Design, Synthesis, and Trypanocidal Activity of New Aminoadamantane Derivatives

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To develop functionalized adamantanes for treating African trypanosomiasis, we report on the synthesis of new 1-alkyl-2-aminoadamantanes **1a**−**i**, 1-alkyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazones **2a**−**g**, and their congeneric thiosemicarbazones **3a**,**b**. The potency of these compounds against *Trypanosoma brucei* was compared to that of amantadine and rimantadine and found to be substantially higher. The most active analogues, **1c**, **1d**, **2c**, **2g**, and **3b**, illustrate the synergistic effect of the lipophilic character of the C1 side chain and the C2 functionality on trypanocidal activity.

Introduction

Sleeping sickness or African trypanosomiasis is a parasitic disease of humans and animals caused by protozoa of the genus *Trypanosoma* and transmitted by the tsetse fly. The disease is endemic in several regions of Sub-Saharan Africa, covering about 36 countries and 60 million people. It is estimated that 50 000−70 000 people are currently infected, the number having declined somewhat in recent years.[1] Three major epidemics have occurred in the past hundred years, one from 1896 to 1906 and the others in 1920 and 1970. The disease had practically disappeared between 1960 and 1965, but since then, screening and effective surveillance have been relaxed and the disease has reappeared in endemic form in several foci over the past 30 years.[2]

Trypanosoma brucei is an extracellular parasite and replicates in the bloodstream of infected individuals, where it avoids immune destruction by a complex system of antigenic variation.[3] As a result, there is little prospect of an effective vaccine. Symptoms begin with fever, headaches, and joint pains, and as the disease progresses, the lymph nodes often swell considerably. Other presentations include anemia and endocrine, cardiac, and kidney disorders. The disease enters its critical stage when the parasite passes through the blood−brain barrier, and the resulting symptoms give the disease its name. Besides confusion and reduced coordination, the sleep cycle is disturbed with bouts of fatigue punctuated with manic periods progressing to daytime slumber and nighttime insomnia. Damage caused in this neurological phase can be irreversible. In addition to the bite of the tsetse fly, the disease can also be contracted by congenital transmission, laboratory-acquired infection, and blood transfusion.

Without treatment, African trypanosomiasis is invariably fatal, with progressive mental deterioration leading to coma and death. However, current drug regimes are unsatisfactory for reasons that include lack of efficacy, toxic side effects, and the need for administration under medical supervision. The standard treatment for first stage disease is intravenous pentamidine (*T.b. gambiense*) or intravenous suramin (*T.b. rhodesiense*). For late stage disease, intravenous melarsoprol is given at 2.2 mg/kg daily for 10 consecutive days.[4] Alternative first line therapies include intravenous eflornithine (difluoromethylornithine) 50 mg/kg every 6 h for 14 days (*T.b. gambiense*).[5] In areas with melarsoprol resistance or in patients who have relapsed after melarsoprol monotherapy, eflornithine is used. More recently, a combination of melarsoprol and nifurtimox has also been shown to be effective.[6]

Pentamidine has been used since 1939. During the 1950s, it was widely used as a prophylactic agent in West Africa, leading to a sharp decline in infection rates. At the time, it was thought that eradication of the disease was at hand. The organoarsenical melarsoprol (Arsobal) was developed in the 1940s and is effective for patients with second stage sleeping sickness. However, 3−10% of those injected have reactive encephalopathy (convulsions, progressive coma, or psychotic reactions), and those that survive can suffer brain damage. Despite this, because of its effectiveness, melarsoprol is still widely used and resistance is increasing. Eflornithine, the most modern treatment, was developed in the 1970s by Albert Sjoerdsmanot and underwent clinical trials in the 1980s. The drug was approved by the U.S. Food and Drug Administration in 1990, but guaranteed production remains a problem.

Recently, we discovered that bloodstream form *T. brucei* are sensitive to the antiviral drug amantadine (**I**, Figure 1) and its congener rimantadine (**II**, Figure 1) and that the potency of these drugs is pH dependent, a factor that could be related to the mechanism of action.[7,8] Derivatives of these compounds (**III**−**V**, Figure 1)[8] were found to have potential as trypanocidal agents.[8] For example, analogue **V** (1-adamantyl-4-aminocyclohexane) ($IC_{50} = 0.33\ \mu M$) was 400 times more potent than amantadine and 20-fold more active than rimantadine. Moreover, as a general trend, we found a correlation between the lipophilicity of derivatives and their trypanocidal activity.

