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Synthesis and antiplasmodial activity of lycorine derivatives

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ABSTRACT

Twenty seven lycorine derivatives were prepared and evaluated for their in vitro antimalarial activity against chloroquine-sensitive strains of *Plasmodium falciparum*. The best antiplasmodial activities were achieved with lycorine derivatives that present free hydroxyl groups at C-1 and C-2 or esterified as acetates or isobutyrates. The double bond C-2–C-3 is also important for the activity. Concerning to the antiplasmodial activity of the secolycorines, the higher values were obtained with the replacement of the methylenedioxy moiety by hydroxyl or acetate groups and with methyl substituent attached to the nitrogen atom.

1. Introduction

Half of the world's population is at risk of malaria, and an estimated 243 million cases led to nearly 863,000 deaths in 2008.[1] The World Health organization (WHO) estimates that 3 billion people live in areas where malaria transmission occurs. Indeed, it is endemic in 109 countries and territories in tropical and subtropical regions, particularly in sub-Saharan Africa.[1] *Plasmodium falciparum* is responsible for the most severe form of the disease, and resistant strains have emerged to many currently used antimalarial agents.[2]

Historically, natural products have played a major role in the treatment of this infectious disease.[3] For centuries, the indigenous people from South America have used the bark from the 'fever tree', *Cinchona succirubra*, for the treatment of malaria.[3] The Chinese medicinal plant, *Artemisia annua*, has likewise been used as an antimalarial herbal remedy for hundreds of years.[3] Chemical investigations of *C. succirubra* and *A. annua*, identified the major active metabolites to be quinine and artemisinin, respectively.[3c] This research has subsequently led to the development of numerous antimalarial drugs based on these two important plant natural products.[3c] Unfortunately, resistance of the malarial parasite to current small molecule therapies and subsequent lack of efficacy makes necessary the development of new antimalarial agents that are structurally different from the existing drugs.[4]

Plants belonging to the Amaryllidaceae family are known by producing an exclusive group of alkaloids, named 'Amaryllidaceae alkaloids', isolated from plants of all genera of this family. Since the isolation of lycorine (**1**) from *Narcissus pseudonarcissus* in 1877, over 300 alkaloids have been isolated from plants of this family,[5] including the recently isolated from *Pancratium canariense*.[6] Amaryllidaceae alkaloids exhibit a wide range of biological activities including cytotoxic,[7] antiviral,[8] antitumour,[9] anticholinergic[10] and anti-inflammatory.[11] For example, galanthamine is used in the treatment of Alzheimer's disease.[12] Some of these alkaloids are of particular interest because of their potential antiprotozoal activity.[13] Thus, lycorine (**1**), augustine and crinamine were found to be the principal antimalarial constituents in *Crinum amabile* bulbs.[14] Several lycorine type-alkaloids were examined for their inhibitory activity against *Trypanosoma brucei* and *P. falciparum*. Among them, 2-*O*-acetyllycorine showed the most potent activity against parasitic *T. brucei*, and 1-*O*-(3*R*)-hydroxybutanoyllycorine, 1,2-di-*O*-butanoyllycorine, and 1-*O*-propanoyllycorine showed significant activity against *P. falciparum*.[15] The antiplasmodial activity of other Amaryllidaceae type-alkaloids have been summarized in a recent review on alkaloids with antiprotozoal activity.[12] Structure–antiplasmodial activity relationships have not been studied in Amaryllidaceae alkaloids. Some results suggest that the methylenedioxy group and a tertiary non-methylated nitrogen contribute to a higher activity in these alkaloids.[16] Additional investigation is required to specify the necessary structural requirements for antiparasitic activity, and, in particular, the possible mode of action.

With these antecedents, in the present study we report the preparation of 27 lycorine derivatives, their inhibitory activity against *P. falciparum* and some preliminary conclusions about structure–activity relationships.

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2. Results and discussion

2.1. Chemistry

Lycorine (**1**) was obtained as the main alkaloid from the bulbs of *P. canariense*.[6] Due to its low solubility in most solvents, many derivatives were obtained from lycorine diacetate **2**, as it is shown in Scheme 1.

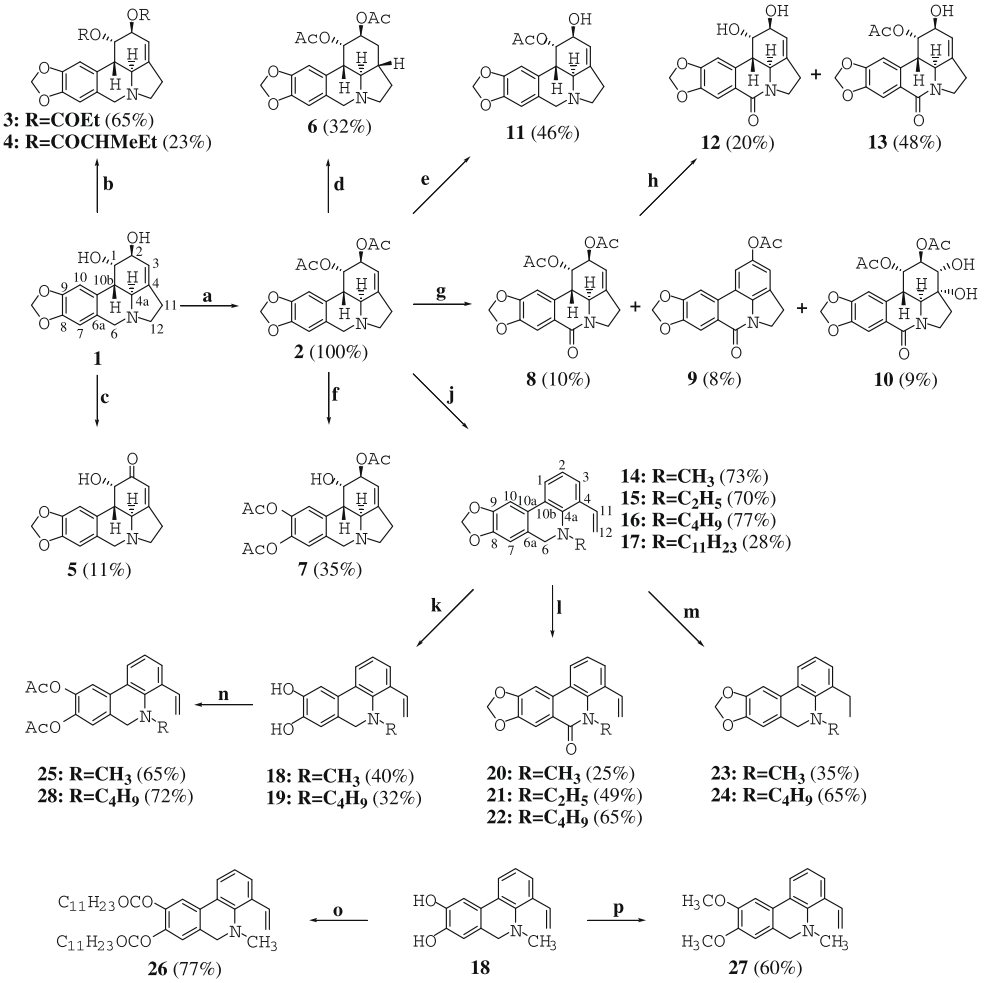
Compounds **2**–**4** were obtained by acylation of lycorine with anhydrides of different sizes, in the presence of pyridine. Treatment of **1** with the Jones reagent yielded the α,β-unsaturated ketone **5**. Compound **6** was obtained by hydrogenation of the double bond of **2** in the presence of 10% Pd/C.[17] Reaction of **2** with BBr_3 followed by acetylation led to compound **7** which does not have the methylenedioxy group and the acetyl group at C-11. Derivatives **8–10** present the ring B as a lactam and they were obtained in low yield by oxidation of **2** with potassium permanganate.[18] Compound **9** showed also the ring C aromatized, while **10** possess a *cis*-diol instead of the double bond. When iodosylbenzene was used as oxidizer,[19] only the lactam **9** was formed quantitatively. Compound **2** was heated with diluted HCl to afford selectively the monoacetylated derivative **11**.[20] Two compounds, the deacetylated **12** and the monoacetylated **13**, were obtained when **8** was treated with HCl under the same conditions followed for **2**.

