European Journal of Medicinal Chemistry 45 (2010) 5022–5030

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design and synthesis of bioactive adamantanaminoalcohols and adamantanamines

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ARTICLE INFO

Article history:
Received 16 April 2010
Received in revised form
4 August 2010
Accepted 6 August 2010
Available online 12 August 2010

Keywords:
Adamantane aminoalcohols and diamines
Anti-influenza A virus agents
H3N2
Rimantadine
Trypanocidal activity
NMR

ABSTRACT

Adamantanamines **16**, **18**, **21**, **24**, **27**, **28**, **30**, **32**, **35**, **36**, **37**, **40**, **46** and **48** were synthesized and tested for anti-influenza A virus and trypanocidal activity. The stereoelectronic requirements for optimal antiviral and trypanocidal potency were investigated. The effect of introducing a hydroxyl group close to the amino group on this class of compounds was examined for the first time. Aminoalcohol **24** proved to be the most active of the compounds tested against influenza A virus, being 6-fold more active than amantadine, equipotent to rimantadine and 26-fold more potent than ribavirin. Aminoalcohols **36** and **37** were found to have considerable activity against bloodstream forms of the African trypanosome, *Trypanosoma brucei*, being almost 10 times more potent than rimantadine.

1. Introduction

Influenza is a highly contagious infectious disease that affects millions of people every year. In the twentieth century, influenza caused more fatalities in Europe than any other infectious disease [1]. Current vaccines against influenza virus have limited effectiveness due to the rapid emergence of strains with mutated viral antigens. Thus, anti-influenza drugs are vital as a first line of defense. At present, two classes of antivirals are available: the neuraminidase inhibitors oseltamivir and zanamivir, and the M2 proton channel blockers amantadine and rimantadine [5].

The cumulative impact of recurrent annual epidemics is generally higher than that of the infrequent pandemics, although the extreme mortality of the H5N1 avian influenza virus is a serious reason for concern. This H5N1 virus originated in 1997 in Hong Kong and has since spread (through birds) to Southeast Asia and other countries, with occasional transmission to humans (almost 500 human cases, more than half of which were fatal). In 2003, another highly pathogenic avian influenza virus (H7N7 subtype) caused some 89 mild infections in the Netherlands and the death of a veterinarian, while in the same year H9N2 viruses were isolated from individuals with mild influenza [2]. The “swine flu” pandemic of 2009 was caused by a new H1N1 reassortant virus containing genome segments from human, avian and swine influenza viruses. Although the source of the outbreak in humans is still unknown, cases were first discovered in Mexico and the U.S.A. [3]. This new influenza pandemic prompted an unprecedented worldwide response consisting of containment measures, antiviral therapy and the development of a vaccine. The disease spectrum of this swine flu H1N1 virus is comparable to that of other human influenza viruses, although it remains unclear how the virus will evolve during the forthcoming months [4].

Amantadine (**1**; Fig. 1) was the first anti-influenza drug to be developed. At micromolar concentrations, amantadine inhibits the function of the M2 proton channel of influenza A virus that is involved in virus uncoating [6,7]. After endocytosis of the virions, the M2 proton channel mediates acidification of the viral interior, resulting in a conformational change of the viral hemagglutinin (to its fusogenic form) and dissociation of viral ribonucleoprotein from the matrix protein. In addition, the M2 protein has a role in virus maturation, since it regulates the pH in the trans-Golgi network to prevent premature conformational rearrangement of

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doi:10.1016/j.ejmech.2010.08.009

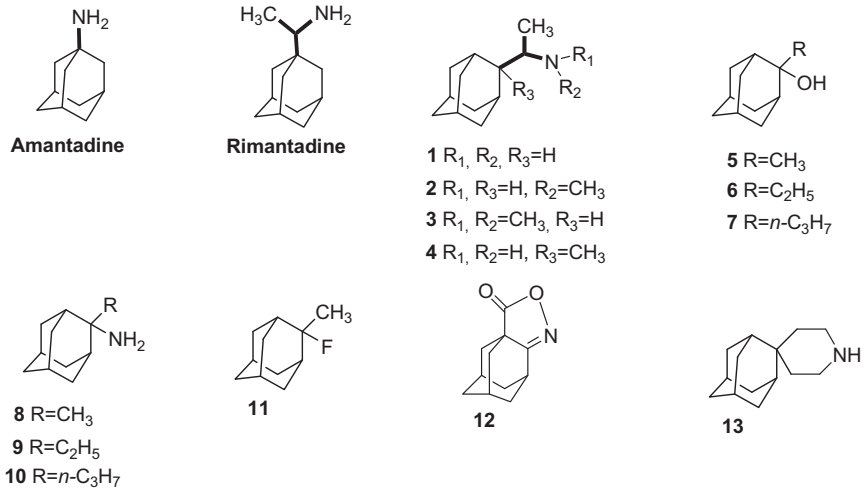


Fig. 1.

the hemagglutinin [6b]. During the past fourteen years, we have synthesized many potent aminoadamantane derivatives (Fig. 1) [8,9]. The protonated forms of these compounds are considered to block the tetrameric M2 ion channel pore [10], formed by its transmembrane domain M2TM [11], and hence, its proton transport function [12,13].

The desired property of new synthetic aminoadamantane derivatives is of course the effective inhibition of virus replication. The amantadine—M2 complex is probably stabilized through formation of hydrogen bonding between the drug's ammonium group and specific residues, probably His-37 or Ser-31, within the M2 acceptor site [10,12]. Here, we have examined the M2 binding properties of aminoadamantane derivatives that have a hydroxyl group at positions close to the amino group; the hydroxyl group could possibly participate as donor or acceptor in hydrogen bonding interaction with the receptor.

Among the many diseases that afflict humankind, those caused by protozoan parasites occupy an important place because of the large number of victims, the lack of efficient therapy, and their continuing spread. Tsetse fly-transmitted parasites of the *Trypanosoma brucei* species complex are the causative agents of Human African Trypanosomiasis (HAT), one of the world's great neglected diseases. The World Health Organization reported 55,000 deaths in 2002 out of 500,000 cases of sleeping sickness in sub-Saharan Africa [14]. Recently, the annual incidence has varied between 50,000 and 300,000 cases, with about 60 million people at risk [15], and in some areas death rates exceed those of HIV/AIDS and malaria. Trypanosomiasis also has a significant affect on human nutrition through its impact on domesticated animals, for example, killing 3 million cattle per year. In humans, the disease is caused by infection with the sub-species *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 drug, eflornithine [(*R*,*S*)-2-difluoromethylornithine (DFMO, initially developed as an anticancer drug)], has been approved for HAT therapy [16]. Moreover, all four front-line drugs (suramin, pentamidine, melarsoprol and eflornithine) require hospitalization for administration, are expensive and are associated with 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 occur when parasites gain access to the central nervous system [17,18]. Treatment of late stage East African trypanosomiasis is a particular problem, since *T. b. rhodesiense* is refractory to eflornithine. Melarsoprol, which is the only available drug, can cause arsenic encephalopathy with 5–10% patient mortality [19]. Although there is an urgent need for new anti-trypanosome drugs, the pharmaceutical industry has paid little attention to this relatively unprofitable area. The development of broad-spectrum, inexpensive, highly efficient, and nontoxic drugs therefore remains a priority.

Recently, 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 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* [20]. 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* (Fig. 1) [9e,f,21]. Here, by investigating the trypanocidal properties of newly synthesized aminoadamantane derivatives, our aim has been to provide greater insight into the chemical features that may enhance this activity.