Over the past 15 years we have sought to develop adamantane derivatives with antiviral properties.[9−11] In extending this work, we describe the synthesis of 1-alkyl-2-aminoadamantanes **1**, 1-alkyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazones **2** and their respective thiosemicarbazones **3** (Figure 2) and report the activity of these compounds against *T. brucei*. The design of analogues **1** was based on our earlier findings, which link lipophilicity with trypanocidal action.[8] The rationale behind the synthesis of **2** and their bioisosters **3** resided in the reported antitrypanosome potency of heterocyclic guanylhydrazones and thiosemicarbazones.[12]

Chemistry

The synthesis of analogues **1a**−**h** is shown in Scheme 1. Protoadamantanone **4**,[13] prepared by a modification of the

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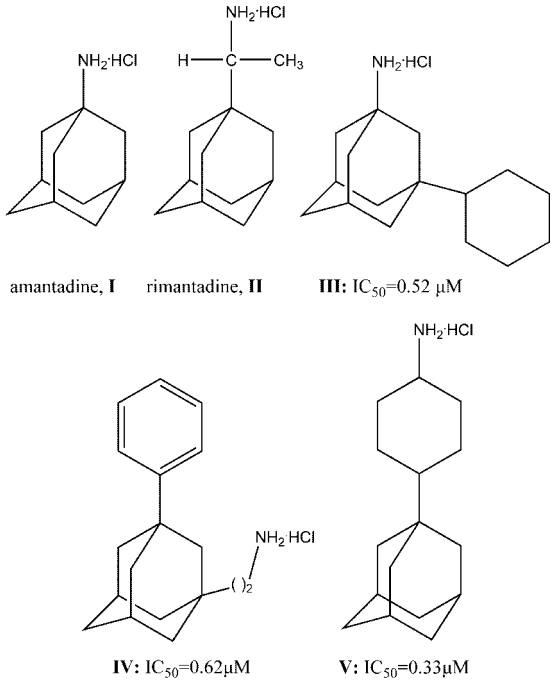
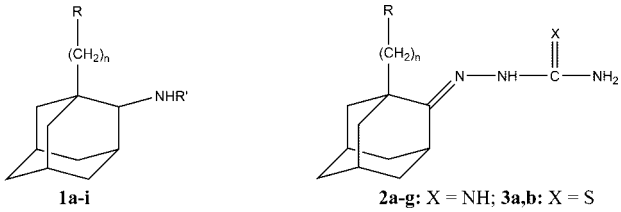


Figure 1. Structures of amantadine (**I**), rimantadine (**II**), and aminoadamantane derivatives with trypanocidal activity (**III**−**V**).[8] The concentrations that inhibit growth of bloodstream form *T. brucei in vitro* by 50% are indicated.



1a: R = C_4H_9, R' = H, n = 2
1b: R = C_6H_{13}, R' = H, n = 2
1c: R = C_8H_{17}, R' = H, n = 2
1d: R = $C_{10}H_{21}$, R' = H, n = 2
1e: R = $C_{12}H_{25}$, R' = H, n = 2
1f: R = C_4H_9, R' = C_2H_5, n = 2
1g: R = C_8H_{17}, R' = C_2H_5, n = 2
1h: R = $C_{10}H_{21}$, R' = C_2H_5, n = 2
1i: R = Ph, R' = H, n = 1

2a: R = C_4H_9, n = 2
2b: R = C_6H_{13}, n = 2
2c: R = C_8H_{17}, n = 2
2d: R = $C_{10}H_{21}$, n = 2
2e: R = $C_{12}H_{25}$, n = 2
2f: R = Ph, n = 0
2g: R = Ph, n = 1
3a: R = C_4H_9, n = 2
3b: R = $C_{12}H_{25}$, n = 2

Figure 2. Structures of the new adamantane derivatives **1a**−**i**, **2a**−**g**, and **3a**,**b**.

