

Cu^I-catalyzed *N,N'*-diarylation of diamines of adamantane series

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A copper(I) complex-catalyzed *N,N'*-diarylation of diamines based on 1,3-disubstituted adamantane, using aryl iodides bearing electron-donating and electron-withdrawing substituents, was studied. In the case of 2,2'-(adamantane-1,3-diyl)ethanediamine, the optimal catalyst system is CuI–2-(isobutyryl)cyclohexanone–Cs₂CO₃–DMF. The highest yield of diarylation product was reached in the case of 4-methoxyiodobenzene (79%). In the case of more spatially hindered adamantane-1,3-diylmethanamine, 1,1'-binaphthalene-2,2'-diol (BINOL) should be used, with the highest yield of the target product (84%) being reached in the reaction with iodobenzene.

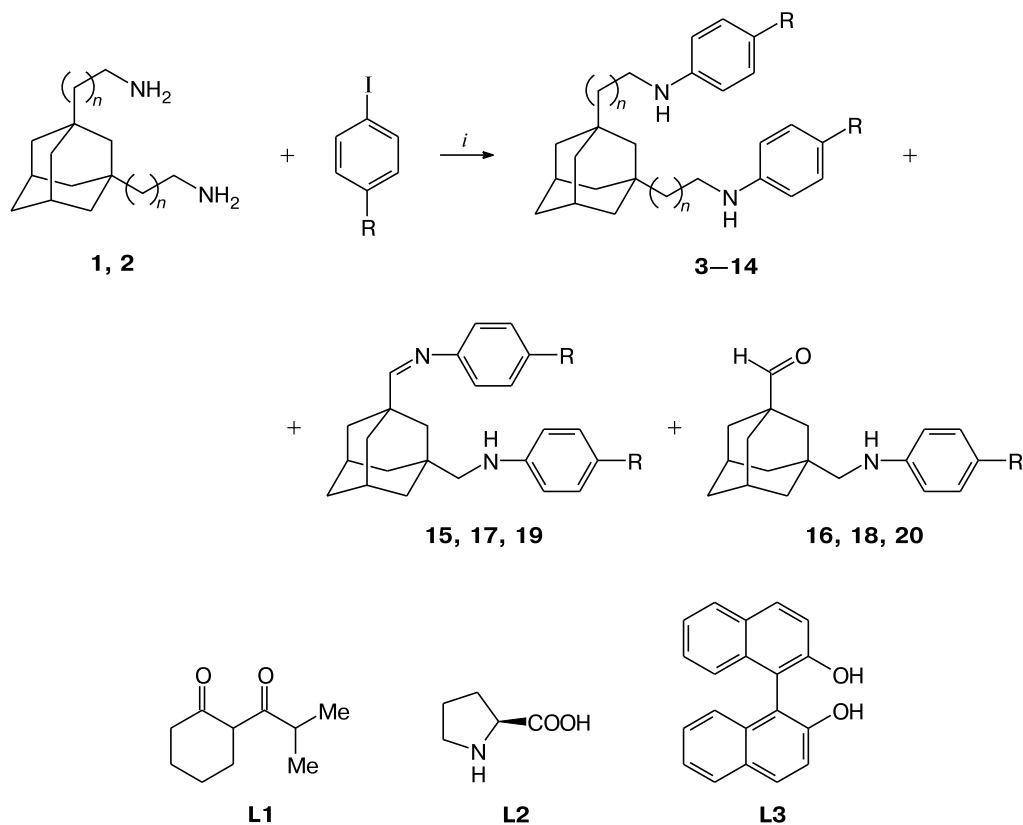
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N-(Hetero)aryl derivatives of adamantane-containing amines are of great interest as compounds exhibiting various biological activity. Some of them, for example, chlodantan (immunopotentiator)¹ and ladasten (neurostimulating agent),² are already used as pharmaceutical agents. A great role in the development of new medicines belongs to compounds containing in the (hetero)aromatic rings such substituents as fluorine and trifluoromethyl group. About 20–25% of modern drugs contain fluorine in the composition,³ most frequently as a substituent in the aromatic or heteroaromatic ring (for example, sitagliptin, atorvastatin, ciproflaxin) or trifluoromethyl group (fluoxetine, sensipar, sustiva). The fluorine atoms present in the molecule of a potential pharmaceutical agent modulate its acidity,⁴ stabilize certain conformations,⁵ modify hydrophobic interactions and hydrogen bonds,⁶ lipophilicity,⁷ solubility,⁸ which leads to the changes in the binding ability with the site of interest and can lead to the improvement of binding selectivity. At the same time, physiological activity of adamantane diamino derivatives is a subject of modern studies. Thus, for example, adamantane-1,3-diylmethanamine dihydrochloride is patented as an antiviral agent for home animals.^{9,10} In this connection, development of versatile methods for the introduction of (hetero)aryl substituents in the adamantane-containing amines and diamines seems an actual problem. One of such methods is the copper complex-catalyzed (hetero)arylation of amines. Recently, we studied a Cu^I-catalyzed heteroarylation of various amines based on ada-

mantane with iodopyridine¹¹ and studied *N,N'*-diarylation of di- and polyamines with a number of aryl iodides and halopyridines.^{12–14} It was found that depending on the structure of polyamines, the relative reactivities of aryl iodides containing electron-donating and electron-withdrawing substituents noticeably differ. In this connection, in the present work we study two diamines based on 1,3-disubstituted adamantane, 2,2'-(adamantane-1,3-diyl)ethanediamine (**1**) and adamantane-1,3-diylmethanamine (**2**), in the reactions of Cu^I-catalyzed arylation.

