Bioorganic & Medicinal Chemistry 19 (2011) 5861–5868

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

New aporphinoid 5-HT$_{2A}$ and α_{1A} antagonists via structural manipulations of nantenine

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ARTICLE INFO

Article history:
Received 2 June 2011
Revised 4 August 2011
Accepted 9 August 2011
Available online 6 September 2011

Keywords:
Aporphine
Nantenine
MDMA
5-HT$_{2A}$
α_{1A}

ABSTRACT

A series of C1, C2, C3 and *N*6 analogs of nantenine (**2**) was synthesized and evaluated in 5-HT$_{2A}$ and α_{1A} receptor functional assays. Alkyl substitution of the C1 and *N*6 methyl groups of nantenine provided selective 5-HT$_{2A}$ and α_{1A} antagonists, respectively. The C2 alkyloxy analogs studied were generally selective for α_{1A} versus 5-HT$_{2A}$. The C3 bromo analog **15** is one of the most potent aporphinoid 5-HT$_{2A}$ antagonists known presently.

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1. Introduction

Aporphines are a group of tetracyclic alkaloids that are a subset of the ubiquitous tetrahydroisoquinoline family. The aporphine template is known to be associated with a range of biological activities. For example, aporphines have been explored as antituberculosis and cytotoxic agents.[1,2] In the realm of central nervous system (CNS) activity, members of the aporphine class are known to inhibit the enzyme acetylcholinesterase—an important therapeutic target in current treatment modalities for Alzheimers disease.[3–5] Behavioral and physiological effects of the designer drug MDMA aka 'Ecstasy' (**1,** Fig. 1) are antagonized by nantenine (**2**), an isolate of a number of Lauraceous plants. With regards to clinically available aporphine drugs, apomorphine (**3,** Fig. 1) is a potent dopamine D1/D2 agonist that is used to treat symptoms of Parkinson's disease.[6]

Naturally occurring aporphines and their synthetic derivatives are known to have affinity for dopaminergic, adrenergic and serotonergic receptors.[7–14] The aporphine chemotype may be regarded as a 'privileged' CNS receptor template. Indeed, this scaffold represents an attractive opportunity to identify and develop selective monopotent as well as multi-potent CNS receptor ligands for dopaminergic, adrenergic and serotonergic receptors. Such molecules will be useful as interrogative chemical tools and potential therapeutic interventions for a variety of neuropsychiatric conditions such as stress, depression, anxiety, psychosis and psychostimulant abuse.

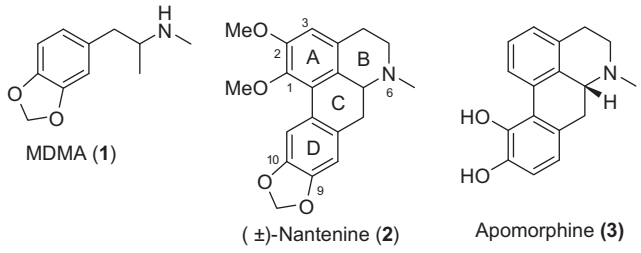

Figure 1. Structures of MDMA (**1**), (±)-Nantenine (**2**) and Apomorphine (**3**).

As indicated earlier, a number of groups have investigated the structure–activity properties of aporphines (particularly apomorphine derivatives) as dopamine D1 and D2 receptor ligands. In contrast, the structure–activity relationships (SAR) of aporphines as 5-HT$_{2A}$ receptor ligands have been little explored. We are particularly interested in 'tooling' aporphines as 5-HT$_{2A}$ and α_{1A} dual antagonists and as probes to study antagonism of MDMA's behavioral and physiological effects. Our interest is propelled by abundant literature studies that implicate 5-HT$_{2A}$ and α_1 adrenergic receptors in mediating physiological and psychobehavioral effects of MDMA in animals and humans.[15–21] Currently, no medications are specifically approved to treat adverse effects of 'Ecstasy' over

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doi:10.1016/j.bmc.2011.08.019

dose although the muscle relaxant, dantrolene, has been effectively used as an antidote in cases of hospitalization due to 'Ecstasy'—induced hyperthermia.[22]

Prior to our forays in this area, only one SAR study on aporphines at the 5-HT_{2A} receptor was reported. In that study, conducted with (±)-nantenine (**2**) as the lead, it was revealed that replacement of the C1 methoxy group with a hydroxyl group gave decreased 5-HT_{2A} affinity.[23] Replacement of the *N*6 methyl group with a hydrogen or ethyl group also gave reduced affinity. We have recently reported further investigations at the C1 position and have identified new 5-HT_{2A} antagonists up to 12 times more potent than nantenine.[24,25]

In addition, we have screened (±)-nantenine in a CNS panel of over 30 receptors, ion-channels and transporters and determined that the molecule is a potent and selective α_{1A} ligand.[26] Others have documented the affinity trends of aporphines at the α_{1A} receptor, but no study has done so with nantenine as the lead.[12] One prior study has investigated the structure-affinity relationships of nantenine at α_1 receptors.[27] Here it was reported that replacement of the C1 methoxy group with a hydroxyl group gave improved α_1 affinity. Substitution of the *N*6 methyl group of nantenine with a hydrogen or ethyl group gave reduced affinities however.

Taken together, the results of previous investigations of (±)-nantenine suggest that the substituents on the aporphine core are important determinants of its 5-HT_{2A} and α_{1A} activity. While the ultimate goal of optimizing aporphines as 5-HT_{2A}/α_{1A} dual antagonist probes seems achievable, more extensive SAR studies are necessary. In this manuscript, we describe an SAR study to further probe the effects of structural manipulations in the ring A and *N*6 regions of the molecule on antagonism of 5-HT_{2A} and α_{1A} receptors. For comparison to our prior work, all evaluations in the following discussion were conducted with racemic aporphine derivatives.

2. Results and discussion

2.1. Chemistry

The ring A C1 modified racemic analogs were prepared using methods analogous to that previously described via the key phenolic precursor **5**.[24,28] Standard Williamson ether O-alkylation of **5** followed by reduction of the carbamate group gave the C1 analogs **6a–i** (Fig. 2). Synthesis of the ring A C2 analogs is shown in Scheme 1. The key intermediate **12** was synthesized from readily available **7** and used to prepare C2 analogs as shown. Thus, coupling of **7** with readily available bromomethylenedioxyphenylacetic acid gave amide **8**.[29] Bischler–Napieralski cyclization of **8** gave an imine which was subsequently reduced to secondary racemic amine **9**[30] (without purification of the imine). Reaction of **9** with Boc anhydride gave the carbamate **10**, which was then cyclized via a palladium-mediated microwave-assisted procedure to afford the aporphine **11**. Removal of the benzyl protecting group of **11** then gave phenol **12**. Alkylation of **12** with respective alkyl bromides afforded the boc protected aporphines **13a–13f**. Removal of the Boc group with $ZnBr_2$ and standard reductive amination gave the target C2 derivatives **14a–14f**. (We attempted to reduce the Boc group directly to the *N*-methyl group with lithium aluminum hydride but found that this gave competing cleavage of the Boc group).

