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Synthesis and antimalarial activity of new haemanthamine-type derivatives

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ABSTRACT

Thirty one derivatives were prepared from the natural alkaloids haemanthamine (**1**), haemanthidine (**2**) and 11-hydroxyvittatine (**3**). They were evaluated for their in vitro antimalarial activity against chloroquine-sensitive strains of *Plasmodium falciparum* and some structure–activity relationships were outlined. For haemanthamine derivatives having a methoxy group at C-3, the presence of a free hydroxyl group at C-11 is important for the activity. The double bond at C-1–C-2 plays also an important role to achieve good inhibitory activity. Compound **35** with two nicotinate groups at C-3 and at C-11 was the most active compound with a $IC_{50} = 0.8 \pm 0.06$ μM.

1. Introduction

AIDS, malaria and tuberculosis cause together more than five million deaths per year, especially in developing countries.[1] Although the development of vaccines for these diseases is in progress, treatment for patients depends on the use of specific drugs. Natural products have made and continue to make an immense contribution to malaria chemotherapy either directly as antimalarial agents or as important lead compounds for the discovery of more potent antimalarials.[2] Chloroquine, and other quinoline antimalarials such as primaquine, mepacrine and mefloquine have been mainstays of antimalarial chemotherapy for more than past 40 years.[3] Artemisinin isolated from the Chinese plant *Artemesia annua* has been used successfully against chloroquine-resistant malarial parasites.[4] But, the poor solubility of artemisinin, coupled with its short plasma half life led to a high rate of parasite recrudescence. The development of semi-synthetic analogues through the reduced lactone dihydroxyartemisinin gave rise to the oil-soluble derivatives artemether and arteether as well as the water-soluble sodium artesunate. However, the rapid spread of drug resistant malarial strains all over the world forces the search for more selective and effective antimalarial drugs.[5,6] Isolation of new lead compounds from plants is one of the strategies that can be in the search for new drugs.[7–9] Alkaloids of the Amaryllidaceae family exhibit a wide and important range of biological activities.[10–12] For example, narciclasine has shown anticancer activity,[13] and galantamine is a worldwide distributed drug for the treatment of Alzheimer's disease.[14] Some of the Amaryllidaceae alkaloids are also of particular interest because of their potential antimalarial activity: lycorine, haemanthamine, haemanthidine and crinamine possess important activity against several strains of *Plasmodium falciparum*.[15–17]

In the present work we have carried out selective modifications on the structures of three haemanthamine-type alkaloids: haemanthamine (**1**), haemanthidine (**2**) and 11-hydroxyvittatine (**3**). These alkaloids were isolated in large amounts from the bulbs of *Pancratium canariense*.[18,19] The 31 obtained derivatives were evaluated as antimalarial agents against *P. falciparum* and some preliminary structure-activity relationships were established for the haemanthamine skeleton.

2. Results and discussion

2.1. Chemistry

Alkaloids haemanthamine **1**, haemanthidine **2**, 11-hydroxyvittatine **3**, vittatine **4**, 8-*O*-demethylmaritidine **5** and 6-*O*-methylmaritidine **6** were isolated from *Pancratium canariense* as published (Fig 1).[18,19]

Modifications achieved on the structure of haemanthamine **1** are shown in Schemes 1 and 2. For the most part, the transformations were carried out on the hydroxyl group at C-11 or on the double bond presents in ring D in order to study their role in the antiplasmodial activity. Compound **7** was obtained quantitatively by acetylation with acetic anhydride. Esterification with *p*-vinylbenzoic acid

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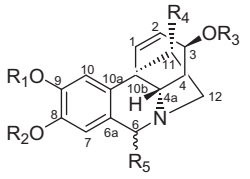
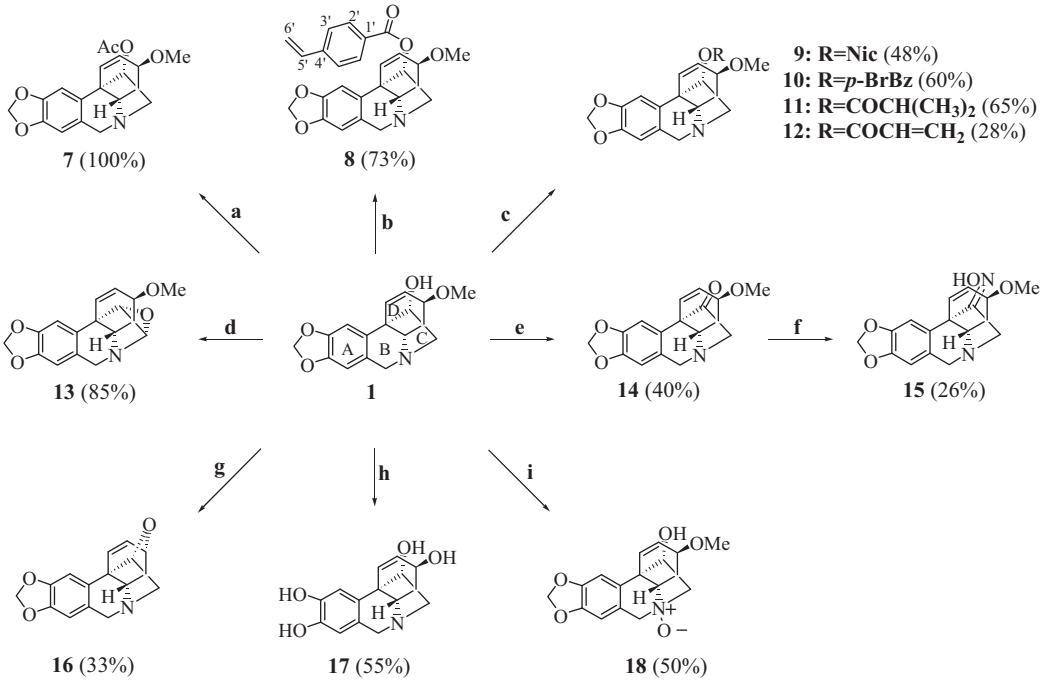
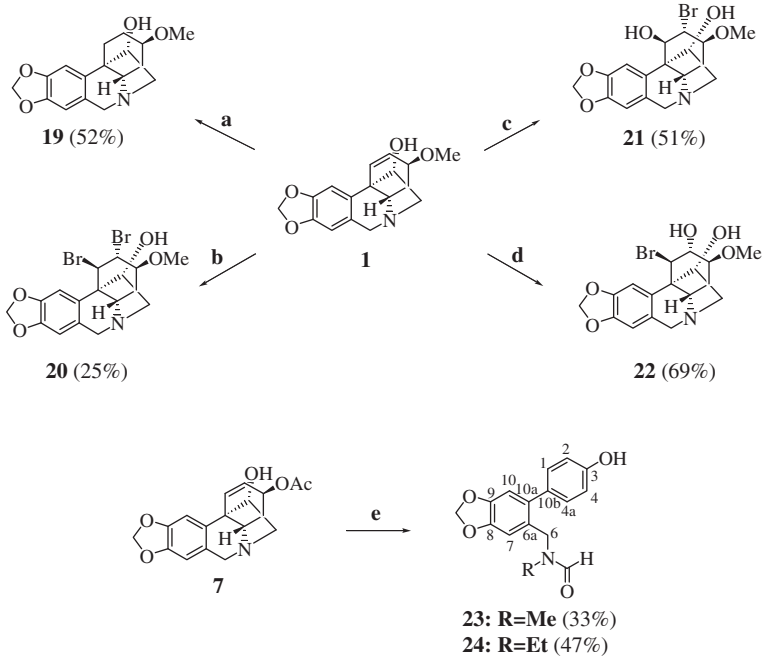


haemanthamine (**1**): R_1+R_2=-CH_2-, R_3=Me, R_4=OH, R_5=H
haemanthidine (**2**): R_1+R_2=-CH_2-, R_3=Me, $R_4=R_5$=OH
11-hydroxyvittatine (**3**): R_1+R_2=-CH_2-, $R_3=R_5$=H, R_4=OH
vittatine (**4**): R_1+R_2=-CH_2-, $R_3=R_4=R_5$=H
8-*O*-demethylmaritidine (**5**): R_1=Me, $R_2=R_3=R_4=R_5$=H
6-*O*-methylmaritidine (**6**): R_1+R_2=-CH_2-, R_3=Me, R_4=OH, R_5=OMe

Figure 1. Structures of haemanthamine-type alkaloids.



Scheme 1. Reagents and conditions: (a) Ac_2O, py; (b) *p*-vinylbenzoic acid, DCC, DCM; (c) RCl, NEt_3, DCM; (d) NBS, DCM; (e) Jones reagent, acetone; (f) NH_3OHCl, NaOAc, EtOH, reflux, 15 h; (g) 6 M HCl, 100 °C, 4 h; (h) BBr_3, DCM, 0 °C; (j) 30% H_2O_2, MeOH, 24 h.



