Med Chem Res (2008) 17:326–334
DOI 10.1007/s00044-007-9068-x

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Amino steroids as antimalarial agents

Upasana Sharma · Kumkum Srivastava · Sunil K. Puri · Chandan Singh

Received: 2 November 2007 / Accepted: 15 November 2007 / Published online: 29 December 2007

Abstract Using easily accessible deoxycholic acid as the starting material, amino compounds **8a-e** and **9a-c** were prepared and screened against *P. falciparum* in vitro. Amino steroid **8d** was the most active of the series with a minimum inhibiting concentration (MIC) of 0.5 μg/mL.

Keywords Malaria · Antimalarials · Sarachine · Deoxycholic acid · Amino steroids

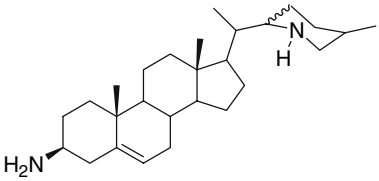
Introduction

Malaria continues to be a major parasitic disease in many parts of the world. Each year 300–500 million people suffer from malaria and about 2–2.5 million die from the disease (WHO, 1999; Wiesner *et al*., 2003). The disease is caused by *Plasmodium* sp., of which *P. falciparum* is the deadliest and is responsible for over 85% cases and much of the mortality due to malaria. Commonly used antimalarials such as chloroquine have become ineffective because of the development of resistance by the parasite against these drugs (Bloland, 2001; Wellems and Plowe, 2002). Thus there is an urgent need to develop new classes of antimalarials.

U. Sharma · C. Singh (✉)
Division of Medicinal & Process Chemistry, Central Drug Research Institute, Lucknow 226001, India
e-mail: chandancdri@yahoo.com

K. Srivastava · S. K. Puri
Division of Parasitology, Central Drug Research Institute, Lucknow 226001, India

Recently a new amino steroid, sarachine **1**, isolated from the leaves of *Saraca punctata*, has been reported to exhibit significant antimalarial activity (IC_{50} 0.01 μg/mL) against *P. falciparum* (Morreti *et al*., 1998).



1

Building on this lead and using deoxycholic acid as the starting material, we have synthesized several new amino steroids (prototypes **8** and **9**), some of which have shown significant antimalarial activity against *P. falciparum* in vitro.

Chemistry

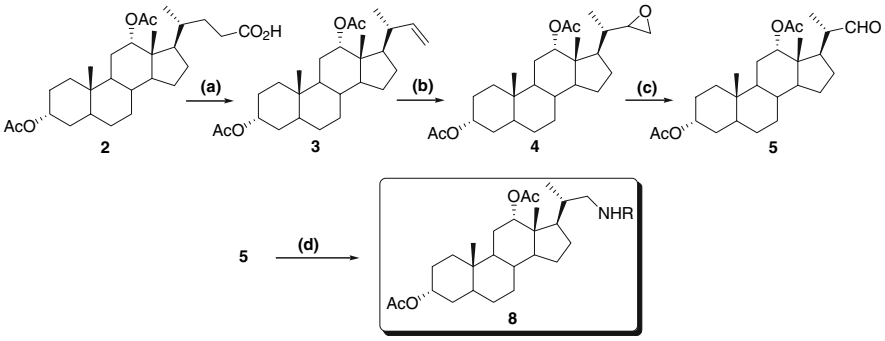
Oxidative decarboxylation of diacetyl deoxycholic acid **2** with $Pb(OAc)_4/Cu(OAc)_2$ furnished olefin **3** at 37% yield (Vaidya *et al*., 1968). Olefin **3** on treatment with *m*-Chloroperbenzoic acid (*m*-CPBA) furnished epoxide **4** at 64% yield. Reaction of **4** with periodic acid furnished aldehyde **5** at 68% yield. Reductive amination of **5** with benzyl amine **7a**, isopropyl amine **7b**, *n*-butyl amine **7c** furnished compounds **8a-c** at 50–73% yields (Abdel-Magid *et al*., 1996). A similar reaction of aldehyde **5** with 4−aminoquinolines **7d,e** furnished steroid-4-aminoquinoline hybrid compounds **8d** and **8e** at 18–51% yields. (Scheme 1). Reaction of diacetyl deoxycholic acid **2** with $Pb(OAc)_4/I_2$ furnished iodo compound **6** at 29% yield, which on reaction with amines **7a-c** furnished amino steroids **9a-c** at 41–57% yields (Oishi *et al*., 2004) (Scheme 2, Table 1, Fig. 1).