literature method from the reaction of 1-adamantanol with iodine and lead tetraacetate,[14] was treated with the appropriate lithiated acetylene to give the corresponding tertiary alcohol **5** as an endo/exo isomeric (1:1) mixture in 82–95% yield. Alcohols **5** were in turn hydrogenated under Adams' conditions to the respective endo/exo saturated products **6**, which on treatment with formic acid were converted to formates **7** via a C2−C3 to C4 metathesis. Saponification of the in situ formed esters **7** gave the respective secondary alcohols **8** in 91–96% yield, and these were then oxidized under Jones reaction conditions to the corresponding 1-alkyl-2-ones **9**. Treatment of ketones **9** with hydroxylamine hydrochloride in the presence of sodium acetate led to the formation of the respective oximes **10**, which on hydrogenation over Raney Ni catalyst were converted to a mixture of amines, **1a**−**e** and **1f**−**h**; the yield of the latter was found to increase upon heating and prolonged hydrogenation. Amine **1i** was obtained from ketone **4** by lithiation with phenyllithium followed by the sequence of the reactions described above.

The ethylation of primary amines, such as **1a**−**e** to their congeners **1f**−**h** by the solvent (ethanol), has been scarcely reported in the literature and only in cases where the reaction is run at high temperatures.[15] It is noteworthy that at 120 °C and after 5 h of hydrogenation only the secondary amines **1f**−**h** were detected in the reaction mixture. Moreover, their formation, albeit partial, was also evident at temperatures below 80 °C. A possible explanation for the observed ethylation of amines **1a**−**e** resides in the disproportionation of the solvent (ethanol), which, under the specific reaction conditions, is rendered sufficiently electrophilic.

The guanylhydrazones **2** were prepared by heating the respective ketones (Scheme 2) with an ethanolic solution of aminoguanidine hydrochloride; the latter was prepared by acidifying (concentrated HCl) an ethanolic suspension of aminoguanidine bicarbonate. For the synthesis of guanylhydrazone **2f**, the organometallic reagent used was phenyllithium, whereas for **2g** it was phenylmagnesium bromide.

The thiosemicarbazones **3** were prepared by heating the respective ketones **9** with an ethanolic solution of thiosemicarbazide (Scheme 3).

