Journal of
Medicinal Chemistry

Article

Synthesis and Structure–Activity Relationships of 5#-Aryl-14-alkoxypyridomorphinans: Identification of a Mu Opioid Receptor Agonist/Delta Opioid Receptor Antagonist Ligand with Systemic Antinociceptive Activity and Diminished Opioid Side Effects.

Rakesh H. Vekariya, Wei Lei, Abhisek Ray, Surendra K. Sainai, Sixue Zhang, Gabriella Molnar, Deborah Barlow, Kelly L. Karlage, Edward Bilsky, Karen Houseknecht, Tally M. Largent-Milnes, John M. Streicher, and Subramaniam Ananthan

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.0c00503 • Publication Date (Web): 12 Jun 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis and Structure–Activity Relationships of 5′-Aryl-14-alkoxypyridomorphinans: Identification of a Mu Opioid Receptor Agonist/Delta Opioid Receptor Antagonist Ligand with Systemic Antinociceptive Activity and Diminished Opioid Side Effects.

Rakesh H. Vekariya,[†] Wei Lei,[‡] Abhisek Ray,[†] Surendra K. Saini,[†] Sixue Zhang,[†] Gabriella Molnar,[‡] Deborah Barlow,[§] Kelly L. Karlage,[‡] Edward J. Bilsky,[‡] Karen L. Houseknecht,[§] Tally M. Largent-Milnes,[‡] John M. Streicher,[‡] and Subramaniam Ananthan[,†]*

[†]Chemistry Department, Southern Research, Birmingham, Alabama 35205, United States, [‡]Department of Pharmacology, College of Medicine, University of Arizona, Tucson, Arizona 85724, United States, [§]Department of Biomedical Sciences, College of Osteopathic Medicine, University of New England, Biddeford, Maine 04005, United States.

ABSTRACT

We previously identified a pyridomorphinan (**6**, SRI-22138) possessing a 4-chlorophenyl substituent at the 5′-position on the pyridine and a 3-phenylpropoxy at the 14-position of the morphinan as a mixed mu opioid receptor (MOR) agonist and delta/kappa opioid receptor (DOR/KOR) antagonist with potent antinociceptive activity and diminished tolerance and dependence in rodents. Structural variations at the 5′- and 14-positions of this molecule gave insights into the structure–activity relationships for binding and functional activity. Subtle structural changes exerted significant influence, particularly on the ability of the compounds to function as agonists at MOR. In vivo evaluation identified compound **20** (SRI-39067) as a MOR agonist/DOR antagonist that produced systemically active potent antinociceptive activity in the tail-flick assay in mice, with diminished tolerance, dependence/withdrawal, reward liability, and respiratory depression versus morphine. These results support the hypothesis that mixed MOR agonist/DOR antagonist ligands may emerge as novel opioid analgesics with reduced side effects.

INTRODUCTION

For relief of moderate to severe acute pain, opioids remain the mainstay of treatment. However, the use of opioid analgesics is associated with severe limiting side effects including abuse liability, respiratory depression, constipation and development of tolerance and dependence.[1-7] Therefore, considerable effort has been expended on the discovery of novel opioid analgesics that are as efficacious as the prototypic opioid analgesic morphine but possessing reduced side effects. Opioid drugs exert their analgesic effects through binding and activation of the three opioid receptor subtypes, namely the mu opioid receptor (MOR), the delta opioid receptor (DOR) and the kappa opioid receptor (KOR).[8,9] Several lines of evidence suggest that there are physical and/or functional interactions between these G-protein coupled receptors (GPCRs), and molecules that interact with multiple receptors may prove advantageous in the search for opioid ligands with diminished side effect profiles.[10-15] Considerable evidence from gene knockout/knockdown studies and studies using pharmacological probes suggests that activation of MOR with simultaneous inhibition of DOR leads to MOR-mediated analgesic activity with diminished development of tolerance, dependence, and potentially other side effects.[13,15-19] Based on these observations, we[20,21] and others[13,22-28] pursued the development of mixed function ligands possessing a MOR agonist/DOR antagonist profile of activity using peptidic, peptidomimetic, and nonpeptide opioid templates. Exemplary MOR agonist/DOR antagonist ligands evaluated in animal models is shown in Figure 1.

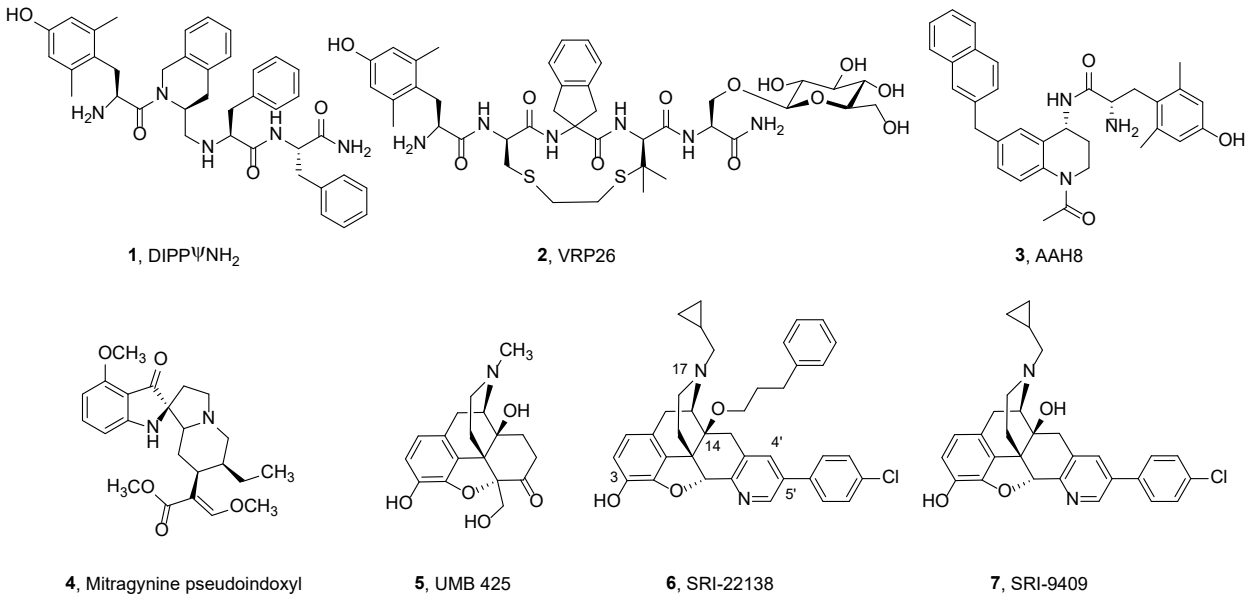


Figure 1. Structures of MOR agonist/DOR antagonist ligands **1–6** and the MOR-DOR antagonist **7**.

We previously synthesized and evaluated a series of 14-alkoxypyridomorphinans possessing a 4-(chlorophenyl) group at the 5′-position on the pyridine ring that led to the identification of compound **6** as a ligand possessing a balanced binding affinity profile at MOR and DOR with agonist activity at MOR and potent antagonist activity at DOR.[21] Pharmacological evaluation with this compound demonstrated antinociceptive activity comparable to morphine in the mouse warm water tail-flick assay. Moreover, on repeated administration, compound **6** displayed diminished development of analgesic tolerance compared to morphine. These studies with compound **6** were performed by intracerebroventricular (icv) administration due to its poor blood brain barrier penetration capacity. The current effort was undertaken to expand the structure–activity relationship (SAR) in the pyridomorphinan scaffold of this prototype compound **6** and to identify improved ligands with mixed MOR agonist/DOR antagonist profile and acceptable absorption,

distribution, metabolism, and excretion (ADME) and pharmacokinetic (PK) properties to enable proof-of-concept studies with systemic administration.

