Supporting Information

Discovery of Adamantane Carboxamides as Ebola Virus Cell Entry and Glycoprotein Inhibitors

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1. Biology Experimental Section

1.1 Pseudotyped virus generation and assay

A vesicular stomatitis virus (VSV) pseudotype system expressing Ebola virus (EBOV) glycoprotein and the *Renilla* luciferase reporter gene were used to generate pseudotyped virus (hereto referred to as pEBOV) to characterize EBOV infectivity and inhibition by compounds. pEBOV was generated with expression of the EBOV (KR063671) glycoprotein (GP) in cultured HEK-293T cells (ATCC CRL-3216) transfected with a pCAGGS plasmid encoding the EBOV glycoprotein and PEI (polyethylenimine) transfection reagent. After transfection, cells were incubated overnight in supplemented DMEM and then infected for one hour with VSV reporter virus whereby the VSV GP gene is replaced with a luciferase reporter gene. Cells were then incubated for 24 hours in supplemented DMEM and supernatant was collected, clarified by centrifugation and filtration, aliquoted and stored at -80°C.

Vero cells (ATCC: CCL-81) grown in supplemented DMEM were used for infectivity and inhibition assays. The pseudotyped virus was titrated for luminescence activity in Vero cell monolayers prepared in 384 well plates. To detect viral entry inhibition by compounds, viral supernatant was diluted to give luminescence signal / background values of >200. Cells were treated with a mixture of compounds at desired concentrations and pEBOV in assay media consisting of 50% Opti-MEM, 50% DMEM, with 1% FBS and supplements. Final DMSO concentration in compound wells was kept < 1% and control wells were treated with assay media and 1% DMSO. Cells were incubated for 24hours and lysed. Cell lysate was added to Coelenterazine substrate according to manufacturer's instructions (Pierce, 16167). Luminescence was read with a plate reader (Beckman Coulter DTX 880 multimode detector, 535 nm emission) for compound-containing and control wells to determine % activity (inhibition of luciferase signal) for each compound. The 50% effective (EC_{50} virus-inhibitory) concentration was calculated by linear regression analysis. Averages and standard deviation (s.d.) were calculated (N=3), with 4 replicates in each experiment, s.d. ≤ 20%.

1.2 In vitro liver microsome metabolic stability assay

Reaction premixtures contained 1uM compound of interest, 1 mg/ml liver microsomes (LM) of desired species, 2.1 mM $MgCl_2$ and 0.1 M sodium phosphate buffer, pH 7.4. This premixture was incubated at 37°C for 30 minutes with gentle agitation to allow the compound to become completely dissolved. Then a freshly made NADPH solution in 0.1M sodium phosphate buffer was added at a concentration of 2mM to start the reaction. A 'Time 0' sample (30uL) was extracted immediately after addition of NADPH and added to 140uL

cold acetonitrile containing 1uM of pre-decided internal standard. The remaining reaction mixture was incubated at 37°C. 'Time 60' sample was extracted after 60 minutes and added to acetonitrile with internal standard. A control compound (Verapamil for human, monkey and dog LM, Lidocaine for Guinea pig LM, and Diphenhydramine for rat and mouse LM) was included and 'Time 0' and 'Time 15' samples were similarly processed. The samples were then spun in a centrifuge for 10 minutes at 4000rpm, supernatant was collected and mixed with equal parts distilled water. These were then analyzed on a Varian 500-MS LC/MS/MS to determine relative analyte concentrations at the different time points (data are an average of two measurements in one experiment).

1.3 Solubility assay

Compound solubility was assessed in phosphate buffer saline solution (PBS) at pH 6.5 and pH 7.4. Compound dilutions were prepared in PBS solution with 1% DMSO, concentrations ranging from 100uM to 1uM in two-fold dilutions in a 96 well polypropylene plate. The HCl salts of prioritized compounds **36**, **38**, **40** and **42** were further tested up to 20 mg/ml in H_20. Control wells contained PBS solution with 1% DMSO. After incubating the plate at 37°C for 2 hours, absorbances were read at 620 nm on a Spectramax Plus 384 spectrophotometer. Relative turbidity was measured in test wells compared to control wells and EC_{90} values calculated to represent aqueous solubility (N=3, s.d. ≤10%).

1.4 Infectious wild type Ebola virus plaque assay

Vero cell culture monolayers in 12-well disposable cell culture plates were prepared in DMEM with 2% FBS and supplements. Test compounds were prepared at four log_{10} final concentrations in 2X DMEM, along with favipiravir as a positive control. After removing growth media, cells were infected with 0.01 MOI of virus or about 50 to 100 plaque forming units (pfu) and incubated for 60 min at 37°C, 5% CO_2 with constant gentle rocking. Virus inoculum was removed, cells washed with PBS and overlaid with 1% methylcellulose diluted 1:1 with 2X DMEM and supplemented with 2% FBS and 1% penicillin/streptomycin and supplemented with the corresponding drug concentration. After incubating for 10 days, the overlays were removed and plates stained with 0.05% crystal violet in 10% buffered formalin for approximately twenty minutes at room temperature. The plates were washed, dried and the number of plaques counted. The number of plaques in each set of compound dilution were converted to a percentage relative to the untreated virus control. The 50% effective (EC_{50} virus-inhibitory) concentration was calculated by linear regression analysis (N=3, s.d. ≤20%).

1.5 Cytotoxicity assay

The cytotoxicity assay (In vitro Toxicology Assay Kit, Neutral red based; Sigma) was performed in 96-well plates following the manufacturer's instructions. Briefly, growth medium was removed from confluent Vero

E6 cell monolayer's and replaced with fresh medium containing the test compound at desired concentrations. Control wells contained medium with the positive control or medium devoid of compound. After incubation for 10 days at 37ºC with 5% CO_2, plates were stained with 0.033% neutral red for approximately two hours. The neutral red medium was removed, cells were washed and the incorporated neutral red was eluted with 1% acetic acid/50% ethanol for at least 30 minutes. The dye content in each well was quantified using a 96-well spectrophotometer at 540 nm wavelength and 690 nm wavelength (background reading). The 50% cytotoxic (CC_{50}, cell-inhibitory) concentrations were calculated by linear regression analysis. The positive control compound (favipiravir) was evaluated in parallel in each test.

1.6 Virus Yield Reduction (VYR) assay

Confluent or near-confluent Vero E6 cell culture monolayers in 96-well disposable cell culture plates were maintained in DMEM with 5% FBS and supplements. The test compounds were prepared at eight half-log_{10} final concentrations in 2x DMEM and mixed 1:1 with virus prior to infection of cells. A virus control, cell control and positive control (favipiravir) were included in the experimental setup. The growth media was removed from the 96-well plates and cells were infected with 0.01 MOI of virus or about 50 to 100 pfu in the presence of antiviral compounds. Cells were incubated for 60 min with 75µl inoculum/ well, at 37°C, 5% CO_2 with constant gentle rocking. After one hour incubation time, 75µl of fresh cell culture medium supplemented with 2x concentration of compound was added. Tissue culture supernatant (TCS) aliquots were collected at 3 days post infection and then used to determine the compounds' inhibitory effect on virus replication. Virus that was replicated in the presence of test compound was titrated and compared to virus from untreated, infected controls. For titration of TCS, serial ten-fold dilutions were prepared and used to infect fresh monolayers of cells. Virus inoculum was removed, cells washed and overlaid with 0.5% methylcellulose diluted 1:1 with 2x DMEM with 2% FBS and 1% penicillin/streptomycin and supplemented with the corresponding drug concentration. Cells were incubated at 37^0C with 5% CO_2 for 10 days. Plotting the log_{10} of the inhibitor concentration versus log_{10} of virus produced at each concentration allowed calculation of the 90% (one log_{10}) effective concentration by linear regression (N=3, s.d. ≤20%).

2. Chemistry Experimental Section: Procedures and Synthetic Schemes

General Information

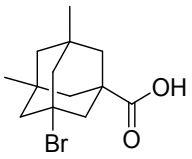
All reactions were run under nitrogen atmosphere unless noted otherwise. Starting materials, reagents and solvents were purchased from commercial suppliers and were used without further purification. Compounds **1**, **2,** and **8** were purchased from commercial screening libraries of compounds. Reaction progress was monitored by TLC using TLC Silica gel 60 F_{254} glass plates or LC-MS using Agilent 1100 Series LC system

connected to the Surveyor MSQ Plus MS detector. Reaction products were purified by silica gel column chromatography or preparative HPLC using Agilent 1100 prep HPLC system (Phenomenex C18 column (30x100 mm), eluted with a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid, at a flow rate of 30 mL/min). ^{1}H NMR spectra were recorded on a BRUKER 300 MHz or BRUKER 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) as internal standard. An Agilent 6230 time-of-flight mass spectrometer (TOFMS) with Jet Stream electrospray ionization source (ESI) was used for high resolution mass spectrometry (HR-MS) analysis. The Jet Stream ESI source was operated under positive ion mode with the following parameters: VCap: 3500V; fragmentor voltage: 160 V; nozzle voltage: 500 V; drying gas temperature: 325 C, sheath gas temperature: 325 C, drying gas flow rate: 7.0 L/Min; sheath gas flow rate: 10 L/Min; nebulizer pressure: 40 psi. According to LC-MS spectra the assayed compounds showed > 95% purity (unless otherwise indicated).

