Design and synthesis of bioactive 1,2-annulated adamantane derivatives

Grigoris Zoidis,[a] Andrew Tsotinis,[a] Nicolas Kolocouris,*[a] John M. Kelly,[b] S. Radhika Prathalingam,[b] Lieve Naesens[c] and Erik De Clercq[c]

Received 25th March 2008, Accepted 6th June 2008
First published as an Advance Article on the web 9th July 2008
DOI: 10.1039/b804907f

Adamantanopyrrolidines **8**, **9** and **10**, adamantanopyrrolidines **16** and **18**, adamantanoxazolone **20**, adamantanopyrazolone **23**, adamantanopyrazolothione **24** and adamantanocyclopentanamine **32** were synthesized and tested for anti-influenza A virus and trypanocidal activity. The stereoelectronic requirements for optimal antiviral and trypanocidal potency were investigated. Pyrrolidine **16** proved to be the most active of the compounds tested against influenza A virus, being 4-fold more active than amantadine, equipotent to rimantadine and 19-fold more potent than ribavirin. Oxazolone **20** showed significant trypanocidal activity against bloodstream forms of the African trypanosome, *Trypanosoma brucei*, being approximately 3 times more potent than rimantadine and almost 50-fold more active than amantadine.

Introduction

The outbreaks of avian influenza A (H5N1) in Southeast Asia, the increasing geographic distribution of this epizootic virus and its ability to transfer to humans and cause severe infection, such as pneumonia, have raised serious concerns regarding the control measures that should be undertaken to curb a potential pandemic[1–3] and about the shortages in both the number and supply of effective anti-influenza virus agents.[4,5] There are, in principle, two mechanisms by which pandemic influenza could originate: first, by direct transmission, perhaps of a mutated virus from animal (bird) to humans, as happened in 1918 with the 'Spanish flu' (H1N1)[6] or second, through reassortment of an avian influenza virus with a human influenza virus, as occurred in 1957 with the 'Asian flu' (H2N2) and, again, in 1968 with the 'Hong Kong flu' (H3N2).[7]

The adamantane derivatives amantadine and rimantadine (α-methyl adamantanemethanamine) are specifically active against influenza A. They interfere with the viral uncoating process through a direct interaction with the matrix (M2) protein, which functions as a channel for hydrogen ions (protons).[8] These drugs have been postulated to block the transmembrane channel formed by the tetrameric M2 helix.[9] Over the past twelve years our group has synthesized many potent aminoadamantane derivatives, mainly heterocycles and carbocycles, the most potent of which usually bear a 5-membered ring (I–IV) and are shown in Fig. 1.[10–12] It is noteworthy that these, bearing the pharmacophore group of rimantadine and a carbon skeleton in the vicinity of the adamantane moiety, have increased anti-influenza A virus activity and exhibit excellent selectivity.

Another major public health problem in many areas of sub-Saharan Africa is sleeping sickness (human African trypanosomiasis, HAT), which currently kills *ca.* 50 000 people each year.[13] Recently, the annual incidence has varied between 50 000 and 300 000 cases, with about 60 million people at risk.[14] The disease is caused by the protozoan parasites *Trypanosoma brucei gambiense* (western and central Africa) and *Trypanosoma brucei rhodesiense* (eastern and southern Africa) and is invariably fatal unless treated. In the past 25 years, only one single drug, eflornithine, has been approved for HAT therapy.[15] Moreover, all four drugs in use (suramin, pentamidine, melarsoprol and eflornithine) require hospitalization for administration, can be expensive and often produce severe side effects. In addition, drug resistance is commonly observed, and suramin and pentamidine are not effective against the later stages of the disease, which occurs when the parasites gain access to the central nervous system.[16,17] Treatment of late stage East African trypanosomiasis is a particular problem, since this sub-species is refractory to eflornithine, and melarsoprol, which is the only effective drug, causes arsenic encephalopathy with 5 to 10% patient mortality.[18] Although there is an urgent need for new antitrypanosome drugs, the pharmaceutical industry pays little attention to this relatively unprofitable area.

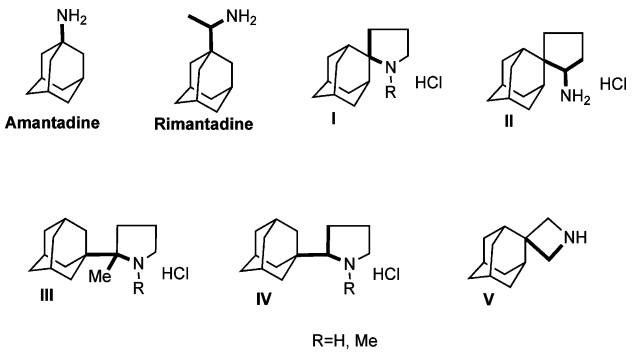


Fig. 1

During the last decade, there have been reports that bloodstream forms of the African trypanosome, *T. brucei*, are sensitive to the anti-influenza virus drug rimantadine ($IC_{50} = 7\ \mu M$) and to a lesser

[a]*Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupoli-Zografou, GR-15771, Athens, Greece*
[b]*London School of Hygiene and Tropical Medicine, Department of Infectious and Tropical Diseases, Keppel Street, London, UK, WC1E 7HT*
[c]*Rega Institute, Department of Microbiology and Immunology, Katholieke Universiteit Leuven, Minderbroedersstraat 10, 3000 Leuven, Belgium*

extent amantadine. The trypanocidal activity is pH-dependent and is enhanced with increasing alkalinity. Rimantadine is also toxic to the trypanosomatid parasites *Trypanosoma cruzi* and *Leishmania major*.[19] More recently, a number of other aminoadamantane derivatives have been evaluated for their trypanocidal properties. These studies revealed a correlation between increased lipophilicity and potency against *T. brucei*.[20] By investigating the trypanocidal properties of other lipophilic aminoadamantane derivatives we hoped to provide greater insight into the chemical features responsible for this activity. Here we report that the compounds adamantanoxazolone **20** and adamantanocyclopentanamine **32** display considerable activity *in vitro* against bloodstream form *T. brucei.*

We now describe the synthesis and biological evaluation of the adamantanopyrrolidines **8**, **9** and **10**, adamantanopyrrolidines **16** and **18**, adamantanoxazolone **20**, adamantanopyrazolone **23**, adamantanopyrazolothione **24** and adamantanocyclopentanamine **32** (Fig. 2), and show that they contain the structural features necessary for antiviral and trypanocidal activity.

