Synthesis of Conformationally Constrained Adamantane Imidazolines with Trypanocidal Activity

Ioannis Papanastasiou[1], Andrew Tsotinis[1], George B. Foscolos[1*], S. Radhika Prathalingam[2], John M. Kelly[2]

[1]Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupoli-Zografou, 157 71 Athens, Greece.
[2]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, U.K.
tsotinis@pharm.uoa.gr

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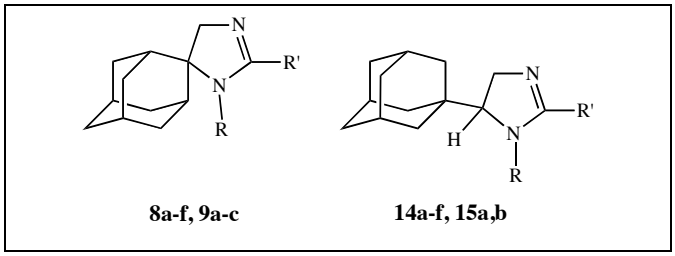

Aiming at the development of new adamantano building blocks for treating African trypanosomiasis, we report on the synthesis of spiro adamantane 2-imidazolines **8a-f** and **9a-c**, and their congeneric 5-(1-adamantyl)imidazolines **14** and **15**. The potency of these compounds against *Trypanosoma brucei* was compared to that of rimantadine and found, in the case of compound **14e**, to be three fold higher. Together with the other active compounds, **14b** and **15b**, which were equipotent to rimantadine, the new molecules illustrate the synergistic effect of the lipophilic character of adamantane and the C1 amidine functionality on trypanocidal activity.

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INTRODUCTION

Human African Trypanosomiasis (HAT) is endemic in several areas of Sub-Saharan Africa. Current estimates are that 70,000 individuals are infected, the number having fallen from 450,000 within the last 10 years as a result of co-ordinated public health campaigns [1]. HAT is caused by tsetse fly transmitted protozoan parasites of the *Trypanosoma brucei* species complex, and is invariably fatal unless treated. For more than fifty years, pentamidine and suramin have been the drugs of choice against first stage disease [2]. However, these compounds are unable to cross the blood brain barrier and are therefore ineffective against second stage HAT, which occurs once the parasites has accessed the central nervous system. The arsenical melarsoprol (Mel B, Asorbal) and eflornithine (Ornidyl) are the only drugs routinely used against this stage of the disease. New drugs are urgently required since melarsoprol is extremely toxic and eflornithine is only effective against *T.b. gambiense* and is relatively expensive.

We have reported that bloodstream forms of *Trypanosoma brucei* are susceptible to the anti-influenza virus drug rimantadine, and to a lesser extent amantadine [3] (compounds **1** and **2**, Fig. 1). This could have relevance for drug development against HAT, since both compounds readily cross the blood brain barrier and are well absorbed from the gastrointestinal tract. Further tests with substituted aminoadamantane derivatives identified compounds with enhanced potency (compounds **3-5**, Figure 1), and we showed that this increased trypanocidal activity could be correlated with hydrophobic substitutions to the adamantane ring [4,5].

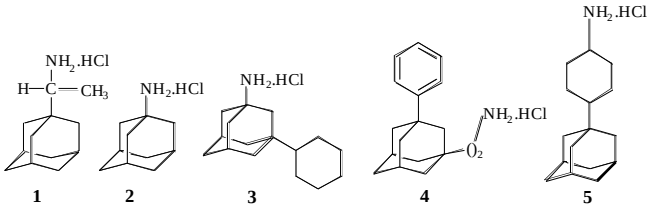


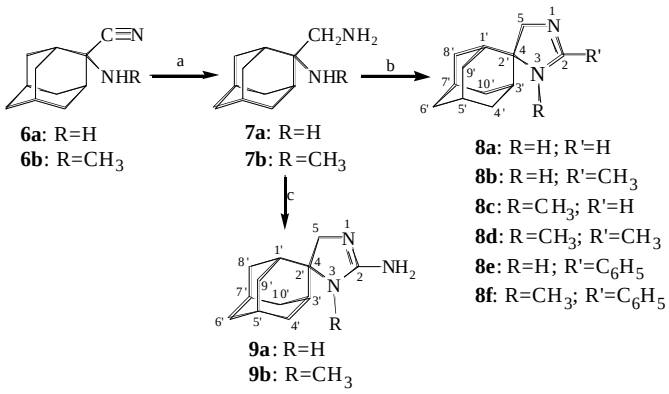
Figure 1. Structures of trypanocidal aminoadamantanes [4]. The concentrations that inhibited growth of bloodstream form *T. brucei* by 50% (IC_{50}) were established as follows: (**1**) 7.04 μM; (**2**) > 132 μM; (**3**) 0.52 μM; (**4**) 0.62 μM; (**5**) 0.33 μM.

To explore further the potential of this class of compound against *T. brucei*, these observations have prompted us to synthesise adamantane 2-imidazolines **8** and **9** (Schemes 1 and 2), and their 1-substituted congeners **14** and **15** (Scheme 3). These compounds combine two distinct structural components: amidine moieties, which have been widely shown to display trypanocidal activity, attached to adamantane, a lipophilic molecule which could facilitate passage of the new derivatives across the blood brain barrier.

