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Probes for narcotic receptor mediated phenomena. 47.¹ Novel C4a- and N-substituted-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ols

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Abstract

A series of *N*-methyl *rac-cis*-4a-aralkyl- and alkyl-substituted-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols have been prepared (**2a–1**) using a simple previously designed synthetic route, in order to find a ligand that would interact with both μ - and δ -opioid receptors. A C4a-phenethyl derivative **2a**, was found to have modest receptor affinity both at μ - ($K_i = 60$ nM) and δ -opioid receptors ($K_i = 64$ nM). The *N*-methyl substituent of **2a** and that of other ligands in the series was then modified to obtain compounds with different N-substituents that might provide higher affinity at both receptors. A number of compounds differently substituted at C4a and N were synthesized and evaluated. Binding studies and functional assays revealed a moderately selective δ -antagonist (**2l**), selective μ - antagonists (**3d**, **3g**), and a μ - antagonist (**3f**).

Keywords

Synthesis; Opioid receptor binding; *cis*-1,2,3,4,4a,9a-Hexahydrobenzofuro[2,3-*c*]pyridin-6-ols; Opioid agonists and antagonists; Oxide-bridged phenylmorphans

1. Introduction

cis-1,2,3,4,4a,9a-Hexahydrobenzofuro[2,3-*c*]pyridin-6-ols (**1**) with suitable substitution on the nitrogen have been shown to have high affinity for μ -, δ - and κ -opioid receptors.² Benzofuro[2,3-*c*]pyridinols are partial structures of oxide-bridged phenylmorphans. Although they appear to be structurally similar to the d-series of the oxide-bridged phenylmorphans,^{3–5} the presence of a truncated C4a group gives the benzofuopyridinols a flexibility that is lacking in the rigid oxide-bridged phenylmorphans. This flexibility may enable them to assume a conformation that is closer to morphine than the oxide-bridged phenylmorphans are able to assume, and their opioid affinity and activity may be correlated with their ability to attain this conformation.⁶ Hutchison et al.² found that the C4a-ethyl-

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substituted *N*-phenethyl- and *N*-cyclopropylmethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols (**1a** and **1b**, respectively), had high affinity for μ -opioid receptors ($K_i = 0.9$ and 4 nM, respectively) and were potent antinociceptives. While Hutchison's work focused on the opioid affinity based on *N*-variations on the piperidine ring, we thought it would be of interest to explore the effect of C4a group as well as the importance of the ethyl group at this position on opioid receptor affinity. As part of our continuing interest in the benzofuro[2,3-*c*]pyridin-ol series of compounds, we had devised a simpler route for the synthesis of these compounds.⁶ This new synthetic route offered us the flexibility to design and study compounds with a variety of substituents in the C4a-position as well as on the piperidine nitrogen atom in the *rac*-*cis*-benzofuro[2,3-*c*]pyridin-6-ol series of compounds. In our present study we initially examined the effect of chain length and substitution at the C4a-position. The *N*-methyl-C4a-alkyl and aralkyl-derivatives (**2**) were synthesized and their affinity for opioid receptors was determined. In the second part of this study we selected a promising compound bearing an *N*-methyl group from the above series of compounds (**2**), and designed a variety of substituents to replace the methyl moiety. The *N*-methyl-C4a phenethyl-compound (**2**, R = phenethyl) having similar (albeit moderate) μ - and κ -affinity and negligible δ -affinity was chosen for further manipulation to obtain compounds based on **3**, where R is not Me, with the hope of obtaining compounds that interact with both μ - and κ -receptors with higher affinity and potency.

Mixed μ - κ ligands are currently of great interest^{7,8} as potential analgesics with fewer side-effects. However, the correct ratio of a ligand's affinities at μ and κ has not been determined that would allow it to act as a potent analgesic with, for example, decreased respiratory depression, physical dependence, and abuse liability. Binding studies and functional assays on the synthesized compounds revealed interesting trends, which are discussed below.

2. Chemistry

The synthesis developed earlier⁶ enabled the preparation of compounds with new alkyl or aralkyl moieties at C-4a. We decided to explore the receptor affinity of compounds with a benzyl, phenethyl, phenylpropyl, phenylbutyl and phenylpentyl group as the aralkyl group, and methyl, propyl, butyl and pentyl, along with the previously known ethyl group, were chosen as alkyl moieties at the C4a position. A general route for the synthesis of the *N*-methyl compounds in the hexahydrobenzofuro[2,3-*c*]pyridin-6-ol series is shown in Scheme 1. We previously found, in the hexahydrobenzofuro[2,3-*c*]pyridin-8-ol series of compounds,⁹ that although a C4a-methyl-*N*-*p*-fluorophenethyl compound showed very weak μ - and κ -affinity, it had better affinity than any of the other substituents examined in that series. We thought it would be of interest, then, to incorporate a 2-fluorophenethyl and a 4-fluorophenethyl moiety in the molecule, at C4a in the *N*-methyl compounds **2k** and **2l**, and as the *N*-substituent in **3c** and **3d** (in the C4a-phenethyl compound).

The starting substrate 4-(2,5-dimethoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (**4**, Scheme 1) was assembled via known literature procedures.³ With compound **4** in hand, functionalization at the C4a position was achieved under Evans conditions,¹⁰ leading to enamines **5a–l**. The desired intermediates possessing an ethyl group, or any alkyl or aralkyl group at C4a were easily obtained using this method. A simple two-step procedure⁶ involving bromination of the alkene with NBS followed by NaBH₃CN reduction in acidic medium gave the late stage intermediates **6a–l**. Hydrobromic acid-assisted deprotection of the two aromatic O-methyl groups gave the diols **7a–l** (Scheme 1), the needed templates for the base-mediated oxide-ring formation. Heating the diol in methanolic Et₃N in a sealed tube gave the *N*-methyl substituted **2a–l** (Scheme 1) in excellent yield. The yields of the *N*-methyl substituted compounds are shown in Table 1. The depicted configuration of the compounds in Schemes 1 and 2 was based on the X-ray crystallographic determination of

the structures of related compounds in the pyridin-8-ol series, compounds **6a**, **7a**, and **2a**,⁶ as well as **2g** and **6g**.⁹

Synthesis of compounds **3a–3i** was carried out as shown in Scheme 2. Acetate protection of the phenol **2a** gave **8**. Sequential treatment of **8** with Troc-Cl, deprotection of the acetate, and Zn-dust mediated removal of the Troc group gave the *N*-nor compound **9**. Compound **9** was alkylated at the N-position to give compounds **3a–3i**.

3. Results and discussion

The opioid receptor binding affinities of the compounds are shown in Table 2. Except for compound **3f**, with an *N*-cyclopropylmethyl group ($K_i = 16$ nM at 10^{-6} M), few of the compounds had <100 nM affinity for the μ -opioid receptor. The μ -receptor affinity of the compounds in Table 2 ranged from affinities comparable to morphine ($K_i = 5$ or 7–8 nM, for **3f**, **3d** and **3e**, respectively) to those with very poor affinity ($K_i = 425$ nM, for **2f**). The δ -receptor affinities ranged from $K_i = 24$ –26 nM for **3d–f**, to inactive ($K_i > 10$ μ M) for **2f**. The compounds with appreciable affinity at an opioid receptor were further evaluated using the [³⁵S]GTP- γ -S assay (Table 3).

Initially we varied the C4a-substituent to see if we could obtain a compound with at least moderate affinity at both the μ - and δ -receptors. In the *N*-methyl, C4a-alkyl series **2a–e**, with the exception of the C4a-phenylpropyl compound **2c** that had little affinity for the μ -opioid receptor, increasing the C4a-chain length resulted in only a moderate increase in μ -affinity (from $K_i = 66$ nM for the C4a-benzyl compound **2b** to 28 nM for the C4a-phenylpentyl compound **2e**). In that series there was great variability in δ -receptor affinity. The affinity for δ -receptors peaked with the C4a-phenylbutyl compound ($K_i = 29$ nM at 10^{-6} M) in **2a–e**. None of these compounds were further evaluated in the functional assay.

In the C4a-alkyl, *N*-methyl series **2f–j**, the affinity for μ receptors was optimal when C4a was ethyl, in **2g**, as found by Hutchison et al.,² and the compound with the highest affinity at δ -receptors was determined to be **2j**, with a C4a-pentyl group ($K_i = 33$ nM, Table 1). The affinity increased with chain-length, from propyl (**2h**, $K_i = 479$ nM) to butyl (**2i**, $K_i = 207$ nM) to pentyl (**2j**, $K_i = 33$ nM). Thus, a 14.5-fold increase in affinity was seen when the C4a-alkyl group chain-length went from C4a-propyl (**2h**) to pentyl (**2j**). Attachment of C4a-fluorophenethyl (*para* or *ortho*, **2k** or **2l**, respectively) did not improve affinity or selectivity for the μ - or δ -receptors. Functional studies ([³⁵S]GTP- γ -S assay) of **2c–2e**, **2j** and **2l** revealed that compound **2l** had moderate antagonist activity ($K_e = 29$ nM), **2c** had less antagonist activity ($K_e = 88$ nM) than **2l** at the δ -receptor, and the others were essentially inactive ($K_e > 200$ nM).

The second part of the study involved selecting a specific C4a-substituent from the *N*-methyl substituted compounds **2a–l** with good affinity for both the μ - and δ -receptors. The C4a-substituent would then be held constant and the N-substituent modified with the hope of finding compounds with suitably mixed μ - and δ -receptor affinities. Toward that end, the C4a-phenethyl substituent in **2a** was chosen as the fixed moiety for the present study. Thus, **2a** with equivalent, if moderate, μ - binding affinity, and negligible δ affinity (Table 2), was used as the template for modification of the N-substituent. A variety of N-substituents were chosen (phenylalkyl, fluorenylalkyl, trifluoromethylphenylalkyl, allyl and cyclopropylmethyl) to examine their effect on the opioid receptor affinity of compounds bearing the C4a-phenethyl moiety (Table 2, **3a–3i**). The *N*-benzyl compounds were not prepared because previous work had shown that opioids with an *N*-benzyl substituent were inactive; for example, an *N*-4-fluorobenzyl compound in the pyridine-8-ol series had almost no affinity for opioid receptors.⁹

Compounds **3a**, **3c**, **3d**, **3e** and **3i** had good to moderate affinity at μ - and δ -receptors and much less affinity for kappa receptors (Table 3). Compound **3f** was more promiscuous and showed good or moderate binding at all three receptors. The μ and δ ratios for **3d** and **3e** were promising and hence were evaluated in the [35 S]GTP- γ -S functional assay along with compounds **3a**, **3c**, **3f**, **3g** and **3i**. The functional assays showed that none of the compounds had any appreciable agonist activity. Compounds **3a–3e** were all found to be partial, and very weak, agonists (Table 3). Most interesting was **3d** with an *o*-fluorophenethyl N-substituent and **3g** with an *N*-allyl substituent both of which were found to have moderate μ - and δ -antagonist activity, and the *N*-cyclopropylmethyl compound **3f**, which was determined to be a moderately potent non-selective antagonist. The antagonist activity of these compounds was in marked contrast with the agonist activity found in the compounds of Hutchison et al.² We have discovered that a change in the substituent at C4a from ethyl to phenethyl completely modified activity in this 1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol series of compounds. For example, a compound with a C4a-ethyl and an *N*-cyclopropylmethyl moiety was formerly found² to be a potent μ -agonist in vivo, with moderate affinity for δ - and somewhat less affinity for κ -receptors (K_i = 4, 34 and 53 nM for μ -, δ - and κ -receptor, respectively). However, when the C4a-ethyl group was changed to the C4a-phenethyl group, as in **3f**, we obtained a moderately potent opioid antagonist with similar receptor affinity and selectivity (K_i = 8, 32 and 64 nM to the μ -, δ - and κ -receptor, respectively); a remarkable change in activity, but not in receptor affinity or selectivity, induced by the substituent at C4a.

4. Conclusion

We evaluated the effect of alkyl and aralkyl chain-length at the C4a position of the *N*-methyl benzofuropyrindin-6-ol series of compounds. We found that increasing the chain length from benzyl to phenylpentyl gave a moderate improvement of μ -affinity. The δ -affinity was found to be highest with the C4a-phenylbutyl group. However, with the C4a-alkyl groups, the highest δ -affinity resides with C4a-ethyl and C4a-pentyl substituents, and these gave better μ -affinity, as well. Except for phenylpentyl, the compounds in the *N*-methyl series had little or no affinity for κ -receptors. Introduction of an *o*-fluoro group on the aromatic ring of the C4a-phenethyl-substituent (**3d**) yielded a moderately selective δ -antagonist. A considerably more potent antagonist had an *N*-cyclopropylmethyl group, **3f** (K_e = 8 nM); it was also more promiscuous, with affinity for all of the opioid receptors. Our search among the C4a-phenethyl compounds with a variety of N-substituents for a selective μ -agonist δ -antagonist resulted in compounds that had opioid antagonist activity at both μ - and δ -receptors. Efforts are underway to study compounds with a more promising N-substituent, changing the C4a-substituent to yet untried moieties. The results from that study will be reported in due course.

5. Experimental

5.1. Chemistry

Mass spectra (CIMS) were obtained using a Finnigan 4600 mass spectrometer unless otherwise noted. ^1H nuclear magnetic resonance (^1H NMR, 500 MHz) was recorded on a Bruker Avance 500 instrument in deuterated solvents (Cambridge Isotope Laboratories, Inc.) as specified. TMS was used as an internal standard. IR spectra were recorded on a Beckman IR 4230 spectrometer. Column chromatography was performed with the use of 230–400-mesh EM silica gel. Melting points were determined on a Buchi B-545 melting point apparatus and are uncorrected. Combustion analyses were determined at Micro-Analysis, Inc., Wilmington, DE or at Atlantic Microlabs, Atlanta, GA.

