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Probes for narcotic receptor mediated phenomena. 40. *N*-Substituted *cis*-4a-ethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ols ☆

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Geometry optimization
Superposition

ABSTRACT

A series of *N*-substituted *rac-cis*-4a-ethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ols have been prepared using a simple synthetic route previously designed for synthesis of related *cis*-2-methyl-4a-alkyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols. The new phenolic compounds, where the aromatic hydroxy moiety is situated *ortho* to the oxygen atom in the oxide-bridged ring, do not interact as well as the pyridin-6-ols with opioid receptors. The *N*-*para*-fluorophenethyl derivative had the highest μ-opioid receptor affinity of the examined compounds (K_i = 0.35 μM).

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1. Introduction

Hexahydrobenzofuro[2,3-*c*]pyridin-8-ols (**1a**–**f**, Fig. 1) and hexahydrobenzofuro[2,3-*c*]pyridin-6-ols[1,2] (**2**, Fig. 1) are partial structures of the oxide-bridged phenylmorphan class of opioids (Fig. 1)[3–14] and although they appear to be structurally similar to the d-series of the oxide-bridged phenylmorphans (**3a**, Fig. 1)[1] we have found that they can assume a conformation that is closer to morphine than to the oxide-bridged phenylmorphans and that their μ-opioid affinity and activity is likely to be due to their ability to attain that conformation.[1] Hutchison et al.[2] found that *N*-phenethyl- and *N*-cyclopropylmethyl-substituted 1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols, had high affinity for μ-opioid receptors (K_i = 0.9 and 4 nM, respectively) and were potent antinociceptives. We have determined that the high affinity of the *N*-phenethyl analogue was ascribable to the 4a*S*,9a*R* enantiomer (K_i = 0.7 nM).[1] In most of the well-known epoxymorphinans, morphinans, 6,7-benzomorphans, and 5-phenylmorphans,[15] the phenolic hydroxyl moiety is situated *meta* to the piperidine ring. The phenolic hydroxy group is also oriented in a *meta*-position with respect to the piperidine ring in the hexahydrobenzofuro[2,3-*c*]pyridin-6-ols (**2**, Fig. 1), and *para* to the oxygen atom in the dihydrofuran ring of the epoxymorphinans. In the hexahydrobenzofuro[2,3-*c*]pyridin-8-ols (**1a**–**f**, Fig. 1), as in the hexahydrobenzofuro[2,3-*c*]pyridin-6-ols, the phenolic hydroxyl moiety is *meta*-oriented to the piperidine ring and, unlike the pyridin-6-ols, oriented *ortho* to the oxygen atom in the dihydrofuran ring. Both the pyridin-6-ols and the pyridin-8-ols might also be expected to show similar affinity for opioid receptors if the *meta*-orientation to the piperidine ring is essential for interaction with opioid receptors. Also, a 7,8-dimethoxy compound in a hexahydrobenzofuro[2,3-*c*]pyridine structure (**2a**, Fig. 1), where the methoxy groups are *meta*- and *para*-oriented to the piperidine ring and *ortho*- and *meta*-oriented to the oxygen in the dihydrofuran ring, was noted, in a patent by Koelsch in 1957,[16,17] to have 'analgesic' action. Some ostensibly similar C-6 and C-8 hydroxy substituted oxide-bridged phenylmorphans (**3**) have been found to be μ-agonists (*N*-phenethyl substituted *para*-e and *para*-f oxide-bridged phenylmorphans, Fig. 1) and κ-antagonists (*N*-phenethyl substituted *ortho*-b and *ortho*-f oxide-bridged phenylmorphans, Fig. 1).[13,14] Based on the data in the Koelsch patent[16] and on our work with oxide-bridged phenylmorphans, we thought that it would be of interest to examine *N*-substituted hexahydrobenzofuro[2,3-*c*]pyri-

☆ See Ref. 1.

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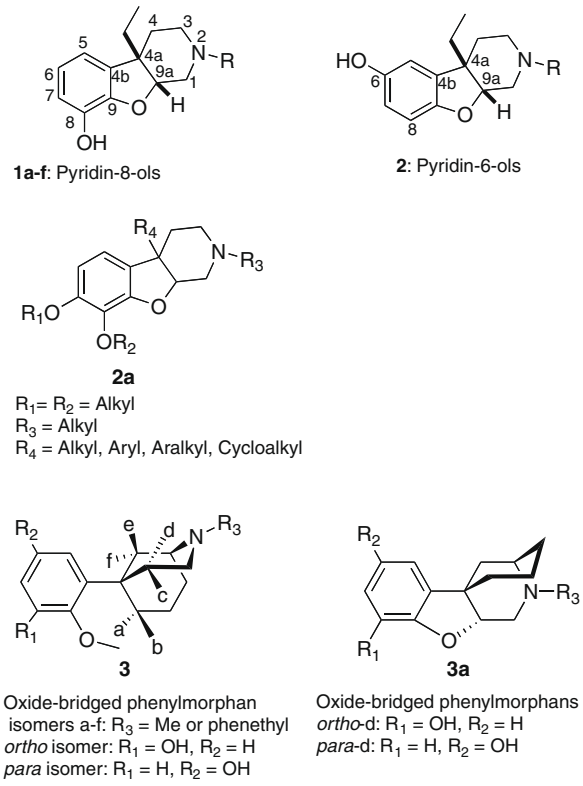


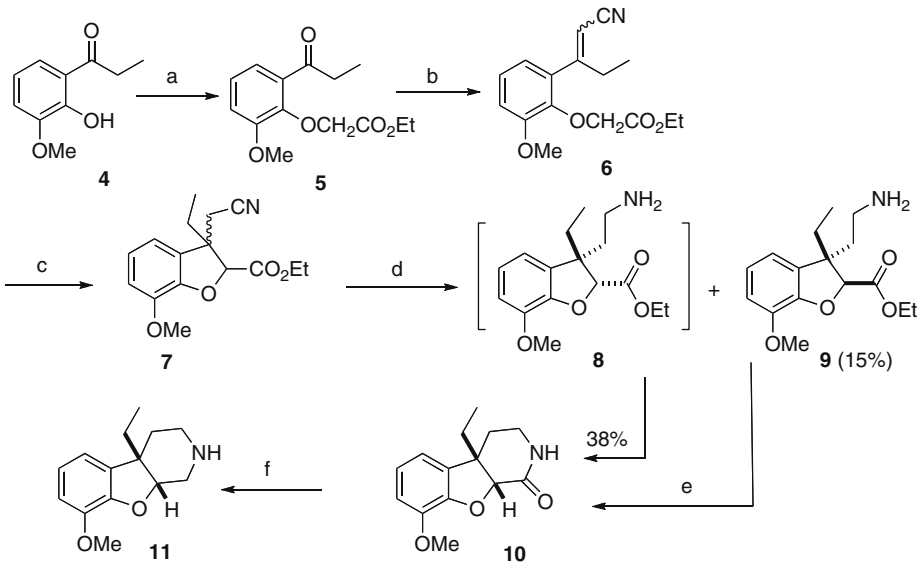
Figure 1. General structures.

din-8-ols (**1a**–**f**, Fig. 1) to see if they interacted with opioid receptors. These compounds were prepared both by the well-known route and by an improved, relatively simple, synthetic procedure that was devised for related compounds.[18] This procedure also enables the synthesis of compounds with new alkyl, or aralkyl moieties at C-4a. In addition to the C4a ethyl group, we prepared one new compound with a phenethyl moiety at that position, as a proof of concept. The phenethyl moiety was chosen because aromatic rings in an aralkyl moiety are known to influence opioid receptor binding and pharmacological activity when present in a morphinan-like structure (e.g., aralkyl amides[19] at C-6, cinnamoyl esters[20] or phenylpropyl ethers[21] at C-14, or various other substituents on the nitrogen atom).[22–24]

