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Semisynthetic Studies on and Biological Evaluation of *N*-Methyllaurotetanine Analogues as Ligands for 5-HT Receptors

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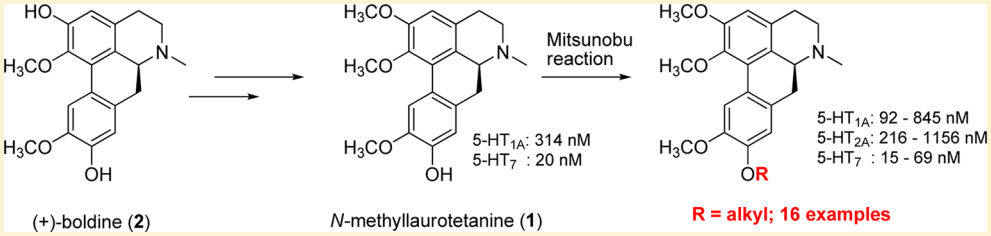
Supporting Information



ABSTRACT: *N*-Methyllaurotetanine (**1**) has been reported to display good affinity for the 5-HT$_{1A}$ receptor, but no structure−affinity studies have been performed to date. The commercially available alkaloid boldine (**2**) was used as the starting material for synthesis of various C-9 alkoxy analogues of *N*-methyllaurotetanine in order to gauge the effect of C-9 alkylation on affinity and selectivity at 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ receptors. Mitsunobu reactions were implemented in the alkylation steps leading to the analogues. Modest improvement in 5-HT$_{1A}$ affinity was observed upon alkylation for most analogues. Thus, the C-9 hydroxy group of **1** is not critical for affinity to the 5-HT$_{1A}$ receptor. Some analogues displayed high affinity for the 5-HT$_7$ receptor, comparable to *N*-methyllaurotetanine, with moderate selectivity vs 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors.

The aporphine scaffold is endowed with a range of biological activities including antiplatelet,[1,2] cytotoxicity,[3−5] antiplasmoidal,[6] antimicrobial,[7,8] and antiviral activities.[9,10] As far as activity at central nervous system (CNS) receptors is concerned, aporphines have been most studied as ligands for dopamine (D$_1$, D$_2$, and D$_3$),[11−19] serotonin (5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$),[20−31] and alpha-adrenergic receptors (α_{1A}, α_{1B}, and α_{1D}).[22,32−35] These receptors are known to play important roles in a myriad of neuropsychiatric disorders and drug abuse. The rich pharmacology of aporphines presents attractive yet challenging opportunities to optimize this naturally occurring scaffold for activity at CNS receptors. Along those lines, the identification of compounds that are selective for a particular receptor will provide a platform for the development of new and useful pharmacological tools, imaging agents, and therapeutics. Given the complex etiology of neuropsychiatric disorders, it is becoming increasingly apparent that compounds with multiple receptor activities may be therapeutically advantageous as compared to single receptor selective compounds.[36−38] The polypharmacology of aporphines provides a good platform for optimization as multireceptor therapeutic agents. Aporphines are thus promising both as monoreceptor selective ligands and as multireceptor agents. Opportunities abound for the exploitation of this scaffold as tools and drugs, particularly in the realms of neuropsychiatric disorders and addiction.

Our own work on aporphines has led to the identification of a number of new 1,2,9,10-tetraoxygenated aporphines that have good affinity and selectivity for 5-HT$_{2A}$ receptors.[22,23,25,30] The 1,2,9,10-tetraoxygenated pattern seems to endow aporphines with a bias for affinity to 5-HT receptors. However, an extensive evaluation of the impact of structural manipulations on the affinity of this scaffold across various 5-HT receptors is in need of attention. The total synthesis of 1,2,9,10-tetraoxygenated aporphines requires several steps and often entails laborious purification. Semisynthetic access to these tetraoxygenated aporphine analogues for structure−activity relationship (SAR) studies at CNS receptors offers considerable advantages as compared to total synthesis, particularly with respect to overall yields and synthetic efficiency.

The 1,2,9,10-tetraoxygenated aporphine *N*-methyllaurotetanine (**1**), isolated from the sedative/anxiolytic plant California poppy (*Eschscholzia californica* Cham., Papaveraceae), has been reported to have good affinity for 5-HT$_{1A}$ receptors and functions as an agonist in vitro.[39] Presumably, *N*-methyllaurotetanine contributes at least partially to the CNS effects of the plant. However, the affinity of *N*-methyllaurotetanine at other CNS receptors is not known, and thus the extent to which other receptors may play a role in its pharmacological activity in vivo remains to be deciphered. Therefore, to help illuminate this issue, one objective was the evaluation of *N*-methyllaurotetanine for affinity across various CNS receptor sites. As a second objective, it was of interest to evaluate the extent to which structural changes on *N*-methyllaurotetanine are tolerated for affinity at 5-HT$_{1A}$ as well as other CNS receptors,

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as a point of entry for obtaining selective and multipotent 5-HT receptor ligands. *N*-Methyllaurotetanine is available in only very low yield from natural sources.[39−42] The demethylated analogue boldine (**2**), however, is commercially available. Hence, it was decided to use boldine as the raw material for synthesis of *N*-methyllaurotetanine and analogues for SAR studies at 5-HT receptors. Herein are described the synthetic and biological experiments that were performed in meeting the objectives of the project.

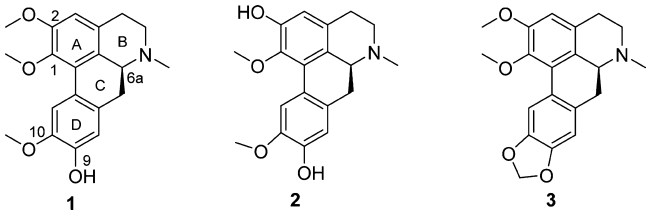

Figure 1. Structures of *N*-methyllaurotetanine (**1**), boldine (**2**), and nantenine (**3**).

RESULTS AND DISCUSSION

Our previous SAR studies on the 1,2,9,10-tetraoxygenated aporphine nantenine (**3**) indicated that homologation of the alkyl group at the C-1 position affords significantly improved affinity for 5-HT_{2A} receptors.[22,25] Thus, it was of interest to determine if a similar alkylation strategy would be beneficial for 5-HT_{1A} affinity in the case of *N*-methyllaurotetanine at the C-9 position.

It is known that phenolic alkylation of aporphines under typical Williamson ether synthesis conditions leads to quaternization of the tertiary nitrogen and subsequent cleavage of ring B to afford a phenanthrene alkaloid nucleus (**4** to **5**, Figure 2).[43] In order to avoid N-alkylation during phenolic alkylation of boldine, it was decided to use a Mitsunobu reaction as the alkylation method. To the best of our knowledge, Mitsunobu phenolic alkylation has not been performed previously on any aporphine.

The route to synthesize the *N*-methyllaurotetanine analogues is outlined in Scheme 1. Boldine was subjected to Mitsunobu alkylation to afford a mixture of *N*-methyllaurotetanine, predicentrine (**6**), and glaucine (**7**). Of the two phenolic groups in boldine, the C-9 hydroxy group is more easily alkylated. This was inferred from the relative yield of *N*-methyllaurotetanine and predicentrine (3:7 by NMR spectroscopy). This result is also in line with other studies involving alkylation of the phenolic groups of boldine, where it has been found that the C-9 phenol is methylated more readily than the C-2 phenol with diazomethane as the methylating agent.[44−46] In a separate experiment, dimethylation of boldine to form glaucine was achieved by using the reactants in excess. Thus, the Mitsunobu procedure is versatile in providing access to the three aporphine natural products, *N*-methyllaurotetanine, predicentrine, and glaucine, or to glaucine exclusively. However, achieving exclusive or even selective alkylation of the C-3 phenol is perhaps not feasible with Mitsunobu conditions. The mixture of *N*-methyllaurotetanine, predicentrine, and glaucine was subjected to column chromatography in order to separate glaucine from the mixture of *N*-methyllaurotetanine and predicentrine. (*N*-Methyllaurotetanine and predicentrine coelute in various solvent systems, and we were not able to separate the compounds from each other chromatographically.) With the aim of separating the compounds via derivatization, the mixture of *N*-methyllaurotetanine and predicentrine was reacted with *tert*-butyldimethylsilyl chloride, affording the silyl ethers **8** and **9**. Fortunately, the silyl ethers proved to be chromatographically separable, though the separation is somewhat tedious owing to the close similarities in R_f. Once separated, the silyl groups in **8** and **9** were removed by treatment with TBAF, thus leading to pure *N*-methyllaurotetanine and predicentrine.