We now describe the synthesis and biological evaluation of adamantanoaminoalcohols **16**, **18**, **21**, **24**, **27**, **28**, **30**, **36** and **37,** adamantanodiamines **32**, **35** and **40** and adamantanamines **46** and **48** (Fig. 2), and show that they contain structural features necessary for antiviral activity.

2. Results and discussion

2.1. Chemistry

2-Aminomethyl-2-hydroxyadamantane **16** (Scheme 1) was prepared by known methods from adamantanone in good yields [22].

In order to synthesize the 2-(2-aminoethyl)-2-hydroxyadamantane **18** we follow a concise and efficient synthesis. In this approach, we have employed *n*-butyl lithium and acetonitrile in dry THF for the preparation of 2-(2-hydroxy-2-adamantyl)acetonitrile **19** from adamantanone **14**. In comparison with the other bases reported in the literature [23], the use of *n*-butyl lithium allows the synthesis of the hydroxyl nitrile **19** quantitatively (97%) without side products and laborious purifications. Nitrile **19** was reduced with $LiAlH_4$ in tetrahydrofuran. As a result, 2-(2-aminoethyl)-2-hydroxyadamantane was obtained in great yield, which was isolated as hydrochloride.

The synthesis of the aminoalcohol **21** is illustrated in Scheme 1. Hydroxymethylation of the 2-nitroadamantane **19** afforded the

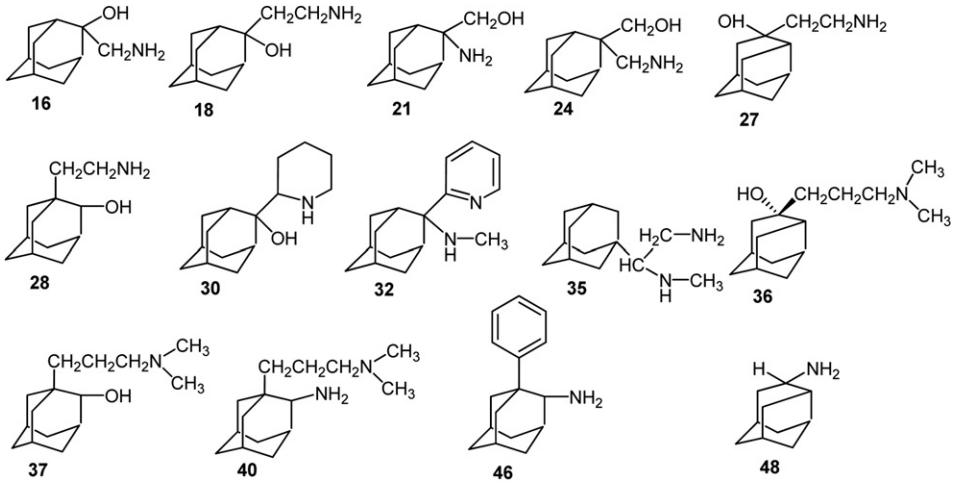


Fig. 2.

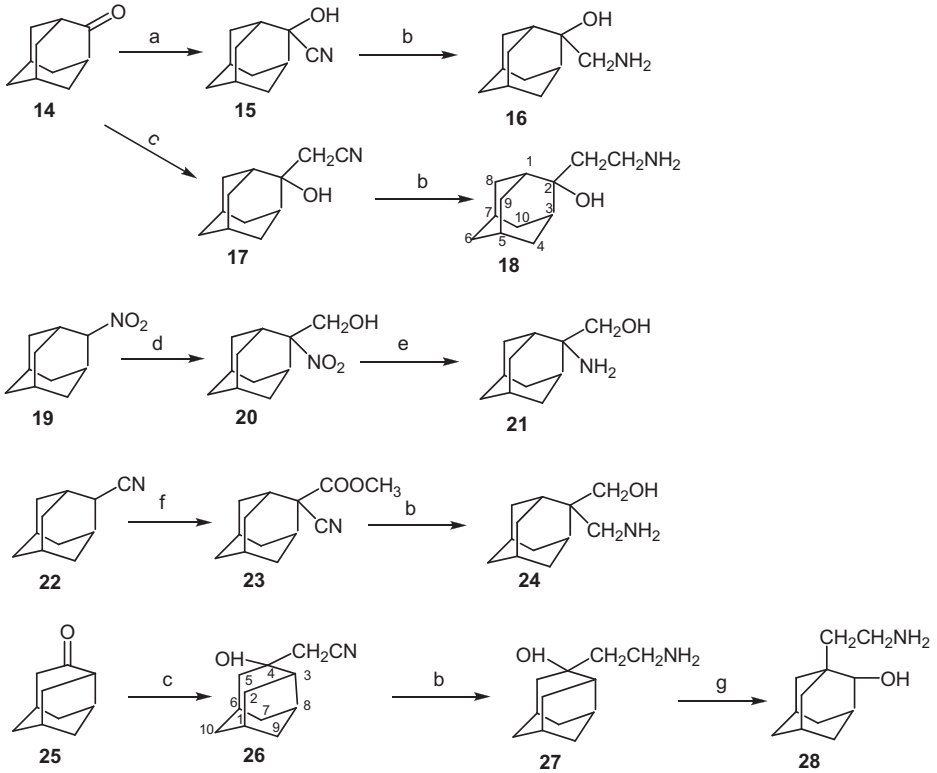
2-nitro-2-adamantanemethanol **20**. Catalytic reduction of the nitro alcohol **20** resulted in the 2-amino-2-adamantanemethanol **21**.

In order to synthesize the aminoalcohol **24** (Scheme 1), 2-adamantanecarbonitrile **22** was used as a starting material [9c]. Thus, lithiation at C-2 using LDA and reaction of the resulting carbanion with methyl chloroformate gave cyanoester **23** in good yield [9e]. Reduction of the latter with $LiAlH_4$ under mild heating afforded the desired aminoalcohol **24**, in excellent yield (93%).

The synthetic route to the aminoalcohol **28** is shown in Scheme 1 and involved protoadamantanone **25** [24a], prepared by a modification of the literature method from the reaction of 1-adamantanol with iodine and lead tetraacetate [24a,b], which on treatment with *n*-butyl lithium and acetonitrile in dry THF afforded the desired hydroxyl nitrile **26** in a 95% yield. Reduction of the latter with $LiAlH_4$ gave aminoalcohol **27**. Heating aminoalcohol **27** in dioxane with H_2SO_4 (15%) afforded the target compound **28** in an excellent yield (95%).

Tertiary alcohol **30** was synthesized from the reaction of adamantanone **14** and 2-pyridinyl lithium. Catalytic hydrogenation of the hydrochloride form of **29** over PtO_2 catalyst led to the aminoalcohol **30** [25].

Diamine **32** was prepared starting from adamantanone **14** which was successively transformed to 2-(*N*-methylimino)adamantane **31** (Scheme 2), in 98% yield, upon treatment with methylamine in dry THF with 3 Å molecular sieves at room temperature under nitrogen overnight [26]. Imine **31** reacted with 2-bromopyridine, *n*-BuLi, in



Scheme 1. a: HCN, Pyridine, r.t., 24 h (82%); b: $LiAlH_4$, THF, 20 °C, 20 h (95%); c: *n*-BuLi, CH_3CN, THF, −80 °C, (97%); d: CH_2O, NaOH, dioxane, reflux (60%); e: H_2/Raney Ni, EtOH, 55 p.s.i., 50 °C (99%); f: LDA, −70 °C, THF, $ClCOOCH_3$, 24 h, 20 °C, (87%); g: dioxane, H_2SO_4 15%, 80 °C, 2 h (96%).

the present of 1-(2-methoxyphenoxy)-*N*,*N*-dimethyl-3-phenylpropan-2-amine to give the target diamine **32**.

