The Synthesis of Adamantane Ring Containing Benzimidazole, Benzoxazole, and Imidazo[4,5-*e*]benzoxazole Derivatives from 3-Aminophenol

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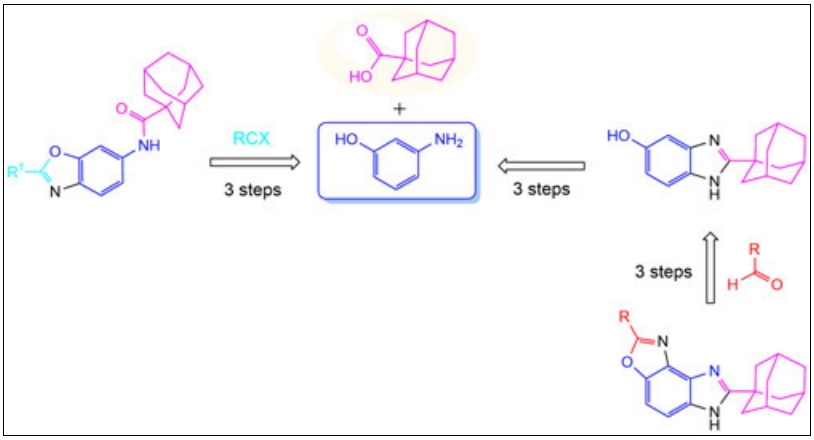

Adamantane derivatives containing heterocycles such as benzimidazoles, benzoxazoles, and fused imidazo[4,5-*e*]benzoxazoles were synthesized from 3-aminophenol. The route started with amidation of adamantane-1-carboxylic acid chloride with 3-aminophenol furnishing *N*-(3-hydroxyphenyl)adamantane-1-carboxamide. Subsequent nitration gave three regioisomers. After reduction of the nitro groups, the respective aniline derivatives were used in the formation of benzimidazole and benzoxazole rings. The cyclization of the 2-substituted benzoxazole ring was performed using two methods: via condensation of *N*-(2-amino-3-hydroxyphenyl)adamantane-1-carboxamide with carbonitriles in the presence of a Lewis acid or via Cu(II)-catalyzed oxidative coupling of aminophenol with aromatic aldehydes. The benzimidazole ring formed by acid-catalyzed cyclization of *N*-(2-amino-5-hydroxyphenyl)adamantane-1-carboxamide was then converted to a tricyclic system after three synthetic steps.

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INTRODUCTION

Benzo-fused nitrogen and oxygen-containing heterocycles such as benzimidazoles [1–3] and benzoxazoles [4,5] are distinguished by a broad spectrum of high bioactivity, and therefore, they are interesting compounds for medicinal chemistry. These important pharmacophores are contained in a vast number of biologically active compounds that are used in agriculture and medicine. Novel-fused tricyclic compounds like 8*H*-imidazo[4,5-*e*][1,3]benzoxazole are also of great interest, and their MPGES-1 enzyme selective inhibitor properties were patented [6]. Diseases associated with hormonal, nervous, and immune system disorders are usually cured by membranotropic drugs such as adamantane-containing medicaments. The main features based on an adamantane moiety are the low toxicity and the variety of biological activities, including anti-viral, immunotropic, psychotropic, anti-cancer, analgesic, anticonvulsant, detoxifying, and many other properties [7]. For example, amino adamantanes like rimantadine and amantadine (Fig. 1) were among the first drugs that were used for the treatment and prevention of viral diseases by inhibition of the influenza proteins, thereby preventing the release of infectious viral nucleic acids into the cell. Furthermore, bromantane and kemantane act as psychoanaleptics, restoring functional activity of the nervous and immune systems and thus enhancing physical and mental functions. Midantane (amantadine hydrochloride), for instance, is effective for treatment of neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, or disseminated sclerosis [8,9]. Recently, adamantane was identified as a key subunit in some synthetic cannabinoid designer drugs like APICA (SDB-001), an indole-based adamantane performing as a potent cannabinoid receptor agonist [10].

The adamantane moiety, besides of its wide range of biological activity, is featured with properties improving

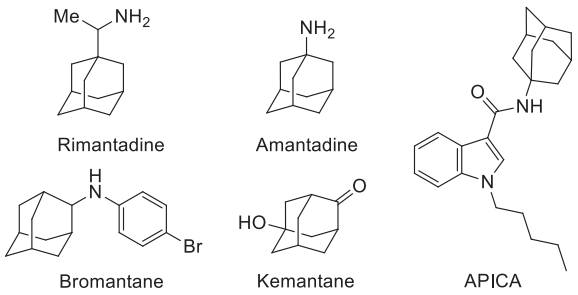

Figure 1. Selected examples of biologically active adamantane derivatives.

the biological characteristics of the medication enhancing the drug's prolonged action and at the same time reducing toxicity and side negative effects [11]. Introducing the bulky, high lipophilic adamantane ring system into the compound provokes an increase of its lipophilicity and stability and improves its pharmacokinetics. Therefore, interaction of the lipophilic adamantane with the lipid layer of cell membranes enhances the permeability and thus facilitates the drug's ability to penetrate into the cells [12].

Considering the unique properties of adamantanyl moieties, there are already many biological studies of adamantane-containing benzimidazoles that revealed anti-virus [13], anti-obesity [14], anti-tumor [15], anti-allergy, and anti-asthma [16] activities. However, compounds of benzoxazoles as well as tricyclic ring systems involving an adamantane motif are insufficiently investigated. Consequently, there is an ongoing need to establish synthetic methodologies for the construction of different adamantane-containing heterocycles. We wish to report herein on the preparation of benzimidazoles, benzoxazoles, and fused imidazo[4,5-*e*]benzoxazoles from 3-aminophenol.

RESULTS AND DISCUSSION

Our approach to synthesize the benzoxazoles **7a**–**j** started with the conversion of 1-adamantane carboxylic acid to the corresponding acid chloride and the reaction of this intermediate product with 3-aminophenol giving *N*-(3-hydroxyphenyl)adamantane-1-carboxamide (**1**) in 80% yield according to a known procedure (Scheme 1) [17]. The subsequent nitration with 65% nitric acid in acetic acid furnished three regioisomers, the *ortho*-isomers **2a** (3%) and **2b** (40%) as well as the *para*-isomer **2c** (30%), which were separated by column chromatography. Reduction of the nitro groups of **2b** and **2c** afforded aminoamides **3b** (91%) and **3c** (95%). The aminophenol moiety of **3b** was utilized for cyclization to the benzoxazoles **7a**–**j** using two methods with yields up to 76% (Table 1). Initially, the Cu(II)-catalyzed, oxidative coupling reactions [18] of **3b** with acetic anhydride **4** (**7a**, entry 1) and diverse aldehydes **5** (**7b**–**g**, entries 2–7) were investigated. While the yields of the reaction with acetic anhydride (entry 1, **7a**, 16%), 4-methoxybenzaldehyde **5f** (entry 7, **7g**, 15%) and 3,4-dimethoxybenzaldehyde **5c** (entry 4, **7d**, 7%) were low, the results with benzaldehyde **5a** (entry 2, **7b**, 50%), with 4-isopropylbenzaldehyde **5b** (Entry 3, **7c**, 32%) and the 4-bromo-substituted benzaldehyde **5e** (entry 6, **7f**, 39%) as well as with