RESULTS AND DISCUSSION

The synthetic route followed for the preparation of spiroadamantanimidazolines **8** and **9** is illustrated in Scheme 1.

Scheme 1



6a: R=H
6b: R=CH_3

7a: R=H
7b: R=CH_3

8a: R=H; R'=H
8b: R=H; R'=CH_3
8c: R=CH_3; R'=H
8d: R=CH_3; R'=CH_3
8e: R=H; R'=C_6H_5
8f: R=CH_3; R'=C_6H_5

9a: R=H
9b: R=CH_3

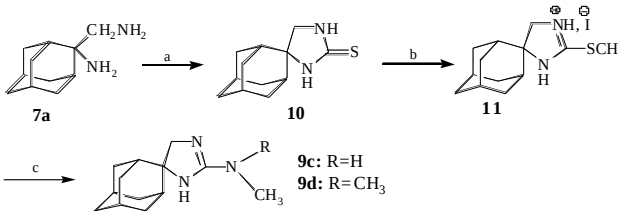
Reagents and Conditions: (a) H_2/PtO_2, gas HCl/EtOH, 55 psi, 90 °C, 1.5 h and then aq. NaOH; (b) formamidine acetate or acetamidine hydrochloride or benzamidine hydrochloride, EtOH, r.t., 30-48 h; (c) BrCN, CH_2Cl_2, 0 °C and then r.t., 70 h.

Catalytic hydrogenation of the hydrochloride salts of α-aminonitriles **6** [7] under Adams' conditions provided the corresponding hydrochloride diamines **7** [8]. These were converted to their respective bases by adding a solution of NaOH. Condensation of diamines **7** with formamidine acetate, acetamidine hydrochloride or benzamidine hydrochloride [7] led to the spiroimidazolines **8**, whereas condensation of diamines **7** with cyanogen bromide gave aminospiroimidazolines **9**. The methylamino- and the dimethylaminoderivatives **9c** and **9d** were obtained by cyclizing the diamines **7** with carbon disulfide [8] in the presence of conc. HCl to give the thione **10**. S-methylation of thione **10** with methyl iodide gave the S-methyl derivative **11**. Displacement of methyl mercaptan by methylamine or dimethylamine in *i*-PrOH under pressure and heating gave amines **9c** and **9d** (Scheme 2). The 2-alkyl and 2-amino-5-(1-adamantyl)imidazolines **14** and **15** were prepared from the nitriles **12** [9] in a similar way as imidazolines **8** and **9** (Scheme 3).

The new adamantane derivatives were initially screened for activity against bloodstream form *T. brucei* at 5 μg/ml (15–20 μM).

With the exception of the methylaminospiroimidazoline derivative (compound **9c**), none of the spiroadamantan-imidazolines (compounds **8a-f**, **9a, b, d**) had any significant effect on the parasite at this concentration. Compound **9c**, on the other hand, completely blocked parasite growth. However, it was ineffective at 1 μg ml^{-1} and was not assessed further at this stage. With the 2-alkyl and 2-amino-5(1-adamantyl)imidazolines (compounds

Scheme 2

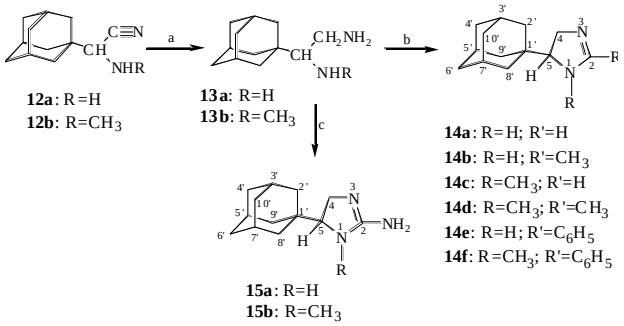


7a **10** **11**

9c: R=H
9d: R=CH_3

Reagents and Conditions: (a) CS_2, H_2O/EtOH, reflux 1 h and then HCl (35%), reflux 7 h; (b) CH_3I, *i*-PrOH, reflux 2 h; (c) CH_3NH_2 or $(CH_3)_2NH$, *i*-PrOH, 130-140 °C, 50 psi, 40 h.

Scheme 3



12a: R=H
12b: R=CH_3

13a: R=H
13b: R=CH_3

14a: R=H; R'=H
14b: R=H; R'=CH_3
14c: R=CH_3; R'=H
14d: R=CH_3; R'=CH_3
14e: R=H; R'=C_6H_5
14f: R=CH_3; R'=C_6H_5

15a: R=H
15b: R=CH_3

Reagents and Conditions: (a) H_2/PtO_2, gas HCl/EtOH, 55 psi, 90 °C, 1.5 h and then aq. NaOH; (b) formamidine acetate or acetamidine hydrochloride or benzamidine hydrochloride, EtOH; (c) BrCN, CH_2Cl_2, 0 °C and then r.t., 70 h.

