Synthesis of Some New Benzimidazole-5(6)-carboxylic Acids

Hakan Göker* [a], Süreyya Ölgen [a], Rahmiye Ertan [a],
Hülya Akgün [b], Süheyla Özbey [c], Engin Kendi [c], and Gül Topçu [d]

[a] Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 06100 Tandogan, Ankara-Turkey; [b] Hacettepe University, Faculty of Pharmacy, Sihhiye, Ankara-Turkey, [c] Hacettepe University, Department of Physics Engineering, 06532, Beytepe, Ankara-Turkey
[d] Marmara Research Center, Gebze, Kocaeli-Turkey

The title compounds, 1,2-dialkyl-benzimidazole-5(6)-carboxylic acids **34-45** were prepared at four steps; 1) preparation of mono amide derivatives **1-11** by the reaction of methyl 3,4-diaminobenzoate and substituted phenyl or phenoxyacetic acid chlorides; 2) preparation of the methyl benzimidazolecarboxylates **12-22**, with zinc chloride and dry hydrogen chloride gas; 3) alkaline hydrolysis of the esters **23-33**; and 4) substitution of the imidazole ring with benzyl or *p*-fluorobenzyl bromide, in alkali medium. 2-Aryl-benzimidazole-5(6)-carboxylic acids **50-53** were prepared *via* the oxidative condensation of 3,4-diaminobenzoic acid and aromatic aldehydes with cupric ion.

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Benzimidazole is an interesting heterocyclic ring because it is present in naturally occurring cyanocobalamine and various drugs such as omeprazole [1], mebendazole [2], astemizole [3], and emedastine difumarate [4,5]. In this study, our aim was to prepare 1-(*p*-substituted benzyl)-2-alkyl **34-45** and 2-aryl **50-53** benzimidazole-5(6)-carboxylic acids, and to examine their chemical properties such as tautomerism and biological activities. In the last decade, the structure of benzimidazole-5(6)-carboxylic acid was widely used in the design of therapeutic agents such as diuretic and natriuretic [6], antiparasitic [7], serotonin antagonist [8], antineoplastic and antifilarial [9], herbicides [10] and antihypertensive [11] compounds.

Synthesis of the targeted benzimidazoles (Scheme 1) involved four steps. Acylation of methyl 3,4-diaminobenzoate with several substituted phenyl or phenoxyacetic acid chlorides gave the corresponding mono amide derivatives **1-11**, following this, cyclization of these compounds with anhydrous zinc chloride and dry hydrogen chloride gas afforded methyl benzimidazolecarboxylates **12-22** in good yield, then alkaline hydrolysis of the **12-22** gave the corresponding carboxylic acids **23-33**. Final products **34-45** were obtained by the reaction of **23-33** with benzyl or *p*-fluorobenzyl bromide in 33% sodium hydroxide solution, some of them as a mixture of isomers (Scheme 1). Some physicochemical properties and spectral data of **34-45** are given in Table 1. At the final stage of preparing **34-45**, since the benzimidazoles **23-33** bear a substituent on the benzenoid ring, a mixture of two regioisomers (5-carboxy and 6-carboxy derivatives) are obtained in different ratios [12]. Tlc Analysis chloroform:acetone:petroleum ether:acetic acid 10:6:15:0.6 v/v) of the mixture **34, 36, 37, 44** and **45** reveals two spots

Scheme 1

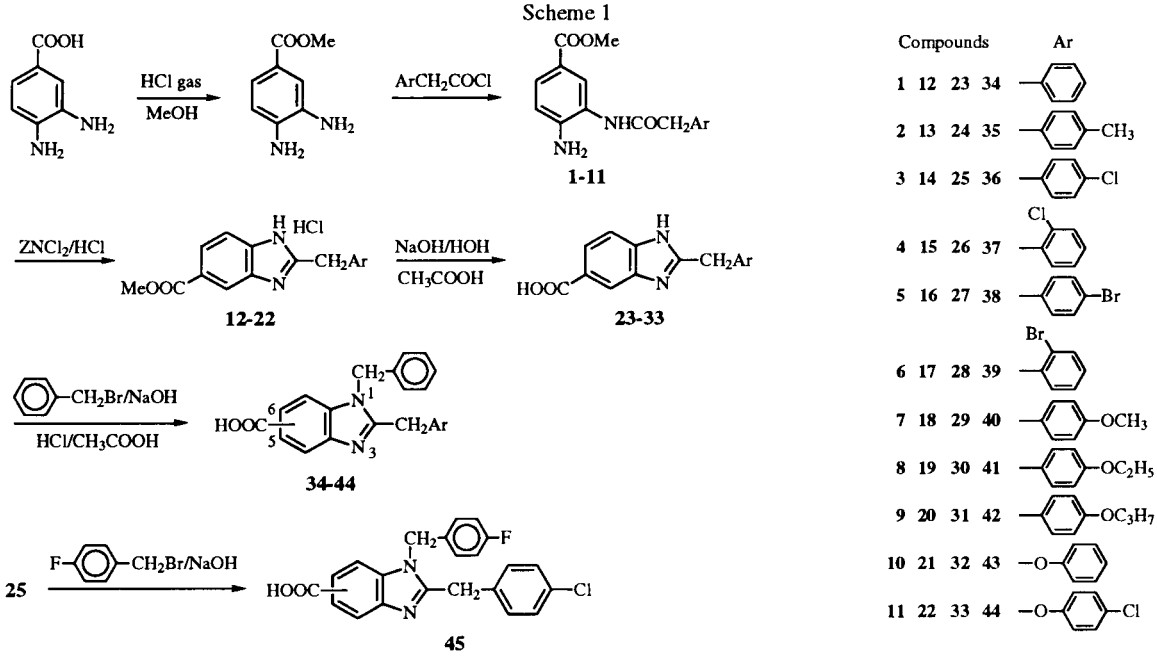
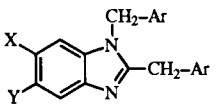