The arylating agents were iodobenzene, its derivatives with electron-withdrawing substituents (4-iodobiphenyl, 4-iodofluorobenzene, and 4-(trifluoromethyl)iodobenzene) and electron-donating groups (4-iodotoluene and 4-iodoanisole). Initially, we carried out the reactions with diamine **1** bearing more spatially available amino groups (Scheme 1). Proceeding from the earlier obtained data on the *N,N'*-diarylation of diamines, we used the catalytic system CuI–2-(isobutyryl)cyclohexanone (**L1**) (10 and 20 mol.%), the reactions were carried out at the molar ratio diamine : aryl iodide 1 : 2.5 in DMF at 110 °C and a concentration of diamine 0.5 mol L^{–1}; cesium carbonate was used as a base. The obtained compounds were isolated by chromatography on silica gel, the yields are given in Table 1. The reaction of diamine **1** with iodobenzene gives the target product **3** in a moderate yield (entry 1), while in the case of electron-deficient 4-iodobiphenyl and 4-iodofluorobenzene, the product yields were much better (entries 4 and 5). The best yields were observed in the case of

Scheme 1



Compound	R	n	Compound	R	n	Compound	R	n	Compound	R	n
1	—	1	6	CF ₃	1	11	F	0	16	CF ₃	—
2	—	0	7	Me	1	12	CF ₃	0	17	Me	—
3	H	1	8	OMe	1	13	Me	0	18	Me	—
4	Ph	1	9	H	0	14	OMe	0	19	OMe	—
5	F	1	10	Ph	0	15	Ph	—	20	OMe	—

i. CuI/L/DMF, Cs₂CO₃, 110–140 °C.

electron-enriched 4-iodotoluene and 4-iodoanisole (70 and 79%, respectively, entries 8 and 9). The activity of 4-(trifluoromethyl)iodobenzene turned out to be unexpectedly the lowest (entry 6). An attempt to improve the result by using another ligand, L-proline (**L2**), was unsuccessful (entry 2).

An increase in the reaction temperature to 140 °C did not lead to a noticeable improvement of the result, as it was inferred from the NMR data of the reaction mixture. Yet another *O,O'*-bidentate ligand, *rac*-BINOL (**L3**), has proved more efficient when used at 140 °C (entry 3), which allowed us to obtain the target compound **3** in 66% yield. This ligand also facilitated the preparation of derivative **6** containing trifluoromethyl substituents in 52% yield (entry 7).

The reactions with diamine **2** containing more spatially hindered amino groups due to their closer position from the adamantane framework were carried out exclusively in the presence of ligand **L3** and at 140 °C, since in the preliminary experiment with iodobenzene in the presence

of the system CuI—**L1**, even at 140 °C the conversion of the starting compounds was low. When catalyzed with the system CuI—**L3**, *N,N'*-diphenyl derivative **9** was isolated in 84% yield (entry 10), however, in the reactions with other iodoarenes the yields were considerably lower. Thus, out of electron deficient aryl iodides only reaction with 4-iodofluorobenzene gave diarylation product **11** in a moderate yield of 41% (entry 12), whereas with electron-enriched iodoarenes the yields were 28% in the case of 4-iodotoluene (entry 14) and 35% in the case of 4-iodoanisole (entry 15). In the latter case, to increase the conversion of the starting compounds we had to increase the amount of the catalyst to 20 mol.%. Apart from that, in a number of cases the formation of imines **17** and **19** was observed as a result of the catalytic reduction of the C—I bond accompanied by the β-hydride elimination from the copper amide complex. In the reaction with 4-iodobiphenyl, imine **15** was the only compound isolated in the individual state (entry 11). The chromatographic separa-

Table 1. Synthesis of *N,N'*-diaryl derivatives of adamantane-containing diamines **3**–**14**

Entry	Diamine	R	Ligand	T/°C	Products	Yield (%)
1	1	H	L1	110	3	33
2	1	H	L2	110	3	27
3	1	H	L3	140	3	66
4	1	Ph	L1	110	4	50
5	1	F	L1	110	5	57
6	1	CF ₃	L1	110	6	21
7	1	CF ₃	L3	140	6	52
8	1	Me	L1	140	7	70
9	1	OMe	L1	110	8	79
10	2	H	L3	140	9	84
11	2	Ph	L3	140	10	Traces
					15	12
12	2	F	L3	140	11	41
13	2	CF ₃	L3	140	12	20
					16	23
14	2	Me	L3	140	13	28
					17	10
					18	10
15	2	OMe	L3*	140	14	35
					19	22
					20	9

* CuI/L3 (20/40 mol.%) was used.

tion of the reaction products was accompanied by partial hydrolysis of imines to the corresponding aldehydes, which also were isolated and characterized (compounds **16**, **18**, and **20**), with their yields being comparable with the yields of the target *N,N'*-diarylation products. In a number of cases, the formation of monoarylation products was observed, however, they were not isolated in the individual state because of the difficulties of separation from the unidentified impurities by chromatography. All the new target compounds **4**–**8** and **10**–**14** were characterized by ¹H and ¹³C NMR spectroscopy (except for the product **12** because of the technical difficulties arising upon acquisition of quaternary carbon atoms in the trifluoromethylphenyl fragment) and high resolution MALDI mass spectrometry. The side compounds **15**–**20** were also characterized by NMR spectroscopy and MALDI.

In conclusion, using the *N,N'*-diarylation reactions of adamantane-containing diamines as an example it was shown that under conditions of the catalysis by copper(I) complexes, a thorough selection of the ligand is required for determination of reagent pairs, whereas the reactivity of aryl iodides in the indicated process is not unambiguously determined by the presence of electron-donating or electron-withdrawing substituents.

