Synthesis and Pharmacological Evaluation of Novel Octahydro-1*H*-pyrido[1,2-a]pyrazine as *μ*-Opioid Receptor Antagonists

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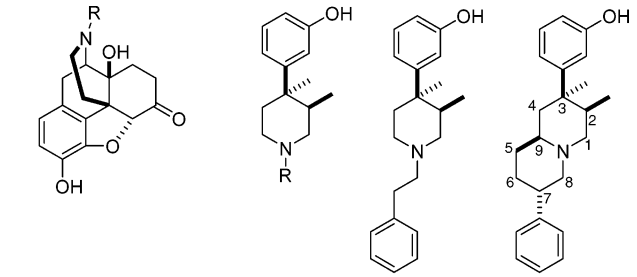
To better understand structural requirements for a *μ* ligand of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine class to interact with the *μ* opioid receptor, we have described in the previous article (Le Bourdonnec, B. et al. *J. Med. Chem.* **2006**, *25*, 7278−7289) new, constrained analogues of the *N*-phenethyl derivative **3**. One of the active constrained analogues, compound **4**, exhibited subnanomolar *μ*-opioid receptor affinity (K_i = 0.62 nM) and potent *μ*-opioid antagonist activity (IC_{50} = 0.54 nM). On the basis of structure **4**, a new series of *μ*-opioid receptor antagonists were designed. In these compounds the octahydroquinolizine template of **4** was replaced by an octahydro-1*H*-pyrido[1,2-a]pyrazine scaffold. The new derivatives were tested for their binding affinities and in vitro functional activity against the cloned human *μ*-, *δ*-, and *κ*-opioid receptors. From this study, we identified compound **36**, which displays high affinity toward the *μ*-opioid receptor (K_i = 0.47 nM), potent *μ* in vitro antagonist activity (IC_{50} = 1.8 nM) and improved binding selectivity profile *μ*/*κ* and *μ*/*δ*, when compared to **4**.

Introduction

Among the opioid receptor antagonists family, naloxone (**1a**), naltrexone (**1b**), and structurally related analogues have received the most attention.[1] The *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**) class of opioid antagonists described for the first time in 1978 by Zimmerman and collaborators [2] has also been widely investigated.[3−6] A representative of this class, (+)-*N*-phenethyl *trans*-3(*R*),4(*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine (**3**), has been previously reported to bind cloned human opioid receptors with good affinity [$K_i(\mu)$ = 1.9 nM; $K_i(\kappa)$ = 17 nM; $K_i(\delta)$ = 33 nM].[3,7]



1a: R = $CH_2CH{=}CH_2$ (naloxone)
1b: R = $CH_2c(C_3H_5)$ (naltrexone) **2** **3** **4**

Due to the fact that the whole phenethyl side chain of **3** can freely rotate relative to the piperidine ring, it is not possible to identify the exact location of this binding site relative to the rest of the molecule. To better understand structural requirements for a ligand of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine class to interact with the *μ*-opioid receptor, in the previous paper[8] we described new, constrained analogues of the *N*-phenethyl derivative **3**. One of the active constrained analogues, compound **4**, exhibited subnanomolar *μ*-opioid receptor affinity ($K_i(\mu)$ = 0.62 nM) and potent *μ*-opioid antagonist activity ($IC_{50}(\mu)$ = 0.54 nM). This novel *μ*-opioid receptor antagonist was prepared in 11 steps and 0.07% overall yield from (+)-4(*R*)-(3-hydroxyphenyl)-3(*R*)-4-dimethyl-1-piperidine.[9] The synthetic complexity of such derivatives prevented structure−activity relationship (SAR) exploration at positions 6 and 7 of the octahydroquinolizine scaffold (Figure 1). On the basis of the structure of **4**, we investigated the bioisosteric replacement of the methylene group at position 6 of the octahydroquinolizine scaffold by an NH or NR moiety. We now wish to report the synthesis, opioid receptor binding properties, and in vitro functional activity of this novel series of octahydro-1*H*-pyrido[1,2-a]pyrazine derivatives.

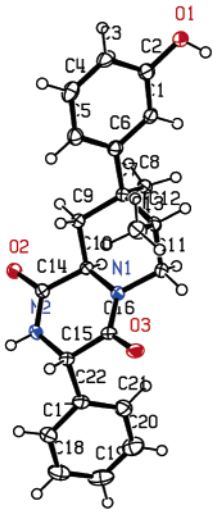


Figure 1. X-ray structure of **62** showing labeling of the nonhydrogen atoms. Displacement ellipsoids are at the 20% probability level.

Chemistry

The synthesis of the octahydro-1*H*-pyrido[1,2-a]pyrazine derivatives **5**−**56** is shown in Schemes 1−6. The preparation of compounds **5**−**7** is described in Scheme 1. The key step of

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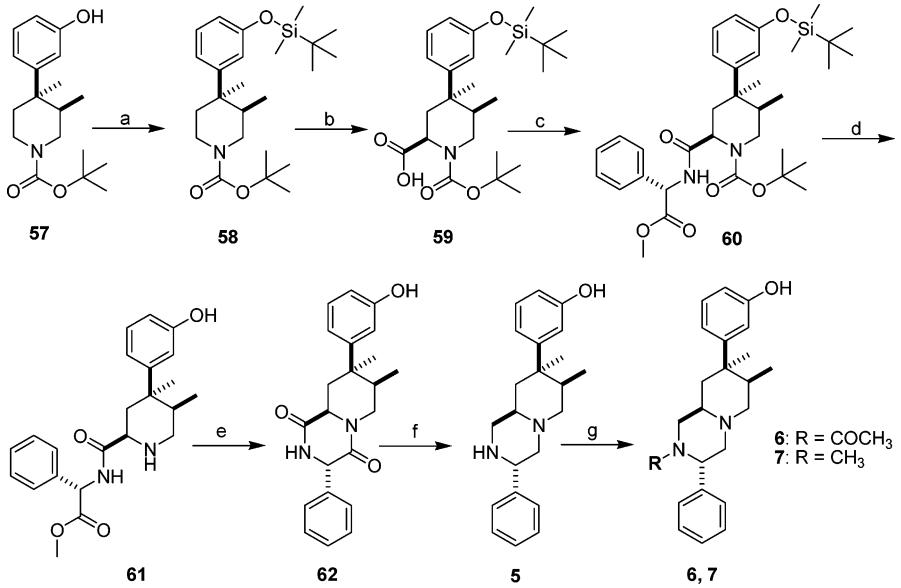
Scheme 1. Synthesis of **5**−**7**[a]



[a] Reagents and conditions: (a) $(CH_3)_3Si(CH_3)_2Cl$, imidazole, DMAP, DMF, 86%; (b) *s*-BuLi, TMEDA, CO_2, Et_2O, 73%; (c) (*S*)-methyl 2-amino-2-phenylacetate, TBTU, IPr_2NEt, CH_3CN, 82%; (d) 4 M HCl in dioxane, 95%; (e) toluene, 47%; (f) $BH_3S(CH_3)_2$, THF, 69%; (g) CH_3COCl, Et_3N, CH_2Cl_2 or CH_2O, $NaCNBH_3$, Et_3N, MeOH, THF, 53% (**6**), 76% (**7**).

the chemistry relied on the regio and stereoselective introduction of a carboxylic acid functionality at the 6β-position of the *N*-*tert*-butoxycarbonyl (*N*-Boc) piperidine derivative **58**, prepared by condensation of (3*R*,4*R*)-*tert*-butyl 4-(3-hydroxyphenyl)-3,4-dimethylpiperidine-1-carboxylate (**57**)[6] with *tert*-butylchlorodimethylsilane in the presence of imidazole and 4-(dimethylamino)-pyridine (DMAP). It has been previously reported that the *N*-Boc group is an effective directing group for the α-lithiation of piperidines.[10−12] Treatment of **58** with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylenediamine (TMEDA) afforded the lithiated intermediate which reacted with carbon dioxide to provide the carboxylic acid **59** isolated in 86% yield.[13] Condensation of **59** with (*S*)-methyl 2-amino-2-phenylacetate in the presence of *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) provided the amide **60**, which was converted to **61** under acidic conditions. Intramolecular cyclization of **61**, conducted in refluxing toluene, provided the lactam derivative **62** in 47% isolated yield. The absolute regio- and stereochemistry of **62** was determined by X-ray crystallography (Figure 1).[14] This crystal structure established by inference the absolute configuration of the synthetic precursors **59**−**61**. Reduction of compound **62** with borane−dimethyl sulfide complex provided the target compound **5**. The acetamide **6** was obtained by treatment of **5** with acetyl chloride. Condensation of **5** with formaldehyde under reductive amination conditions afforded the *N*-methyl derivative **7**.

The preparation of compounds **8**−**13** is described in Scheme 2. Coupling of **5** with benzaldehyde under reductive amination conditions, using borane−pyridine complex (BAP) as reducing agent, afforded the *N*-benzyl derivative **8**, which was converted to the triflate **63** by condensation with *N*-phenyltrifluoromethanesulfonimide. The derivative **9** was obtained by palladium-catalyzed reduction of the triflate **63**. Palladium-catalyzed carbonylation of the triflate **63** provided the methyl ester **10**, which was hydrolyzed under basic conditions to give the carboxylic acid **11**. Coupling of **11** with ammonium chloride in the presence of triethylamine and TBTU provided the primary amide **12**, which was converted to **13** by hydrogenation.

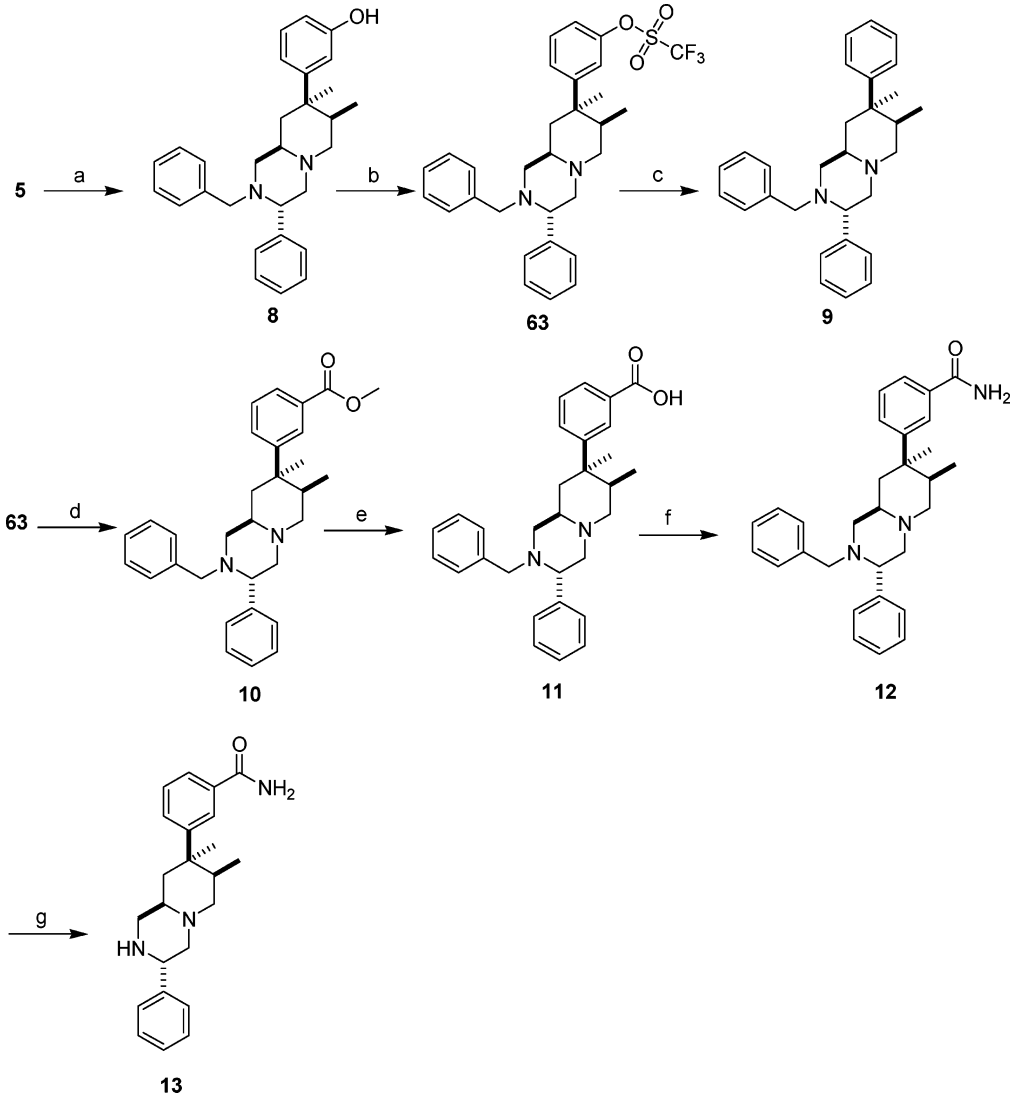
The compounds **14**−**19** were prepared from **59** according to a reaction sequence (Scheme 3) similar to the one described for the synthesis of **5**. The intramolecular cyclization of compounds **65** was performed in either toluene (**65a**,**c**,**d**) or *o*-xylene (**65e**,**f**). Compound **66b** was synthesized in quantitative yield from **64a** in a one-pot, two-step procedure.

The preparation of compounds **20**−**28** and **30**−**32** is described in Scheme 4. Condensation of **15** with formaldehyde under reductive amination conditions afforded the *N*-methyl derivative **20**. Coupling of **15** with acetyl chloride, benzoyl chloride, 2-phenylacetyl chloride, or 3-phenylpropanoyl chloride provided the amides **21**−**24**, respectively. Reduction of **22**−**24** with borane−dimethyl sulfide complex provided the target compounds **26**−**28**, respectively. Condensation of **15** with methanesulfonyl chloride or phenylisocyanate, under standard conditions, provided the sulfonamide **30** or the urea **32**, respectively. The *O*-benzyl derivative **67**, prepared from **15** in three steps (Boc protection, alkylation of the phenol hydroxyl group with benzyl bromide, and acid-mediated *N*-Boc deprotection) was used as starting material for the preparation of compounds **25** and **31**. Condensation of **67** with potassium phenyltrifluoroborate at room temperature, in the presence of triethylamine, molecular sieves, and copper(II) acetate, provided the corresponding *N*-phenyl derivative, which was converted to the target compound **25** by hydrogenation. Coupling of **67** with benzenesulfonyl chloride, followed by debenzylation of the sulfonamide intermediate, provided compound **31**. Compound **29** was prepared in four steps from **59**, using a chemical route (Scheme 5) similar to the one described for the synthesis of **5**. Condensation of **15** with a selected range of aldehydes under reductive amination conditions in trimethylorthoformate/methanol/acetic acid using resin-supported cyano borohydride as reducing agent afforded the corresponding derivatives **33**−**56**. These library compounds were purified by preparative HPLC. Representative compounds (**33**, **36**, **39**, **54**, and **56**) were resynthesized according to Scheme 6 to confirm the biological data obtained for the library compounds.

Results and Discussion

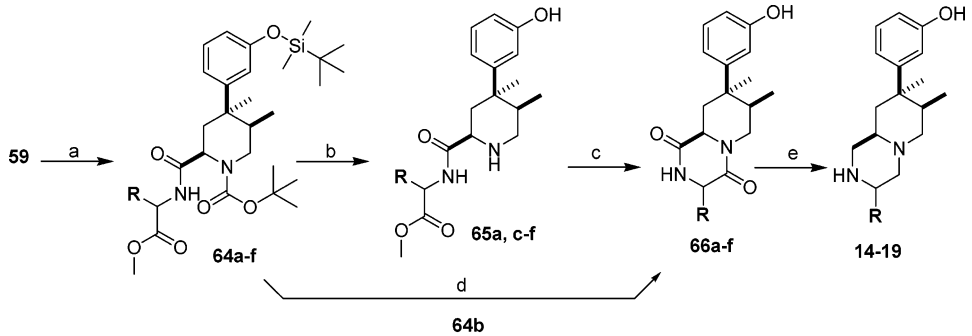
The derivatives **1a**,**b**, and **3**−**56** were tested for their affinities toward the cloned human μ-, δ-, and κ-opioid receptors as measured by their abilities to displace [^{3}H]-diprenorphine from

Scheme 2. Synthesis of **8**−**13**[a]



[a] Reagents and conditions: (a) C_6H_5CHO, BH_3·pyridine, EtOH, 71%; (b) $C_6H_5N(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, 72%; (c) Et_3N, HCO_2H, PPh_3, $Pd(OAc)_2$, DMF, 57%; (d) Et_3N, $Pd(OAc)_2$, dppf, MeOH, CO, DMSO, 76%; (e) LiOH·H_2O, H_2O, THF, MeOH, 100%; (f) NH_4Cl, Et_3N, TBTU, DMF, 91%; (g) Pd/C, H_2, EtOH, 12%.

