Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 95–99

TETRAHEDRON

# First synthesis of aza-calanolides—a new class of anti-HIV active compounds☆

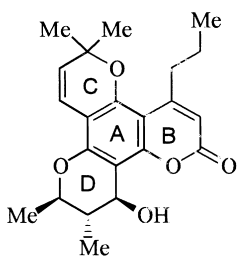
G. V. Madhava Sharma,[a,*] A. Ilangovan,[a] Ven L. Narayanan[b] and Mukund K. Gurjar[c]

[a]*Discovery Laboratory D-211, Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD 20692, USA*
[c]*Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India*

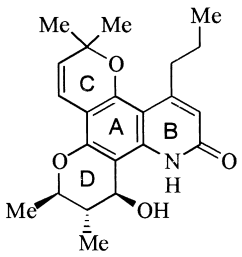
Received 2 September 2002; revised 14 October 2002; accepted 7 November 2002

**Abstract**—First synthesis of (±)-aza-calanolides, starting from dimethoxy aniline, is achieved. These new compounds exhibited potent in vitro anti-HIV reverse transcriptase activity. 

An urge to identify non-nucleoside reverse transcriptase inhibitors (NNRTI)[1,2] resulted in isolation of a novel class of pyranocoumarin derivatives from *Calophyllum lanigerum*.[3] One such compound, calanolide A (**1**) is in clinical testing and hence arose unprecedented interest particularly in developing its analogues.[4–6] But so far, most of the analogues were either less potent or devoid of anti-HIV activity. The limitations associated with **1** are its instability and bio-availability in physiological medium. We envisaged that replacing oxygen in ring B with a nitrogen atom would lead to aza-calanolide A (**2**), which might circumvent these limitations due to the presence of stable quinolinone ring system. Herein, we describe the first synthesis, characterization, optical resolution and in vitro biological evaluation of (±) aza-calanolide A **2**.




Calanolide A
(**1**)




Aza-Calanolide A
(**2**)

The target molecule **2** was visualized as a hexa-substituted aromatic system (ring A) fused on either side with 2-(1-H)-quinolinone (ring B), chromene (ring C) and dimethyl-chromanol (ring D) rings. Successive introduction of these three rings on commercially available 3,5-dimethoxyaniline forms the basic strategy of our synthetic endeavor.

The synthesis was first initiated with the construction of quinolinone system (ring B) onto 3,5-dimethoxyaniline (**3**) by reacting with ethyl 3-oxo-hexanoate under reflux to give the acetanilide intermediate (**4**), albeit in low yield with number of products. However, by adopting the modified approach described by Avendano et al.[7] wherein **3** was treated with 2,2-dimethyl-6-*n*-propyl-4*H*-1,3-dioxin-4-one[8,9] in xylene at 130°C, **4** was obtained in 77% yield. The $^1$H NMR spectrum of **4** revealed H-2′ and H-6′ at a downfield region $\delta$ 6.75 and 6.76 compared to H-4′ located at $\delta$ 6.20. Subsequent treatment of **4** with conc. $H_2SO_4$ at room temperature effected cyclisation to afford the quinolinone derivative **5** in 90% yield. The two aromatic protons H-6 and H-8 of **5** appeared at $\delta$ 6.22 and 6.50 respectively in its $^1$H NMR spectrum. This confirmed the fusion of ring B on the centrally located ring A. The demethylation of both the methoxyl groups was conveniently effected with $AlCl_3$ in chlorobenzene at 100°C to give the substituted resorcinol derivative **6** (Scheme 1).