Scheme 1. Preparation of benzoxazoles **7a**–**j**. Reagents and conditions: (a) 1) $SOCl_2$, 60°C, 30 min; 2) Et_3N, CH_2Cl_2, 23°C, 3 h. (b) 1.3 equiv HNO_3, AcOH, 23°C, 1 h; (c) Pt/C (cat.), 1 atm H_2, EtOH, 23°C, 24–32 h; (d) 2.0 equiv Ac_2O (**4**), $Cu(OAc)_2 \cdot H_2O$ (cat.), toluene, 110°C, air, 7 h; (e) 1.0 equiv aldehyde **5a**–**f**, $Cu(OAc)_2 \cdot H_2O$ (cat.), toluene, 110°C, air, 16–20 h; (f) 1.0 equiv carbonitrile **6a**–**c**, $ZnCl_2$ (cat.), PhCl, 135°C, inert atmosphere (N_2), 24 h.

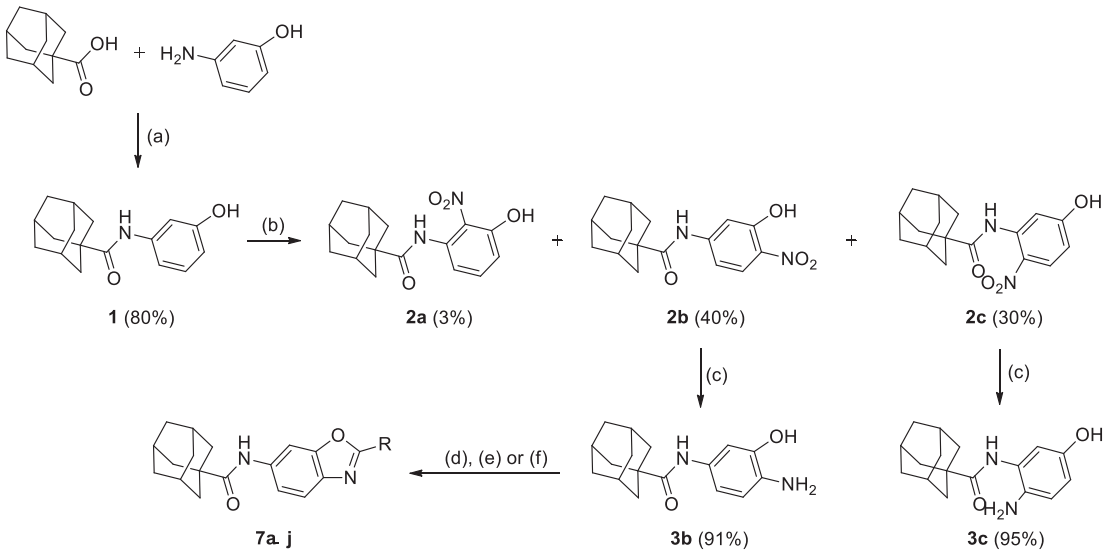

Table 1

Scope and yields of the synthesis of products **7a**–**j** and **11a**–**b**.

Entry		Starting material	Method		Product (R)	Yield[a] (%)
1	**4**	Acetic anhydride	(d)	**7a**	(Me)	16
2	**5a**	Benzaldehyde	(e)	**7b**	(Ph)	50
3	**5b**	4-Isopropylbenzaldehyde	(e)	**7c**	(4-*i*PrC_6H_4)	32
4	**5c**	3,4-Dimethoxybenzaldehyde	(e)	**7d**	[3,4-$(MeO)_2C_6H_4$]	7
5	**5d**	Thiophene-2-carbaldehyde	(e)	**7e**	(2-thienyl)	53
6	**5e**	3-Bromobenzaldehyde	(e)	**7f**	(3-BrC_6H_4)	39
7	**5f**	4-Methoxybenzaldehyde	(e)	**7g**	(4-MeOC_6H_4)	15
8	**6a**	4-Bromobenzonitrile	(f)	**7h**	(4-BrC_6H_4)	17
9	**6b**	Terephthalodinitrile	(f)	**7i**	(4-NCC_6H_4)	76
10	**6c**	3-Methoxypropionitrile	(f)	**7j**	(2-MeOC_2H_4)	19
11	**5a**	Benzaldehyde	(g)	**11a**	(Ph)	11
12	**5f**	4-Methoxybenzaldehyde	(g)	**11b**	(4-MeOC_6H_4)	9

[a]Yields of isolated products after chromatographic purification.

thiophene-2-carbaldehyde **5d** (entry 5, **7e**, 53%) were moderate, but yet preparative useful. The results could not be significantly improved by switching the method to the condensation of **3b** with carbonitriles **6** in the presence of the Lewis acid $ZnCl_2$ (**7h**–**j**, entries 8–10) [19]. Only the utilization of terephthalodinitrile **6b** gave a good yield of 76% (entry 9, product **7i**).

While isomer **3b** was applied in the synthesis of benzoxazoles **7**, isomer **3c** was converted to benzimidazole **8** in 99% yield by acid-catalyzed cyclization using trifluoroacetic acid in toluene (Scheme 2). The nitration of compound **8** gave three nitro products, **9a**–**c**, with the mono nitrated **9a** (44%) being the main product of this reaction. After reduction of the nitro group in **9a** to the aminophenol **10** (99%), compound **10** was coupled with aromatic aldehydes **5a** and **5f**, catalyzed by $Cu(OAc)_2 \cdot H_2O$ [18], to provide access to the tricyclic systems (Table 1, entries 11 and 12), products **11a** (11%) and **11b** (9%)] with an imidazo[4,5-*e*]benzoxazole moiety.

Scheme 2. Preparation of benzimidazole **5** and imidazo[4,5-*e*]benzoxazoles **8a** and **8b**. Reagents and conditions: (a) CF_3COOH, toluene, 110°C, 11 h; (b) 1.0 equiv HNO_3, AcOH, 23°C, 30 min; (c) Pd/C (cat.), 1 atm H_2, EtOH, 23°C, 1 d; (g) 2.6 equiv aldehyde **5a** or **5f**, $Cu(OAc)_2 \cdot H_2O$ (cat.), toluene, 110°C, air, 9–15 h.