5.1.1. General procedure A—A solution of **4** in dry THF was stirred under argon at -20°C . A solution of *n*-butyllithium, 2.5 M in hexane (1.5 equiv), was added to the reaction, producing a deep red color. The mixture was stirred at -20°C for 2 h. Alkyl bromide (1.5 equiv) was added, producing a yellow solution, which was then stirred and brought to 20°C over 1 h. The reaction mixture was then treated with saturated NH_4Cl solution. The reaction mixture was partitioned between Et_2O and H_2O . The organic layer was dried over anhyd Na_2SO_4 and removal of the solvent gave an orange oil. Column chromatography of the crude material using 20% hexanes in Et_2O gave compound **5** as a pure yellow oil.

5.1.2. General procedure B—To a solution of **5** in dry THF at -78°C was added *N*-bromosuccinimide (1 equiv) in dry THF (15 mL). The mixture was stirred at 20°C for 1 h and the solvent was removed to give a brown oil. The crude product was suspended in MeOH and 37% HCl (1 mL) was added to the suspension. Solid NaBH_3CN (1.5 equiv) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then diluted with aqueous saturated NaHCO_3 and the organic layer was washed with H_2O and extracted into CH_2Cl_2 . Evaporation of the solvent gave a brown oil. Purification of the crude product by column chromatography using 30% hexanes in Et_2O gave either sticky oils or crystalline solids **6**.

5.1.3. General procedure C—To **6** was added 48% HBr (20 mL) and the emulsion was refluxed for 10 h. After completion of the reaction, the excess HBr was removed by distillation to give **7** as a brown solid. Neutralization of the HBr salt by partitioning between NaHCO_3 and CHCl_3 gave the free base. A small batch of **7** was recrystallized from MeOH to give crystalline **7** as a free base that could be converted to the pure HBr salt.

5.1.4. General procedure D—Compound **7** was treated with MeOH (1 mL) and excess Et_3N (15 mL). The reaction mixture was placed in a sealed tube and heated at 100°C for 3 h. The reaction mixture was cooled, and the excess Et_3N removed to give a brown solid. Silica-gel column chromatography of the brown solid using 15% MeOH in CH_2Cl_2 gave an off-white solid **2**.

5.1.5. General procedure E—A mixture of the amine **9**, alkyl bromide (1.2 equiv) and NaHCO_3 (2 equiv) in DMF (20 mL) was heated at 50°C for 20 h. After cooling to room temperature, the reaction mixture was poured into ice- H_2O , and the product was extracted with Et_2O . The ethereal extracts were washed with saturated NH_4Cl solution. After drying over Na_2SO_4 , the solvent was removed in vacuo to afford an oil. The crude oil was subjected to flash chromatography on silica gel using 75% EtOAc in hexanes as the eluent to give the compounds **3a–h** as a solid.

5.1.6. 4-Benzyl-4-(2,5-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydropyridine (5a)—Using general procedure A, 12.75 g of **4** was converted to **5a** (13.4 g, 76%). ^1H NMR (500 MHz; CDCl_3): 7.02 (d, $J = 6.1$ Hz, 4H), 6.81–6.76 (m, 3H), 6.71 (d, $J = 3.1$ Hz, 1H), 6.63 (dd, $J = 8.7, 3.1$ Hz, 1H), 5.84 (d, $J = 8.1$ Hz, 1H), 4.54–4.52 (m, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.51 (d, $J = 12.9$ Hz, 1H), 2.86 (d, $J = 12.9$ Hz, 1H), 2.69 (dt, $J = 11.2, 3.7$ Hz, 1H), 2.60 (dt, $J = 13.4, 2.1$ Hz, 1H), 2.46–2.42 (m, 3H), 1.91–1.85 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3): 152.9, 151.7, 139.3, 137.3, 136.4, 130.5, 127.4, 125.6, 119.8, 111.7, 110.4, 110.3, 103.8, 55.6, 55.4, 47.0, 45.6, 42.4, 41.9, 33.6. HRMS (TOF MS ES^+) calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_2$ ($\text{M}+\text{H}^+$): 324.1964; found: 324.1957. Anal. Calcd for $(\text{C}_{21}\text{H}_{25}\text{NO}_2 \cdot 0.1\text{H}_2\text{O})$: C, 77.55; H, 7.81; N, 4.31; found: C, 77.44; H, 7.82; N, 4.18.

5.1.7. 4-Benzyl-3-bromo-4-(2,5-dimethoxyphenyl)-1-methylpiperidine (6a)—Using general procedure B, 13.4 g of **5a** was converted to **6a** (7.0 g, 42%). IR (neat) 2941

cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 7.04 (m, 3H), 6.89 (d, 1H, *J* = 9.0 Hz), 6.76 (dd, 1H, *J* = 2.0 and 8.5 Hz), 6.58 (d, 2H, *J* = 7.0 Hz), 6.24 (s, 1H), 5.66 (s, 1H), 3.96 (s, 3H), 3.63 (s, 3H), 3.45 (d, 1H, *J* = 15.0 Hz), 3.24 (d, 1H, *J* = 13.5 Hz), 3.18 (d, 1H, *J* = 13.0 Hz), 3.02 (d, 2H, *J* = 13.5 Hz), 2.66 (t, 1H, *J* = 12.0 Hz), 2.45 (s, 3H), 2.36 (t, 1H, *J* = 9.5 Hz), 1.70 (d, 1H, *J* = 13.0 Hz); ¹³C NMR (126 MHz, CDCl₃): 153.2, 152.7, 137.9, 135.1, 130.3, 127.5, 126.2, 115.8, 111.7, 111.2, 110.5, 58.9, 58.0, 56.0, 55.7, 51.8, 46.4, 45.7, 36.8, 27.4; HRMS (TOF MS ES⁺) calcd for C₂₁H₂₇NBrO₂ (M+H)⁺: 404.1225; found: 404.1206. Anal. Calcd for (C₂₁H₂₆NBrO₂): C, 62.38; H, 6.48; N, 3.46; found: C, 62.44; H, 6.39; N, 3.55.

5.1.8. 2-(4-Benzyl-3-bromo-1-methylpiperidin-4-yl)benzene-1,4-diol (7a)—Using general procedure C, 2.7 g of **6a** was converted to **7a** (2.4 g, 96%). ¹H NMR (500 MHz; CD₃OD): 7.00 (d, *J* = 7.4 Hz, 3H), 6.66 (t, *J* = 8.4 Hz, 3H), 6.51 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.03 (d, *J* = 2.5 Hz, 1H), 5.89 (s, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.35 (m, 2H), 3.25 (t, *J* = 11.4 Hz, 1H), 3.00 (dd, *J* = 28.1, 10.7 Hz, 2H), 2.52 (s, 3H), 2.28 (td, *J* = 13.2, 4.3 Hz, 1H), 1.68 (d, *J* = 13.6 Hz, 1H). ¹³C NMR (126 MHz, CD₃OD): 150.3, 150.2, 139.2, 133.3, 131.4, 128.4, 127.1, 117.2, 116.2, 114.7, 59.2, 58.1, 52.3, 49.8, 49.5, 49.3, 48.6, 48.5, 46.2, 45.7, 36.6, 27.4. HRMS (TOF MS ES⁺) calcd for C₁₉H₂₃N⁸¹BrO₂ (M+H)⁺: 378.0892; found: 378.0901.

5.1.9. (4a-Benzyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2a)—Using general procedure D, 2.4 g of **7a** was converted to **2a** (1.2 g, 64%). Mp 148–151 °C; IR (neat) 3055 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): 7.18 (d, 3H, *J* = 7.5 Hz), 6.95 (d, 2H, *J* = 6.5 Hz), 6.55 (m, 2H), 6.35 (s, 1H), 4.43 (t, 1H, *J* = 6.0 Hz), 2.87 (s, 2H), 2.77 (dd, 1H, *J* = 5.5 and 12.5 Hz), 2.49 (dd, 1H, *J* = 5.5 and 11.5 Hz), 2.22 (m, 1H), 2.19 (s, 3H), 2.09 (dt, 1H, *J* = 3.5 and 11.5 Hz), 1.94 (m, 2H); ¹³C NMR (126 MHz, CD₃OD): 152.7, 152.3, 137.9, 134.9, 131.6, 128.7, 127.3, 115.3, 112.0, 111.4, 107.6, 84.2, 56.8, 52.4, 46.0, 45.9, 32.7; HRMS (TOF MS ES⁺) calcd for C₁₉H₂₂NO₂ (M+H)⁺: 296.1651; found: 296.1640. Anal. Calcd for (C₁₉H₂₁NO₂·0.25H₂O): C, 76.52; H, 7.54; N, 4.46; found: C, 76.30; H, 7.47; N, 4.56.

5.1.10. 4-(2,5-Dimethoxyphenyl)-1-methyl-4-(3-phenylpropyl)-1,2,3,4-tetrahydropyridine (5c)—Using general procedure A, 5.0 g of **4** was converted to **5c** (3.0 g, 41%). ¹H NMR (500 MHz; CDCl₃): 7.30 (t, *J* = 7.4 Hz, 2H), 7.19 (dd, *J* = 20.6, 7.3 Hz, 3H), 7.11 (d, *J* = 2.8 Hz, 1H), 6.82–6.73 (m, 2H), 6.00 (d, *J* = 8.0 Hz, 1H), 4.74 (d, *J* = 7.9 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.80 (d, *J* = 11.1 Hz, 1H), 2.63 (d, *J* = 14.9 Hz, 4H), 2.59–2.54 (m, 3H), 2.37 (td, *J* = 12.7, 4.1 Hz, 1H), 1.96 (t, *J* = 12.5 Hz, 1H), 1.74 (td, *J* = 12.6, 4.0 Hz, 1H), 1.61 (dd, *J* = 12.6, 6.0 Hz, 1H), 1.30 (dd, *J* = 12.2, 7.4 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): 152.8, 151.8, 142.9, 137.7, 136.2, 128.5, 128.1, 125.4, 119.7, 111.8, 109.9, 104.5, 55.5, 55.33, 55.32, 47.0, 42.4, 40.8, 39.60, 39.61, 39.59, 39.58, 36.6, 36.57, 36.52, 33.80, 33.78, 26.51, 26.48, 26.46, 26.44. HRMS (TOF MS ES⁺) calcd for C₂₃H₃₀NO₂ (M+H)⁺: 352.2277; found: 352.2288. Anal. Calcd for (C₂₃H₂₉NO₂): C, 78.59; H, 8.32; N, 3.99; found: C, 78.38; H, 8.39; N, 3.98.

5.1.11. 3-Bromo-4-(2,5-dimethoxyphenyl)-1-methyl-4-(3-phenylpropyl)piperidine (6c)—Using general procedure B, 3.0 g of **5c** was converted to **6c** (3.0 g, 81%). ¹H NMR (500 MHz; CDCl₃): 7.16–7.14 (m, 1H), 7.01–6.97 (m, 4H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.81–6.78 (m, 2H), 5.46 (s, 1H), 3.87 (s, 4H), 3.81 (s, 4H), 3.02 (dd, *J* = 23.2, 12.3 Hz, 2H), 2.81 (d, *J* = 13.4 Hz, 1H), 2.56 (dd, *J* = 13.0, 3.4 Hz, 1H), 2.49–2.38 (m, 6H), 2.20 (dd, *J* = 11.9, 9.0 Hz, 1H), 2.02 (d, *J* = 12.9 Hz, 1H), 1.90 (t, *J* = 10.4 Hz, 1H). ¹³C NMR (126 MHz, CD₃OD): 162.0, 160.1, 153.3, 152.7, 135.4, 130.7, 130.6, 129.5, 129.4, 127.64, 127.58, 124.1, 124.0, 115.8, 115.4, 115.2, 111.9, 110.6, 110.5, 76.8, 58.4, 58.2, 55.9, 55.7, 51.2, 46.2, 44.6, 32.3, 27.5, 25.6. HRMS (TOF MS ES⁺) calcd for C₂₃H₃₁BrNO₂

(M+H)⁺: 432.1538; found: 432.1529. Anal. Calcd for (C₂₃H₃₀BrNO₂·0.25H₂O): C, 63.22; H, 7.03; N, 3.20; found: C, 63.35; H, 7.16; N, 3.46.

5.1.12. 2-(3-Bromo-1-methyl-4-(3-phenylpropyl)piperidin-4-yl)benzene-1,4-diol (7c)

—Using general procedure C, 15.5 g of **6c** was converted to **7c** (12.0, 83%). ¹H NMR (500 MHz; CDCl₃): 7.19 (t, *J* = 7.1 Hz, 3H), 7.10 (t, *J* = 6.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 2H), 6.58 (d, *J* = 10.4 Hz, 2H), 6.45 (s, 1H), 5.91 (s, 1H), 3.96 (d, *J* = 14.1 Hz, 1H), 3.75 (d, *J* = 14.1 Hz, 1H), 3.48 (s, 1H), 3.31–3.23 (m, 3H), 2.96 (s, 3H), 2.58–2.44 (m, 3H), 2.20 (d, *J* = 14.2 Hz, 1H), 2.00–1.98 (m, 1H), 1.43–1.42 (m, 1H), 1.07 (s, 1H). ¹³C NMR (126 MHz, CD₃OD): 150.7, 149.9, 143.2, 131.7, 129.3, 129.2, 126.7, 117.5, 115.6, 115.3, 107.8, 57.9, 55.0, 51.8, 49.5, 49.32, 49.26, 49.14, 49.10, 48.9, 48.80, 48.76, 44.6, 44.1, 36.8, 30.6, 28.5, 26.4. HRMS (TOF MS ES⁺) calcd for C₂₁H₂₇NBr⁷⁹O₂ (M+H)⁺: 404.1225; found: 404.1206. Anal. Calcd for (C₂₁H₂₆BrNO₂·HBr·0.75H₂O): C, 50.56; H, 5.76; N, 2.80; found: C, 50.59; H, 5.88; N, 2.80.