Antimalarial activity

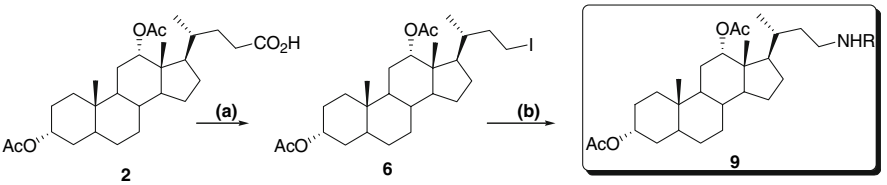
Amino compounds **8a-e** and **9a-c** and the 4-aminoquinolines **7d** and **7e** were evaluated against a chloroquine-sensitive strain of *P. falciparum* in vitro using minor modifications to the technique of Rieckmann and co-workers (Reickmann *et al*., 1978). Results are summarized in Table 2.

In vitro antimalarial efficacy

All the amino compounds **8a-e** and **9a-c** were evaluated in vitro against a chloroquine-sensitive strain of *P. falciparum* (NF-54). The asynchronous parasites obtained from cultures of *P. falciparum* were synchronized after 5% sorbitol treatment so as to contain only ring-stage parasites (Lambros and Vanderverg, 1979). Parasite suspension in medium RPMI 1640 at 1–2% parasitaemia and 3% hematocrit was dispensed

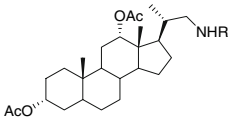
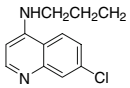
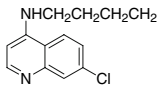
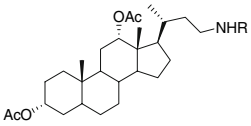


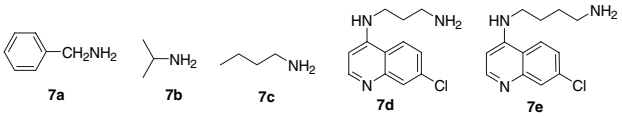
Scheme 1 Reagents and conditions: (a) $Pb(OAc)_4$, $Cu(OAc)_2$, C_5H_5N (Cat.), C_6H_6, reflux, 10 h. (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C-rt, 4.5 h. (c) $HIO_4.2H_2O$, THF, 0°C-rt, 4–5 h. (d) RNH_2 (**7a-e**), $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt, 3–10 h



Scheme 2 Reagents and conditions: (a) $Pb(OAc)_4$, I_2, CCl_4, reflux, 30 min. (b) RNH_2 (**7a-c**), K_2CO_3, CH_3CN, reflux, 0.5–1 h

Table 1 Yields of compounds **8a-e** and **9a-c**

general structure	Comp.	R	% yield
	**8a**		50%
	8b	$CH(CH_3)_2$	73%
	8c	$CH_2CH_2CH_2CH_3$	53%
	8d		51%
	8e		18%
	**9a**		41%
	9b	$CH(CH_3)_2$	57%
	9c	$CH_2CH_2CH_2CH_3$	44%



7a 7b 7c 7d 7e

Fig. 1 Structures of amines **7a-e**

into the wells of sterile 96-well plates. Test compounds were serially diluted in duplicate wells to obtain the final test concentration. Thin blood smears from each well prepared at the end of the incubation period were microscopically examined and the concentration that inhibited the maturation of rings into schizonts stage was recorded as the MIC. The assay was performed at concentrations of 50, 10, 2, 1, and 0.5 μg/mL and a few of them showed moderate activity.

