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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

New aminoadamantane derivatives with antiproliferative activity

Ioannis Papanastasiou · Andrew Tsotinis · Nicolas Kolocouris · Spyros P. Nikas · Alexandre Vamvakides

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Abstract 1-Benzyl-2-aminoadamantanes **2a–c**, conformationally constrained aminoadamantanes **3a**, **b** and **4** and diaminoadamantanes derivatives **5a–c**, **6a–c** were synthesized and tested as antiproliferative agents. The in vitro biological evaluation showed a significant difference in activity between 1-phenyl and 1-benzyl derivatives.

Keywords Aminoaromatic adamantanes · Synthesis · Antiproliferative activity

Introduction

Adamantane derivatives have a broad pharmacological profile, involving antibacterial (Aigami *et al.*, 1975), antifungal (Kadi *et al.*, 2007), antiviral (Kolocouris *et al.*, 1994, 1996), trypanocidal (Papanastasiou *et al.*, 2008) and anti-*Parkinson* (Chakrabarti *et al.*, 1976) activity. Moreover, it is well documented that the incorporation of the adamantyl moiety into the skeleton of various molecules increases their antiproliferative potency, possibly due to the lipophilic character of adamantane or its unique structure. Such examples include aromatic carboxylic acids (Cincinelli *et al.*, 2003; Dawson *et al.*, 2008), pyrimidines, pyridines (Kazimierczuk *et al.*, 2001) and cyclic imides (Shibata *et al.*, 1995; Tsuji *et al.*, 2000; Wang *et al.*, 1997, 1998, 2002) with anticancer activity. Recently, aminoaromatic adamantane (Wang *et al.*, 2004) and bisubstituted adamantane derivatives, with marked antiproliferative activity on different human cell lines, were reported (Zefirova *et al.*, 2002; Smith *et al.*, 2006; Wang *et al.*, 2003). In our effort to develop new antiproliferative agents, we have synthesized 1-benzyl-2-aminoadamantanes **2a–c** and the conformationally constrained fused three-membered ring systems **3** and **4**. We have also introduced into the skeleton of derivatives **2** a second nitrogen atom, 2 or 3 carbon atoms away from the first nitrogen (diamines **5** and **6**, respectively) to probe the influence on anticancer potency of two nitrogens in these scaffolds (Fig. 1).

Materials and methods

Cell cultures and cell lines

All human cancer cell lines were obtained from the National Cancer Institute, NIH (Bethesda, MD, USA). All cell lines were adapted to propagate in RPMI 1640 medium supplemented with 5 % heat-inactivated fetal calf serum, 2 mM L-glutamine and antibiotics. The cultures were grown in a humidified 37 °C incubator in 5 % CO_2 atmosphere.

I. Papanastasiou (✉) · A. Tsotinis · N. Kolocouris
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Panepistimioupoli-Zografou, 157 71 Athens, Greece
e-mail: papanastasiou@pharm.uoa.gr

S. P. Nikas
Center for Drug Discovery, Northeastern University, 116 Mugar Life Sciences Building, 360 Huntington Avenue, Boston, MA 02115, USA

S. P. Nikas
Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 48 Vass. Constantinou, 116 35 Athens, Greece

A. Vamvakides
Anavex Life Sciences, 27 Marathonos Avenue, 153 51 Pallini, Athens, Greece

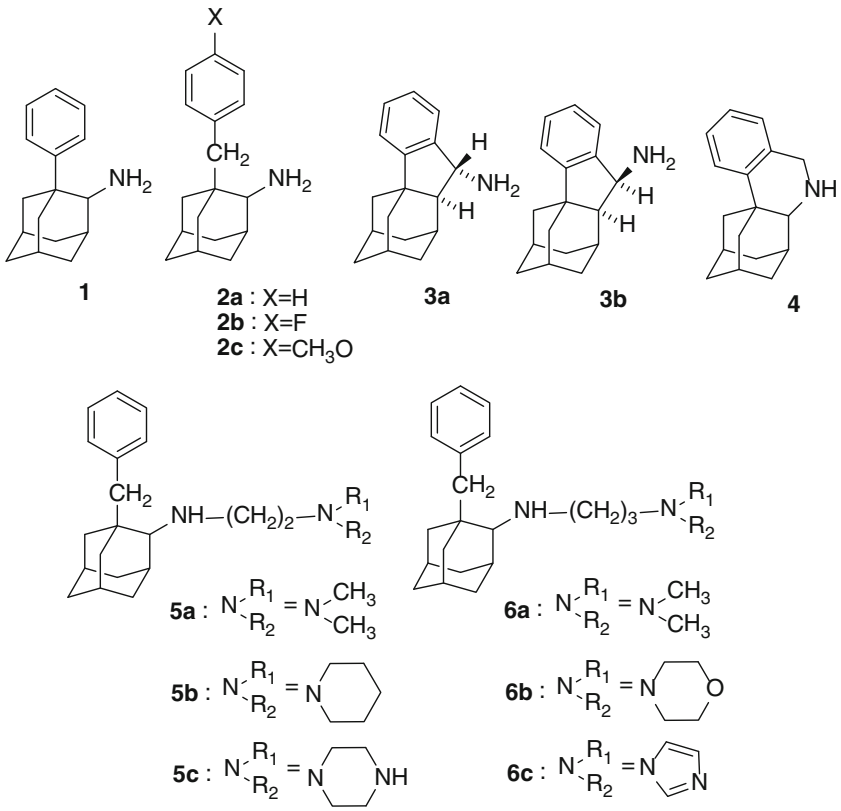


Fig. 1 New adamantane derivatives with antiproliferative activity

In vitro cytotoxic activity

Cell viability was assessed at the beginning of each experiment by the trypan blue dye exclusion method and was always greater than 95 %. Cells were seeded into 96-well microtiter plates in 100 μL of medium at the corresponding density (3,500–30,000 cells per well) and, subsequently, the plates were incubated at standard conditions for 24 h to allow the cells to resume exponential growth prior to addition of the agents to be tested. Then to measure the cell population, cells in one plate were fixed in situ with TCA followed by SRB staining, as described elsewhere (Skehan *et al.*, 1990; Keepers *et al.*, 1991). To determine the activity, each compound was dissolved in DMSO and then added at tenfold dilutions (from 100 to 0.01 μM) and incubation continued for an additional period of 48 h. The assay was terminated by addition of cold TCA followed by SRB staining and absorbance measurement at 540 nm, in a DAS plate reader, to determine GI_{50}, that is, the concentration required in the cell culture to inhibit cell growth by 50 %, and TGI, the concentration that is required to completely inhibit cell growth (Skehan *et al.*, 1990; Keepers *et al.*, 1991).