2.1 Synthesis of adamantanecarboxylic and noradamantanecarboxylic acids

Preparation of intermediates B (Scheme 1)

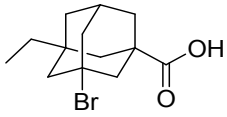
3-Bromo-5,7-dimethyladamantane-1-carboxylic acid:



Bromine (0.61 mL, 12 mmol) was cooled to 0 ^{o}C in a 25 mL round-bottomed flask. Then, iron (0.11 g, 1.92 mmol) was added in small portions, and the mixture was stirred at 0 ^{o}C for 30 min. Then, 3,5-dimethyladamantane-1-carboxylic acid (0.1 g, 0.48 mmol) was added, and the mixture was stirred at r.t. for 8 h. After adding ice and 6N aqueous HCl (5 mL), ethyl acetate and saturated aqueous Na_2SO_3 were added. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous Na_2SO_3. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 3-bromo-5,7-dimethyladamantane-1-carboxylic acid as

a white solid, which was used in the next step without further purification.[1] Yield: 89 mg (65%); R_f (hexanes / ethyl acetate 6:4) 0.5.

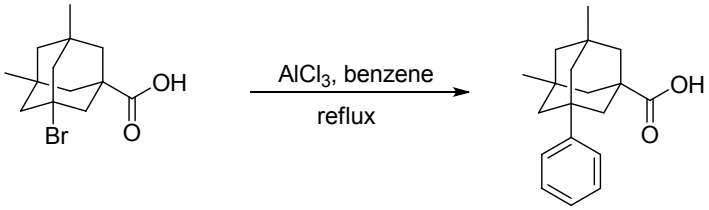
3-Bromo-5-ethyladamantane-1-carboxylic acid:



The desired compound[2] was prepared from 3-ethyladamantane-1-carboxylic acid in the same manner as described above for 3-bromo-5,7-dimethyladamantane-1-carboxylic acid and was used in the next step without further purification. White solid, Yield: 0.11 g (80%); R_f (hexanes / ethyl acetate 7:3) 0.4.

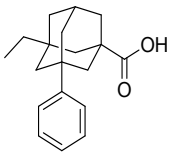
Preparation of intermediates C (Scheme 1)

3,5-Dimethyl-7-phenyladamantane-1-carboxylic acid:



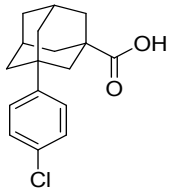
3-Bromo-5,7-dimethyladamantane-1-carboxylic acid (0.033 g, 0.11 mmol) was added to a mixture of $AlCl_3$ (0.018 g, 0.14 mmol) in 1 mL anhydrous benzene. The reaction mixture was heated to reflux for 6 h, then diluted with EtOAc. The organic phase was washed with 0.5 M aq. HCl and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid as a white solid, which was used directly in the next step without further purification. Yield: 0.03 g (91%); R_f (hexanes / ethyl acetate 7:3) 0.4.

3-Ethyl-5-phenyladamantane-1-carboxylic acid:



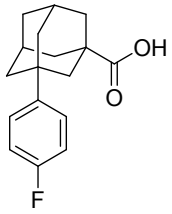
The desired compound was prepared from 3-bromo-5-ethyladamantane-1-carboxylic acid and benzene in the same manner as described above for 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid. White solid, Yield: 66 mg (74%); R_f (hexanes / ethyl acetate 7:3) 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.22 – 7.16 (m, 1H), 2.34 – 2.27 (m, 1H), 2.01 (br. s, 2H), 1.91 – 1.79 (m, 4H), 1.70 – 1.62 (m, 2H), 1.59 (br. s, 2H), 1.51 – 1.42 (m, 2H), 1.25 (q, 2H), 0.83 (t, 3H).

3-(4-Chlorophenyl)adamantane-1-carboxylic acid:



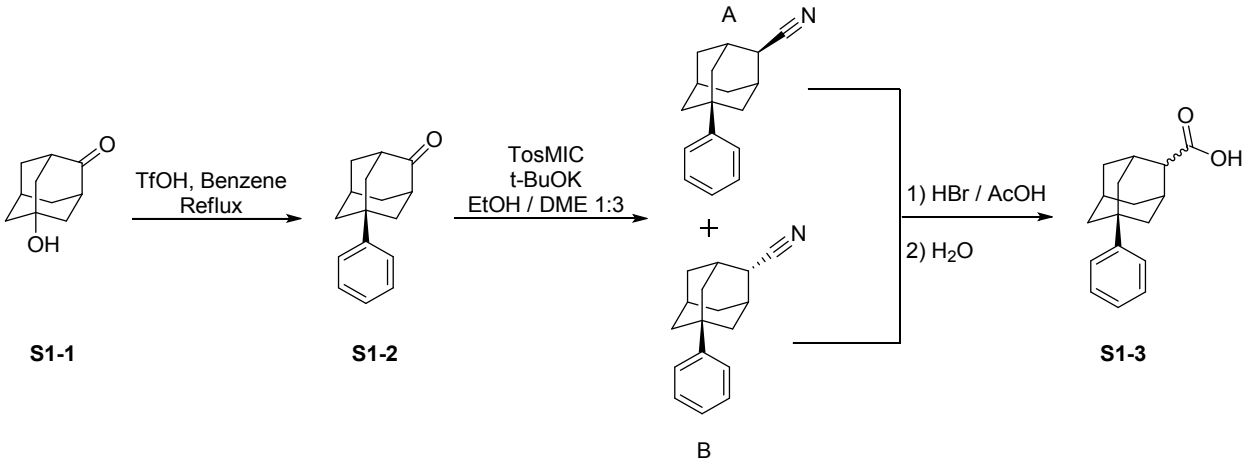
The desired compound[3] was prepared from 3-bromoadamantane-1-carboxylic acid and chlorobenzene in the same manner as described above for 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid and used directly in the next step without further purification. White solid, Yield: 90 mg (81%); R_f (hexanes / ethyl acetate 6:4) 0.6.

3-(4-Fluorophenyl)adamantane-1-carboxylic acid:



The title compound[4] was prepared from 3-bromoadamantane-1-carboxylic acid and fluorobenzene in the same manner as described above for 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid and used directly in the next step without further purification. White solid, Yield: 38 mg (72%); R_f (hexanes / ethyl acetate 6:4) 0.7.

Scheme S1. Synthesis of 5-phenyladamantane-2-carboxylic acid (**S1-3**).



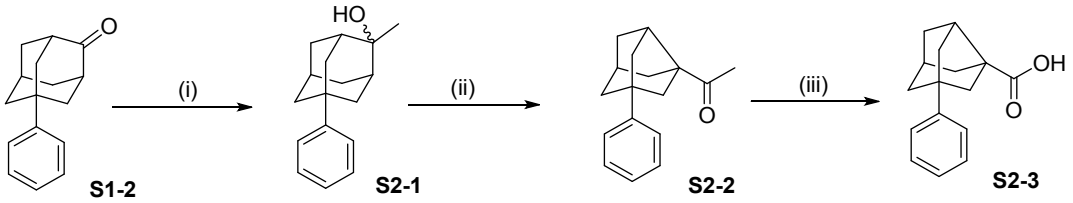
Step 1: 5-phenyladamantan-2-one (**S1-2**). To 5-hydroxyadamantan-2-one (5 g, 150 mmol) was added benzene (20 mL) and triflic acid (3 mL). The heterogenous mixture was heated to reflux, at which time all starting materials dissolved, and reflux was continued overnight. The mixture was cooled to room temperature and partitioned between water and *tert*-butylmethyl ether (50 mL), and the organic phase was washed 3 times with water, followed by saturated $NaHCO_3$ and brine. The organics were dried over Na_2SO_4

and evaporated to give 4.7g of crude product. Purification with flash chromatography on silica gel using 8:2 hexanes:ethyl acetate eluent gave 3.7 g (54%) of pure product as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) δ: 7.41-7.32 (m, 4H), 7.27-7.21 (m, 1H), 2.70 (br:s, 2H), 2.37-2.03 (m, 11H).

Step 2: *cis*-5-phenyladamantane-2-carbonitrile (**A**) and *trans*-5-phenyladamantane-2-carbonitrile (**B**).
To 5-phenyladamantan-2-one (1.1 g, 4.87 mmol) in a flask with strong stirrer was added dimethoxyethane (20 mL), ethanol (7 mL), and p-toluenesulfonylmethylisocyanide (1.23 g, 6.33 mmol).[5] The mixture was cooled to 0 ^{o}C, and potassium *tert*-butoxide (1.31 g, 11.7 mmol) was added in 3 portions (mild exotherm). The reaction mixture was heated to 35 ^{o}C overnight and then cooled to room temperature and filtered to remove potassium tosylate. The filtrate was partitioned between water and *tert*-butylmethyl ether and washed three times with water, then brine, dried (Na_2SO_4), and evaporated. The crude residue was purified via flash chromatography on silica gel using 95:5 hexanes:ethyl acetate eluent. Purification gave 200 mg (17%) and 234 mg (20%) of the less and more polar isomers, respectively, and 410 mg (36%) of mixed fractions containing co-eluted meso-isomers **A** and **B**. Top isomer on TLC, configuration unknown: ^{1}H NMR (500MHz, $CDCl_3$) δ: 7.38-7.30 (m, 4H), 7.20 (t, 1H), 2.93 (s, 1H), 2.39 (s, 2H), 2.25-2.15 (m, 3H), 2.07 (d, 2H), 1.94 (t, 4H), 1.77 (d, 2H). Bottom isomer on TLC, configuration unknown: ^{1}H NMR (500MHz, $CDCl_3$) δ: 7.38-7.31 (m, 4H), 7.20 (t, 1H), 2.94 (s, 1H), 2.39 (s, 2H), 2.35 (d, 2H), 2.15 (s, 1H), 1.97 (s, 1H), 1.90 (d, 4H), 1.78 (d, 2H).