When **2** was reacted with different alkyl halides followed by treatment with *t*-BuOK/*t*-BuOH the corresponding secolycorines **14–17** were formed by Hofmann elimination.[21] In order to generate diversity on the structure of the secolycorines formed (**14**–**17**), some modifications were achieved. First, the methylenedioxy group was removed with BBr_3 and the corresponding compounds **18** and **19** were formed. Secolycorines **14**, **15**, and **16** were converted into the corresponding lactams **20**, **21**, and **22** when treated with 3 equiv of iodosylbenzene. Hydrogenation of the double bond of **14** and **16** yielded derivatives **23** and **24**, respectively. The catechol group on the structure of **18** and **19** was also modified. Thus, acetylation, acylation with undecyl chloride and methoxylation employing trimethylsilyldiazomethane were performed on **23**, yielding the corresponding derivatives **25**, **26**, and **27**, respectively. Acetylation of **19** was also performed yielding compound **28**.

2.2. Biological assay and SAR

Results of the antiplasmodial evaluation are summarized in Table 1. Lycorine (**1**) resulted be the most active alkaloid, with an IC_{50} value of 0.13 μM. Compounds **2**, **4**, **11**, **25**, and **28** showed also important antiplasmodial activity, with IC_{50} values less than 1 μM.

From the obtained results we can establish some structure–activity relationships. The presence of the hydroxyl groups at C-1 and C-2 in the lycorine skeleton seems important for the activity. For example, acylation of the hydroxyl groups of lycorine **1** produced a decrease in the activity (i.e., **1** vs **2**, **1** vs **3**, **1** vs **4**).



Scheme 1. Reagents and conditions: (a) Ac_2O, py; (b) R_2O, py; (c) Jones reagent, acetone; (d) H_2, 10% Pd/C, THF; (e) 10% HCl, 50 °C, 30 min; (f) (1) BBr_3, DCM, 0 °C; (2) Ac_2O, py; (g) $KMnO_4$, acetone, 1 h; (h) 10% HCl, 50 °C, 30 min; (i) (1) RX, CH_3CN, 24 h; (2) *t*-BuOK/*t*-BuOH, reflux, 4 h; (j) BBr_3, DCM, 0 °C; (k) PhIO, NBu_4I, CH_3CN/H_2O 9:1; (l) H_2, 10% Pd/C, THF; (m) Ac_2O, py; (n) $C_{11}H_{23}COCl$, NEt_3, DCM; (o) Me_3SiCHN_2, DCM/MeOH 1:1.

Table 1
In vitro activity against *Plasmodium falciparum* F32

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1	0.13	**15**	86.0
2	0.26	**16**	9.7
3	2.7	**17**	7.4
4	0.6	**18**	1.1
5	14.7	**19**	>100
6	34.8	**20**	>100
7	8.4	**21**	>100
8	>100	**22**	>100
9	9.2	**23**	>100
10	>100	**24**	7.4
11	0.9	**25**	0.9
12	No tested	**26**	47.0
13	>100	**27**	12.4
14	11.3	**28**	0.8
Chloroquine	0.04		

The oxidation of the hydroxyl group at C-2 also led to a less active compound (**5**). Comparison of the activity of compounds **2** and **6** indicated that the presence of the double bond C-3–C-4 plays an important role for the activity. In addition, oxidation of the carbon C-6 to the corresponding lactam led to inactive compounds (i.e., **2** vs **8**, **1** vs **12**, **11** vs **13**). Compound **9** having the D ring aromatized and a lactam moiety presented an IC_{50} = 9.2 μM. With respect to the secolycorine series (**14–28**), the most potent compounds were compounds **16**, **17**, **18**, **24**, **25**, and **28**. The role of the alkyl group attached to the nitrogen is not too clear. When we compared the antiplasmodial activity of compounds **14–17**, we obtain similar values of activity except for compound **15** with a *N*-ethyl group which was inactive. In the case of compound **18** (R = Me) and **19** (R = C_4H_9) which present a catechol moiety, **19** was inactive while **18** showed good activity. Compound **25** (R = Me) and **28** (R = C_4H_9) with two acetates showed the same good activity. As it happened with the lycorine series, the oxidation at C-6 yielded inactive compounds (**20–22**). When compound **14** (R = Me) was hydrogenated the inactive derivative **23** was obtained, while in the case of **16** (R = Bu) the corresponding hydrogenated derivative (**24**) showed similar activity. We also analyzed the replacement of the methylenedioxy moiety at the aromatic ring A by other groups. Thus, the best activity was achieved with the hydroxyl groups (i.e., **18** vs **14**), the presence of two acetyl groups or two methoxy groups led to similar activity (i.e., **25** vs **14**, **27** vs **14**), while the replacement by two lauroyl groups produced a drastic loss of activity (i.e., **18** vs **26**).

In conclusion, we have prepared several lycorines and secolycorine derivatives. The best antiplasmodial activities were achieved with lycorine derivatives that present free hydroxyl groups at C-1 and C-2 or esterified as acetates or isobutyrates. The double bond C-2–C-3 is also important for the activity. Concerning to the antiplasmodial activity of the secolycorines, the higher values were obtained with the replacement of the methylenedioxy moiety by hydroxyl or acetate groups and with methyl substituent attached to the nitrogen atom.

Our results represent a starting point for the preparation of a new series of lycorine and secolycorine derivatives with the aim of improving the antiplasmodial activity.

3. Experimental

3.1. General

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F. Purification of Laboratory Chemicals, third edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. Reactions were monitored by TLC (on silica gel POLYGRAM SIL G/UV $_{254}$ foils). IR spectra were obtained using a Bruker IFS28/55 spectrophotometer. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or MeOD at 300 and 75 MHz respectively using a Bruker AMX300. 2D NMR experiments were conducted on a Bruker AVANCE 400 NMR spectrometer. MS and HRMS were obtained on a VG Autospec spectrometer. Analtech Silica Gel GF preparative layer with UV254 was used for preparative-TLC purification. Silica gel (0.2–0.63 mm) was employed for column chromatography. Silica gel 60 (Merck) was used on a Harrison Research 7924T Chromatotron.

Lycorine **1** was isolated from the bulbs of *P. canariense* as described in Ref. 6.

3.2. General procedure for acylation of 1

Lycorine **1** (20–30 mg) was dissolved in 1 mL of pyridine and an excess of the corresponding anhydride was added. After stirring at rt for 16 h the solvent was removed under reduced pressure and the residue was purified by preparative-TLC using DCM/MeOH 9:1, to yield the corresponding esters **2–4**.

3.2.1. 1,2-Diacetyllycorine (2)

Following the procedure described above, 30 mg (0.105 mmol) of **1** was treated with 0.3 mL (3.18 mmol) of acetic anhydride. After purification, 39 mg of **2** (100%) were obtained as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ: 6.73 (1H, s, H-10), 6.56 (1H, s, H-7), 5.89 (2H, br s, OCH_2O), 5.71 (1H, s, H-1), 5.51 (1H, s, H-3), 5.23 (1H, s, H-2), 4.14 (1H, d, J = 14.1 Hz, H-6), 3.51 (1H, d, J = 14.1 Hz, H-6), 3.35 (1H, dd, J = 4.1 Hz, J = 8.4 Hz, H-12), 2.86 (1H, d, J = 10.1 Hz, H-10b), 2.75 (1H, d, J = 10.2 Hz, H-4a), 2.62 (2H, br s, H-11), 2.39 (1H, dd, J = 8.6 Hz, J = 17.4 Hz, H-12), 2.05 (3H, s, $OCOCH_3$), 1.93 (3H, s, $OCOCH_3$) ppm. ^{13}C NMR ($CDCl_3$) δ: 169.7 (s, $OCOCH_3$), 169.5 (s, $OCOCH_3$), 146.1 (s, C-8), 146.0 (s, C-9), 145.8 (s, C-4), 129.1 (s, C-6a), 126.3 (s, C-10a), 113.5 (d, C-3), 107.0 (d, C-7), 104.8 (d, C-10), 100.7 (t, OCH_2O), 70.6 (d, C-2), 68.9 (d, C-1), 60.9 (d, C-4a), 56.6 (t, C-6), 53.3 (t, C-12), 40.2 (d, C-10b), 28.4 (t, C-11), 20.9 (q, $OCOCH_3$), 20.7 (q, $OCOCH_3$). EIMS m/z (%): 371 ([M]$^+$, 17); 311 (16); 268 (13); 252 (100); 238 (4); 226 (31); 222 (9); 192 (4). HREIMS m/z 371.1383 (calcd for $C_{20}H_{21}NO_6$ [M]$^+$ 371.1369). IR (neat) ν_{max} 2925, 1734, 1645, 1485, 1370, 1316, 1234, 1132, 1035, 965, 900, 736 cm^{-1}. $[\alpha]_D^{20}$ = +3.9 (c 0.1, MeOH).