The Strecker reaction [27] has been employed for the preparation of diamine **35** (Scheme 2). The conditions for preparing the latter are consistent with mixing the bulky 1-adamantanecarboxaldehyde **33** with NaCN and CH_3NH_2, in a mixture of DMSO/water, and leaving the mixture to react at ambient temperature. Catalytic hydrogenation of the α-aminonitrile **34** over PtO_2 provided the desired α-aminomethyl adamantanemethanamine **35** [28].

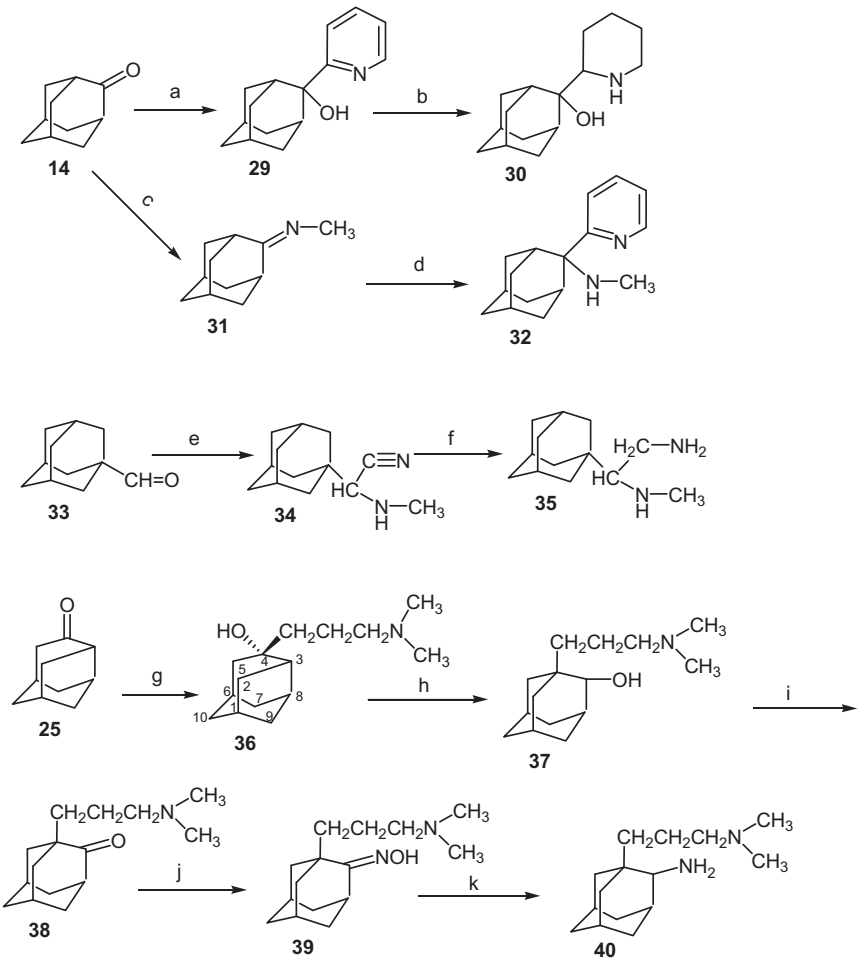
The key intermediate **36** for the synthesis of compounds **37** and **40** was prepared from protoadamantanone **25**, which was first converted to the aminoalcohol **36** *via* a Grignard reaction between ketone **25** and the magnesium derivative of 3-chloro-*N*,*N*-dimethylpropan-1-amine hydrochloride (Scheme 2). Heating aminoalcohol **36** in dioxane with H_2SO_4 (15%) afforded compound **37** quantitatively via a C2–C3 to C4 metathesis [24b]. Oxidation of the latter under Jones reaction conditions led to the aminoketone **38**, which was in turn converted to the respective oxime **39**. Catalytic hydrogenation of **39** over Raney Nickel afforded diamine **40** in a 91% yield.

The synthesis of analogue **46** is shown in Scheme 3. Protoadamantanone **25**, was treated with phenyl lithium to give the corresponding tertiary alcohol **41** as an endo/exo (1:1) isomeric mixture in 96% yield, which on treatment with formic acid was converted to formate **42** via a C2–C3 to C4 metathesis. Saponification of the in situ formed ester **42** gave the respective secondary alcohol **43** in 96% yield, and that was then oxidized under Jones reaction conditions to the corresponding 1-phenyl-2-one **44** [9d]. Treatment of ketone **44** with hydroxylamine hydrochloride in the presence of sodium acetate led to the formation of the respective oxime **45** quantitatively, which on hydrogenation over Raney Ni catalyst was converted to amine **46**, the yield of the latter was found to increase upon heating and prolonged hydrogenation.

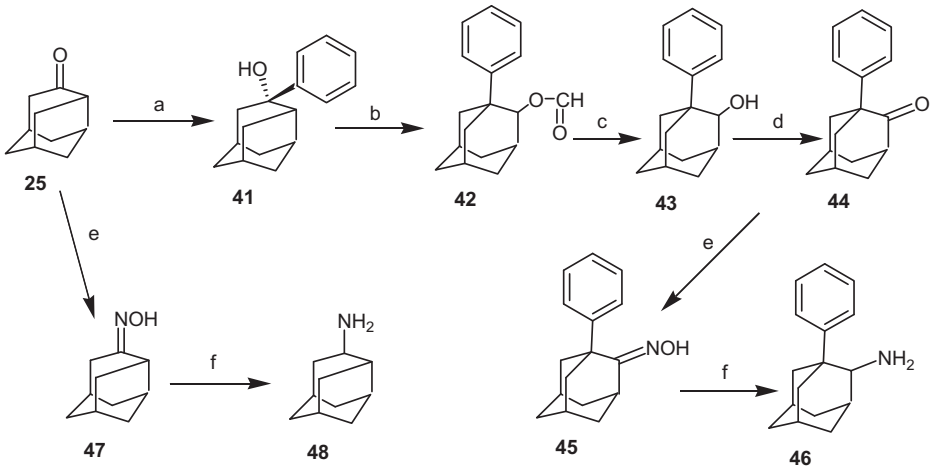
Finally, treatment of ketone **25** with hydroxylamine hydrochloride in the presence of sodium acetate led to the formation of the respective oxime **47**, which on hydrogenation over Raney Ni catalyst was converted to protoadamantanamine **48**.