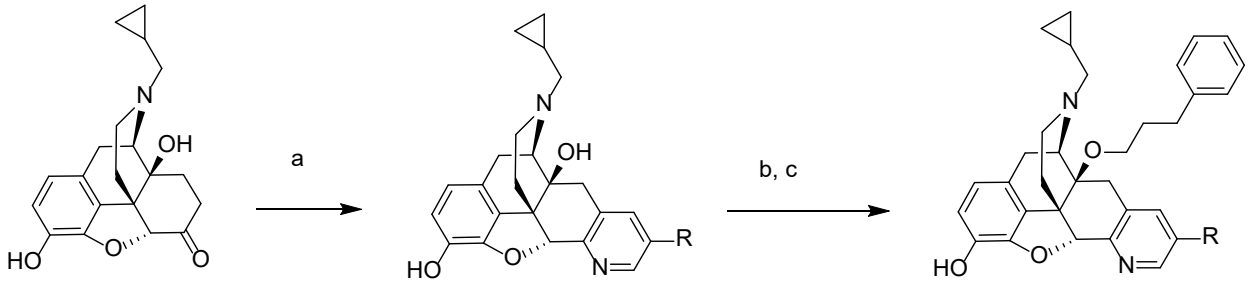
RESULTS AND DISCUSSION

Compound Design. The design principle that led to the identification of compound **6** was that a non-selective dual MOR/DOR antagonist pyridomophinan **7** (Figure 1) possessing a C-14 hydroxyl group could be transformed to a MOR agonist with retention of DOR antagonist profile by installation of a 3-(phenylpropyl) group on the C-14 oxygen atom.[21] In our previous DOR antagonist-focused effort, we had demonstrated that a number of compounds related to **7** possessing various aryl and heteroaryl groups at the 5′-position displayed a dual MOR/DOR antagonist profile similar to that of **7**.[20,29-31] Therefore, we pursued the installation of a 3-(phenylpropyl) group on C-14 oxygen on a series of pyridomorphinans possessing substituent variations on the phenyl group at the 5′-position (compounds **8–29**, Table 1) and a few heteroaryl variants in place of the phenyl group at the 5′-position (compounds **30–42**, Table 2). In addition, we pursued targeted changes to the alkyl group on the oxygen at C-14 using **6** and its deschloro analogue **8** as the templates. This study was intended to explore the consequence of installation of a substituent other than a 3-(phenylpropyl) group (compounds **43–52**, Table 3) on opioid receptor binding and functional activity.

Synthesis. Several synthetic approaches were utilized for the preparation of the desired target compounds. The original synthetic route developed for the preparation of compound **6** was adopted for the preparation of the 5′-aryl target compounds **8–10** and the 5′-heteroaryl target compounds **36** and **38**, as depicted in Scheme 1. The starting materials **54–58** were synthesized by annulation of the pyridine ring on the C-ring of naltrexone (**53**) by condensation with substituted

malondialdehydes and ammonium acetate in acetic acid. Dialkylation of the phenol and the tertiary alcohol groups with phenylpropyl bromide followed by selective removal of the phenypropyl group from the phenolic oxygen using BBr_3 yielded the desired target compounds.

Scheme 1. Synthesis of Pyridomorphinans **8–10, 36**, and **38**[a]



53

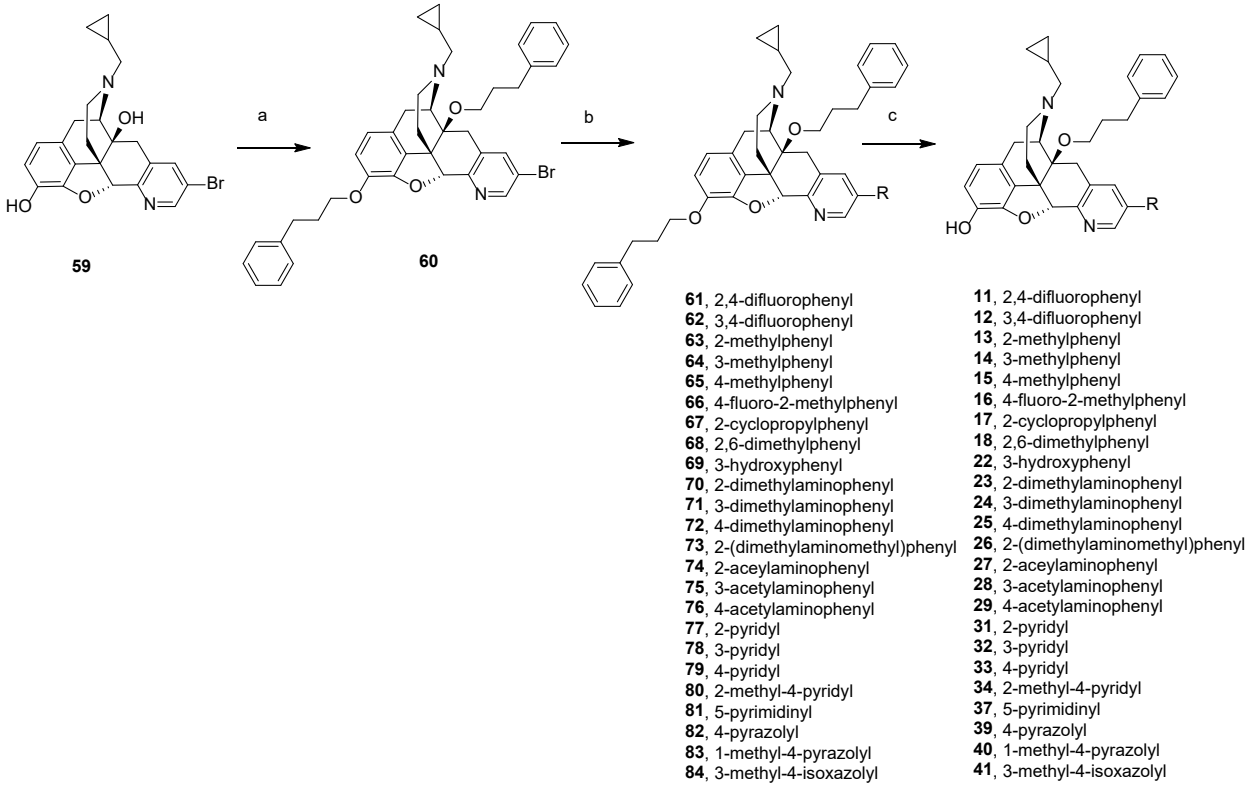
54, R = phenyl
55, R = 4-bromophenyl
56, R = 4-fluorophenyl
57, R = 4-pyrimidinyl
58, R = 2-pyrazinyl

8, R = phenyl
9, R = 4-bromophenyl
10, R = 4-fluorophenyl
36, R = 4-pyrimidinyl
38, R = 2-pyrazinyl

[a]Reagents and conditions: (a) $RCH(CHO)_2$, $AcONH_4$, AcOH, reflux, 16 h; (b) NaH, $Ph(CH_2)_3Br$, DMF, 0 °C to rt, 4 h; (c) BBr_3, CH_2Cl_2, –78 °C to 0 °C, 1 h.

We also developed an alternative, more versatile approach utilizing the 3-bromopyridine **60**, prepared by dialkylation of the previously described **59**,[30] as the key starting material. Suzuki coupling of **60** with arylboronic acids or esters, followed by deprotection of the phenol, as depicted in Scheme 2, gave the desired target compounds **11**–**18**, **22**–**29**, **31**–**34**, **37,** and **39–41**. Similarly, coupling of **60** with pyrrole using $Pd_2(dba)_3$ as the catalyst in the presence of Cs_2CO_3 and P(*t*-Bu)$_3$ in toluene followed by 3-*O*-dealkylation with BBr_3 gave **30** (Table 2).

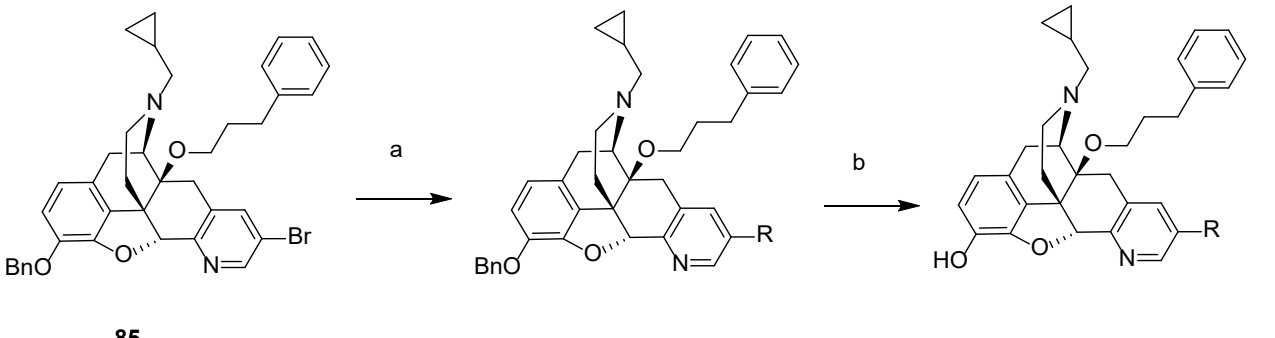
Scheme 2. Synthesis of Pyridomorphinans **11**–**18**, **22**–**29**, **31**–**34**, **37,** and **39–41**[a]



[a]Reagents and conditions: (a) NaH, $Ph(CH_2)_3Br$, DMF, 0 °C to rt, 4 h; (b) $RB(OH)_2$ or RBpin, $Pd(PPh_3)_4$, K_2CO_3, 10:1 DMF/H_2O, mw, 100 °C, 1 h; (c) BBr_3, CH_2Cl_2, –78 °C to 0 °C, 1 h.