Experimental

¹H and ¹³C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) at 298 K. Chemical shifts in the ¹H

and ¹³C NMR spectra are given in δ scale relative to Me₄Si as an internal standard. MALDI mass spectra of positive ions were recorded on a Bruker Autoflex II instrument using 1,8,9-trihydroxyanthracene as a matrix and poly(ethylene glycols) as internal standards. Preparative column chromatography was carried out using Merck silica gel (40/60). The starting iodoarenes, 2-isobutyrylcyclohexanone, L-proline, *rac*-BINOL, and cesium carbonate from Sigma-Aldrich were used without purification. Amines **1** and **2** were synthesized according to the procedure described earlier.¹⁵

Synthesis of *N*-aryl-substituted adamantane-containing amines (general procedure). A corresponding iodoarene (1.25–2.5 mmol), CuI (10 mol.%, 9.5–19 mg), a corresponding ligand (20 mol.%), cesium carbonate (1.25–2.5 mmol, 408–916 mg), DMF (1–2 mL), and adamantane-containing diamine **1** or **2** (0.5–1 mmol, 111–222 or 97–194 mg, respectively) were placed in a one-neck flask equipped with a magnetic stirrer and a reflux condenser and filled with anhydrous argon. The reaction mixture was stirred at 110 or 140 °C for 24 h. After the reaction reached completion, the mixture was cooled to room temperature and diluted with dichloromethane (5 mL), a precipitate was filtered off and washed additionally with dichloromethane (5 mL), the combined organic fractions were concentrated *in vacuo*, the residue was analyzed by NMR spectroscopy and subjected to chromatography on silica gel using the following sequence of eluents: light petroleum ether–CH₂Cl₂ (10 : 1)→(1 : 4), CH₂Cl₂, CH₂Cl₂–MeOH (100 : 1)→(3 : 1).

***N,N'*-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]dianiline (**3**)** was obtained from diamine **1** (222 mg) and iodobenzene (510 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (33 mg) in DMF (2 mL). Eluent CH₂Cl₂→CH₂Cl₂–MeOH (50 : 1). The yield was 124 mg (33%), a white crystalline powder, m.p. 85–87 °C. When *rac*-BINOL (28.5 mg, 20 mol.%) was used as the ligand, diamine **1** (111 mg, 0.5 mmol) and iodobenzene (255 mg, 1.25 mmol) gave the yield of 123 mg (66%). The spectral data are given in the work.¹⁶

***N,N'*-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]bis(biphenyl-4-amine) (**4**)** was obtained from diamine **1** (222 mg), 4-iodobiphenyl (700 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (33 mg) in DMF (2 mL). Eluent light petroleum ether–CH₂Cl₂ (1 : 4), CH₂Cl₂. The yield was 265 mg (50%), a yellow crystalline powder, m.p. 150–152 °C. ¹H NMR (CDCl₃), δ: 1.38 (br.s, 2 H, H_{Ad}); 1.45–1.49 (m, 4 H, CH₂–Ad); 1.50–1.54 (m, 4 H, H_{Ad}); 1.57–1.62 (m, 4 H, H_{Ad}); 1.66 (br.s, 2 H, H_{Ad}); 2.10 (br.s, 2 H, HC_{Ad}); 3.16–3.20 (m, 4 H, CH₂NPh); 3.61 (br.s, 2 H, NH); 6.69 (d, 4 H, H_{Ar}, ³J_{obs} = 8.5 Hz); 7.27 (t, 2 H, H_{Ar}, ³J = 7.3 Hz); 7.40 (t, 4 H, H_{Ar}, ³J_{obs} = 7.8 Hz); 7.47 (d, 4 H, H_{Ar}, ³J_{obs} = 8.5); 7.53–7.57 (m, 4 H, H_{Ar}). ¹³C NMR (CDCl₃), δ: 28.9 (2 C, HC_{Ad}); 32.7 (2 C, C_{Ad}); 36.4 (1 C, H₂C_{Ad}); 38.7 (2 C, CH₂–Ad); 42.0 (4 C, H₂C_{Ad}); 43.7 (2 C, CH₂NPh); 47.8 (1 C, H₂C_{Ad}); 112.9 (4 C, HC_{Ar}); 126.0 (2 C, HC_{Ar}); 126.2 (4 C, HC_{Ar}); 127.9 (4 C, HC_{Ar}); 128.6 (4 C, HC_{Ar}); 130.0 (2 C, C_{Ar}); 141.3 (2 C, C_{Ar}); 147.9 (2 C, NC_{Ar}). MS (MALDI), found: *m/z* 527.3403 [M + H]⁺. C₃₈H₄₃N₂. Calculated: 527.3426.

***N,N'*-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]bis(4-fluoroaniline) (**5**)** was obtained from diamine **1** (222 mg), 4-iodofluorobenzene (555 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (33 mg) in DMF (2 mL). Eluent CH₂Cl₂, CH₂Cl₂–MeOH (100 : 1)→(50 : 1). The yield was 271 mg (66%), a colorless dense oil. ¹H NMR (CDCl₃), δ: 1.33 (br.s, 2 H, H_{Ad}); 1.39–1.44 (m, 4 H, CH₂–Ad); 1.45–1.50 (m, 4 H, H_{Ad}); 1.52–1.58 (m, 4 H, H_{Ad}); 1.63 (br.s, 2 H, H_{Ad}); 2.07 (br.s, 2 H,

H_{Ad}); 3.05–3.09 (m, 4 H, CH_2N); 3.34 (br.s, 2 H, NH); 6.50–6.55 (d, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{H,F} = 4.3$ Hz); 6.86–6.93 (d, 4 H, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{H,F} = 8.8$ Hz). ^{13}C NMR ($CDCl_3$), δ : 28.9 (2 C, HC_{Ad}); 32.6 (2 C, C_{Ad}); 36.4 (1 C, H_2C_{Ad}); 39.2 (2 C, CH_2-Ad); 41.9 (4 C, H_2C_{Ad}); 43.6 (2 C, CH_2N); 47.8 (1 C, H_2C_{Ad}); 113.4 (d, 4 C, $C_{Ph}(2)$, $C_{Ph}(2')$, $^3J_{C,F} = 7.6$ Hz); 115.6 (d, 4 C, $C_{Ph}(3)$, $C_{Ph}(3')$, $^2J_{C,F} = 21.9$ Hz); 144.9 (2 C, $C_{Ph}(1)$); 155.5 (d, 2 C, $C_{Ph}(4)$, $^1J_{C,F} = 234.4$ Hz). MS (MALDI), found: m/z 409.2481 $[M - H_2 + H]^+$. $C_{26}H_{31}F_2N_2$. Calculated: 409.2455.