Synthesis

Melting points were determined using a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^{1}H NMR spectra were recorded on a Bruker MSL 400 and ^{13}C NMR spectra were taken on a Bruker AC 200 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Carbon multiplicities were established by DEPT experiments. 2D NMR experiments (HMQC, COSY and NOESY) were performed for the elucidation of the structures of the new compounds. Microanalyses were carried out by the Service Central de Microanalyse (CNRS), France, and the results obtained had a maximum deviation of ±0.4 % from the theoretical values.

*General procedure for the synthesis of 1-benzyltricyclo[3.3.1.1^{3,7}]decan-2-ketoxime (**8a**), 1-(4-fluorobenzyl)-tricyclo[3.3.1.1^{3,7}]decan-2-ketoxime (**8b**) and 1-(4-methoxybenzyltricyclo[3.3.1.1^{3,7}]decan-2-ketoxime (**8c**)*

Hydroxylamine hydrochloride (1.4 g, 20.2 mmol) and sodium acetate trihydrate (4.26 g, 31.3 mmol) were added to a 90° ethanolic solution (50 mL) of ketones **7a** (Papanastasiou *et al.*, 2008), **7b** (Papanastasiou *et al.*, 2009) and **7c** (Papanastasiou *et al.*, 2009) (10.1 mmol), respectively, and the resulting mixture was refluxed for 5 h. Upon completion of the reaction, ethanol was evaporated, chilled water (20 mL) was added and the precipitate formed was filtered off, washed with water and dried to give **8a**, **8b** and

8c, respectively, as solids in quantitative yield; **8a**: mp 210 °C (ether), **8b**: mp 216 °C (ether–pentane), **8c**: mp 182 °C (ether–pentane).

*General procedure for the synthesis of 1-benzyltricyclo[3.3.1.1^{3,7}]decan-2-amine (**2a**), 1-(4-fluorobenzyl)tricyclo[3.3.1.1^{3,7}]decan-2-amine (**2b**) and 1-(4-methoxybenzyltricyclo[3.3.1.1^{3,7}]decan-2-amine (**2c**)*

Oximes **8a**, **8b** and **8c** (13.7 mmol) in absolute ethanol (40 mL) were hydrogenated under pressure (55 psi) over Raney-Ni (200 mg) for 5 h, at 70 °C. The catalyst was filtered off through Celite and the solvent was evaporated under vacuum to give the crude title compounds as viscous oils; amines **2a** and **2b** were crystallized upon standing. **2a** mp 38 °C (Papanastasiou *et al.*, 2008); **2b** mp 40 °C. ^{1}H NMR ($CDCl_3$) δ 1.26–1.97 (13H, m, H_{3-10}), 1.98 (2H, brs, NH_2, D_2O exchangeable), 2.36–2.49 (2H, AB, $J = 13.2$, $\Delta\nu = 0.05$, CH_2Ph), 2.61 (1H, s, H_2), 6.84–7.03 (4H, m, $H_{2,3,5,6}$-arom.); ^{13}C NMR ($CDCl_3$) δ 28.0 (C_5), 28.1 (C_7), 30.4 (C_6), 35.64 (C_4), 35.8 (C_3), 36.8 (C_1), 37.0 (C_{10}), 37.4 (C_9), 40.9 (C_8), 45.0 (*C*H_2Ph), 57.8 (C_2), 114.2–114.4 ($C_{3,5}$-arom.), 131.8–133.9 ($C_{2,6}$-arom.), 133.4 (C_1-arom.), 162.6 (C_4-arom.); **2c**, ^{1}H NMR ($CDCl_3$): δ 1.25–1.83 (13H, m, H_{3-10}), 1.85 (2H, brs, NH_2, D_2O exchangeable), 2.39–2.50 (2H, AB, $J = 13.6$, $\Delta\nu = 0.04$, CH_2Ph), 2.66 (1H, s, H_3), 3.78 (3H, s, CH_3O), 6.78–7.05 (4H, m, $H_{2,3,5,6}$-arom.); ^{13}C NMR ($CDCl_3$) δ 28.1 (C_5), 28.2 (C_7), 30.5 (C_6), 35.7 (C_4), 35.8 (C_3), 37.1 (C_{10}), 37.5 (C_9), 42.6 (C_1), 40.9 (C_8), 44.9 (*C*H_2Ph), 55.1 (*C*H_3O) 55.7 (C_2), 112.9–113.1 ($C_{3,5}$-arom.), 129.8 (C_1-arom.), 131.4 ($C_{2,6}$-arom.), 157.7 ppm (C_4-arom.). Elemental analyses measurements were performed on the hydrochloride salts of amines **2b** and **2c**. **2b** (hydrochloride, mp >250 °C); Anal calcd for $C_{17}H_{23}ClFN$: C 69.02, H 7.84, found C 68.86, H 7.86. **2c** (hydrochloride, mp >250 °C); Anal calcd for $C_{18}H_{26}ClNO$: C 70.22, H 8.51, found C 70.31, H 8.43.

