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Heterocyclic rimantadine analogues with antiviral activity

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Abstract—2-(1-Adamantyl)-2-methyl-pyrrolidines **3** and **4**, 2-(1-adamantyl)-2-methyl-azetidines **5** and **6**, and 2-(1-adamantyl)-2-methyl-aziridines **7** and **8** were synthesized and tested for their antiviral activity against influenza A. Parent molecules **3**, **5**, and **7** contain the α-methyl-1-adamantan-methanamine **2** pharmacophoric moiety (rimantadine). The ring size effect on anti-influenza A activity was investigated. Pyrrolidine **3** was the most potent anti-influenza virus A compound, 9-fold more potent than rimantadine **2**, 27-fold more potent than amantadine **1**, and 22-fold more potent than ribavirin. Azetidines **5** and **6** were both markedly active against influenza A H2N2 virus, 10- to 20-fold more potent than amantadine. Aziridine **7** was almost devoid of any activity against H2N2 virus but exhibited borderline activity against H3N2 influenza A strain. Thus, it appears that changing the five-, to four- to a three-membered ring results in a drop of activity against influenza A virus.

1. Introduction

Influenza A is a major respiratory tract disease affecting millions of people every year. 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] Conditions that affect the likelihood of suffering a severe case of influenza include those that compromise: heart, lungs, renal system, and immune system. In some people, the infection can cause pulmonary or cardiac disease or lead to secondary bacterial pneumonia or primary viral pneumonia. 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.[2,3]

Influenza A viruses have the ability to undergo changes by the mechanisms of antigenic drift and shift, and new evolving strains can be a serious threat to the human population.[4] Thus, pandemic influenza A viruses appeared in 1918 (''Spanish'' H1N1), 1957 (''Asian'' H2N2), and 1968 (''Hong Kong'' H3N2). In the winter of 1918–1919, 21 million deaths from influenza were recorded worldwide—one of the most catastrophic consequences of an infectious disease ever known. Recent (for example, Hong Kong 1997) and current epidemics in Asia with highly pathogenic avian influenza (H5N1) result in a high fatality rate in infected human, which underlines the danger of influenza to cause new pandemics.

Amantadine **1** and rimantadine **2** are *anti*-influenza virus A drugs that inhibit virus replication at micromolar concentrations.[5] They inhibit influenza A virus replication by blocking the ion channel of the small virus membrane protein M2.

During the last decade, potent anti-influenza aminoadamantane carbocycles and heterocycles have been synthesized in our laboratory.[6] The activity of the most potent compounds against influenza A H2N2 virus is presented in Table 1. Several compounds showed marked biological activity and exhibited excellent selectivity. Compounds bearing the pharmacophore group of drug Rimantadine and a carbon skeleton in the vicinity of

Keywords: Adamantanamines; Anti-influenza A; Heterocyclic rimantadine analogues; NMR.
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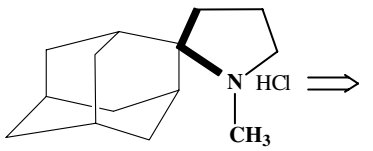
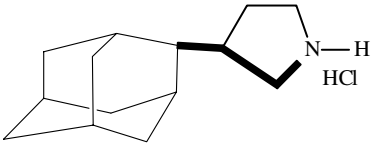
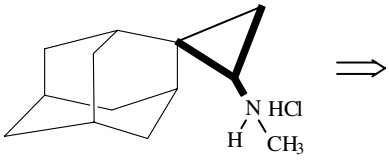
Table 1.



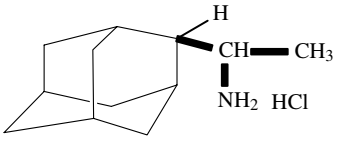
230 times more active than amantadine and 12 than rimantadine SI>357



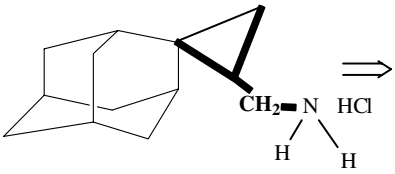
4.3 times more active than amantadine and 5 times less potent than rimantadine SI=207



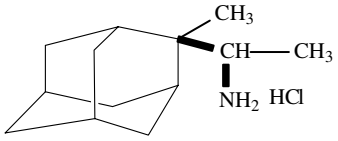
101 times more active than amantadine SI=83.4



8 times more active than amantadine and 4 than rimantadine SI=611



151 times more active than amantadine and 7 than rimantadine SI=24.5



4 times more active than amantadine and 2 than rimantadine SI=160

the adamantane moiety have increased anti-influenza A virus activity.

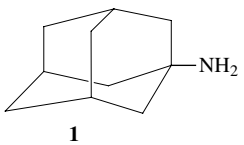
In the context of our ongoing research in this area, we present herein the synthesis and antiviral activity of some heterocyclic rimantadine analogues and specifically 2-(1-adamantyl)-2-methyl-pyrrolidines **3**,**4**, 2-(1-adamantyl)-2-methyl-azetidines **5**, **6**, and 2-(1-adamantyl)-2-methyl aziridines **7** and **8**.