***N,N'*-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]bis(4-trifluoromethylaniline) (6)** was obtained from diamine **1** (222 mg), 4-trifluoromethyl iodobenzene (680 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (33 mg) in DMF (2 mL). Eluent light petroleum ether– CH_2Cl_2 (2 : 1)→(1 : 1). The yield was 107 mg (21%), a white crystalline powder, m.p. 107–109 °C. When *rac*-BINOL (28.5 mg, 20 mol.%) was used as the ligand, diamine **1** (111 mg, 0.5 mmol) and 4-trifluoromethyl iodobenzene (340 mg, 1.25 mmol) gave the yield of 134 mg (52%). 1H NMR ($CDCl_3$), δ : 1.41–1.45 (m, 4 H, CH_2-Ad); 1.46–1.51 (m, 4 H, H_{Ad}); 1.54–1.60 (m, 4 H, H_{Ad}); 1.64 (br.s, 4 H, H_{Ad}); 2.08 (br.s, 2 H, HC_{Ad}); 3.12–3.16 (m, 4 H, CH_2NPh); 3.82 (br.s, 2 H, NH); 6.57 (d, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{obs} = 8.6$ Hz); 7.39 (d, 4 H, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = 8.6$ Hz). ^{13}C NMR ($CDCl_3$), δ : 28.8 (2 C, HC_{Ad}); 32.7 (2 C, C_{Ad}); 36.3 (1 C, H_2C_{Ad}); 38.2 (2 C, CH_2-Ad); 41.9 (4 C, H_2C_{Ad}); 43.4 (2 C, CH_2NPh); 47.8 (1 C, H_2C_{Ad}); 111.7 (4 C, $C_{Ph}(2)$, $C_{Ph}(2')$); 118.5 (q, 2 C, $C_{Ph}(4)$, $^2J_{C,F} = 32.6$ Hz); 125.1 (q, 2 C, CF_3 , $^1J_{C,F} = 270.2$ Hz); 126.6 (4 C, $C_{Ph}(3)$, $C_{Ph}(3')$); 150.8 (2 C, $C_{Ph}(1)$). MS (MALDI), found: m/z 491.2510 $[M - F]^+$. $C_{28}H_{32}F_5N_2$. Calculated: 491.2486.

***N,N'*-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]bis(4-methylaniline) (7)** was obtained from diamine **1** (111 mg), 4-iodotoluene (273 mg) in the presence of CuI (9.5 mg) and 2-isobutyrylcyclohexanone (17 mg) in DMF (1 mL). Eluent CH_2Cl_2 . The yield was 141 mg (70%), a beige crystalline powder, m.p. 86–88 °C. 1H NMR ($CDCl_3$), δ : 1.33 (br.s, 2 H, H_{Ad}); 1.38–1.44 (m, 4 H, $Ad-CH_2$); 1.44–1.56 (m, 8 H, H_{Ad}); 1.62 (br.s, 2 H, H_{Ad}); 2.06 (br.s, 2 H, HC_{Ad}); 2.25 (s, 6 H, CH_3); 3.08–3.12 (m, 4 H, CH_2N); 3.46 (br.s, 2 H, NH); 6.55 (d, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{obs} = 8.3$ Hz); 6.99 (d, 4 H, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = 8.3$ Hz). ^{13}C NMR ($CDCl_3$), δ : 20.4 (2 C, CH_3); 28.9 (2 C, HC_{Ad}); 32.7 (2 C, C_{Ad}); 36.5 (1 C, H_2C_{Ad}); 39.1 (2 C, $Ad-CH_2$); 42.0 (4 C, H_2C_{Ad}); 43.7 (2 C, CH_2N); 47.8 (1 C, H_2C_{Ad}); 113.1 (4 C, $C_{Ph}(2)$, $C_{Ph}(2')$); 126.5 (2 C, $C_{Ph}(4)$); 129.7 (4 C, $C_{Ph}(3)$, $C_{Ph}(3')$); 146.1 (2 C, $C_{Ph}(1)$). MS (MALDI), found: m/z 403.3089 $[M + H]^+$. $C_{28}H_{39}N_2$. Calculated: 403.3113.

***N,N'*-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]bis(4-methoxyaniline) (8)** was obtained from diamine **1** (222 mg), 4-iodoanisole (585 mg) in the presence of CuI (19 mg) and 2-isobutyrylcyclohexanone (33 mg) in DMF (2 mL). Eluent CH_2Cl_2 –MeOH 10 : 1. The yield was 346 mg (79%), a brown dense oil. 1H NMR ($CDCl_3$), δ : 1.31 (br.s, 2 H, H_{Ad}); 1.37–1.42 (m, 4 H, CH_2-Ad); 1.43–1.48 (m, 4 H, H_{Ad}); 1.52–1.56 (m, 4 H, H_{Ad}); 1.61 (br.s, 2 H, H_{Ad}); 2.04 (br.s, 2 H, HC_{Ad}); 3.03–3.07 (m, 4 H, CH_2NPh); 3.32 (br.s, 2 H, NH); 3.73 (s, 6 H, OCH_3); 6.57 (d, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{obs} = 8.8$ Hz); 6.77 (d, 2 H, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = 8.8$ Hz). ^{13}C NMR ($CDCl_3$), δ : 28.8 (2 C, HC_{Ad}); 32.5 (2 C, C_{Ad}); 36.3 (1 C, H_2C_{Ad}); 39.4 (2 C, CH_2-Ad); 41.8 (4 C, H_2C_{Ad}); 43.6 (2 C, CH_2NPh); 47.6 (1 C, H_2C_{Ad}); 55.6 (2 C, OCH_3); 113.9 (4 C, HC_{Ph}); 114.7 (4 C, HC_{Ph}); 142.7 (2 C, $C_{Ph}(1)$); 151.8 (2 C, $C_{Ph}(4)$). MS (MALDI), found: m/z 435.3052 $[M + H]^+$. $C_{28}H_{39}N_2O_2$. Calculated: 435.3012.