*1-Phenyltricyclo[3.3.1.1^{3,7}]decan-2-carboxylic acid (**12**)*

Dry dimethylsulfoxide (105 mL) was added dropwise to a mixture of trimethylsulfoxonium iodide (7.92 g, 36 mmol) and sodium hydride 60 % (1.44 g, 36 mmol), under an argon atmosphere, and stirred for 30 min before ketone **9** (Lenoir, 1973; Tseng *et al.*, 1998) (6 g, 26.5 mmol) was added. The resulting mixture was stirred at 20 °C for 30 min and then heated at 55–58 °C for 2 h. The mixture was then poured into chilled water and extracted with *n*-hexane 3 × 20 mL without shaking the separatory funnel. The combined organic layers were dried over Na_2SO_4 and evaporated at 40 °C to afford 6.21 g of a liquid, which was diluted with dry benzene (120 mL) and shaken well with $BF_3{\cdot}Et_2O$ complex (3.6 g, recently distilled) in the separatory funnel. After 3 min at rest, the organic phase was washed with H_2O (3 × 15 mL) and dried over Na_2SO_4. The organic phase was partially evaporated (40–50 mL) at 30 °C, acetone was added, followed by evaporation; this procedure was repeated twice. Then, acetone was added to give a volume of 150–200 mL, and the solution was oxidized with Jones reagent (~33 mL, 1 M) at 15 °C. The reaction mixture was stirred overnight at 20 °C, then quenched by the addition of isopropyl alcohol (3 mL) and filtered through cotton wool. H_2O (20 mL) was added to the filtrate and acetone was removed under reduced pressure. The residue was extracted with ether and the organic extracts were washed with an aqueous solution of NaOH (5 %). The combined aqueous phases were washed with ether and acidified with conc. HCl at 0 °C. The crystals formed were filtered off, washed with H_2O and dried to afford carboxylic acid **12** (4.73 g, 70 %); mp: 127 °C (ether); ^{1}H NMR ($CDCl_3$) δ 1.51–2.75 (13H, m, H_{3-10}), 3.04 (1H, s, H_2), 7.06–7.24 (5H, m, H-arom.), 10.5 (1H, brs, CO*OH*); ^{13}C NMR ($CDCl_3$) δ 27.9 (C_5), 28.8 (C_7), 31.6 (C_6), 31.8 (C_3), 35.1 (C_4), 36.8 (C_{10}), 37.5 (C_1), 38.0 (C_9), 47.1 (C_8), 53.8 (C_2), 124.9 ($C_{2,6}$-arom.), 125.8 (C_4-arom.), 128.1 ($C_{3,5}$-arom.), 148.5 (C_1-arom.), 179.0 (CO); IR (Nujol): ν = 1,689–1,634 cm^{-1}(CO).

*Indeno[1,2-a]tricyclo[3.3.1.1^{3,7}]decan-5(5aH)-one (**13**)*

Carboxylic acid **12** (3 g, 11.7 mmol) was treated with freshly distilled thionyl chloride (8 mL), at 65 °C, during 15–20 min. After removal of residual thionyl chloride by co-evaporation with benzene under reduced pressure, carbon disulfide (45 mL) and anhydrous aluminum chloride (1.8 g, 13.4 mmol) were added to the reaction mixture, which was stirred at RT for 30 min and then refluxed for 30 min. The reaction was cooled, quenched by the addition of ice and extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with H_2O, dried over Na_2SO_4 and evaporated to afford a residue, which crystallized upon standing. Further purification by flash column chromatography over silica gel at gradient eluent (pentane to pentane:ether, 6:1) gave compound **13** (2.81 g, almost quantitative) mp: 56 °C; 1H NMR ($CDCl_3$) δ 1.93–2.57 (13H, m, H_{6-13}), 2.57 (1H, s, H_{5a}), 7.19–7.66 (4H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 26.9 (C_8), 27.9 (C_{10}), 28.6 (C_6), 32.10 (C_9), 36.0 (C_7), 38.2 (C_{13}), 38.7 (C_{12}), 41.5 (C_{11a}), 46.9 (C_{11}), 62.8 (C_{5a}), 121.6 (C_1), 124.0 (C_3), 127.0 (C_2), 133.3 (C_4), 135.7 (C_{11b}), 164.5 (C_{4a}), 204.6 (CO); IR (Nujol): ν = 1,724 cm^{-1}(CO).

*Indeno[1,2-a]tricyclo[3.3.1.1^{3,7}]decan-5-ketoxime (**14**)*

A mixture of ketone **13** (0.31 g, 1.3 mmol), hydroxylamine hydrochloride (0.27 g, 3.9 mmol) and sodium acetate trihydrate (0.81 g, 6 mmol) in ethanol (90°) (15 mL) was

refluxed for 7 h. The reaction mixture was then cooled to room temperature, ethanol was evaporated and chilled water was added. The precipitate formed was filtered off, washed with water and dried to give ketoxime **14** as a solid (0.32 g, yield quantitative) mp: 164 °C (ethanol–water, then dried with hexane).

*5,5a-Dihydroindeno[1,2-a]tricyclo[3.3.1.1^{3,7}]decan-5-amines (**3a**) and (**3b**)*