Parent molecules **3**, **5**, and **7** contain the pharmacophore group of the α-methyl-1-adamantan-methanamine **2** (drug rimantadine). Thus, we sought to compare the anti-influenza A virus potency of these structurally modified rimantadines with the activity of rimantadine **2** and to investigate the effect of reducing the size of the heterocyclic ring to the M2 ion channel blocking. The study is limited to three-, four-, and five-membered heterocycles because from our experience in SAR of adamantane compounds, extension from a four or five- to a six- or seven-membered ring reduced the potency against influenza A virus.[6a,b]

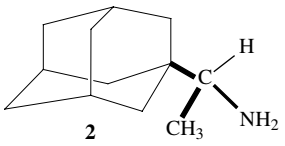
2. Results and discussion

2.1. Chemistry

The synthetic route followed for the synthesis of pyrrolidine **3** is presented in Scheme 1. Initially, we synthesized the nitro compound **9** by oxidizing rimantadine **2** with *meta*-chloroperoxybenzoic acid (mCPBA).[7] The Michael condensation of nitro compound **9** with acrylic ethyl ester afforded the corresponding nitroethyl ester **10** as a crude oil. This was purified by saponification, and the intermediate carboxylic acid **11** was then esterified in MeOH–HCl to the solid methyl ester **12**. The conversion of



1



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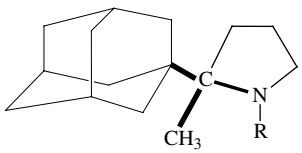
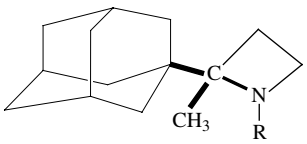
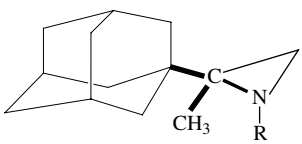


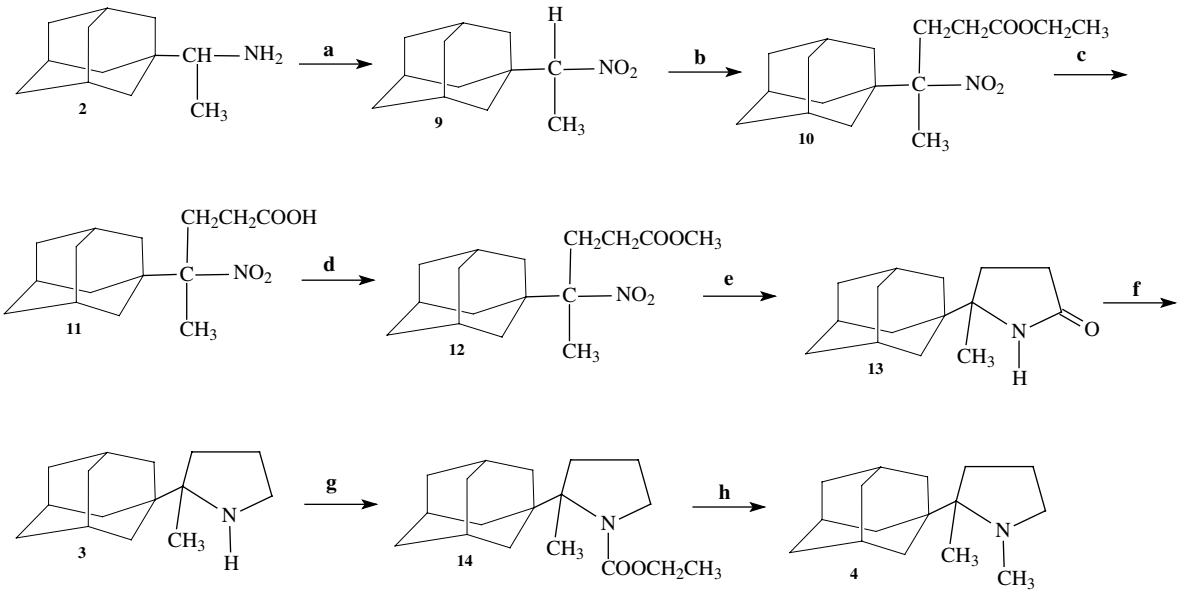
3 R=H
4 R=CH_3



5 R=H
6 R=CH_3



7 R=H
8 R=CH_3



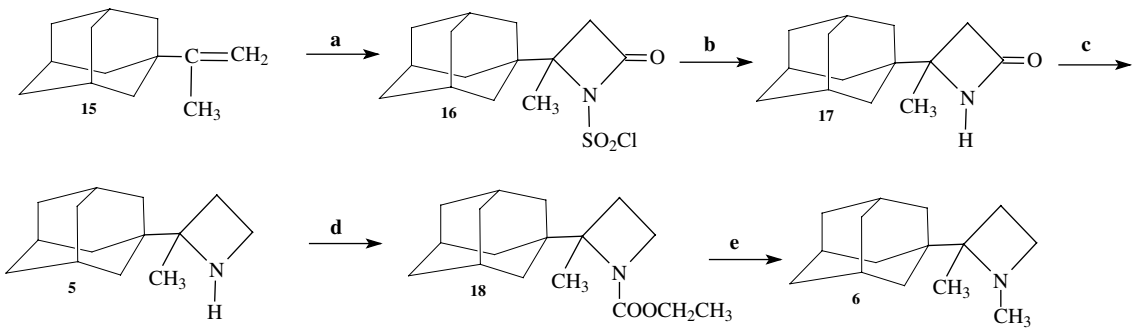
Scheme 1. Reagents and conditions: (a) mCPBA, CH_2Cl–CH_2Cl, reflux, 3 h (96%); (b) ^{t}BuOH, Triton B, CH_2=$CHCOOC_2H_5$, 65–70 °C, 3 h; (c) H_2O, EtOH, NaOH, reflux, 3 h and then HCl (87%); (d) CH_3OH–HCl, 3 h, 50 °C, 24 h, 20 °C (96%); (e) EtOH, H_2, Ni-Raney, 50 psi, 75 °C, 4 h (90%); (f) $LiAlH_4$, THF, reflux, 25 h (97%); (g) Et_3N, $ClCOOC_2H_5$, ether, 24 h, 25 °C (98%); (h) $LiAlH_4$, THF, 24 h, 25 °C (86%).

the liquid ethyl ester **10** to the solid methyl ester **12** was important not only for the purification of the product, but also for the quantitative γ-lactamization, which occurred during hydrogenation of the nitro ester **12** over Raney nickel catalyst in boiling ethanol. Subsequent reduction of the γ-lactam **13** with $LiAlH_4$ in THF led to the parent pyrrolidine **3**. N-Acylation of the latter followed by reduction of the intermediate carbamate **14** with $LiAlH_4$ gave the *N*-methyl derivative **4**.

