HETEROCYCLES, Vol. 75, No. 8, 2008, pp. 2043 - 2061. © The Japan Institute of Heterocyclic Chemistry
Received, 29th February, 2008, Accepted, 11th April, 2008, Published online, 14th April, 2008. COM-08-11377

CONFORMATIONALLY CONSTRAINED ADAMANTANE-OXAZOLINES OF PHARMACOLOGICAL INTEREST

Ioannis Papanastasiou,[a] George B. Foscolos,[a*] Andrew Tsotinis,[a] Judit Oláh,[b] Judit Ovádi,[b] S. Radhika Prathalingam,[c] and John M. Kelly [c]

[a]Faculty of Pharmacy, Department of Pharmaceutical Chemistry, University of Athens, Panepistimioupoli-Zografou, 15771 Athens, Greece tsotinis@pharm.uoa.gr

[b]Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, H-1113 Budapest, Hungary

[c]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, U.K.

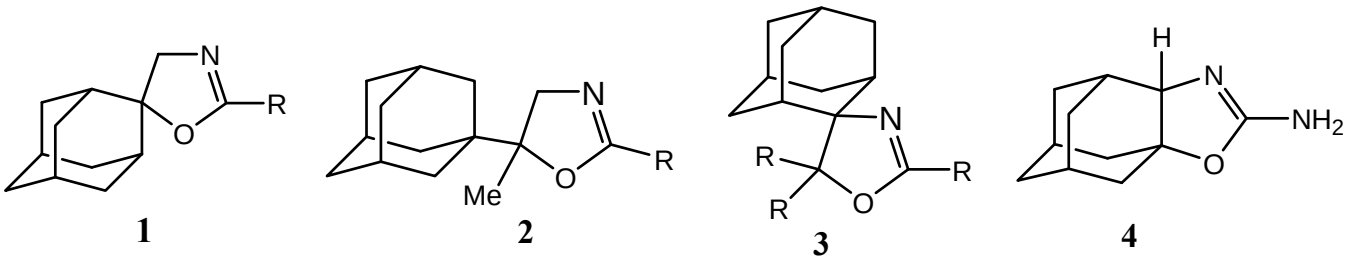
Abstract – New conformationally constrained adamantane 2-oxazoline building blocks **1-4** were synthesized and their antimicrotubule and antitrypanosomal potency was investigated. Although most of the new compounds affect tubulin polymerization, this does not make a major contribution to trypanocidal activity.

The bulk and lipophilicity of the adamantane skeleton confers interesting biological features to its derivatives. Thus aminoadamantanes, such as amantadine and rimantadine,[1] have a significant activity against influenza A virus, inhibiting virus replication by blocking the ion channel of the small virus membrane protein M2. Previously, our laboratory has synthesized many aminoadamantanes,[2] which have a greatly increased potency compared to amantadine and rimantadine. Recently, we and others have shown that aminoadamantanes[3] also exhibit activity against the protozoan parasite *Trypanosoma brucei*, the causative agent of African trypanosomiasis.

Oxazoline bearing agents, such as rhizoxin[4] and 2-indolyloxazolines,[5] display anticancer activity that has been linked to their ability to block mitosis via inhibition of tubulin polymerization. Reports that rhizoxin also exhibits trypanocidal activity[4] has led us to synthesise conformationally constrained adamantane

2-oxazoline derivatives **1-4** (**Figure 1**) and investigate their antimicrotubule and antitrypanosomal potency.

Figure 1

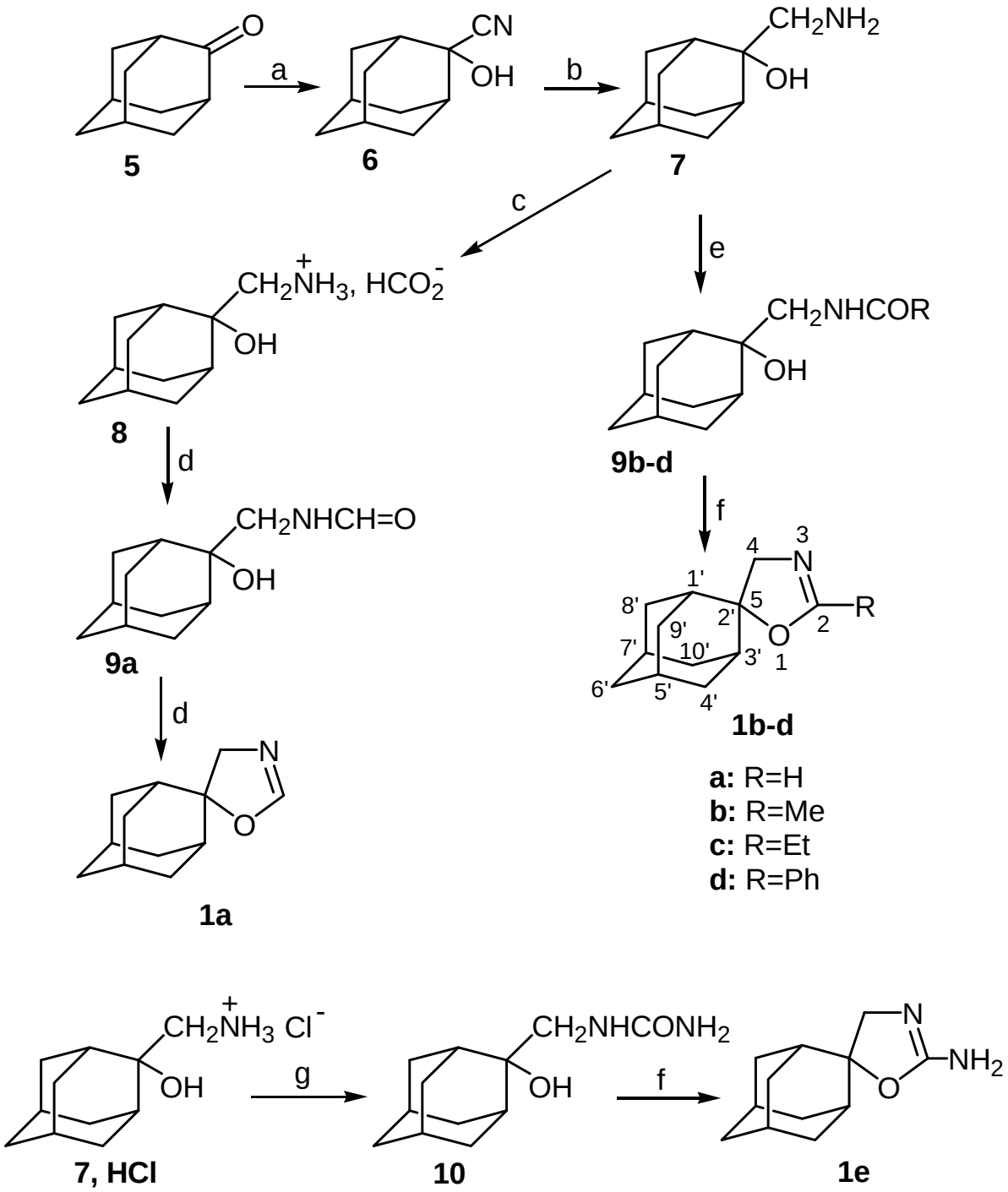


The synthetic route leading to spiroadamantaneoxazolines **1** is depicted in **Scheme 1**. Reaction of adamantanone **5** with KCN and ammonium chloride gave cyanohydrin **6**,[6] which was then reduced to the aminoalcohol **7** with $LiAlH_4$. 2-Adamantanol was formed as a by-product of the reduction because of displacement of the "cyanohydrin-ketone equilibrium" towards the ketone owing to the basicity of $LiAlH_4$. The formation of this by-product could be minimized by using ether rather than THF as a solvent and conducting the reaction at ambient temperature.

Addition of excess formic acid[7] to aminoalcohol **7** followed by removal of formic acid in vacuo gave the formate **8**, which, when azeotropically distilled with a mixture of toluene-water, gave the formamide **9a** that on heating ring-closed to the spirooxazoline **1a**. The 2-substituted spirooxazolines **1b-d** were prepared from **7** by acylation with the appropriate anhydride or acid chloride to give the intermediates **9b-d** which were then cyclised with sulphuric acid.[8] The 2-aminospirooxazoline **1e** was prepared from the hydrochloride **7** by treatment with potassium cyanate[9] to give **10,** which was then cyclised with concentrated H_2SO_4 (**Scheme 1**).