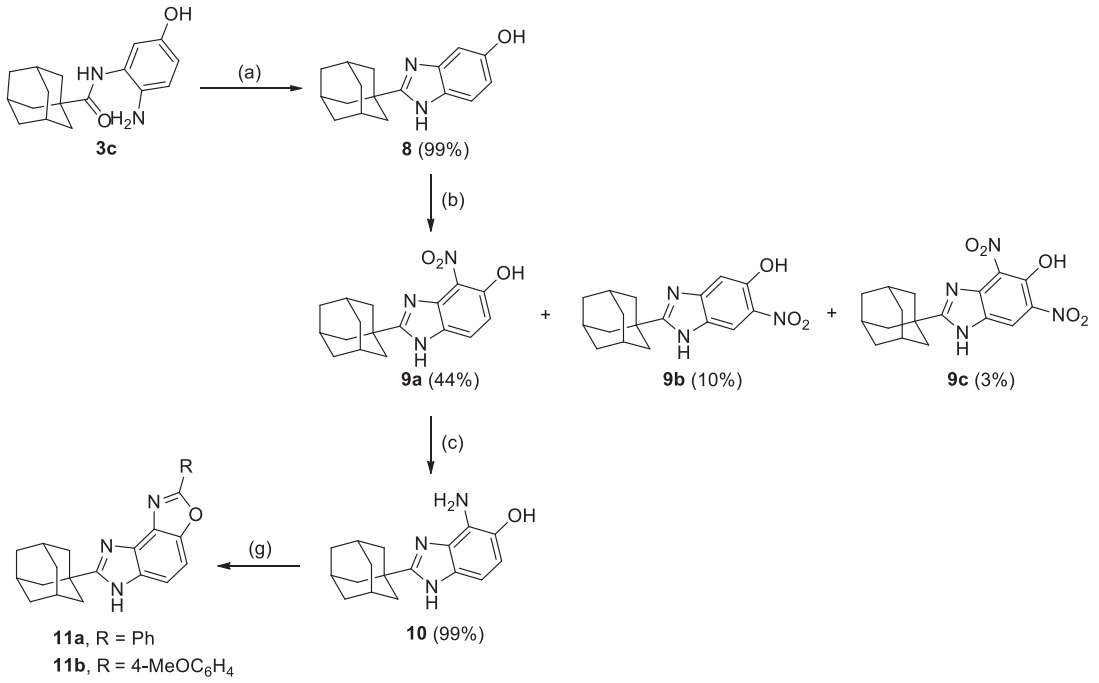

Table 2

P_a and P_i values for the renal disease treatment activity of compounds **11a**–**b** and their structural analogs.

Entry		Compound name	Renal disease treatment	
			P_a	P_i
1	**11a**	7-(1-Adamantyl)-2-phenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.882	0.003
2		7-Cyclohexyl-2-phenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.392	0.008
3		7-Methyl-2-phenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.630	0.004
4		2-Phenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.451	0.005
5		7-Isopropyl-2-phenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.526	0.011
6		2,7-Diphenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.537	0.007
7		7-*tert*-Butyl-2-phenyl-6*H*-imidazo[4,5-*e*]benzoxazole	0.677	0.004
8	**11b**	7-(1-Adamantyl)-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-e]benzoxazole	0.810	0.003
9		7-Cyclohexyl-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-*e*]benzoxazole	0.350	0.011
10		7-Methyl-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-*e*]benzoxazole	0.540	0.004
11		2-(4-Methoxyphenyl)-6*H*-imidazo[4,5-*e*]benzoxazole	0.398	0.008
12		7-Isopropyl-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-*e*]benzoxazole	0.468	0.005
13		7-Phenyl-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-*e*]benzoxazole	0.459	0.005
14		7-*tert*-Butyl-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-*e*]benzoxazole	0.520	0.005

CONCLUSIONS

In summary, adamantane derivatives containing heterocycles such as benzoxazoles, benzimidazoles, and fused imidazo[4,5-*e*]benzoxazoles were synthesized from the starting material 3-aminophenol. Key steps of the reaction sequences were the amidation of adamantane-1-carboxylic acid chloride with 3-aminophenol, nitration reactions followed by reduction of the nitro groups using a palladium catalyst. The final cyclizations toward the desired adamantane-containing heterocycles were performed either by Cu(II)-catalyzed oxidative coupling or by Lewis acid-catalyzed condensation reactions.

Biological activity spectra prediction. Estimation of possible biological activity for the synthesized compounds was made on the basis of a PASS (prediction of activity spectra for substances) prediction results by ParmaExpert software. The PASS program predicts the pharmacological effects of a molecule based on the analysis of structure–activity relationship for the training set of database including about 300.000 thoroughly selected data records about structure and biological activity of organic compounds [20]. Activity spectrum of a compound is estimated as probable active (P_a) or probable inactive (P_i), and their value varies from 0.000 to 1.000. Only activities with $P_a > P_i$ are considered as possible for a particular compound. The average accuracy of a prediction is reported to be as high as 95% [21].

According to the predicted results, amides **1**, **2a**–**c**, and **3b**–**c** revealed high activity ($P_a > 0.7$) as anti-viral agents against picornavirus and influenza. The benzoxazoles **7a**–**j** gave good results as 5-hydroxytryptamine release inhibitors while benzimidazoles **8**, **9a**–**c** and **10** as kidney function stimulants. Compounds **11a**–**b** shown $P_a > 0.8$ on renal disease treatment activity. Furthermore, among the wide spectrum of predicted activities for synthesized compounds, the high P_a values for revealed activities were compared with the structural analogs of obtained compounds with some functional groups on the place of adamantyl moiety. As it was expected, replacing of adamantyl group from the molecule in most cases decreased its predicted activity. Molecules with methyl, phenyl, cyclohexyl, isopropyl, and *tert*-butyl moiety showed much lower P_a value than the same molecule with adamantane. For example, P_a values for the renal disease treatment activity of fused tricyclic compounds are shown in Table 2.

EXPERIMENTAL

Preparative column chromatography was carried out using Merck SiO_2 (35–70 μm, type 60 Å) with hexanes and ethyl acetate (EtOAc) as eluents. TLC was performed on aluminum plates coated with SiO_2 F_{254}. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance DRX 500 instruments. Multiplicities of carbon signals were determined with DEPT experiments. MS and HRMS spectra were obtained with a Finnigan MAT95 (EI) and a Waters Q-TOF Premier (ESI, pos. mode) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. Elemental analyses were measured with a Euro EA-CHNS instrument from HEKAtech. Melting points of crystalline compounds were determined on a Gallenkamp Melting Point apparatus and are uncorrected.

Reagents and starting materials were purchased from common commercial suppliers and used without further purification. Solvents were purified and dried following standard procedures. Compound **1** was synthesized according to a literature procedure [16].