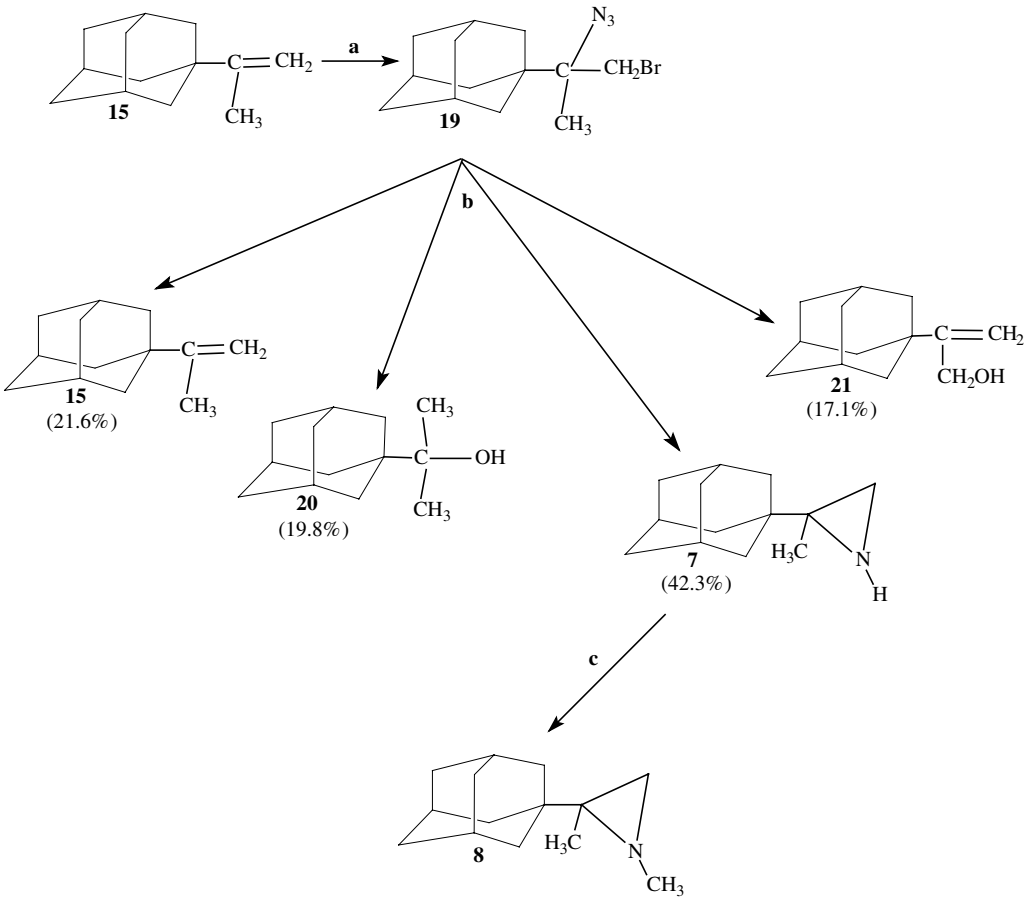
For the synthesis of the azetidine **5**, 2-(1-adamantyl)propene **15** was used as starting material (Scheme 2). This was successively cyclized to the *N*-chlorosulfonyl azetidinone **16** upon treatment with chlorosulfonyl isocyanate,[8] via a [2+2] polar cycloaddition. Hydrolysis of the chlorosulfonyl azetidinone **16** under mild conditions resulted in the azetidinone **17**, which was converted to the parent azetidine **5** by means of $LiAlH_4$ reduction. N-Methylation of the latter was accomplished according to the procedures used for the preparation of the corresponding pyrrolidine analogue **4** (Scheme 1).

The synthesis of the aziridine **7** (Scheme 3) involved the same starting material, alkene **15**. The bromoazide **19** was obtained from the addition of bromine azide, prepared in situ by the reaction of NBS with NaN_3,[8h] to the alkene **15** via a mechanism that involves the formation of a cyclic bromonium ion.[8i] Along with the desired product some unreacted alkene was also isolated.

Reduction of the bromo azide **19** with $LiAlH_4$, under mild reaction conditions, resulted in the formation of a mixture consisting of four different products: (a) the aziridine **7**, after cyclization of the intermediate β-bromo amine in a yield of 42.3%, (b) the 2-(1-adamantyl)allylic alcohol **21** in 17.1% yield; the formation of the alcohol **21** could be explained by the attack of $LiAlH_4$, as a base, on the bromo azide **19** and E_2 elimination of HN_3 led to the allylic bromide **22**, which was in turn hydrolyzed (H_2O–NaOH) to afford alcohol **21**, (c) the tertiary alcohol **20** (yield 19.8%), the formation of which is explained by the Lewis acid character of $LiAlH_4$; in detail, the alkene **15** complexes with $LiAlH_4$ and via a tertiary carbonium ion and hydrolysis of it, leads to the alcohol **20**,



Scheme 2. Reagents and conditions: (a) $ClSO_2$–N=C=O, ether, −75 °C then 24 h, 25 °C (86%); (b) KOH, Na_2SO_3, H_2O, ether, pH ~ 8–9 (98%); (c) $LiAlH_4$, THF, reflux, 25 h (98%); (d) Et_3N, $ClCOOC_2H_5$, ether, 24 h, 25 °C (98%); (e) $LiAlH_4$, THF, 24 h, 25 °C (93%).