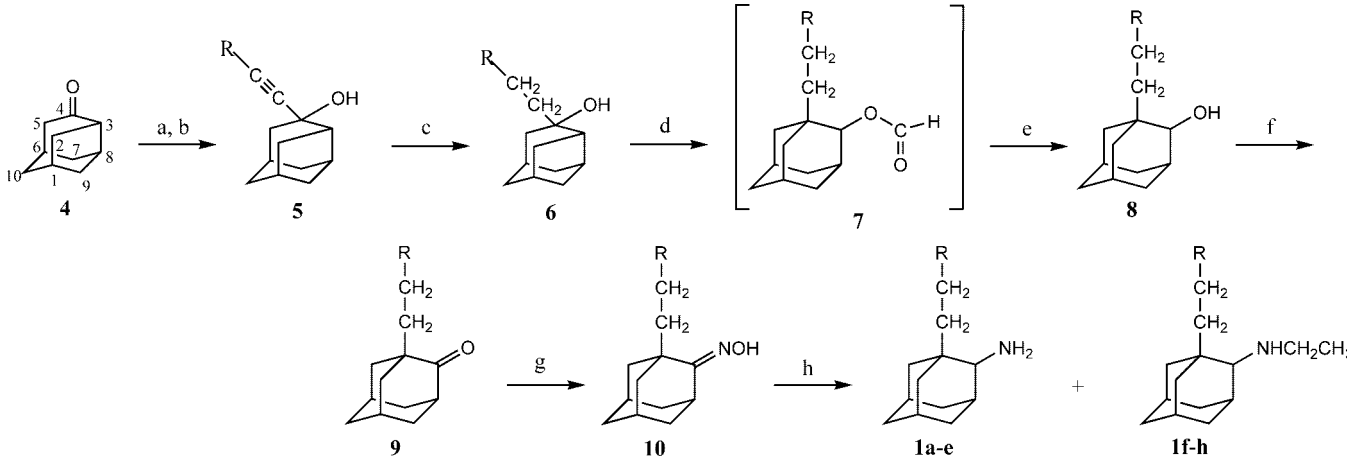
Results and Discussion

The 18 new adamantane derivatives were tested for activity against bloodstream form *T. brucei.* The aminoadamantane analogues (**1a**−**i**) allowed us to explore the synergism of the amino and alkyl/aryl moieties. From Table 1, it can be seen that increasing the size of the alkyl chain from *n*-hexyl (**1a**) to *n*-dodecyl (**1d**, **1h**) leads to an enhancement in potency. Analogues **1d** and **1h** are ∼280- and 15-fold more active than amantadine and rimantadine, respectively. However, the introduction of a tetradecyl at the 1 position of 2-aminoadamantane (**1e**) or a benzylic group (compound **1i**) leads to a decrease in activity. A difference in potency was also noticed between the primary amines **1c** and **1d** (**1c**, IC_{90} = 0.67 μM; **1d**, IC_{90} = 0.67 μM) and their respective *N*-ethyl congeners **1g** (IC_{90} = 1.65 μM) and **1h** (IC_{90} = 1.06 μM). Taking amantadine and rimantadine as the basic structures, these results nicely illustrate the effect of adding alkyl and phenyl groups at C1 and converting the C2 amine from primary to secondary.

Comparison of the 1-amino derivatives (**1a**−**i**) with their guanylhydrazone congeners (**2a**−**g**) shows that the nature of the C2 substitution is even more important in the latter series (Table 2). Compound **2c** (R = C_8H_{17}) is an exceptionally potent adamantane derivative, being 1460- and 77-fold more active than amantadine and rimantadine, respectively, and warrants further investigation. Interestingly, this activity was reduced by approximately 10-fold by lengthening the alkyl group from *n*-decyl (**2c**) to *n*-dodecyl (**2e**). Another derivative that displayed considerable trypanocidal activity was **2g** (R = Ph), which was 323- and 17-fold more potent than amantadine and rimantadine, respectively. The differences between the 1-amino derivatives (**1a**−**i**) and guanylhydrazones (**2a**−**g**) demonstrate that the latter compounds show an enhanced activity that is not linked to the degree of lipophilicity of the R group and/or its aliphatic or aromatic nature but to the characteristic stereoelectronic features of the guanylhydrazone component.

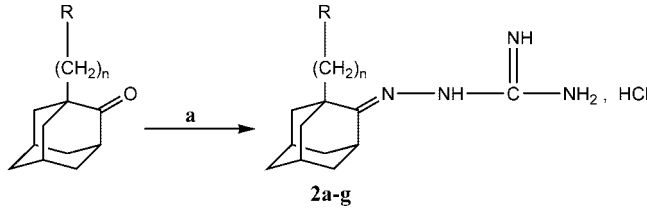
This hypothesis is further strengthened by the trypanocidal activity data obtained for thiosemicarbazones **3a** and **3b** (Table 3), which are structurally related to guanylhydrazones (**2a**−**g**). Thus, compound **3a** (R = C_4H_9; IC_{90} = 5.64 μM) is ∼3-fold less potent than its aminoadamantane congener **1a** (R = C_4H_9; IC_{90} = 1.73 μM) while **3b** (R = $C_{12}H_{25}$; IC_{90} = 0.54 μM) is 4 times as active as **1e** (R = $C_{12}H_{25}$; IC_{90} = 1.98 μM). However,

Scheme 1. Synthesis of the New Adamantane Derivatives **1a**−**h**[a]



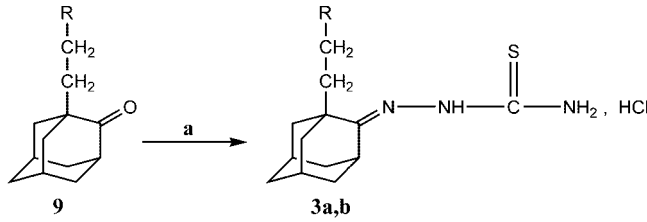
[a] Reagents and conditions: (a) RC≡CH, *n*-BuLi, THF; (b) H_2O; (c) H_2/PtO_2, EtOH, room temp; (d) HCOOH, reflux, 30 min; (e) NaOH/EtOH, Δ; (f) CrO_3, aqueous H_2SO_4 (8 N), acetone, 15 °C; (g) $H_2NOH \cdot HCl$, AcONa, EtOH; (h) H_2/Raney Ni, EtOH, 80 °C.

Scheme 2. Synthesis of the New Adamantane Derivatives **2a**−**e** ($n = 2$), **2f** ($n = 0$), and **2g** ($n = 1$)[a]



[a] Reagents and conditions: (a) aminoguanidine bicarbonate, HCl, EtOH, Δ.