Bromination of (±)-nantenine with bromine/acetic acid (Fig. 3) gave the C3-bromo analog **15**. This reaction also produced a substantial amount of tribromo derivative **16**.

The preparation of *N*6 analogs was achieved by *N*-alklyation of secondary (±)-amine **17** (see Ref. 4) under reductive amination conditions (Fig. 4).

2.2. Pharmacology

All analogs were screened at 10 μM in multi-well format for intrinsic (agonist) and antagonist activity at the human 5-HT_{2A} receptor using FLIPR Tetra (Molecular Devices, Sunnydale, CA) functional assays that detect receptor-mediated mobilization of internal calcium with a calcium sensitive fluorescent dye. Compounds that showed no intrinsic activity in the functional assay and inhibited the increase in basal fluorescence elicited by the EC_{80} of 5-HT by at least 50%, had their K_e (apparent affinity in a functional assay) determined. K_e values were determined by running an 8-point half-log 5-HT concentration response curve in the presence and absence of a single concentration of antagonist. EC_{50} values were calculated for 5-HT (A) and 5-HT + test compound (A'), and these used to calculate the test compound K_e using the formula: $K_e = [L]/(DR-1)$, where [L] equals the concentration of test compound in the assay and DR equals the dose ratio or A′/A. A similar set of assays was performed for the α_{1A}-adrenergic receptor.

In our previous SAR study, we found that successive alkyl homologation of the C1 methyl group of nantenine resulted in a progressive increase in 5-HT_{2A} antagonist activity (ethyl to *n*-pentyl: 890–171 nM).[24] Additionally, the C1 cyclopropylmethyloxy analog was the most potent 5-HT_{2A} antagonist (68 nM) identified in that study. Therefore, we continued our exploration of this position by investigating other alkyloxy, and cycloalkyloxy analogs. *n*-Hexyloxy analog **6a** (K_e = 71 nM, Table 1), showed activity comparable to the cyclopropylmethyloxy compound and two fold improved activity as compared to the previously reported *n*-pentyloxy analog. Compound **6b** was prepared as a ring-opened analog for comparison to the cyclopropylmethyloxy compound but this had five fold lower

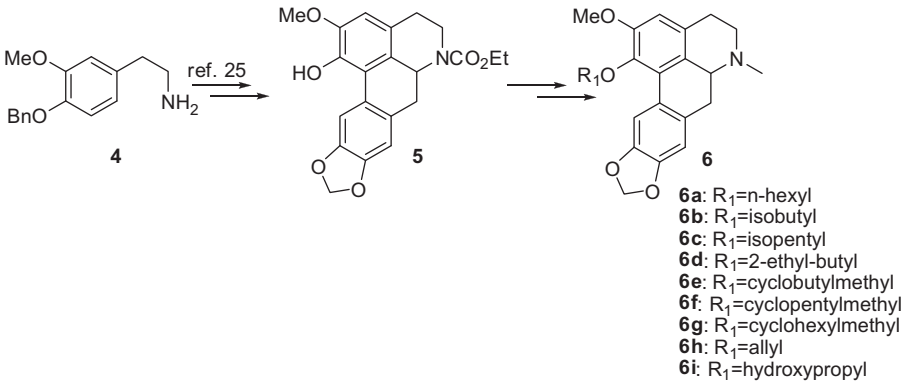
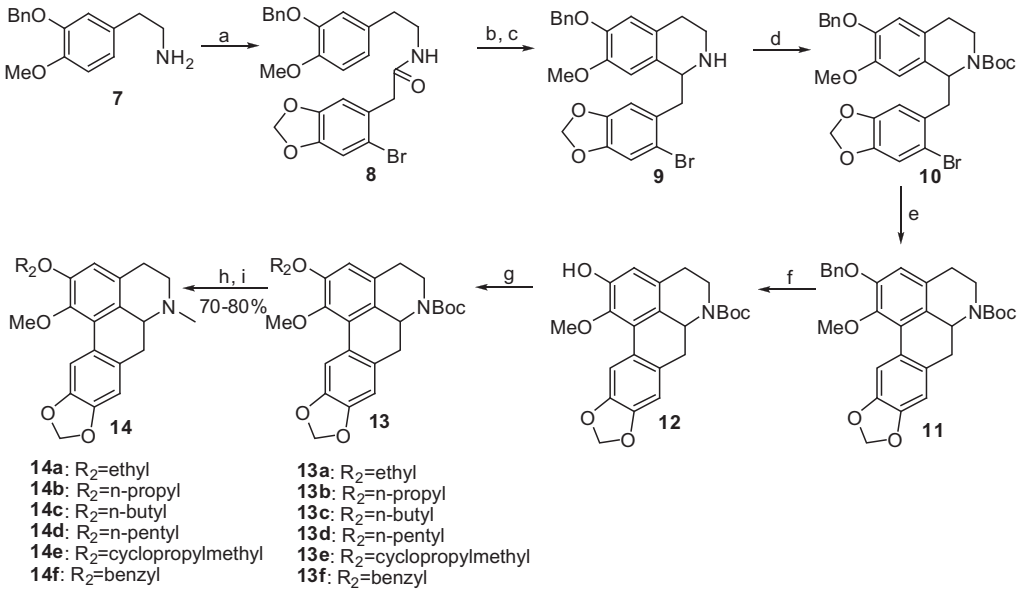


Figure 2. Preparation of C1 analogs.



Scheme 1. Synthesis of C2 ring A analogs. Reagents and conditions: (a) bromomethylenedioxyphenylacetic acid, CDI, THF, 0 °C-rt. (b) PCl_5, DCM, 0 °C-rt. (c) $NaBH_4$, MeOH, 0 °C. (d) $(Boc)_2O$, DMAP, iPr_2EtN, DCM, rt. (e) $Pd(OAc)_2$, Cs_2CO_3, PPh_3, 175 °C, DMF, microwaves. (f) H_2/Pd, rt. (g) alkyl bromide, KI, K_2CO_3, acetone, 70 °C. (h) $ZnBr_2$, DCM, rt. (i) HCHO, $Na(OAc)_3BH$, DCM, rt.