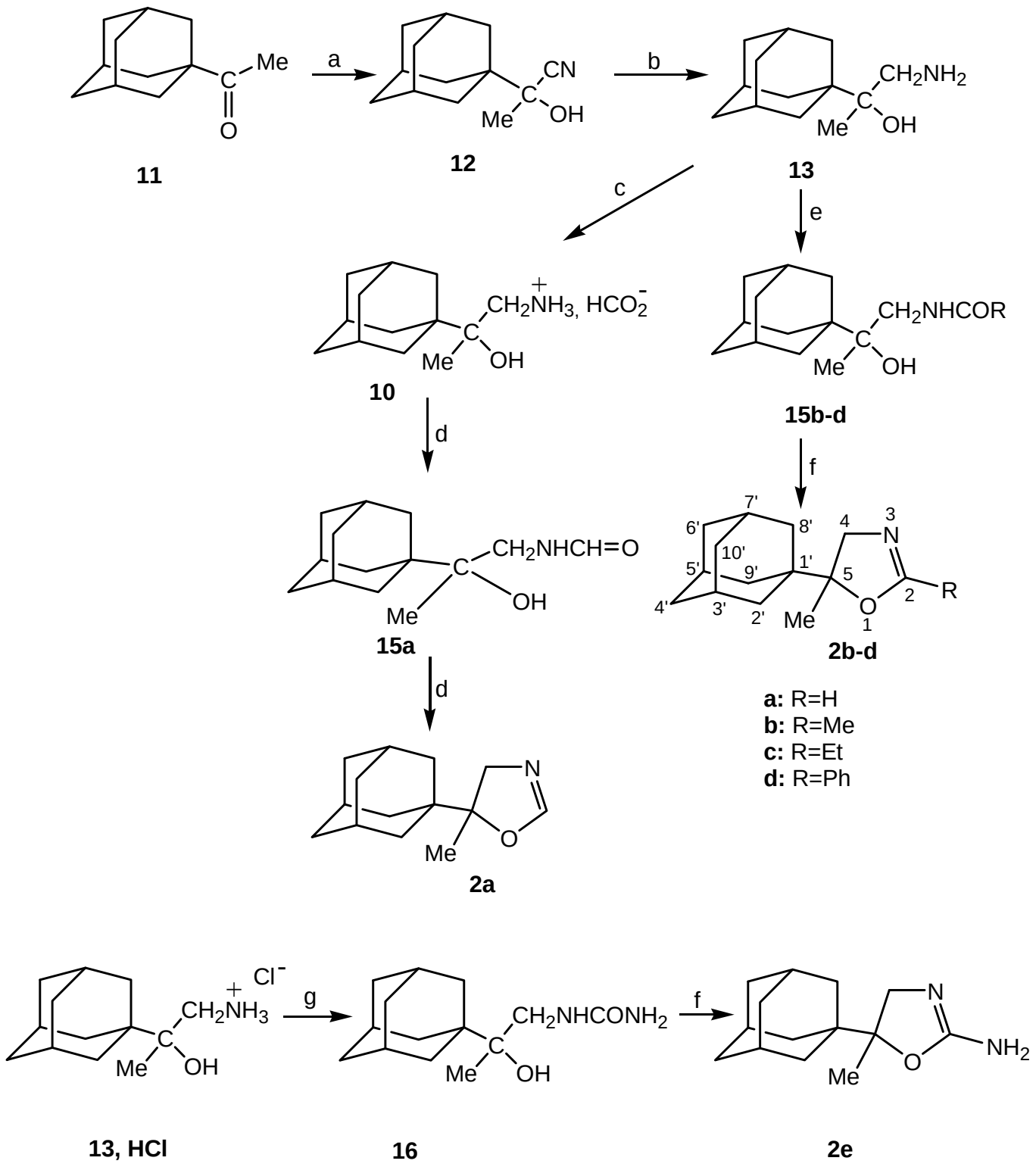
Scheme 2 illustrates the synthetic route followed for the preparation of exocyclic adamantane oxazolines **2**, from 1-adamantyl methyl ketone **11**.[10] The reaction of the aminoalcohol **13** with acyl chlorides and triethylamine gave a mixture of the desired amides **15b-d** together with some *N,O*-bisacyl derivatives. Treatment of the reaction mixture with 1M NaOH at room temperature afforded the desired amides. The exocyclic 2-aminoxazoline **2e** was prepared from the hydrochloride **13** in a similar way to the spirooxazoline **1e**.

Scheme 1



Reagents and conditions: (a) KCN-NH_4Cl/EtOH-H_2O, rt. (b) $LiAlH_4$/Et_2O and then H_2O/NaOH. (c) HCO_2H (98%), reflux, 2 h. (d) toluene/140 ^oC, Dean-Stark. (e) $(RCO)_2O$/THF, rt or RCOCl/Et_3N/THF, rt. (f) i) conc. H_2SO_4 , 45-50 ^oC, ii) H_2O ~0 ^oC, iii) NaOH (10%). (g) KOCN.

Scheme 2

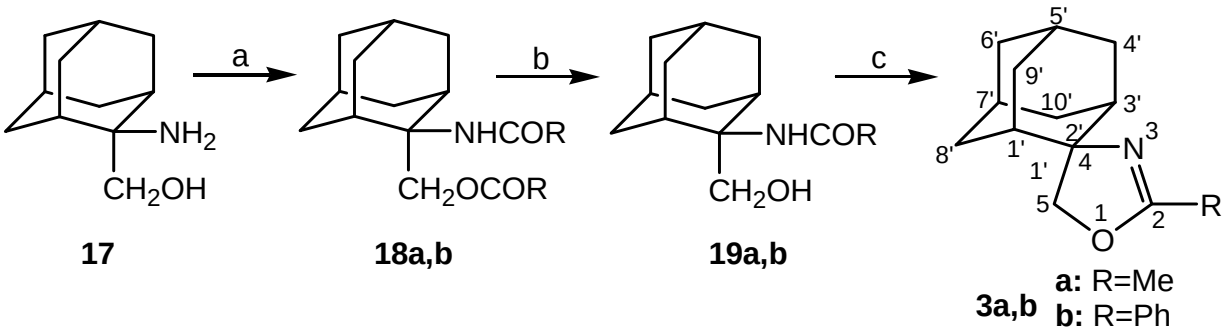


Reagents and conditions: (a) KCN-NH_4Cl/EtOH-H_2O rt. (b) $LiAlH_4$/Et_2O and then aq NaOH (2N). (c) HCO_2H (98%), reflux 2 h. (d) toluene/140 ^oC – Dean Stark. (e) $(RCO)_2O$/THF, rt or RCOCl/Et_3N/THF, rt. (f) i) conc. H_2SO_4 , 45-50 ^oC, ii) H_2O ~0 ^oC, iii) NaOH (10%). (g) KOCN.

Oxazolines **3a,b** were synthesized from 2-amino-2-adamantanemethanol **17**[2(b)] as illustrated in Scheme 3. Again *N*,*O*-bisacyl derivatives (**18a,b**) were formed. These were hydrolysed with NaOH to the amides **19a,b** which were cyclised to the oxazolines **3a,b** (**Scheme 3**).

During the reaction of acylchlorides to aminoalcohol **17**, *N*,*O*-bisacyl derivatives **18a**,**b** were again formed, which were hydrolyzed to amides **19a,b**. The latter molecules were cyclized to their respective oxazolines **3a,b** with tosyl chloride[11] in pyridine.

Scheme 3



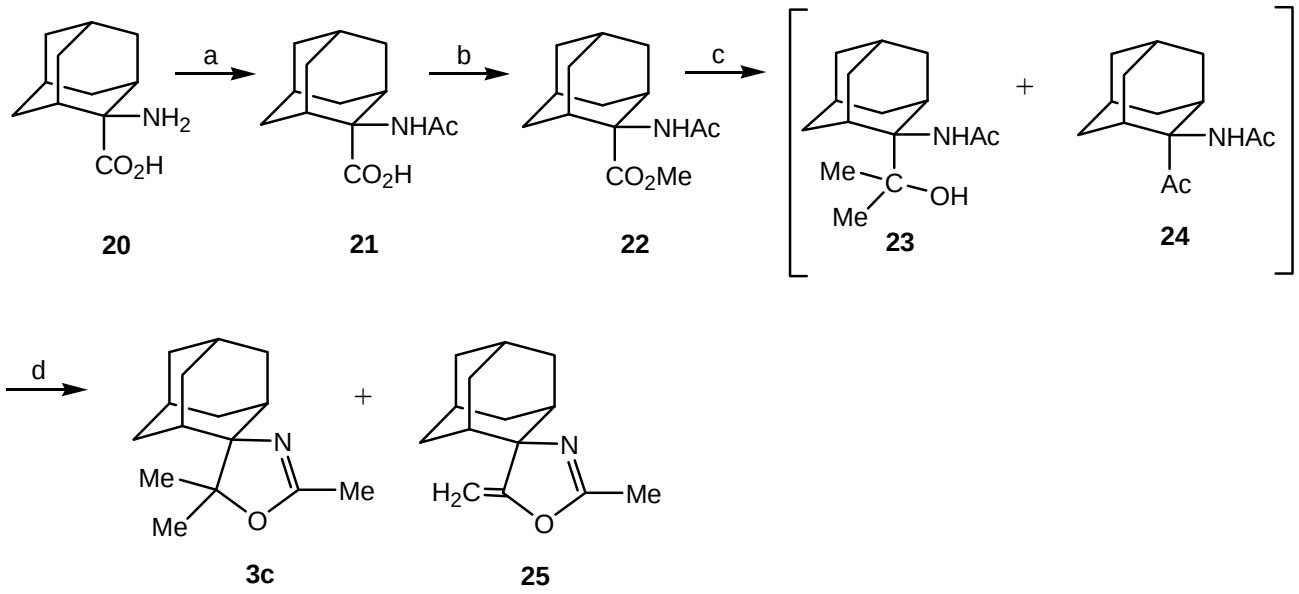
Reagents and conditions: (a) RCOCl/Et_3N/THF, rt. (b) NaOH (1N), rt, 12 h. (c) TsCl/Py, 115-120 ^oC, 15 h.

The synthesis of trimethyl derivative **3c** from 2-amino-2-adamantanecarboxylic acid **20**[12] as starting material is shown in **Scheme 4**. The amino acid **20** was acylated to acetamido acid **21**, which was then converted into methyl ester **22**. Addition of excess methylmagnesium iodide to the amidoester **22** gave a mixture of aminoalcohol **23** and aminoketone **24**, which was cyclized without further purification with sulphuric acid to trimethyloxazoline **3c** and the methylene derivative **25**.

Finally, the fused system **4** was prepared by reaction of potassium cyanate with the hydrochloride **26**[13] followed by cyclisation with concentrated HCl (**Scheme 5**).