Results and discussion

As seen from Table 2, the amino steroids **8a-e** were more active than **9a-c**. Compound **8d** with an MIC of 0.5 μg/mL was the most active compound of the series and was several times more active than the corresponding 4-aminoquinoline **7d** (MIC of 10 μg/mL). Compound **8e** with an MIC of 1 μg/mL was the next most active compound of the series and was twice as active as the corresponding 4-aminoquinoline **7e** (MIC of 2 μg/mL). Among the nonchloroquinoline amino derivatives **8a-c**, only **8a** shows significant activity (MIC of 2 μg/mL). The fact that quinoline-containing steroids **8d,e** are more active than other amino steroids **8a-c** suggests that the quinoline moiety might be contributing towards biological activity. All of the amino steroids **9a-c**, which have one carbon more in their side chain as compared with **8a-e,** exhibited very poor activity. Thus amino steroids having side chain similar to that of sarachine **1** show significant activity and increase in side chain length even by one carbon has a deleterious effect on antimalarial activity.

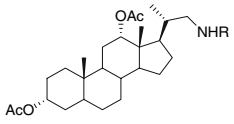
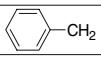
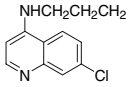
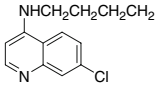
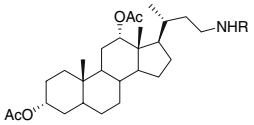
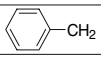
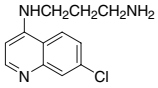
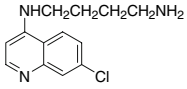
Conclusion

Using sarachine **1**, a naturally occurring amino steroid, as a lead and easily accessible deoxycholic acid as the starting material, we prepared a new series of amino steroids, some of which have shown significant antimalarial activity against *P. falciparum* in vitro. Compound **8d** with an MIC of 0.5 μg/mL was the most active compound of the series.

Experimental section

All glass apparatus were properly cleaned and oven dried prior to use. Yields refer to purified products and are not optimized. Infrared spectra (cm^{-1}) were recorded on a Perkin-Elmer RXI Fourier-transform (FT)-IR spectrophotometer. ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Supercon Magnet DPX-200/DRX-300 MHz using $CDCl_3$ as solvent and tetramethylsilane (δ 0.00

Table 2 In vitro antimalarial activity of compounds **8a-e**, **9a-c,** and **7d,e** against a chloroquine-sensitive strain of *P. falciparum* (NF-54)

general structure	Comp.	R	[a,b]MIC (g/mL)
	**8a**		2.0
	8b	$CH(CH_3)_2$	10.0
	8c	$CH_2CH_2CH_2CH_3$	>10.0
	8d		0.5
	8e		1.0
	**9a**		50.0
	9b	$CH(CH_3)_2$	>50.0
	9c	$CH_2CH_2CH_2CH_3$	>50.0
	**7d**	-	10.0
	**7e**	-	2.0
Chloroquine	-	-	0.04

[a] MIC is the minimum concentration inhibiting development of ring-stage parasites into the schizonts

[b] 50.00 μg/mL is the highest concentration used in this study

ppm) as an internal standard. Fast atom bombardment mass spectra (FAB-MS) were obtained on a JEOL SX-102 spectrometer using glycerol or *m*-nitrobenzyl alcohol as the matrix. Reactions were monitored on silica gel thin-layer chromatography (TLC) plates. Column chromatography was performed over silica gel (60–120 Mesh) procured from Qualigens (India) using freshly distilled solvents. All the chemicals and reagents were obtained from Aldrich (USA), Lancaster (England) or Spectrochem (India) and were used without purification.