Scheme 3. Synthesis of **14**−**19**[a]

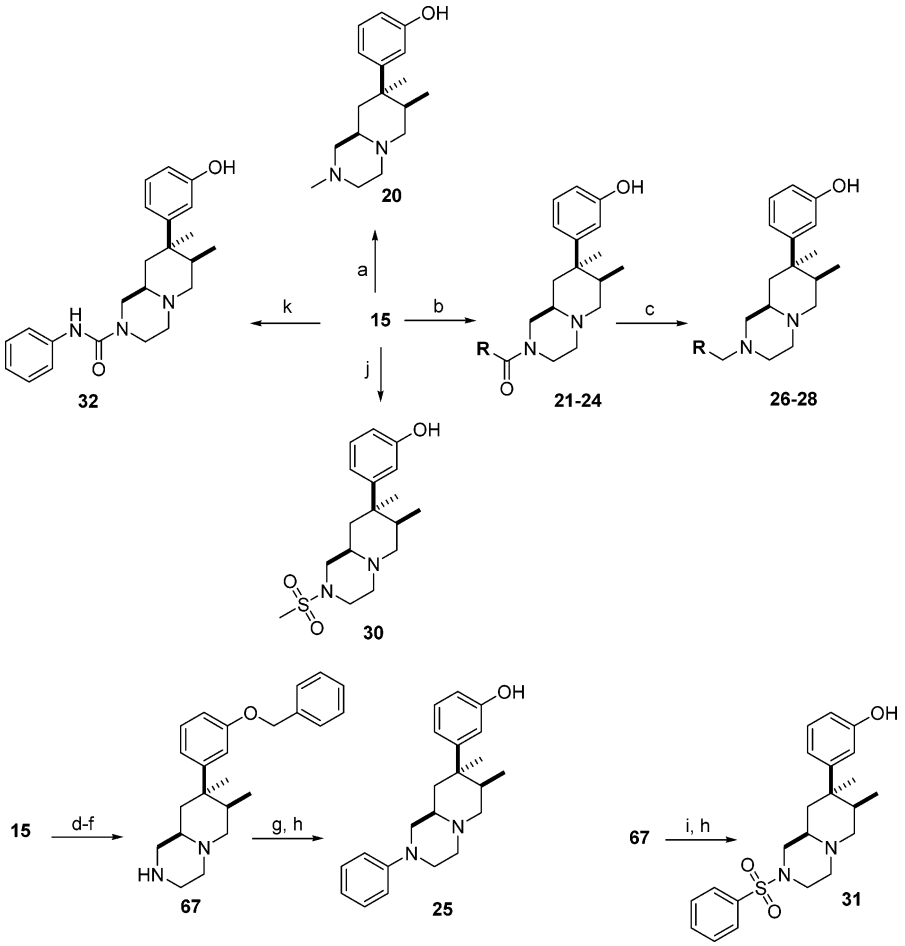


a: R = (*R*)-C_6H_5
b: R = H
c: R = (*S*)-$CH_2C_6H_5$
d: R = (*R*)-$CH_2C_6H_5$
e: R = (*S*)-C_6H_{11}
f: R = (*S*)-$CH(CH_3)_2$

[a] Reagents and conditions: (a) $H_2NCHRCO_2Me$, TBTU, *i*-Pr_2NEt, CH_3CN, 83% (**64a**), 95% (**64b**), 81% (**64c**), 71% (**64d**), 82% (**64e**), 75% (**64f**); (b) 4 M HCl in dioxane, 84% (**65a**), 99% (**65c**), 77% (**65d**), 97% (**65e**), 100% (**65f**); (c) toluene (**66a**,**c**,**d**) or *o*-xylene (**66e**,**f**), 99% (**66a**), 38% (**66c**), 70% (**66d**), 37% (**66e**), 43% (**66f**); (d) (i) 4 M HCl in dioxane; (ii) Et_3N, 100%; (e) BH_3·$S(CH_3)_2$, THF, 69% (**14**), 73% (**15**), 43% (**16**), 80% (**17**), 68% (**18**), 22% (**19**).

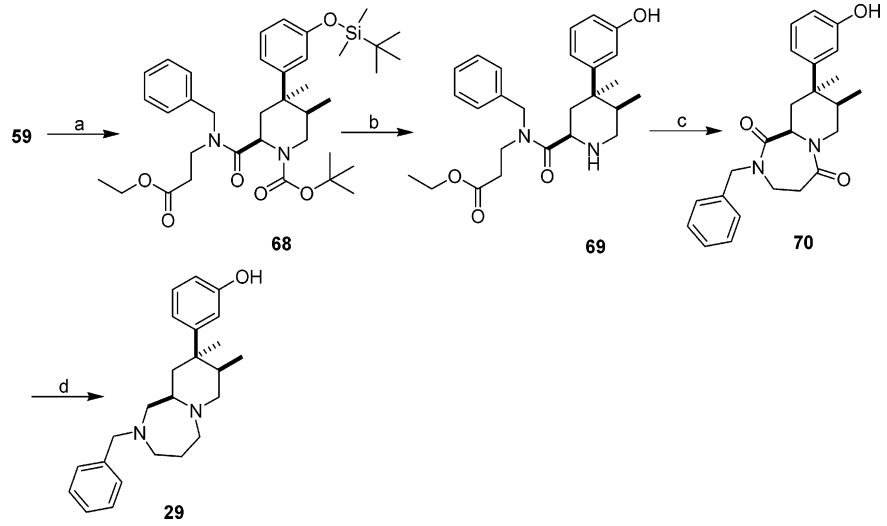
its specific binding sites. The μ antagonist potencies of the compounds were assessed by their abilities to inhibit agonist (loperamide)-stimulated guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding to membranes containing μ-opioid recep-

Scheme 4. Synthesis of **20**−**28** and **30**−**32**[a]



[a] Reagents and conditions: (a) HCHO, $NaCNBH_3$, Et_3N, THF, EtOH, 4%; (b) ROCl, Et_3N, THF, 22% (**21**), 57% (**22**), 96% (**23**), 54% (**24**); (c) $BH_3{\cdot}S(CH_3)_2$, THF, 100% (**26**), 42% (**27**), 45% (**28**); (d) $((CH_3)_3COCO)_2O$, Et_3N, THF, 74%; (e) $C_6H_5CH_2Br$, K_2CO_3, DMF, 99%; (f) 2 M HCl in ether, MeOH, 100%; (g) Et_3N, $Cu(OAc)_2$, $CH_3C_6H_4BF_3K$, Et_3N, CH_2Cl_2, 30%; (h) Pd/C, H_2, EtOH, 50% (**25**), 85% (**31**); (i) $C_6H_5SO_2Cl$, Et_3N, THF, 70%; (j) CH_3SO_2Cl, Et_3N, THF, 15%; (k) C_6H_5NCO, Et_3N, CH_2Cl_2, 58%.

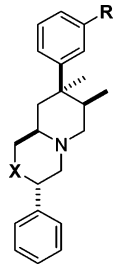
Scheme 5. Synthesis of **29**[a]



[a] Reagents and conditions: (a) $C_6H_5NHCH_2CH_2CO_2CH_2CH_3$, TBTU, *i*-$Pr_2NEt$, CH_3CN, 60%; (b) 4 M HCl in dioxane, 92%; (c) *o*-xylene, 25%; (d) $BH_3{\cdot}S(CH_3)_2$, THF, 10%.

tors. As shown in Table 1, bioisosteric replacement of the methylene group at position 6 of the octahydroquinolizine scaffold of **4** by an NH functionality was successful. Indeed the octahydro-1*H*-pyrido[1,2-a]pyrazine derivative **5**, NH analogue of **4**, displayed high affinity toward the μ-opioid receptor (K_i = 3.6 nM) and potent μ in vitro antagonist activity (IC_{50} = 1.1 nM). No μ agonist activity was detectable for compound **5** at concentrations up to 10 μM, demonstrating that this new ligand was a pure μ antagonist. We then explored the effect of substituting the NH functionality of **5** by various lipophilic

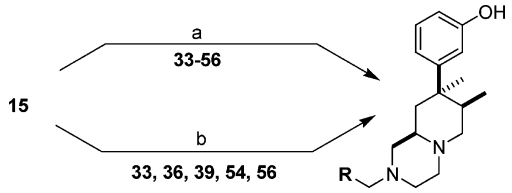
Table 1. Opioid Receptor (μ, κ, and δ) Binding Data and in Vitro Antagonist Activity (μ) of Compounds **1a**, **1b**, and **3**−**13**



compd	X	R	$K_i(\mu)$[a] (nM) or % inh.[b] @ 10 μM	$IC_{50}(\mu)$[c] (nM)	$K_i(\kappa)$[a] (nM) or % inh.[b] @ 10 μM	$K_i(\delta)$[a] (nM) or % inh.[b] @ 10 μM
1a			3.7 (3.1−4.5)	7.3 (5.0−10)	9.2 (6.9−13)	33 (27−41)
1b			1.0 (0.78−1.3)	4.1 (1.8−9.1)	4.4 (3.4−5.6)	14 (9.8−20)
3			1.8 (0.76−4.4)	1.1 (0.3−2.0)	17 (12−25)	33 (19−57)
4[d]	CH^2	OH	0.62 (0.41−0.81)	0.54 (0.32−2.0)	9.0 (6.3−12)	31 (21−45)
5[d]	NH	OH	3.6 (2.2−6.0)	1.1 (0.52−2.2)	18 (13−25)	89 (68−120)
6	$NCOCH_3$	OH	94 (55−160)	220 (120−390)	620 (300−1300)	57% ± 1%
7[d]	NCH_3	OH	3.3 (1.9−5.9)	26 (17−42)	13 (3.4−47)	2300 (190−4700)
8[d]	$NCH_2C_6H_5$	OH	4.7 (0.85−26)	40 (20−79)	120 (78−180)	340 (68−1700)
9	$NCH_2C_6H_5$	H	1600 (450−6200)	nd[e]	11% ± 3%	26% ± 2%
10	$NCH_2C_6H_5$	CO_2CH_3	24% ± 2%	nd[e]	6% ± 4%	39% ± 5%
11	$NCH_2C_6H_5$	CO_2H	44% ± 2%	nd[e]	9% ± 2%	2500 (1000−5700)
12	$NCH_2C_6H_5$	$CONH_2$	17 (9.3−30)	28 (14−56)	460 (280−770)	1100 (760−1700)
13[d]	NH	$CONH_2$	1.8 (0.81−4.1)	1.5 (1.0−2.3)	11 (8.3−13)	60 (37−99)

[a] The potencies of the compounds were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the nonselective opioid antagonist, [^{3}H]diprenorphine, to cloned human μ, κ, and δ opioid receptors, expressed in separate cell lines. K_i values are geometric means and 95% confidence intervals computed from at least three separate determinations. [b] The % inhibition of [^{3}H]diprenorphine binding to the cloned human μ-, κ-, and δ-opioid receptors using a concentration of the competitor of 10 μM. Mean ± S.E.M. [c] The potencies of the antagonists were assessed by their abilities to inhibit agonist (μ: loperamide; κ: U50, 488; δ: BW373U86) stimulated [^{35}S]GTPγS binding to membranes containing the respective cloned human opioid receptor. [d] The κ and δ antagonist potency of selected ligands. **4**: $IC_{50}(\kappa)$ = 3.2 nM (0.81−13), $IC_{50}(\delta)$ = 51 nM (45−58). **5**: $IC_{50}(\kappa)$ = 3.2 nM (0.39−27), $IC_{50}(\delta)$ = 98 nM (9.3−1000). **7**: $IC_{50}(\kappa)$ = 2.4 nM (0.43−13), $IC_{50}(\delta)$ = 580 nM (220−1500). **8**: $IC_{50}(\kappa)$ = 99 nM (54−180), $IC_{50}(\delta)$ = 1300 nM (730−2400). **13**: $IC_{50}(\kappa)$ = 2.3 nM (0.37−14), $IC_{50}(\delta)$ = 110 nM (33−380). [e] Not determined.

Scheme 6. Synthesis of **33**−**56**[a]

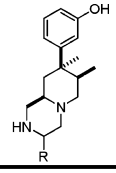


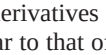
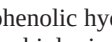
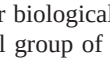
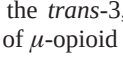
[a] Reagents and conditions: (a) RCHO, PS-$CNBH_3$, TMOF, MeOH, CH_3COOH; (b) RCHO, BH_3·pyridine, EtOH, 39% (**33**), 62% (**36**), 38% (**39**), 47% (**54**), 65% (**56**).

moieties. *N*-Acetylation of **5** resulted in a 20-fold decrease in μ binding (**6**: K_i = 94 nM). In contrast, the *N*-methyl (**7**) and the *N*-benzyl (**8**) derivatives displayed μ-opioid receptor binding affinities similar to that of the precursor from which they were derived. The phenolic hydroxy group of opiate-derived ligands is important for biological activity.[1] As expected, replacement of the hydroxyl group of **8** with a hydrogen atom (compound **9**) resulted in a significant (340-fold) decrease in μ binding. The methyl ester **10** and its carboxylic acid analogue **11** were also devoid of appreciable opioid receptor binding. We showed previously in the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine series of μ-opioid receptor antagonists that the $CONH_2$ group was an effective isostere of the phenolic OH moiety.[7] As shown in Table 1, the carboxamide derivative **12** retained good μ binding affinity (K_i = 17 nM). Furthermore, replacement of the phenolic OH functionality of **5** with a $CONH_2$ group resulted in a 2-fold increase in the binding affinity toward the μ-opioid receptor (**13**: K_i = 1.8 nM). The presence and spatial orientation of the phenyl ring of the octahydroquinolizine derivative **4** are of critical importance for good binding affinity toward the μ-opioid receptor.[8]

As shown in Table 2, comparison of the μ binding affinity of **5** with the binding affinity of its diastereoisomeric analogue

Table 2. Opioid Receptor (μ, κ, and δ) Binding Data and in Vitro Antagonist Activity (μ) of Compounds **5** and **14**−**19**

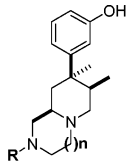


compd	R	$K_i(\mu)$ (nM)[a] or %inh.@10μM[b]	$IC_{50}(\mu)$ (nM)[c]	$K_i(\kappa)$ (nM)[a] or %inh.@10μM[b]	$K_i(\delta)$ (nM)[a] or %inh.@10μM[b]
5[d]	(*S*) 	3.6 (2.2-6.0)	1.1 (0.52-2.2)	18 (13-25)	89 (68-120)
14	(*R*) 	180 (71-450)	52 (39-71)	430 (280-680)	660 (380-1100)
15		49%±6%	nd[e]	46%±3%	35%±4%
16[d]	(*S*) 	8.9 (3.2-24)	2.8 (2.1-3.7)	86 (34-210)	36 (31-43)
17	(*R*) 	25 (10-62)	22 (18-27)	130 (110-150)	410 (220-760)
18[d]	(*S*) 	2.7 (0.66-11)	1.3 (0.79-2.1)	16 (8.9-28)	68 (20-220)
19	(*S*) 	380 (210-730)	66 (34-130)	57 (28-120)	15%±6%

[a] See Table 1, footnote a. [b] See Table 1, footnote b. [c] See Table 1, footnote c. [d] The κ and δ antagonist potency of selected ligands. **5**: $IC_{50}(\kappa)$ = 3.2 nM (0.39−27), $IC_{50}(\delta)$ = 98 nM (9.3−1000). **16**: $IC_{50}(\kappa)$ = 16 nM (4.1−64), $IC_{50}(\delta)$ = 33 nM (3.6−290). **18**: $IC_{50}(\kappa)$ = 1.2 nM (0.47−3.0), $IC_{50}(\delta)$ = 28 nM (18−44). [e] See Table 1, footnote e.

14 demonstrated that the *S*-stereochemistry at the carbon atom bearing the phenyl ring was highly preferred. Furthermore, the binding data for compound **15**, which differs from **5** by the absence of the phenyl group, supported the necessity of this lipophilic substituent for good μ-opioid receptor binding affinity. Replacement of the phenyl moiety of **5** (K_i = 3.6 nM) with a

Table 3. Opioid Receptor (μ, κ, and δ) Binding Data and in Vitro Antagonist Activity (μ) of Compounds **15** and **20**−**32**



compd	n	R	$K_i(\mu)$ (nM)[a] or %inh.@10μM[b]	$IC_{50}(\mu)$ (nM)[c]	$K_i(\kappa)$ (nM)[a] or %inh.@10μM[b]	$K_i(\delta)$ (nM)[a] or %inh.@10μM[b]
15	1		49%±6%	nd[e]	46%±3%	35%±4%
20	1		69%±10%	nd[e]	60%±4%	11%±3%
21	1		520 (140-1800)	nd[e]	36%±5%	47%±7%
22[d]	1		2.0 (1.1-3.7)	2.1 (1.3-3.2)	180 (130-250)	25 (21-30)
23	1		17 (4.2-73)	6.7 (5.0-9.4)	540 (69-4200)	71 (4.6-1100)
24	1		160 (72-360)	78 (25-240)	65%±5%	140 (39-490)
25	1		220 (98-490)	54 (35-81)	3700 (1900-7400)	960 (300-3000)
26[d]	1		1.2 (0.50-2.7)	0.73 (0.54-0.97)	43 (21-85)	140 (66-290)
27[d]	1		5.5 1.5-19)	2.0 (1.3-2.9)	110 (9.5-1300)	240 (9.3-6400)
28	1		36 (17-74)	13 (11-16)	950 (600-1500)	960 (820-1100)
29	2		160 (78-340)	15 (7.4-30)	540 (190-1500)	2900 (1100-7400)
30	1		45%±9%	nd[e]	14%±6%	5%±4%
31	1		210 (69-600)	140 (68-270)	34%±9%	1700 (600-4800)
32	1		31 (14-69)	16 (13-20)	420 (160-1100)	540 (46-6300)

[a] See Table 1, footnote a. [b] See Table 1, footnote b. [c] See Table 1, footnote c. [d] The κ and δ antagonist potency of selected ligands. **22**: $IC_{50}(\kappa)$ = 50 nM (7.2−350), $IC_{50}(\delta)$ = 14 nM (3.4−58). **26**: $IC_{50}(\kappa)$ = 8.4 nM (2.3−31), $IC_{50}(\delta)$ = 150 nM (120−200). **27**: $IC_{50}(\kappa)$ = 20 nM (10−39), $IC_{50}(\delta)$ = 310 nM (98−1000). [e] See Table 1, footnote e.

benzyl substituent (compound **16**; K_i = 8.9 nM) or a cyclohexyl group (compound **18**; K_i = 2.7 nM) was well tolerated. However, replacement of the phenyl ring of **5** with an isopropyl moiety (compound **19**) resulted in a 100-fold decrease in μ binding, suggesting that the isopropyl group of **19** is of insufficient size for an optimal lipophilic contact with the μ-opioid receptor. On the basis of the structure of **4**, we then demonstrated that the bioisosteric replacement of the methylene group at position 6 of the octahydroquinolizine scaffold by an NH or NR moiety successfully led to a new series of potent μ-opioid receptor antagonists. As expected from the limited SAR obtained in the octahydroquinolizine series,[8] we further provided evidence that the presence and proper orientation of a lipophilic substituent (phenyl, benzyl, or cyclohexyl) connected to the octahydro-1*H*-pyrido[1,2-a]pyrazine template are of primary importance for good μ binding and antagonist activity. As indicated previously, the absence of this key pharmacophoric element in structure **15** is likely to explain the weak μ binding affinity of this ligand. On the basis of this assumption, we hypothesized that introduction of various lipophilic substituents at the secondary amine functionality of **15** could lead to compounds with improved μ-opioid receptor binding affinity.