Preparation of compounds 2a–c. HNO_3 (65%, 7 mL, 15 mmol) was added dropwise within 15 min to a cold suspension (ice-water bath) of compound **1** (2.99 g, 11.0 mmol) in acetic acid (15 mL), and the reaction mixture was stirred at ambient temperature for 1 h. Subsequently, the suspension was poured into ice (200 mL), and the yellow participate formed was collected by filtration and washed with water (3 × 100 mL). The crude product was purified by column chromatography (SiO_2, hexanes/EtOAc 3:1) to yield the isomer **2a** (104 mg, 0.33 mmol, 3%, R_f = 0.85) in the first fraction. Secondly, compound **2b** (1.39 g, 5.13 mmol, 40%, R_f = 0.80) and as the third fraction isomer **2c** (1.05 g, 3.32 mmol, 30%, R_f = 0.71) was isolated.

N-(3-Hydroxy-2-nitrophenyl)adamantane-1-carboxamide (2a). This compound was obtained as a red solid, mp 155–157°C. IR (ATR): 3351, 2912, 2850, 1695, 1611, 1579 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.60–1.76 (m, 6H, Ad), 1.77–1.96 (m, 6H, Ad), 1.96–2.05 (m, 3H, Ad), 6.81 (d, *J* = 7,9 Hz, 1H, Ar), 6.90 (d, *J* = 8.2 Hz, 1H, Ar), 7.33 (t, *J* = 8.2 Hz, 1H, Ar), 9.27 (s, 1H, OH), 10.86 (s, 1H, NH) ppm; $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 27.56 (3 CH), 36.00 (3 CH_2), 38.22 (3 CH_2), 40.39 (C), 114.30 (CH), 117.31 (CH), 131.31 (CH), 131.63 (C), 135.96 (C), 150.37 (C), 176.03 (C) ppm. MS (ESI): *m*/*z* (%) = 339.1 (100) $[M + Na]^+$. *Anal*. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.03; H, 6.83; N, 8.34.

N-(3-Hydroxy-4-nitrophenyl)adamantane-1-carboxamide (2b). This compound was obtained as a yellow solid, mp 192–194°C. IR (ATR): 3434, 2904, 2849, 1686, 1628, 1589 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.66–1.78 (m, 6H, Ad), 1.87–1.97 (m, 6H, Ad), 1.90–2.12 (m, 3H, Ad), 7.27 (d, *J* = 9.1 Hz, 1H, Ar), 7.75 (s, 1H, Ar), 7.94 (d, *J* = 9.2 Hz, 1H, Ar), 9.54 (s, 1H, OH), 10.85 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 27.55 (3 CH), 35.85 (3 CH_2), 37.88 (3 CH_2), 41.37 (C), 108.03 (CH), 111.21 (CH), 126.06 (CH), 130.40 (C), 146.36 (C), 154.15 (C), 176.79 (C) ppm. MS (ESI): *m*/*z* (%) = 339.2 (100) $[M + Na]^+$. *Anal*. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.63; H, 6.41; N, 8.61.

N-(5-Hydroxy-2-nitrophenyl)adamantane-1-carboxamide (2c). This compound was isolated as a dark yellow solid, mp 280–285°C. IR (ATR): 3094, 2920, 2851, 1660, 1598, 1559 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.64–1.80 (m, 6H, Ad), 1.85–1.97 (m, 6H, Ad), 2.01–2.06 (m, 3H, Ad), 6.62 (dd, *J* = 9.2 Hz, *J* = 2.2, 1H, Ar), 7.98 (d, *J* = 2.1 Hz, 1H, Ar), 8.08 (d, *J* = 9.3 Hz, 1H, Ar), 10.57 (s, 1H, OH), 11.17 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 27.58 (3 CH), 35.93 (3 CH_2), 38.42 (3 CH_2), 41.69 (C), 107.27 (CH), 111.40 (CH), 128.55 (CH), 129.74 (C), 137.05 (C), 164.39 (C), 176.32 (C) ppm. MS (ESI): *m*/*z* (%) = 339.2 (100) $[M + Na]^+$. *Anal*. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.36; H, 6.62; N, 8.90.

Preparation of compounds 3b and 3c. The catalyst (5% Pt, 1% Fe, on charcoal, 100 mg) was added to a solution of nitro compound **2b** or **2c** (0.78 g, 2.37 mmol) in EtOH (25 mL). The reaction mixture was degased and then stirred at ambient temperature for 24 h under an atmosphere of hydrogen (1 atm). Then the catalyst was removed by filtration, and the solvent was removed in *vacuo*. The crude product was recrystallized from chloroform (10 mL) to give the aminoamides **3b** and **3c**.

N-(4-Amino-3-hydroxyphenyl)adamantane-1-carboxamide (3b). Yield: 0.64 g (2.24 mmol, 91%); white-gray solid, mp 200–202°C. IR (ATR): 3356, 3326, 3291, 3899, 2850, 1646, 1619, 1544 cm^{-1}. ^1H NMR (methanol-d_4): δ 1.73–1.81 (m, 6H, Ad), 1.92–1.96 (m, 6H, Ad), 2.02–2.06 (m, 3H, Ad), 6.63–6.72 (m, 2H, 2 Ar), 6.98 (d, *J* = 1.9 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR (methanol-d_4): δ 30.16 (3 CH), 38.01 (3 CH_2), 40.53 (3 CH_2), 42.81 (C), 111.24 (CH), 115.46 (CH), 117.44 (CH), 131.64 (C), 133.66 (C), 146.75 (C), 179.57 (C) ppm. MS (ESI): *m*/*z* (%) = 287.2 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* [M + H] + calcd for $C_{17}H_{23}N_2O_2$: 287.1760; found: 287.1747.

N-(2-Amino-5-hydroxyphenyl)adamantane-1-carboxamide (3c). Yield: 0.67 g (2.34 mmol, 95%); white-gray solid, mp 180–182°C. IR (ATR): 3312, 3006, 2906, 2850, 1629 cm^{-1}. ^1H NMR (methanol-d_4): δ 1.78–1.84 (m, 6H, Ad), 1.98–2.03 (m, 6H, Ad), 2.04–2.09 (m, 3H, Ad), 6.55 (dd, *J* = 8.5 Hz, *J* = 2.7 Hz, 1H, Ar), 6.69 (d, *J* = 2.6 Hz, 1H, Ar), 6.75 (d, *J* = 8.5 Hz, 1H, Ar), 7.90 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (methanol-d_4): δ 29.70 (3 CH), 37.56 (3 CH_2), 40.24 (3 CH_2), 42.47 (C), 113.68 (CH), 114.98 (CH), 120.51 (CH), 127.55 (C), 134.69 (C), 151.79 (C), 179.47 (C) ppm. MS (ESI): *m*/*z* (%) = 309.2 (100) $[M + Na]^+$. *Anal*. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.26; H, 7.78; N, 9.55.