3.2.2. 1,2-Dipropionyllycorine (3)

Following the procedure described above, 20 mg (0.7 mmol) of **1** was reacted with 0.5 mL (3.9 mmol) of propionic anhydride to yield after purification, 17.8 mg of **3** (65%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ: 6.73 (1H, s, H-10), 6.56 (1H, s, H-7), 5.90 (2H, br s, OCH_2O), 5.73 (1H, s, H-1), 5.52 (1H, s, H-3), 5.24 (1H, s, H-2), 4.15 (1H, d, J = 14.1 Hz, H-6), 3.52 (1H, d, J = 14.1 Hz, H-6), 3.36 (1H, ddd, J = 4.7 Hz, J = 9.0 Hz, J = 9.0 Hz, H-12), 2.88 (1H, d, J = 10.2 Hz, H-10b), 2.78 (1H, J = 10.4 Hz, H-4a), 2.63 (2H, br s, H-11), 2.41 (1H, m, H-12), 2.33 (2H, q, J = 7.5 Hz, CH_2CH_3), 2.19 (2H, q, J = 7.5 Hz, CH_2CH_3), 1.14 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.00 (3H, t, J = 7.5 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ: 173.2 (s, C=O), 172.9 (s, C=O), 146.1 (s, C-8), 146.0 (s, C-9), 145.6 (s, C-4), 129.0 (s, C-6a), 126.4 (s, C-10a), 113.7 (d, C-3), 107.0 (d, C-7), 104.8 (d, C-10), 100.7 (t, OCH_2O), 70.5 (d, C-2), 68.8 (d, C-1), 61.0 (d, C-4a), 56.6 (t, C-6), 53.4 (t, C-12), 40.3 (d, C-10b), 28.4 (t, C-11), 27.3 (t, CH_2CH_3), 27.2 (t, CH_2CH_3), 8.7 (q, CH_2CH_3), 8.7 (q, CH_2CH_3). EIMS m/z (%): 399 (M$^+$, 7); 325 (13); 268 (11); 252 (100); 226 (19); 194 (5). HREIMS m/z 399.1704 (calcd for $C_{22}H_{25}NO_6$ [M]$^+$ 399.1682). IR (neat) ν_{max} 2980, 2939, 1740, 1621, 1485, 1349, 1318, 1265, 1236, 1176, 1079, 1037, 936, 855, 807, 736 cm^{-1}. $[\alpha]_D^{20}$ = +111.2 (c 0.16, MeOH).

3.2.3. 1,2-Bis(2-methylbutyryl)lycorine (4)

Following the procedure described above, 20 mg (0.7 mmol) of **1** was treated with 0.5 mL (2.51 mmol) of (+)-(*R*)-2-metylbutyric anhydride. After purification, 7.1 mg of **4** (23%) was obtained as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ 6.73 (1H, s, H-10), 6.57 (1H, s, H-7), 5.90 (2H, br s, OCH_2O), 5.72 (1H, s, H-1), 5.52 (1H, s, H-3), 5.23 (1H, s, H-2), 4.15 (1H, d, *J* = 14.1 Hz, H-6), 3.53 (1H, d, *J* = 13.9 Hz, H-6), 3.38 (1H, br s, H-12), 2.89 (1H, d, *J* = 10.3 Hz, H-10b), 2.81 (1H, br s, H-4a), 2.65 (2H, br s, H-11), 2.39 (2H, m, H-12, C*H*MeCH$_2$CH$_3$), 2.23 (1H, m, C*H*MeCH$_2$CH$_3$), 1.69 (2H, m, CHMeC*H*$_2$CH$_3$), 1.56 (2H, m, CHMeC*H*$_2$CH$_3$), 1.14 (3H, d, *J* = 6.9 Hz, CH*Me*CH$_2$CH$_3$), 0.96 (3H, d, *J* = 6.9 Hz, CH*Me*CH$_2$CH$_3$), 0.92 (3H, t, *J* = 7.4 Hz, CHMeCH$_2$C*H*$_3$), 0.75 (3H, t, *J* = 7.4 Hz, CHMeCH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 175.2 (s, C=O), 175.1 (s, C=O), 146.1 (s, C-8), 145.9 (s, C-9), 145.5 (s, C-4), 129.1 (s, C-6a), 126.4 (s, C-10a), 113.7 (d, C-3), 107.0 (d, C-7), 105.0 (d, C-10), 100.6 (t, OCH_2O), 70.4 (d, C-2), 68.6 (d, C-1), 61.2 (d, C-4a), 56.6 (t, C-6), 53.4 (t, C-12), 40.7 (d, *C*HMeCH$_2$CH$_3$), 40.7 (d, *C*HMeCH$_2$CH$_3$), 28.4 (t, C-11), 26.5 (t, CHMe*C*H$_2$CH$_3$), 26.3 (t, CHMe*C*H$_2$CH$_3$), 16.3 (q, CHMeCH$_2$*C*H$_3$), 16.2 (q, CHMeCH$_2$*C*H$_3$), 11.3 (q, CH*Me*CH$_2$CH$_3$), 11.1 (q, CH*Me*CH$_2$CH$_3$). EIMS *m/z* (%): 455 (M^+, 5); 353 (9); 268 (10); 252 (100); 226 (9); 194 (3). HREIMS *m/z* 455.2293 (calcd for $C_{26}H_{33}NO_6$ $[M]^+$ 455.2308). $[\alpha]_D^{20}$ = +11.9 (*c* 0.32, MeOH). IR (neat) ν_{max} 2968, 2928, 1736, 1650, 1544, 1462, 1368, 1263, 1178, 1139, 1036, 738 cm^{-1}.

3.2.4. 2-Oxolycorine (5)

To a solution of 50 mg (0.17 mmol) of **1** in acetone (2 mL) at 0 °C, was added the Jones reagent dropwise, until the solution turned orange. The reaction was stirred for 30 min and then was filtered through Florisil. The residue was concentrated and purified by preparative-TLC using DCM/MeOH (9:1) to yield 5 mg of **5** (11%) as an amorphous yellow solid. ^{1}H NMR ($CDCl_3$) δ: 6.77 (1H, s, H-10), 6.59 (1H, s, H-7), 5.96 (2H, br s, OCH_2O), 5.93 (1H, d, *J* = 1.2 Hz, H-3), 4.55 (1H, d, *J* = 3 Hz, H-1), 4.16 (1H, d, *J* = 14.1 Hz, H-6), 3.60 (1H, d, *J* = 14.4 Hz; H-6), 3.45 (1H, m, H-12), 3.24 (1H, d, *J* = 9.6 Hz, H-10b), 3.12 (1H, d, *J* = 9.8 Hz, H-4a), 2.85 (2H, m, H-11), 2.52 (1H, dd, *J* = 8.6 Hz, *J* = 17.2 Hz, H-12). ^{13}C NMR ($CDCl_3$) δ: 197.1 (s, C-2), 147.8 (s, C-8), 147.7 (s, C-9), 146.4 (s, C-4), 128.9 (s, C-6a), 125.6 (s, C-10a), 119.4 (d, C-3), 107.3 (d, C-7), 104.7 (d, C-10), 100.8 (t, OCH_2O), 70.0 (d, C-1), 61.5 (d, C-4a), 56.1 (t, C-6), 53.1 (t, C-12), 45.6 (d, C-10b), 29.4 (t, C-11). EIMS *m/z* (%):285 (M^+, 18); 266 (100); 240 (8); 226 (16); 208 (4); 180 (3). HREIMS *m/z* 285.0999 (calcd for $C_{16}H_{15}NO_4$ $[M]^+$ 285.1001). IR (neat) ν_{max} 2920, 2851, 1661, 1469, 1360, 1318, 1232, 1146, 1071, 1030, 925, 895, 845, 796, 733 cm^{-1}. $[\alpha]_D^{20}$ = −20.5 (*c* 0.4, MeOH).