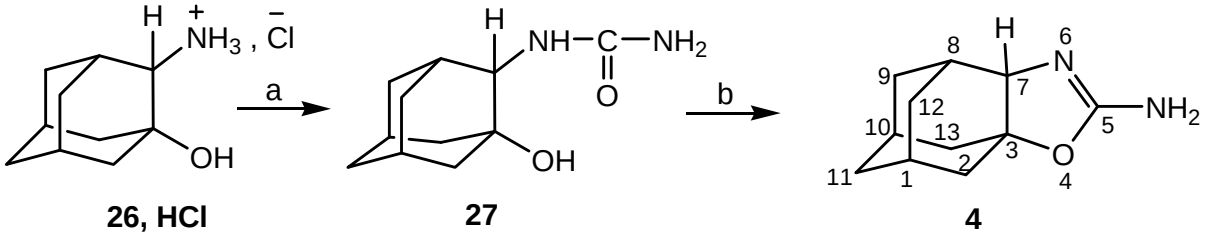
A preliminary pharmacological investigation with selected compounds was carried out on Microtubule Associated Protein-depleted tubulin, which was purified from bovine brain.[14] The tubulin polymerization was initiated by addition of paclitaxel and then the effect of the compounds on polymerization was evaluated. Some of the adamantaneoxazolines inhibit tubulin polymerization and the results for the active compounds are presented in **Table 1**.

Scheme 4



Reagents and conditions: (a) $(CH_3CO)_2O/CHCl_3$, 60 ^oC, 18 h. (b) gas HCl/CH_3OH, rt. (c) CH_3MgI/Et_2O and then NH_4Cl/H_2O. (d) i) conc. H_2SO_4, rt, 15 min, ii) H_2O ~0 ^oC, iii) NaOH (10%).

Scheme 5



Reagents and conditions: (a) KOCN. (b) i) conc. HCl, 40-50 ^oC, 6 h, ii) H_2O ~0 ^oC, iii) NaOH (10%).

To investigate if the new adamantane derivatives also had trypanocidal properties, they were tested[3(a),15] against the bloodstream form of *T. brucei*. None of the spiroadamantaneoxazolines (**1a-d**), the exocyclic adamantine oxazolines **2a-d,** or 4-oxa-6-azatetracyclo[6.3.1.1.^{3,10}.0^{3,7}]tridec-5-en-5-amine (**4**) displayed any activity at 5 μg mL^{-1}. Oxazolines **3a-c** had a **s**light effect, inhibiting parasite growth in the range of 25-50% under the conditions tested. The only compound to show significant activity was the aminoxazoline **2e,** which caused 100% cell death at 5 μg mL^{-1}. Further investigation, carried out in triplicate, demonstrated that this compound was about 6-fold more effective than rimantadine against bloodstream form *T. brucei*, with an IC_{50} of 0.89 $\pm$ 0.23 μM and an IC_{90} of 2.40 $\pm$ 0.11 μM.

Table 1. Effects of compounds on paclitaxel-induced tubulin polymerization

Compound	Inhibition of tubulin polymerization at 50 μM drug concentration (%)	Inhibition of tubulin polymerization at 100 μM drug concentration (%)
1a	45	50
1c	20	45
1d	60	80
2c	0	0
2d	70	86
3f	0	10
4	59	64

There was no obvious correlation between inhibition of tubulin polymerization and the activity of the derivatives against bloodstream form *T. brucei*. Compounds **1a**, **1c**, **1d** and **2d** and **4** resulted in moderate to significant inhibition of tubulin polymerization (Table 1), but had no effect on trypanosomes. Interestingly, the only derivative which had a high level of activity was the aminoxazoline **2e**. Previously, we have shown that trypanocidal adamantanes derivatives require an amino group.[3] This can be attached directly to the adamantane ring, or via a side group, and can be substituted or non-substituted. It is a reasonable assumption therefore, that the enhanced activity displayed by **2e**, compared to the other oxazoline derivatives, can be attributed to the amino group. Furthermore, it can be inferred that the primary target in the trypanosome is probably the same as that of the other aminoadamantane derivatives we have previously tested.[3] The mechanism of action of these derivatives in the case of *T. brucei* is unknown, but in other systems, such as influenza A virus infected cells, the therapeutic effect is mediated by channel blocking activity.[3] Although we cannot exclude the possibility that oxazoline derivatives may affect tubulin polymerization in trypanosomes, our results suggest that this does not make a major contribution to trypanocidal activity.

EXPERIMENTAL

Melting points were determined using a Büchi capillary apparatus and an uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 833 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AC 200 and MSL 400 spectrometers operating at 200 and 400 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C proton decoupled NMR spectra were recorded on a Bruker AC 200 at 50 MHz using $CDCl_3$ or DMSO as solvent. 2D NMR experiments (HMQC and COSY) were used for the elucidation of the structures of selected compounds. Service Central de Microanalyse (CNRS) in

France carried out microanalyses and the results obtained had a maximum deviation of ± 0.4% from the theoretical value.

2-Hydroxy-2-tricyclo[3.3.1.1.^{3,7}]decanecarbonitrile (6)

To a solution of adamantanone **5** (2.00 g, 13.3 mmol) in EtOH (30 mL) was added a solution of ammonium chloride (2.13 g, 39.9 mmol) in water (10 mL) and a solution of potassium cyanide (2.60 g, 39.9 mml) in water (10 mL). The mixture of reaction was stirred overnight at rt. Then the solvent was evaporated under vacuum and water was poured into the residue. The mixture was extacted with Et_2O and the organic phase was washed with water, dried over sodium sulfate and evaporated to give 2.30 g (98%) of **6**, mp 232-233 ^oC. The IR spectrum has shown the existence of ketone **5** as by product. Compound **6** was used without further purification for the preparation of amine **7**.

2-Hydroxy-2-tricyclo[3.3.1.1.^{3,7}]decane-2-methanamine (7)

To a stirred suspension of $LiAlH_4$ (1.97 g, 52.0 mmol) in dry Et_2O (50 mL) was added dropwise a solution of cyanohydrin **6** (2.30 g, 13.0 mmol) in dry ether (20 mL). The reaction mixture was stirred at rt for 4 h and then left standing overnight. Afterwards, it was hydrolyzed with aqueous sodium hydroxide (10%) under ice cooling. The inorganic precipitate formed was filtered off, washed with hot THF, and the filtrate was concentrated *in vacuo*. Water was poured into the residue followed by the addition of hydrochloric acid (3%). The aqueous layer was washed with Et_2O, made alkaline with solid sodium carbonate and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated to give 1.27 g (54%) of **7**, mp (hydrochloride) > 250 ^oC; ^1H NMR ($CDCl_3$) δ 1.50-1.54 (brd, 2H, $4'_{eq}$, $9'_{eq}$ -H), 1.65-1.84 (complex m, 13H, 1, 3, 5, 6, 7, 8, 10-H, OH, NH_2), 2.18-2.21 (brd, 2H, $4'_{ax}$, $9'_{ax}$-H), 2.82 (s, 2H, CH_2N).

***N*-(2-Hydroxy-2-tricyclo[3.3.1.1.^{3,7}]decylmethyl)acetamide (9b)**

To a stirred suspension of aminoalcohol **7** (1.0 g, 5.5 mmol) in dry THF (10 mL) was added dropwise under ice cooling acetic anhydride (3.0 mL, 33.0 mmol). A white precipitate was immediately formed and the mixture was stirred overnight at ambient temperature. Afterwards, it was poured onto chilled water and extracted with EtOAc. The organic layer was washed with water, hydrochloric acid (5%), a solution of aqueous sodium carbonate and dried over sodium sulfate. The solvent was evaporated under vacuum to give 1.06 g (86%) of **9b** in crystalline form, mp 191-193 ^oC. The product was used without further purification for the preparation of the spiro compound **1b**. IR (Nujol) *v* 3334 (OH), 1643 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.34-1.37 (brd, 2H, 4_{eq}, 9_{eq}-H), 1.52-1.56 (m, 6H, 6, 8, 10-H), 1.69 (brs, 2H, 5,7-H), 1.76 (brs, 2H, 1, 3-H), 1.80 (s, 3H, CH_3), 2.10-2.13 (brd, 2H, 4_{ax}, 9_{ax}-H), 3.26-3.28 (d, J ~ 6 Hz, 2H, CH_2N), 7.55 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 22.8 (CH_3), 26.9 (5-C), 27.3 (7-C), 32.4 (4, 9-C), 34.2 (8, 10-C), 34.8 (1, 3-C), 38.2 (6-C), 46.1 (CH_2N), 73.7 (2-C), 170.2 (C=O).

***N*-(2-Hydroxy-2-tricyclo[3.3.1.1.^{3,7}]decylmethyl)propanamide (9c)**

To a stirred suspension of aminoalcohol **7** (1.27 g, 7.0 mmol) in dry THF (20 mL) was added dropwise under ice cooling propionic anhydride (1.97 g, 21.0 mmol). The mixture was stirred overnight at rt and then filtered off. The precipitate was washed with water, hydrochloric acid (5%) and water, and dried to give 0.92 g (55%) of **9c** in crystalline form, mp 134-135 ^{o}C. The product was used without further purification for the preparation of the spiro derivative **1c.** ^{1}H NMR ($CDCl_3$) δ 1.10-1.14 (t, J_{AX} = 7.5 Hz, 3H, A_3X_2, CH_3CH_2CO), 1.52-1.55 (brd, 2H, 4_{eq}, 9_{eq}-H), 1.64-1.69 (m, 6H, 1, 3, 6, 7, 8_{eq}, 10_{eq}-H), 1.79 (brs, 2H, 5, 7-H), 1.84-1.87 (brd, 2H, 8_{ax}, 10_{ax}-H), 2.07-2.10 (brd, 2H, 4_{ax}, 9_{ax}-H), 2.18-2.24 (q, J_{AX} = 7.5 Hz, 2H, A_3X_2, CH_3CH_2CO), 2.80 (brs, 1H, OH), 3.49-3.51(d, J = 6.0 Hz, 2H, CH_2N), 6.15 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 10.0 (CH_3CH_2CO), 27.0 (5-C), 27.3 (7-C), 29.6 (CH_3CH_2CO), 32.6 (4, 9-C), 34.4 (8, 10-C), 35.3 (1, 3-C), 38.0 (6-C), 46.3 (CH_2N), 75.1 (2-C), 174.8 (C=O).