Although very similar in their ^{1}H NMR and ^{13}C NMR spectra, *N*-methyllaurotetanine and predicentrine may be distinguished based on the chemical shifts of the methoxy group protons. In the case of compound *N*-methyllaurotetanine, the methoxy signals appear at δ 3.65 (3H, s) and 3.88 (6H, br s), while predicentrine had three singlet methoxy signals at δ 3.58, 3.89, and 3.92 ppm. It was found also that the lower field methoxy group signals for *N*-methyllaurotetanine appeared as two singlets (δ 3.88 and 3.89 ppm) rather than a broad singlet when the NMR sample was less concentrated; in this case distinguishing the isomers as described above was made more difficult due to the similarity in their chemical shifts. NOESY spectra are also useful in distinguishing the regioisomers with the aromatic protons and methoxy group cross-peaks being diagnostic. In 1,2,9,10-tetraoxygenated aporphines, the aromatic proton chemical shifts increase in the order H-3 < H-8 < H-11. For predicentrine, a NOESY cross-peak was observed between the lowest field aromatic proton (H-11) and a methoxy group. A similar cross-peak was observed in the NOESY spectrum of *N*-methyllaurotetanine. *N*-Methyllaurotetanine also showed a cross-peak between the furthest upfield aromatic proton (H-3) and the methoxy protons, thus placing a methoxy group at C-2. In predicentrine, this corresponding NOESY cross-peak was absent, but cross-peaks appeared between H-8 and a methoxy group, indicating that a methoxy group is attached to C-9. Key NOESY cross-peaks are summarized in Figure 3.

N-Methyllaurotetanine was reacted with a variety of alcohols under Mitsunobu conditions to afford analogues **10a−10n**, with the reaction proceeding in high yield.

N-Methyllaurotetanine (**1**) was screened at a number of CNS receptor, ion-channel, and transporter sites. In this

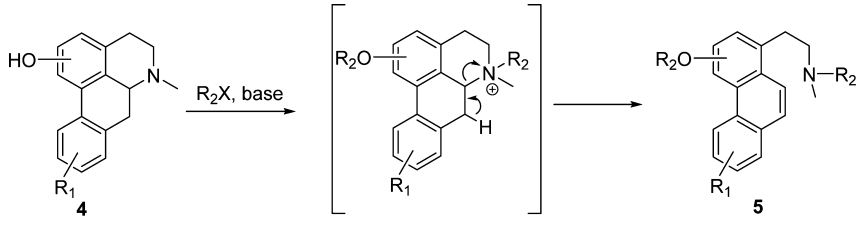

Figure 2. Ring opening of aporphines under Williamson ether synthesis conditions.

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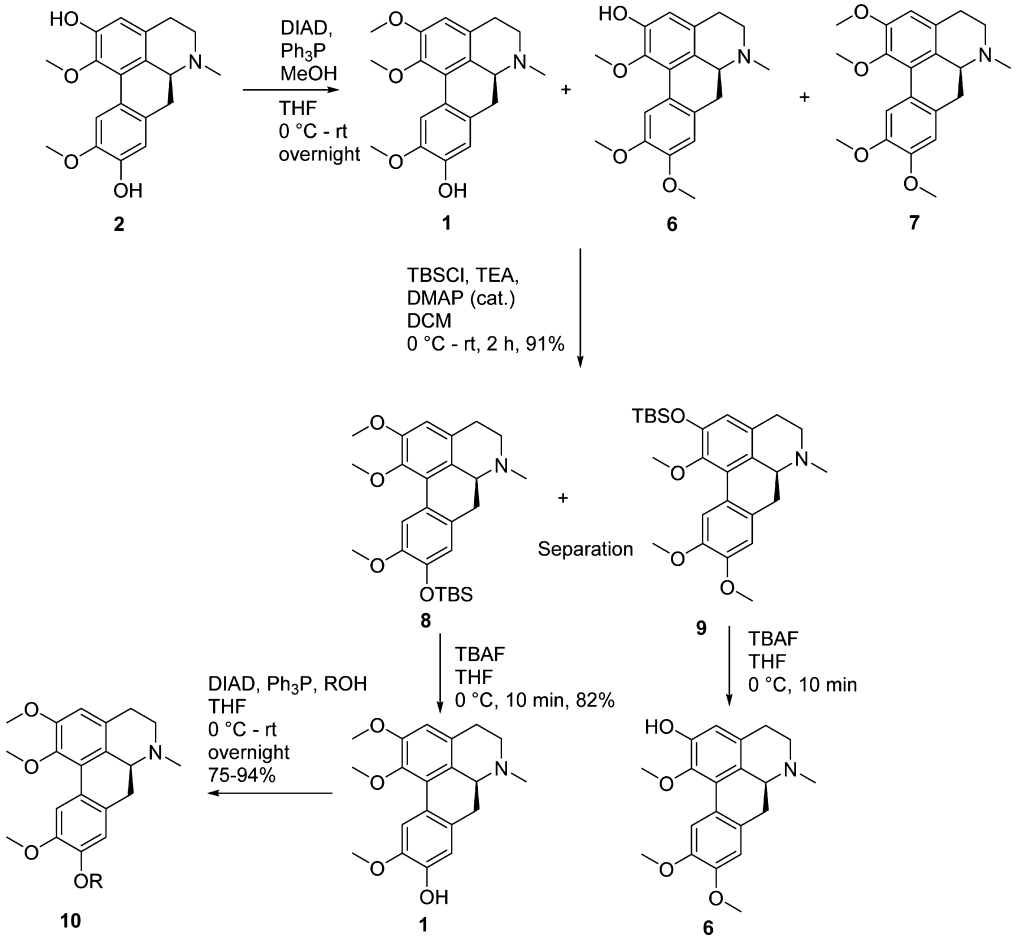
Scheme 1. Synthesis of *N*-Methyllaurotetanine Analogues from Boldine



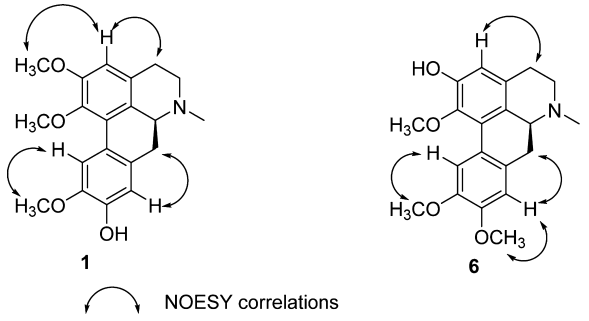


Figure 3. Key NOESY correlations for *N*-methyllaurotetanine (**1**) and predicentrine (**6**).

screening, conducted by the Psychoactive Drug Screening Program (PDSP), *N*-methyllaurotetanine was first screened at the various receptor sites in primary radioligand binding assays that measure percent inhibition. If <50% inhibition was observed in the primary assay at a particular receptor, the compound was considered inactive at that receptor and was not evaluated further in secondary assays. Secondary assays were performed at those receptors sites where >50% inhibition was obtained in order to obtain affinity (K_i) values.