***N,N'*-[Adamantane-1,3-diylbis(methanediyl)]dianiline (9)** was obtained from diamine **2** (97 mg) and iodobenzene (255 mg) in the presence of CuI (9.5 mg) and *rac*-BINOL (28.5 mg) in DMF (1 mL). Eluent light petroleum ether– CH_2Cl_2 (1 : 1)→(1 : 2). The yield was 145 mg (84%), a white crystalline powder, m.p. 101–103 °C. The spectral data are given in the work.¹⁶

***N,N'*-[Adamantane-1,3-diylbis(methanediyl)]bis(4-fluoroaniline) (11)** was obtained from diamine **2** (97 mg) and 4-fluoroiodobenzene (278 mg) in the presence of CuI (9.5 mg) and *rac*-BINOL (28.5 mg) in DMF (1 mL). Eluent light petroleum ether– CH_2Cl_2 (1 : 1)→(1 : 2). The yield was 78 mg (41%), a yellow dense oil. 1H NMR ($CDCl_3$), δ : 1.41 (br.s, 2 H, H_{Ad}); 1.49–1.59 (m, 8 H, H_{Ad}); 1.66 (br.s, 2 H, H_{Ad}); 2.12 (br.s, 2 H, HC_{Ad}); 2.80 (s, 4 H, CH_2N); 3.57 (br.s, 2 H, NH); 6.56 (dd, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{obs} = 8.6$ Hz, $^4J_{H,F} = 4.0$ Hz); 6.86 (dd, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = ^3J_{H,F} = 8.6$ Hz). ^{13}C NMR ($CDCl_3$), δ : 28.4 (2 C, HC_{Ad}); 34.5 (2 C, C_{Ad}); 36.4 (1 C, H_2C_{Ad}); 40.2 (4 C, H_2C_{Ad}); 43.7 (1 C, H_2C_{Ad}); 57.0 (2 C, CH_2N); 113.6 (4 C, $C_{Ph}(2)$, $C_{Ph}(2')$); 115.6 (d, 4 C, $C_{Ph}(3)$, $C_{Ph}(3')$, $^2J_{C,F} = 22.8$ Hz); 145.3 (2 C, $C_{Ph}(1)$); 155.7 (d, 2 C, $C_{Ph}(4)$, $^1J_{C,F} = 234.4$ Hz). MS (MALDI), found: m/z 383.2324 $[M + H]^+$. $C_{24}H_{29}F_2N_2$. Calculated: 383.2299.

***N,N'*-[Adamantane-1,3-diylbis(methanediyl)]bis(4-trifluoromethylaniline) (12)** was obtained from diamine **2** (97 mg) and 4-(trifluoromethyl)iodobenzene (340 mg) in the presence of CuI (9.5 mg) and *rac*-BINOL (28.5 mg) in DMF (1 mL). Eluent light petroleum ether– CH_2Cl_2 (10 : 1). The yield was 48 mg (20%), a light yellow dense oil. 1H NMR ($CDCl_3$), δ : 1.41 (br.s, 2 H, H_{Ad}); 1.47–1.59 (m, 8 H, H_{Ad}); 1.65 (br.s, 2 H, H_{Ad}); 2.12 (br.s, 2 H, HC_{Ad}); 2.88 (s, 4 H, CH_2N); 4.05 (br.s, 2 H, NH); 6.63 (br.s, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$); 7.37 (d, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = 8.3$ Hz). MS (MALDI), found: m/z 463.2120 $[M - F]^+$. $C_{26}H_{28}F_5N_2$. Calculated: 463.2173.

***N,N'*-[Adamantane-1,3-diylbis(methanediyl)]bis(4-methylaniline) (13)** was obtained from diamine **2** (97 mg) and 4-iodotoluene (273 mg) in the presence of CuI (9.5 mg) and *rac*-BINOL (28.5 mg) in DMF (1 mL). Eluent light petroleum ether– CH_2Cl_2 (1 : 2). The yield was 53 mg (28%), a beige crystalline powder, m.p. 132–134 °C. 1H NMR ($CDCl_3$), δ : 1.42 (br.s, 2 H, H_{Ad}); 1.51–1.62 (m, 8 H, H_{Ad}); 1.67 (br.s, 2 H, H_{Ad}); 2.13 (br.s, 2 H, HC_{Ad}); 2.25 (s, 6 H, CH_3); 2.84 (s, 4 H, CH_2N); 3.50 (s, 2 H, NH); 6.57 (d, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{obs} = 8.2$ Hz); 6.99 (d, 4 H, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = 8.2$ Hz). ^{13}C NMR ($CDCl_3$), δ : 20.3 (2 C, CH_3); 28.5 (2 C, HC_{Ad}); 34.6 (2 C, C_{Ad}); 36.5 (1 C, H_2C_{Ad}); 40.2 (4 C, H_2C_{Ad}); 43.8 (1 C, H_2C_{Ad}); 56.4 (2 C, CH_2N); 112.6 (4 C, $C_{Ph}(2)$, $C_{Ph}(2')$); 126.1 (2 C, $C_{Ph}(4)$); 129.7 (4 C, $C_{Ph}(3)$, $C_{Ph}(3')$); 146.8 (2 C, $C_{Ph}(1)$). MS (MALDI), found: m/z 375.2767 $[M + H]^+$. $C_{26}H_{35}N_2$. Calculated: 375.2800.

