Dedicated to the memory of
acad. Ecaterina Cioranescu-Nenitzescu

New Secondary Amines from the Adamantane Group Having a Potential CNS Biological Activity (NMDA Receptors)

RODICA GUTA[1]*, CORINA ILIE[1], DOINA NANAU-ANDREESCU[1], AURA EDU[1], MIRON TEODOR CĂPROIU[2]

[1] National Institute for Chimical-Pharmaceutical Research & Development – ICCF, 112 Vitan Av., Bucharest, Romania

[2] Romanian Academy, "C.D. Neniţescu" Institute of Organic Chemistry, Splaiul Independenţei nr.202 B, Bucharest, Romania

*The paper presents experimental data regarding the synthesis of new compounds of the class of adamantanamines. Row materials in obtaining of these new compounds are adamantan-1-yl-amine (**1a**) or 3,5-dimethyl-1-yl-amine (**1b**) and substituted aromatic aldehydes (**2a-g**). The new compounds were characterized by m.p., IR and NMR (^{1}H- and ^{13}C) spectral data and elemental analysis. The new compounds will be tested as antagonists of the NMDA receptors (Alzheimer disease).*

Key words: adamantane derivatives, aromatic aldehydes, reductive alkylation

Alzheimer disease is a brain progressive degenerative disorder which occurs especially at old age people causing more and more deterioration of the cognitive functions of the brain.

It has been pointed out that antiglutamatergic therapy (with N-methyl-D-aspartate receptors antagonists) is useful for the treatment of Alzheimer and vascular dementia by decreasing the neuronal degradation owing to the glutamatergic excess.[1,2] The specific NMDA receptor antagonist activity of aminoadamantane derivatives has been demonstrated by recent investigations and therefore the first drug in this field (Memantine) has been developed.

In the last years, our research works focused (concentrated) to get new (amino)adamantane derivatives having a potential biological activity.

Experimental part

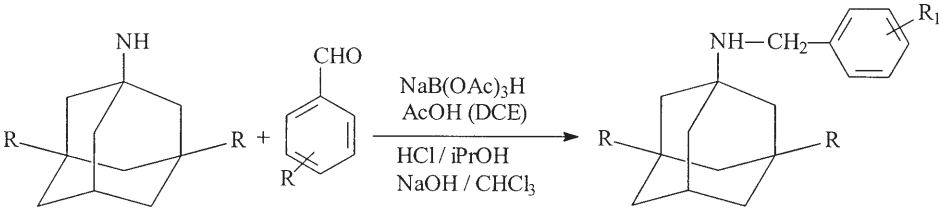
Melting points have been determined in open capillaries and are not corrected.

IR spectra have been recorded on a Bruker Vertex 70 instrument and the NMR spectra were recorded on a Varian Gemini 300BB (^{1}H at 300 MHz and ^{13}C at 76MHz) and on a Unity 400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100MHz).

The thin layer chromatography analysis (TLC) has been effected on silica 60 F_{254} Merck plates, unidimensional working method (ethyl acetate/ cyclohexane 4: 6 V/V eluent). The plates were detected by UV light irradiation (λ = 254 nm).

The synthesis of the secondary amines

The synthesis of the original secondary amines is presented in scheme 1 and is based on the reductive alkylation of adamantan-1-yl-amine **(1a)** and respectively of 3,5-dimethyladamantan-1-ylamine **(1b)** with various mono- and disubstituted aromatic aldehydes **(2a-g),** in the presence of triacetoxy sodium borohydride [$NaB(O_2CCH_3)_3H$] as a reductive agent [3,4].



1(a-b)

1a: R=H

1b: R= CH_3

2(a-g)

2a: R_1 = 4-OH

2b: R_1 = 3-NO_2

2c: R_1 = 4-NO_2

2d: R_1 = 2-F

2e: R_1 = 3-F

2f: R_1 = 2,5-Cl_2

2g: R_1 = 2,6-Cl_2

3(a-j)