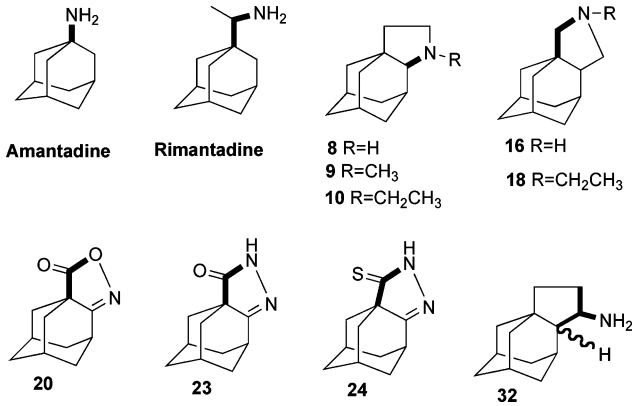


Fig. 2

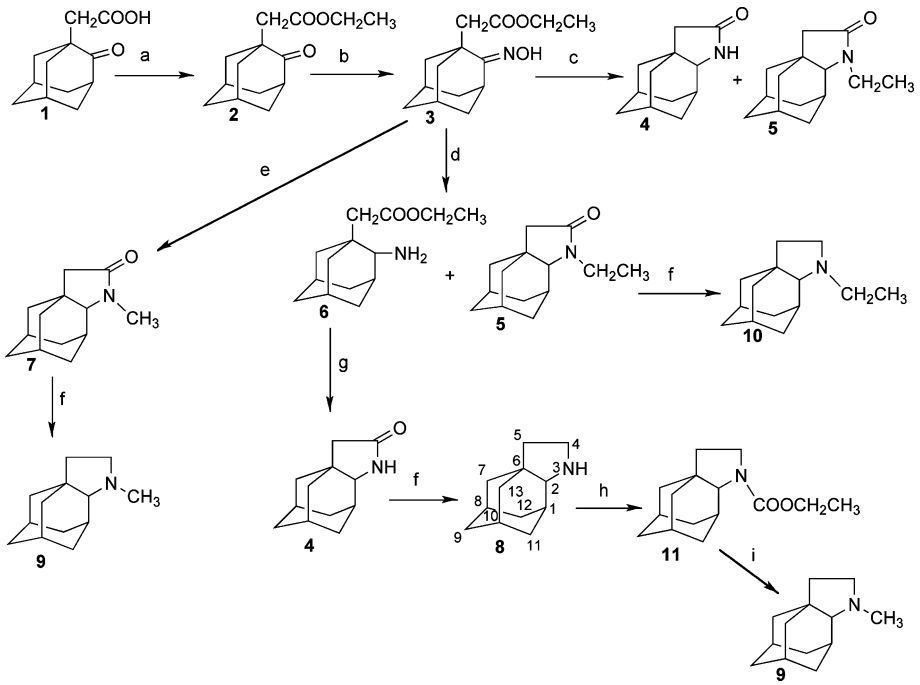
Results and discussion

Chemistry

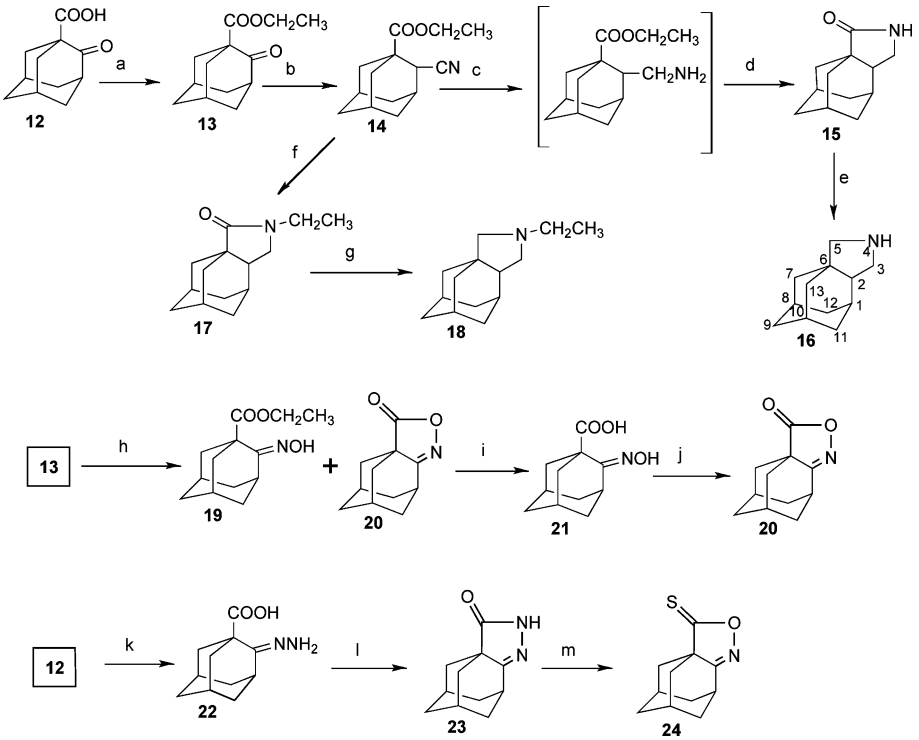
For the synthesis of the pyrrolidine **8**, 2-oxo-1-adamantanacetic acid **1**[21,22] was used as the starting material (Scheme 1). The acid **1** was esterified to the ethyl ester **2**, which on treatment with hydroxylamine hydrochloride in the presence of sodium acetate gave the oxime ester **3**. Catalytic hydrogenation of **3** over Raney nickel, under different reaction conditions, gave either a mixture of lactams **4** and **5** or lactam **7**. Reduction of lactams **4**, **5** and **7** with $LiAlH_4$ in THF gave the pyrrolidines **8**[23], **9** and **10**. *N*-Acylation of the pyrrolidine **8** followed by reduction of the intermediate carbamate **11** with $LiAlH_4$ gave the *N*-methyl derivative **9**.

The synthetic route to the pyrrolidine **16** is shown in Scheme 2 and involved ketoacid **12**[24] as the starting material, which was esterified to the ketoester **13**. Reductive cyanation of **13** was accomplished in high yield using toluenesulphonylmethyl isocyanide (TOSMIC).[25] Hydrogenation of cyanoester **14** over Raney nickel catalyst in ethanol gave either lactams **15** or **17**, which were reduced with $LiAlH_4$ in THF to the pyrrolidines **16** and **18**, respectively.

N-Alkylation of heterocyclic secondary amines during hydrogenation has rarely been reported in the literature and only



Scheme 1 *Reagents and conditions*: (a) (I) $SOCl_2$, 50 °C, 30 min, (II) abs. CH_3CH_2OH (quant.); (b) $NH_2OH{\cdot}HCl$, $CH_3COONa{\cdot}3H_2O$, CH_3CH_2OH : H_2O (5 : 1), reflux, 1 h (97%); (c) (I) H_2/Ni-Raney, EtOH, 55 psi, 120 °C, 10 h, (II) xylene, reflux, 12 h (**5**: 58%, **4**: 40%); (d) H_2/Ni-Raney, EtOH, 55 psi, 100 °C, 3 h, (**5**: 23%, **6**: 34%); (e) (I) H_2/Ni-Raney, MeOH, 55 psi, 200 °C, 4 h, (II) xylene, reflux, 20 h (64%); (f) $LiAlH_4$, THF, 5 h, reflux (94–96%); (g) xylene, reflux, 12 h, (quant.); (h) Et_3N, $ClCOOC_2H_5$, ether, 24 h, 25 °C (96%); (i) $LiAlH_4$, THF, 24 h, 25 °C (93%).



Scheme 2 *Reagents and conditions*: (a) (I) $SOCl_2$, 65 °C, 15 min, (II) abs. EtOH (quant.); (b) TOSMIC, abs. EtOH, DME, *t*-BuOK, 0 °C, argon, 20 °C, 30 min and 48 °C, 1 h (74%); (c) H_2/Ni-Raney, MeOH, 62 psi, 60 °C, 6 h; (d) xylene, reflux, 10 h (40%); (e) $LiAlH_4$, THF, 18 h, reflux (70%); (f) H_2/Ni-Raney, EtOH, 65 psi, 140 °C, 3 h (46%); (g) $LiAlH_4$, THF, 13 h, reflux (92%); (h) $NH_2OH{\cdot}HCl$, $CH_3COONa{\cdot}3H_2O$, EtOH : H_2O (5 : 1), reflux, 3 h (**19**: 85%, **20**: 15%); (i) NaOH, EtOH, H_2O, 3.5 h, 60 °C and then conc. HCl (97%); (j) sublimation, 10^{-2} mmHg (79%); (k) NH_2NH_2, abs. EtOH, 30 min, reflux (72%); (l) sublimation, 10^{-2} mmHg (93%); (m) Lawesson's reagent, toluene, 12 h, reflux (93%).

in cases where the reaction is run at high temperatures.[26] It is noteworthy that at 140 °C, and after 3 h of hydrogenation, only the *N*-ethyl lactam **17** was isolated from the reaction mixture. Moreover, its formation, though partial, was also noticed at temperatures below 100 °C. A plausible explanation for the observed *N*-alkylation of lactams **4** and **15** might be the anticipated stability to disproportionation of the solvent (primary alcohols: ethanol, methanol), which, under the specific reaction conditions is rendered sufficiently electrophilic. Nucleophilic attack on the latter by the primary aminoesters, formed during the hydrogenation, gives the secondary aminoesters which, in turn, cyclize to the corresponding *N*-alkylated lactams.

