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Heterocyclic Rimantadine Analogues with Antiviral Activity

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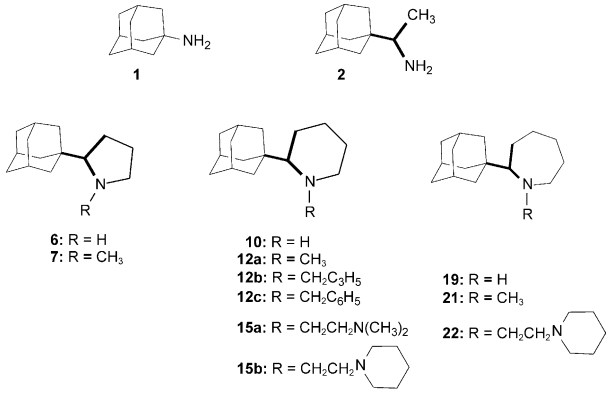
Abstract—2-(1-Adamantyl)pyrrolidines **6**, **7**, 2-(1-adamantyl)piperidines **10**, **12a–c**, **15a**,**b** and 2-(1-adamantyl)hexahydroazepines **19**, **21**, **22** were synthesized and tested for their antiviral activity against influenza A, B viruses and the human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2). The synthetic procedure followed for the preparation of the parent piperidine **10** represents a general method for the synthesis of 2-alkyl- or cycloalkyl-substituted piperidine alkaloids. Parent aminoadamantanes **6**, **10** and **19** contain the 1-aminoethyl pharmacophore group of rimantadine drug **2**, extended into a saturated nitrogen heterocycle: pyrrolidine, piperidine and hexahydroazepine, respectively. The ring size effect in anti-influenza A activity was investigated. Rimantadine analogues **6** and **10** were, respectively, 6- and 4-fold more active than the drug Rimantadine **2**, whereas the hexahydroazepine derivative **19** was inactive. Thus, enlargement from a 5-(pyrrolidine)- or 6-(piperidine)- to a 7-(hexahydroazepine)- membered heterocyclic ring dramatically reduced the anti-influenza virus A activity. Substitution of piperidine **10** with a dialkyaminoethyl group led to the active compounds **15a** and **15b**: compound **15a** was active against influenza A virus whereas both **15a** and **15b** were active against HIV-1.

Introduction

Millions of people each year become infected with the influenza A virus. Influenza A is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, nonproductive cough, sore throat and rhinitis).[1] In some persons the infection can cause pulmonary or cardiac disease or lead to secondary bacterial pneumonia or primary viral pmeumonia. Epidemics of influenza occur during the winter months nearly every year and are responsible for an average of approximately 20,000 deaths per year in the United States.[2] Pandemic lethal influenza A viruses appeared in 1918 ('Spanish' flu), 1957 ('Asian' flu) and 1968 ('Hong Kong' flu).[3] Given that influenza shifts occur every 20–30 years and that a new lethal variant appeared in Hong Kong in 1997,[4] the danger of future influenza A pandemics is real and new more effective drugs are needed.

Amantadine **1** and Rimantadine **2** are *anti*-influenza virus A drugs that inhibit virus replication at micromolar concentrations.[5,6] Many aminoadamantane carbocycles and heterocycles with activity against influenza A virus were synthesized in our laboratory during the past 8 years.[6,7] The antiviral activity of synthetic 2-(1-adamantyl)pyrrolidines **6**, **7**, 2-(1-adamantyl)piperidines **10**, **12a–c**, **15a**,**b** and 2-(1-adamantyl) azepines **19**, **21**, **22** is described in the present paper.



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Parent molecules **6**, **10**, **19** contain the 1-aminoethyl pharmacophore group of drug Rimantadine **2** extended into a pyrrolidine, piperidine or hexahydroazepine heterocycle. Thus, we sought mainly to compare the anti-influenza A virus potency of these structurally modified rimantadines with the activity of Rimantadine **2**. The effect of *N*-dialkylaminoethyl group substitution was also investigated since it appeared to be important for activity against influenza A virus and HIV-1, as was shown previously in preliminary reports.[7c,e]

Results and Discussion

Chemistry

The synthetic protocol used for the synthesis of pyrrolidines was based on the dry distillation of *N*-acylpyrrolidinone **4** in the presence of CaO, as has already been described elsewhere in detail.[7b] From this reaction, 2-(1-adamantyl)-1-pyrroline **5** was obtained which was easily converted to the parent pyrrolidine **6** (Scheme 1). Reductive methylation of pyrrolidine **6** with CH_2O/$NaCNBH_3$[8] afforded the *N*-methyl derivative **7**.

The synthetic route followed for the preparation of piperidines **10**, **12a–c** and **15a**,**b** is illustrated in Scheme 2. Tertiary alcohol **8** was synthesized from ester **7** and 1,4-bis(bromomagnesium)butane.[9] The reaction of tertiary alcohol **8** with trichloroacetic acid or concd sulfuric acid — the last giving the best results — and sodium azide led to tetrahydropyridine **9**, the formation of which was accomplished by cyclopentane ring expansion of the intermediate alkylazide via nitrenium ion.[10] Reduction of imine **9** with $NaBH_4$ gave 2-(1-adamantyl)piperidine **10**. The above described sequence, based on the reaction between 1,4-bis(bromomagnesium)butane and an ester function to form 1-substituted-1-cyclopentanols, can be considered as general route for the synthesis of 2-alkyl- or cycloalkyl-substituted piperidine alkaloid analogues.