Acetic anhydride (4.32 g, 42.4 mmol) was added to a chilled solution of oxime **14** (0.59 g, 2.34 mmol) in pyridine (10 mL). The reaction mixture was stirred at 0 °C for 7 h and 18 h at 3 °C and then diluted with diethyl ether prior to addition of ice. The aqueous phase was discarded and the organic layer sequentially washed with H_2O, saturated aqueous solution of $NaHCO_3$ and H_2O. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to give oxime-ester **15** (0.72 g, yield almost quantitative); IR (net): $\nu = 1{,}764$ cm^{-1} (CO), 1,644 cm^{-1} (CN). To a stirred solution of oxime-ester **15** (0.7 g, 2.17 mmol) in anhydrous tetrahydrofuran (10 mL) was added sodium borohydride (0.65 g, 17.4 mmol) and a solution of iodine (1.67 g, 6.61 mmol) in dry tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was refluxed for 8 h and then quenched at 0 °C by the addition of an aqueous solution of HCl (3N). The mixture was then made alkaline with aqueous conc. KOH, extracted with diethyl ether, washed with H_2O and dried over anhydrous Na_2CO_3. The ethereal phase was treated with a saturated ethanolic solution of gaseous HCl under ice cooling and the precipitate formed was filtered off, washed with cold diethyl ether and dried to afford the respective hydrochloride salts of the desired compounds, which were then converted to the free bases by the addition of a solution of Na_2CO_3. These were further purified by flash column chromatography, eluting with a 1:1 MeOH–Et_2O solution to give viscous oils, which were then separated to the two diastereomers, respectively, eluting with a 13:1 Et_2O–MeOH mixture. The less polar compounds correspond to the *cis*-diastereomers, which are solids, while the more polar to the *trans*-diastereomers, which are liquid (80 mg each diastereomer, total yield 31.5 %). **3a**: ^{1}H NMR ($CDCl_3$) δ 1.35–2.22 (16H, m, H_{5a-13}, NH_2), 4.12 (1H, d, $J = 10.6$, H_5), 6.99–7.14 (4H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 27.7 (C_8), 28.1 (C_{10}), 29.1 (C_6), 31.10 (C_9), 37.4 (C_7), 39.1 (C_{13}), 40.6 (C_{12}), 40.8 (C_{11}), 42.5 (C_{11a}), 55.7 (C_{5a}), 64.0 (C_5), 120.6–123.7–126.4–126.9 (C_{1-4}), 146.7–151.5 (C_{4a-11b}). **3b**: ^{1}H NMR ($CDCl_3$) δ 1.66–2.29 (16H, m, H_{5a-13}, NH_2), 4.25 (1H, d, $J = 7.16$, H_5), 7.05–7.15 (4H, m, H-arom); ^{13}C NMR ($CDCl_3$) δ 28.2 (C_8), 29.7 (C_{10}), 30.0 (C_6), 33.0 (C_9), 37.5 (C_7), 39.1 (C_{11a}), 40.9 (C_{13}), 42.0 (C_{12}), 44.3 (C_{11}), 54.0 (C_{5a}), 58.6 (C_5), 121.6–125.3–126.7–127.5 (C_{1-4}), 146.9–152.6 (C_{4a-11b}). The precipitation of the hydrochloride salts from the ethereal solution of the amine was effected by the addition of *n*-pentane. Hydrochloride (*trans*-amine) **3a**; mp >255 °C. Anal. calcd for $C_{17}H_{22}ClN$: C 74.03, H 8.04, found C 73.91, H 8.12. Hydrochloride (*cis*-amine) **3b**; mp >255 °C. Anal. calcd for $C_{17}H_{22}ClN$: C 74.03, H 8.04, found C 73.96, H 8.05.

*5H,6H-tricyclodecan[1,2-a]isoquinoline (**4**)*

A mixture of oxime **14** (0.9 g, 3.55 mmol) and phosphorus pentachloride (1 g, 4.79 mmol) in benzene (20 mL) was refluxed for 1 h. After cooling, ice was added and the mixture extracted with benzene. The organic phase was washed sequentially with a saturated aqueous solution of $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to give a residue, which was treated with a mixture of ether: *n*-pentane (1:1) and chilled to give a precipitate, which was filtered off and washed with *n*-pentane. Recrystallization from methanol gave **16** (260 mg, 29 %); mp >250 °C; IR (Nujol): $\nu = 3{,}435$–$3{,}175$ cm^{-1}(NH), 1,667 cm^{-1}(CO). Compound **16** (238 mg, 0.94 mmol) was then added dropwise into a suspension of lithium aluminum hydride (400 mg, 10.5 mmol) in anhydrous tetrahydrofuran (30 mL) and the reaction mixture was refluxed for 12 h. Quenching by the sequential addition of H_2O and an aqueous solution of NaOH (5 %) gave a suspension, which was filtered off, the filtrate dried over Na_2CO_3 and the solvent evaporated to give a residue, which was transformed into the hydrochloride salt of **4**. The salt was recrystallized from ethanol–ether and then converted to the free base **4** upon treatment with Na_2CO_3. Base **4** was further purified by flash column chromatography using a 1:9 MeOH–Et_2O mixture as eluent to give **4** as a viscous oil, which was crystallized on standing (0.13 g, 58 %); mp: 79 °C; ^{1}H NMR ($CDCl_3$) δ 1.50–2.31 (13H, m, H_{6a-14}, NH), 2.83 (1H, s, H_{6a}), 4.01–4.18 (2H, AB, $J = 16$, H_5), 6.91–7.22 (4H, m, H-arom.); ^{13} C NMR ($CDCl_3$) δ 28.4 (C_9), 28.9 (C_{11}), 30.68 (C_{10}), 33.9 (C_7), 35.5 (C_{12a}), 37.2 (C_8), 37.6 (C_{14}), 40.6 (C_{13}), 41.2 (C_{12}), 49.4 (C_5), 62.2 (C_{6a}), 124.9–125.5–126.0–126.2 (C_{1-4}), 134.6–144.5 (C_{4a-12b}); hydrochloride salt: mp >250 °C. Anal calcd for $C_{17}H_{22}ClN$: C 74.03, H 8.04, found C 74.15, H 8.08.

*General procedure of synthesis of 1-benzyltricycle [3.3.1.1^{3,7}] decan-2-(2-dimethylaminoethyl)amine (**5a**), 1-benzyltricycle [3.3.1.1^{3,7}]decan-2-(N-piperidinylethyl)amine (**5b**), 1-benzyltricyclo[3.3.1.1^{3,7}]decan-2-(N-piperazinylethyl) amine (**5c**), 1-benzyltricyclo[3.3.1.1^{3,7}]decan-2-(3-dimethyl aminopropyl)amine (**6a**), 1-benzyltricyclo[3.3.1.1^{3,7}]decan-2-(N-morpholinopropyl)amine (**6b**) and 1-benzyltricyclo [3.3.1.1^{3,7}]decan-2-(1-imidazolylpropyl)amine (**6c**)*

A mixture of ketone **7a** (8.66 mmol) and the requisite diamine (10 mmol) in anhydrous toluene (20 mL) was refluxed for 6 h, while removing H_2O azeotropically. The solvent was then evaporated to give a viscous oil, which was reduced with