Scheme 3. Reagents and conditions: (a) NaN_3, H_2O, DMF, NBS, 6 h, 0 °C, 20 h, 4 °C (89%); (b) $LiAlH_4$, ether, 24 h, 25 °C; (c) CH_3CN, HCHO 37%, $NaCNBH_3$ and then CH_3COOH, 2 h, 25 °C (90%).

and (d) the alkene **15** (yield 21.6%); the presence of **15** in the mixture can be explained either by the fact that part of it might had remained unreacted after the addition of bromine azide or that it is formed during the reduction of the allylic bromide **22** with $LiAlH_4$.

In order to obtain the *N*-methyl derivative **8**, two different synthetic pathways were examined. The first procedure involved N-acylation of the aziridine **7** followed by reduction of the intermediate carbamate with $LiAlH_4$. The carbamate derivative, which was obtained from the reaction of aziridine **7** with $ClCOOCH_2CH_3$ in the presence of Et_3N using ether as solvent, was found to be a mixture of *E* and *Z* stereoisomers. The stereochemistry around the C–N bond was investigated using NOE spectroscopy and it was found to be in favor of the *E*-stereoisomer.

Interestingly, the reduction of the carbamate gave the parent aziridine **7** instead of the expected *N*-methyl aziridine **8**. A reasonable explanation for this might be the steric hindrance present in the intermediate complex, due to the bulky adamantane moiety at the C-2 of the aziridine ring; this hypothesis convolutes with the data obtained from molecular mechanics calculations. A possible mechanism of the reaction could include the attack of the hydride on the carbonyl of the carbamate and simultaneous cleavage of the C–N bond to give the parent amine. In our case, the greater stability of the aziridine anions compared to that of the secondary amines provided the necessary driving force to lead the reaction toward the observed product.

Finally, the synthesis of the *N*-methyl aziridine **8** was achieved, in high yield, by the Borch–Hassid reductive methylation ($NaCNBH_3$, CH_2O, and CH_3CN) of the parent amine **7**.[9]

The *E*-stereoisomers **4**, **6**, and **8** were obtained from the corresponding amines due to the steric hindrance between adamantane and the *N*-CH_3 group. Structures were assigned using NOE spectroscopy.

NOE interactions between the methyl protons (*N*-CH_3, *C*-CH_3), for all the *N*-methyl-substituted compounds **4**, **6**, and **8**, showed that methyl groups were on the same face of the molecule, which led to the *E*-stereochemistry proposed in Figure 1. The *trans* to the adamantane conformation of the *N*-CH_3 is entirely in keeping with the NOE correlations, indicating spatial proximity, in the 2D NOESY experiments. Having *trans* conformation, *N*-methyl exhibits space proximity with the *C*-methyl.

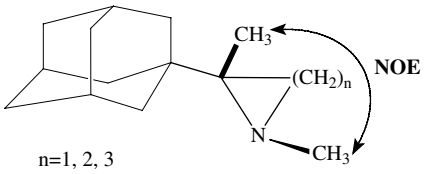


Figure 1.

3. Antiviral activity evaluation

The potency of the new aminoadamantane heterocycles **3**–**8** was examined in vitro against two influenza A virus strains (H2N2 and H3N2) and was compared to the activity of amantadine **1**, rimantadine **2**, and ribavirin (Table 2). The new compounds were synthesized and tested in their racemic form. It has been reported that different configuration of chiral center of rimantadine **2** did not affect anti-influenza A potency.[10] The sources of viruses, the methods, and the antiviral assays used were as previously reported.[11]

Data presented in Table 2 indicate that compounds **3**, **5**, and **6** elicit potent anti-influenza virus A activity (H2N2). Pyrrolidine **3** was endowed with the most potent anti-influenza virus A activity and is at least 9-fold more potent than rimantadine **2**, 27-fold more potent than amantadine **1**, and 22-fold more potent than ribavirin. Although pyrrolidine **3** was more cytotoxic than amantadine, rimantadine or ribavirin, it resulted in a higher selectivity.

Methyl substitution at the nitrogen atom of the pyrrolidine **3** caused a dramatic reduction in anti-influenza virus A potency against both strains (124-fold less potent than the parent amine, H2N2 and 8-fold, H3N2) (compound **4**). Azetidines **5** and **6** were both markedly active against influenza A H2N2 virus, 20- to 10-fold higher than that of amantadine, but azetidine **5** exhibited increased cytotoxicity than the pyrrolidines **3** and **4**. Ring size reduction resulted in aziridine **7**, which was less potent against influenza A H2N2 virus than the other parent amines and cytotoxic, but was relatively active against H3N2. The *N*-methyl derivative **8** was cytotoxic as well.

Table 2. Anti-influenza virus A (H2N2 and H3N2) activity and cytotoxicity of heterocyclic rimantadine analogues—aziridines **7**–**8**, azetidines **5**, **6**, and pyrrolidines **3**, **4**[a]—in MDCK cells[b]

Compound	EC_{50}[c] (μM)		MTC[d] (μM)
	H2N2	H3N2	
3	1.56	1.8 ± 1.3	205
4	>194	14	194
5	1.96	2.3	51
6	4.1 ± 1.3	11 ± 9	240
7	>55	4.1	55
8	>259	>259	259
Amantadine, **1**	42	6	1240
Rimantadine, **2**	14	0.4	1160
Ribavirin	34	6	>1077

All data represent mean values for at least two separate experiments.