Scheme 2. Reagents and conditions: (a) H_2, 10% Pd/C, THF; (b) Br_2, DCM, 24 h; (c) $CH_3CONHBr$, $SnCl_4$, H_2O, CH_3CN, 0 °C; (d) $CH_3CONHBr$, $SnCl_4$, CH_3CN, 0 °C; (e) (1) RX, CH_3CN, 24 h; (2) *t*-BuOK/*t*-BuOH, reflux, 4 h.

produced derivative **8**, which possesses a terminal vinyl group. The hydroxyl group was also acylated with several acyl chlorides of different size, lipophilicity and stereoelectronic properties (nicotyl, p-bromobenzoyl, isobutyryl and acryloyl chloride), to yield the corresponding esters **9–12**. When **1** was treated with NBS one product was obtained in good yield, being identified as the epoxide **13**. Since the absolute configuration of haemanthamine is known the stereochemistry of the epoxy ring was established as 11*S*, 12*R* on the basis of the following NOEs observed in the Roesy spectrum H-4a/H-6b, H-12/H-4a, H-12/H-6a. Oxidation of the hydroxyl group to the corresponding ketone **14** was achieved by using the Jones reagent and treatment of **14** with hydroxylamine hydrochloride led to the oxime **15**. The treatment of **1** with concentrated HCl under reflux conditions yielded derivative **16**, which was identified as apohaemanthamine, a natural alkaloid isolated from *Eucharis amazonica*.[20] The polyhydroxylated compound **17** was obtained by treatment of **1** with BBr_3. The reaction of **1** with H_2O_2 afforded the corresponding N-oxide derivative **18**.

The double bond at C-1–C-2 of haemanthamine was modified as shown in Scheme 2: Hydrogenation and bromination led to derivatives **19** and **20**, respectively. Treatment of **1** with N-bromoacetamide according to the published conditions for haloamidation[21] produced compound **21**. However, when this reaction was performed under anhydrous conditions only one product, after work-up, was obtained, being identified as **22**. Thus, the presence or absence of water allowed us the regioselective preparation of the corresponding bromohydrines. Hofmann elimination[22] was performed on 11-acetylhaemanthamine. Thus, the reaction of **7** with different alkyl halides followed by treatment with *t*-BuOK/*t*-BuOH yielded the corresponding new biphenyl derivatives **23** and **24**. The formation of these compounds occurred with aromatization of ring C and ring D opening, and they were obtained as a mixture of *anti* and *syn* formamide conformers.

The structure of haemanthidine (**2**) was also modified as shown in Scheme 3. Acetylation with Ac_2O/py and acylation with different acyl chlorides afforded derivatives **25–28**. When **2** reacted with the Jones reagent only the hydroxyl group at C-11 was chemoselectively oxidized, yielding compound **29**. With the aim of oxidizing the hydroxyl group at C-6, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy)[23] was employed, but derivative **30** was obtained instead of the desired lactam. The structure of **30** was unequivocally established on the basis of the correlations observed in the HMBC spectrum. The derivatives **31** and **32** were prepared from **2** using BBr_3 and HCl, respectively in a similar way to that followed for haemanthamine.

Modifications carried out on the hydroxyl groups of 11-hydroxyvittatine (**3**) are shown in Scheme 4. Acetylation of **3** yielded compound **33**. The derivative **34** was obtained by esterification using (*R*)-(−)-methoxyphenylacetic acid (MPA), while acylation of **3** with different acyl chlorides led the corresponding compounds **35–37**.

2.2. Biological assay and SAR

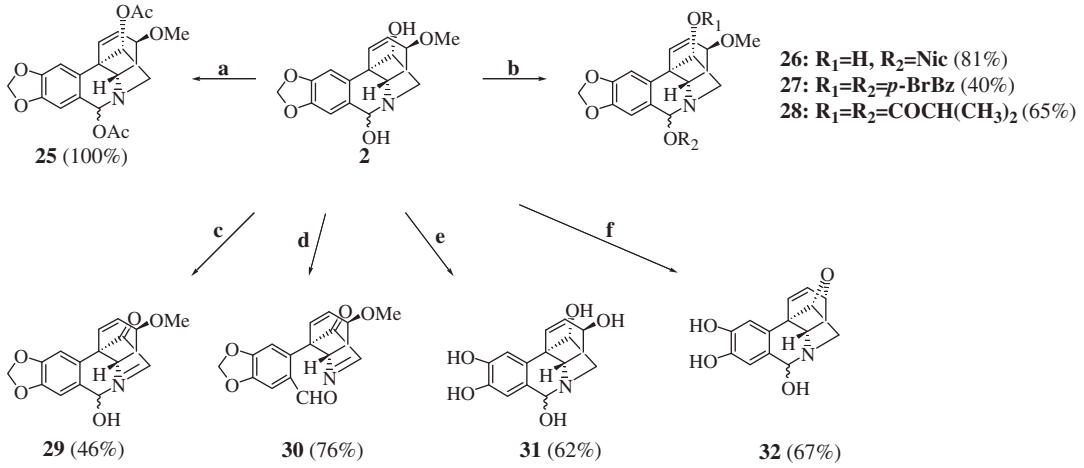
Results of the antiplasmodial evaluation are summarized in Table 1, indicating that haemanthamine (**1**) and haemanthidine (**2**) are the most active natural alkaloids, with IC_{50} values of 1.3 and 1.2 μM, respectively. However, derivative **35** presented the best antiplasmodial activity, with an IC_{50} value under 1 μM.

From the obtained results presented in Table 1, we can establish some structure–activity relationships for the haemanthamine skeleton. When **1** was converted into the corresponding acyl derivatives **7–10** and **12**, a dramatic decrease in the activity was observed (i.e., **1** vs **7**, **1** vs **8**, **1** vs **9**, **1** vs **10**, **1** vs **12**). These results indicated that a hydrogen-bond-donor (HBD) at C-11 is an important requirement for the antiplasmodial activity. Only in the case of compound **12** which presents an acryloyl moiety, a 6-fold lower activity than **1**, was detected. Probably, in this case the acryloyl moiety at C-11 could act as a Michael acceptor.

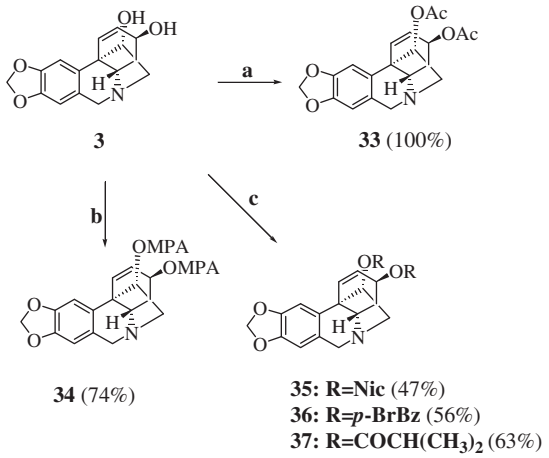
The oxidation of the hydroxyl group at C-11 also led to a less active compound (**1** vs **14**). The replacement of the methoxy group at C-3 by a hydroxyl group produced a decrease in the activity (**1** vs **17**). The N-oxide derivative **18** obtained by oxidation of **1** with H_2O_2 was inactive. The epoxy derivative **13** showed similar antiplasmodial activity than compound **1**, while the derivative **16** was inactive. The similar antiplasmodial activity of compounds **1** and **13** could be attributed to a possible hydrolysis of the oxirane ring.

Concerning the modifications on the double bond at C-1–C-2 of the ring D, derivatives **19–22** were less active than **1**, indicating that this double bond seems to play an important role in the activity. A simplification of the haemanthamine skeleton achieved by the formation of the biphenyl compounds **23** and **24** produced a drastic loss of activity.

With respect to the haemanthidine series (**2**, **25–32**), the presence of a hydroxyl group at C-6 produces similar antiplasmodial activity (i.e., **1** vs **2**). The diacetylated compounds were less active than compound **2** (i.e., **2** vs **25**, **2** vs **27**, **2** vs **28**). In this case, the introduction of two nicotinates (**26**) or two *p*-bromo benzoates (**27**) produced a lower loss of activity than the introduction of



Scheme 3. Reagents and conditions: (a) Ac_2O, py; (b) RCl, NEt_3, DCM; (c) Jones reagent, acetone; (d) TEMPO, NBu_4I, *m*-CPBA, DCM, 24 h; (e) BBr_3, DCM, 0 °C; (f) 6 M HCl, 100 °C, 4 h.



Scheme 4. Reagents and conditions: (a) Ac_2O, py; (b) (*R*)-(−)-MPA, DCC, DCM; (c) RCl, NEt_3, DCM.

Table 1
In vitro activity against *Plasmodium falciparum* F32

Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)
1	1.3 ± 0.2	20	6.5 ± 0.9
2	1.2 ± 0.09	21	62.6 ± 7.5
3	13.2 ± 1.4	22	72.6 ± 5.0
4	7.3 ± 0.1	23	73.4 ± 10.5
5	91.5 ± 10.4	24	>100
6	75.5 ± 9.0	25	52.3 ± 7.5
7	75.8 ± 8.7	26	7.1 ± 0.9
8	>100	27	2.9 ± 0.6
9	51.7 ± 4.9	28	52.5 ± 6.6
10	43.3 ± 4.1	29	85.7 ± 9.5
11	56.6 ± 8.1	30	76.6 ± 9.6
12	8.4 ± 1.7	31	72.1 ± 10.0
13	1.6 ± 0.1	32	84.2 ± 10.5
14	73.5 ± 10.0	33	>100
15	95.5 ± 9.5	34	5.1 ± 0.7
16	92.9 ± 14.8	35	0.8 ± 0.06
17	13.4 ± 1.8	36	3.0 ± 0.6
18	>100	37	7.0 ± 1.2
19	9.9 ± 1.3	Chloroquine	0.04

[a] Data are expressed as mean standard deviation of three determinations.

two acetates (**25**), or two isobutiryl groups (**28**). These results indicate that the presence of an aromatic moiety at C-6 favours the antiplasmodial activity (i.e., **9** vs **26**, 10 vs **27**).The replacement of the methylenedioxy moiety at the aromatic ring A by other groups led to a decreased activity (i.e., **1** vs **5**, **1** vs **17** and **2** vs **31**). The formation of compounds **29**, **30**, **31**, and **32** led to similar results that those obtained from haemanthamine (**1**). Regarding to the derivatives (**33–37**) obtained from 11-hydroxyvittatine (**3**), the acylation of the hydroxyl groups led to different results depending on the type of esters at C-3 and C-11. Thus, the diacetate compound **33** was inactive (i.e., **3** vs **33**), the introduction of isobutyrates produced a slight improved activity (i.e., **3** vs **37**) and the best activity was achieved with the presence of two nicotinates (i.e., **3** vs **35**).

