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SYNTHESIS AND REACTIONS OF SOME 5(6)-(1-ADAMANTYL)BENZIMIDAZOLES

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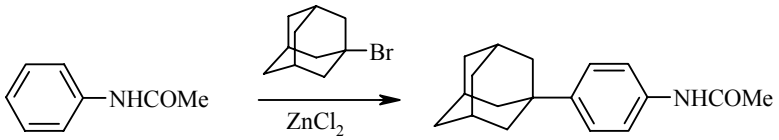
4-(1-Adamantyl)-1,2-diaminobenzene, previously unreported in the literature, has been prepared and a novel series of 5(6)-(1-adamantyl)benzimidazole derivatives synthesized. Nitration, hydrogenation, and side chain reactions have been carried out.

Keywords: adamantane, benzimidazole, *o*-phenylenediamine, hydrogenation, hydrolysis, condensation, nitration, cyclization.

Substances with an adamantane fragment in the molecule have a broad spectrum of biological activity [1-3]. We have previously reported [4, 5] the synthesis and reactions of 5(6)-(1-adamantyl)benzimidazoles. The synthesized benzimidazoles were assayed for their biocide, antihelmintic, antitumor, and anti HIV activity [6, 7] revealing compounds with identified activity. The results obtained point to the promise of a directed synthesis of benzimidazoles with adamantane substituents. Hence the search for novel biologically active compounds through the synthesis of adamantane-containing benzimidazoles and a study of their physicochemical and biological properties is a very timely scientific task.



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It is known that the main problem in the synthesis of benzimidazoles is the preparation of the corresponding substituted *o*-phenylenediamine. The aim of our work was the discovery of optimum conditions for synthesizing adamantane-containing *o*-phenylenediamine. The key reagent in the synthesis of 4-(1-adamantyl)-1,2-diaminobenzene (**4**) is 1-(4-acetamidophenyl)adamantane (**1**). The methods of preparing compound **1** in the literature [8, 9] are multistage demanding the use of acetanilide in a tenfold excess and are characterized by further technical difficulties. The authors of [8] have noted that an attempt to prepare compound **1** by treating 1-bromoadamantane with acetanilide under Friedel-Crafts catalytic conditions was unsuccessful.

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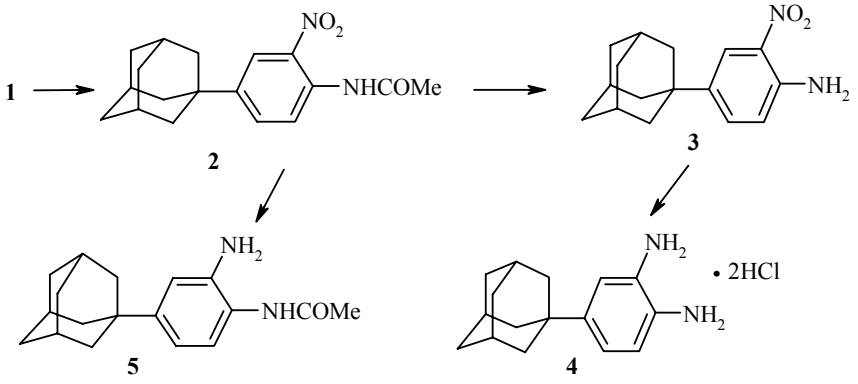
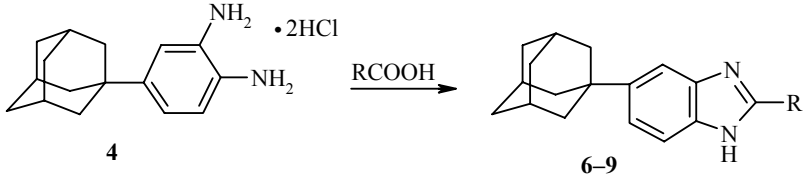
1-(4-Acetamidophenyl)adamantane (**1**) was synthesized by the alkylation of acetanilide by 1-bromoadamantane in tetrachloroethane or nitrobenzene medium in the presence of zinc chloride [10]. The synthesis was carried out at 75ºC in a single stage using an equimolar ratio of reagents.

Compound **1** melts at 197-199ºC instead of the literature figures of 164-165 [8] and 173-175ºC [9]. Nitration of the product **1** obtained by us gave the 1-(4-acetamido-3-nitrophenyl)adamantane (**2**) with mp 212-214ºC, in agreement with literature data [11, 12]. Hydrolysis of compound **1** gives the corresponding aniline which additionally confirms the correctness of structure **1**.