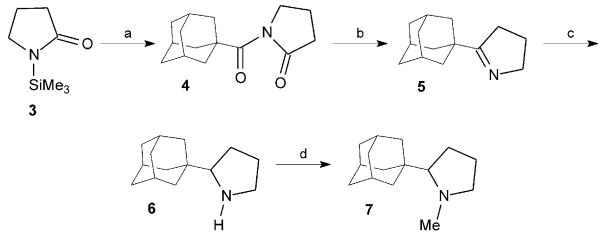
Piperidine **10** was suitably *N*-acylated to afford amides **11a**,**c**,**d**, which were converted to piperidines **12a–c** by reduction with $LiAlH_4$. Alternatively *N*-methylpiperidine **12a** was obtained through $NaBH_4$ reduction of quaternary salt **11b**.[11] *N*-Bromoacetylation of parent piperidine **10** resulted in bromoacetamide **13**, which after treatment with the appropriate secondary amines gave dialkylaminoacetamides **14a**,**b**. These compounds were converted to the corresponding diamines **15a**,**b** by means of $LiAlH_4$.

For the synthesis of the hexahydroazepine derivatives **19** and **21**, **22**, 1-adamantyl lithium was needed. This reagent was prepared from 1-bromoadamantane **16**, using the procedure of Kraus and Siclovan.[12] 1-Adamantyl lithium was then reacted with cyclohexanone to afford the tertiary alcohol **17**.[12] Tetrahydroazepine **18** was obtained from the tertiary alcohol **17** through cyclohexane ring expansion of the intermediate alkylazide. Parent hexahydroazepine **19** and its *N*-substituted derivatives **21**, **22** were obtained according to the procedures used for the preparation of the corresponding piperidine analogues **10**, **12a** and **15a** (Scheme 3).

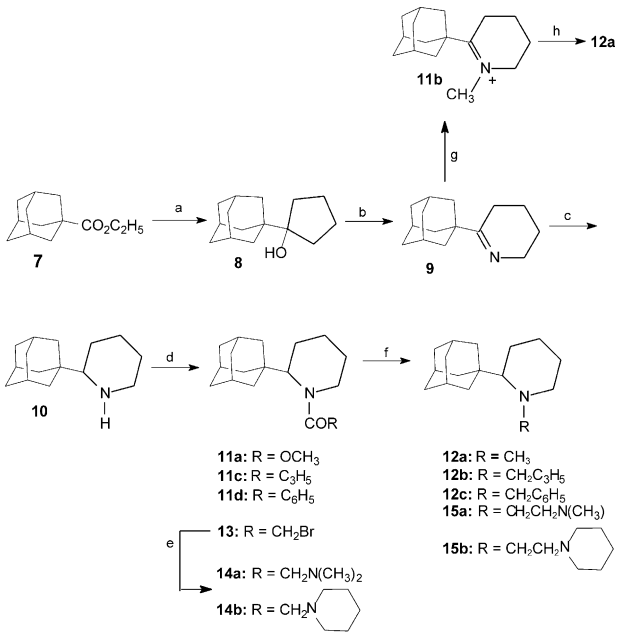
Antiviral activity evaluation

The potency of the new aminoadamantane heterocycles **6**, **7**, **10**, **12a–c**, **15a**,**b**, **19** and **21**, **22**, was examined in vitro against influenza A (H_2N_2) and B viruses, and was compared to the activity of Amantadine **1**, Rimantadine **2** and Ribavirin (Table 1). The compounds were also evaluated against HIV-1 and -2; AZT, Nevirapine (BI-RG587) and Ritonavir (ABT538) were used as controls (Table 1). The sources of viruses, and methods and antiviral assays used were as previously reported.[13–18]

From the MIC_{50} values shown in Table 1, it is obvious that **6**, **10** and, to a lesser extent, **15a** were potent anti-influenza virus A compounds. Compounds **6** and **10**



Scheme 1. Reagents and conditions: (a) 1-AdCOCl, THF, reflux 7 h, (94%); (b) CaO, Δ (35%); (c) $NaBH_4$, MeOH–AcOH (3:1), −30 °C, and then rt 4 h (83%); (d) 37% CH_2O, CH_3CN, 10 min, then $NaCNBH_3$, 30 min, AcOH, 45 min (83%).

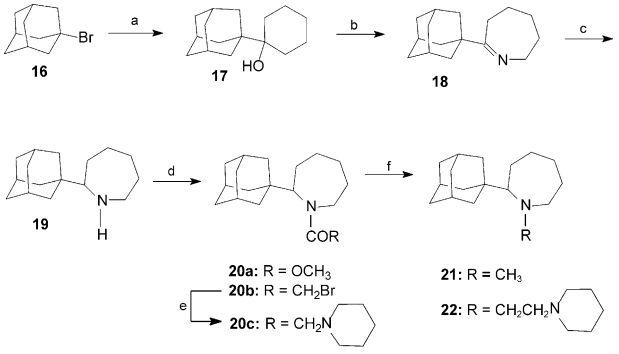


Scheme 2. Reagents and conditions: (a) $BrMg(CH_2)_4MgBr$/THF and then NH_4Cl, H_2O (67%); (b) NaN_3/trichloroacetic acid, $CHCl_3$, 0 °C, 29 h and then concd H_2SO_4, $CHCl_3$, 0 °C, 0.5 h (method A, 51%) or NaN_3/concd H_2SO_4, $CHCl_3$, 0 °C 1.5 h (method B, 73%); (c) $NaBH_4$, MeOH, 1 h, 0 °C, and then rt 20 h (92%); (d) RCOCl, Et_3N, ether or THF, 0 °C, and then rt 24 h (66–91%) for **11a**,**c**,**d** or $BrCH_2COCl$/K_2CO_3, $CHCl_3$/H_2O, 0 °C, and then rt for 2.5 h (52%) for **13** (e) diethylamine or piperidine, benzene, 30 min, 0 °C, and then 24 h rt (76–86%); (f) $LiAlH_4$, THF, reflux (70–89%); (g) MeI, reflux, 3 h (60%); (h) $NaBH_4$, $CHCl_3$/MeOH 2:1, 0 °C, 1 h, and then rt 24 h (87%).