For the preparation of the targets containing a methoxy group (**19–21** and **35**), intermediates carrying benzyl as the phenolic protecting group were utilized to facilitate selective deprotection under reductive or acidic conditions (Scheme 3). The benzyl protected bromopyridine **85** was accessible from **59** via benzylation of the phenolic OH followed by phenypropylation of the 14-OH group.

Scheme 3. Synthesis of Pyridomorphinans **19–21** and **35**[a]



85

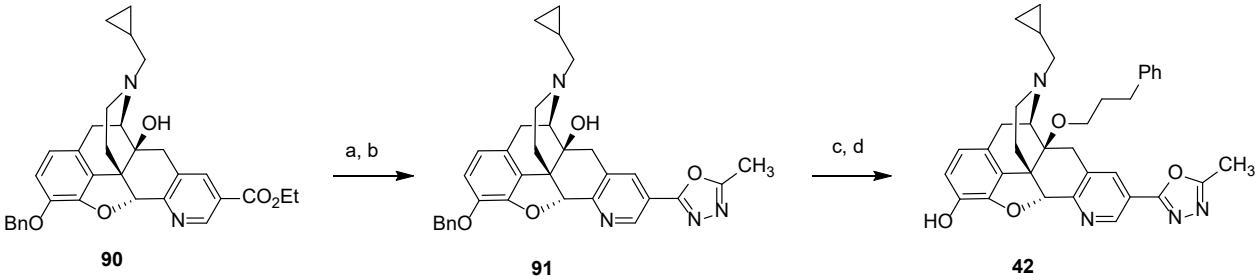
86, R = 2-methoxyphenyl
87, R = 3-methoxyphenyl
88, R = 4-methoxyphenyl
89, R = 3-methoxy-4-pyridyl

19, R = 2-methoxyphenyl
20, R = 3-methoxyphenyl
21, R = 4-methoxyphenyl
35, R = 2-methoxy-4-pyridyl

[a]Reagents and conditions: (a) RBpin, $Pd(PPh_3)_4$, K_2CO_3, 10:1 DMF/H_2O, mw, 100 °C, 1 h; (b) TFA, reflux, 1.5 h or H_2, 10% Pd/C, 1:1 CH_2Cl_2/MeOH, 20 h.

The oxadiazolyl compound **42** was prepared from the carbethoxypyridine **90** via conversion to hydrazide, cyclization to oxadiazole with triethyl orthoacetate, followed by etherification of the 14-OH and deprotection of the phenol as shown in Scheme 4.

Scheme 4. Synthesis of Oxadiazolyl Pyridomorphinan **42**[a]

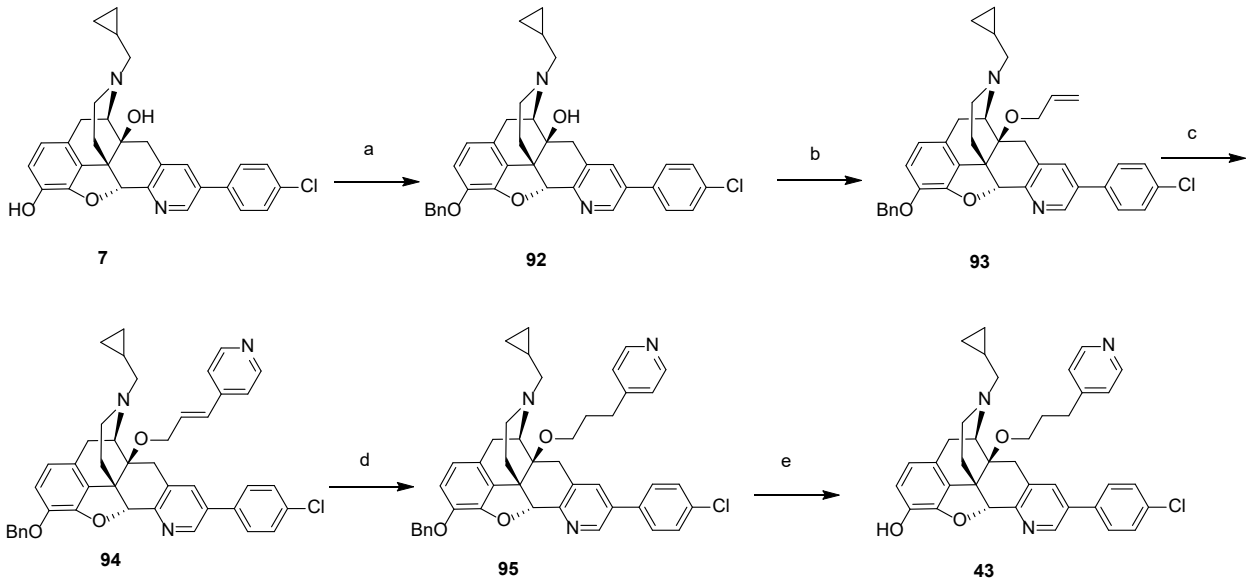


90 **91** **42**

[a]Reagents and conditions: (a) $N_2H_4 \cdot H_2O$, EtOH, reflux, 16 h; (b) $CH_3C(OEt)_3$, AcOH, 150 °C, 3 h; (c) NaH, $Ph(CH_2)_3Br$, DMF, 0 °C to rt, 4 h; (d) H_2, 10% Pd/C, 1:1 CH_2Cl_2/MeOH, 20 h.

For the synthesis of the target compound **43** possessing a pendant 4-pyridyl group in the 14-*O*-alkyl substituent, we initially attempted dialkylation of **7** or monoalkylation of **92** with 3-(4-pyridylpropyl)bromide and related alkylating agents. However, all our attempts under a variety of reaction conditions failed to yield the desired alkylated intermediates, possibly due to base promoted elimination reaction predominating over nucleophilic substitution reaction. This difficulty was overcome by a stepwise derivatization involving 14-*O*-allylation, Heck coupling with 4-bromopyridine, saturating the double bond, followed by acid catalyzed deprotection of the 3-*O*-benzyl group as shown in Scheme 5.

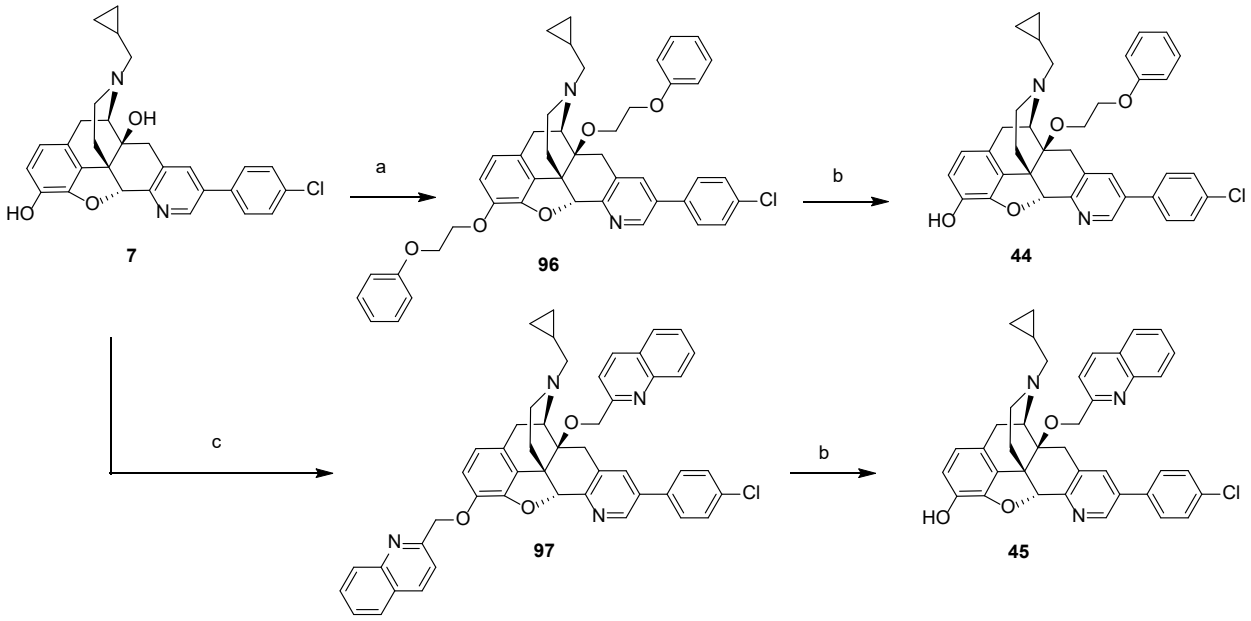
Scheme 5. Synthesis of 14-(3(4-Pyridyl)propoxy)pyridomorphinan **43**[a]