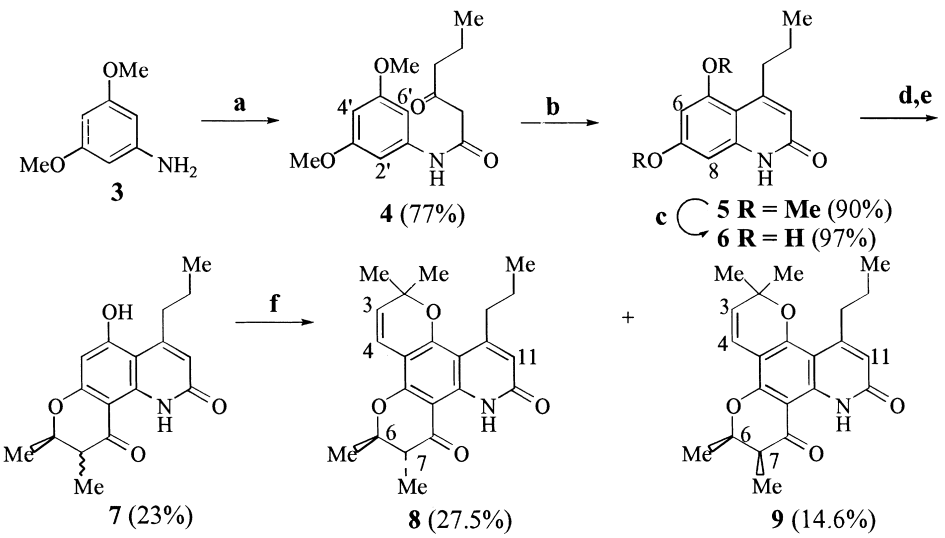
The next step was to build the dimethylchromanone ring (ring D) on the intermediate **6,** for which the Friedel–Crafts acylation with tigloyl chloride–$AlCl_3$ was sought. However, the issue of regioselectivity was our main concern, although literature[10] published during the synthesis of calanolide A clearly indicated that the acylation at C-8 was highly preferred. Accordingly, **6** was treated with tigloyl chloride and $AlCl_3$ in $CS_2$-nitrobenzene at 50°C followed by exposure of the crude reaction mixture to $Et_3N$

☆ IICT Communication 4421

*Keywords*: pyranocoumarin; calanolide; aza-calanolide; anti-HIV; quinolinone synthesis.

* Corresponding author. Fax: +91-40-717-3387;
e-mail: esmvee@iict.ap.nic.in

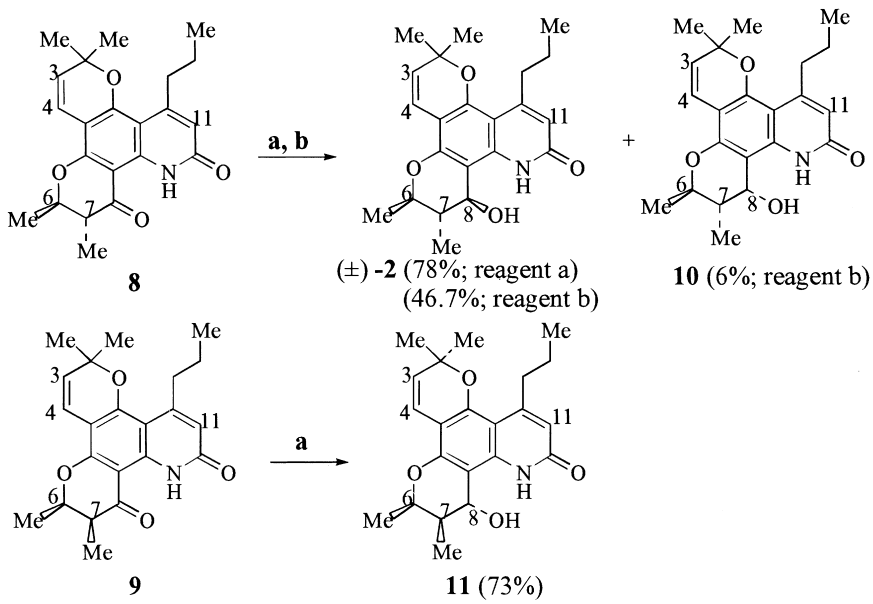
0040–4020/03/$ - see front matter 
PII: S0040-4020(02)01456-4