***N*-(2-Methylbenzoxazol-6-yl)adamantane-1-carboxamide (7a)**. A mixture of compound **3b** (92 mg, 0.30 mmol), $Cu(OAc)_2 \cdot H_2O$ (19 mg, 0.10 mmol) and acetic anhydride **4** (61 mg, 0.60 mmol) in glacial acetic acid (2 mL) was heated to reflux at 118°C for 7 h. Subsequently, the solvent was removed *in vacuo,* and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc 2:1) to give the title compound **7a** (15 mg, 0.05 mmol, 16%, R_f = 0.30) as pink crystals, mp 235–237°C. IR (ATR): 3261, 2900, 2849, 1644, 1623, 1582, 1527 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.60–2.09 (m, 15H, Ad), 2.81 (s, 3H, CH_3), 7.07 (dd, *J* = 8.5 Hz, *J* = 2.1 Hz, 1H, Ar), 7.43 (s, 1H, NH), 7.53 (d, *J* = 8.5 Hz, 1H, Ar), 8.17 (d, *J* = 2.0 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 14.65 (CH_3), 28.30 (3 CH), 36.59 (3 CH_2), 39.46 (3 CH_2), 41.73 (C), 103.09 (CH), 116.54 (CH), 119.07 (CH), 135.28 (C), 138.06 (C), 151.49 (C), 164.13 (C), 176.21 (C) ppm. MS (ESI): *m*/*z* (%) = 333.1 (100) $[M + Na]^+$. HRMS (ESI): *m*/*z* calcd 333.1579 (for $C_{19}H_{22}N_2NaO_2^+$); found 333.1576 $[M + Na]^+$.

Benzoxazoles 7b–g: general procedure A. A mixture of compound **3b** (1.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.4 equiv) and an aldehyde **5a–f** (1.0 equiv) in absolute toluene (10 L/mol **3b**) was heated to reflux for 16–20 h using a Dean-Stark trap. Upon completion of the reaction (monitored by TLC), the solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the final products **7b–g** (Table 1, entries 2–7).

N-(2-Phenylbenzoxazol-6-yl)adamantane-1-carboxamide (7b). According to general procedure A (GPA), the reaction of **3b** (143 mg, 0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.20 mmol) and benzaldehyde **5a** (53 mg, 0.50 mmol) in absolute toluene (50 mL) was heated to reflux for 16 h to give the title compound **7b** (93 mg, 0.25 mmol, 50%, R_f = 0.25) after column chromatography (SiO_2, hexanes/EtOAc 4:1) as pale beige crystals, mp 196–198°C. IR (ATR): 3433, 3901, 2819, 1665, 1620, 1556, 1523, 1481 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.71–1.79 (m, 6H, Ad), 1.95–1.99 (m, 6H, Ad), 2.08–2.11 (m, 3H, Ad), 7.11–7.19 (m, 1H, Ar), 7.44–7.54 (m, 3H, Ar), 7.58 (s, 1H, NH), 7.62 (d, *J* = 8.4 Hz, 1H, Ar), 8.20 (dd, *J* = 6.7, *J* = 3.0 Hz, 2H, Ar), 8.28 (d, *J* = 2.1 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.19 (3 CH), 36.47 (3 CH_2), 39.31 (3 CH_2), 41.67 (C), 103.21 (CH), 117.12 (CH), 119.57 (CH), 127.20 (C), 127.52 (CH), 128.96 (2 CH), 131.44 (2 CH), 135.82 (C), 138.51 (C), 151.20 (C), 163.29 (C), 176.28 (C) ppm. MS (ESI): *m*/*z* (%) = 395.1 (100) [M + Na^+]. HRMS (ESI): *m*/*z* calcd 373.1916 (for $C_{24}H_{25}N_2O_2^+$); found 373.1908 $[M + H]^+$.

N-[2-(4-Isopropylphenyl)benzoxazol-6-yl]adamantane-1-carboxamide (7c). According to GPA, the reaction of **3b** (100 mg, 0.35 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol) and 4-isopropylbenzaldehyde **5b** (52 mg, 0.35 mmol) in absolute toluene (30 mL) was heated to reflux for 16 h to give the title compound **7c** (46 mg, 0.11 mmol, 32%, R_f = 0.68) after column chromatography (SiO_2, hexanes/EtOAc 3:1) as colorless crystals, mp 225–226°C. IR (ATR): 3434, 2906, 2851, 1620, 1565, 1485 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30 (d, *J* = 6.8 Hz, 6H, 2 CH_3), 1.69–1.86 (m, 6H, Ad), 1.98–2.02 (m, 6H, Ad), 2.07–2.17 (m, 3H, Ad), 2.99 (p, *J* = 6.8 Hz, 1H, CH), 7.12 (dd, *J* = 8.5 Hz, *J* = 2.2 Hz, 1H, Ar), 7.37 (d, *J* = 8.4 Hz, 2H, Ar), 7.45 (s, 1H, NH), 7.64 (d, *J* = 8.5 Hz, 1H, Ar), 8.15 (d, *J* = 8.3 Hz, 2H, Ar), 8.28 (d, *J* = 2.2 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 23.84 (2 CH_3), 28.23 (3 CH), 34.34 (CH), 36.52 (3 CH_2), 39.36 (3 CH_2), 41.69 (C), 103.20 (CH), 116.99 (CH), 119.44 (CH), 124.80 (C), 127.13 (2 CH), 127.67 (2 CH), 135.62 (C), 138.65 (C), 151.16 (C), 152.83 (C), 163.59 (C), 176.25 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 414.3 (30), 135.1 (100), 83.9 (75) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 414.2307 (for $C_{27}H_{30}N_2O_2^+$); found 414.2301 $[M]^+$.

N-[2-(3,4-Dimethoxyphenyl)benzoxazol-6-yl]adamantane-1-carboxamide (7d). According to GPA, the reaction of **3b** (100 mg, 0.35 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol), and 3,4-dimethoxybenzaldehyde **5c** (58 mg, 0.35 mmol) in absolute toluene (30 mL) was heated to reflux for 20 h to give the title compound **7d** (10 mg, 0.02 mmol, 7%, R_f = 0.25) after column chromatography (SiO_2, hexanes/EtOAc 2:1) as colorless crystals, mp 140–145°C. IR (ATR): 3259, 2902, 2850, 1650, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.56–2.13 (m, 15H, Ad), 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.99 (d, *J* = 8.4 Hz, 1H, Ar), 7.11 (dd, *J* = 8.5 Hz, *J* = 1.9 Hz, 1H, Ar), 7.45 (s, 1H, NH), 7.63 (d, *J* = 8.5 Hz, 1H, Ar), 7.73 (d, *J* = 1.8 Hz, 1H, Ar), 7.83 (dd, *J* = 8.3 Hz, *J* = 1.9 Hz, 1H, Ar), 8.27 (d, *J* = 1.8 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.27 (3 CH), 36.57 (3 CH_2), 39.44 (3 CH_2), 41.75 (C), 56.20 (CH_3), 56.29 (CH_3), 103.12 (CH), 110.04 (CH), 111.18 (CH), 116.89 (CH), 119.30 (CH), 119.96 (C), 121.23 (CH), 135.50 (C), 138.75 (C), 149.39 (C), 151.26 (C), 152.05 (C), 163.54 (C), 176.21 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 432.6 (100), 135.1 (100), 93.1 (14) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 432.2049 (for $C_{26}H_{28}N_2O_4^+$); found 432.2036 $[M]^+$.