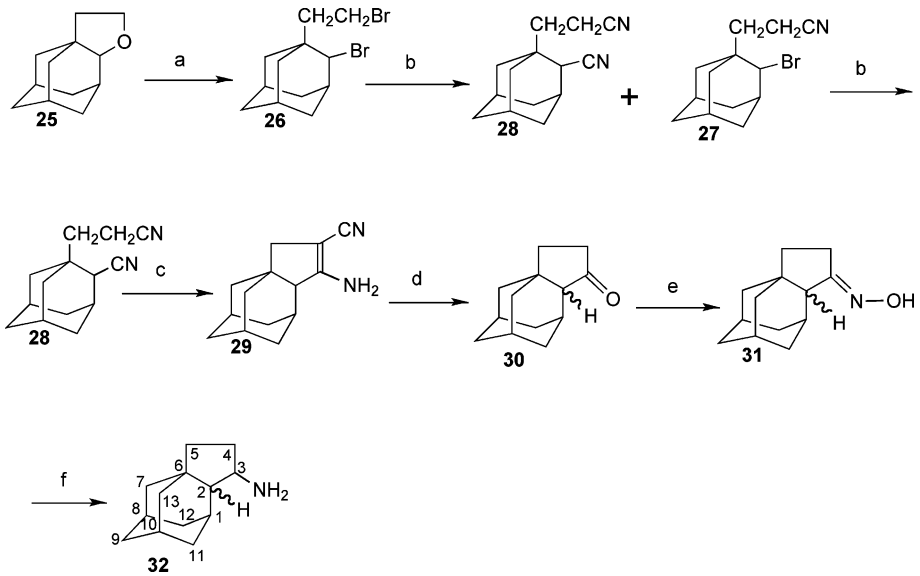
Treatment of the ketoester **13** with hydroxylamine gave a mixture of the oxime **19** and the oxazolone **20**. Saponification of this mixture followed by sublimation gave **20**.[27] Treatment of 2-oxo-1-adamantane carboxylic acid **12** with hydrazine followed by sublimation gave the pyrazolone **23**.[28] Compound **23** was refluxed in toluene with *p*-methoxyphenylthionophosphine sulfide (Lawesson's reagent) to give the pyrazolothione **24** in 93% yield.[29]

The condensed cyclopentanamine **32** was prepared by the route shown in Scheme 3. Reaction of tetrahydrofuranic derivative **25**[21b] with triphenyldibromophosphorane in benzonitrile gave the dibromine **26** in 84% yield,[30] which on heating for 1 h with NaCN–DMSO at 155 °C gave a separable mixture of bromonitrile **27** and dinitrile **28** in a 4 : 1 ratio. A subsequent treatment of this mixture with NaCN–DMSO gave **28** in 89% yield. The dinitrile **28** was converted to the cyanoenamine **29** through Thorpe–Ziegler reaction, using LDA in THF.[31] Acidic hydrolysis of the enamine **29** with 33% H_2SO_4 and glacial acetic acid led to the key cyclopentanone **30**. The desired amine **32** was obtained as a single racemic diastereomer on Raney-Ni hydrogenation of the racemic ketone oxime **31**.

Biological activity

The antiviral efficacy of the new aminoadamantane heterocycles **8**, **9**, **10**, **16**, **18**, **20**, **23**, **24** and **32** was examined *in vitro* against influenza A (H3N2) and was compared to the activity of amantadine, rimantadine and ribavirin (Table 1). The antiviral assay used was identical to that previously reported.[32,33]

The data presented in Table 1 indicate that compounds **8** and **16** elicit potent anti-influenza A virus activity, with a selectivity index (SI) of 217 and 200, respectively. Pyrrolidine **16** was endowed with the most potent anti-influenza A virus activity; it proved to be at least 4-fold more potent than amantadine, equipotent to rimantadine and 19-fold more active than ribavirin. Cyclopentanamine **32** exhibited a 2-fold higher potency than amantadine and had slightly lower potency than rimantadine. The activity of **32** is not expected to be impaired by the fact that this compound is racemic, as we[11d] and others[34] have found that the absolute configuration of the chiral centre in rimantadine and its analogues does not affect their biological behaviour. It is noteworthy that pyrrolidine **8** exhibited 6-fold lower potency than rimantadine, but displayed the highest selectivity index (more than 4-fold higher than that of amantadine) of any of the test



Scheme 3 *Reagents and conditions*: (a) Br_2, C_6H_5CN, Ph_3P, 124 °C, 4 h, (84%); (b) NaCN, DMSO, 145 °C, 2 h (**27**: 75%, **28**: 18%); (c) LDA, THF, −80 °C (quant.); (d) H_2SO_4 (33%), glacial CH_3COOH, reflux, 20 h (quant.); (e) $NH_2OH{\cdot}HCl$, $CH_3COONa{\cdot}3H_2O$, abs. EtOH–H_2O (14 : 1), 6h, reflux (94%); (f) EtOH, Ni-Raney, 50 psi, 70 °C, 4 h (86%).

Table 1 Anti-influenza virus A (H3N2) activity and cytotoxicity of 1,2-annulated adamantane five-membered heterocyclic and carbocyclic analogues **8**, **9**, **10**, **16**, **18**, **20**, **23**, **24** and **32**[a]—in MDCK cells[b]

Compound	EC_{50}[c,e]/μM	MCC[d,e]/μM	SI (ratio MCC : EC_{50})
8	2.20 ± 1.10 (4)	468	217
9	3.40 ± 2.70 (4)	439	128
10	7.70 ± 2.90 (3)	83	11
16	0.46 ± 0.28 (4)	94	200
18	2.40 ± 1.60 (3)	83	35
20	N/A[f]	105	< 5
23	≥ 323±189(3)	> 525	≥ 2
24	N/A[f]	> 525	< 5
32	1.10 ± 1.60 (3)	88	77
Amantadine	2.00	> 100	> 51
Rimantadine	0.36	> 100	> 276
Ribavirin	8.70	20	2

[a] Pyrrolidines **8**, **9**, **10**, **16** and **18** were tested as hydrochlorides. Oxazolone **20**, pyrazolone **23** and pyrazolothione **24** were tested as free bases. [b] MDCK, Madin-Darby canine kidney cells; virus strain: influenza A/Hong Kong/7/87 (H3N2). [c] Concentration producing 50% inhibition of the virus-induced cytopathic effect, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay. [d] Minimal cytotoxic concentration, or concentration that causes microscopically detectable changes in cell morphology. [e] Data are shown as mean ± SD (in brackets: number of independent determinations). [f] N/A: not active at subtoxic concentrations or the highest concentration tested (~500 μM).

compounds. Methyl and ethyl substitution at the nitrogen atom of all heterocycles (compounds **9**, **10** and **18**) caused a reduction in anti-influenza virus A activity.

The numbered compounds in Table 2 were first tested at 5 μg ml^{-1} (20–30 μM, depending on the compound) against bloodstream form *T. brucei* (strain 427) cultured at pH 7.4. Compounds displaying significant activity were assessed further and their IC_{50} and IC_{90} values determined by investigating growth inhibition over a range of concentrations, from 1–20 μM.

Table 2 Susceptibility of cultured bloodstream form *T. brucei* to aminoadamantane derivatives

Compound	IC_{50}/μM	IC_{90}/μM
8	>20	—
9	>20	—
10	>20	—
16	18.06 ± 0.56	>25
18	>20	—
20	2.87 ± 0.36	3.91 ± 0.36
23	>20	—
24	>20	—
32	4.47 ± 0.87	7.46 ± 0.43
Rimantadine	7.04 ± 0.12	13.97 ± 1.7

The values shown are the mean ± standard deviation from three experiments, with the values for rimantadine shown for comparison.

In the preliminary screen, bloodstream form *T. brucei*, seeded at an initial density of 0.25 × 10^5 ml^{-1}, were cultured for 3 days in the presence of aminoadamantane derivatives at 5 μg ml^{-1}. At this concentration, compounds **8**, **9**, **10**, **18** and **23** showed a slight (30–60%) inhibition of parasite growth, while pyrrolidine **16** was more active (70% growth inhibition). Further assessment showed this analogue to be at least 7-fold more potent than amantadine, although 2-fold less active than rimantadine (Table 2). Oxazolone **20** and cyclopentanamine **32** were the most active of the compounds tested, resulting in lysis of all trypanosomes in the culture at 5 μg ml^{-1}. Oxazolone **20** was found to be around 3 times more active than rimantadine and at least 45 times more active than amantadine, while cyclopentanamine **32** exhibited around 2-fold higher potency than rimantadine and 30-fold more than amantadine. This contrasted with the limited activity displayed by the pyrrolidines **8** and **16**, and their *N*-alkyl derivatives **9**, **10** and **18**.

Conclusion

The aim of this study was to examine the anti-influenza A virus and trypanocidal activity of 1,2-annulated adamantane analogues **8**, **9**, **10**, **16**, **18**, **20**, **23**, **24** and **32** and to correlate their potency with the distance of the amine nitrogen atom from the 2-adamantyl carbon. Two interesting points arise from this analysis in the case of compounds active against influenza A virus: (i) moving the amine nitrogen atom from the 2-adamantyl carbon enhances activity (*compound* **8** *vs.* **16** *and* **32**, Table 1) (ii) nonsubstituted compounds are more active, with *N*-alkylation causing a dramatic reduction in potency (*compound* **8** *vs.* **9** *and* **10**, *and compound* **16** *vs.* **18**).[33] For the most active compounds, the amine nitrogen lies a distance of 1.5–2.5 Å away from the 2-adamantyl carbon. Interestingly, we could find no obvious correlation between the trypanocidal activity of the analogues and their anti-influenza virus properties. For example, compound **20** displayed significant activity against *T. brucei*, but was relatively ineffective in the antiviral assays. In contrast, compounds **8–10** displayed considerable potency against the influenza virus, but only minimal trypanocidal activity. On the other hand, compound **32** was active in both cases (Table 1 and 2). This lack of correlation is consistent with what we previously observed for other aminoadamantanes.[20] Determination of the mechanism of action of the aminoadamantane derivatives in trypanosomes, including the identification of the target, will therefore be of considerable importance. Such information should aid the design of derivatives with enhanced activity. The predominant anti-influenza virus properties of aminoadamantanes are mediated by their channel-blocking activities. The interaction between the drugs and the M2 protein is highly specific. In other cases where aminoadamantanes are therapeutically active, channel blocking activity is thought to be the predominant mechanism involved.[35–37] One possible explanation for the trypanocidal activities of aminoadamantanes, is that they also target an essential membrane-localized ion channel or transporter in *T. brucei*, but that the differences observed here, in terms of efficacy between derivatives, reflect structural/functional aspects of the target.