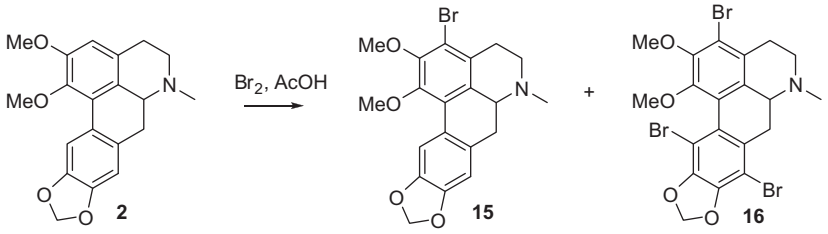


Figure 3. Bromination of nantenine.

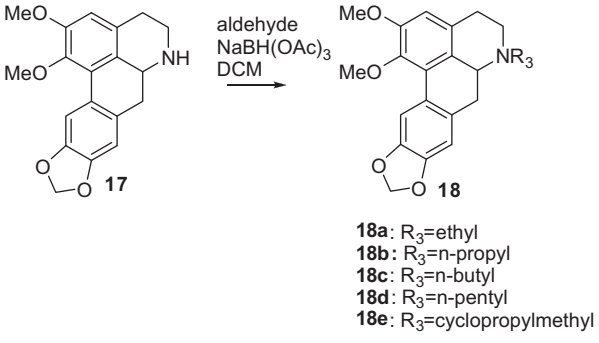


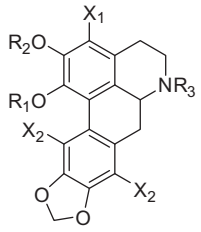
Figure 4. Synthesis of *N*-alkyl analogs.

5-HT_{2A} antagonist activity. Nevertheless, we anticipated that homologation of **6b** would cause a rebound in antagonist activity as seen with the C1 *n*-alkyloxy series and so we prepared and evaluated isopentyloxy analog **6c** and 2-ethylbutyloxy analog **6d**. However, homologation did not improve the antagonist activity. In fact in the case of **6c**, this compound had weak agonist activity (19% of 5-HT E_{max}). Next we decided to investigate other cycloalkyloxy analogs. The cyclohexylmethyloxy analog (**6g**) showed moderate activity, albeit 25-fold lower than the cyclopropyloxy analog. Other cycloalkyloxy derivatives tested showed weak agonist activity (25% and 35% of 5-HT E_{max} for **6e** and **6f**, respectively). However, we were pleased to observe that the allyloxy analog (**6h**) had activity comparable to the cyclopropylmethyloxy analog. Since the alkene functionality of **6h** is electronically similar to a cyclopropyloxy group, this may account for the similar activities seen; this is in need of further investigation. We then decided to test the tolerance for a polar group in this region. Addition of a hydroxypropyloxy moiety (**6i**) was associated with a reduction in 5-HT_{2A} antagonist activity. Compounds **6a–6i** were evaluated in α_{1A} assays but were devoid of activity.

We then progressed to examine C2 nantenine analogs. With regards to 5-HT_{2A} activity, the ethyloxy and n-propyloxy analogs (**14a** and **14b**, respectively) were equipotent. Further extension of the alkyl chain resulted in decreased antagonist activity with a plummet in activity in going from the *n*-butyloxy analog to the *n*-pentyloxy homolog (**14c** to **14d**). The C2 cyclopropylmethyloxy analog was found to have moderate activity that was comparable to **14a** and **14b**. Benzyloxy analog (**14f**) was the most potent C2 analog tested. In the α_{1A} assay a clear SAR trend was observed. The C2 ethyloxy analog had the highest activity though this was slightly lower than that obtained for nantenine in this assay. Increasing the alkyl chain length at this position led to a progressive decrease in α_{1A} antagonist activity. The C2 alkyloxy analogs (**14a–14d**) are generally more selective for α_{1A} versus 5-HT_{2A}. Interestingly, this selectivity is reversed with the benzyloxy analog **14e**.

The C3 bromo analog (**15**) had high 5-HT_{2A} antagonist activity (K_e = 53 nM). Polybromination of ring D (**16**) did not affect this activity. Compounds **15** and **16** are the most potent 5-HT_{2A} aporphine antagonists identified up to now. Both of these halogenated analogs were found to be highly selective for the 5-HT_{2A} receptor versus the α_{1A} receptor.

Table 1
K_e values for ring A and *N*6 analogs at 5-HT_{2A} and α_{1A} receptors



Compd	R_1	R_2	R_3	X_1	X_2	$K_e \pm$ SEM[a] (nM)	
						5-HT_{2A}	α_{1A}
6a	*n*-Hex	Me	Me	H	H	71 ± 19	>10,000
6b	Isobu	Me	Me	H	H	367 ± 82	>10,000
6c	Isopen	Me	Me	H	H	ND[b]	>10,000
6d	2-EthylBu	Me	Me	H	H	806 ± 152	>10,000
6e	CyclobutylMe	Me	Me	H	H	ND[b]	>10,000
6f	CyclopentylMe	Me	Me	H	H	ND[b]	>10,000
6g	CyclohexylMe	Me	Me	H	H	1722 ± 258	>10,000
6h	Allyl	Me	Me	H	H	70 ± 15	>10,000
6i	HydroxyPr	Me	Me	H	H	708 ± 316	>10,000
14a	Me	Et	Me	H	H	378 ± 92	52 ± 13
14b	Me	*n*-Pr	Me	H	H	389 ± 93	133 ± 45
14c	Me	*n*-Bu	Me	H	H	943 ± 283	234 ± 52
14d	Me	*n*-Pen	Me	H	H	>10,000	449 ± 169
14e	Me	CyclopropylMe	Me	H	H	484 ± 123	195 ± 86
14f	Me	Benzyl	Me	H	H	154 ± 76	1917 ± 226
15	Me	Me	Me	Br	H	53 ± 14	>10,000
16	Me	Me	Me	Br	Br	43 ± 11	>10,000
18a	Me	Me	Et	H	H	>10,000	26 ± 6
18b	Me	Me	*n*-Pr	H	H	>10,000	38 ± 3
18c	Me	Me	*n*-Bu	H	H	>10,000	210 ± 50
18d	Me	Me	*n*-Pen	H	H	>10,000	720 ± 204
18e	Me	Me	CyclopropylMe	H	H	>10,000	319 ± 60
2	Me	Me	Me	H	H	850 ± 6[c]	36 ± 7
Prazosin							1.1 ± 0.4
Ketanserin						32[c,d]	

[a] Values represent mean ± SEM for three independent experiments.
[b] ND = K_e not determined (compounds were weak agonists).
[c] Data from Ref. 25.
[d] IC_{50} determined in the presence of 5-HT EC_{80}.

None of the *N*6 analogs tested had activity at the 5-HT_{2A} receptor. The *N*6 ethyl (**18a**) and *N*6 *n*-propyl (**18b**) congeners had activities that were comparable to nantenine in the α_{1A} assay. Further lengthening of the alkyl chain gave reduced α_{1A} antagonist activity.