3. Conclusion

We have prepared 31 derivatives from the natural alkaloids haemanthamine (**1**), haemanthidine (**2**) and 11-hydroxyvittatine (**3**) with the aim of identifying the structural requirements to achieve good inhibitory activity against *P. falciparum*. The presence of the double bond at C-1–C-2 of the ring D and the methylenedioxi group at the ring A seem to play an important role in the activity since they are present in the most active compounds. From the results obtained in the acylation of haemanthamine (**7–12**), haemanthidine (**25–28**) and 11-hydroxy vittatine (**33–37**), we can conclude that the free hydroxyl at C-11 is essential in the haemanthamine series with only one hydroxyl group at C-11. In the haemanthidine series with hydroxyl groups at C-11 and at C-6 or in the 11-hydroxy vittatine series with hydroxyl groups at C-3 and at C-11, the nature of the acyl groups at C-6 or at C-3 modulate the loss of antiplasmodial activity associated with the acylation of the OH at C-11. The presence of two aromatic ester groups at C-3 and at C-11 produces good inhibitory activity. The findings of the present study suggest that some haemantamine derivatives are good inhibitors of *P. falciparum* and provided a useful starting point for the preparation of new haemanthamine-type derivatives with improved antiplasmodial activity.

4. Experimental

4.1. Chemistry

IR spectra were obtained using a Bruker IFS28/55 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter. ^1H and ^{13}C NMR spectra were recorded, unless any other indication, in $CDCl_3$ or MeOD at 300 and 75 MHz respectively. 2D NMR experiments were conducted on a Bruker WP-400 SY NMR spectrometer at 400 MHz. High- and low-resolution mass spectra were obtained on a VG Autospec spectrometer. Analtech Silica Gel GF preparative layer with UV254 was used for TLC. Silica gel (0.2–0.63 mm) was employed for column chromatography. Silica gel 60 (Merck) was used on a Harrison Research 7924T Chromatotron.

Alkaloids **1–6** were extracted from the bulbs of *Pancratium canariense* as described in Reference[15].

4.1.1. 11-Acetylhaemanthamine (7)

To 14 mg (0.046 mmol) of **1** in 1 mL of pyridine was added 0.3 mL (3.18 mmol) of acetic anhydride. After 3 h stirring, the solvent was evaporated and the residue was purified by preparative TLC using DCM/MeOH 19:1 as eluent to yield 15 mg (99%) of **7** as an amorphous white solid. $[\alpha]_D^{20}$ −5.6 (*c* 0.98, EtOH). ^1H NMR ($CDCl_3$) δ: 4.97 (1H, t, J = 5.0 Hz, H-11), 1.96 (3H, s, $OCOCH_3$), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 169.8 (s, $OCOCH_3$), 79.9 (d, C-11), 21.0 (q, $OCOCH_3$), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2933, 1735, 1648, 1483, 1373, 1240, 1086, 1036, 933, 847, 755, 662. EIMS *m/z* (%): 343 (M^+, 100); 300 (4); 284 (17); 268 (12); 252 (16); 224 (28); 211 (16); 188 (11); 181 (19). HRMS *m/z* 343.1410 (calcd for $C_{19}H_{21}NO_5$ $[M]^+$ 343.1420).

4.1.2. 11-(*p*-Vinylbenzoyl)-haemanthamine (8)

To a solution of 23.4 mg (0.08 mmol) of **1** in 3 mL of DCM were added 33 mg (2 equiv) of 1,3-dicyclohexylcarbodiimide (DCC) and 19 mg (2 equiv) of *p*-vinylbenzoic acid. The mixture was stirred for 24 h. Then, the solvent was evaporated and the residue was purified by preparative TLC using DCM/MeOH 9:1 to yield 24.4 mg (73%) of compound **8** as an amorphous white solid. $[\alpha]_D^{20}$ +46.2 (*c* 0.08, MeOH). ^1H NMR ($CDCl_3$) δ 7.86 (2H, d, J = 8.0 Hz, H-2′), 7.45 (2H, d, J = 8.0 Hz, H-3′), 6.74 (1H, dd, J = 10.8 Hz, J = 17.5 Hz, H-5′), 5.86 (1H, d, J = 19.9 Hz, H-6′), 5.39 (1H, d, J = 10.8 Hz, H-6′), 5.20 (1H, br s, H-11) for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 164.9 (s, C=O), 141.9 (s, C-1′), 135.6 (d, C-5′), 129.4 (d, C-2′), 127.3 (s, C-4′), 125.9 (d, C-3′), 116.4 (t, C-6′), 80.5 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2922, 2848, 1710, 1621, 1481, 1270, 1239, 1178, 1097, 1020, 930, 848, 783, 683. EIMS *m/z* (%): 432 ($[M+1]^+$, 100);

356 (4); 342 (5); 315 (4); 288 (11); 277 (3). HREIMS *m/z* 432.1814 (calcd for $C_{26}H_{26}NO_5$ $[M+1]^+$ 432.1811).

4.1.3. General procedure for acylation of 1

To a solution of haemanthamine (**1**) in 3 mL of dry DCM were added Et_3N (2.5 equiv) and 1.5 equiv of the corresponding acyl chloride. The mixture was stirred at room temperature until disappearance of the starting material. Then, the solvent was evaporated and the residue was purified by preparative TLC using DCM/MeOH 9:1 to afford the corresponding esters **9–12**.

4.1.4. 11-Nicotylhaemanthamine (9)

Following the procedure described above, 17.6 mg (0.06 mmol) of **1** was treated with 21 μL (2.5 equiv) of Et_3N and 16 mg (0.09 mmol) of nicotinoyl chloride. After purification, 11 mg (48%) of **9** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +30.0 (*c* 0.95, EtOH). ^{1}H NMR ($CDCl_3$) δ 9.10 (1H, s, CC*H*N), 8.78 (1H, d, *J* = 3.5 Hz, NC*H*CHCHC), 8.20 (1H, d, *J* = 7.9 Hz, NCHCHC*H*C), 7.41 (1H, dd, *J* = 2.9 Hz, *J* = 7.8 Hz, NCHC*H*CHC), 5.22 (1H, dd, *J* = 2.2 Hz, *J* = 3.9 Hz, H-11), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 163.9 (s, C=O), 153.3 (d, *C*CHN), 150.3 (d, NCHCHCHC), 136.9 (d, NCHCHCHC), 125.9 (s, *C*CHN), 123.3 (d, NCHCHCH), 81.0 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2927, 1721, 1591, 1482, 1328, 1283, 1239, 1115, 1039, 935, 848, 754, 701, 664. EIMS *m/z* (%): 406 (M^+, 100); 375 (5); 300 (8); 283 (27); 268 (18); 252 (20); 224 (38); 181 (14). HREIMS *m/z* 406.1562 (calcd for $C_{23}H_{22}N_2O_5$ $[M]^+$ 406.1529).

4.1.5. 11-(*p*-Bromobenzoyl)-haemanthamine (10)

Following the procedure described above, 20.6 mg (0.7 mmol) of **1** was reacted with 24 μL (2.5 equiv) of Et_3N and 23 mg (1.05 mmol) of *p*-bromobenzoyl chloride to yield, after purification, 19 mg (60%) of **10** as an amorphous white solid. $[\alpha]_D^{20}$ +27.3 (*c* 0.9, EtOH). ^{1}H NMR ($CDCl_3$) δ 7.77 (2H, d, *J* = 8.4 Hz, H-2′), 7.57 (2H, d, *J* = 8.4 Hz, H-3′), 5.91 (2H, s, OCH_2O), 5.21 (1H, br s, H-11), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 163.8 (s, C=O), 131.6 (d, C-2′), 130.6 (d, C-3′), 126.2 (s, C-1′), 123.0 (s, C-4′), 106.5 (d, C-7), 103.7 (d, C-10), 100.8 (t, OCH_2O), 80.9 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3443, 2928, 1721, 1645, 1483, 1270, 1240, 1173, 1100, 1039, 936, 847, 755. EIMS *m/z* (%): 485 ($[M+1]^+$, 100); 483 ($[M-1]^+$, 99); 456 (5); 441 (7); 371 (9); 300 (20); 283 (65); 268 (52); 252 (37); 224 (61); 184 (54). HREIMS *m/z* 485.0672 (calcd for $C_{24}H_{22}NO_5Br$ $[M]^+$ 485.0661).

4.1.6. 11-Isobutyrylhaemanthamine (11)

Following the procedure described above, 16.5 mg (0.055 mmol) of **1** was treated with 20 μL (2.5 equiv) of Et_3N and 9 μL (0.17 mmol) of isobutyryl chloride. After purification, 13 mg (65%) of **11** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +3.8 (*c* 1.3, EtOH). ^{1}H NMR ($CDCl_3$) δ 4.97 (1H, t, *J* = 5.0 Hz, H-11), 2.44 (1H, m, C*H*$(CH_3)_2$), 1.10 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3)_2$), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 175.6 (s, C=O), 79.0 (d, C-11), 33.7 (d, *C*H$(CH_3)_2$), 18.8 (q, CH(*C*H$_3)_2$), 18.4 (q, CH(*C*H$_3)_2$), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2973, 2932, 1731, 1483, 1325, 1240, 1155, 1086, 1039, 934, 850, 755, 663. EIMS *m/z* (%): 371 (M^+, 100); 342 (6); 300 (12); 283 (30); 268 (35); 252 (20); 224 (53); 181 (24). HREIMS *m/z* 371.1748 (calcd for $C_{21}H_{25}NO_5$ $[M]^+$ 371.1733).