4-(1-Adamantyl)-1,2-diaminobenzene (**4**) was prepared from compound **1** by successive nitration, hydrolysis, and reduction. In the nitration of adamantane **1** we used 58-60% HNO_3 in place of 82% HNO_3 [11, 12]. Nitration using a mixture of nitric and sulfuric acids in the presence of glacial acetic acid and acetic anhydride gave the corresponding compound **2**, hydrolysis of which led to the nitroaniline **3** [11, 12] and hydrogenation gave compound **5**. The reduction of 1-(4-amino-3-nitrophenyl)adamantane (**3**) was carried out in several systems including Fe–NH_4Cl, Fe–HCl, and $SnCl_2 \cdot 2H_2O$–ethanol. The best result was obtained by hydrogenation using molecular hydrogen in absolute ethanol in the presence of Raney nickel. Compound **4** was converted to the dihydrochloride due to its susceptibility to oxidation.



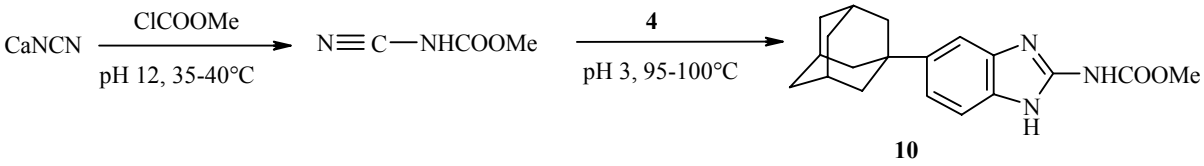
6 R = 1-Ad; **7** R = *o*-C_6H_4Cl; **8** R = *p*-C_6H_4Cl; **9** R = CH_2OPh

Condensation of compound **4** with carboxylic acids was carried out *via* heating the reagents in the ratios 1: 5 and 1: 10 in order to prepare the novel 5(6)-(1-adamantyl)benzimidazoles **6-9**.

The basic properties of compound **4** were greater than *o*-phenylenediamine due to the electron-donor effects of an adamantyl radical. It is known [13] that heating *o*-phenylenediamine with adamantane carboxylic acid at atmospheric pressure does not lead to cyclization to a benzimidazole whereas condensation of compound **4** gave the cyclization product **6** in 97% yield under the same conditions.

Condensation of compound **4** with aromatic acids occurs at high temperature, e.g. in the case of *p*-chlorobenzoic acid at 230-240ºC.

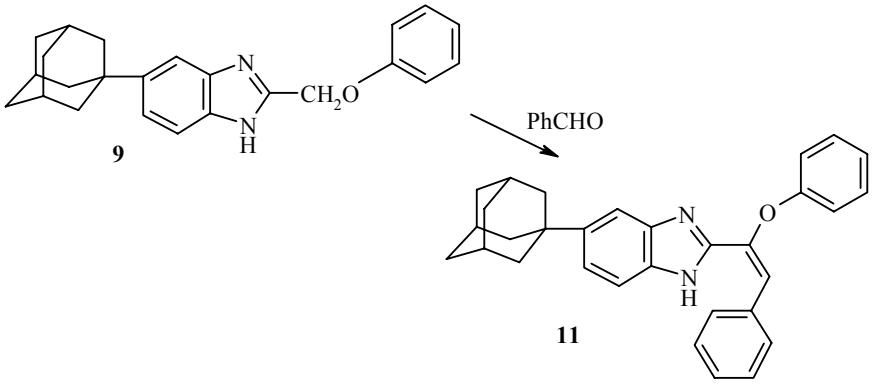
Benzimidazolylcarbamates are widely used in the preparation of fungicide and antihelmintic preparations but the majority of them show embriotoxic and teratogenic properties [14]. With the aim of decreasing the possible appearance of similar side effects we have prepared the adamantyl-substituted benzimidazolylcarbamate **10** [15].



10

5(6)-(1-Adamantyl)-2-methoxycarbonylaminobenzimidazole (**10**) was synthesized in two stages. The optimum conditions found for the process were: stage 1, treatment of calcium cyanamide with methyl chloroformate at 35-40ºC and pH 12; stage 2, reaction of the N-cyanomethylcarbamate with compound **4** at 90-100ºC and pH 3. The product **10** was obtained in 49% yield.

In order to study the mobility of the methylene group protons of the 5(6)-(1-adamantyl)-2-phenoxymethylbenzimidazole (**9**) we have condensed compound **9** with benzaldehyde at 175-179ºC and obtained the product **11** in 50% yield.