The preceding evaluations were conducted with the compounds in racemic form. It will be interesting to evaluate enantiomers of these molecules to ascertain whether there is any enantio-preference with respect to selectivity and activity. This is especially necessary in light of the fact that series of aporphine enantiomers have been shown to have opposing effects (agonism and antagonism) at the related 5-HT_{1A} receptor.[11,31,32]

3. Conclusions

In summary, we have identified a number of new aporphine 5-HT_{2A} and α_{1A} antagonists via manipulation of the ring A and *N*6 substituents of nantenine. The results of our SAR study suggest that C1 and C3 substituents may be modified to develop potent 5-HT_{2A} antagonists that are highly selective versus the α_{1A} receptor. In contrast, the C2 alkyloxy analogs are generally more selective for the α_{1A} receptor versus. 5-HT_{2A}. However, it would appear that only relatively small alkyl groups are tolerated at this position for optimal activity at either receptor. Similarly, at *N*6 the relatively small methyl group is best tolerated. Compounds **15** and **16** are the most potent aporphine 5-HT_{2A} antagonists known. It is clear that the aporphine skeleton is sensitive to structural changes and that this template is amenable to the development of selective 5-HT_{2A} versus α_{1A} and selective α_{1A} versus 5-HT_{2A} antagonists.

Altogether, these results suggest that it is possible to synthesize potent dual-acting 5-HT_{2A}/α_{1A} aporphine ligands because the receptor selectivity can be directed through modifications of different substituents. Evaluation of the aporphine enantiomers is an important direction for future work. Our research team is actively investigating these avenues.

4. Experimental section

4.1. General experimental procedures

Reagent grade chemicals and solvents were purchased from Sigma–Aldrich Inc. or Fisher Scientific Inc. Reactions were monitored by TLC with Analtech Uniplate silica gel G/UV 254 precoated plates (0.2 mm). TLC plates were visualized by UV (254 nm), by iodine vapor or by staining with phosphomolybdic acid reagent followed by heating. Microwave reactions were conducted on a CEM Discover microwave reactor. Flash column chromatography was performed with Silicagel 60 (EMD Chemicals, 230–400 mesh, 0.04–0.063 μm particle size). High Resolution Electrospray Mass

Spectra (HRESIMS) were obtained using an Agilent 6520 Q-TOF instrument. NMR data were collected on a Bruker 500 MHz machine with TMS as internal standard. Chemical shift (δ) values are reported in ppm and coupling constants in Hertz (Hz). Melting points were obtained on a Mel-Temp capillary electrothermal melting point apparatus.

4.2. Synthesis of C1 analogs (6)

C1 analogs were prepared from **4** using methods as described in Ref. 25.

4.2.1. 1-(Hexyloxy)domesticine (6a)

Off white solid; mp: 68–70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.97 (d, J = 1.5 Hz, 1H), 5.95 (d, J = 1.5 Hz, 1H), 3.84 (s, 3H), 3.83.3.81 (m, 1H), 3.61-3.59 (m, 1H), 3.16–3.11 (m, 1H), 3.03 (dd, J = 11.3, 6.0 Hz, 1H), 2.98–2.95 (m, 2H), 2.68–2.64 (br d, J = 16 Hz, 1H), 2.54–2.49 (m, 5H), 1.74–1.60 (m, 2H), 1.45–1.26 (m, 6H), 0.88–0.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 146.48, 143.9, 130.8, 129.9, 128.8, 128.5, 127.5, 126.0, 110.8, 109.5, 108.3, 101.0, 73.4, 64.5, 56.0, 53.4, 44.1, 35.3, 31.8, 30.3, 29.3, 26.0, 22.8, 14.2; HRMS (ESI) m/z calcd for $C_{25}H_{31}NO_4$ ([M+H]$^+$), 410.2326, found 410.2330.

4.2.2. 1-(Isobutyloxy)domesticine (6b)

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.97 (s, 1H), 5.94 (s, 1H), 3.84 (s, 3H), 3.61 (t, J = 7.6 Hz, 1H), 3.36 (t, J = 7.6 Hz, 1H), 3.16–3.10 (m, 1H), 3.04–2.95 (m, 2H), 2.67–2.64 (br d, J = 15.7 Hz, 1H), 2.54–2.48 (m, 5H), 2.04–1.99 (m, 1H), 1.01–0.95 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 146.4 (×2), 144.1, 130.7, 128.4, 127.4, 125.8, 110.9, 109.6, 108.2, 101.0, 100.84, 79.8, 62.8, 56.1, 53.5, 44.2, 35.3, 29.3, 29.2, 19.7, 19.5; HRMS (ESI) m/z calcd for $C_{23}H_{27}NO_4$ ([M+H]$^+$), 382.2013, found 382.2017.

4.2.3. 1-(Isopentyloxy)domesticine (6c)

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.96 (s, 1H), 5.95 (s, 1H), 3.86–3.82 (m, 4H), 3.66–3.61 (m, 1H), 3.17–3.10 (m, 1H), 3.04–3.01 (m, 1H), 2.98–2.94 (m, 2H), 2.68–2.64 (m, 1H), 2.55–2.48 (m, 5H), 1.84–1.76 (m, 1H), 1.63–1.52 (m, 2H), 0.88–0.87 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 146.4, 144.1, 143.7, 130.7, 129.7, 128.5, 127.3, 125.7, 110.5, 109.2, 108.1, 100.8, 71.5, 62.5, 55.8, 53.2, 40.3, 39.1, 35.1, 24.7, 22.6, 22.4; HRMS (ESI) m/z calcd for $C_{24}H_{29}NO_4$ ([M+H]$^+$), 396.4914, found 396.4914.

4.2.4. 1-(2-Ethylbutyloxy)domesticine (6d)

Brown solid; mp: 62–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.95 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 3.84 (s, 3H), 3.74 (dd, J = 9.1, 5.3 Hz, 1H), 3.49 (dd, J = 9.0, 5.3 Hz, 1H), 3.17–3.10 (m, 1H), 3.03 (dd, J = 11.3, 5.1 Hz, 1H), 2.98–2.94 (m, 2H), 2.66 (dd, J = 16.3, 3.4 Hz, 1H), 2.54–2.48 (m, 5H), 1.56–1.34 (m, 5H), 0.86 (d, J = 7.2 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 146.4, 146.3, 144.1, 130.6, 128.3, 127.5, 127.4, 125.8, 110.8, 109.6, 108.2, 100.9, 75.2, 62.7, 55.9, 53.4, 44.1, 42.1, 35.2, 29.3, 23.4, 23.2, 11.3, 11.1; HRMS (ESI) m/z calcd for $C_{25}H_{31}NO_4$ ([M+H]$^+$), 410.2326, found 410.2329.