Scheme 3. Synthesis of the New Adamantane Derivatives **3a**,**b**[a]



[a] Reagents and conditions: (a) thiosemicarbazide, EtOH, Δ.

Table 1. Trypanocidal Activity of 1-Alkyl-2-aminoadamantanes[a]

compd	1-alkyl side chain	IC_{50} (μM)	IC_{90} (μM)
amantadine		>132.4	>132.4
rimantadine		7.04 ± 0.27	13.97 ± 1.67
1a	C6	1.32 ± 0.00	1.73 ± 0.03
1b	C8	0.80 ± 0.36	1.06 ± 0.46
1c	C10	0.48 ± 0.03	0.67 ± 0.09
1d	C12	0.47 ± 0.02	0.67 ± 0.00
1e	C14	0.92 ± 0.05	1.98 ± 0.05
1i	$PhCH_2$	2.07 ± 0.03	2.65 ± 0.00
1f	C6	>2	
1g	C10	1.09 ± 0.28	1.65 ± 0.28
1h	C12	0.59 ± 0.05	1.06 ± 0.02

[a] Several 2-aminoadamantane derivatives were tested for in vitro activity against bloodstream form *T. brucei* (pH 7.4), and the concentrations that inhibited growth by 50% (IC_{50}) and 90% (IC_{90}) were calculated (Supporting Information). The lengths or nature of the 1-alkyl side chains is indicated. The derivatives contained primary (**1a**−**e**) or *N*-ethyl substituted (**1f**−**i**) amino groups at the 2 position. IC_{50} and IC_{90} data are the mean of triplicate experiments ± SEM.

the activity of the more lipophilic compound **3b** is 10 times higher than that of **3a**. Both thiosemicarbazones were considerably more active than amantadine and rimantadine, **3b** being respectively 315- and 17-fold more potent.

Table 2. Trypanocidal Activity of 1-Alkyltricyclodecan-2-guanylhydrazones[a]

compd	1-alkyl side chain	IC_{50} (μM)	IC_{90} (μM)
2a	C6	>6.0	
2b	C8	>6.0	
2c	C10	0.09 ± 0.02	0.11 ± 0.00
2e	C14	0.84 ± 0.50	1.30 ± 0.50
2f	Ph	2.12 ± 0.09	2.81 ± 0.03
2g	$PhCH_2$	0.41 ± 0.06	0.47 ± 0.01

[a] Derivatives **2a**−**g** were tested against in vitro bloodstream form *T. brucei* (pH 7.4) as outlined in the Supporting Information. The lengths or nature of the 1-alkyl side chains is indicated. IC_{50} and IC_{90} data are the mean of triplicate experiments ± SEM.

Table 3. Trypanocidal Activity of 1-Alkyl-tricyclodecan-2-thiosemicarbazones[a]

compd	1-alkyl side chain	IC_{50} (μM)	IC_{90} (μM)
3a	C6	2.81 ± 0.09	5.64 ± 0.54
3b	C14	0.42 ± 0.04	0.54 ± 0.02

[a] Derivatives **3a** and **3b** were tested against in vitro bloodstream form *T. brucei* (pH 7.4) (Supporting Information). The lengths of the 1-alkyl side chains are indicated. IC_{50} and IC_{90} data are the mean of triplicate experiments ± SEM.

The five most active adamantane analogues identified in this report, **1c**, **1d**, **2c**, **2g**, and **3b**, illustrate the synergistic effect on antitrypanosome activity of the lipophilic character of the C1 side chain and C2 functionality. Continuing attempts to define the characteristics of adamantane-based structures required for effective activity against *T. brucei* are currently underway. This would be greatly facilitated if the target of these adamantine analogues in the trypanosome could be identified. Our current model is that these drugs probably block/perturb a parasite membrane-localized ion channel/transporter, since this is the only known mechanism by which this class of compound are therapeutically effective. Channel blocking activity is the basis for the anti-influenza virus properties of aminoadamantanes and is also the mechanism behind their effects on neurodegenerative disorders. Respectively, this involves blockage of the M2 proton channel[16] and the transmembrane channel in the *N*-methyl-D-aspartate receptor.[17] The activity of amantadine against hepatitis C virus is also mediated by blocking of an ion channel, in this instance that formed by the viral encoded protein p7.[18]