3a: R = H; R_1 = 4-OH

3b: R = H; R_1 = 3-NO_2

3c: R = CH_3; R_1 = 3-NO_2

3d: R = H; R_1 = 4-NO_2

3e: R = CH_3; R_1 = 4-NO_2

3f: R = H; R_1 = 2-F

3g: R = CH_3; R_1 = 2-F

3h: R = CH_3; R_1 = 3-F

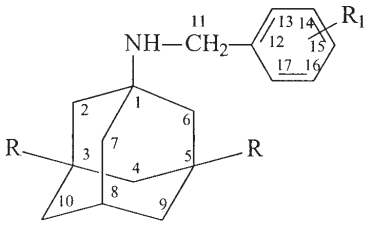
3i: R = CH_3; R_1 = 2,5-Cl_2

3j: R = CH_3; R_1 = 2,6- Cl_2

Scheme 1

* *Tel.: 021 322 29 10 / 203, 211*

Table 1



Compound	R	R_1	Compound	R	R_1
3a	H	4-OH	**3f**	H	2-F
3b	H	3-NO_2	**3g**	CH_3	2-F
3c	CH_3	3-NO_2	**3h**	CH_3	3-F
3d	H	4-NO_2	**3i**	CH_3	2,5-dichloro
3e	CH_3	4-NO_2	**3j**	CH_3	2,6-dichloro

General working method

On 55 mmol triacetoxy sodium borohydride suspended in 75 mL dichloroethane 154 mmol glacial acetic acid and 32 mmol adamantan-1-yl-amine (**1a)** or 3,5-dimethyl-adamantan-1-yl-amine (**1b)** solved in 30 mL dichloroethane are added. Then, a solution from 28 mmol of the aromatic aldehyde **(2a-g)** solved in 30 mL dichloroethane is added dropwise during 1-1,5 h. The reaction mixture is stirred at 30-35 ^{0} for 24 h. After neutralization with a solution of 3N sodium hydroxide, the dichloroethane solution is washed with water and is acidified with HCl/ i-Pr-OH 26% to *p*H= 2-2,5.

The hydrochloride salt which is formed is filtered, taken in $CHCl_3$ and neutralized with a solution of 3N NaOH. The layers are separated and the chloroformic solution is concentrated (under vacuum) to an oily residue, (some of these oils crystallize on freezing).

4-(Adamantan-1-yl-amino-methyl)-phenol (3a)

White crystals , with m.p: 96-100 ^{0}C; Yield : 38 %

$C_{17}H_{23}NO$: M= 257, C% calculated/ found = 79.38/ 77.79
N% calculated/ found = 5.45/ 5.34

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 7.03(d, 2H, H-13-17, 8.2); 6.54(d, 2H, H-14-16, 8.2); 5.46(s, 1H, NH); 3.65(s, 2H, H-11); 2.11(sl, 3H, H-3-5-8); 2.06(sl, 6H, H-2-6-7); 1.77(sl, 6H, H-4-9-10).

^{13}C-RMN($CDCl_3$, δ ppm): 165.87(C-11); 156.66(C-15); 131.80(C-12); 129.78(C-13-17); 116.10(C-14-16); 51.21(C-1); 46.28(C-11); 42.94(C-2-6-7); 36.48(C-4-9-10); 29.89(C-3-5-8).

FT-IR(solid in ATR, ν cm^{-1}): 3332; 3272; 2899; 2846; 1640; 1587; 1514; 1451; 1358; 1312; 1280; 1249; 1143; 1095; 1047; 1007; 825; 710; 651; 616; 468.

Adamantan-1-yl-(3-nitro-benzyl)-amine (3b)

Yellowish crystals with m.p: 42-45^{0}C; Yield = 60%.

$C_{17}H_{22}N_2O_2$: M= 286
C% calculated/ found = 71.33/ 68.47
N% calculated/ found = 9.79/10.28

^{1}H-RMN ($CDCl_3$, δ ppm, *J* Hz): 8,24(t, 1H, H-13, 1,7); 8,07(dd, 1H, H-15, 1,7 , 8,1) ; 7,70 (dd, 1H, H-17, 1,7 , 8,1); 7,46 (t, 1H, H-16, 8,1); 3,87(s, 2H, H-11); 2,10(m, 4H, H-admnt.); 1,74-1,60(m, 11H, H-admnt.).