Step 3: 5-phenyladamantane-2-carboxylic acid (**S1-3**). In two separate reactions, 140 mg of the top nitrile on TLC (absolute configuration unknown) and 230 mg of the bottom nitrile on TLC (absolute configuration unknown) were combined with 5 mL of 33% HBr/glacial acetic acid solution. Each reaction was brought to reflux until TLC indicated that the nitriles had hydrolyzed to the primary amide, and the maximum amount of water that does not cause the amide to precipitate was titrated into the reaction mixtures through their condensers. The separate reactions were refluxed overnight and then cooled to room temperature. On cooling, both reactions produced precipitates that were filtered off into sintered glass funnels, washed 3 times with 1 M HCl, and dried on a rotary evaporator to yield fine white crystals. The top nitrile on TLC yielded 105 mg (70%), while the bottom nitrile produced 185 mg (75%). ^{13}C NMR of both reaction products confirms that both nitriles hydrolyze to identical carboxylic acids, presumably the most thermodynamically stable product. The absolute cis / trans configuration of the single carboxylic acid product is unknown. HPLC and TLC also indicate the formation of a single, identical carboxylic acid isomer from both reactions. ^{1}H NMR (500MHz, $CDCl_3$) δ: 7.37 – 7.29 (m, 4H), 7.22 – 7.16 (m, 1H), 2.72 (d, 1H), 2.60 – 2.53 (m, 2H), 2.15 – 1.96 (m, 3H), 2.00 – 1.80 (m, 7H), 1.67 (d, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 180.35, 150.64, 128.45, 125.96, 125.01, 49.04, 48.76, 43.76, 43.33, 39.16, 37.43, 35.83, 32.96, 30.40, 28.41.

Scheme S2. Synthesis of 1-Phenyltricyclo[3.3.1.0^{3,7}]nonane-3-carboxylic acid (**S2-3**). [6]



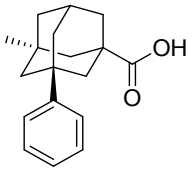
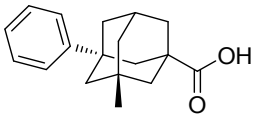
Reagents and Conditions: (i) MeMgBr, THF, 0^0C-RT; (ii) NaOCl, AcOH, n-Bu_4NI, THF, 0^0C-RT then KOH, MeOH, RT; (iii) Br_2, NaOH, 1,4-Dioxane/H_2O, 0^0C-RT.

Step1: 2-methyl-5-phenyladamantan-2-ol (**S2-1**). To a solution of 5-phenyladamantan-2-one (3.25 g, 14.38 mmol) in THF (40 mL) cooled to 0 ^{0}C was added MeMgBr (1M/THF) (44 ml, 44 mmol) and was gradually brought to RT and stirred for 12h to complete the reaction. Reaction was quenched by slow addition of saturated aqueous NH_4Cl solution, and extracted with ethyl acetate (2x100 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated to give the title compound as an oil, which was used without purification in the next step, Yield : 2.86 (82%).

Step 2: 2-phenylhexahydro-2,5-methanopentalen-3a(1H)-yl)ethan-1-one (**S2-2**). A solution of 2-methyl-5-phenyladamantan-2-ol (0.300 g, 1.24 mmol) in a mixture of THF (0.70 mL) and AcOH (1600 uL) was added dropwise to aqueous NaOCl (2.4 mL) at 0 ^{0}C with stirring. Then n-Bu_4NI (24 mg) was added in one portion and reaction mixture was stirred while temperature gradually reaches to RT for 2h to complete the reaction. Extracted with methyl tert-butyl ether (5 mL), dried (Na_2SO_4), filtered and concentrated to give a crude residue, which was dissolved in MeOH (1 mL), then KOH (82 mg, 1.24 mmol) was added and the reaction mixture was stirred at RT for 12 h. Extracted with tert-butyl ether (5 mL), dried (Na_2SO_4), filtered and concentrated to give the title compound as a colorless syrup, which was used without purification in the next step, Yield : 164 mg (54%).

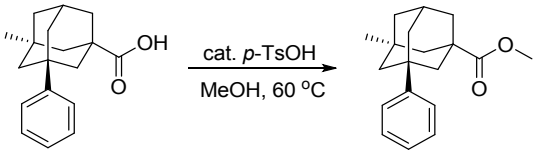
Step 3: 1-Phenyltricyclo[3.3.1.$0^{3,7}$]nonane-3-carboxylic acid **(S2-3)**. To a stirred mixture of NaOH (0.396g, 9.9 mmol) in a mixture of H_2O (2.7 mL) and 1,4-dioxane (1.4 mL) solution cooled to 0 ^{0}C was added Br_2 (0.09 mL, 1.71 mmol) dropwise and stirred for 15 min. Resulting hypobromite solution was added dropwise to a stirred solution of 2-phenylhexahydro-2,5-methanopentalen-3a(1H)-yl)ethan-1-one (0.160 g, 0.66 mmol) in 1,4-dioxane (1.4 mL) at 0 ^{0}C. Gradually brought to RT and stirred for 1h, then quenched by adding AcOH (0.6 mL). Diluted with water, and extracted with ethyl acetate (2x5 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated to give the title compound as a white solid, which was used without purification in the next step, Yield : 90 mg (56%).

(1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyladamantane-1-carboxylic acid and (1*R*,3*S*,5*S*,7*R*)-3-methyl-5-phenyladamantane-1-carboxylic acid:

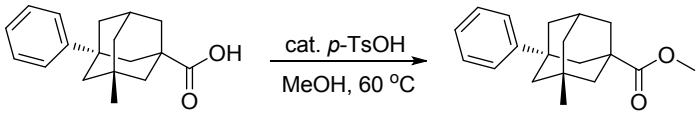
The desired compounds were obtained by chiral separation of racemic 3-methyl-5-phenyladamantane-1-carboxylic acid (commercially available from Enamine, product number EN300-54568] on a prep. Agilent 1200 (Chiralpak AS 20X250 mm, 10 um; mobile phase: n-hexane-2-propanol-TFA, 97-3-0; flow rate: 13 mL/min, injection: 40 mg). Each enantiomer was separately converted to the corresponding methyl ester whose optical rotation was compared with published data.[7]

Methyl (1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyladamantane-1-carboxylate.



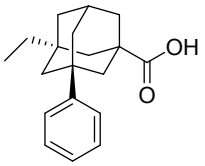
To a solution of (1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyladamantane-1-carboxylic acid (15mg, 0.055 mmol) in MeOH (1 mL) was added cat. *p*-toluenesulfonic acid. The reaction mixture was stirred at 60 ^{0}C for 3h. Then, the solvent was removed *in vacuo*, the residue was partitioned between EtOAc and water; organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (hexanes / EtOAc 4:1) to give 8 mg (50%) of the title compound as a colorless oil. $[\alpha]_D^{23}$ = -1.93 (c = 0.124, $CHCl_3$); Lit. $[\alpha]_D^{23}$ = -1.50 (c = 0.1, $CHCl_3$).

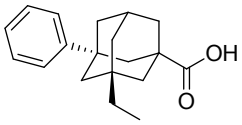
Methyl (1*R*,3*S*,5*S*,7*R*)-3-methyl-5-phenyladamantane-1-carboxylate.



To a solution of (1*R*,3*S*,5*S*,7*R*)-3-methyl-5-phenyladamantane-1-carboxylic acid(15 mg, 0.055 mmol) in MeOH (1 mL) was added cat. *p*-toluenesulfonic acid. The reaction mixture was stirred at 60 ^{0}C for 3 h. Then, the solvent was removed *in vacuo*, the residue was partitioned between EtOAc and water; organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*.The residue was purified by flash chromatography on SiO_2 (hexanes / EtOAc 4:1) to give 9 mg (56%) of the title compound as a colorless oil. $[\alpha]_D^{23}$ = +4.48 (c = 0.154, $CHCl_3$); Lit. $[\alpha]_D^{23}$ = +1.50 (c = 0.1, $CHCl_3$).

(1*S*,3*R*,5*R*,7*S*)-3-ethyl-5-phenyladamantane-1-carboxylic acid and (1*R*,3*S*,5*S*,7*R*)-3-ethyl-5-phenyladamantane-1-carboxylic acid:





The desired compounds were obtained by chiral separation of racemic 3-ethyl-5-phenyladamantane-1-carboxylic acid in a similar way described above for the separation of 3-methyl-5-phenyladamantane-1-carboxylic acid.

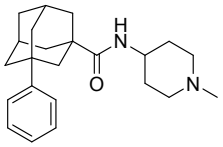
2.2 Synthesis of compounds 3-7, 9-43

General Procedure 1 for preparation of adamantane carboxamides

To a solution of corresponding adamantanecarboxylic or noradamantanecarboxylic acid (1 eq.) in 1 mL of anhydrous CH_2Cl_2 was added *N*,*N*-diisopropylethylamine (2.5 eq.), EDC hydrochloride (1.3 eq.), and 1-hydroxy-7-azabenzotriazole (HOAt, 1.1 eq.) sequentially. The resulting reaction mixture was stirred at room temperature for 0.5 h, then corresponding mono Boc protected diamine (1 eq.) was added. The reaction mixture was stirred at room temperature for 12 h, diluted with CH_2Cl_2 and washed with saturated aq. $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. It was dissolved in 1 mL of CH_2Cl_2, and trifluoroacetic acid (0.1 mL) was added and stirred for 2 h at r.t. The solvent was evaporated, the residue was treated with saturated aq. $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporation of solvent gave a residue which was purified by preparative HPLC using a gradient from 5 to 95% acetonitrile in water containing 0.1% trifluoroacetic acid. HPLC fractions were concentrated *in vacuo*. The residue was dissolved in methanol and filtered through an Agilent StratoSpheres PL-HCO_3 ion exchange resin. The filtrate was concentrated to provide the title compound.