***N,N'*-[Adamantane-1,3-diylbis(methanediyl)]bis(4-methoxyaniline) (14)** was obtained from diamine **2** (97 mg) and 4-iodoanisole (293 mg) in the presence of CuI (19 mg) and *rac*-BINOL (57 mg) in DMF (1 mL). Eluent CH_2Cl_2 , CH_2Cl_2 –MeOH (100 : 1). The yield was 71 mg (35%), a brown oil. 1H NMR ($CDCl_3$), δ : 1.42 (br.s, 2 H, H_{Ad}); 1.50–1.60 (m, 8 H, H_{Ad}); 1.65 (br.s, 2 H, H_{Ad}); 2.11 (br.s, 2 H, HC_{Ad}); 2.79 (s, 4 H, CH_2N); 3.47 (br.s, 2 H, NH); 3.74 (s, 6 H, OCH_3); 6.60 (d, 4 H, $H_{Ph}(2)$, $H_{Ph}(2')$, $^3J_{obs} = 8.7$ Hz); 6.76 (d, 4 H, $H_{Ph}(3)$, $H_{Ph}(3')$, $^3J_{obs} = 8.7$ Hz). ^{13}C NMR ($CDCl_3$), δ : 28.5 (2 C, HC_{Ad}); 34.5 (2 C, C_{Ad}); 36.5 (1 C, H_2C_{Ad}); 40.3 (4 C, H_2C_{Ad}); 43.8 (1 C, H_2C_{Ad}); 55.8 (2 C, CH_2N); 57.4 (2 C, CH_3O); 114.1 (4 C, $C_{Ph}(2)$, $C_{Ph}(2')$); 114.9 (4 C, $C_{Ph}(3)$, $C_{Ph}(3')$); 143.2 (2 C, $C_{Ph}(1)$);

151.9 (2 C, C_{Ph}(4)). MS (MALDI), found: m/z 407.2752 [M + H]⁺. C₂₆H₃₅N₂O₂. Calculated: 407.2699.

N-((3-[(Biphenyl-4-ylamino)methyl]-1-adamantyl)methylidene)biphenyl-4-amine (15) was obtained in the attempt to synthesize compound **10** from diamine **2** (97 mg) and 4-iodobiphenyl (350 mg) in the presence of CuI (9.5 mg) and *rac*-BINOL (28.5 mg) in DMF (1 mL). Eluent light petroleum ether—CH₂Cl₂ 1 : 2. The yield was 30 mg (12%), a yellow dense oil. ¹H NMR (CDCl₃), δ: 1.63–1.89 (m, 12 H, H_{Ad}); 2.24 (br.s, 2 H, HC_{Ad}); 2.98 (s, 2 H, CH₂N); 3.80 (br.s, 1 H, NH); 6.72 (d, 2 H, H_{Ar}, ³J_{obs} = 8.5 Hz); 7.10 (d, 2 H, H_{Ar}, ³J_{obs} = 8.3 Hz); 7.24–7.48 (m, 8 H, H_{Ar}); 7.53–7.63 (m, 6 H, H_{Ar}); 7.66 (s, 1 H, CH=N). ¹³C NMR (CDCl₃), δ: 28.1 (2 C, HC_{Ad}); 34.5 (1 C, C_{Ad}); 36.1 (1 C, H₂C_{Ad}); 38.9 (2 C, H₂C_{Ad}); 39.6 (1 C, C_{Ad}); 39.9 (2 C, H₂C_{Ad}); 42.0 (1 C, H₂C_{Ad}); 55.8 (1 C, CH₂N); 112.8 (2 C, HC_{Ar}); 121.0 (2 C, HC_{Ar}); 125.9 (1 C, HC_{Ar}); 126.2 (2 C, HC_{Ar}); 126.4 (1 C, HC_{Ar}); 126.9 (2 C, HC_{Ar}); 127.6 (2 C, HC_{Ar}); 127.9 (2 C, HC_{Ar}); 128.6 (2 C, HC_{Ar}); 128.7 (2 C, HC_{Ar}); 131.5 (1 C, C_{Ar}); 138.2 (1 C, C_{Ar}); 140.7 (1 C, C_{Ar}); 141.3 (1 C, C_{Ar}); 148.5 (1 C, NC_{Ar}); 151.8 (1 C, NC_{Ar}); 172.3 (1 C, CH=N). MS (MALDI), found: m/z 497.2930 [M + H]⁺. C₃₆H₃₇N₂. Calculated: 497.2957.

3-[(4-Trifluoromethylphenylamino)methyl]adamantane-1-carbaldehyde (16) was obtained as a second product in the synthesis of compound **12**. Eluent light petroleum ether—CH₂Cl₂ 1 : 1–1 : 2. The yield was 39 mg (23%), a colorless dense oil. ¹H NMR (CDCl₃), δ: 1.52–1.56 (m, 4 H, H_{Ad}); 1.59–1.65 (m, 4 H, H_{Ad}); 1.68–1.77 (m, 4 H, H_{Ad}); 2.20 (br.s, 2 H, HC_{Ad}); 2.93 (s, 2 H, CH₂N); 6.64 (d, 2 H, H_{Ph}(2), H_{Ph}(2'), ³J_{obs} = 8.4 Hz); 7.37 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.4 Hz); 9.35 (s, 1 H, CHO); the proton of the NH group was not found. ¹³C NMR (CDCl₃), δ: 27.5 (2 C, HC_{Ad}); 34.6 (1 C, C_{Ad}); 35.4 (2 C, H₂C_{Ad}); 35.8 (1 C, H₂C_{Ad}); 38.7 (1 C, H₂C_{Ad}); 39.7 (2 C, H₂C_{Ad}); 45.4 (1 C, C_{Ad}); 55.3 (1 C, CH₂N); 112.0 (2 C, C_{Ph}(2), C_{Ph}(2')); 126.6 (2 C, C_{Ph}(3), C_{Ph}(3')); 205.2 (1 C, CHO), three quaternary carbon atoms were not found. MS (MALDI), found: m/z 338.18 [M + H]⁺. C₁₉H₂₃F₃NO. Calculated: 338.17.