14a-f and **15a,b**, respectively), we observed a range of trypanocidal activity. For example, compounds **14a** and **15a** inhibited parasite growth by approximately 50% at 5 μg/ml, whereas **14d** and **14f** displayed no activity. The most active compounds tested were **14b, c, e** and **15 b** (Table 1). Of these, **14e** was found to be at least three times as effective at killing bloodstream form *T. brucei* as rimantadine, with an IC_{50} close to 2 μM. The results presented in this paper show that exocyclic imidazolines have significant activity against bloodstream form *T. brucei*. Other adamantane 2-imidazoline derivatives that we tested exhibited little effect. In the absence of information on the biological target, it is difficult to be definitive about the physicochemical parameters responsible for this lack of activity. The degree of lipophilicity may be one factor, although it could be that the rigidness of the spiro arrangement, in relation to the bulk of adamantane skeleton, hinders the approach towards the biological target. The adamantane imidazoline with the greatest trypanocidal activity was a 2-alkyl derivative (**14e**), which we found to be three fold more effective than rimantadine. By exploring the properties of other derivatives of this class, it should be possible to identify compounds that display significantly higher activity.

Table 1

Trypanocidal activity of 2-alkyl (**14b, c, e**) and 2-amino-5-(1-adamantyl)imidazoline (**15b**)

Compound	IC_{50} (μM)
14b[a]	7.40 ± 2.28
14c[a]	11.55 ± 0.36
14e[b]	2.13 ± 0.51
15b[c]	6.27 ± 2.04
rimantadine[b]	7.04 ± 0.27

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}) were calculated. Data are the mean of triplicate experiments ± SEM. The value obtained with rimantadine is shown for comparison. [a] fumarate salt; [b] hydrochloride salt; [c] hydrobromide salt.

The design of more effective derivatives would be greatly aided if their target in the trypanosome could be identified. Channel blocking activity is the only known mechanism for the therapeutic activity of amantadine and its derivatives. Targets of these compounds include the hepatitis C virus encoded protein p7 [10], the potassium channel of the PBCV-1 chlorella virus [11] and the transmembrane channel of the *N*-methyl-*D*-aspartate receptor [12]. In the case of influenza virus A infected cells, the most studied system, the target is the virus-encoded M2 proton channel. Whether the main antiviral activity results from physical blockage of the channel, or by an allosteric effect mediated by binding of the drug to a site external to the channel, remains to be resolved [13,14]. It seems reasonable, by analogy with other cases, to assume that the mechanism of action of these compounds in trypanosomes involves blockage/ perturbation of a parasite membrane-localized ion channel/transporter. This would correlate with our observations that drug potency appears to be associated an increase in the lipophilic nature of side chains on the adamantane ring [4,5].

EXPERIMENTAL

General

Melting points were determined on a Büchi 530 apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 833 spectrophotometer. ^{1}H NMR spectra were taken in Deuteriochloroform or DMSO-d_6 and recorded on a Bruker DRX 400 (400 MHz) spectrometer, and the spectra are reported in δ. ^{13}C NMR spectra were taken at 50 MHz or 100 MHz on a Bruker AC 200 or Bruker DRX 400 spectrometer, respectively. Tetramethylsilane was used as internal standard. 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.

Bloodstream-form *T. brucei* (strain 427) were cultured in 25 cm^3 flasks at 37 ºC in modified Iscove's medium (pH 7.4) [6]. To establish the extent of activity, parasites were grown for 3 days in the presence of test compounds and the concentrations which inhibited growth by 50% (IC_{50}) and 90% (IC_{90}) were determined. In these experiments, which were performed at least in triplicate, the densities of untreated cultures increased from 0.25 x 10^5 to 4 x 10^6 cells ml^{-1}. After determination of cell densities at each drug concentration with a hemocytometer (Weber Scientific International Ltd.), drug sensitivity was expressed as a percentage of growth of control cells.

3,5-Dihydrospiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]decane] (8a). To a solution of diamine **7a** (650 mg, 3.6 mmol) in absolute ethanol (20 ml) was added formamidine acetate (427 mg, 4.1 mmol). The solution was stirred under an argon atmosphere at ambient temperature for 48 h. The solvent was then evaporated under vacuum and the residue was treated with 4% HCl (50 ml). The mixture was taken up with ethyl acetate, made alkaline with 4% NaOH (50 ml), and extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 380 mg (56%) of imidazoline **8a**, which was then converted to its fumarate salt; $mp_{fumarate}$ 161-163 ºC (EtOH-Et_2O). ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.58-1.75 (m, 12H, 1', 3', 4'$_{eq}$, 5', 6', 7', 8', 9'$_{eq}$, 10'-H), 1.99-2.03 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 3.66 (s, 2H, 5-H), 6.42 (s, 2H, CH= fumarate), 8.34 (s, 1H, 2-H); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 25.8 (5'-C), 26.2 (7'-C), 32.3 (4', 9'-C), 33.2 (8', 10'-C), 36.5 (1', 3'-C), 37.0 (6'-C), 54.2 (5-C), 69.6 (4,2'-C), 135.6 (CH= fumarate), 155.6 (2-C), 168.6 (C=O fumarate). *Anal*. Calcd. for $C_{16}H_{22}N_2O_4$ (306.4): C, 62.73%; H, 7.24%. Found: C, 62.48%; H, 7.39%.