Experimental

Melting points were determined using a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker MSL 400 and AC 200 spectrometers, respectively, using $CDCl_3$ as the solvent and TMS as the 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.

Ethyl (2-oxotricyclo[3.3.1.1^{3,7}]dec-1-yl)acetate (2)

A mixture of ketoacid **1** (4.00 g, 19.1 mmol) and thionyl chloride (6 ml) was heated at 50 °C for 30 min. The excess thionyl chloride was removed under vacuum, and the resulting chloride was esterified in an ethanolic solution (30 ml). After 24 h, **2** was isolated in quantitative yield (4.50 g) as a clear oil; ν_{max}/cm^{-1} 1731 (CO), 1711 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.24 (3H, t, *J* 7.1, C*H*$_3$) 1.58–2.08 (12H, complex m, 4, 5, 6, 7, 8, 9, 10-H), 2.34 (2H, s, -C*H*$_2$CO$_2$), 2.58 (1H, s, 3-H), 4.11 (2H, d, *J* 7.1, CO$_2$C*H*$_2$CH$_3$).

Ethyl [2-(hydroxyimino)tricyclo[3.3.1.1^{3,7}]dec-1-yl]acetate (3)

To a solution of ketoester **2** (4.11 g, 17.4 mmol) in ethanol (30 ml) was added hydroxylamine hydrochloride (1.20 g, 17.4 mmol) and $CH_3COONa{\cdot}3H_2O$ (2.50 g, 19.0 mmol). The mixture was refluxed for 1 h and was then evaporated to dryness under reduced pressure. Water was added and the mixture was extracted with Et_2O (4 × 35 ml). The organic phase was washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure to afford oxime ester **3** (4.21 g, 97%); mp 102 °C (*n*-hexane); ν_{max}/cm^{-1} 3475 (OH), 1727 (CO), 1653(CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.22 (3H, t, *J* 7.1, C*H*$_3$), 1.73–1.94 (10H, complex m, 4, 6, 8, 9, 10-H), 2.03 (2H, br s, 5, 7-H), 2.40 (2H, s, C*H*$_2$CO$_2$-), 3.66 (1H, s, 3-H), 4.08 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 8.52 (1H, br s, N-O*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.2 (*C*H$_3$), 28.0 (5, 7-C), 28.4 (3-C), 35.6 (8, 10-C), 37.2 (4, 9-C), 39.9 (1-C), 42.2 (*C*H$_2$COO-), 43.4 (6-C), 60.0 (*C*H$_2$), 166.5 (*C*=NOH), 172.0 (C=O). Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42. Found: C, 66.77; H, 8.40.

3-Azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecan-4-one (4) and 3-ethyl-3-azatetracyclo [6.3.1.1^{6,10}.0^{2,6}]tridecan-4-one (5)

A solution of the oxime ester **3** (4.60 g, 18.3 mmol) in dry ethanol (30 ml) was hydrogenated in the presence of Raney nickel catalyst under a pressure of 55 psi, at 120 °C, for 10 h. The solution was filtered to remove the catalyst, and the filtrate evaporated to dryness to afford an oily product, which was refluxed in xylenes (20 ml) for 12 h. The solvent was removed by evaporation, and the residue extracted with petroleum ether. The precipitated lactam was filtered and washed with *n*-pentane (0.89 g). The filtrate was evaporated under vacuum, and the oily residue was purified by flash column chromatography on silica gel eluting with Et_2O–THF (1 : 1) to give first the liquid *N*-ethyl lactam **5** (2.31 g, 58%) and then lactam **4** (0.5 g, overall yield 40%). Compound **4**, white solid; mp 156 °C (ether) (lit:[21a] 153–155 °C); ν_{max}/cm^{-1} 3185, 3088 (NH), 1684 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.37 (1H, d, *J* 12.2, 13e-H), 1.57 (1H, d, *J* 10.5, 11e-H), 1.64–1.86 (10H, complex m, 5*H*$_A$, 7, 9, 10, 11a, 12, 13a-H), 2.02 (3H, q, 1, 5*H*$_B$, 8-H), 3.43 (1H, s, 2-H), 6.29 (1H, s, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.2 (10-C), 28.9 (8-C), 29.4 (1, 11-C), 36.7 (9-C), 37.0 (13-C), 37.1 (12-C), 38.5 (6-C), 40.0 (7-C), 46.2 (5-C), 64.0 (2-C), 179.2 (C=O).

N-ethyl lactam **5**; ν_{max}/cm^{-1} 1696 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.01 (3H, t, *J* 14.4, C*H*$_3$), 1.32 (1H, br d, *J* 13.4, 11e-H), 1.57–1.95 (11H, complex m, 5, 7, 8, 9, 11a, 12, 13e-H), 1.98 (1H, br s, 10-H), 2.10 (2H, br s, 1, 13a-H), 2.88 (1H, m, C*H*$_A$), 3.26 (1H, d, *J* 2.4, 2-H), 3.59 (1H, m, C*H*$_B$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 12.7 (*C*H$_3$), 27.0 (8-C), 28.1 (1-C), 28.8 (10-C), 30.1 (11-C), 34.2 (*C*H$_2$), 36.1 (6-C), 36.7 (13-C), 36.8 (9-C), 37.6 (7-C), 40.0 (12-C), 46.0 (5-C), 65.8 (2-C), 176.0 (C=O). Anal. calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.94; H, 9.38.

3-Methyl-3-azatetracyclo [6.3.1.1^{6,10}.0^{2,6}]tridecan-4-one (7)

A solution of oxime ester **3** (1.30 g, 5.1 mmol) in methanol was hydrogenated over Ni-Raney catalyst for 4 h, at 200 °C, and

under pressure (55 psi). The catalyst was filtered off and the solvent was evaporated under vacuum to give an oily product, which was refluxed in xylenes (10 ml) for 20 h. The solvent was evaporated, and the residue was then worked up with *n*-pentane. The precipitated lactam was filtered and washed with petroleum ether (0.41 g). The filtrate was evaporated under vacuum, and the residue was purified by flash column chromatography on silica gel using as eluents CH_2Cl_2 and then CH_2Cl_2–MeOH (1 : 1) to afford 0.26 g of *N*-methyl lactam **7** (overall yield 0.67 g, 64%) as a white solid; mp 50 °C (*n*-pentane, −20 °C); ν_{max}/cm^{-1} 1688 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.35 (1H, br d, *J* 13.0, 13e-H), 1.53–1.95 (10H, complex m, 7, 8, 9, 11, 12, 13a-H), 1.89 and 1.97 (2H, AB, J_{AB} 16.4, $5H_A$, $5H_B$), 1.99 (1H, br d, 10-H), 2.12 (1H, br d, 1-H), 2.72 (3H, s, CH_3), 3.16 (1H, d, *J* 2.0, 2-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.3 (CH_3), 27.1 (8-C), 28.4 (3-C), 29.0 (10-C), 30.0 (11-C), 36.4 (6-C), 36.6 (13-C), 36.8 (7-C), 37.7 (9-C), 39.9 (12-C), 45.9 (5-C), 68.0 (2-C), 176.5 (C=O). Anal. calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33. Found: C, 76.34; H, 9.51.

General procedures for the synthesis of pyrrolidines 8–10, 16 and 18

To a stirred suspension of $LiAlH_4$ (4 equiv.) in dry THF (50 ml) was added a solution of the requisite lactam (1 equiv.) in dry THF (40 ml). The reaction mixture was refluxed for 12 h and was then hydrolyzed with water and a 20% NaOH solution under ice-cooling. The inorganic precipitate was filtered off and washed with Et_2O, and the filtrate was evaporated under vacuum to afford a viscous oily product (yield almost quantitative). The residue was dissolved in ether and the resulting dry Et_2O solution of the free amine was treated with a saturated ethanolic solution of gaseous HCl under ice cooling. The precipitate was filtered off, washed with cold Et_2O and dried to afford the hydrochloride salt as a white solid.