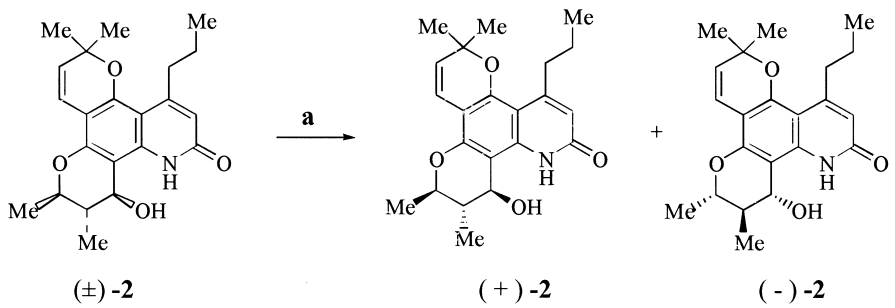

**Scheme 1.** *Reagents*: (a) 2,2-Dimethyl-6-*n*-propyl-4*H*-1,3-dioxin-4-one, xylene, 130°C, 3 h; (b) conc. $H_2SO_4$, rt, 1 h; (c) $AlCl_3$, $C_6H_5Cl$, 120°C, 16 h; (d) $CH_3CH{=}(Me)$ COCl, $AlCl_3$, $CS_2$, $C_6H_5NO_2$, 50°C, 48 h; (e) $Et_3N$, $CHCl_3$, rt, 16 h; (f) $\equiv C(Me)_2-Cl$, $K_2CO_3$, *n*-$Bu_4NI$, $ZnCl_2$, EtCOMe–DMF (9:1), 70°C, 16 h.

in $CHCl_3$ at room temperature and gave compound **7** in 23% yield as a *cis* and *trans* diastereomeric mixture in 1:2 ratio. The regioselectivity of the above acylation reaction was amply indicated by the $^1H$ NMR spectrum of the mixture in which the resonances due to H-8, as expected, were missing from the region of $\delta$ 6.5 while those of H-6 were present at $\delta$ 6.20.

The chromene segment (ring C) was fused on **7** by essentially adopting the procedure described by Dreyer et al.[10] Thus the reaction of **7** with 3-chloro-3-methyl-1-butyne in 2-butanone–DMF in the presence of $K_2CO_3$, *n*-$Bu_4NI$ and $ZnCl_2$ at 70°C afforded a mixture of *trans* and *cis* ketones (**8** and **9**) in 42% yield. The *trans*–*cis* mixture was separated by silica gel chromatography and analysed by $^1H$ NMR spectroscopy; particularly important were the coupling constants between H-5 and H-6 of ring D. In the $^1H$ NMR spectrum of the *trans*-ketone (**8**), the methyl groups in ring D resonated at separately at $\delta$ 1.22 (d, $J$=6.9 Hz) and 1.78 (multiplet) while H-6 appeared at $\delta$ 4.20–4.40 ($J_{5,6}$=11.1 Hz). For the *cis*-ketone (**9**), the resonances due to two methyl groups appeared at $\delta$ 1.22 and 1.50 as doublets ($J$=6.1 Hz each) while H-6 appeared at $\delta$ 4.60–4.75 ($J_{5,6}$=3.0 Hz). Individually both ketones **8** and **9** were reduced with $NaBH_4$ in EtOH to give **2** (78%) and **11** (73%), respectively. Whereas, the corresponding reduction of **8** with $NaBH_4$–$CeCl_3$ under Luche condition[11] at −30°C afforded a 8:1 mixture of (±)-aza-calanolide A (**2**) and (±)-aza-calanolide B (**10**) respectively which were separated by silica gel chromatography. In the $^1H$ NMR spectrum of compound **2**, the chemical shift of H-8 was localized at $\delta$ 4.59 and the observed $J$ value of 9.0 Hz clearly indicated the *trans* relationship with H-7. The protons H-3 and H-4 resonated as doublets at $\delta$ 5.49 and 6.63 ($J$=9.9 Hz). The




**Scheme 2.** *Reagents*: (a) $NaBH_4$, EtOH, 0°C to rt, 1 h; (b) $NaBH_4$ $CeCl_3$, EtOH, −30°C, 10 h.




**Scheme 3.** (a) Chiral HPLC.

minor isomer **10** showed in its $^1$H NMR spectrum a signal due to H-8 at $\delta$ 4.78 ($J_{7,8}$=3.1 Hz) indicating a *cis* relationship with H-7 (Scheme 2).