3,5-Dihydro-2-methylspiro[imidazole-4,2'-tricyclo[3.3.1.1.3,7]-decane] (8b). Imidazoline **8b** was prepared by following the procedure used for the synthesis of **8a**, by reacting diamine **7a** with acetamidine hydrochloride. Yield 56%; $mp_{fumarate}$ 170-172 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.56-1.75 (m, 12H, 1', 3', 4'$_{eq}$, 5', 6', 7', 8', 9'$_{eq}$, 10'-H), 1.99-2.03 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 2.15 (s, 3H, CH_3), 3.62 (s, 2H, 5-H), 6.38 (s, 2H, CH= fumarate); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 12.4 (CH_3), 25.8 (5'-C), 26.2 (7'-C), 32.3 (4', 9'-C), 33.2 (8', 10'-C), 36.5 (1', 3'-C), 37.0 (6'-C), 54.1 (5-C), 69.5 (4,2'-C), 135.6 (CH= fumarate), 165.6 (2-C), 168.6 (C=O fumarate). *Anal*. Calcd. for $C_{17}H_{24}N_2O_4$ (320.4): C, 63.73%; H, 7.55%. Found: C, 63.40%; H, 7.81%.

3,5-Dihydro-3-methylspiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]-decane] (8c). Imidazoline **8c** was prepared by following the procedure used for the synthesis of **8a**, by reacting diamine **7b** with formamidine acetate. Yield 82%; $mp_{fumarate}$ 158-160 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.60-1.99 (m, 12H, 1', 3', 4'$_{eq}$, 5', 6', 7', 8', 9'$_{eq}$, 10'-H), 2.19-2.22 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 3.39 (s, 3H, CH_3), 3.76 (s, 2H, 5-H), 6.42 (s, 2H, CH= fumarate), 8.20 (s, 1H, 2-H); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 26.1 (5', 7'-C), 32.6 (4', 9'-C), 35.0 (8', 10'-C), 35.5 (1', 3'-C), 38.0 (CH_3), 38.1 (6'-C), 55.8 (5-C), 72.2 (4,2'-C), 135.2 (CH= fumarate), 159.2 (2-C), 167.9 (C=O fumarate). *Anal*. Calcd. for $C_{17}H_{24}N_2O_4$ (320.4): C, 63.73%; H, 7.55%. Found: C, 63.61%; H, 7.59%.

3,5-Dihydro-2,3-dimethylspiro[imidazole-4,2'-tricyclo-[3.3.1.1.^{3,7}]decane] (8d). Imidazoline **8d** was prepared by following the procedure used for the synthesis of **8a**, by reacting diamine **7b** with acetamidine hydrochloride. The reaction mixture was stirred under an argon atmosphere at 65-70º for 30 h. Yield 42%; mp 40-41º ($mp_{fumarate}$ 65-67 ºC, resolidifies at 110 ºC and melts again at 144-146 ºC); ir (Nujol): 3419 (H_2O) cm^{-1}; ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.56-1.73 (m, 8H, 4'$_{eq}$, 8', 9'$_{eq}$, 10'-H), 1.84-1.87 (m, 7H, 1', 3', 5', 6', 7'-H, 2-CH_3), 2.26-2.30 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 3.15 (s, 3H, N-CH_3), 3.54 (s, 2H, 5-H); ^{13}C nmr (deuteriochloroform, 100 MHz, free

base): δ 16.1 (2-CH_3), 26.8 (5'-C), 27.0 (7'-C), 33.2 (4', 9'-C), 35.0 (N-CH_3), 35.8 (8', 10'-C), 36.8 (1', 3'-C), 39.0 (6'-C), 64.3 (5-C), 68.9 (4,2'-C), 164.1 (2-C). *Anal*. Calcd. for $C_{18}H_{26}N_2O_4$ (fumarate) x 1 H_2O (352.4): C, 61.34%; H, 8.01%. Found: C, 61.02%; H, 8.01%.

3,5-Dihydro-2-phenylspiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]-decane] (8e). Imidazoline **8e** was prepared by following the procedure used for the synthesis of **8d**, by reacting diamine **7a** with benzamidine hydrochloride. Yield 52%; mp 127-129 ºC ($mp_{fumarate}$ 218-220 ºC (dec) (EtOH-Et_2O). ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.69-1.89 (m, 14H, adamantane-H), 3.78 (s, 2H, 5-H), 5.22 (brs, 1H, 3-H), 7.31-7.39 (m, 3H, 3, 4, 5-H_{arom}), 7.71-7.72 (m, 2H, 2, 6-H_{arom}); ^{13}C nmr (deuteriochloroform, 100 MHz, free base): δ 26.5 (5'-C), 26.9 (7'-C), 34.1 (4', 9'-C), 34.1 (8', 10'-C), 37.2 (1', 3'-C), 37.5 (6'-C), 64.7 (5-C), 71.9 (4,2'-C), 126.9 (2, 6-C_{arom}), 128.4 (3, 5-C_{arom}), 130.4 (4-C_{arom}), 130.9 (1-C_{arom}), 161.9 (2-C). *Anal*. Calcd. for $C_{22}H_{26}N_2O_4$ (fumarate) (382.4): C, 69.09%; H, 6.85%. Found: C, 68.85%; H, 6.97%.