The following K_i values were obtained for *N*-methyllaurotetanine (**1**) in this broad panel screening: 5-HT_{1A} (314 nM), 5-HT_{2B} (323 nM), 5-HT_{5A} (566 nM), 5-HT_6 (306 nM), 5-HT_7 (20 nM), D_1 (373 nM). Compound **1** was inactive (>50% inhibition in the primary assay) at the following receptors: 5-HT_{1e}, 5-HT_{2A}, 5-HT_3, α_{1A}, α_{1D}, α_{2B}, BZP rat brain site, D2, D4, D5, DOR, $GABA_A$, H_1, H_3, H_4, KOR, M_1, M_2, M_3, M_4, M_5, MOR, PBR, σ_1, σ_2. At the following sites, **1** had low affinity (K_i values >950 nM): 5-HT_{2C}, α_{1B}, α_{2C}, β_2, D3, DAT, NET, SERT.

In a similar fashion to that described above for *N*-methyllaurotetanine, all analogues were assayed for their affinity to human 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors. K_i data are collated in Table 1. As alluded to above, *N*-methyllaurotetanine showed 16-fold higher affinity for the 5-HT_7 receptor as compared to the 5-HT_{1A} receptor. In general, the analogues had moderate affinity for the 5-HT_{1A} receptor with K_i values ranging from 92 to 845 nM. With the exception of the ethyl analogue (**10a**), the addition of *n*-alkyl groups to the C-9 position gave compounds (**10b**, **10c**, and **10d**) with slightly higher affinity for the 5-HT_{1A} receptor (153, 179, and 273 nM, respectively) as compared to *N*-methyllaurotetanine. Addition of a fluoroethyl group (compound **10e**), however, led to the loss of affinity at 5-HT_{1A} (K_i = 845 nM, the lowest affinity among this series), which tends to suggest that the electronic nature of the C-9 substituent is important (based on the similarity of size of ethyl and fluoroethyl groups; compare **10a** and **10e**). An isopropyl group (**10f**) led to a 2-fold loss of affinity at the 5-HT_{1A} receptor (K_i = 563 nM). However, the inclusion of other branched alkyl chain groups (**10g**–**10i**) and a cyclohexyl moiety (**10k**) provided molecules with up to 3-fold higher affinity for the 5-HT_{1A} receptor than *N*-methyllaurotetanine. The presence of a cyclopropyl methyl group also gave slightly improved 5-HT_{1A} receptor affinity (**10j**; 224 nM).

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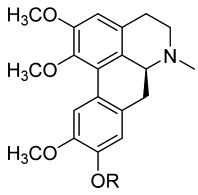
Table 1. Affinity (K_i in nM) of Analogues at 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 Receptors



		K_i (nM) ± SEM[a]			selectivity	
compound	R	5-HT_{1A}	5-HT_{2A}	5-HT_7	1A/7	2A/7
1	H	314 ± 47	nd[b]	20 ± 2.2	16	
7	Me	171 ± 29	966 ± 120	43 ± 4.7	4	22
10a	Et	506 ± 55	818 ± 72	69 ± 7.5	7	12
10b	*n*-butyl	153 ± 17	268 ± 29	15 ± 1.9	10	18
10c	*n*-pentyl	179 ± 16	239 ± 26	24 ± 3.1	7	10
10d	*n*-hexyl	273 ± 24	570 ± 62	58 ± 8.6	5	10
10e	fluoroethyl	845 ± 92	1,156 ± 130	52 ± 6.7	16	22
10f	isopropyl	563 ± 61	750 ± 82	28 ± 4.7	20	27
10g	*sec*-butyl	244 ± 21	377 ± 41	34 ± 4.4	7	7
10h	2-pentyl	117 ± 13	244 ± 27	24 ± 3.1	5	5
10i	2-hexyl	152 ± 13	446 ± 49	38 ± 6.4	4	12
10j	cyclopropyl methyl	224 ± 24	582 ± 63	22 ± 3.3	10	10
10k	cyclohexyl	163 ± 18	570 ± 62	50 ± 7.4	3	11
10l	allyl	361 ± 32	383 ± 42	20 ± 2.6	18	18
10m	benzyl	92 ± 10	216 ± 19	23 ± 2.5	4	9
10n	*p*-bromobenzyl	102 ± 9	418 ± 45	54 ± 8	2	8
8-OH-DPAT		0.71				
clozapine			18			
clozapine				37		

[a]From at least three experiments performed in triplicate. [b]nd - not determined; % inhibition <50% in primary assay.

The allyl analogue (**10l**) had similar 5-HT_{1A} affinity as compared to *N*-methyllaurotetanine. The compounds with the highest affinity for the 5-HT_{1A} receptor were the benzyl analogues **10m** and **10n**, with K_i values of 92 and 102 nM, respectively, representing an approximate 3-fold increase in affinity with respect to *N*-methyllaurotetanine.

The analogues in general had moderate affinity for the 5-HT_{2A} receptor, with most compounds having K_i values in the 200−1000 nM range. At the 5-HT_{2A} receptor, an increase in alkyl chain length led to an increase in affinity (up to five carbons in length, i.e., compounds **7** and **10a**−**10c**). A similar trend was observed for branched-chain analogues in the series **10f**, **10g**, and **10h**. A five-carbon alkyl unit seems to be best tolerated at this site for 5-HT_{2A} affinity. The *n*-pentyl (**10c**) and 2-pentyl (**10h**) analogues were among the top three compounds with respect to 5-HT_{2A} receptor affinity (239 and 244 nM, respectively); the benzyl analogue (**10m**) had a similar affinity to **10c** and **10h** (216 nM). Paralleling the SAR at the 5-HT_{1A} receptor, the fluoroethyl analogue (**10e**) had the lowest affinity for 5-HT_{2A} of the compounds assayed (K_i = 1156 nM).

Interestingly, most of the compounds displayed high affinity for the 5-HT_7 receptor and were comparable to *N*-methyllaurotetanine (**1**) in this regard (K_i values were in the 15−69 nM range). However, no clear SAR trend could be discerned. Nevertheless, all of the compounds were selective for the 5-HT_7 receptor, with selectivities ranging from 2- to 20-fold for 5HT_7 vs 5-HT_{1A} and 5- to almost 30-fold for 5-HT_7 vs 5-HT_{2A}.

The results above suggest that the C-9 phenol is not required for affinity to the 5-HT_7 receptor and indicate very good tolerance for alkoxy groups at this position. The phenolic groups present in aporphine alkaloids are metabolic liabilities for drug development. In the case of boldine (**2**) for example, the phenolic groups are glycosylated and sulfated, which predictably leads to low bioavailability of the compound.[47] Therefore, "capping" these phenolic groups is an important strategy for improving the pharmacokinetic properties of these molecules.

CONCLUSION

In conclusion, Mitsunobu reactions have been implemented that allow for rapid and high-yielding semisynthetic access to phenol alkyl ether analogues of *N*-methyllaurotetanine (**1**) from commercially available boldine (**2**). The synthetic procedure implemented is valuable for producing naturally occurring alkaloids as well as various phenol ether variants. *N*-Methyllaurotetanine was found to have high affinity for the 5-HT_7 receptor. Given this high 5-HT_7 receptor affinity, it is reasonable to presume that this receptor plays a significant role in the CNS effects of *N*-methyllaurotetanine and by extension, *E. californica*. However, contributory roles by other receptors for which *N*-methyllaurotetanine has affinity cannot be excluded at this stage. Biological evaluation of the compounds revealed high affinity for the 5-HT_7 receptor with moderate selectivity vs 5-HT_{1A} and 5-HT_{2A} receptors. The retention of high 5-HT_7 affinity in this series of compounds should engender improved metabolic stability in vivo owing to protection of the metabolically labile phenol functionality. This SAR study revealed that the C-9 phenol of *N*-methyllaurotetanine is detrimental to 5-HT_{2A} affinity and is not essential for 5-HT_{1A} and 5-HT_7 receptor activity. A number of new 5-HT receptor ligands have been uncovered, and this

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work has enriched knowledge on the SAR of aporphines as CNS receptor ligands.