3. Biological activity

The antiviral efficacy of the new aminoadamantane derivatives **16**, **18**, **21**, **24**, **27**, **28**, **30**, **32**, **35**, **36**, **37**, **40**, **46** and **48** was determined *in vitro* against influenza A (H3N2 subtype; strain A/HK/7/87, which carries a serine at position 31 of the M2 protein) and was compared to the activity of amantadine, rimantadine and ribavirin (Table 1). The antiviral assay used was identical to that previously reported [29], and is based on inhibition of the virus-induced cytopathic effect (CPE) after multiple replication cycles at 72 h post infection, as



Scheme 2. a: 2-pyridinyl lithium, Et_2O/THF, −60 °C (82%); b: (1) gas HCl, EtOH; (2) H_2/PtO_2, EtOH and then Na_2CO_3 10% (97%); c: CH_3NH_2, THF, molecular sieves (3 Å), 24 h (82%); d: 2-bromopyridine, *n*-BuLi, dry ether, 1-(2-methoxyphenoxy)-*N*,*N*-dimethyl-3-phenylpropan-2-amine, dry toluene, 3 h (53%); e: NaCN, $CH_3NH_3^+Cl^-$, DMSO/H_2O 29:1, rt, 48 h, and then HCl(g)/Et_2O (66%); f: H_2, PtO_2, HCl(g)/MeOH, 45 lb/in^2, rt, 6 h, and then NaOH 20% (85% for **8**, 90% for **11**); g: $(CH_3)_2NCH_2CH_2CH_2MgCl$, THF, C_6H_6, reflux, 4 h (97%); h: dioxane, H_2SO_4 15%, 80 °C, 2 h (93%); i: CrO_3, aq. H_2SO_4 (1 N), acetone, 15 °C, then r.t., 24 h (87%); j: NH_2OH–HCl, $CH_3COONa.3H_2O$, abs. EtOH, H_2O (14:1), 3 h, reflux (quantitative); k: EtOH, Ni-Raney, 55 p.s.i., 65 °C, 5 h (95%).



Scheme 3. a: PhLi, THF; b: HCOOH, reflux, 30 min; c: NaOH/EtOH, Δ; d: CrO_3, aqueous H_2SO_4 (8 N), acetone, 15 °C; e: NH_2OH–HCl, $CH_3COONa.3H_2O$, abs. EtOH, H_2O (10:1) (70%), 3 h, reflux (quantitative); f: EtOH, Ni-Raney, 55 p.s.i., 90 °C, 8 h (70–81%).

assessed by microscopical scoring of the CPE and a formazan-based cell viability assay. There was a good correlation between the antiviral EC_{50} values obtained by the CPE reduction and MTS cell viability assay, and, hence, only the latter values are shown in Table 1.

The data presented in Table 1 indicate that compounds **21** and **24** elicit potent anti-influenza A virus activity, with a selectivity index (SI) of at least 314 and 256, respectively. Aminoalcohol **24** was endowed with the most potent anti-influenza A virus activity; it proved to be at least 6-fold more potent than amantadine, equipotent to rimantadine and 26-fold more active than ribavirin. Protoadamantanamine **48** was less active than rimantadine, while this compound was comparable to amantadine in both antiviral activity and cytotoxicity. Aminoalcohol **18**, **27**, and its metathesis product **28**, had intermediate activity (EC_{50} ranging from 6 to 9 μM), with **27** and **28** having promising selectivity (SI above 60). Compounds **16**, **30**, **32**, **35**, **36**, **37**, **40** and **46** were devoid of anti-influenza virus activity.

All compounds were inactive against influenza B virus, which is in accordance with their putative mode of action, namely interaction with the influenza A virus M2 protein, which is different in influenza B virus. This is further supported by our observation that none of the new derivatives displayed activity against the influenza virus strain X-31, which carries the V27T and S31N substitutions in M2, associated with amantadine resistance.

The numbered compounds in Table 2 were first tested at 5 μg ml^{-1} against bloodstream form *T. brucei* (strain 427) cultured at pH 7.4. Compounds displaying significant inhibitory activity (>50%) at this concentration were assessed further and their IC_{50} and IC_{90} values determined (Experimental section). The values shown are the mean ± standard deviation from three experiments, with the values for rimantadine shown for comparison. N/A: compounds with marginal activity at 5 μg ml^{-1} which were not examined further.

In the preliminary screen, bloodstream form *T. brucei*, were cultured for 2 days in the presence of aminoadamantane derivatives at 5 μg ml^{-1} (20–30 μM, depending on the compound). At this

Table 1
Anti-influenza A virus (H3N2) activity and cytotoxicity of aminoadamantane derivatives[a] in MDCK cells.[b]

Compound	EC_{50}[c,e] (μM)	MCC[d] (μM)	SI (ratio MCC/EC_{50})
16	N/A	–	–
18	6.24 ± 7.80 (4)	17	3
21	1.46 ± 0.27 (3)	>459	>314
24	0.34 ± 0.12 (4)	87	256
27	7.68 ± 1.68 (3)	512	67
28	8.60 ± 1.99 (3)	512	60
30	N/A	208	–
32	N/A	264	–
35	N/A	404	–
36	N/A	>250	–
37	N/A	>250	–
40	N/A	>200	–
46	N/A	218	–
48	1.5 ± 0.3 (4)	107	69
Amantadine	2.0	>100	>51
Rimantadine	≤0.362	>100	>276
Ribavirin	8.7	20	2

N/A: not active at subtoxic concentrations or the highest concentration tested (~500 μM).

[a] All compounds were tested as hydrochlorides. Aminoalcohols **27** and **36** 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 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).

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

Compound	IC_{50} (μM)	IC_{90} (μM)
16	N/A	–
18	N/A	–
21	9.4 ± 1.1	18.2 ± 1.1
24	N/A	–
27	N/A	–
28	N/A	–
30	N/A	–
32	24.6 ± 0.7	>25
35	5.2 ± 0.4	7.8 ± 0.4
36	0.84 ± 0.04	1.7 ± 0.1
37	0.84 ± 0.08	1.8 ± 0.1
40	N/A	–
46	11.1 ± 5.7	>20
48	N/A	–
Rimantadine	7.0 ± 0.1	14.0 ± 1.7

concentration, compounds **16**, **18**, **24**, **27**, **28**, **30, 40** and **48** showed only slight inhibition (up to 30%) of parasite growth, while dianamine **32** was marginally more active (Table 2). In contrast, amine **46**, aminoalcohol **21** and diamine **35** each exhibited trypanocidal activity in a concentration range similar to that of rimantadine, with lysis of all trypanosomes in the culture at 5 $\mu g\,ml^{-1}$. Aminoalcohols **36** and **37** were the most active of the compounds tested. They displayed significant trypanocidal activity at sub-micromolar levels and were found to be approximately 10-fold more potent than rimantadine (Table 2).

The targets of adamantane derivatives in trypanosomes are unknown. Likewise, the mechanisms of action of other trypanocidal drugs, including pentamidine, suramin and melarsoprol have yet to been identified [30]. However, the mode of action of the nitroheterocycle nifurtimox has been resolved [31]. This drug, in combination with eflornithine, is now recommended as the treatment of choice for late stage West African sleeping sickness [32]. Nifurtimox-resistance is due to down-regulation of the type I nitroreductase which activates the drug *in vivo*. There is no cross-resistance with rimantadine [31].

4. Conclusion

The major conclusions from this study can be summarized as follows: (a) Introduction of the hydroxyl group adjacent to the amine resulted in good antiviral activity, comparable to that of rimantadine. (b) It is apparent that for a series of aminoadamantane compounds, the relative antiviral activity is not directly comparable to the relative trypanocidal potencies in cell culture. (c) The two most active adamantane analogues identified in this report, **36** and **37**, illustrate the synergistic effect on anti-trypanosome activity of the lipophilic character of the side chain and the hydroxyl group. Finally, the simultaneous anti-influenza virus A and trypanocidal activity of aminoalcohol **21**, along with its very low cytotoxicity, are of particular interest and merit further investigation.

5. Experimental

Melting points were determined using 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 a Bruker MSL 400 spectrometer, 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.