5.1.13. 2-Methyl-4a-(3-phenylpropyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2c)

—Using general procedure D, 12.0 g of **7c** was converted to **2c** (8.0 g, 83%). Mp 180–183 °C; IR (neat) 3055 cm⁻¹; ¹H NMR (500 MHz, CD₃OD) 7.24 (t, 2H, *J* = 7.0 Hz), 7.13 (m, 3H), 6.56 (m, 3H), 4.38 (t, 1H, *J* = 6.0 Hz), 2.74 (dd, 1H, *J* = 5.0 and 12.5 Hz), 2.54 (t, 2H, *J* = 7.0 Hz), 2.46 (dd, 1H, *J* = 5.5 and 11.0 Hz), 2.30 (dd, 1H, *J* = 7.0 and 12.5 Hz), 2.21 (s, 3H), 2.14 (dt, 1H, *J* = 2.5 and 11.5 Hz), 2.00 (m, 1H), 1.71–1.77 (m, 2H), 1.53–1.59 (m, 3H); ¹³C NMR (126 MHz, CD₃OD) 153.1, 152.9, 143.4, 135.7, 129.4, 129.3, 126.8, 115.2, 111.42, 111.37, 107.9, 85.3, 57.1, 52.7, 46.6, 46.2, 39.8, 37.2, 33.6, 27.1; HRMS (TOF MS ES⁺) calcd for C₂₁H₂₆NO₂ (M+H)⁺: 324.1964; found: 324.1961. Anal. Calcd for (C₂₁H₂₅NO₂·0.25H₂O): C, 76.91; H, 7.83; N, 4.27; found: C, 77.20; H, 7.73; N, 4.31.

5.1.14. 4-(2,5-Dimethoxyphenyl)-1-methyl-4-(4-phenylbutyl)-1,2,3,4-tetrahydropyridine (5d)

—Using general procedure A, 15.0 g of **4** was converted to **5d** (11.5 g, 49%). ¹H NMR (500 MHz, CDCl₃): 7.29 (t, *J* = 7.4 Hz, 3H), 7.18 (dd, *J* = 15.1, 7.3 Hz, 2H), 7.08 (d, *J* = 3.0 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.73 (dd, *J* = 8.7, 3.0 Hz, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 4.70 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 6H), 2.79 (d, *J* = 10.9 Hz, 1H), 2.60 (s, 3H), 2.58–2.52 (m, 3H), 2.29 (td, *J* = 12.7, 4.3 Hz, 1H), 1.96–1.91 (m, 1H), 1.73 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.57 (dd, *J* = 12.7, 6.3 Hz, 2H), 1.31 (q, *J* = 6.7 Hz, 2H), 1.01 (dt, *J* = 12.3, 5.0 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): 152.9, 151.9, 143.1, 138.0, 136.2, 128.4, 128.2, 125.5, 119.8, 111.9, 110.0, 104.8, 55.6, 55.5, 47.1, 42.5, 41.0, 39.8, 35.9, 33.8, 32.4, 24.5, 14.3. HRMS (TOF MS ES⁺) calcd for C₂₄H₃₂NO₂ (M+H)⁺: 366.2069; found: 366.2061. Anal. Calcd for (C₂₄H₃₁NO₂): C, 78.86; H, 8.55; N, 3.83; found: C, 78.47; H, 8.67; N, 3.65.

5.1.15. 3-Bromo-4-(2,5-dimethoxyphenyl)-1-methyl-4-(4-phenylbutyl)piperidine (6d)

—Using general procedure B, 9.4 g of **5d** was converted to **6d** (9.7 g, 85%). ¹H NMR (500 MHz, CDCl₃): 7.24–7.19 (m, 3H), 7.12 (t, *J* = 6.9 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 3H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.73–6.71 (m, 1H), 6.65 (s, 1H), 5.45 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.03 (d, *J* = 13.3 Hz, 1H), 2.88 (d, *J* = 11.0 Hz, 1H), 2.82 (d, *J* = 13.4 Hz, 1H), 2.43 (t, *J* = 8.0 Hz, 2H), 2.35 (s, 3H), 2.30 (t, *J* = 12.1 Hz, 1H), 2.10–2.05 (m, 1H), 1.93–1.83 (m, 1H), 1.46 (q, *J* = 7.5 Hz, 2H), 1.12 (t, *J* = 6.3 Hz, 1H), 0.67 (d, *J* = 4.3 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃): 153.0, 152.4, 142.4, 135.8, 128.2, 128.1, 125.5, 115.5, 111.8, 110.1, 105.6, 58.39, 58.36, 55.8, 55.4, 51.1, 46.0, 44.3, 35.4, 31.9, 31.0, 27.4, 24.7. HRMS (TOF MS ES⁺) calcd for C₂₄H₃₃NBrO₂ (M+H)⁺: 446.1695; found: 446.1685. Anal. Calcd for (C₂₄H₃₂NBrO₂·0.75H₂O): C, 62.57; H, 7.34; N, 3.05; found: C, 62.51; H, 7.46; N, 3.15.

5.1.16. 2-(3-Bromo-1-methyl-4-(4-phenylbutyl)piperidin-4-yl)benzene-1,4-diol (7d)—Using general procedure C, 9.0 g of **6d** was converted to **7d** (7.0 g, 83%). ¹H NMR (500 MHz, CD₃OD): 6.99 (t, *J* = 7.5 Hz, 3H), 6.90 (t, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 6.45 (d, *J* = 8.5 Hz, 1H), 6.39 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 5.75 (s, 1H), 3.86 (d, *J* = 14.1 Hz, 1H), 3.58 (d, *J* = 14.3 Hz, 1H), 3.36–3.33 (m, 1H), 3.21–3.19 (m, 1H), 2.81 (s, 3H), 2.32–2.26 (m, 4H), 1.99 (d, *J* = 14.6 Hz, 1H), 1.85 (dt, *J* = 12.0, 6.3 Hz, 1H), 1.40–1.38 (m, 1H), 1.33–1.30 (m, 1H), 1.02 (t, *J* = 6.3 Hz, 1H), 0.62–0.58 (m, 1H). ¹³C NMR (126 MHz, CD₃OD): 150.6, 149.8, 143.6, 132.0, 129.3, 129.2, 126.5, 117.6, 115.6, 115.2, 57.9, 55.1, 51.8, 44.7, 44.2, 36.3, 32.8, 30.7, 26.4, 25.9. HRMS (TOF MS ES⁺) calcd for C₂₂H₂₉NBrO₂ (M+H)⁺: 418.1382; found: 418.1376. Anal. Calcd for (C₂₂H₂₈NBrO₂·1.5HBr): C, 48.96; H, 5.51; N, 2.60; found: C, 48.60; H, 5.22; N, 2.55.

5.1.17. 2-Methyl-4a-(4-phenylbutyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2d)—Using general procedure D, 6.8 g of **7d** was converted to **2d** (4.5 g, 86%). Mp 175–178 °C; ¹H NMR (500 MHz, CDCl₃): 7.24 (t, *J* = 7.5 Hz, 2H), 7.14–7.13 (m, 4H), 6.61–6.56 (m, 2H), 4.39 (t, *J* = 5.9 Hz, 1H), 2.75 (dd, *J* = 12.3, 5.1 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 3H), 2.49–2.47 (m, 1H), 2.37 (dd, *J* = 12.3, 6.6 Hz, 1H), 2.25 (s, 2H), 2.20–2.15 (m, 1H), 2.03–2.00 (m, 1H), 1.81–1.79 (m, 1H), 1.67–1.52 (m, 3H), 1.29 (t, *J* = 1.2 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD): 153.1, 152.7, 143.8, 136.0, 129.4, 129.2, 126.6, 115.2, 111.4, 111.3, 110.4, 85.3, 57.1, 52.7, 46.7, 46.2, 40.0, 36.7, 33.8, 32.5, 30.7, 24.9. HRMS (TOF MS ES⁺) calcd for C₂₂H₂₈NO₂ (M+H)⁺: 338.2120; found: 338.2111. Anal. Calcd for (C₂₂H₂₇NO₂): C, 78.30; H, 8.06; N, 4.15; found: C, 78.17; H, 8.06; N, 4.21.

5.1.18. 4-(2,5-Dimethoxyphenyl)-1-methyl-4-(5-phenylpentyl)-1,2,3,4-tetrahydropyridine (5e)—Using general procedure A, 6.0 g of **4** was converted to **5e** (6.8 g, 70%). ¹H NMR (500 MHz, CDCl₃): 7.25–7.22 (m, 3H), 7.12 (t, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 3.1 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.66 (dd, *J* = 8.7, 3.1 Hz, 1H), 5.90 (d, *J* = 8.0 Hz, 1H), 4.64 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.74 (d, *J* = 2.7 Hz, 4H), 2.73–2.70 (m, 1H), 2.53 (s, 3H), 2.50 (d, *J* = 7.7 Hz, 3H), 2.46–2.44 (m, 2H), 2.17 (td, *J* = 12.4, 4.3 Hz, 1H), 1.88–1.83 (m, 1H), 1.59–1.51 (m, 3H), 1.22 (td, *J* = 9.1, 5.8 Hz, 3H), 0.90 (d, *J* = 5.8 Hz, 2H). ¹³C NMR (126 MHz, CD₃OD): 152.8, 151.9, 143.0, 138.1, 136.2, 128.5, 128.2, 125.5, 119.8, 111.9, 109.9, 104.9, 55.60, 55.56, 47.1, 42.5, 41.0, 39.9, 36.0, 33.8, 31.4, 30.0, 24.4. HRMS (TOF MS ES⁺) calcd for C₂₅H₃₄NBrO₂ (M+H)⁺: 380.2590; found: 380.2589. Anal. Calcd for (C₂₅H₃₃NBrO₂·0.5H₂O): C, 63.96; H, 7.51; N, 2.98; found: C, 64.12; H, 7.51; N, 2.84.

5.1.19. 3-Bromo-4-(2,5-dimethoxyphenyl)-1-methyl-4-(5-phenylpentyl)piperidine (6e)—Using general procedure B, 6.8 g of **5e** was converted to **6e** (5.2 g, 63%). ¹H NMR (500 MHz, CDCl₃): 7.28–7.25 (m, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.76–6.73 (m, 1H), 6.69 (s, 1H), 5.46 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.05 (d, *J* = 13.4 Hz, 1H), 2.92 (d, *J* = 11.0 Hz, 1H), 2.84 (d, *J* = 13.4 Hz, 1H), 2.49 (t, *J* = 7.6 Hz, 3H), 2.44 (d, *J* = 12.3 Hz, 1H), 2.37 (d, *J* = 7.9 Hz, 2H), 2.07–2.02 (m, 1H), 1.89–1.87 (m, 2H), 1.49 (t, *J* = 7.5 Hz, 3H), 1.20 (dd, *J* = 16.1, 7.8 Hz, 2H), 1.10 (t, *J* = 6.2 Hz, 1H), 0.64 (s, 1H). ¹³C NMR (126 MHz, CD₃OD): 153.1, 152.6, 142.7, 136.1, 128.4, 128.3, 125.6, 115.7, 111.9, 110.1, 105.7, 58.6, 58.5, 56.0, 55.5, 51.2, 46.2, 44.5, 35.8, 31.3, 31.1, 29.7, 27.5, 24.9. HRMS (TOF MS ES⁺) calcd for C₂₅H₃₅NBrO₂ (M+H)⁺: 460.1851; found: 460.1837. Anal. Calcd for (C₂₅H₃₄NBrO₂·0.25H₂O): C, 78.19; H, 8.79; N, 3.65; found: C, 78.34; H, 8.76; N, 3.25.

5.1.20. 2-Methyl-4a-(5-phenylpentyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2e)—Using general procedure C and D, 4.7 g of **6e** was converted to **2e** (2.9 g, 81%). Mp 182–185 °C; ¹H NMR (500 MHz, CDCl₃): 7.22 (t, *J* = 7.4 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 3H), 6.58–6.55 (m, 3H), 4.38 (t, *J* = 5.9 Hz, 1H), 2.77 (dd, *J* = 12.4, 5.1 Hz,

1H), 2.56 (t, $J = 7.6$ Hz, 3H), 2.50 (t, $J = 5.8$ Hz, 1H), 2.37 (dd, $J = 12.3, 6.7$ Hz, 1H), 2.26 (s, 3H), 2.20–2.15 (m, 1H), 2.00 (ddd, $J = 13.9, 5.9, 3.0$ Hz, 1H), 1.81–1.68 (m, 2H), 1.57 (q, $J = 7.3$ Hz, 3H), 1.34–1.27 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.1, 152.8, 143.7, 135.9, 129.4, 129.3, 126.7, 115.2, 111.44, 111.37, 85.2, 57.0, 52.7, 46.7, 46.2, 39.9, 36.6, 33.63, 33.60, 33.2, 24.6. HRMS (TOF MS ES^+) calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_2$ ($\text{M}+\text{H}^+$): 352.2277; found: 352.2287. Anal. Calcd for ($\text{C}_{23}\text{H}_{29}\text{NO}_2$): C, 78.59; H, 8.32; N, 3.99; found: C, 78.31; H, 8.22; N, 3.94.