4.1.7. 11-Acryloylhaemanthamine (12)

Following the procedure described above, 30 mg (0.1 mmol) of **1** were treated with 28 μL (2 equiv) of Et_3N and 13 μL (0.15 mmol) of acryloyl chloride. After purification, 9.6 mg (28%) of **12** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +13.9 (*c* 0.18, MeOH). ^{1}H NMR ($CDCl_3$) δ 6.30 (1H, d, *J* = 8.6 Hz, OCOCHC*H*$_2$), 6.03 (1H, dd, *J* = 10.4 Hz, *J* = 17.2 Hz, OCOC*H*CH$_2$), 5.81 (1H, d, *J* = 10.4 Hz, OCOCHC*H*$_2$), 5.06 (1H, t, *J* = 5.1 Hz, H-11), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 164.8 (s, C=O), 130.6 (t, OCOCH*C*H$_2$), 128.1 (d, OCOCH*C*H$_2$), 80.0 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3036, 2929, 1722, 1619, 1483, 1405, 1326, 1267, 1239, 1086, 1041, 932, 849, 808, 733. EIMS *m/z* (%): 355 ($[M]^+$, 100); 340 (3); 324 (4); 300 (8); 283 (18); 268 (14); 252 (17); 225 (26); 210 (16), 185 (5). HREIMS *m/z* 355.1414 (calcd for $C_{20}H_{21}NO_6$ $[M]^+$ 355.1420).

4.1.8. 11,12-Epoxyhaemanthamine (13)

To 20 mg (0.066 mmol) of **1** dissolved in DCM (3 mL) were added 24 mg (2 equiv) of N-bromosuccinimide (NBS). The reaction was stirred for 12 h and then the solvent was evaporated. The residue was purified by preparative TLC using DCM/MeOH 9:1 to yield 19 mg (85%) of compound **13** as an amorphous white solid. $[\alpha]_D^{20}$ +2.8 (*c* 1.2, EtOH). ^{1}H NMR ($CDCl_3$) δ 4.27 (1H, br s, H-11), 3.78 (2H, m, H-4a, H-12), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 76.7 (d, C-12), 64.7 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2928, 1643, 1485, 1244, 1035, 929, 855, 733, 591. EIMS *m/z* (%): 300 ($[M+1]^+$, 8); 269 (75); 257 (60); 240 (31); 227 (100); 211 (43); 181 (84). HREIMS *m/z* 300.1235 (calcd for $C_{17}H_{18}NO_4$ $[M+1]^+$ 300.1236).

4.1.9. 11-Oxohaemanthamine (14)

To a solution of 20 mg (0.066 mmol) of **1** in acetone (2 mL) at 0 °C, was added the Jones reagent dropwise, until the solution turned orange. The reaction mixture was stirred for 30 min and then isopropanol was added. The solution was filtered through Florisil and the filtrate was concentrated and purified by preparative TLC using DCM/MeOH 9:1 to yield 8 mg (40%) of compound **14** as an amorphous white solid. $[\alpha]_D^{20}$ +38.3 (*c* 0.6, EtOH). ^{1}H NMR ($CDCl_3$) δ 3.52 (4H, m, H-6, H-12, H-4a), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 205.2 (s, C-11), 58.7 (t, C-12), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2925, 1734, 1646, 1482, 1239, 1085, 1038, 932, 849, 758, 666. EIMS *m/z* (%): 299 (M^+, 2); 271 (100); 211 (25); 181 (65). HREIMS *m/z* 299.1140 (calcd for $C_{17}H_{17}NO_4$ $[M]^+$ 299.1158).

4.1.10. 11-Oxohaemanthamine oxime (15)

To a solution of 17 mg (0.057 mmol) of **14** in 2 mL of EtOH were added 12 mg (3 equiv) of hydroxylamine hydrochloride and a solution of 10 mg (2 equiv) of sodium acetate in 0.5 mL of H_2O. The mixture was refluxed for 15 h. Then, the solvent was evaporated and water was added to the residue. The mixture was extracted with DCM and the organic phase was then dried over anhydrous magnesium sulphate, filtered and concentrated. Further purification by preparative TLC using DCM/MeOH 9:1 yielded 4.6 mg (26%) of compound **15** as an amorphous white solid. $[\alpha]_D^{20}$ −7.4 (*c* 0.23, EtOH). ^{1}H NMR ($CDCl_3$) δ 3.84 (2H, m, H-12), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 168.0 (s, C-11), 53.1 (t, C-12), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3421, 2926, 1645, 1483, 1329, 1240, 1086, 1038, 932, 854, 796, 736. EIMS *m/z* (%): 314 (M^+, 19); 297 (8); 266 (21); 238 (12); 224 (100); 210 (12); 181 (5). HREIMS *m/z* 314.1266 (calcd for $C_{17}H_{18}N_2O_4$ $[M]^+$ 314.1267).

4.1.11. Apohaemanthamine (16)

A solution of 20 mg (0.066 mmol) of **1** in 5 mL of a solution 6 M HCl was heated at 100 °C for 4 h. Then, a 20% NH_4OH solution was added until basic pH and the mixture was extracted with DCM. The organic phase was dried over anhydrous magnesium sulphate and

concentrated. After purification by preparative TLC, using DCM/MeOH 22:3, 5.8 mg (33%) of compound **16** was obtained as an amorphous white solid. $[\alpha]_D^{20}$ +91.5 (*c* 0.6, MeOH). ^{1}H NMR (MeOD) δ 4.40 (1H, br s, H-3), 3.69 (1H, s, H-11), 3.21 (2H, s, H-12), for the rest of the signals see Supplementary data. ^{13}C NMR (MeOD) δ 80.2 (d, C-11), 64.6 (d, C-3), 60.5 (t, C-12), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3055, 2927, 1645, 1482, 1384, 1264, 1233, 1037, 936, 870, 738, 703. EIMS *m/z* (%): 269 (M$^+$, 100); 240 (21); 224 (10); 214 (24); 186 (22); 181 (34); 152 (15); 128 (16). HREIMS *m/z* 269.1058 (calcd for $C_{16}H_{15}NO_3$ [M]$^+$ 269.1052).

4.1.12. 12 8,9-Nor-11-hydroxyvittatine (17)

To a solution of 22 mg (0.073 mmol) of **1** in 5 mL of dry DCM, at 0 °C, was added dropwise 0.22 mL (3 equiv) of a 1 M BBr_3 solution in DCM. The reaction mixture was stirred for 7 h, then the solvent was removed and the residue was chromatographied with preparative TLC using DCM/MeOH 9:1. 15.5 mg (55%) of compound **17** was obtained as an amorphous white solid. $[\alpha]_D^{20}$ +50.5 (*c* 1.55, EtOH). ^{1}H NMR (MeOD) δ 4.53 (1H, br s, H-3), for the rest of the signals see Supplementary data. ^{13}C NMR (MeOD) δ 145.5 (s, C-9), 145.3 (s, C-8), 63.7 (d, C-3), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3437, 2928, 1644, 1250, 613. EIMS *m/z* (%): 275 (M$^+$, 4); 257 (100); 228 (26); 214 (11); 199 (22); 181 (43). HREIMS *m/z* 275.1139 (calcd for $C_{15}H_{17}NO_4$ [M]$^+$ 275.1158).

4.1.13. Haemanthamine N-oxide (18)

To a solution of 24.4 mg (0.083 mmol) of **1** in 2 mL of MeOH, at 0 °C, was added dropwise 0.1 mL (11 equiv) of 30% H_2O_2. The reaction mixture was stirred at room temperature for 24 h. Then, an excess of manganese dioxide was added and the resulting mixture was filtered through Celite. After evaporation of the solvent, 13 mg (50%) of compound **18** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +2.8 (*c* 0.91, EtOH). ^{1}H NMR (MeOD) δ 4.68 (2H, d, *J* = 4.5 Hz, H-6), 3.67 (2H, dd, *J* = 4.5 Hz, *J* = 8.6 Hz, H-12), for the rest of the signals see Supplementary data. ^{13}C NMR (MeOD) δ 75.4 (t, C-12), 74.0 (t, C-6), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3430, 2925, 1725, 1645, 1487, 1249, 1038, 930. EIMS *m/z* (%): 317 ([M]+, 5); 301 (85); 269 (61); 257 864); 240 (34); 227 (100); 211 (45); 181 (83). HREIMS *m/z* 317.1263 (calcd for $C_{17}H_{21}NO_5$ [M]$^+$ 317.1259).

4.1.14. 1,2-Dihydrohaemanthamine (19)

15.3 mg (0.047 mmol) of compound **1** dissolved in 3 mL of THF were hydrogenated in the presence of catalytic amounts of Pd/C. The reaction mixture was stirred for 5 days. The solution was filtered through Celite and the solvent was evaporated. After purification by preparative TLC with DCM/MeOH 9:1, 8 mg (52%) of compound **19** was obtained as an amorphous white solid. $[\alpha]_D^{20}$ +39.8 (*c* 0.6, EtOH). ^{1}H NMR ($CDCl_3$) δ 1.88 (4H, m, H-1, H-2), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 26.5 (t, C-2), 22.5 (t, C-1), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3441, 2926, 2857, 1720, 1644, 1487, 1354, 1245, 1087, 1041, 939, 852, 758, 670. EIMS *m/z* (%): 303 (M$^+$, 100); 287 (18); 272 (20); 259 (41); 244 (12); 226 (33); 211 (38); 186 (50). HREIMS *m/z* 303.1454 (calcd for $C_{17}H_{21}NO_4$ [M]$^+$ 303.1471).