Table 1

Some Physicochemical Properties and Spectral Findings of **34-45**



No.	X	Y	mp (°) [a]	Yield (%)	Formula	IR ν (CO)	^{1}H nmr (δ ppm) [c]	MS (EI, 70 eV)	Elemental Analyses Calcd./Found C	H	N
34	H COOH	COOH H	[b]	80	$C_{22}H_{18}N_2O_2$ 0.4 EtOH	1680	6.8-7.4 (11H, aromatic)	342 (M^+, 81), 251 (86), 205 (9.5), 167 (40.5), 91 (100)	75.91 75.94	5.66 5.76	7.76 7.69
35	H	COOH	205-207	83	$C_{23}H_{20}N_2O_2$	1690	2.2 (s, 3H, -CH_3) 6.7-7.3 (10H, aromatic)	356 (M^+85.5), 341(18), 265(100), 250 (18), 181 (64.5), 91 (87.5)	77.51 77.52	5.66 5.63	7.86 7.82
36	H COOH	COOH H	[b]	76	$C_{22}H_{17}ClN_2O_2$ 0.5 EtOH	1685	6.8-7.4 (10H, aromatic)	376 (M^+, 96), 378 (M+2, 31), 285 (97), 250 (88), 201(100), 203 (31), 125 (35), 91 (61)	69.17 68.88	5.01 4.92	7.02 6.92
37	H COOH	COOH H	[b]	77	$C_{22}H_{17}ClN_2O_2$ EtOH	1690	6.8-7.7 (10H, aromatic)	376 (M^+, 4.2), 378 (M+2, 1.2), 341 (96), 285 (4.3), 287 (1.3), 250 (12), 91 (100)	68.16 67.83	5.48 5.35	6.62 6.51
38	H	COOH	216-221	79	$C_{22}H_{17}BrN_2O_2$	1685	6.7-7.4 (10H, aromatic)	420 (M^+, 65), 422 (63.5), 341 (5.5), 329 (26.5), 331 (25.5), 250 (76), 245 (37), 247 (36), 91 (100)	62.72 62.59	4.07 4 03	6.65 6 69
39	H	COOH	232-235	82	$C_{22}H_{17}BrN_2O_2$	1685	6.8-7.4 (10H, aromatic)	420 (M^+, 2.1), 422 (M+2, 1.9), 341 (91.5), 250 (12.5), 91 (100)	62.72 62.69	4.07 4.08	6.65 6.61
40	H	COOH	204-205	80	$C_{23}H_{20}N_2O_3$	1690	3.7 (s, 3H; - OCH_3) 6.7-7.35 (10H, aromatic)	372 (M^+, 92), 357 (37.5), 282 (78), 250 (78.5), 198 (82.5), 121 (100), 91 (61)	74.18 74.21	5.41 5.38	7.52 7.49
41	H	COOH	203-205	86	$C_{24}H_{22}N_2O_3$	1690	1.3 (t, 3H, -OCH_2CH_3) 3.9 (q, 2H, -OCH_2CH_3) 6.7-7.3 (10H, aromatic)	386 (M^+, 11), 371 (21), 294 (6.5), 212 (9), 197 (8), 117 (28), 91 (58.5), 57 (100)	74.59 74.49	5.74 5.76	7.25 7.24
42	H	COOH	207-208	80	$C_{25}H_{24}N_2O_3$	1690	0.95 (t, 3H, -CH_3) 1.75 (m, 2H, -OCH_2CH_2) 3.85 (t, 2H, -OCH_2) 6.7-7.3 (10H, aromatic)	400 (M^+, 70.5), 357 (30), 309 (83.5), 267 (76), 250 (25.5), 225 (100), 183 (79.5), 107 (62.3), 92 (82), 91 (54)	74.98 74.94	6.04 6.11	7.00 6.96
43	H	COOH	236	76	$C_{22}H_{18}N_2O_3$	1690	5.6 (s, 2H, -[2]-CH_2-O-) 6.7-7.4 (11H, aromatic)	358 (M^+, 66.5), 265 (100), 250 (7.3), 183 (7.5), 91 (57)	73.73 73.57	5.06 5.08	7.82 7.73
44	H COOH	COOH H	[b]	82	$C_{22}H_{17}ClN_2O_3$ 0.5 EtOH	1690	5.6 (s, 2H, -[2]-CH_2-O-) 6.7-7.4 (10H, aromatic)	392 (M^+, 17), 394 (M+2, 6.1), 265 (100), 220 (4.5), 128 (5.7), 91 (71.5)	66.50 66.41	4.82 4.69	6.75 6.84
45	H COOH	COOH H	[b]	74	$C_{22}H_{16}ClFN_2O_2$ 0.3 EtOH	1690	6.7-7.6 (9H, aromatic)	394 (M^+, 43), 396 (M+2, 15), 285 (39), 287 (13), 250 (23), 219 (29), 221 (9.8), 109 (100)	66.51 66.81	4.36 4.41	7.10 NA [d]