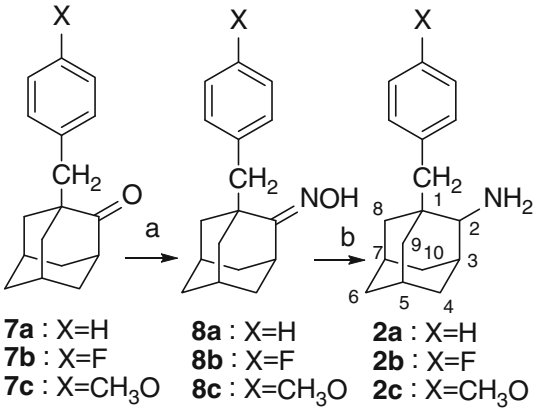
lithium aluminum hydride (50 mmol) in anhydrous diethyl ether (30 mL), upon refluxing for 10 h. The reaction was then quenched by the sequential addition of H_2O and an aqueous solution of NaOH (5 %) and the solid filtered off. The filtrate was dried over Na_2CO_3 and evaporated to give a residue, which was further purified by flash column chromatography over silica gel using a mixture of Et_2O:MeOH as eluent to give the desired amine, as an oil, which was transformed to the respective fumarate salt. Compound **5a**: purification by column chromatography-eluent system Et_2O:MeOH (2:1), yield 67 %; ^{1}H NMR ($CDCl_3$) δ 1.32–1.90 (13H, m, H_{3-10}), 2.18 (7H, s, (CH_3)$_2$N, C*H*NH), 2.31–2.63 (2H, AB, $J = 12.8$, CH_2Ph), 2.40–2.43 (3H, m, NHC*H*H + CH_2N(CH$_3$)$_2$), 2.74 (1H, m, NHCH*H*CH$_2$N(CH$_3$)$_2$), 7.07–7.17 (5H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 28.1 (C_5), 28.2 (C_7), 30.3 (C_3), 30.7 (C_6), 37.2 (C_4), 37.3 (C_{10}), 37.4 (C_9), 41.6 (C_8), 45.0 (NHCH$_2$*C*H$_2$N(CH$_3$)$_2$), 45.5 ((*C*H$_3$)$_2$N), 45.8 (*C*H$_2$Ph), 59.7 (NH*C*H$_2$CH$_2$N(CH$_3$)$_2$), 63.7 (C_2), 71.8 (C_1), 125.5 (C_4-arom.), 127.4 ($C_{2,6}$-arom), 130.8 ($C_{3,5}$-arom.), 138.5 (C_1-arom.); fumarate, mp: 171 °C. Anal calcd for $C_{25}H_{36}N_2O_4$: C 70.06, H 8.47, found C 69.97, H 8.41. Compound **5b**: purification by column chromatography-eluent system Et_2O:MeOH (1:1), yield 92 %;^{1}H NMR ($CDCl_3$) δ 1.13–1.78 (19H, m, H_{3-10}, $H_{3,4,5}$-piper.), 2.20 (1H, ~d, C*H*NH), 2.33–2.45 (8H, AB, $J = 12.8$, C*H*HPh, NHC*H*H + CH_2N, $H_{2,6}$-piper.), 2.64 (1H, AB, $J = 12.8$, CH*H*Ph), 2.60–2.64 (1H, m, NHC*H*HCH$_2$N), 7.08–7.18 (5H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 24.4 (C_4-pip), 26.0 ($C_{3,5}$-piper.), 28.1 (C_5), 28.2 (C_7), 30.3 (C_3), 30.7 (C_6), 37.1–37.2–37.3 ($C_{4,9,10}$), 41.5 (C_8), 44.36 (NH*C*H$_2$CH$_2$N), 45.8 (*C*H$_2$Ph), 54.7 ($C_{1,6}$-piper.), 59.0 (NHCH$_2$*C*H$_2$N), 64.0 (C_2), 71.8 (C_1), 125.5(C_4-arom.), 127.4 ($C_{2,6}$-arom.), 130.7 ($C_{3,5}$-arom.), 138.5 (C_1-arom.); fumarate, mp: 187 °C. Anal calcd for $C_{28}H_{40}N_2O_4$: C 71.76, H 8.60, found C 71.82, H 8.63. Compound **5c**: purification by column chromatography-eluent system Et_2O:MeOH (3:2), yield 40 %; ^{1}H NMR ($CDCl_3$) δ 1.43–1.97 (13H, m, H_{3-10}), 2.27 (1H, ~s, $J = 0.2$, C*H*NH), 2.40–2.53 (8H, AB, $J = 12.8$, C*H*HPh, NHC*H*H + CH_2N, $H_{3,5}$-piperaz.), 2.64 (1H, AB, $J = 12.8$, CH*H*Ph), 2.81 (1H, m, NHC*H*HCH$_2$N), 2.90 (4H, m, $H_{2,6}$-piperaz.), 7.14–7.26 (5H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 28.2 (C_5), 28.3 (C_7), 30.4 (C_3), 30.8 (C_6), 37.2–37.3–37.4 ($C_{4,9,10}$), 41.6 (C_8), 44.1 (NH*C*H$_2$CH$_2$N), 45.9 (*C*H$_2$Ph), 46.3 (C_4-piperaz.), 54.7 (C_2-piperaz.), 59.0 (NHCH$_2$*C*H$_2$N), 64.0 (C_2), 125.5 (C_4-arom.), 127.4 ($C_{2,6}$-arom.), 130.7 ($C_{3,5}$-arom.), 138.5 (C_1-arom.); fumarate, mp: 168 °C. Anal calcd for $C_{27}H_{39}N_3O_4$: C 69.05, H 8.37, N 8.95, found C 69.12, H 8.32. Compound **6a**: purification by column chromatography-eluent system Et_2O:MeOH (3:2), yield 61 %; ^{1}H NMR ($CDCl_3$) δ 1.25–2.00 (15H, m, H_{3-10}, CH$_2$C*H*$_2$CH$_2$), 2.24 (6H, s, (CH_3)$_2$N), 2.28 (1H, ~s, C*H*NH), 2.36–2.43 (4H, m, AB, $J = 12.8$, C*H*HPh, NHC*H*HCH$_2$C*H*$_2$N(CH$_3$)$_2$), 2.68–2.78 (2H, m, AB, $J = 12.8$, CH*H*Ph, NHCH*H*CH$_2$CH$_2$N(CH$_3$)$_2$), 7.14–7.26 (5H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 28.1 (C_5), 28.2 (C_7), 28.9 (CH$_2$*C*H$_2$CH$_2$), 30.1 (C_3), 30.8 (C_6), 37.16 (C_4), 37.3 (C_{10}), 37.4 (C_9), 41.7 (C_8), 45.6 ((*C*H$_3$)$_2$N), 45.8 (NH*C*H$_2$CH$_2$CH$_2$N(CH$_3$)$_2$), 45.8 (*C*H$_2$Ph), 58.3 (NHCH$_2$CH$_2$ *C*H$_2$N(CH$_3$)$_2$), 63.7 (C_2), 71.8 (C_1), 125.5 (C_4-arom.), 127.4 ($C_{2,6}$-arom.), 130.7 ($C_{3,5}$-arom.), 138.6 (C_1-arom.); fumarate, mp: 170 °C. Anal calcd for $C_{26}H_{38}N_2O_4$: C 70.56, H 8.65, found C 70.45, H 8.71. Compound **6b**:purification by column chromatography-eluent system Et_2O:MeOH (3:2), yield 52 %; ^{1}H NMR ($CDCl_3$) δ 1.24–2.00 (15H, m, H_{3-10}, CH$_2$C*H*$_2$CH$_2$), 2.27 (1H, ~s, C*H*NH), 2.37–2.70 (8H, m, AB, $J = 14$, C*H*HPh, NHC*H*HCH$_2$C*H*$_2$N, $H_{3,5}$-morph.), 2.73–2.85 (2H, m, AB, $J = 14$, CH*H*Ph, NHCH*H*CH$_2$CH$_2$N), 3.72–3.77 (4H, m, $H_{2,6}$-morph.), 7.13–7.26 (5H, m, H-arom.); ^{13}C NMR ($CDCl_3$) δ 27.5 (CH$_2$*C*H$_2$CH$_2$), 28.2 (C_5), 28.3 (C_7), 30.1 (C_3), 30.9 (C_6), 37.2 (C_4), 37.3 (C_{10}), 37.6 (C_9), 41.7 (C_8), 45.9 (NH*C*H$_2$CH$_2$CH$_2$N), 46.0 (*C*H$_2$Ph), 53.9 ($C_{3,5}$-morph.), 57.9 (NHCH$_2$CH$_2$*C*H$_2$N), 63.6 (C_2), 67.1 ($C_{2,6}$-morph.), 71.8 (C_1), 125.5 (C_4-arom.), 127.4 ($C_{2,6}$-arom), 130.7 ($C_{3,5}$-arom.), 138.6 (C_1-arom.); fumarate, mp: 178 °C. Anal calcd for $C_{28}H_{40}N_2O_5$: C 69.39, H 8.32, found C 69.43, H 8.47. Compound **6c**: purification by column chromatography-eluent system Et_2O:MeOH (2:1), yield 60 %; ^{1}H NMR ($CDCl_3$) δ 1.26–1.97 (15H, m, H_{3-10}, CH$_2$C*H*$_2$CH$_2$), 2.27 (1H, ~s, C*H*NH), 2.41 (1H, quint, NHCH*H*CH$_2$CH$_2$N), 2.58 (8H, AB, $J = 13.2$, C*H*HPh), 2.72 (1H, quint, NHC*H*HCH$_2$CH$_2$N), 4.12 (2H, t, NHCH$_2$CH$_2$C*H*$_2$N), 6.94–7.50 (8H, m, H-phen.+i-mid.); ^{13}C NMR ($CDCl_3$) δ 27.9 (C_5), 28.1 (C_7), 30.1 (C_3), 30.7 (C_6), 32.07 (NHCH$_2$*C*H$_2$CH$_2$N) 36.9 (C_4), 37.0 (C_{10}), 37.3 (C_9), 41.7 (C_8), 43.6 (NH*C*H$_2$CH$_2$CH$_2$N), 44.9 (NHCH$_2$CH$_2$*C*H$_2$N), 46.0 (*C*H$_2$Ph), 64.0 (C_2), 118.8 (C-imid.), 125.6 (C_4-phen.), 127.5 ($C_{2,6}$-phen.), 129.3 (C-imid.),130.6 ($C_{3,5}$-arom.), 137.2 (C-imid.), 138.3 (C_1-phen.); fumarate, mp: 171 °C. Anal calcd for $C_{27}H_{35}N_3O_4$: C 69.65, H 7.58, found C 69.54, H 7.66.