It may be expected that obtaining ligands that are highly potent and selective for a particular receptor using this template will be challenging. The bias for the 5-HT_7 receptor exhibited by these compounds provides a basis for further work in optimizing 5-HT_7 affinity and selectivity. Aporphine-based multireceptor agents that are potent at all three receptors seem to be a reachable goal. Further SAR studies will enable enlightenment in that direction. The functional activity of the analogues at the various 5-HT receptors remains to be determined. This is critical for understanding the pharmacological basis for activity of these molecules in vivo, since it is possible that receptor-mediated synergistic or antagonistic effects are in operation. Nevertheless, optimization of potency and selectivity of the aporphine scaffold to various 5-HT receptors (irrespective of functional activity) will lead to structurally unique ligands that are valuable for understanding receptor−ligand interactions that control receptor affinity, activity, and selectivity. The synthetic and biological work described herein sets the stage for such an optimization.

EXPERIMENTAL SECTION

General Experimental Procedures. All moisture-sensitive reactions were carried out in vacuum-oven-dried glassware under a nitrogen atmosphere. Anhydrous solvents and reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Melting points were obtained on a Mel-Temp capillary electrothermal melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DPX-500 spectrometer (operating at 500 MHz for ^{1}H; 125 MHz for ^{13}C) using $CDCl_3$ as solvent. TMS (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR as solvent unless stated otherwise. Chemical shift (δ 0.00 ppm) values are reported in parts per million, and coupling constants in hertz (Hz). Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). HRESIMS were obtained using an Agilent 6520 QTOF instrument. Reactions were monitored by TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm). Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230−400 mesh, 0.04e0.063 mm particle size) and basic alumina 60A (Acros Chemicals, 50−200 mesh).

Mitsunobu Reaction on Boldine (1): Synthesis of Compounds 1, 6, and 7. To a stirring solution of Ph_3P (4.81 g, 18.34 mmol) in anhydrous THF (50 mL) was slowly added DIAD (3.71 g, 18.34 mmol) at 0 °C under an inert (N_2) atmosphere. The reaction mixture was stirred for 15 min, and then methanol (0.55 mL, 13.75 mmol) was added slowly. After 15 min, a solution of **2** (3.0 g, 9.17 mmol) in anhydrous THF was added to the reaction mixture. The resulting reaction mixture was allowed to attain ambient temperature, and stirring was continued overnight. The solvent was removed by evaporation under reduced pressure, and the resulting residue was dissolved in ethyl acetate (100 mL) and washed consecutively with brine solution and water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a residue, which was purified by column chromatography on silica gel using 2:98 and 4:96 MeOH−CH_2Cl_2 as eluent to afford glaucine [**7** (0.85 g, 26%)] and a mixture of *N*-methyllaurotetanine, **1**, and predicentrine [**6** (1.40 g, 45%)].

Synthesis of Compounds 8 and 9. To a stirred solution of a mixture of compounds **1** and **6** (1.40 g, 4.10 mmol) in anhydrous CH_2Cl_2 (15 mL) were added TEA (0.85 mL, 6.15 mmol), DMAP (5 mg, 0.041 mmol), and TBSCl (0.74 g, 4.92 mmol) at 0 °C, under N_2. The reaction mixture was allowed to attain room temperature, and stirring was continued for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with brine solution and water, dried over Na_2SO_4, and concentrated under reduced pressure to obtain a residue. The resulting residue was purified by silica gel column chromatography using 2:98 to 3:97 MeOH−CH_2Cl_2 as eluent to afford compounds **8** (0.50 g, 27%) and **9** (1.2 g, 64%).

Synthesis of Compound 1. To a stirred solution of compound **8** (0.50 g, 1.09 mmol) in THF (10 mL) was added TBAF (0.57 g, 2.19 mmol) at 0 °C under N_2, and the stirring continued for 10 min. Thereafter the reaction mixture was quenched with water and extracted with ethyl acetate (3 × 20 mL). The combined organic solution was washed with brine solution, dried over Na_2SO_4, and concentrated to yield the crude product, which was purified via silica gel column chromatography using MeOH−CH_2Cl_2 (5:95) as eluent to afford pure compound **1** (0.31, 84%).

General Procedure for Preparation of C-9 Analogues (10a−10n). To a stirred solution of Ph_3P (1.5 equiv) in anhydrous THF (5 mL) was slowly added DIAD (1.5 equiv) at 0 °C under an inert (N_2) atmosphere, and the stirring was allowed to continue for 15 min. Thereafter, the appropriate alcohol (1.2 equiv) was added to the reaction mixture, which was further stirred for 20 min. Then, the solution of *N*-methyllaurotetanine (1.0 equiv) in THF (1 mL) was added to the reaction mixture. The resulting reaction mixture was allowed to reach ambient temperature, and stirring was continued for completion of the reaction (8−12 h). Thereafter, the reaction solvent was removed by evaporation under reduced pressure, and the resulting residue was dissolved in ethyl acetate (20 mL) and washed with brine solution and then water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a residue, which was purified by column chromatography on neutral alumina using 8−12% acetone in hexanes as eluent to afford **10a−10n** in high yield (75−94%).

(*S*)-9-Ethoxy-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline (10a). Yield: 81% (88 mg), light brown gum; R_f = 0.52 on a silica gel TLC plate in 5:95 MeOH−CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (1H, s, H-11), 6.77 (1H, s, H-8), 6.58 (1H, s, H-3), 4.19−4.12 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.89 (3H, s, OCH_3-2), 3.88 (3H, s, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.98 (3H, m, H-5, 6a, 7), 2.67 (1H, dd, J = 16.2, 3.2 Hz, H-7), 2.60−2.48 (5H, m, H-5, 4, NCH_3), 1.50 (3H, t, J = 7.0 Hz, OCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9 (C-2), 147.6 (C-10), 147.3 (C-9), 144.2 (C-1), 129.2 (C-7a), 128.9 (C-1a), 127.2 (C-3a), 126.9 (C-1b), 124.4 (C-11a), 112.0 (C-8), 111.7 (C-11), 110.3 (C-3), 64.1 (OCH$_2$CH$_3$), 62.5 (C-6a), 60.1 (C-1-OCH$_3$), 55.9 (C-10-OCH$_3$), 55.7 (C-2-OCH$_3$), 53.3 (C-5), 44.0 (NCH$_3$), 34.5 (C-7), 29.3 (C-4), 14.9 (OCH$_2$CH$_3$); HRESIMS m/z 370.2018 [M + H]$^+$ (calcd for $C_{22}H_{27}NO_4$, 370.2018).

(*S*)-9-Butoxy-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10b. Yield: 77% (90 mg), light brown solid; R_f = 0.54 on a silica gel TLC plate in 5:95 MeOH−CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, s, H-11), 6.78 (1H, s, H-8), 6.58 (1H, s, H-3), 4.10−4.04 (2H, m, OCH_2CH$_3$), 3.88 (6H, br s, OCH_3-2, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.04−2.98 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.2, 3.2 Hz, H-7b), 2.60−2.47 (5H, m, H-5, 4, NCH_3), 1.87 (2H, m, OCH$_2$CH_2CH$_2$CH$_3$), 1.54−1.48 (2H, m, OCH$_2$CH$_2$CH_2CH$_3$), 1.00 (3H, t, J = 7.4 Hz, OCH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9 (C-2), 147.7 (C-10), 147.6 (C-9), 144.2 (C-1), 129.3 (C-7a), 128.9 (C-1a), 127.3 (C-3a), 126.9 (C-1b), 124.3 (C-11a), 112.2 (C-8), 111.9 (C-11), 110.3 (C-3), 68.8 (OCH$_2$CH$_2$CH$_2$CH$_3$), 62.6 (C-6a), 60.1 (C-1-OCH$_3$), 56.0 (C-10-OCH$_3$), 55.7 (C-2-OCH$_3$), 53.3 (C-5), 44.1 (NCH$_3$), 34.5 (C-7), 31.3 (OCH$_2$CH$_2$CH$_2$CH$_3$), 29.3 (C-4), 19.2 (OCH$_2$CH$_2$CH$_2$CH$_3$), 13.9 (OCH$_2$CH$_2$CH$_2$CH$_3$); HRESIMS m/z 398.2299 [M + H]$^+$ (calcd for $C_{24}H_{31}NO_4$, 398.2331).