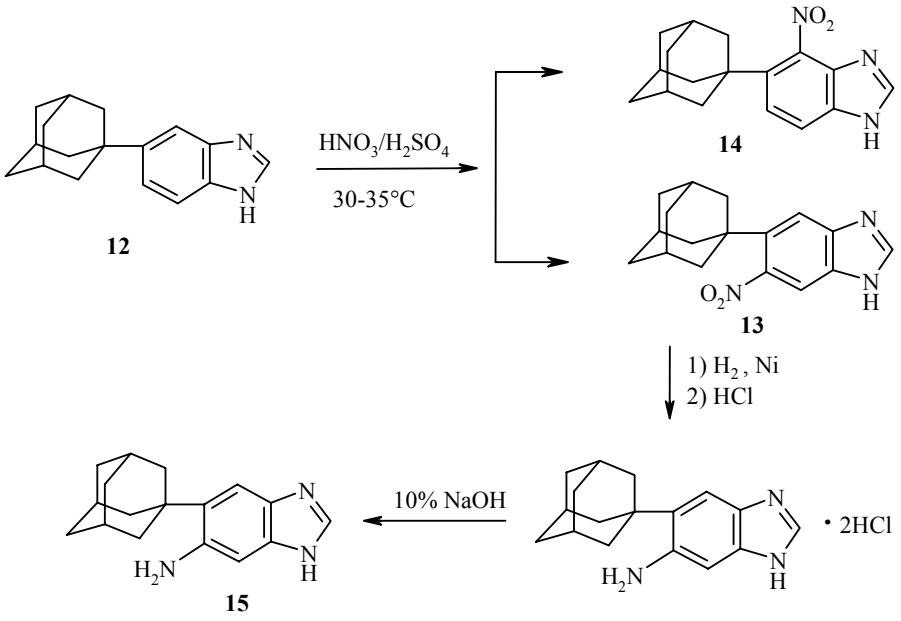
9 **11**

We have further studied the nitration reaction of 5(6)-(1-adamantyl)benzimidazole (**12**), the synthesis of which has been described by us before [4]. The positive inductive effect of the adamantyl radical leads to an increase in electron density in the corresponding *ortho* positions, i.e. in positions 4 and 6 of the benzimidazole ring. This explains the formation of a mixture of isomers **13** and **14** as a result of the nitration reaction.

The nitration was performed at 30-35ºC with an experimentally established optimum ratio of the reacting components benzimidazole-HNO_3-H_2SO_4 of 1:2:6. The yield of the nitration products **13** and **14** was 95%. Recrystallization from ethanol gave the product **14** with R_f 0.67 in 90% yield. Using column chromatography it was possible to separate the product **13** with R_f 0.79 in 4% yield.

Hydrogenation of the mixture of nitro products **13** and **14** in the presence of Raney nickel in absolute ethanol and subsequent treatment with HCl gave the aminobenzimidazole dihydrochloride mixture in 30% yield. Treatment of the latter with an aqueous solution of 10% NaOH gave a mixture of the bases. Multi-crystallization from a mixture of chloroform and hexane gave the less soluble isomer **15** with R_f 0.46.

Mass spectroscopic and elemental analytical data (Table 1) confirmed the composition of the compounds prepared. The structure of the products was confirmed by IR, UV, and ^{1}H NMR data. The IR spectra of compounds **6-15** showed absorption bands for the following groups: benzimidazole N–H at



3460-3100, aromatic ring (Ar) C–H at 3085-3005, and adamantane (Ad) C–H at 2980-2820 cm^{-1}. The IR spectrum of compound **10** showed absorption bands for the ester carbonyl group at 1700 and 1650 and C–O–C at 1270 and 1090 cm^{-1}. The IR spectrum of compound **11** showed absorption bands typical of a vinyl C=C group at 1640 as well as bands corresponding to (C=)C–H at 3060 and C–O–Ph at 1230 and 1200 cm^{-1}. Bands typical of a C–NO_2 group were seen at 1520 and 1320 and at 1525 and 1330 cm^{-1} respectively in the IR spectra of compounds **13** and **14**. These bands are not observed in the reduction product **15** but absorption bands characteristic of the NH_2 group appear at 3490 and 3380 cm^{-1}.

The ^{1}H NMR spectra of compounds **6-11, 13-15** showed broadened singlet signals in the region 12.84-8.95 ppm for NH groups as well as signals in the form of singlets, doublets, double doublets, and multiplets typical of benzimidazole and benzene rings protons at 8.28-6.85 ppm while multiplets were observed in the region 2.17-1.70 ppm characteristic of adamantyl radical protons. In compound **7** the proton *ortho* to the chlorine atom appears as a double doublet at 8.26 ppm, the two benzimidazole ring protons H-4 and H-7 as a broadened singlet and doublet at 7.66 and 7.65 ppm, and the H-4',5',6' and H-6 are seen as a multiplet at 7.45-7.29 ppm. In compound **8** the four benzene ring protons H-3',5' and H-2',6' occur as two double doublets at 8.16 and 7.61 ppm respectively, the benzimidazole ring H-7 proton as a doublet at 7.58 ppm, and the H-4 and H-6 signals as multiplets at 7.47-7.24 ppm (DMSO-d_6). In the spectrum recorded in $CDCl_3$ the H-6 proton appears as a double doublet at 7.36 ppm with $J_{6,7}$ = 8.6 and $J_{6,4}$ = 1.2 Hz. Compound **9** shows two phenyl group protons H-2' and H-6' as double doublets at 7.33 ppm with the remaining three phenyl group protons as a multiplet at 7.05-7.03 ppm. The benzimidazole protons H-4, H-6, and H-7 are seen as a multiplet at 7.29-7.25 ppm respectively while the methylene group protons are observed as a singlet at 5.75 ppm. The benzimidazole ring H-4 and H-7 protons for compound **10** appear as doublets at 7.54 and 7.48 ppm and H-6 as a double doublet at 7.42 ppm while the three CH_3 group protons occurred as a singlet at 3.93 ppm. The three benzimidazole ring protons and ten phenyl group protons in compound **11** occur as multiplets at 7.78-7.48 and 7.46-6.99 ppm while the vinyl group proton is seen as a broadened singlet at 6.54 ppm. In the minor nitration product **13** the H-2 proton appears as a singlet at 8.22 ppm and the H-7 and H-4 protons as double doublets at 8.28 and 8.20 ppm respectively with spin-spin coupling $J_{4,7}$ = 1.6 Hz and so indicate that the nitro group substitutes position 6. In nitration product **14** the H-2 proton is a singlet at 8.17 ppm and the H-7 and H-6 protons are two doublets at 8.15 and 7.76 ppm with a spin-spin coupling of $J_{6,7}$ = 11 Hz inferring that the nitro group occurs in position 4. On the