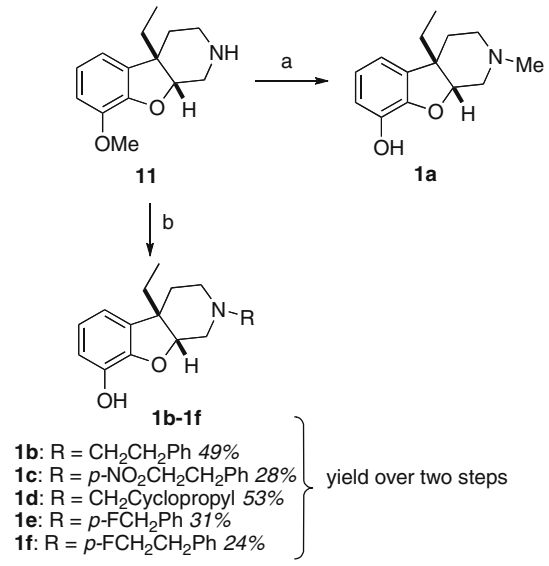
2. Results and discussion

2.1. Chemistry

The basic route for assembling the *cis*-benzofuropyridin-8-ol system (**1a**–**f**, Fig. 1) was initially based on the method developed by Hutchison et al.[2] Starting from the known hydroxypropiophenone **4** (Scheme 1),[25] alkylation with ethyl bromoacetate in DMF with K_2CO_3 afforded the ester **5** in 91% yield. This material was subjected to the Horner–Emmons reaction with diethyl(cyanomethy1)phosphonate and NaH in THF to give the alkenic cyano ester **6** in 90% yield as a mixture of alkene stereoisomers (Scheme 1). The isomeric mixture was carried through without separation and treated with fresh sodium ethoxide to yield the benzofuronitrile **7** via an intramolecular Michael addition as a 1:l mixture of diastereomers in 82% yield. These diastereomers were subjected to hydrogenation under pressure with platinum oxide in acetic acid to afford a separable mixture of *cis*-lactam **10** in 38% yield and *trans*-amine ester **9** in 15% yield. As reported by the Hutchison group,[2] the *cis*-amine **8** cyclizes in situ under the acidic reaction conditions to give the *cis*-lactam **10** whereas *trans*-amine **9** fails to undergo a similar cyclization to form the presumably strained *trans*-lactam under the same conditions. Upon subjecting the *trans*-amine **9** to epimerizing conditions (sodium ethoxide in refluxing ethanol), *cis*-lactam **10** could be isolated in 82% yield, and the *trans*-lactam was not observed. Though an appreciable amount of the *cis*-lactam was obtained for the synthesis, the inconsistent yields from the hydrogenation step pointed to the need for some modification of the synthetic route. The stereochemistry of the ring junction for benzofurolactam **10** as well as for all subsequent intermediates was assigned on the basis of the ^{1}H NMR spectra of **10** in which the proton on C-9a showed $J_{AX} = J_{BX} = 5.0–6.0$ Hz, a result consistent with a *cis* ring junction. Additionally, 2D NOESY experiments provided further proof for the *cis* stereochemistry. Lactam **10** was reduced under refluxing LAH conditions to the amine **11**, which represents the common intermediate from which the new racemic compounds **1a**–**1f** are derived.



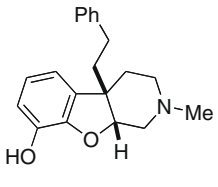
Scheme 1. Synthesis of *rac*-4a-ethyl-8-methoxy-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridine. Reagents and conditions: (a) K_2CO_3, $BrCH_2CO_2Et$, DMF, reflux, 91%; (b) NaH, $(OEt)_2OPCH_2CN$, 90%; (c) NaOEt, EtOH, reflux, 82%; (d) Pt/C, AcOH, H_2, 50 psi; (e) NaOEt/EtOH, 82%; (f) LAH, THF, reflux, 92%.



Scheme 2. Synthesis of *rac*-*N*-substituted 4a-ethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ols. Reagents and conditions: (a) (1) HCHO/MeOH/PtO_2, H_2, 1 atm; (2) BBr_3, 53% over two steps; (b) (1) alkyl bromide/$NaHCO_3$; (2) BBr_3.

The conversion of amine **11** to *cis*-benzofuropyridin-8-ols **la** and **1b**–**1f** is shown in Scheme 2. Analogue **la** was prepared by the treatment of amine with HCHO in MeOH under hydrogenating conditions in presence of catalytic Pd/C, followed by subsequent O-demethylation. Analogues **1b**–**1f** were obtained by directly alkylating the amine with an alkyl halide/$NaHCO_3$ in DMF system followed by BBr_3 deprotection of the aromatic methoxy group (see General Method for the synthesis of **1b**–**f** in the Section 4).

Since the hydrogenation step gave inconsistent yields, we focused on modifying the synthesis of **1a**, using a procedure that would enable introduction of alkyl or aralkyl substituents at C-4a, to obtain, for example, compound **12**.



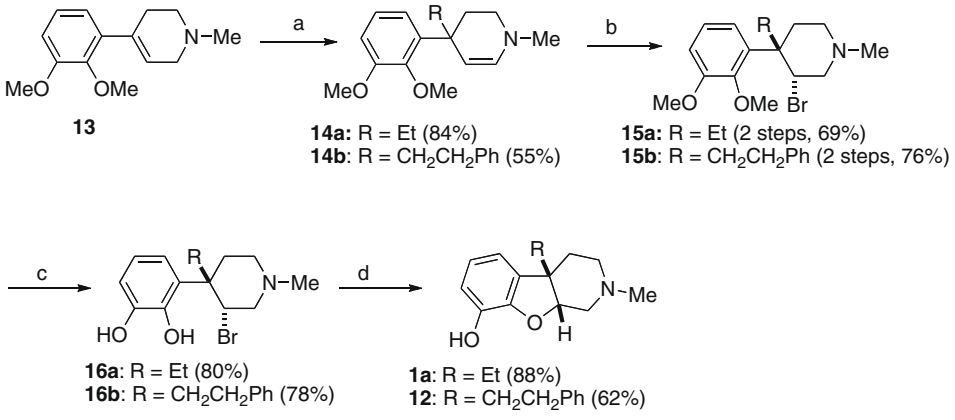
12

Toward that end the starting alkene substrate **13** (Scheme 3) was assembled via known literature procedures.[6] With the alkene **13** in hand, functionalization leading to the enamine **14** bearing the desired ethyl group, or any alkyl or aralkyl group was easily achieved using the method of Evans et al.[26] and earlier reports from our laboratory.[6,7,9–11] A simple two-step procedure, originally conceived for the synthesis of the pyridin-6-ols,[18] involved bromination of the alkene with NBS followed by $NaCNBH_3$ reduction in acidic medium and gave the late stage intermediate **15**. The relative stereochemistry of the bromo compound **15a** was determined by single crystal X-ray diffraction analysis of the salt **15a**·HCl (Fig. 2).

Hydrobromic acid-assisted deprotection of the two aromatic O-methyl groups gave the diol **16** (Scheme 3) that is the needed template for the base-mediated oxide-ring formation. The base Et_3N worked well in this reaction. Refluxing the diol in methanolic Et_3N gave **1a** (Scheme 3) in excellent yield. The same route was put to use in the synthesis of **12**. Following similar manipulations noted in Scheme 3, the analogue **12** was synthesized and its stereochemistry was confirmed by X-ray diffraction analysis (Fig. 2).

2.2. Opioid receptor binding studies

The *N*-methyl substituted pyridin-8-ol, **1a**, had little affinity for opioid receptors (K_i = 795 nM, Table 1). It had 40 times less affinity for μ-receptors than the comparable pyridin-6-ol. Even a greater difference between the pyridin-8- and 6-ols was seen with the *N*-cyclopropylmethyl and *N*-phenethyl analogues (K_i = 4670 and 1630 nM, respectively, in Table 1), both of these pyridin-8-ols showing about three orders of magnitude less affinity for μ-receptors than the comparable pyridin-6-ols. Clearly, interaction with the μ-receptor was greatly facilitated by a phenolic hydroxyl at the C-6 position. We formerly observed, in overlay studies with the pyridin-6-ols, that the likely pharmacologically active conformer of 4a*S*,9a*R*-(−)-*cis*-4a-ethyl-2-(2-phenylethyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (**17**, Table 1) had its aromatic hydroxyl group is in the same general area of three-dimensional space as that of morphine.[1] In order to map the spatial region of these phenolic hydroxyl groups with respect to the phenolic hydroxyl group of morphine, geometry optimization on compound **1b** and its superposition onto morphine were carried out as previously noted.[1] While the backbone of both **1b** and **17** has considerable overlap with morphine, it can be seen in Figure 3 that the overlap between the phenolic hydroxy groups of compound **17** and morphine cannot be attained by compound **1b**. The effect of the *N*-substituent on μ-receptor



Scheme 3. Simplified synthesis of *rac*-hexahydrobenzofuro[2,3-*c*]pyridin-8-ols. Reagents and conditions: (a) *n*-BuLi −40 °C, alkyl bromide; (b) (1) NBS, THF; (2) $NaCNBH_3$, HCl; (c) 48% HBr, reflux; (d) Et_3N, 100 °C, sealed tube.