(*S*)-1,2,10-Trimethoxy-6-methyl-9-(pentyloxy)-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10c. Yield: 75% (63 mg), light brown gum; R_f = 0.54 on silica gel TLC plate in 5:95 MeOH−CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, s, H-11), 6.78 (1H, s, H-8), 6.58 (1H, s, H-3), 4.10−4.00 (2H, m, OCH_2CH$_2$CH$_2$CH$_2$CH$_3$), 3.88 (6H, s, OCH_3-2, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.98 (3H, m, H-5, 6a, 7), 2.67 (1H, dd, J = 16.1, 3.0 Hz, H-7a), 2.60−2.48 (5H, m, H-5,

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4, NCH_3), 1.89 (2H, m, OCH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.50−1.37 (4H, m, OCH$_2$CH$_2$CH_2CH_2CH$_3$), 0.94 (3H, t, J = 7.2 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 147.8 (C-10), 147.6 (C-9), 144.2 (C-1), 129.3 (C-7a), 128.9 (C-1a), 127.3 (C-3a), 126.9 (C-1b), 124.3 (C-11a), 112.2 (C-8), 111.9 (C-11), 110.3 (C-3), 68.8 (OCH_2CH$_2$CH$_2$CH$_2$CH$_3$), 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.1 (NCH_3), 34.6 (C-7), 29.3 (C-4), 28.9 (OCH$_2$CH_2CH$_2$CH$_2$CH$_3$), 28.1 (OCH$_2$CH$_2$CH_2CH$_2$CH$_3$), 22.5 (OCH$_2$CH$_2$CH$_2$CH_2CH$_3$), 14.0 (OCH$_2$CH$_2$CH$_2$CH$_2$CH_3); HRESIMS m/z 412.2456 [M + H]$^+$ (calcd for $C_{25}H_{33}NO_4$, 412.2488).

(*S*)-9-(Hexyloxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10d. Yield: 83% (72 mg), light brown gum; R_f = 0.54 on silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (1H, s, H-11), 6.77 (1H, s, H-8), 6.58 (1H, s, H-3), 4.10−4.02 (2H, m, OCH_2CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 3.88 (6H, s, OCH_3-2, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.98 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.1, 3.1 Hz, H-7b), 2.60−2.48 (5H, m, H-5, 4, NCH_3), 1.88 (2H, m, OCH$_2$CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.51−1.45 (2H, m, OCH$_2$CH$_2$CH_2-CH$_2$CH$_2$CH$_3$), 1.39−1.33 (4H, m, OCH$_2$CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.92−0.89 (3H, m, 3H, OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 147.8 (C-10), 147.6 (C-9), 144.2 (C-1), 129.3 (C-7a), 128.8 (C-1a), 127.2 (C-3a), 126.9 (C-1b), 124.3 (C-11a), 112.2 (C-8), 111.9 (C-11), 110.3 (C-3), 68.9 (OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 34.5 (C-7), 31.6 (OCH$_2$CH$_2$CH$_2$CH_2CH$_2$CH$_3$), 29.3 (C-4), 29.2 (OCH$_2$CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 25.7 (OCH$_2$CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 22.6 (OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 14.0 (OCH_2CH$_2$CH$_2$-CH$_2$CH$_2$CH_3); HRESIMS m/z 426.2644 [M + H]$^+$ (calcd for $C_{26}H_{35}NO_4$, 426.2644).

(*S*)-9-(2-Fluoroethoxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10e. Yield: 80% (63 mg), light brown gum; R_f = 0.57 on a silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (1H, s, H-11), 6.82 (1H, s, H-8), 6.60 (1H, s, H-3), 4.85 (2H, dt, J = 47.5, 4.5 Hz, OCH$_2$CH_2F), 4.39−4.27 (2H, m, OCH_2CH$_2$F), 3.89 (3H, s, OCH_3-2), 3.88 (3H, s, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.97 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.2, 3.2 Hz, H-7b), 2.59−2.47 (5H, m, H-5, 4, NCH_3); ^{13}C NMR (125 MHz, CDCl$_3$): δ 151.9 (C-2), 148.1 (C-10), 146.8 (C-9), 144.3 (C-1), 129.3 (C-7a), 128.9 (C-1a), 127.3 (C-3a), 126.7 (C-1b), 125.6 (C-11a), 113.6 (C-8), 112.3 (C-11), 110.5 (C-3), 82.6 (OCH$_2$CH$_2$F), 68.4 (OCH$_2$CH$_2$F), 62.5 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 34.4 (C-7), 29.3 (C-4); HRESIMS m/z 388.2548 [M + H]$^+$ (calcd for $C_{22}H_{26}FNO_4$, 388.1924).

(*S*)-9-Isopropoxy-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10f. Yield: 83% (65 mg), light brown gum; R_f = 0.55 on silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (1H, s, H-11), 6.78 (1H, s, H-8), 6.58 (1H, s, H-3), 4.60 [1H, sept., J = 6.1 Hz, OCH(CH$_3$)$_2$], 3.88 (3H, s, OCH_3-2), 3.87 (3H, s, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.12 (1H, m, H-4), 3.05−2.96 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.2, 3.2 Hz, H-7b), 2.59−2.48 (5H, m, H-5, 4, NCH_3), 1.43−1.40 [6H, d, J = 6.1 Hz, OCH(CH_3)$_2$]; ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 148.6 (C-10), 146.4 (C-9), 144.2 (C-1), 129.2 (C-7a), 128.8 (C-1a), 127.3 (C-3a), 126.9 (C-1b), 124.6 (C-11a), 114.5 (C-8), 112.1 (C-11), 110.3 (C-3), 71.1 [OCH(CH$_3$)$_2$], 62.5 (C-6a), 60.1 (C-1-OCH_3), 55.9 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 34.5 (C-7), 29.3 (C-4), 22.3 [OCH(CH_3)$_2$], 22.3 [OCH(CH_3)$_2$]; HRESIMS m/z 384.2163 [M + H]$^+$ (calcd for $C_{23}H_{29}NO_4$, 384.2175).

(*S*)-9-(*sec*-Butoxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10g. Yield: 75% (61 mg), light brown gum; R_f = 0.55 on silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (1H, s, H-11), 6.77 (1H, s, H-8), 6.58 (1H, s, H-3), 4.37−4.31 [1H, m, CH(CH$_3$CH$_2$)CH$_3$], 3.88 (3H, s, OCH_3-2), 3.87 (3H, s, OCH_3-10), 3.66 (3H, s, OCH_3-1), 3.15−3.11 (1H, m, H-4), 3.05−2.96 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.1, 3.0 Hz, H-7b), 2.59−2.47 (5H, m, H-5, 4, NCH_3), 1.89−1.85 [1H, m, CH(CH$_3$CH_2)CH$_3$], 1.70−1.65 [1H, m, CH(CH$_3$CH_2)-CH$_3$], 1.39−1.35 [3H, m, CH(CH$_3$CH$_2$)CH_3], 1.04−0.99 [3H, m, CH(CH_3CH$_2$)CH$_3$]; ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 148.8 (C-10), 146.8 (C-9), 144.3 (C-1), 129.2 (C-7a), 128.8 (C-1a), 127.3 (C-3a), 126.9 (C-1b), 124.6 (C-11a), 114.7 (C-8), 112.3 (C-11), 110.3 (C-3), 76.5 [CH(CH$_3$CH$_2$)CH$_3$], 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.1 (NCH_3), 34.5 (C-7), 29.3 (C-4), 29.2 [CH(CH$_3$CH$_2$)CH$_3$], 19.4 [CH(CH$_3$CH$_2$)CH$_3$], 10.0 [CH(CH_3CH$_2$)CH$_3$]; HRESIMS m/z 398.2328 [M + H]$^+$ (calcd for $C_{24}H_{31}NO_4$, 398.2331).