basis of this data we can conclude that, as in the case of 5(6)-hydroxybenzimidazole [16], the nitration of 5(6)-(1-adamantyl)benzimidazole **(12)** occurs principally at the benzimidazole ring 4 position to form compound **14** (in 90% yield). In compound **15** the H-2, H-4, and H-7 protons appear as singlets at 7.91, 7.53, and 6.85 ppm respectively.

The ^{13}C NMR spectra of compounds **6-11, 13-15** show signals typical of benzimidazole and benzene ring carbon atoms at 95.0-161.0 ppm and four peaks characteristic of the adamantyl radical in the region 28.2-43.8 ppm, of which three signals correspond to nine carbon atoms and one signal to the carbon atom bound to the benzimidazole. Because of the presence of two adamantyl radicals in compound **6** eight signals characteristic of an adamantyl radical are observed at 28.2 (3C), 29.1 (3C), 35.3 (1C), 36.3 (1C), 36.5 (3C), 36.9 (3C), 41.5 (3C), and 43.8 ppm (3C). Compound **9** shows the absorption bands for the adamantyl radical (29.0, 36.3, 36.8, 43.6 ppm) together with a signal typical of a CH_2 carbon atom (64.42) ppm and signals in the region 114.6-157.6 ppm for the carbon atoms of the benzimidazole and benzene rings. Compound **10** shows the adamantyl radical signals (28.3, 35.8, 36.1, 43.0 ppm), the CH_3 group carbon peak at 53.1 ppm, and a peak at 153.8 ppm assigned to the C=O carbonyl group carbon.

The UV absorption spectra of compounds **7, 8, 11** show absorption bands which typify benzimidazole derivatives with λ_{max} 204-212, 230-249, 253-265, and 301-335 nm.

The anti HIV and antitumor activities of compounds **7-9** were studied in the National Cancer Institute (Bethesda, Maryland, USA). The anti HIV activity was determined on 60 different lines in 9 cancer tissue types. The antitumor activity was studied to find compounds affecting the reproductive cycle of the AIDS virus.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			M, g/mol	*m/z**
		C	H	N		
1	$C_{18}H_{23}NO$	79.96 / 80.25	8.83 / 8.61	5.50 / 5.20	269.39	269
2	$C_{18}H_{22}N_2O_3$	68.96 / 68.77	7.35 / 7.05	8.99 / 8.91	314.39	314
3	$C_{16}H_{20}N_2O_2$	70.44 / 70.56	7.30 / 7.40	10.40 / 10.29	272.35	—
4·2HCl	$C_{16}H_{24}Cl_2N_2$	60.95 / 60.46	7.67 / 8.43	8.88 / 8.59	315.29	242 (–2HCl)
5	$C_{18}H_{24}N_2O$	75.62 / 76.02	8.54 / 8.51	9.93 / 9.95	284.41	284
6	$C_{27}H_{34}N_2$	83.98 / 83.89	9.51 / 8.86	7.18 / 7.25	386.58	386
7	$C_{23}H_{23}ClN_2$	76.55 / 76.12	6.36 / 6.39	8.21 / 7.72	362.90	362
8	$C_{23}H_{23}ClN_2$	75.95 / 76.12	5.81 / 6.39	7.36 / 7.72	362.90	362
9	$C_{24}H_{26}N_2O$	80.38 / 80.41	7.38 / 7.31	7.83 / 7.81	358.49	—
10	$C_{19}H_{23}N_3O_2$	70.53 / 70.13	6.99 / 7.12	12.59 / 12.91	325.41	325
11	$C_{31}H_{30}N_2O$	83.46 / 83.40	6.79 / 6.77	6.44 / 6.27	446.59	446
13	$C_{17}H_{19}N_3O_2$	68.42 / 68.67	6.72 / 6.44	13.78 / 14.13	297.36	297
14	$C_{17}H_{19}N_3O_2$	68.33 / 68.67	6.56 / 6.44	13.99 / 14.13	297.36	297
15	$C_{17}H_{21}N_3$	76.59 / 76.37	7.87 / 7.90	15.85 / 15.72	267.38	—

* Values of *m/z* for the molecular ions [$M^{+\cdot}$] according to electron impact mass-spectrometric data.