5.1. 2-Hydroxy-tricyclo[3.3.1.1]decane-2-acetonitrile (*17*) [3,7]

To a stirred solution of *n*-butyl lithium 2.5 M in hexanes (22 ml, 50 mmol), in dry THF (22 ml) was added, over a period of 7 min, a solution of acetonitrile (2.05 g, 50 mmol) in dry THF (50 ml) at −80 °C under an argon atmosphere. After stirring the mixture for 1 h at −80 °C, a solution of adamantanone **1** (7.50 g, 50 mmol), in dry THF (50 ml) was added over a period of 5 min. The cold bath was removed and the resulting suspension was stirred for 10 min. The mixture was treated with ice-water (50 ml) and concd HCl (5 ml), extracted with Et_2O (3 × 50 ml) and the organic phase was washed with water (40 ml), dried (Na_2SO_4) and concentrated *in vacuo* to afford 9.26 g of the solid hydroxy nitrile **2** (97%), mp 140 °C (THF − petr. ether). I.R. (Nujol): *ν*: (OH) 3437, (CN) 2259 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.62 (br d, 2H, H-4e, 9e), 1.71 (br d, 4H, H-6, 8), 1.83 (br d, 4H, H-5, 7, 10), 1.91 (br s, 2H, H-1, 3), 2.18 (br d, 3H, H-4a, 9a, OH), 2.77 (s, 2H, CH_2-CN); ^{13}C NMR (100 MHz, $CDCl_3$): 26.6 (C-5), 26.8 (C-7), 28.9 (CH_2-CN), 32.4 (C-4, 9), 34.4 (C-8, 10), 36.7 (C-1, 3), 37.7 (C-6), 73.9 (C-2), 117.7 (C*N*). Anal. Calcd. for $C_{12}H_{17}NO$. Calcd, %: C 75.35; H 8.96. Found, %: C 75.33; H 8.90.

5.2. 2-(2-Aminoethyl)tricyclo[3.3.1.1]decan-2-ol (*18*) [3,7]

To a stirred suspension of $LiAlH_4$ (1.50 g, 31 mmol), in dry THF (20 mL) was added dropwise a solution of hydroxy nitrile **2** (1.13 g, 5.9 mmol) in dry THF (10 ml). The reaction mixture was stirred for 20 h at 20 °C 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* ($T < 40$ °C) to give 1.13 g of the solid aminoalcohol **4** (quantitative yield), mp 131 °C (ether). I.R. (Nujol): *ν*: 3349, 3269, 3171 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.47 (br d, 2H, H-4e, 9e), 1.67 (br d, 4H, H-6, 8), 1.77 (br t, 8H, H-1, 3, 5, 7, 10, CH_2CH$_2$NH$_2$), 2.27 (br d, 2H, H-4a, 9a), 2.98 (t, 2H, $J = 11.6$ Hz, CH$_2$CH_2NH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 27.4 (C-5), 27.6 (C-7), 32.7 (C-4, 9), 34.6 (C-8, 10), 37.0 (CH$_2$CH$_2$NH$_2$), 37.3 (CH$_2$CH$_2$NH$_2$), 37.5 (C-1, 3), 38.5 (C-6), 75.5 (C-2). Anal. Calcd. for $C_{12}H_{22}NOCl$. Calcd, %: C 62.19; H 9.57. Found, %: C 62.42; H 9.63.

5.3. 2-Cyano- tricyclo[3.3.1.1]decane-2-carboxylic acid methyl ester (*23*) [3,7]

A solution of nitrile **22** (14.20 g, 88.0 mmol) in dry THF (60 ml) was added dropwise to a solution of LDA, prepared by adding a dry THF solution of freshly distilled diisopropylamine (17.20 g, 170.5 mmol) to a solution of *n*-BuLi (54.52 ml, 2.5 M or 60 mmol) in hexane and stirring the resulting solution for 30 min at −70 °C under an argon atmosphere. After stirring the mixture for 2 h, a solution of freshly distilled methyl chloroformate (48.28 g, 510 mmol) in dry THF (50 ml) was added and the mixture was stirred overnight to slowly reach room temperature. The solution was then poured into crashed ice, extracted with ether; the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude oil was purified by *vacuum* distillation ($bp_{0.01} = 120$ °C) to afford 16.85 g (88%) of ester **23** as a low melting point solid. mp 45 °C (Et_2O-*n*-pentane); I.R.(Nujol): *ν* (CN) 2238, (C═O) 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), *δ* (ppm) 1.65–2.15 (m, 12H, H-4, 5, 6, 7, 8, 9, 10), 2.44 (br s, 2H, H-1, 3), 3.74 (s, 3H, CH_3).

5.4. 2-(2-Aminoethyl)tricyclo[3.3.1.1]decan-2-ol (*24*) [3,7]

To a stirred suspension of $LiAlH_4$ (10.6 g, 279 mmol) in dry THF (150 ml) was added dropwise a solution of the cyanoester **23** (14.8 g, 67.5 mmol) in dry THF (150 ml). The reaction mixture was refluxed for 30 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*. The liquid residue dissolved in ether (150 ml) and extracted with HCl 5% (100 ml) (the aqueous layer must be kept acid). The aqueous layer extracted with ether and alkalized with KOH 30% under ice cooling. The solution was cooled and the precipitated aminoalcohol **24** was filtered, washed with cool water and dried: yield 12.3 g (93%); mp 133 °C (THF-*n*-pentane); IR (Nujol) *ν* 3378 cm^{-1}, 3175 cm^{-1} (OH); ^1H NMR (400 MHz, $CDCl_3$), *δ*: 1.51 (br t, 4H, H-4e, 8, 9e), 1.64 (br d, 4H, H-1, 3, 6), 1.81 (br s, 2H, H-5, 7), 1.89 (br d, 1H, H-10), 2.00 (br d, 2H, H-4a, 9a), 2.59 (br s, 2H, NH_2), 3.04 (s, 2H, CH_2NH$_2$), 3.83 (br s, 2H, CH_2OH) (ppm); ^{13}C NMR ($CDCl_3$, 100 MHz), *δ*: 28.0 (C-5), 28.2 (C-7), 29.8 (C-1, 3), 32.7 (C-4, 9), 32.9 (C-8, 10), 39.4 (C-6), 40.9 (C-2), 48.8 (CH_2NH$_2$), 70.8 (CH_2OH) (ppm).

Anal. Calcd. for $C_{12}H_{22}NOCl$ Calcd. (%): C: 62.19, H: 9.57, N: 6.04. Found (%): C: 62.48, H: 6.50, N: 5.87.