[a] Aziridines **7**, **8** and azetidines **5**, **6** were tested as bases. Pyrrolidines **3**, **4** were tested as hydrochlorides.

[b] Abbreviations and strains used: MDCK, Madin–Darby canine kidney cells, influenza A H_2N_2 (A2 Japan/305/57).

[c] Concentration required to reduce virus-induced CPE in MDCK cells by 50%. For the compounds showing reproducible activity, data are shown as means ± SD.

[d] Minimal toxic concentration or concentration that causes microscopically detectable toxicity in virus infected cultures.

The compounds proved inactive against unrelated viruses such as HIV-1, vesicular stomatitis virus (VSV, a rhabdovirus) in HeLa cells and in E6SM cells, coxsackie virus B4 (picornavirus) in HeLa cells and Vero cells, respiratory syncytial virus (a paramyxovirus) in HeLa cells and parainfluenza virus (a paramyxovirus) type 3 (in Vero cells), herpes simplex virus type 1 (strain Kos), type 2 (strain G) (herpesviruses) in E6SM cells, vaccinia virus (poxvirus) in E6SM cells, reovirus type 1 (orthoreovirus) in Vero cells, sindbis virus (alphavirus) in Vero cells, and Punta Toro virus (bunyavirus) in Vero cells. Pyrrolidine **7** has an MTC of 312 μM in HeLa cells; $\geqslant$51.2 μM in E6SM cells and 312 μM in Vero cells. For the other compounds values in each cell line are either above 400 or 2000 μM. The lack of activity of compounds **3**–**7** against other viruses further points to the selectivity against influenza A virus.

4. Conclusion

The prime target of this study was to examine the anti-influenza A virus activity of rimantadine analogues **3**, **5**, and **7**, and to correlate their potency to the size of the heterocyclic ring they bear in their skeleton. Comparing the antiviral activity of compounds **3**–**8** two interesting points arise: (i) changing a five-, to four- to a three-membered ring reduces the activity against influenza A virus; (ii) nonsubstituted heterocyclic compounds are more active, whereas N-methylation caused a dramatic reduction in anti-influenza virus A potency. The N-substitution of the parent amines with homologous alkyls was not attempted, as it has already been reported that the small size of the *N*-alkyl group enhances the activity of the respective compounds against influenza A H2N2 and H3N2 strains.[6a]

5. Experimental

5.1. Chemistry

Melting points were determined with a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker MSL 400 and AC 200 spectrometers, respectively, using $CDCl_3$ as solvent and TMS as internal standard. Carbon multiplicities were established by DEPT experiments. The 2D NMR experiments (HMQC, COSY, and NOESY) were performed for the elucidation of the structures of the new compounds.

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

2-(1-Adamantyl)propene **15** was synthesized from the dehydration of 2-(1-adamantyl)-2-propanol in the presence of $KHSO_4$. 2-(1-Adamantyl)-2-propanol was obtained from the nucleophilic attack of CH_3MgI to ethyl 1-adamantanecarboxylate, using ether as solvent.

5.2. 1-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)nitroethane (9)

To a stirred solution of rimantadine **2** (7.2 g, 40 mmol), freshly prepared from its hydrochloride salt, in boiling 1,2-dichloroethane (DCE) (15 mL), was added dropwise within 5 min a solution of *m*-chloroperoxybenzoic acid (mCPBA) (38.4 g, 222 mmol) in DCE (100 mL). Refluxing was continued for 3 h and then the mixture was chilled to 0 °C. The precipitated material was filtered off, washed with dichloromethane, and the filtrate was extracted three times with a solution of NaOH (1 N) (150 mL). The organic phase was dried (Na_2SO_4) over a period of 24 h and evaporated in vacuo to afford a yellow viscous oil, which was partially solidified at 3 °C. The product was purified by fractional distillation in vacuo (Eb. 105 °C/10^{-2} mmHg) (8.3 g, 96%); mp 48 °C (MeOH–H_2O); IR (Nujol) ν 1548 cm^{-1} (NO_2); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.41 (d, 3H, A_3 region, A_3X, $J \sim 7$ Hz, CH_3), 1.47–1.72 (complex m, 12H, 2, 4, 6, 8, 9, 10-H), 2.01 (br s, 3H, 3, 5, 7-H), 4.23 (q, 4H, X region, A_3X, $J \sim 7$ Hz, C*H* NO_2). Anal. ($C_{12}H_{19}NO_2$) C, H.

5.3. 4-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-4-nitropentanoic acid (11)

To a stirred mixture of **9** (12.47 g, 59.6 mmol) in *tert*-butyl alcohol (65 mL) and ethyl acrylate (20 g, 200 mmol) was added dropwise a methanolic solution (40%) of Triton B (6.5 mL). The reaction mixture was heated at 65–70 °C for 3 h. The mixture was saponified with NaOH (1/1 in an aqueous ethanolic solution) at 80 °C for 3 h. Most of the ethanol was removed under vacuum, and the residue was diluted with water and extracted with ether (3×50 mL). The aqueous layer was acidified under ice cooling with HCl (36%), and the precipitated acid **11** was filtered, washed with water, and dried: yield 14.51 g (87%); mp 164 °C (Et_2O–petr. ether); IR (Nujol) ν 1695 cm^{-1} (C=O), 1532 cm^{-1} (NO_2); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.44 (s, 3H, CH_3), 1.56 (br s, 2H, 2-H), 1.56 (br s, 2H, 8-H), 1.60 (br s, 2H, 9-H), 1.67 (br s, 4H, 6, 10-H), 1.70 (br s, 2H, 4-H), 1.88–1.95 (8let, 1H, X region, ABXY, NO_2–C–CH_x), 2.03 (br s, 3H, 3, 5, 7-H), 2.15–2.23 (7let, 1H, A region, ABXY, CH_A–CO_2), 2.30–2.38 (7let, 1H, B region, ABXY, CH_B–CO_2), 2.71–2.78 (7let, 1H, Y region, ABXY, NO_2–C–CH_Y), 11.00 (very br s, 1H, COO*H*); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 17.3 (CH_3), 27.8 (NO_2–C–*C*H_2), 28.6 (3, 5, 7-C), 29.2 (*C*H_2CO), 36.4 (4, 6, 10-C), 36.5 (2, 8, 9-C), 39.2 (1-C), 97.6 (NO_2–*C*), 178.9 (C=O). Anal. ($C_{15}H_{23}NO_4$) C, H.