Experimental Section

General Procedure for the Preparation of 1-Alkyltricyclo-[3.3.1.1^{3,7}]decan-2-amines 1a−e and *N*-Ethyl-1-alkyltricyclo-[3.3.1.1^{3,7}]decan-2-amines 1f−h. A solution of the appropriate ketoxime (1.63 mmol) in absolute EtOH (50 mL) under H_2 (55 psi) in the presence of Raney Ni was heated at 80–100 °C for 4–5 h. The resulting suspension was filtered through Celite, and the filtrate was concentrated in vacuo to give a liquid product, which was flash-chromatographed (eluent Et_2O) to give the title amines. Both primary amines **1a**−**e** and their *N*-ethyl congeners **1f**−**h** were treated with an HCl saturated ethanolic solution. The solvent was evaporated, and *n*-pentane (**1c**), acetone (**1b**,**d**,**e**,**h**), ether (**1a**), or water (**1f**,**g**) was added to the resulting residue, which was chilled to 0 °C. The precipitate formed was filtered, washed with *n*-pentane, acetone, ether, or water and dried to give the hydrochloride salts of the title amines.

1-Hexyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1a). This compound was obtained in 45% yield following the general method by hydrogenating ketoxime **10** at 55 psi for 4 h at 100 °C. Mp 128 °C (hydrochloride salt, Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 6.9 Hz, 3H, CH_3), 0.91–1.19 (m, 10H, $(CH_2)_5$), 1.31–1.82 (m, 13H, H_{3-10}), 2.66 (s, 1H, H_2-adamantane). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.8 CH_3CH_2NH), 28.5 (C_7), 30.2 (C_4), 30.7 (C_4), 31.9 (C_3), 35.5 (C_3), 35.7 (C_1), 36.8 (C_1), 37.6 (C_9), 37.8 (C_6), 39.8 (C_{10}), 41.1 (C_8), 57.2 (C_2). Anal. ($C_{16}H_{30}NCl$) C, H.

1-Decyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1c). This compound was obtained in 31% yield following the general method by hydrogenating ketoxime **10** at 55 psi for 5 h at 80 °C. Mp 101 °C (hydrochloride salt, EtOH/Et_2O/*n*-pentane).

1-Dodecyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1d). This compound was obtained in 53% yield following the general method by hydrogenating ketoxime **10** at 55 psi for 2 h at 105 °C. Mp 73 °C (hydrochloride salt, methanol−acetone).

***N*-Ethyl-1-hexyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1f).** This compound was obtained in 23% yield following the general method by hydrogenating ketoxime **10** at 55 psi for 4 h at 100 °C. Mp 137 °C (hydrochloride salt, Et_2O/*n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 6.8 Hz, 3H, CH_3), 1.03 (t, J = 7.0 Hz, 3H, CH_3CH_2NH), 1.12–1.32 (m, 10H, $(CH_2)_5$), 1.33–1.86 (m, 13H, H_{3-10}), 2.39 (bs, 1H, H_2-adamantane), 2.45 (m, 1H, CH_3CH_2NH), 2.66 (m, 1H, CH_3CH_2NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (CH_3), 15.7 (CH_3CH_2NH), 21.8 (C_5), 22.6 ($C_{2'}$), 28.2 (C_5), 28.4 (C_7), 30.2 (C_4), 30.6 (C_3), 31.0 ($C_{4'}$), 31.9 ($C_{3'}$), 35.6 (C_1), 37.4 (C_9), 38.1 ($C_{1'}$), 39.8 (C_{10}), 41.7 (C_8), 42.0 (CH_3CH_2NH), 63.6 (CHNHCH$_2$CH$_3$). Anal. ($C_{18}H_{34}NCl$) C, H.

***N*-Ethyl-1-decyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1g).** This compound was obtained in 43% yield following the general method by hydrogenating ketoxime **10** at 55 psi for 5 h at 80 °C. Yield 43%. Mp 69 °C (hydrochloride salt, H_2O).

***N*-Ethyl-1-dodecyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1h).** This compound was obtained in 30% yield following the general method by hydrogenating ketoxime **10** at 55 psi for 2 h at 105 °C. Mp 105 °C (hydrochloride salt, acetone).

1-Benzyltricyclo[3.3.1.1^{3,7}]decan-2-amine (1i). 1-Benzyladamantan-2-one oxime (3.40 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. Yield 82%. Mp >255 °C (hydrochloride salt, EtOH/Et_2O).