4.2.5. 1-(Cyclobutylmethoxy)domesticine (6e)

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 6.74 (s, 1H), 6.56 (s, 1H), 5.98 (d, J = 1.5 Hz 1H), 5.94 (d, J = 1.5 Hz, 1H), 3.85 (s, 3H), 3.83 (dd, J = 9.4, 6.7 Hz, 1H), 3.59 (dd, J = 9.4, 7.4 Hz, 1H), 3.18–3.11 (m, 1H), 3.05 (dd, J = 6.0, 5.5 Hz, 1H), 3.0–2.95 (m, 2H), 2.69–2.64 (m, 2H), 2.56–2.50 (m, 5H), 2.06–1.95 (m, 2H), 1.92–1.85 (m, 1H), 1.83–1.66 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 146.4, 146.7, 143.7, 130.7, 128.4, 127.5, 127.2, 125.9, 110.7, 109.7, 108.2, 101.0, 62.6, 56.1, 53.3, 44.0, 35.5, 35.2, 29.8, 29.1, 25.5, 25.0, 18.6; HRMS (ESI) m/z calcd for $C_{24}H_{27}NO_4$ ([M+H]$^+$), 394.2013, found 394.2017.

4.2.6. 1-(Cyclopentylmethoxy)domesticine (6f)

Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.97 (d, J = 1.3 Hz, 1H), 5.94 (d, J = 1.3 Hz, 1H), 3.85 (s, 3H), 3.73 (dd, J = 7.0, 7.0 Hz, 1H), 3.47 (dd, J = 7.6, 7.6 Hz, 1H), 3.16–3.10 (m, 1H), 3.03 (dd, J = 11.6, 5.5 Hz, 1H), 2.98–2.94 (m, 2H), 2.66 (br d, J = 16.1 Hz, 1H), 2.54–2.47 (m, 4H), 2.31–2.25 (m, 1H), 1.92–1.85 (m, 1H), 1.80–1.71 (m, 2H), 1.55–1.49 (m, 4H), 1.33–1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 146.4, 146.3, 144.0, 130.7, 128.4, 127.4, 127.2, 125.9, 110.8, 109.7, 108.2, 101.0, 62.7, 56.0, 53.4, 44.1, 40.2, 35.2, 29.9, 29.4, 29.3, 25.6, 25.0, 25.5; HRMS (ESI) m/z calcd for $C_{25}H_{29}NO_4$ ([M+H]$^+$), 408.2169, found 408.2172.

4.2.7. 1-(Cyclohexylmethoxy)domesticine (6g)

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.97 (s, 1H), 5.94 (s, 1H), 3.84 (s, 3H), 3.60 (dd, J = 8.7, 6.1 Hz, 1H), 3.40 (t, J = 7.6 Hz, 1H), 3.17–3.10 (m, 1H), 3.05–2.94 (m, 3H), 2.66 (br d. J = 16.0 Hz, 1H), 2.53–2.49 (m, 5H), 1.90–1.63 (m, 10H), 1.17–1.10 (m,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 146.49, 146.45, 144.2, 130.7, 128.4, 127.4 (×2), 125.8, 110.9, 109.7, 108.2, 101.0, 78.7, 62.7, 56.1, 53.4, 44.1, 38.7, 35.2, 30.2, 29.9, 29.1, 26.7, 26.1, 26.0; HRMS (ESI) m/z calcd for $C_{26}H_{31}NO_4$ ([M+H]$^+$), 422.2326, found 422.2329.

4.2.8. 1-(Allyloxy)domesticine (6h)

Brown solid; mp: 63–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.74 (s, 1H), 6.58 (s, 1H), 6.01–5.93 (m, 3H), 5.27 (ddd, J = 17.3, 3.0, 1.4 Hz, 1H), 5.14 (dd, J = 10.4, 1.4 Hz, 1H), 4.37–4.33 (m, 1H), 4.22–4.21 (m, 1H), 3.86 (s, 3H), 3.17–3.10 (m, 1H), 3.04–2.94 (m, 3H), 2.66 (dd, J = 16.3, 3.35 Hz, 1H), 2.54–2.48 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 146.5, 146.4, 143.1, 134.4, 130.8, 128.8, 127.6, 127.3,125.8, 117.6, 110.7, 109.4, 108.3, 101.0, 73.8, 62.6, 56.0, 53.3, 44.1, 35.2, 29.3; HRMS (ESI) m/z calcd for $C_{22}H_{23}NO_4$ ([M+Na]$^+$), 388.1519, found 388.1520.

4.2.9. 1-(3-Hydroxy-propanyloxy)domesticine (6i)

Brown Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.74 (s, 1H), 6.59 (s, 1H), 5.98 (s, 1H), 5.96 (s, 1H), 3.97–3.92 (m, 2H), 3.90–3.84 (m, 5H), 3.82–3.77 (m, 1H), 3.19–3.13 (m, 1H), 3.07–2.95 (m, 3H), 2.68 (dd, J = 16.2, 2.8 Hz, 1H), 2.54 (m, 5H), 2.05–1.97 (s, 1H), 1.85–1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 146.7, 146.6, 143.4, 130.8, 128.9, 127.4, 125.6, 110.6, 108.7, 108.5, 101.1, 71.0, 62.6, 61.2, 56.0, 53.3, 44.1, 44.0, 35.1, 29.9; HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_5$ ([M+H]$^+$), 384.4376, found 384.4376.

4.3. 3-(6-Bromobenzo[d][1,3] dioxol-5-yl)-N-(3,4-dimethoxyphenethyl) ethanamide (8)

A solution of bromomethylenedioxyphenylacetic acid (4.76 g, 17.5 mmol) and 1,10-carbonyldiimidazole (2.84 g, 17.5 mmol) in anhydrous THF (40 mL) was stirred at 0 °C for 1.5 h and then at room temperature for 1 h. The mixture was cooled in an ice-bath and stirred for 1 h. Then 3-benzyloxy-4-methoxyphenethylamine (**7**) (4.50 g, 17.5 mmol) was added and the solution was stirred at 0 °C for 4 h and left to stir overnight at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in EtOAc and washed sequentially with 1 N HCl (25 mL), water (50 mL), satd $NaHCO_3$ solution (25 mL) and finally with brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was crystallized from EtOAc/diethylether to furnish amide **8** (6.65 g, 76.5%).

White solid; mp: 163–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.39 (m, 2H), 7.30 (m, 1H), 7.00 (s, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.75 (s, 1H), 6.70 (br s., 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.00 (s, 2H), 5.38 (br s, 1H), 5.12 (s, 2H), 3.89 (s, 3H), 3.55 (s, 2H), 3.44 (dd, J = 13.0, 6.5 Hz, 2H), 2.69 (dd, J = 6.9, 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 148.4, 148.3, 147.9, 147.7, 137.1, 131.0, 128.5, 127.9, 127.5, 127.4, 121.4, 115.3, 114.6, 112.9, 112.0, 110.9, 102.0, 71.1, 56.1, 43.8, 40.6, 34.9; HRMS (ESI) m/z calcd for $C_{25}H_{24}BrNO_5$ ([M+H]$^+$), 498.0838, found 498.0840.