5.4. 4-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-4-nitropentanoic methyl ester (12)

To a stirred mixture of a saturated methanolic solution of gaseous HCl (80 mL, ~45%) was added, under ice cooling, nitro acid **11** (11.5 g, 40 mmol). The reaction mixture was heated at 50 °C for 3 h and at room temperature for 24 h. The resulting mixture was chilled (−20 °C) and the precipitated methyl ester **12** was filtered, washed with cool methanol, and dried: yield 11.52 g methyl ester **12** (96%); mp 95 °C (methanol); IR (Nujol) ν 1741 cm^{-1} (C=O), 1531 cm^{-1} (NO_2).

5.5. 5-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-5-methyl-2-pyrrolidinone (13)

A solution of the nitro ester **12** (5 g, 16.9 mmol) in ethanol (25 mL) was hydrogenated in the presence of Raney nickel catalyst under a pressure of 50 psi, at 75 °C, for 4 h. The suspension was filtered through Celite to remove the catalyst, and the filtrate was evaporated to dryness. The precipitated pyrrolidinone was filtered and washed with cool petroleum ether to afford neat lactone **13** (3.55 g, 90%); mp 168 °C (Et_2O); IR (Nujol) ν 3190 cm^1 (NH), 1690 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.17 (s, 3H, CH_3), 1.49–1.66 (very complex m, 13H, 1× 4-H, 2, 4, 6′, 8′, 9′, 10′-H), 1.99 (br s, 3H, 3, 5, 7′-H), 2.24–2.35 (m, 3H, 2× 3-H, 1× 4-H), 6.59 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 22.8 (CH_3), 28.2 (3, 5, 7-C), 28.3 (4-C), 30.8 (3-C), 36.0 (4, 6′, 10′-C), 36.8 (2, 8′, 9′-C), 38.4 (1′-C), 64.5 (5-C), 177.5 (2-C). Anal. ($C_{15}H_{23}NO$) C, H.

5.6. 2-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-methyl-2-pyrrolidine (3)

To a stirred suspension of $LiAlH_4$ (1.17 g, 31 mmol) in dry THF (20 mL) was added dropwise a solution of lactam **13** (2.9 g, 12.4 mmol) in dry THF (10 mL). The reaction mixture was refluxed for 25 h and then hydrolyzed with water and NaOH (10%), under ice cooling, and dried (Na_2CO_3). The inorganic precipitate was filtered off and washed with THF; the filtrate was concentrated in vacuo to give 1.05 g of the pyrrolidine **3** (quantitative yield). Recrystallization of the product from petroleum ether at −20 °C; mp 59 °C (petr. ether); ^1H NMR (400 MHz, $CDCl_3$), δ: 0.99 (s, 3H, CH_3), 1.08–1.24 (m, 1H, 3-H), 1.57–1.62 (complex m, 15H, 2′, 4′, 6′, 8′, 9′, 10′, 4-H, NH), 1.68–1.85 (m, 1H, 3-H), 1.89–1.95 (br s, 3H, 3′, 5′, 7′-H), 2.69–2.81 (m, 1H, 5-H), 2.86–2.98 (m, 1H, 5-H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 23.0 (CH_3), 26.9 (4-C), 28.6 (3′, 5′, 7′-C), 32.6 (3-C), 36.7 (4′, 6′, 9′-C), 37.2 (2′, 8′, 10′-C), 38.2 (1′-C), 47.3 (5-C), 66.3 (2-C). Hydrochloride: mp >270 °C (EtOH-Et_2O). Anal. ($C_{15}H_{26}NCl$) C, H.

5.7. (*E*)-2-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-*N*,2-dimethylpyrrolidine (14)

To a solution of pyrrolidine **3** (1.5 g, 6.8 mmol) and triethylamine (4.12 g, 40.8 mmol) in dry ether (20 mL) was added dropwise and under ice cooling a solution of ethyl chloroformate (2.95 g, 27.2 mmol) in dry ether (15 mL). The mixture was stirred for 24 h at 25 °C, poured into an ice–water mixture, and extracted with ether. The organic phase was washed with water, cold HCl (3%), water, dried (Na_2SO_4), and evaporated in vacuo. The liquid product obtained was filtered through silica gel to

afford liquid carbamate ester **14** (1.9 g, quantitative yield); IR ν 1712 cm^{-1} (C=O).