***N*-(2-Hydroxy-2-tricyclo[3.3.1.1.^{3,7}]decylmethyl)benzamide (9d)**

To a stirred suspension of aminoalcohol **7** (1.0 g, 5.5 mmol) in dry THF (10 mL) was added triethylamine (734 mg, 7.2 mmol) and then dropwise a solution of benzoyl chloride (928 mg, 6.6 mmol) in dry THF (10 mL) at 0 ^{o}C. Following the work up used for **9b** the title compound was obtained in 80% yield (1.25 g) in crystalline form, mp 179-181 ^{o}C. The product was used without further purification for the preparation of the spiro derivative **1d**. ^{1}H-NMR ($CDCl_3$) δ 1.56-1.59 (d, 2H, 4_{eq}, 9_{eq}-H), 1.67 (brs, 2H, 6-H), 1.69-1.81 (m, 6H, 1, 3, 5, 7, 8_{eq}, 10_{eq}-H), 1.92-1.95 (d, 2H, 8_{ax}, 10_{ax}-H), 2.08-2.11 (d, 2H, 4_{ax}, 9_{ax}-H), 2.56 (brs, 1H, OH), 3.71-3.72 (d, J = 6.0 Hz, 2H, CH_2N), 6.74 (brs, 1H, NH), 7.35-7.39 (m, 2H, 3, 5-H_{arom}), 7.43-7.47 (m, 1H, 4-H_{arom}), 7.75-7.77 (m, 2H, 2, 6-H_{arom}); ^{13}C-NMR ($CDCl_3$) δ 27.0 (5-C), 27.3 (7-C), 32.6 (4, 9-C), 34.4 (8, 10-C), 35.4 (1, 3-C), 38.0 (6-C), 46.7 (CH_2N), 75.5 (2-C), 127.0 (2, 6-C_{arom}), 128.4 (3, 5-C_{arom}), 131.4 (4-C_{arom}), 134.4 (1-C_{arom}), 168.1 (C=O).

Spiro[oxazol-5(4*H*),2′-tricyclo[3.3.1.1.^{3,7}]decane] (1a)

Aminoalcohol **7** (850 mg, 4.7 mmol) was dissolved in formic acid (98%, 10 mL) and then refluxed for 2 h. The excess of formic acid was removed *in vacuo* under heating, and dry toluene (20 mL) was added to the mixture, which was heated at 140 ^{o}C in a Dean-Stark apparatus for 2 h after the start of azeotropic distillation of toluene-water. The gluey residue was crystallized with Et_2O and *n*-pentane, and then filtered and dried to give 470 mg of formamide **9a** in crystalline form, mp 117 ^{o}C. The filtrate was evaporated to give 300 mg of a ropy residue, which was purified by flash column chromatography (Et_2O) to give 90 mg of **1a**. Formamide **9a** (470 mg) was re-dissolved in dry toluene and heated with formic acid (98%, 5 mL) in a Dean-Stark apparatus for 3 h after the start of azeotropic distillation of toluene-water. The solvent was evaporated under vacuum and the residue was purified by flash chromatography (Et_2O) to give 172 mg of **1a**. Total yield of **1a** 29% (262 mg); ^{1}H NMR ($CDCl_3$) δ 1.56-1.79 (m, 12H, 1′, 3′, $4'_{eq}$, 5′, 6′, 7′, 8′, $9'_{eq}$, 10′-H), 2.03-2.06 (brd, 2H, $4'_{ax}$, $9'_{ax}$-H), 3.54-3.55(d, J = 2.0 Hz, 2H, 4-H), 6.75 (s, 1H,

2-H); ^{13}C NMR δ 26.4 (5′-C), 26.6 (7′-C), 33.4 (4′, 9′-C), 34.6 (8′, 10′-C), 36.6 (1′, 3′-C), 37.1 (6′-C), 62.6 (4-C), 89.3 (5, 2′-C), 154.5 (2-C); mp (picrate) 166-168 ^{o}C (decomp) (MeOH-Et_2O). *Anal*. Calcd for $C_{26}H_{28}N_4O_8$ (picrate): C, 51.43; H, 4.80. Found: C, 51.19; H, 4.90.

2-Methylspiro[oxazol-5(4*H*),2′-tricyclo[3.3.1.1.^{3,7}]decane] (1b)

Amide **9b** (860 mg, 3.9 mmol) was dissolved in small portions into sulphuric acid (98%, 2mL) under ice cooling. The solution formed was left for 25 min and then heated under stirring at 45-50 ^{o}C for 15 min. Chilled water was then poured onto the mixture, which was made alkaline on addition of a solution of aqueous sodium hydroxide. The resulting mixture was extracted with Et_2O and the organic layer dried over sodium sulfate. Evaporation of Et_2O *in vacuo* gave 750 mg (94%) of **1b** in crystalline form, mp 111-113 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.57-1.82 (m, 12H, 1′, 3′, 4′$_{eq}$, 5′, 6′, 7′, 8′, 9′$_{eq}$, 10′-H), 1.92(s, 3H, CH_3), 2.06-2.09 (brd, 2H, 4′$_{ax}$, 9′$_{ax}$-H), 3.54-3.55 (d, J = 1.0 Hz, 2H, 4-H); ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3), 26.35(5′-C), 26.6 (7′-C), 33.4 (4′, 9′-C), 34.4 (8′, 10′-C), 36.7 (1′, 3′-C), 37.1 (6′-C), 63.7 (4-C), 89.9 (5,2′-C), 164.4 (2-C); mp (picrate) 202-204 ^{o}C (decomp) (MeOH-Et_2O). *Anal*. Calcd for $C_{19}H_{22}N_4O_8$ (picrate): C, 52.53; H, 5.10. Found: C, 52.70; H, 5.10.

2-Ethylspiro[oxazol-5(4*H*),2′-tricyclo[3.3.1.1.^{3,7}]decane] (1c)

Oxazoline **1c** was prepared from amide **9c** following the procedure used for **1b**; yield 73%. ^{1}H-NMR ($CDCl_3$) δ 1.11-1.15 (t, J_{AX} = 7.5 Hz, 3H, A_3X_2, CH_3), 1.57-1.76 (m, 12H, 1′, 3′, 4′$_{eq}$, 5′, 6′, 7′, 8′, 9′$_{eq}$, 10′-H), 2.06-2.09 (brd, 2H, 4′$_{ax}$, 9′$_{ax}$-H), 2.20-2.26 (q, J_{AX} = 7.5 Hz, 2H, A_3X_2, CH_2), 3.55 (s, 2H, 4-H); ^{13}C NMR ($CDCl_3$) δ 10.3 (CH_3), 21.9 (CH_2), 26.4 (5′-C), 26.6 (7′-C), 33.5 (4′, 9′-C), 34.5 (8′, 10′-C), 36.7 (1′, 3′-C), 37.2 (6′-C), 63.5 (4-C), 89.5 (5,2′-C), 168.4 (2-C); mp (picrate) 201-202 ^{o}C (decomp) (MeOH-Et_2O). *Anal*. Calcd for $C_{20}H_{24}N_4O_8$ (picrate): C, 53.57; H, 5.39. Found: C, 53.47; H, 5.35.

2-Phenylspiro[oxazol-5(4*H*),2′-tricyclo[3.3.1.1.^{3,7}]decane] (1d)

Oxazoline **1c** was prepared from amide **9d** following the procedure used for **1b**; yield 70%. The solvent used for the extraction was $CHCl_3$; mp 118-120 ^{o}C; ^{1}H NMR ($CDCl_3$) δ 1.66-1.92 (m, 12H, 1′, 3′, 4′$_{eq}$, 5′, 6′, 7′, 8′, 9′$_{eq}$, 10′-H), 2.24-2.27 (brd, 2H, 4′$_{ax}$, 9′$_{ax}$-H), 3.83 (s, 2H, 4-H), 7.36-7.46(m, 3H, 3, 4, 5-H_{arom}), 7.94-7.96 (~d, 2H, 2, 6- H_{arom}); ^{13}C NMR ($CDCl_3$) δ 26.4 (5′-C), 26.7 (7′-C), 33.6 (4′, 9′-C), 34.5 (8′, 10′-C), 36.8 (1′, 3′-C), 37.2 (6′-C), 63.9 (4-C), 90.1 (5,2′-C), 128.0 (2, 6-C_{arom}), 128.2 (1, 3, 5-C_{arom}), 131.0 (4-C_{arom}), 163.2 (2-C). mp (picrate) 206-208 ^{o}C (decomp) (MeOH-Et_2O). *Anal*. Calcd for $C_{24}H_{24}N_4O_8$ (picrate); C, 58.06; H, 4.87. Found C, 58.19; H, 4.88.

***N*-[2-Hydroxy-2-(tricyclo[3.3.1.1.^{3,7}]decylmethyl)]urea (10)**

To a stirred solution of the hydrochloride of **7** (476 mg, 2.2 mmol) in water (8 mL) was added potassium cyanate (178 mg, 2.2 mmol). The mixture was refluxed for 4 h and then the solvent was evaporated under vacuum to give a solid residue, which was dissolved in boiling EtOH. The solution was filtered through a fluted filter paper and the filtrate was evaporated *in vacuo* to give 370 mg (75%) of crystalline **10**, mp

202-204 °C. The product was used without further purification for the preparation of spiro amine **1e**. ^{1}H NMR ($CDCl_3$) δ 1.35-1.38 (brd, 2H, 4_{eq}, 9_{eq}-H), 1.53-1.79 (m, 10H, 1, 3, 5, 6, 7, 8, 10-H), 1.69 (brs, 2H, 5, 7-H), 2.11-2.14 (brd, 2H, 4_{ax}, 9_{ax}-H), 3.18-3.20 (d, J = 5.5 Hz, 2H, CH_2N), 5.52 (s, 2H, NH_2), 5.93 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 27.0 (5-C), 27.4 (7-C), 32.5 (4, 9-C), 34.1 (8, 10-C), 34.8 (1, 3-C), 38.2 (6-C), 46.5 (CH_2N), 73.9 (2-C), 159.8 (C=O).