Table 1. Anti-influenza virus A, B and anti-HIV activity and cytotoxicity of heterocyclic Rimantadine analogues — pyrrolidines **6**, **7**, piperidines **10**, **12a–c**, **15a**,**b** and hexahydroazepines **19**, **21**, **22**[a] — in MDCK[b] and MT-4 cells[b]

Compd	Influenza			HIV		
	EC_{50}[c] (μM)		MTC[d] (μM)	EC_{50}[e] (μM)		CC_{50}[f] (μM)
	A H_2N_2[b]	B		HIV-1	HIV-2	
6	2.5	>1035	1035	—	—	—
7	>196	>196	196	—	—	—
10	3.3	>978	978	>403	>403	403
12a	>978	>928	928	>415	>415	413
12b	244	>162	162	75.2	>265	263
12c	522	>724	145	>64	>694	63
15a	51.3	>616	616	40.8	>276	275
15b	>561	>561	561	3.6	>54	53
19	186	>186	186	>101	>101	101
21	>39	>35	39	>281	>281	281
22	>840	>840	840	>66	>6.6	6.6
Amantadine, 1	45	—	>1333	—	—	—
Rimantadine, 2	13.9	—	>1160	—	—	—
Ribavirin	22.1	19.9	>710	—	—	—
AZT	—	—	—	0.001	0.002	36.8
Nevirapine	—	—	—	0.05	>75.1	75.1
Ritonavir	—	—	—	0.06	0.14	>14.2

[a]Aminoadamantanes **6**, **7**, **10**, **12a–c**, **15a**,**b**, **19**, **21**, **22** were tested as hydrochlorides or fumarate salts.
[b]Abbreviations and strains used: MDCK, Madin–Darby canine kidney cells, human epithelial cells; influenza A H2N2 (A2 Japan/305/57); MT-4 represents a human T-4 lymphocytic cell line.
[c]Concentration required to reduce virus-induced CPE in MDCK cells by 50%, as determined by the MTS method.
[d]Minimal toxic concentration or concentration that causes microscopically detectable toxicity in virus infected cultures.
[e]50% Effective concentration, or concentration which inhibited virus-induced cytopathogenicity by 50%.
[f]50% Cytotoxic concentration, or concentration which inhibited MT-4 cell growth by 50%, as compared with control cultures. All data represent mean values for at least two separate experiments.



Scheme 3. Reagents and conditions: (a) (i) Li/THF, sonication, (ii) cyclohexanone, THF, 0 °C 5 h, and then MeOH–H_2O 1:1 (72%); (b) NaN_3/concd. H_2SO_4, $CHCl_3$, 0 °C 1.5 h (30%) (c) $NaBH_4$, MeOH, 0 °C 1 h, and then rt 2 h (73%); (d) RCOCl, Et_3N, ether or THF, rt 24 h (84–94%) for **21a** or $BrCH_2COCl/K_2CO_3$, $CHCl_3/H_2O$, 0 °C 3 h, rt for 30 min (86%) for **21b** (e) piperidine, benzene, 30 min 0 °C, 24 h rt (90%); (f) $LiAlH_4$, THF, reflux (73% for **22** and 96% for **23**).

were, respectively, 18- and 14-fold more potent than Amantadine **1**, and 9 and 7 times more potent than Ribavirin, whereas **15a** proved equipotent to Amantadine **1** and was 2.3 times less potent than Ribavirin.

Compounds **6**, **10** and **19** contain a 1-aminoethyl pharmacophore group of Rimantadine **2** extended into a saturated nitrogen heterocycle: pyrrolidine, piperidine and hexahydroazepine, respectively. Pyrrolidine **6** was somewhat more potent than the piperidine analogue **10**, but both the heterocyclic Rimantadine analogues **6** and **10** were, respectively, 6- and 4-fold more potent, and than Rimantadine **2**. The hexahydroazepine **19** was an inactive compound. It appears that enlargement from a five-, six- to a seven-membered ring detrimentally reduced the activity against influenza A virus. This provides a novel observation regarding the SAR in aminoadamantane series.

N-Alkylation of parent amines **6** and **10** caused a dramatic reduction in anti-influenza virus A potency. However, *N*-dimethylaminoethyl substitution of the piperidine derivative **10** led to the active analogue **15a**. This result has also been observed in a previous work concerning a different class of aminoadamantane heterocycles.[7e] The specific activity of compound **15a** could be attributed to three pharmocophore groups, that is, adamantane and two amine groups.

All compounds were inactive against influenza B virus, which is in accordance with their putative mode action, that is their interaction with influenza A M2 protein which is absent from influenza B virion.

N-H, *N*-methyl and *N*-benzyl piperidines **10**, **12a** and **12c** proved to be inactive against HIV-1, whereas the *N*-cyclopropylmethyl derivative **12b** showed an EC_{50} of 75.2 μM. *N*-Substitution by a dialkylaminoethyl group further improved the activity. Indeed, compounds **15a** and **15b** showed an EC_{50} of 40.8 and 3.6 μM, respectively. Interestingly, replacement of the dimethylamino moiety in **15a** by a piperidino group in **15b** led to a substantial increase in potency. The active compounds **12b**, **15a**, **16b** showed selectivity against HIV-1. The hexahydroazepines **19** and **21**, **22** were found inactive against HIV.

Aminoadamantane derivatives have not primarily been pursued as inhibitors of HIV replication. This fact makes the activity of **12b** and **15a** and **15b** against HIV-1 even more intriguing; although their potency is considerably lower compared to that of the control compounds Azidothymidine, Nevirapine and Ritonavir. The new aminoadamantane derivatives may be considered as the starting point for the development of new anti-HIV-1 agents. In analogy to the mechanism of anti-influenza A virus activity exhibited by adamantanamines,[5] the new compounds can be surmised to interact with an early step (i.e., fusion/uncoating) of the HIV replicative cycle. Since conversion of **10** to **15b** results in a marked shift from anti-influenza to anti-HIV activity, studies are currently underway to obtain further insight in the structure–activity relationships of this series of compounds.