As shown in Table 3, the *N*-methyl (compound **20**) and *N*-acetyl (compound **21**) analogues of **15** displayed weak μ binding affinity. However, as anticipated, changing the acetyl group of **21** to a benzoyl moiety (compound **22**) resulted in a 250-fold increase in the affinity toward the μ receptor. This result demonstrated that both the increased binding affinity and potency of **22**, when compared to **15**, were directly related to the *N*-benzoyl functionality. Introduction of a phenacetyl (**23**), phenpropionyl (**24**), or phenyl (**25**) group in place of the benzoyl functionality of **22** gave rise to compounds of lower binding affinity (Table 3). The *N*-benzyl derivative **26** displayed comparable μ-opioid affinity to the *N*-benzoyl analogue **22**, indicating that the pK_a of the nitrogen atom attaching the benzyl or benzoyl functionalities does not have an effect on μ-opioid binding affinity. To explore the size of the lipophilic pocket in which the benzyl group of **26** interacts, we prepared the *N*-phenethyl (compound **27**) and *N*-phenpropyl (compound **28**) analogues of **26**. These structural modifications led to a decrease in the affinity toward the μ-opioid receptor, indicating that the hydrophobic cavity in which the benzyl group of **26** interacts is relatively small. Furthermore, extending the octahydro-1*H*-pyrido[1,2-a]pyrazine scaffold of **26** to a decahydropyrido[1,2-a][1,4]diazepine template (compound **29**) resulted in a 130-fold decrease in μ binding. Replacement of the benzyl group of **26** with a phenylsulfonamide (compound **31**) also led to a decrease in μ binding. These data showed that subtle structural modifications have an important impact on μ-opioid receptor binding.

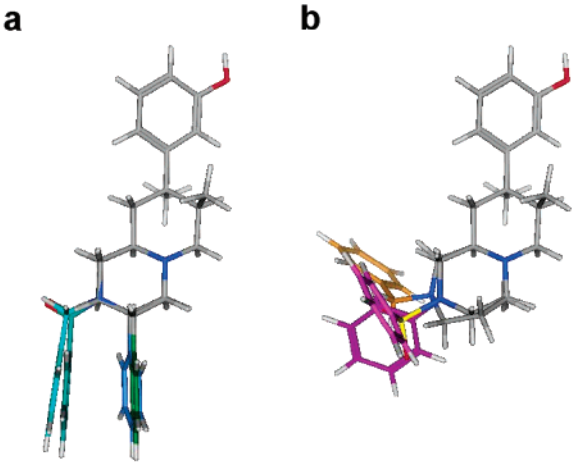


Figure 2. Lowest-energy conformers of (a) set A and (b) set B. Side chain coloring: **4**, green; **5**, blue; **22**, teal; **26**, aqua; **25**, dark magenta; **29**, orange; **31**, magenta.

In an attempt to rationalize these findings, we compared the low-energy conformations of the potent μ ligands (set A: **4**, K_i = 0.62 nM; **5**, K_i = 3.6 nM; **22**, K_i = 2.0 nM; **26**, K_i = 1.2 nM) with the low-energy conformations of weaker μ ligands (set B: **25**, K_i = 220 nM; **29**, K_i = 160 nM; **31**, K_i = 210 nM), structurally related to **5**, **22**, and **26**. To examine the conformational behavior of the investigated ligands, a conformational analysis was performed. All calculations were conducted using the MOE software.[15] Stochastic conformational searches using the default MMFF94x force field without solvation were performed to identify the global minimum energy conformers for the ligands of set A (**4**, **5**, **22**, and **26**) and set B (**25**, **29**, and **31**). Antagonist structures were aligned in MOE by superposing the piperidine ring common to the central fused bicyclic templates. As shown in Figure 2, the ligands of set A (potent μ ligands) assume an extended conformation as their lowest-energy conformer.

In the low-energy conformations of the high-affinity ligands (set A), the phenyl moieties of compounds **4** and **5** are restricted to the downward region shown in Figure 2a. As expected, the *N*-benzoyl and *N*-benzyl side chains of compounds **22** and **26**

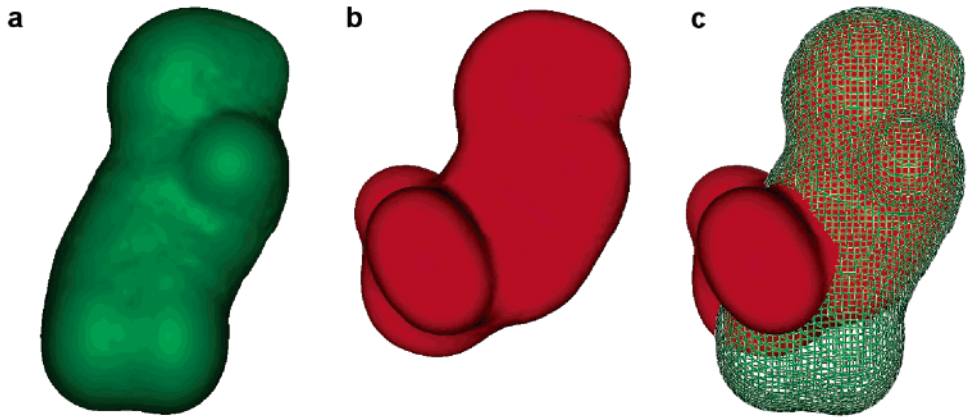


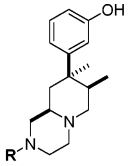
Figure 3. Molecular volumes enclosing (a) high-potency μ antagonists (set A) and (b) lower-potency μ antagonists (set B). The overlay of the two volumes is shown in Figure 4c. Lipophilic substituents in the lower green region, unique to set A, are essential for high μ binding affinity.

are more flexible, and compounds **22** and **26** have low-energy conformations (0.6 and 0.1 kcal/mol above the lowest-energy conformers, respectively) in which the phenyl moiety is positioned to the side of the bicyclic template. In the lowest-energy conformations of ligands of set B (weaker μ ligands), the phenyl moiety is positioned to the side of the bicyclic template in an orientation different to the one adopted for the phenyl rings of the constrained analogues **4** and **5**. There are no conformers in which the phenyl group of **25** can reach the putative hydrophobic pocket occupied by the phenyl groups in the lowest-energy conformers of **4**, **5**, **22**, and **26**. Conformers of **29** and **31** with the benzyl and phenyl sulfonamide side chains extended like the low-energy conformers of **22** and **26** are 2.6 and 2.8 kcal/mol higher in energy, respectively, than their lowest-energy conformers. This molecular modeling study combined with SAR analysis led us to hypothesize that the phenyl groups of **25**, **29**, and **31** are positioned in such an orientation that they are less likely to interact efficiently with the putative hydrophobic pocket of the μ receptor that is of critical importance for ligand recognition. We also generated the molecular volume maps for each set of ligands (Figure 3).

The molecular volume can be visualized using a Gaussian approximation of the Connolly surface, representing the solvent accessible surface area of the molecule.[16] The overlay of the two volumes (Figure 3c) further highlighted the differences between the placement of phenyl groups in the two sets of antagonists. The weaker binding affinity of ligands of set B, when compared with ligands of set A, could also be explained by unfavorable steric interactions of the phenyl groups of **25**, **29**, and **31** with the μ-opioid receptor.

With the identification of **26** as a novel μ-opioid antagonist, the SAR at the benzyl functionality was investigated. This additional study was conducted to further characterize the lipophilic pocket in which the benzyl group of **26** interacts. The biological data obtained for the library compounds **33**−**56** are summarized in Tables 4 and 5. Representative compounds (**33**, **36**, **39**, **54**, and **56**) were resynthesized according to Scheme 6 and further purified to confirm the binding data obtained for the library compounds. The K_i values obtained for the purified products were generally within 2−4-fold of the K_i values obtained for the library compounds. Various substituents were introduced at the 2-, 3-, and 4-position of the benzyl group of **26**. Comparison of the in vitro profile of **33**, **34**, and **35** suggested that substitution at the 2- and 3-position of the benzyl group is preferred. Hence, substitution in the *para* position might hinder the locking of the aromatic moiety within the binding pocket. Introduction of a chloro substituent at the 2-position of the benzyl group of **26** resulted in a slight increase in affinity toward the μ receptor. Indeed, compound **36** displayed high affinity toward the μ-opioid receptor (K_i = 0.47 nM) and potent μ in vitro antagonist activity (IC_{50} = 1.8 nM). This compound

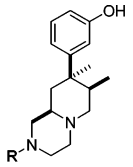
Table 4. Opioid Receptor (μ, κ, and δ) Binding Data and in Vitro Antagonist Activity (μ) of Compounds **26** and **33**−**43**

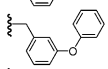
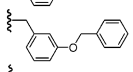


compd	R	$K_i(\mu)$ (nM)[a] or %inh.@10μM[b]	$IC_{50}(\mu)$ (nM)[b]	$K_i(\kappa)$ (nM)[a] or %inh.@10μM[b]	$K_i(\delta)$ (nM)[a] or %inh.@10μM[b]
26		1.2 (0.50-2.7)	0.73 (0.54-0.97)	43 (21-85)	140 (66-290)
33[d]		1.2 (0.86-1.7) **0.98[e] (0.27-3.6)**	1.5 (0.79-2.8) **1.8[e] (1.1-3.0)**	30 (23-37) **42[e] (13-130)**	190 (180-210) **89[e] (20-400)**
34		1.3 (1.0-1.7)	1.5 (2.0-4.9)	130 (100-170)	510 (480-550)
35		14 (9.8-19)	9.5 (8.1-11)	300 (220-400)	350 (210-560)
36[d]		0.95 (0.42-2.2) **0.47 (0.32-1.3)**	2.5 (1.6-3.7) **1.8 (1.3-2.6)**	48 (7.4-310) **16 (5.3-51)**	200 (32-1200) **57 (16-200)**
37		1.5 (1.2-1.7)	1.8 (0.34-9.3)	83 (31-230)	360 (74-1700)
38		17 (8.3-36)	42 (25-69)	280 (180-450)	420 (340-510)
39[d]		2.4 (1.8-3.2) **1.8 (0.72-4.4)**	2.5 (0.89-6.8) **1.6 (0.65-4.3)**	120 (24-660) **76 (26-220)**	550 (220-1300) **300 (30-2900)**
40		4.3 (3.7-5.1)	4.5 (1.9-11)	56 (42-76)	310 (110-860)
41		10 (5.9-18)	5.7 (3.1-11)	270 (220-340)	220 (87-550)
42		750 (380-1500)	190 (38-940)	34%±3%	26%±3%
43		11 (8.3-14)	6.9 (3.0-16)	140 (130-150)	43%±2%

[a] See Table 1, footnote a. [b] See Table 1, footnote b. [c] See Table 1, footnote c. [d] The κ and δ antagonist potency of selected ligands. **26**: $IC_{50}(\kappa)$ = 8.4 nM (2.3−31), $IC_{50}(\delta)$ = 150 nM (120−200). **33**: $IC_{50}(\kappa)$ = 15 nM (4.4−52), $IC_{50}(\delta)$ = 62 nM (1.5−5800). **36**: $IC_{50}(\kappa)$ = 10 nM (6.8−16), $IC_{50}(\delta)$ = 190 nM (27−1400). **39**: $IC_{50}(\kappa)$ = 9.4 nM (3.9−23), $IC_{50}(\delta)$ = 570 nM (38−8600). [e] Biological data of purified library compound expressed as the geometric mean, and 95% confidence intervals of at least three separate determinations.

Table 5. Opioid Receptor (μ, κ, and δ) Binding Data and in Vitro Antagonist Activity (μ) of Compounds **26** and **45**−**56**



compd	R	$K_i(\mu)$ (nM)[a] or %inh.@10μM[b]	$IC_{50}(\mu)$ (nM)[c]	$K_i(\kappa)$ (nM)[a] or %inh.@10μM[b]	$K_i(\delta)$ (nM)[a] or %inh.@10μM[b]
26		1.2 (0.50-2.7)	0.73 (0.54-0.97)	43 (21-85)	140 (66-290)
44		21 (8.4-52)	9.7 (5.1-18)	24 (11-49)	55%±14%
45		13 (3.7-44)	22 (0.50-960)	33 (9.7-110)	43%±14%
46		90 (30-270)	74 (27-210)	980 (370-2600)	49%±12%
47		3.5 (0.78-16)	16 (2.0-120)	230 (110-460)	60%±16%
48		88 (76-100)	80 (60-100)	55%±8%	28%±0.4%
49		20 (14-27)	13 (1.9-92)	390 (98-1500)	1100 (240-5300)
50		13 (11-15)	7.5 (1.4-39)	400 (360-450)	840 (170-4100)
51		(15-18)	18 (13-25)	67%±0.8	1300 (890-2000)
52		7.4 (6.5-8.4)	7.2 (2.5-21)	430 (40-4700)	1500 (1100-1900)
53		12 (3.1-49)	6.1 (1.6-24)	120 (78-190)	740 (350-1500)
54[d]		1.8 (1.5-2.1) **1.4**[e] **(0.21-9.7)**	3.8 (0.25-59) **0.63**[e] **(0.41-0.98)**	110 (35-340) **37**[e] **(32-41)**	310 (260-390) **260**[e] **(59-1100)**
55		3.0 (2.4-3.6)	1.4 (0.21-10)	38 (13-110)	340 (260-440)
56[d]		1.4 (1.2-1.6) **1.1 (0.46-2.4)**	1.7 (0.47-6.2) **1.1 (0.49-2.3)**	160 (62-410) **84 (80-87)**	230 (210-570) **65 (19-220)**

[a] See Table 1, footnote a. [b] See Table 1, footnote b. [c] See Table 1, footnote c. [d] The κ and δ antagonist potency of selected ligands. **26**: $IC_{50}(\kappa)$ = 8.4 nM (2.3−31), $IC_{50}(\delta)$ = 150 nM (120−200); **54**: $IC_{50}(\kappa)$ = 6.6 nM (2.0−22), $IC_{50}(\delta)$ = 340 nM (20−5800); **56**: $IC_{50}(\kappa)$ = 36 nM (15−87), $IC_{50}(\delta)$ = 85 nM (9.4−770). [e] Biological data of purified library compound expressed as the geometric mean of at least three separate determinations.

also displayed improved selectivity profile (μ/κ, 34-fold; μ/δ, 120-fold) when compared to the selectivity profile of **4** (μ/κ, 13-fold; μ/δ, 40-fold) from which it derived. As shown in Table 4, the phenolic derivative **39** was also found to be a potent μ-opioid receptor antagonist. The in vitro profile of compounds **44** and **45** (Table 5) showed that introduction of additional lipophilic functionalities at the 3-position of the benzyl group of **26** resulted in a decrease in μ binding. This confirmed that the size and depth of this lipohilic pocket might be relatively small. However, replacement of the benzyl group of **26** by a naphthalen-1-yl-methyl moiety (compound **47**) was well tolerated. Replacing the phenyl ring of **26** by various heterocycles (compounds **48**−**55**) also provided ligands with good affinity for the μ-opioid receptor. In particular, the thiophene derivative **54** bound to the μ-opioid receptor with high affinity (K_i = 1.4 nM) and was a potent μ antagonist in vitro ($IC_{50}(\mu)$ = 0.74 nM). The interaction of these compounds with the hypothesized lipophilic pocket may either be of $\pi-\pi$-type stacking with an aromatic receptor moiety or simply hydrophobic in nature. The biological data for compound **56** (K_i = 1.1 nM) demonstrated that the benzyl group of **26** could be efficiently replaced by a cyclohexylmethyl moiety. This result is consistent with a non $\pi-\pi$-type hydrophobic interaction. Comparison of the μ binding affinity of **5** (K_i = 3.6 nM) with the μ binding affinity of its cyclohexyl analogue (**18**: K_i = 2.7 nM) conclusively supports that statement.

Conclusion

There are multiple reasons for the use of bioisosterism to design new drugs, including the necessity to improve pharmacological activity, gain selectivity for a determined receptor or enzymatic isoform subtype, or optimize pharmacokinetics. In this study, we explored the concept of bioisosterism to prepare synthetically simplified analogues of the conformationally constrained μ-opioid antagonist **4**, thereby allowing us to potentially expand SAR studies. The bioisosteric replacement of the methylene group at position 6 of the octahydroquinolizine scaffold of **4** ($K_i(\mu)$ = 0.62 nM) by an NH functionality (compound **5**; $K_i(\mu)$ = 3.6 nM) was well tolerated. In addition, the new octahydro-1*H*-pyrido[1,2-a]pyrazine series offers several advantages over the octahydroquinolizine series, including ease of preparation, stereochemical control, and potential for scale-up. Indeed, the preparation of compound **5** (7 steps; 15% overall yield) was conducted in a more straightforward manner when compared to the synthesis of **4** (11 steps; 0.07% yield). This new series of octahydro-1*H*-pyrido[1,2-a]pyrazine provided numerous ligands with good affinity toward the μ-opioid receptor and potent μ in vitro antagonist activity. The SAR studies indicated that the presence of a lipophilic group at position 2 or 3 of the octahydro-1*H*-pyrido[1,2-a]pyrazine template is essential for high μ-opioid receptor binding affinity. This key lipophilic moiety, which can be an aromatic, heteroaromatic, or an aliphatic group, is thought to interact with the μ receptor by hydrophobic contacts. The SAR showed that the nature of the linker connecting this lipophilic moiety to the fused bicyclic heterocyclic template has an important impact on μ-opioid receptor binding affinity. Hence, some of the best ligands incorporated an *N*-benzoyl (**22**), *N*-benzyl (**26**), or *N*-cyclohexylmethyl (**56**) moieties. From this study, we identified compound **36**, which displayed high affinity toward the μ-opioid receptor (K_i = 0.47 nM) and potent μ in vitro antagonist activity (IC_{50} = 1.8 nM). Furthermore, this compound also showed an improved binding selectivity profile (μ/κ and μ/δ) when compared to the selectivity profile of **4** from which it evolved. This new series of octahydro-1*H*-pyrido[1,2-a]-pyrazines has much latitude for structural manipulation. In particular, variations of the substituents at position 2 and/or 3 of this template could be further explored to identify new subtype selective compounds. The SAR data as well as modeling studies obtained with these rigid structures provided insights into the pharmacophoric features (hydroxyphenyl, piperidine nitrogen, and lipophilic moieties) important for μ binding and expression of antagonist activity. This information provides useful tools for further refinement of receptor modeling and docking studies in this class of μ antagonists.