5.1.21. 4-(2,5-Dimethoxyphenyl)-1,4-dimethyl-1,2,3,4-tetrahydropyridine (5f)—

Using general procedure A, 7.0 g of **4** was converted to **5f** (5.0 g, 67%). ^1H NMR (500 MHz, CDCl_3): 7.07 (d, $J = 3.2$ Hz, 1H), 6.78 (d, $J = 8.7$ Hz, 2H), 6.68 (dd, $J = 8.8, 3.1$ Hz, 1H), 5.89 (d, $J = 7.9$ Hz, 1H), 4.53–4.52 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.74 (dd, $J = 7.3, 4.0$ Hz, 1H), 2.55 (s, 3H), 2.49–2.44 (m, 1H), 1.83 (ddd, $J = 13.4, 11.6, 3.2$ Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.2, 152.3, 139.7, 136.0, 118.7, 112.6, 110.5, 107.6, 56.0, 55.9, 47.6, 42.8, 37.5, 35.2, 28.9. HRMS (TOF MS ES^+) calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}^+$): 248.1645; found: 248.1651.

5.1.22. 3-Bromo-4-(2,5-dimethoxyphenyl)-1,4-dimethylpiperidine (6f)—

Using general procedure B, 5.0 g of **5f** was converted to **6f** (2.0 g, 30%). ^1H NMR (500 MHz, CDCl_3): 6.82 (d, $J = 8.7$ Hz, 1H), 6.73 (dd, $J = 13.1, 4.3$ Hz, 2H), 5.45 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.03 (d, $J = 13.4$ Hz, 1H), 2.94 (d, $J = 12.1$ Hz, 1H), 2.74 (d, $J = 13.4$ Hz, 1H), 2.62 (td, $J = 12.7, 3.8$ Hz, 1H), 2.40 (d, $J = 11.7$ Hz, 1H), 2.36 (s, 3H), 1.68 (d, $J = 12.7$ Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.7, 152.8, 138.9, 114.2, 112.4, 110.5, 59.0, 58.1, 56.2, 55.9, 51.8, 46.5, 41.2, 32.2, 22.1. HRMS (TOF MS ES^+) calcd for $\text{C}_{15}\text{H}_{23}\text{NBr}^{79}\text{O}_2$ ($\text{M}+\text{H}^+$): 328.0912; found: 328.0875. Anal. Calcd for ($\text{C}_{15}\text{H}_{22}\text{NBrO}_2 \cdot 0.5\text{H}_2\text{O}$): C, 53.42; H, 6.87; N, 4.15; found: C, 53.12; H, 6.86; N, 4.12.

5.1.23. 2,4a-Dimethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2f)—

Using general procedure C and D, 2.0 g of **6f** was converted to **2f** (0.65 g, 49%). Mp 275–278 °C ^1H NMR (500 MHz, CDCl_3): 6.75–6.63 (m, 3H), 4.40 (d, $J = 0.4$ Hz, 1H), 3.84 (d, $J = 0.4$ Hz, 1H), 3.55 (dd, $J = 13.9, 2.4$ Hz, 1H), 3.31 (s, 3H), 3.27–3.22 (m, 2H), 2.97 (s, 3H), 2.05–2.01 (m, 1H), 1.90–1.89 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD): 153.6, 151.5, 138.4, 115.6, 111.7, 110.4, 85.5, 53.0, 51.0, 44.0, 41.6, 34.0, 20.4. HRMS (TOF MS ES^+) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_2$ ($\text{M}+\text{H}^+$): 220.1338; found: 220.1335. Anal. Calcd for ($\text{C}_{13}\text{H}_{17}\text{NO}_2 \cdot \text{HBr}$): C, 52.01; H, 6.04; N, 4.67; found: C, 51.73; H, 6.12; N, 4.65.

5.1.24. 4-(2,5-Dimethoxyphenyl)-1-methyl-4-propyl-1,2,3,4-tetrahydropyridine (5h)—

Using general procedure A, 7.5 g of **4** was converted to **5h** (4.0 g, 45%). ^1H NMR (500 MHz, CDCl_3): 7.02 (d, $J = 3.0$ Hz, 1H), 6.78 (s, 2H), 6.68 (d, $J = 3.0$ Hz, 2H), 5.91 (d, $J = 8.0$ Hz, 1H), 4.66 (d, $J = 8.0$ Hz, 1H), 3.77 (d, $J = 9.5$ Hz, 6H), 2.75–2.72 (m, 1H), 2.55 (s, 3H), 2.51–2.45 (m, 2H), 2.16 (td, $J = 12.7, 4.1$ Hz, 2H), 1.87 (td, $J = 12.2, 2.2$ Hz, 1H), 1.57 (td, $J = 12.5, 4.2$ Hz, 1H), 1.16 (s, 1H), 0.80 (t, $J = 7.1$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3): 153.2, 152.4, 138.6, 136.5, 120.1, 112.4, 110.3, 105.4, 55.98, 55.96, 47.5, 42.9, 42.8, 41.4, 34.2, 18.3, 15.3. HRMS (TOF MS ES^+) calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_2$ ($\text{M}+\text{H}^+$): 276.1964; found: 276.1964.

5.1.25. 3-Bromo-4-(2,5-dimethoxyphenyl)-1-methyl-4-propylpiperidine (6h)—

Using general procedure B, 4.0 g of **5h** was converted to **6h** (2.5 g, 48%). Mp 120–124 °C; ^1H NMR (500 MHz, CDCl_3): 6.79 (d, $J = 8.8$ Hz, 1H), 6.72 (dd, $J = 8.8, 2.8$ Hz, 1H), 6.66 (s, 1H), 5.44 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.04 (d, $J = 13.3$ Hz, 1H), 2.87 (dd, $J = 33.7, 12.1$ Hz, 2H), 2.43 (td, $J = 12.9, 2.2$ Hz, 1H), 2.36–2.31 (m, 5H), 1.98 (td, $J = 12.7, 3.8$ Hz, 1H), 1.86 (td, $J = 12.5, 3.7$ Hz, 2H), 1.07 (t, $J = 6.2$ Hz, 1H), 0.76 (t, $J = 7.2$ Hz, 2H),

0.60 (d, J = 5.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD): 153.2, 152.7, 136.3, 115.7, 112.1, 110.2, 58.6, 56.1, 55.6, 51.3, 46.3, 44.6, 34.0, 27.6, 18.6, 14.8. HRMS (TOF MS ES^+) calcd for $\text{C}_{17}\text{H}_{27}\text{NBrO}_2$ ($\text{M}+\text{H}^+$): 356.1225; found: 356.1222. Anal. Calcd for $(\text{C}_{17}\text{H}_{26}\text{NBrO}_2)$: C, 57.31; H, 7.36; N, 3.93; found: C, 57.39; H, 7.61; N, 3.90.

5.1.26. 2-(3-Bromo-3-propyl-1-methylpiperidin-4-yl)benzene-1,4-diol (**7h**)—

Using general procedure C, 2.5 g of **6h** was converted to **7h** (2.0 g, 87%). ^1H NMR (500 MHz, CD_3OD): 6.56 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 8.5 Hz, 1H), 6.41 (s, 1H), 5.89 (s, 1H), 3.98 (d, J = 14.2 Hz, 1H), 3.73 (d, J = 14.2 Hz, 1H), 3.50 (d, J = 12.5 Hz, 1H), 3.37 (t, J = 13.2 Hz, 1H), 2.96 (s, 3H), 2.43 (t, J = 13.8 Hz, 1H), 2.29 (t, J = 12.7 Hz, 1H), 2.17 (d, J = 14.8 Hz, 1H), 1.96–1.91 (m, 1H), 1.12 (t, J = 6.0 Hz, 1H), 0.80 (t, J = 6.9 Hz, 3H), 0.73–0.69 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD): 150.7, 149.8, 132.1, 117.6, 115.6, 115.1, 57.9, 55.2, 51.9, 44.7, 44.1, 33.5, 26.5, 19.9, 14.8. HRMS (TOF MS ES^+) calcd for $\text{C}_{15}\text{H}_{23}\text{NBr}^{79}\text{O}_2$ ($\text{M}+\text{H}^+$): 328.0912; found: 328.0875. Anal. Calcd for $(\text{C}_{15}\text{H}_{22}\text{NBrO}_2\cdot\text{HBr})$: C, 44.03; H, 5.67; N, 3.42; found: C, 44.15; H, 5.79; N, 3.35.

5.1.27. 2-Methyl-4a-propyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (**2h**)—

Using general procedure D, 0.7 g of **7h** was converted to **2h** (0.4 g, 76%). Mp 179 °C; ^1H NMR (500 MHz, CDCl_3): 6.57 (q, J = 8.1 Hz, 3H), 4.39 (t, J = 5.9 Hz, 1H), 2.75 (dd, J = 12.4, 5.2 Hz, 1H), 2.49–2.46 (m, 1H), 2.35 (dd, J = 12.4, 6.7 Hz, 1H), 2.24 (s, 3H), 2.19–2.14 (m, 1H), 2.03–2.00 (m, 1H), 1.80 (td, J = 9.4, 4.5 Hz, 1H), 1.65 (td, J = 12.9, 4.7 Hz, 1H), 1.51 (td, J = 12.8, 4.4 Hz, 1H), 1.27 (ddd, J = 25.4, 12.9, 6.4 Hz, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.1, 152.7, 136.0, 115.1, 111.4, 111.3, 85.3, 57.1, 52.7, 49.5, 48.5, 46.7, 46.2, 42.6, 41.4, 37.2, 36.8, 33.9, 33.77, 33.75, 29.0, 18.4, 15.0. HRMS (TOF MS ES^+) calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2$ ($\text{M}+\text{H}^+$): 248.1651; found: 248.1655. Anal. Calcd for $(\text{C}_{15}\text{H}_{21}\text{NO}_2)$: C, 72.84; H, 8.56; N, 5.66; found: C, 72.82; H, 8.53; N, 5.62.

5.1.28. 4-Butyl-4-(2,5-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydropyridine (**5i**)—

Using general procedure A, 8.5 g of **4** was converted to **5i** (9.0 g, 82%). ^1H NMR (500 MHz, CDCl_3): 7.04 (d, J = 3.0 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 6.70 (dd, J = 8.7, 3.1 Hz, 1H), 5.94 (d, J = 8.0 Hz, 1H), 4.68 (d, J = 8.0 Hz, 1H), 3.79 (d, J = 6.6 Hz, 6H), 2.77–2.75 (m, 1H), 2.57 (s, 3H), 2.54–2.48 (m, 2H), 2.22 (dt, J = 12.5, 6.3 Hz, 1H), 1.92–1.87 (m, 1H), 1.62 (dt, J = 12.6, 6.4 Hz, 1H), 1.24–1.20 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3): 152.8, 152.0, 138.2, 136.2, 119.8, 112.0, 109.9, 105.8, 105.1, 55.62, 55.59, 47.2, 42.5, 41.0, 39.8, 33.8, 26.9, 23.5, 14.2. HRMS (TOF MS ES^+) calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_2$ ($\text{M}+\text{H}^+$): 290.2120; found: 290.2104. Anal. Calcd for $(\text{C}_{18}\text{H}_{27}\text{NO}_2)$: C, 74.70; H, 9.40; N, 4.84; found: C, 74.46; H, 9.57; N, 4.48.

5.1.29. 3-Bromo-4-butyl-4-(2,5-dimethoxyphenyl)-1-methylpiperidine (**6i**)—

Using general procedure B, 10.4 g of **5i** was converted to **6i** (6.0 g, 48%). ^1H NMR (500 MHz, CDCl_3): 6.88 (d, J = 8.7 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.75 (s, 1H), 5.53 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.12 (d, J = 13.2 Hz, 1H), 2.98 (d, J = 10.5 Hz, 1H), 2.92 (d, J = 13.3 Hz, 1H), 2.51 (s, 1H), 2.43 (d, J = 11.1 Hz, 4H), 2.12 (s, 2H), 1.97–1.94 (m, 2H), 1.24 (dd, J = 14.8, 7.4 Hz, 2H), 1.10 (t, J = 6.0 Hz, 1H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.0, 152.5, 136.1, 115.5, 111.8, 110.0, 58.6, 58.5, 55.8, 55.4, 51.1, 46.1, 44.3, 31.1, 31.0, 27.3, 23.2, 13.9. Using general procedure B, 10.4 g of **5i** was converted to **6i** (6.0 g, 48%). HRMS (TOF MS ES^+) calcd for $\text{C}_{18}\text{H}_{29}\text{NBrO}_2$ ($\text{M}+\text{H}^+$): 370.1382; found: 370.1393. Anal. Calcd for $(\text{C}_{18}\text{H}_{28}\text{NBrO}_2\cdot 0.5\text{H}_2\text{O})$: C, 56.99; H, 7.71; N, 3.69; found: C, 57.27; H, 7.43; N, 3.53.

5.1.30. 4a-Butyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (**2i**)—

Using general procedure C and D, 12.75 g of **6i** was converted to **2i** (13.4 g, 76%).