N-[2-(2-Thienyl)benzoxazol-6-yl]adamantane-1-carboxamide (7e). According to GPA, the reaction of **3b** (100 mg, 0.35 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol), and thiophene-2-carbaldehyde **5d** (39 mg, 0.35 mmol) in absolute toluene (30 mL) was heated to reflux for 17 h to give the title compound **7e** (70 mg, 0.18 mmol, 53%, R_f = 0.70) after column chromatography (SiO_2, hexanes/EtOAc 2:1) as orange crystals, mp 203–205°C. IR (ATR): 3440, 3070, 2909, 2849, 1659, 1618, 1575 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.72–1.79 (m, 6H, Ad), 1.95–1.99 (m, 6H, Ad), 2.12–2.08 (m, 3H, Ad), 7.13 (dd, *J* = 8.5 Hz, *J* = 1.9 Hz, 1H, Ar), 7.16 (dd, *J* = 4.8 Hz, *J* = 3.9 Hz, 1H, thienyl), 7.52 (m, 2H, thienyl; NH), 7.59 (d, *J* = 8.5 Hz, 1H, Ar), 7.83–7.89 (m, 1H, thienyl), 8.24 (d, *J* = 1.8 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.22 (3 CH), 36.51 (3 CH_2), 39.36 (3 CH_2), 41.71 (C), 103.06 (CH), 117.15 (CH), 119.40 (CH), 128.35 (CH), 129.72 (C), 129.87 (CH), 130.15 (CH), 135.82 (C), 138.41 (C), 150.94 (C), 159.33 (C), 176.24 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 378.5 (70) 135.0 (100), 78.9 (23) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 378.1402 (for $C_{22}H_{22}N_2O_2S^+$); found 378.1395 $[M]^+$.

N-[2-(3-Bromophenyl)benzoxazol-6-yl]adamantane-1-carboxamide (7f). According to GPA the reaction of **3b** (100 mg, 0.35 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 0.15 mmol), and 3-bromobenzaldehyde **5e** (65 mg, 0.35 mmol) in absolute toluene (30 mL) was heated to reflux for 16 h to give the title compound **7f** (61 mg, 0.14 mmol, 39%, R_f = 0.50) after column chromatography (SiO_2, hexanes/EtOAc 3:1) as beige crystals, mp 216–218°C. IR (ATR): 3437, 2902, 2849,

1674, 1621, 1571, 1530, 1492 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.74–1.82 (m, 6H, Ad), 2.00–2.01 (m, 6H, Ad), 2.12–2.14 (m, 3H, Ad), 7.15 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz, 1H, Ar), 7.39 (t, *J* = 7.9 Hz, 1H, Ar), 7.48 (s, 1H, NH), 7.60–7.69 (m, 2H, Ar), 8.15 (d, *J* = 7.8 Hz, 1H, Ar), 8.31 (d, *J* = 2.1 Hz, 1H, Ar), 8.38 (d, *J* = 1.9 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.26 (3 CH), 36.54 (3 CH_2), 39.41 (3 CH_2), 41.78 (C), 103.17 (CH), 117.28 (CH), 119.91 (CH), 123.12 (C), 126.05 (CH), 129.03 (C), 130.43 (CH), 130.57 (CH), 134.36 (CH), 136.24 (C), 138.35 (C), 151.36 (C), 161.78 (C), 176.28 (C) ppm. HRMS (EI, 70 eV): *m*/*z* calcd 450.0943 (for $C_{24}H_{23}BrN_2O_2^+$); found 450.0933 $[M]^+$.

N-[2-(4-Methoxyphenyl)benzoxazol-6-yl]adamantane-1-carboxamide (7g). According to GPA, the reaction of **3b** (72 mg, 0.25 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.10 mmol), and 4-methoxybenzaldehyde **5f** (34 mg, 0.25 mmol) in absolute toluene (20 mL) was heated to reflux for 20 h to give the title compound **7g** (15 mg, 0.04 mmol, 15%, R_f = 0.25) after column chromatography (SiO_2, hexanes/EtOAc 3:1) as pale beige crystals, mp 235–239°C. IR (ATR): 3262, 2898, 2850, 1644, 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.74–1.84 (m, 6H, Ad), 2.00–2.04 (m, 6H, Ad), 2.11–2.13 (m, 3H, Ad), 3.89 (s, 3H, OCH_3), 6.98–7.07 (m, 2H, Ar), 7.11 (dd, *J* = 8.5 Hz, *J* = 2.1 Hz, 1H, Ar), 7.45 (s, 1H, NH), 7.61 (d, *J* = 8.5 Hz, 1H, Ar), 8.11–8.21 (m, 2H, Ar), 8.24 (d, *J* = 1.9 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.32 (3 CH), 36.61 (3 CH_2), 39.48 (3 CH_2), 41.77 (C), 55.60 (CH_3), 103.18 (CH), 114.52 (2 CH), 116.88 (CH), 119.30 (CH), 119.92 (C), 129.41 (2 CH), 135.43 (C), 138.86 (C), 151.24 (C), 162.42 (C), 163.58 (C), 176.19 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 402.01 (90) 135.01 (100), 93.3 (44), 79.3 (42) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 402.1943 (for $C_{25}H_{26}N_2O_3^+$); found 402.1945 $[M]^+$.

Benzoxazoles 7h–j: general procedure B. A mixture of compound **3b** (1.0 equiv), $ZnCl_2$ (0.3 equiv) and a carbonitrile (1.0 equiv) in PhCl (12 L/mol **3b**) was heated to reflux under an atmosphere of nitrogen at 135°C for 24 h. Subsequently, the solvent was removed in *vacuo* and the residue was purified by column chromatography to give the products **7h–j** (Table 1, entries 8–10).

N-[2-(4-Bromophenyl)benzoxazol-6-yl]adamantane-1-carboxamide (7h). According to general procedure B (GPB), the reaction of **3b** (70 mg, 0.24 mmol), $ZnCl_2$ (10 mg, 0.07 mmol), and 4-bromobenzonitrile **6a** (44 mg, 0.24 mmol) in PhCl (3 mL) was heated to reflux for 24 h to give the title compound **7h** (19 mg, 0.04 mmol, 17%, R_f = 0.60) after column chromatography (SiO_2, hexanes/EtOAc 3:1) as colorless crystals, mp 180–182°C. IR (ATR): 3434, 2910, 2851, 1674, 1619, 1520 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.76–1.82 (m, 6H, Ad), 1.93–2.04 (m, 6H, Ad), 2.07–2.15 (m, 3H, Ad), 7.11 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H, Ar), 7.49 (s, 1H, NH), 7.59–7.73 (m, 4H, Ar), 8.08 (d, *J* = 8.7 Hz, 1H, Ar), 8.30 (d, *J* = 2.1 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.27 (3 CH), 36.55 (3 CH_2), 39.43 (3 CH_2), 41.78 (C), 103.18 (CH), 117.21 (CH), 119.79 (CH), 126.21 (C), 128.99 (2 CH), 132.36 (2 CH), 136.09 (C), 138.47 (C), 151.34 (C), 162.48 (C), 176.30 (C) ppm. HRMS (EI, 70 eV): *m*/*z* calcd 450.0943 (for $C_{24}H_{23}BrN_2O_2^+$); found 450.0950 $[M]^+$.