3.2.5. 1,2-Diacetyl-3,4*S*-dihydrolycorine (6)

24 mg (0.065 mmol) of compound **2** dissolved in 3 mL of dry THF were hydrogenated in the presence of catalytic amounts of Pd/C (10%). The reaction mixture was left at room temperature for 24 h until disappearance of the starting material. Then the mixture was filtered through Celite and the solvent was evaporated. After purification by preparative-TLC using DCM/MeOH (9:1), 7.7 mg of **6** (32%) was obtained as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ: 6.64 (1H, s, H-10), 6.57 (1H, s, H-7), 5.90 (2H, br s, OCH_2O), 5.67 (1H, s, H-1), 4.93 (1H, m, H-2), 4.00 (1H, d, *J* = 14,6 Hz, H-6), 3.82 (1H, d, *J* = 14.6 Hz, H-6), 3.07 (2H, m, H-12), 2.68 (2H, m, H-4a, H-10b), 2.38 (1H, dd, *J* = 8.9 Hz, *J* = 14.6 Hz, H-4), 2.14 (2H, m, H-11), 2.10 (3H, s, $OCOCH_3$), 1.96 (3H, s, $OCOCH_3$), 1.66 (2H, m, H-3). ^{13}C NMR ($CDCl_3$) δ: 170.0 (s, O*C*OCH$_3$), 169.6 (s, O*C*OCH$_3$), 146.2 (s, C-8), 145.9 (s, C-9), 131.8 (s, C-6a), 127.9 (s, C-10a), 106.9 (d, C-7), 104.8 (d, C-10), 100.6 (t, OCH_2O), 74.1 (d, C-2), 70.7 (d, C-1), 59.2 (d, C-4a), 54.7 (t, C-6), 53.2 (t, C-12), 37.1 (d, C-4), 32.7 (d, C-10b), 30.7 (t, C-11), 29.4 (t, C-3), 20.9 (q, OCO*C*H$_3$), 20.7 (q, OCO*C*H$_3$). EIMS *m/z* (%):373 (M^+, 92); 314 (27); 254 (100); 226 (5); 212 (6); 187 (4). HREIMS *m/z* 373.1511 (calcd for $C_{20}H_{23}NO_6$ $[M]^+$ 373.1525). IR (neat) ν_{max} 2923, 1738, 1649, 1485, 1372, 1244, 1118, 1035, 934, 855, 735, 605 cm^{-1}. $[\alpha]_D^{20}$ = −66.9 (*c* 0.16, MeOH).

3.2.6. 8,9-Nor-2,8,9-triacetyllycorine (7)

A solution of 20 mg (0.054 mmol) of **2** in 2 mL of DCM at 0 °C was treated with 0.11 mL (2 equiv) of a solution 2 M BBr_3 in DCM. The reaction mixture was stirred for 4 h until disappearance of the starting material. Then it was treated with 2 mL of MeOH and the solvent removed. The residue was dissolved in 1 mL of pyridine and reacted with 0.3 mL (3.18 mmol) of acetic anhydride for 24 h. After evaporation of the solvent and purification by preparative-TLC using DCM/MeOH (19:1), 7.6 mg of **7** (35%) were obtained as an pale yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ: 7.04 (1H, s, H-10), 6.96 (1H, s, H-7), 6.02 (1H, d, *J* = 4.7 Hz, H-3), 5.50 (1H, s, H-2), 4.70 (1H, s, H-1), 4.19 (1H, br d, *J* = 14.0 Hz, H-6), 3.66 (2H, m, H-6, H-12), 3.02 (2H, br s, H-4a, H-10b), 2.66 (3H, br s, H-11, H-12), 2.22 (6H, s, $OCOCH_3$), 2.03 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 171.7 (s, $OCOCH_3$), 168.1 (s, O*C*OCH$_3$), 168.1 (s, O*C*OCH$_3$), 143.7 (s, C-8), 141.9 (s, C-9), 140.5 (s, C-4), 131.8 (s, C-6a), 122.0 (s, C-10a), 119.4 (d, C-3), 112.2 (s, C-7), 108.8 (d, C-10), 69.8 (d, C-2), 67.3 (d, C-1), 60.9 (d, C-4a), 56.3 (t, C-6), 53.5 (t, C-12), 43.4 (d, C-10b), 29.4 (t, C-11), 20.7 (q, OCO*C*H$_3$), 20.4 (q, OCO*C*H$_3$), 20.4 (q, OCO*C*H$_3$). EIMS *m/z* (%): 401 (M^+, 5); 359 (2); 339 (8); 323 (10); 297 (11); 282 (22); 254 (27); 238 (100); 210 (15). HREIMS *m/z* 401.1461 (calcd for $C_{21}H_{23}NO_7$ $[M]^+$ 401.1475). IR (neat) ν_{max} 3398, 2922, 2852, 1737, 1619, 1560, 1460, 1370, 1238, 1117, 1034, 918, 883, 664 cm^{-1}. $[\alpha]_D^{20}$ = −34.4 (*c* 0.18, MeOH).

3.3. Oxidation of 2 with potassium permanganate to obtain derivatives 8, 9, and 10

100 mg (0.27 mmol) of **2** dissolved in 3 mL of acetone were treated with a solution of 0.25 g of $KMnO_4$ in 1 mL of water. The reaction mixture was stirred for 4 h. Then H_2O was added and the aqueous phase was extracted several times with DCM. The organic phases were collected and dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting residue was purified using DCM/MeOH (9:1) to yield 10.1 mg of **8** (10%), 6.2 mg of **9** (8%) and 10 mg of **10** (9%) as white amorphous solids.

3.3.1. 1,2-Diacetyl-6-oxolycorine (8)

^{1}H NMR ($CDCl_3$) δ: 7.55 (1H, s, H-7), 6.67 (1H, s, H-10), 6.01 (2H, br s, OCH_2O), 5.74 (1H, s, H-1), 5.61 (1H, s, H-3), 5.28 (1H, s, H-2), 4.23 (1H, d, *J* = 12.3 Hz, H-12), 3.82 (2H, m, H-4a, H-10b), 3.04 (1H, d, *J* = 12.6 Hz, H-12), 2.81 (2H, m, H-11), 2.09 (3H, s, $OCOCH_3$), 2.03 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$) δ 169.6 (s, O*C*OCH$_3$), 169.2 (O*C*OCH$_3$), 162.3 (s, C-6), 150.5 (s, C-4), 146.8 (s, C-8), 143.4 (s, C-9), 131.6 (s, C-6a), 126.0 (s, C-10a), 115.2 (d, C-3), 108.7 (d, C-7), 103.3 (d, C-10), 101.5 (t, OCH_2O), 69.9 (d, C-2), 67.1 (d, C-1), 54.9 (d, C-4a), 43.3 (t, C-12), 40.2 (d, C-10b), 28.3 (t, C-11), 20.8 (q, OCO*C*H$_3$), 20.6 (q, OCO*C*H$_3$). EIMS *m/z* (%): 385 (M^+, 17); 370 (2); 325 (34); 283 (56); 266 (100); 241 (11); 208 (9); 191 (6); 180 (5). HREIMS *m/z* 385.1175 (calcd for $C_{20}H_{19}NO_7$ $[M]^+$ 385.1162). IR (neat) ν_{max} 3056, 2914, 1741, 1651, 1612, 1482, 1416, 1371, 1235, 1039, 967, 933, 735, 702 cm^{-1}. $[\alpha]_D^{20}$ = +73.3 (*c* 0.18, MeOH).

3.3.2. 2-Acetyl-1-deoxy-1,2,4a,10b-tetradehydro-6-oxolycorine (9)

^{1}H NMR ($CDCl_3$) δ: 7.90 (1H, s, H-7), 7.43 (2H, s, H-1, H-3), 7.03 (1H, s, H-10), 6.13 (2H, br s, OCH_2O), 4.97 (2H, t, *J* = 8.0 Hz, H-12), 3.43 (2H, t, *J* = 8.1 Hz, H-11), 2.35 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 170.1 (s, O*C*OCH$_3$), 159.1 (s, C-6), 151.7 (s, C-2), 148.6 (s, C-9), 146.8 (s, C-8), 137.0 (s, C-4), 132.1 (s, C-4a), 130.0 (s, C-10a), 123.0 (s, C-6a), 118.0 (d, C-3), 116.7 (s, C-10b), 112.1 (d, C-1),

106.6 (d, C-10), 101.9 (d, C-7), 100.7 (t, OCH_2O), 46.5 (t, C-12), 27.1 (t, C-11), 20.8 (q, $OCOCH_3$). EIMS *m/z* (%): 323 (M^+, 26); 281 (100); 250 (3); 222 (10); 194 (6); 166 (3). HREIMS *m/z* 323.0804 (calcd for $C_{18}H_{13}NO_5$ $[M]^+$ 323.0794). IR (neat) ν_{max} 3042, 2917, 1752, 1647, 1616, 1496, 1469, 1365, 1256, 1206, 1136, 1095, 1035, 956, 935, 908 cm^{-1}.