Mp 176 °C; ¹H NMR (500 MHz, CDCl₃): 6.63 (d, *J* = 9.1 Hz, 1H), 6.57 (dd, *J* = 7.0, 2.2 Hz, 2H), 4.45 (t, *J* = 6.0 Hz, 1H), 2.81–2.79 (m, 1H), 2.48 (t, *J* = 5.5 Hz, 1H), 2.36 (s, 1H), 2.28 (s, 3H), 2.16 (t, *J* = 9.0 Hz, 1H), 1.98 (ddd, *J* = 10.4, 6.3, 3.4 Hz, 1H), 1.83–1.81 (m, 1H), 1.63–1.61 (m, 1H), 1.48 (t, *J* = 3.2 Hz, 1H), 1.21 (ddd, *J* = 7.0, 5.8, 5.1 Hz, 4H), 0.85–0.82 (m, 3H). ¹³C NMR (126 MHz, CDCl₃): 152.4, 150.6, 135.2, 114.5, 111.5, 111.0, 110.7, 84.5, 56.3, 51.9, 45.8, 45.7, 39.2, 32.6, 26.3, 23.4, 14.1. HRMS (TOF MS ES⁺) calcd for C₁₆H₂₄NO₂ (M+H)⁺: 262.1807; found: 262.1815. Anal. Calcd for (C₁₆H₂₃NO₂): C, 73.53; H, 8.87; N, 5.36; found: C, 73.23; H, 8.90; N, 5.40.

5.1.31. 4-Pentyl-4-(2,5-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydropyridine (5j)—Using general procedure A, 10.0 g of **4** was converted to **5j** (9.0 g, 69%).

¹H NMR (500 MHz, CDCl₃): 7.06 (d, *J* = 3.1 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.72 (d, *J* = 3.1 Hz, 1H), 5.95 (d, *J* = 8.0 Hz, 1H), 4.70–4.69 (m, 1H), 3.81 (s, 6H), 2.78–2.76 (m, 1H), 2.59 (s, 3H), 2.52 (t, *J* = 13.4 Hz, 3H), 2.22 (d, *J* = 4.4 Hz, 2H), 1.90 (d, *J* = 7.1 Hz, 2H), 1.64–1.59 (m, 1H), 1.45 (d, *J* = 7.1 Hz, 1H), 0.85 (t, *J* = 7.0 Hz, 5H). ¹³C NMR (126 MHz, CD₃OD): 152.8, 152.0, 138.2, 136.1, 119.8, 114.7, 111.9, 109.9, 105.1, 55.58, 55.56, 47.1, 42.5, 41.0, 40.0, 33.8, 32.7, 32.6, 30.4, 24.3, 22.6, 22.0, 14.19, 14.00. HRMS (TOF MS ES⁺) calcd for C₁₉H₃₀NO₂ (M+H)⁺: 304.2277; found: 304.2273. Anal. Calcd for (C₁₉H₂₉NO₂·0.5H₂O): C, 73.04; H, 9.68; N, 4.48; found: C, 73.07; H, 9.56; N, 4.27.

5.1.32. 3-Bromo-4-pentyl-4-(2,5-dimethoxyphenyl)-1-methylpiperidine (6j)—

Using general procedure B, 9.0 g of **5j** was converted to **6j** (4.5 g, 39%). Mp 219 °C; ¹H NMR (500 MHz, CD₃OD): 6.77 (d, *J* = 8.8 Hz, 1H), 6.72–6.69 (m, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 5.43 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.02 (d, *J* = 13.4 Hz, 1H), 2.89 (d, *J* = 11.1 Hz, 1H), 2.83–2.80 (m, 1H), 2.40 (dd, *J* = 12.8, 2.8 Hz, 1H), 2.34 (s, 3H), 2.30 (d, *J* = 12.5 Hz, 1H), 2.03–1.99 (m, 2H), 1.86 (dd, *J* = 12.4, 3.6 Hz, 2H), 1.15–1.02 (m, 5H), 0.76 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD): 153.1, 152.6, 136.2, 115.6, 111.9, 110.1, 58.7, 58.5, 55.9, 55.5, 51.2, 46.2, 44.4, 32.4, 31.3, 27.5, 24.8, 22.4, 14.1. HRMS (TOF MS ES⁺) calcd for C₁₉H₃₁NBr⁷⁹O₂ (M+H)⁺: 384.1538; found: 384.1537. Anal. Calcd for (C₁₉H₃₀NBrO₂·0.5H₂O): C, 58.01; H, 7.94; N, 3.56; found: C, 58.29; H, 8.03; N, 3.49.

5.1.33. 4a-Pentyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2j)—Using general procedure C and D, 4.5 g of **6j** was converted to **2j** (1.5 g, 47%).

Mp 185–188 °C; ¹H NMR (500 MHz, CDCl₃): 6.57 (q, *J* = 8.2 Hz, 3H), 4.39 (t, *J* = 5.9 Hz, 1H), 4.39 (t, *J* = 5.9 Hz, 1H), 2.75 (dd, *J* = 12.4, 5.1 Hz, 1H), 2.49–2.46 (m, 1H), 2.36 (dd, *J* = 12.4, 6.7 Hz, 1H), 2.25 (s, 3H), 2.17 (td, *J* = 10.4, 2.9 Hz, 1H), 2.02 (ddd, *J* = 14.2, 6.3, 3.4 Hz, 1H), 1.80 (td, *J* = 9.4, 4.5 Hz, 1H), 1.67–1.64 (m, 1H), 1.54 (d, *J* = 11.6 Hz, 1H), 1.27 (dt, *J* = 24.2, 5.1 Hz, 5H), 0.87 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CD₃OD): 153.0, 152.6, 135.9, 115.1, 111.34, 111.27, 85.3, 57.0, 52.7, 49.5, 48.4, 46.6, 46.19, 46.16, 40.0, 33.7, 33.5, 24.8, 23.5, 14.3. HRMS (TOF MS ES⁺) calcd for C₁₇H₂₆NO₂ (M+H)⁺: 276.1964; found: 276.1951. Anal. Calcd for (C₁₇H₂₅NO₂): C, 74.14; H, 9.15; N, 5.09; found: C, 73.89; H, 9.12; N, 5.02.

5.1.34. 4-(2,5-Dimethoxyphenyl)-4-(4-fluorophenethyl)-1-methyl-1,2,3,4-tetrahydropyridine (5k)—Using general procedure A, 12.75 g of **4** was converted to **5k** (13.4 g, 76%).

¹H NMR (500 MHz, CDCl₃): 7.12 (d, *J* = 3.1 Hz, 1H), 7.05 (dd, *J* = 8.3, 5.7 Hz, 2H), 6.92 (t, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.74 (dd, *J* = 8.7, 3.1 Hz, 1H), 6.01 (d, *J* = 8.0 Hz, 1H), 4.74 (dd, *J* = 8.0, 1.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.78 (dt, *J* = 7.5, 3.6 Hz, 1H), 2.62–2.58 (m, 3H), 2.58–2.52 (m, 3H), 2.52–2.43 (m, 1H), 2.18 (td, *J* = 12.9, 4.4 Hz, 1H), 1.92 (dtd, *J* = 17.2, 12.8, 4.1 Hz, 2H). ¹³C NMR (126 MHz, CD₃OD): 162.0, 160.1, 152.9, 151.9, 139.31, 139.29, 137.3, 136.6, 129.7, 129.6, 120.0, 114.9, 114.77, 111.8, 110.2, 104.0, 55.6, 55.4, 47.0, 42.5, 42.3, 41.1, 33.9, 30.6. HRMS (TOF MS ES⁺)

calcd for $C_{22}H_{27}FNO_2$ ($M+H$)⁺: 356.2026; found: 356.2024. Anal. Calcd for ($C_{22}H_{26}FNO_2 \cdot 0.25H_2O$): C, 73.41; H, 7.42; N, 3.89; found: C, 73.36; H, 7.30; N, 3.73.

5.1.35. 3-Bromo-4-(2,5-dimethoxyphenyl)-4-(4-fluorophenethyl)-1-methylpiperidine (6k)—Using general procedure B, 12.75 g of **5k** was converted to **6k** (13.4 g, 76%).

IR (neat) 2941 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (m, 4H), 6.77 (d, 1H, $J = 8.5$ Hz), 6.68 (m, 2H), 5.35 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.96 (d, 1H, $J = 13.0$ Hz), 2.94 (d, 1H, $J = 11.0$ Hz), 2.73 (d, 1H, $J = 13.5$ Hz), 2.46 (dt, 1H, $J = 3.0$ and 13.0 Hz), 2.34 (m, 2H), 2.28 (s, 3H), 2.22 (m, 1H), 2.11 (dt, 1H, $J = 4.5$ and 12.5 Hz), 1.88 (d, 1H, $J = 13.0$ Hz), 1.81 (dt, 1H, $J = 3.0$ and 11.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 160.3, 153.3, 152.6, 138.22, 138.20, 135.5, 129.7, 129.6, 115.8, 115.2, 115.0, 112.0, 110.5, 58.4, 58.1, 56.0, 55.6, 51.2, 46.2, 44.6, 33.1, 31.3, 27.5; HRMS (TOF MS ES⁺) calcd for $C_{22}H_{28}NBrFO_2$ ($M+H$)⁺: 436.1287; found: 436.1288. Anal. Calcd for ($C_{22}H_{27}NBrFO_2$): C, 60.55; H, 6.24; N, 3.21; found: C, 60.59; H, 6.24; N, 3.26.

5.1.36. 2-(3-Bromo-4-(4-fluorophenethyl)-1-methylpiperidin-4-yl)benzene-1,4-diol (7k)—Using general procedure C, 12.75 g of **6k** was converted to **7k** (13.4 g, 76%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, $J = 6.8$ Hz, 2H), 6.92 (t, $J = 8.7$ Hz, 3H), 6.67 (d, $J = 8.5$ Hz, 1H), 6.62–6.60 (m, 1H), 6.53 (s, 1H), 5.92 (s, 1H), 4.01–3.98 (m, 1H), 3.76 (d, $J = 14.0$ Hz, 1H), 3.59–3.56 (m, 1H), 3.50–3.45 (m, 1H), 3.00 (s, 3H), 2.69–2.65 (m, 1H), 2.59–2.54 (m, 1H), 2.42 (d, $J = 4.9$ Hz, 1H), 2.31 (s, 1H), 2.04 (dd, $J = 11.7$, 2.0 Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 163.6, 161.7, 150.9, 149.8, 139.12, 139.10, 131.6, 131.1, 131.0, 117.7, 115.9, 115.8, 115.7, 115.5, 108.3, 107.9, 57.9, 54.9, 51.8, 49.5, 49.3, 48.5, 44.9, 44.1, 33.4, 32.3, 26.4. HRMS (TOF MS ES⁺) calcd for $C_{20}H_{22}FBrNO_2$ ($M+H$)⁺: 406.0818; found: 406.0798. Anal. Calcd for ($C_{20}H_{21}FBrNO_2 \cdot HBr$): C, 49.10; H, 4.94; N, 2.86; found: C, 48.89; H, 4.86; N, 2.88.

5.1.37. 4a-(4-Fluorophenethyl)-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2k)—Using general procedure D, 12.75 g of **7k** was converted to **2k** (13.4 g, 76%).

Mp 207–210 °C; IR (neat) 3055 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 7.13 (t, 2H, $J = 8.0$ Hz), 6.95 (d, 2H, $J = 8.5$ Hz), 6.66 (s, 1H), 6.60 (m, 2H), 4.49 (t, 1H, $J = 5.5$ Hz), 2.83 (dd, 1H, $J = 5.0$ and 12.5 Hz), 2.58 (m, 3H), 2.35 (dd, 1H, $J = 7.0$ and 12.5 Hz), 2.26 (s, 3H), 2.15 (dt, 1H, $J = 2.5$ and 11.0 Hz), 2.09 (m, 1H), 1.94 (dt, 1H, $J = 5.0$ and 13.5 Hz), 1.76–1.86 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 153.2, 152.9, 139.47, 139.45, 135.3, 130.84, 130.77, 125.4, 116.0, 115.8, 115.4, 111.5, 111.4, 85.1, 57.1, 46.9, 46.2, 42.79, 33.7, 30.8; HRMS (TOF MS ES⁺) calcd for $C_{20}H_{23}NFO_2$ ($M+H$)⁺: 328.1713; found: 328.1702. Anal. Calcd for ($C_{20}H_{22}FNO_2 \cdot 0.25H_2O$): C, 72.37; H, 6.83; N, 4.22; found: C, 72.61; H, 6.89; N, 4.28.

5.1.38. 4-(2,5-Dimethoxyphenyl)-4-(2-fluorophenethyl)-1-methyl-1,2,3,4-tetrahydropyridine (5l)—Using general procedure A, 12.75 g of **4** was converted to **5l** (13.4 g, 76%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.12–7.08 (m, 3H), 6.98 (dt, $J = 25.8$, 8.3 Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 1H), 6.73 (dd, $J = 8.7$, 3.1 Hz, 1H), 6.00 (d, $J = 8.0$ Hz, 1H), 4.78 (dd, $J = 8.0$, 1.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.77 (dt, $J = 7.2$, 3.7 Hz, 1H), 2.60 (d, $J = 8.1$ Hz, 4H), 2.55–2.46 (m, 3H), 2.23 (td, $J = 12.7$, 4.3 Hz, 1H), 1.96–1.86 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 162.1, 160.2, 152.9, 152.0, 137.2, 136.6, 130.69, 130.65, 130.5, 130.4, 127.1, 127.0, 123.84, 123.81, 120.0, 115.2, 115.0, 111.7, 110.5, 110.3, 104.0, 55.7, 55.4, 47.0. HRMS (TOF MS ES⁺) calcd for $C_{22}H_{27}FNO_2$ ($M+H$)⁺: 356.2026; found: 356.2024. Anal. Calcd for ($C_{22}H_{26}FNO_2 \cdot 0.25H_2O$): C, 73.41; H, 7.42; N, 3.89; found: C, 73.36; H, 7.30; N, 3.73.