General Procedure for the Preparation of 1-Alkyltricyclo-[3.3.1.1^{3,7}]decan-2-guanylhydrazones 2a−g. A suspension of aminoguanidine bicarbonate (0.17 g, 1.28 mmol) in absolute EtOH (15 mL) was cautiously acidified with concentrated HCl until the mixture became soluble (pH ~2) and CO_2 gas ceased to evolve. The requisite 1-substituted-2-adamantanone (1.28 mmol) was then added, and the mixture was refluxed for 5 h. The solvent was evaporated in vacuo, and the residue obtained was treated with Et_2O/*n*-pentane. The precipitate formed was filtered, washed with *n*-pentane, and dried to give the desired compound.

1-Hexyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2a). Yield 92%. Mp 173 °C (hydrochloride salt, EtOH/Et_2O). IR (free base, nujol) ν_{max} 3441, 3315, 2588, 2425, 1598 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H, CH_3), 1.27–1.44 (m, 10H, $(CH_2)_5$), 1.59–1.97 (m, 12H, H_{4-10}), 3.70 (bs, 1H, H_3-adamantane), 4.82 (bs, 4H, NHC(=NH)NH$_2$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.2 (CH_3), 21.8 ($C_{5'}$), 22.4 ($C_{2'}$), 27.4 ($C_{5,7}$), 29.6 ($C_{3'}$), 30.3 (C_3), 31.1 ($C_{4'}$), 35.4 (C_6), 37.2 ($C_{4,10}$), 37.3 ($C_{1'}$), 40.9 (C_1), 43.2 ($C_{8,9}$), 157.2 (C=N), 168.0 (NH*C*(=NH)NH$_2$). Anal. ($C_{17}H_{31}N_4Cl$) C, H.

1-Octyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2b). Yield 85%. Mp 177 °C (hydrochloride salt, EtOH/Et_2O). Anal. ($C_{19}H_{35}N_4Cl$) C, H.

1-Decyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2c). Yield 94%. Mp 133 °C (hydrochloride salt, EtOH/Et_2O). Anal. ($C_{21}H_{39}N_4Cl$) C, H.

1-Dodecyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2d). Yield 78%. Mp 172 °C (hydrochloride salt, EtOH/Et_2O). Anal. ($C_{23}H_{43}N_4Cl$) C, H.

1-Tetradecyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2e). Yield 85%. Mp 98 °C (hydrochloride salt, EtOH/Et_2O/*n*-pentane).

1-Phenyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2f). Yield 96%. Mp 251 °C (hydrochloride salt, EtOH/Et_2O).

1-Benzyltricyclo[3.3.1.1^{3,7}]decan-2-guanylhydrazone (2g). Yield 78%. Mp >255 °C (hydrochloride salt, EtOH/Et_2O).

General Procedure for the Preparation of 1-Alkyltricyclo-[3.3.1.1^{3,7}]decan-2-thiosemicarbazones 3a,b. A mixture of the appropriate ketone **10** (1.28 mmol) and thiosemicarbazide (0.12 g, 1.28 mmol) in absolute EtOH (15 mL) was refluxed for 5 h. The resulting suspension was concentrated in vacuo to $^1/_3$ of its original value, the solution chilled (0 °C), and the resulting precipitate filtered and washed with cold EtOH to give the title compounds.

1-Hexyltricyclo[3.3.1.1^{3,7}]decan-2-thiosemicarbazone (3a). Yield 82%. Mp 173 °C (hydrochloride salt, EtOH). IR (nujol) ν_{max} 3416, 3254, 3148 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 6.4 Hz, 3H, CH_3), 1.21–1.37 (m, 10H, $(CH_2)_5$), 1.58–1.94 (m, 12H, H_{4-10}), 3.13 (s, 1H, H_3-adamantane).

1-Tetradecyltricyclo[3.3.1.1^{3,7}]decan-2-thiosemicarbazone (3b). Yield 89%. Mp 108 °C (hydrochloride salt, EtOH). IR (nujol) ν_{max} 3424, 3255, 3143 cm^{-1}. Anal. ($C_{25}H_{45}N_3S$) C, H.

Supporting Information Available: Experimental details of the synthesis of the compounds described in this paper; NMR, IR, and 2-D NMR spectra of selective compounds; elemental analysis data for key target molecules; and pharmacological assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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