Experimental Section

A. Chemistry. General. All chemicals were reagent grade and used without further purification. Thin-layer chromatography (TLC) was performed on silica gel 6F glass-backed plates (250 microns) from Analtech and visualized by UV 254 irradiation and iodine. Flash chromatography was conducted using the ISCO CombiFlash with RediSep silica gel cartridges (4, 12, 40, and 120 g). Chromatographic elution solvent systems are reported as volume/volume ratios. All ^{1}H NMR spectra were recorded at ambient temperature on a Bruker 400-MHz spectrometer. They are reported

in ppm on the δ scale from TMS. LC-MS data were obtained using a Thermo-Finnigan Surveyor HPLC and a Thermo-Finnigan AQA MS using either positive or negative electrospray ionization. Program (positive); solvent A, 10 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B, acetonitrile; column, Michrom Bioresources Magic C18 Macro Bullet; detector, PDA λ = 220−300 nm; gradient, 96% A−100% B in 3.2 min and hold 100% B for 0.4 min. Program (negative); solvent A, 1 mM ammonium acetate, pH 4.5, 1% acetonitrile; solvent B, acetonitrile; column, Michrom Bioresources Magic C18 Macro Bullet; detector, PDA λ = 220−300 nm; gradient, 96% A−100% B in 3.2 min and hold 100% B for 0.4 min. Mass spectra were obtained on a Finnigan 4000 or VG707EHF spectrometer by the mass spectrometry laboratories at the Department of Chemistry, University of Minnesota. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA and are within ±0.4% of theoretical values.

(3*R*,4*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-3,4-dimethylpiperidine-1-carboxylate (58). To a solution of **57** (72.69 g, 238 mmol) in *N*,*N*-dimethylformamide (500 mL) was added imidazole (43.13 g, 309 mmol), DMAP (2.9 g, 23.8 mmol), and *tert*-butyldimethylsilyl chloride (43.13 g, 286 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then poured into water and extracted with hexanes. The combined organic extracts were washed successively with water and brine solution, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent, hexane/ethyl acetate mixtures of increasing polarity). Yield 86% (colorless oil); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.62 (d, J = 6 Hz, 3H), 0.98 (s, 9H), 1.26 (s, 1H), 1.34 (s, 3H), 1.46 (s, 9H), 1.96 (m, 1H), 2.17 (m, 1H), 3.03 (m, 1H), 3.30 (m, 1H), 3.79 (m, 0.6H), 3.88 (m, 0.4H), 4.06 (m, 0.5H), 4.23 (m, 0.5H), 6.67 (dd, J = 8 and 2 Hz, 1H), 6.73 (s, 1H), 6.84 (d, J = 7 Hz, 1H), 7.16 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 420 (M + H$^+$).

(2*R*,4*R*,5*R*)-1-(*tert*-Butoxycarbonyl)-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-4,5-dimethylpiperidine-2-carboxylic acid (59). An oven-dried flask under nitrogen atmosphere was charged with a solution of **58** (5.73 g, 13.64 mmol) and ¢¢TMEDA in diethyl ether (30 mL). The solution was cooled to −78 °C and *sec*-butyllithium (1.4 M in cyclohexane, 14.6 mL, 20.46 mmol) was added dropwise over 30 min. After stirring at −78 °C for 4.5 h, carbon dioxide was bubbled through the solution, and the reaction mixture was allowed to warm to room temperature overnight. The mixture was poured into saturated ammonium chloride solution, and the aqueous layer was extracted once with diethyl ether. The ether extract was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent, dichloromethane/methanol/acetic acid mixtures of increasing polarity). Yield 73% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 6H), 0.69 (d, J = 7 Hz, 3H), 0.98 (s, 9H), 1.37 (s, 3H), 1.46 (s, 9H), 2.01 (dd, J = 14 and 6 Hz, 2H), 2.40 (t, J = 12 Hz, 1H), 3.37 (dd, J = 14 and 8 Hz, 1H), 3.74 (m, 1H), 4.30 (dd, J = 11 and 6 Hz, 1H), 6.67 (dd, J = 8 and 2 Hz, 1H), 6.77 (s, 1H), 6.88 (d, J = 7 Hz, 1H), 7.14 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 464 (M + H$^+$).

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-((*S*)-2-methoxy-2-oxo-1-phenylethylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (60). To a stirred solution of **59** (2 g, 4.32 mmol) in acetonitrile (20 mL) under a nitrogen atmosphere was added, sequentially, *N*,*N*-diisopropylethylamine (3 mL, 17.28 mmol), (*S*)-methyl 2-amino-2-phenylacetate (1.04 g, 5.18 mmol), and ¢¢TBTU (2.08 g, 6.48 mmol). The reaction was stirred at room temperature overnight, poured into saturated ammonium chloride solution, and extracted with ethyl acetate. The organic extracts were washed with saturated brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent, hexane/ethyl acetate mixtures of increasing polarity). Yield 82% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.54 (d, J = 6 Hz, 3H), 0.98 (s, 9H), 1.34 (s, 3H), 1.38 (s, 9H), 2.03 (m, 2H), 2.40 (t, J = 13 Hz, 1H), 3.03 (dd, J = 13 and 8 Hz, 1H), 3.74 (s, 3H), 3.92 (dd, J = 11 and 8 Hz, 1H), 4.33 (dd, J = 12 and 6 Hz, 1H), 5.59 (d, J = 7 Hz, 1H), 6.68 (dd, J = 8 and 2 Hz, 1H), 6.75 (t, J = 2 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 2H), 7.33 (m, 1H), 7.35 (m, 4H); LCMS (ESI) m/z 611 (M + H$^+$).

(*S*)-Methyl-2-((2*R*,4*R*,5*R*)-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)-2-phenylacetate (61). To a solution of **60** (2.16 g, 3.54 mmol) in methanol (75 mL) was added a 4 M solution of anhydrous hydrogen chloride in dioxane (3.8 mL, 14.4 mmol). The mixture was heated to reflux for 2 h. The mixture was concentrated under reduced pressure, and the residue was taken up in ethyl acetate (75 mL). A saturated solution of sodium bicarbonate was added to the mixture, which was stirred for 2 h at room temperature. The layers were separated, and the organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was washed with hexanes and used for the next step without further purification. Yield 95% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.73 (d, J = 7 Hz, 3H), 1.28 (s, 4H), 1.92 (m, 1H), 2.03 (m, 1H), 2.81 (dd, J = 12 and 2 Hz, 1H), 3.29 (dd, J = 12 and 3 Hz, 1H), 3.61 (dd, J = 11 and 4 Hz, 1H), 3.74 (s, 3H), 5.63 (d, J = 13 Hz, 1H), 6.64 (dd, J = 8 and 2 Hz, 1H), 6.72 (s, 1H), 6.79 (d, J = 7 Hz, 1H), 7.15 (t, J = 8 Hz, 1H), 7.38 (m, 5H), 7.92 (d, J = 7 Hz, 1H); LCMS (ESI) m/z 397 (M + H$^+$).

(3*S*,7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenylhexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (62). A solution of **61** (1.33 g, 3.36 mmol) in toluene (200 mL) was heated to reflux for 60 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). Yield 47% (yellow solid); ^{1}H NMR ($CDCl_3$) δ 0.64 (d, J = 7 Hz, 3H), 1.39 (s, 3H), 2.11 (m, 1H), 2.26 (t, J = 13 Hz, 1H), 2.43 (dd, J = 14 and 2 Hz, 1H), 3.12 (dd, J = 14 Hz and 3 Hz, 1H), 4.35 (dd, J = 12 and 3 Hz, 1H), 4.41 (dd, J = 14 and 2 Hz, 1H), 5.16 (s, 1H), 6.51 (s, 1H), 6.67 (dd, J = 8 and 2 Hz, 1H), 6.73 (s, 1H), 6.79 (d, J = 8 Hz, 2H), 7.19 (t, J = 8 Hz, 1H), 7.39 (m, 5H); LCMS (ESI) m/z 363 (M − H$^+$).

3-((3*S*,7*R*,8*R*,9α*R*)-7,8-Dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (5). To a solution of **62** (0.57 g, 1.57 mmol) in anhydrous tetrahydrofuran (10 mL) was added borane−dimethyl sulfide complex (2 M solution in tetrahydrofuran, 4.7 mL, 9.4 mmol), and the reaction was heated to reflux under a nitrogen atmosphere for 16 h. The mixture was then cooled to 0 °C. Methanol (20 mL) was added to the reaction mixture, which was stirred at 0 °C for 1 h. A 2 M anhydrous solution of hydrogen chloride in diethyl ether (5 mL) was then added to the reaction, which was heated to reflux for 1 h. After cooling to room temperature, an aqueous ammonium hydroxide solution (5 mL) was added to the mixture, which was stirred for 10 min at room temperature. The mixture was concentrated under reduced pressure. The residue was dissolved in methanol and concentrated under reduced pressure. This process was repeated three times. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 69% (white solid); ^{1}H NMR (CD_3OD) δ 0.79 (d, J = 7 Hz, 3H), 1.38 (s, 3H), 1.57 (d, J = 13 Hz, 1H), 1.95 (t, J = 12 Hz, 1H), 2.06 (m, 1H), 2.30 (t, J = 13 Hz, 1H), 2.49 (t, J = 11 Hz, 1H), 2.57 (dd, J = 12 and 2 Hz, 1H), 2.81 (m, 3H), 3.06 (dd, J = 13 and 2 Hz, 1H), 4.04 (dd, J = 11 and 3 Hz, 1H), 6.59 (dd, J = 8 and 2 Hz, 1H), 6.72 (t, J = 2 Hz, 1H), 6.76 (d, J = 7 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.30 (m, 1H), 7.36 (t, J = 7 Hz, 2H), 7.41 (d, J = 7 Hz, 2H); LCMS (ESI) m/z 337 (M + H$^+$). Anal. ($C_{22}H_{28}N_2O\cdot 0.33H_2O$) C, H, N.

1-((3*S*,7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)ethanone (6). To a solution of **5** (0.1 g, 0.30 mmol) in tetrahydrofuran (5 mL) was added triethylamine (0.09 g, 0.90 mmol) and acetyl chloride (0.05 mL, 0.65 mmol), and the reaction was stirred at room temperature for 1 h. Aqueous 1 N solution of sodium hydroxide (10 mL) was then added to the reaction mixture, which was stirred for 1 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent:

dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 53% (white solid); ^{1}H NMR (CD_3OD) δ 0.79 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.66 (d, J = 12 Hz, 1H), 2.05 (m, 5H), 2.82 (dd, J = 11 and 2 Hz, 1H), 3.09 (m, 1H), 3.61 (br m, 1H), 3.81 (dd, J = 14 and 6 Hz, 1H), 4.98 (dd, J = 10 and 6 Hz, 1H), 6.60 (dd, J = 8 and 2 Hz, 1H), 6.74 (s, 1H), 6.77 (d, J = 7 Hz, 1H), 7.12 (t, J = 8 Hz, 1H), 7.26 (m, 3H), 7.33 (m, 2H); LCMS (ESI) m/z 379 (M + H$^+$). Anal. ($C_{24}H_{30}N_2O_2 \cdot 0.2H_2O$) C, H, N.

3-((3*S*,7*R*,8*R*,9α*R*)-2,7,8-Trimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (7). To a solution of **5** (0.1 g, 0.30 mmol) in tetrahydrofuran (5 mL) and ethanol (5 mL) was added triethylamine (0.067 g, 0.66 mmol) and formaldehyde (40% aqueous solution; 0.05 mL, 0.60 mmol). After 10 min, sodium cyanoborohydride (0.03 g, 0.36 mmol) was added to the mixture, which was stirred at room temperature for 60 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 76% (white solid); ^{1}H NMR (CD_3OD) δ 0.77 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.57 (d, J = 13 Hz, 1H), 1.96 (t, J = 13 Hz, 1H), 2.07 (s, 4H), 2.24 (t, J = 11 Hz, 1H), 2.32 (t, J = 11 Hz, 1H), 2.55 (m, 1H), 2.66 (m, 2H), 2.74 (m, 1H), 2.92 (d, J = 10 Hz, 1H), 3.24 (d, J = 9 Hz, 1H), 6.58 (dd, J = 8 and 2 Hz, 1H), 6.72 (t, J = 2 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 7.29 (m, 1H), 7.36 (m, 4H); LCMS (ESI) m/z 351 (M + H$^+$). Anal. ($C_{23}H_{30}N_2O \cdot 0.4H_2O$) C, H, N.

3-((3*S*,7*R*,8*R*,9α*R*)-2-Benzyl-7,8-dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (8). To a solution of **5** (1 g, 2.98 mmol) in ethanol (20 mL) was added benzaldehyde (0.95 g, 8.93 mmol), and the reaction mixture was stirred at room temperature for 10 min. To this was then added BAP (0.82 g, 8.93 mmol), and the reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate. The mixture was washed with a saturated aqueous sodium bicarbonate solution, water, and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 71% (white solid); ^{1}H NMR (CD_3OD) δ 0.76 (d, J = 7 Hz, 3H), 1.31 (s, 3H), 1.38 (d, J = 13 Hz, 1H), 1.89 (t, J = 13 Hz, 1H), 2.04 (m, 2H), 2.32 (t, J = 11 Hz, 1H), 2.48 (m, 1H), 2.54 (dd, J = 11 and 2 Hz, 1H), 2.69 (t, J = 3 Hz, 1H), 2.72 (t, J = 3 Hz, 1H), 2.79 (dd, J = 11 and 2 Hz, 1H), 2.90 (d, J = 13 Hz, 1H), 3.51 (dd, J = 10 and 3 Hz, 1H), 3.74 (d, J = 13 Hz, 1H), 6.55 (dd, J = 7 and 1 Hz, 1H), 6.67 (t, J = 2 Hz, 1H), 6.71 (d, J = 7 Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.21 (m, 1H), 7.28 (m, 5H), 7.37 (t, J = 8 Hz, 2H), 7.53 (d, J = 6 Hz, 2H); LCMS (ESI) m/z 427 (M + H$^+$). Anal. ($C_{29}H_{34}N_2O$) C, H, N.

3-((3*S*,7*R*,8*R*,9α*R*)-2-Benzyl-7,8-dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenyl trifluoromethanesulfonate (63). To a solution of **8** (0.9 g, 2.11 mmol) in dichloromethane (10 mL) at 0 °C under a nitrogen atmosphere was added *N*-phenyltrifluoromethane sulfonimide (0.83 g, 2.32 mmol) and triethylamine (0.71 mL, 5.06 mmol). The reaction mixture was allowed to warm to room temperature overnight and then concentrated under reduced pressure. The residue was taken up in ethyl acetate. The organic mixture was washed successively with brine, a 1 N aqueous solution of sodium hydroxide, and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). Yield 72% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.75 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.44 (d, J = 12 Hz, 1H), 1.57 (s, 1H), 1.88 (t, J = 12 Hz, 1H), 2.05 (m, 1H), 2.32 (t, J = 11 Hz, 1H), 2.44 (m, 1H), 2.51 (dd, J = 12 and 2 Hz, 1H), 2.67 (dd, J = 12 and 3 Hz, 1H), 2.76 (dd, J = 11 and 3 Hz, 1H), 2.83 (dd, J = 11 and 2 Hz, 1H), 2.88 (d, J = 14 Hz, 1H), 3.51 (dd, J = 11 and 3 Hz, 1H), 3.82 (d, J = 13 Hz, 1H), 7.09 (m, 2H), 7.24 (m, 4H), 7.30 (m, 4H), 7.37 (m, 3H), 7.53 (m, 1H); LCMS (ESI) m/z 559 (M + H$^+$)

(3*S*,7*R*,8*R*,9α*R*)-2-Benzyl-7,8-dimethyl-3,8-diphenyl-octahydro-1*H*-pyrido[1,2-α]pyrazine (9). A solution of **63** (0.35 g, 0.63 mmol) in *N*,*N*-dimethylformamide (20 mL) under a nitrogen atmosphere was treated with triethylamine (0.35 mL, 2.52 mmol), formic acid (0.1 mL, 2.52 mmol), palladium(II) acetate (0.02 g, 0.09 mmol), and triphenylphosphine (0.03 g, 0.13 mmol), and the mixture was heated to 60 °C for 18 h. After cooling to room temperature, the reaction was treated with a 0.5 N aqueous solution of hydrochloric acid (20 mL) and stirred for 30 min at room temperature. The reaction mixture was poured into dichloromethane, and the layers were separated. The organic extracts were washed with water until the washings attained a pH of 7. The organic extracts were then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). Yield 57% (white solid); ^{1}H NMR (CD_3OD) δ 0.72 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.43 (d, J = 13 Hz, 1H), 1.93 (t, J = 13 Hz, 1H), 2.08 (m, 2H), 2.31 (t, J = 12 Hz, 1H), 2.48 (m, 1H), 2.54 (dd, J = 12 and 2 Hz, 1H), 2.70 (dd, J = 11 and 2 Hz, 2H), 2.81 (dd, J = 11 and 2 Hz, 1H), 2.90 (d, J = 13 Hz, 1H), 3.51 (dd, J = 11 and 2 Hz, 1H), 3.74 (d, J = 13 Hz, 1H), 7.12 (m, 1H), 7.26 (m, 10H), 7.37 (t, J = 8 Hz, 2H), 7.52 (m, 2H); LCMS (ESI) m/z 411 (M + H$^+$). Anal. ($C_{29}H_{34}N_2$) C, H, N.

Methyl-3-((3*S*,7*R*,8*R*,9α*R*)-2-benzyl-7,8-dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)benzoate (10). To a solution of **63** (0.5 g, 0.90 mmol) in methanol (6 mL) and dimethyl sulfoxide (8 mL) was added triethylamine (0.28 mL, 1.97 mmol). Carbon monoxide was then bubbled through the solution for 5 min. Palladium(II) acetate (0.02 g, 0.09 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (dppf; 0.1 g, 0.18 mmol) were added to the mixture. Carbon monoxide was bubbled through the reaction mixture for 15 min while the reaction was heated to 65 °C. The reaction mixture was heated at 65 °C under an atmosphere of carbon monoxide for 18 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic extracts were washed with water and saturated brine solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). Yield 76% (white solid); ^{1}H NMR (CD_3OD) δ 0.72 (d, J = 7 Hz, 3H), 1.36 (s, 3H), 1.50 (d, J = 13 Hz, 1H), 1.98 (t, J = 13 Hz, 1H), 2.11 (m, 2H), 2.35 (t, J = 11 Hz, 1H), 2.54 (m, 2H), 2.74 (m, 2H), 2.84 (dd, J = 11 and 2 Hz, 1H), 2.92 (d, J = 13 Hz, 1H), 3.52 (dd, J = 10 and 3 Hz, 1H), 3.74 (d, J = 13 Hz, 1H), 3.89 (s, 3H), 7.22 (m, 1H), 7.28 (m, 5H), 7.39 (m, 3H), 7.53 (d, J = 8 Hz, 3H), 7.82 (dd, J = 8 and 2 Hz, 1H), 7.90 (s, 1H); LCMS (ESI) m/z 469 (M + H$^+$). Anal. ($C_{31}H_{36}N_2O_2 \cdot 0.33H_2O$) C, H, N.