(*S*)-1,2,10-Trimethoxy-6-methyl-9-(pentan-2-yloxy)-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10h. Yield: 86% (72 mg), light brown gum; R_f = 0.56 on a silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (1H, s, H-11), 6.78 (1H, s, H-8), 6.58 (1H, s, H-3), 4.43−4.39 [1H, m, OCH(CH$_2$CH$_2$CH$_3$)-CH$_3$], 3.88 (3H, s, OCH_3-2), 3.86 (3H, s, OCH_3-10), 3.66 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.96 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.1, 2.8 Hz, H-7b), 2.59−2.48 (5H, m, H-5, 4, NCH_3), 1.89−1.81 [1H, m, OCH(CH_2CH$_2$CH$_3$)CH$_3$], 1.65−1.35 [6H, m, OCH(CH$_2$CH_2CH_3)CH$_3$], 0.98−0.94 [3H, m, OCH-(CH$_2$CH$_2$CH$_3$)CH_3]; ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 148.8 (C-10), 146.8 (C-9), 144.3 (C-1), 129.2 (C-7a), 128.8 (C-1a), 127.3 (C-3a), 126.9 (C-1b), 124.6 (C-11a), 114.7 (C-8), 112.3 (C-11), 110.3 (C-3), 75.0 [OCH(CH$_2$CH$_2$CH$_3$)CH$_3$], 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 38.8 [OCH(CH_2CH$_2$CH$_3$)CH$_3$], 34.5 (C-7), 29.3 (C-4), 19.9 (OCH(CH$_2$CH$_2$CH$_3$)CH$_3$), 18.9 [OCH(CH$_2$CH_2CH$_3$)CH$_3$], 14.1 [OCH(CH$_2$CH$_2$CH_3)CH$_3$]; HRESIMS m/z 412.2485 [M + H]$^+$ (calcd for $C_{25}H_{33}NO_4$, 412.2488).

(*S*)-9-(Hexan-2-yloxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10i. Yield: 74 mg, 85% (74 mg), light brown gum; R_f = 0.56 on a silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (1H, s, H-11), 6.77 (1H, s, H-8), 6.58 (1H, s, H-3), 4.42−4.38 [1H, m, OCH(CH$_2$CH$_2$CH$_2$CH$_3$)CH$_3$], 3.88 (3H, s, OCH_3-2), 3.86 (3H, s, OCH_3-10), 3.66 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.96 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.1, 3.0 Hz, H-7b), 2.59−2.47 (5H, m, H-5, 4, NCH_3), 1.90−1.82 (1H, m, OCH-(CH_2CH$_2$CH$_2$CH$_3$)CH$_3$), 1.67−1.59 [1H, m, OCH-(CH_2CH$_2$CH$_2$CH$_3$)CH$_3$], 1.53−1.49 [1H, m, OCH-(CH$_2$CH_2CH$_2$CH$_3$)CH$_3$], 1.48−1.35 [6H, m, OCH-(CH$_2$CH$_2$CH$_2$CH$_3$)CH$_3$], 0.94−0.90 [3H, m, OCH(CH$_2$CH$_2$CH$_2$CH$_3$)CH_3]; ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 148.8 (C-10), 146.8 (C-9), 144.3 (C-1), 129.2 (C-7a), 128.8 (C-1a), 127.3 (C-3a), 127.0 (C-1b), 124.6 (C-11a), 114.7 (C-8), 112.3 (C-11), 110.3-(C-3), 75.3 [OCH(CH$_2$CH$_2$CH$_2$CH$_3$)CH$_3$], 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.1 (NCH_3), 36.3 [OCH(CH$_2$CH$_2$CH$_2$CH$_3$)CH$_3$], 34.6 (C-7), 29.3 (C-4), 27.9 (OCH(CH$_2$CH$_2$CH$_2$CH$_3$)CH$_3$), 22.7 [OCH-(CH$_2$CH$_2$CH_2CH$_3$)CH$_3$], 20.0 [OCH(CH$_2$CH$_2$CH$_2$CH$_3$)CH_3], 14.1 [OCH(CH$_2$CH$_2$CH$_2$CH_3)CH$_3$]; HRESIMS m/z 426.2631 [M + H]$^+$ (calcd for $C_{26}H_{35}NO_4$, 426.2644).

(*S*)-9-(Cyclopropylmethoxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10j. Yield: 84% (68 mg), light brown gum; R_f = 0.55 on a silica gel TLC plate in 5:95 MeOH−CH$_2$Cl$_2$; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (1H, s, H-11), 6.77 (1H, s, H-8), 6.58 (1H, s, H-3), 3.90−3.88 [8H, m, OCH_2CH(CH$_2$CH$_2$)], OCH_3-2, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.18−3.11 (1H, m, H-4), 3.05−2.97 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, J = 16.2, 2.8 Hz, H-7b), 2.59−2.48 (5H, m, H-5, 4, NCH_3), 1.42−1.36 [1H, m, OCH$_2$CH(CH$_2$CH$_2$)], 0.68−0.64 [2H, m, OCH$_2$CH-(CH_2CH$_2$)], 0.39−0.36 [2H, m, OCH_2CH(CH$_2$CH_2)]; ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.9 (C-2), 147.8 (C-10), 147.5 (C-9), 144.2 (C-1), 129.2 (C-7a), 128.9 (C-1a), 127.2 (C-3a), 126.9 (C-1b), 124.5 (C-11a), 112.5 (C-8), 111.9 (C-11), 110.3 (C-3), 73.8 [OCH$_2$CH-(CH$_2$CH$_2$)], 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 34.5 (C-7), 29.3 (C-4), 10.3 [OCH$_2$CH(CH$_2$CH$_2$)], 3.5 [OCH$_2$CH(CH_2CH$_2$)], 3.5 [OCH$_2$CH-

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(CH_2CH_2)]; HRESIMS *m/z* 396.2159 $[M + H]^+$ (calcd for $C_{24}H_{29}NO_4$, 396.2175).

(*S*)-9-(Cyclohexyloxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10k. Yield: 82% (71 mg), light brown gum; R_f = 0.57 on a silica gel TLC plate in 5:95 MeOH–CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, s, H-11), 6.79 (1H, s, H-8), 6.58 (1H, s, H-3), 4.27–4.24 [1H, m, $OCH(CH_2)_2(CH_2)_2CH_2$], 3.88 (3H, s, OCH_3-2), 3.87 (3H, s, OCH_3-10), 3.66 (3H, s, OCH_3-1), 3.15–3.11 (1H, m, H-4), 3.05–2.96 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, *J* = 16.2, 3.0 Hz, H-7b), 2.58–2.47 (5H, m, H-5, 4, NCH_3), 2.10–2.09 (2H, m, $[OCH(CH_2)_2(CH_2)_2CH_2]$, 1.87–1.83 [2H, m, $OCH(CH_2)_2(CH_2)_2CH_2$], 1.62–1.58 [3H, m, $OCH(CH_2)_2(CH_2)_2CH_2$], 1.43–1.36 [3H, m, $OCH(CH_2)_2(CH_2)_2CH_2$]; ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8 (C-2), 148.8 (C-10), 146.3 (C-9), 144.2 (C-1), 129.2 (C-7a), 128.8 (C-1a), 127.3 (C-3a), 126.9 (C-1b), 124.7 (C-11a), 115.0 (C-8), 112.3 (C-11), 110.3 (C-3), 76.7 $[OCH(CH_2)_2(CH_2)_2CH_2]$, 62.6 (C-6a), 60.1 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.1 (NCH_3), 34.5 (C-7), 32.2 $[OCH(CH_2)_2(CH_2)_2CH_2]$, 32.2 $[OCH(CH_2)_2(CH_2)_2CH_2]$, 29.3 (C-4), 25.6 $[OCH(CH_2)_2(CH_2)_2CH_2]$, 24.3 $[OCH(CH_2)_2(CH_2)_2CH_2]$, 24.3 $[OCH(CH_2)_2(CH_2)_2CH_2]$; HRESIMS *m/z* 424.2461 $[M + H]^+$ (calcd for $C_{26}H_{33}NO_4$, 424.2488).