Spiro[oxazol-5(4*H*),2′-tricyclo[3.3.1.1.^{3,7}]decane]-2-amine (1e)

Urea **10** (250 mg, 1.1 mmol) was dissolved in small portions in sulphuric acid (98%, 1 mL) under ice cooling. The solution was heated at 45-50 °C for 2 h and then poured onto chilled water. The resulting mixture was washed with EtOAc, made alkaline with a solution of aqueous sodium hydroxide, extracted with EtOAc and then the organic layer was dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 200 mg (88%) of crystalline **1e**, mp 162-164 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ 1.58-1.80 (m, 10H, $4'_{eq}$, 5′, 6′, 7′, 8′, $9'_{eq}$, 10′-H), 1.96 (brs, 2H, 1′, 3′-H), 2.04-2.07 (brd, 2H, $4'_{ax}$, $9'_{ax}$ -H), 3.52 (s, 2H, 4-H), 4.66 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 26.4 (5′-C), 26.6 (7′-C), 33.5 (4′, 9′-C), 34.5 (8′, 10′-C), 36.5 (1′, 3′-C), 37.2 (6′-C), 61.1 (4-C), 91.0 (5, 2′-C), 164.1 (2-C). *Anal*. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80. Found: C, 70.11; H, 8.72.

1-Tricyclo[3.3.1.1.^{3,7}]decylethanone (11)

A mixture of *β*-oxo-1-tricyclo[3.3.1.1.^{3,7}]decanepropanoic acid ethyl ester[10] (10.44 g, 41.8 mmol) in sulphuric acid (98%, 2.4 mL) and water (12.5 mL) was refluxed for 4 h and then poured onto chilled water, where some of the product crystallized. The mixture was taken up with ether and the organic layer was exhaustively washed with water and a solution of aqueous sodium carbonate, dried over sodium sulfate and evaporated under reduced pressure to give 6.26 g (84%) of **11**, mp 53-54 °C.

***α*-Hydroxy-*α*-methyl-1-tricyclo[3.3.1.1.^{3,7}]decaneacetonitrile (12)**

Ketone **11** (6.26 g, 35.2 mmol), sodium cyanide (6.9 g, 140.8 mmol) and ammonium chloride (7.53 g 140.8 mmol) in a mixture of Et_2O, water and THF (1:1:1, 90 mL) was vigorously stirred overnight. Then water was poured onto the mixture, which was extracted with Et_2O. The organic layer was washed with water, hydrochloric acid (5%) and water. After drying over sodium sulfate the solvent was removed under vacuum to give 6.45 g of the title compound, along with some amount of **11** (IR spectral data). The product was used without further purification for the preparation of amine **13**.

***α*-Hydroxy-*α*-methyl-1-tricyclo[3.3.1.1.^{3,7}]decanemethanamine (13)**

To a chilled (0 °C) stirred suspension of $LiAlH_4$ (2.0 g, 53.3 mmol) in dry Et_2O (60 mL) was added dropwise a solution of cyanohydrin **12** (3.00 g, 14.6 mmol) in dry Et_2O (40 mL). The reaction mixture was stirred at rt for 4 h, and then hydrolyzed by adding water and a solution of aqueous sodium hydroxide (10%) under ice cooling. The inorganic precipitate formed was filtered off, washed with hot THF, and the filtrate was concentrated *in vacuo*. Water was poured onto the residue and then hydrochloric acid (3%).

The aqueous layer was washed with Et_2O, made alkaline with solid sodium carbonate and extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate and evaporated in vacuo to give 1.2 g (39%) of amine **13**. Melting of this material commences at 120-121^oC and ceases at 126-127 ^oC (decomp). The product was used without further purification for the preparation of acetamide **15b**. ^1H NMR ($CDCl_3$) δ 1.01 (s, 3H, CH_3), 1.58-1.68 (m, 14H, 2, 4, 6, 8, 9, 10-H, NH_2), 1.95 (brs, 4H, 3, 5, 7-H, OH), 2.45-2.79 (q, J_{AB} = 12.6 Hz, 2H, AB, CH_2N); ^{13}C NMR ($CDCl_3$) δ 19.4 (CH_3), 28.5 (3, 5, 7-C), 36.3 (4, 6, 10-C), 37.2 (2, 8, 9-C), 38.4 (1-C), 44.8 (CH_2N), 74.2 (C-O).

***N*-[2-Hydroxy-2-(1-tricyclo[3.3.1.1.^{3,7}]decyl)propyl]acetamide (15b)**

To a stirred suspension of aminoalcohol **13** (1.48 g, 7.1 mmol) in dry THF (25 mL) was added triethylamine (1.88 g, 18.46 mmol) and then dropwise under ice cooling a solution of acetyl chloride (725 mg, 9.23 mmol) in dry THF (10 mL). The mixture was stirred at ambient temperature overnight, poured onto chilled water and extracted with CH_2Cl_2. The organic layer was washed with water, hydrochloric acid (5%), water and dried over sodium sulfate. The solvent was then evaporated under vacuum to give 1.52 g of a product, which was dissolved in EtOH (20 mL) and saponified with a solution of aqueous sodium hydroxide (976 mg, 24.4 mmol) in water (2 mL) for 2 h. EtOH was then removed *in vacuo* and water was poured onto the residue. The mixture was extracted with CH_2Cl_2, the organic layer dried over sodium sulfate and evaporated to give 1.38 g (78%) of **15b**, mp 147-149 ^oC. The product was used without further purification for the preparation of oxazole **2b**. IR (Nujol) *v* 3335 (OH), 1654 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01(s, 3H, CH_3), 1.57-1.68 (m, 14H, 2, 4, 6, 8, 9, 10-H, NH_2), 1.97 (brs, 4H, 3, 5, 7-H), 2.00 (s, 3H, CH_3CO), 2.48 (brs, 1H, OH), 3.19-3.26 (m, 1H, ABX, CH_AHNH), 3.33-3.38 (m, 1H, ABX, CHH_BNH), 6.18 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 19.0 (CH_3), 23.3 (CH_3CO), 28.4 (3, 5, 7-C), 36.0 (4, 6, 10-C), 36.9 (2, 8, 9-C), 38.6 (1-C), 44.2 (CH_2N), 76.2 (C-OH), 171.4 (C=O).

***N*-[2-Hydroxy-2-(1-tricyclo[3.3.1.1.^{3,7}]decyl)propyl]propanamide (15c)**

To a stirred suspension of aminoalcohol **13** (840 mg, 4.0 mmol) in dry THF (20 mL) was added triethylamine (813 mg, 8.0 mmol) and then dropwise under ice cooling a solution of propionyl chloride (444 mg, 4.8 mmol) in dry THF (10 mL). Amide **15c** (1.0 g, 95%) was obtained in crystalline form after employing the same work up used for 15**b**; mp 112-114 ^oC. The product was used without further purification for the preparation of oxazole **2c**. IR (Nujol) *v* 3350 (OH), 3286 (NH), 1648 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01(s, 3H, CH_3), 1.11-1.15 (t, J_{AX} = 7.5 Hz, 3H, A_3X_2, CH_3CH_2CO), 1.57-1.67 (m, 14H, 2, 4, 6, 8, 9, 10-H, NH_2), 1.97 (brs, 4H, 3, 5, 7-H), 2.19-2.25 (q, J_{AX} = 7.5 Hz, 2H, A_3X_2, CH_3CH_2CO), 2.46 (brs, 1H, OH), 3.22-3.26 (m, 1H, ABX, CH_AHNH), 3.33-3.38 (m, 1H, ABX, CHH_BNH), 6.18 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 10.0 (CH_3CH_2CO), 18.9 (CH_3), 28.4 (3, 5, 7-C), 29.7 (CH_3CH_2CO), 36.0 (4, 6, 10-C), 36.9 (2, 8, 9-C), 38.7 (1-C), 44.0 (CH_2N), 76.2 (C-OH), 175.1 (C=O).

***N*-[2-Hydroxy-2-(1-tricyclo[3.3.1.1.^{3,7}]decyl)propyl]benzamide (15d)**

To a stirred suspension of aminoalcohol **13** (1.12 g, 5.4 mmol) in dry THF (20 mL) was added triethylamine (1.42 g, 13.9 mmol) and then dropwise under ice cooling a solution of benzoyl chloride (980 mg, 6.9 mmol) in dry THF (10 mL). Benzamide **15d** (1.05 g, 63%) was obtained as an off-white soilid after employing the same work up used for 15**b**. Melting of this compound commences at 135 ^{o}C and ceases at 150 ^{o}C. The product was used without further purification for the preparation of oxazole **2d**. IR (Nujol) *v* 3339 (OH), 1637 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 3H, CH_3), 1.59-1.70 (m, 12H, 2, 4, 6, 8, 9, 10-H,), 1.99 (s, 3H, 3, 5, 7-H), 2.47 (brs, 1H, OH), 3.39-3.43 (m, 1H, ABX, CH_AHNH), 3.59-3.64 (m, 1H, ABX, CHH_BNH), 6.76 (brs, 1H, NH), 7.35-7.39 (m, 2H, 3, 5-H_{arom}), 7.43-7.47 (m, 1H, 4-H_{arom}), 7.74-7.76 (d, J = 7.5 Hz, 2H, 2, 6-H_{arom}); ^{13}C NMR ($CDCl_3$) δ 19.2 (CH_3), 28.4 (3, 5, 7-C), 36.0 (4, 6, 10-C), 36.9 (2, 8, 9-C), 38.8 (1-C), 44.4 (CH_2N), 76.5 (C-OH), 126.9 (2, 6-C_{arom}), 128.5 (3, 5-C_{arom}), 131.4 (4-C_{arom}), 134.5 (1-C_{arom}), 168.5 (C=O).