Results and discussion

Chemical synthesis

For the preparation of 1-benzyl-2-aminoadamantanes **2a–c**, the previously reported ketones **7a–c** (Papanastasiou *et al.*, 2009) were converted to their respective oximes **8a–c**, which were then catalytically reduced to the desired amines **2a–c** (Scheme 1).

Amine **1** was prepared from 1-phenyl-2-adamantanone (Lenoir, 1973; Tseng *et al.*, 1998; Zoidis *et al.*, 2010), in a similar way to amines **2**. For the preparation of the diastereomeric amines **3a** and **3b**, phenylketone **9** (Lenoir, 1973; Tseng *et al.*, 1998) was treated with the appropriate sulfur ylide to give epoxide **10**. This was treated with $BF_3{\cdot}Et_2O$ complex to give aldehyde **11**, which was immediately oxidized, under Jones conditions, to the

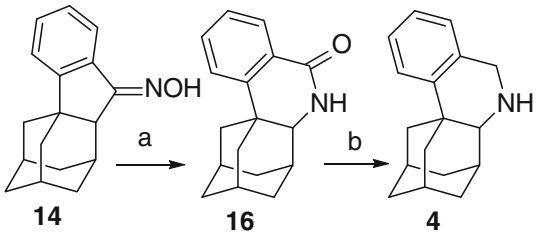


Scheme 1 Reagents and conditions: *a* NH_2OH HCl, CH_3CO-$ONa{\cdot}3H_2O$, EtOH, reflux for 5 h, (quant.); *b* H_2/Ni-Raney, EtOH, 55 psi, 70 °C for 5 h, (91–95 %)

carboxylic acid **12** in good yield. This acid was then converted to its chloride, which, in the presence of $AlCl_3$, was cyclized to ketone **13**. Treatment of **13** with hydroxylamine gave oxime **14**, which was transformed to the oxime-ester **15**. This was reduced by diborane, prepared in situ from $NaBH_4$ and iodine, to the diastereomeric amines **3a** and **3b**. The two diastereomers were separated by flash column chromatography and characterized by NMR spectral analysis. $J_{6H–6aH} \approx 7.16$ Hz coupling is attributed to the *cis*-**3b** amine and $J_{6H–6aH} \approx 10.6$ Hz to the *trans*-**3a** amine (Scheme 2).