The optical resolution of racemic **2** (Scheme 3) was conveniently carried out by chiral HPLC (Chiracel (OD), 9:1 isopropanol–hexane, 1 mL/min) to afford (+)-aza-calanolide A (+)-**2** {$[\alpha]_D$=+50.7 (*c* 2.2, $CHCl_3$)} and (−)-aza-calanolide A (−)-**2** {$[\alpha]_D$=−48.4 (*c* 1.65, $CHCl_3$)}. The absolute stereochemistry was defined based on the correlation of their sign of rotation with those of natural calanolides.[3] The spectral data of (+)-**2** and (−)-**2** were in agreement with the structures assigned.

Compound (±)-**2** was evaluated[12,13] for anti-HIV reverse transcriptase activity using CEM-SS cell line at a maximum concentration of 100 μM. The assay basically involves the killing of T-4 lymphocytes by HIV. The $EC_{50}$ value of (±)-**2** (0.12 μM) is much lower than that of the natural product (+)-**1** (0.27 μM). Similarly, the $IC_{50}$ values for (±)-**2** and (+)-**1** are $IC_{50}$=15 and $IC_{50}$=23, respectively. The $EC_{50}$ and $IC_{50}$ values infer that (±)-**2** is active and cytotoxic at lesser concentrations when compared to (+)-**1**. Thus, the higher therapeutic index value observed for (±)-aza-calanolide (**2**) (TI=126) over naturally occurring (+) calanolide A **1** (TI=82) indicates that (+)-**2** could certainly be a better choice for further pre-clinical development.

In conclusion, a new class of synthetic NNRTI, e.g. aza-calanolide A (**2**), has been synthesized evaluated and optically resolved. Its enhanced anti-HIV activity compared to the natural product calanolide A has been demonstrated. The detailed synthetic work on other analogues of aza-calanolides and their anti-HIV activity will be dealt with separately.

## 1. Experimental

### 1.1. General

**1.1.1. 1*N*-(3,5-Dimethoxyphenyl)-3-oxo-hexanamide (4).** A solution of 3, 5-dimethoxy aniline (**3**; 14.15 g, 92.48 mmol) in xylene (50 mL) was heated at 130°C under nitrogen atmosphere and treated with 2,2-dimethyl-6-*n*-propyl-4*H*-1,3-dioxin-4-one (17.3 g, 101.7 mmol) dropwise for 25 min. After 6 h, the reaction mixture was cooled to 50°C and xylene removed under vacuum and the residue obtained was purified by column chromatography (silica gel hexane–EtOAc, 4:1) to give *1N-(3,5-dimethoxyphenyl)-3-oxo-hexanamide* **4** (18.87 g) in 77% yield as an oily liquid. $\nu_{max}$ (Neat) 3325, 2960, 2925, 1710, 1650 cm$^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 0.96 (t, 3H, *J*=6.2 Hz, $CH_2CH_3$), 1.55–1.75 (m, 2H, $CH_2CH_2$), 2.54 (t, 2H, *J*=6.2 Hz, $CH_2CH_2$), 3.50 (s, 2H, $COCH_2$), 3.80 (s, 6H, 2-$OCH_3$), 6.20 (s, 1H, *H-4′*), 6.75, 6.76 (2s, 2H, *H-2′* and *H-6′*); *m/z* (EI) 265 ($M^+$, 62), 203 (20), 186 (10), 179 (21), 153 (100%); HRMS: found 265.1315. $C_{14}H_{19}NO_4$ requires 265.1314.

**1.1.2. 1,2-Dihydro-5,7-dimethoxy-4-*n*-propyl-2-quinolinone (5).** Compound **4** (19 g, 71.69 mmol) was cooled to 0°C, Conc. $H_2SO_4$ (88.298 g, 901 mmol) added dropwise for 10 min and allowed to raise to room temperature over a period of 30 min. After completion of the reaction (TLC, hexane–EtOAc, 1:1, $R_f$=0.3) it was poured into water (200 mL) and the solid which separated was filtered, washed with water to a neutral pH and dried under vacuum to give product *1,2-dihydro-5,7-dimethoxy-4-n*-propyl-2-quinolinone **5** (15.93 g) in 90% yield as a white solid, mp 193–196°C; $\nu_{max}$ (Neat) 1670, 1625, 1605 cm$^{-1}$;$\delta_H$ (200 MHz, $CDCl_3$+DMSO-$d_6$) 1.00 (t, 3H, *J*=6.3 Hz, $CH_2CH_3$), 1.54–1.74 (m, 2H, $CH_2CH_2$), 2.90 (t, 2H, *J*=6.3 Hz, $CH_2CH_2$), 3.80 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 6.15 (s, 1H, *H-3*), 6.22 (s, 1H, *H-6*), 6.50 (s, 1H, *H-8*), 11.70 (br.s, 1H, *NH*); *m/z* (EI) 247 ($M^+$, 95), 230 (22), 219 (44), 204 (100%); HRMS: found 247. 1219. $C_{14}H_{17}NO_3$ requires 247. 1208.