3-Azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecane (8)

mp_{HCl} >260 °C (EtOH–Et_2O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.23 (1H, d, *J* 12.7, 13e-H), 1.32 (1H, q, 5A-H), 1.42–1.50 (2H, complex m, 5B, 7a-H), 1.52 (1H, br d, *J* 12.7, 11e-H), 1.67 (4H, m, 9, 12-H), 1.76–1.83 (5H, m, 7e, 11a, 10, 13a-H, N*H*), 1.94 (2H, m, 8-H, N*H*), 2.07 (1H, m, 1-H), 2.58 (1H, d, *J* 2.0, 2-H), 2.93 (1H, td, *J* 3.2, 4A-H), 3.04 (1H, m, 4B-H);); δ_C (100 MHz; $CDCl_3$; Me_4Si) 28.2 (10-C), 29.3 (8-C), 30.0 (11-C), 30.5 (1-C), 36.8 (13-C), 37.5 (9-C), 37.7 (12-C), 38.1 (5-C), 39.2 (6-C), 41.8 (7-C), 43.0 (4-C), 67.6 (2-C). Anal. calcd for $C_{12}H_{20}NCl$: C, 67.43; H, 9.43. Found: C, 67.13; H, 9.39.

3-Methyl-3-azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecane (9)

mp_{HCl} 237 °C (EtOH–Et_2O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.23 (1H, d, *J* 12.2, 13e-H), 1.31 (2H, t, *J* 8.2, 5-H), 1.45 (2H, m, 7, 11e-H), 1.59 (3H, m, 9, 12a-H), 1.77–1.96 (8H, complex m, 1, 2, 7e, 8, 11a, 10, 12e, 13a-H), 2.09 (1H, m, 4A-H), 2.22 (3H, s, CH_3), 3.19 (1H, m, 4B-H);); δ_C (100 MHz; $CDCl_3$; Me_4Si) 28.6 (8, 10-C), 29.3 (1-C), 30.1 (11-C), 35.9 (5-C), 37.0 (12-C), 37.6 (9-C), 39.3 (13-C), 39.5 (6-C), 40.6 (CH_3), 42.6 (7-C), 53.7 (4-C), 75.2 (2-C). Anal. calcd for $C_{13}H_{22}NCl$: C, 68.55; H, 9.73. Found: C, 68.14; H, 9.77.

3-Ethyl-3-azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecane (10)

mp_{HCl} >250 °C (EtOH–Et_2O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.03 (3H, t, *J* 7.3, CH_3), 1.18 (1H, d, *J* 12.2, 13e-H), 1.28 (2H, m, 12-H), 1.39 (3H, m, 5A, 9-H), 1.55–1.64 (3H, m, 7a, 9-H), 1.76 (3H, m, 5B, 7e, 10-H), 1.90–1.98 (6H, complex m, 1, 2, 8, 13a-H, CH_A, N*H*), 2.07 (1H, m, 4A-H), 2.75 (1H, m, CH_B), 3.16 (1H, m, 4B-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 13.6 (CH_3), 28.6 (10-C), 29.4 (8-C), 29.6 (1-C), 30.0 (11-C), 35.8 (12-C), 36.9 (8-C), 37.6 (9-C), 39.0 (13-C), 39.4 (6-C), 42.4 (5-C), 47.9 (CH_2), 50.4 (4-C), 73.3 (2-C). Anal. calcd for $C_{14}H_{24}NCl$: C, 69.54; H, 10.00. Found: C, 69.74; H, 10.11.

3-Methyl-3-azatetracyclo [6.3.1.1^{6,10}.0^{2,6}]tridecane (9)

To a solution of pyrrolidine **8** (0.40 g, 2.2 mmol) and triethylamine (1.39 g, 13.8 mmol) in dry ether (20 ml) was added, dropwise and under ice cooling, a solution of ethyl chloroformate (1.00 g, 9.2 mmol) in dry ether (10 ml). The mixture was stirred for 24 h at 25 °C, poured onto an ice–water mixture and extracted with ether. The organic phase was washed with water, cold HCl (3%) and water, dried (Na_2SO_4) and evaporated *in vacuo*. The liquid carbamate ester **11** (0.54 g, 96%) was used without further purification for the preparation of the derivative **9**.

A solution of the carbamate **11** (0.50 g, 2.0 mmol) in dry THF (10 ml) was added dropwise under ice cooling to a suspension of $LiAlH_4$ (1.00 g, 26 mmol) in dry THF (10 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*. The residue was dissolved in ether and extracted with a 10% HCl solution. The aqueous phase was made alkaline with solid Na_2CO_3, and the oil that separated was extracted with ether, dried (Na_2CO_3), and evaporated to dryness under vacuum to give 0.37 g (93%) of a viscous oily, free amine **9**, which was converted to its hydrochloride salt (0.42 g); hydrochloride: mp >237 °C.

Ethyl (2-oxotricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (13)

A mixture of the acid **12** (1.08 g, 5.5 mmol) and thionyl chloride (4 ml) was heated at 65 °C for 15 min. The excess thionyl chloride was removed under vacuum, and the resulting chloride was esterified in an ethanolic solution (20 ml) to give, after 1 h at rt and 0.5 h at 70 °C, 1.14 g (quantitative yield) of ethyl **13** as a white solid; ν_{max}/cm^{-1} 1731 (CO), 1711 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.26 (3H, t, *J* 7.2, CH_3) 1.60–1.96 (7H, complex m, 4e, 6, 8a, 9e, 10-H), 2.01–2.06 (4H, m, 4a, 5, 7, 8e-H), 2.12 (1H, d, 9a-H), 4.13 (2H, d, *J* 7.2, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.1 (CH_3), 26.7 (5-C), 26.8 (7-C), 30.8 (3-C), 32.1 (4-C), 34.0 (9-C), 35.7 (8, 10-C), 39.4 (6-C), 42.7 (1-C), 61.1 ($COOCH_2CH_3$), 174.4 (C=O), 217.4 (2-C).

Ethyl 2-cyanotricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (14)

Solid *t*-BuOK (0.60 g, 4.3 mmol) was added portionwise to a stirred (argon atmosphere) solution of ketoester **13** (0.48 g, 2.17 mmol) and TosMIC (0.55 g, 2.8 mol) in a mixture of 8 ml of DME and 0.3 ml of absolute EtOH maintained at 0 °C. The cooling was removed and stirring continued for 30 min at ambient temperature and the mixture was then heated to 47 °C for 30 min. The suspension thus obtained was cooled to room temperature

with stirring. The precipitate (TosK) was filtered and washed with DME. The combined DME solutions were concentrated and purified by flashing the concentrate over silica gel using as eluents *n*-pentane–Et_2O (3 : 1) to afford cyanoester **14** (370 mg, 74%); mp 39 °C (*n*-hexane); ν_{max}/cm^{-1} 2237 (CN), 1727 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.26 (3H, t, *J* 7.2, CH_3), 1.67–1.94 (7H, complex m, 4e, 6, 8a, 9e, 10-H), 2.00–2.06 (4H, m, 4a, 5, 7, 8e-H), 2.13 (1H, d, *J* 14.0, 9a-H), 2.28 (1H, br s, 3-H), 3.18 (1H, s, 2-H), 4.15 (2H, m, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.0 (CH_3), 26.7 (5-C), 26.8 (7-C), 30.9 (3-C), 32.1 (4-C), 34.1 (9-C), 35.7 (8, 10-C), 38.5 (2-C), 39.4 (6-C), 42.7 (1-C), 61.1 ($COOCH_2CH_3$), 174.4 (C=O). Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 71.84; H, 8.01.

4-Azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecan-5-one (15)

Cyanoester **14** (0.52 g, 2.3 mmol) in dry methanol (20 ml) was hydrogenated in the presence of Raney-Ni under a pressure of 65 psi, at 60 °C, for 6 h. The solution was filtered to remove catalyst, and the filtrate was evaporated to dryness to give the aminoester as an oil; IR (film) *ν* 3374 cm^{-1} (NH), 1729 cm^{-1} (C=O). The aminoester was refluxed in xylenes (10 ml) for 10 h. The solvent was evaporated and the residue triturated with *n*-pentane. The solid formed was filtered and washed with *n*-pentane to give lactam **15** (190 mg, 40%) as a white solid; mp 168 °C (Et_2O–*n*-hexane); ν_{max}/cm^{-1} 3123 (NH), 1695 (CO); lactam **15** δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.62–1.82 (9H, complex m, 7, 9, 11, 12a, 13-H), 1.93–2.06 (4H, m, 1, 8, 10, 12e-H), 2.25 (1H, t, *J* 8.7, 2-H), 3.17 (1H, t, *J* 9.1, 3H_A), 3.37 (1H, t, *J* 9.1, 3H_B), 6.22 (1H, s, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 26.9 (1-C), 28.5 (8, 10-C), 31.3 (11-C), 33.7 (12-C), 36.9 (13-C), 37.1 (7-C), 38.3 (9-C), 40.8 (6-C), 42.7 (3-C), 48.0 (2-C), 182.6 (C=O). Anal. calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96. Found: C, 75.55; H, 8.99.