^{13}C-RMN($CDCl_3$, δ ppm): 148,44(C-14); 144,54(C-12); 134,44(C-15); 129,20(C-13); 123,07(C-17); 121,82(C-16); 51,07(C-1); 44,48(C-11); 43,12(C-2-6-7); 36,81(C-4-9-10); 29,73 (C-3-5-8).

FT-IR(solid in ATR, ν cm^{-1}): 3324; 3082; 2900; 2847; 1520; 1474; 1449; 1345; 1310; 1207; 1147; 1091; 974; 901; 807; 739; 704.

3,5-Dimethyl-adamantan-1-yl-(3-nitro-benzoyl)-amine (3c)

Yellowish crystals, with m.p: 28- 30^{0}C; Yield = 45%

$C_{19}H_{26}N_2O_2$: M= 314
C% calculated/found = 72.61 / 70.43
N% calculated/ found = 8.92/ 8.60

^{1}H-RMN ($CDCl_3$, δ ppm, *J* Hz): 8,23(t, 1H, H-13, 1,7); 8,08(dd, 1H, H-15, 1,3, 8,2); 7,69(dd, 1H, H-17, 1,7, 8,2); 7,46(t, 1H, H-16, 8,2); 3,86(s, 2H, H-11); 2,17(spt, 1H, H-8, 3,0); 1,53 (d, 2H, H-17); 1,36(d, 2H, H-2A, H-6A, sist. AB, 11,9); 1,13(d, 2H, H-9B, H-10B, sist. AB, 11,9); 0,87(s, 6H, H-3'-5').

^{13}C-RMN($CDCl_3$, δ ppm): 148,48(C-14); 144,44(C-12); 134,45 (C-15); 129,23(C-13); 123,10(C-17); 121,88(C-16); 52,92(C-1); 51,09(C-7); 49,36(C-2-6); 44,72(C-4); 43,14(C-9-10); 41,63 (C-8); 32,61(C-3-5); 30,45(C-3'-5').

FT-IR (solid in ATR, ν cm^{-1})**:** 3306; 3081; 2938; 2900; 2842; 1518; 1477; 1451; 1344; 1192; 1149; 1105; 984; 924; 891; 800; 764; 732; 694; 671.

Adamantan-1-yl-(4-nitro-benzyl)-amine (3d)

Yellowish crystals, with m.p: 90-94^{0}C; Yield: 38%

$C_{17}H_{22}N_2O_2$: M= 286
C% calculated/ found= 71.33/ 70,.24
N% calculated/ found= 9.79/ 10.12

^{1}H-RMN ($CDCl_3$, δ ppm, *J* Hz): 8,16(d, 2H, H-14-16, 8,9); 7,53(d, 2H, H-15-17, 8,9); 3,87(s, 2H, H-11); 2,10(m, 4H, H-admnt.); 1,73-1,60(m, 11H, H-admnt.).

^{13}C-RMN($CDCl_3$, λδ ppm): 150,26(C-15); 146,95(C-12); 128,80(C-14-16); 123,64(C-13-17); 51,12(C-1); 44,64(C-11); 43,16(C-2-6-7); 36,83(C-4-9-10); 29,74(C-3-5-8).

FT-IR (solid in ATR, ν cm^{-1})**:** 3315; 3059; 2899; 2845; 2672; 1598; 1506; 1343; 1309; 1178; 1145; 1099; 1037; 979; 853; 741; 706; 649; 583; 498; 455.

3,5-Dimethyl-adamantan-1-yl-(4-nitro-benzoyl)-amine (3e)

Yellowish crystals with m.p: 42-45^{0}C; Yield: 35%

$C_{19}H_{26}N_2O_2$: M= 314
C% calculated/found= 72.61/ 71.16
N% calculated/ found= 8.92/ 8.74

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 8.15(d, 2H, H-16-18, 8.8); 7.53(d, 2H, H-15-19, 8.8); 3.87(s,2H, H-13); 1.52(d, 2H, H-7, 2.6); 1.38÷1.27(m, 8H, H-2-6, H-9-10); 1.19÷1.14(m, 3H, 2H-4, H-8);

^{13}C-RMN($CDCl_3$, δ ppm): 150.15(C-17); 144.93(C-14); 128.75(C-16-18); 123.59(C-15-19); 52.89(C-1); 51.06(C-13); 49.33(C-2-6); 44.81(C-7); 43.10(C-9-10); 41.61(C-4); 32.57(C-3-5); 30.99(C-8); 30.42(CH_2-11); 30.40(CH_3-12).