The following compounds were prepared according to General Procedure 1 using the appropriate commercially available amine and carboxylic acid as starting materials.

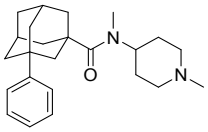
***N*-(1-methylpiperidin-4-yl)-3-phenyladamantane-1-carboxamide (3)**:



The desired compound was prepared from 3-phenyl-adamantane-1-carboxylic acid and 1-methylpiperidin-4-amine using General Procedure 1. Colorless syrup, Yield: 23 mg (47%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.38 (m, 4H) 7.14 - 7.21 (m, 1H) 5.67 (d, 1H) 3.83 - 4.01 (m, 1H) 3.22 (d, 2H) 2.57 (s, 4H) 2.25 (br.

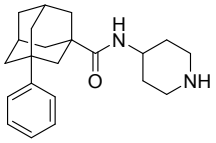
s., 2H) 1.98 (br. s., 3H) 1.79 - 1.95 (m, 10H) 1.72 (br. s., 2H); LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.26, found 353.37.

_N_-methyl-_N_-(1-methylpiperidin-4-yl)-3-phenyl adamantane-1-carboxamide (4):



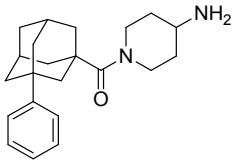
The desired compound was prepared from 3-phenyl-adamantane-1-carboxylic acid and *N*,1-dimethylpiperidin-4-amine using General Procedure 1 omitting cleavage of the Boc-group under acidic conditions. Colorless syrup, Yield: 11 mg (43%); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.36.

3-phenyl-_N_-(piperidin-4-yl) adamantane-1-carboxamide (5):



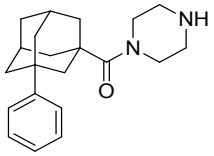
The desired compound was prepared from 3-phenyl-adamantane-1-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 6 mg (49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (br. s., 1H) 7.28 - 7.37 (m, 4H) 7.15 - 7.22 (m, 1H) 5.66 (d, 0.5 H) 5.46 (d, 0.5H) 4.28 (d, 1H) 4.01 (dd, 1H) 3.49 (d, 1H) 2.84 - 3.11 (m, 2 H) 2.26 (br. s., 2 H) 2.10 (d, 1H) 1.99 (br. s., 1H) 1.78 - 1.95 (m, 10H) 1.72 (br. s., 2H); LC/MS *m/z*: calculated for $C_{22}H_{30}N_2O$ $[M+H]^+$ 339.24, found 339.45.

1-[(3-phenyladamantan-1-yl) carbonyl]piperidin-4-amine (6):



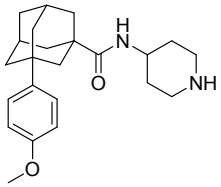
The desired compound was prepared from 3-phenyl-adamantane-1-carboxylic acid and *tert*-butyl *N*-(piperidin-4-yl)carbamate using General Procedure 1. Colorless oil, Yield: 16 mg (15%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 - 7.30 (m, 4H), 7.22 - 7.17 (m, 1H), 4.43 (d, 2H), 2.97 – 2.81 (m, 3H), 2.25 (br. s, 2H), 2.12 (s, 2H), 2.02 (s, 4H), 1.90 (d, 4H), 1.87 – 1.83 (m, 2H), 1.74 (d, 2H), 1.28 – 1.20 (m, 2H); LC/MS *m/z*: calculated for $C_{22}H_{30}N_2O$ $[M+H]^+$ 339.24, found 339.34.

1-[(3-phenyladamantan-1-yl)carbonyl]piperazine (7):



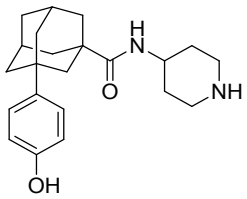
The desired compound was prepared from 3-phenyl-adamantane-1-carboxylic acid and *tert*-butyl piperazine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 8.1 mg (76%); LC/MS *m/z*: calculated for $C_{21}H_{28}N_2O$ $[M+H]^+$ 325.23, found 325.24.

3-(4-methoxyphenyl)-*N*-(piperidin-4-yl)adamantane-1-carboxamide (9):



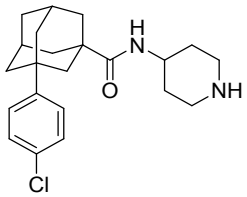
The desired compound was prepared from 3-(4-methoxyphenyl) adamantane-1-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 11.5 mg (36.5%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 6.88 – 6.85 (m, 2H), 5.53 (d, 0.85H), 5.46 (d, 0.15H), 3.93 – 3.85 (m, 1H), 3.79 (s, 3H), 3.15 – 3.10 (m, 2H), 2.88 – 2.85 (m, 0.3H), 2.76 – 2.70 (m, 1.7H), 2.25 (br. s, 2H), 1.95 – 1.89 (m, 4H), 1.87 (s, 4H), 1.85 (d, 4H), 1.72 (br. s, 2H), 1.42 – 1.33 (m, 2H); LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O_2$ $[M+H]^+$ 369.25, found 369.35.

3-(4-hydroxyphenyl)-*N*-(piperidin-4-yl)adamantane-1-carboxamide (10):



The desired compound was prepared from 3-(4-hydroxyphenyl) adamantane-1-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. White solid, Yield: 5.6 mg (20%); LC/MS *m/z*: calculated for $C_{22}H_{30}N_2O_2$ $[M+H]^+$ 355.24, found 355.31.

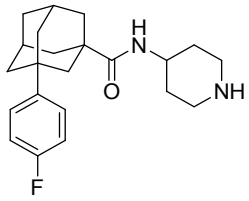
3-(4-chlorophenyl)-*N*-(piperidin-4-yl)adamantane-1-carboxamide (11):



The desired compound was prepared from 3-(4-chlorophenyl) adamantane-1-carboxylic acid and *tert*-butyl 4-amino piperidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 18.5 mg (45%); ^{1}H NMR

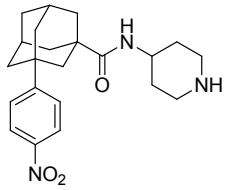
(500 MHz, $CDCl_3$) δ 7.28 (d, 4H), 5.58 (d, 0.7H), 5.46 (d, 0.3H), 3.94 – 3.87 (m, 0.7H), 3.81 – 3.74 (m, 0.3H), 3.16 (d, 1H), 2.88 – 2.72 (m, 4H), 2.26 (br. s, 2H), 1.97 – 1.93 (m, 1H), 1.92 (s, 2H), 1.86 (br. s, 8H), 1.72 (br. s, 2H), 1.48 – 1.33 (m, 2H); LC/MS *m/z*: calculated for $C_{22}H_{29}ClN_2O$ $[M+H]^+$ 373.20, found 373.31.

3-(4-fluorophenyl)-*N*-(piperidin-4-yl)adamantane-1-carboxamide (12):



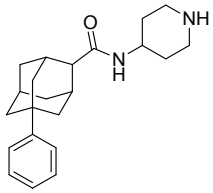
The desired compound was prepared from 3-(4-fluorophenyl) adamantane-1-carboxylic acid and *tert*-butyl 4-amino piperidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 10 mg (24%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 7.02 – 6.97 (m, 2H), 5.59 (d, 0.7H), 5.47 (d, 0.3H), 3.96 – 3.88 (m, 0.7H), 3.82 – 3.74 (m, 0.3H), 3.20 (d, 1H), 2.89 – 2.72 (m, 4H), 2.26 (br. s, 2H), 1.99 – 1.95 (m, 1H), 1.93 (s, 2H), 1.88 – 1.84 (m, 8H), 1.73 (br. s, 2H), 1.54 – 1.45 (m, 1.4H), 1.42 – 1.33 (m, 0.6H); LC/MS *m/z*: calculated for $C_{22}H_{29}FN_2O$ $[M+H]^+$ 357.23, found 357.29.

3-(4-nitrophenyl)-*N*-(piperidin-4-yl)adamantane-1-carboxamide (13):



The desired compound was prepared from 3-(4-nitrophenyl) adamantane-1-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. White solid, Yield: 13.3 mg (30%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, 2H), 7.52 (d, 2H), 5.48 (d, 1H), 3.91 – 3.83 (m, 1H), 3.07 (dt, 2H), 2.70 (td, 2H), 2.30 (br. s, 2H), 1.99 (s, 2H), 1.94 – 1.84 (m, 10H), 1.76 (br. s, 2H), 1.30 (qd, 2H); LC/MS *m/z*: calculated for $C_{22}H_{29}N_3O_3$ $[M+H]^+$ 384.23, found 384.30.

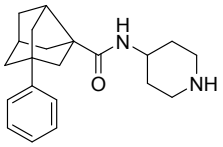
5-phenyl-*N*-(piperidin-4-yl) adamantane-2-carboxamide (14):



The desired compound was prepared from 5-phenyladamantane-2-carboxylic acid and *tert*-butyl 4-amino piperidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 5.3 mg (8%); ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.36 (d, 1H), 7.34-7.23 (m, 3H), 7.13 (q, 1H), 4.04-3.93 (m, 1H), 3.46-3.37 (m, 2H), 3.09 (q,

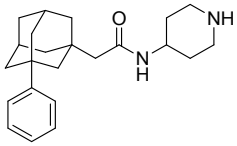
2H), 2.57 (d, 1H), 2.40 (br:s, 2H), 2.22 (d, 1H), 2.13-1.83 (m, 10H), 1.81-1.67 (m, 3H), 1.63 (d, 1H); LC/MS *m/z*: calculated for $C_{22}H_{30}N_2O$ $[M+H]^+$ 339.24, found 339.34.