(*S*)-9-(Allyloxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10l. Yield: 78% (61 mg), brown gum; R_f = 0.50 on a silica gel TLC plate in 5:95 MeOH–CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (1H, s, H-11), 6.78 (1H, s, H-8), 6.59 (1H, s, H-3), 6.17–6.09 (1H, m, $OCH_2CH{=}CH_2$), 5.44 (1H, dd, *J* = 17.3, 1.4 Hz, $OCH_2CH{=}CH_2$), 5.31 (1H, dd, *J* = 10.5, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.67–4.66 (2H, m, $OCH_2CH{=}CH_2$), 3.89 (3H, s, OCH_3-2), 3.88 (3H, s, OCH_3-10), 3.65 (3H, s, OCH_3-1), 3.19–3.12 (1H, m, H-4), 3.05–2.96 (3H, m, H-6a, 7a), 2.67 (1H, dd, *J* = 16.2, 3.1 Hz, H-7b), 2.60–2.48 (5H, m, H-5, 4, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6 (C-2), 147.5 (C-10), 146.7 (C-9), 144.0 (C-1), 133.1 ($OCH_2CH{=}CH_2$), 128.9 (C-7a), 128.6 (C-1a), 126.9 (C-3a), 126.6 (C-1b), 124.5 (C-11a), 117.7 ($OCH_2CH{=}CH_2$), 112.4 (C-8), 111.6 (C-11), 110.1 (C-3), 69.4 ($OCH_2CH{=}CH_2$), 62.2 (C-6a), 59.9 (C-1-OCH_3), 55.6 (C-10-OCH_3), 55.4 (C-2-OCH_3), 53.0 (C-5), 43.7 (NCH_3), 34.2 (C-7), 28.9 (C-4); HRESIMS *m/z* 382.2006 $[M + H]^+$ (calcd for $C_{23}H_{27}NO_4$, 382.2018).

(*S*)-9-(Benzyloxy)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10m. Yield: 92% (81 mg), light yellow solid, mp 112–116 °C; R_f = 0.60 on a silica gel TLC plate in 5:95 MeOH–CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (1H, s, H-11), 7.48–7.30 (5H, m, $OCH_2C_6H_5$), 6.81 (1H, s, H-8), 6.58 (1H, s, H-3), 5.19 (2H, d, *J* = 12.2 Hz, $OCH_2C_6H_5$), 3.90 (3H, s, OCH_3-2), 3.88 (3H, s, OCH_3-10), 3.66 (3H, s, OCH_3-1), 3.18–3.12 (1H, m, H-4), 3.04–2.93 (3H, m, H-5, 6a, 7a), 2.66 (1H, dd, *J* = 16.2, 3.2 Hz, H-7b), 2.57–2.47 (5H, m, H-5, 4, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9 (C-2), 148.1 (C-9), 147.3 (C-10), 144.3 (C-1), 137.2 ($OCH_2C_6H_5$), 129.2 (C-7a), 128.9 (C-1a), 128.5 (2 × $OCH_2C_6H_5$), 127.8 ($OCH_2C_6H_5$), 127.3 (2 × $OCH_2C_6H_5$), 127.2 (C-3a), 126.8 (C-1b), 125.0 (C-11a), 113.2 (C-8), 112.1 (C-11), 110.4 (C-3), 70.9 ($OCH_2C_6H_5$), 62.5 (C-6a), 60.2 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 34.4 (C-7), 29.2 (C-4); HRESIMS *m/z* 432.2921 $[M + H]^+$ (calcd for $C_{27}H_{29}NO_4$, 432.2175).

(*S*)-9-[(4-Bromobenzyl)oxy]-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de*,*g*]quinoline, 10n. Yield: 94% (70 mg), brown crystalline solid, mp 56–60 °C, R_f = 0.62 on a silica gel TLC plate in 5:95 MeOH–CH_2Cl_2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (1H, s, H-11), 7.51 (2H, d, *J* = 8.3 Hz, $OCH_2C_6H_4Br$), 7.35 (2H, d, *J* = 8.3 Hz, $OCH_2C_6H_4Br$), 6.77 (1H, s, H-8), 6.59 (1H, s, H-3), 5.13 (2H, d, *J* = 12.2 Hz, $OCH_2C_6H_4Br$), 3.90 (3H, s, OCH_3-2), 3.88 (3H, s, OCH_3-10), 3.66 (3H, s, OCH_3-1), 3.18–3.12 (1H, m, H-4), 3.05–2.92 (3H, m, H-5, 6a, 7a), 2.67 (1H, dd, *J* = 16.2, 3.2 Hz, H-7b), 2.57–2.48 (5H, m, H-5, 4, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9 (C-2), 148.1 (C-9), 146.9 (C-10), 144.3 (C-1), 136.2 ($OCH_2C_6H_4Br$), 131.7 (2 × $OCH_2C_6H_4Br$), 129.2 (C-7a), 128.9 (2 × $OCH_2C_6H_4Br$), 127.2 (C-3a), 126.8 (C-1b), 126.7 (C-1a), 125.3 (C-11a), 121.7 ($OCH_2C_6H_4Br$), 113.3 (C-11), 112.2 (C-8), 110.5 (C-3), 70.2 ($OCH_2C_6H_4Br$), 62.5 (C-6a), 60.2 (C-1-OCH_3), 56.0 (C-10-OCH_3), 55.7 (C-2-OCH_3), 53.3 (C-5), 44.0 (NCH_3), 34.4 (C-7), 29.2 (C-4); HRESIMS *m/z* 510.1264 $[M + H]^+$ (calcd for $C_{27}H_{28}BrNO_4$, 510.1280)

Receptor Binding Assays. All receptor binding assays were performed by the PDSP/NIMH. Complete details of the assays performed may be found online in the PDSP assay protocol book (http://pdsp.med.unc.edu/PDSP%20Protocols%20II%202013-03-28.pdf).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR data for all new compounds and NOESY spectra for compounds **1** and **6** are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Coy Barrera, E. D.; Cuca Suarez, L. E. *Nat. Prod. Commun.* **2010**, *5*, 383–386.

(2) Jantan, I.; Raweh, S. M.; Yasin, Y. H.; Murad, S. *Phytother. Res.* **2006**, *20*, 493–496.

(3) Sun, R.; Jiang, H.; Zhang, W.; Yang, K.; Wang, C.; Fan, L.; He, Q.; Feng, J.; Du, S.; Deng, Z.; Geng, Z. *Evid.-Based Complementary Altern. Med.* **2014**, *2014*, 580483.

(4) Thuy, T. T.; Quan, T. D.; Anh, N. T.; Sung, T. V. *Nat. Prod. Res.* **2012**, *26*, 1296–1302.

(5) Ponnala, S.; Chaudhary, S.; Gonzalez-Sarrias, A.; Seeram, N. P.; Harding, W. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4462–4464.

(6) Baghdikian, B.; Mahiou-Leddet, V.; Bory, S.; Bun, S. S.; Dumetre, A.; Mabrouki, F.; Hutter, S.; Azas, N.; Ollivier, E. *J. Ethnopharmacol.* **2013**, *145*, 381–385.

(7) Makarasen, A.; Sirithana, W.; Mogkhuntod, S.; Khunnawutmanotham, N.; Chimnoi, N.; Techasakul, S. *Planta Med.* **2011**, *77*, 1519–1524.