3,5-Dihydro-3-methyl-2-phenylspiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]decane] (8f). Imidazoline **8f** was prepared by following the procedure used for the synthesis of **8d**, by reacting diamine **7b** with benzamidine hydrochloride. Yield 58%; mp 83-85 ºC; $mp_{fumarate}$ 187-188 ºC (dec) (EtOH - Et_2O); $mp_{picrate}$ 180-182 ºC (dec) (MeOH-Et_2O); ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.68-1.73 (m, 6H, 4'$_{eq}$, 6', 8'$_{eq}$, 9'$_{eq}$, 10'$_{eq}$-H), 1.82-1.93 (m, 6H, 1', 3', 5', 7', 8'$_{ax}$, 10'$_{ax}$-H), 2.25-2.28 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 3.00 (s, 3H, CH_3), 3.77 (s, 2H, 5-H), 7.34-7.41 (m, 3H, 3, 4, 5-H_{arom}), 7.62-7.65(m, 2H, 2, 6-H_{arom}); ^{13}C nmr (deuteriochloroform, 100 MHz, free base): δ 27.0 (5'-C), 27.2 (7'-C), 33.7 (4', 9'-C), 35.2 (8', 10'-C), 35.2 (1', 3'-C), 35.4 (CH_3), 38.4 (6'-C), 64.2 (5-C), 68.9 (4, 2'-C), 128.2 (2, 6-C_{arom}), 128.9 (3, 5-C_{arom}), 130.0 (4-C_{arom}), 132.2 (1-C_{arom}), 168.8 (2-C). *Anal*. Calcd. for $C_{25}H_{27}N_5O_7$ (picrate) (509.5): C, 58.93%; H, 5.34%. Found: C, 58.69%; H, 5.50%.

3,5-Dihydrospiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]decan]-2-amine hydrobromide (9a). To a solution of diamine **7a** (670 mg, 4.0 mmol) in dichloromethane (10 ml) was added dropwise a solution of cyanogen bromide (530 mg, 5.0 mmol) in dichloromethane (30 ml) under ice cooling. The reaction mixture was stirred at ambient temperature for 70 h, and the solvent was then evaporated under vacuum to leave a residue, which was triturated with anhydrous ether. The crystalline compound formed was filtered and dried to give 560 mg (49%) of salt **9a**; mp 174-176 ºC (EtOH- Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.64-1.80 (m, 12H, 1', 3', 4'$_{eq}$, 5', 6', 7', 8', 9'$_{eq}$, 10'-H), 1.90-1.93 (brd, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 3.46 (s, 2H, 5-H), 7.36 (br s, 2H, NH_2), 7.94 (s, 1H, 3-H), 8.78 (s, 1H, 1-H); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 25.8 (5'-C), 26.2 (7'-C), 32.8 (4', 9'-C), 33.5 (8', 10'-C), 36.4 (1', 3'-C), 37.0 (6'-C), 52.2 (5-C), 66.5 (4,2'-C), 157.9 (2-C). *Anal*. Calcd. for $C_{12}H_{20}N_3Br$ (286.2): C, 50.36%; H, 7.04%. Found: C, 50.16%; H, 7.34%.

3,5-Dihydro-3-methylspiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]-decan]-2-amine hydrobromide (9b). Imidazoline **9b** was prepared by the procedure used for the synthesis of **9a**, using diamine **7b** as starting material. Yield 79%; mp > 240 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.61-1.93 (m, 12H, 1', 3', 4'$_{eq}$, 5', 6', 7', 8', 9'$_{eq}$, 10'-H), 2.20-2.23 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 3.19 (s, 3H, CH_3), 3.42 (s, 2H, 5-H), 7.83 (br s, 2H, NH_2), 7.88 (s, 1H, 3-H); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 26.4 (5', 7'-C), 32.5 (4', 9'-C), 34.1 (CH_3), 35.0 (1', 3'-C), 35.6 (8', 10'-C), 38.4 (6'-C), 51.6 (5-C), 70.2 (4, 2'-C), 158.8 (2-C). *Anal*. Calcd. for $C_{13}H_{22}N_3Br$ (300.2): C, 52.01%; H, 7.38%. Found: C, 51.80%; H, 7.60%.

1,5-Dihydrospiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]decan]-2(3*H*)-thione (10). To a suspension of diamine **7a** (850 mg, 4.7 mmol) in a solution of EtOH:H_2O (10 ml, 8/2) was added carbon disulfide (400 mg, 5.3 mmol) and the reaction mixture was heated at reflux for 1 h. To the refluxing mixture 2 drops of HCl (~35%) were added and heating was continued for 7 h. Then, the suspension was left stirring at ambient temperature for 24 h. Water was poured onto the mixture, which was filtered and the residue was washed with water to give 1.01 g (97%) of **10** as an off-white solid; mp 209-211 ºC; ^{1}H nmr (deuteriochloroform, 400 MHz): δ 1.60-1.83 (m, 14H, adamantane H), 3.54 (s, 2H, 5-H), 6.68 (s, 1H, 3-H), 7.02 (s, 1H, 1-H); ^{13}C nmr (deuteriochloroform, 50 MHz): δ 26.1 (5'-C), 26.3 (7'-C), 33.2 (4', 9'-C), 35.1 (8', 10'-C), 36.5 (1', 3'-C), 37.2 (6'-C), 54.6 (5-C), 68.4 (4,2'-C), 181.0 (2-C). *Anal*. Calcd. for $C_{12}H_{18}N_2S$ (222.4): C, 64.82%; H, 8.16%. Found: C, 64.61%; H, 8.33%.