5.5. 4-Hydroxy-tricyclo[4.3.1.0]decan-4-acetonitrile (**26**) [3,8]

To a stirred solution of *n*-butyl lithium 2.5 M in hexanes (10.6 ml, 26.6 mmol), in dry THF (10 ml) was added, over a period of 4 min, a solution of acetonitrile (1.09 g, 26.6 mmol) in dry THF (20 ml) at −80 °C under an argon atmosphere. After stirring the mixture for 1 h at −80 °C, a solution of protoadamantanone **25** (2.0 g, 13.3 mmol), in dry THF (20 ml) was added over a period of 10 min. The cold bath was removed and the resulting suspension was stirred for 10 min. The mixture was treated with ice-water (50 ml), extracted with Et_2O (3 × 30 ml) and the organic phase was washed with water (3 × 10 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography using as eluents Et_2O-*n*-hexane 2/1 to afford 2.83 g of the solid hydroxy nitrile **26** (95%), mp 61 °C (Et_2O-*n*-pentane). I.R. (Nujol): *ν* 3464 cm^{-1} (OH), 2253 cm^{-1} (CN); ^1H NMR (400 MHz, $CDCl_3$) **endo**–**exo**, *δ* (ppm) 1.22–2.16 (complex m, 12H, H-1, 2, 5, 6, 7, 9e, 10, O*H*), 2.30–2.36 (q, 2H, H-3, 8), 2.52–2.72 (m, 3H, H-9a, CH_2CN); ^{13}C NMR ($CDCl_3$, 100 MHz), *δ* (ppm) 28.2/29.2 (C-6), 32.0 (*C*H_2CN), 33.0 (C-8), 33.6/34.3 (C-9), 35.3/35.6 (C-1), 35.8 (C-2), 39.5/39.6 (C-10), 41.6/41.8 (C-7), 42.2/42.6 (C-5), 44.7/45.5 (C-3), 72.2/73.6 (C-4), 118.0/118.2 (*C*N). Anal. Calcd. for $C_{12}H_{17}NO$ Calcd. (%): C: 75.35, H: 8.96, N: 7.32. Found (%): C: 75.12, H: 8.89, N: 7.67.

5.6. 4-(2-Aminoethyl)tricyclo[4.3.1.0]decan-4-ol (**27**) [3,8]

To a stirred suspension of $LiAlH_4$ (2.00 g, 52.0 mmol), in dry ether (30 ml) was added dropwise a solution of hydroxy nitrile **26** (2.21 g, 11.5 mmol) in dry ether (20 ml). The reaction mixture was stirred for 20 h at 20 °C 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 ether; the filtrate was concentrated *in vacuo* ($T < 40$ °C) to give 2.15 g of the solid aminoalcohol **27** (yield 95%), mp 100 °C (Et_2O-*n*-pentane), I.R.(Nujol) *ν* 3364 cm^{-1} (OH), 3290 cm^{-1} (NH_2); ^1H NMR (400 MHz, $CDCl_3$) **endo**–**exo**, *δ* (ppm) 1.25–2.00 (complex m, 14H, H-2, 5, 6, 7, 9, 10, CH_2CH_2NH_2, OH), 2.07–2.11 (t, 1H, H-1), 2.22–2.30 (m, 2H, H-3, 8), 2.74 (br s, 2H, NH_2), 3.00–3.04 (m, 2H, CH_2NH_2); ^{13}C NMR ($CDCl_3$, 100 MHz), *δ* (ppm) 28.7/29.7 (C-6), 32.6 (C-9), 33.3/33.6 (C-8), 33.9/35.3 (C-2), 35.4/35.8 (C-1), 37.8/38.3 (*C*H_2NH_2), 40.0/40.1 (C-10), 42.3/42.6 (C-7), 42.6/42.8 (C-5), 42.9/43.1 (*C*H_2CH_2NH_2), 45.3/45.5 (C-3), 74.4/75.5 (C-4). Anal. Calcd. for $C_{12}H_{21}NO$ Calcd. (%): C: 73.80, H: 10.84, N: 7.17. Found (%): C: 73.71, H: 10.81, N: 7.27.

5.7. 1-(2-Aminoethyl)tricyclo[3.3.1.1]decan-2-ol (**28**) [3,7]

A solution of aminoalcohol **27** (1.10 g, 5.64 mmol), dioxane (13 ml) and H_2SO_4 10% (4 ml) was heated for 2 h in a steam bath. After evaporation of the dioxani *in vacuo*, water was added and the mixture was alkalized with a solution of NaOH 20%. The aqueous solution was extracted with ether (3 × 25 ml), dried (Na_2CO_3) and concentrated *in vacuo* to give aminoalcohol **28** as a white solid (1.05 g, 96%). Mp 87 °C (Et_2O-*n*-hexane), I.R.(Nujol): *ν* 3358 cm^{-1}, 3282 cm^{-1} (NH); ^1H NMR (400 MHz, $CDCl_3$), *δ* (ppm) 0.98–1.00 (d, 1H, H-9e), 1.12–1.15 (m, 1H, CH_ACH_2NH_2), 1.29–1.46 (complex m, 4H, 4e, 6, CH_B-H), 1.53–1.66 (complex m, 3H, H-8, 10a), 1.72–1.83 (complex m, 3H, H-5, 7, 10e), 1.91 (d, 1H, H-3), 2.00–2.05 (m, 2H, 4a, H-9a), 2.66–2.80 (m, 2H, CH_2CH_2NH_2), 3.17 (br s, 3H, NH_2, O*H*), 3.45–3.46 (d, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz), *δ* (ppm) 28.1 (C-5, 7), 30.8 (C-4), 34.5 (C-3), 35.3 (*C*H_2NH_2), 35.6 (C-9), 36.6 (C-10), 37.0 (C-1), 37.4 (C-8), 44.0 (C-6), 44.8 (*C*H_2CH_2NH_2), 75.6 (C-2). Anal. Calcd. for $C_{12}H_{21}NO$ Calcd. (%): C: 73.80, H: 10.84, N: 7.17. Found (%): C: 73.71, H: 10.81, N: 7.31.

5.8. N-methyl-2-(2-pyridinyl)-tricyclo[3.3.1.1]decan-2-amine (**32**) [3,7]

To a stirred solution of 2.5 M n-BuLi in hexanes (12.2 ml, 30.5 mmol), a solution of 2-bromopyridine (4.81 g, 30.5 mol) in dry ether (30 ml) was added dropwise at −85 °C under argon atmosphere. The mixture was then warmed to −42 °C and a solution of imine **31** (2.0 g, 12.2 mmol) and 1-(2-methoxyphenoxy)-*N*,*N*-dimethyl-3-phenylpropan-2-amine (2.0 g, 13.3 mmol) in dry toluene (25 ml) was added dropwise over 30 min. The reaction mixture was stirred at −42 °C for 3 h and allowed to reach slowly room temperature and poured into water under ice cooling. The organic layer was separated and the aqueous layer was extracted with ether and the combined organic extracts were washed several times with water, dried (Na_2SO_4), and evaporated *in vacuo* to give a viscuous oil. After purification with flash column chromatography through silica gel using ether as eluent the solid base **32** was obtained (1.55 g, 53%); mp 71 °C (*n*-hexane); ^1H NMR (400 MHz, $CDCl_3$), *δ* (ppm): 1.25 (bs, 1H, N*H*), 1.56–1.76 (m, 9H, H-4e, 6, 7, 8, 9e, 10), 1.82 (s, 1H, H-5), 1.84 (s, 3H, CH_3), 2.32 (d, 2H, *J* = 11.6 Hz, H-4a, 9a), 2.52 (s, 2H, H-1, 3), 7.02 (t, *J* = 7.2 Hz, 5.2 Hz, 5-Hpyr), 7.25 (d, *J* = 8.0 Hz, 3-Hpyr), 7.58 (t, *J* = 15.6 Hz, 8.0 Hz, 4-Hpyr), 8.54 (d, *J* = 4.8 Hz, 6-Hpyr); ^{13}C NMR (100 MHz, $CDCl_3$), *δ* (ppm): 27.1 (C-5), 27.5 (*C*H_3), 27.9 (C-7), 32.0 (C-1, 3), 32.4 (C-4, 9), 34.1 (C-8, 10), 38.1 (C-6), 63.1 (C-2), 120.8 (C-5pyr), 121.2 (C-3pyr), 135.2 (C-4pyr), 149.1 (C-6pyr), 163.9 (C-2pyr). Anal. Calcd. for $C_{16}H_{22}N_2$ Calcd. (%): C: 79.29, H: 9.15. Found (%): C: 79.61, H: 9.49.