3.3.3. 1,2-Diacetyl-3,4-dihydroxy-6-oxolycorine (10)

^1H NMR ($CDCl_3$) δ: 7.53 (1H, s, H-7), 6.45 (1H, s, H-10), 6.02 (2H, br s, OCH_2O), 5.32 (1H, s, H-1), 5.23 (1H, d, *J* = 10.5 Hz, H-2), 4.21 (1H, d, *J* = 7.5 Hz, H-3), 4.06 (1H, d, *J* = 10.1 Hz, H-4a), 3.91 (1H, d, *J* = 17.9 Hz, H-12), 3.47 (1H, m, H-10b), 3.32 (1H, d, *J* = 14.4 Hz, H-12), 2.21 (3H, s, $OCOCH_3$), 2.09 (3H, s, $OCOCH_3$), 2.02 (2H, m, H-11). ^{13}C NMR ($CDCl_3$) δ: 170.9 (s, $OCOCH_3$), 170.3 (s, $OCOCH_3$), 161.3 (s, C-6), 151.0 (s, C-9), 147.2 (s, C-8), 131.1 (s, C-10a), 124.7 (s, C-6a), 108.7 (d, C-7), 104.4 (d, C-10), 101.8 (t, OCH_2O), 79.5 (s, C-4), 77.6 (d, C-2), 74.1 (d, C-3), 71.2 (d, C-1), 63.6 (d, C-4a), 43.6 (t, C-12), 40.0 (t, C-11), 38.1 (d, C-10b), 21.0 (q, $OCOCH_3$), 20.8 (q, $OCOCH_3$). EIMS *m/z* (%): 419 (M^+, 1); 383 (2); 341 (20); 299 (53); 282 (35); 257 (100); 228 (6); 190 (10). HREIMS *m/z* 419.1216 (calcd for $C_{20}H_{21}NO_9$ $[M]^+$ 419.1216). $[\alpha]_D^{20}$ = −115.2 (*c* 0.21, MeOH). IR (neat) ν_{max} 3401, 2916, 1737, 1641, 1606, 1466, 1421, 1368, 1245, 1037, 932, 880, 736 cm^{-1}.

3.4. General procedure for deacetylation

A solution of the corresponding acetylated compound (20–30 mg) in 5 mL of 10% HCl is heated at 50 °C for 30 min. Then the reaction mixture is treated with 20% NH_4OH solution until basic pH is reached, and extracted several times with DCM. The organic phases are dried over $MgSO_4$, concentrated and purified by preparative-TLC using DCM/MeOH (9:1).

3.4.1. 1-Acetyllycorine (11)

Following the general procedure described above, 30 mg (0.08 mmol) of **2** yielded 12.2 mg of the derivative **11** (46%) as an amorphous white solid.

^1H NMR ($CDCl_3$) δ: 6.63 (1H, s, H-10), 6.56 (1H, s, H-7), 5.91 (2H, s, OCH_2O), 5.58 (1H, s, H-1), 5.53 (1H, s, H-3), 4.17 (1H, s, H-2), 4.14 (1H, d, *J* = 13.9 Hz, H-6), 3.50 (1H, d, *J* = 14.0 Hz, H-6), 3.34 (1H, m, H-12), 2.85 (1H, d, *J* = 10.3 Hz, H-10b), 2.75 (1H, d, *J* = 10.3 Hz, H-4a), 2.61 (2H, s, H-11), 2.40 (1H, m, H-12), 1.93 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 170.5 (s, $OCOCH_3$), 146.2 (s, C-8), 145.9 (s, C-9), 143.4 (s, C-4), 128.9 (s, C-6a), 126.7 (s, C-10a), 117.1 (d, C-3), 107.0 (d, C-7), 104.5 (d, C-10), 100.7 (t, OCH_2O), 72.3 (d, C-2), 69.1 (d, C-1), 61.2 (d, C-4a), 56.4 (t, C-6), 53.4 (t, C-12), 38.8 (d, C-10b), 28.3 (t, C-11), 20.8 (q, $OCOCH_3$). EIMS *m/z* (%): 329 (M^+, 52); 268 (37); 250 (24); 240 (9); 226 (100); 192 (3). HRMS *m/z* 329.1260 (calcd for $C_{18}H_{19}NO_5$ $[M]^+$ 329.1263). IR (neat) ν_{max} 3393, 2893, 1735, 1650, 1485, 1371, 1239, 1179, 1153, 1130, 1037, 995, 933, 867, 735 cm^{-1}. $[\alpha]_D^{20}$ = −118.9 (*c* 0.09, MeOH).

3.5. Reaction of 8 to obtain derivatives 12 and 13

Following the general procedure described above, 26.3 mg (0.068 mmol) of **8** afforded 4.8 mg of compound **12** (20%) and 9.7 mg of compound **13** (48%) as amorphous white solids.

3.5.1. 6-Oxolycorine (12)

^1H NMR (400 MHz, MeOD,) δ: 7.37 (1H, s, H-7), 6.93 (1H, s, H-10), 6.03 (2H, s, OCH_2O), 5.63 (1H, s, H-3), 4.47 (1H, s, H-2), 4.21 (2H, s, H-1, H-12), 3.74 (2H, m, H-4a, H-12), 2.83 (3H, m, H-10b, H-11). ^{13}C NMR (100 MHz, MeOD) δ: 163.5 (s, C-6), 151.0 (s, C-8), 146.7 (s, C-9), 140.4 (s, C-4), 134.8 (s, C-6a), 125.5 (s, C-10a), 119.0 (d, C-3), 107.4 (d, C-7), 103.8 (d, C-10), 101.8 (t, OCH_2O), 71.3 (d, C-2), 68.4 (d, C-1), 54.9 (d, C-4a), 43.4 (t, C-12), 40.2 (d, C-10b), 27.8 (t, C-11). EIMS *m/z* (%): 301 (M^+, 41); 283 (29); 265 (74); 257 (29); 241 (100); 226 (14); 206 (9); 191 (13); 178 (9). HREIMS *m/z* 301.0949 (calcd for $C_{16}H_{15}NO_5$ $[M]^+$ 301.0950) IR ν_{max} (neat) 3394, 2923, 2856, 1632, 1596, 1460, 1419, 1373, 1266, 1118, 1036, 817, 564 cm^{-1}. $[\alpha]_D^{20}$ = +25.9 (*c* 0.58, MeOH).

3.5.2. 1-Acetyl-6-oxolycorine (13)

^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (1H, s, H-7), 6.61 (1H, s, H-10), 6.03 (2H, s, OCH_2O), 5.68 (1H, s, H-1), 5.63 (1H, s, H-3), 4.32 (1H, s, H-2), 4.20 (1H, d, *J* = 12.9 Hz, H-12), 3.80 (2H, m, H-4a, H-10b), 3.02 (1H, d, *J* = 12.9 Hz, H-12), 2.82 (2H, s, H-11), 2.05 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (s, $OCOCH_3$), 162.7 (s, C-6), 150.7 (s, C-4), 147.0 (s, C-8), 141.9 (s, C-9), 132.3 (s, C-6a), 128.2 (s, C-10a), 118.6 (d, C-3), 108.9 (d, C-7), 103.3 (d, C-10), 101.7 (t, OCH_2O), 70.6 (d, C-2), 69.3 (d, C-1), 55.3 (d, C-4a), 43.6 (t, C-12), 39.4 (d, C-10b), 28.5 (t, C-11), 20.9 (q, $OCOCH_3$). EIMS *m/z* (%): 343 (M^+, 36); 325 (2); 283 (20); 266 (44); 254 (9); 241 (100); 226 (9); 208 (4). HREIMS *m/z* 343.1059 (calcd for $C_{18}H_{17}NO_6$ $[M]^+$ 343.1056) IR (neat) ν_{max} 3280, 2921, 1738, 1640, 1598, 1463, 1420, 1373, 1270, 1227, 1172, 1123, 1031, 929, 780 cm^{-1}. $[\alpha]_D^{20}$ = +17.1 (*c* 0.14, MeOH).

3.6. Preparation of secolycorines 14–17

Compounds **14–17** were prepared from **2** according to the procedure described in Ref. 21. Spectroscopic data for **14–16** resulted identical to those published.[21]

3.6.1. 5-Methyl-8,9-methylenedioxy-4-vinyl-5,6-dihydrophenantridine (14)

Compound **14** was obtained as a pale yellow amorphous solid in 73% yield. HRMS *m/z* 264.1021 (calcd for $C_{17}H_{14}NO_2$ $[M-1]^+$ 264.1025). IR (neat) ν_{max} 3058, 2909, 1731, 1641, 1501, 1466, 1380, 1332, 1247, 1175, 1121, 1082, 1038, 934, 809, 772, 736 cm^{-1}.

3.6.2. 5-Ethyl-8,9-methylenedioxy-4-vinyl-5,6-dihydrophenantridine (15)

Compound **15** was obtained as a pale yellow amorphous solid in 70% yield. HRMS *m/z* 278.1172 (calcd for $C_{18}H_{16}NO_2$ $[M]^+$ 278.1181). IR (neat) ν_{max} 3060, 2969, 1731, 1653, 1502, 1468, 1380, 1239, 1176, 1116, 1038, 935, 811, 736, 612 cm^{-1}.