N-[2-(4-Cyanophenyl)benzoxazol-6-yl]adamantane-1-carboxamide (7i). According to GPB, the reaction of **3b** (70 mg, 0.24 mmol), $ZnCl_2$ (10 mg, 0.07 mmol), and terephthalodinitrile **6b** (31 mg, 0.24 mmol) in PhCl (3 mL) was heated to reflux for 24 h to give the title compound **7i** (37 mg, 0.09 mmol, 76%, R_f = 0.33) after column chromatography (SiO_2, hexanes/EtOAc 3:1) as colorless crystals, mp > 340°C. IR (ATR): 3429, 2907, 2852, 2228, 1669, 1622, 1527 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75–1.82 (m, 6H, Ad), 1.99–2.03 (m, 6H, Ad), 2.09–2.15 (m, 3H, Ad), 7.15 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H, Ar), 7.52 (s, 1H, NH), 7.68 (d, *J* = 8.5 Hz, 1H, Ar), 7.80 (d, *J* = 8.0 Hz, 2H, Ar), 8.32 (d, *J* = 8.4 Hz, 2H, Ar), 8.37 (d, *J* = 2.1 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.24 (3 CH), 36.53 (3 CH_2), 39.42 (3 CH_2), 41.83 (C), 103.14 (CH), 114.63 (C), 117.51 (CH), 118.38 (C), 120.29 (CH), 127.91 (2 CH), 131.24 (C), 132.81 (2 CH), 136.78 (C), 138.27 (C), 151.55 (C), 161.21 (C), 176.37 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 397.2 (35), 135.1 (100) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 397.1790 (for $C_{25}H_{23}N_3O_2^+$); found 397.1789 $[M]^+$.

N-[2-(2-Methoxyethyl)benzoxazol-6-yl]adamantane-1-carboxamide (7j). According to GPB, the reaction of **3b** (70 mg, 0.24 mmol), $ZnCl_2$ (10 mg, 0.07 mmol), and 3-methoxypropionitrile **6c** (20 mg, 0.24 mmol) in PhCl (3 mL) was heated to reflux for 24 h to give the title compound **7j** (16 mg, 0.05 mmol, 19%, R_f = 0.15) after column chromatography (SiO_2, hexanes/EtOAc 2:1) as colorless crystals, mp 175–177°C. IR (ATR): 3259, 2900, 2849, 1644, 1618, 1526 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.70–1.74 (m, 6H, Ad), 1.90–1.95 (m, 6H, Ad), 2.01–2.05 (m, 3H, Ad), 3.15 (t, *J* = 6.3 Hz, 2H, CH_2), 3.26 (s, 3H, OCH_3), 3.79 (t, *J* = 6.4 Hz, 2H, OCH_2), 7.51 (dd, *J* = 8.6 Hz, *J* = 1.9 Hz, 1H, Ar), 7.56 (d, *J* = 8.6 Hz, 1H, Ar), 8.11 (d, *J* = 1.8 Hz, 1H, Ar) 9.26 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 27.63 (3 CH), 28.65 (CH_2), 35.97 (3 CH_2), 38.24 (3 CH_2), 40.94 (C), 57.86 (CH_3), 68.43 (CH_2), 102.24 (CH), 117.09 (CH), 118.43 (CH), 136.37 (C), 136.57 (C), 150.09 (C), 164.31 (C), 176.01 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 354.2 (15), 135.1 (100) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 354.1943 (for $C_{21}H_{26}N_2O_3^+$); found 354.1942 $[M]^+$.

2-(1-Adamantyl)-5-hydroxybenzimidazole (8). Trifluoroacetic acid (0.10 mL, 1.30 mmol) was added to a stirred solution of compound **3c** (54 mg, 0.20 mmol) in toluene (5 mL). The reaction mixture was heated to

reflux for 11 h, and the formed precipitate was collected by filtration, washed with toluene, and dried. The crude product was purified by recrystallization from chloroform (5 mL) to give the titled compound **8** (50 mg, 0.19 mmol, 99%) as a gray-white solid, mp. 220–222°C. IR (ATR): 2912, 2856, 2280, 1778, 1663, 1638, 1503 cm^{-1}. ^1H NMR (methanol-d_4): δ 1.75–1.93 (m, 6H, Ad), 2.14 (s, 9H, Ad), 6.95–7.04 (m, 2H, 2 Ar), 7.48 (d, J = 8.6 Hz, 1H, Ar) ppm. $^{13}C\{^1H\}$ NMR (methanol-d_4): δ 29.16 (3 CH), 36.57 (C), 36.87 (3 CH_2), 40.93 (3 CH_2), 99.16 (CH), 115.27 (CH), 117.07 (CH), 125.51 (C), 133.38 (C), 158.05 (C), 160.45 (C) ppm. MS (ESI): m/z (%) = 269.2 (100) $[M + H]^+$. HRMS (ESI): m/z calcd 269.1654 (for $C_{17}H_{21}N_2O^+$); found 269.1655 $[M + H]^+$.

Preparation of compounds 9a–c. To a cold (ice-water bath) suspension of benzimidazole **8** (1.24 g, 4.60 mmol) in glacial acetic acid (10 mL) nitric acid (65%, 0.2 mL, 4.60 mmol) was added dropwise within 5 min. The reaction mixture was stirred at ambient temperature for 15 min and then diluted with water (10 mL). The yellow precipitate formed was collected by filtration, washed with water and dried. The crude product was purified by column chromatography (SiO_2, hexanes/EtOAc 3:1) to yield the compound **9a** (0.64 g, 2.02 mmol, 44%, R_f = 0.49) in the first fraction. Secondly, compound **9b** (114 mg, 0.46 mmol, 10%, R_f = 0.32) and the third fraction the dinitro product **9c** (49 mg, 0.14 mmol, 3%, R_f = 0.15) was isolated.