4-(3,12-Diacetoxy-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoic acid (**2**)

Deoxycholic acid (5 g, 12.7 mmol) and acetic anhydride (6.5 g, 5 eq., 63.8 mmol) in dry dichloromethane (75 mL) were reacted in the presence of triethysilyl triflurom-ethanesulfonate (0.2 mL) at 0°C for 1 h. The reaction mixture was quenched with water

(50 mL) and extracted with dichloromethane (3 × 50 mL), dried over anhydrous Na_2SO_4, and concentrated, and the crude product was purified by column chromatography over silica gel to furnish compound **2** (5.5 g, 90.59% yield). IR (KBr, cm^{-1}) 3449, 1727; ^1H NMR (200 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.81 (d, 3H, $J = 5.9$ Hz), 0.91 (s, 3H), 1.21–1.85 (m, 24H), 2.03 (s, 3H), 2.10 (s, 3H), 2.20–2.41 (m, 2H), 4.61–4.80 (m, 1H), 5.08 (bs, 1H); FAB-MS (*m/z*): 477 $[M + H]^+$.

Acetic acid 3-acetoxy-10,13-dimethyl-17-(1-methyl-allyl)-hexadecahydro-cyclopenta [a]phenanthren-12-yl ester (**3**)

To a refluxing mixture of diacetyl deoxycholic acid **2** (4.5 g, 9.45 mmol), $Cu(OAc)_2$ (0.5 g, 0.25 eq.) and pyridine (0.3 g, 0.25 eq.) in benzene (50 mL) was added $Pb(OAc)_4$ (8.86 g, 2 eq.) over 3 h and the reaction mixture was stirred at the same temperature for 6 h. It was cooled to room temperature and filtered through celite, the residue was washed with benzene (75 mL), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and the crude product was purified by column chromatography over silica gel to furnish compound **3** (1.5 g, 37% yield). FT-IR (KBr, cm^{-1}) 1726; ^1H NMR (200 MHz, $CDCl_3$) δ 0.75 (s, 3H), 0.91 (s, 3H), 0.92 (d, 3H, $J = 6.3$ Hz), 1.08–1.85 (m, 22H), 2.03 (s, 3H), 2.11 (s, 3H), 4.61–4.78 (m, 1H), 4.79–4.94 (m, 1H), 5.08 (bs, 1H), 5.52–5.75 (m, 1H); FAB-MS (*m/z*): 431 $[M + H]^+$.

Acetic acid 3-acetoxy-10,13-dimethyl-17-(1-oxiranyl-ethyl)-hexadecahydro-cyclo-penta[a]phenanthren-12-yl ester (**4**)

Olefin **3** (1.5 g, 3.5 mmol) and $NaHCO_3$ (1.5 g, 5 eq.) in dry dichloromethane (50 mL) were stirred at 0°C and *m*-CPBA (1.5 g, 2.5 eq.) was added over 10 min. The resulting mixture was stirred for an additional 4 h at room temperature. The mixture was quenched with saturated Sodium bicarbonate ($NaHCO_3$) solution (40 mL), extracted with Dichloromethane (DCM) (3 × 25 mL), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography over silica gel to furnish compound **4** (1 g, 64% yield). FT-IR (KBr, cm^{-1}) 1724; ^1H NMR (200 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.85 (d, 3H, $J = 6.8$ Hz), 0.99 (s, 3H), 0.96–1.82 (m, 22H), 2.04 (s, 3H), 2.12 (s, 3H), 2.59–2.79 (m, 2H), 4.58–4.79 (m, 1H), 5.01 (bs, 1H); FAB-MS (*m/z*): 447 $[M + H]^+$.

Acetic acid 3-acetoxy-10,13-dimethyl-17-(1-methyl-2-oxo-ethyl)-hexadecahydro-cyclopenta[a]phenanthren-12-yl ester (**5**)

To a magnetically stirred, ice-cooled solution of **4** (1 g, 2.24 mmol) in Tetrahydrofuran (THF) (20 mL) was added a solution of periodic acid (0.5 g, 1 eq., 2.24 mmol) in THF (5 mL) dropwise over 5 min. The resulting mixture was stirred for an additional 4 h at room temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ solution (20 mL), water (50 mL) was added,

extracted with ether (4 × 25 mL), solvent was distilled off, and the crude product was purified by column chromatography over silica gel to furnish compound **5** (660 mg, 68% yield). IR (KBr, cm^{-1}) 1727; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 (s, 3H), 0.88 (s, 3H), 1.01 (d, 3H, $J = 6.8$ Hz), 1.26–1.85 (m, 21H), 2.04 (s, 3H), 2.12 (s, 3H), 2.18–2.31 (m, 1H), 4.07–4.09 (m, 1H), 5.06 (bs, 1H), 9.55 (d, 1H, $J = 2.9$ Hz), FAB-MS (*m/z*): 433 $[M + H]^+$.