Beckmann rearrangement of oxime **14** on treatment with PCl_5 led to the formation of lactam **16**, which was selectively reduced by $LiAlH_4$ to provide amine **4** (Scheme 3).

The selectivity of this reaction can be attributed to the stability of the produced cation **16a**, which leads to lactam **16**. Conversely, cation **17a** is less stable and thus the corresponding lactam **17** is not formed (Fig. 2).



Scheme 3 Reagents and conditions: *a* PCl_5, anhydrous C_6H_6, reflux for 1 h. *b* $LiAlH_4$, anhydrous THF, reflux 12 h

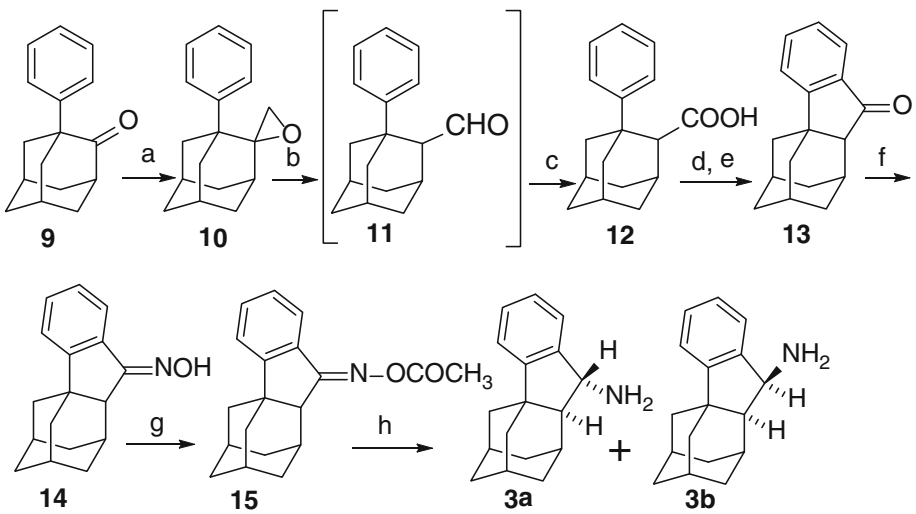
The elucidation of the structure of amine **4** was based on the NMR spectra. Thus, the 5-CH_2 peak appears as an AB system with $J = 16.1$ Hz, which justifies its linkage to the phenolic ring and not with the C2 carbon atom of the adamantane skeleton.

The synthesis of the ethanodiamines **5** and propanodiamines **6** was effected by heating the appropriate diamines with ketone **7a**, followed by azeotropic removal of water. The intermediate imines **18** were not isolated, but reduced directly to the corresponding amines **5a**, **5b**, **5c** and **6a**, **6b**, **6c** (Scheme 4).

Pharmacology

The results from the in vitro drug screening of the new compounds on cancer cell lines (colon, prostate, breast, ovarian, central nervous system, leukemia, pancreas, liver) and on normal cell lines are shown in Table 1.

Considering the antiproliferative activity of the active analogs on various cancer cell lines, it appears that aminoadamantanes **2a–c** are the most potent compounds, derivative **2b** being the most active across all examined cancer cell lines. Moreover, the OMe-substituted analog **2c** proved to be more efficient than the parent compound **2a**. The C2-diamino-substituted adamantanes (compounds **5b** and **6a**) show a



Scheme 2 Reagents and conditions: *a* trimethylsulfoxonium iodide, NaH, anhydrous DMSO, 20 °C for 30 min, 55–58 °C for 2 h. *b* $BF_3{\cdot}Et_2O$, anh. C_6H_6. *c* CrO_3, H_2SO_4 (8N), 15–20 °C. *d* $SOCl_2$, 65 °C for 15 min. *e* $AlCl_3$, CS_2, rt for 30 min, reflux for 30 min. *f* $NH_2OH.HCl$, $CH_3COONa{\cdot}3H_2O$, EtOH, reflux for 7 h, (quant.). *g* $(CH_3CO)_2O$, Py, 0 °C for 7 h and 3 °C for 18 h, (quant.). *h* $NaBH_4/I_2$, anhydrous. THF, reflux for 8 h

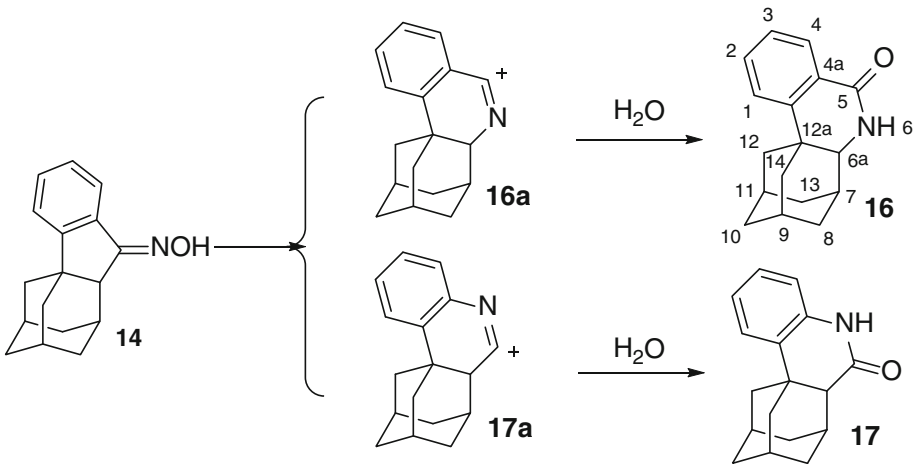
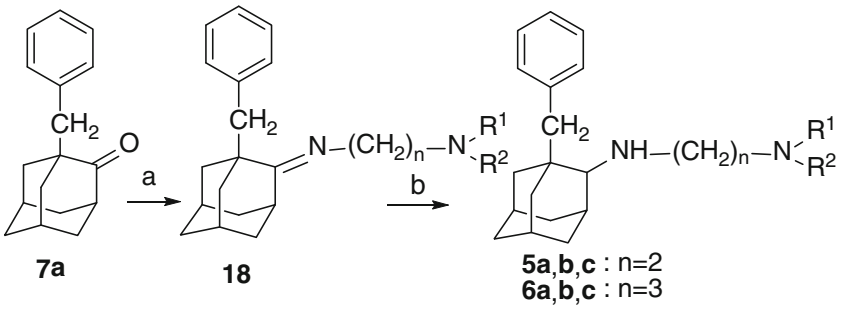