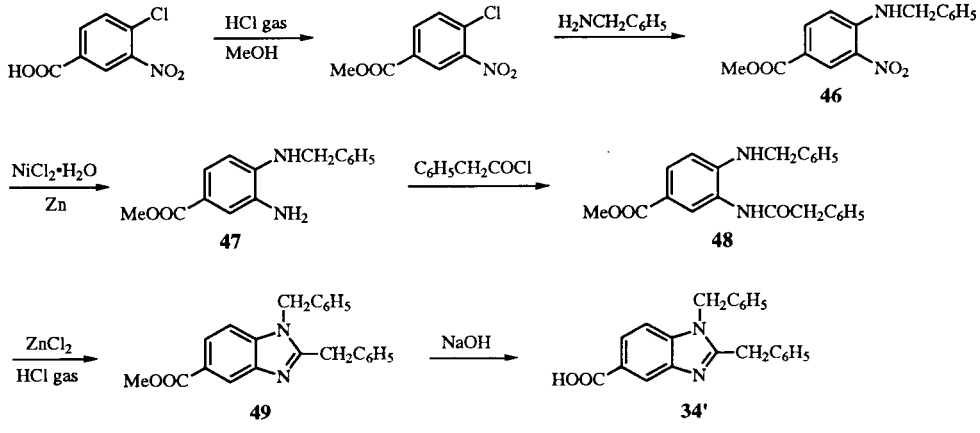
[a] Recrystallization solvents for **35** and **38**: 2-propanol others ethanol. [b] Due to a mixture of two positional isomer, they have no sharp mp. [c] Common protons: δ (deuteriochloroform) 4.2-4.35 (s, 2H, -[2]-CH_2-φ, if not stated otherwise), 5.2-5.5 (s, 2H, -[1]-CH_2-φ), 7.85-8.00 (dd, 1H, J_o = 9-10 Hz, J_m = 1 Hz, H-6), 8.4-8.75 (d, 1H, J_m = 1 Hz, H-4). [d] Not available.

with very close R_f values and they have no sharp mp. Their ^1H nmr spectra also showed double proton signals [particularly, (C-2)-C*H*$_2$ (4.2 and 4.3 δ ppm), (N-1)-C*H*$_2$ (5.2 and 5.25 δ ppm) and (C6,7)-H] and are not suitable for the differentiation between these regioisomers as a mixture. Since the isomers have very close R_f values the separation of mixtures is usually difficult [13], therefore no efforts were made to separate the mixtures by chromatography. However a regioselective synthesis of **34'** (5-carboxy) was accomplished using the route in Scheme 2, in order to see if it has a similar biological activity as **34**. Aromatic nucleophilic substitution of the chlorine atom of methyl 4-chloro-3-nitrobenzoate with benzylamine afforded **46**. According to the method Nose and Kudo [14] reduction of **46** with nickel(II) chloride hexahydrate and zinc gave **47** in good yield. Amidification of **47** with phenylacetyl chloride, followed by cyclization of **48**, yielded **49**, then alkaline hydrolysis of **49** gave **34'**. One of the tlc spots of **34** (0.75 and 0.84) corresponds to **34'** with R_f 0.75.

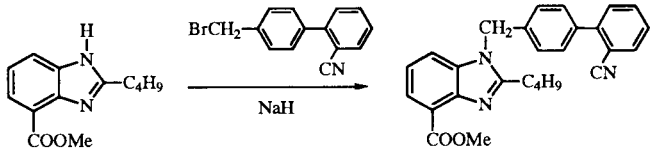
It was reported [11] that only one regioisomer could be obtained if the benzimidazole ring possesses a carboxymethyl group at C-4(7). This selectivity was attributed to the steric hindrance caused by the methoxycarbonyl group on the nearest nitrogen atom (Scheme 3).

On the other hand, it was reported that the electronic effect of the substituents on the benzonoid ring does not influence the ratio of the isomers. Even a very strong electron withdrawing substituents C-5(6)-nitro could not differentiate the proportion of the isomers [13]. In contrast Louvet *et al.* [15] stated that, while the reaction of 4-chloro-*o*-phenylendiamine with 2-acetoxybenzoic acid afforded the isomeric mixture **I** and **II** (Scheme 4), but the same reaction with 3,5-dichloro-*o*-phenylenediamine afforded just one isomeric derivative

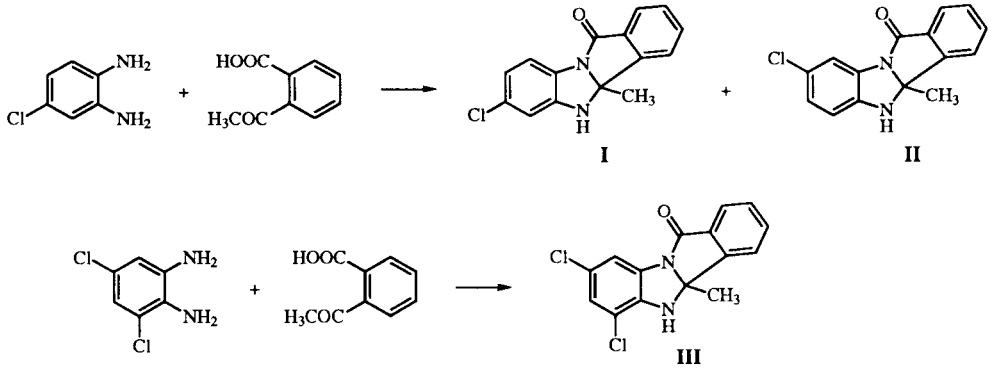
Scheme 2



Scheme 3



Scheme 4



III, even after a much longer reaction period. They concluded that, these results could be attributed to the additive electron withdrawing nature of the two chlorine atoms.