3,5-Dihydro-2-methylthiospiro[imidazole-4,2'-tricyclo-[3.3.1.1.^{3,7}]decane]hydroiodide (11). To a suspension of thione **10** (2.0 g, 9.0 mmol) in *i*-PrOH (15 ml) was added dropwise methyl iodide (1.42 g, 10.0 mmol). The reaction mixture was heated at reflux for 2 h, the solvent evaporated to half of its initial volume and anhydrous ether was added. The precipitate formed was removed by filtration to give 2.1 g (64%) of salt **11**; mp 214-215 ºC (EtOH-Et_2O). *Anal*. Calcd. for $C_{13}H_{21}N_2IS$ (364.3): C, 42.86%; H, 5.81%. Found: C, 42.63%; H, 5.98%.

3,5-Dihydro-N-methylspiro[imidazole-4,2'-tricyclo[3.3.1.1.^{3,7}]-decan]]-2-amine (9c). To a suspension of salt **11** (2.5 g, 6.8 mmol) in *i*-PrOH (20 ml) in an autoclave was added a solution of methylamine (2.5 g, 80.6 mmol) in *i*-PrOH (40 ml). The reaction mixture was heated at 130-140 ºC under a pressure of 50 psi for 40 h. The solvent was then evaporated under vacuum and the residue dissolved in 4% HCl (50 ml). The solution was taken up with ether and made alkaline with a solution of 4% NaOH (50 ml). The aqueous layer was extracted with chloroform, the organic phase was decolorized by adding activated charcoal, dried (Na_2SO_4) and evaporated to give 940 mg (74%) of imidazoline **9c**; mp 238-239 ºC (CH_2Cl_2-*n*-pentane), $mp_{hydrochloride}$ 247-248 ºC (EtOH-Et_2O); ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.62-1.85 (m, 12H, 1', 3', 4'$_{eq}$, 5', 6', 7', 8', 9'$_{eq}$, 10'-H), 1.98-2.01 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 2.94 (s, 3H, CH_3), 3.54 (s, 2H, 5-H); ^{13}C nmr (deuteriochloroform, 50 MHz, free base): δ 26.0 (5'-C), 26.4 (7'-C), 29.1 (CH_3), 33.2 (4', 9'-C), 34.0 (8', 10'-C), 36.9 (1'-C), 37.1 (6'-C), 52.5 (5-C), 66.4 (4, 2'-C), 77.2 (3'-C), 158.4 (2-C). *Anal*. Calcd. for $C_{13}H_{22}N_3Cl$ (hydrochloride) (255.8): C, 61.04%; H, 8.67%. Found: C, 61.40%; H, 8.70%.

3,5-Dihydro-N,N-dimethylspiro[imidazole-4,2'-tricyclo-[3.3.1.1.^{3,7}]decan]]-2-amine (9d). To a suspension of salt **11** (1.7 g, 4.6 mmol) in *i*-PrOH (40 ml) in an autoclave was added a solution of dimethylamine (9.0 ml, 33% in absolute ethanol) and the reaction mixture was heated at 100 ºC under a pressure of 50 psi for 30 h. Following the work up as described for the preparation of **9c**, imidazoline **9d** was obtained as a pale yellow liquid (400 mg, 37%), which was then converted to the fumarate salt, mp 208-209 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.46-1.50 (br d, 2H, 4'$_{eq}$, 9'$_{eq}$ -H), 1.66-1.69 (m, 1', 3', 5', 6', 7', 8', 10'-H), 2.12-2.16 (br d, 2H, 4'$_{ax}$, 9'$_{ax}$-H), 2.95 (s, 6H, 2×CH_3), 3.43 (s, 2H, 5-H), 5.62 (br s, 1H, 3-H), 6.32 (s, 2H, CH= fumarate), 8.08 (s, 1H, CO_2H); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 25.2 (5'-C), 25.6 (7'-C), 31.3 (4', 9'-C), 33.1 (8', 10'-C),

35.8 (1', 3'-C), 36.6 (6'-C), 38.0 (2×CH_3), 51.9 (5-C), 67.0 (4, 2'-C), 134.9 (CH= fumarate), 157.3 (2-C), 167.8 (C=O fumarate). *Anal*. Calcd. for $C_{18}H_{27}N_3O_4$ (349.4): C, 61.87%; H, 7.79%. Found: C, 61.90%; H, 7.90%.

4,5-Dihydro-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole (14a). Imidazoline **14a** was prepared by the method employed for the synthesis of **8a**, by the reacting diamine **13a** with formamidine acetate. Yield 60%; $mp_{fumarate}$ 179-180 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.29-1.48 (m, 6H, 2´, 8´, 9´-H), 1.53-1.63 (m, 6H, 4´, 6´, 10´-H), 1.91 (br s, 3´, 5´, 7´-H), 3.60-3.75 (m 3H, 4-H, 5-H), 6.40(s, 2H, CH= fumarate), 8.36 (s, 2H, 2-H), 10.22 (br s, 2H, 2×CO_2H); ^{13}C nmr (DMSO-d_6, 50 MHz): δ 27.5 (3´, 5´, 7´-C), 35.0 (1´-C), 36.5 (4´, 6´, 10´-C), 36.8 (2´, 8´, 9´-C), 44.1 (4-C), 66.2 (5-C), 135.3 (CH= fumarate), 157.2 (2-C), 168.1 (C=O fumarate). *Anal*. Calcd. for $C_{17}H_{24}N_2O_4$ (320.4): C, 63.73%; H, 7.55%. Found: C, 64.01%; H, 7.85%.