[a]Reagents and conditions: (a) BnBr, K_2CO_3, Me_2CO, reflux, 3h; (b) CH_2=$CHCH_2Br$, NaH, DMF, 0 °C to rt, 4 h; (c) 4-bromopyridine hydrochloride, $Pd(PPh_3)_4$, $Pd(OAc)_2$, K_2CO_3, 130 °C, 1 h; (d) H_2, 10% Pd/C, 1:1 CH_2Cl_2/MeOH, 20 h; (e) TFA, reflux, 1.5 h.

A dialkylation and selective mono-dealkylation sequence (Scheme 6) was successful for the preparation of the 2-phenoxyethoxy (**44**) and the 2-quinolinylmethoxy (**45**) target compounds using 2-phenoxyethyl triflate and 2-(chloromomethyl)quinoline as the alkylating agent, respectively.

Scheme 6. Synthesis of 14-Alkoxypyridomorphinans **44** and **45**[a]

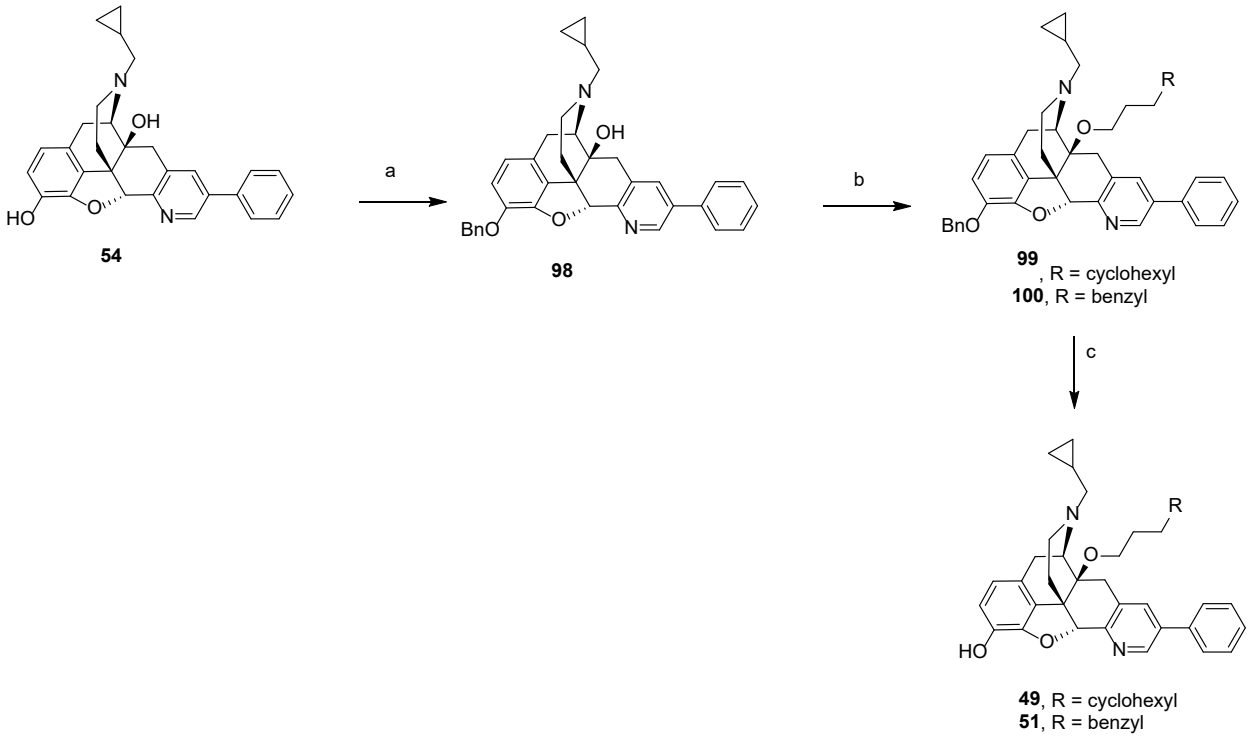


[a]Reagents and conditions: (a) $PhOCH_2CH_2OSO_2CF_3$, PMP, CH_3NO_2, 50 °C, 1 h; (b) BBr_3, CH_2Cl_2, –78 ºC to 0 °C, 1 h; (c) 2-(chloromethyl)quinoline, NaH, DMF, 0 °C to rt, 4 h.

The allylation–Heck coupling route shown in Scheme 5 for the preparation of **43** was adapted for the synthesis of the 3-(3-pyridylpropoxy) compound **46** and the 3-(4-pyridylpropoxy) compound **47** (Table 3) using the 5′-phenylpyridomorphinan **54**[29] as the starting material. In the preparation of these compounds, saturation of the double bond and removal of the phenolic-*O* benzyl protecting group were accomplished by catalytic hydrogenation in a single step. Dialkylation of

54 with 4-(fluorophenyl)propyl bromide followed by treatment with BBr_3 to selectively remove the alkyl group from the phenolic oxygen delivered the desired target compound **48** (Table 3). The cyclohexylpropoxy (**49**) and the 4-phenylbutoxy (**51**) compounds were synthesized as depicted in Scheme 7.

Scheme 7. Synthesis of 14-Alkoxypyridomorphinans **49** and **51**[a]



[a]Reagents and conditions: (a) BnBr, K_2CO_3, Me_2CO, reflux, 3h; (b) 3-cyclohexylpropyl bromide or 4-phenylbutyl bromide, NaH, DMF, 0 °C to rt, 4 h; (c) BBr_3, CH_2Cl_2, –78 °C to rt (for **49**) or TFA, 70 °C, 2 h (for **51**).

A synthetic sequence similar to that described in Scheme 5 was deployed for the preparation of compound **50** using compound **98** as the starting material. Thus, allylation of **98** and palladium

catalyzed coupling of the allyl derivative with 4-bromo-3,6-dihydro-2*H*-pyran gave benzyl protected diene intermediate which was subjected to catalytic hydrogenation to saturate the double bonds with simultaneous removal of the benzyl protecting group to obtain the desired compound **50**. Similarly, catalytic hydrogenation of the 14-*O*-allyl derivative of **98** gave the propoxy compound **52** (Table 3).

In Vitro Pharmacology and ADME Evaluation. The binding affinity of the compounds at MOR, DOR, and KOR were evaluated using well-established radioligand displacement assays. Membranes prepared from CHO cells stably expressing human MOR, DOR, or KOR and [^{3}H]diprenorphine as the radioligand were used in determining the binding affinities.[32,33] The functional activity evaluations were performed using the [^{35}S]-GTPγS coupling assay using membranes from the same cells. For MOR agonist experiments, DAMGO was used as the reference agonist and the E_{max} values were calculated relative to DAMGO as the full agonist (E_{max} 100%). For DOR antagonist evaluation, SNC80 was used as the agonist ligand to determine the ability of the test compounds to inhibit SNC80 mediated stimulation of [^{35}S]-GTPγS binding. KOR agonist evaluations were performed similar to MOR agonist experiments with (±)-U50,488 as the standard agonist ligand (E_{max} 100%). Since the goal of our effort was to identify compounds with agonist activity at MOR and antagonist activity at DOR, the compounds were evaluated first as agonists at MOR and antagonists at DOR. Only selected compounds that were of interest based on binding and functional profiles at MOR and DOR were then evaluated at KOR to determine whether they displayed undesirable agonist activity.