4.4. 6-(Benzyloxy)-1-((6-bromobenzo[d][1,3]dioxol-5-yl) methyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (9)

To a magnetically stirred ice-cooled solution of **8** (5.00 g, 10.05 mmol) in dry DCM (40 mL) was added solid phosphorus pentachloride (4.19 g, 20.1 mmol) in portions over 10 min. The reaction mixture was stirred at 0 °C for 1 h and then left to stir at room temperature for 20 h. The reaction mixture was then poured onto a saturated solution of aqueous $NaHCO_3$ (100 mL) and the contents of the flask were stirred for 1 h. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (100 mL) and brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. To a magnetically stirred ice-cooled solution of the crude imine thus obtained in a mixture of dry MeOH (40 mL) and dry DCM (20 mL), was added powdered $NaBH_4$ (3.60 g, 98 mmol) in three portions over 10 min. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with water and extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography over deactivated silica gel using 0.7% MeOH/DCM as eluant to furnish pure **9** (3.92 g, 81% yield from **8**).

White solid; mp: 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.36 (m, 2H), 7.30 (m, 1H), 7.05 (s, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 6.63 (s, 1H), 6.00 (s, 2H), 5.12 (s, 2H), 4.21 (t, J=6.5 Hz, 1H), 3.84 (s, 3H), 3.28–3.20 (m, 2H), 2.99–2.89 (m, 2H), 2.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 147.3, 147.2, 147.0, 137.3, 131.6, 130.8, 128.5, 127.8, 127.3, 127.1, 115.0, 114.5, 112.9, 111.4, 110.4, 101.7, 71.1, 56.2, 55.2, 42.8, 40.0, 29.1; HRMS (ESI) m/z calcd for $C_{25}H_{24}BrNO_4$ ([M+H]$^+$), 482.0889, found 482.0886.

4.5. *tert*-butyl-6-(benzyloxy)-1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-7-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (10)

To a stirred solution of **9** (3.67 g, 7.63 mmol) in DCM (30 mL) was added DIPEA (2.66 mL, 15.3 mmol), a catalytic amount of DMAP (0.01 g) followed by BOC anhydride (3.26 mL, 15.3 mmol) at room temperature and the solution stirred under inert atmosphere for 18 h. The reaction mixture was washed with saturated NH_4Cl solution and water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using 30% EtOAc/hexanes as eluant to furnish pure **10** (5.10 g, 65%).

Off-white solid; mp: 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (m, 2H), 7.36 (m, 2H), 7.29 (m, 1H), 7.02 (s, 1H), 6.96 (s,1H), 6.63 (s, 1H), 6.65 (s, 1H), 5.97 (s, 1H), 5.93 (s, 1H), 5.27 (m, 1H), 5.10–5.09 (s, 2H), 4.35 (dd, J = 13.2, 5.3 Hz, 1H), 3.85 (s, 3H), 3.21 (m, 2H), 2.89 (m, 2H), 1.40–1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 148.3, 147.2, 137.8, 131.3, 128.6, 127.9, 127.8, 127.3, 126.6, 115.3, 114.2, 112.5, 111.4, 111.0, 110.6, 101.6, 79.5, 71.1, 56.2, 54.0, 42.6, 36.4, 28.1; HRMS (ESI) m/z calcd for $C_{30}H_{32}BrNO_6$ ([M]$^+$), 581.1413, found 581.1415.

4.6. 2-(Benzyloxy)*N*-boc-*nor*-isodomesticine (11)

In a microwave reaction vial, compound **10** (0.12 g, 0.21 mmol), $Pd(OAc)_2$ (0.009 g, 0.04 mmol), triphenylphosphine (0.02 g, 0.08 mmol) and Cs_2CO_3 (0.13 g, 0.4 mmol),) were added and dissolved in degassed DMF (2 mL). The mixture was irradiated in the CEM microwave reactor for 15 min at 175 °C with the power level at 300 W. After cooling to room temperature, the reaction mixture was loaded directly onto a deactivated silica gel column and eluted in gradient fashion with 15–30% EtOAc/hexanes to furnish compound **11** (0.05 g, 52%).

Off-white solid; mp: 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.52–7.29 (m, 5H), 6.76 (s, 1H), 6.68 (s, 1H), 6.01 (s, 2H), 5.15 (m, 2H), 4.65 (m, 1H), 4.42 (m, 1H), 3.75 (s, 3H), 2.86–2.64 (m, 5H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 146.6, 146.5, 145.5, 137.1, 129.7, 128.6, 127.9, 127.3, 125.2, 112.8, 109.1, 100.9, 79.9, 71.0, 60.1, 51.8, 30.3, 28.6; HRMS (ESI) m/z calcd for $C_{30}H_{31}NO_6$ ([M]$^+$), 501.2151, found 501.2154.

4.7. *N*-boc-*nor*-isodomesticine (12)

To a solution of 11 (0.50 g, 1 mmol) in dry methanol (10 mL) was added 10% Pd/C (25 mg) under inert atmosphere. The reaction was purged with H_2 and stirred under a balloon of H_2 for 6 h. Pd/C was filtered through a Celite pad and the filtrate was evaporated to give the corresponding phenol **12** (0.38 g, 92%).

White solid; mp: 218–220 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 6.79 (s, 1H), 6.73 (s, 1H), 6.02 (s, 2H), 5.86 (s, 1H), 4.70–4.68 (m, 1H), 4.61 (m, 1H), 4.40 (m, 1H), 3.61 (s, 3H), 2.92–2.76 (m, 4H), 2.66–2.62 (m, 1H), 1.57–1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 146.9, 146.8, 142.6, 131.5, 131.1, 126.5, 125.4, 124.9, 124.8, 113.4, 108.6, 107.8, 101.0, 79.9, 60.2, 51.8, 30.2, 28.6; HRMS (ESI) m/z calcd for $C_{23}H_{25}NO_6$ ([M]$^+$), 411.1682, found 411.1684.

4.8. General procedure for preparation of C2 analogs (14)

*O-methylation of **12***: To a stirred solution of phenol (1 equiv) in acetone (10 mL) was added solid K_2CO_3 (2 equiv) and potassium iodide (2 equiv) at rt The resulting mixture was stirred for 5 min and then alkyl halide (1.5 equiv) was added and refluxed for 7 h. The solvent was evaporated and the resulting solid dissolved in water and extracted with dichloromethane twice (20 mL each). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 12.5% EtOAc/hexanes.