1-phenyl-*N*-(piperidin-4-yl)tricyclo [3.3.1.0^{3,7}] nonane-3-carboxamide (15):



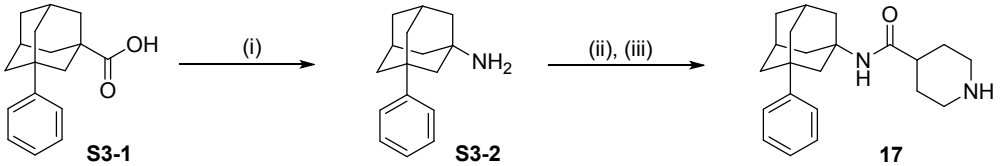
The desired compound was prepared from 1-phenyltricyclo [3.3.1.0^{3,7}]nonane-3-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 17.6 mg (27%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.26 (m, 4 H), 7.21 - 7.18 (m, 1 H), 5.48 (d, 1 H), 3.88 – 3.86 (m, 1 H), 3.05 (d, 2 H), 2.69 (t, 2 H), 2.31-2.29 (m, 1 H), 1.91-1.79 (m, 5 H), 1.80-1.76 (m, 3 H), 1.62 (br. s., 2 H), 1.57 (br. s., 2 H), 1.47 (br. s., 2 H), 1.33-1.25 (m, 2 H); LC/MS *m/z*: calculated for $C_{21}H_{28}N_2O$ $[M+H]^+$ 325.23, found 325.32.

2-(3-phenyladamantan-1-yl)-*N*-(piperidin-4-yl)acetamide (16):



The desired compound was prepared from 2-(3-phenyladamantan-1-yl)acetic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 7.8 mg (45%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.29 (m, 4 H), 7.17 (t, 1 H), 5.24 (d, 1 H), 3.92 – 3.86 (m, 1 H), 3.05 (d, 2 H), 2.69 (t, 2 H), 2.18 (br. s., 1 H), 1.98 (s, 2 H), 1.92 – 1.76 (m, 10 H), 1.70 – 1.64 (m, 6 H), 1.34 – 1.25 (m, 2 H); LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.26, found 353.39.

Scheme S3. Synthesis of compound **17**.



S3-1 **S3-2** **17**

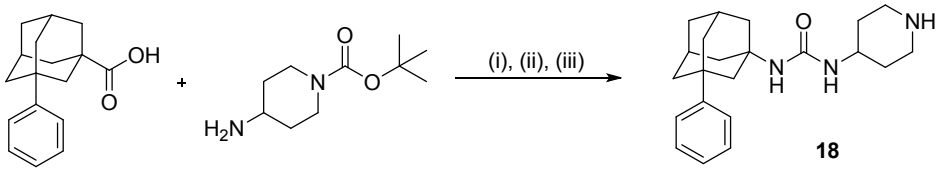
Reagents and Conditions: (i) DPPA, Et_3N, reflux; (ii) *N*-BOC-piperidine-4-carboxylic acid, EDCI·HCl, DIEA; (iii) TFA, DCM, RT.

Step1: 3-phenyladamantan-1-amine (**S3-2**). To a solution of 3-phenyladamantane-1-carboxylic acid (0.064 g, 0.25 mmol) in toluene (0.75 mL) was added Et_3N (0.04 ml, 0.29 mmol) followed by diphenylphosphorylazide (0.060 ml, 0.28 mmol) and the resulting reaction mixture was stirred at 70 ^{0}C for 2 h. After cooling rt, aq. $NaHCO_3$ solution was added and the mixture was stirred for 0.5 h, and extracted

with ethyl acetate (2 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated to give the title compound which was used without purification in the next step.

Step 2: *N*-(3-phenyladamantan-1-yl)piperidine-4-carboxamide (**17**). To a solution of *N*-BOC-piperidine-4-carboxylic acid (0.057 g, 0.25 mmol) in DCM (1 mL) was added EDCI·HCl (0.059 g, 0.30 mmol) followed by DIEA (0.06 ml, 0.29 mmol). The mixture was stirred for 0.5 h, then 3-phenyl-adamantane-1-amine obtained from step 1 was added and the resulting mixture was stirred for 3 h, then TFA was added and stirring was continued for 2 h. The solvent was evaporated and the crude residue was purified by preparative HPLC to give *N*-(3-phenyladamantan-1-yl)piperidine-4-carboxamide (1.5 mg, 1.8%) as a syrup. LC/MS *m/z*: calculated for $C_{22}H_{30}N_2O$ $[M+H]^+$ 339.24, found 339.40

Scheme S4. Synthesis of compound **18**.

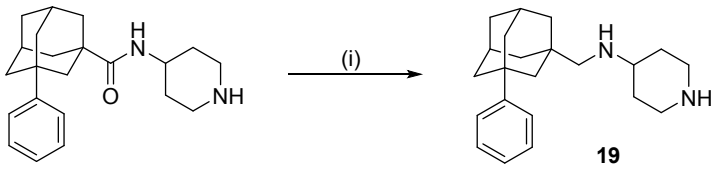


18

Reagents and Conditions: (i) DPPA, Et_3N, reflux; (ii) *tert*-butyl-4-aminopiperidine-1-carboxylate; (iii) TFA, DCM, RT.

3-(3-phenyladamantan-1-yl)-1-(piperidin-4-yl)urea (18). To a solution of 3-phenyladamantane-1-carboxylic acid (0.064 g, 0.25mmol) in toluene (0.75 mL) was added Et_3N (0.04 ml, 0.29 mmol) followed by diphenylphosphorylazide (0.060 ml, 0.28 mmol) and the resulting reaction mixture was stirred at 70^0C for 2 h. It was cooled to room temperature, then *tert*-butyl-4-aminopiperidine-1-carboxylate (0.050 g, 0.25 mmol) was added and the mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in DCM (0.5 mL). TFA (0.2 mL) was added and the mixture was stirred for 2h. The solvent was evaporated and the crude residue was purified by preparative HPLC to give 3-(3-phenyladamantan-1-yl)-1-(piperidin-4-yl)urea (9.1mg, 10.3%) as an off- white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.26 (m, 4 H), 7.18 (t, 1 H), 4.14 (br. s., 2 H), 3.63 – 3.58 (m, 1 H), 3.02 (d, 2 H), 2.65 (t, 2 H), 2.26 (br. s., 2 H), 2.13 (br. s., 2 H), 2.03 – 1.83 (m, 8 H), 1.76 – 1.65 (m, 5 H), 1.28 – 1.21 (m, 2 H); LC/MS *m/z*: calculated for $C_{22}H_{31}N_3O$ $[M+H]^+$ 354.25, found 354.36.

Scheme S5. Synthesis of compound **19**.

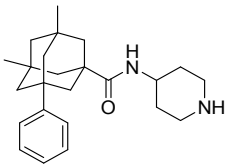


19

Reagents and Conditions: (i) $LiAlH_4$, THF, reflux.

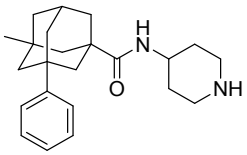
***N*-((3-phenyladamantan-1-yl)methyl)piperidin-4-amine (19)**. To a suspension of $LiAlH_4$ (0.030 g, 0.78 mmol) in THF (1 mL) cooled to 0 ^{0}C was added a solution of 3-phenyl-N-(piperidin-4-yl)adamantane-1-carboxamide (0.060 g, 0.14 mmol) in THF (1 mL) dropwise. The resulting reaction mixture was brought to room temperature and then refluxed for 6 h, cooled to 0 ^{0}C and quenched with sat. aq. Na_2SO_4 solution, filtered and the solvent was evaporated to give a crude residue that was purified using preparative HPLC to give the title compound as pale yellow syrup. Yield : 0.012 g (28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.38 (m, 4 H) 7.12 - 7.20 (m, 1 H) 3.19 - 3.33 (m, 1 H) 3.13 (s, 1 H) 2.68 - 2.88 (m, 3 H) 2.54 - 2.68 (m, 1 H) 2.25 - 2.37 (m, 2 H) 2.16 (br. s., 2 H) 1.99 (d, 1 H) 1.75 - 1.92 (m, 4 H) 1.38 - 1.75 (m, 10 H); LC/MS *m/z*: calculated for $C_{22}H_{32}N_2$ $[M+H]^+$ 325.26, found 325.34.

3,5-dimethyl-7-phenyl-*N*-(piperidin-4-yl)adamantane-1-carboxamide (20):



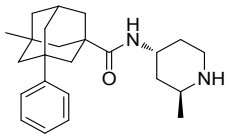
The desired compound was prepared from 3,5-dimethyl-7-phenyladamantane-1-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. White solid, Yield: 4.3 mg (11%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 2H), 7.34 – 7.30 (m, 2H), 7.22 – 7.18 (m, 1H), 5.46 (d, 1H), 3.92 – 3.84 (m, 1H), 3.08 (dt, 2H), 2.69 (dd, 2H), 1.94 – 1.88 (m, 2H), 1.83 (s, 2H), 1.61 – 1.48 (m, 8H), 1.35 – 1.24 (m, 2H), 1.22 (s, 2H), 0.96 (s, 6H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.36.