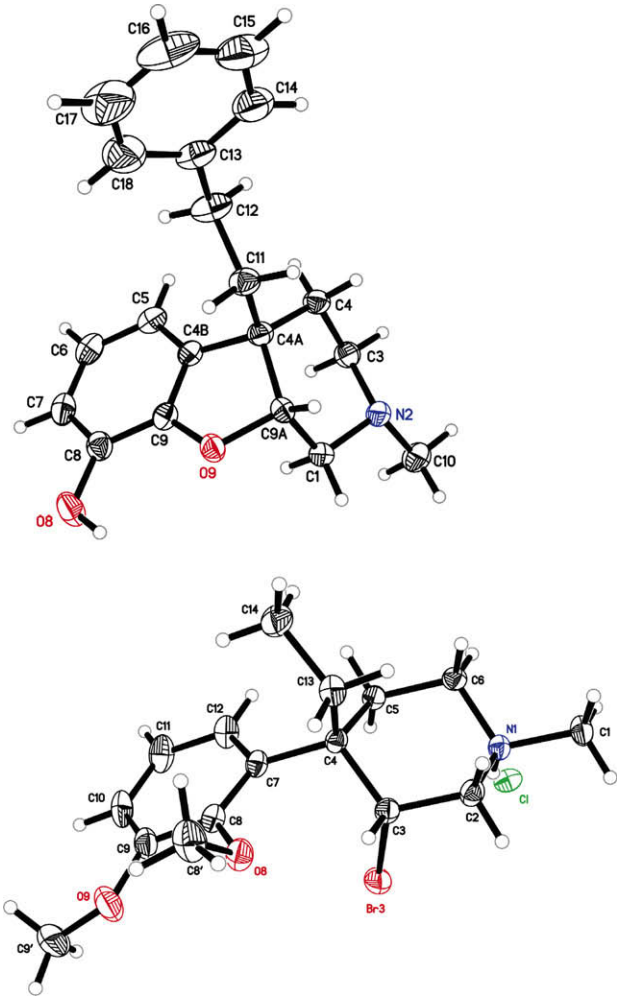
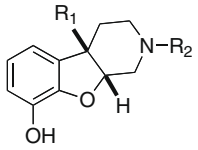
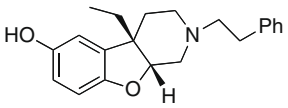


Figure 2. X-ray crystal structure of 2-methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (**12**, top) and 3-bromo-4-(2,3-dimethoxyphenyl)-4-ethyl-1-methylpiperidine hydrochloride (**15a**·HCl, bottom). Displacement ellipsoids are shown at the 50% level.

Table 1
[^{3}H] Binding data for *rac-cis*-benzofuro[2,3-*c*]pyridin-8-ols



rac-**1a-f**, **12**



4a*S*,9a*R*-**17**[1]

Cmpd	R_1	R_2	K_i (nM ± SD)		
			μ[a]	δ[b]	κ[c]
1a	Et	Me	795 ± 65	7480 ± 890	>10,000
1b	Et	CH_2CH_2Ph	1630 ± 170	7210 ± 670	2220 ± 290
1c	Et	*p*-$NO_2CH_2CH_2Ph$	670 ± 50	2260 ± 145	720 ± 40
1d	Et	Cyclopropylmethyl	4670 ± 350	6150 ± 470	10,000 ± 1500
1e	Et	*p*-FCH_2Ph	>2700	>4500	3380 ± 205
1f	Et	*p*-FCH_2CH_2Ph	354 ± 45	>4500	935 ± 60
12	PhEt	Me	740 ± 86	>4300	2880 ± 259
17[1]	—	—	0.70 ± 0.06	75 ± 8.8	88 ± 8

Assays were conducted using CHO cells, which were stably transfected and express the μ-, δ- or κ-opiate receptors, respectively. All results $n = 3$.
[a] [^{3}H]DAMGO binding.
[b] [^{3}H]DADLE binding.
[c] [^{3}H]U69,593 binding.

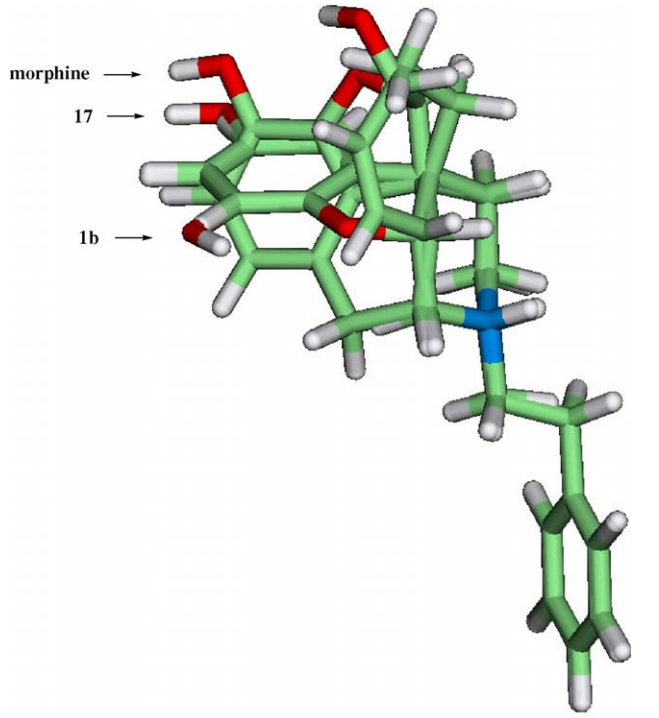


Figure 3. Overlay of the piperidine ring of conformers of compounds **1b** and **17**[1] onto that of morphine, illustrating the topographical similarity of the high affinity ligand **17** with morphine, and the lack of overlap of the oxygen atoms in **1b**, a compound with little affinity for μ-opioid receptors. The distance between the phenolic oxygen atoms of **17** and morphine is 1.4 Å, and it is 4.5 Å between the phenolic oxygen atoms in **1b** and morphine.

affinity in the pyridin-8-ols was relatively slight, and the bulky phenethyl moiety at C-4a in **12** (K_i = 740 nM) did not appear to have much influence on affinity, possibly because of the overwhelming detrimental effect of the poorly situated phenolic hydroxyl group. Compared with the ethyl group in **1a** (K_i = 795 nM); the phenethyl's aromatic ring in the spatial area around C4a did not appear to influence interaction with the opioid receptor. Of the compounds examined, the *N*-*p*-fluorophenethyl substituted pyridin-8-ol (**1f**) had the highest affinity for the μ-receptor, it had five fold better affinity than the unsubstituted *N*-phenethyl compound **1b** (K_i = 354 nM vs 1630 nM for **1b**). The fluorine atom in the phenyethyl moiety at C4a increased receptor affinity in the pyridin-8-ols. That finding is of interest and will be explored in further studies in the pyridin-6-ol series.

3. Conclusion

A surprisingly large difference in binding affinity was found between comparably substituted pyridin-6-ol and pyridin-8-ol compounds. Some showed about a thousand-fold difference in their ability to bind to μ-opioid receptors. As we discussed with the pyridin-6-ols,[1] compound **17** was able to reach a conformation in which its phenolic hydroxyl group was in the same vicinity as that of morphine, whereas compound **1b** could not attain such overlap. Thus, it is apparent that the spatial location of the phenolic hydroxyl in these *cis*-4a-alkyl or aralkyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6 and -8-ols, not just the *meta*-orientation to the piperidine ring as in the well-known epoxymorphinans, morphinans, 6,7-benzomorphans, and 5-phenylmorphans, is one of the most important factors in determining their ability to interact with opioid receptors.

4. Experimental

4.1. Chemistry

4.1.1. General

Mass spectra (CIMS) were obtained using a Finnigan 4600 mass spectrometer unless otherwise noted. ^{1}H nuclear magnetic resonance (^{1}H 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 Atlantic Microlabs, Atlanta, GA.

4.1.2. Ethyl 2-(2-methoxy-6-propionylphenoxy)acetate (5)

A mixture of 1-(2-hydroxy-3-methoxyphenyl)propan-1-one (**4**) (50.0 g, 0.28 mol),[25] ethyl bromoacetate (37.0 mL, 0.33 mol) and powdered K_2CO_3 (77.4 g, 0.56 mol) in dry DMF (750 mL) was vigorously stirred at 90 °C for 6 h. The reaction mixture was cooled and then poured onto ice water (200 mL) and the product was extracted with Et_2O (2 × 300 mL). After drying over $MgSO_4$, the solvent was removed in vacuo and the residue was distilled under aspirator pressure at 200 °C to give 67.7 g (91%) of **5** as a colorless viscous oil. IR (neat): 1756, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (dd, 2H, J = 2.0 and 8.0 Hz), 7.01 (dd, 1H, J = 2.0 and 7.5 Hz), 4.67 (s, 2H), 4.22 (q, 2H, J = 7.0 Hz), 3.85 (s, 3H), 3.05 (q, 2H, J = 7.0 Hz), 1.26 (t, 3H, J = 7.0 Hz), 1.15 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.06, 169.21, 152.14, 145.54, 134.67, 124.54, 120.77, 115.26, 69.83, 61.14, 56.07, 36.79, 14.23, 8.31; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{19}O_5$ (M+H)$^+$: 267.1232; found: 267.1227. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.04; H, 6.88.