*N-Boc deprotection and reductive amination of **13**:* To a solution of the boc-protected amine (1 equiv) in dichloromethane (15 mL) was added dry $ZnBr_2$ (2 equiv) and the reaction allowed to stir at rt overnight under N_2. The mixture was diluted with dichloromethane (20 mL) and washed with saturated aqueous $NaHCO_3$ twice (10 mL each). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude amine product was purified by column chromatography on water-deactivated silica gel in 5% methanol/dichloromethane. To a solution of this amine (1 equiv) in dichloromethane (10 mL) was added the aldehyde (3 equiv) and sodium triacetoxyborohydride (3 equiv) under N_2. The reaction mixture was allowed to stir at rt overnight. The reaction was quenched with water and extracted with dichloromethane twice (20 mL each). The combined organic layer was washed with 10% aq $NaHCO_3$, then with brine, dried over anhydrous Na_2SO_4, and concentrated to give crude product. The crude product was subjected to column chromatography over water-deactivated silica gel using methanol/dichloromethane (2:98) as eluant, to furnish *N*-alkylated final product.

4.8.1. 2-(Ethoxy)isodomesticine (14a)

Yellow solid; mp: 101–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 5.96 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 4.12–4.02 (m, 2H), 3.67 (s, 3H), 3.15–3.08 (m, 1H), 3.02–2.94 (m, 3H), 2.66–2.62 (m, 1H), 2.54–2.45 (m, 5H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 146.5, 146.4, 144.7, 130.5, 128.9, 127.3, 127.1, 125.6, 111.6, 109.1, 108.4, 100.9, 64.2, 62.4, 60.2, 53.4, 44.2, 35.3, 29.3, 15.1; HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_4$ ([M+H]$^+$), 354.4116, found 354.4120.

4.8.2. 2-(Propyloxy)isodomesticine (14b)

Yellow solid; mp: 76–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.76 (s, 1H), 6.59 (s, 1H), 5.98 (d, J = 1.4 Hz, 1H) 5.95 (d, J = 1.4 Hz, 1H), 4.04–3.90 (m, 2H), 3.69 (s, 3H), 3.17–3.10 (m, 1H), 3.04–2.96 (m, 3H), 2.65 (m, 1H), 2.55–2.48 (m, 5H), 1.93–1.85 (m, 3H), 1.09 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 146.5, 146.4, 144.7, 131.0, 128.6, 127.3, 127.1, 125.8, 111.8, 109.1, 108.4, 101.0, 70.3, 62.6, 60.3, 53.4, 44.2, 35.3, 29.4, 22.9, 10.9; HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_4$ ([M+H]$^+$), 368.1882, found 368.1888.

4.8.3. 2-(Butyloxy)isodomesticine (14c)

Yellow solid; mp: 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.76 (s, 1H), 6.60 (s, 1H), 5.98 (d, J = 1.4 Hz, 1H), 5.97 (d, J = 1.4 Hz, 1H), 4.05–3.94 (m, 2H), 3.68 (s, 3H), 3.17–3.10 (m, 1H), 3.04–2.95 (m, 3H), 2.68–2.64 (m, 1H), 2.55–2.46 (m, 5H), 1.92–1.78 (m, 2H), 1.63–1.47 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 146.5, 146.4, 144.7, 130.9, 128.6, 127.3, 127.0, 125.8, 111.7, 109.1, 108.3, 100.9, 68.4, 62.6, 60.3, 53.4, 44.2, 35.3, 31.6, 27.4, 19.5, 14.0; HRMS (ESI) m/z calcd for $C_{23}H_{27}NO_4$ ([M+H]$^+$), 382.2016 found 382.2013.

4.8.4. 2-(Pentyloxy)isodomesticine (14d)

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 6.75 (s, 1H), 6.59 (s, 1H), 5.97 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 4.05–3.94 (m, 2H), 3.68 (s, 3H), 3.15–3.09 (m, 1H), 3.03–2.95 (m, 3H), 2.67–2.63 (m, 1H), 2.54–2.46 (m, 5H), 1.92–1.81 (m, 2H), 1.55–1.37 (m, 4H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 146.5, 146.4, 144.7, 130.9, 128.6, 127.3, 127.1, 125.8, 111.8, 109.1, 108.4, 100.9, 68.7, 62.6, 60.3, 53.4, 44.2, 35.3, 29.4, 29.2, 28.4, 22.6, 14.2; HRMS (ESI) m/z calcd for $C_{24}H_{29}NO_4$ ([M+H]$^+$), 396.2194, found 396.2192.

4.8.5. 2-(Cyclopropylmethyloxy)isodomesticine (14e)

Yellow solid; mp: 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 6.74 (s, 1H), 6.56 (s, 1H), 5.97 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 3.94–3.90 (m, 1H), 3.79–3.75 (m, 1H), 3.70 (s, 3H), 3.14–3.07 (m, 1H), 3.02–2.94 (m, 3H), 2.65–2.61 (m, 1H), 2.54–2.45 (m, 5H), 1.37–1.24 (m, 1H), 0.64 (m, 2H), 0.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 146.5, 146.4, 144.7, 130.9, 128.6, 127.3, 127.1, 125.8, 111.8, 109.1, 108.4, 100.9, 68.7, 62.6, 60.3, 53.4, 44.2, 35.3, 29.4, 29.2, 28.4, 22.6, 14.2; HRMS (ESI) m/z calcd for $C_{23}H_{25}NO_4$ ([M+H]$^+$), 380.1872 found 380.1874.

4.8.6. 2-(Benzyloxy)isodomesticine (14f)

Brown solid; mp: 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.50–7.32 (m, 5H), 6.77 (s, 1H), 6.67 (s, 1H), 5.98 (d, J = 1.4 Hz, 1H), 5.97 (d, J = 1.4 Hz, 1H), 5.12 (d, J = 11.8 Hz, 1H), 5.11 (d, J = 11.8 Hz, 1H), 3.72 (s, 3H), 3.11 (m, 1H), 3.09–2.97 (m, 3H), 2.64 (m, 1H), 2.56–2.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 146.5, 146.4, 145.0, 137.2, 130.8, 128.6, 128.5, 127.9, 127.8, 127.4, 127.3, 127.2, 125.6, 112.7, 109.0, 108.3, 100.9, 70.9, 62.5, 60.3, 53.2, 44.0, 35.1, 29.1; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_4$ ([M+H]$^+$), 416.1784, found 416.1788.

4.9. Synthesis of 3-bromonantenine (15) and 3,8,11-tribromonantenine (16)

To a solution of nantenine (**2**) (25 mg, 1 equiv) in acetic acid (5 mL) was slowly added a solution of bromine (3 equiv) dissolved in acetic acid (2 mL) at room temperature. The mixture was stirred overnight at room temperature and the solvent evaporated in vacuo. The residue was dissolved in toluene and the solvent again removed by rotary evaporation. The residue was purified by column chromatography with elution in 2% MeOH/DCM to give compounds **15** (5 mg, 16%) and **16** (22 mg, 52%).