The analysis was based on the death of T-4 lymphocytes induced by the human AIDS virus. Compound **7** proved inactive but 5(6)-(1-adamantyl)-2-(4-chlorophenyl)benzimidazole (**8**) and 5(6)-(1-adamantyl)-2-phenoxymethyl-benzimidazole (**9**) showed weak *in vitro* cytostatic activity and suppressed the capability of the HIV reproductive cycle.

The results obtained point to the promise of further, targeted synthesis of benzimidazoles with adamantane substituents.

EXPERIMENTAL

The course of the reaction and purity of the substances was monitored by TLC on Silufol UV-254 plates using acetone–CCl_4 as eluent and revealed using iodine vapor. silica gel with particle size 100-400 μm was used as sorbent for column chromatography. IR spectra were taken on a Specord IR-75 spectrophotometer using hexachlorobutadiene or vaseline oil and UV spectra on a Specord UV-vis spectrometer using ethanol. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-400, Varian UNITY-400 (400 and 100 MHz respectively) (compounds **9** and **13**) and Tesla BS 567A (100 MHz) spectrometers (compounds **1,2,4,5** and **14**). The internal standard was HMDS for compounds **1** and **2**, and TMS for compounds **4-15**. Mass spectra were taken on a Ribermag 10-10-B spectrometer with electron impact ionization and electron ionization energy of 70 eV. Melting points were measured on a Boetius apparatus with a PHMKO5 visual attachment.

1-Bromoadamantane from the Swiss company Fluka AG (CH-9470 Buchs) was used as the starting material.

1-(4-Acetamidophenyl)adamantane (1) was prepared by method [10] in 80% yield with mp 197-199ºC (ethanol); R_f 0.38 (acetone–CCl_4, 1:3). IR spectrum (thin film), ν, cm^{-1}: 3295, 3180, 3100 (NH), 3050 (C–H Ar), 2980-2850 (Ad), 1650 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.76 (1H, s, NH); 7.37, 7.20 (4H, dd, AA'BB', C_6H_4, $^3J_{2,3} = {}^3J_{5,6} = 8.7$, $^4J_{2,6} = {}^4J_{3,5} = 3.3$); 2.06 (3H, s, CH_3); 2.05-1.69 (15H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.2, 28.8, 35.8, 36.7, 43.1, 119.9, 125.2, 135.3, 147.5, 168.4

1-(4-Acetamido-3-nitrophenyl)adamantane (2). A nitrating mixture prepared from 59% HNO_3 (20 ml, 380 mmol) and 95% H_2SO_4 (105 ml, 1860 mmol) was added dropwise to a cooled mixture of the amide **1** (50 g, 190 mmol), glacial acetic acid (100 ml), and acetic anhydride (40 ml). The mixture was stirred at room temperature for 12 h and poured into iced water. The precipitate was filtered off, washed with water to neutral reaction, and dried to give lemon colored crystals (52.2 g, 90%) with mp 212-214ºC (benzene–ethanol) and R_f 0.81 (acetone–CCl_4, 1: 3). IR spectrum (thin film), ν, cm^{-1}: 3350 (NH), 3090, 3030 (C–H Ar), 2980-2840 (Ad), 1700 (C=O), 1580, 1330 (C–NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 10.13 (1H, s, NH); 8.58 (1H, d, $^3J_{5,6} = 8.8$, H-5); 8.07 (1H, d, $^4J_{2,6} = 2.4$, H-2); 7.59 (1H, dd, $^3J_{6,5} = 8.8$, $^4J_{6,2} = 2.4$, H-6); 2.21 (3H, s, CH_3); 2.06-1.71 (15H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 25.3, 28.6, 35.9, 36.4, 42.7, 121.7, 122.0, 132.3, 132.8, 136.4, 147.1, 168.4.

1-(4-Amino-3-nitrophenyl)adamantane (3). Yield 89%; mp 224-226ºC (benzene–ethanol, 1:1), (mp 218-219 [11] and 222-224ºC [12]).