As depicted in Table 1, 1,2-disubstituted 5(6)-benzimidazolecarboxylic acids yielded a mixture of regioisomers of **34, 36, 37, 44** and **45** in different proportions. Surprisingly compounds **39-43** were obtained only as 5-carboxy regioisomers. These results may be explained with the electron withdrawing effect of the carboxy group. Steric effect could not be considered due to the position of the carboxy group. In addition, since the one of the isomers of **35** and **38** were seen in rather small quantities upon tlc, after the first crystallization from the ethanol, then recrystallization from the 2-propanol gave the completely pure (5-carboxy) isomers of **35** and **38**. Crystallization was not a suitable separation procedure for the other isomeric mixtures. Further studies are necessary to explain the effect of the 5(6)-carboxy substituent for producing the ratio of the isomers.

When a N^1-substituted benzimidazole compound possessing a 5-carboxy group, the signal of H-4 will be expected to resonate as a doublet with *meta* coupling (J_m = 1-2 Hz) at lower field due to the anisotropic effect of the double bond in the imidazole ring [11,12] and the carbonyl group. Similarly H-6 must appear as a doublet of doublets with *meta* and *ortho* coupling constants (J_m = 1-2 Hz, J_o = 8-10 Hz) at higher field than H-4. These expectations are confirmed by the ^{1}H nmr spectrum of **34'**. Since the ^{1}H nmr spectra of **35, 38, 39-43** appears as completely expected without any extra peaks belong to the other isomer, their structures were proposed as 5-carboxy substituted. X-ray structure analysis (Tables 2-5) of **35** also revealed that this compound possesses the COOH group at C5 as shown in Figure 1 and the carboxyl group is slightly twisted out of the plane of the benzene ring plane by 8.5°. The phenyl rings at the N1 and C2 are essentially planar. In addition the benzimidazole nucleus is also planar with the 2.68° dihedral angles between the imidazole and benzene ring planes. Both of the phenyl rings are almost perpendicular to the benzimidazole nucleus (the torsion angles C2-N1-C10-C11 and N3-C2-C20-C21 are 108.6 and 105.6°, respectively).

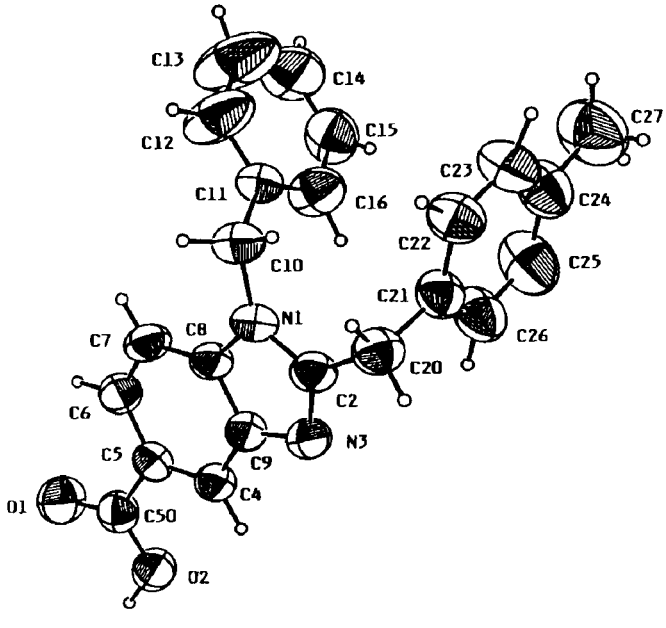


Figure 1. An ORTEP-II drawing of the molecule **35** with 50% probability ellipsoids. The H atoms are shown as circles of an arbitrary small diameter.

Table 2

Experimental Data for the Crystallographic Analysis

Molecular formula	$C_{23}H_{20}N_2O_2$
Molecular weight	356.43
Crystal system	Monoclinic
Space group	P21/n
a, Å	11.574(1)
b, Å	12.034(1)
c, Å	14.694(1)
β, deg.	109.64(5)
V, Å^3	1927(1)
Z	4
ρ calcd., g.cm^{-3}	1.23
F(000)	752
μ, cm^{-1}	0.7
Temperature, °C	23
Crystal size, mm	0.64 x 0.30 x 0.92
Scan type	ω-2θ
Scan width	0.7+1.90tan(θ)
θ range, deg.	10-18
Standard reflections	three, measured every two hours
Nb of measured reflections	4315
Nb of reflections used Fo>3.0(Fo)	1796
Min-max height in final Δρ, e.Å^{-3}	-0.061-0.14
Nb of refined parameters	321
$R = [\Sigma(\Delta F)/\Sigma Fo]$	0.045
$Rw = [\Sigma(\Delta F)^2 / \Sigma w\, Fo^2]^{\frac{1}{2}}$	0.055
$W = 4Fo/\sigma Fo$	