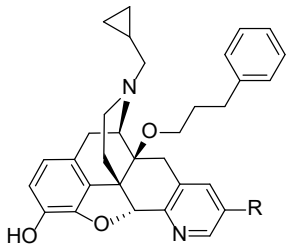
All compounds were also evaluated via in vitro ADME assays to determine aqueous solubility, log *D*, and mouse liver and human liver microsomal stability. Mouse liver microsomal stability and log *D* data are presented along with binding affinity and functional activity data of the compounds

in Tables 1–3. Human liver microsomal stability, solubility, and calculated physicochemical properties of the target compounds are given in Table S1 (Supplementary Information).

Structure–Activity Relationships (SAR).

Binding affinity of 5′-aryl compounds at MOR. The data for the group of compounds possessing structural variations on the 5′-phenyl ring are presented in Table 1. Most of the 5′-aryl compounds displayed only modest binding affinity at MOR. The lead compound **6** possessing the 4-chlorophenyl substituent displayed single-digit nanomolar binding affinity at MOR (K_i = 7.55 nM). Among compounds with other substituent groups on the phenyl ring, only three compounds, the 4-fluorophenyl compound **10**, the 2-(dimethylamino)phenyl compound **23**, and the 4-(dimethylamino)phenyl compound **25** showed improved binding affinity at MOR with K_i values of 2.33 nM, 6.97 nM, and 4.70 nM, respectively. Compounds that displayed moderate binding affinity with K_i value in the range of 10 nM – 100 nM include the unsubstituted (**8**), 3-methyl (**14**) 2-methyl-4-fluoro (**16**), 2-methoxy (**19**), 3-methoxy (**20**), 3-hydroxy (**22**), and 3-dimethylamino (**24**) phenyl derivatives. In contrast to the 4-fluoro compound with high affinity, the difluoro compounds **11** and **12** displayed a marked reduction in binding affinity. Other substituents that also had a deleterious effect on MOR affinity include 4-bromo (**9**), 2-methyl (**13**), 2,6-dimethyl (**18**), 4-methyl (**15**), 2-cyclopropyl (**17**), 4-methoxy (**21**), and 2-, 3- or 4-acetylamino (compounds **27**, **28** and **29**) groups.

Table 1. Binding, Functional Activity, and In Vitro ADME Data for 5′-Aryl-14-(phenylpropoxy) Compounds 8–29.



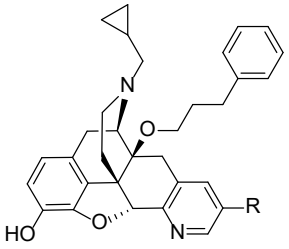
compd	R	Binding K_i (nM)[a]			[^{35}S]GTPγS Coupling[b]						Log D[c]	MLM $t_{1/2}$ (min)[d]
		MOR	DOR	KOR	MOR Agonist EC_{50} (nM)	MOR Agonist E_{max} (%)	DOR Antagonist IC_{50} (nM)	DOR Antagonist I_{max} (%)	KOR Agonist EC_{50} (nM)	KOR Agonist E_{max} (%)		
6[e]		7.55 ± 1.23	2.1 ± 0.2	60.9 ± 31	8.20 ± 4.78	47.5 ± 18.7	4.88 ± 2.75	67.0 ± 16.4	12.6 ± 5.5	10.9 ± 1.7	0.393	9.72
8		23.1 ± 12.9	19.3 ± 9.8	132 ± 18	1.27 ± 0.07	105 ± 3	0.93 ± 0.07	98.3 ± 0.9	>3333	(19.1)[f]	0.868	8.96
9		138 ± 22	20.9 ± 1.8	75.9 ± 10.2	26.6 ± 15.0	78.3 ± 2.7	< 0.51	90.7 ± 5.7	5.52 ± 0.96	34.3 ± 1.2	3.64	9.64
10		2.33 ± 0.14	3.42 ± 0.29	6.69 ± 0.39	117 ± 27	37 ± 4	34.5 ± 18.5	101 ± 4	56.6 ± 11.3	15.3 ± 0.9	0.428	10.4
11		171 ± 4	53.7 ± 8.1	35.9 ± 7.5	130 ± 61	68.0 ± 5.3	3.20 ± 0.62	103 ± 4	ND[g]	ND[g]	2.84	10.4
12		370 ± 13	7.52 ± 0.20	71.2 ± 4.8	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	2.92	8.08
13		235 ± 20	97.2 ± 14.4	152 ± 18	5.53 ± 0.70	92.0 ± 1.7	14.3 ± 6.3	92.6 ± 4.1	ND[g]	ND[g]	2.68	6.48
14		24.4 ± 5.0	26.8 ± 4.7	17.6 ± 2.9	20.6 ± 10.0	111 ± 4	< 0.169	105 ± 9	NC[h]	NC[h]	3.39	7.09
15		191 ± 13	34.4 ± 4.5	102 ± 6.2	2.31± 0.41	115 ± 3	3.63 ± 1.1	104 ± 0.6	ND[g]	ND[g]	2.44	7.86
16		29.9 ± 0.6	3.78 ± 0.61	129 ± 46	25 ± 5	58 ± 3	28.2 ± 20.7	136 ± 7	NC[h]	NC[h]	4.52	8.27
17		135 ± 29	64.1 ± 8.9	175 ± 44	141 ± 78	122 ± 6	2.48 ± 0.50	81.3 ± 6.9	ND[g]	ND[g]	3.73	8.28
18		249 ± 27	93.4 ± 2.3	134 ± 15	3.40 ± 1.19	101 ± 1	51.6 ± 31.0	74.3 ± 1.2	ND[g]	ND[g]	3.08	8.27
19		61.9 ± 4.3	29.7 ± 9.4	126 ± 7	7.18 ± 2.13	79.0 ± 1.0	0.79 ± 0.07	94.3 ± 1.9	NC[h]	NC[h]	2.01	8.65
20		91.3 ± 14.1	48.0 ± 8.9	103 ± 16	13.0 ± 1.2	78.7 ± 2.0	2.40 ± 0.28	85.7 ± 1.2	NC[h]	NC[h]	2.58	10.5
21		148 ± 13	30.6 ± 9.1	140 ± 24	23.5 ± 6.5	81.0 ± 1.2	22.0 ± 2.7	92.3 ± 0.7	2.02 ± 0.64	20.2 ± 0.2	1.93	9.03
22		12.9 ± 0.8	8.37 ± 0.33	18.1 ± 3.2	1.12 ± 0.04	104 ± 5	1.28 ± 0.14	90.3 ± 10.5	ND[g]	ND[g]	3.73	7.36
23		6.97 ± 0.70	69.6 ± 5.1	7.96 ± 1.65	233 ± 24	94.7 ± 0.3	12.3 ± 3.9	82.7 ± 1.7	NC[h]	NC[h]	1.93	9.78
24		15.8 ± 1.6	68.9 ± 7.9	11.9 ± 2.4	1.50 ± 0.19	98.0 ± 11.1	3.76 ± 1.54	99.3 ± 3.8	NC[h]	NC[h]	3.38	7.10
25		4.70 ± 0.58	53.1 ± 4.6	6.18 ± 1.88	2.10 ± 0.26	116 ± 3	2.53 ± 0.99	96.3 ± 2.7	NC[h]	NC[h]	1.87	7.83
26		56.4 ± 5.6	14.0 ± 3.4	22.7 ± 10.0	28.9 ± 16.5	57.0 ± 2.1	11.7 ± 0.4	74.0 ± 1.0	NC[h]	NC[h]	3.65	12.7
27		141 ± 62	> 3333	13.5 ± 2.9	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	2.52	10.3
28		337 ± 80	> 3333	608 ± 343	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	2.60	14.0
29		159 ± 37	394 ± 338	15.1 ± 3.9	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	ND[g]	3.15	11.0
DAMGO					25.5 ± 1.4	100						
Naloxone		59.5 ± 2.9	98.1 ± 3.0				153 ± 6	100				
U50,488				31.9 ± 9.0					35.8 ± 2.0	100		

[a]Binding affinities determined by competitive displacement of [^{3}H]diprenorphine in membrane preparations from CHO cells expressing human MOR, DOR, or KOR. [b][^{35}S]GTPγS binding for functional activity performed using the same membrane preparations. MOR and KOR agonist efficacy expressed as percent stimulation versus standard agonists DAMGO and U50,4888, respectively. DOR antagonist potency (IC_{50}) and efficacy (I_{max}) determined versus the standard agonist SNC80 (100 nM). DOR antagonist efficacy (I_{max}) calculated as percent of the reference antagonist naloxone. KOR efficacy in parenthesis is the maximum stimulation produced at 10 μM. All values expressed as mean ± SEM for N=3–4 independent experiments. [c]The log *D* measured at pH 7.4. [d]In vitro mouse liver microsomal half-life values in minutes. [e]Data for compound **6** included for comparison. [f]Percent maximum stimulation at 10 μM. [g]ND = Not Determined. [h]NC = Not Converged (no agonist activity detected).