4-Ethyl-4-azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecan-5-one (17)

A solution of the cyanoester **14** (0.35 g, 1.6 mmol) in dry ethanol (20 ml) was hydrogenated in the presence of Raney-Ni catalyst under a pressure of 65 psi, at 140 °C, for 3 h. The solution was filtered to remove catalyst, and the filtrate was evaporated to dryness to afford an oily product, which was chromatographed on a silica gel column (Et_2O–THF 1 : 1) to afford pure *N*-ethyl lactam **17** (160 mg, 46%) as a white solid; mp 84 °C; ν_{max}/cm^{-1} 1687 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (3H, t, *J* 7.2, CH_3), 1.56–1.70 (7H, m, 7a, 9, 11e, 12a, 13-H), 1.74–1.78 (2H, m, 7e, 11a-H), 1.91 (1H, t, 10-H), 1.98–2.10 (3H, m, 1, 8, 12e-H), 2.13 (1H, m, 2-H), 3.08 (1H, dd, *J* 7.2, 3H_A), 3.18 (1H, sextet, CH_A), 3.33 (1H, dd, *J* 7.2, 3H_B), 3.38 (1H, sextet, CH_B); δ_C (100 MHz; $CDCl_3$; Me_4Si) 12.6 (CH_3), 26.9 (10-C), 28.2 (8-C), 28.4 (1-C), 31.3 (11-C), 33.5 (13-C), 36.8 (9-C), 37.1 (12-C), 37.2 (CH_2), 38.5 (7-C), 41.8 (6-C), 45.8 (2-C), 46.6 (3-C), 178.7 (C=O). Anal. calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.42; H, 9.44.

4-Azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecane (16)

Compound **16** was prepared in accordance with the general procedure for the synthesis of pyrrolidines **8–10**, **16** and **18**. Mp 189 °C (dec.) (EtOH–Et_2O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.18–1.96 (16H, m, 1, 2, 7, 8, 9, 11, 10, 12, 13-H, N*H*), 2.42 (1H, dd, *J* 7.2, 3H_A), 2.62 (1H, dd, *J* 7.2, 3H_B), 2.95 (2H, br d, 5-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.4 (10-C), 27.5 (8-C), 28.0 (1-C), 29.6 (11-C), 35.1 (13-C), 36.7 (7-C), 37.8 (9-C), 38.4 (6-C), 40.3 (12-C), 45.6 (5-C), 48.6 (2-C), 56.8 (3-C). Anal. calcd for $C_{12}H_{20}NCl$: C, 67.43; H, 9.43. Found: C, 67.03; H, 9.38.

4-Ethyl-4-azatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecane (18)

Compound **18** was prepared in accordance with the general procedure for the synthesis of pyrrolidines **8–10**, **16** and **18**. Mp 235 °C (EtOH–Et_2O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.03 (3H, t, *J* 7.2, CH_3), 1.33 (1H, br d, 13e-H), 1.42–1.51 (2H, m, 7a, 11e-H), 1.55–1.65 (3H, m, 9, 12a-H), 1.72–1.79 (4H, m, 7e, 11a, 12e, 13a-H), 1.82 (1H, br s, 10-H), 1.88–1.94 (3H, m, 1, 2, 8-H), 2.39 (2H, AB, J_{AB} 9.2, 5-H), 2.58–2.64 (2H, m, CH_2), 2.69 (1H, dd, *J* 7.6, 3H_A), 2.83 (1H, dd, *J* 7.6, 3H_B); δ_C (100 MHz; $CDCl_3$; Me_4Si) 14.3 (CH_3), 28.6 (8, 10-C), 29.3 (1-C), 30.9 (11-C), 37.7 (13-C), 37.9 (9-C), 38.9 (12-C), 39.2 (6-C), 41.9 (7-C), 48.9 (2-C), 51.9 (CH_2), 54.0 (3-C), 65.6 (5-C). Anal. calcd for $C_{14}H_{24}NCl$: C, 69.54; H, 10.00. Found: C, 69.19; H, 10.24.

2-(Hydroxyimino)tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic acid (21)

A mixture of ketoester **13** (540 mg, 2.43 mmol), $NH_2OH{\cdot}HCl$ (180 mg, 2.7 mmol) and $CH_3COONa{\cdot}3H_2O$ (367 mg, 2.7 mmol) in EtOH 93% (30 ml) was refluxed for 3 h. After evaporation of the solvent, the mixture was cooled to room temperature, water was added and the precipitate formed removed by filtration, washed with water and dried (400 mg oxime ester **19** and 50 mg azalactone **20**).

The above mixture (450 mg) was saponified with a solution of NaOH (0.55 g, 13.7 mmol) in EtOH–H_2O (10 ml, 1 : 1) over 3.5 h at 60 °C. After evaporation of the solvent, the mixture was extracted twice with Et_2O (20 ml) and the aqueous layer was acidified with concd HCl at 0 °C. The white solid acid oxime **21** was removed by filtration, washed with water and dried (0.37 g, 97%); mp 210 °C (dec.) (EtOH–H_2O); ν_{max}/cm^{-1} 3286 (OH), 1713 (CO), 1665 (CN); δ_H (400 MHz; DMSO-d_6; Me_4Si) 1.67–1.89 (8H, m, 4e, 6, 8, 9e, 10-H), 2.06 (2H, br d, 5, 7-H), 2.17 (2H, br d, 4a, 9a-H), 3.51 (1H, br s, 3-H); δ_C (100 MHz; DMSO-d_6; Me_4Si) 28.2 (5, 7-C), 28.6 (3-C), 35.8 (6-C), 37.4 (4, 9-C), 41.4 (8, 10-C), 48.4 (1-C), 162.4 (C=N), 175.3 (C=O). Anal. calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22. Found: C, 63.03; H, 7.16.

3-Oxa-2-azatetracyclo[6.3.1.1^{6,10}.1^{2,6}]tridec-2-en-5-one (20)

A 460 mg (2.2 mmol) portion of acid oxime **21** was melted in an oil bath at 220 °C and then sublimed (10^{-2} mmHg, heated over a Bunsen burner flame) to yield 330 mg of azalactone **20** (79%); mp 184 °C (Et_2O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.83–1.88 (6H, m, 7a, 9, 11e, 12a, 13e-H), 2.09 (2H, m, 11a, 13a-H), 2.22 (4H, m, 7e, 8, 10, 12e-H), 3.05 (1H, t, *J* = 2.8 Hz, 1-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.6 (8, 10-C), 32.0 (1-C), 35.0 (9-C), 37.6 (11, 13-C), 39.3 (7, 12-C), 46.0 (6-C), 175.0 (C=N), 180.3 (C=O). Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 7.32. Found: C, 69.12; H, 7.21.

3,4-Diazatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridec-2-en-5-one (23)

A mixture of ketoacid **12** (400 mg, 2.0 mmol), abs. EtOH (2 ml) and hydrazine hydrate (126 mg, 2.4 mmol) was heated at reflux for 0.5 h. After evaporation of the solvent, the solid formed (300 mg)

was sublimed (10^{-2} mmHg, heated over a Bunsen burner flame) to yield 260 mg of pyrazolone **23** (67%); mp 213 °C (EtOH); ν_{max}/cm^{-1} 3142 (NH), 1693 (CO), 1653 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.68 (2H, d, *J* 12.2, 11e, 12e-H), 1.78 (2H, br d, *J* 12.5, 7a, 13a-H), 1.85 (2H, br s, 9-H), 2.04 (2H, br d, *J* 12.5, 7e, 13e-H), 2.12 (2H, br s, 8, 10-H), 2.18 (2H, d, *J* 12.5, 11a, 12a-H), 2.92 (1H, t, *J* 2.7, 1-H), 9.1 (1H, br s, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.6 (8, 10-C), 33.6 (1-C), 35.2 (9-C), 38.7 (7, 12-C), 39.1 (11, 13-C), 47.7 (6-C), 171.2 (C=N), 180.8 (C=O). Anal. calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42. Found: C, 69.69; H, 7.31.