4.1.3. Ethyl 2-(2-(1-cyanobut-1-en-2-yl)-6-methoxyphenoxy)acetate (6)

To an ice-cooled suspension of 60% NaH (3.6 g, 90.0 mmol), which had been washed free of oil with hexane in THF (300 mL), was added diethyl(cyanomethy1)phosphonate (13.2 mL, 82.5 mmol) in a dropwise fashion. After 15 min at room temperature, a solution of **5** (20.0 g, 75.0 mmol) in THF (350 mL) was added dropwise at 0 °C. After 2 h at 0 °C, the reaction mixture was poured on ice water and the product was extracted with Et_2O. After drying over $MgSO_4$, the solvent was removed in vacuo to give a dark yellow oil. Purification by flash chromatography using 30% EtOAc in hexanes gave 19.5 g (90%) of an isomeric mixture **6** as a yellow oil. IR (neat) 1746, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (mixture of isomers) 7.20 (m, 1H), 7.02 (m, 1H), 6.84 (m, 1H), 5.53 (s, 1H), 4.64 (s, 2H), 4.36 (m, 2H), 3.95 (s, 3H), 3.03 (q, 2H, J = 7.2 Hz), 1.38 (m, 3H), 1.15 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (mixture of isomers) 168.86, 165.80, 152.13, 144.27, 132.53, 124.648, 124.53, 12 152.133, 204.06, 169.21, 152.14, 145.54, 134.67, 124.64, 124.53, 121.08, 120.88, 116.93, 113.43, 113.25, 98.28, 96.65, 69.79, 61.08, 55.92, 55.83, 31.24, 28.67, 14.23, 12.73, 120.77, 115.26, 69.83, 61.14, 56.07, 36.79, 14.23, 8.31; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{20}NO_4$ (M+H)$^+$: 290.1392; found: 290.1390. Anal. Calcd for $C_{16}H_{19}NO_4{\cdot}0.25H_2O$: C, 65.40; H, 6.69; N, 4.77. Found: C, 65.36; H, 6.78; N, 4.46.

4.1.4. Ethyl 3-(cyanomethyl)-3-ethyl-7-methoxy-2,3-dihydrobenzofuran-2-carboxylate (7)

Compound **6** (17.0 g, 58.8 mmol) in 20 mL EtOH was carefully added to a solution of freshly cut sodium metal (850 mg, 37.0 mmol) in EtOH (20 mL). The mixture was heated at 80 °C for 90 min. After cooling to room temperature, the reaction mixture was poured onto ice water, and the product was treated with 37% HCl (5 mL) to neutralize the excess base. The organic layer was extracted with Et_2O (2 × 200 mL), and after drying over $MgSO_4$ the solvent was removed in vacuo to give a dark oil. Purification by flash chromatography using 50% EtOAc in hexanes gave 14.0 g (82%) of isomeric mixture **7** as a sticky solid. IR (neat) 1755, 1493 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (single isomer) 6.96 (t, 1H, J = 7.5 Hz), 6.85 (t, 2H, J = 7.5 Hz), 5.07 (s, 1H), 4.35 (m, 2H), 3.89 (s, 3H), 2.99 (d, 1H, J = 16.5 Hz), 2.89 (d, 1H, J = 16.5 Hz), 1.86 (m, 1H), 1.67 (m, 1H), 1.33 (t, 3H, J = 7.5 Hz), 0.80 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ single isomer) 168.03, 146.54, 145.07, 129.77, 122.84, 116.98, 115.34, 112.86, 87.40, 61.95, 56.07, 51.62, 26.83, 14.36, 14.34; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{20}NO_4$ (M+H)$^+$: 290.1392; found: 290.1382. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.42; H, 6.60; N, 4.84.

4.1.5. General procedure for the synthesis of ethyl 3-(2-aminoethyl)-3-ethyl-7-methoxy-2,3-dihydrobenzofuran-2-carboxylate (9) and 4a-ethyl-8-methoxy-2,3,4,4a-tetrahydrobenzofuro[2,3-*c*]pyridin-1(9a*H*)-one (10)

A mixture of the nitrile **7** (3.4 g, 11.7 mmol) and PtO_2 (0.5 g) in acetic acid (50 mL) was hydrogenated at 50 psi at room temperature for 6 h. After filtration, the solvent was removed in vacuo and the reaction mixture was poured on an ice water and NH_4OH mixture, the product was extracted with $CHCl_3$ (2 × 100 mL) and washed with a saturated $NaHCO_3$ solution. After drying over Na_2SO_4, the solvent was removed in vacuo and the residue was subjected to flash chromatography on silica gel with 90:9:1 CH_2Cl_2/MeOH/NH_4OH to give 1.1 g of the *cis*-lactam **10** in 38% yield as a sticky foam. Eluting the above column with 50% MeOH in CH_2Cl_2 gave 0.5 g (15%) of **9** as a sticky solid.

4.1.5.1. Ethyl 3-(2-aminoethyl)-3-ethyl-7-methoxy-2,3-dihydrobenzofuran-2-carboxylate (9). IR (neat) 3278, 1746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (t, 1H, J = 7.5 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.76 (d, 1H, J = 7.2 Hz), 5.17 (br s, 2H), 5.08 (s, 1H), 4.38 (m, 2H), 3.96 (s, 3H), 2.88 (m, 2H), 2.19 (m, 2H), 1.83 (m, 1H), 1.58 (m, 1H), 1.41 (t, 1H, J = 7.2 Hz), 0.86 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.93, 148.05, 146.06, 133.47, 123.02, 117.13, 113.67, 88.27, 62.46, 56.64, 53.71, 40.33, 38.19, 30.23, 14.51, 8.78; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{24}NO_4$ (M+H)$^+$: 294.1705; found: 294.1711. Anal. Calcd for $C_{16}H_{23}NO_4{\cdot}0.75H_2O$: C, 62.62; H, 8.04; N, 4.56. Found: C, 62.95; H, 7.87; N, 4.62.

4.1.5.2. 4a-Ethyl-8-methoxy-2,3,4,4a-tetrahydrobenzofuro[2,3-*c*]pyridin-1(9a*H*)-one (10). Compound **10** was alternatively obtained from compound **9**. The *trans* amino ester **9** (500 mg, 1.76 mmol) was carefully added to a solution of freshly cut sodium metal (23 mg, 1.0 mmol) in EtOH (5 mL). The mixture was heated at 80 °C for 90 min. After cooling to room temperature, the reaction mixture was poured onto ice water, and the product was treated with 37% HCl (2 mL) to neutralize the excess base. The organic layer was extracted with $CHCl_3$ (2 × 30 mL), and after drying over Na_2SO_4 the solvent was removed in vacuo to give a dark oil. Purification by flash chromatography using 90:9:1 CH_2Cl_2/MeOH/NH_4OH gave 345 mg (82%) of **10** as a foam. IR (neat) 3211, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (br s, 1H), 6.85 (t, 1H, J = 7.5 Hz), 6.73 (t, 1H, J = 8.0 Hz), 6.62 (d, 1H, J = 7.5 Hz), 4.64 (s, 1H), 3.80 (s, 3H), 3.17 (ddd, 1H, J = 4.5, 9.0 and 17.0 Hz), 3.05 (t, 1H, J = 10.5 Hz), 2.16 (m, 2H), 1.71 (m, 2H), 0.80 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.25, 147.86, 144.63, 131.86, 121.97, 114.9, 112.08, 99.34, 85.47, 55.94, 50.00, 38.30, 32.78, 8.26; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{18}NO_3$ (M+H)$^+$: 248.1287; found: 248.1295. Anal. Calcd for $C_{14}H_{17}NO_3{\cdot}0.1H_2O$: C, 67.51; H, 6.96; N, 5.62. Found: C, 67.43; H, 6.95; N, 5.43.