3-((3*S*,7*R*,8*R*,9α*R*)-2-Benzyl-7,8-dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)benzoic acid (11). A solution of **10** (0.29 g, 0.62 mmol) in tetrahydrofuran (4 mL) and water (2 mL) was treated with lithium hydroxide monohydrate (0.08 g, 1.86 mmol) and methanol (10 mL), and the mixture was stirred at room temperature for 2 days. The reaction mixture was neutralized to pH ~6−7 by the addition of a 1 N aqueous solution of hydrochloric acid. The mixture was then concentrated under reduced pressure. The residue was taken up in dichloromethane. The organic solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was isolated without further purification. Yield 100% (white solid); ^{1}H NMR (CD_3OD) δ 0.76 (d, J = 7 Hz, 3H), 1.42 (s, 3H), 1.69 (d, J = 13 Hz, 1H), 2.14 (t, J = 13 Hz, 1H), 2.27 (m, 1H), 2.34 (m, 1H), 2.80 (t, J = 11 Hz, 1H), 2.88 (dd, J = 13 and 2 Hz, 1H), 2.95 (dd, J = 12 and 2 Hz, 1H), 3.02 (m, 3H), 3.11 (dd, J = 12 and 3 Hz, 1H), 3.75 (m, 2H), 7.22 (m, 1H), 7.28 (m, 4H), 7.36 (m, 2H), 7.42 (m, 3H), 7.56 (d, J = 7 Hz, 2H), 7.81 (d, J = 8 Hz, 1H), 7.90 (s, 1H); LCMS (ESI) m/z 455 (M + H$^+$). Anal. ($C_{30}H_{34}N_2O_2 \cdot 2HCl \cdot 3H_2O$) C, H, N.

3-((3*S*,7*R*,8*R*,9α*R*)-2-Benzyl-7,8-dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)benzamide (12). To a stirred solution of **11** (0.22 g, 0.48 mmol) in *N*,*N*-dimethylformamide (10 mL) were added, sequentially, triethylamine (0.15 mL, 1.06 mmol), ammonium chloride (0.1 g, 2.40 mmol), and ¢¢TBTU (0.23 g, 0.72

mmol). The reaction was stirred at room temperature for 4 h, poured into saturated ammonium chloride solution, and extracted with ethyl acetate. The organic extracts were washed with saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 91% (white solid); ^{1}H NMR (CD_3OD) δ 0.74 (d, J = 7 Hz, 3H), 1.39 (s, 3H), 1.64 (d, J = 13 Hz, 1H), 2.06 (t, J = 13 Hz, 1H), 2.22 (m, 2H), 2.59 (t, J = 12 Hz, 1H), 2.76 (m, 2H), 2.89 (m, 1H), 2.95 (m, 3H), 3.61 (dd, J = 11 and 3 Hz, 1H), 3.75 (d, J = 13 Hz, 1H), 7.22 (m, 1H), 7.28 (m, 6H), 7.40 (t, J = 8 Hz, 3H), 7.47 (d, J = 8 Hz, 1H), 7.54 (m, 2H), 7.68 (m, 2H), 7.778 (s, 1H); LCMS (ESI) m/z 454 (M + H$^+$); HRMS for $C_{30}H_{35}N_3O$ (M, 453.2780 [M + H]) calcd, 454.2853; found, 454.2853.

3-((3*S*,7*R*,8*R*,9α*R*)-7,8-Dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)benzamide (13). To a solution of **12** (0.1 g, 0.22 mmol) in ethanol (20 mL) was added 10% palladium on charcoal (0.01 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The mixture was then filtered through Celite. The Celite was washed with ethanol, and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 12% (white solid); ^{1}H NMR (CD_3OD) δ 0.77 (d, J = 7 Hz, 3H), 1.43 (s, 3H), 1.67 (d, J = 12 Hz, 1H), 2.02 (t, J = 12 Hz, 1H), 2.18 (m, 1H), 2.24 (t, J = 11 Hz, 1H), 2.46 (m, 1H), 2.58 (dd, J = 11 and 2 Hz, 1H), 2.79 (m, 3H), 3.04 (dd, J = 12 and 3 Hz, 1H), 3.97 (dd, J = 11 and 3 Hz, 1H), 7.27 (m, 1H), 7.33 (t, J = 8 Hz, 2H), 7.42(m, 3H), 7.52 (d, J = 8 Hz, 1H), 7.70 (dd, J = 8 and 2 Hz, 1H), 7.83 (s, 1H); LCMS (ESI) m/z 364 (M + H$^+$). Anal. ($C_{23}H_{29}N_3O\cdot0.33H_2O$) C, H, N.

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-((*R*)-2-methoxy-2-oxo-1-phenylethylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (64a). To a stirred solution of **59** (2 g, 4.32 mmol) in acetonitrile (20 mL) under a nitrogen atmosphere were added, sequentially, *N*,*N*-diisopropylethylamine (3 mL, 17.28 mmol), (*R*)-methyl 2-amino-2-phenylacetate (1.04 g, 5.18 mmol), and ¢¢TBTU (2.08 g, 6.48 mmol). The reaction mixture was stirred at room temperature overnight, poured into a saturated aqueous solution of ammonium chloride, and extracted with ethyl acetate. The organic extracts were washed with saturated brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity). Yield 83% (white foam); ^{1}H NMR ($CDCl_3$) δ 0.17(s, 6H), 0.47 (d, J = 7 Hz, 3H), 0.97 (s, 9H), 1.34 (s, 3H), 1.46 (s, 9H), 2.00 (m, 2H), 2.37 (t, J = 12 Hz, 1H), 2.94 (dd, J = 14 and 9 Hz, 1H), 3.73 (s, 3H), 3.90 (m, 1H), 4.37 (dd, J = 12 and 6 Hz, 1H), 5.57 (d, J = 7 Hz, 1H), 6.66 (dd, J = 8 and 2 Hz, 1H), 6.73 (s, 1H), 6.85 (d, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 1H), 7.35 (m, 5H); LCMS (ESI) m/z 611 (M + H$^+$).

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-(2-methoxy-2-oxoethylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (64b). Compound **64b** was synthesized in a manner similar to **64a**, using methyl 2-aminoacetate. Yield 95% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.53 (d, J = 6 Hz 3H), 0.98 (s, 9H), 1.35 (s, 3H), 1.48 (s, 9H), 2.39 (t, J = 13 Hz, 1H), 3.04 (dd, J = 14 and 9 Hz, 1H), 3.76 (s, 3H), 3.89 (dd, J = 14 and 6 Hz, 1H), 4.05 (dd, J = 10 and 5 Hz, 2H), 4.35 (dd, J = 11 and 6 Hz, 1H), 6.60 (br s, 1H), 6.67 (dd, J = 8 and 2 Hz, 1H), 6.76 (t, J = 2 Hz, 1H), 6.87 (dd, J = 8 and 1 Hz, 1H), 7.14 (t, J = 8 Hz, 3H); LCMS (ESI) m/z 535 (M + H$^+$).

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (64c). Compound **64c** was synthesized in a manner similar to **64a** using (*S*)-methyl 2-amino-3-phenylpropanoate. Yield 81% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.45 (d, J = 7 Hz, 3H), 0.98 (s, 9H), 1.32 (s, 3H), 1.45 (s, 9H), 1.98 (m, 2H), 2.33 (t, J = 13 Hz, 1H), 2.89 (dd, J = 14 and 9 Hz, 1H), 3.12 (t, J = 6 Hz, 2H), 3.70 (s, 3H), 3.88 (dd, J = 8 and 3 Hz, 1H), 4.33 (dd, J = 12 and 6 Hz, 1H), 4.84 (q, J = 6 Hz, 1H), 6.66 (dd, J = 8 and 2 Hz, 1H), 6.73 (t, J = 2 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 7.13 (m, 3H), 7.24 (m, 1H), 7.29 (m, 2H); LCMS (ESI) m/z 625 (M + H$^+$).

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (64d). Compound **64d** was synthesized in a manner similar to **64a**, using (*R*)-methyl 2-amino-3-phenylpropanoate. Yield 71% (white foam); ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 6H), 0.43 (d, J = 7 Hz, 3H), 0.99 (s, 9H), 1.30 (s, 3H), 1.44 (s, 9H), 1.98 (dd, J = 14 and 6 Hz, 2H), 2.14 (m, 1H), 2.79 (m, 1H), 3.05 (dd, J = 14 and 6 Hz, 1H), 3.22 (dd, J = 14 and 6 Hz, 1H), 3.74 (s, 3H), 3.82 (dd, J = 12 and 4 Hz, 1H), 4.25 (q, J = 6 Hz, 1H), 4.92 (m, 1H), 6.55 (m, 1H), 6.68 (m, 1H), 6.72 (t, J = 2 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 7.12 (m, 1H), 7.16 (t, J = 8 Hz, 2H), 7.24 (m, 3H); LCMS (ESI) m/z 625 (M + H$^+$).

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-((*S*)-3-cyclohexyl-1-methoxy-1-oxopropan-2-ylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (64e). Compound **64e** was synthesized in a manner similar to **64a**, using (*S*)-methyl 2-amino-2-cyclohexyl acetate. Yield 82% (white foam); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.50 (d, J = 7 Hz, 3H), 0.98 (s, 9H), 1.04−1.16 (m, 2H), 1.19−1.28 (m, 2H), 1.34 (s, 3H), 1.50 (s, 9H), 1.59 (s, 2H), 1.60−1.69 (m, 2H), 1.70−1.84 (m, 3H), 2.00 (m, 2H), 2.34 (t, J = 13 Hz, 1H), 2.92 (dt, J = 14 and 4 Hz, 1H), 3.73 (s, 3H), 3.96 (br s, 1H), 4.38 (dd, J = 11 and 6 Hz, 1H), 4.54 (dd, J = 9 and 5 Hz, 1H), 6.67 (dd, J = 8 and 2 Hz, 1H), 6.74 (t, J = 2 Hz, 1H), 6.86 (dd, J = 9 and 1 Hz, 1H), 7.13 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 617 (M + H$^+$).

(2*R*,4*R*,5*R*)-*tert*-Butyl-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-2-((*S*)-1-methoxy-4-methyl-1-oxopentan-2-ylcarbamoyl)-4,5-dimethylpiperidine-1-carboxylate (64f). Compound **64f** was synthesized in a manner similar to **64a**, using (*S*)-methyl 2-amino-3-methylbutanoate. Yield 75% (white foam); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.50 (d, J = 7 Hz, 3H), 0.90 (d, J = 7 Hz, 3H), 0.98 (s, 12H), 1.34 (s, 3H), 1.49 (s, 9H), 1.61 (br s, 1H), 2.05 (m, 2H), 2.19 (m, 1H), 2.36 (t, J = 13 Hz, 1H), 2.93 (dd, J = 14 and 11 Hz, 1H), 3.74 (s, 3H), 4.40 (dd, J = 12 and 6 Hz, 1H), 4.56 (dd, J = 9 and 5 Hz, 1H), 6.67 (dd, J = 8 and 2 Hz, 1H), 6.75 (t, J = 2 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 7.13 (m, 1H); LCMS (ESI) m/z 577 (M + H$^+$).

(*R*)-Methyl-2-((2*R*,4*R*,5*R*)-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)-2-phenylacetate (65a). To a solution of **64a** (2.18 g, 3.49 mmol) in methanol (100 mL) was added a 2 M solution of hydrogen chloride in diethyl ether (7.2 mL, 14.4 mmol), and the mixture was heated to reflux for 2 h. The solvents were removed under vacuum, and the residue was taken up in ethyl acetate (75 mL). A saturated aqueous solution of sodium bicarbonate (100 mL) was then added to the mixture, which was stirred for 2 h at room temperature. The layers were separated, and the organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was washed with hexanes and used in the next step without further purification. Yield 84% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.69 (d, J = 7 Hz, 3H), 1.26 (m, 1H), 1.32 (s, 3H), 1.95 (m, 4H), 2.83 (dd, J = 12 and 2 Hz, 1H), 3.32 (dd, J = 12 and 3 Hz, 1H), 3.68 (dd, J = 13 and 2 Hz, 1H), 3.73 (s, 3H), 5.60 (d, J = 8 Hz, 1H), 6.64 (dd, J = 8 and 2 Hz, 1H), 6.68 (s, 1H), 6.76 (d, J = 8 Hz, 1H), 7.15 (t, J = 8 Hz, 1H), 7.37 (m, 5H), 7.80 (d, J = 7 Hz, 1H); LCMS (ESI) m/z 397 (M + H$^+$).

(*S*)-Methyl-2-((2*R*,4*R*,5*R*)-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)-3-phenylpropanoate (65c). Compound **65c** was synthesized in a manner similar to **65a**, using **64c** as starting material. Yield 99% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.67 (d, J = 7 Hz, 3H), 1.28 (s, 3H), 1.92 (m, 3H), 2.75 (dd, J = 13 and 2 Hz, 1H), 3.08 (d, J = 13 Hz, 0.5H), 3.11 (d, J = 6 Hz, 0.5H), 3.21 (d, J = 6 Hz, 1H), 3.27 (m, 2H), 3.55 (dd, J = 11 and 6 Hz, 1H), 3.74 (s, 3H), 4.88 (q, J = 6 Hz, 1H), 6.64 (dd, J = 8 and 2 Hz, 1H), 6.70 (s, 1H), 6.77 (d, J = 7 Hz, 1H), 7.15 (m, 3H), 7.21 (m, 2H), 7.31 (m, 3H); LCMS (ESI) m/z 411 (M + H$^+$).

Author: In the paragraph below, the starting material information seems to be missing.

(*R*)-Methyl-2-((2*R*,4*R*,5*R*)-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)-3-phenylpropanoate (65d). Compound **65d** was synthesized in a manner similar to **65a**, using as starting material. Yield 77% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.68 (d, J = 7 Hz, 3H), 1.28 (s, 3H), 1.73 (m, 1H), 1.86 (m, 1H), 1.94 (m, 1H), 2.79 (dd, J = 12 and 2 Hz, 1H), 3.07 (dd, J = 14 and 8 Hz, 1H), 3.23 (dd, J = 14 and 6 Hz, 1H), 3.30 (dd, J = 13 and 3 Hz, 1H), 3.59 (dd, J = 12 and 3 Hz, 1H), 3.75 (s, 3H), 4.96 (m, 1H), 6.66 (m, 2H), 6.74 (d, J = 9 Hz, 1H), 7.17 (m, 2H), 7.27 (m, 4H), 7.38 (d, J = 9 Hz, 1H); LCMS (ESI) m/z 411 (M + H$^+$).

(*S*)-Methyl-3-cyclohexyl-2-((2*R*,4*R*,5*R*)-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)propanoate (65e). Compound **65e** was synthesized in a manner similar to **65a**, using **64e** as starting material. Yield 97% (white foam); ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 7 Hz, 3H), 1.02−1.16 (m, 3H), 1.18−1.23 (m, 1H), 1.30 (s, 3H), 1.64 (m, 4H), 1.76 (m, 3H), 1.81−1.89 (m, 1H), 1.93 (m, 1H), 1.99 (m, 1H), 2.84 (dd, J = 13 and 2 Hz, 1H), 3.32 (dd, J = 12 and 3 Hz, 1H), 3.63 (dd, J = 10 and 6 Hz, 1H), 3.76 (s, 3H), 4.56 (dd, J = 9 and 5 Hz, 1H), 6.65 (dd, J = 7 and 2 Hz, 1H), 6.72 (t, J = 2 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.44 (d, J = 9 Hz, 1H); LCMS (ESI) m/z 403 (M + H$^+$).

(*S*)-Methyl-2-((2*R*,4*R*,5*R*)-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)-4-methylpentanoate (65f). Compound **65f** was synthesized in a manner similar to **65a**, using **64f** as starting material. Yield 100% (yellow foam); ^{1}H NMR ($CDCl_3$) δ 0.71 (d, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 1.29 (s, 3H), 1.93 (m, 3H), 2.00 (d, J = 8 Hz, 1H), 2.21 (m, 1H), 2.83 (dd, J = 13 and 2 Hz, 1H), 3.32 (dd, J = 12 and 3 Hz, 1H), 3.65 (t, J = 8 Hz, 1H), 3.76 (s, 3H), 4.58 (dd, J = 9 and 5 Hz, 1H), 6.65 (dd, J = 8 and 2 Hz, 1H), 6.72 (t, J = 2 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 7.15 (t, J = 8 Hz, 1H), 7.47 (d, J = 9 Hz, 1H); LCMS (ESI) m/z 363 (M + H$^+$).

(3*R*,7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-3-phenylhexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (66a). A solution of **65a** (1.28 g, 3.23 mmol) in toluene (100 mL) was heated to reflux for 60 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). Yield 99% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.40 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.75 (br s, 1H), 2.09 (m, 1H), 2.24 (t, J = 13 Hz, 1H), 2.43 (dd, J = 13 and 2 Hz, 1H), 3.11 (dd, J = 13 and 3 Hz, 1H), 4.27 (dd, J = 13 and 2 Hz, 1H), 4.38 (dd, J = 13 and 2 Hz, 1H), 5.15 (s, 1H), 6.64 (dd, J = 8 and 2 Hz, 1H), 6.71 (s, 1H), 6.75 (m, 2H), 7.16 (t, J = 8 Hz, 1H), 7.37 (m, 4H); LCMS (ESI) m/z 363 (M − H$^+$).

(7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (66b). To a solution of **64b** (1.55 g, 2.90 mmol) in methanol (20 mL) was added a 4 M anhydrous solution of hydrogen chloride in dioxane (2.2 mL, 8.8 mmol), and the mixture was heated to reflux for 2 h. Triethylamine (3.51 g, 34.8 mmol) was then added, and the mixture was heated to reflux for 60 h. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). Yield 100% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.64 (d, J = 6 Hz, 3H), 1.43 (s, 3H), 1.59 (s, 1H), 2.16 (m, 1H), 2.22 (t, J = 13 Hz, 1H), 2.37 (m, 1H), 3.16 (dd, J = 14 and 3 Hz, 1H), 3.49 (s, 1H), 4.23 (dd, J = 14 and 3 Hz, 1H), 4.50 (dd, J = 14 and 3 Hz, 1H), 6.26 (br s, 1H), 6.70 (m, 2H), 6.81 (d, J = 8 Hz, 1H), 7.20 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 287 (M − H$^+$).