**1.1.3. 8,9-Dimethyl-5-hydroxy-4-*n*-propyl-1,8,9,10-tetrahydro-2*H*-pyrano[2,3-*h*]quinolin-2,10-dione (7).** To a stirred solution of **5** (12 g, 48.58 mmol) in chlorobenzene (100 mL), was added aluminium chloride (25.8 g, 195.45 mmol) in portions over a period of 10 min. and heated at 100°C for 12 h (TLC, chloroform–methanol, 9:1, $R_f$=0.2). The reaction mixture was cooled to room temperature, poured on crushed ice (300 g) and stirred well for 30 min. The solid precipitate was filtered, washed with water to a neutral pH then washed with hexane (50 mL) and dried at 60°C for 1 h to give *1,2-dihydro-5,7-dihydroxy-4-n-propyl-2-quinolinone* ***6*** (10.32 g) in 97% yield as a dark brown solid, mp (300°C; $\nu_{max}$ (KBr): 3280, 3220, 3140, 1650 cm$^{-1}$.

A mixture of the above crude **6** (7.0 g, 31.96 mmol), $AlCl_3$ (21.60 g, 162 mmol) and $CS_2$ (140 mL) was taken in a 500 mL round bottom flask equipped with a mechanical stirrer and a reflux condenser. The reaction mixture was heated at 50°C for 30 min. Nitrobenzene (45 mL) was added dropwise in 30 min. and stirred for additional 30 min. to get a homogeneous mixture. Tigloyl chloride (4.621 g,

39 mmol) in nitrobenzene (20 mL) was added dropwise in 30 min and stirred at 50°C for 48 h. The reaction mixture was cooled to room temperature after completion of reaction (TLC, chloroform–MeOH, 9:1, $R_f$=0.4), poured on crushed ice (500 g) and stirred for 30 min. The solid separated was filtered and washed with water till neutral to pH. It was dried under vacuum to get the compound, which was used as such for next reaction.

A dispersion of the above crude solid in chloroform (150 mL) was treated with triethylamine (4.97 mL, 3.61 g, 35.7 mmol) and stirred at room temperature for 12 h. The reaction mixture was filtered and residue was extracted with hot chloroform (3×200 mL). Combined chloroform extracts were evaporated and the residue was purified by column chromatography (silica gel, chloroform–methanol, 9:1) to afford *8,9-dimethyl-5-hydroxy-4-n-propyl-1,8,9,10-tetrahydro-2H-pyrano[2,3-h]quinolin-2,10-dione* ***7*** (2.212 g) in 23% yield as a solid, mp 295–296°C; $\nu_{max}$ (Neat): 3425, 2958, 2920, 2860, 1595 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$+ DMSO-$d_6$) 1.00 (t, 3H, *J*=7.2 Hz, $CH_2CH_3$), 1.16–1.30 (m, 3H, $CHCH_3$), 1.44 (d, 1.2H, *J*=6.5 Hz, $CHCH_3$), 1.52 (d, 1.8H, *J*=6.7 Hz, $CHCH_3$), 1.60–1.68 (m, 2H, $CH_2CH_2$), 2.50–2.70 (m, 1H, *H-9*), 2.95 (t, 2H, *J*=6.3 Hz, $CH_2CH_2$), 4.20–4.38 (m, 0.6H, *J*=6.4 Hz, 11.4 Hz, *H-8*), 4.62–4.78 (m, 0.4H, *J*=3.4 Hz, 6.2 Hz, *H-8*), 6.12 (s, 1H, *H-3*), 6.20 (s, 1H, *H-6*), 11.32 (br. s, 1H, *OH*), 12.88 (br. s, 1H, *NH*); *m/z* (EI) 301 ($M^+$, 46), 286 (15), 273 (41), 245 (12), 217 (15%); HRMS: found 301.1317. $C_{17}H_{19}NO_4$ requires 301.1314.