4.1.6. 4a-Ethyl-8-methoxy-1,2,3,4,4a,9a-hexahydrobenzofuro-[2,3-*c*]pyridine (11)

To a solution of LAH (1.8 g, 4.25 mmol) in THF (30 mL) was added *cis*-lactam **10** (3.0 g, 1.21 mmol) in THF (20 mL) and the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction was quenched with EtOAc and treated with 50% NaOH, the organic layer was then extracted with $CHCl_3$ (2 × 50 ml), dried over Na_2SO_4 and the solvent was removed in vacuo to afford a brown oil. Purification on a silica gel column using 90:10 CH_2Cl_2/MeOH gave 2.6 g (92%) of compound **11** as a pale yellow oil. IR (neat) 2938, 1489 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.97 (t, 1H, J = 7.5 Hz), 6.86 (dd, 1H, J = 1.2 and 8.1 Hz), 6.79 (dd, 1H, J = 1.5 and 7.5 Hz), 4.47 (t, 1H, J = 4.5 Hz), 3.99 (s, 3H), 3.21 (d, 1H, J = 4.5 Hz), 2.88 (m, 1), 2.80 (m, 1H), 1.75–1.93 (m, 4H), 0.96 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.23, 144.98, 135.70, 121.28, 115.17, 111.08, 84.37, 59.97, 55.85, 46.68, 46.11, 41.63, 33.96, 30.79, 29.74, 8.69; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{20}NO_2$ $(M+H)^+$: 234.1494; found: 234.1491. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H, 7.90; N, 5.70.

4.1.7. 4a-Ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro-[2,3-*c*]pyridin-8-ol (1a)

A deoxygenated solution of compound **11** (600 mg, 2.57 mmol), HCHO (2 mL) and 10% Pd on carbon (20 mg) in MeOH (10 mL) was stirred at room temperature under H_2 at 1 atm for 2 h. The resultant mixture was filtered through Celite and concentrated in vacuo to give a yellow oil. The oil was taken up in $CHCl_3$ and treated with neat BBr_3 (0.97 mL, 10.3 mmol) and refluxed for 2 h. The reaction mixture was cooled and treated with MeOH to quench the excess BBr_3, poured in to a mixture of water and NH_4OH and extracted with CH_2Cl_2. After evaporation of the solvent in vacuo the crude compound was subjected to flash chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to give **1a** (320 mg, 53% over two steps) as a pale yellow solid, mp 158–160 °C. IR (neat) 2983, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (t, 1H, J = 7.5 Hz), 6.76 (d, 1H, J = 8.0 Hz), 6.62 (d, 1H, J = 7.0 Hz), 4.65 (t, 1H, J = 6.0 Hz), 2.97 (dd, 1H, J = 5.5 and 11.5 Hz), 2.57 (dd, 1H, J = 6.0 and 11.5 Hz), 2.26 (m, 1H), 2.21 (s, 3H), 2.11 (m, 2H), 1.89 (ddd, 1H, J = 3.5, 11.0 and 15.0 Hz), 1.70 (m, 1H), 1.56 (m, 1H), 0.83 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.66, 141.99, 134.27, 121.67, 115.90, 114.61, 85.08, 56.65, 52.04, 46.52, 46.15, 32.70, 31.80, 8.54; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{20}NO_2$ $(M+H)^+$: 234.1494; found: 234.1505. Anal. Calcd for $C_{14}H_{19}NO_2{\cdot}0.2H_2O$: C, 70.97; H, 8.25; N, 5.91. Found: C, 71.17; H, 8.12; N, 5.91.

4.1.8. General method for the synthesis of 1b through 1f

A mixture of the amine **11**, alkyl bromide (1.2 equiv) and $NaHCO_3$ (2 equiv) in DMF (20 mL) was heated at 100 °C for 3 h. After cooling to room temperature, the reaction mixture was poured on ice water, and the product was extracted with Et_2O. The ethereal extracts were washed with a saturated NH_4Cl solution. After drying over Na_2SO_4, the solvent was removed in vacuo to afford an oil. This oil was taken up in $CHCl_3$ and treated with neat BBr_3 (4 equiv) and refluxed for 2 h. The reaction mixture was cooled and treated with MeOH to quench the excess BBr_3, poured in to a mixture of H_2O and NH_4OH and extracted with CH_2Cl_2. After evaporation of the solvent in vacuo the crude compound was subjected to flash chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to give the compounds **1b**–**f** as a solid.

4.1.9. 4a-Ethyl-2-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro-[2,3-*c*]pyridin-8-ol (1b)

Using the general method of **4.1.9**, the amine **11** (1.1 g, 4.85 mmol), 2-bromoethylbenzene (0.78 mL, 5.82 mmol) and subsequent treatment with BBr_3 (1.84 mL, 19.4 mmol) gave 0.76 g of **1b** (49% over two steps) as a white solid, mp 195–198 °C. IR (neat) 3019, 1264 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 7.24 (t, 2H, J = 7.5 Hz), 7.15 (m, 3H), 6.72 (t, 1H, J = 8.0 Hz), 6.63 (d, 1H, J = 7.0 Hz), 6.59 (d, 1H, J = 7.5 Hz), 4.61 (br s, 1H), 4.48 (t, 1H, J = 6.0 Hz), 2.94 (dd, 1H, J = 5.5 and 12.5 Hz), 2.77 (m, 2H), 2.63 (m, 1H), 2.56 (d, 1H, J = 8.0 Hz), 2.42 (dd, 1H, J = 7.0 and 12.0 Hz), 2.22 (ddd, 1H, J = 2.5, 10.0 and 12.0 Hz), 2.05 (ddd, 1H, J = 3.0, 5.5 and 14.0 Hz), 1.78 (ddd, 1H, J = 4.0, 9.5 and 14.0 Hz), 1.70 (m, 1H), 1.59 (m, 1H), 0.80 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.02, 141.56, 136.30, 132.71, 128.80 (2C), 128.76 (2C), 126.99 122.65, 116.78, 114.46, 81.719, 59.06, 50.03, 48.62, 46.31, 30.66, 30.33, 30.31, 29.65, 8.42; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{26}NO_2$ $(M+H)^+$: 324.1964; found: 324.1972. Anal. Calcd for $C_{21}H_{25}NO_2{\cdot}0.25H_2O$: C, 76.91; H, 7.83; N, 4.27. Found: C, 77.02; H, 7.84; N, 4.22.

4.2. 4a-Ethyl-2-(4-nitrophenethyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (1c)

Using the general method of 4.1.9, amine **11** (600 mg, 2.57 mmol) 1-(2-bromoethyl)-4-nitrobenzene (651 mg, 2.83 mmol) and subsequent treatment with BBr_3 (977 μL, 10.3 mmol) gave 270 mg (28% over two steps) of **1c** as a pale yellow crystalline solid, mp 144–146 °C. IR (neat) 3020, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 6.82 (t, 1H, J = 7.5 Hz), 6.79 (d, 1H, J = 8.0 Hz), 6.64 (d, 1H, J = 7.0 Hz), 4.56 (t, 1H, J = 5.5 Hz), 2.94 (d, 1H, J = 7.5 Hz), 2.89 (t, 1H, J = 7.5 Hz), 2.63 (d, 1H, J = 6.5 Hz), 2.48 (dd, 1H, J = 6.5 and 11.0 Hz), 2.27 (t, 1H, J = 9.5 Hz), 2.08 (dt, 1H, J = 4.5 and 10.5 Hz), 1.83 (t, 1H, J = 9.5 Hz), 1.70 (m, 1H), 1.60 (m, 1H), 0.83 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.12, 146.69, 145.63, 141.26, 134.36, 129.62 (2C), 123.81 (2C), 121.75, 115.53, 115.12, 85.47, 59.49, 54.57, 49.74, 47.12, 33.35, 32.30, 32.12, 8.54 145.66, 141.99, 134.27, 121.67, 115.90, 114.61, 85.08, 56.65, 52.04, 46.52, 46.15, 32.70, 31.80, 8.54; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{25}N_2O_4$ $(M+H)^+$: 369.1814; found: 369.1816. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.24; H, 6.70; N, 7.51.