2-(1-Adamantyl)-5-hydroxy-4-nitrobenzimidazole (9a).
This compound was obtained as yellow crystals, mp 188–187°C. IR (ATR): 3435, 3016, 2906, 2854, 1626, 1601, 1509, 1489 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–1.88 (m, 6H, Ad), 2.10–2.19 (m, 9H, Ad), 6.96 (d, J = 8.7 Hz, 1H, Ar), 7.93 (d, J = 8.6 Hz, 1H, Ar), 10.16 (br, s, 1H, NH), 10.82 (s, 1H, OH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.21 (3 CH), 35.51 (C), 36.49 (3 CH_2), 41.38 (3 CH_2), 112.90 (CH), 120.81 (C), 128.19 (C), 130.58 (CH), 137.86 (C), 153.74 (C), 162.58 (C) ppm. MS (ESI): m/z (%) = 314.2 (100) $[M + H]^+$. *Anal*. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.22; H, 6.19; N, 13.54.

2-(1-Adamantyl)-5-hydroxy-6-nitrobenzimidazole (9b).
This compound was obtained as a yellow solid, mp 258–260°C. IR (ATR):3311, 2919, 2850, 1640, 1600, 1551 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.80–1.87 (m, 6H, Ad), 2.03–2.15 (m, 9H, Ad), 7.09 (s, 1H, Ar), 8.38 (s, 1H, Ar), 10.67 (s, 1H, NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.19 (3 CH), 35.92 (C), 36.51 (3 CH_2), 41.19 (3 CH_2), 130.46 (C), 152.16 (C) ppm. MS (ESI): m/z (%) = 314.1 (100) $[M + H]^+$. HRMS (ESI): m/z calcd 314.1505 (for $C_{17}H_{20}N_3O_3)^+$; found 314.1511 $[M + H]^+$.

2-(1-Adamantyl)-5-hydroxy-4,6-dinitrobenzimidazole (9c).
This compound as a dark yellow solid, mp 133–135°C. IR (ATR): 3850, 2905, 2852, 1641, 1515 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75–1.96 (m, 6H, Ad), 2.04–2.32 (m, 9H, Ad), 8.78 (s, 1H, Ar), 10.38 (s, 1H, NH), 12.16 (s, 1H, OH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.06 (3 CH), 35.98 (C), 36.35 (3 CH_2), 41.07 (3 CH_2), 124.57 (CH), 132.11 (C), 134.62(C), 135.81(C), 149.59 (C) ppm. MS (ESI): m/z (%) = 359.2 (95), 301.2 (100) $[M + H]^+$. HRMS (ESI): m/z calcd 359.1355 (for $C_{17}H_{19}N_4O_5)^+$; found 359.1353 $[M + H]^+$.

2-(1-Adamantyl)-4-amino-5-hydroxybenzimidazole (10).
Pd/C (10% *w*/w, 140 mg) was added to a solution of nitro compound **9a** (575 mg, 1.80 mmol) in EtOH (60 mL). The reaction mixture was degased and then stirred under an atmosphere of hydrogen (1 atm) at room temperature for 24 h. Then the catalyst was removed by filtration, and the solvent was removed *in vacuo*. The title compound **7** (450 mg, 1.6 mmol, 87%) was isolated as a brown solid, mp 185.190°C without further purification. IR (ATR): 3402, 3308, 2910, 1665, 1639 cm^{-1}. ^1H NMR (methanol-d_4): δ 1.55–2.32 (m, 15H, Ad), 3.27 (s, 3H, NH_2, NH) 6.67 (d, J = 2.9 Hz, 2H, 2 Ar) ppm. $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 27.71 (3 CH), 34.83 (C), 38.13 (3 CH_2), 40.80 (3 CH_2), 101.23 (C), 111.77 (CH), 123.09 (C), 137.59 (C), 159.52 (2 C) ppm. MS (EI, 70 eV): m/z (%) = 283.1 (100), 226 (10) $[M]^+$. HRMS (EI, 70 eV): m/z calcd 283.1685 (for $C_{17}H_{21}N_3O^+$); found 283.1683 $[M]^+$.

7-(1-Adamantyl)-2-phenyl-6*H*-imidazo[4,5-*e*]benzoxazole (11a). A mixture of amino alcohol **10** (50 mg, 0.14 mmol), $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.20 mmol) and benzaldehyde **5a** (162 mg, 0.37 mmol) in toluene (30 mL) was heated to reflux for 9 h. Subsequently, the solvent was removed *in vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc 2:1) to give the title compound **11a** (7 mg, 0.02 mmol, 11%, R_f = 0.45) as beige crystals, mp 303–306°C. IR (ATR): 2901, 2849, 1553 1530 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.78–1.88 (m, 6H, Ad), 2.11–2.22 (m, 9H, Ad), 7.47 (d, J = 8.7 Hz, 1H, Ar), 7.49–7.57 (m, 3H, Ar), 7.66 (br. s, 1H, Ar), 8.27 (dd, J = 6.7 Hz, J = 3.0 Hz, 2H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.43 (3 CH), 35.64 (C), 36.71 (3 CH_2), 41.66 (3 CH_2), 104.94 (CH), 127.51 (2 CH), 127.61 (C), 129.09 (3 CH), 131.38 (CH), 148.05 (C), 161.91 (C), 162.79 (C) ppm. MS (EI, 70 eV): m/z (%) = 369.2 (100), 312.1 (17) $[M]^+$. HRMS (EI, 70 eV): m/z calcd 369.1841 (for $C_{24}H_{23}N_3O^+$); found 369.1833 $[M]^+$.

7-(Adamantyl)-2-(4-methoxyphenyl)-6*H*-imidazo[4,5-*e*] benzoxazole (11b). A mixture of amino alcohol **10** (50 mg, 0.14 mmol), $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.20 mmol) and 4-methoxybenzaldehyde **5f** (50 mg, 0.37 mmol) in toluene (30 mL) was heated to reflux for 15 h. Subsequently, the solvent was removed *in vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc 3:1) to give the title compound **11b**

(12 mg, 0.03 mmol, 9%, R_f = 0.25) as beige crystals, mp 293–296°C. IR (ATR): 3072, 3003, 2903, 2847, 1610, 1529, 1498 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.78–1.88 (m, 6H, Ad), 2.10–2.24 (m, 9H, Ad), 3.90 (s, 3H, CH_3O), 6.95–7.09 (m, 2H, Ar), 7.46 (d, *J* = 8.6 Hz, 1H, Ar), 7.66 (s, 1H, Ar), 8.27–8.12 (m, 2H, Ar) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.42 (3 CH), 35.62 (C), 36.69 (3 CH_2), 41.62 (3 CH_2), 55.61 (CH_3), 104.87 (2 CH), 114.56 (2 CH), 120.16 (C), 129.25 (2 CH), 147.90 (2 C), 161.83 (2 C), 162.32 (C), 162.97 (2 C) ppm. MS (EI, 70 eV): *m*/z (%) = 399.1 (100), 342.1 (58), 171.2 (25) $[M]^+$. HRMS (EI, 70 eV): *m*/*z* calcd 399.1947 (for $C_{25}H_{25}N_3O_2^+$); found 399.1948 $[M]^+$.

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