Binding affinity of 5'-aryl compounds at DOR. At DOR, the structure of the ligands had significant effects on the binding affinities. Removal of the chlorine at the *para*-position on the phenyl ring in the lead compound **6** yielded compound **8** that displayed nearly 10-fold reduction in affinity**.** Replacement with other substituents such as bromine (compound **9**), methyl (compound **15**), methoxy (compound **21**), dimethylamino (compound **25**) or acetylamino (compound **29**) all led to moderate to significant reductions in affinity at DOR. While the 4-fluoro compound **10** maintained high affinity, the 3,4-difluoro (**12**) and the 2,4-difluoro (**11**) compounds displayed ~3- and ~25-fold reductions in affinity, respectively. Substitution at the 2-position of the phenyl ring in general appears to result in significant reductions in binding affinity at DOR as exemplified by the data on the 2-methyl, 2-cyclopropyl, 2,6-dimethyl, 2-methoxy, 2-dimethylamino and 2-acetylamino compounds **13, 17, 18, 19, 23,** and **27**, respectively. Among *ortho*-, *meta*- and *para*- substituted

isomers, the *ortho*- methyl compound **13** shows lower affinity (DOR K_i = 97.2 nM) than the *meta*- and *para*- methyl compounds **14** and **15** (DOR K_i = 26.8 nM and 34.4 nM, respectively). In contrast, the methoxy (**19–21**) and dimethylamino (**23–25**) positional isomers did not display significant differences in their binding affinity at DOR. The acetylamino substituent at the *ortho*-, *meta*-, or *para*- position (compounds **27**, **28**, and **29**) proved detrimental to binding at DOR.

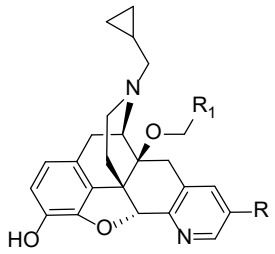
Table 2. Binding Affinity, Functional Activity, and In Vitro ADME Data for 5′-Heteroaryl-14-(phenylpropoxy) Compounds 30–42



compd	R	Binding K i (nM)[a]			[^{35}S]GTPγS Coupling[b]						log D[c]	MLM t ½ (min)[d]
		MOR	DOR	KOR	MOR Agonist EC_{50} (nM)	MOR Agonist E_{max} (%)	DOR Antagonist IC_{50} (nM)	DOR Antagonist I_{max} (%)	KOR Agonist EC_{50} (nM)	KOR Agonist E_{max} (%)		
30		14.7 ± 1.5	< 0.169	13.8 ± 2.6	1.61 ± 0.28	84.7 ± 8.7	0.98 ± 0.12	101 ± 0.3	NC[e]	NC[e]	3.30	7.07
31		105 ± 1	6.52 ± 0.28	19.2 ± 4.3	526 ± 83	37.7 ± 4.6	0.51 ± 0.05	99.3 ± 0.7	ND[f]	ND[f]	2.32	6.25
32		82.7 ± 2.5	30.6 ± 7.9	27.8 ± 0.8	>3333	(30.2 ± 5.3)[g]	0.67 ± 0.03	93.3 ± 0.7	NC[e]	NC[e]	3.67	8.22
33		47.1 ± 2.1	6.43 ± 1.49	15.8 ± 1.8	56.3 ± 26.5	49.3 ± 8.7	18.3 ± 0.6	91.0 ± 2.0	NC[e]	NC[e]	3.53	11.1
34		1.05 ± 0.37	63.5 ± 51.2	<0.51	1.88 ± 0.18	81.0 ± 4.0	0.39 ± 0.03	86.7 ± 0.9	NC[e]	NC[e]	1.74	9.60
35		10.7 ± 0.6	3.50 ± 1.14	6.62 ± 2.88	2.69± 0.37	93.5 ± 3.5	0.70 ± 0.08	89.3 ± 0.3	NC[e]	NC[e]	4.32	13.4
36		66.2 ± 4.7	22.1 ± 7.8	30.8 ± 8.5	>3333	(37.3 ± 5.1)[g]	0.71 ± 0.02	92.0 ± 2.1	NC[e]	NC[e]	3.30	10.1
37		47.9 ± 5.8	5.18 ± 0.37	24.8 ± 1.3	>3333	(29.3 ± 5.9)[g]	0.87 ± 0.14	92.3 ± 0.3	NC[e]	NC[e]	2.00	26.8
38		88.7 ± 1.4	40.1 ± 8.8	19.8 ± 0.9	>3333	(40.8 ± 3.8)[g]	1.27 ± 0.15	96.7 ± 0.7	NC[e]	NC[e]	3.55	8.72
39		121 ± 66	257 ± 211	29.8 ± 21.3	3.29 ± 0.82	115 ± 3	0.62 ± 0.08	92.3 ± 1.2	NC[e]	NC[e]	0.707	7.00
40		3.79 ± 1.63	7.96 ± 2.22	8.40 ± 5.25	659 ± 484	44 ± 2	19.6 ± 8.7	106 ± 6	NC[e]	NC[e]	0.943	21.7
41		99.3 ± 17.8	64.5 ± 3.3	23.1 ± 4.0	3.46 ± 1.19	74.7 ± 3.4	0.68 ± 0.05	92.0 ± 3.1	ND[f]	ND[f]	2.11	18.5
42		3.18 ± 0.07	8.12 ± 1.97	14.8 ± 4.8	17.5 ± 6.1	70.0 ± 2.5	< 0.17	101 ± 3	NC[e]	NC[e]	2.85	6.35
DAMGO					25.5 ± 1.4	100						
Naloxone		59.5 ± 2.9	98.1 ± 3.0				153 ± 6	100				
U50,488				31.9 ± 9.0					35.8 ± 2.0	100		

[a-d]See corresponding footnotes in Table 1. [e]NC = Not Converged (no agonist activity detected). [f]ND = Not Determined. [g]Percent maximum stimulation at 10 μM.

Table 3. Binding Affinity, Functional Activity, and In Vitro ADME Data for 5′-Aryl-14-alkoxy Compounds 43–52.[a]