4.1.15. 1,2-Dibromohaemanthamine (20)

A solution of 22 mg (0.073 mmol) of **1** in 4 mL of dry DCM was treated with 5 μL (1 equiv) of Br_2. The reaction mixture was stirred at room temperature for 24 h. Then, the solvent was evaporated and the residue was purified by preparative TLC using DCM/MeOH 17:3 to afford 8 mg (25%) of compound **20** as an orange solid. $[\alpha]_D^{20}$ +4.3 (*c* 0.8, EtOH). ^{1}H NMR ($CDCl_3$) δ 4.87 (2H, s, H-1, H-2), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 63.8 (d, C-2), 60.1 (t, C-1), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3440, 2927, 1644, 1503, 1483, 1241, 1037, 933, 734, 600. EIMS *m/z* (%): 460 (M$^+$, 3); 459 (2); 382 (29); 380 (29); 331 (5); 300 (100); 270 (11); 245 (34); 238 (18); 181 (21). HREIMS *m/z* 460.9663 (calcd for $C_{17}H_{19}NO_4Br_2$ [M]$^+$ 460.9660).

4.1.16. 2-Bromo-1-hydroxyhaemanthamine (21)

20 mg (0.066 mmol) of **1** was added to a cold (0 °C) mixture of 10 mg (1.2 equiv) of N-bromoacetamide, 27 μL (0.4 equiv) of a 1 M solution of tin chloride ($SnCl_4$) in DCM, and 1.5 μL (1.2 equiv) of H_2O in 5 mL of MeCN. After 12 h stirring, water was added and the mixture was extracted with DCM. The organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated and purified by preparative TLC using DCM/MeOH 9:1 to yield 13.5 mg (51%) of compound **21** as an amorphous white solid. $[\alpha]_D^{20}$ +135.0 (*c* 0.6, MeOH). ^{1}H NMR (MeOD) δ 4.90 (1H, m, H-2), 4.39 (1H, d, *J* = 5.4 Hz, H-1), for the rest of the signals see Supplementary data. ^{13}C NMR (MeOD) δ 76.8 (d, C-1), 41.0 (d, C-2), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3422, 2930, 1670, 1484, 1378, 1330, 1236, 1095, 1034, 935, 839, 768, 740, 670. FABMS *m/z* (%): 399 (M$^+$, 4); 382 (46); 380 (48); 350 (7); 289 (17); 273 (4); 241 (8); 181 (6); 176 (11), 154 (100). HRMS *m/z* 399.0486 (calcd for $C_{17}H_{20}NO_5Br$ [M]$^+$ 399.0500).

4.1.17. 1-Bromo-2-hydroxyhaemanthamine (22)

A solution of 20 mg (0.066 mmol) of **1** in 5 mL of dry MeCN, at 0 °C, was added to a mixture of 10 mg (1.2 equiv) of N-bromoacetamide and 27 μL (0.4 equiv) of a 1 M solution of tin chloride ($SnCl_4$) in DCM. The reaction mixture was stirred for 5 h. After that period, water was added and the mixture was extracted with DCM. The organic phase was concentrated and purified by preparative TLC, using DCM/MeOH 9:1 to yield 18 mg (69%) of compound **22** as an amorphous white solid. $[\alpha]_D^{20}$ +88.0 (*c* 0.9, MeOH). ^{1}H NMR (MeOD) δ 6.77 (1H, s, H-10), 6.60 (1H, s, H-7), 5.92 (1H, br s, OCH_2O), 5.90 (1H, br s, OCH_2O), 4.91 (1H, d, *J* = 5.3 Hz, H-1), 4.45 (1H, d, *J* = 17.1 Hz, H-6), 4,.42 (1H, d, *J* = 5.3 Hz, H-2), 4.19 (1H, dd, *J* = 2.9 Hz, *J* = 6.3 Hz, H-11), 3.89 (1H, d, *J* = 17.1 Hz, H-6), 3.63 (1H, m, H-3), 3.54 (2H, m, H-12), 3.39 (3H, s, OMe), 3.30 (1H, m, H-4a), 2.40 (1H, m, H-4), 2.27 (1H, d, *J* = 9.3 Hz, H-4). ^{13}C NMR (MeOD) δ 147.0 (s, C-8), 146.6 (s, C-9), 129.7 (s, C-10a), 125.2 (s, C-6a), 106.1 (d, C-7), 101.8 (d, C-10), 100.8 (t, OCH_2O), 87.5 (d, C-11), 79.4 (d, C-3), 76.9 (d, C-2), 63.7 (d, C-4a), 62.9 (t, C-12), 59.5 (t, C-6), 55.6 (q, OMe), 54.9 (s, C-10b), 40.6 (d, C-1), 28.8 (t, C-4). IR (neat, cm^{-1}): 3458, 2932, 1730, 1503, 1484, 1385, 1236, 1100, 1035, 935, 845, 735, 671. FABMS *m/z* (%): 398 ([M-1]$^+$, 8); 382 (18); 380 (16); 350 (7); 289 (14); 273 (6); 242 (5); 226 (3); 176 (14), 154 (100). HRMS *m/z* 398.0444 (calcd for $C_{17}H_{19}NO_5Br$ [M-1]$^+$ 398.0422).

4.1.18. General procedure for the preparation of formamides 23 and 24

A solution of compound **7** in 5 mL of CH_3CN was treated with an excess of the corresponding alkyl halide. The reaction mixture was refluxed for 24 h. Then, the solvent was evaporated and the residue was dissolved in 5 mL of *t*-butanol. An excess of potassium *t*-butoxide (7 equiv) was added and the mixture was refluxed for 4 h. After this period, a saturated solution of NH_4Cl was added and the mixture was extracted with DCM. The organic phase was dried over anhydrous $MgSO_4$, filtered, concentrated and purified by preparative TLC using DCM/MeOH 99:1 as eluent.

4.1.19. *N*-{[6-(4-Hydroxyphenyl)-1,3-benzodioxol-5-yl]methyl}-*N*-methylformamide (23)

Following the general procedure, 19 mg (0.055 mmol) of **1** were treated with 0.5 mL (8 mmol) of methyl iodide, to yield 5.1 mg

(33%) of compound **23** as an amorphous pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.01 (1H, s, CHO), 7.48 (1H, s, CHO), 7.08 (2H, d, J = 8.4 Hz, H-1, H-4a), 7.02 (2H, d, J = 8.4 Hz, H-1, H-4a), 6.88 (2H, d, J = 8.4 Hz, H-2, H-4), 6.85 (2H, d, J = 8.3 Hz, H-2, H-4), 6.74 (1H, s, H-7), 6.72 (2H, s, H-7, H-10), 6.70 (1H, s, H-10), 6.00 (2H, s, OCH_2O), 5.97 (2H, s, OCH_2O), 4.44 (2H, s, H-6), 4.23 (2H, s, H-6), 2.63 (3H, s, NMe), 2.61 (3H, s, NMe). ^{13}C NMR ($CDCl_3$) δ 162.5 (d, CHO), 162.4 (d, CHO), 155.7 (s, C-3), 155.0 (s, C-3), 147.0 (s, C-9), 146.9 (s. C-9), 146.6 (s, C-8), 146.5 (s. C-8), 136.2 (s, C-10a), 135.6 (s. C-10a), 132.1 (s, C-10b), 131.3 (s, C-10b), 130.2 (d, C-1, C-4a), 129.9 (d, C-1, C-4a), 126.3 (s, C-6a), 125.8 (s, C-6a), 115.3 (d, C-2, C-4), 115.0 (d, C-2, C-4), 110.7 (d, C-10), 110.0 (d, C-10), 108.8 (d, C-7), 107.9 (d, C-7), 101.1 (t, OCH_2O), 100.9 (t, OCH_2O), 51.5 (t, C-6), 44.7 (t, C-6), 33.6 (q, NMe), 28.7 (q, NMe). IR (neat, cm^{-1}): 3272, 2923, 1720, 1612, 1502, 1447, 1394, 1268, 1171, 1090, 1038, 930, 834, 735, 666. EIMS *m/z* (%): 285 ([M]$^+$, 66); 254 (4); 226 (100); 214 (6); 197 (27); 168 (21); 139 (11). HREIMS *m/z* 285.1002 (calcd for $C_{16}H_{15}NO_4$ [M]$^+$ 285.1001).