3,4-Diazatetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridec-2-en-5-thione (24)

A mixture of the pyrazolone **23** (500 mg, 2.6 mmol) and *p*-methoxyphenylthionophosphine sulfide (Lawesson's reagent) (530 mg, 1.3 mmol) in toluene (30 ml) was heated for 12 h. After cooling at ambient temperature the solvent was removed by evaporation and the mixture was purified on silica gel, using ether as the eluent, to give pyrazolothione **24** (500 mg, 93%) as a solid; mp 167–169 °C; ν_{max}/cm^{-1} 3112, 3074 (NH), 1618 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.62 (2H, d, *J* 12.0, 11e, 13e-H), 1.82 (2H, d, *J* 12.4, 7a, 12a-H), 1.93 (2H, br s, 9-H), 2.14 (2H, d.d, *J* 12.4, 1.6, 7e, 12e-H), 2.20 (2H, s, 8, 10-H), 2.33 (2H, d, *J* 12, 11a, 13a-H), 3.21 (1H, s, 1-H), 11.20 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 27.7 (8, 10-C), 33.6 (1-C), 34.9 (9-C), 39.2 (7, 13-C), 43.0 (11, 12-C), 61.1 (6-C), 179.3 (C=N), 204.8 (C=S). Anal. calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84. Found: C, 63.87; H, 6.70.

2-Bromo-1-(2-bromoethyl)tricyclo[3.3.1.1^{3,7}]decane (26)

A solution of triphenyldibromophosphorane was prepared by the dropwise addition of Br_2 (3.20 g, 20.0 mmol) in benzonitrile (15 ml) to a solution of triphenylphosphine (5.24 g, 20.0 mmol) in benzonitrile (15 ml) and the resulting solution was stirred at 124 °C under an argon atmosphere. To this solution was added in one portion the tetrahydrofuran derivative **25** (3.00 g, 16.8 mmol) and the mixture was heated at 124 °C for 4 h. The mixture was cooled to room temperature, *n*-pentane was added and the precipitate formed was removed by filtration and washed with *n*-pentane. The washings were combined and the upper layer was removed and evaporated under vacuum to give a viscous oil. The product was purified by fractional distillation *in vacuo* to give **26** ($Eb_{0.01mmHg}$ 120 °C) (4.50 g, 84%); ν_{max}/cm^{-1} 733 (C-Br); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.32–2.28 (15H, complex m, 3, 4, 5, 6, 7, 8, 9, 10-H, C*H*$_2$CH$_2$Br), 3.31–3.44 (2H, complex m, CH$_2$C*H*$_2$Br), 4.34 (1H, s, 2-H).

1-(2-Cyanoethyl)tricyclo[3.3.1.1^{3,7}]decane-2-carbonitrile (28)

A mixture of dibromide **26** (3.00 g, 9.3 mmol) and NaCN (4.20 g, 85.0 mmol) in DMSO (50 ml) was stirred at 115 °C for 1 h and at 145 °C for a further hour. The mixture was cooled to room temperature, poured onto 40 ml of water and extracted with Et_2O. The organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel, using *n*-hexane–Et_2O (6 : 1) and Et_2O as the eluents, to give 3-(2-bromotricyclo[3.3.1.1^{3,7}]dec-1-yl)propanenitrile **27** (75%) and the title compound **28** (18%); ν_{max}/cm^{-1} 2249 (CN), 733 (C-Br); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.34 (1H, m, 9e-H), 1.57–1.80 (8H, complex m, 4e, 6e, 8, 10-H, C*H*$_2$CH$_2$CN), 1.87–1.95 (3H, m, 5, 6a, 9a-H), 2.00 (1H, m, 7-H), 2.25–2.34 (4H, m, 3, 4a, C*H*$_2$CN), 4.30 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 10.5 (*C*H$_2$CN), 27.5 (5-C), 27.9 (7-C), 31.2 (4-C), 36.8 (1-C), 37.0 (8, 10-C), 37.2 (3-C), 37.5 (9-C), 38.1 (6-C), 41.0 (*C*H$_2$CH$_2$CN), 66.8 (2-C), 120.2 (CN). Anal. calcd for $C_{13}H_{18}NBr$: C, 58.22; H, 6.76. Found: C, 58.51; H, 6.92.

A mixture of bromonitrile **27** (2.53 g, 7.8 mmol) and NaCN (4.20 g, 85.0 mmol) in DMSO (50 ml) was stirred at 155 °C for 1 h. The mixture was cooled to ambient temperature, poured onto 40 ml of water and extracted with Et_2O. The organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo* the residue was crystallized from a mixture of Et_2O–*n*-pentane (5 : 1). The precipitated dinitrile **28** was filtered off, washed with the above mixture of solvents and dried (1.80 g, 89%); mp 83 °C (Et_2O); ν_{max}/cm^{-1} 2233, 2139 (CN); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.51–1.86 (11H, complex m, 4e, 6, 8, 9, 10-H, C*H*$_2$CH$_2$CN), 2.06 (3H, br d, 4a, 5, 7-H), 2.26 (1H, s, 3-H), 2.34 (2H, t, *J* 8.0, C*H*$_2$CN), 2.65 (1H, br s, 2-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 10.9 (*C*H$_2$CN), 27.1 (5-C), 27.3 (7-C), 31.2 (3-C), 32.4 (4-C), 34.0 (1-C), 35.8 (8-C), 35.9 (10-C), 36.7 (6-C), 37.9 (9-C), 39.7 (*C*H$_2$CH$_2$CN), 41.4 (2-C), 119.7 (CH$_2$CN), 120.0 (CN). Anal. calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47. Found: C, 78.54; H, 8.41.

Tetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecan-3-one (30)

A THF (20 ml) solution of freshly distilled diisopropylamine (0.94 g, 9.34 mmol) was added to a solution of *n*-BuLi (3.2 ml, 2.5 M, 0.81 mmol) in hexanes and the resulting solution was stirred for 45 min at −80 °C under argon. To this solution was added dropwise a solution of dinitrile **28** (1.25 g, 5.8 mmol) in dry THF (20 ml) and the mixture was left overnight to slowly reach room temperature. The mixture was treated with an ice–water mixture, extracted with ether and the organic phase was washed with water, HCl (5%), water, and then dried (Na_2SO_4) and evaporated *in vacuo* to give enaminenitrile **29** (1.23 g, quantitative yield) as a solid, which was decolorized with activated charcoal; mp 188 °C (ether); ν_{max}/cm^{-1} 3447, 3345, 3259 (NH$_2$), 2173 (CN), 1654, 1594 (C=C).

A vigorously stirring mixture of enaminenitrile **29** (0.89 g, 4.1 mmol), 33% H_2SO_4 (15 ml) and glacial acetic acid (10 ml) was gently refluxed for 20 h. After cooling to room temperature, water was added and the mixture extracted with ether. The organic phase was separated, washed with water, aqueous Na_2CO_3, water, and dried (Na_2SO_4). The solvent was evaporated and the residue was filtered through silica gel to give ketone **30** (0.80 g, 100%); mp 61 °C; ν_{max}/cm^{-1} 1743 (CO).

Tetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecan-3-one oxime (31)

A mixture of ketone **30** (0.60 g, 3.1 mmol), NH$_2$OH·HCl (0.43 g, 6.2 mmol) and CH$_3$COONa·3H$_2$O (1.26 g, 9.3 mmol) and ethanol 90% (15 ml) was refluxed for 6 h. The mixture was cooled at room temperature, ice–water was added and the precipitate formed was filtered off, washed with water and dried to give **31** as a solid (0.60 g, 94%); mp 179 °C (Et_2O, petr. ether); ν_{max}/cm^{-1} 3307 (OH); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.24–1.32 (2H, m, 5A, 13e-H), 1.45–1.53 (4H, m, 5B, 7a, 11e, 13a-H), 1.61–1.67 (3H, m, 9, 12a-H), 1.80–1.86 (4H, m, 7e, 8, 11a, 12e-H), 2.00 (1H, br s, 1-H), 2.25

(1H, s, 10-H), 2.37–2.45 (1H, br s, 2-H), 2.40 (1H, m, $4H_A$), 2.52–2.62 (1H, m, $4H_B$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 24.3 (4-C), 27.8 (10-C), 28.0 (1-C), 29.2 (8-C), 30.8 (11-C), 34.9 (13-C), 37.0 (9-C), 37.2 (5-C), 38.0 (12-C), 39.8 (6-C), 43.4 (7-C), 54.3 (2-C), 165.6 (*C*=NOH). Anal. calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33. Found: C, 75.92; H, 9.28.