5.1.39. 3-Bromo-4-(2,5-dimethoxyphenyl)-4-(2-fluorophenethyl)-1-methylpiperidine (6l)—Using general procedure B, 12.75 g of **5l** was converted to **6l** (13.4 g, 76%). Mp °C; IR (neat) 2941 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) 7.13 (q, 1H, $J=7.0$ Hz), 6.99 (m, 2H), 6.85 (d, 2H, $J=8.5$ Hz), 6.77 (m, 2H), 5.43 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.03 (d, 1H, $J=13.5$ Hz), 2.98 (d, 1H, $J=11.0$ Hz), 2.79 (d, 1H, $J=13.5$ Hz), 2.56 (dt, 1H, $J=3.5$ and 12.5 Hz), 2.43 (m, 2H), 2.38 (m, 1H), 2.33 (s, 3H), 2.22 (dd, 1H, $J=2.5$ and 9.0 Hz), 2.00 (d, 1H, $J=13.0$ Hz), 1.93 (t, 1H, $J=9.0$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) 162.0, 160.1, 153.3, 152.7, 135.4, 130.7, 130.6, 129.5, 129.4, 127.64, 127.58, 124.1, 124.0, 115.8, 115.4, 115.2, 111.9, 110.6, 110.5, 58.4, 58.2, 55.9, 55.6, 51.2, 46.2, 44.6, 32.3, 27.5, 25.6, 153.23, 152.53, 142.56, 135.52, 128.34 (2C), 128.24 (2C), 125.74, 115.67, 111.92, 110.42, 58.36, 58.15, 55.90, 55.53, 51.12, 46.10, 44.55, 33.76, 31.97, 27.45; HRMS (TOF MS ES^+) calcd for $\text{C}_{22}\text{H}_{28}\text{NFB}^9\text{O}_2$ ($\text{M}+\text{H}^+$): 436.1287; found: 436.1288. Anal. Calcd for ($\text{C}_{22}\text{H}_{27}\text{NBrFO}_2$): C, 60.55; H, 6.24; N, 3.21; found: C, 60.59; H, 6.24; N, 3.26.

5.1.40. 2-(3-Bromo-4-(2-fluorophenethyl)-1-methylpiperidin-4-yl)benzene-1,4-diol (7l)—Using general procedure C, 12.75 g of **6l** was converted to **7l** (13.4 g, 76%). ^1H NMR (500 MHz, CDCl_3): 7.08 (s, 1H), 6.96 (d, $J=6.1$ Hz, 1H), 6.89 (d, $J=8.2$ Hz, 1H), 6.62 (t, $J=5.8$ Hz, 2H), 6.56 (t, $J=1.8$ Hz, 1H), 6.50 (s, 1H), 5.87–5.86 (m, 1H), 3.94 (d, $J=12.7$ Hz, 1H), 3.72–3.69 (m, 1H), 3.57 (d, $J=0.7$ Hz, 1H), 3.38 (t, $J=1.8$ Hz, 1H), 3.16 (d, $J=1.0$ Hz, 2H), 2.95 (s, 3H), 2.65–2.64 (m, 1H), 2.54 (d, $J=1.4$ Hz, 1H), 2.40–2.39 (m, 1H), 2.31–2.28 (m, 1H), 2.18 (s, 1H), 1.97 (d, $J=0.7$ Hz, 1H). ^{13}C NMR (126 MHz, CD_3OD): 163.0, 161.05, 161.04, 150.6, 149.8, 131.73, 131.70, 131.1, 129.7, 129.5, 128.8, 128.7, 125.08, 125.05, 117.5, 115.9, 115.7, 115.5, 115.4, 107.70, 57.8, 54.6, 51.7, 49.29, 49.1, 49.0, 48.8, 48.69, 48.65, 48.6, 48.52, 48.49, 48.33, 48.28, 44.6, 44.21, 44.19, 31.7, 26.2, 26.1. HRMS (TOF MS ES^+) calcd for $\text{C}_{20}\text{H}_{24}\text{FBrNO}_2$ ($\text{M}+\text{H}^+$): 406.0818; found: 406.0798. Anal. Calcd for ($\text{C}_{20}\text{H}_{23}\text{FBrNO}_2 \cdot 1.5\text{HBr}$): C, 45.35; H, 4.66; N, 2.64; found: C, 45.57; H, 4.76; N, 2.70.

5.1.41. 4a-(2-Fluorophenethyl)-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (2l)—Using general procedure D, 12.75 g of **7l** was converted to **2l** (13.4 g, 76%). Mp 218–221 °C; IR (neat) 3055 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) 7.17 (t, 2H, $J=6.5$ Hz), 7.06 (t, 1H, $J=7.0$ Hz), 6.99 (t, 1H, $J=9.0$ Hz), 6.68 (s, 1H), 6.61 (m, 2H), 4.51 (t, 1H, $J=6.0$ Hz), 2.81 (dd, 1H, $J=4.5$ and 11.5 Hz), 2.62 (dt, 1H, $J=5.0$ and 13.0 Hz), 2.53 (m, 2H), 2.40 (dd, 1H, $J=6.5$ and 11.5 Hz), 2.26 (s, 3H), 2.16 (m, 1H), 2.09 (m, 1H), 1.94 (dt, 1H, $J=5.0$ and 13.0 Hz), 1.76–1.87 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) 152.9, 152.5, 134.9, 131.4, 131.3, 129.8, 128.61, 128.55, 125.04, 125.01, 116.0, 115.8, 115.3, 111.4, 111.3, 107.6, 84.8, 56.9, 52.5, 46.6, 46.2, 35.6, 24.8; HRMS (TOF MS ES^+) calcd for $\text{C}_{20}\text{H}_{23}\text{NFO}_2$ ($\text{M}+\text{H}^+$): 328.1713; found: 328.1702. Anal. Calcd for ($\text{C}_{20}\text{H}_{22}\text{FNO}_2 \cdot 0.1\text{H}_2\text{O}$): C, 72.97; H, 6.79; N, 4.25; found: C, 72.84; H, 6.72; N, 4.19.

5.1.42. 2-Methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-yl acetate (8)—Compound **2a** was treated with acetic anhydride (10 mL) and heated to reflux. After completion of the reaction the acetic anhydride was evaporated off to give a sticky solid. This solid was applied to silica-gel column and the desired product was eluted using 75% EtOAc in hexanes to give a sticky solid **8**. ^1H NMR (500 MHz, CDCl_3): 7.26 (t, $J=7.0$ Hz, 2H), 7.18 (d, $J=6.8$ Hz, 1H), 7.12 (d, $J=6.8$ Hz, 2H), 6.88–6.81 (m, 3H), 4.59 (d, $J=4.7$ Hz, 1H), 2.80 (t, $J=6.1$ Hz, 1H), 2.58–2.53 (m, 2H), 2.43 (dt, $J=13.8$, 6.4 Hz, 2H), 2.29 (d, $J=7.1$ Hz, 6H), 2.19 (t, $J=10.2$ Hz, 1H), 2.10 (d, $J=14.5$ Hz, 1H), 2.04–1.96 (m, 1H), 1.91–1.85 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD): 170.0, 156.5, 144.7, 142.0, 134.7, 128.5, 128.3, 126.0, 121.1, 116.6, 110.9, 85.2, 56.5, 56.4, 51.85, 51.83, 46.3, 45.8, 41.3, 33.20, 33.18, 33.1, 30.6, 21.3. HRMS (TOF MS ES^+) calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_3$

(M+H)⁺: 352.1913; found: 352.1901. Anal. Calcd for (C₂₂H₂₅NO₃): C, 75.19; H, 7.17; N, 3.99; found: C, 74.96; H, 7.35; N, 3.99.

5.1.43. 4a-Phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (**9**)—

Compound **8** was treated with Troc-Cl and proton sponge in dichloroethane and stirred overnight. After completion of the reaction, the organic layer was evaporated and the reaction mixture was taken in water and treated with 1 M HCl (1 mL). The organic layer was then extracted with ethyl acetate (20 mL), dried over Na₂SO₄ and solvent evaporated to give a pale yellow oil. The compound was dissolved in MeOH and H₂O (1:1) and treated with excess K₂CO₃ and stirred for 2 h. The organic layer was then extracted into CH₂Cl₂, washed with water and dried over Na₂SO₄. The organic layer was then evaporated to give a brown oil. This oil was treated with AcOH (6 mL) and powdered Zn dust () and stirred for 2 h. After completion of the reaction, the organic layer was filtered over cotton and washed with CH₂Cl₂. The excess AcOH was quenched with satd. NaHCO₃ dried over Na₂SO₄ and solvent evaporated. This solid was applied to silica-gel column and the desired product was eluted using 15% MeOH in CH₂Cl₂ to give an off-white solid **9**. ¹H NMR (500 MHz, CDCl₃): 7.21 (t, *J* = 7.4 Hz, 2H), 7.10 (t, *J* = 8.9 Hz, 3H), 6.65–6.58 (m, 3H), 4.37 (t, *J* = 5.1 Hz, 1H), 3.07 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.79 (dd, *J* = 13.5, 5.7 Hz, 2H), 2.56 (dt, *J* = 11.7, 5.4 Hz, 2H), 2.45 (td, *J* = 12.8, 4.4 Hz, 1H), 1.99–1.89 (m, 3H), 1.79 (dtd, *J* = 31.2, 11.3, 4.5 Hz, 2H). ¹³C NMR (126 MHz, CD₃OD): 153.5, 152.9, 143.6, 135.8, 129.4, 129.3, 126.82, 126.80, 115.4, 111.4, 84.7, 49.5, 49.4, 49.2, 49.0, 48.8, 48.7, 48.5, 47.8, 46.8, 42.6, 42.4, 34.2, 31.6. HRMS (TOF MS ES⁺) calcd for C₁₉H₂₂NO₂ (M+H)⁺: 296.1651; found: 296.1651.

5.1.44. 2,4a-Diphenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (**3a**)—

Using general procedure E, **9** (50 mg, 0.17 mmol) was converted to **3a** (38 mg, 56%). Mp 205–208 °C; ¹H NMR (500 MHz, CDCl₃): 7.21 (dt, *J* = 25.8, 8.6 Hz, 8H), 7.10 (d, *J* = 7.2 Hz, 3H), 6.71–6.61 (m, 2H), 4.77 (d, *J* = 0.4 Hz, 1H), 4.58–4.56 (m, 1H), 3.00–2.96 (m, 1H), 2.80 (t, *J* = 7.9 Hz, 2H), 2.62–2.53 (m, 1H), 2.50 (td, *J* = 13.0, 4.5 Hz, 1H), 2.43–2.41 (m, 1H), 2.27–2.24 (m, 1H), 2.15–2.11 (m, 1H), 1.99 (td, *J* = 13.1, 5.0 Hz, 1H), 1.90–1.80 (m, 1H), 1.65–1.56 (m, 3H). ¹³C NMR (126 MHz, CD₃OD): 153.1, 150.0, 142.2, 140.3, 134.7, 128.8, 128.56, 128.54, 128.4, 126.2, 126.0, 114.7, 110.9, 84.9, 60.6, 54.7, 49.9, 46.7, 42.1, 33.6, 32.9, 30.6. HRMS (TOF MS ES⁺) calcd for C₂₇H₃₀NO₂ (M+H)⁺: 400.2277; found: 400.2271. Anal. Calcd for (C₂₇H₂₉NO₂·0.5H₂O): C, 79.38; H, 7.40; N, 3.43; found: C, 79.31; H, 7.34; N, 3.60.

5.1.45. 4a-Phenethyl-2-(3-phenylpropyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (**3b**)—

Using general procedure E, **9** (50 mg, 0.17 mmol) was converted to **3b** (27 mg, 39%). Mp 137–141 °C; ¹H NMR (500 MHz, CDCl₃): 7.18–7.05 (m, 8H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 6.49 (dd, *J* = 8.4, 2.3 Hz, 1H), 4.47 (t, *J* = 6.6 Hz, 1H), 2.85 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.48 (dq, *J* = 25.9, 6.7 Hz, 4H), 2.37 (td, *J* = 13.0, 4.4 Hz, 1H), 2.29 (d, *J* = 4.6 Hz, 2H), 2.19 (dd, *J* = 12.0, 7.6 Hz, 1H), 2.04–1.97 (m, 2H), 1.75 (m, 6H). ¹³C NMR (126 MHz, CDCl₃): 152.7, 150.5, 142.2, 141.9, 134.3, 128.5, 128.4, 126.0, 125.9, 114.9, 111.1, 110.9, 84.6, 58.0, 54.6, 49.9, 46.7, 42.3, 33.8, 32.1, 30.5, 28.2. HRMS (TOF MS ES⁺) calcd for C₂₈H₃₂NO₂ (M+H)⁺: 414.2433; found: 414.2457. Anal. Calcd for (C₂₈H₃₁NO₂): C, 81.32; H, 7.56; N, 3.39; found: C, 81.41; H, 7.56; N, 3.35.