FT-IR(solid in ATR, ν cm^{-1}): 3292; 2943; 2898; 2839; 1598; 1507; 1448; 1338; 1251; 1191; 1150; 1102; 1015; 990; 832; 770; 731; 586; 475.

Adamantan-1-yl-(2-fluoro-benzyl)-amine (3f)

Whith crystals, with m. p: 38-40^{0}C; Yield = 70%

$C_{17}H_{22}FN$: M = 259

C% calculated/ found = 78.76/ 77.18

N% calculated/ found = 5.41/ 5.50

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 7.39(td, 1H, H-14, 7.5, 1.8); 7.21(m, 1H, H-17); 7.08(td, 1H, H-15, 7.4, 1.4); 7.00(ddd, 1H, H-16, 1.2, 7.4, 8.1); 3.81(s, 2H, H-11); 2.09(m, 4H, H-admnt.); 1.72-1.65(m, 11H, H-admnt.).

$^3J(^{19}F\text{-}^1H)$=7.5 Hz; $^4J(^{19}F\text{-}^1H\text{-}17)$=5.3 Hz;

^{13}C-RMN($CDCl_3$, δ ppm): 161.18(d, C-13, $J(^{19}F\text{-}^{13}C)$=245.0 Hz); 131.42(d, C-12, $J(^{19}F\text{-}^{13}C)$=34.8 Hz); 130.49(d, CH, $J(^{19}F\text{-}^{13}C)$=4.7 Hz); 128.34(d, CH, $J(^{19}F\text{-}^{13}C)$=8.1 Hz); 124.17(d, CH, $J(^{19}F\text{-}^{13}C)$=3.4 Hz); 115.26(d, C-14, $J(^{19}F\text{-}^{13}C)$=21.9 Hz); 50.99(C-1); 42.96(C-2-6-7); 38.71(C-11); 36.91(C-4-9-10); 29.80(C-3-5-8).

FT-IR(solid in ATR, ν cm^{-1}): 3041w; 2902vs; 2846vs; 1640w; 1583w; 1488w; 1455m; 1359w; 1342w; 1311w; 1266w; 1224m; 1179w; 1143w; 1100w; 1074w; 1034w; 1004w; 977w; 932w; 841w; 817w; 795w; 745m; 716w; 570w; 532w; 444w.

(3,5-Dimethyl-adamantan-1-yl)-(2-fluoro-benzyl)-amine (3g)

Colorless oil; Yield = 50,5 %

$C_{19}H_{26}FN$: M= 287

C% calculated/ found= 79.44 / 78.10

N% calculated/ found= 4.88/ 4.75

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 7.39(td, 1H, H-14, 7.5, 1.8); 7.21(m, 1H, H-17); 7.08(td, 1H, H-15, 7.4, 1.4); 7.00(ddd, 1H, H-16, 1.2, 7.4, 8.1); 3.79(s, 2H, H-11); 2.16(spt, 1H, H-8, 3.2); 1.55(d, 2H, H-7, 3.2); 1.40÷1.26(m, 8H, H-2-6-9-10); 1.13 (m, 2H, sist. AB, H-4A, H-4B, 14.1); 0.86(s, 6H, CH_3).

^{13}C-RMN($CDCl_3$, δ ppm): 161.20(d, C-13, $J(^{19}F\text{-}^{13}C)$=245.0 Hz); 131.42(d, C-12, $J(^{19}F\text{-}^{13}C)$=34.8 Hz); 130.52(d, CH, $J(^{19}F\text{-}^{13}C)$=4.7 Hz); 128.39(d, CH, $J(^{19}F\text{-}^{13}C)$=8.1 Hz); 124.26(d, CH, $J(^{19}F\text{-}^{13}C)$=3.4 Hz); 115.23(d, C-14, $J(^{19}F\text{-}^{13}C)$=21.9 Hz); 52.81(C-1); 51.19(C-7); 49.20(C-2-6); 43.23(C-9-10); 41.47(C-4); 38.90(C-3-5); 32.60(C-8); 30.49($2CH_3$).