4.9.1. 3-Bromonantenine (15)

Off white solid; mp: 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.75 (s, 1H), 5.98 (d, J = 1.2 Hz, 1H), 5.97 (d, J = 1.2 Hz, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.10-3.07 (dd, J = 10.7, 5.2 Hz, 1H), 2.98–2.89 (m, 3H), 2.83–2.79 (m, 1H), 2.52 (s, 3H), 2.49–2.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 149.3, 146.77, 146.76, 132.6, 130.7, 129.4, 127.0, 124.9, 118.5, 108.8, 108.3, 101.1, 62.9, 60.8, 60.6, 53.2, 44.0, 34.8, 30.5; HRMS (ESI) m/z calcd for $C_{20}H_{20}BrNO_4$ ([M+H]$^+$), 418.0648, found 418.0651.

4.9.2. 3,8,11-Tribromonantenine (16)

White solid; mp: 193–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (s, 1H), 6.14 (s, 1H), 3.95 (s, 3H), 3.54 (s, 3H), 3.08 (dd, J = 11.5, 5.2 Hz, 1H), 2.96–2.90 (m, 1H), 2.85–2.77 (m, 2H), 2.54 (s, 3H), 2.49 (dt, J = 11.8, 4.1 Hz, 1H), 2.18 (dd, J = 14.5, 12.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 145.9, 145.0, 133.8, 132.6, 128.7, 127.5, 127.1, 125.7, 119.7, 101.7, 101.5, 101.4, 63.0, 61.5, 61.1, 53.0, 44.1, 34.9, 30.3; HRMS (ESI) m/z calcd for $C_{20}H_{18}$ Br_3NO_4 ([M+H]$^+$), 572.8859, found 572.8859.

4.10. Synthesis of *N*6 analogs (18)

These compounds were prepared by reductive amination on amine **17** using the procedure as described above for synthesis of the C2 analogs.

4.10.1. *N*-Ethyl-nornantenine (18a)

Brown solid; mp: 220–222 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.76 (s, 1H), 6.60 (s, 1H), 5.98 (d, J = 1.4 Hz, 1H), 5.95 (d, J = 1.4 Hz, 1H), 3.88 (s, 3H), 3.65 (s, 3H), 3.27 (d, J = 8 Hz, 1H), 3.19–3.17 (m, 1H), 3.12–3.08 (m, 2H), 2.99–2.96 (m, 1H), 2.71–2.48 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 146.6, 146.4, 144.6, 131.0, 129.0, 127.3, 125.7, 110.7, 109.1, 109.0, 108.4, 101.0, 60.4, 59.2, 55.9, 48.4, 47.9, 35.0, 29.3, 10.8; HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_4$ ([M+H]$^+$), 354.4116, found, 354.4115.

4.10.2. *N*-Propyl-nornantenine (18b)

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.76 (s, 1H), 6.59 (s, 1H), 5.98 (d, J = 1.1 Hz, 1H), 5.97 (d, J = 1.1 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.23–3.20 (d, 1H), 3.17–3.14 (m, 2H), 2.98–2.95 (m, 1H), 2.69–2.66 (d, 1H), 2.51–2.41 (m, 4H), 1.60–1.57 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 151.9, 146.5, 146.4, 144.5, 131.2, 129.2, 128.2, 128.1, 127.3, 125.7, 110.8, 109.0, 108.3, 101.0, 60.3, 60.0, 56.4, 55.9, 49.3, 35.3, 29.8, 29.5, 19.7,12.2; HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_4$ ([M+H]$^+$), 368.4382, found, 368.4380.

4.10.3. *N*-butyl-nornantenine (18c)

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.77 (s, 1H), 6.60 (s, 1H), 5.99 (d, J = 1.5 Hz, 1H), 5.97 (d, J = 1.5 Hz, 1H), 3.88 (s, 3H), 3.65 (s, 3H), 3.17–3.15 (m, 2H), 2.99–2.95 (m, 3H), 2.70 (m, 1H), 2.54–2.43 (m, 3H), 1.59–1.54 (m, 2H), 1.41–1.37 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.6, 146.4, 144.5, 131.3, 129.3, 128.6, 127.3, 125.8, 110.7, 109.0, 108.4, 101.0, 60.4, 60.0, 56.0, 54.2, 49.3, 35.3, 29.6, 28.7, 21.0, 14.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_4$ ([M+H]$^+$), 382.4648, found 382.4645.

4.10.4. *N*-Pentyl-nornantenine (18d)

Yellow Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 6.77 (s, 1H), 6.59 (s, 1H), 5.99 (d, J = 1.4 Hz, 1H), 5.97 (d, J = 1.4 Hz, 1H), 3.87 (s, 3H), 3.65 (s, 3H), 3.20–3.15 (m, 1H), 2.98–2.94 (m, 4H), 2.69 (m, 1H), 2.54 (m, 1H), 2.45–2.42 (m, 2H), 1.57 (m, 2H), 1.39–1.33 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.6, 146.4, 144.54, 131.3, 129.2, 128.1, 127.3, 125.8, 110.7, 109.0, 108.4, 101.0, 60.4, 60.0, 56.0, 54.5, 49.3, 35.3, 30.1, 29.6, 26.2, 22.9, 14.3; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}NO_4$ ([M+H]$^+$), 396.4914, found 396.4918.

4.10.5. *N*-Cyclopropylmethyl-nornantenine (18e)

Yellow Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.76 (s, 1H), 6.60 (s, 1H), 5.98 (d, 1.5 Hz, 1H), 5.97 (d, 1.5 Hz, 1H), 3.88 (s, 3H), 3.65 (s, 3H) 3.38–3.37 (m, 1H), 2.99–2.92 (m, 4H), 2.72–2.71 (m, 1H), 2.57–2.56 (m, 1H), 2.53–2.47 (m, 1H), 2.40–2.36 (m, 1H), 0.96 (m, 1H), 0.59 (dd, J = 8.0, 8.0 Hz, 1H), 0.54 (dd, J = 8.0, 8.0 Hz, 1H), 0.19 (d, J = 4.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.6, 146.4, 144.5, 131.2, 129.2, 128.0, 127.2, 125.8, 110.7, 109.0, 108.3, 101.0, 60.4, 59.5, 59.2, 56.0, 49.5, 35.2, 29.5, 7.7, 5.2, 3.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_4$ ([M+H]$^+$), 380.4489, found 380.4490.

Acknowledgments

This publication was made possible by Grant Number RR03037 and R03DA025910 from the National Center for Research Resources (NCRR) and National Institute of Drug Abuse (NIDA) respectively, components of the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or its divisions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.08.019.

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