***rac*-3-methyl-5-phenyl-*N*-(piperidin-4-yl)adamantane-1-carboxamide (21)**:



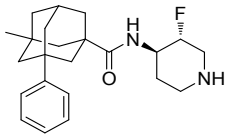
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl 4-amino piperidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 11.4 mg (57%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 4H), 7.21 – 7.16 (m, 1H), 5.73 (d, 0.6H), 5.50 (dd, 0.4H), 4.28 (d, 0.4H), 4.07 – 3.91 (m, 1H), 3.60 (d, 0.6H), 3.42 (d, 1H), 3.03 –2.86 (m, 2H), 2.30 (br. s, 1H), 2.23 –2.00 (m, 2H), 1.91 – 1.71 (m, 8H), 1.61 (br. s, 2H), 1.55 (br. s, 2H), 1.47 (br. s, 2H), 0.93 (s, 3H); LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.26, found 353.39.

***rac-trans*-3-methyl-*N*-[(2*S*,4*R*)-2-methylpiperidin-4-yl]-5-phenyladamantane-1-carboxamide (22)**:



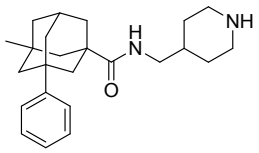
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *trans-tert*-butyl-4-amino-2-methylpiperidine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 34.1 mg (62%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.37 (m, 4H) 7.14 - 7.21 (m, 1H) 5.78 (d, 1H) 4.17 (dt, 1 H) 3.44 (s, 3H) 2.70 - 3.02 (m, 3H) 2.29 (dt, 1H) 2.22 (br. s., 2H) 1.52 - 1.90 (m, 9H) 1.38 - 1.51 (m, 2H) 1.10 (d, 2H) 0.93 (s, 3H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.35;

***rac-trans-N*-3-fluoropiperidin-4-yl]-3-methyl-5-phenyladamantane-1-carboxamide (23)**:



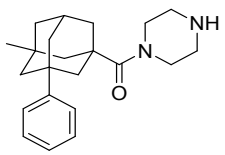
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *trans-tert*-butyl-4-amino-3-fluoropiperidine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 11.8 mg (28%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.39 (m, 4H) 7.13 - 7.22 (m, 1H) 5.62 (d, 1 H) 4.19 - 4.37 (m, 0.5H) 4.05-4.17 (m, 0.5H) 3.98-4.03 (m, 1H) 3.22-3.86 (m, 1H) 2.84 - 2.98 (m, 1H) 2.59 - 2.84 (m, 1H) 2.25 - 2.34 (m, 1H) 1.99 - 2.17 (m, 2H) 1.70 - 1.93 (m, 6H) 1.51 - 1.67 (m, 4H) 1.19 - 1.40 (m, 2H) 0.93 (s, 3H); LC/MS *m/z*: calculated for $C_{23}H_{31}FN_2O$ $[M+H]^+$ 371.25, found 371.40.

***rac*-3-methyl-5-phenyl-*N*-(piperidin-4-ylmethyl) adamantane-1-carboxamide (24)**:



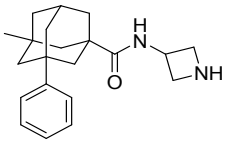
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate using General Procedure 1. The product was purified by flash chromatography on silica gel using a mixture of 10% methanol and 0.1% NH4OH in DCM. Colorless oil, Yield: 9.2 mg (26%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.21 – 7.17 (m, 1H), 5.92 (t, 1H), 3.39 (d, 2H), 3.18 (t, 2H), 2.83 (td, 2H), 2.33 – 2.29 (m, 1H), 1.93 – 1.75 (m, 10H), 1.62 (s, 2H), 1.58 (s, 2H), 1.57 – 1.53 (m, 1H), 1.48 (s, 2H), 0.94 (s, 3H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.38; calculated for $C_{24}H_{34}N_2O$ $[2M+H]^+$ 733.54, found 733.62.

***rac*-1-[(3-methyl-5-phenyl adamantan-1-yl)carbonyl] piperazine (25)**:



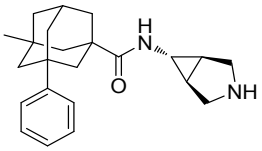
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl piperazine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 4.7 mg (22%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 4H), 7.22 – 7.18 (m, 1H), 3.72 – 3.69 (m, 2H), 2.90 – 2.87 (m, 2H), 2.32 – 2.28 (m, 1H), 2.10 – 1.79 (m, 10H), 1.73 (d, 2H), 1.61 (s, 2H), 1.48 (s, 2H), 0.94 (s, 3H); LC/MS *m/z*: calculated for $C_{22}H_{30}N_2O$ $[M+H]^+$ 339.24, found 339.42; calculated for $C_{22}H_{30}N_2O$ $[2M+H]^+$ 677.48, found 677.63.

***rac*-*N*-(azetidin-3-yl)-3-methyl-5-phenyl adamantane-1-carboxamide (26)**:



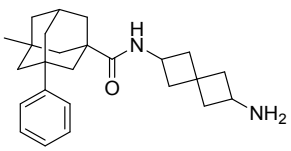
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl 3-aminoazetidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 3.4 mg (16%); LC/MS *m/z*: calculated for $C_{21}H_{28}N_2O$ $[M+H]^+$ 325.23, found 325.32; calculated for $C_{21}H_{28}N_2O$ $[2M+H]^+$ 649.45, found 649.59.

***rac*-*N*-[(1*R*,5*S*)-3-azabicyclo[3.1.0]hexan-6-yl]-3-methyl-5-phenyladamantane-1-carboxamide (27)**:



The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl (1*R*,5*S*,6*S*)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate using General Procedure 1.Colorless oil, Yield: 3.7 mg (15%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.21 – 7.17 (m, 1H), 6.07 (br. s, 1H), 3.53 (d, 2H), 3.45 (d, 2H), 2.77 (br. s, 1H), 2.31 – 2.27 (m, 1H), 1.88 (br. s, 2H), 1.85 – 1.70 (m, 6H), 1.60 (s, 2H), 1.52 (br. s, 2H), 1.46 (br. s, 2H), 0.92 (s, 3H); LC/MS *m/z*: calculated for $C_{23}H_{30}N_2O$ $[M+H]^+$ 351.24, found 351.29.

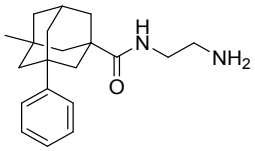
***rac*-*N*-{6-aminospiro [3.3] heptan-2-yl}-3-methyl-5-phenyladamantane-1-carboxamide (28)**:



The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl *N*-{6-aminospiro[3.3]heptan-2-yl}carbamate using General Procedure 1. The product was purified by flash chromatography on silica gel using a mixture of 10% methanol and 0.1% NH4OH in DCM. Colorless oil, Yield: 7 mg (20%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (br. s, 2H), 7.37 – 7.27 (m, 4H), 7.21 – 7.14 (m, 1H), 6.25 – 6.14 (m, 0.6H), 5.76 – 5.69 (m, 0.4H), 4.32 – 4.13 (m, 1H), 3.88 – 3.72 (m, 1H), 2.55 – 2.27 (m,

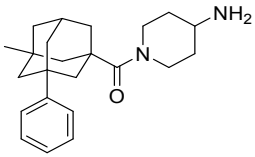
7H), 1.94 –1.76 (m, 8H), 1.61 – 1.51 (m, 4H), 1.49 – 1.41 (m, 2H), 0.93 (s, 1.2H), 0.91 (s, 1.8H); LC/MS *m/z*: calculated for $C_{25}H_{34}N_2O$ $[M+H]^+$ 379.27, found 379.31.

***rac-N*-(2-aminoethyl)-3-methyl-5-phenyladamantane-1-carboxamide (29)**:



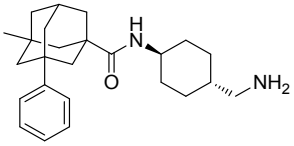
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl *N*-(2-aminoethyl)carbamate using General Procedure 1. The product was purified by flash chromatography on silica gel eluting with 100% EtOAc, followed by 5% methanol in DCM. Colorless oil, Yield: 5.7 mg (16%); LC/MS *m/z*: calculated for $C_{20}H_{28}N_2O$ $[M+H]^+$ 313.23, found 313.47.

***rac*-(4-aminopiperidin-1-yl)(3-methyl-5-phenyladamantan-1-yl)methanone (30)**:



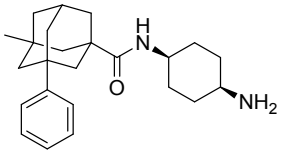
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl (piperidin-4-yl) carbamate using General Procedure 1. Colorless oil, Yield: 2.8 mg (7%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.22 – 7.17 (m, 1H), 4.42 (d, 2H), 2.97 – 2.83 (m, 3H), 2.32 – 2.27 (m, 1H), 2.10 – 1.91 (m, 4H), 1.88 – 1.78 (m, 4H), 1.73 (d, 2H), 1.61 (s, 2H), 1.48 (br. s, 2H), 1.29 – 1.22 (m, 2H), 0.94 (s, 3H); LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.26, found 353.39.

***rac-trans-N*-[4-(aminomethyl) cyclohexyl]-3-methyl-5-phenyladamantane-1-carboxamide (31)**:



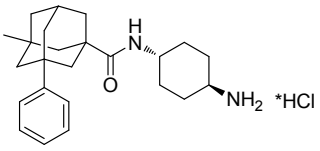
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *trans-tert*-butyl *N*-[(4-aminocyclohexyl)methyl]carbamate using General Procedure 1. The product was purified by flash chromatography on silica gel using a mixture of 10% methanol and 0.1% NH4OH in DCM. Colorless oil, Yield: 11.8 mg (30%). The compound purity was ~92% according to LC-MS spectrum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (br. s, 2H), 7.37 – 7.27 (m, 4H), 7.21 – 7.15 (m, 1H), 5.72 (d, 0.7H), 5.45 (d, 0.3H), 3.78 – 3.61 (m, 1H), 3.00 – 2.91 (m, 2H), 2.90 – 2.80 (m, 1H), 2.33– 2.24 (m, 1H), 2.01 – 1.69 (m, 10H), 1.61 – 1.51 (m, 4H), 1.49 – 1.41 (m, 2H), 1.24 – 1.07 (m, 4H), 0.93 (s, 0.9H), 0.91 (s, 2.1H); LC/MS *m/z*: calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.29, found 381.39.