Acetic acid 3-acetoxy-17-(3-iodo-1-methyl-propyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-12-yl ester (**6**)

A solution of diacetyl deoxycholic acid **2** (0.5 g, 1.1 mmol), $Pb(OAc)_4$ (0.6 g, 1.2 eq.) and iodine (0.66 g, 2.5 eq.) in CCl_4 (15 mL) was irradiated with a 500-W tungsten-halogen lamp for 30 min. The reaction mixture was quenched by adding saturated $Na_2S_2O_3$ solution and extracted with dichloromethane (3 × 25 mL), dried over Na_2SO_4, concentrated, and the crude product was purified by column chromatography over silica gel to furnish compound **6** (0.2 g, 29% yield). IR (KBr, cm^{-1}) 1727; ^1H NMR (200 MHz, $CDCl_3$) δ 0.75 (s, 3H), 0.81 (d, 3H, $J = 5.8$ Hz), 0.91 (s, 3H), 1.01–1.95 (m, 24H), 2.03 (s, 3H), 2.09 (s, 3H), 3.01–3.13 (m, 1H), 3.24–3.33 (m, 1H), 4.65–4.76 (m, 1H), 5.08 (bs, 1H); FAB-MS (*m/z*): 559 $[M + H]^+$, 497 $[M + H - AcOH]^+$, 439 $[M + H - 2\ AcOH]^+$.

General procedure for the preparation of compounds **8a–e** (preparation of **8d** as representative)

Aldehyde **5** (300 mg, 0.7 mmol), 4-aminoquinoline **7d** (330 mg, 1.4 mmol), and glacial acetic acid (0.1 mL) in CH_2Cl_2 (50 mL) were stirred at room temperature for 30 min. $NaBH(OAc)_3$ (330 mg, 1.03 mmol) was added portionwise for over 3 h and the reaction mixture was stirred for another 6 h. The reaction mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL), solvent was removed under reduced pressure, and the crude product was purified by column chromatography over silica gel to furnish compound **8d** (230 mg, 51% yield). mp 113–115°C. IR (KBr, cm^{-1}) 3399; ^1H NMR (200 MHz, $CDCl_3$) δ 0.72 (s, 3H), 0.91 (s, 3H), 0.99 (d, 3H, $J = 6.0$ Hz), 1.08–1.84 (m, 25H), 2.03 (s, 3H), 2.09 (s, 3H), 2.48 (t, 1H, $J = 8.0$ Hz), 2.81 (t, 1H, $J = 8.0$ Hz), 3.01 (bs, 2H), 3.46 (bs, 2H), 4.70 (m, 1H), 5.07 (bs, 1H), 5.96 (bs, 1H, NH), 6.27 (d, 1H, $J = 5.8$ Hz), 7.34 (dd, 1H, $J = 8.8$ and 1.4 Hz), 7.89 (d, 1H, $J = 1.4$ Hz), 8.11 (d, 1H, $J = 8.8$ Hz), 8.31 (d, 1H, $J = 5.8$ Hz); FAB-MS (*m/z*): 652 $[M + H]^+$, 592 $[M + H - AcOH]^+$, 532 $[M + H - 2\ AcOH]^+$.

Compounds **8a-c** and **8e** were prepared by the above procedure.