Table 3

Fractional Atomic Coordinates for Non-hydrogen Atoms of **35**

Atom	x/a	y/b	z/c	B(eqv)
O1	0.1301(2)	0.2716(2)	0.2319(1)	6.81(5)
O2	0.2656(2)	0.1392(1)	0.2985(1)	6.11(5)
N1	-0.1258(2)	-0.1691(2)	0.0231(1)	4.44(5)
N3	0.0640(2)	-0.2140(2)	0.1156(1)	4.62(5)
C2	-0.0379(2)	-0.2505(2)	0.0508(2)	4.53(6)
C4	0.1213(2)	-0.0241(2)	0.1889(2)	4.34(6)
C5	0.0775(2)	0.0836(2)	0.1863(2)	4.29(6)
C6	-0.0418(2)	0.1113(2)	0.1276(2)	4.86(6)
C7	-0.1188(2)	0.0335(2)	0.0707(2)	4.89(6)
C8	-0.0756(2)	-0.0740(2)	0.0726(2)	4.18(6)
C9	0.0433(2)	-0.1036(2)	0.1310(2)	4.11(6)
C10	-0.2492(2)	-0.1774(2)	-0.0479(2)	5.02(6)
C11	-0.3512(2)	-0.1773(2)	-0.0060(2)	4.61(6)
C12	-0.4611(3)	-0.1376(4)	-0.0616(2)	9.9(1)
C13	-0.5593(3)	-0.1389(5)	-0.0294(3)	13.6(2)
C14	-0.5487(3)	-0.1775(3)	0.0585(2)	8.9(1)
C15	-0.4413(3)	-0.2163(3)	0.1151(2)	7.49(9)
C16	-0.3406(3)	-0.2172(3)	0.0827(2)	6.83(8)
C20	-0.0572(2)	-0.3662(2)	0.0137(2)	5.41(7)
C21	-0.1403(2)	-0.4315(2)	0.0547(2)	5.17(7)
C22	-0.2484(2)	-0.4777(2)	-0.0035(2)	5.96(7)

Table 3 (continued)

Atom	x/a	y/b	z/c	B(eqv)
C23	-0.3261(3)	-0.5321(3)	0.0350(2)	7.22(9)
C24	-0.2992(3)	-0.5423(3)	0.1327(2)	7.50(9)
C25	-0.1900(3)	-0.4980(3)	0.1905(2)	8.8(1)
C26	-0.1110(3)	-0.4445(3)	0.1527(2)	7.38(9)
C27	-0.3903(4)	-0.5926(4)	0.1755(3)	11.3(1)
C50	0.1585(2)	0.1734(2)	0.2412(2)	4.82(6)

Table 4

Interatomic Distances (Å) of **35**

O1 - C50	1.221(3)	C10 - C11	1.504(4)
O2 - C50	1.310(3)	C11 - C12	1.346(4)
N1 - C2	1.371(3)	C11 - C16	1.356(4)
N1 - C8	1.376(3)	C12 - C13	1.369(6)
N1 - C10	1.463(3)	C13 - C14	1.339(6)
N3 - C2	1.317(3)	C14 - C15	1.327(4)
N3 - C9	1.382(3)	C15 - C16	1.399(5)
C2 - C20	1.485(4)	C20 - C21	1.515(4)
C4 - C5	1.388(3)	C21 - C22	1.374(3)
C4 - C9	1.392(3)	C21 - C26	1.372(4)
C5 - C6	1.401(3)	C22 - C23	1.379(5)
C5 - C50	1.479(3)	C23 - C24	1.367(4)
C6 - C7	1.366(3)	C24 - C25	1.372(4)
C7 - C8	1.384(4)	C24 - C27	1.524(6)
C8 - C9	1.402(3)	C25 - C26	1.379(5)

Compounds **50-53** were prepared by the method of Scheme 5, *via* the oxidative condensation of 3,4-diaminobenzoic acid and aromatic aldehydes with cupric ion [16]. Copper complexes were obtained at the room temperature and treatment of this complexes with hydrogen sulfide gave the expected 2-arylbenzimidazole5-(6)-carboxylic acids **50-51**. Deprotection of **50-51** by heating under reflux in hydrochloric acid (37%) gave the final products **52-53**. Biological activities of these compounds are under examination and will be published later.