4.2.1. 2-(Cyclopropylmethyl)-4a-ethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (1d)

Using the general method of 4.1.9, amine **11** (320 mg, 1.37 mmol) (bromomethyl)cyclopropane (147 μL, 1.51 mmol) and subsequent treatment with BBr_3 (520 μL, 5.48 mmol) gave 200 mg of **1d** (53% over two steps) as a pale yellow solid, mp 139–141 °C. IR (neat) 3019 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.80 (t, 1H, J = 7.5 Hz), 6.77 (d, 1H, J = 8.0 Hz), 6.61 (d, 1H, J = 7.0 Hz), 4.83 (t, 1H, J = 7.0 Hz), 3.35 (dd, 1H, J = 6.0 and 10.5 Hz), 2.89 (d, 1H, J = 10.0 Hz), 2.32 (dd, 1H, J = 6.5 and 12.5 Hz), 2.23 (dd, 1H, J = 6.5 and 12.5 Hz), 2.16 (m, 3H), 2.00 (ddd, 1H, J = 4.0, 11.0 and 15.0 Hz), 1.64 (m, 1H), 1.54 (m, 1H), 0.84 (m, 1H), 0.79 (t, 3H, J = 7.5 Hz) 0.45 (t, 2H, J = 3.5 Hz), 0.03 (d, 2H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.88, 142.30, 133.81, 121.66, 116.41, 114.52, 84.83, 63.56, 54.65, 50.03, 47.28, 33.83, 30.52, 8.38, 7.59, 4.29, 4.27; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{24}NO_2$ $(M+H)^+$: 274.1807; found: 274.1814. Anal. Calcd for $C_{17}H_{23}NO_2{\cdot}0.25H_2O$: C, 73.48; H, 8.52; N, 5.04. Found: C, 73.11; H, 8.50; N, 4.93.

4.2.2. 4a-Ethyl-2-(4-fluorobenzyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (1e)

Using the general method of 4.1.9, amine **11** (233 mg, 1 mmol), 1-(bromomethyl)-4-fluorobenzene (147 μL, 1.2 mmol) and subsequent treatment with BBr_3 (379 μL, 4 mmol) gave 60 mg of **1e** (31% over two steps) as light white crystals, mp 138–140 °C. IR (neat) 3019, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (m, 2H), 6.97 (t, 2H, J = 8.5 Hz), 6.79 (t, 1H, J = 7.5 Hz), 6.76 (d, 1H, J = 7.0 Hz), 6.63 (d, 1H, J = 7.0 Hz), 5.51 (br s, 1H), 4.52 (t, 1H,

J = 6.0 Hz), 3.44 (m, 2H), 2.88 (dd, 1H, J = 5.0 and 11.5 Hz), 2.53 (dd, 1H, J = 5.5 and 11.0 Hz), 2.26 (dd, 1H, J = 7.5 and 12.0 Hz), 2.04–2.13 (m, 2H), 1.80 (ddd, 1H, J = 3.5, 10.0 and 13.5 Hz), 1.68 (m, 1H), 1.55 (m, 1H), 0.81 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.16, 161.21, 145.70, 141.25, 134.43, 133.63, 130.80, 130.73, 121.56, 115.363, 115.27, 115.18, 115.10, 85.76, 62.12, 54.75, 49.73, 47.25, 32.77, 31.94, 8.48; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{23}FNO_2$ (M+H)$^+$: 328.2713; found: 328.1706. Anal. Calcd for $C_{20}H_{22}FNO_2$: C, 73.37; H, 6.77; N, 4.28. Found: C, 73.34; H, 6.78; N, 4.30.

4.2.3. 4a-Ethyl-2-(4-fluorophenethyl)-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (1f)

Using the general method of 4.1.9, amine **11** (288 mg, 1.23 mmol), 1-(2-bromoethyl)-4-fluorobenzene (208 μL, 1.48 mmol) and subsequent treatment with BBr_3 (467 μL, 4.92 mmol) gave 100 mg of **1f** (24% over two steps) as a light yellow crystalline compound, mp 156–158 °C. IR (neat) 3019, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (t, 2H, J = 8.0 Hz), 7.10 (d, 2H, J = 8.5 Hz), 6.80 (t, 1H, J = 7.5 Hz), 6.77 (d, 1H, J = 7.5 Hz), 6.65 (d, 1H, J = 7.0 Hz), 5.15 (br s, 1H), 4.55 (t, 1H, J = 6.0 Hz), 2.92 (dd, 1H, J = 5.0 and 12.0 Hz), 2.75 (t, 2H, J = 8.0 Hz), 2.54 (m, 3H), 2.46 (dd, 1H, J = 7.0 and 12.0 Hz), 2.25 (dd, 1H, J = 3.0 and 12.0 Hz), 2.08 (ddd, 1H, J = 3.5, 5.5 and 14.0 Hz), 1.81 (ddd, 1H, J = 3.5, 9.0 and 13.5 Hz), 1.73 (m, 1H), 1.61 (m, 1H), 0.82 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.51, 160.57, 145.63, 141.23, 135.89, 134.65, 130.18, 130.11, 121. 65, 115.38, 115.32, 115.22, 115.16, 85.72, 60.57, 54.61, 49.88, 47.11, 32.78, 32.50, 32.08, 8.60; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{25}NFO_2$ (M+H)$^+$: 342.1869; found: 342.1857. Anal. Calcd for $C_{21}H_{24}NFO_2$: C, 73.88; H, 7.09; N, 4.10. Found: C, 73.99; H, 7.08; N, 4.29.

4.2.4. 4-(2,3-Dimethoxyphenyl)-4-ethyl-1-methyl-1,2,3,4-tetrahydropyridine (14a)

A solution of **13** (33.0 g, 141 mmol) in dry THF (350 mL) was stirred under argon at −40 °C. A solution of *n*-butyllithium, 2.5 M in hexane (113 mL, 283 mmol), was added to the reaction, producing a deep red color. The mixture was stirred at −40 °C for 3 h. Bromoethane (21.1 mL, 283 mmol) 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 aqueous NH_4Cl solution (40 mL). The reaction mixture was partitioned between Et_2O (2 × 300 mL) and H_2O (300 mL). The organic layer was dried over anhydrous Na_2SO_4 and removal of the solvent in vacuo gave an orange oil. Column chromatography of the crude material using 10% hexanes in Et_2O gave 31.0 g (84%) of **14a** as a pure yellow oil. IR (neat) 2932, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (m, 2H), 6.90 (d, 1H, J = 7.8 Hz), 6.02 (d, 1H, J = 7.8 Hz), 4.82 (d, 1H, J = 7.8 Hz), 4.00 (s, 6H), 2.89 (d, 1H, J = 10.5 Hz), 2.65 (s, 3H), 2.59 (m, 2H), 2.24 (m, 1H), 2.02 (t, 1H, J = 12.0 Hz), 1.84 (m, 1H), 0.79 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.12, 147.53, 141.32, 135.89, 124.09, 122.36, 110.54, 105.07, 60.07, 55.73, 47.20, 42.47, 41.37, 34.49, 33.56, 9.13; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{24}NO_2$ (M+H)$^+$: 262.1807; found: 262.1820. Anal. Calcd for $C_{16}H_{24}NO_2$: C, 73.53; H, 8.87; N, 5.08. Found: C, 73.42; H, 8.89; N, 5.36.

4.2.5. 3-Bromo-4-(2,3-dimethoxyphenyl)-4-ethyl-1-methylpiperidine (15a)

To a solution of compound **14a** (10.0 g, 38.0 mmol) in dry THF (75 mL) at −78 °C was added *N*-bromosuccinimide (6.8 g, 38.0 mmol) in dry THF (40 mL). The mixture was stirred at 20 °C for 1 h and then evaporated to an orange oil. The crude product was taken in MeOH (75 mL) and 37% HCl (2 mL) was added to the suspension. To this suspension was added solid $NaBH_3CN$ (2.4 g, 38.0 mmol), and the reaction mixture was stirred at room temperature for 45 min. The reaction mixture was then diluted with aqueous saturated $NaHCO_3$ and the organic layer was washed with H_2O (50 mL) and extracted into CH_2Cl_2 (150 mL). Removal of the solvent in vacuo gave a brown oil. Purification of the crude product by column chromatography using 30% hexanes in Et_2O gave a pale yellow solid (9.0 g, 69% over two steps). A small batch of the yellow solid was dissolved in MeOH and treated with 37% HCl to give white crystals of **15a**·HCl that were used for X-ray crystallography (Fig. 2). Mp 220–223 °C; IR (neat) 2937 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.99 (t, 1H, J = 8.0 Hz), 6.88 (d, 1H, J = 8.0 Hz), 6.69 (d, 1H, J = 7.5 Hz), 5.29 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.15 (d, 1H, J = 13.0 Hz), 3.00 (m, 2H), 2.50 (t, 1H, J = 14.0 Hz), 2.47 (s, 3H), 2.43 (m, 1H), 2.05 (m, 2H), 1.92 (d, 1H, J = 12.5 Hz), 0.51 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.67, 147.92, 138.72, 122.79, 120.01, 111.48, 60.33, 58.46, 55.78 (2C), 51.14, 46.13, 45.13, 26.77, 24.86, 9.65; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{25}NBr^{79}O_2$ (M+H)$^+$: 342.1069; found: 342.1055. Anal. Calcd for $C_{16}H_{24}NBrO_2$·HCl: C, 50.74; H, 6.65; N, 3.70. Found: C, 50.74; H, 6.71; N, 3.74.