Acetic acid 12-acetoxy-10,13-dimethyl-17-(1-methyl-2-phenylamino-ethyl)-hexadecahydro-cyclopenta[a]phenanthren-3-yl ester (**8a**)

IR (KBr, cm^{-1}) 3433; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.73 (s, 3H), 0.89 (d, 3H, $J = 5.4$ Hz), 0.90 (s, 3H), 1.01–1.88 (m, 23H), 2.03 (s, 3H), 2.09 (s, 3H), 2.29 (dd,

1H, $J = 11.7$ and 8.4 Hz), 2.65 (dd, 1H, $J = 11.7$ and 3.0 Hz), 3.72 (d, 1H, $J = 13.2$ Hz), 3.81 (d, 1H, $J = 13.2$ Hz), 4.68 (m, 1H), 5.08 (bs, 1H), 7.24–7.33 (m, 5H); FAB-MS: (*m/z*): 524 $[M + H]^+$, 464 $[M + H - AcOH]^+$, 404 $[M + H - 2\ AcOH]^+$.

Acetic acid 12-acetoxy-17-(2-isopropylamino-1-methyl-ethyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-3-yl ester (**8b**)

IR (KBr, cm^{-1}) 3342; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.75 (s, 3H), 0.91 (s, 3H), 0.96 (d, 3H, $J = 5.4$ Hz), 1.18 (d, 6H, $J = 6.3$ Hz), 1.20–1.88 (m, 23H), 2.03 (s, 3H), 2.10 (s, 3H), 2.33 (dd, 1H, $J = 12.0$ and 9.0 Hz), 2.76 (bd, 1H, $J = 12.0$ Hz), 2.97 (septate, 1H, $J = 6.3$ Hz), 4.70 (m, 1H), 5.08 (bs, 1H), FAB-MS (*m/z*): 476 $[M + H]^+$, 416 $[M + H - AcOH]^+$, 356 $[M + H - 2\ AcOH]^+$.

Acetic acid 3-acetoxy-17-(2-butylamino-1-methyl-ethyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-12-yl ester (**8c**)

IR (KBr, cm^{-1}) 3342; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.79 (s, 3H), 0.91 (s, 3H), 0.99 (d, 3H, $J = 7.2$ Hz), 1.06–1.83 (m, 30H), 2.03 (s, 3H), 2.10 (s, 3H), 2.37 (t, 2H, $J = 10.0$ Hz), 2.80 (bd, 1H, $J = 11.4$ Hz), 3.02–3.09 (m, 1H), 4.70 (m, 1H), 5.07 (bs, 1H); FAB-MS (*m/z*): 490 $[M + H]^+$, 430 $[M + H - AcOH]^+$, 370 $[M + H - 2\ AcOH]^+$.

Acetic acid 3-acetoxy-17-{2-[4-(7-chloro-quinolin-4-ylamino)-butylamino]-1-methyl-ethyl}-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-12-yl ester (**8e**)

IR (KBr, cm^{-1}) 3279; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.78 (s, 3H), 0.90 (s, 3H), 0.99 (d, 3H, $J = 6.0$ Hz), 1.09–1.90 (m, 27H), 2.03 (s, 3H), 2.11 (s, 3H), 2.65–2.81 (m, 1H), 2.92–3.80 (m, 3H), 3.50 (bs, 2H), 4.67 (m, 1H), 5.01 (bs, 1H), 5.97 (bs, 1H, NH), 6.52 (d, 1H, $J = 5.6$ Hz), 7.10 (d, 1H, $J = 8.4$ Hz), 7.45 (bs, 1H), 8.12–8.17 (m, 2H); FAB-MS (*m/z*): 666 $[M + H]^+$, 606 $[M + H - AcOH]^+$, 546 $[M + H - 2\ AcOH]^+$.

General procedure for the preparation of compounds **9a–c** (preparation of **9a** as representative).