***rac-cis-N*-(4-aminocyclohexyl)-3-methyl-5-phenyl adamantane-1-carboxamide (32)**:



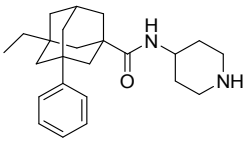
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *cis*-*tert*-butyl *N*-(4-aminocyclohexyl) carbamate using General Procedure 1. The product was purified by flash chromatography on silica gel eluting with 100% EtOAc, followed by 5% methanol in DCM. Colorless oil, Yield: 3 mg (8%); ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.37 (d, 2H), 7.28 (t, 2H), 7.16 (t, 1H), 3.80 (m, 1H), 3.04 (m, 1H), 2.29 (m 1H), 1.90 (t, 3H), 1.82 (t, 3H), 1.75-1.67 (m, 4H), 1.66-1.58 (m, 8H), 1.51 (br:s, 2H), 0.96 (s, 3H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.43.

***rac-trans-N*-(4-aminocyclohexyl)-3-methyl-5-phenyl adamantane-1-carboxamide hydrochloride (33)**:



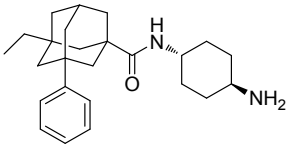
The desired compound was prepared from *rac*-3-methyl-5-phenyladamantane-1-carboxylic acid and *trans*-*tert*-butyl *N*-(4-aminocyclohexyl)carbamate using General Procedure 1. For this example, HCl in MeOH was used for the Boc-group cleavage. White solid, Yield: 7 mg (18%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (br. s, 3H), 7.36 (d, 2H), 7.30 (t, 2H), 7.20 (d, 1H), 7.16 (t, 1H), 3.54 – 3.47 (m, 1H), 2.91–2.86 (m,1H), 2.20 – 2.15 (m, 1H), 1.97–1.90 (m, 2H), 1.81 – 1.64 (m, 8H), 1.54 – 1.44 (m, 4H), 1.40 (br. s, 2H), 1.37 – 1.22 (m, 4H), 0.87 (s, 3H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.42; calculated for $C_{24}H_{34}N_2O$ $[2M+H]^+$ 733.54, found 733.73.

***rac*-3-ethyl-5-phenyl-*N*-(piperidin-4-yl)adamantane-1-carboxamide (34)**:



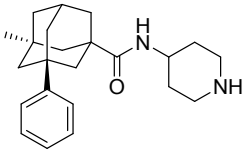
The desired compound was prepared from *rac*-3-ethyl-5-phenyladamantane-1-carboxylic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate using General Procedure 1. Colorless oil, Yield: 6 mg (37%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H), 7.22 – 7.16 (m, 1H), 5.70 (d, 0.7H), 5.48 (d, 0.3H), 4.29 (d, 0.3H), 4.08 – 3.84 (m, 1H), 3.48 (d, 0.7H), 3.40 – 3.21 (m, 1H), 3.03 – 2.88 (m, 1.4H), 2.68 – 2.53 (m, 0.6H), 2.32 (br. s, 1H), 2.15 –2.05 (m, 1H), 2.00 – 1.75 (m, 9H), 1.59 (br. s, 2H), 1.56 – 1.52 (m, 2H), 1.46 (br. s, 2H), 1.26 (q, 2H), 0.84 (t, 3H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.40.

***rac-trans-N*-(4-aminocyclo hexyl)-3-ethyl-5-phenyl adamantane-1-carboxamide (35)**:



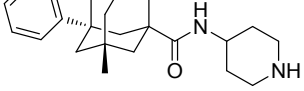
The desired compound was prepared from *rac*-3-ethyl-5-phenyladamantane-1-carboxylic acid and *trans-tert*-butyl *N*-(4-amino cyclohexyl)carbamate using General Procedure 1. Colorless oil, Yield: 6.1 mg (24%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (br. s, 2H), 7.38– 7.27 (m, 4H), 7.21 – 7.15 (m, 1H), 5.73 – 5.63 (m, 0.6H), 5.40 – 5.32 (d, 0.4H), 3.79 – 3.65 (m, 1H), 3.36 – 3.06 (m, 1H), 2.33 – 2.21 (m, 2H), 2.02 –1.76 (m, 11H), 1.60 – 1.50 (m, 4H), 1.48 – 1.40 (m, 2H), 1.30 – 1.14 (m, 4H), 0.82 (td, 3H); LC/MS *m/z*: calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.29, found 381.35.

(1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyl-*N*-(piperidin-4-yl) adamantane-1-carboxamide (36):



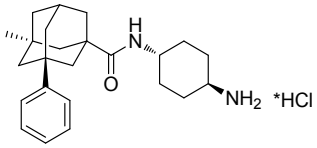
The desired compound was prepared from (1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyl adamantane-1-carboxylic acid and *tert*-butyl 4-amino piperidine-1-carboxylate using General Procedure 1. Colorless syrup,Yield: 15.6 mg (64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 4H), 7.21 – 7.16 (m, 1H), 5.73 (d, 0.6H), 5.50 (dd, 0.4H), 4.28 (d, 0.4H), 4.07 – 3.91 (m, 1H), 3.60 (d, 0.6H), 3.42 (d, 1H), 3.03 –2.86 (m, 2H), 2.30 (br. s, 1H), 2.23 –2.00 (m, 2H), 1.91 – 1.71 (m, 8H), 1.61 (br. s, 2H), 1.55 (br. s, 2H), 1.47 (br. s, 2H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.71, 149.76, 128.45, 126.16, 125.10, 50.82, 49.38, 46.67, 45.57, 45.55, 44.49, 42.87, 42.76, 41.52, 38.08, 37.85, 33.58, 32.43, 31.55, 30.84, 29.65; LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.26, found 353.38; HRMS (ESI): calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.2587, found 353.2585.

(1*R*,3*S*,5*S*,7*R*)-3-methyl-5-phenyl-*N*-(piperidin-4-yl) adamantane-1-carboxamide (37):



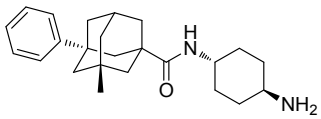
The desired compound was prepared from (1*R*,3*S*,5S,7*R*)-3-methyl-5-phenyl adamantane-1-carboxylic acid and *tert*-butyl 4-amino piperidine-1-carboxylate using General Procedure 1. Colorless syrup, Yield: 19 mg (73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.25 (m, 4 H), 7.21 - 7.18 (m, 1 H), 5.48 (d, 1 H), 3.94 – 3.92 (m, 1 H), 3.11 (d, 2 H), 2.87 (t, 1 H), 2.75 (t, 2 H), 2.70 (br. s., 2 H), 2.50 (br. s., 1 H), 2.19 (d, 1 H), 2.08 – 2.05 (m, 2 H), 1.99 – 1.92 (m, 4 H), 1.84 – 1.82 (m, 5 H), 1.69 – 1.67 (m, 1 H), 1.41 – 1.37 (m, 2 H); LC/MS *m/z*: calculated for $C_{23}H_{32}N_2O$ $[M+H]^+$ 353.26, found 353.38.

(1*S*,3*R*,5*R*,7*S*)-*trans*-*N*-(4-aminocyclohexyl)-3-methyl-5-phenyladamantane-1-carboxamide hydrochloride (38):



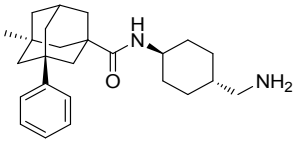
The desired compound was prepared from (1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyl adamantane-1-carboxylic acid and *trans-tert*-butyl *N*-(4-aminocyclohexyl)carbamate using General Procedure 1. For this example, HCl in MeOH was used for the Boc-group cleavage. White solid, Yield: 13 mg (65%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (br. s, 3H), 7.36 (dd, 2H), 7.30 (t, 2H), 7.20 – 7.15 (m, 2H), 3.54 – 3.47 (m, 1H), 2.93 – 2.86 (m,1H), 2.20 – 2.15 (m, 1H), 1.94 – 1.89 (m, 2H), 1.81 – 1.64 (m, 8H), 1.55 – 1.44 (m, 4H), 1.40 (br. s, 2H), 1.37 – 1.23 (m, 4H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.80, 149.82, 128.06, 125.62, 124.75, 56.20, 48.69, 48.66, 46.50, 44.72, 43.47, 42.17, 41.73, 40.85, 37.22, 30.86, 30.54, 29.77, 29.20, 28.96; LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.40; HRMS (ESI): calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.2744, found 367.2742.