Scheme 5

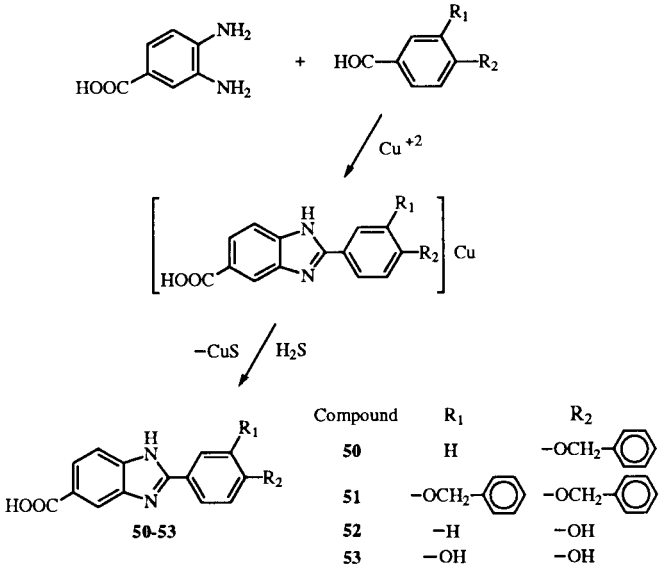


Table 5

Bond Tables (degrees) of **35**

C2 - N1 - C8	107.4(2)	C10 - C11 - C16	124.3(2)
C2 - N1 - C10	127.7(2)	C12 - C11 - C16	118.1(3)
C8 - N1 - C10	124.9(2)	C11 - C12 - C13	120.8(3)
C2 - N3 - C9	106.1(2)	C12 - C13 - C14	121.3(3)
N1 - C2 - N3	111.7(2)	C13 - C14 - C15	119.3(3)
N1 - C2 - C20	123.8(2)	C14 - C15 - C16	120.1(3)
N3 - C2 - C20	124.5(2)	C11 - C16 - C15	120.5(2)
C5 - C4 - C9	118.0(2)	C2 - C20 - C21	112.2(2)
C4 - C5 - C6	120.9(2)	C20 - C21 - C22	121.9(2)
C4 - C5 - C50	120.6(2)	C20 - C21 - C26	120.7(2)
C6 - C5 - C50	118.3(2)	C22 - C21 - C26	117.4(3)
C5 - C6 - C7	121.3(2)	C21 - C22 - C23	121.3(2)
C6 - C7 - C8	118.1(2)	C22 - C23 - C24	121.6(3)
N1 - C8 - C7	133.0(2)	C23 - C24 - C25	116.9(3)
N1 - C8 - C9	105.4(2)	C23 - C24 - C27	121.6(3)
C7 - C8 - C9	121.6(2)	C25 - C24 - C27	121.3(3)
N3 - C9 - C4	130.4(2)	C24 - C25 - C26	122.0(3)
N3 - C9 - C8	109.4(2)	C21 - C26 - C25	120.9(3)
C4 - C9 - C8	120.1(2)	O1 - C50 - O2	122.5(2)
N1 - C10 - C11	114.9(2)	O1 - C50 - C5	123.3(2)
C10 - C11 - C12	117.6(2)	O2 - C50 - C5	114.2(2)

EXPERIMENTAL

Instrumentation.

Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded with a Bruker AC 200L and Bruker AC 80 spectrophotometer, in DMSO-d_6 unless otherwise stated, δ scale (ppm) from internal standard TMS. The ir spectra were recorded on a PYE-UNICAM SP-1025 spectrophotometer as potassium bromide pellets. All ν N-C=O 1650-1665 cm^{-1}, all ν MeO-C=O 1730-1735 cm^{-1}, if not stated otherwise. The mass spectra (in El mode at 70 eV) and elemental analysis were determined at Marmara Research Center. Methyl 3-nitro-4-phenylmethylaminobenzoate **46** and methyl 3-amino 4-phenylmethylaminobenzoate **47** were prepared according to the literature [17].

Methyl 3,4-Diaminobenzoate.

The mixture of 3,4-diaminobenzoic acid (5 g, 32.9 mmoles) and methanolic hydrogen chloride (9%, 50 ml) were refluxed for 1 hour. Methanol was removed, under pressure made alkaline with sodium carbonate solution. The precipitate was collected and crystallized from ethanol:water, light pink coloured, 66% yield, mp 107°, lit [18] mp 108°.

Compounds **1-11**.

The phenyl or phenoxyacetic acids (7.35 mmoles) were refluxed in benzene (5 ml) with thionyl chloride (2.5 ml) for 1 hour at 80°. The solvent and excess thionyl chloride were evaporated and methyl 3,4-diaminobenzoate (7.5 mmoles in 15 ml of benzene) and 7.35 mmoles of pyridine were added. The mixture was refluxed for 3 hours. Removal of the solvent gave a residue which was crystallized from chloroform:ethanol (1:4, v/v) to give compounds **1-11**.

Compound	1	2	3	4	5	6	7	8	9	10	11
mp	219	202	225	221	235	229	200	202	189	184	212
Yield %	49	56	62	56	47	48	58	73	74	68	67

The ^{1}H nmr spectra of **1-11** are: δ 2.3 (s, 3H, *p*-tolyl C*H*$_3$ protons of **2**), 3.65-3.8 (s, 3H, COOC*H*$_3$), 3.55-4.75 (s, 2H, COC*H*$_2$), 1.05-4.05 (alkyloxy protons of **7-9**), 6.8-7.3 (aromat), 7.75-7.85 (2H, *H*-2,6), 8.05-8.2 (s, 1H, N*H*CO), 9.40-9.90 (s, 2H, N*H*$_2$). The integral values support the proton numbers.

Compounds **12-22**.