Conclusion

The major aim of this study was to examine the anti-influenza A virus activity of heterocyclic Rimantadine **2** analogues **6**, **10** and **19**. The effect of ring size was investigated. Pyrrolidine and piperidine analogues **6** and **10** were more potent in vitro, by 6- and 4-fold, respectively, than the drug Rimantadine 2, whereas hexahydroazepine **19** was inactive. Extension from a five- or six- to a seven-membered ring detrimentally reduced the potency against influenza A virus.

Substitution of piperidine **10** with a dialkyaminoethyl group led to compounds **15a** and **b**, with compound **15a** showing modest activity against both influenza A virus and HIV-1, and **15b** being markedly active against HIV-1.

As it has been proposed by molecular modelling studies, amantadine 1 blocks the M2 channel activity because its two pharmacophoric groups, that is, adamantane and amine groups, are complementary in shape, hydrophobicity and polarity with the luminal space between M2 Leu26 and His37.[5c] The anti-influenza A virus activity of compound **15a** may be determined by three pharmocophore groups, the adamantane and the two amine groups. Since this result has also been observed previously with a different class of compounds,[7e] it will be of interest to verify in the future whether this effect is general for aminoadamantanes.

Aminoadamantanes **15a** and, in particular, **15b** have interesting activity against HIV-1 and can possibly be considered as lead compounds for the development of a new class of anti-HIV-1 agents.

Experimental

Chemistry

Melting points were determined using a Buchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 and MSL 400 spectrometers, respectively, using $CDCl_3$ as solvent and TMS as internal standard. Carbon multiplicities were established by DEPT experiments. The 2D NMR techniques (HMQC and COSY) were used for the elucidation of the structures of some derivatives.

Microanalyses were carried out by the Service Central de Microanalyse (CNRS) France, and the results obtained had a maximum deviation of $\pm 0.4\%$ from the theoretical value.

1-(1-Adamantyl)cyclopentanol **8** was synthesized from the reaction of 1,4-bis(bromomagnesium) butane with ethyl 1-adamantanecarboxylate in 67% yield.[8] 1-(1-Adamantyl)cyclohexanol **17** was synthesized from the reaction of 1-adamantyl lithium with cyclohexanone in 72% yield.[12] 2-(1-Adamantyl)pyrrolidines **6**, **7** were synthesized according a previous publication.[7b]

3,4,5,6-Tetrahydro-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)pyridine, 9. Method A. A mixture of trichloroacetic acid (37.5 g, 0.230 mol) and NaN_3 (4.57 g, 0.070 mol) in chloroform (110 mL) was stirred for 15 min at 0 °C. To the resulting suspension was added in one portion adamantylcyclopentanol **8** (5 g, 22.7 mmol) and stirring was continued for 5 h at 0 °C. The mixture was allowed to stand for 24 h at 0 °C and then poured into a mixture of ice and 26% aqueous ammonia solution. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic extracts were washed three times with water, dried (Na_2SO_4) and concentrated under vacuum at ambient temperature to a volume of ~80 mL. To the resulting solution concentrated sulfuric acid (7.5 mL) was added dropwise at 0 °C and the mixture was stirred for 30 min and then poured into a mixture of ice and 26% aqueous ammonia solution. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic extracts were washed with water and evaporated almost to dryness. The residue was dissolved in ether and extracted with 5% hydrochloric acid solution. The acidic aqueous phase was washed with ether and then made alkaline with solid Na_2CO_3. The resulting oil was extracted with ether and the organic extracts were dried and evaporated to dryness. The oily residue was solidified on cooling and was filtered through neutral aluminum oxide (100–125 mesh) with ether as the eluent to afford 2.50 g of piperideine **9**: yield 51%.

Method B. To a vigorously stirred mixture of adamantylcyclopentanol **8** (880 mg, 4.0 mmol) and NaN_3 (1.4 g, 21.0 mmol) in chloroform (30 mL) was added dropwise concentrated sulfuric acid (4 mL) under ice cooling. The mixture was stirred for 1.5 h and poured into a mixture of ice and 26% aqueous ammonia solution. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic extracts were washed many times with water and evaporated almost to dryness. The residue was dissolved in ether and extracted with 5% hydrochloric acid solution. The acidic aqueous phase was washed with ether and then made alkaline with solid Na_2CO_3. The resulting oil was extracted with ether and the organic

extracts were dried (Na_2SO_4) and evaporated to dryness. The oily residue was heated at 30–35 °C under vacuum (1 mm Hg) and the yellow solid was chromatographed on neutral aluminum oxide (100–125 mesh) with ether as the eluent to afford 630 mg of piperideine **9**: yield 73%; mp 34–36 °C (*n*-pentane); IR (Nujol): ν (C=N) 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.44–1.70 (m, 16H, 2,4,6,8,9,10-adamantane H, 4,5-tetrahydropyridine H), 1.96 (s, 3H, 3,5,7-adamantane H), 2.06–2,12 (t, 2H, 3-tetrahydropyridine H), 3.50–3.60 (m, 2H, 6-tetrahydropyridine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 19.6 (4-tetrahydropyridine C), 21.9 (5-tetrahydropyridine C), 23.5 (3-tetrahydropyridine C), 28.4 (3,5,7-adamantane C), 36.8 (4,6,10-adamantane C), 39.6 (2,8,9-adamantane C), 41.3 (1-adamantane C), 49.1 (6-tetrahydropyridine C), 177.0 (2-tetrahydropyridine C). Picrate: mp 177–179 °C (MeOH) Anal. ($C_{21}H_{26}N_4O_7$) C, H.