A solution of the carbamate **14** (2 g, 6.8 mmol) in dry THF (20 mL) was added dropwise under ice cooling to a suspension of $LiAlH_4$ (744 mg, 20.4 mmol) in dry THF (20 mL). The mixture was stirred for 24 h at 25 °C, hydrolyzed with water and NaOH (5%), dried (Na_2CO_3), filtered off, and concentrated in vacuo to afford a viscous oily, free amine **4**, which was converted to its hydrochloride salt (1.6 g salt, 86% yield); Hydrochloride: mp >270 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.86 (s, 3H, 2-CH_3), 1.14–1.22 (m, 1H, 3-H), 1.50–1.66 (complex m, 14H, 2′, 4′, 6′, 8′, 9′, 10′, 4-H), 1.94 (br s, 3H, 3′, 5′, 7′-H), 2.03–2.12 (m, 1H, 3-H), 2.28 (N-CH_3), 2.33–2.39 (∼q, 1H, 5-H), 2.93–2.97 (m, 1H, 5-H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 15.2 (2-CH_3), 23.7 (4-C), 28.6 (3′, 5′, 7′-C), 36.1 (3-C), 36.9 (4′, 6′, 9′-C), 37.3 (2′, 8′, 10′-C), 39.0 (N–CH_3), 40.0 (1′-C), 57.5 (5-C), 65.9 (2-C). Anal. ($C_{16}H_{28}NCl$) C, H.

5.8. 4-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-4-methyl-2-azetidinone (17)

To a solution of alkene **15** (4.16 g, 23.6 mmol) in dry ether was added dropwise at −75 °C under an argon atmosphere a solution of chlorosulfonyl isocyanate (7.41 g, 52.3 mmol) in dry ether (30 mL). After the addition, the mixture was left overnight to slowly reach ambient temperature and then concentrated under reduced pressure to 25% of its initial volume. The precipitate formed was treated with petroleum ether, the mixture was chilled to −20 °C, filtered rapidly, and washed again with cold petroleum ether. The sulfochloride **16** that was formed was then dried in vacuo: yield 6.4 g (85.3%); mp 107 °C (Et_2O/pentane); IR (Nujol) ν 1820 cm^1 (C=O).

To a solution of the sulfochloride **16** (3.5 g, 11.5 mmol) in ether (180 mL) was added an aqueous solution of Na_2SO_3 (20%). The reaction mixture was vigorously stirred for 48 h, during which time the pH of the aqueous phase was kept between 8 and 9 by adding aq KOH (10%). The organic layer was separated, the aqueous layer was extracted twice with ether, and the combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to afford β-lactam **17** (2.4 g, quantitative yield); mp 144 °C (Et_2O); IR (Nujol) ν 3221 cm^1 (NH), 1722 cm^{-1} (C=O); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.33 (s, 3H, CH_3), 1.48–1.97 (complex m, 15H, adamantane-H), 2.30–2.98 (q, 2H, AB, $J_{AB} \sim 15$ Hz, 3-H), 6.39 (s, 1H, NH). Anal. ($C_{14}H_{21}NO$) C, H.

5.9. 2-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-methyl azetidine (5)

To a stirred suspension of $LiAlH_4$ (0.8 g, 21 mmol) in dry THF (20 mL) was added dropwise a solution of the β-lactam **17** (1.82 g, 8.3 mmol) in dry THF (20 mL). The reaction mixture was refluxed for 25 h and then hydrolyzed with water and NaOH (10%) under ice cooling and dried (Na_2CO_3). The inorganic precipitate was filtered off, washed with THF, and the filtrate was concentrated in vacuo to give 1.68 g of the solid azetidine **5** (quantitative yield). The product was recrystallized from *n*-pentane at −20 °C; mp 82 °C (*n*-pentane); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.28 (s, 3H, CH_3), 1.56–1.71 (complex m, 13H, 2′, 4′, 6′, 8′, 9′, 10′, 3-H), 1.97 (br s, 3H, 3′, 5′, 7′-H), 2.12 (br s, 1H, NH), 2.34–2.48 (m, 1H, 3-H), 3.08–3.20 (m, 1H, 4-H), 3.42–3.54 (∼q, 1H, 4-H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 23.4 (CH_3), 26.9 (3-C), 28.3 (3′, 5′, 7′-C), 35.3 (4′, 6′, 9′-C), 37.0 (2′, 8′, 10′-C), 39.9 (1′, 4-C), 67.5 (2-C). Anal. ($C_{14}H_{23}N$) C, H.

5.10. (*E*)-2-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-*N*,2-dimethyl azetidine (6)

To a solution of azetidine **5** (1.6 g, 7.8 mmol) and triethylamine (4.72 g, 46.8 mmol) in dry ether (30 mL) was added dropwise and under ice cooling a solution of ethyl chloroformate (3.38 g, 31.2 mmol) in dry ether (20 mL). The mixture was stirred for 24 h at 25 °C, poured into an ice–water mixture, and extracted with ether. The organic phase was washed with water, cold HCl (3%), water, and dried (Na_2SO_4). The mixture was evaporated in vacuo to afford the carbamate ester **18** as a liquid (2.1 g, quantitative yield); IR ν 1706 cm^{-1} (C=O).

A solution of carbamate **18** (2.2 g, 7.9 mmol) in dry THF (20 mL) was added dropwise under ice cooling to a suspension of $LiAlH_4$ (900 mg, 23.8 mmol) in dry THF (20 mL). The mixture was stirred for 24 h at 25 °C, hydrolyzed with water and NaOH (5%), dried (Na_2CO_3), filtered off, and evaporated in vacuo to afford amine **6** as a viscous oil, which was chromatographed on silica gel (pet. ether/ether 1:1 as an eluent) to afford 1.6 g of the solid *N*-methyl azetidine (92.5%). The product can alternatively be purified by a recrystallization from *n*-pentane at −20 °C; mp 60 °C (*n*-pentane); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.09 (s, 3H, 2-CH_3), 1.19–1.28 (m, 1H, 3-H), 1.40–1.69 (complex m, 12H, 2′, 4′, 6′, 8′, 9′, 10′-H), 1.94 (br s, 3H, 3′, 5′, 7′-H), 2.14 (s, 3H, N-CH_3), 2.15–2.29 (∼q, 1H, 3-H), 2.66–2.78 (m, 1H, 4-H), 3.15–3.24 (m, 1H, 4-H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 12.0 (2-CH_3), 24.4 (3-C), 28.5 (3′, 5′, 7′-C), 36.4 (4′, 6′, 9′-C), 37.2 (2′, 8′, 10′-C), 37.9 (1′-C), 39.3 (N-CH_3), 50.2 (4-C), 70.4 (2-C). Anal. ($C_{15}H_{25}N$) C, H.