(1*R*,3*S*,5*S*,7*R*)-*trans*-*N*-(4-aminocyclohexyl)-3-methyl-5-phenyladamantane-1-carboxamide (39):



The desired compound was prepared from (1*R*,3*S*,5*S*,7*R*)-3-methyl-5-phenyl adamantane-1-carboxylic acid and *trans-tert*-butyl *N*-(4-aminocyclohexyl)carbamate using General Procedure 1. White solid, Yield: 10 mg (50%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38– 7.27 (m, 4H), 7.16 (t, 1H), 7.08 (d, 1H), 3.54 – 3.43 (m, 1H), 2.46–2.41 (m,1H), 2.20 – 2.14 (m, 1H), 1.82– 1.59 (m, 10H), 1.54 – 1.44 (m, 4H), 1.39 (br. s, 2H), 1.30 – 1.16 (m, 2H), 1.09 – 0.96 (m, 2H), 0.87 (s, 3H); LC/MS *m/z*: calculated for $C_{24}H_{34}N_2O$ $[M+H]^+$ 367.27, found 367.44.

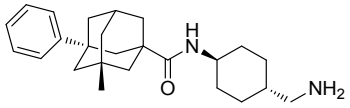
(1*S*,3*R*,5*R*,7*S*)-*trans*-*N*-[4-(aminomethyl)cyclohexyl]-3-methyl-5-phenyl adamantane-1-carboxamide (40):



The desired compound was prepared from (1*S*,3*R*,5*R*,7*S*)-3-methyl-5-phenyl adamantane-1-carboxylic acid and *trans-tert*-butyl *N*-[(4-aminocyclohexyl)methyl]carbamate using General Procedure 1. Colorless syrup, Yield: 16.5 mg (63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (br. s, 2H), 7.37 – 7.27 (m, 4H), 7.21 – 7.15 (m, 1H), 5.72 (d, 0.7H), 5.45 (d, 0.3H), 3.78 – 3.61 (m, 1H), 3.00 – 2.91 (m, 2H), 2.90 – 2.80 (m, 1H), 2.33–2.24 (m, 1H), 2.01 – 1.69 (m, 10H), 1.61 – 1.51 (m, 4H), 1.49 – 1.41 (m, 2H), 1.24 – 1.07 (m, 4H), 0.93 (s, 0.9H), 0.91 (s, 2.1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.71, 149.81, 128.44, 126.14, 125.10, 49.40, 48.51, 48.34, 45.61, 44.53, 42.89, 42.74, 41.55, 40.49, 38.10, 37.87, 33.01, 31.54, 30.84, 29.66, 29.54; LC/MS

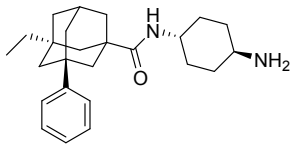
m/z: calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.29, found 381.41; HRMS (ESI): calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.2900, found 381.2897.

(1*R*,3*S*,5*S*,7*R*)-*trans*-*N*-[4-(aminomethyl)cyclohexyl]-3-methyl-5-phenyl adamantane-1-carboxamide (41):



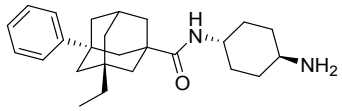
The desired compound was prepared from (1*R*,3*S*,5*S*,7*R*)-3-methyl-5-phenyl adamantane-1-carboxylic acid and *trans*-*tert*-butyl N-[(4-aminocyclohexyl)methyl]carbamate using General Procedure 1. Colorless syrup, Yield: 16.7 mg (59%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.21 – 7.18 (m, 1H), 5.39 (d, 1H), 3.75 – 3.68 (m, 1H), 2.54 (d, 2H), 2.31 – 2.28 (m, 1H), 1.99 (d, 2H), 1.92-1.74 (m, 8H), 1.61 – 1.54 (m, 7H), 1.47 (br. s., 2 H), 1.12 – 1.04 (m, 4H), 0.94 (s, 3H); LC/MS *m/z*: calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.29, found 381.39.

(1*S*,3*R*,5*R*,7*S*)-*trans*-*N*-(4-aminocyclohexyl)-3-ethyl-5-phenyladamantane-1-carboxamide (42):



The desired compound was prepared from (1*S*,3*R*,5*R*,7*S*)-3-ethyl-5-phenyladamantane-1-carboxylic acid and *trans*-*tert*-butyl *N*-(4-aminocyclohexyl)carbamate using General Procedure 1. Colorless syrup, Yield: 14.2 mg (42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (br. s, 2H), 7.38– 7.27 (m, 4H), 7.21 – 7.15 (m, 1H), 5.73 – 5.63 (m, 0.6H), 5.40 – 5.32 (d, 0.4H), 3.79 – 3.65 (m, 1H), 3.36 – 3.06 (m, 1H), 2.33 – 2.21 (m, 2H), 2.02 –1.76 (m, 11H), 1.60 – 1.50 (m, 4H), 1.48 – 1.40 (m, 2H), 1.30 – 1.14 (m, 4H), 0.82 (td, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.97, 149.94, 128.46, 126.16, 125.10, 50.20, 47.82, 47.08, 44.83, 43.26, 42.62, 41.85, 40.24, 38.46, 37.70, 36.27, 35.45, 34.08, 32.10, 29.52, 7.21; LC/MS *m/z*: calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.29, found 381.42; HRMS (ESI): calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.2900, found 381.2896.

(1*R*,3*S*,5*S*,7*R*)-*trans*-*N*-(4-aminocyclohexyl)-3-ethyl-5-phenyladamantane-1-carboxamide (43):



The desired compound was prepared from (1*R*,3*S*,5*S*,7*R*)-3-ethyl-5-phenyl adamantane-1-carboxylic acid and *trans*-*tert*-butyl *N*-(4-aminocyclohexyl)carbamate using General Procedure 1. Colorless syrup, Yield: 15.8 mg (46%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38– 7.30 (m, 4H), 7.21 – 7.18 (m, 1H), 5.38 (d, 1H), 3.74 – 3.69 (m, 1H), 2.66 – 2.61 (m, 1H), 2.32 – 2.31 (m, 1H), 1.96 (d, 2H), 1.89-1.78 (m, 10H), 1.59 (br. s., 2 H), 1.54 (d, 2 H), 1.46 (br. s., 2 H), 1.26 – 1.12 (m, 6H), 0.84 (t, 3H); LC/MS *m/z*: calculated for $C_{25}H_{36}N_2O$ $[M+H]^+$ 381.29, found 381.42.

3. Ebola GP protein expression, purification, crystallization and structure determination

The Ebola GP protein was produced as a single polypeptide as described by Zhao *et al*.[8] Briefly, the expression construct contains two linked domains with amino acids 32-312 linked to amino acids 464-632 with mutations T42A and H613A, and the foldon trimerization sequence with a 6x His tag at the C-terminus. Transiently transfected HEK293 cells (5L) were growth in the presence of 5 uM kifunensin to reduce complex glycosylation. After 5 days the conditioned media was collected, then concentrated 5-fold and buffer exchanged by tangential flow filtration into 1X PBS, pH 7.4. The protein was purified by Ni affinity chromatography. After size exclusion chromatography the protein was concentrated to 4.98 mg/ml for crystallization trials.

Apo protein was crystallized in vapor diffusion sitting drop trays with 0.2 ul protein plus 0.2 ul well solution at 14 ˚C. Crystals were initially obtained from theJCSG$^+$, condition B8: 0.2 M $MgCl_2$ hexahydrate. 0.1 M Tris-HCl, pH7.0, 10% (w/v) PEG 8000. Initial crystals diffracted to greater than 3Å and optimized with a screen of 0.2 M $MgCl_2$ hexahydrate. 0.1 M Tris-HCl, pH 6.3-7.7, 9-11% (w/v) PEG 8000. Apo crystals were soaked in well solution supplemented with 1 mM ARN0074898 for 4 hours at 14 ˚C. Diffraction data was collected at the APS LS-CAT beamline 21-ID-F equipped with a C(111) monochromator, and a Rayonix MX-300 detector at a wavelength of 0.97872 Å. .

Diffraction data for all complexes were reduced and scaled to 2.75 Å with XDS/XSCALE. The ARN0074898-bound structure was determined by molecular replacement using 6F5U as a starting model and the programs Phaser (McCoy et al., 2007)[9] and Molrep (Vagin and Teplyakov, 2010),[10] in the CCP4 (Collaborative Computational Project, 1994; Winn et al., 2011)[11] and Phenix (Adams et al., 2010)[12] program suite. The structure was refined using iterative cycles restrained refinement with Phenix Refine and manual model-building using COOT (Emsley et al., 2010)[13] and validated using Molprobity. Data collection and refinement statistics are reported in Table S1. The structure was validated using Molprobity (Chen et al., 2010)[14] and deposited in the Protein Data Bank (Berman et al., 2003; Berman et al., 2000).[15,16] as 6NAE.

Table S1. Data collection and refinement statistics for the crystal structure of *EBOV* GP with bound ARN0074898.

Data collection	
PDB code	6NAE
Resolution (Å)	50-2.75 (2.82-2.75)
Space Group	H 3 2
Unit Cell Dimensions	
• a, b, c (Å)	113.250, 113.250, 307.210
• α, β, γ, (˚)	90.00, 99.0, 120.00

No. of unique reflections	20154 (1491)
$R_{,merge}$	6.5 (52.8)
Redundancy	7.4 (7.5)
Completeness (%)	100.0 (100.0)
I/σ	23.09 (4.15)
$CC_{1/2}$	99.9 (94.7)
Refinement	
Resolution (Å)	2.75 (2.81-2.75)
No. of protein atoms	2647
No. of heteroatoms	209
No. of water molecules	88
$R_{working}$ (R_{free})	19.3 (24.0)
R.M.S. deviations	
• Bond lengths (Å)	0.003
• Bond angles (°)	0.641
Ave. B factors (Å^2)	
• Protein	63.42
• Heteroatom	98.55
• Water	55.22
Ramachandran plot	
• Favored region (%)	96.19
• Allowed regions (%)	3.52
• Outlier regions (%)	0.29

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