4,5–Dihydro-5-methyl-5-(1-tricyclo[3.3.1.1.^{3,7}]decyl)oxazole (2a)

Oxazoline **2a** was prepared by the procedure used for the synthesis of **1a**, by reacting aminoalcohol **13** with formic acid; yield 35%, mp (formamide **15a**) 142-143 ^{o}C; mp (oxazoline **2a**) 159-161 ^{o}C (Et_2O); ^{1}H NMR ($CDCl_3$) (oxazoline **2a**) δ 1.23 (s, 3H, 5-CH_3), 1.52 (br.s, 6H, 2′, 8′, 9′-H), 1.58-1.68 (brq, 6H, 4′, 6′, 10′-H), 1.98 (brs, 3H, 3′, 5′, 7′-H), 3.20-3.83 (q, J_{AB} = 14.5 Hz, 2H, AB, 4-H), 6.72 (s, 1H, 2-H); ^{13}C NMR. ($CDCl_3$) (oxazoline **2a**) δ 20.8 (CH_3), 27.9 (3′, 5′, 7′-C), 35.7 (4′, 6′, 10′-C), 36.7 (2′, 8′, 9′-C), 37.5 (1′-C), 59.9 (4-C), 89.9 (5-C), 154.4 (2-C). *Anal*. Calcd for $C_{20}H_{24}N_4O_8$: C, 76.67; H, 9.65. Found: C, 76.91; H, 9.62.

4,5–Dihydro-2,5-dimethyl-5-(1-tricyclo[3.3.1.1.^{3,7}]decyl)oxazole (2b)

Amide **15b** (640 mg, 2.6 mmol) was dissolved in small portions into sulphuric acid (98%, 2 mL) under ice cooling. The solution was chilled for 15 min and then cold water was poured onto the mixture, which was made alkaline by adding a solution of aqueous sodium hydroxide. The mixture was extracted with Et_2O and the organic layer dried over sodium sulfate and concentrated *in vacuo* to give a gluey residue, which was purified by flash column chromatography (Et_2O) to give 515 mg (87%) of **2b**; mp 192-193 ^{o}C (MeOH-Et_2O). ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 3H, 5-CH_3), 1.51 (brs, 6H, 4′, 6′,10′-H), 1.57-1.68 (brq, 6H, 2′, 8′, 9′-H), 1.90 (s, 3H, 2-CH_3), 1.97 (brs, 3H, 3′, 5′, 7′-H), 3.18-3.81 (q, J_{AB} = 14.0 Hz, 2H, AB 4-H); ^{13}C NMR ($CDCl_3$) δ 14.2 (2-CH_3), 20.8 (5-CH_3), 28.1 (3′, 5′, 7′-C), 35.8 (4′, 6′, 10′-C), 36.9 (2′, 8′, 9′-C), 37.7 (1′-C), 61.1 (4-C), 90.5 (5-C), 164.4 (2-C). *Anal.* Calcd for $C_{21}H_{26}N_4O_8$ (picrate): C, 54.54; H, 5.67. Found: C, 54.53; H, 5.92.

4,5–Dihydro-2-ethyl-5-methyl-5-(1-tricyclo[3.3.1.1.^{3,7}]decyl)oxazole (2c)

Oxazoline **2c** was prepared by the procedure used for the synthesis of **2b**; mp (picrate) 148-150 ^{o}C (MeOH-Et_2O); yield 63%; ^{1}H NMR ($CDCl_3$) δ 1.12-1.15 (t, J_{AX} = 7.5 Hz, 3H, A_3X_2, CH_3), 1.20 (s, 3H, 5-CH_3), 1.51 (brs, 6H, 4′, 6′, 10′-H), 1.57-1.68 (brq, 6H, 2′, 8′, 9′-H), 1.90 (s, 3H, 2-CH_3), 1.96 (brs, 3H,

3′, 5′, 7′-H), 2.19-2.24 (q, J_{AX} = 7.5 Hz, 2H, A_3X_2, CH_2), 3.19-3.82 (q, J_{AB} = 14.0 Hz, 2H, AB, 4-H); ^{13}C NMR ($CDCl_3$) δ 10.3 (CH_3), 20.8 (5-CH_3), 21.7 (CH_2), 28.1 (3′, 5′, 7′-C), 35.8 (4′, 6′, 10′-C), 36.9 (2′, 8′, 9′-C), 37.8 (1′-C), 60.9 (4-C), 90.1 (5-C), 168.4 (2-C). *Anal*. Calcd for $C_{22}H_{28}N_4O_8$ (picrate): C, 55.45; H, 5.92. Found: C, 55.73; H, 6.20.

4,5–Dihydro-5-methyl-2-phenyl-5-(1-tricyclo[3.3.1.1.^{3,7}]decyl)oxazole (2d)

Oxazoline **2d** was prepared by the procedure used for the synthesis of **2b**, but the reaction mixture was stirred at rt for 15 min; yield 51%; mp (picrate) 198-200 ^{o}C (MeOH-Et_2O). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.58-1.70 (m, 12H, 2′, 4′, 6′, 8′, 9′, 10′-H), 1.99 (brs, 3H, 3′, 5′, 7′-H), 3.45-4.09 (q, J_{AB} = 15 Hz, 2H, AB, 4-H), 7.36-7.43 (m, 3H, 3, 4, 5-H_{arom}), 7.91-7.93 (m, 2H, 2, 6-H_{arom}); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 28.1 (3′, 5′, 7′-C), 35.9 (4′, 6′, 10′-C), 36.9 (2′, 8′, 9′-C), 38.1 (1′-C), 61.5 (4-C), 90.7 (5-C), 128.0 (2-C_{arom}), 128.2 (1, 4-C_{arom}), 131.0 (3, 5-C_{arom}), 163.3 (2-C). *Anal*. Calcd for $C_{26}H_{28}N_4O_8$: C, 59.53; H, 5.38. Found: C, 59.31; H, 5.52.

***N*-[2-Hydroxy-2-(1-tricyclo[3.3.1.1.^{3,7}]decyl)propyl]urea (16)**

To a stirred suspension of hydrochloride of **13** (693 mg, 2.8 mmol) in water (15 mL) was added potassium cyanate (229 mg, 2.8 mmol). The mixture was refluxed for 3.5 h, filtered and the residue was washed well with water, and dried to give 525 mg (74%) of crystalline **16**, mp 209-211 ^{o}C (decomp). ^{1}H NMR (DMSO-d_6) δ 0.80 (s, 3H, CH_3), 1.48-1.56 (m, 12H, 2, 4, 6, 8, 9, 10-H), 1.84 (brs, 3H, 3, 5, 7-H), 2.82-2.86 (m, 1H, CHN), 2.98-3.03 (m, 1H, CHN), 5.50 (s, 2H, NH_2), 5.73 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 18.2 (CH_3), 27.6 (3, 5, 7-C), 35.3 (4, 6, 10-C), 36.3 (2, 8, 9-C), 37.8 (1-C), 43.7 (CH_2N), 74.5 (C-OH), 159.3 (C=O). The product was used without further purification for the preparation of oxazolamine **2e**.

4,5–Dihydro-5-methyl-5-(1-tricyclo[3.3.1.1.^{3,7}]decyl)oxazol-2-amine (2e)

Urea **10** (250 mg, 1.1 mmol) was dissolved in small portions into sulphuric acid (98%, 1 mL) under ice cooling. The solution was then heated at 45-50 ^{o}C for 2 h and poured onto chilled water. After following the work up used for **1e**, oxazoline **2e** was obtained in 85% yield (200 mg); mp (fumarate) 181 ^{o}C (decomp). ^{1}H NMR (DMSO-d_6) δ 1.32 (s, 3H, CH_3), 1.35-1.57 (m, 12H, 2′, 4′, 5′, 6′, 7′, 8′, 9′, 10′-H), 1.91 (s, 3′, 5′, 7′-H), 3.20-3.24 (m, 1H, 4-H), 3.78-3.82 (m, 1H, 4-H), 3.72 (brs, 4H, NH_2, 2×CO_2H), 6.35 (s, 2H, CH= fumarate); ^{13}C-NMR (DMSO-d_6) δ 14.7 (CH_3), 26.8 (3′, 5′, 7′-C), 34.3 (4′, 6′, 10′-C), 35.6 (2′, 8′, 9′-C), 48.7 (4-C), 52.2 (1′-C), 94.7 (5-C), 134.9 (CH= fumarate), 161.6 (2-C), 168.6 (C=O fumarate). *Anal*. Calcd for $C_{18}H_{26}N_2O_5$ (fumarate): C, 64.65; H, 7.84. Found: C, 65.01; H, 7.97.

***N*-(2-Hydroxymethyl-2-tricyclo[3.3.1.1.^{3,7}]decyl)acetamide (19a)**

To a stirred suspension of aminoalcohol **17** (1.5 g, 8.3 mmol) in dry THF (15 mL) was added triethylamine (3.36 g, 33.2 mmol) and then dropwise, under ice cooling, a solution of acetyl chloride (1.44 g, 18.3 mmol) in dry THF (10 mL). The mixture was stirred at 0 ^{o}C for 10 min and then refluxed for

6 h. The solvent was evaporated under vacuum, water was added to the residue and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, hydrochloric acid (5 %), water and dried over sodium sulfate. The solvent was removed *in vacuo* to give 2.04 g of **18a** as an oily product; IR (Nujol) *v* 3501-3289, 1737, 1644 cm^{-1}. The above mixture consisting of the *N*-acetyl and *N,O*-bisacetyl derivatives (2.04 g) was dissolved in EtOH (30 mL) and saponified with a solution of sodium hydroxide (320 mg, 8.0 mmol) in water (11 mL) for 18 h at rt. The solvent was evaporated under vacuum and water was poured onto the residue. The resulting mixture was filtered and the precipitate was washed with water, hydrochloric acid (5%) and water, and dried to give 1.8 g (97%) of **19a**; IR (Nujol) *v* 3388-3239, 1644 cm^{-1}. Melting of **19a** commences at 187 ^oC and ceases at 195-196 ^oC with decomposition. ^1H NMR (DMSO-d_6) δ 1.66-1.87 (m, 10H, 4_{eq}, 5, 6, 7, 8, 9_{eq}, 10-H), 1.98-2.02 (brd, 2H, 4_{ax}, 9_{ax}-H), 2.03 (s, 3H, CH_3), 2.20 (brs, 2H, 1, 3-H), 3.95-3.96 (s, 2H, CH_2O), 4.68 (brs, 1H, OH), 5.56 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 24.1 (CH_3), 26.9 (5-C), 27.2 (7-C), 30.8 (1-C), 31.0 (3-C), 32.9 (4, 9-C), 33.2 (8, 10-C), 38.3 (6-C), 62.8 (2-C), 67.4 (CH_2O), 171.4 (C=O). The product was used without further purification for the preparation of the spiro derivative **3a**.