4,5-Dihydro-2-methyl-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole (14b). Imidazoline **14b** was prepared by the method used for the synthesis of **8a**, by reacting diamine **13b** with acetamidine hydrochloride. The solution was stirred under an argon atmosphere at 40 ºC for 7 h and then at room temperature for 42 h. Yield 60%; $mp_{fumarate}$ 150-152 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.30-1.48 (br q, 6H, 2´, 8´, 9´-H), 1.54-1.64 (m, 6H, 4´, 6´, 10´-H), 1.91 (br s, 3H, 3´, 5´, 7´-H), 2.13 (s, 3H, CH_3), 3.59-3.72 (m 3H, 4-H, 5-H), 6.36 (s, 2H, CH= fumarate); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 12.1 (CH_3), 27.5 (3´, 5´, 7´-C), 35.0 (1´-C), 36.5 (4´, 6´, 10´-C), 37.8 (2´, 8´, 9´-C), 44.3 (4-C), 66.4 (5-C), 135.6 (CH= fumarate), 167.4 (2-C), 168.4 (C=O fumarate). *Anal*. Calcd. for $C_{18}H_{26}N_2O_4$ (334.4): C, 64.65%; H, 7.84%. Found: C, 64.29%; H, 7.81%.

4,5-Dihydro-1-methyl-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole (14c). Imidazoline **14c** was prepared by the method used for **8a**, by reacting diamine **13b** with formamidine acetate. The reaction mixture was stirred under an argon atmosphere at 40-45 ºC for 10 h and then at ambient temperature for 24 h. Yield 75%; $mp_{fumarate}$ 166-168 Cº (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz): δ 1.40-1.55 (m, 6H, 2´, 8´, 9´-H), 1.60 (m, 6H, 4´, 6´, 10´-H), 1.91 (br s, 3H, 3´, 5´, 7´-H), 3.08 (s, 3H, CH_3), 3.44-3.49 (t, J = 10.0 Hz 1H, 5-H), 3.72-3.74 (d, J = 10.0 Hz, 2H, 4-H), 6.42 (s, 2H, CH= fumarate), 8.01 (s, 2H, 2-H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 27.6 (3´, 5´, 7´-C), 36.4 (1´, 4´, 6´, 10´-C), 37.4 (CH_3, 2´, 8´, 9´-C), 48.2 (4-C), 71.1 (5-C), 135.3 (CH= fumarate), 160.0 (2-C), 167.9 (C=O fumarate). *Anal*. Calcd. for $C_{18}H_{26}N_2O_4$ (334.4): C, 64.65%; H, 7.84%. Found: C, 64.39%; H, 7.93%.

4,5-Dihydro-1,2-dimethyl-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole (14d). Imidazoline **14d** was prepared by following the procedure employed for the synthesis **8a**, by reacting diamine **13b** with acetamidine hydrochloride. The reaction mixture was stirred under an argon atmosphere at 65-70 ºC for 28.5 h. Yield 55%; mp 94-96 ºC; $mp_{fumarate}$ 132-134 ºC (EtOH-Et_2O); $mp_{picrate}$ 168-170 ºC (MeOH-Et_2O); ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.38-1.52 (m, 6H, 2´, 8´, 9´-H), 1.57-1.67 (m, 6H, 4´, 6´, 10´-H), 1.87 (s, 3H, 1-CH_3), 1.93 (br s, 3H, 3´, 5´, 7´-H), 2.82 (s, 3H, 2-CH_3), 2.84-2.89 (m, 1H, 5-H), 3.49-3.60 (m, 2H, 4-H); ^{13}C NMR (deuteriochloroform, 100 MHz, free base): δ 14.8 (1-CH_3), 28.1 (3´, 5´, 7´-C), 36.9 (1´-C), 36.1 (4´, 6´, 10´-C), 37.2 (2-CH_3), 38.3 (2´, 8´, 9´-C), 53.7 (4-C), 73.4 (5-C), 166.0 (2-C). *Anal*. Calcd. for $C_{21}H_{27}N_5O_7$ (picrate) (461.5): C, 54.66%; H, 5.90%. Found: C, 54.75%; H, 5.70%.

4,5-Dihydro-2-phenyl-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole (14e). Imidazoline **14e** was prepared by the method used for **8a**, by reacting diamine **13a** with benzamidine hydrochloride. The reaction mixture was stirred under an argon atmosphere at 65-70 ºC for 21 h. Yield 77%, mp 127-129 ºC; $mp_{hydrochloride}$ 205-207 ºC (dec) (acetone-Et_2O); $mp_{fumarate}$ 214-216 ºC (dec) (EtOH-Et_2O); $mp_{picrate}$ 151-153 ºC (MeOH-Et_2O); ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.39-1.50 (m, 6H, 2´, 8´, 9´-H), 1.56-1.67 (m, 6H, 4´, 6´, 10´-H), 1.93 (br s, 3H, 3´, 5´, 7´-H), 3.44-3.49 (t, J = 9.5 Hz, 1H, 5-H), 3.68-3.70 (d, J = 9.5 Hz, 2H, 4-H), 4.20 (s, 1H, 1-H), 7.32-7.34 (m, 3H, 3, 4, 5- H_{arom}), 7.70-7.72 (m, 2H, 2, 6-H_{arom}); ^{13}C nmr (deuteriochloroform, 100 MHz, free base): δ 28.1 (3´, 5´, 7´-C), 35.4 (1´-C), 37.1 (4´, 6´, 10´-C), 38.3 (2´, 8´, 9´-C), 52.3 (4-C), 69.5 (5-C), 127.0 (2, 6-C_{arom}), 128.3 (3, 5-C_{arom}), 130.5 (1, 4-C_{arom}), 163.5 (2-C). *Anal*. Calcd. for $C_{25}H_{27}N_5O_7$ (picrate) (509.5): C, 58.93%; H, 5.34%. Found: C, 58.69%; H, 5.50%.