FT-IR(solid in ATR, ν cm^{-1}): 3043w; 2943s; 2897vs; 2864m; 2840s; 1585w; 1489m; 1453s; 1358w; 1338w; 1226m; 1195w; 1150w; 1108w; 1033w; 937w; 839w; 795w; 753s; 631w; 532w; 443w.

(3,5-Dimethyl-adamantan-1-yl)- (3-fluoro-benzyl)-amine (3h)

Colorless oil; Yield: 48%

$C_{19}H_{26}FN$: M= 287

C% calculated/ found= 79.44 / 77.85

N% calculated/ found= 4.88/ 4.90

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 7.25(m, 1H, H-15); 7.11÷7.06(m, 2H, H-13, H-17); 6.90(td, 1H, H-16, 8.3, $^4J(^{19}F\text{-}^1H\text{-}16)$=2.5 Hz); 3.75(s, 2H, H-11); 2.16(spt, 1H, H-8, 3.2); 1.53(d, 2H, H-7, 3.2); 1.39÷1.26(m, 8H, syst. AB, H-2-6-9-10); 1.14 (m, 2H, sist. AB, H-4A, H-4B, 14.1); 0.87(s, 6H, CH_3).

^{13}C-RMN($CDCl_3$, δ ppm): 163.09(d, C-14, $J(^{19}F\text{-}^{13}C)$=245.3 Hz); 144.73(d, C-12, $J(^{19}F\text{-}^{13}C)$=6.9 Hz); 129.82(d, C-16, $J(^{19}F\text{-}^{13}C)$=8.3 Hz); 123.73(d, C-17, $J(^{19}F\text{-}^{13}C)$=2.6 Hz); 115.11(d, C-15, $J(^{19}F\text{-}^{13}C)$=21.2 Hz); 113.57(d, C-13, $J(^{19}F\text{-}^{13}C)$=21.2 Hz); 52.72(C-1); 51.14(C-7); 49.31(C-2-6); 45.00(C-9-10); 43.19(C-3-5); 41.58(C-4); 32.58(C-8); 30.48($2CH_3$).

FT-IR(solid in ATR, ν cm^{-1}): 2943s; 2897vs; 2865m; 2840s; 1615w; 1590m; 1485w; 1451m; 1356w; 1338w; 1252m; 1195w; 1133w; 1110w; 1072w; 988w; 939w; 867w; 779m; 727w; 685w; 563w; 520w; 443w.

(2,5-Dichloro-benzyl)- (3,5-dimethyl-adamantan-1-yl)-amine (3i)

White crystals, with m.p: 100-102^{0}C; Yield: 40%

$C_{19}H_{25}Cl_2N$: M= 338

C% calculated/ found = 67.46/ 66.32

N% calculated/found = 4.14/ 4.23

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 8.38(bs, 1H, NH); 8.17(d, 1H, H-19, 1.8); 7.34(d, 1H, H-16, 8.9); 7.21(dd, 1H, H-17, 1.8, 8.9); 4.12(s, 2H, H-11); 2.20(spt, 1H, H-8, 3.2); 1.88(d, 2H, H-7, 3.2); 1.73(d, 2H, syst.AB, H-2A, H-6A, 11.3); 1.67(d, 2H, syst.AB, H-2B, H-6B, 11.3); 1.40(d, 2H, syst.AB, H-9A, H-10A, 12.4); 1.30(d, 2H, syst.AB, H-9B, H-10B, 12.4); 1.18 (m, 2H, sist. AB, H-4A, H-4B, 14.1); 0.86(s, 6H, $2CH_3$).

^{13}C-RMN($CDCl_3$, δ ppm): 142.41(C-14); 132.30(Cq); 130.40(Cq); 133.04(CH); 130.92(CH); 130.57(CH); 54.47(C-1); 50.10(C-7); 46.47(C-2, C-6); 42.06(C-9, C-10); 39.25(C-3, C-5); 32.68(C-8); 29.94($2CH_3$).

FT-IR(solid in ATR, ν cm^{-1}): 2980m; 2943s; 2997vs; 2861vs; 2841s; 1611w; 1574w; 1512w; 1454m; 1360w; 1263w; 1188w; 1099w; 1056w; 962w; 936w; 907; 875w; 836w; 812w; 570w; 540w; 474w.