N-((3-[(4-Methylphenylamino)methyl]-1-adamantyl)methylidene)-4-methylphenylamine (17) was obtained as a second product in the synthesis of compound **13**. Eluent light petroleum ether—CH₂Cl₂ 1 : 4. The yield was 18 mg (10%), a pale yellow dense oil. ¹H NMR (CDCl₃), δ: 1.55–1.83 (m, 12 H, H_{Ad}); 2.20 (br.s, 2 H, CH(Ad)); 2.24 (s, 3 H, CH₃); 2.34 (s, 3 H, CH₃); 2.88 (s, 2 H, CH₂N); 3.60 (br.s, 1 H, NH); 6.56 (d, 2 H, H_{Ph}(2), H_{Ph}(2'), ³J_{obs} = 8.2 Hz); 6.92 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.2 Hz); 6.98 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.2 Hz); 7.13 (d, 2 H, H_{Ph}(2), H_{Ph}(2')); 7.58 (s, 1 H, CH=N). ¹³C NMR (CDCl₃), δ: 20.3 (1 C, CH₃); 20.8 (1 C, CH₃); 28.1 (2 C, HC_{Ad}); 34.1 (1 C, C_{Ad}); 36.0 (1 C, H₂C_{Ad}); 38.9 (2 C, H₂C_{Ad}); 39.4 (1 C, C_{Ad}); 40.0 (2 C, H₂C_{Ad}); 42.1 (1 C, H₂C_{Ad}); 56.3 (1 C, CH₂N); 112.8 (2 C, C_{Ph}(2), C_{Ph}(2')); 120.4 (2 C, C_{Ph}(2), C_{Ph}(2')); 126.1 (1 C, C_{Ph}(4)); 129.5 (2 C, C(3), C_{Ph}(3')); 129.6 (2 C, C_{Ph}(3), C_{Ph}(3')); 134.8 (1 C, C_{Ph}(4')); 146.8 (1 C, C_{Ph}(1)); 150.1 (1 C, C_{Ph}(1')); 171.7 (1 C, CH=N). MS (MALDI), found: m/z 373.25 [M + H]⁺. C₂₆H₃₃N₂. Calculated: 373.26.

3-[(4-Methylphenylamino)methyl]adamantane-1-carbaldehyde (18) was obtained as a second product in the synthesis of compound **13**. Eluent light petroleum ether—CH₂Cl₂ 1 : 4. The yield was 14 mg (10%), a yellow dense oil. ¹H NMR (CDCl₃), δ: 1.55–1.83 (m, 12 H, H_{Ad}); 2.20 (br.s, 2 H, HC_{Ad}); 2.24 (s, 3 H, CH₃); 2.89 (s, 2 H, CH₂N); 3.60 (br.s, 1 H, NH); 6.56 (d, 2 H,

H_{Ph}(2), H_{Ph}(2'), ³J_{obs} = 8.2 Hz); 6.98 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.2 Hz); 9.36 (s, 1 H, CHO). ¹³C NMR (CDCl₃), δ: 20.3 (1 C, CH₃); 27.6 (2 C, HC_{Ad}); 34.4 (1 C, C_{Ad}); 35.5 (2 C, H₂C_{Ad}); 36.2 (1 C, H₂C_{Ad}); 38.8 (1 C, H₂C_{Ad}); 39.8 (2 C, H₂C_{Ad}); 45.5 (1 C, C_{Ad}); 56.1 (1 C, CH₂N); 112.9 (2 C, C_{Ph}(2), C_{Ph}(2')); 126.2 (1 C, C_{Ph}(4)); 129.6 (2 C, C_{Ph}(3), C_{Ph}(3')); 146.6 (1 C, C_{Ph}(1)); 205.4 (1 C, CHO). MS (MALDI), found: m/z 284.22 [M + H]⁺. C₁₉H₂₆NO. Calculated: 284.20.

N-((3-[(4-Methoxyphenylamino)methyl]-1-adamantyl)methylidene)-4-methoxyphenylamine (19) was obtained as a second product in the synthesis of compound **14**. Eluent CH₂Cl₂. The yield was 36 mg (18%), a brown dense oil. ¹H NMR (CDCl₃), δ: 1.52–1.82 (m, 12 H, H_{Ad}); 2.19 (br.s, 2 H, HC_{Ad}); 2.85 (s, 2 H, CH₂N); 3.74 (s, 3 H, OCH₃); 3.79 (s, 3 H, OCH₃); 6.60 (d, 2 H, H_{Ph}(2), H_{Ph}(2'), ³J_{obs} = 8.7 Hz); 6.77 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.7 Hz); 7.00 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.7 Hz); 7.59 (d, 2 H, H_{Ph}(2), H_{Ph}(2'), ³J_{obs} = 8.7 Hz); 7.59 (s, 1 H, CH=N), the proton of the NH group was not found. ¹³C NMR (CDCl₃), δ: 28.1 (2 C, HC_{Ad}); 34.2 (1 C, C_{Ad}); 36.2 (1 C, H₂C_{Ad}); 38.8 (1 C, C_{Ad}); 38.9 (2 C, H₂C_{Ad}); 40.0 (2 C, H₂C_{Ad}); 42.1 (1 C, H₂C_{Ad}); 55.4 (1 C, CH₂N); 57.0 (1 C, OCH₃); 57.3 (1 C, OCH₃); 114.0 (2 C, C_{Ph}(2), C_{Ph}(2')); 114.9 (4 C, C_{Ph}(3), C_{Ph}(3'), C_{Ph}(3), C_{Ph}(3')); 121.7 (2 C, C_{Ph}(2), C_{Ph}(2')); 143.3 (1 C, C_{Ph}(1)); 145.6 (1 C, C_{Ph}(1')); 151.8 (1 C, C_{Ph}(4)); 157.6 (1 C, C_{Ph}(4')); 170.9 (1 C, CH=N). MS (MALDI), found: m/z 405.23 [M + H]⁺. C₂₆H₃₃N₂O₂. Calculated: 405.25.