5.9. 4-[3-(Dimethylamino)propylo]-4-tricyclo[4.3.1.0]decanol (**36**) [3,8]

A solution of (3-chloropropyl)dimethylamine (8.09 g, 66.6 mmol) in dry benzene (50 ml) was added dropwise to magnesium turnings (1.7 g, 0.071 g-at)] and the mixture was stirred and heated until complete dissolution. Then a solution of protoadamantanone **25** (2.00 g, 13.3 mmol) in dry benzene (25 ml) was added and the mixture was refluxed for 4 h and then was hydrolyzed under ice cooling by the addition of saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O (3 × 20 ml) and the combined organic extracts were washed with water (3 × 20 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue formed was crystallized upon treatment with *n*-pentane. The solid was filtered off and washed with a cold *n*-pentane to give aminoalcohol **36** (3.06 g, 97%) as a white solid; mp 67 °C (*n*-hexane) I.R. (Nujol) *ν* (OH) 3288 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), *δ* (ppm): 1.26 (d, *J* = 12.8 Hz, 1H, H-9e), 1.39 (dd, *J* = 13.4 Hz, 1.6 Hz, 1H, H-10e), 1.45 (dd, *J* = 11.2 Hz, 2.8 Hz, 1H, H-5e), 1.52–1.83 (complex m, 9H, H-4e, 5a, 7e, 9a, 10a, $CH_2CH_2CH_2N$, $CH_2CH_2CH_2N$), 1.89–1.92 (m, 2H, H-6, 7a), 1.97 (dd, *J* = 13.6 Hz, 2.8 Hz, 1H, H-2a), 2.06–2.12 (m, 3H, H-1, 3, 8), 2.19 (s, 6H, 2xCH_3), 2.28 (t, *J* = 11.6 Hz, 5.6 Hz, 2H, $CH_2CH_2CH_2N$), 6.30 (bs, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$), *δ* (ppm): 22.2 (CH_2**C**H_2CH_2N), 29.9 (C-6), 32.6 (C-9), 33.5 (C-1), 34.2 (C-2), 35.5 (C-8), 40.2 (C-10), 41.4 (CH_2**C**H_2CH_2N), 42.6 (C-7), 43.0 (C-5), 45.0 (2xCH_3), 46.3 (C-3), 60.1 (CH_2**C**H_2CH_2N), 71.5 (C-4). Anal. Calcd. for $C_{15}H_{27}NO$ Calcd. (%): C: 75.90, H: 11.46, N: 5.90. Found (%): C: 76.11, H: 11.19, N: 6.27.

5.10. 1-[3-(dimethylamino)propyl]-tricyclo[3.3.1.1]decan-2-ol (**37**) [3,7]

A solution of aminoalcohol **36** (2.30 g, 9.7 mmol) and H_2SO_4 15% (10 ml) in dioxane (25 ml) was heated in a boiling steam bath for

2 h. After removal *in vacuo* of diaxane, the residue was alkalized with an aq solution of NaOH 10%, extracted with Et_2O and the combined organic extracts were dried (Na_2CO_3). The solvent was evaporated *in vacuo* to give **37** as a viscous oil (2.15 g, 93%), which was converted to its hydrochloride salt. Mp_{HCl} 206 °C (EtOH-Et_2O). I.R.(Nujol) *v* (OH) 3190 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.03 (t, $J = 13.2$ Hz, 4.6 Hz, 2H, $CH_2CH_2CH_2N$), 1.11 (bs, 1H, H-9e), 1.14 (bs, 1H, H-10e), 1.28–1.94 (complex m, 13H, H-3, 4, 5, 6, 7, 8 9a, 10a, $CH_2CH_2CH_2N$), 2.16 (s, 6H, 2xCH_3), 2.27 (t, $J = 11.6$ Hz, 5.6 Hz, 2H, $CH_2CH_2CH_2N$), 3.51 (s, 1H, H-2), 3.82 (bs, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 19.7 (CH_2**C**H_2CH_2N), 28.1 (C-5), 28.2 (C-7), 30.9 (C-4), 34.7 (C-3), 36.5 (C-10), 36.9 (C-1), 37.0 ($CH_2CH_2CH_2N$), 37.4 (C-6), 37.9 (C-9), 40.4 (C-8), 45.3 (2xCH_3), 60.6 ($CH_2CH_2CH_2N$), 75.2 (C-2). Anal. Calcd. for $C_{15}H_{27}NO$ Calcd. (%): C: 75.90, H: 11.46, N: 5.90. Found (%): C: 76.25, H: 11.30, N: 6.07.

5.11. 1-[3-(dimethylamino)propyl]-tricyclo[3.3.1.1]decan-2-one (**38**) [3,7]

To a solution of aminoalcoholol **37** (1.34 g, 5.6 mmol) in acetone (25 ml) was added, during a 0.5 h period, Jones reagent (20.0 ml, 1 mM) at 15 °C. After stirring for 24 h at ambient temperature, isopropanol (3 ml) was added and stirring was continued for an additional 1 h. The reaction mixture was filtered off and the filtrate was evaporated *in vacuo*. The residue was alkalified with Na_2CO_3 and then was extracted with Et_2O (3 × 20 ml). The combined organic extracts were washed with water (2 × 10 ml), dried (Na_2CO_3), concentrated *in vacuo* to afford aminoketone **38** (1.14 g, 87%) as a viscous oil; I.R. (Nujol): *v* (C=O) 1710=cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 1.30–1.35 (m, 2H, $CH_2CH_2CH_2N$), 1.37–1.46 (m, 2H, $CH_2CH_2CH_2N$), 1.56–2.08 (complex m, 12H, H-4, 5, 6, 7, 8, 9, 10), 2.19 (s, 6H, 2xCH_3), 2.23 (t, $J = 14.4$ Hz, 6.8 Hz, 2H, $CH_2CH_2CH_2N$), 2.51 (bs, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm) 21.5 (−**C**H_2CH_2N), 28.1 (C-5, 7), 30.7 (−**C**$H_2CH_2CH_2N$), 39.3 (C-4, 9), 44.1 (C-8, 10), 45.5 (2xCH_3), 47.1 (C-3), 49.2 (C-1), 60.5 (CH_2**C**H_2CH_2N), 218.2 (C=O). Anal. Calcd. for $C_{15}H_{25}NO$: C: 76.55, H: 10.71. Found: C: 76.86, H: 10.95.

5.12. 1-[3-(dimethylamino)propyl]-tricyclo[3.3.1.1]decan-2-one oxime (**39**) [3,7]

A mixture of ketone **38** (0.70 g, 2.9 mmol), $NH_2OH{\cdot}HCl$ (0.41 g, 6.0 mmol) and $CH_3COONa.3H_2O$ (1.36 g, 10.0 mmol) and ethanol 90% (10 ml) was refluxed for 3 h. The ethanol was removed *in vacuo* and the residue was alkalized with Na_2CO_3, extracted with ether, dried (Na_2CO_3) and concentrated under reduced pressure to give **39** as a white low melting solid (0.77 g, quantitative yield); mp 64 °C (*n*-hexane). IR. (Nujol): *v* 1648 cm^{-1} (C=N).