5.11. 2-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-2-methyl aziridine (7)

To a well-stirred and ice-cooled solution of alkene **15** (4 g, 22.7 mmol) in dimethylformamide (35 mL) were slowly added sodium azide (7.3 g, 112 mmol) in water (12 mL) and then *N*-bromosuccinimide (5.65 g, 31.7 mmol) in small successive portions. After stirring for 6 h under ice-cooling, the reaction mixture was left overnight at 4 °C and then extracted with petroleum ether. The organic extracts were washed with water and dried (Na_2SO_4). Removal of the solvent at 40 °C under reduced pressure afforded bromoazide **19** as an oil (6 g, 89%) and some unreacted alkene **15**; IR ν

2106 cm^{-1} (–N=N^+=N^-); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.47 (s, 3H, CH_3), 1.58–1.82 (complex m, 12H, 2, 4, 6, 8, 9, 10-H), 2.05 (br s, 3H, 3, 5, 7-H), 3.57–3.80 (m, 2H, CH_2Br).

The bromoazide **16** was used without any further purification for the preparation of the aziridine **7**.

To a stirred suspension of $LiAlH_4$ (10 g, 263 mmol) in dry ether (80 mL) was added dropwise a solution of the bromoazide **19** (8.25 g, 27.6 mmol) in dry ether (80 mL). The reaction mixture was stirred for 24 h at room temperature. Work-up as usual afforded 6 g of an oily residue, which was purified by column chromatography on silica gel with ether, ether–methanol (3:1), and ether–methanol (1:1) as eluents. The second fraction was characterized as the aziridine **7** (2.5 g, 42.3%) and the third fraction as the allylic alcohol **21** (1.02 g, 17.1%). IR ν 1634 cm^{-1} (C=C), 3366–3294 cm^{-1} (OH); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.35–2.02 (complex m, 15H, adamantane-H, CH_2OH), 3.28 (s, 2H, CH_2OH), 4.83–4.93 (d, 2H, vinyl-H). Anal. ($C_{12}H_{20}O$) C, H.

The first fraction was found to be a mixture of two different products, which were also separated by column chromatography on silica gel, with pentane, pentane–ether (1:1) to afford the liquid alkene **15** (1.17 g) and the solid tertiary alcohol **20** (1.19 g, 19.8%): mp 77 °C (hexane); IR (Nujol) ν 3499–3230 cm^{-1} (OH); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.11 (s, 6H, methyl-H), 1.55–1.98 (complex m, 16H, adamantane-H,-O*H*).

5.11.1. Aziridine 7. Mp 42 °C (pentane); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.33 (s, 3H, CH_3), 1.27 (~s, 1H, 3-H), 1.47–1.67 (complex m, 12H, 2′, 4′, 6′, 8′, 9′, 10′-H), 1.71 (~s, 1H, 3-H), 1.95 (br s, 3H, 3′, 5′, 7′-H), 3.42 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 20.5 (CH_3), 28.4 (3′, 5′, 7′-C), 29.0 (3-C), 33.7 (2-C), 36.9 (4′, 6′, 9′-C), 38.0 (2′, 8′, 10′-C), 40.6 (1′-C). Anal. ($C_{13}H_{21}N$) C, H.

5.12. (*E*)-2-(1-Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-*N*,2-dimethyl aziridine (8)

To a stirred mixture of aziridine **7** (0.7 g, 3.6 mmol), acetonitrile (15 mL), and an aqueous formaldehyde solution (37%) (3 mL, 37 mmol) was added $NaCNBH_3$ (0.69 g, 10.9 mmol) in one portion. Acetic acid (0.36 mL) was added during a 10 min period, under stirring, until the pH of the solution became neutral. Stirring was continued for two additional hours during which time the pH was maintained neutral by the addition of acetic acid (0.36 mL). After 0.5 h of stirring, ether (70 mL) was added and the mixture was washed three times with KOH (20 mL, 1 M), brine, dried over Na_2CO_3, and evaporated to dryness under vacuum to give 1.0 g of a viscous oil. Flash chromatography on silica gel using ether as an eluent gave the solid aziridine **8** (0.6 g, 90%); mp 135 °C (pentane); ^1H NMR (400 MHz, $CDCl_3$), δ: 1.20 (s, 3H, 2-CH_3), 1.43–1.80 (complex m, 12H, 2′, 4′, 6′, 8′, 9′, 10′-H), 1.93 (s, 1H, 3-H), 2.00 (br s, 3H, 3′, 5′, 7′-H), 2.23 (s, 3H, N-CH_3), 2.61 (s, 1H, 3-H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 16.4 (2-CH_3), 19.1 (N-CH_3), 27.9 (3′, 5′, 7′-C), 34.6 (1′, 2-C), 34.8 (3-C), 36.4 (4′, 6′, 9′-C), 37.8 (2′, 8′, 10′-C). Anal. ($C_{14}H_{23}N$) C, H.

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