4.2.6. 2-(3-Bromo-4-ethyl-1-methylpiperidin-4-yl)benzene-1,2-diol (16a)

To compound **15a** (7.5 g, 21.9 mmol) in a clean round-bottom flask was added 48% HBr (30 mL) and the emulsion was refluxed at 105 °C for 10 h. After completion of the reaction, the excess HBr was removed by distillation to leave **16a**·HBr as a pale yellow solid (7.0 g, 80%). A small batch was recrystallized from MeOH to give off-white crystals of **16a**·HBr, mp 248–251 °C. IR (neat) 3458 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 6.76 (d, 1H, J = 7.0 Hz), 6.65 (t, 1H, J = 8.0 Hz), 6.51 (d, 1H, J = 7.0 Hz), 5.95 (s, 1H), 4.04 (d, 1H, J = 14.0 Hz), 3.81 (d, 1H, J = 14.0 Hz), 3.54 (d, 1H, J = 12.0 Hz), 3.41 (t, 1H, J = 16.5 Hz), 3.00 (s, 3H), 2.50 (dt, 1H, J = 3.5 and 14.5 Hz), 2.45 (dd, 1H, J = 7.0 and 13.5 Hz), 2.28 (d, 1H, J = 14.5 Hz), 2.08 (m, 1H) 0.63 (t, 3H, J = 7.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 146.06, 145.10, 130.77, 119.55, 119.47, 114.89, 57.95, 55.19, 51.80, 45.22, 44.14, 25.86, 23.85, 10.04; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{21}NBrO_2$ (M+H)$^+$: 314.0756; found: 314.0744. Anal. Calcd for $C_{14}H_{20}NBrO_2$·HBr: C, 42.56; H, 5.36; N, 3.54. Found: C, 42.59; H, 5.42; N, 3.55.

4.2.7. 4a-Ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro-[2,3-*c*]pyridin-8-ol (1a)

Compound **16a** (2.0 g, 6.37 mmol) (free base was obtained after neutralization of the HBr salt of **16a** partitioned between $NaHCO_3$ and $CHCl_3$) was treated with excess Et_3N (30 mL). The reaction mixture was placed in a sealed tube and heated at 100 °C for 4 h. Cooling of the reaction mixture, followed by evaporation of the excess Et_3N gave a brown solid. This solid was subject to silica gel column chromatography and the desired product **1a** was eluted using 15% MeOH in CH_2Cl_2 to give an off-white solid (1.3 g, 88%), mp 158–160 °C. IR (neat) 2983, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.82 (t, 1H, J = 7.5 Hz), 6.76 (d, 1H, J = 8.0 Hz), 6.62 (d, 1H, J = 7.0 Hz), 4.65 (t, 1H, J = 6.0 Hz), 2.97 (dd, 1H, J = 5.5 and 11.5 Hz), 2.57 (dd, 1H, J = 6.0 and 11.5 Hz), 2.26 (m, 1H), 2.21 (s, 3H), 2.11 (m, 2H), 1.89 (ddd, 1H, J = 3.5, 11.0 and 15.0 Hz), 1.70 (m, 1H), 1.56 (m, 1H), 0.83 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.66, 141.99, 134.27, 121.67, 115.90, 114.61, 85.08, 56.65, 52.04, 46.52, 46.15, 32.70, 31.80, 8.54; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{20}NO_2$ (M+H)$^+$: 234.1470; found: 234.1480. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.85; H, 8.10; N, 6.00.

4.2.8. 4-(2,3-Dimethoxyphenyl)-1-methyl-4-phenethyl-1,2,3,4-tetrahydropyridine (14b)

A solution of **13** (10.0 g, 42.9 mmol) in dry THF (100 mL) was stirred under argon at −40 °C. A solution of *n*-butyllithium, 2.5 M in hexane (34.5 mL, 85.8 mmol), was added to the reaction, producing a deep red color. The mixture was stirred at −40 °C for

2 h. Phenethyl bromide (11.7 mL, 85.8 mmol) 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 (15 mL). The reaction mixture was partitioned twice between Et_2O (100 mL) and H_2O (100 mL). The organic layer was dried over anhydrous 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 8.0 g (55%) of compound **14b** as pure yellow oil. IR (neat) 2929, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.20 (t, 2H, J = 7.5 Hz), 7.12 (d, 3H, J = 7.5 Hz), 7.05 (d, 1H, J = 7.5 Hz), 6.97 (t, 1H, J = 7.5 Hz), 6.83 (d, 1H, J = 8.0 Hz), 5.95 (d, 1H, J = 8.0 Hz), 4.79 (d, 1H, J = 7.5 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 2.78 (dd, 1H, J = 4.0 and 8.0 Hz), 2.56 (s, 3H), 2.43–2.51 (m, 4 H), 2.39–2.43 (m, 2 H), 2.26 (dt, 1H, J = 5.5 and 12.5 Hz), 1.98 (dt, 1H, J = 3.0 and 12.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.22, 147.69, 143.46, 141.16, 128.46 2C, 128.28 2C); HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{28}NO_2$ (M+H)$^+$: 338.2120; found: 338.2113.

4.2.9. 3-Bromo-4-(2,3-dimethoxyphenyl)-1-methyl-4-phenethylpiperidine (15b)

To a solution of compound **14b** (9.5 g, 28.1 mmol) in dry THF (75 mL) at −78 °C was added *N*-bromosuccinimide (5.0 g, 28.1 mmol) in dry THF (30 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 placed in MeOH (75 mL) and 37% HCl (2 mL) was added to the suspension. To this suspension was added solid $NaBH_3CN$ (1.76 g, 28.1 mmol), 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 (50 mL) and extracted into CH_2Cl_2 (150 mL). Removal of the solvent gave a brown oil. Purification of the crude product by column chromatography using 30% hexanes in Et_2O gave **15b** (9.0 g, 76% over two steps) as a white crystalline solid, mp 132–135 °C. IR (neat) 2940 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (t, 2H, J = 7.5 Hz), 7.15 (t, 1H, J = 7.5 Hz), 7.04 (d, 3H, J = 7.0 Hz), 6.92 (d, 1H, J = 8.0 Hz), 6.78 (d, 1H, J = 7.5 Hz), 5.29 (s, 1H), 4.00 (s, 3H), 3.89 (s, 3H), 3.09 (d, 1H, J = 13.5 Hz), 2.99 (d, 1H, J = 11.0 Hz), 2.88 (d, 1H, J = 13.0 Hz), 2.60 (dt, 1H, J = 2.5 and 12.5 Hz), 2.47 (t, 1H, J = 11.5 Hz), 2.38 (s, 3H), 2.27 (m, 3H), 2.03 (dt, 1H, J = 13.0 Hz), 1.90 (dt, 1H, J = 3.0 and 11.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.69, 148.08, 142.37, 138.82, 128.38 (2C), 128.32 (2C), 125.81, 122.79, 119.77, 111.77, 60.27, 8.95, 58.44, 55.81, 51.13, 46.11, 44.87, 34.56, 31.92, 27.69; HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{29}NBr^{79}O_2$ (M+H)$^+$: 418.1382; found: 418.1382. Anal. Calcd for $C_{22}H_{28}NBrO_2$: C, 63.16; H, 6.75; N, 3.35. Found: C, 63.22; H, 6.78; N, 3.40.