compd	R	R1	Binding K_i (nM)[a]			^{35}S-GTPγS Coupling[b]						log D[c]	MLM t ½ (min)[d]
			MOR	DOR	KOR	MOR Agonist EC_{50} (nM)	MOR Agonist E_{max} (%)	DOR Antagonist IC_{50} (nM)	DOR Antagonist I_{max} (%)	KOR Agonist EC_{50} (nM)	KOR Agonist E_{max} (%)		
43			5.37 ± 0.51	5.24 ± 1.65	10.3 ± 5.7	NC[e]	NC[e]	4.69 ± 2.45	16.7 ± 1.2	ND[f]	ND[f]	1.73	12.2
44			819 ± 96	172 ± 85	21.3 ± 2.3	NC[e]	NC[e]	25.4 ± 21	102 ± 3.1	ND[f]	ND[f]	2.72	160
45			799 ± 131	32.5 ± 12.6	31 ± 4.6	NC[e]	NC[e]	10.8 ± 9	101 ± 0.6	ND[f]	ND[f]	2.79	9.40
46			3.96 ± 0.43	5.89 ± 3.70	5.3 ± 1.4	>3333	64 ± 9.8	< 0.51	93 ± 1	NC[e]	NC[e]	0.0434	8.60
47			3.82 ± 0.06	29.2 ± 9.2	21.9 ± 5.6	NC[e]	NC[e]	< 0.51	96 ± 2	ND[f]	ND[f]	0.818	8.88
48			70.9 ± 3.4	11.0 ± 0.8	60.2 ± 20.3	93.9 ± 9.1	60.0 ± 1.5	63.8 ± 40.3	100	NC[e]	NC[e]	2.38	81.1
49			95.3 ± 8.2	12.9 ± 2.1	57.9 ± 3.8	23.6 ± 1.4	66.0 ± 4.6	28.7 ± 11.9	100	34.5 ± 14.2	9.54 ± 0.19	3.27	27.6
50			5.99 ± 0.53	64.5 ± 28.9	24.8 ± 7.3	9.12 ± 4.93	68.3 ± 1.2	< 0.17	96.3 ± 2.7	ND[f]	ND[f]	3.37	6.49
51			92.1 ± 4.1	14.6 ± 0.2	57.1 ± 12.4	24.8 ± 2.7	24.3 ± 2.6	66.6 ± 16.5	100	ND[f]	ND[f]	2.33	16.8
52			499 ± 47	7.48 ± 0.97	252 ± 20	ND[f]	ND[f]	ND[f]	ND[f]	ND[f]	ND[f]	2.60	6.67
DAMGO						25.5 ± 1.4	100						
Naloxone			59.5 ± 2.9	98.1 ± 3.0				153 ± 6	100				
U50,488					31.9 ± 9.0					35.8 ± 2.0	100		

[a-d]See corresponding footnotes in Table 1. [e]NC = Not Converged (no agonist activity detected). [f]ND = Not Determined.

Binding affinity of 5′-aryl compounds at KOR. Most of the 5′-aryl compounds displayed weak binding affinity at KOR. Exceptions include the 4-fluoro (**10**), 2-dimethylamino (**23**), and 4-dimethylamino (**25**) compounds that display KOR binding K_i values of <10 nM. Significant binding affinity at KOR was also displayed by compounds possessing a 3-dimethylamino (**24**, K_i

= 11.9 nM), 2-acetylamino (**27**, K_i = 13.5 nM), 4-acetylamino (**29**, K_i = 15.1 nM), and 3-OH (**22**, K_i = 18.1 nM) group.

Functional activity of 5′-aryl compounds at MOR. The evaluated 5′-arylpyridomorphinans displayed a partial to full agonist profile with efficacy (E_{max}) ranging from 37% to 122%. A wide range in potencies were also displayed by these ligands (EC_{50} ranging from 1.12 nM to 233 nM). Surprisingly, the functional potency of the compounds did not always reflect the binding affinity of the compounds. Except for compounds **10**, **17**, and **23**, all of the phenyl substituted compounds displayed much stronger functional potency compared to their binding affinity. For example, the MOR affinity of compounds 4-methyl (**15**) and 2,6-dimethyl (**18**) compounds are in the 200 nM range but are >70-fold more potent as functional full agonists with EC_{50} < 4 nM. Interestingly, among the dimethylamino isomers, while the *ortho*-substituted compound **23** displayed greatly diminished agonist potency (EC_{50} = 233 nM) the *meta*- and *para*-substituted compounds **24** and **25** emerged as highly potent, full agonists with EC_{50} values of 1.50 nM and 2.10 nM, respectively. These findings suggest that these ligands have high intrinsic efficacy at MOR, enabling high potency functional activity even with modest binding affinity.

Functional activity of 5′-aryl compounds at DOR. At DOR, most of these compounds consistently displayed an antagonist profile of activity with high potency and efficacy (I_{max} >70%). Subnanomolar antagonist IC_{50} were displayed by the unsubstituted (**8**), 4-bromo (**9**), 3-methyl (**14**), and 2-methoxy (**19**) compounds. The presence of a 4-fluoro (**10**), 2- methyl (**13**), 2,6-dimethyl (**18**), or 4-methoxy (**21**) group tended to diminish DOR antagonist potency. The 2-(dimethylamino)methyl compound **26** also displayed moderate potency and efficacy as an antagonist.

Functional activity of 5′-aryl compounds at KOR. Only compounds that emerged as promising MOR agonist/DOR antagonists were evaluated for potential agonist activity at KOR. The evaluated compounds were found to be devoid of significant agonist efficacy at KOR. Most of the compounds did not produce detectable activation. These are designated as non-converged (NC) in Table 1. The 4-bromo compound **9** and the 4-methoxy compound **21** displayed agonist potencies of 5.52 nM and 2.02 nM, respectively. These compounds, however, displayed <35% efficacy indicating a partial agonist profile at KOR. Since these compounds displayed strong to moderate KOR binding affinity but little agonist activity, they likely act as KOR antagonists. However, this was not explicitly tested.

Binding affinity of 5′-heteroaryl compounds at MOR. Among 5′-heterocyclic analogues, high affinity binding (K_i < 10 nM) was displayed by compounds possessing 2-methyl-4-pyridyl (**34**), 2-methoxy-4-pyridyl (**35**), 1-methyl-4-pyrazolyl (**40**) and 2-(5-methyl-1,3,4-oxadiazolyl) (**42**) substituents. All three pyridyl isomers (**31–33**) displayed modest to weak binding affinity. The introduction of a methoxy (**35**) or methyl (**34**) group at the 2-position of the 4-pyridyl moiety led to significant (4-fold and 45-fold, respectively) improvements in binding affinity. Whereas the *N*-methyl-4-pyrazolyl compound **40** displayed high affinity (K_i = 3.79 nM), the *N*-unsubstituted pyrazole **39** displayed significantly decreased affinity (K_i = 121 nM). This >30-fold reduction in binding affinity could be due to the hydrogen-bond donor feature present in the latter.

Binding affinity of 5′-heteroaryl compounds at DOR. Among the 5′-heteroaryl compounds, the 1-pyrrolyl compound **30** displayed subnanomolar binding affinity at DOR. The 2-pyridyl (**31**) and 4-pyridyl (**33**) isomers displayed higher affinity (DOR K_i <10 nM) than the 3-pyridyl isomer (**32**, DOR K_i = 30.6 nM). Among the 5-membered heterocyclic compounds, the 1-methyl-4-pyrazolyl compound **40** and the 2-(5-methyl-1,3,4-oxadiazolyl) compound **42** displayed DOR binding

affinity of <10 nM. Similar to the profile at MOR, the *N*-unsubstituted pyrazole **39** displayed significantly decreased affinity in comparison to the *N*-methyl congener **34** (K_i value of 257 nM for **39** vs. 7.96 nM for **40**).

Binding affinity of 5'-heteroaryl compounds at KOR. Most of the compounds displayed moderate binding affinity with K_i values in the 10–30 nM range. The 2-methyl-4-pyridyl compound (**34**) and the 1-methyl-4-pyrazolyl compound (**40**) that displayed high affinity at MOR also displayed high affinity at KOR.

Functional activity of 5'-heteroaryl compounds at MOR. More disparate results were seen in the agonist functional activity in this series of compounds. The 1-pyrrolyl compound **30** displayed high potency (EC_{50} 1.61 nM) and efficacy (E_{max} 84.7%). However, some of the compounds, for example, compounds **32**, and **36–38**, displayed very weak potency as agonists. The low potency of these compounds prevented full evaluation of their efficacy with fully saturated concentration–response curves. For these compounds, the efficacy listed in parenthesis in Table 2 is the maximum stimulation produced at 10 μM concentration in the GTPγS assay, which was <50%. Among isomeric pyridyl compounds only the 4-pyridyl isomer **33** displayed moderate potency and efficacy. Interestingly, introduction of a methyl group (compound **34**) or a methoxy group (compound **35**) at the 2-position of the 4-pyridyl ring gave ligands with high potency (EC_{50} <3 nM) and efficacy (E_{max} >80%).

Functional activity of 5'-heteroaryl compounds at DOR. All of the compounds displayed high antagonist potency (IC_{50} <1.0 nM – 2.0 nM) and efficacy (I_{max} >85%) except for the 4-pyridyl compound **33** and the *N*-methylpyrazolyl compound **40** that displayed moderate potencies of 18.3 nM and 19.6 nM, respectively.