3.6.3. 5-Butyl-8,9-methylenedioxy-4-vinyl-5,6-dihydrophenantridine (16)

Compound **16** was obtained as a pale yellow amorphous solid in 77% yield. HREIMS *m/z* 307.1574 (calcd for $C_{20}H_{21}NO_2$ $[M]^+$ 307.1572). IR (neat) ν_{max} 2959, 2874, 1731, 1651, 1467, 1381, 1239, 1176, 1038, 935, 865, 812, 737, 700 cm^{-1}.

3.6.4. 8,9-Methylenedioxy-5-undecyl-4-vinyl-5,6-dihydrophenantridine (17)

Compound **17** was obtained as a pale yellow amorphous solid in 28% yield. ^1H NMR ($CDCl_3$) δ: 7.55 (1H, d, *J* = 7.5 Hz, H-1), 7.44 (1H, d, *J* = 7.6 Hz, H-3), 7.20 (2H, m, H-10, H-11), 7.12 (1H, t, *J* = 7.7 Hz, H-2), 6.68 (1H, s, H-7), 5.97 (2H, s, OCH_2O), 5.70 (1H, d, *J* = 17.8 Hz, H-12), 5.26 (1H, d, *J* = 11.1 Hz, H-12), 4.02 (2H, s, H-6), 2.63 (2H, t, *J* = 7.3 Hz, $NCH_2(C_9H_{18})CH_3$), 1.21 (18H, br s, $NCH_2(C_9H_{18})CH_3$), 0.86 (3H, t, *J* = 6.9 Hz, $NCH_2(C_9H_{18})CH_3$). ^{13}C NMR ($CDCl_3$) δ: 147.0 (s, C-9), 146.9 (s, C-8), 145.2 (s, C-4a), 133.5 (d, C-11), 132.9 (s, C-6a), 129.3 (s, C-10a), 126.9 (s, C-4), 126.2 (s, C-10b), 124.7 (d, C-1), 123.6 (d, C-3), 122.3 (d, C-2), 113.7 (t, C-12), 106.6 (d, C-7), 103.4 (d, C-10), 100.7 (t, OCH_2O), 52.8 (t, C-6), 49.8 (t, $NCH_2(C_9H_{18})CH_3$), 31.6, 29.3, 29.2, 29.0, 27.9, 26.7, 22.4 (t, $NCH_2(C_9H_{18})CH_3$), 13.8 (q, $NCH_2(C_9H_{18})CH_3$). EIMS *m/z* (%): 405 ($[M]^+$, 51); 292 (3); 264 (92); 250 (100); 234 (10); 220 (4); 206 (9); 191 (6). HREIMS *m/z* 405.2643 (calcd for $C_{27}H_{35}NO_2$ $[M]^+$ 405.2668). IR (neat) ν_{max}

2925, 2854, 1733, 1650, 1502, 1466, 1382, 1239, 1175, 1037, 936, 811, 768 cm^{-1}.

3.7. General procedure for preparation of derivatives 18 and 19

To a solution of the corresponding compound in 5 mL of dry DCM at 0 °C, was added dropwise 2 equiv of a solution 1 M of in DCM. The reaction mixture was stirred for ~4 h until disappearance of the starting material. Then, the solvent was evaporated and the residue was purified by preparative-TLC using DCM/MeOH (19:1).

3.7.1. 8,9-Dihydroxy-5-methyl-4-vinyl-5,6-dihydrophenantridine (18)

According to the procedure described above, 30.9 mg (0.12 mmol) of compound **14** was reacted with 0.25 mL of a solution 1 M of BBr_3 in DCM. After purification, 11.8 mg of **23** (40%) was obtained as an amorphous pale yellow solid. ^{1}H NMR ($CDCl_3$) δ: 7.55 (1H, d, J = 7.7 Hz, H-1), 7.44 (1H, d, J = 7.7 Hz, H-3), 7.21 (2H, m, H-10, H-11), 7.13 (1H, t, J = 7.7 Hz, H-2), 6.73 (1H, s, H-7), 5.72 (1H, d, J = 17.7 Hz, H-12), 5.30 (1H, d, J = 10.9 Hz, H-12), 3.99 (2H, s, H-6), 2.49 (3H, s, NMe). ^{13}C NMR ($CDCl_3$) δ: 145.0 (s, C-9), 143.4 (s, C-8), 142.7 (s, C-4a), 133.2 (d, C-11), 133.0 (s, C-6a), 128.7 (s, C-10a), 125.5 (s, C-4), 124.8 (s, C-10b), 124.6 (d, C-1), 124.1 (d, C-3), 122.4 (d, C-2), 114.2 (t, C-12), 113.4 (d, C-7), 110.1 (d, C-10), 54.0 (t, C-6), 41.5 (q, NMe). EIMS m/z (%): 253 ([M]$^+$, 27); 252 (59); 251 (100); 236 (10); 223 (34); 208 (24); 191 (11); 178 (14). HRMS m/z 253.1096 (calcd for $C_{16}H_{15}NO_2$ [M]$^+$ 253.1103). IR (neat) ν_{max} 3367, 2924, 2853, 1733, 1653, 1619, 1543, 1461, 1115, 1038, 813 cm^{-1}.

3.7.2. 5-Butyl-8,9-dihydroxy-4-vinyl-5,6-dihydrophenantridine (19)

According to the procedure described above, 36 mg (0.12 mmol) of compound **16** was reacted with 0.25 mL of a solution 1 M of BBr_3 in DCM. After purification, 11.8 mg of **24** (40%) was obtained as an amorphous pale yellow solid. ^{1}H NMR ($CDCl_3$) δ: 7.51 (1H, br s, H-1), 7.43 (1H, d, J = 7.3 Hz, H-3), 7.17 (3H, m, H-2, H-10, H-11), 6.74 (1H, s, H-7), 5.69 (1H, d, J = 17.6 Hz, H-12), 5.27 (1H, d, J = 10.9 Hz, H-12), 4.00 (2H, s, H-6), 2.64 (2H, t, J = 7.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.46 (2H, m, $NCH_2CH_2CH_2CH_3$), 1.20 (2H, m, $NCH_2CH_2CH_2CH_3$), 0.83 (3H, t, J = 7.1 Hz, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 144.8 (s, C-4a), 143.6 (s, C-9), 143.0 (s, C-8), 133.4 (d, C-11), 132.9 (s, C-6a), 129.0 (d, C-1), 125.2 (s, C-10a), 124.7 (d, C-3), 124.0 (s, C-4), 123.9 (s, C-10b), 122.3 (d, C-2), 113.9 (t, C-12), 113.3 (d, C-7), 110.1 (d, C-10), 52.9 (t, C-6), 49.4 (t, $NCH_2CH_2CH_2CH_3$), 28.9 (t, $NCH_2CH_2CH_2CH_3$), 19.9 (t, $NCH_2CH_2CH_2CH_3$), 13.7 (q, $NCH_2CH_2CH_2CH_3$). EIMS m/z (%): 295 ([M]$^+$, 56); 252 (100); 238 (94); 220 (7); 209 (9); 191 (7); 178 (8). HREIMS m/z 295.1563 (calcd for $C_{19}H_{21}NO_2$ [M]$^+$ 295.1572). IR (neat) ν_{max} 3395, 2958, 2929, 1667, 1609, 1511, 1393, 1336, 1300, 1250, 1196, 1056, 907, 858, 809, 739 cm^{-1}.

3.8. General procedure for preparation of the lactam derivatives 20–22

To a suspension of the corresponding compound (10–20 mg) in 5 mL of CH_3CN/H_2O (9:1) were added 0.2 equiv of tetrabutylammonium iodide (TBAI) and 3 equiv of iodosylbenzene. The reaction mixture was stirred for ~4 h until disappearance of the starting material. The solvent was evaporated and the residue was purified by preparative-TLC using DCM as eluent.