2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)piperidine, 10. To a stirred solution of tetrahydropyridine **9** (2.68 g, 12.3 mol) in methanol (50 mL) $NaBH_4$ (2.0 g, 53.0 mmol) was added in small portions under ice cooling. The reaction mixture was stirred for 20 h at ambient temperature and the solvent was removed under reduced pressure. The residue was treated with HCl (10%) and the aqueous mixture was washed with ether and then made alkaline with solid Na_2CO_3. The oil formed was extracted with ether, the combined organic extracts were dried and evaporated to give piperidine **10** as a white solid: yield 2.51 g (93%); mp 73–74 °C (ether–*n*-pentane); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.04–1.80 (complex m, 20H, 2,4,6,8,9,10-adamantane H, 2,3,4,5-piperidine H, *N*H), 1.91 (s, 3H, 3,5,7-adamantane H), 2.46–2.58 (m, 1H, 6-piperidine H), 3.06–3.11 (m, 1H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 25.40 (3-piperidine C), 25.50 (5-piperidine C), 26.70 (4-piperidine C), 28.50 (3,5,7-adamantane C), 35.10 (1-adamantane C), 37.30 (4,6,10-adamantane C), 38.70 (2,8,9-adamantane C), 48.0 (6-piperidine C), 66.90 (2-piperidine C). Hydrochloride: mp > 300 °C (EtOH–Et_2O); Picrate: mp 221–223 °C (MeOH–Et_2O) anal. ($C_{21}H_{28}N_4O_7$) C, H.

1-Methyl-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)piperidine, 12a.
Method A. Ethyl chloroformate (1.09 g, 10.0 mmol) in dry ether (20 mL) was added dropwise under ice cooling to a stirred solution of the piperidine **10** (1.30 g, 5.93 mmol) and triethylamine (1.95 g, 19.3 mmol) in dry ether (20 mL). The mixture was stirred at room temperature for 24 h and water was added. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with water, HCl (2%), water and dried. The solvent was evaporated in vacuo to afford carbamate **11a** as an oil (1.33 g, 77%); IR (film) 1700 cm^{-1}, which was used without further purification for the preparation of derivative **12a**.

To a stirred suspension of $LiAlH_4$ (1.40 g, 36.9 mmol) in dry THF (40 mL) was added dropwise a solution of the carbamate **11a** (1.0 g, 3.40 mmol) in dry THF (20 mL). The reaction mixture was refluxed for 20 h and then hydrolyzed with water and NaOH 20% under ice cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was concentrated under vacuum. The residue was dissolved in ether and extracted with HCl 5%. The aqueous layer was made alkaline with solid Na_2CO_3 and the solid formed was extracted with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent was evaporated. The resulting residue was chromatographed on silica gel with ether as an eluent to give the piperidine **12a** (710 mg, 89%).

Method B. A suspension of tetrahydropyridine **9** (510 mg, 2.30 mmol) and CH_3I (12 mL) was refluxed for 3 h. The reaction mixture was ice-cooled and the precipitated crystalline salt **11b** was filtered off, washed with ether and dried: yield 500 mg (60%); 162–164 °C (EtOH–Et_2O); anal. ($C_{16}H_{26}IN$) C, H.

To a stirred solution of tetrahydropyridinium iodide **11b** (1.08 g, 3.0 mmol) in chloroform–methanol 2:1 (20 mL) was added portionwise under ice cooling $NaBH_4$ (500 mg, 13.0 mmol) and stirring was continued for 24 h at ambient temperature. The solvent was evaporated under vacuum at room temperature and water was added into the residue with vigorous stirring. The aqueous mixture was extracted with chloroform, and the combined organic phases were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in ether and the ethereal solution was extracted many times with HCl 5%. The acidic aqueous phase was made alkaline with solid Na_2CO_3, extracted with ether and the organic solution was dried (Na_2SO_4). After evaporation of the solvent the residue was chromatographed to afford crystalline piperidine **12a**: (610 mg, 87%); mp 54–55 °C (ether–*n*-pentane); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.31–1.84 (complex m, 18H, 2,4,6,8,9,10-adamantane H, 3,4,5-piperidine H), 1.92 (s, 3H, 3,5,7-adamantane H), 2.09 (dd, $J = 2.7$, 10.8 Hz, 1H, 2-piperidine H), 2.41 (s, 3H, CH_3), 2.70–2.96 (m, 2H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 17.71 (3-piperidine C), 19.05 (5-piperidine C), 24.53 (4-piperidine C), 28.68 (3,5,7-adamantane C), 36.32 (1-adamantane C), 37.22 (4,6,10-adamantane C), 39.17 (CH_3), 39.75 (2,8,9-adamantane C), 55.75 (6-piperidine C), 70.80 (2-piperidine C). Hydrochloride: mp > 260 °C (EtOH–Et_2O); Picrate: mp 159–161 °C (MeOH), anal. ($C_{22}H_{30}N_4O_7$) C, H.7

1-Cyclopropylmethyl-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)piperidine, 12b. Cyclopropanecarbonyl chloride (2.68 g, 25.6 mmol) in dry THF (10 mL) was added dropwise under ice cooling to a stirred solution of the piperidine **10** (1.70 g, 7.76 mmol) and triethylamine (4.04 g, 39.9 mmol) in dry THF (40 mL). The mixture was stirred at 75 °C for 2 h and the precipitated triethylamine hydrochloride was filtered off and washed with THF. The filtrate was evaporated under vacuum and the residue was dissolved in ether. The organic solution was washed with water, HCl 5%, NaOH 5%, water and dried (Na_2SO_4). The solvent was evaporated in vacuo and the oil residue was chromatographed on aluminum oxide using ether as an eluent to afford amide **11c** as an oil (2.04 g, 91%); IR (Film) 1637 cm^{-1}.