4.1.20. *N*-Ethyl-N-{[6-(4-Hydroxyphenyl)-1,3-benzodioxol-5-yl]methyl}formamide (24)

Following the general procedure described above, 37.7 mg (0.11 mmol) of **1** were treated with 0.5 mL (6.7 mmol) of ethyl bromide, to yield 15.4 mg (47%) of compound **24** as an amorphous pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, s, CHO), 7.72 (1H, s, CHO), 7.38 (4H, m, H-1, H-4a), 7.22 (4H, m, H-2, H-4), 6.81 (1H, s, H-7), 6.73 (2H, s, H-7, H-10), 6.71 (1H, s, H-10), 6.00 (2H, s, OCH_2O), 5.97 (2H, s, OCH_2O), 4.44 (2H, s, H-6), 4.22 (2H, s, H-6), 3.12 (2H, q, J = 7.1 Hz, NCH_2CH_3), 2.98 (2H, q, J = 7.1 Hz, NCH_2CH_3), 0.83 (3H, t, J = 7.1 Hz, NCH_2CH_3), 0.77 (3H, t, J = 7.1 Hz, NCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 162.3 (d, CHO), 162.0 (d, CHO), 154.2 (s, C-3), 154.0 (s, C-3), 147.2 (s, C-9), 146.8 (s, C-8), 136.0 (s, C-10a), 135.5 (s, C-10a), 129.2 (d, C-1, C-4a), 128.9 (d, C-1, C-4a), 128.2 (d, C-2, C-4), 128.1 (C-2, C-4), 127.2 (s, C-10b), 127.2 (s, C-10b), 126.9 (s, C-6a), 126.5 (s, C-6a), 110.2 (d, C-10), 109.5 (d, C-10), 108.1 (d, C-7), 108.0 (d, C-7), 101.1 (t, OCH_2O), 100.9 (t, OCH_2O), 48.0 (t, C-6), 41.2 (t, NCH_2CH_3), 41.0 (t, NCH_2CH_3), 36.0 (t, C-6), 13.7 (q, NCH_2CH_3), 11.7 (q, NCH_2CH_3). IR (neat, cm^{-1}): 3445, 3057, 2975, 2893, 1699, 1503, 1481, 1443, 1398, 1375, 1224, 1100, 1037, 930, 872, 769, 704. EIMS *m/z* (%): 299 ([M]$^+$, 6); 283 (54); 254 (5); 224 (3); 210 (100); 181 (26); 167 (5); 152 (31); 139 (6). HREIMS *m/z* 299.1158 (calcd for $C_{17}H_{17}NO_4$ [M]$^+$ 299.1153).

4.1.21. 6,11-Diacetylhaemanthidine (25)

To 13.8 mg (0.044 mmol) of compound **2** dissolved in 1 mL of pyridine, 0.3 mL (3.18 mmol) of acetic anhydride were added. The reaction mixture was stirred at room temperature for 3 h, then the solvent was evaporated and the residue was purified by preparative TLC with DCM/MeOH 19:1 to yield 17 mg (99%) of compound **25** as an amorphous white solid. $[\alpha]_D^{20}$ −.7 (*c* 1.19, EtOH). ^{1}H NMR ($CDCl_3$) δ 6.12 (1H, s, H-6), 4.90 (1H, t, J = 6.6 Hz, H-11), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 170.1 (s, $OCOCH_3$), 169.9 (s, $OCOCH_3$), 86.3 (d, C-6), 78.5 (d, C-11), 21.2 (q, $OCOCH_3$), 20.9 (q, $OCOCH_3$) for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3055, 2932, 1737, 1483, 1370, 1245, 1089, 1036, 936, 864, 815, 737. EIMS *m/z* (%): 401 (M$^+$, 32); 386 (20); 359 (19); 342 (47); 327 (16); 299 (36); 284 (100); 268 (37); 254 (27); 224 (49); 209 (66); 181 (18). HREIMS *m/z* 401.1461 (calcd for $C_{21}H_{23}NO_7$ [M]$^+$ 401.1475).

4.1.22. General procedure for acylation of 2

To a solution of haemanthidine **2** in 3 mL of dry DCM were added 5 equiv of Et_3N and 3 equiv of the corresponding acyl chloride. After stirring at rt for 18 h, the solvent was evaporated and the residue was purified by preparative TLC using DCM/MeOH 92:8 yielding the corresponding esters **26–28**.

4.1.23. 6-Nicotylhaemanthidine (26)

Following the procedure described above, 15 mg (0.047 mmol) of **2** were treated with 33 μL (0.235 mmol) of Et_3N and 25.2 mg (0.141 mmol) of nicotinoyl chloride. After purification, 16 mg (81%) of compound **26** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +22.2 (*c* 0.09, MeOH). ^{1}H NMR ($CDCl_3$) δ 9.29 (1H, s, CCHN), 9.22 (1H, s, CCHN), 8.80 (1H, d, J = 3.8 Hz, NC*H*CHCHC), 8.76 (1H, d, J = 4.6 Hz, NC*H*CHCHC), 8.37 (1H, d, J = 7.8 Hz, NCHCHC*H*C), 8.30 (1H, d, J = 7.9 Hz, NCHCHC*H*C), 7.42 (1H, dd, J = 4.8 Hz, J = 7.7 Hz, NCHC*H*CHC), 7.37 (1H, dd, J = 5.0 Hz, J = 7.8 Hz, NCHC*H*CHC), 6.86 (1H, s, H-6), 3.98 (1H, s, H-11), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 164.0 (s, C=O), 153.6 (d, C*C*HN), 153.3 (d, C*C*HN), 150.9 (d, N*C*HCHCHC), 150.8 (d, N*C*HCHCHC), 137.2 (d, NCHCH*C*HC), 137.2 (d, NCHCH*C*HC), 125.5 (s, *C*CHN), 123.2 (d, NCH*C*HCHC), 123,0 (d, NCH*C*HCHC), 86.8 (d, C-6), 78.0 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3399, 2925, 2855, 1724, 1603, 1483, 1387, 1249, 1195, 1098, 1036, 933, 870, 737, 700, 663. EIMS *m/z* (%): 422 (M$^+$, 2); 406 (3); 323 (10); 284 (7); 257 (18); 248 (31); 225 (63); 166 (12); 123 (100). HREIMS *m/z* 422.1469 (calcd for $C_{23}H_{22}N_2O_6$ [M]$^+$ 422.1478).

4.1.24. 6,11-Bis(*p*-bromobenzoyl)-haemanthidine (27)

Following the procedure described above, 15.6 mg (0.049 mmol) of **2** was reacted with 33 μL (0.245 mmol) of NEt_3 and 31.1 mg of *p*-bromobenzoyl chloride (0.147 mmol) to yield, after purification, 13 mg (40%) of compound **27** as an amorphous white solid. $[\alpha]_D^{20}$ +25.0 (*c* 0.22, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d, J = 8.4 Hz, H-2′), 7.75 (2H, d, J = 8.4 Hz, H-2′), 7.61 (2H, d, J = 8.6 Hz, H-3′), 7.57 (2H, d, J = 8.4 Hz, H-3′), 6.91 (1H, s, H-6), 5.18 (1H ,d, J = 4.4 Hz, H-11), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 164.9 (s, C=O), 164.6 (s, C=O), 164,5 (s, C=O), 164,5 (s, C=O), 131.7 (d, C-2′), 131.6 (d, C-2′), 131.5 (d, C-2′), 131.2 (d, C-3′), 130.5 (d, C-3′), 128.7 (s, C-1′), 128.5 (s, C-1′), 128.5 (s, C-1′), 128.2 (s, C-1′), 128.2 (s, C-4′), 128.1 (s, C-4′), 87.7 (d, C-6), 80.3 (d, C-11), 76.9 (d, C-11), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2926, 1720, 1589, 1482, 1398, 1262, 1173, 1092, 1010, 935, 848, 754. EIMS *m/z* (%): 682 (M$^+$, 7); 680 (4); 500 (30); 482 (37); 457 (10); 299 (52); 284 (63); 266 (40); 254 (29); 182 (100). HREIMS *m/z* 682.9946 (calcd for $C_{31}H_{25}NO_7Br_2$ [M]$^+$ 682.9977).

4.1.25. 6,11-Diisobutyrylhaemanthidine (28)

Following the procedure described above, 15 mg (0.047 mmol) of **2** were treated with 33 μL of Et_3N (0.245 mmol) and 15 μL of isobutyryl chloride (0.147 mmol). After purification, 14 mg (65%) of compound **28** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +51.2 (*c* 0.16, MeOH). ^{1}H NMR ($CDCl_3$) δ 6.57 (1H, s, H-6), 4.88 (1H, br s, H-11), 2.64 (1H, m, C*H*$(CH_3)_2$), 2.44 (1H, m, C*H*$(CH_3)_2$), 1.25 (6H, d, J = 6.8 Hz, CH(C*H*$_3)_2$), 1.09 (6H, d, J = 6.9 Hz, CH(C*H*$_3)_2$), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 176.1 (s, C=O), 175.8 (s, C=O), 175.7 (s, C=O), 175.4 (s, C=O), 86.6 (d, C-6), 85.2 (d, C-6), 78.9 (d, C-11), 78.0 (d, C-11), 34.0 (d, *C*H$(CH_3)_2$), 33.8 (d, *C*H$(CH_3)_2$), 33.6 (d, *C*H$(CH_3)_2$), 33.6 (d, *C*H$(CH_3)_2$), 18.8 (q, CH(*C*H$_3)_2$), 18.7 (q, CH(*C*H$_3)_2$), 18.6 (q, CH(*C*H$_3)_2$), 18.5 (q, CH(*C*H$_3)_2$), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2974, 2935, 1734, 1647, 1483, 1387, 1335, 1248, 1190, 1150, 1094, 1023, 934, 858, 808, 736. EIMS *m/z* (%): 457 (M$^+$, 31); 442 (18); 386 (41); 370 (78); 343 (6); 299 (74); 284 (100); 273 (11); 254 (40); 209 (27). HREIMS *m/z* 457.2111 (calcd for $C_{25}H_{31}NO_7$ [M]$^+$ 457.2101).