4-(1-Adamantyl)-1,2-diaminobenzene Dihydrochloride (4). A solution of compound **3** (10.57 g, 39 mmol) in absolute ethanol (100 ml) was hydrogenated over 12 h at 18ºC (730 mm Hg) in the presence of Raney nickel. The mixture was filtered and the filtrate was treated with ethanol saturated with HCl to pH 1. The mixture was held for 1 day and white crystals were precipitated with dry ether, filtered off, washed with ether, and dried. Yield 12 g (98%); mp 258-260 (ethanol–ether) and 266-267ºC (ethanol). The dihydrochloride **4**·2HCl
was treated with a 10% solution of NaOH to give the 4-(1-adamantyl)-1,2-diaminobenzene **4** as white crystals with mp 135-137ºC, unstable in air. R_f 0.42 (acetone–CCl_4, 1:3). IR spectrum (thin film), ν, cm^{-1}: 3400, 3290, 3230, 1625 (NH_2), 3040 (C–H Ar), 2990-2850 (Ad), 1275 (C–N). UV spectrum (EtOH), λ_{max}, (log ε): 211 (4.28). ^{1}H NMR spectrum (CD_3OD), δ, ppm (*J*, Hz): 7.67-7.57 (3H, m, C_6H_5); 5.27 (4H, s, 2 NH_2); 2.20-1.80 (15H, m, Ad).

1-(4-Acetamido-3-aminophenyl)adamantane (5). A solution of nitroamide **2** (2.62 g, 8 mmol) in absolute ethanol (80 ml) was hydrogenated using molecular hydrogen at 21ºC for 6 h (736 mm Hg) in the presence of Raney nickel. The precipitate was filtered off, dissolved in benzene, and the solution was evaporated to give 1.92 g (81%) of crystals with mp 228-230ºC (benzene–ethanol) and R_f 0.61 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3380, 3310, 3220 (NH_2), 3160, 3110 (NH), 3040 (C–H Ar), 2980-2840 (C–H Ad), 1650 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.89 (1H, br. s, NH); 7.16 (1H, d, $^3J_{5,6}$ = 8.2, H-5); 6.83 (1H, d, $^4J_{2,6}$ = 2.1, H-2); 6.64 (1H, dd, $^3J_{6,5}$ = 8.2, $^4J_{6,2}$ = 2.1, H-6); 3.18 (2H, s, NH_2); 2.09 (3H, s, CH_3); 2.07-1.80 (15H, m, Ad).

2,5(6)-Di(1-adamantyl)benzimidazole (6). A mixture of compound **4** (1 g, 3.17 mmol) and adamantane carboxylic acid (5.4 g, 30 mmol) was heated at 195-200ºC for 2 h. The mixture was cooled, poured into iced water, and treated with a 10% solution of NaOH to pH 10. The precipitate was held in a basic medium until full conversion of excess acid to AdCOONa. The precipitate was then filtered, washed with water to neutral pH and dried. Yield 1.19 g (96%); mp 272-275ºC, crystals melting and again melting at 282-284ºC (chloroform–hexane), R_f 0.44 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3200-3100 (NH), 3040 (C–H Ar), 2980-2840 (Ad). Hydrochloride mp 335-336ºC (ethanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.95 (1H, br. s, NH); 7.73-7.33 (2H, m, H-4,7); 7.28 (1H, dd, $^3J_{6,7}$ = 8.4, $^4J_{6,4}$ = 1.2, H-6); 2.17-2.05 (12H, m, Ad); 2.02-1.91 (6H, m, Ad); 1.85-1.74 (12H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.2, 29.1, 35.3, 36.3, 36.5, 36.9, 41.5, 43.8, 119.6, 122.8, 126.9, 140.2, 142.5, 146.0, 161.8.

5(6)-(1-Adamantyl)-2-(2-chlorophenyl)benzimidazole (7). A mixture of the diamine dihydrochloride **4** (3.15 g, 10 mmol) and *o*-chlorobenzoic acid (7.85 g, 50 mmol) was heated for 2 h at 170-180ºC. The mixture was cooled, iced water was added, and the product was treated with 10% aqueous NaOH solution to pH 10. The precipitate was filtered off, washed initially with 10% NaOH and then water to neutral reaction, and dried. The yield of dry product was 3.35 g (93%). Recrystallization from a mixture of ethanol and water gave creamish colored crystals (2.6 g, 72%). Column chromatography using chloroform eluent gave white crystals with mp 284-285ºC (chloroform–hexane), R_f 0.84 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3400 (NH), 3050 (C–H Ar), 2980-2840 (Ad), 790, 750 (C–Cl). UV spectrum (EtOH), λ_{max}, nm (log ε): 211 (4.68), 246 (4.22), 301 (4.25). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 10.12 (1H, br. s, NH); 8.26 (1H, dd, $^3J_{3',4'}$ = 8.5, $^4J_{3',5'}$ = 4.3, H-3'); 7.66 (1H, br. s, H-4); 7.65 (1H, d, $^3J_{7,6}$ = 9.3, H-7); 7.45-7.29 (4H, m, H-4',5',6',6); 2.16-2.07 (3H, m, Ad); 2.01-1.89 (6H, m, Ad); 1.86-1.71 (6H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.0, 36.5, 36.8, 43.6, 100.0, 114.8, 121.7, 127.1, 127.5, 130.7, 131.3, 131.4, 132.2, 147.9, 148.0.