Compound **12b** was prepared by the $LiAlH_4$ (1.98 g, 52.2 mmol) reduction (9 h) of *N*-cyclopropanecarbonyl derivative **11c** (1.50 g, 5.22 mmol) in dry THF (40 mL), using the procedure followed for the preparation of **12a** (method A): yield 70% (oil); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.04–0.51 (m, 4H, 2,3-cyclopropane H), 0.75–0.94 (m, 1H, 1-cyclopropane H), 1.23–1.75 (complex m, 18H, 2,4,6,8,9,10-adamantane H, 3,4,5-piperidine H), 1.92 (s, 3H, 3,5,7-adamantane H), 2.04–2.11 (m, 1H, 2-piperidine H), 2.38–2.62 (m, 2H, $C_3H_5C\underline{H}_2N$), 2.77–3.10 (m, 2H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 3.68, 3.86 (2,3-cyclopropane C), 10.52 (1-cyclopropane C), 18.26, 18.65, 22.13 (3,4,5-piperidine C), 28.69 (3,5,7-adamantane C), 36.90 (1-adamantane C), 37.32 (4,6,10-adamantane C), 39.68 (2,8,9-adamantane C), 46.60 (6-piperidine C), 57.93 ($C_3H_5C\underline{H}_2N$), 70.37 (2-piperidine C). Hydrochloride: mp 219–221 °C ($EtOH–Et_2O$); Picrate: mp 152–154 °C (MeOH); anal. ($C_{25}H_{34}N_4O_7$) C, H.

1-Phenylmethyl-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)piperidine, 12c. Amide **11d** was prepared by the procedure used for **11c**, by the reaction of benzoyl chloride (2.81 g, 20.0 mmol) with piperidine **10** (1.77 g, 8,08 mmol) in the presence of triethylamine (3.30 g, 32.6 mmol): yield 84%; mp 123–125 °C (ether–*n*-pentane); anal. ($C_{22}H_{29}NO$) C, H.

Compound **12c** was prepared by the $LiAlH_4$ (1.75 g, 46.1 mmol) reduction (20 h) of *N*-benzoylcarbonyl derivative **11d** (1.40 g, 4.33 mmol) in dry THF (45 mL), using the procedure followed for the preparation of **12b**: yield 83%; mp 77–78 °C (*n*-pentane); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.42–1.83 (complex m, 18H, 2,4,6,8,9,10-adamantane H, 3,4,5-piperidine H), 1.97 (s, 3H, 3,5,7-adamantane H), 2.15–2.26 (m, 1H, 2-piperidine H), 2.42–2.76 (m, 2H, 6-piperidine H), 3.69–4.0 (m, 2H, $C\underline{H}_2C_6H_5$), 7.22–7.45 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 17.80, 19.10, 21.80 (3,4,5-piperidine C), 28.70 (3,5,7-adamantane C), 37.40 (4,6,10-adamantane C), 38.10 (1-adamantane C), 39.70 (2,8,9-adamantane C), 44.60 ($\underline{C}H_2C_6H_5$), 57.6 (6-piperidine C), 70.80 (2-piperidine C), 126.50, 128.10, 128.50, 141.10 (C_6H_5). Hydrochloride: mp 121–123 °C dec ($EtOH–Et_2O$). Anal. ($C_{22}H_{31}N$) C, H.

1-[2-(Dimethylamino)ethyl]-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)piperidine, 15a. To a vigorously stirred mixture of adamantylpiperidine **10** (1.70 g, 7.76 mmol) and K_2CO_3 (850 mg, 6.10 mmol) in dichloromethane (10 mL)/water (10 mL) was added dropwise under ice cooling a solution of bromoacetyl chloride (1.23 g, 7.81 mmol) in dichloromethane (5 mL). The mixture was stirred for 3 h at 0 °C and 30 min at room temperature. Water was added, the organic phase was separated and the aqueous was extracted with dichloromethane. The combined organic extracts were evaporated and the oily residue was dissolved in ether. The ether solution was washed successively with water, Na_2CO_3 (5%), water, HCl (5%), brine and dried (Na_2SO_4). Evaporation of the solvent afford crystalline bromoamide **13**; yield 2.21 g (84%); mp 61–63 °C (ether–*n*-pentane); IR (Nujol) 1648 cm^{-1}; anal. ($C_{17}H_{26}BrNO$) C, H.

To a stirred solution of bromoacetamide **13** (750 mg, 2.20 mmol) in dry benzene (10 mL) was added dropwise under ice cooling a solution of Me_2NH (300 mg, 6.60 mmol) in the same solvent (8 mL). The mixture was stirred for 30 min at 0 °C and 24 h at ambient temperature. The solvent was evaporated in vacuo and water was added to the residue. The aqueous mixture was extracted with ether and the organic extracts were washed with water and extracted with HCl (5%). The acidic aqueous solution was washed with ether and was made alkaline with solid Na_2CO_3. The mixture was extracted many times with ether and the combined organic extracts were dried (Na_2SO_4) and evaporated under vacuum. The solid residue was chromatographed on silica gel with a mixture of ether–*n*-hexane 2:1 as an eluent to afford compound **14a**; yield 580 mg (86%); mp 91–93 °C (ether–*n*-pentane); IR (Nujol) 1629 cm^{-1}; Picrate: mp 178–180 °C ($MeOH–Et_2O$); anal. ($C_{25}H_{35}N_5O_8$) C, H.