To a mixture of 2 mmoles of compounds **1-11** in anhydrous ethanol (20 ml), freshly prepared anhydrous zinc chloride (10 mmoles) was added. After dissolving all of the zinc chloride, dry hydrogen chloride gas (1.5 g) was passed through the clear solution which was refluxed until the starting materials were used up (at least 3 hours). Then ethanol was evaporated, dilute ammonium hydroxide solution was added, and the mixture was extracted with chloroform. The extract was washed with water 3 times, dried (sodium sulfate) and evaporated. The oily residue was dissolved in ethanol, a few drops of concentrated hydrochloric acid were added and stirred vigorously. After addition of ether, hydrochloride salts **12-22** were precipitated.

Compound	12	13	14	15	16	17	18	19	20	21	22
mp	232	234	238	234	245	225	232	225	229	233	237
Yield %	68	53	21	24	31	45	43	47	53	54	51

The ^{1}H nmr spectra of **12-22** are: δ 3.5-3.7 (s, 3H, COOC*H*$_3$). Other nmr data are the same for **23-33**.

Compounds **23-33**.

The ester derivatives (5.5 mmoles) in ethanol were refluxed in 3% sodium hydroxide (10 ml) for 40 minutes on the water bath. The reaction mixture was cooled, diluted with water and neutralized with glacial acetic acid. The crude product was precipitated and then crystallized with ethanol.

Compound	23	24	25	26	27	28	29	30	31	32	33
mp	155	96	153	155	165	173	149	151	145	123	118
Yield %	79	93	53	55	54	50	63	66	70	88	77

The ^{1}H nmr spectra of **23-33** are: δ 2.1 (s, 3H, *p*-tolyl C*H*$_3$ protons of **24**), 4.25-5.3 (s, 2H, C*H*$_2$), 0.95-3.9 (alkyloxy protons of **29-31**), 6.9-7.6 (aromat), 7.7-7.9 (dd, 1H, J_o = 10 Hz, J_m = 1.5 Hz, H-6), 8.1 (d,1H, J_m = 1 Hz, H-4), 12-13 (broad s, -COOH).

Compounds **34-44**.

A mixture of **23-33** (2 mmoles), benzyl bromide (4 mmoles) and 33% w/w aqueous sodium hydroxide (10 ml) were stirred at 60° for 0.5 hour, hydrochloric acid (37%, 6.5 ml) was added and stirred, then the reaction mixture was acidified with glacial acetic acid. The precipitate was filtered and washed with water, then crystallized from ethanol. Compound **35** and **38** were recrystallized from 2-propanol.

1-(*p*-Fluorophenylmethyl)-2-(*p*-chlorophenyl)-1*H*-benzimidazole-5 and 6-carboxylic Acid (**45**). (Mixture of Isomers).

The above compound was prepared in analogy to **34-44,** starting from **25** (0.71 g, 2.5 mmoles) and *p*-fluorobenzyl bromide (0.945 g, 5 mmoles).

Methyl 3-Phenylmethylcarbonylamino-4-phenylmethylaminobenzoate (**48**).

The mixture of compound **47** (0.9 g, 2.72 mmoles) and phenylacetyl chloride (0.42 g, 2.72 mmoles) in benzene (20 ml) were refluxed with pyridine (0.25 g, 3 mmoles) for 4 hours. The solvent was evaporated and the residue was extracted with chloroform. The chloroform layer was washed with sodium carbonate solution (5%) and water. The solvent was evaporated, and the product was crystallised from ethanol, colorless crystals, 0.3 g (25%), mp 165°; ir: ν COOMe 1720, ν NHCO 1660 cm^{-1}; ^{1}H nmr: δ 3.71 (s, 2H, NHCOC*H*$_2$-ϕ), 3.75 (s, 3H, COOMe), 4.43 (d, J = 5.49 Hz, 2H, NHC*H*$_2$-ϕ), 6.39 (t, J = 5.18 Hz, 1H, N*H*CH$_2$), 6.68 (d, 1H, J_o = 8.68 Hz, H-5), 7.25-7.4 (10H, aromat), 7.56 (d, 1H, J_o = 8.28 Hz, H-6), 7.70 (s, 1H, H-2), 9.3 (s, 1H, NHCO).

Methyl 1,2-Di-(phenylmethyl)-1*H*-benzimidazole-5-carboxylate (**49**).

The compound was prepared in analogy to **12-22,** starting from **48** (0.5 g, 1.11 mmoles). After evaporation of the chloroform, the product was crystallised from ethanol, colorless crystals, 0.1 g (21%), mp 121°; ir: ν CONH 1720 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.75 (s, 3H, COOMe), 4.2 (s, 2H, 2 C*H*$_2$-ϕ), 5.2 (s, 2H, 1 C*H*$_2$-ϕ), 6.8-7.4 (11H, aromat), 7.9 (dd,1H, J_o =10 Hz, J_m = 1 Hz, H-6), 8.5 (s, 1H, J_m = 1 Hz, H-4).

1,2-Di-(phenylmethyl)-1*H*-benzimidazole-5-carboxylic Acid (**34'**).

This compound was prepared in analogy to **23-33** starting from **49** (0.2 g, 0.46 mmole). The precipitate was filtered and crystallised from 2-propanol, colorless crystals, 0.135 g (85%), mp 232°; ^{1}H nmr: δ 4.2 (s, 2H, 2 C*H*$_2$-ϕ), 5.25 (s, 2H, 1 C*H*$_2$-ϕ), 6.8-7.4 (12H, aromat), 7.85 (dd, 1H, J_o = 10 Hz, J_m = 1 Hz, H-6), 8.3 (d, 1H, J_m = 1 Hz, H-4).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.16; H, 5.30; N, 8.19. Found: C, 76.89; H, 5.34; N, 8.21.