5(6)-(1-Adamantyl)-2-(4-chlorophenyl)benzimidazole (8). A mixture of the diamine dihydrochloride **4** (3.15 g, 10 mmol) and *p*-chlorobenzoic acid (7.85 g, 50 mmol) was heated for 2 h at 230-240ºC. The mixture was cooled, iced water was added and the product was treated with 10% NaOH solution to pH 10. The precipitate was filtered off, washed with 10% NaOH and water to neutral reaction, and dried. Yield of dry product 3.32 g (91%). Recrystallization from a mixture of ethanol and water gave creamish colored crystals (2.9 g, 80%). Column chromatography with chloroform eluent gave white crystals with mp 173-175ºC (chloroform–hexane), R_f 0.91 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3460 (NH), 3150 (C–H Ar), 2980-2840 (Ad), 820, 780 (C–Cl). UV spectrum (EtOH), λ_{max}, nm (log ε): 204 (4.62), 230 (4.2), 249 (4.09), 314 (4.28), 328 sh (4.19). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.84 (1H, s, NH); 8.16 (2H, dd, $^3J_{3',2'} = {}^3J_{5',6'}$ = 8.5, $^4J_{3',5'}$ = 2.0, H-3',5'); 7.61 (2H, dd, $^3J_{2',3'} = {}^3J_{6',5'}$ = 8.5, $^4J_{2',6'}$ = 2.0, H-2',6'); 7.58 (1H, d, $^3J_{7,6}$ = 8.6, H-7); 7.47-7.24 (2H, m, H-6,4); 2.12-2.04 (3H, m, Ad); 1.98-1.91 (6H, m, Ad); 1.81-1.71 (6H, m, Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.4, 35.7, 36.2, 43.0, 106.9, 110.6, 114.6, 118.3, 119.3, 127.9, 129.0, 135.0, 143.8, 149.8.

5(6)-(1-Adamantyl)-2-phenoxymethylbenzimidazole (9). A mixture of the diamine dihydrochloride **4** (1.55 g, 4.92 mmol) and phenoxyacetic acid (3.8 g, 25 mmol) was heated for 3 h at 140-145ºC. The mixture was cooled and 10% NaOH solution was added to pH 10. The precipitate was held in alkaline medium for conversion of the excess acid to the sodium salt. The principitate was filtred off, washed with water to neutral

reaction. Yield 1.75 g (99%); mp 223-224ºC (methanol), R_f 0.69 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3250-3100 (NH), 3040 (C–H Ar), 2960-2840 (C–H Ad), 1230, 1040 (C–O–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.50 (1H, br. s, NH); 7.33 (2H, dd, $^3J_{2',3'} = {}^3J_{6',5'} = 8.8$, $^4J_{2',6'} = 1.6$, H-2',6'); 7.29-7.25 (3H, m, H-4,6,7); 7.05-7.03 (3H, m, C_6H_5); 5.75 (2H, s, CH_2); 2.17-1.71 (15H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.0, 36.3, 36.8, 43.6, 64.2, 114.6, 120.3, 121.8, 129.7, 144.0, 150.0, 157.6.

5(6)-(1-Adamantyl)-2-(methoxycarbonylamino)benzimidazole (10). KOH solution (10%, 25 ml) was added to technical 38% CaNCN (8.4 g, 3.2 g, 40 mmol). The mixture was cooled and methyl chloroformate (3.78 g, 40 mmol) was added dropwise with stirring. The mixture was stirred for 30 min at pH 12 and 35-40ºC, filtered, and the precipitate was washed with distilled water (10 ml). The filtrate and water wash were poured into a round bottomed flask, acidified with conc. HCl to pH 3, and compound **4** (4.8 g, 20 mmol) was added portionwise. The mixture was heated for 3 h at 95-100°C, periodically conc. HCl was added to keep pH 3. The mixture was then cooled, filtered, and the precipitate was washed with hot water, acetone, and ether, and dried. Yield 3.16 g (49%). For purification it was converted to the hydrochloride and then again to the base, mp > 330ºC with decomposition (chloroform). Hydrochloride mp > 350ºC with decomposition. R_f 0.81 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3380 (NH), 3070, 3020 (C–H Ar), 2980-2830 (C–H Ad), 1700, 1650 (C=O), 1275, 1090 (C–O–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.54 (1H, d, $^4J_{4,6} = 1.5$, H-4); 7.48 (1H, d, $^3J_{7,6} = 8.5$, H-7); 7.42 (1H, dd, $^3J_{6,7} = 8.5$, $^4J_{6,4} = 1.5$, H-6); 6.05 (2H, br. s, 2 NH); 3.93 (3H, s, CH_3); 2.17-2.09 (3H, m, Ad); 1.96-1.88 (6H, m, Ad); 1.86-1.72 (6H, m, Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.3, 35.8, 36.1, 43.0, 53.1, 99.4, 109.0, 112.7, 120.3, 138.7, 139.8, 146.4, 153.8.