Compound **6** (50 mg, 0.09 mmol), benzyl amine **7a** (24 mg, 2.5 eq., 0.22 mmol) and K_2CO_3 (5.0 mg, 0.035 mmol) in CH_3CN (20 mL) were refluxed for 2 h. The reaction mixture was cooled to room temperature and solvent was removed under reduced pressure. Residue was taken in CH_2Cl_2 (50 mL) and washed with water (2×25 mL), dried and concentrated, and the crude product was purified by column chromatography over silica gel to furnish compound **9a** (20 mg, 41% yield). IR (KBr, cm^{-1}) 3471; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 3H), 0.80 (d, 3H, $J = 6.0$

Hz), 0.90 (s, 3H), 1.00–1.87 (m, 26H), 2.03 (s, 3H), 2.09 (s, 3H), 2.55–2.57 (m, 1H), 3.75 (d, 1H, $J = 13.5$ Hz), 3.76 (d, 1H, $J = 13.5$ Hz), 4.70–4.71 (m, 1H), 5.08 (bs, 1H), 7.24–7.41 (m, 5H); FAB-MS: (*m/z*) 538 $[M + H]^+$, 478 $[M + H - AcOH]^+$, 418 $[M + H - 2\ AcOH]^+$.

Compounds **9b** and **9c** were prepared by the above procedure.

Acetic acid 3-acetoxy-17-(3-benzylamino-1-methyl-propyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-12-yl ester (**9b**)

IR (KBr, cm^{-1}) 3420; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 3H), 0.84 (d, 3H, $J = 6.0$ Hz), 0.91 (s, 3H), 1.02–1.87 (m, 31H), 2.03 (s, 3H), 2.11 (s, 3H), 2.74–2.88 (m, 1H), 2.91–3.11 (m, 1H), 3.32–3.43 (m, 1H), 4.69 (m, 1H), 5.07 (bs, 1H), FAB-MS (*m/z*): 490 $[M + H]^+$, 430 $[M + H - AcOH]^+$, 370 $[M + H - 2\ AcOH]^+$.

Acetic acid 3-acetoxy-17-(3-butylamino-1-methyl-propyl)-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-12-yl ester (**9c**)

IR (KBr, cm^{-1}) 3358; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.73 (s, 3H), 0.83 (d, 3H, $J = 5.9$ Hz), 0.91 (s, 3H), 1.08–1.90 (m, 32H), 2.03 (s, 3H), 2.11 (s, 3H), 2.81–3.32 (m, 4H), 4.69 (m, 1H), 5.07 (bs, 1H); FAB-MS (*m/z*): 504 $[M + H]^+$.

Acknowledgment Upasana Sharma is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of a Senior Research Fellowship.

References

Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD (1996) Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. J Org Chem 61:3849–3862

Bloland BP (2001) Drug Resistance in Malaria, WHO, Geneva. Report no. WHO/CDS/CSR/DRS/2001.4

Lambros C, Vanderberg JP (1979) Synchronization of *Plasmodium falciparum* erythrocytic stages in culture. J Parasitol 65:418–420

Moretti C, Sauvain M, Lavaud C, Massiot G, Bravo JA, Munoz V (1998) A novel antiprotozoal aminosteroid from Saracha punctata. J Nat Prod 61:1390–1393

Oishi T, Tsuchikawa H, Murata M, Yoshida M, Morisawa M (2004) Synthesis and identification of an endogenous sperm activating and attracting factor isolated from eggs of the ascidian Ciona intestinalis, an example of nanomolar-level structure elucidation of novel natural compound. Tetrahedron 60:6971–6980

Ridley RG (2002) Medical need, scientific opportunity and the drive for antimalarial drugs. Nature 415:686–693

Rieckmann KH, Campbell GH, Sax LJ, Mrema JE (1978) Drug sensitivity of plasmodium falciparum. An in-vitro microtechnique. Lancet 1:22–23

Vaidya AS, Dixit SM, Rao AS (1968) Degradation of bile acid side chain with lead tetraacetate. Tet Lett 50:5173–5174

Wellems J, Plowe C (2001) Chloroquine-resistant malaria. J Infec Dis 184:770–776

Wiesner J, Ortmann R, Jomaa H, Schlitzer M (2003) New antimalarial drugs. Angew Chem Int Ed 42: 5274–5293

WHO (1999) Drug Information Bulletin 13:9