2-(4-Benzyloxyphenyl)-1*H*-benzimidazole-5(6)-carboxylic Acid (**50**).

A solution of 3,4-diaminobenzoic acid (2.05 g, 13.5 mmoles) in 5% acetic acid and a solution of 4-benzyloxybenzaldehyde (3.90 g, 18.5 mmoles) in methanol (100 ml) was mixed, followed by adding a solution of cupric acetate (3.7 g, 18.5 mmoles) in water 50 ml. The mixture was stirred vigorously and heated briefly to boiling and then filtered hot. The precipitate was washed with water and dissolved in ethanol containing concentrated hydrochloric acid (5 ml). A solution of sodium sulfide nonahydrate (5 g) in water was added, then filtered hot to remove the copper(II) sulfide. The *p*H of the solution was adjusted to 5-6 by sodium hydroxide solution and diluted with water, then the precipitate was collected. The crude product was dissolved in 5% sodium hydroxide solution, filtered and acidified with acetic acid. The precipitate was collected and washed with water then crystallized from aqueous ethanol with the aid of active carbon, white needle crystals, 2.1 g (47%), mp 263°; ir : ν CO 1700 cm^{-1}; ^{1}H nmr: δ 5.25 (s, 2H, -OC*H*$_2$-ϕ), 7.0-7.4 (m, 6H, aromat), 7.6 (d, 2H, J_o = 9 Hz, H-3' and 5'), 7.85 (d, 2H, J_o = 9 Hz, H-2' and 6'), 8.25 (m, 2H, H-4 and H-6).

2-(3,4-Dibenzyloxyphenyl)-1*H*-benzimidazole-5(6)-carboxylic Acid (**51**).

The compound was prepared in analogy to **50**, starting from 3,4-diaminobenzoic acid (2.05 g, 13.5 mmoles) and 3,4-dibenzyloxybenzaldehyde (5.88 g, 18.5 mmoles). The crude product was directly crystallized from aqueous ethanol with active carbon, white powder, 1.95 g (32%), mp 259°; ir: ν CO 1700 cm^{-1}; ^1H nmr: δ 5.25 (s, 4H, -OCH_2-ϕ), 7.15-8.0 (m, 15H, aromat), 8.25 (d, 1H, J_m = 1 Hz, H-4).

2-(4-Hydroxyphenyl)-1*H*-benzimidazole-5(6)-carboxylic Acid (**52**).

Compound **50** (0.45 g, 1.3 mmoles) was refluxed in 6*M* aqueous hydrochloric acid for 30 hours, the solution allowed to cool, and the resulting precipitate collected by filtration. The solid was washed with water and dried in vacuum to give pure **52** as its hydrochloride salt, 0.28 g (74%), mp >285°; ir: ν CO 1705 cm^{-1}; ^1H nmr: δ 7.05 (d, 1H, J_o = 9 Hz, H-7), 7.75 (d, 2H, J_o = 8 Hz, H-3',5'), 8.0 (d, 2H, J_o = 8 Hz, H-2',6'), 8.3 (m, 2H, H-4,6); ms: m/z 254 ($M^{+\cdot}$, 100), 237 (26.64), 209 (10.89).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$•HCl•0.6H_2O: C, 55.76; H, 4.05; N, 9.29. Found: C, 56.01; H, 4.06; N, 9.15.

2-(3,4-Dihydroxyphenyl)-1*H*-benzimidazole-5(6)-carboxylic Acid (**53**).

The compound was prepared in analogy to **52**, starting from **51** (0.65 g, 1.44 mmoles). Recrystallization of the crude product from ethanol:water gave the **53**, with active carbon as light yellow coloured product, 0.25 g (56%), mp >285°; ir: ν CO 1705 cm^{-1}; ^1H nmr: δ 7.0 (d, 1H, J_o = 9 Hz, H-7), 7.6-7.8 (m, 3H, H-2',5',6'), 8.0 (dd, 1H, J_o = 9 Hz, J_m = 1 Hz, H-6), 8.3 (d, 1H, J_m = 1 Hz, H-4); ms: m/z 270 ($M^{+\cdot}$, 100), 253 (25.24), 225 (18.33).

Anal. Calcd. for $C_{14}H_{10}N_2O_4$•HCl•H_2O: C, 51.78; H, 4.04; N, 8.63. Found: C, 51.89; H, 4.13; N, 8.98.

X-Ray Crystallography of Compound **35**.

Crystallographic and refinement parameters are summarized in Table 2. The data were collected on a Nonius CAD 4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Three standard reflections were measured every two hours, insignificant change was observed. The structure was solved by direct methods. Refinements were carried out by full-matrix least square techniques. Non-hydrogen atoms were anisotropically refined. The hydrogen atoms were generated in idealized positions 0.95Å from the bonded carbon atom and refined isotropically. An empirical ψ-scan absorption correction was applied from the MolEN [19] which has been used to carry out all the calculations. The final atomic parameters for non-hydrogen atoms are reported in Table 3. Bond lengths and bond angles are listed in Tables 4 and 5, respectively. The view of the molecule was performed using ORTEP [20].

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