5(6)-(1-Adamantyl)-2-(1-phenoxy-2-phenylvinyl)benzimidazole (11). A mixture of compound **9** (0.5 g, 1.4 mmol) and benzaldehyde (4 ml, 39 mmol) was heated for 5 h at 175-179ºC. The mixture was cooled, dissolved in ether (50 ml), and treated with saturated $NaHCO_3$ solution. The ether was washed with water to neutral reaction, dried over Na_2SO_4, and evaporated. The residue was washed with hexane and then recrystallized from hexane. Yield 0.32 g (50%); mp 246-248ºC (hexane), R_f 0.63 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3280 (NH), 3060, 3040 (C–H Ar), 2950, 2895, 2840 (C–H Ad), 1640 (C=C), 1230, 1200 (C–O–Ph). UV spectrum, λ_{max}, nm (log ε): 208 (4.67), 265 (4.15), 332 (4.49). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 9.23 (1H, br. s, NH); 7.78-7.48 (3H, m, C_6H_5); 7.46-7.19 (7H, m, C_6H_5); 7.19-6.99 (3H, m, C_6H_5); 6.54 (1H, s, =CH); 2.17-2.05 (3H, m, Ad); 2.04-1.86 (6H, m, Ad); 1.83-1.73 (6H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 29.0, 36.7, 36.8, 43.6, 115.2, 123.0, 128.5, 128.7, 129.8, 130.2, 133.3, 133.6, 144.0, 159.2

5(6)-(1-Adamantyl)-6(5)-nitrobenzimidazole (13) and 5(6)-(1-Adamantyl)-4(7)-nitrobenzimidazole (14). A nitrating mixture prepared from 59% HNO_3 (0.25 ml, 3 mmol) and conc. H_2SO_4 (0.5 ml, 9 mmol) was added dropwise with stirring and cooling to 5(6)-(1-adamantyl)benzimidazole (**12)** (0.39 g, 1.5 mmol). The mixture was stirred for 4 h at 30-35ºC and poured into iced water. The precipitate was filtered off, washed with water to neutral reaction, and dried. Yield of the mixture of the two isomers **13** and **14** 0.44 g (95%). Recrystallization from ethanol gave compound **14** (0.41 g, 90%) with mp 242-244ºC (ethanol), R_f 0.67 (acetone–CCl_4, 1:1). Compound **13** remained in the filtrate. The ethanol was evaporated to dryness and the residue was column chromatographed using chloroform eluent to give the nitro product **13** (0.018 g, 3.98%) with mp 333-335ºC (chloroform–hexane), R_f 0.79 (acetone–CCl_4, 1:1). **Compound 13**. IR spectrum (thin film), ν, cm^{-1}: 3300-2700 (NH), 3085, 3025 (C–H Ar), 2950, 2900, 2845 (C–H Ad), 1525, 1330 (C–NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.28 (1H, d, $^4J_{7,4} = 1.6$, H-7); 8.22 (1H, s, H-2); 8.20 (1H, d, $^4J_{4,7} = 1.6$, H-4); 2.17-1.70 (15H, m, Ad). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.8, 36.5, 43.5, 94.4, 117.4, 118.6, 124.7, 134.0, 141.5, 142.4. **Compound 14**. IR spectrum (thin film), ν, cm^{-1}: 3390 (NH), 3100, 3040 (C–H Ar), 2980-2840 (C–H Ad), 1520, 1320 (C–NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 10.6 (1H, br. s, NH); 8.17 (1H, s, H-2); 8.15 (1H, d, $^3J_{7,6} = 11$, H-7); 7.76 (1H, d, $^3J_{6,7} = 11$, H-6); 2.14-1.70 (15H, m, Ad).

5(6)-(1-Adamantyl)-6(5)aminobenzimidazole (15). A solution of the mixture of nitro products **13** and **14** (1.12 g, 3.7 mmol) in absolute ethanol (80 ml) was hydrogenated for 4 h at 20ºC (729 mm Hg) in the presence of Raney nickel. The mixture was filtered and ethanol was added saturated with HCl to pH 1. The

product was held for 1 day and crystals were precipitated with dry ether, washed with ether, and dried. Yield 0.38 g (30%); mp > 350ºC. The dihydrochloride was treated with 10% NaOH solution to liberate the products as their free bases to give a mixture of the aminobenzimidazoles (0.27 g) with mp 230-235ºC. After repeated recrystallizations the less soluble isomer **15** was obtained; mp 254-256ºC, the melt crystallizing and again melting at 264-266ºC (chloroform–hexane), R_f 0.46 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 3490, 3380 (NH_2), 3120 (NH), 3075, 3020 (C–H Ar), 2960, 2910, 2850 (C–H Ad), 1625 (NH deformation). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.91 (1H, s, H-2); 7.53 (1H, s, H-4); 6.85 (1H, s, H-7); 4.22 (2H, br. s, NH_2); 2.17-2.09 (9H, m,Ad); 1.83-1.75 (6H, m, Ad). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 28.4, 36.3, 39.9, 99.4, 113.0, 129.0, 130.6, 133.4, 139.3, 142.8.

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