(3*S*,7*R*,8*R*,9α*R*)-3-Benzyl-8-(3-hydroxyphenyl)-7,8-dimethyl-hexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (66c). Compound **66c** was synthesized in a manner similar to **66a**, using **65c** as starting material. Yield 38% (yellow solid); ^{1}H NMR ($CDCl_3$) δ 0.59 (d, J = 7 Hz, 3H), 1.21 (s, 3H), 2.00 (m, 1H), 2.16 (m, 1H), 2.87 (dd, J = 14 and 3 Hz, 1H), 3.05 (d, J = 11 Hz, 1H), 3.20 (t, J = 4 Hz, 2H), 4.38 (m, 2H), 6.31 (br s, 1H), 6.64 (m, 1H), 6.69 (m, 1H), 6.76 (d, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 2H), 7.21 (dd, J = 8 and 2 Hz, 2H), 7.31 (t, J = 7 Hz, 1H), 7.36 (m, 2H); LCMS (ESI) m/z 377 (M − H$^+$).

(3*R*,7*R*,8*R*,9α*R*)-3-Benzyl-8-(3-hydroxyphenyl)-7,8-dimethyl-hexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (66d). Compound **66d** was synthesized in a manner similar to **66a**, using **65d** as starting material. Yield 70% (white solid); ^{1}H NMR (CD_3OD) δ 0.17 (d, J = 7 Hz, 3H), 0.98 (t, J = 13 Hz, 1H), 1.30 (s, 3H), 1.80 (d, J = 12 Hz, 1H), 1.93 (m, 1H), 3.01 (dd, J = 14 and 5 Hz, 1H), 3.07 (dd, J = 13 and 3 Hz, 1H), 3.30 (m, 1H), 4.07 (m, 1H), 4.24 (dd, J = 13 and 2 Hz, 1H), 4.43 (t, J = 4 Hz, 1H), 6.45 (m, 2H), 6.58 (dd, J = 8 and 2 Hz, 1H), 7.07 (t, J = 8 Hz, 1H), 7.22 (m, 5H); LCMS (ESI) m/z 377 (M − H$^+$).

(3*S*,7*R*,8*R*,9α*R*)-3-Cyclohexyl-8-(3-hydroxyphenyl)-7,8-dimethyl-hexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (66e). Compound **66e** was synthesized in a manner similar to **66a**, using **65e** as starting material. The reaction was performed in *o*-xylene instead of toluene. Yield 37% (yellow solid); ^{1}H NMR (DMSO-d_6) δ 0.49 (d, J = 7 Hz, 3H), 1.00−1.29 (m, 6H), 1.34 (s, 3H), 1.45 (m, 1H), 1.53 (d, J = 8 Hz, 1H), 1.62 (d, J = 8 Hz, 1H), 1.72 (t, J = 8 Hz, 1H), 1.84 (m, 1H), 1.96 (t, J = 13 Hz, 1H), 2.10 (m, 1H), 2.50 (m, 1H), 3.12 (dd, J = 14 and 3 Hz, 1H), 3.74 (t, J = 2 Hz, 1H), 4.15 (dd, J = 12 and 2 Hz, 1H), 4.24 (dd, J = 13 and 2 Hz, 1H), 6.57 (dd, J = 8 and 1 Hz, 1H), 6.65 (d, J = 2 Hz, 1H), 6.69 (d, J = 8 Hz, 1H), 7.11 (t, J = 8 Hz, 1H), 8.24 (d, J = 3 Hz, 1H), 9.24 (s, 1H); LCMS (ESI) m/z 369 (M − H$^+$).

(3*S*,7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-3-isopropyl-7,8-dimethyl-hexahydro-6*H*-pyrido[1,2-α]pyrazine-1,4-dione (66f). Compound **66f** was synthesized in a manner similar to **66e**, using **65f** as starting material. Yield 43% (yellow foam); ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.97 (d, J = 7 Hz, 3H), 1.32 (s, 3H), 1.99 (d, J = 8 Hz, 2H), 2.32 (s, 0.5H), 2.37 (s, 0.5H), 2.45 (s, 1H), 2.83 (dd, J = 14 and 3 Hz, 1H), 3.34 (m, 1H), 3.64 (m, 1H), 4.58 (dd, J = 9 and 5 Hz, 1H), 6.66 (m, 1H), 6.72 (m, 1H), 6.80 (d, J = 8 Hz, 1H), 7.11 (m, 1H); LCMS (ESI) m/z 329 (M − H$^+$).

3-((3*R*,7*R*,8*R*,9α*R*)-7,8-Dimethyl-3-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (14). Compound **14** was synthesized in a manner similar to **5**, using **66a**. Yield 69% (white solid); ^{1}H NMR (CD_3OD) δ 0.85 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.47 (d, J = 13 Hz, 1H), 1.59 (m, 1H), 1.88 (t, J = 12 Hz, 1H), 2.08 (m, 1H), 2.48 (m, 1H), 2.58 (m, 3H), 2.74 (m, 2H), 3.11 (d, J = 12 Hz, 1H), 3.57 (m, 1H), 4.07 (d, J = 3 Hz, 1H), 6.58 (dd, J = 8 and 2 Hz, 1H), 6.71 (s, 1H), 6.75 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 7.22 (t, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 2H), 7.74 (t, J = 8 Hz, 2H); LCMS (ESI) m/z 337 (M + H$^+$). Anal. ($C_{22}H_{28}N_2O\cdot 0.75H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (15). Compound **15** was synthesized in a manner similar to **5**, using **66b** as starting material. Yield 73% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.79 (d, J = 8 Hz, 3H), 1.36 (s, 3H), 1.46 (d, J = 12 Hz, 1H), 1.95 (t, J = 12 Hz, 1H), 2.03 (br s, 1H), 2.17 (dt, J = 11 and 7 Hz, 1H), 2.25 (t, J = 11 Hz, 1H), 2.52 (dd, J = 11 and 2 Hz, 1H), 2.74 (m, 3H), 3.02 (m, 3H), 6.60 (s, 1H), 6.63 (dd, J = 9 and 1 Hz, 1H), 6.78 (d, J = 9 Hz, 1H), 7.19 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 261 (M + H$^+$); HRMS for $C_{16}H_{24}N_2O$ (M, 260.1889 [M + H]) calcd, 261.1961; found, 261.1981.

3-((3*S*,7*R*,8*R*,9α*R*)-3-Benzyl-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (16). Compound **16** was synthesized in a manner similar to **5**, using **66c** as starting material. Yield 43% (white solid); ^{1}H NMR (CD_3OD) δ 0.67 (d, J = 7 Hz, 3H), 1.29 (s, 3H), 1.43 (d, J = 8 Hz, 1H), 1.79 (t, J = 12 Hz, 1H), 1.87 (t, J = 11 Hz, 1H), 1.96 (m, 3H), 2.25 (dt, J = 13 and 3 Hz, 1H), 2.40 (dd, J = 12 and 2 Hz, 1H), 2.52 (d, J = 12 Hz, 1H), 2.56 (m, 1H), 2.67 (m, 2H), 2.82 (dd, J = 12 and 2 Hz, 1H), 3.03 (m, 1H), 6.52 (dd, J = 8 and 2 Hz, 1H), 6.64 (t, J = 2 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 7.04 (t, J = 8 Hz, 1H), 7.17 (d, J = 7 Hz, 3H), 7.25 (t, J = 7 Hz, 2H); LCMS (ESI) m/z 351 (M + H$^+$). Anal. ($C_{23}H_{30}N_2O\cdot 0.2H_2O$) C, H, N.

3-((3*R*,7*R*,8*R*,9α*R*)-3-Benzyl-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (17). Compound **17** was synthe-

sized in a manner similar to **5**, using **66d** as starting material. Yield 80% (white solid); ^{1}H NMR (CD_3OD) δ 0.89 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.56 (d, J = 14 Hz, 1H), 2.06 (m, 2H), 2.29 (dd, J = 12 and 3 Hz, 1H), 2.38 (dd, J = 12 and 2 Hz, 1H), 2.50 (m, 2H), 2.70 (dd, J = 12 and 3 Hz, 1H), 2.92 (m, 2H), 3.10 (t, J = 11 Hz, 1H), 3.38 (d, J = 10 Hz, 2H), 6.60 (dd, J = 8 and 2 Hz, 1H), 6.73 (t, J = 2 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 1H), 7.23 (d, J = 7 Hz, 3H), 7.30 (t, J = 8 Hz, 2H); LCMS (ESI) m/z 351 (M + H$^+$); HRMS for $C_{23}H_{30}N_2O$ (M, 350.2358 [M + H]) calcd, 351.2431; found, 351.2438.

3-((3*S*,7*R*,8*R*,9α*R*)-3-Cyclohexyl-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (18). Compound **18** was synthesized in a manner similar to **5**, using **66e** as starting material. Yield 68% (white solid); ^{1}H NMR (CD_3OD) δ 0.76 (d, J = 7 Hz, 3H), 1.12 (m, 2H), 1.25 (m, 2H), 1.34 (m, 4H), 1.47 (m, 1H), 1.56 (d, J = 13 Hz, 1H), 1.70 (d, J = 10 Hz, 1H), 1.84 (m, 5H), 2.09 (m, 2H), 2.46 (m, 1H), 2.59 (dd, J = 11 and 2 Hz, 1H), 2.77 (m, 2H), 2.93 (m, 2H), 3.13 (dd, J = 12 and 3 Hz, 1H), 6.59 (dd, J = 8 and 2 Hz, 1H), 6.73 (m, 2H), 7.10 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 343 (M + H$^+$). Anal. ($C_{22}H_{34}N_2O\cdot1.5H_2O$) C, H, N.

3-((3*S*,7*R*,8*R*,9α*R*)-3-Isopropyl-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (19). Compound **19** was synthesized in a manner similar to **5**, using **66f** as starting material. Yield 22% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (d, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 0.98 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.47 (d, J = 13 Hz, 1H), 1.58 (sx, J = 7 Hz, 1H), 1.83 (d, J = 8 Hz, 1H), 1.88 (t, J = 9 Hz, 1H), 2.03 (m, 1H), 2.26 (m, 1H), 2.55 (m, 3H), 2.72 (dd, J = 12 and 3 Hz, 1H), 2.79 (dd, J = 11 and 3 Hz, 1H), 2.88 (dd, J = 12 and 3 Hz, 1H), 6.57 (dd, J = 8 and 3 Hz, 1H), 6.70 (d, J = 2 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 7.09 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 303 (M + H$^+$). Anal. ($C_{19}H_{30}N_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-2,7,8-Trimethyl-octahydro-1*H*-pyrido[1,2-α]-pyrazin-8-yl)phenol (20). To a solution of **15** (0.1 g, 0.39 mmol) in tetrahydrofuran (5 mL) and ethanol (5 mL) was added triethylamine (0.085 g, 0.85 mmol) and formaldehyde (40% aqueous solution; 0.06 mL, 0.77 mmol). After 10 min, sodium cyanoborohydride (0.03 g, 0.46 mmol) was added to the mixture, which was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 4% (white solid); ^{1}H NMR (CD_3OD) δ 0.80 (d, J = 7 Hz, 3H), 1.42 (s, 3H), 1.77 (d, J = 13 Hz, 1H), 2.10 (t, J = 13 Hz, 1H), 2.26 (m, 1H), 2.94 (s, 3H), 3.00 (d, J = 12 Hz, 2H), 3.15 (m, 2H), 3.59 (m, 2H), 6.63 (dd, J = 8 and 2 Hz, 1H), 6.71 (t, J = 2 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 7.15 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 275 (M + H$^+$); HRMS for $C_{17}H_{26}N_2O$ (M, 274.2045 [M + H]) calcd, 274.2118; found, 275.2122.

1-((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)ethanone (21). A solution of **15** (0.02 g, 0.08 mmol) in tetrahydrofuran (2 mL) was treated with triethylamine (0.03 g, 0.32 mmol) and acetyl chloride (0.01 g, 0.17 mmol), and the mixture was stirred overnight at room temperature. A 1 N aqueous solution of sodium hydroxide (2 mL) was added to the mixture, and stirring was continued at room temperature for an additional 12 h. The mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 22% (white solid); ^{1}H NMR (CD_3OD) δ 0.78 (d, J = 7 Hz, 3H), 1.33 (s, 1.5H), 1.35 (s, 1.5H), 1.59 (dd, J = 12 and 2 Hz, 1H), 1.92 (t, J = 13 Hz, 1H), 2.07 (m, 1H), 2.11 (s, 1.5H), 2.13 (s, 1.5H), 2.23 (m, 2H), 2.49 (t, J = 12 Hz, 0.5H), 2.59 (d, J = 12 Hz, 1H), 2.79 (m, 2.5H), 3.00 (t, J = 12 Hz, 0.5H), 3.38 (m, 0.5H), 3.79 (dt, J = 13 and 2 Hz, 0.5H), 3.86 (dt, J = 13 and 2 Hz, 0.5H), 4.40 (dt, J = 13 and 2 Hz), 4.48 (dd, J = 13 and 2 Hz, 0.5 H), 6.59 (d, J = 8 Hz, 1H), 6.72 (d, J = 2 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 303 (M + H$^+$); HRMS for $C_{18}H_{26}N_2O_2$ (M, 302.1994 [M + Na]) calcd, 325.1886; found, 325.1880.

((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)(phenyl)methanone (22). Compound **22** was synthesized in a fashion similar to compound **21**, using benzoyl chloride as starting material. Yield 57% (white solid); ^{1}H NMR (CD_3OD) δ 0.78 (br s, 3H), 1.29 (br s, 1.5H), 1.37 (br s, 1.5H), 1.63 (m, 0.5H), 1.82 (m, 0.5H), 1.99 (m, 0.5H), 2.06 (br s, 1H), 2.25−2.35 (m, 1.4H), 2.38 (m, 0.6H), 2.61 (m, 1H), 2.70 (m, 1H), 2.79 (dd, J = 12 and 2 Hz, 1H), 2.86 (m, 0.5H), 3.06 (m, 1H), 3.37 (m, 1H), 3.59 (m, 1H), 4.60 (m, 1H), 6.58 (m, 1H), 6.67 (m, 1H), 6.77 (m, 1H), 7.11 (m, 1H), 7.44 (m, 2H), 7.48 (m, 3H); LCMS (ESI) m/z 365 (M + H$^+$); HRMS for $C_{23}H_{28}N_2O_2$ (M, 364.2151 [M + H]) calcd, 365.2224; found, 365.2235.

1-((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)-2-phenylethanone (23). Compound **23** was synthesized in a fashion similar to compound **21**, using phenylacetyl chloride as starting material. Yield 96% (yellow foam); ^{1}H NMR (CD_3OD) δ 0.72 (d, J = 7 Hz, 1H), 0.75 (d, J = 7 Hz, 2H), 1.13 (s, 1.5H), 1.30 (s, 1.5H), 1.55 (d, J = 14 Hz, 0.5H), 1.79 (m, 1H), 1.89 (d, J = 11 Hz, 0.5H), 1.98 (m, 1.4H), 2.04 (m, 1H), 2.19 (m, 0.6H), 2.53 (m, 2H), 2.65 (m, 1.7H), 2.86 (m, 1.3H), 3.78 (d, J = 15 Hz, 1.5H), 3.86 (d, J = 15 Hz, 1H), 3.96 (dd, J = 13 and 2 Hz, 0.5H), 4.43 (dt, J = 13 and 2 Hz, 0.5H), 4.49 (dd, J = 13 and 2 Hz, 0.5H), 6.57 (d, J = 8 Hz, 1H), 6.65 (s, 1H), 6.70 (s, 1H), 6.74 (d, J = 8 Hz, 1H), 7.09 (m, 1H), 7.25 (m, 1H), 7.32 (m, 3H); LCMS (ESI) m/z 379 (M + H$^+$). Anal. ($C_{24}H_{30}N_2O_2\cdot0.1H_2O$) C, H, N.

1-((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)-3-phenylpropan-1-one (24). Compound **24** was synthesized in a fashion similar to compound **21**, using phenylpropanoyl chloride as starting material. Yield 54% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (m, 3H), 1.28 (s, 1.4H), 1.31 (s, 1.6H), 1.43 (d, J = 11 Hz, 0.5H), 1.53 (d, J = 13 Hz, 0.5H), 1.85 (m, 2H), 2.03 (m, 2H), 2.47 (m, 2H), 2.64 (m, 3H), 2.77 (m, 2H), 2.93 (m, 2.5H), 3.17 (dt, J = 13 and 3 Hz, 0.5H), 3.68 (d, J = 13 Hz, 0.5H), 3.82 (d, J = 13 Hz, 0.5H), 4.41 (dd, J = 13 and 3 Hz, 0.5H), 4.48 (d, J = 12 Hz, 0.5H), 6.59 (dd, J = 8 and 1 Hz, 1H), 6.71 (m, 2H), 7.11 (m, 1H), 7.19 (m, 1H), 7.25 (m, 4H); LCMS (ESI) m/z 393 (M + H$^+$). Anal. ($C_{25}H_{32}N_2O_2\cdot0.25H_2O$) C, H, N.

(7*R*,8*R*,9α*R*)-8-(3-(Benzyloxy)phenyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazine (67). To a stirred solution of **15** (1 g, 3.85 mmol) in tetrahydrofuran (20 mL) under nitrogen at 0 °C was added triethylamine (2.14 mL, 15.40 mmol) and di-*tert*-butyl dicarbonate (1.84 g, 8.46 mmol). The solution was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (20 mL). The solution was then washed with a 0.5 M aqueous solution of hydrochloric acid (2 × 25 mL) and dried over sodium sulfate. The mixture was filtered, and the residue was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity) to give (7*R*,8*R*,9α*R*)-*tert*-butyl 8-(3-hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazine-2(6*H*)-carboxylate. Yield 74% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.73 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.48 (s, 9H), 1.52 (s, 1H), 1.66 (s, 1H), 1.97 (m, 2H), 2.19 (dt, J = 12 and 4 Hz, 1H), 2.26 (m, 1H), 2.56 (dd, J = 12 and 2 Hz, 1H), 2.68 (m, 3H), 3.02 (br s, 1H), 4.00 (br s, 1H), 6.64 (dd, J = 8 and 2 Hz, 1H), 6.74 (t, J = 2 Hz, 1H), 6.80 (d, J = 8 Hz 1H), 7.17 (t, J = 8 Hz 1H); LCMS (ESI) m/z 361 (M + H$^+$).