(8) Orhana, I.; Ozcelik, B.; Karaoglu, T.; Sener, B. *Z. Naturforsch. C* **2007**, *62*, 19–26.

(9) Mohamed, S. M.; Hassan, E. M.; Ibrahim, N. A. *Nat. Prod. Res.* **2010**, *24*, 1395–1402.

(10) Boustie, J.; Stigliani, J. L.; Montanha, J.; Amoros, M.; Payard, M.; Girre, L. *J. Nat. Prod.* **1998**, *61*, 480–484.

(11) Ye, N.; Wu, Q.; Zhu, L.; Zheng, L.; Gao, B.; Zhen, X.; Zhang, A. *Bioorg. Med. Chem.* **2011**, *19*, 1999–2008.

(12) Herm, L.; Berenyi, S.; Vonk, A.; Rinken, A.; Sipos, A. *Bioorg. Med. Chem.* **2009**, *17*, 4756–4762.

DOI: 10.1021/np500893h
J. Nat. Prod. XXXX, XXX, XXX–XXX

(13) Si, Y. G.; Gardner, M. P.; Tarazi, F. I.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3971−3973.
(14) Liu, Z.; Chen, X.; Yu, L.; Zhen, X.; Zhang, A. *Bioorg. Med. Chem.* **2008**, *16*, 6675−6681.
(15) Sipos, A.; Csutoras, C.; Berenyi, S.; Uustare, A.; Rinken, A. *Bioorg. Med. Chem.* **2008**, *16*, 4563−4568.
(16) Si, Y. G.; Gardner, M. P.; Tarazi, F. I.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2008**, *51*, 983−987.
(17) Asencio, M.; Hurtado-Guzman, C.; Lopez, J. J.; Cassels, B. K.; Protais, P.; Chagraoui, A. *Bioorg. Med. Chem.* **2005**, *13*, 3699−3704.
(18) Si, Y. G.; Choi, Y. K.; Gardner, M. P.; Tarazi, F. I.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 51−53.
(19) Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171−181.
(20) Zhao, R.; Lu, W.; Fang, X.; Guo, L.; Yang, Z.; Ye, N.; Zhao, J.; Liu, Z.; Jia, J.; Zheng, L.; Zhao, B.; Zhang, A.; Zhen, X. *Pharmacol., Biochem. Behav.* **2014**, *124*, 204−210.
(21) Munusamy, V.; Yap, B. K.; Buckle, M. J.; Doughty, S. W.; Chung, L. Y. *Chem. Biol. Drug Des.* **2013**, *81*, 250−256.
(22) Chaudhary, S.; Ponnala, S.; Legendre, O.; Gonzales, J. A.; Navarro, H. A.; Harding, W. W. *Bioorg. Med. Chem.* **2011**, *19*, 5861−5868.
(23) Pecic, S.; Makkar, P.; Chaudhary, S.; Reddy, B. V.; Navarro, H. A.; Harding, W. W. *Bioorg. Med. Chem.* **2010**, *18*, 5562−5575.
(24) Liu, Z.; Zhang, H.; Ye, N.; Zhang, J.; Wu, Q.; Sun, P.; Li, L.; Zhen, X.; Zhang, A. *J. Med. Chem.* **2010**, *53*, 1319−1328.
(25) Chaudhary, S.; Pecic, S.; Legendre, O.; Navarro, H. A.; Harding, W. W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2530−2532.
(26) Linnanen, T.; Brisander, M.; Mohell, N.; Johansson, A. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 367−370.
(27) Cannon, J. G.; Mohan, P.; Bojarski, J.; Long, J. P.; Bhatnagar, R. K.; Leonard, P. A.; Flynn, J. R.; Chatterjee, T. K. *J. Med. Chem.* **1988**, *31*, 313−318.
(28) Si, Y. G.; Gardner, M. P.; Tarazi, F. I.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4128−4130.
(29) Ponnala, S.; Kapadia, N.; Navarro, H. A.; Harding, W. W. *Chem. Biol. Drug Des.* **2014**, *84*, 558−566.
(30) Ponnala, S.; Gonzales, J.; Kapadia, N.; Navarro, H. A.; Harding, W. W. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1664−1667.
(31) Indra, B.; Matsunaga, K.; Hoshino, O.; Suzuki, M.; Ogasawara, H.; Ishiguro, M.; Ohizumi, Y. *Can. J. Physiol. Pharmacol.* **2002**, *80*, 198−204.
(32) Ivorra, M. D.; Valiente, M.; Martinez, S.; Madrero, Y.; Noguera, M. A.; Cassels, B. K.; Sobarzo, E. M.; D'Ocon, P. *Planta Med.* **2005**, *71*, 897−903.
(33) Indra, B.; Matsunaga, K.; Hoshino, O.; Suzuki, M.; Ogasawara, H.; Ohizumi, Y. *Eur. J. Pharmacol.* **2002**, *437*, 173−178.
(34) Martinez, S.; Madrero, Y.; Elorriaga, M.; Noguera, M. A.; Cassels, B.; Sobarzo, E.; D'Ocon, P.; Ivorra, M. D. *Life Sci.* **1999**, *64*, 1205−1214.
(35) Madrero, Y.; Elorriaga, M.; Martinez, S.; Noguera, M. A.; Cassels, B. K.; D'Ocon, P.; Ivorra, M. D. *Br. J. Pharmacol.* **1996**, *119*, 1563−1568.
(36) Anighoro, A.; Bajorath, J.; Rastelli, G. *J. Med. Chem.* **2014**, *57*, 7874−7887.
(37) Carrieri, A.; Perez-Nueno, V. I.; Lentini, G.; Ritchie, D. W. *Curr. Top. Med. Chem.* **2013**, *13*, 1069−1097.
(38) Bolognesi, M. L. *Curr. Med. Chem.* **2013**, *20*, 1639−1645.
(39) Gafner, S.; Dietz, B. M.; McPhail, K. L.; Scott, I. M.; Glinski, J. A.; Russell, F. E.; McCollom, M. M.; Budzinski, J. W.; Foster, B. C.; Bergeron, C.; Rhyu, M. R.; Bolton, J. L. *J. Nat. Prod.* **2006**, *69*, 432−435.
(40) Correa, J. E.; Rios, C. H.; del Rosario Castillo, A.; Romero, L. I.; Ortega-Barria, E.; Coley, P. D.; Kursar, T. A.; Heller, M. V.; Gerwick, W. H.; Rios, L. C. *Planta Med.* **2006**, *72*, 270−272.
(41) Gan, L. S.; Yao, W.; Mo, J. X.; Zhou, C. X. *Nat. Prod. Commun.* **2009**, *4*, 43−46.
(42) Nafiah, M. A.; Mukhtar, M. R.; Omar, H.; Ahmad, K.; Morita, H.; Litaudon, M.; Awang, K.; Hadi, A. H. *Molecules* **2011**, *16*, 3402−3409.
(43) Moreno, L.; Cabedo, N.; Ivorra, M. D.; Sanz, M. J.; Castel, A. L.; Carmen Alvarez, M.; Cortes, D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4824−4827.
(44) Asencio, M.; Cassels, B. K.; Speisky, H. *Bol. Soc. Chil. Quim.* **1993**, *38*, 331−334.
(45) Thomet, F. A.; Pinyol, P.; Villena, G. J.; Reveco, P. G. *Inorg. Chim. Acta* **2012**, *384*, 255−259.
(46) Asencio, M.; Hurtado-Guzman, C.; Lopez, J. J.; Cassels, B. K.; Protais, P.; Chagraoui, A. *Bioorg. Med. Chem.* **2005**, *13*, 3699−3704.
(47) Hroch, M.; Micuda, S.; Cermanova, J.; Chladek, J.; Tomsik, P. *J. Chromatogr. B* **2013**, *936*, 48−56.

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