Diamine **15a** was prepared by the $LiAlH_4$ (1.12 g, 29.6 mmol) reduction (10 h) of dimethylaminoacetamide **14a** (900 mg, 2.96 mmol) in dry THF (45 mL), using the procedure followed for the preparation of **12a**. The product was purified by column chromatography on silica gel using ether as an eluent: yield 78% (oil); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.40–1.75 (complex m, 18H, 2,4,6,8,9,10-adamantane H, 3,4,5-piperidine H), 1.93 (s, 3H, 3,5,7-adamantane H), 2.04–2.10 (m, 1H, 2-piperidine H), 2.25 (s, 6H, 2×CH_3), 2.41–2.94 (complex m, 6H, NCH_2CH_2N, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 18.40, 19.0, 22.20 (3,4,5-piperidine C), 28.70 (3,5,7-adamantane C), 37.30 (4,6,10-adamantane C), 38.70 (1-adamantane C), 39.90 (2,8,9-adamantane C), 45.90 (CH_3), 48.10 ($NC\underline{H}_2CH_2NMe_2$), 50.80 ($NCH_2C\underline{H}_2NMe_2$), 58.70 (6-piperidine C), 71.40 (2-piperidine C). Fumarate: mp 167–170 °C dec ($EtOH–Et_2O$); anal. ($C_{23}H_{38}N_2O_4$) C, H.

1-[2-(1-Piperidino)ethyl]-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)piperidine, 15b. Compound **14b** was prepared by the procedure used for **14a**, by the reaction of bromacetamide **13** (1.30 g, 3.82 mmol) with piperidine (800 mg, 9.40 mmol) in dry benzene (20 mL). The solid residue was chromatographed on silica gel with ether–*n*-hexane 2:1 as an eluent: yield 1.0 g (76%); mp 36–38 °C (ether–*n*-pentane); IR (film) 1642 cm^{-1}; Picrate: mp 195–197 °C (MeOH); anal. ($C_{28}H_{39}N_5O_8$) C, H.

The solid diamine **15b** was prepared by the $LiAlH_4$ (450 mg, 11.6 mmol) reduction (12 h) of piperidinocetamide **14b** (450 mg, 11.6 mmol) in dry THF (40 mL), using the procedure followed for the preparation of **15a**: yield 730 mg (76%); mp 46–47 °C (ether–*n*-pentane); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.34–1.67 (complex m, 24H, 2,4,6,8,9,10-adamantane H, 3,4,5-piperidine H, 3′,4′,5′-piperidine H), 1.86–2.01 (m, 4H, 2-piperidine H, 3,5,7-adamantane H), 2.31–2.46 (m, 6H, 6-piperidine H, 2′,6′-piperidine H), 2.52–2.88 (m, 4H, NCH_2CH_2N) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 18.40, 19.0, 22.20 (3,4,5-piperidine C), 24.30 (4′-piperidine C), 25.90 (3′,5′-piperidine C), 28.60 (3,5,7-adamantane C), 37.30 (4,6,10-adamantane C), 39.90 (2,8,9-adamantane C),

40.10 (1-adamantane C), 47.60 (NCH_2CH_2N), 50.50 (NCH_2CH_2N), 55.1 (2′,6′-piperidine C), 58.90 (6-piperidine C), 71.20 (2-piperidine C). Fumarate: mp 193–195 °C (EtOH–Et_2O); Bipicrate: mp 209–211 °C (MeOH); anal. ($C_{34}H_{44}N_8O_{14}$) C, H.

4,5,6,7-Tetrahydro-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-3*H*-azepine, 18. Compound **18** was prepared by the procedure used for the tetrahydropyridine analogue **9** (method B), by treating a chloroform solution (30 mL) of 1-adamantylcyclohexanol **17** (1.0 g, 4.30 mmol) with sodium azide (1.50 g, 23.0 mmol) and concd H_2SO_4 (4 mL): yield 300 mg (30%); mp 47–49 °C (*n*-pentane); IR (Nujol) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.23–1.37 (m, 2H, 4-azepine H), 1.38–1.50 (m, 2H, 6-azepine H), 1.52–1.77 (m, 14H, 2,4,6,8,9,10-adamantane H, 5-azepine H), 1.96 (br s, 3H, 3,5,7-adamantane H), 2.32 (~t, 2H, J = ~8 Hz, 3-azepine H), 3.53 (~t, 2H, J = ~6 Hz, 1H, 7-azepine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 23.98 (4-azepine C), 26.20 (6-azepine C), 27.07 (3-azepine C), 28.15 (3,5,7-adamantane C), 31.33 (5-azepine C), 36.72 (4,6,10-adamantane C), 38.97 (2,8,9-adamantane C), 42.17 (1-adamantane C), 51.44 (7-azepine C), 183.55 (2-azepine C). Picrate: mp 161–163 °C (MeOH–Et_2O); anal. ($C_{22}H_{28}N_4O_7$) C, H.

Hexahydro-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1*H*-azepine, 19. Compound **19** was prepared by the procedure used for the piperidine analogue **10**, by treating a methanol solution (20 mL) of tetrahydroazepine **18** (1.0 g, 4.33 mmol) with $NaBH_4$ (730 mg, 19.3 mmol) for 1 h at 0 °C and 2 h at ambient temperature: yield 740 mg (73%); mp 65–67 °C (*n*-pentane); IR (Nujol) 3365 cm^{-1}; ‘p^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.23–1.74 (m, 21H, 2,4,6,8,9,10-adamantane H, 1,3,4,5,6-azepine H), 1.96 (dd, 1H, J = 2.7, 10.1 Hz, 1H, 2-azepine H), 1.91 (br s, 3H, 3,5,7-adamantane H), 2.52–2.61 (m, 1H, 7-azepine H), 2.91–3.0 (m, 1H, 7-azepine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 26.70, 27.10, 28.90, 31.60 (3,4,5,6-azepine C), 28.50 (3,5,7-adamantane C), 36.60 (1-adamantane C), 37.30 (4,6,10-adamantane C), 38.70 (2,8,9-adamantane C), 49.0 (7-azepine C), 67.9 (2-azepine C). Hydrochloride mp >280 °C (EtOH–Et_2O); Picrate: mp 172–174 °C (MeOH–Et_2O); anal. ($C_{22}H_{30}N_4O_7$) C, H.