***N*-(2-Hydroxymethyl-2-tricyclo[3.3.1.1.^{3,7}]decyl)benzamide (19b)**

To a stirred suspension of aminoalcohol **17** (1.5 g, 8.3 mmol) in dry THF (20 mL) was added triethylamine (3.36 g, 33.2 mmol) and then dropwise under ice cooling a solution of benzoyl chloride (2.57 g, 18.3 mmol) in dry THF (10 mL). The mixture was reluxed for 3 h, stirred at ambient temperature for 24 h, and then the solvent was evaporated under vacuum. Water was poured onto the residue and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, hydrochloric acid (5%), water and dried over sodium sulfate. The solvent was removed *in vacuo* to give 3.6 g of a product, which was purified by flash column chromatography (EtOAc: *n*-hexane = 1 : 1, v/v) to give 1.94 g (82%) of **19b**. IR (Nujol) *v* 3342 (NH), 3272, (OH), 1636, (C=O) cm^{-1}. Melting of **19b** commences at 148 ^oC and ceases at 168-170 ^oC (decomp). ^1H NMR (DMSO-d_6) δ 1.74-2.14 (m, 12H, 4, 5, 6, 7, 8, 9,10-H), 2.36 (s, 2H, 1, 3-H), 4.04 (s, 2H, CH_2O), 4.81 (brs, 1H, OH), 6.27 (brs, 1H, NH), 7.40-7.44 (m, 2H, 3, 5-H_{arom}), 7.47-7.4 (m, 1H, 4-H_{arom}), 7.73-7.75 (m, 2H, 2, 6-H_{arom}); ^{13}C NMR (DMSO-d_6) δ 27.1 (5-C), 27.2 (7-C), 31.0 (1, 3-C), 33.0 (4, 9-C), 33.3 (8, 10-C), 38.3 (6-C), 63.0 (2-C), 67.2 (CH_2O), 126.9 (2, 6-C_{arom}), 128.7 (3, 5-C_{arom}), 131.6 (4-C_{arom}), 134.9 (1-C_{arom}), 168.3 (C=O). The product was used without further purification for the preparation of the spiro derivative **3b**.

2-Methylspiro[oxazol-4(5*H*),2´-tricyclo[3.3.1.1.^{3,7}]decane] (3a)

To a solution of acetamidealcohol **19a** (1.0 g, 4.5 mmol) in pyridine (6 mL) was added tosyl chloride (858 mg, 4.5 mmol) in small portions under ice cooling. The reaction mixture was heated at 115-120 ºC for 15 h and then poured onto water. The resulting mixture was extracted with $CHCl_3$ and the organic layer was exhaustively washed with water, dried over sodium sulfate and concentrated *in vacuo* to give

510 mg of a product, which was purified by flash column chromatography (Et_2O) to give 380 mg (41%) of crystalline **3a**, mp 105-107 ^oC mp (picrate) 179-180 ^oC (decomp) (MeOH-Et_2O). ^1H NMR ($CDCl_3$) δ 1.56-1.85 (m, 12H, 1′, 3′, $4'_{eq}$, 5′, 6′, 7′, 8′, $9'_{eq}$, 10′-H), 1.96 (s, 3H, CH_3), 2.31-2.33 (brd, 2H, $4'_{ax}$, $9'_{ax}$-H), 4.01 (s, 2H, 5-H); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 25.5 (5′-C), 26.2 (7′-C), 29.1 (CH_3), 33.6 (4′, 9′-C), 35.5 (8′, 10′-C), 36.7 (6′-C), 36.9 (1′, 3′-C), 74.6 (4, 2′-C), 76.7 (5-C), 160.7 (2-C). *Anal*. Calcd for $C_{19}H_{22}N_4O_8$ (picrate): C, 52.53; H, 5.10. Found: C, 52.27; H, 5.16.

2-Phenylspiro[oxazol-4(5*H*),2′-tricyclo[3.3.1.1.^{3,7}]decane] (3b)

To a suspension of benzylamidealcohol **19b** (1.0 g, 3.5 mmol) in pyridine (8 mL) was added tosyl chloride (667 mg, 3.5 mmol) in small portions under ice cooling, and the resulting mixture was heated for10 h. Oxazole **3b** 230 mg (25%) was obtained as a crystalline solid after applying the same work up used for the isolation of **3a**, and having the residue obtained chromatographed using as eluents *n*-hexane : Et_2O = 1 : 1, v/v; mp 118-120 ^oC; mp (picrate) 205-207 ^oC (MeOH-Et_2O) (decomp). ^1H NMR ($CDCl_3$) δ 1.66-1.92 (m, 12H, 1′, 3′, $4'_{eq}$, 5′, 6′, 7′, 8′, $9'_{eq}$, 10′-H), 2.24-2.27 (brd, 2H, $4'_{ax}$, $9'_{ax}$-H), 3.83 (s, 2H, 5-H), 7.36-7.46 (m, 3H, 3, 4, 5-H_{arom}), 7.94-7.96 (m, 2H, 2, 6-H_{arom}); ^{13}C NMR ($CDCl_3$) δ 26.4 (5′-C), 26.7 (7′-C), 33.6 (4′, 9′-C), 34.5 (8′, 10′-C), 36.7 (1′, 3′-C), 37.2 (6′-C), 64.0 (5-C), 90.0 (4,2′-C), 128.0 (2, 6-C_{arom}), 128.2 (3, 5-C_{arom}), 128.5 (1-C_{arom}), 131.0 (4-C_{arom}), 163.1 (2-C). *Anal*. Calcd for $C_{24}H_{24}N_4O_8$ (picrate): C, 58.06; H, 4.87. Found: C, 58.20; H, 4.91.

2-Acetamido-2-tricyclo[3.3.1.1.^{3,7}]decanecarboxylic acid (21)

To a stirred suspension of amino acid **21** (2.12 g, 10.9 mmol) in $CHCl_3$ (20 mL) was added dropwise at 60 ^oC acetic anhydride (0.75 mL). After the mixture had been stirred for 6 h a second portion of acetic anhydride (0.75 mL) was added and heating was continued for 12 h. The solvent was then evaporated and water was added dropwise under ice cooling onto the residue. The resulting mixture was filtered off, and the precipitate washed with water, and dried to give 1.85 g (72%) of the title compound; mp 215 ^oC. ^1H NMR ($CDCl_3$) δ 1.62-1.65 (brd, 4H, 8_{eq}, 4_{eq}, 9_{eq}, 10_{eq}-H), 1.75 (brs, 4H, 1, 3, 6-H), 1.92 (m, 2H, 5, 7-H), 2.18 (s, 3H, CH_3), 2.31-2.35 (brd, 2H, 8_{ax}, 10_{ax}-H), 2.48-2.51 (brd, 2H, 4_{ax}, 9_{ax}-H), 2.56 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 15.3 (CH_3), 26.2 (5-C), 27.4 (7-C), 31.0 (4, 9-C), 33.5 (8,10-C), 35.0 (1, 3-C), 37.7 (6-C), 72.2 (2-C), 159.2 (CON), 179.1 (CO_2H). The product was used without further purification for the preparation of methyl ester **22**.

2-Acetamido-2-tricyclo[3.3.1.1.^{3,7}]decanecarboxylic acid methyl ester (22)

To a saturated solution of hydrogen chloride in MeOH (15 mL) was sequentially added MeOH (5 mL) and carboxylic acid **21** (2.0 g, 8.4 mmol) in small portions under ice cooling. The mixture was stirred at rt overnight, the solvent evaporated and water was added onto the residue The mixture was extracted with $CHCl_3$ and the organic layer was washed with water, dried over sodium sulfate and concentrated *in vacuo* to give 2.0 g (95%) of the title compound **22**; mp 103-105 ^oC.

2,5,5-Trimethylspiro[oxazol-4,2′-tricyclo[3.3.1.1.^{3,7}]decane] (3c)

To the Grignard reagent, prepared from methyl iodide (5.79 g, 40.8 mmol) and magnesium turnings (0.99 g, 40.8 mmol) in dry Et_2O (20 mL), was added dropwise under argon a solution of ester **22** (1.7 g, 6.8 mmol) in dry Et_2O (20 mL). The mixture was stirred at ambient temperature overnight and then hydrolyzed by adding a saturated aqueous ammonium chloride solution. The aqueous layer formed was extracted with Et_2O and a small quantity of THF. The combined organic layers were washed with sodium thiosulfate, dried over sodium sulfate and concentrated under vacuum. The residue obtained was worked up as in the procedure used for **2b** to give a gluey product, which was purified by flash column chromatography (Et_2O : *n*-hexane = 1 : 1, v/v) to afford 380 mg (24%) of **3c**; mp (picrate) 203-205 ^oC (decomp) (MeOH-Et_2O); ^1H NMR ($CDCl_3$) δ 1.39 (s, 6H, 2×5-CH_3), 1.49-1.53 (m, 2H, 4′$_{eq}$, 9′$_{eq}$-H), 1.67 (brs, 2H, 6-H), 1.65-1.67 (m, 4H, 6′, 8′$_{eq}$, 10′$_{eq}$-H), 1.82-1.90 (m, 6H, 1′, 3′, 5′, 7′, 8′$_{ax}$, 10′$_{ax}$-H), 1.89 (s, 3H, 2-CH_3), 2.45-2.48 (m, 2H, 4′$_{ax}$, 9′$_{ax}$-H); ^{13}C NMR ($CDCl_3$) δ 14.8 (2-CH_3), 25.0 (2×5-CH_3), 27.1 (5′-C), 27.5 (7′-C), 33.9 (1′, 3′-C), 34.2 (8′, 10′-C), 34.8 (4′, 9′-C), 38.4 (6′-C), 75.5 (4,2′-C), 88.6 (5-C), 159.6 (2-C). *Anal*. Calcd for $C_{21}H_{26}N_4O_8$ (picrate): C, 54.54; H, 5.67. Found: C, 54.33; H, 5.82.