5.1.46. 2-(4-Fluorophenethyl)-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (**3c**)—

Using general procedure E, **9** (50 mg, 0.17 mmol) was converted to **3c** (28 mg, 40%). Mp 194–197 °C; ¹H NMR (500 MHz, CDCl₃): 7.26–7.23 (m, 3H), 7.16 (s, 1H), 7.11 (dd, *J* = 12.2, 6.4 Hz, 3H), 6.95 (t, *J* = 8.7

Hz, 2H), 6.71–6.62 (m, 3H), 4.56 (t, J = 6.2 Hz, 1H), 2.96 (dd, J = 11.4, 5.7 Hz, 1H), 2.76 (t, J = 8.1 Hz, 2H), 2.61–2.49 (m, 4H), 2.40 (dd, J = 12.0, 7.2 Hz, 1H), 2.27–2.22 (m, 1H), 2.12 (ddd, J = 13.8, 4.9, 3.5 Hz, 1H), 1.99 (td, J = 13.1, 4.9 Hz, 1H), 1.91–1.80 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): 162.5, 160.6, 153.1, 150.1, 142.2, 135.9, 134.6, 130.2, 130.1, 128.5, 128.4, 126.0, 115.4, 115.2, 114.7, 110.9, 110.8, 84.9, 60.5, 54.7, 49.9, 46.6, 42.1, 32.8, 30.6. HRMS (TOF MS ES^+) calcd for $\text{C}_{27}\text{H}_{29}\text{NFO}_2$ ($\text{M}+\text{H}^+$): 418.2182; found: 418.2163. Anal. Calcd for $(\text{C}_{27}\text{H}_{28}\text{NFO}_2 \cdot 0.5\text{H}_2\text{O})$: C, 77.84; H, 6.81; N, 3.32; found: C, 76.75; H, 6.68; N, 3.40.

5.1.47. 2-(2-Fluorophenethyl)-4a-phenethyl-1,2,3,4,9a-

hexahydrobenzofuro[2,3-c]pyridin-6-ol (3d)—Using general procedure E, **9** (50 mg, 0.17 mmol) was converted to **3d** (32 mg, 42%). Mp 209–213 °C; ^1H NMR (500 MHz, CDCl_3): 7.27–7.24 (m, 3H), 7.18 (t, J = 8.0 Hz, 3H), 7.11 (d, J = 7.3 Hz, 2H), 7.03 (dt, J = 24.5, 8.2 Hz, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.67–6.62 (m, 1H), 4.57 (t, J = 6.2 Hz, 1H), 3.00 (dd, J = 11.6, 5.2 Hz, 1H), 2.84 (t, J = 7.9 Hz, 2H), 2.67–2.56 (m, 4H), 2.50 (td, J = 13.0, 4.6 Hz, 1H), 2.41 (dd, J = 11.8, 7.3 Hz, 1H), 2.29–2.25 (m, 1H), 2.15–2.12 (m, 1H), 1.99 (td, J = 13.1, 5.0 Hz, 1H), 1.92–1.80 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): 162.3, 160.3, 160.2, 153.1, 150.1, 142.2, 134.6, 131.1, 128.5, 128.0, 126.0, 124.2, 115.5, 115.3, 114.7, 110.94, 110.85, 110.6, 84.9, 58.8, 54.58, 49.8, 46.7, 42.2, 32.8, 30.6, 26.8. HRMS (TOF MS ES^+) calcd for $\text{C}_{27}\text{H}_{29}\text{NFO}_2$ ($\text{M}+\text{H}^+$): 418.2182; found: 418.2163. Anal. Calcd for $(\text{C}_{27}\text{H}_{28}\text{NFO}_2)$: C, 77.67; H, 6.76; N, 3.35; found: C, 77.41; H, 6.68; N, 3.32.

5.1.48. 4a-Phenethyl-2-(4-(trifluoromethyl)phenethyl)-1,2,3,4,9a-

hexahydrobenzofuro[2,3-c]pyridin-6-ol (3e)—Using general procedure E, **9** (50 mg, 0.17 mmol) was converted to **3e** (32 mg, 40%). Mp 163–166 °C; ^1H NMR (500 MHz, CDCl_3): 7.52 (d, J = 7.9 Hz, 2H), 7.25 (q, J = 8.7 Hz, 5H), 7.16 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 7.3 Hz, 2H), 6.71–6.61 (m, 2H), 4.56 (t, J = 5.8 Hz, 1H), 2.99–2.96 (m, 1H), 2.84 (d, J = 7.7 Hz, 2H), 2.58 (dt, J = 14.0, 7.4 Hz, 4H), 2.52–2.42 (m, 2H), 2.26 (t, J = 9.2 Hz, 1H), 2.13–2.10 (m, 1H), 1.98 (td, J = 13.0, 5.0 Hz, 1H), 1.91–1.80 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.1, 150.2, 142.1, 129.1, 128.6, 128.4, 126.0, 125.5, 114.8, 110.92, 110.86, 84.8, 59.9, 54.53, 54.51, 49.8, 46.7, 42.0, 33.4, 32.7, 30.6. HRMS (TOF MS ES^+) calcd for $\text{C}_{28}\text{H}_{29}\text{NF}_3\text{O}_2$ ($\text{M}+\text{H}^+$): 468.2150; found: 468.2139. Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{NF}_3\text{O}_2$: C, 71.93; H, 6.04; N, 3.00; found: C, 72.16; H, 6.22; N, 3.07.

5.1.49. 2-(Cyclopropylmethyl)-4a-phenethyl-1,2,3,4,9a-

hexahydrobenzofuro[2,3-c]pyridin-6-ol (3f)—Using general procedure E, **9** (200 mg, 0.68 mmol) was converted to **3f** (90 mg, 38%). Mp 170–173 °C; ^1H NMR (500 MHz, CDCl_3): 7.17 (t, J = 6.8 Hz, 3H), 7.09 (d, J = 7.0 Hz, 1H), 7.02 (d, J = 6.9 Hz, 2H), 6.60 (dd, J = 26.5, 11.2 Hz, 2H), 4.52 (d, J = 5.8 Hz, 1H), 3.01 (t, J = 5.8 Hz, 1H), 2.65 (d, J = 5.4 Hz, 1H), 2.47 (dd, J = 38.2, 6.3 Hz, 2H), 2.28–2.14 (m, 4H), 2.06–2.04 (m, 1H), 1.88 (dd, J = 13.4, 4.1 Hz, 2H), 1.75 (dd, J = 12.4, 3.8 Hz, 2H), 0.8 (br s, 1H), 0.5 (d, J = 1.0 Hz, 2H), 0.06 (br s, 2H). ^{13}C NMR (126 MHz, CD_3OD): 165.5, 152.9, 150.3, 142.2, 136.4, 134.5, 128.5, 128.4, 125.9, 115.9, 114.8, 111.0, 110.9, 84.8, 63.7, 54.6, 50.0, 46.7, 42.2, 32.4, 30.5, 8.2, 4.2. HRMS (TOF MS ES^+) calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_2$ ($\text{M}+\text{H}^+$): 350.2120; found: 350.2117. Anal. Calcd for $(\text{C}_{23}\text{H}_{27}\text{NO}_2 \cdot 0.25\text{H}_2\text{O})$: C, 78.04; H, 7.83; N, 3.95; found: C, 78.16; H, 7.95; N, 3.89.

5.1.50. 2-Allyl-4a-phenethyl-1,2,3,4,9a-hexahydrobenzofuro[2,3-c]pyridin-6-

ol (3g)—Using general procedure E, **9** (50 mg, 0.17 mmol) was converted to **3g** (22 mg, 39%). Mp 155–158 °C; ^1H NMR (500 MHz, CDCl_3): 7.21–7.17 (m, 2H), 7.11 (d, J = 7.0 Hz, 1H), 7.04 (d, J = 7.5 Hz, 3H), 6.64–6.56 (m, 2H), 5.79 (t, J = 8.3 Hz, 1H), 5.12–5.09 (m, 2H), 4.48 (t, J = 6.2 Hz, 1H), 2.93 (t, J = 7.9 Hz, 2H), 2.84 (dd, J = 11.8, 5.3 Hz, 1H), 2.50–

2.40 (m, 2H), 2.25 (dd, $J = 11.9, 6.9$ Hz, 1H), 2.09–2.02 (m, 2H), 1.94–1.88 (m, 2H), 1.82–1.71 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): 153.1, 150.1, 142.2, 134.8, 128.5, 128.4, 126.0, 118.5, 114.7, 110.9, 110.8, 84.9, 61.8, 54.5, 49.8, 46.6, 42.0, 32.8, 30.6. HRMS (TOF MS ES^+) calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_2$ ($\text{M}+\text{H}^+$): 336.1964; found: 336.1962. Anal. Calcd for ($\text{C}_{22}\text{H}_{25}\text{NO}_2$): C, 78.77; H, 7.51; N, 4.18; found: C, 78.88; H, 7.54; N, 4.16.

5.1.51. 4a-Phenethyl-2-(2-(trifluoromethyl)phenethyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (3h)—Using general procedure E, **9** (350 mg, 1.18 mmol) was converted to **3h** (210 mg, 38%). Mp 180–183 °C; ^1H NMR (500 MHz, CD_3OD): 7.60 (d, $J = 7.7$ Hz, 1H), 7.45 (t, $J = 7.4$ Hz, 1H), 7.31–7.23 (m, 5H), 7.16 (d, $J = 7.3$ Hz, 1H), 7.10 (d, $J = 7.2$ Hz, 2H), 6.71–6.61 (m, 2H), 4.57 (t, $J = 6.3$ Hz, 1H), 3.01–2.95 (m, 4H), 2.66–2.57 (m, 4H), 2.47 (dt, $J = 31.1, 6.2$ Hz, 2H), 2.30–2.25 (m, 1H), 2.15–2.12 (m, 1H), 2.02–1.80 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD): 153.1, 150.1, 142.2, 138.9, 134.6, 131.9, 131.8, 128.5, 128.4, 126.4, 126.14, 126.09, 126.0, 114.7, 111.0, 110.9, 105.8, 84.9, 77.4, 60.3, 54.5, 49.7, 46.7, 42.1, 32.8, 30.6, 30.1. HRMS (TOF MS ES^+) calcd for $\text{C}_{28}\text{H}_{29}\text{NF}_3\text{O}_2$ ($\text{M}+\text{H}^+$): 468.2150; found: 468.2139. Anal. Calcd for ($\text{C}_{28}\text{H}_{28}\text{NF}_3\text{O}_2$): C, 71.93; H, 6.04; N, 3.00; found: C, 71.65; H, 5.98; N, 2.96.

5.1.52. 4a-Phenethyl-2-(3-(trifluoromethyl)phenethyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ol (3i)—Using general procedure E, **9** (350 mg, 1.18 mmol) was converted to **3i** (240 mg, 43%). Mp 168–171 °C; ^1H NMR (500 MHz, CDCl_3): 7.52–7.48 (m, 2H), 7.42 (dt, $J = 16.4, 8.0$ Hz, 2H), 7.30 (dd, $J = 14.2, 6.9$ Hz, 3H), 7.22 (d, $J = 7.2$ Hz, 1H), 7.15 (d, $J = 7.5$ Hz, 2H), 6.77–6.67 (m, 2H), 4.63 (t, $J = 6.3$ Hz, 1H), 3.05 (dd, $J = 12.0, 5.4$ Hz, 1H), 2.91 (t, $J = 8.0$ Hz, 2H), 2.67 (dt, $J = 16.9, 9.1$ Hz, 4H), 2.53 (ddd, $J = 38.7, 12.3, 5.9$ Hz, 2H), 2.34–2.30 (m, 1H), 2.19–2.17 (m, 1H), 1.96 (dddd, $J = 50.0, 26.9, 13.3, 7.3, 6.1$ Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): 152.8, 150.3, 142.1, 141.0, 134.4, 132.2, 130.9, 130.6, 128.9, 128.5, 128.3, 125.9, 125.5, 123.11, 123.08, 114.8, 110.93, 110.88, 84.6, 59.9, 54.5, 49.8, 46.6, 42.0, 33.3, 32.5, 30.5. HRMS (TOF MS ES^+) calcd for $\text{C}_{28}\text{H}_{29}\text{NF}_3\text{O}_2$ ($\text{M}+\text{H}^+$): 468.2150; found: 468.2139. Anal. Calcd for ($\text{C}_{28}\text{H}_{28}\text{NF}_3\text{O}_2$): C, 71.93; H, 6.04; N, 3.00; found: C, 71.80; H, 6.13; N, 2.93.

5.2. Pharmacology

5.2.1. Opioid binding affinity—As previously described,^{1,11} the recombinant CHO cells (hMOR-CHO, hDOR-CHO and hKOR-CHO) were produced by stable transfection with the respective human opioid receptor cDNA, and provided by Dr. Larry Toll (SRI International, CA). The cells were grown in plastic flasks in DMEM (90%) (hDOR-CHO and hKOR-CHO) or DMEM/F-12 (45/45%) medium (hMOR-CHO) containing 5% FBS (Invitrogen), 5% FetalClone II (HyClone), and Geneticin (G-418: 0.10–0.2 mg/ml) (Invitrogen) under 95% air/5% CO_2 at 37 °C. Cell monolayers were harvested and frozen in –80 °C. The hKOR-CHO, hMOR-CHO and hDOR-CHO cells are used for opioid binding experiments. For the [^{35}S]-GTP- γ -S binding experiments, we use hKOR-CHO and hMOR-CHO cells for assaying KOR and MOR receptor function. Currently, we use the NG108-15 neuroblastoma $\times$ glioma cell for the DOR [^{35}S]-GTP- γ -S binding assay, and obtain an excellent signal-to-noise ratio. In summary, we use the hDOR-CHO cells for DOR binding assays, and the NG108-15 cells for the DOR [^{35}S]-GTP- γ -S binding assay.