**1.1.4. (±)-12-*n*-Propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2*H*,6*H*-dipyrano[2,3-*f*:2,3-*h*]quinoline-8,10-dione (8 *trans* and 9 *cis*).** To a solution of **7** (2.0 g, 6.64 mmol) in mixture of 2-butanone-DMF (35 mL, 9:1), 3-chloro-3-methyl-1-butyne (3.40 g, 33.2 mmol), $K_2CO_3$ (2.292 g, 16.6 mmol), *n*-$Bu_4N^+I^-$ (2.45 g, 6.63 mmol) and $ZnCl_2$ (1.128 g, 8.27 mmol) were added sequentially and heated at 70°C for 12 h (TLC, hexane–EtOAc, 7:3, $R_f$=0.4). It was cooled to room temperature, water (20 mL) added and 2-butanone was evaporated under reduced pressure. The residue was extracted with EtOAc (3×30 mL) and combined organic layers were washed with water (20 mL), dried ($Na_2SO_4$) and evaporated. The residue obtained was purified through column chromatography (silica gel, finer than 200 mesh, hexane–EtOAc, 4:1) first to afford *(±)-trans-12-n-propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2H,6H-dipyrano[2,3-f:2,3-h]quinoline-8,10-dione* ***8*** (0.67 g) in 27.5% yield as a white solid, mp 120–121°C; $\nu_{max}$ (KBr): 3180, 2986, 2963, 2892, 1690, 1664 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.04 (t, 3H, *J*=7.1 Hz, $CH_2CH_3$), 1.22 (d, 3H, *J*=6.9 Hz, $CHCH_3$), 1.54 (s, 3H, $CH_3$), 1.58 (s, 3H, $CH_3$), 1.69–1.78 (m, 5H, $CHCH_3$ and $CH_2CH_2$), 2.50–2.65 (m, 1H, *J*=6.9 Hz, 11.1 Hz, *H-7*), 2.91 (t, 2H, *J*=6.9 Hz, $CH_2CH_2$), 4.20–4.40 (dq, 1H, *J*=6.3, 11.1 Hz, *H-6*), 5.55 (d, 1H, *J*=10.1 Hz, *H-3*), 6.24 (s, 1H, *H-11*), 6.62 (d, 1H, *J*=10.1 Hz, *H-4*), 12.95 (br. s, 1H, *NH*); *m/z* (EI) 367 ($M^+$, 22), 352 (100), 296 (39%); HRMS: found: 367.1767. $C_{22}H_{25}NO_4$ requires 367.1783.

Second eluted was compound *(±)-cis-12-n-propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2H,6H-dipyrano-[2,3-f:2,3-h]quinoline-8,10-dione* ***9*** (0.356 g) in 14.6% yield as a syrupy liquid. $\delta_H$ (200 MHz, $CDCl_3$) 1.05 (t, 3H, *J*=7.3 Hz, $CH_2CH_3$), 1.22 (d, 3H, *J*=6.1 Hz, $CHCH_3$), 1.50 (d, 3H, *J*=6.1 Hz, $CHCH_3$), 1.60 (s, 3H, $CH_3$), 1.62 (s, 3H, $CH_3$), 1.63–1.69 (m, 2H, $CH_2CH_2$), 2.60–2.74 (m, 1H, *J*=3.4, 6.0 Hz, *H-7*), 2.95 (t, 2H, *J*=8.1 Hz, $CH_2CH_2$), 4.60–4.75 (m, 1H, *J*=3.0, 6.2 Hz, *H-6*), 5.55 (d, 1H, *J*=10.2 Hz, *H-3*), 6.28 (s, 1H, *H-11*), 6.64 (d, 1H, *J*=10.2 Hz, *H-4*), 12.9 (br. s, 1H, *NH*); *m/z* (EI) 367 ($M^+$, 22); HRMS: found: 367.1766. $C_{22}H_{25}NO_4$ requires 367.1783.