Hexahydro-1-methyl-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1*H*-azepine, 21. The oily carbamate ester **20a** was prepared by the procedure used for **11a** (method A), by the reaction of ethyl chloroformate (760 mg, 7.0 mmol) with hexahydroazepine **19** (990 mg, 4.25 mmol) in the presence of triethylamine (1.40 g, 13.8 mmol) in dry ether (15 mL): yield 1.01 g (78%); IR (film) 1697 cm^{-1}.

The solid azepine **21** was prepared by the $LiAlH_4$ (1.20 g, 31.6 mmol) reduction of carbamate ester **20a** (960 mg, 3.15 mmol) in dry THF (60 mL), using the procedure followed for the preparation of **12a** (method A): yield 570 mg (73%); mp 56–58 °C (*n*-pentane); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.12–1.92 (complex m, 24H, adamantane H, 2,3,4,5,6-azepine H), 2.52 (s, 3H, *N*-CH_3), 2.69–2.93 (m, 2H, 7-azepine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.39, 26.81, 27.93, 30.16 (3,4,5,6-azepine C), 28.71 (3,5,7-adamantane C), 36.81 (1-adamantane C), 37.45 (4,6,10-adamantane C), 39.28 (2,8,9-adamantane C), 45.31 (*N*-CH_3), 52.01 (7-azepine C), 73.67 (2-azepine C). Hydrochloride mp 206–208 °C (EtOH–Et_2O); Picrate: mp 199–201 °C (MeOH); anal. ($C_{23}H_{32}N_4O_7$) C, H.

1-[2-(1-Piperidine)ethyl]-2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-hexahydro-1*H*-azepine, 22. The solid bromacetylated hexahydroazepine **20b** was prepared by the procedure used for **13**, by treating hexahydroazepine **19** (900 g, 3.90 mmol) in dichloromethane (18 mL) — water (10 mL) with bromacetyl chloride (680 mg, 4.30 mmol) in dichloromethane (10 mL) in the presence of K_2CO_3 (600 mg, 4.30 mmol) in water (4 mL): yield 1.21 g (86%); mp 85–87 °C (ether–*n*-pentane); IR (Nujol) 1635 cm^{-1}; anal. ($C_{18}H_{28}BrNO$) C, H.

Treating a solution of bromacetylated derivative **20b** (1.0 g, 2.80 mmol) in dry benzene (8 mL) with piperidine (720 mg, 8.50 mmol) in dry benzene (10 mL) using the same procedure described for compound **14b** afforded 910 mg of acylated azepine **20c**: yield 90%; mp 136–138 °C (*n*-pentane); IR (Nujol) 1646 cm^{-1}; anal. ($C_{23}H_{38}N_2O$) C, H.

Piperidinoethyl hexahydroazepine **22** was prepared by the $LiAlH_4$ (370 mg, 9.80 mmol) reduction of piperidinoacetyl hexahydroazepine **20c** (700 mg, 1.95 mmol) in dry THF (30 mL), using the procedure followed for the preparation of **15b**. The residue was chromatographed on silica gel with ether as an eluent to afford solid compound **22**: yield 620 mg (92%); mp 49 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.23–2.03 (complex m, 30H, adamantane H, 2,3,4,5,6-azepine H, 3,4,5-piperidine H), 2.35–2.71 (m, 10H, NCH_2CH_2N, 7-azepine H, 2,6-piperidine-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.46 (4-piperidine C), 26.04 (3,5-piperidine C), 23.84, 26.28, 27.74, 26.69 (3,4,5,6-azepine C), 28.75 (3,5,7-adamantane C), 36.81 (1-adamantane C), 37.48 (4,6,10-adamantane C), 38.88, 39.44 (2,8,9-adamantane C), 47.51, 50.47 (NCH_2CH_2N), 55.35 (2,6-piperidine C), 58.46 (7-azepine C), 74.49 (2-azepine C). Monofumarate: mp 209–211 °C (EtOH–Et_2O); anal. ($C_{27}H_{44}N_2O_4$) C, H.

Biological evaluation

Reference compounds. Dextran sulfate with an average molecular weight of 5000 was purchased from Sigma (St. Louis, MO). AZT (azdothymidine) was synthesized as previously described.[14] Nevirapine (BI-RG587) was obtained from Boehringer Ingelheim (Ridgefield, CN). Ritonavir (ABT538) was kindly provided by J. M. Leonard, Abbott Laboratories (Abbott Park, IL, USA).

Cells and viruses. The MT-4 cells[15] were grown in humidified atmosphere with 5% CO_2 and maintained in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, 2 mM L-glutamine, 0.1% sodium bicarbonate and 20 μg/mL of gentamicin. The origin of HIV-1(III_B) and HIV-2 (ROD) virus stocks

has been described previously.[16] HIV-1 and HIV-2(ROD) stocks were obtained from the culture supernatant of HIV-1- or HIV-2-infected MT-4 cells, respectively. Influenza A viruses (H_2N_2) and B were kindly provided by Dr. K. Andries (Janssen Pharmaceutica, Beerse, Belgium) and stocks were prepared on MDCK cells.

Antiviral activity and cytotoxicity assays. The inhibitory effects of the rimantadine derivatives on HIV-1 strain III_B and HIV-2 strain ROD replication were monitored by measuring the viability of MT-4 cells 5 days after infection. Cytotoxicity of the compounds was determined in parallel by measuring the viability of mock-infected cells on day 5. The number of viable cells was quantified semi-automatically by a tetrazolium-based colorimetric method using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT), as described by Pauwels et al.[17,18] Anti-influenza virus activity was assessed in 96-well plates on 1-day confluent MDCK cells. Cells were infected with $100CCID_{50}$ virus/well. After 1 h of virus absorption virus was removed and serial dilutions of the test compounds were added after which cultures were further incubated at 35 °C (5% CO_2) for 4–5 days. Cytopathic effects (and, in parallel, cytotoxic effects in non-infected cultures) were read using the MTS-method (Promega).

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