3-[(4-Methoxyphenylamino)methyl]adamantane-1-carbaldehyde (20) was obtained as a second product in the synthesis of compound **14**. Eluent CH₂Cl₂. The yield was 13 mg (9%), a brown dense oil. ¹H NMR (CDCl₃), δ: 1.52–1.83 (m, 12 H, H_{Ad}); 2.19 (br.s, 2 H, HC_{Ad}); 2.84 (s, 2 H, CH₂N); 3.74 (s, 3 H, CH₃O); 6.60 (d, 2 H, H_{Ph}(2), H_{Ph}(2'), ³J_{obs} = 8.7 Hz); 6.77 (d, 2 H, H_{Ph}(3), H_{Ph}(3'), ³J_{obs} = 8.7 Hz); 9.35 (s, 1 H, CHO); the proton of the NH group was not found. ¹³C NMR (CDCl₃), δ: 27.6 (2 C, HC_{Ad}); 34.0 (1 C, C_{Ad}); 35.5 (2 C, H₂C_{Ad}); 36.0 (1 C, H₂C_{Ad}); 39.3 (1 C, H₂C_{Ad}); 39.8 (2 C, H₂C_{Ad}); 45.5 (1 C, C_{Ad}); 55.8 (1 C, CH₂N); 56.9 (1 C, OCH₃); 113.9 (2 C, C_{Ph}(2), C_{Ph}(2')); 114.9 (2 C, C_{Ph}(3), C_{Ph}(3')); 143.3 (1 C, C_{Ph}(1)); 151.8 (1 C, C_{Ph}(4)); 205.4 (1 C, CHO). MS (MALDI), found: m/z 300.22 [M + H]⁺. C₁₉H₂₆NO₂. Calculated: 300.20.

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References

1. A. Baxter, J. Bent, K. Bowers, M. Braddock, S. Brough, M. Fagua, M. Lawson, T. McNally, M. Mortimore, M. Robertson, R. Wever, P. Webborn, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4047.
2. M. N. Levina, *Byul. Eksp. Biol. Med. [Bull. Exp. Biol. Med.]*, 2005, **139**, 337 (in Russian).
3. N. A. Menwell, K. J. Estman, E. P. Gillis, *Tactical Applications of Fluorine in Drug Design and Development*, in: *Fluorine in Heterocyclic Chemistry Volume 1: 5-Membered Heterocycles and Macrocycles*, Ed. V. Nenajdenko, Springer International Publishing, Cham, 2014, p. 1–54.
4. C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.
5. D. O'Hagan, *J. Org. Chem.*, 2012, **77**, 3689.

6. N. J. Barbarich, C. D. Rithner, S. M. Miller, O. P. Anderson, S. H. Strauss, *J. Am. Chem. Soc.*, 1999, **121**, 4280.
7. Z-K. Wan, E. Chenail, J. Xiang, H-Q. Li, M. Ipeak, J. Bard, K. Svenson, N. S. Mansour, X. Xu, V. Suri, S. Hahm, Y. Xing, C. E. Johnson, X. Li, A. Qadri, D. Panza, M. Perreult, J. F. Tobin, E. Saiah, *J. Med. Chem.*, 2009, **52**, 5449.
8. M. Ishikawa, Y. Hashimoto, *J. Med. Chem.*, 2011, **54**, 1539.
9. Y. Inamoto, K. Aigami, T. Kadono, *Jpn Pat. 50108252*, 1975; *Chem. Abstr.*, 1976, **84**, 58783.
10. Y. Inamoto, K. Aigami, K. Hattori, T. Kakuno, *Jpn Pat. 50111218*, 1975; *Chem. Abstr.*, 1975, **83**, 188517.
11. A. S. Abel, A. D. Averin, M. V. Anokhin, O. A. Maloshitskaya, G. M. Butov, E. N. Savelyev, B. S. Orlinson, I. A. Novakov, I. P. Beletskaya, *Russ. J. Org. Chem. (Engl. Transl.)*, 2015, **51**, 301 [*Zh. Org. Khim.*, 2015, **51**, 301].
12. M. V. Anokhin, A. D. Averin, I. P. Beletskaya, *Eur. J. Org. Chem.*, 2011, 6240.
13. S. P. Panchenko, A. D. Averin, M. V. Anokhin, O. A. Maloshitskaya, I. P. Beletskaya, *Beilstein J. Org. Chem.*, 2015, **11**, 2297.
14. M. V. Anokhin, A. D. Averin, S. P. Panchenko, O. A. Maloshitskaya, A. K. Buryak, I. P. Beletskaya, *Helv. Chim. Acta*, 2015, **98**, 47.
15. A. D. Averin, E. R. Ranyuk, S. L. Golub, A. K. Buryak, E. N. Savelyev, B. S. Orlinson, I. A. Novakov, I. P. Beletskaya, *Synthesis*, 2007, 2215.
16. A. D. Averin, M. A. Ulanovskaya, A. K. Buryak, E. N. Savelyev, B. S. Orlinson, I. A. Novakov, I. P. Beletskaya, *Russ. J. Org. Chem. (Engl. Transl.)*, 2011, **47**, 30 [*Zh. Org. Khim.*, 2011, **47**, 35].

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