**1.1.5. (±)-8-Hydroxy-12-*n*-propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2*H*,6*H*-dipyrano[2,3-*f*:2,3-*h*] quinolin-10-one (2).** To a solution of compound **8** (0.15 g, 0.408 mmol) in ethanol (3 mL), cooled to 0°C, $NaBH_4$ (0.015 g, 0.408 mmol) was added and the reaction mixture allowed to raise to room temperature over a period of 1 h. After completion of reaction (TLC, hexane–EtOAc, 6:4, $R_f$=0.2)), water (2 mL) was added and extracted with EtOAc (3×5 mL). The combined organic layers were successively washed with water (4 mL), brine (4 mL), dried ($Na_2SO_4$) and evaporated. The residue was subjected to chromatographic purification (silica gel, hexane–EtOAc, 1:8) to afford product *(±)-8-hydroxy-12-n-propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2H,6H-dipyrano[2,3-f:2,3-h]quinolin-10-one* ***2*** (0.117 g) in 78% yield as a white solid, mp 164–166°C; $\nu_{max}$ (neat): 3250, 2988, 2945, 2875, 1660 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 1.0 (t, 3H, *J*=7.3 Hz, $CH_2CH_3$), 1.19 (d, 3H, *J*=6.6 Hz, $CHCH_3$), 1.45–1.52 (br. s, 9H, *J*=7.1 Hz, $3CH_3$), 1.50–1.70 (m, 2H, $CH_2CH_2$), 2.0–2.15 (m, 1H, *H-7*), 2.80–3.05 (m, 2H, $CH_2CH_2$), 3.88–4.04 (m, 1H, *J*=6.4, 11.2 Hz, *H-6*), 4.59 (d, 1H, *J*=9.0 Hz, *H-8*), 5.49 (d, 1H, *J*=9.9 Hz, *H-3*), 6.10 (s, 1H, *H-11*), 6.63 (d, 1H, *J*=9.9 Hz, *H-4*); *m/z* (EI) 352 ($M^+-OH$, 17), 351 ($M^+-H_2O$, 17), 336 (100), 284 (10%); HRMS: found: 369.1922. $C_{22}H_{27}NO_4$ requires 369.1940.

**1.1.6. (±)-8-Hydroxy-12-*n*-propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2*H*,6*H*-dipyrano [2,3-*f*:2,3-*h*] quinolin-10-one (2 and 10).** A solution of **8** (0.1 g, 0.272 mmol) and $CeCl_3{\cdot}7H_2O$ (0.202 g, 0.54 mmol) in ethanol (5 mL) was stirred at room temperature for 2 h. The reaction mixture was cooled to −30°C, $NaBH_4$ (0.01 g, 0.272 mmol) was added and stirred for 10 h (TLC, hexane–EtOAc, 3:2, $R_f$=0.2). The reaction mixture was allowed to rise to room temperature, quenched with water (3 mL) and extracted with ethyl acetate (3×5 mL). Combined organic layers were washed with brine (5 mL), dried ($Na_2SO_4$) and evaporated to get a gummy residue. The residue was purified by column chromatography (silica gel, finer than 200 mesh, hexane–EtOAc, 3:7) first to give **10** (0.006 g) in 6% yield, as a solid, m. p. 183–185°C; $\delta_H$ (200 MHz, $CDCl_3$) 1.02 (t, 3H, *J*=7.3 Hz, $CH_2CH_3$), 1.20 (d, 3H, *J*=6.5 Hz, $CHCH_3$), 1.35–1.59 (m, 9H, $3CH_3$), 1.60–1.78 (m, 3H, $CH_2CH_2$ and *H-7*), 2.90–3.08 (m, 2H, $CH_2CH_2$), 4.18–4.30 (m, 1H, *J*=10.5, 6.2 Hz, *H-6*), 4.78 (d, 1H, *J*=3.1 Hz, *H-8*), 5.49 (d, 1H, *J*=9.8 Hz, *H-3*), 6.18 (s, 1H, *H-11*), 6.64 (d, 1H, *J*=9.9 Hz, *H-4*), 11.55 (br. s, 1H, *NH*); HRMS: found: 369.1923. $C_{22}H_{27}NO_4$ requires 369.1940.