Fig. 2 Mechanism of formation of lactam **16** versus **17**



Scheme 4 Reagents and conditions: *a* $n = 2$, i, 2-dimethylaminoethylamine, toluene, reflux for 6 h. ii, 2-(piperidin-1-yl)ethylamine, toluene, reflux for 6 h. iii, 2-(piperazin-1-yl)ethylamine, reflux for 6 h; $n = 3$, i, 3-dimethylaminopropylamine, toluene, reflux for 6 h. ii, 3-morpholinopropylamine, toluene, reflux for 6 h. iii, 3-(1*H*-imidazol-1-yl)propylamine, toluene, reflux for 6 h. *b* $LiAlH_4$, anhydrous Et_2O, reflux 10 h, (40–92 %)

Table 1 Results from the in vitro drug screening

		Cancer cell lines								
		Colon			Renal	Prostate			Breast	
Compound	Values[a]	Colo205	HCT-116	HCT-15	Caki	DU145	PC3	LNCap	MDA MB231	MCF7
1[b]	TGI	100				100	89.3			100
	GI_{50}	84.53				100	82.92			69.3
2a[b]	TGI	33.23	35.84		26.84	29.77			46.6	9.5
	GI_{50}	7.12	6.59		6.54	6.68			6.68	5.5
2b[b]	TGI		17.46	53.82						8.7
	GI_{50}		5.6	19.39						4.6
2c[b]	TGI		52.17	75.05						42.3
	GI_{50}		18.49	38.81						7.4
3a[b]	TGI	69.89				37.62		61.2		62.47
	GI_{50}	34.95				26.63		28.53		32.62
3b[b]	TGI					66.13	56.74			
	GI_{50}					31.45	21.34			
4	TGI		100.0							100.0
	GI_{50}		63.92							52.0
5a[c]	TGI	59.94	55.87					54.7		54.09
	GI_{50}	25.44	24.02					24.36		25.86

Table 1 continued

Compound	Values[a]	Cancer cell lines									
		Colon			Renal	Prostate			Breast		
		Colo205	HCT-116	HCT-15	Caki	DU145	PC3	LNCap	MDA MB231		MCF7
5b[c]	TGI		51.69								33.2
	GI_{50}		9.94								6.75
5c[c]	TGI		50.0								52.72
	GI_{50}		7.02								21.1
6a[c]	TGI		34.8								42.85
	GI_{50}		6.76								9.11
6b[c]	TGI		100.0								58.54
	GI_{50}		43.98								28.94
6c[c]	TGI		64.7								56.15
	GI_{50}		26.82								26.96
5-FU	TGI		>100								>100
	GI_{50}		9.51								8.40
ETO	TGI										
	GI_{50}										

Compound	Values[a]	Cancer cell lines											
		Ovarian				CNS		Non small lung			Small lung	Melanoma	Normal cells	
		IGROV-1	OVCAR-5	ADR-res	NCI	SF268	U251	NCI-H460	EKVX	A549	DMS 114	SK-MEL-28	hMSC	NHDF
1[b]	TGI					100	100	100						
	GI_{50}					100	100	100						
2a[b]	TGI	36.5	37.8	30.00		56.82			29.25	43.7			45.56	
	GI_{50}	7.6	8.35	6.7		20.98			6.94	8.67			9.55	
2b[b]	TGI			24.4		37.44	50.87	51.95			50.39	44.98		52.8
	GI_{50}			7.4		7.83	21.81	13.72			9.38	13.24		17.9
2c[b]	TGI			55.3		50.7	57.98	62.38			73.94	60.71	56.05	58.8
	GI_{50}			29.3		21.17	31.23	31.18			40.05	31.79	24.83	27.7
3a[b]	TGI						56.23							
	GI_{50}						31.15							
3b[b]	TGI						56.56							
	GI_{50}						33.05							
4	TGI					100.0		100.0						
	GI_{50}					100.0		100.0						
5a[c]	TGI					57.05					58.07			
	GI_{50}					29.34					26.48			
5b[c]	TGI					45.85		32.18						
	GI_{50}					13.09		6.32						
5c[c]	TGI					53.61		46.78						
	GI_{50}					22.19		7.49						
6a[c]	TGI					40.93		25.83						
	GI_{50}					9.09		5.78						
6b[c]	TGI					100.0		100.0						
	GI_{50}					56.39		50.73						
6c[c]	TGI					62.77		67.52						
	GI_{50}					28.78		31.48						

Table 1 continued

		Cancer cell lines											
		Ovarian			CNS		Non small lung			Small lung	Melanoma	Normal cells	
Compound	Values[a]	IGROV-1	OVCAR-5	ADR-res NCI	SF268	U251	NCI-H460	EKVX	A549	DMS 114	SK-MEL-28	hMSC	NHDF
5-FU	TGI				>100		>100						
	GI_{50}				49.21		5.95						
ETO	TGI				92.67								
	GI_{50}				4.21								

5-FU 5-fluorouracil, *ETO* etoposide

[a] TGI is the concentration (μM) resulting in total growth inhibition, GI_{50} is the concentration (μM) resulting in growth inhibition of 50 %

[b] Hydrochloride

[c] Monofumarate

similar profile, while the tricyclic derivative **4** is inactive and **3a–c** are marginally active. The presence of morpholine in analog **6b** does not contribute to antiproliferative activity. On the other hand, the presence of piperidine, piperazine and imidazole moieties on aminoadamantanes **5b**, **5c** and **6c**, respectively, has similar contribution to potency. The size of $(CH_2)_n$ linker, 2 or 3 methylene units, does not affect the antiproliferative potency. Interestingly, 1-phenyl-2-amino-adamantane **1** proved to be inactive, while its 1-benzyl congener **2a** is sufficiently potent. It seems that the increase of the distance between the aromatic ring and the adamantane moiety enhances the antiproliferative potency. The activity shown by the benzylic compounds is consistent with previous reported findings on diaryl-substituted adamantanes (Riganas *et al.*, 2012a, b, c). These results should aid in the future design of more effective antiproliferative aminoadamantanes.

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