5.13. 2-Amino-N,N-dimethyl-tricyclo[3.3.1.1]decane-1-propanamine (**40**) [3,7]

A solution of oxime **39** (550 mg, 2.2 mmol) in dry EtOH was hydrogenated over Raney-Ni catalyst for 5 h, at 65 °C, and under pressure (55 psi). The catalyst was filtered off and the solvent was evaporated under vacuum to afford a viscous oil (amine **40**) (570 mg, 95% yield), which was converted to its hydrochloride salt; $Mp_{HCl} > 250$ °C (EtOH); ^1H NMR (400 MHz, $CDCl_3$), δ (ppm) 0.93 (bd, 1H, 9e), 1.16–1.85 (complex m, 18H, H-3, 4a, 5, 6, 7, 8, 9, 10, $CH_2CH_2CH_2N$, $CH_2CH_2CH_2N$, NH_2), 2.18 (s, 6H, 2xCH_3), 2.19 (t, $J = 14.2$ Hz, 6.5 Hz, 2H, $CH_2CH_2CH_2N$), 2.67 (bs, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm) 20.2 (−**C**H_2CH_2N), 28.2 (C-5), 28.4 (C-7), 30.6 (−**C**$H_2CH_2CH_2N$), 35.6 (C-3), 35.7 (C-1), 36.8 (C-4), 37.2 (C-10), 37.4 (C-6), 37.5 (C-9), 41.1 (C-8), 45.5 (2xCH_3), 57.3 (C-2), 60.6 (CH_2**C**H_2CH_2N). Anal. Calcd. for $C_{15}H_{29}ClN_2$: C: 66.03, H: 10.71. Found: C: 66.39, H: 11.09.

5.14. (2E)-1-phenyl tricyclo[3.3.1.1]decan-2-one oxime (**45**) [3,7]

A mixture of the ketone **44** [9d] (900 mg, 3.9 mmol), hydroxylamine hydrochloride (490 mg, 7.0 mmol), and sodium acetate trihydrate (1.90 g, 14.0 mmol) in EtOH (25 ml) and H_2O (2.5 ml) was refluxed for 3 h. After evaporation under reduced pressure of 1/3 of the volume of the solvents, H_2O was added to the residue and the solid material formed was filtered, washed with H_2O and dried to give after recrystallization (EtOH/H_2O) the desired oxime **45** as a white crystalline solid (923 mg, 98%); mp 250 °C (dec.). IR. (Nujol): *v* 1662 cm^{-1} (C=N).

5.15. 1-Phenyl-tricyclo[3.3.1.1]decan-2-amine (**46**) [3,7]

1-Phenyladamantan-2-one oxime (819 mg 3.4 mmol) in absolute EtOH (25 ml) under H_2 (55 psi) in the presence of Raney Ni was heated at 90 °C for 8 h. The resulting suspension was filtered through Celite, and the filtrate was concentrated *in vacuo* to give 0.63 g of a viscous liquid product, which was treated with an HCl saturated ethanolic solution. The solvent was evaporated, and water was added to the resulting residue, which was chilled to 0 °C. The precipitate formed was filtered, washed with water, and dried to give the hydrochloride salt of the title amine **46**. Yield 81%. $Mp > 255$ °C (hydrochloride salt, EtOH/Et_2O). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (d, 1H, $J = 12.0$ Hz, H-9e), 1.31–2.03 (m, 14H, H-3, 3, 4, 5, 6, 7, 8, 9a, 10, NH_2), 2.61 (s, 1H, H-2), 7.00–7.27 (m, 5H, H-aromatic); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm) 28.3 (C-5, 7), 30.5 (C-9), 35.9 (C-4), 36.1 (C-3), 37.2 (C-6), 37.6 (C-1, 8), 41.1 (C-10), 59.4 (C-2), 126.1 (C_{arom}-4), 128.6 (C_{arom}-2, 6), 131.6 (C_{arom}-3, 5), 148.4 (C_{arom}-1). Anal. Calcd. for $C_{16}H_{22}ClN$: C: 72.85, H: 8.41. Found: C: 72.52, H: 8.09.

5.16. Tricyclo[4.3.1.0]decan-4-one oxime (**47**) [3,8]

A mixture of protoadamantanone **25** (700 mg, 4.7 mmol), hydroxylamine hydrochloride (590 mg, 8.4 mmol), and sodium acetate trihydrate (2.28 g, 16.8 mmol) in EtOH (25 ml) and H_2O (5 ml) was refluxed for 3 h. After evaporation under reduced pressure of 1/3 of the volume of the solvents, H_2O was added to the residue and the solid material formed was filtered, washed with H_2O and dried to give after recrystallization (Et_2O/PE) the desired oxime **47** as a white crystalline solid (543 mg, 70%); mp 128 °C (dec.). IR. (Nujol): *v* 3209 cm^{-1} (OH), 1666 cm^{-1} (C=N).

5.17. 4-Tricyclo[4.3.1.0]decanamime (**48**) [3,8]

Oxime **47** (330 mg 2.0 mmol) in absolute EtOH (15 ml) under H_2 (55 psi) in the presence of Raney Ni was heated at 90 °C for 8 h. The resulting suspension was filtered through Celite, and the filtrate was concentrated *in vacuo* to give 0.63 g of a viscous liquid product, which was treated with an HCl saturated ethanolic solution. The solvent was evaporated, and water was added to the resulting residue, which was chilled to 0 °C. The precipitate formed was filtered, washed with water, and dried to give the hydrochloride salt of the title amine **48**. Yield 70%. $Mp > 250$ °C (hydrochloride salt, EtOH/Et_2O). I.R.(Nujol) *v* 3280 cm^{-1} (NH_2); ^1H NMR (400 MHz, $CDCl_3$) **endo/exo**, **1/1**,, δ (ppm) 0.98–2.20 (complex m, 14H, 1, 2, 3, 5, 6, 7, 8, 9, 10-H, NH_2), 2.34 (t, 1H, 4-H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm) 28.8/28.9 (6-C), 31.1 (7-C), 31.8/31.9 (2-C), 34.6/34.7 (8-C), 35.1/35.2 (1-C), 39.7/39.9 (5-C), 41.3/41.6 (10-C), 42.6 (9-C), 43.3/43.5 (3-C), 49.5/49.9 (4-C). Anal. Calcd. for $C_{10}H_{18}ClN$: C: 63.99, H: 9.67. Found: C: 63.75, H: 9.35.

5.18. T. brucei culturing and drug test

Bloodstream form *T. brucei* (strain 427) were cultured at 37 °C in modified Iscove's medium [33]. Trypanocidal activity was assessed by growing parasites in 4 ml cultures for 48 h in the presence of a range of drug concentrations, from 0.1 to 25 μM, and determining the levels which inhibited growth by 50% (IC_{50}) and 90% (IC_{90}). In the case of untreated cultures, cell densities increased from 0.25×10^5 to 1×10^6 over this period. Cell densities at each drug concentration were determined using a hemocytometer and drug sensitivity was expressed as a percentage of growth of control cells.

Acknowledgments

Dr. Zoidis would like to thank the State Scholarship Foundation of Greece and the University of Athens (ELKE Account) for financial support. L. Naesens acknowledges the financial support from the International Consortium for Anti-Virals (ICAV); the Flemish Fonds voor Wetenschappelijk Onderzoek (FWO No. 9.0188.07) and the Geconcerteerde Onderzoeksacties (GOA/10/014); and the technical assistance from Leentje Persoons and Frieda De Meyer. J. Kelly acknowledges support from the Wellcome Trust (Ref. 5632).

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