To a stirred solution of (7*R*,8*R*,9α*R*)-*tert*-butyl 8-(3-hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazine-2(6*H*)-carboxylate (1.03 g, 2.86 mmol) in *N*,*N*-dimethylformamide (10 mL) was added benzyl bromide (0.41 mL, 3.43 mmol) and potassium carbonate (1.18 g, 8.58 mmol), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then poured into water (20 mL) and extracted with hexanes. The combined organics were washed with water and brine and dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated

under reduced pressure to give (7*R*,8*R*,9αR)-*tert*-butyl 8-(3-(benzyloxy)phenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazine-2(6*H*)-carboxylate which was used for next step without further purification. Yield 99% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.75 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.48 (s, 10H), 1.51 (s, 1H), 1.60 (s, 1H), 1.87 (t, J = 12 Hz, 1H), 2.01 (m, 1H), 2.18 (m, 1H), 2.52 (dd, J = 11 Hz and 2 Hz, 2H), 2.67 (m, 2H), 2.96 (br s, 1H), 3.98 (br s, 1H), 5.05 (s, 2H), 6.81 (dd, J = 8 and 2 Hz, 1H), 6.89 (m, 2H), 7.23 (d, J = 9 Hz 1H), 7.34 (m, 1H), 7.39 (t, J = 8 Hz, 2H), 7.45 (d, J = 9 Hz, 2H); LCMS (ESI) m/z 451 (M + H$^+$).

To a stirred solution of (7*R*,8*R*,9αR)-*tert*-butyl 8-(3-(benzyloxy)-phenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazine-2(6*H*)-carboxylate (1.27 g, 2.82 mmol) in methanol (10 mL) was added a 2 M anhydrous solution of hydrogen chloride in diethyl ether (6 mL), and the reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated under reduced pressure. A saturated sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL) were added to the residue, and the resultant mixture was stirred at room temperature for 1 h. The layers were separated, and the organic layer was washed with brine and dried over sodium sulfate. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give **67**, which was used without further purification. Yield 100% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.75 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.45 (d, J = 13 Hz, 1H), 1.88 (t, J = 12 Hz, 1H), 2.00 (m, 1H), 2.27 (m, 2H), 2.48 (dd, J = 12 and 2 Hz, 1H), 2.60 (t, J = 11 Hz, 1H), 2.70 (m, 2H), 2.94 (m, 2H), 2.99 (m, 2H), 5.05 (s, 2H), 6.79 (dd, J = 9 and 2 Hz, 1H), 6.87 (m, 2H), 7.23 (t, J = 8 Hz 1H), 7.32 (m, 1H), 7.38 (t, J = 8 Hz, 2H), 7.44 (m, 2H); LCMS (ESI) m/z 351 (M + H$^+$)

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-phenyl-octahydro-1*H*-pyrido-[1,2-α]pyrazin-8-yl)phenol (25). To a solution of **67** (0.5 g, 1.43 mmol) in dichloromethane (10 mL) was added potassium phenyltrifluoroborate (0.5 g, 2.71 mmol), triethylamine (0.4 mL, 2.86 mmol), and cupric acetate (0.2 g, 1.43 mmol). The mixture was stirred at room temperature for 2 days. The mixture was poured into water and extracted with dichloromethane. The organic extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity) to give (7*R*,8*R*,9α*R*)-8-(3-(benzyloxy)phenyl)-7,8-dimethyl-2-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazine. Yield 30% (yellow solid); ^{1}H NMR ($CDCl_3$) δ 0.78 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.55 (t, J = 12 Hz, 1H), 2.02 (m, 2H), 2.44 (m, 1H), 2.49 (m, 1H), 2.60 (t, J = 12 Hz, 1H), 2.75 (dd, J = 11 and 3 Hz, 1H), 2.81 (dd, J = 11 and 3 Hz, 1H), 2.94 (dt, J = 12 and 3 Hz, 1H), 3.51 (dd, J = 11 and 2 Hz, 1H), 3.57 (d, J = 11 Hz, 1H), 5.06 (s, 2H), 6.81 (dd, J = 8 and 2 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 6.88 (d, J = 5 Hz, 1H), 6.91 (s, 2H), 6.96 (d, J = 7 Hz, 2H), 7.28 (m, 2H), 7.33 (d, J = 7 Hz, 1H), 7.39 (t, J = 8 Hz, 2H), 7.46 (d, J = 7 Hz, 2H); LCMS (ESI) m/z 427 (M + H$^+$).

To a solution of (7*R*,8*R*,9α*R*)-8-(3-(benzyloxy)phenyl)-7,8-dimethyl-2-phenyl-octahydro-1*H*-pyrido[1,2-α]pyrazine (0.18 g, 0.42 mmol) in ethanol (20 mL) was added 10% palladium on charcoal (0.02 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The mixture was then filtered through Celite. The Celite was washed with ethanol, and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity) to give **25**. Yield 50% (white solid); ^{1}H NMR (CD_3OD) δ 0.79 (d, J = 7 Hz, 3H), 1.37 (s, 3H), 1.61 (d, J = 12 Hz, 1H), 1.99 (t, J = 12 Hz, 1H), 2.08 (m, 1H), 2.44 (dt, J = 11 and 2 Hz, 1H), 2.54 (m, 2H), 2.63 (dd, J = 11 and 2 Hz, 1H), 2.77 (dd, J = 12 and 3 Hz, 1H), 2.84 (m, 1H), 2.90 (m, 1H), 3.55 (t, J = 11 Hz, 2H), 6.58 (dd, J = 8 and 2 Hz, 1H), 6.74 (m, 1H), 6.77 (d, J = 8 Hz, 1H), 6.83 (t, J = 7 Hz, 1H), 6.99 (d, J = 8 Hz, 2H), 7.11 (t, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 2H); LCMS (ESI) m/z 337 (M + H$^+$). Anal. ($C_{22}H_{28}N_2O\cdot 0.2H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-2-Benzyl-7,8-dimethyl-octahydro-1*H*-pyrido-[1,2-α]pyrazin-8-yl)phenol (26). Compound **26** was synthesized in a manner similar to **5**, using **22** as starting material. Yield 100% (white solid); ^{1}H NMR (CD_3OD) δ 0.73 (d, J = 7 Hz, 3H), 1.32 (s, 3H), 1.41 (d, J = 13 Hz, 1H), 1.65 (m, 1H), 1.84 (m, 2H), 2.00 (m, 1H), 2.33 (m, 1H), 2.43 (t, J = 11 Hz, 1H), 2.56 (dd, J = 11 and 2 Hz, 1H), 2.70 (m, 1H), 2.74 (m, 1H), 2.82 (dd, J = 8 and 2 Hz, 1H), 3.56 (m, 2H), 3.58 (m, 1H), 6.56 (dd, J = 8 and 2 Hz, 1H), 6.68 (m, 1H), 6.72 (d, J = 8 Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.27 (m, 1H), 7.34 (m, 4H); LCMS (ESI) m/z 351 (M + H$^+$); HRMS for $C_{23}H_{30}N_2O$ (M, 350.2358 [M + H]) calcd, 351.2446; found, 351.2431.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-phenethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (27). Compound **27** was synthesized in a similar fashion as compound **5**, using compound **23** as starting material. Yield 42% (white solid); ^{1}H NMR (CD_3OD) δ 0.76 (d, J = 7 Hz, 3H), 1.36 (s, 3H), 1.53 (d, J = 13 Hz, 1H), 1.65 (m, 0.5H), 1.93 (t, J = 13 Hz, 1H), 1.98 (m, 0.5H), 2.07 (m, 1H), 2.16 (t, J = 11 Hz, 1H), 2.44 (m, 2H), 2.61 (d, J = 12 Hz, 1H), 2.71 (m, 2H), 2.79 (d, J = 10 Hz, 1H), 2.87 (m, 2H), 3.00 (d, J = 9 Hz, 1H), 3.05 (d, J = 9 Hz, 1H), 3.58 (m, 1H), 6.58 (dd, J = 7 and 2 Hz, 1H), 6.70 (s, 1H), 6.74 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 7.19 (m, 1H), 7.24 (m, 2H), 7.28 (m, 2H); LCMS (ESI) m/z 365 (M + H$^+$); HRMS for $C_{24}H_{32}N_2O$ (M, 364.2515 [M + H]) calcd, 365.2587; found, 365.2582.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(3-phenylpropyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (28). Compound **28** was synthesized in a similar fashion as compound **5**, using compound **24** as starting material. Yield 45% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.50 (d, J = 12 Hz, 1H), 1.87 (m, 3H), 1.97 (t, J = 11 Hz, 1H), 2.05 (m, 1H), 2.32 (t, J = 12 Hz, 2H), 2.43 (m, 3H), 2.57 (dd, J = 12 and 2 Hz, 1H), 2.65 (t, J = 8 Hz, 2H), 2.72 (m, 2H), 2.84 (d, J = 11 Hz, 1H), 2.91 (d, J = 9 Hz, 1H), 6.59 (dd, J = 8 and 2 Hz, 1H), 6.70 (t, J = 2 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 7.16 (m, 1H), 7.22 (m, 2H), 7.27 (m, 2H); LCMS (ESI) m/z 379 (M + H$^+$). Anal. ($C_{25}H_{34}N_2O\cdot 0.5H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(methylsulfonyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (30). To a solution of **15** (0.1 g, 0.39 mmol) in methylene chloride (5 mL) was added triethylamine (0.16 mL, 1.17 mmol) and methanesulfonyl chloride (0.04 mL, 0.47 mmol). The mixture was stirred at room temperature for 3 h. A 1 N aqueous solution of sodium hydroxide was added, and the reaction was heated to 70 °C for 1 h. The reaction mixture was concentrated in vacuo, and the residue was stirred with ethyl acetate for 1 h. The mixture was filtered, and the solvents were evaporated. The crude product was subjected to LC separation. Yield 15% (white solid); ^{1}H NMR (CD_3OD) δ 0.77 (d, J = 7 Hz, 3H), 1.35 (s, 3H), 1.57 (dt, J = 13 and 2 Hz, 1H), 1.93 (t, J = 13 Hz, 1H), 2.07 (m, 1H), 2.33 (dt, J = 12 and 3 Hz, 1H), 2.42 (m, 1H), 2.61 (m, 2H), 2.80 (dt, J = 12 and 2 Hz, 2H), 2.86 (s, 3H), 2.95 (dt, J = 12 and 2 Hz, 1H), 3.55 (dt, J = 12 and 2 Hz, 1H), 3.61 (dt, J = 11 and 2 Hz, 1H), 6.58 (dd, J = 8 and 2 Hz, 1H), 6.71 (t, J = 2 Hz, 1H), 6.76 (d, J = 7 Hz, 1H), 7.11 (t, J = 8 Hz, 1H); LCMS (ESI) m/z 339 (M + H$^+$). Anal. ($C_{17}H_{26}N_2O_3S\cdot 0.5H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(phenylsulfonyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (31). To a solution of **67** (0.5 g, 1.43 mmol) in tetrahydrofuran (10 mL) was added triethylamine (0.6 mL, 4.26 mmol) and benzenesulfonyl chloride (0.22 mL, 1.72 mmol). The mixture was stirred at room temperature for 2 h. The mixture was poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: hexane/ethyl acetate mixtures of increasing polarity) to give (7*R*,8*R*,9α*R*)-8-(3-(benzyloxy)phenyl)-7,8-dimethyl-2-(phenylsulfonyl)-octahydro-1*H*-pyrido[1,2-α]pyrazine. Yield 70% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.64 (d, J = 7 Hz, 3H), 1.33 (s, 3H), 1.49 (dd, J = 12 and 2 Hz, 1H), 1.78 (t, J = 12 Hz, 1H), 1.99 (m, 1H), 2.09 (t, J = 11 Hz, 1H), 2.39 (m, 1H), 2.48 (m, 3H), 2.71 (m, 2H), 3.60 (dt, J = 11 and 2 Hz, 1H), 3.69 (dt, J = 8 and 2 Hz, 1H), 5.04 (s, 2H),

6.78 (m, 1H), 6.82 (m, 2H), 7.22 (t, $J = 8$ Hz, 1H), 7.34 (m, 1H), 7.39 (t, $J = 8$ Hz, 2H), 7.45 (d, $J = 8$ Hz, 2H), 7.56 (m, 2H), 7.61 (m, 1H), 7.78 (d, $J = 8$ Hz, 1H); LCMS (ESI) *m*/*z* 491 ($M + H^+$).

To a solution of (7*R*,8*R*,9α*R*)-8-(3-(benzyloxy)phenyl)-7,8-dimethyl-2-(phenylsulfonyl)-octahydro-1*H*-pyrido[1,2-α]pyrazine (0.52 g, 1.06 mmol) in ethanol (20 mL) was added 10% palladium on charcoal (0.05 g), and the mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. The mixture was then filtered through Celite. The Celite was washed with ethanol, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity) to give **31**. Yield 85% (white solid); ^{1}H NMR (CD_3OD) δ 0.65 (d, $J = 7$ Hz, 3H), 1.31 (s, 3H), 1.52 (d, $J = 12$ Hz, 1H), 1.77 (t, $J = 12$ Hz, 1H), 2.00 (m, 1H), 2.10 (t, $J = 11$ Hz, 1H), 2.30 (dt, $J = 11$ and 3 Hz, 1H), 2.37 (m, 1H), 2.43 (dd, $J = 12$ and 3 Hz, 1H), 2.52 (m, 2H), 3.60 (d, $J = 11$ Hz, 1H), 3.65 (d, $J = 11$ Hz, 1H), 6.57 (dd, $J = 8$ and 3 Hz, 1H), 6.67 (s, 1H), 6.70 (d, $J = 7$ Hz, 1H), 7.08 (t, $J = 8$ Hz, 1H), 7.63 (m, 2H), 7.68 (m, 1H), 7.79 (d, $J = 8$ Hz, 2H); LCMS (ESI) *m*/*z* 401 ($M + H^+$). Anal. ($C_{22}H_{28}N_2O_3S$) C, H, N.

(7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-*N*-phenylhexahydro-1*H*-pyrido[1,2-α]pyrazine-2(6*H*)-carboxamide (32). To a solution of **15** (0.1 g, 1.43 mmol) in methylene chloride (5 mL) was added triethylamine (0.11 mL, 0.76 mmol) and phenylisocyanate (0.05 mL, 0.46 mmol). The mixture was stirred at room temperature overnight. The mixture was concentrated in vacuo. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity) Yield 58% (white solid); ^{1}H NMR (CD_3OD) δ 0.80 (d, $J = 7$ Hz, 3H), 1.37 (s, 3H), 1.60 (d, $J = 13$ Hz, 1H), 1.94 (t, $J = 13$ Hz, 1H), 2.08 (m, 1H), 2.26 (dt, $J = 12$ and 3 Hz, 1H), 2.34 (t, $J = 11$ Hz, 1H), 2.62 (dd, $J = 11$ and 2 Hz, 1H), 2.76 (m, 3H), 3.13 (m, 1H), 4.05 (dt, $J = 13$ and 2 Hz, 1H), 4.09 (m, 1H), 6.60 (dd, $J = 8$ and 2 Hz, 1H), 6.73 (t, $J = 2$ Hz, 1H), 6.77 (d, $J = 8$ Hz, 1H), 7.03 (t, $J = 8$ Hz, 1H), 7.12 (t, $J = 8$ Hz, 1H), 7.27 (t, $J = 8$ Hz, 2H), 7.36 (dd, $J = 8$ and 1 Hz, 2H); LCMS (ESI) *m*/*z* 380 ($M + H^+$). Anal. ($C_{23}H_{29}N_3O_2 \cdot 0.33H_2O$) C, H, N.

(2*R*,4*R*,5*R*)-*tert*-Butyl-2-(benzyl(3-ethoxy-3-oxopropyl)carbamoyl)-4-(3-(*tert*-butyldimethylsilyloxy)phenyl)-4,5-dimethylpiperidine-1-carboxylate (68). Compound **68** was synthesized in a fashion similar to compound **60**, using ethyl 3-(benzylamino)-propanoate. Yield 60% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.47 (m, 3H), 0.88 (m, 1H), 0.98 (s, 9H), 1.14 (s, 2H), 1.24 (m, 4H), 1.47 (s, 9H), 1.64 (s, 1H), 1.89 (m, 1H), 2.01 (m, 0.5H), 2.35 (m, 0.5H), 2.47 (m, 0.5H), 2.56 (m, 0.5H), 2.70 (t, $J = 7$ Hz, 1H), 3.36 (m, 1H), 3.54 (m, 1H), 3.89 (m, 1H), 4.11 (m, 2H), 4.46 (m, 0.5H), 4.61 (m, 2H), 4.96 (m, 0.5H), 6.65 (m, 2H), 6.77 (m, 1H), 6.90 (m, 1H), 7.13 (m, 1H), 7.30 (m, 4H); LCMS (ESI) *m*/*z* 654 ($M + H^+$).

Ethyl-3-((2*R*,4*R*,5*R*)-*N*-benzyl-4-(3-hydroxyphenyl)-4,5-dimethylpiperidine-2-carboxamido)propanoate (69). Compound **69** was synthesized in a fashion similar to compound **61**, using compound **68** as starting material. Yield 92% (white solid); ^{1}H NMR ($CDCl_3$) δ 0.65 (d, $J = 7$ Hz, 2H), 0.69 (d, $J = 7$ Hz, 1H), 1.23 (m, 5.5H), 1.38 (m, 0.5H), 1.46 (m, 1H), 1.50 (m, 0.5H), 1.66 (d, $J = 13$ Hz, 0.5H), 1.82 (m, 0.5H), 1.90 (m, 0.5H), 2.08 (m, 1H), 2.20 (t, $J = 13$ Hz, 0.5H), 2.47 (m, 0.5H), 2.59 (m, 1H), 2.67 (m, 1H), 2.81 (m, 0.5H), 2.86 (m, 1H), 3.27 (dd, $J = 14$ and 3 Hz, 0.5H), 3.37 (dd, $J = 14$ and 3 Hz, 0.5H), 3.62 (m, 1H), 3.71 (m, 1H), 3.93 (dd, $J = 12$ and 3 Hz, 0.5H), 4.11 (m, 2H), 4.63 (m, 2H), 6.66 (m, 2H), 6.75 (m, 1H), 7.14 (m, 1H), 7.20 (m, 2H), 7.28 (m, 3H); LCMS (ESI) *m*/*z* 439 ($M + H^+$).