4.1.26. 11-Oxohaemanthidine (29)

To a solution of 20 mg (0.063 mmol) of compound **2** in 2 mL of acetone at 0 °C, the Jones reagent was added dropwise, until the solution turned orange. The reaction mixture was stirred for

30 min and then isopropanol was added. The solution was filtered through Florisil and the residue was concentrated and purified by preparative TLC using DCM/MeOH 9:1 as eluant, to yield 9 mg (46%) of compound **29** as an amorphous white solid. $[\alpha]_D^{20}$ +51.4 (*c* 0.7, MeOH). ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, m, H-12, H-4a), 3.51 (1H, d, *J* = 18.7 Hz, H-12), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 209.1 (s, C-11), 209.0 (s, C-11), 53.6 (t, C-12), 49.1 (t, C-12), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3416, 2924, 1747, 1503, 1482, 1400, 1246, 1118, 1084, 1037, 935, 871, 736, 670. EIMS *m/z* (%): 315 (M^+, 11); 300 (5); 287 (59); 258 (28); 225 (57); 209 (28); 200 (100); 141 (22). HREIMS *m/z* 315.1091 (calcd for $C_{17}H_{17}NO_5$ $[M]^+$ 315.1107).

4.1.27. 6-(6-Methoxy-3-oxo-3,6,7,7a-tetrahydro-3a*H*-indol-3a-yl)-1,3-benzodioxole-5-carbaldehyde (30)

To 20 mg (0.063 mmol) of **2** in 5 mL of DCM were added 5 mg (0.2 equiv) of tetrabutylammonium iodide, 7 mg (0.7 equiv) of TEMPO and 33 mg (3 equiv) of *m*-chloroperbenzoic acid. The reaction mixture was stirred at room temperature for 24 h. Then, it was treated with a saturated solution of sodium bicarbonate and the mixture was extracted with DCM. The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by preparative TLC using DCM/MeOH 97:3 to yield 15 mg (76%) of compound **30** as an amorphous white solid. $[\alpha]_D^{20}$ −4.0 (*c* 1.2, MeOH). ^{1}H NMR ($CDCl_3$) δ 9.68 (1H, s, CHO), 7.29 (1H, s, H-7), 7.26 (1H, s, H-12), 7.08 (1H, s, H-10), 6.31 (1H, d, *J* = 10.1 Hz, H-2), 6.12 (2H, s, OCH_2O), 5.63 (1H, d, *J* = 10.1 Hz, H-1), 4.60 (1H, t, *J* = 3.2 Hz, H-3), 3.90 (1H, m, H-4a), 3.45 (3H, s, OMe), 3.08 (1H, m, H-4), 1.51 (1H, dt, *J* = 2.5 Hz, *J* = 10.4 Hz, H-4). ^{13}C NMR ($CDCl_3$) δ 193.9 (s, C-11), 191.3 (d, CHO), 152.4 (s, C-9), 147.7 (s, C-8), 133.9 (C-12), 133.9 (d, C-2), 132.5 (s, C-6a), 127.7 (s, C-10a), 125.8 (d, C-1), 115.9 (d, C-7), 112.9 (d, C-10), 102.6 (t, OCH_2O), 74.3 (d, C-3), 69.9 (d, C-4a), 57.2 (s, C-10b), 56.5 (q, OMe), 24.4 (t, C-4). IR (neat, cm^{-1}): 2924, 1718, 1691, 1605, 1547, 1507, 1360, 1330, 1263, 1198, 1095, 1034, 926, 878, 788, 600. EIMS *m/z* (%): 313 (M^+, 30); 294 (7); 268 (5); 256 (4); 225 (5); 200 (11); 178 (18); 125 (100). HRMS *m/z* 313.0963 (calcd for $C_{17}H_{15}NO_5$ $[M]^+$ 313.0950).

4.1.28. 8,9-Nor-6,11-dihydroxyvittatine (31)

To a solution of 22 mg (0.07 mmol) of compound **2** in 5 mL of dry DCM at 0 °C, was added dropwise 0.4 mL (6 equiv) of a 1 M BBr_3 solution in DCM. After 5 h stirring, the solvent was removed and the residue was purified by preparative TLC using DCM/MeOH 4:1. 13 mg (62%) of compound **31** were obtained as an amorphous orange solid. $[\alpha]_D^{20}$ +27.9 (*c* 1.1, EtOH). ^{1}H NMR (MeOD) δ 6.98 (1H, m, H-2), 6.92 (1H, s, H-7), 6.91 (1H, s, H-10), 6.86 (1H, s, H-10), 6.82 (1H, s, H-7), 6.69 (1H, d, *J* = 8.5 Hz, H-1), 6.66 (1H, d, *J* = 8.5 Hz, H-1), 6.27 (1H, s, H-6), 5.67 (1H, s, H-6), 4.56 (1H, br s, H-3), 3.99 (1H, m, H-12), 3.96 (1H, m, H-4a), 3.79 (1H, br s, H-11), 3.76 (1H, br s, H-11), 3.49 (1H, d, *J* = 5.8 Hz, H-12), 2.10 (2H, t, *J* = 5.1 Hz, H-4). ^{13}C NMR (MeOD) δ 147.1 (s, C-9), 146.4 (s, C-9), 145.9 (s, C-8), 145.7 (s, C-8), 139.1 (d, C-2), 139.0 (d, C-2), 126.0 (d, C-1), 125.8 (d, C-1), 122.0 (s, C-10a), 120.0 (s, C-6a), 115.0 (d, C-7), 113.7 (d, C-7), 111.9 (d, C-10), 111.6 (d, C-10), 86.3 (d, C-6), 85.7 (d, C-6), 77.1 (d, C-11), 76.3 (d, C-11), 63.4 (d, C-3), 60.9 (d, C-4a), 56.2 (t, C-12), 54.2 (d, C-4a), 51.8 (t, C-12), 47.0 (s, C-10b), 32.0 (t, C-4), 30.4 (t, C-4). IR (neat, cm^{-1}): 3443, 2925, 1643, 1247, 668. EIMS *m/z* (%): 291 (M^+, 4); 273 (48); 255 (100); 228 (17); 213 (10); 199 (31); 181 (28). HREIMS *m/z* 291.1084 (calcd for $C_{15}H_{17}NO_5$ $[M]^+$ 291.1103).

4.1.29. Apohaemanthidine (32)

20 mg (0.063 mmol) of compound **2** in 5 mL of a 6 M HCl solution were heated at 100 °C for 4 h. Then a 20% NH_4OH solution was added until basic pH and the mixture was extracted with DCM. The organic phase was dried over anhydrous magnesium sulphate filtered and concentrated. After purification by preparative TLC, using DCM/MeOH 22:3, 12 mg (67%) of compound **32** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ +81.5 (*c* 0.4, MeOH). ^{1}H NMR ($CDCl_3$) δ 6.99 (1H, s, H-7), 6.82 (4H, d, *J* = 8.3 Hz, H-1), 6.79 (2H, s, H-10), 6.60 (2H, dd, *J* = 4.1 Hz, *J* = 8.3 Hz, H-2), 5.96 (2H, br s, OCH_2O), 5.95 (2H, br s, OCH_2O), 5.81 (1H, s, H-6), 5.19 (1H, s, H-6), 4.46 (2H, d, *J* = 3.6 Hz, H-3), 3.81 (1H, dd, *J* = 4.6 Hz, *J* = 14.3 Hz, H-12), 3.65 (3H, m, H-4a, H-11), 3.41 (1H, d, *J* = 9.7 Hz, H-12), 3.28 (1H, d, *J* = 13.6 Hz, H-12), 3.03 (2H, m, H-4a, H-12), 1.90 (4H, m, H-4). ^{13}C NMR ($CDCl_3$) δ 147.9 (s, C-9), 147.7 (s, C-9), 147.2 (s, C-8), 147.1 (s, C-8), 138.0 (d, C-2), 137.9 (d, C-2), 131.1 (s, C-10a), 128.2 (d, C-1), 128.1 (d, C-1), 126.1 (s, C-6a), 108.7 (d, C-7), 107.6 (d, C-7), 105.4 (d, C-10), 105.3 (d, C-10), 101.0 (t, OCH_2O), 86.6 (d, C-6), 85.2 (d, C-6), 79.0 (d, C-11), 64.4 (d, C-3), 64.2 (d, C-3), 59.5 (d, C-4a), 56.8 (t, C-12), 53.0 (d, C-4a), 52.1 (t, C-12), 47.4 (s, C-10b), 46.8 (s, C-10b), 33.6 (t, C-4), 29.4 (t, C-4). IR (neat, cm^{-1}): 3418, 3058, 2927, 1730, 1673, 1617, 1483, 1386, 1299, 1248, 1118, 1082, 1037, 932, 872, 817, 736, 700. EIMS *m/z* (%): 285 (M^+, 99); 268 (100); 256 (11); 239 (10); 225 (11); 209 (31); 201 (28); 185 (15). HREIMS *m/z* 285.1009 (calcd for $C_{16}H_{15}NO_4$ $[M]^+$ 285.1001).