Apart from **3c**, a second fraction was isolated from the flash column (110 mg, 8 %), the spectral data of which correspond to the structure of by-product **25**. ^1H NMR ($CDCl_3$) δ 1.57-1.65 (m, 6H, 1′, 3′, 4′$_{eq}$, 8′$_{eq}$, 9′$_{eq}$, 10′$_{eq}$-H), 1.75 (brs, 2H, 6-H), 1.87 (brs, 2H, 5′, 7′-H), 2.04 (s, 3H, 2-CH_3), 2.18-2.21(brd, 2H, 8′$_{ax}$, 10′$_{ax}$-H), 2.40-2.43 (brd, 2H, 4′$_{ax}$, 9′$_{ax}$-H), 4.52-4.53 (d, J_{AX}= 2.5Hz, 1H, CH_A=), 4.80-4.81 (d, J_{AX} = 2.5Hz, 1H, CH_X=); ^{13}C NMR ($CDCl_3$) δ 14.1 (2-CH_3), 26.3 (5′-C), 27.6 (7′-C), 31.3 (8′, 10′-C), 34.0(4′, 9′-C), 37.0 (1′, 3′-C), 38.6 (6′-C), 76.0 (4,2′-C), 87.9 (C=), 158.7 (2-C), 165.9 (5-C).

***N*-[1-Hydroxy-2-(tricyclo[3.3.1.1.^{3,7}]decyl)]urea (27)**

To a stirred solution of the hydrochloride salt of **26** (750 mg, 3.7 mmol) in water (15 mL) was added potassium cyanate (300 mg, 3.7 mmol). The mixture was refluxed for 4 h and the solvent was then evaporated under vacuum to give 660 mg (85 %) of **27**; mp > 230 ^oC (water); ^1H NMR (DMSO-d_6) δ 1.24-1.73(m, 10H, 4, 5, 6, 8, 10-H), 1.90 (m, 3H, 3, 5, 7-H), 3.38 (brs, 1H, 2-H), 5.38 (brs, 1H, OH), 5.52 (s, 2H, NH_2), 6.04-6.05(m, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 29.1 (5-C), 29.6 (7-C), 29.9 (6-C), 34.2 (3-C), 35.8 (4, 10-C), 38.9 (9-C), 45.4 (8-C), 58.7 (2-C), 67.7 (1-C), 159.6 (C=O). The product was used without further purification for the preparation of amine **4**.

4-Oxa-6-azatetracyclo[6.3.1.1.^{3,10}.0^{3,7}]tridec-5-en-5-amine (4)

Urea **27** (230 mg, 1.1 mmol) was dissolved in small portions in sulphuric acid (98%, 1 mL) under ice cooling. The solution was heated at 45-50 ^oC for 6 h and then poured onto chilled water. The mixture was diluted with EtOAc, made alkaline with a solution of aqueous sodium hydroxide and extracted with EtOAc. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give 70 mg (33%) of crystalline **4**; mp 222-223 ^oC (decomp) (water); ^1H NMR ($CDCl_3$) δ 1.67-1.89 (m, 6H, 2$_{eq}$, 9$_{eq}$, 11, 12$_{eq}$,

13_{eq} -H), 2.08-2.88 (m, 7H, 1, 2_{ax}, 8 , 9_{ax}, 10, 12_{ax}, 13_{ax}-H), 3.18 (brs, 1H, 7-H), 7.50 (brs, 2H, NH_2); ^{13}C NMR ($CDCl_3$) 28.5 (1, 8, 10-C), 34.6 (11-C), 36.2 (7-C), 38.5 (9, 12-C), 44.9 (2, 13-C), 64.4 (3-C), 168.9 (5-C, amino form), 202.5 (5-C, imino form). *Anal.* Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39. Found: C, 69.05; H, 8.52.

REFERENCES

1. (a) A. J. Hay, J. J Skehel, and M. H. Smith, *EMBO J*., 1985, **4**, 3021. (b) A. J. Hay, *Semin. Virol.*, 1992, **3**, 21. (c) L. H. Pinto, L. J. Holsinger, and R. A. Lamb, *Cell*, 1992, **69**, 517.
2. (a) N. Kolocouris, G. B. Foscolos, A. Kolocouris, P. Marakos, N. Pouli, G. Fytas, S. Ikeda, and E. De Clercq, *J. Med. Chem*., 1994, **37**, 2896. (b) N. Kolocouris, A. Kolocouris, G. B. Foscolos, G. Fytas, J. Neyts, E. Padalko, J. Balzarini, R. Snoeck, G. Andrei, and E. De Clercq, *J. Med. Chem*., 1996, **39**, 3307. (c) A. Kolocouris, D. Tataridis, G. Fytas, G. B. Foscolos, T. Mavromoustakos, N. Kolocouris, and E. De Clercq, *Bioorg. Med. Chem. Lett*., 1999, **9**, 3465. (d) G. Stamatiou, A. Kolocouris, N. Kolocouris, G. Fytas, G. B. Foscolos, J. Neyts, and E. De Clercq, *Bioorg*. *Med. Chem*. *Lett*., 2001, **11**, 2137. (e) G. Zoidis, N. Kolocouris, G. B. Foscolos, A. Kolocouris, G. Fytas, P. Karayannis, E. Padalko, J. Neyts, and E. De Clercq, *Antiviral Chem. Chemother*., 2003, **14**, 153. (f) G. Stamatiou, G. B. Foscolos, G. Fytas, A. Kolocouris, N. Kolocouris, C. Pannecouque, M. Witvrouw, E. Padalko, J. Neyts, and E. De Clercq, *Bioorg. Med. Chem.*, 2003, **11**, 5485. (g) I. Stylianakis, A. Kolocouris, N. Kolocouris, G. Fytas, G. B. Foscolos, E. Padalko, J. Neyts, and E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1699. (h) D. Setaki, D. Tatarides, G. Stamatiou, A. Kolocouris, N. Kolocouris, G. B. Foscolos, G. Fytas, E. Padalko, J. Neyts, and E. De Clercq, *Bioorg. Med. Chem*., 2006, **34**, 248. (i) D. Tataridis, G. Fytas, A. Kolocouris, Ch. Fytas, N. Kolocouris, G. B. Foscolos, E. Padalko, J. Neyts, and E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 692.
3. (a) J. M. Kelly, M. A. Miles, and A. C. Skinner, *Antimicrob. Agents Chemopher*., 1999, **43**, 985. (b) J. M. Kelly, G. Quack, and M. A. Miles, *Antimicrob. Agents Chemopher*., 2001, **45**, 1360. (c) I. Papanastasiou, A. Tsotinis, N. Kolocouris, S. R. Prathalingam, and J. M. Kelly, *J. Med. Chem.,* 2008, **51**, 1496.
4. A. Ploubidou, D. R. Robinson, R. C. Docherty, E. O. Ogbadoyi, and K. Gull, *J. Cell Sci.*, 1999, **112**, 4641.
5. Q. Li, K. W. Woods, A. Claiborne, S. L. Gwaltney, II, K. J. Barr, G. Liu, L. Gehrke, R. B. Credo, Y. H. Hui, J. Lee, R. B. Warner, P. Kovar, M. A. Nukkala, N. A. Zielinski, S. K. Tahir, M. Fitzgerald, K. H. Kim, K. Marsh, D. Frost, S.-C. Ng, S. Rosenberg, and H. L. Sham, *Bioorg. Med*. *Chem*. *Lett.*, 2002, **12**, 465.

6. J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, 1970, **26**, 949.
7. J. F. Schindler, K. B. Berst, and B. V. Plapp, *J. Med. Chem*., 1998, **41**, 1696.
8. (a) S .P. McManus, J. T. Carrol, and C. U. Pittman, *J. Org. Chem*., 1970, **35**, 3768. (b) R. N. Boyd and R. C. Rittner, *J. Am. Chem. Soc*., 1960, **82**, 2032. (c) E. E. van Tamelen, *J. Am. Chem. Soc.*, 1952, **74**, 2074.
9. C. Zhi, Z-Y. Long, J. Gambino, W.-C. Xu, N. C. Brown, M. Barnes, M. Butler, W. LaMarr, and G. E. Wright, *J. Med. Chem*., 2003, **46**, 2731.
10. H. Stetter and El. Ruscher, *Chem. Ber.*, 1960, **93**, 2054.
11. (a) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, 1974, **39**, 2787. (b) R. N. Boyd and R. H. Hansen, *J. Am. Chem. Soc*., 1953, **75**, 5896.
12. H. T. Nagasawa, J. A. Elberling, and F. N. Shirota, *J. Med. Chem*., 1973, **16**, 823.
13. W. V. Curran and R .B. Angier, *J. Org. Chem.*, 1969, **34***,* 3668.
14. G. C. Na and S. N. Timasheff, *Biochem.*, 1986, **25**, 6214.
15. H. Hirumi and K. Hirumi, *J. Parasitol*., 1989, **75**, 985.