3.8.1. 5-Methyl-8,9-methylenedioxy-6-oxo-4-vinyl-5,6-dihydrophenantridine (20)

Following the general procedure, 18.2 mg (0.07 mmol) of **14** was treated with 6 mg of TBAI and 46 mg of iodosylbenzene. After purification 4.8 mg of **20** (25%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ: 7.97 (1H, d, J = 7.6 Hz, H-1), 7.85 (1H, s, H-10), 7.57 (1H, s, H-7), 7.46 (1H, d, J = 7.1 Hz, H-3), 7.25 (1H, br s, H-2), 7.08 (1H, dd, J = 10.9 Hz, J = 16.1 Hz, H-11), 6.12 (2H, br s, OCH_2O), 5.62 (1H, d, J = 16.9 Hz, H-12), 5.37 (1H, d, J = 10.7 Hz, H-12), 3.78 (3H, s, NMe). ^{13}C NMR ($CDCl_3$) δ: 162.9 (s, C-6), 152.0 (s, C-9), 148.1 (s, C-8), 137.6 (d, C-11), 136.9 (s, C-4a), 130.3 (s, C-6a), 130.0 (d, C-1), 128.3 (s, C-10a), 122.4 (d, C-3), 121.9 (d, C-2), 120.9 (s, C-4), 120.7 (s, C-10b), 114.0 (t, C-12), 106.3 (d, C-7), 101.7 (t, OCH_2O), 100.4 (d, C-10), 39.0 (q, NMe). EIMS m/z (%): 279 ([M]$^+$, 92); 264 (100); 250 (6); 234 (8); 220 (7); 206 (22); 191 (8). HREIMS m/z 279.0886 (calcd for $C_{17}H_{13}NO_3$ [M]$^+$ 279.0895). IR (neat) ν_{max} 2981, 2912, 1641, 1501, 1461, 1380, 1331, 1249, 1122, 1082, 1037, 935, 881, 774, 739, 669 cm^{-1}.

3.8.2. 5-Ethyl-8,9-methylenedioxy-6-oxo-4-vinyl-5,6-dihydrophenantridine (21)

Following the general procedure, 13.3 mg (0.048 mmol) of **15** was treated with 4 mg of TBAI and 33 mg of iodosylbenzene. After purification, 6.8 mg of **21** (49%) was obtained as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, d, J = 7.8 Hz, H-1), 7.85 (1H, s, H-10), 7.57 (1H, s, H-7), 7.43 (1H, d, J = 7.3 Hz, H-3), 7.23 (1H, m, H-2), 7.15 (1H, dd, J = 10.7 Hz, J = 17.1 Hz, H-11), 6.10 (2H, br s, OCH_2O), 5.62 (1H, d, J = 17.1 Hz, H-12), 5.36 (1H, d, J = 10.7 Hz, H-12), 4.53 (2H, q, J = 6.8 Hz, NCH_2CH_3), 1.30 (3H, t, J = 6.8 Hz, NCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ: 162.6 (s, C-6), 152.0 (s, C-9), 148.1 (s, C-8), 137.7 (d, C-11), 135.8 (s, C-4a), 130.8 (d, C-1), 130.3 (s, C-6a), 128.4 (s, C-10a), 122.3 (d, C-3), 122.2 (d, C-2), 121.1 (s, C-4), 120.9 (s, C-10b), 114.9 (t, C-12), 106.4 (d, C-7), 101.6 (t, OCH_2O), 100.4 (d, C-10), 42.7 (t, NCH_2CH_3), 14.4 (q, NCH_2CH_3). EIMS m/z (%):293 ([M]$^+$, 75); 278 (77); 264 (100); 248 (7); 234 (7); 220 (10); 206 (19); 191 (7).HREIMS m/z 293.1052 (calcd for $C_{18}H_{15}NO_3$ [M]$^+$ 293.1052). IR (neat) ν_{max} 2962, 2916, 1732, 1643, 1501, 1461, 1382, 1299, 1247, 1163, 1037, 935, 843, 774, 739 cm^{-1}.

3.8.3. 5-Butyl-8,9-methylenedioxy-6-oxo-4-vinyl-5,6-dihydrophenantridine (22)

Following the general procedure, 15.1 mg (0.049 mmol) of **16** was treated with 4 mg of TBAI and 33 mg of iodosylbenzene. After purification, 10.2 mg of **22** (65%) was obtained as an amorphous white solid. ^{1}H NMR ($CDCl_3$) δ: 7.98 (1H, d, J = 7.9 Hz, H-1), 7.84 (1H, s, H-10), 7.56 (1H, s, H-7), 7.41 (1H, d, J = 7.3 Hz, H-3), 7.22 (1H, m, H-2), 7.10 (1H, dd, J = 10.7 Hz, J = 17.2 Hz, H-11), 6.10 (2H, br s, OCH_2O), 5.62 (1H, d, J = 17.2 Hz, H-12), 5.36 (1H, d, J = 10.7 H-12), 4.49 (2H, t, J = 7.3 Hz, $NCH_2CH_2CH_2CH_3$), 1.62 (2H, q, J = 7.3 Hz, $NCH_2CH_2CH_2CH_3$), 1.23 (2H, sext, J = 7.3 Hz, $NCH_2CH_2CH_2CH_3$), 0.85 (3H, t, J = 7.3 Hz, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 162.8 (s, C-6), 152.0 (s, C-9), 148.1 (s, C-8), 137.7 (d, C-11), 135.9 (s, C-4a), 130.6 (d, C-1), 130.2 (s, C-6a), 128.6 (s, C-10a), 122.3 (d, C-3), 122.2 (d, C-2), 121.1 (s, C-4), 120.9 (s, C-10b), 114.7 (t, C-12), 106.5 (d, C-7), 101.6 (t, OCH_2O), 100.4 (d, C-10), 47.4 (t, $NCH_2CH_2CH_2CH_3$), 30.6 (t, $NCH_2CH_2CH_2CH_3$), 19.5 (t, $NCH_2CH_2CH_2CH_3$), 13.5 (q, $NCH_2CH_2CH_2CH_3$). EIMS m/z (%):321 ([M]$^+$, 48); 304 (22); 292 (32); 278 (39); 264 (100); 234 (4); 220 (7); 206 (12); 191 (7). HREIMS m/z 321.1357 (calcd for $C_{20}H_{19}NO_3$ [M]$^+$ 321.1365). IR (neat) ν_{max} 2959, 2929, 1732, 1644, 1500, 1461, 1382, 1247, 1204, 1162, 1087, 1038, 934, 882, 845, 775, 739 cm^{-1} .

3.9. Preparation of dihydrosecolycorines 23 and 24

Derivatives **23** and **24** were prepared by hydrogenation according to the method described in Ref. 21. Compounds **23** and **24** showed identical spectroscopic data to those published.[21]

3.9.1. 4-Ethyl-5-methyl-8,9-methylenedioxy-5,6-dihydrophenantridine (23)

Compound **23** was isolated as a pale yellow solid in 35% yield. HREIMS *m/z* 267.1248 (calcd for $C_{17}H_{17}NO_2$ $[M]^+$ 267.1259). IR (neat) ν_{max} 2965, 2932, 1644, 1620, 1501, 1467, 1380, 1298, 1237, 1167, 1080, 1038, 934, 861, 809, 760, 737 cm^{-1}.

3.9.2. 5-Butyl-4-ethyl-8,9-methylenedioxy-5,6-dihydrophenantridine (24)

Compound **24** was isolated as a pale yellow solid in 65% yield. IR (neat) ν_{max} 2961, 2930, 1731, 1651, 1467, 1377, 1238, 1176, 1095, 1038, 937, 861, 806, 737 cm^{-1}. HREIMS *m/z* 309.1720 (calcd for $C_{20}H_{23}NO_2$ $[M]^+$ 309.1729).

3.9.3. 8,9-Diacetyl-5-methyl-4-vinyl-5,6-dihydrophenantridine (25)

To a solution of 9.3 mg (0.037 mmol) of compound **18** in 1 mL of pyridine, was added 0.3 mL (3.18 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 24 h. Then the solvent was removed and the crude purified by preparative-TLC using DCM as eluent to yield 8 mg of **25** (65%) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ: 7.60 (1H, d, J = 7.7 Hz, H-1), 7.53 (1H, s, H-10), 7.50 (1H, d, J = 7.7 Hz, H-3), 7.19 (2H, m, H-2, H-11), 7.08 (1H, s, H-7), 5.74 (1H, d, J = 17.7 Hz, H-12), 5.32 (1H, d, J = 11.0 Hz, H-12), 4.09 (2H, s, H-6), 2.53 (3H, s, NMe), 2.32 (3H, s, $OCOCH_3$), 2.30 (3H, s, $OCOCH_3$). ^{13}C NMR ($CDCl_3$) δ: 168.2 (s, $OCOCH_3$), 168.1 (s, $OCOCH_3$), 145.3 (s, C-4a), 145.3 (s, C-8), 141.1 (s, C-9), 133.1 (s, C-6a), 133.0 (d, C-11), 130.7 (s, C-10b), 130.5 (s, C-10a), 127.6 (s, C-4), 125.9 (d, C-2), 124.1 (d, C-1), 123.1 (d, C-3), 121.2 (d, C-10), 117.7 (d, C-7), 114.4 (t, C-12), 53.9 (t, C-6), 41.8 (q, NMe), 20.5 (q, $OCOCH_3$), 20.4 (q, $OCOCH_3$). EIMS *m/z* (%): 337 ($[M]^+$, 53); 322 (7); 294 (26); 280 (18); 252 (100); 238 (23); 224 (12); 208 (10). HREIMS *m/z* 337.1308 (calcd for $C_{20}H_{19}NO_4$ $[M]^+$ 337.1314). IR (neat) ν_{max} 2939, 1768, 1672, 1616, 1504, 1465, 1372, 1210, 1122, 1042, 1011, 919, 812, 760, 735 cm^{-1}.