As noted formerly,^{1,12} [^3H][D-Ala²-MePhe⁴, Gly⁵]enkephalin ([^3H]DAMGO, SA = 44–48 Ci/mmol) was used to label MOR, [^3H][D-Ala², D-Leu⁵]enkephalin ([^3H]DADLE, SA = 40–50 Ci/mmol) to label DOR and [^3H](–)-U69,593 (SA = 50 Ci/mmol) to label KOR binding sites. On the day of the assay, cell pellets were thawed on ice for 15 min then homogenized with a polytron in 10 mL/pellet of ice-cold 10 mM Tris–HCl, pH 7.4. Membranes were then centrifuged at 30,000 $\times g$ for 10 min, resuspended in 10 mL/pellet ice-

cold 10 mM Tris-HCl, pH 7.4 and again centrifuged $30,000 \times g$ for 10 min. Membranes were then resuspended in 25 °C 50 mM Tris-HCl, pH 7.4 (~100 mL/pellet hMOR-CHO, 50 mL/pellet hDOR-CHO and 120 mL/pellet hKOR-CHO). All assays took place in 50 mM Tris-HCl, pH 7.4, with a protease inhibitor cocktail [bacitracin (100 µg/mL), bestatin (10 µg/mL), leupeptin (4 µg/mL) and chymostatin (2 µg/mL)], in a final assay volume of 1.0 mL. All drug dilution curves were made up with buffer containing 1 mg/mL BSA. Nonspecific binding was determined using 20 µM levallorphan ([³H]DAMGO and [³H]DADLE) and 1 µM (-)-U69,593 (for [³H]U69,593 binding). [³H]Radioligands were used at ~2 nM concentrations. Triplicate samples were filtered with Brandel Cell Harvesters (Biomedical Research & Development Inc., Gaithersburg, MD), over Whatman GF/B filters, after a 2 h incubation at 25 °C. The filters were punched into 24-well plates to which was added 0.6 mL of LSC-cocktail (Cytoscint). Samples were counted, after an overnight extraction, in a Trilux liquid scintillation counter at 44% efficiency. Opioid binding assays had ~30 µg protein per assay tube. Inhibition curves were generated by displacing a single concentration of radioligand by 10 concentrations of drug. The pooled data of three experiments (typically 30 data points) were fit to the two-parameter logistic equation for the best-fit estimates of the IC_{50} and N values: $Y = 100 / (1 + ([INHIBITOR] / IC_{50})^N)$, where 'Y' is the percent of control value. K_i values for test drugs are calculated according to the standard equation: $K_i = IC_{50} / (1 + [radioligand] / K_d)$. For the [³H]radioligands, the following K_d values (nM ± SD, $n = 3$) were used in the K_i calculation: [³H]DAMGO (0.93 ± 0.04), [³H]DADLE (1.9 ± 0.3) and [³H](-)-U69,593 (11 ± 0.6).

5.2.2. [³⁵S]GTP-γ-S binding assays—As previously described,^{1,12} the assays were conducted with minor modifications of published methods.¹³ In this description, buffer 'A' is 50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 10 mM MgCl₂, 1 mM EDTA and buffer 'B' is buffer A plus 1.67 mM DTT and 0.15% BSA. On the day of the assay, cells were thawed on ice for 15 min and homogenized using a polytron in 50 mM Tris-HCl, pH 7.4, containing 4 µg/mL leupeptin, 2 µg/mL chymostatin, 10 µg/mL bestatin and 100 µg/mL bacitracin. The homogenate was centrifuged at $30,000 \times g$ for 10 min at 4 °C, and the supernatant discarded. The membrane pellets were resuspended in buffer B and used for [³⁵S]GTP-γ-S binding assays. Test tubes received the following additions: 50 µL buffer A plus 0.1% BSA, 50 µL GDP in buffer A/0.1% BSA (final concentration = 40 µM), 50 µL drug in buffer A/0.1% BSA, 50 µL [³⁵S]-GTP-γ-S in buffer A/0.1% BSA (final concentration = 50 pM), and 300 µL of cell membranes (50 µg of protein) in buffer B. The final concentrations of reagents in the [³⁵S]GTP-γ-S binding assays were: 50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 10 mM MgCl₂, 1 mM EDTA, 1 mM DTT, 40 µM GDP and 0.1% BSA. Incubations proceeded for 3 h at 25 °C. Nonspecific binding was determined using GTP-γ-S (40 µM). Bound and free [³⁵S]GTP-γ-S was separated by vacuum filtration (Brandel) through GF/B filters. The filters were punched into 24-well plates to which was added 0.6 mL LSC-cocktail (Cytoscint). Samples were counted, after an overnight extraction, in a Trilux liquid scintillation counter at 27% efficiency.

For the [³⁵S]GTP-γ-S binding experiments,^{1,12} K_e values were determined using the 'shift' experimental design, agonist (DAMGO) dose-response curves were generated, using hMOR-CHO cells, in the absence and presence (ten points/curve) of a test compound. The data of several experiments, three or more, were pooled, and the K_e values were calculated according to the equation: $[Test\ drug] / (EC_{50-2} / EC_{50-1} - 1)$, where EC_{50-2} is the EC_{50} value in the presence of the test drug and EC_{50-1} is the value in the absence of the test drug.

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Scheme 1.

Reagents and conditions: (a) *n*-BuLi, aralkyl or alkyl Br; (b) (1) NBS, (2) NaBH₃CN; (c) HBr, reflux; (d) Et₃N, sealed tube, 100 °C. Yields are shown in Table 1.

Scheme 2.

Reagents and conditions: (a) Ac₂O (neat), reflux, 71%; (b) (1) proton sponge, Troc-Cl, (2) K₂CO₃, MeOH, (3) Zn, AcOH, 77%; (c) (1) RBr, DMF, NaHCO₃, (2) K₂CO₃, MeOH, 38–56% (see Section 5 for details).

Table 1Yields of *N*-methyl substituted compounds

Compd	R	5 (%)	6 (%)	7 (%)	2 (%)
a	PhCH ₂	76	42	96	64
b	Ph(CH ₂) ₂	<i>a</i>			
c	Ph(CH ₂) ₃	41	81	83	83
d	Ph(CH ₂) ₄	49	85	83	86
e	Ph(CH ₂) ₅	70	63	<i>c</i>	94
f	CH ₃	67	30	<i>c</i>	49
g	CH ₂ CH ₃	<i>b</i>			
h	(CH ₂) ₂ CH ₃	45	48	87	76
i	(CH ₂) ₃ CH ₃	82	48	<i>c</i>	92
j	(CH ₂) ₄ CH ₃	69	39	<i>c</i>	65
k	4-F-Ph(CH ₂) ₂	35	75	80	62
l	2-F-Ph(CH ₂) ₂	34	82	95	64

^aSee Iyer et al.⁶^bSee Hutchison et al.²^cTaken directly to next step (diol not purified).

Table 2

Opioid receptor binding studies

Compd	K_i (nM $\pm$ SD)							
	R	R ₁	μ^a	b	c	μ'	/ μ	/
2a	Me	Ph(CH ₂) ₂	60 $\pm$ 5	64 $\pm$ 5	2882 $\pm$ 259	0.9	48	45
2b	Me	PhCH ₂	66 $\pm$ 5	551 $\pm$ 37	3544 $\pm$ 167	0.1	54	6
2c	Me	Ph(CH ₂) ₃	165 $\pm$ 18	36 $\pm$ 2	238 $\pm$ 10	5	1.4	7
2d	Me	Ph(CH ₂) ₄	45 $\pm$ 5	29 $\pm$ 1	163 $\pm$ 19	2	4	6
2e	Me	(CH ₂) ₅ Ph	28 $\pm$ 2	75 $\pm$ 4	71 $\pm$ 9	0.4	3	0.95
2f	Me	CH ₃	425 $\pm$ 45	>10,000	4182 $\pm$ 240	0.04	>10	>0.4
2g ^d	Me	CH ₂ CH ₃	19 $\pm$ 0.5	212 $\pm$ 13	>5000	0.09	>263	>23
2h	Me	(CH ₂) ₂ CH ₃	84 $\pm$ 10	479 $\pm$ 29	1651 $\pm$ 162	0.2	20	3
2i	Me	(CH ₂) ₃ CH ₃	97 $\pm$ 5	207 $\pm$ 21	1913 $\pm$ 70	0.5	20	9
2j	Me	(CH ₂) ₄ CH ₃	91 $\pm$ 5	33 $\pm$ 3.3	971 $\pm$ 55	3	11	29
2k	Me	4-F-Ph(CH ₂) ₂	166 $\pm$ 14	128 $\pm$ 8	2879 $\pm$ 131	1.3	17	22
2l	Me	2-F-Ph(CH ₂) ₂	96 $\pm$ 8	52 $\pm$ 2	2217 $\pm$ 90	2	23	43
3a	Ph(CH ₂) ₂	Ph(CH ₂) ₂	9 $\pm$ 0.8	39 $\pm$ 4	730 $\pm$ 48	0.2	81	19
3b	Ph(CH ₂) ₃	Ph(CH ₂) ₂	49 $\pm$ 3	111 $\pm$ 11	670 $\pm$ 26	0.4	14	6
3c	4-F-Ph(CH ₂) ₂	Ph(CH ₂) ₂	22 $\pm$ 3	34 $\pm$ 3	721 $\pm$ 40	0.7	33	21
3d	2-F-Ph(CH ₂) ₂	Ph(CH ₂) ₂	7 $\pm$ 0.43	26 $\pm$ 1	826 $\pm$ 67	0.3	118	32
3e	4-CF ₃ -Ph(CH ₂) ₂	Ph(CH ₂) ₂	8 $\pm$ 0.4	26 $\pm$ 2	2459 $\pm$ 222	0.3	307	95
3f	CPM ^e	Ph(CH ₂) ₂	5 $\pm$ 0.36	24 $\pm$ 2	16 $\pm$ 0.75	0.2	3	0.7
3g	CH ₂ CH=CH ₂	Ph(CH ₂) ₂	23 $\pm$ 2	55 $\pm$ 4	80 $\pm$ 3	0.4	3	1.5
3h	2-CF ₃ -Ph(CH ₂) ₂	Ph(CH ₂) ₂	174 $\pm$ 17	136 $\pm$ 14	1922 $\pm$ 144	1.3	11	14
3i	3-CF ₃ -Ph(CH ₂) ₂	Ph(CH ₂) ₂	16 $\pm$ 2	63 $\pm$ 5	541 $\pm$ 44	0.3	34	9
	Morphine		2.6 $\pm$ 0.01	605 $\pm$ 36	299 $\pm$ 49			
	DAMGO		1.2 $\pm$ 0.1	1500 $\pm$ 170				
	U69,593		>2 μ M	>12 μ M	3.5 $\pm$ 0.3			

Assays were conducted using CHO cells that were stably transfected and express the μ -, δ -, or κ -opioid receptors, respectively. All results $n = 3$.

^a[³H]DAMGO binding.

^b[³H]DADLE binding.

^c[³H]u69,593 binding.

^dData from Hutchison et al.²

^eCPM = cyclopropylmethyl.

Table 3

Agonist (ED_{50} , nM, and E_{max}) and antagonist (K_e , nM) activities from [35 S]GTP- γ -S functional assays

Compd	R	μED_{50} & E_{max}^a	ED_{50} & E_{max}^a	ED_{50} & E_{max}^a	μK_e	K_e	K_e
3a	Ph(CH ₂) ₂	567 $\pm$ 93 75 $\pm$ 3	395 $\pm$ 6 29 $\pm$ 1	ND	229 $\pm$ 10	258 $\pm$ 45	ND
3c	4-F-Ph(CH ₂) ₂	1186 $\pm$ 211 43 $\pm$ 2	350 $\pm$ 110 29 $\pm$ 1	ND	218 $\pm$ 15	213 $\pm$ 17	ND
3d	2-F-Ph(CH ₂) ₂	248 $\pm$ 35 82 $\pm$ 2	N	ND	48 $\pm$ 8	37 $\pm$ 7	2160 $\pm$ 252
3e	4-CF ₃ -Ph(CH ₂) ₂	2149 $\pm$ 556 60 $\pm$ 5	1250 $\pm$ 261 46 $\pm$ 3	ND	111 $\pm$ 13	827 $\pm$ 97	ND
3f	CPM ^b	N	N	135 $\pm$ 36 18 $\pm$ 0.01	8 $\pm$ 1	64 $\pm$ 10	32 $\pm$ 8
3g	CH ₂ CH=CH ₂	N	ND	ND	37 $\pm$ 7	43 $\pm$ 3	ND
3i	3-CF ₃ -Ph(CH ₂) ₂	N	ND	ND	248 $\pm$ 36	455 $\pm$ 47	ND
DAMGO		34 $\pm$ 4 100 $\pm$ 2					
SNC80			55 $\pm$ 10 104 $\pm$ 1				
(-)-U50,488				27 $\pm$ 3 99 $\pm$ 2			
Naloxone					2.3 $\pm$ 0.3		

ND = not determined; N = no agonist activity.

^aCPM = cyclopropylmethyl.

^b E_{max} = the percent the compound stimulated GTP- γ -S binding as compared to the stimulation produced by 1000 nM DAMGO, 500 nM SNC80 or 500 nM (-)-U50,488 (when the% stimulation is considerably less than 100%, the compound is said to be a partial agonist).