Second eluted was compound **2** (0.047 g) in 46.7% yield, which was identical in all respect with the material prepared in the earlier experiment.

**1.1.7. (±)-8-Hydroxy-12-*n*-propyl-7,8,9,10-tetrahydro-2,2,6,7-tetramethyl-2*H*,6*H*-dipyrano [2,3-*f*:2,3-*h*] quinolin-10-one (11).** Compound **9** (0.15 g, 0.408 mmol) in ethanol (3 mL) was treated with $NaBH_4$ (0.015 g, 0.408 mmol) for a period of 1 h. Worked up and purified as described for **2** to afford **11** (0.11 g) in 73% yield as a white solid, mp 185–188°C; $\delta_H$ (200 MHz, $CDCl_3$) 1.05 (t, 3H, $J$=7.2 Hz, $CH_2CH_3$), 1.12 (d, 3H, $J$=6.5 Hz, $CHCH_3$), 1.42 (d, 3H, $J$=6.5 Hz, $CHCH_3$), 1.46 (s, 3H, $CH_3$), 1.48 (s, 3H, $CH_3$), 1.64–1.68 (m, 2H, $CH_2CH_2$), 2.35–2.4 (m, 1H, *H-7*), 2.95–3.08 (m, 2H, $CH_2CH_2$), 4.30–4.42 (m, 1H, $J$=3.0, 6.1 Hz, *H-6*), 5.34 (d, 1H, $J$=7.6 Hz, *H-8*), 5.47 (d, 1H, $J$=10.0 Hz, *H-3*), 6.19 (s, 1H, *H-11*), 6.62 (d, 1H, $J$=10.0 Hz, *H-4*); HRMS: found: 369.1923. $C_{22}H_{27}NO_4$ requires 369.1940.

## Acknowledgements

Authors wish to thank DST, New Delhi and the Government of USA for the award of PL-480 scheme.

## References

1. Barre-Sinoussi, F.; Chermann, J. C.; Rey, F.; Chameret, M. T.; Guruest, J.; Dauguet, C.; Axler-Blin, C.; Veinet-Brun, F.; Rouzioux, C.; Rosenbaum, W.; Montaigner, L. *Science* **1983**, *220*, 868–871.
2. De Clerq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517.
3. (a) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, II., J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, Jr. R. W.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735–2743. (b) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Haltiwagner, R. C.; Bean, M. F.; Taylor, P. B.; Caranfa, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westley, J. W. *J. Med. Chem.* **1993**, *36*, 4131–4138. (c) Kling, J. *Modern Drug Discovery* **1999**, *2*(6), 31–36.
4. Zembower, D. E.; Liao, S.; Flavin, M. T.; Xu, Z. Q.; Stup, T. L.; Buckheit, Jr. R. W.; Khilevich, A.; Mar, A. A.; Sheinkman, A. K. *J. Med. Chem.* **1997**, *40*, 1005–1017.
5. Xu, Z. Q.; Buckheit, Jr. R. W.; Stup, T. L.; Flavin, M. T.; Liao, S.; Khilevich, A.; Rizzo, J. D.; Lin, L.; Zembower, D. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2179–2183.
6. Newman, R. A.; Chen, W.; Madden, T. L. *J. Pharm. Sci.* **1998**, *87*, 1077–1080.
7. Avendano, C. E de la Cuesta; Gesto, C. *Synthesis* **1991**, 727–730.
8. Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848–3856.
9. Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896–1901.
10. (a) Chenera, B.; West, M. L.; Finkelstein, J. A.; Dreyer, G. B. *J. Org. Chem.* **1993**, *58*, 5605–5606. (b) Pedersen, O. S.; Pedersen, E. B. *Synthesis* **2000**, 479–495.
11. Germal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *34*, 5454–5459.
12. Weislo, O. W.; Kiser, R.; Fine, D.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *J. Natl Cancer Inst.* **1989**, *81*, 586.
13. Gurjar, M. K.; Sharma, G. V. M.; Ilangovan, A.; Narayanan, V. L.; Indian Patent Application No. 1441/DEL/98; US Patent 6,191,279, 2001.