3.9.4. 8,9-Dilauroyl-5-methyl-4-vinyl-5,6-dihydrophenantridine (26)

To a solution of 9.5 mg (0.038 mmol) of compound **18** in 3 mL of DCM, were added 16 μL (3 equiv) of triethylamine and 27 μL (3 equiv) of lauroyl chloride. The reaction mixture was stirred for 18 h stirring at room temperature. Then the solvent was eliminated and the residue was the mixture was purified by preparative-TLC using DCM as eluent, to yield 17.7 mg of **26** (77%) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ: 7.61 (1H, d, J = 7.7 Hz, H-1), 7.51 (1H, s, H-10), 7.49 (1H, d, J = 8.3 Hz, H-3), 7.19 (2H, m, H-2, H-11), 7.07 (1H, s, H-7), 5.74 (1H, d, J = 17.7 Hz, H-12), 5.31 (1H, d, J = 11.0 Hz, H-12), 4.08 (2H, s, H-6), 2.56 (4H, t, J = 7.0 Hz, $COCH_2(C_9H_{18})CH_3$), 2.52 (3H, s, NMe), 1.26 (36H, s, $COCH_2(C_9H_{18})CH_3$), 0.87 (6H, t, J = 5.2 Hz, $COCH_2(C_9H_{18})CH_3$). ^{13}C NMR ($CDCl_3$) δ: 171.0 (s, C=O), 170.9 (s, C=O), 146.1 (s, C-4a), 141.3 (s, C-8), 141.3 (s, C-9), 133.1 (s, C-6a), 133.0 (d, C-11), 130.5 (s, C-10b), 130.3 (s, C-10a), 127.6 (s, C-4), 125.8 (d, C-2), 124.1 (d, C-1), 123.1 (d, C-3), 121.2 (d, C-10), 117.7 (d, C-7), 114.3 (t, C-12), 54.0 (t, C-6), 41.7 (q, NMe), 33.8 (t, $COCH_2(C_9H_{18})CH_3$), 31.6, 29.2, 29.1, 29.0, 29.0, 28.9, 28.9, 24.7, 22.4 (t, $COCH_2(C_9H_{18})CH_3$), 13.8 (q, $COCH_2(C_9H_{18})CH_3$). EIMS *m/z* (%):617 ($[M]^+$, 92); 435 (81); 252 (100); 238 (17); 224 (19); 208 (5). HREIMS *m/z* 617.4471 (calcd for $C_{40}H_{59}NO_4$ $[M]^+$ 617.4444). IR (neat) ν_{max} 2917, 2851, 1747, 1502, 1466, 1390, 1312, 1240, 1149, 1122, 1085, 909, 814, 760, 718 cm^{-1}.

3.9.5. 5-Methyl-8,9-dimethoxy-4-vinyl-5,6-dihydrophenantridine (27)

To a solution of 6.1 mg (0.024 mmol) of compound **18** in 5 mL of a mixture DCM/MeOH 1:1, was added 0.5 mL (42 equiv) of a solution 2 M of trimethylsilyldiazomethane in ethyl ether. The reaction mixture was stirred for 24 h, then the solvent was evaporated and the residue was purified by preparative-TLC using DCM as eluent, to yield 4 mg of **27** (60%) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ: 7.63 (1H, d, J = 7.7 Hz, H-1), 7.45 (1H, d, J = 7.7 Hz, H-3), 7.23 (2H, m, H-10, H-11), 7.16 (1H, t, J = 7.7 Hz, H-2), 6.73 (1H, s, H-7), 5.74 (1H, d, J = 17.7 Hz, H-12), 5.31 (1H, d, J = 11.0 Hz, H-12), 4.06 (2H, s, H-6), 3.96 (3H, s, OMe), 3.93 (3H, s, OMe), 2.52 (3H, s, NMe). ^{13}C NMR ($CDCl_3$) δ: 148.7 (s, C-9), 148.2 (s, C-8), 144.8 (s, C-4a), 133.2 (d, C-11), 133.1 (s, C-6a), 128.9 (s, C-10a), 124.8 (s, C-4), 124.8 (d, C-1), 124.5 (s, C-10b), 124.2 (d, C-3), 122.2 (d, C-2), 114.1 (t, C-12), 109.5 (d, C-7), 106.1 (d, C-10), 55.8 (q, OMe), 55.7 (q, OMe), 54.2 (t, C-6), 41.6 (q, NMe). EIMS *m/z* (%): 280 ($[M-1]^+$, 100); 264 (21); 250 (4); 235 (6); 222 (3); 207 (4); 191 (5). HREIMS *m/z* 280.1341 (calcd for $C_{18}H_{18}NO_2$ $[M-1]^+$ 280.1338). IR (neat) ν_{max} 2929, 1640, 1610, 1515, 1466, 1380, 1273, 1211, 1064, 1025, 809, 772, 734 cm^{-1}.

3.9.6. 5-Butyl-8,9-diacetyl-4-vinyl-5,6-dihydrophenantridine (28)

To a solution of 5.9 mg (0.02 mmol) of compound **19** in 1 mL of pyridine, was added 0.3 mL (3.18 mmol) of acetic anhydride. The reaction mixture was stirred for 24 h at room temperature, then the solvent was eliminated and the residue was purified by preparative-TLC using DCM as eluent, to yield 5.4 mg of **28** (72%) as a pale yellow solid. ^1H NMR ($CDCl_3$) δ: 7.60 (1H, d, J = 7.6 Hz, H-1), 7.52 (1H, s, H-10), 7.50 (1H, d, J = 9.6 Hz, H-3), 7.14 (2H, m, H-2, H-11), 7.07 (1H, s, H-7), 5.72 (1H, d, J = 17.7 Hz, H-12), 5.30 (1H, d, J = 11 Hz, H-12), 4.11 (2H, s, H-6), 2.68 (2H, t, J = 7.1 Hz, $NCH_2CH_2CH_2CH_3$), 2.32 (3H, s, $OCOCH_3$), 2.31 (3H, s, $OCOCH_3$), 1.49 (2H, q, J = 7.5 Hz, $NCH_2CH_2CH_2CH_3$), 1.25 (2H, m, $NCH_2CH_2CH_2CH_3$), 0.86 (3H, t, J = 7.2 Hz, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 168.2 (s, $OCOCH_3$), 168.1 (s, $OCOCH_3$), 145.9 (s, C-4a), 145.6 (s, C-8), 141.1 (s, C-9), 133.3 (s, C-6a), 133.1 (d, C-11), 131.5 (s, C-10a), 131.0 (s, C-10b), 127.8 (s, C-4), 126.1 (d, C-2), 123.7 (d, C-1), 123.0 (d, C-3), 120.9 (d, C-10), 117.7 (d, C-7), 114.0 (t, C-12), 52.9 (t, C-6), 49.2 (t, $NCH_2CH_2CH_2CH_3$), 30.2 (t, $NCH_2CH_2CH_2CH_3$), 20.5 (q, $OCOCH_3$), 20.4 (q, $OCOCH_3$), 19.8 (t, $NCH_2CH_2CH_2CH_3$), 13.7 (q, $NCH_2CH_2CH_2CH_3$). EIMS *m/z* (%): 379 ($[M]^+$, 62); 336 (86); 322 (84); 294 (100); 280 (54); 252 (60); 238 (34); 210 (13). HREIMS *m/z* 379.1779 (calcd for $C_{23}H_{25}NO_4$ $[M]^+$ 379.1784). IR (neat) ν_{max} 2959, 2931, 1766, 1667, 1613, 1504, 1466, 1394, 1208, 1128, 1055, 921, 811, 737 cm^{-1}.

3.10. Antiplasmodial assay

F-32 Tanzania (chloroquine-sensitive) strains of *P. falciparum* were cultured according to Trager and Jensen[22] on glucose-enriched RPMI 1640 medium, supplemented with 10% human serum at 37 °C. After 24 h of incubation at 37 °C, the medium was replaced by fresh medium supplemented with the compound to be evaluated at three different concentrations (0.1, 1, and 10 μg/mL) and incubation was continued for further 48 h. On the third day of the test, a blood smear was taken from each well and parasitemia was calculated for each concentration of sample compared to the control. IC_{50} values were determined graphically by plotting concentrations versus percent inhibition. Chloroquine (0.04 μM) was used as a positive control. All tests were performed in triplicate.

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