Tetracyclo[6.3.1.1^{6,10}.0^{2,6}]tridecan-3-amine (32)

A solution of oxime **31** (370 mg, 1.8 mmol) in dry EtOH was hydrogenated over Raney-Ni catalyst for 4 h, at 70 °C, and under pressure (50 psi). The catalyst was filtered off and the solvent was evaporated under vacuum to afford a viscous oil (amine **32**), which was converted to its hydrochloride salt (350 mg, 86% yield); hydrochloride: mp >250 °C (EtOH); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.16–1.81 (17H, complex m, 1, 2, 4A, 5, 7, 9, 11, 12, 13-H, NH_2), 1.90 (1H, br s, 10-H), 1.98 (1H, br s, 8-H), 2.06–2.16 (1H, m, 4B-H), 3.31 (1H, m, 3-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 28.2 (10-C), 28.7 (8-C), 29.3 (1-C), 30.8 (11-C), 32.3 (4-C), 36.8 (13-C), 37.7 (9-C), 38.4 (5-C), 38.8 (12-C), 40.0 (6-C), 44.7 (7-C), 52.5 (3-C), 60.0 (2-C). Anal. calcd for $C_{13}H_{22}NCl$: C, 68.55; H, 9.73. Found: C, 67.92; H, 9.68.

Acknowledgements

Dr Zoidis would like to thank the State Scholarship Foundation of Greece for financial support. John Kelly acknowledges the support of the Wellcome Trust. L. Naesens and E. De Clercq wish to thank L. Persoons, F. De Meyer and V. Broeckx for excellent technical assistance, and the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (FWO Project No. G.0188.07) and the International Consortium for Antivirals (ICAV) for financial support.

References

1 *Lancet Infect. Dis.*, 2007, **7**,175 .
2 N. M. Ferguson, D. A. T. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn and D. S. Burke, *Nature*, 2005, **437**(7056), 209–214.
3 N. M. Ferguson, D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley and D. S. Burke, *Nature*, 2006, **442**(7101), 448–452.
4 D. Kaye and C. R. Pringle, *Clin. Infect. Dis.*, 2005, **40**, 108–112.
5 J. H. Beigel, J. Farrar, A. M. Han, F. G. Hayden, R. Hyer, M. D. De Jong, S. Lochindarat, N. T. K. Tien, N. T. Hien, T. T. Hien, A. Nicoll, S. Touch and K. Y. Yuen, *N. Engl. J. Med.*, 2005, **353**, 1374–1385.
6 J. K. Taubenberger and D. M. Morens, *Emerging Infect. Dis.*, 2006, **12**, 15–22.
7 (*a*) E. D. Kilbourne, *Emerging Infect. Dis.*, 2006, **12**, 9–14; (*b*) R. B. Beishe, *N. Engl. J. Med.*, 2005, **353**, 2209–2211.
8 (*a*) A. J. Hay, A. J. Wolstenholme, J. J. Skehel and M. H. Smith, *EMBO J.*, 1985, **4**, 3021–3024; (*b*) A. J. Hay, *Semin. Virol.*, 1992, **3**, 21–30; (*c*) L. H. Pinto, L. J. Holsinger and R. A. Lamb, *Cell*, 1992, **69**, 517–528.
9 M. S. Samson and I. D. Kerr, *Protein Eng.*, 1993, **6**, 65–74.
10 *Burger's Medicinal Chemistry*, ed. M. E. Wolff, John Wiley & Sons, New York, 1998; part II, pp. 590–591.
11 (*a*) N. Kolocouris, G. B. Foscolos, A. Kolocouris, P. Marakos, N. Pouli, G. Fytas, S. Ikeda and E. De Clercq, *J. Med. Chem.*, 1994, **37**, 2896–2902; (*b*) N. Kolocouris, A. Kolocouris, G. B. Foscolos, G. Fytas, J. Neyts, E. Padalko, J. Balzarini, R. Snoeck, A. Graciela and E. De Clercq, *J. Med. Chem.*, 1996, **39**, 3307–3318; (*c*) G. Zoidis, N. Kolocouris, G. B. Foscolos, A. Kolocouris, G. Fytas, P. Karayannis, E. Padalko, J. Neyts and E. De Clercq, *Antiviral Chem. Chemother.*, 2003, **14**, 153–164; (*d*) G. Zoidis, C. Fytas, I. Papanastasiou, G. B. Foscolos, G. Fytas, E. Padalko, E. De Clercq, L. Naesens, J. Neyts and N. Kolocouris, *Bioorg. Med. Chem.*, 2006, **14**, 3341–3348.
12 E. De Clercq, *Nat. Rev. Drug Discovery*, 2006, **5**, 1015–1025.
13 World Health Report 2004, Statistical Annex Table 2.
14 P. G. E. Kennedy, *J. Clin. Invest.*, 2004, **113**, 496–504.
15 S. L. Croft, M. P. Barrett and J. A. Urbina, *Trends Parasitol.*, 2005, **21**, 508–512.
16 W. E. Gutteridge, *Br. Med. Bull.*, 1985, **41**, 162–168.
17 F. Doua and F. B. Yapo, *Acta Trop.*, 1993, **54**, 163–168.
18 P. G. E. Kennedy, *Int. J. Parasitol.*, 2006, **36**, 505–512.
19 J. M. Kelly, M. A. Miles and A. C. Skinner, *Antimicrob. Agents Chemother.*, 1999, **43**, 985–987.
20 (*a*) J. M. Kelly, G. Quack and M. A. Miles, *Antimicrob. Agents Chemother.*, 2001, **45**, 1360–1366; (*b*) I. Papanastasiou, A. Tsotinis, N. Kolocouris, S. Radhika Prathalingam and J. M. Kelly, *J. Med. Chem.*, 2008, **51**, 1496–1500.
21 (*a*) J. Chakrabarti, S. Szinai and A. Todd, *J. Chem. Soc. C*, 1970, 1303–1309; (*b*) J. Chakrabarti, T. Hotten, D. Rackham and D. Tupper, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1893–1900; (*c*) W. H. W. Lunn, W. D. Podmore and S. Szinai, *J. Chem. Soc. C*, 1968, 1657–1660.
22 N. Kolocouris, G. Zoidis and C. Fytas, *Synlett*, 2007, **7**, 1063–1066.
23 *Br. Pat.*, 1 265 794, 1968.
24 D. Farcasiu, *J. Am. Chem. Soc.*, 1976, **98**, 5301–5305.
25 O. Oldenziel, D. van Leusen and A. van Leusen, *J. Org. Chem.*, 1977, **42**, 3114–3118.
26 G. M. Badger, J. W. Cook and T. Walker, *J. Chem. Soc.*, 1948, 2011–2017.
27 I. K. Moiseev, T. A. Mratkhuzina, P. G. Belyaev, G. F. Nafikov, E. B. Tkacheva and L. B. Sechkareva, *J. Org. Chem. USSR (Engl. Transl.)*, 1979, **15**, 2120–2122.
28 I. K. Moiseev and V. P. Konovalova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1982, **18**, 405–408.
29 S. Scheibye, J. Kristensen and S. O. Lawesson, *Tetrahedron*, 1979, **35**, 1339–1343.
30 A. Anderson and F. Freenor, *J. Org. Chem.*, 1972, **37**, 626–630.
31 J. P. Schaefer and J. J. Bloomfield, *Org. React.*, 1967, **15**, 1–203.
32 G. Stamatiou, G. B. Foscolos, G. Fytas, A. Kolocouris, N. Kolocouris, C. Pannecouque, M. Witvrouw, E. Padalko, J. Neyts and E. De Clercq, *Bioorg. Med. Chem.*, 2003, **11**, 5485–5492.
33 N. Kolocouris, G. Zoidis, G. B. Foscolos, G. Fytas, R. S. Prathalingham, J. M. Kelly, L. Naesens and E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4358–4362.
34 P. E. Aldrich, E. C. Hermann, W. E. Meier, M. Paulshock, W. W. Prichard, J. A. Snyder and J. C. Watts, *J. Med. Chem.*, 1971, **14**, 535–543.
35 S. D. Griffin, L. P. Beales, D. S. Clarke, O. Worsfold, S. D. Evans, J. Jaeger, M. P Harris and D. J. Rowlands, *FEBS Lett.*, 2003, **535**, 34–38.
36 B. Plugge, S. Gazzarrini, M. Nelson, R. Cerana, J. L. Van Etten, C. Derst, D. DiFrancesco, A. Moroni and G. Thiel, *Science*, 2000, **287**, 1641–1644.
37 K. Mizoguchi, H. Yokoo, M. Yoshida, T. Tanaka and M. Tanaka, *Brain Res.*, 1994, **662**, 25–58.