(8*R*,9*R*,10α*R*)-2-Benzyl-9-(3-hydroxyphenyl)-8,9-dimethylhexahydropyrido[1,2-α][1,4]diazepine-1,5(2*H*,7*H*)-dione (70). A solution of **69** (2.58 g, 5.89 mmol) in *o*-xylene (200 mL) was heated to reflux for 60 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol mixtures of increasing polarity). Yield 25% (yellow oil); ^{1}H NMR ($CDCl_3$) δ 0.52 (d, $J = 7$ Hz, 2H), 0.63 (d, $J = 7$ Hz, 1H), 1.36 (s, 1H), 1.41 (s, 2H), 2.02 (m, 2H), 2.68 (m, 2H), 3.12 (m, 0.5H), 3.46 (m, 1H), 3.55 (m, 1H), 3.63 (dd, $J = 14$ and 4 Hz, 1H), 3.86 (dd, $J = 14$ and 6 Hz, 1H), 4.22 (m, 0.5H), 4.54 (m, 1H), 4.63 (dd, $J = 12$ and 3 Hz, 1H), 4.75 (d, $J = 14$ Hz, 1H), 6.70 (m, 1H), 6.78 (m, 1H), 7.11 (m, 3H), 7.29 (m, 2H), 7.34 (m, 2H); LCMS (ESI) *m*/*z* 391 ($M - H^+$).

3-((8*R*,9*R*,10α*R*)-2-Benzyl-8,9-dimethyl-decahydropyrido[1,2-α][1,4]diazepin-9-yl)phenol (29). Compound **29** was synthesized in a fashion similar to compound **5**, using compound **70** as starting material. Yield 10% (white solid); ^{1}H NMR (CD_3OD) δ 0.71 (d, $J = 7$ Hz, 3H), 1.27 (s, 3H), 1.58 (m, 0.5H), 1.84 (m, 2H), 1.95 (m, 2H), 2.60 (m, 4H), 2.73 (m, 2H), 2.81 (m, 2H), 2.88 (m, 1H), 3.56 (m, 0.5H) 3.69 (q, $J = 13$ Hz, 2H), 6.65 (dd, $J = 8$ and 2 Hz, 1H), 6.69 (s, 1H), 7.07 (t, $J = 8$ Hz, 1H), 7.24 (m, 1H), 7.31 (t, $J = 8$ Hz, 2H), 7.37 (m, 1H); LCMS (ESI) *m*/*z* 365 ($M + H^+$). Anal. ($C_{24}H_{32}N_2O \cdot 0.33H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(2-methylbenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (33). To a 10 μM solution of compound **15** (100 μL) in methanol/acetic acid (8:1) was added tetramethyl orthoformate (TMOF; 100 μL) and a 12 μM solution of 2-methylbenzaldehyde (100 μL) in methanol/acetic acid (8:1). The reaction mixture was shaken for 16 h at room temperature. To this mixture was added resin-bound cyanoborohydride, and shaking was continued for 60 h. The reaction mixture was filtered through a SCX-2 cartridge, and the resin was washed with methanol. The product was eluted from the cartridge by washing with a 2 M solution of ammonia in methanol. The product was purified by liquid chromatographic methods. LCMS (ESI) *m*/*z* 365 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(3-methylbenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (34). Compound **34** was synthesized in a fashion similar to compound **33**, using 3-methylbenzaldehyde as starting material. LCMS (ESI) *m*/*z* 365 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(4-methylbenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (35). Compound **35** was synthesized in a fashion similar to compound **33**, using 4-methylbenzaldehyde as starting material. LCMS (ESI) *m*/*z* 365 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(2-chlorobenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (36). Compound **36** was synthesized in a fashion similar to compound **33** using 2-chlorobenzaldehyde as starting material. LCMS (ESI) *m*/*z* 385 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(3-chlorobenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (37). Compound **35** was synthesized in a fashion similar to compound **33** using 3-chlorobenzaldehyde as starting material. LCMS (ESI) *m*/*z* 385 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(4-chlorobenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (38). Compound **38** was synthesized in a fashion similar to compound **33**, using 4-chlorobenzaldehyde as starting material. LCMS (ESI) *m*/*z* 385 ($M + H^+$).

2-(((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)methyl)phenol (39). Compound **39** was synthesized in a fashion similar to compound **33**, using 2-hydroxybenzaldehyde as starting material. LCMS (ESI) *m*/*z* 367 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-2-(3-Hydroxybenzyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (40). Compound **40** was synthesized in a fashion similar to compound **33**, using 3-hydroxybenzaldehyde as starting material. LCMS (ESI) *m*/*z* 367 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-2-(4-Hydroxybenzyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (41). Compound **41** was synthesized in a fashion similar to compound **33**, using 4-hydroxybenzaldehyde as starting material. LCMS (ESI) *m*/*z* 367 ($M + H^+$).

3-((7*R*,8*R*,9α*R*)-2-(4-(Dimethylamino)benzyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (42). Compound **42** was synthesized in a fashion similar to compound **33**, using 4-(dimethylamino)benzaldehyde as starting material. LCMS (ESI) *m*/*z* 394 ($M + H^+$).

**Methyl 3-(((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)methyl)benzo-

ate (43). Compound **43** was synthesized in a fashion similar to compound **33**, using methyl 3-formylbenzoate as starting material. LCMS (ESI) *m*/*z* 409 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(3-phenoxybenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (44). Compound **44** was synthesized in a fashion similar to compound **33**, using 3-phenoxybenzaldehyde as starting material. LCMS (ESI) *m*/*z* 443 (M + H^+).

3-((7*R*,8*R*,9α*R*)-2-(3-(Benzyloxy)benzyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (45). Compound **45** was synthesized in a fashion similar to compound **33**, using 3-(benzyloxy)benzaldehyde as starting material. LCMS (ESI) *m*/*z* 457 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(naphthalen-2-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (46). Compound **46** was synthesized in a fashion similar to compound **33**, using 2-naphthaldehyde as starting material. LCMS (ESI) *m*/*z* 401 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(naphthalen-1-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (47). Compound **47** was synthesized in a fashion similar to compound **33**, using 1-naphthaldehyde as starting material. LCMS (ESI) *m*/*z* 401 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(quinolin-4-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (48). Compound **48** was synthesized in a fashion similar to compound **33**, using quinoline-4-carbaldehyde as starting material. LCMS (ESI) *m*/*z* 402 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(pyridin-2-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (49). Compound **49** was synthesized in a fashion similar to compound **33**, using picolinaldehyde as starting material. LCMS (ESI) *m*/*z* 352 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(pyridin-3-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (50). Compound **50** was synthesized in a fashion similar to compound **33**, using nicotinaldehyde as starting material. LCMS (ESI) *m*/*z* 352 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(pyridin-4-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (51). Compound **51** was synthesized in a fashion similar to compound **33**, using isonicotinaldehyde as starting material. LCMS (ESI) *m*/*z* 352 (M + H^+).

3-((7*R*,8*R*,9α*R*)-2-(Furan-2-ylmethyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (52). Compound **52** was synthesized in a fashion similar to compound **33**, using furan-2-carbaldehyde as starting material. LCMS (ESI) *m*/*z* 341 (M + H^+).

3-((7*R*,8*R*,9α*R*)-2-(Furan-3-ylmethyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (53). Compound **53** was synthesized in a fashion similar to compound **33**, using furan-3-carbaldehyde as starting material. LCMS (ESI) *m*/*z* 341 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(thiophen-2-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (54). Compound **54** was synthesized in a fashion similar to compound **33**, using thiophene-2-carbaldehyde as starting material. LCMS (ESI) *m*/*z* 357 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(thiophen-3-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (55). Compound **55** was synthesized in a fashion similar to compound **33**, using thiophene-3-carbaldehyde as starting material. LCMS (ESI) *m*/*z* 357 (M + H^+).

3-((7*R*,8*R*,9α*R*)-2-(Cyclohexylmethyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (56). Compound **56** was synthesized in a fashion similar to compound **33**, using cyclohexanecarbaldehyde as starting material. LCMS (ESI) *m*/*z* 357 (M + H^+).

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(2-methylbenzyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (33). To a solution of **15** (0.1 g, 0.4 mmol) in ethanol (10 mL) under a nitrogen atmosphere was added 2-methylbenzaldehyde (0.13 mL, 1.15 mmol), and the reaction mixture was stirred at room temperature for 10 min. To this was then added BAP (0.12 mL, 1.15 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: dichloromethane/methanol/ammonium hydroxide mixtures of increasing polarity). Yield 39% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (d, J = 7 Hz, 3H), 1.32 (s, 3H), 1.42 (d, J = 13 Hz, 1H), 1.90 (t, J = 12 Hz, 1H), 2.03 (m, 2H), 2.35 (m, 2H), 2.38 (s, 4H), 2.57 (d, J = 11 Hz, 1H), 2.74 (m, 4H), 3.52 (s, 2H), 6.57 (dd, J = 8 and 2 Hz, 1H), 6.69 (t, J = 2 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 7.09 (t, J = 8 Hz, 1H), 7.15 (m, 3H), 7.25 (d, J = 8 Hz, 2H); LCMS (ESI) *m*/*z* 365 (M + H^+). Anal. ($C_{24}H_{32}N_2O \cdot 0.16H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-2-(2-Chlorobenzyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (36). Compound **36** was synthesized in a fashion similar to compound **33**, using 2-chlorobenzaldehyde as starting material. Yield 62% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.45 (d, J = 13 Hz, 1H), 1.91 (t, J = 12 Hz, 1H), 2.05 (m, 1H), 2.12 (t, J = 10 Hz, 1H), 2.45 (m, 2H), 2.60 (m, 1H), 2.79 (m, 5H), 3.69 (s, 2H), 6.57 (dd, J = 8 and 2 Hz, 1H), 6.69 (s, 1H), 6.73 (d, J = 7 Hz, 1H), 7.09 (t, J = 7 Hz, 1H), 7.27 (m, 2H), 7.39 (dd, J = 7 and 2 Hz, 1H), 7.51 (dd, J = 8 and 2 Hz, 2H); LCMS (ESI) *m*/*z* 385 (M + H^+). Anal. ($C_{23}H_{29}ClN_2O \cdot 0.33H_2O$) C, H, N.

2-(((7*R*,8*R*,9α*R*)-8-(3-Hydroxyphenyl)-7,8-dimethyl-hexahydro-1*H*-pyrido[1,2-α]pyrazin-2(6*H*)-yl)methyl)phenol (39). Compound **39** was synthesized in a fashion similar to compound **33**, using 2-hydroxybenzaldehyde as starting material. Yield 38% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.47 (d, J = 12 Hz, 1H), 1.90 (t, J = 12 Hz, 1H), 2.06 (m, 2H), 2.34 (m, 1H), 2.41 (m, 2H), 2.58 (dd, J = 12 and 2 Hz, 1H), 2.75 (dd, J = 12 and 2 Hz, 2H), 2.84 (d, J = 11 Hz, 1H), 2.90 (d, J = 11 Hz, 1H), 3.59 (m, 1H), 3.66 (m, 1H), 3.74 (s, 2H), 6.56 (dd, J = 8 and 2 Hz, 1H), 6.68 (t, J = 2 Hz, 1H), 6.74 (m, 2H), 6.78 (m, 1H), 7.09 (m, 3H); LCMS (ESI) *m*/*z* 367 (M + H^+); HRMS for $C_{23}H_{30}N_2O_2$ (M, 366.2307 [M + H]) calcd, 367.2380; found, 367.2403.

3-((7*R*,8*R*,9α*R*)-7,8-Dimethyl-2-(thiophen-2-ylmethyl)-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (54). Compound **54** was synthesized in a fashion similar to compound **33**, using thiophene-2-carbaldehyde as starting material. Yield 47% (white solid); ^{1}H NMR (CD_3OD) δ 0.74 (d, J = 7 Hz, 3H), 1.34 (s, 3H), 1.48 (m, 1H), 1.91 (t, J = 12 Hz, 1H), 2.06 (br s, 2H), 2.40 (br s, 2H), 2.62 (m, 1H), 2.82 (m, 4H), 3.80 (s, 2H), 6.58 (dd, J = 8 and 2 Hz, 1H), 6.69 (s, 1H), 6.72 (d, J = 8 Hz, 1H), 6.98 (d, J = 5 Hz, 1H), 7.01 (s, 1H), 7.10 (t, J = 8 Hz, 1H), 7.34 (d, J = 5 Hz, 1H); LCMS (ESI) *m*/*z* 357 (M + H^+). Anal. ($C_{21}H_{28}N_2OS \cdot 0.33H_2O$) C, H, N.

3-((7*R*,8*R*,9α*R*)-2-(Cyclohexylmethyl)-7,8-dimethyl-octahydro-1*H*-pyrido[1,2-α]pyrazin-8-yl)phenol (56). Compound **56** was synthesized in a fashion similar to compound **33**, using cyclohexanecarboxaldehyde as starting material. Yield 65% (white solid); ^{1}H NMR (CD_3OD) δ 0.75 (d, J = 7 Hz, 3H), 0.91 (m, 2H), 1.25 (m, 3H), 1.35 (s, 3H), 1.47 (d, J = 13 Hz, 1H), 1.57 (m, 1H), 1.89 (m, 3H), 2.05 (dd, J = 13 Hz and 2 Hz, 1H), 2.21 (m, 3H), 2.36 (t, J = 12 Hz, 1H), 2.45 (t, J = 12 Hz, 1H), 2.58 (d, J = 11 Hz, 1H), 2.71 (m, 2H), 2.75 (m, 1H), 2.84 (dd, J = 12 and 2 Hz, 1H), 6.58 (dd, J = 8 and 2 Hz, 1H), 6.70 (s, 1H), 6.74 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H); LCMS (ESI) *m*/*z* 357 (M + H^+). Anal. ($C_{23}H_{36}N_2O \cdot 0.25H_2O$) C, H, N.

B. Biological Methods. Radioligand Binding Assays. Membrane preparations from Chinese hamster ovary (CHO) cells stably expressing human κ-, μ-, or δ-opioid receptors were prepared as described previously.[17] The assay buffer used is composed of 50 mM tris(hydroxymethyl) aminomethane HCl, pH 7.8, 1.0 mM ethylene glycol bis(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA-free acid), 5.0 mM $MgCl_2$, 10 mg/L leupeptin, 10 mg/L pepstatin A, 200 mg/L bacitracin, and 0.5 mg/L aprotinin. After dilution in assay buffer and homogenization in a Polytron homogenizer (Brinkmann, Westbury, NY) for 30 s at a setting of 1, membrane proteins (10−80 μg) in 250 μL of assay buffer were added to mixtures containing test compound and [^{3}H]diprenorphine (0.5−1.0 nM, 25 000−50 000 dpm) in 250 μL of assay buffer in 96-well deep-well polystyrene titer plates (Beckman) and incubated at room temperature for 60 min. Reactions were terminated by vacuum filtration with a Brandel MPXR-96T harvester through GF/B filters that had been pretreated with a solution of 0.5%

polyethylenimine and 0.1% bovine serum albumin for at least 1 h. The filters were washed four times with 1.0 mL each of ice-cold 50 mM Tris-HCl, pH 7.8, and 30 μL of Microscint-20 (Packard Instrument Company, Meriden, CT) was added to each filter. Radioactivity on the filters was determined by scintillation spectrometry in a Packard TopCount.

[^{3}H]Diprenorphine with a specific activity of 50 Ci/mmol was purchased from Perkin-Elmer Life Sciences, Inc. (Boston, MA). The K_D values for [^{3}H]diprenorphine binding were 0.33 nM for the κ and μ receptors and 0.26 nM for the δ receptor. Receptor expression levels, determined as B_{max} values from Scatchard analyses, were 4400, 4700, and 2100 fmol/mg of protein for the κ, μ, and δ receptors, respectively. Preliminary experiments were performed to show that no specific binding was lost during the wash of the filters, that binding achieved equilibrium within the incubation time and remained at equilibrium for at least an additional 60 min, and that binding was linear with regard to protein concentration. Nonspecific binding, determined in the presence of 10 μM unlabeled naloxone, was less than 10% of total binding. Protein was quantified by the method of Bradford.[18]

The data from competition experiments were fit by nonlinear regression analysis with the program Prism (GraphPad Software, Inc., San Diego, CA) using the four-parameter equation for one-site competition, and K_i values were subsequently calculated from EC_{50} values by the Cheng−Prusoff equation.

Receptor-Mediated [^{35}S]GTPγS Binding. Receptor-mediated [^{35}S]GTPγS binding was performed by modifications of the methods of Selley and co-workers[19] and Traynor and Nahorski.[20] Assays were carried out in 96-well FlashPlates (Perkin-Elmer Life Sciences, Inc., Boston, MA). Membranes prepared from CHO cells expressing the appropriate receptor (50−100 μg of protein) were added to assay mixtures containing agonist with or without antagonists, approximately 100 000 dpm (100 pM) [^{35}S]GTPγS, 3.0 μM GDP, 75 mM NaCl, 15 mM $MgCl_2$, 1.0 mM EGTA, 1.1 mM dithiothreitol, 10 mg/L leupeptin, 10 mg/L pepstatin A, 200 mg/L bacitracin, and 0.5 mg/L aprotinin in 50 mM Tris-HCl buffer, pH 7.8. After incubation at room temperature for 1 h, the plates were sealed and centrifuged at 800 *g* in a swinging bucket rotor for 5 min, and bound radioactivity was determined with a TopCount microplate scintillation counter (Packard Instrument Co., Meriden, CT).

Antagonist activities were obtained by titration in the presence of a concentration of loperamide (50 nM) that yielded 80% of its maximal stimulation (EC_{80}), and the data were analyzed by nonlinear regression fit using Prism. Potency was expressed as the concentration of antagonist that achieved 50% of the maximum inhibition of that antagonist.

Supporting Information Available: Table of crystallographic data for compound **62**. Table of elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) This material also contained, as an impurity (i.e., up to 20% dependent upon reaction scale; percentage determined by ^{1}H NMR), an additional carboxylic acid derivative, an isomer of **59**. The mixture was used for the next step without further purification.

(14) Crystallographic data for compound **62** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 604294. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Rd., Cambridge CB2 1EZ, U.K., (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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