4.1.30. 3,11-Diacetyl-11-hydroxyvittatine (33)

To 14 mg (0.049 mmol) of compound **3** in 1 mL of pyridine were added 0.3 mL (3.18 mmol) of acetic anhydride. The reaction mixture was stirred for 3 h, then the solvent was evaporated and the residue was purified by preparative TLC with DCM/MeOH 19:1 to yield 18 mg (100%) of compound **33** as an amorphous white solid. $[\alpha]_D^{20}$ −35.0 (*c* 0.06, MeOH). ^{1}H NMR ($CDCl_3$) δ 5.36 (1H, br s, H-3), 4.96 (1H, m, H-11), 1.99 (3H, s, $OCOCH_3$), 1.96 (3H, s, $OCOCH_3$), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 170.2 (s, $OCOCH_3$), 169.8 (s, $OCOCH_3$), 80.0 (d, C-11), 66.1 (d, C-3), 20.9 (q, $OCOCH_3$), 20.9 (q, $OCOCH_3$), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3048, 2927, 2720, 1650, 1503, 1437, 1372, 1323, 1100, 948, 854, 794, 735. EIMS *m/z* (%): 371 (M^+, 100); 312 (29); 269 (47); 252 (36); 240 (35); 224 (83); 209 (67); 181 (54). HREIMS *m/z* 371.1357 (calcd for $C_{20}H_{21}NO_6$ $[M]^+$ 371.1369).

4.1.31. 3,11-Bis(methoxyphenylacetyl)-11-hydroxyvittatine (34)

To a solution of 10 mg (0.035 mmol) of compound **3** in 5 mL of DCM, 29 mg (4 equiv) of 1,3-dicyclohexylcarbodiimide (DCC) and 23 mg (4 equiv) of (*R*)-(−)-methoxyphenylacetic acid were added. The reaction mixture was refluxed for 12 h. Then the solvent was evaporated. Further purification of the residue by preparative TLC using DCM/MeOH 19:1 yielded 15 mg (74%) of compound **34** as an amorphous white solid. ^{1}H NMR (CD_3CN) δ 7.35 (5H, s, Ph), 7.31 (5H, s, Ph), 5.21 (1H, br s, H-3), 4.83 (1H, m, H-11), 4.73 (1H, s, C*H*OMe), 4.72 (1H, s, C*H*OMe), 4.13 (1H, d, *J* = 17.7 Hz, H-6), 3.70 (1H, d, *J* = 17.7 Hz, H-6), for the rest of the signals see Supplementary data.13C NMR (CD_3CN) δ 169.7 (s, C=O), 169.3 (s, C=O), 135.5 (s, Ph), 128,7 (s, Ph), 127.3 (d, Ph), 126.8 (d, Ph), 82.5 (d, CHOMe), 82.0 (d, CHOMe), 80.2 (d, C-11), 66.8 (d, C-3), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 2924, 2849, 1742, 1621, 1574, 1482, 1238, 1171, 1104, 1023, 934, 732, 695. HRMS *m/z* 583.2642 (calcd for $C_{34}H_{33}NO_8$ $[M]^+$ 583.2660).

4.1.32. General procedure for acylation of compound 3

To a solution of 11-hydroxyvittatine (**3**) in 3 mL of dry DCM were added 5 equiv of Et_3N and 3 equiv of the corresponding acyl chloride. After stirring at rt for 18 h, the solvent was evaporated and the residue was purified by preparative TLC using DCM/MeOH 92:8 as eluent, to afford the corresponding esters **35–37**.

4.1.33. 3,11-Dinicotyl-11-hydroxyvittatine (35)

Following the procedure described above, 16 mg (0.056 mmol) of compound **3** were treated with 39 μL (0.28 mmol) of Et_3N and

30 mg (0.17 mmol) of nicotinoyl chloride. After purification, 13 mg (47%) of compound **35** were obtained as an amorphous white solid. $[\alpha]_D^{20}$ −50.0 (*c* 0.05, MeOH). ^{1}H NMR ($CDCl_3$) δ 9.14 (2H, s, CCHN), 8.80 (1H, dd, *J* = 1.5 Hz, *J* = 4.8 Hz, NC*H*CHCHC), 8.73 (1H, dd, *J* = 1.5 Hz, *J* = 4.8 Hz, NC*H*CHCHC), 8.23 (1H, d, *J* = 8.2 Hz, NCHCHC*H*C), 8.19 (1H, d, *J* = 8.2 Hz, NCHCHC*H*C), 7.42 (1H, dd, *J* = 5.0 Hz, *J* = 7.9 Hz, NCHC*H*CHC), 7.34 (1H, dd, *J* = 5.0 Hz, *J* = 7.9 Hz, NCHC*H*CHC), 5.66 (1H, br s, H-3), 5.26 (1H, dd, *J* = 3.5 Hz, *J* = 6.5 Hz, H-11), 4.43 (1H, d, *J* = 17.0 Hz, H-6), 3.71 (1H, d, *J* = 17.0 Hz, H-6), for the rest of the signals see Supplementary data. ^{13}C NMR ($CDCl_3$) δ 164.3 (s, C=O), 163.9 (s, C=O), 153.5 (d, C*C*HN), 153.2 (d, C*C*HN), 150.7 (d, N*C*HCHCHC), 150.4 (d, N*C*HCHCHC), 136.9 (d, NCHCH*C*HC), 136.6 (d, NCHCH*C*HC), 125.8 (s, *C*CHN), 125.5 (s, *C*CHN), 123.2 (d, NCH*C*HCHC), 123.0 (d, NCH*C*HCHC), 80.8 (d, C-11), 67.1 (d, C-3), 60.7 (t, C-6), for the rest of the signals see Supplementary data. IR (neat, cm^{-1}): 3050, 2925, 1719, 1591, 1482, 1421, 1329, 1278, 1239, 1114, 1023, 935, 852, 738, 701. EIMS *m/z* (%): 497 (M^+, 51); 374 (32); 268 (47); 252 (32); 238 (16); 224 (75); 209 (51); 181 (27). HREIMS *m/z* 497.1594 (calcd for $C_{28}H_{23}N_3O_6$ $[M]^+$ 497.1587).

4.1.34. 3,11-Bis(*p*-bromobenzoyl)-11-hydroxyvittatine (36)

Following the procedure described above, 16 mg (0.056 mmol) of compound **3** were treated with 39 μL (0.28 mmol) of Et_3N and 37 mg (0.17 mmol) of *p*-bromobenzoyl chloride to yield, after purification, 20 mg (56%) of compound **36** as an amorphous white solid. $[\alpha]_D^{20}$ +10.5 (*c* 0.19, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.82 (2H, d, *J* = 8.4 Hz, H-2′), 7.78 (2H, d, *J* = 8.4 Hz, H-2′), 7.59 (2H, d, *J* = 8.4 Hz, H-3′), 7.51 (2H, d, *J* = 8.4 Hz, H-3′), 5.59 (1H, br s, H-3), 5.21 (1H, dd, *J* = 3.6 Hz, *J* = 6.3 Hz, H-11). ^{13}C NMR ($CDCl_3$) δ 165.0 (s, C=O), 164.5 (s, C=O), 146.7 (s, C-9), 146.6 (s, C-8), 133.4 (s, C-10a), 131.7 (d, C-2′), 131.4 (d, C-2′), 130.9 (d, C-3′), 130.6 (d, C-3′), 128.8 (s, C-1′), 128.5 (s, C-1′), 128.2 (s, C-4′), 127.9 (s, C-4′), 80.7 (d, C-11), 66.9 (d, C-3). IR (neat, cm^{-1}): 3044, 2926, 1715, 1590, 1482, 1398, 1327, 1100, 1014, 936, 849, 737, 681. EIMS *m/z* (%): 652 (M^+, 17); 452 (20); 408 (3); 269 (70); 251 (39); 238 (18); 224 (82); 182 (100). HREIMS *m/z* 652.9899 (calcd for $C_{30}H_{23}NO_6Br_2$ $[M]^+$ 652.9872).

4.1.35. 3,11-Diisobutyryl-11-hydrovittatine (37)

Following the procedure described above, 16 mg (0.056 mmol) of compound **3** were treated with 39 μL (0.28 mmol) of Et_3N and 18 μL (0.17 mmol) of isobutyryl chloride. After purification, 15 mg (63%) of compound **37** were obtained as a white solid. $[\alpha]_D^{20}$ −118.9 (*c* 0.09, MeOH). ^{1}H NMR ($CDCl_3$) δ 4.93 (1H, dd, *J* = 3.3 Hz, *J* = 6.5 Hz, H-11), 4.35 (1H, d, *J* = 16.9 Hz, H-6), 3.72 (1H, d, *J* = 16.9 Hz, H-6), 2.44 (2H, dq, *J* = 2.4 Hz, *J* = 4.4 Hz, C*H*$(CH_3)_2$), 1.09 (12H, d, *J* = 6.9 Hz, CH(C*H*$_3)_2$). ^{13}C NMR ($CDCl_3$) δ 176.3 (s, C=O), 175.7 (s, C=O), 79.7 (d, C-11), 65.7 (d, C-3), 33.7 (d, *C*H$(CH_3)_2$), 33.6 (d, *C*H$(CH_3)_2$), 18.7 (q, CH(*C*H$_3)_2$), 18.7 (q, CH(*C*H$_3)_2$), 18.6 (q, CH(*C*H$_3)_2$), 18.6 (q, CH(*C*H$_3)_2$). IR (neat, cm^{-1}): 2974, 2934, 1729, 1621, 1503, 1483, 1387, 1239, 1192, 1154, 1064, 1038, 992, 938, 852, 736. EIMS *m/z* (%): 427 (M^+, 62); 398 (6); 340 (27); 269 (100); 252 (24); 238 (14); 224 (49); 181 (37). HREIMS *m/z* 427.2011 (calcd for $C_{24}H_{29}NO_6$ $[M]^+$ 427.1995).

4.2. Antiplasmodial assay

F-32 Tanzania (chloroquine sensitive) strains of *Plasmodium falciparum* were cultured according to Trager and Jensen[24] 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 in DMSO 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 vs. percent inhibition. Chloroquine (0.04 μM) was used as a positive control. All tests were performed in triplicate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.07.036.

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