(2,6-Dichlorobenzyl)-(3,5-dimethyl-adamantan-1-yl)-amine (3j)

White crystals, with m.p: 74- 76^{0}C; Yield: 42%

$C_{19}H_{25}Cl_2N$: M= 338

C% calculated/ found= 67.46/ 65.44

N% calculated/ found= 4.14/ 4.20

^{1}H-RMN($CDCl_3$, δ ppm, *J* Hz): 7.28(d, 2H, H-16, H-18, syst. A2B, 7.7); 7.11(m, 1H, H-17, syst. A_2B, 7.4, 8.5); 4.02(s, 2H, H-11); 2.19(spt, 1H, H-8, 3.0); 1.61(d, 2H, H-7, 3.0); 1.48÷1.28(m, 8H, syst. AB, H-2, H-6, H-9, H-10); 1.19(m, 1H, syst. AB, H-4A, 13.8); 1.13(m, 1H, syst. AB, H-4B, 13.8); 0.89(s, 6H, $2CH_3$).

^{13}C-RMN($CDCl_3$, δ ppm): 137.03(C-14); 135.98(C-15, C-19); 128.71(C-17); 128.55(C-16, C-18);

53.01(C-1); 51.16(C-7); 48,96(C-2, C-6); 43.21(C-9, C-10); 41.24(C-3, C5); 40.97(C-4); 32.63(C-8); 30.52($2CH_3$).

FT-IR(solid in ATR, ν cm^{-1}): 2945m; 2907vs; 2839vs; 1655w; 1584w; 1564w; 1437m; 1355w; 1336w; 1288w; 1259w; 1220w; 1178w; 1103m; 1086w; 1020w; 975w; 921w; 881w; 790w; 764m; 720m; 679w; 640w; 572w; 518w; 489w; 469w; 432w.

Results and discussions

Our purpose was to obtain new compounds **(3a-j)** with a secondary amine structure from the adamantane group in order to check out their biological activity as N-methyl-D-aspartate (NMDA) receptors.

The new compounds have been obtained by the reductive alkylation of two amino-adamantane derivatives **(1a-b)** [5] with substituted aromatic aldehydes **(2a-g)** in (the) presence of sodium triacetoxyborohydride [$NaB(O_2CCH_3)_3H$] as a reducing agent, according to scheme 1. 10 new secondary amines **(3a-j)** have been obtained by this synthetic procedure and they were characterized by melting points, IR and NMR (^{1}H and ^{13}C)

spectra and their purity has been determined by TLC and elemental analysis.

Conclusions

Ten new secondary amines (**3a-j)** from the adamantane groups have been synthetized by the reductive alkylation of adamantan-1-yl-amine **(1a)** or of 3,5-dimethyl-adamantan-1-yl-amine **(1b)** with mono- and disubstituted aromatic aldehydes **(2a-g)**. The complete characterization was done by elemental analysis, FT-IR and H^1-NMR, ^{13}C-NMR spectroscopy. The spectral data confirm the chemical structures of the new compounds.

The new compounds are tested in order to investigate their biological activity against Alzheimer disease (as NMDA receptors).

References

1. AERASA, S.A., Sherrff, F. Memantine for dementia, Cochrane Database Syst. Rev., 2003
2. JARVIS, B., FIGGIT, D.P Memantine Drugs Aging 2003, p. 477
3.ABDEL- MAGID, A.F., CARSAN, K.G., HARRIS, B.D MARYANOFF, C.A. SHAH R.D – J.Org Chem., **61**, nr. 11, 1996, p. 3849
4.GUŢĂ R., ILIE C., PUTINĂ G., NĂNĂU-ANDREESCU D., NEGREŞ, S., CĂPROIU M. T. Rev. Chim. (Bucuresti), **58**, nr. 10, 2007, p. 937
5. ILIE, C., GUTA, R., HAU, R, NANAU-ANDREESCU, D., PUTINA, G., PUTINA, G., CAPROIU, M.T., Rev. Chim. (Bucuresti), **60**, nr. 7, 2009, p. 653

Manuscript received: 5.08.2008