4.3. 2-(3-Bromo-1-methyl-4-phenethylpiperidin-4-yl)benzene-1,2-diol (16b)

To compound **15b** (2.2 g, 5.26 mmol) in a round-bottom flask was added 48% HBr (25 mL) and the emulsion was refluxed at 105 °C for 10 h. After completion of the reaction, the excess HBr was removed by distillation to leave compound **16b**·HBr as a light brown solid. Neutralization of the HBr salt by partitioning between $NaHCO_3$ and $CHCl_3$ gave 1.6 g (78%) of the free base. A small batch of **16b**·HBr was recrystallized from MeOH to give white crystals of **16b**·HBr, mp 190–193 °C. IR (neat) 3479 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 7.20 (t, 2H, J = 7.5 Hz), 7.12 (d, 1H, J = 7.0 Hz), 7.07 (d, 2H, J = 7.5 Hz), 6.82 (d, 1H, J = 7.5 Hz), 6.70 (t, 1H, J = 8.0 Hz), 6.58 (d, 1H, J = 8.0 Hz), 5.92 (s, 1H), 4.02 (d, 1H, J = 14.5 Hz), 3.76 (d, 1H, J = 14.0 Hz), 3.56 (d, 1H, J = 12.0 Hz), 3.44 (t, 1H, J = 13.0 Hz), 2.98 (s, 3H), 2.75 (dt, 1H, J = 3.5 and 12.5 Hz), 2.56 (dt, 1H, J = 2.0 and 13.0 Hz), 2.41 (dt, 1H, J = 7.5 and 13.0 Hz), 2.31 (m, 2H), 2.03 (dt, 1H, J = 3.5 and 12.0 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 146.17, 145.17, 143.22, 130.94, 129.47 (2C), 129.30 (2C), 126.81, 119.75, 119.39, 115.13, 57.87, 55.06, 51.84, 45.06, 44.16, 33.54, 33.21, 26.50; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{25}NBr^{79}O_2$ (M+H)$^+$: 390.1069; found: 390.1070. Anal. Calcd for $C_{20}H_{24}NBrO_2 \cdot HBr \cdot H_2O$: C, 49.10; H, 5.56; N, 2.86. Found: C, 48.90; H, 5.62; N, 2.77.

4.3.1. 2-Methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (12)

Compound **16b** (820 mg, 2.1 mmol) 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. Cooling of the reaction mixture followed by evaporation of the excess Et_3N gave a brown solid. This solid was subjected to silica gel column chromatography and the desired product was eluted using 15% MeOH in CH_2Cl_2 to give an off-white solid **12** (400 mg, 62%), mp 187–189 °C. IR (neat) 3020 cm^{-1}. The X-ray crystallographic analysis confirmed the molecular structure (Fig. 2). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.23 (t, 2H, J = 7.0 Hz), 7.15 (t, 1H, J = 7.0 Hz), 7.08 (d, 2H, J = 7.5 Hz), 6.86 (t, 1H, J = 7.5 Hz), 6.80 (d, 1H, J = 8.0 Hz), 6.71 (d, 1H, J = 7.0 Hz), 4.68 (t, 1H, J = 5.5 Hz), 2.90 (dd, 1H, J = 4.0 and 11.5 Hz), 2.55 (m, 3H), 2.42 (dd, 1H, J = 7.0 and 11.5 Hz), 2.28 (s, 3H), 2.23 (t, 1H, J = 11.0 Hz), 2.14 (m, 1H), 1.97 (m, 2H), 1.85 (dt, 1H, J = 5.0 and 13.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.62, 142.17, 141.79, 134.34, 128.54 (2C), 128.37 (2C), 125.99, 122.00, 115.92, 114.68, 85.25, 56.37, 51.87, 46.36, 46.20, 41.56, 32.85, 30.68; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{24}NO_2$ (M+H)$^+$: 310.1807; found: 310.1817. Anal. Calcd for $C_{20}H_{23}NO_2 \cdot 0.25\ H_2O$: C, 76.52; H, 7.54; N, 4.46. Found: C, 76.70; H, 7.33; N, 4.52.

4.3.2. X-ray crystal structures (Fig. 2) of 2-methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-8-ol (12) and 3-bromo-4-(2,3-dimethoxyphenyl)-4-ethyl-1-methylpiperidine hydrochloride (15a·HCl)

Single-crystal X-ray diffraction data on compounds **12** and **15a**·HCl were collected using MoKα radiation and a Bruker APEX 2 CCD area detector. The structures was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C–H distance set at 0.96 Å. Atomic coordinates for these compounds have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 729148 and 729149 for compounds **12** and **15a**·HCl, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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Supplementary data

Supplementary data (atomic coordinates and crystallographic data for compounds **15a**·HCl and **12**) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.11.022.

References and notes

1. Zhang, Y.; Lee, Y. S.; Rothman, R. B.; Dersch, C. M.; Deschamps, J. R.; Jacobson, A. E.; Rice, K. C. J. Med. Chem. (2009), doi:10.1021/jm9004225.
2. Hutchison, A. J.; de Jesus, R.; Williams, M.; Simke, J. P.; Neale, R. F.; Jackson, R. H.; Ambrose, F.; Barbaz, B. J.; Sills, M. A. *J. Med. Chem.* **1989**, *32*, 2221.
3. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Silverton, J. V. In *Problems of Drug Dependence 1983*; Harris, L. S., Ed.; National Institute on Drug Abuse Research Monograph 49; DHHS ((ADM) 84-1316): Washington, DC, 1984; Vol. 49, 109.
4. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. *J. Org. Chem.* **1984**, *49*, 1051.
5. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V. *J. Org. Chem.* **1984**, *49*, 2508.
6. Burke, T. R., Jr.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Huang, H. C.; Silverton, J. V. *J. Med. Chem.* **1986**, *29*, 748.
7. Yamada, K.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *Synthesis-Stuttgart* **2002**, 2359.
8. Kodato, S.; Linders, J. T. M.; Gu, X.-H.; Yamada, K.; Flippen-Anderson, J. L.; Deschamps, J. R.; Jacobson, A. E.; Rice, K. C. *Org. Biomol. Chem.* **2004**, *2*, 330.
9. Hashimoto, A.; Przybyl, A. K.; Linders, J. T. M.; Kodato, S.; Tian, X. R.; Deschamps, J. R.; George, C.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *J. Org. Chem.* **2004**, *69*, 5322.
10. Tadic, D.; Linders, J. T. M.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *Tetrahedron* **2003**, *59*, 4603.
11. Linders, J. T. M.; Mirsadeghi, S.; Flippen-Anderson, J. L.; George, C.; Jacobson, A. E.; Rice, K. C. *Helv. Chim. Acta* **2003**, *86*, 484.
12. Zezula, J.; Jacobson, A. E.; Rice, K. C. *Heterocycles* **2007**, *71*, 881.
13. Zezula, J.; Singer, L. B.; Przybyl, A. K.; Hashimoto, A.; Dersch, C. M.; Rothman, R. B.; Deschamps, J.; Lee, Y. S.; Jacobson, A. E.; Rice, K. C. *Org. Biomol. Chem.* **2008**, *6*, 2868.
14. Kurimura, M.; Liu, H.; Sulima, A.; Przybyl, A. K.; Ohshima, E.; Kodato, S.; Deschamps, J. R.; Dersch, C.; Rothman, R. B.; Lee, Y. S.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2008**, *51*, 7866.
15. May, E. L. *J. Org. Chem.* **1956**, *21*, 899.
16. Koelsch, C. F. U.S.A. Patent 2,809,201, 1957, 8.
17. Koelsch, C. F. *Chem. Abstr.* **1958**, *52*, 3871f.
18. Iyer, M. R.; Deschamps, J. R.; Jacobson, A. E.; Rice, K. C. *Heterocycles* **2009**, *79*, 1061.
19. Cami-Kobeci, G.; Neal, A. P.; Bradbury, F. A.; Purington, L. C.; Aceto, M. D.; Harris, L. S.; Lewis, J. W.; Traynor, J. R.; Husbands, S. M. *J. Med. Chem.* **2009**, *52*, 1546.
20. Moynihan, H.; Jales, A. R.; Greedy, B. M.; Rennison, D.; Broadbear, J. H.; Purington, L.; Traynor, J. R.; Woods, J. H.; Lewis, J. W.; Husbands, S. M. *J. Med. Chem.* **2009**, *52*, 1553.
21. Greiner, E.; Spetea, M.; Krassnig, R.; Schullner, F.; Aceto, M.; Harris, L. S.; Traynor, J. R.; Woods, J. H.; Coop, A.; Schmidhammer, H. *J. Med. Chem.* **2003**, *46*, 1758.
22. May, E. L.; Jacobson, A. E.; Mattson, M. V.; Traynor, J. R.; Woods, J. H.; Harris, L. S.; Bowman, E. R.; Aceto, M. D. *J. Med. Chem.* **2000**, *43*, 5030.
23. May, E. L.; Aceto, M. D.; Bowman, E. R.; Bentley, C.; Martin, B. R.; Harris, L. S.; Medzihradsky, F.; Mattson, M. V.; Jacobson, A. E. *J. Med. Chem.* **1994**, *37*, 3408.
24. McLamore, S.; Ullrich, T.; Rothman, R. B.; Xu, H.; Dersch, C.; Coop, A.; Davis, P.; Porreca, F.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2001**, *44*, 1471.
25. Parker, K. A.; Petraitis, J. J. *Tetrahedron Lett.* **1981**, *22*, 397.
26. Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robbey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955.