4,5-Dihydro-1-methyl-2-phenyl-5(1-tricyclo[3.3.1.1.^{3,7}]-decyl)-1*H*-imidazole (14f). Imidazoline **14f** was prepared by the method used for the synthesis of **8a**, by reacting diamine **13b** with benzamidine hydrochloride. The reaction mixture was stirred under an argon atmosphere at 65-70 ºC for 24 h. Yield 70%. mp 75-77 ºC; $mp_{fumarate}$ 130-132 ºC (EtOH-Et_2O); $mp_{picrate}$ 179-181 ºC (MeOH-Et_2O); ^{1}H nmr (deuteriochloroform, 400 MHz, free base): δ 1.46-1.54 (m, 6H, 2´, 8´, 9´-H), 1.59-1.68 (m, 6H, 4´, 6´, 10´-H), 1.94 (br s, 3H, 3´, 5´, 7´-H), 2.80 (s, 3H, CH_3), 2.88-2.93 (t, J = 8.0 Hz, 1H, 5-H), 3.76-3.79 (d, J = 8.0 Hz, 2H, 4-H), 7.32-7.34 (m, 3H, 3, 4, 5-H_{arom}), 7.59-7.62(m, 2H, 2, 6-H_{arom}). ^{13}C nmr (deuteriochloroform, 100 MHz, free base): δ 28.1 (3´, 5´, 7´-C), 37.2 (4´, 6´, 10), 37,4 (2´, 8´, 9´-C), 39.4 (1´-C), 40.4 (CH_3), 54.4 (4-C), 74.6 (5-C), 128.2 (2, 6-C_{arom}), 128.6 (3, 5-C_{arom}), 130.0 (4-C_{arom}), 131.4 (1-C_{arom}), 168.9 (2-C). *Anal*. Calcd. for $C_{26}H_{29}N_5O_7$ (picrate) (523.5): C, 59.65%; H, 5.58%. Found: C, 59.91%; H, 5.86%.

4,5-Dihydro-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole-2-amine hydrobromide (15a). Imidazoline **15a** was prepared from diamine **13a** by the method used for **9a**. Yield 89%, $mp_{hydrobromide}$ 240-241º (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz, hydrobromide): δ 1.28-1.44 (m, 6H, 2´, 8´, 9´-H), 1.53-1.64 (m, 6H, 4´, 6´, 10´-H), 1.91 (br s, 3´, 5´, 7´-H), 3.38-3.49 (m 3H, 4-H, 5-H), 7.49 (s, 2H, NH_2), 7.81 (s, 1H, 1-H), 8.20 (s, 1H, 3-H); ^{13}C nmr (DMSO-d_6, 100 MHz, hydrobromide): δ 27.5 (3´, 5´, 7´-C), 35.0 (1´-C), 36.5 (4´, 6´, 10´-C), 37.1 (2´, 8´, 9´-C), 42.4 (4-C), 63.9 (5-C), 159.5 (2-C). *Anal*. Calcd. for $C_{13}H_{22}N_3Br$ (hydrobromide) (300.2): C, 52.01%; H, 7.38%. Found: C, 51.66%; H, 7.55%.

4,5-Dihydro-1-methyl-5(1-tricyclo[3.3.1.1.^{3,7}]decyl)-1*H*-imidazole-2-amine hydrobromide (15b). Imidazoline **15a** was prepared from diamine **13b** by the method used for the synthesis of **9a**. Yield 69%; $mp_{hydrobromide}$ > 250 ºC (EtOH-Et_2O); ^{1}H nmr (DMSO-d_6, 400 MHz, hydrobromide): δ 1.44-1.53 (m, 6H, 2´, 8´, 9´-H), 1.61-1.69 (m, 6H, 4´, 6´, 10´-H), 1.97 (br s, 3´, 5´, 7´-H), 2.99 (s, 3H, CH_3), 3.38-3.41 (m, 1H, 5-H), 3.49-3.50 (m, 2H, 4-H), 7.86 (s, 1H, 3-H), 7.89 (s, 2H, NH_2); ^{13}C nmr (DMSO-d_6, 100 MHz): δ 27.5 (3´, 5´, 7´-C), 35.8 (CH_3, 1´-C), 36.4 (4´, 6´, 10´-C), 37.1 (2´, 8´, 9´-C), 41.8 (4-C), 70.2 (5-C), 159.9 (2-C). *Anal*. Calcd. for $C_{14}H_{24}N_3Br$ (hydrobromide) (314.3): C, 53.51%; H, 7.70%. Found: C, 53.32%; H, 7.90%.

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