Functional activity of 5′-heteroaryl compounds at KOR. Similar to the 5′-aryl compounds, all of the evaluated 5′-heteroaryl compounds displayed non-converged (NC) dose-response curves indicating their non-agonist profile at KOR. Similar to the 5′-aryl series, these compounds likely act as KOR antagonists.

Binding affinity and functional activity of 14-alkoxy compounds. Conversion of the pendant phenyl group in the 14-*O*-substituent of **6** to a 4-pyridyl group gave a compound **43** that retained high affinity binding at MOR, DOR, and KOR. However, the functional activity at MOR was drastically altered to a non-agonist profile. Moreover, the antagonist efficacy at DOR was also greatly diminished (I_{max} 16.7%). Exchanging an oxygen atom for the benzylic methylene group of the propyl chain of **6** led to compound **44** that displayed greatly diminished binding at MOR and DOR. The drastic reduction of binding affinity at MOR could be attributed to favorable hydrophobic interactions sustained by the methylene group of the $C_6H_5CH_2$ substituent and unfavorable repulsion encountered by the electron rich oxygen atom of the of C_6H_5O group. The fused benzene ring of the quinolinylmethyl substituent present in **45** could potentially mimic the phenyl group of the phenylpropyl substituent of **6**. However, this compound while retaining moderate binding potency at DOR and KOR, lost affinity at MOR. Interestingly, in the functional assay, these three compounds **43–45** failed to function as agonists at MOR. On the 5′-phenylpyridomorphinan template, the 14-*O*-3-(3-pyridylpropyl) compound **46** and the 14-*O*-3-(4-pyridylpropyl) compound **47** displayed moderate to high binding affinity at all three receptors. These two compounds also lost agonist potency and efficacy at MOR while retaining potent and efficacious antagonist activity at DOR. The introduction of a fluorine at the *para*-position on the phenyl ring of **8** gave a compound **48** that displayed diminished MOR binding and agonist potency. Saturating the pendant phenyl to a cyclclohexyl group (compound **49**) also led to a reduction in binding affinity and

agonist activity at MOR. Interestingly, replacement of the cyclohexyl group with a 4-pyranyl group gave a compound (**50**) that displayed single digit nanomolar binding and agonist potency but moderate efficacy at MOR. Despite its weak binding affinity at DOR, in the functional assay, the compound displayed potent DOR antagonist activity. Since in principle antagonist activity should rely on intrinsic efficacy, this disparity may reflect allosteric binding for this ligand, producing strong functional activity but weak orthosteric competition. Extension of the linker chain length from propyl to butyl (compound **51**) also had a deleterious effect on MOR binding and MOR agonist activity. Removal of the pendant aryl group altogether (compound **52**) also resulted in poor binding affinity at both MOR and KOR. Thus, the nature of the alkoxy substituent has a significant influence on binding and functional activity, and subtle changes in the structure lead to drastic changes in binding and activation of MOR.

ADME Properties. In vitro ADME screens were used to profile lead compounds for drug- like properties and to help prioritize potent compounds for in vivo proof-of-concept studies. Our strategy focused on profiling compounds for aqueous solubility and lipophilicity (Log *D*) as these properties are important predictors of drug bioavailability.[34,35] As our ideal lead candidate profile includes CNS drug exposure, we sought leads with physicochemical properties indicative of good brain permeability/CNS exposure.[36,37] Additionally, we screened compounds for metabolic stability using mouse and human liver microsomes to help predict drug exposure to rank the lead compounds. For the majority of compounds screened, aqueous solubility was moderate to high (Table S1). In an effort to identify leads with good permeability, we prioritized compounds with Log *D* in the range of 0–3.[38-40] With only a few exceptions, all compounds screened fell within this range (Tables 1-3).

Most of the compounds screened were rapidly metabolized in mouse liver microsome preparations, with t½ values falling less than 30 minutes, with the exception of compounds **44** (t½ = 160 min) possessing an oxygen in place of benzylic methylene group and **48** (t½ = 81 min) possessing a fluorine at the *para* position of the phenyl ring of the phenylpropyl group. Oxidative *N*-dealkylation of the cyclopropylmethyl group at N17 as well as the metabolic susceptibility of benzylic methylene and the aryl ring of the 14-*O*-substituent could potentially be contributing to the observed poor MLM stability of most of the compounds. Rapid metabolism in MLM suggests poor exposure in vivo and influenced our decision to dose iv or sc for in vivo studies. Overall, compounds were significantly more stable in HLM preparations (Table S1). Species differences in microsomal stability are not uncommon; additional studies are needed to determine the mechanism of this apparent species difference.

Molecular Modeling. In an effort to gain insights into the SAR, we performed molecular docking studies using the X-ray crystal structures of the active state of MOR (PDB ID 5C1M),[41] and inactive state of DOR and KOR (PDB IDs 4N6H and 4DJH, respectively).[42,43] Since the binding affinities of most of the ligands spanned a relatively narrow range, the differences in the docking scores in general were subtle. Nevertheless, the type and complementarity of interactions between the ligand and the receptor residues seen in the docking poses gave useful insights. The general binding mode of the ligands is illustrated using the docking pose of compound **8** and **46** at MOR (Figure 2A and 2B, respectively). The epoxymorphinan core binds to the bottom of the orthosteric pocket defined by residues W293$^{6.48}$, H297$^{6.52}$, D147$^{3.32}$, and M151$^{3.36}$. The cyclopropylmethyl group forms hydrophobic contact with W293$^{6.48}$ while the basic nitrogen N17, which is protonated at physiological pH, forms a salt bridge interaction with D147$^{3.32}$. The phenolic hydroxyl forms a

hydrogen bond with H297$^{6.52}$ either directly or through a network of two water molecules. These interactions are shown by all ligands and are conserved in all three receptor subtypes.

The aryl/heteroaryl substituent at the 5′-position on the pyridine ring, on the other hand, plays a role in influencing binding selectivity at MOR, DOR, and KOR. This is due to the extracellular region that these substituents occupy, which varies in volume and the nature of the residues among the three receptor subtypes. As shown in the docking pose of compound **8** at MOR (Figure 2A), the phenyl group at the 5′-position forms π-π stacking interaction with W318$^{7.34}$ and a potential π-cation interaction with K233$^{5.40}$ and with the subtype variant K303$^{6.58}$ residue.[41,44,45] Besides selectivity, such interactions may also influence conformational changes that play a role in the functional state of the receptor. At DOR, the volume of this extracellular region is even larger than in MOR and is capable of accommodating a phenyl ring in its favorable orientation. Indeed, in the docking pose of compound **8** at DOR (Figure 3A), the phenyl group adopts an orientation that positions it near W284$^{6.58}$ and K214$^{5.40}$ which could form π-π stacking and π-cation interaction. In contrast, when docked to KOR (Figure 3B) in which the volume of this region is smaller than that of MOR, the phenyl group comes in close unfavorable contact with glutamate E297$^{6.58}$ (corresponding to K303$^{6.58}$ in MOR), thus providing a possible explanation for the 5 to 7-fold lower affinity at KOR compared to its affinity at MOR and DOR.

The substituent extending from the oxygen at 14-position binds to a hydrophobic region in all three receptor subtypes. A group such as the phenylpropoxy at the C-14 has the appropriate size and hydrophobicity to fit into this hydrophobic region and interact with residues such as I144$^{3.29}$ in MOR. As discussed, compounds with some of the substituent variations at C-14 did not effectively stimulate MOR. For example, in contrast to the MOR agonist profile of compound **8**, its 3-pyridyl analogue **46** displayed neither efficacious agonism nor antagonism at MOR. A plausible

explanation is provided by the docking result with **46**, which indicates that the pendant pyridyl ring of **46** binds in a different orientation than the phenyl ring of **8**. Instead of the hydrophobic contact that the phenyl ring of **8** has with residues such as I144$^{3.29}$ (Figure 2A), the pyridyl ring adopts an orientation that forms a polar hydrogen bond interaction with N127$^{2.63}$ (Figure 2B). Thus, the new pattern of interaction displayed by **46** in this middle region of TM2/TM3 might affect the conformational change in a manner that is different from that induced by a typical agonist of MOR. Moreover, the specific interaction brought about by the pendant group of the substituent on C-14 might prevent the ligand from going deeper into the pocket, thus, reducing its ability to interact with residues at the bottom of the orthosteric site that play a key role in the conformational switch needed for the activation of the receptor.[41,46]

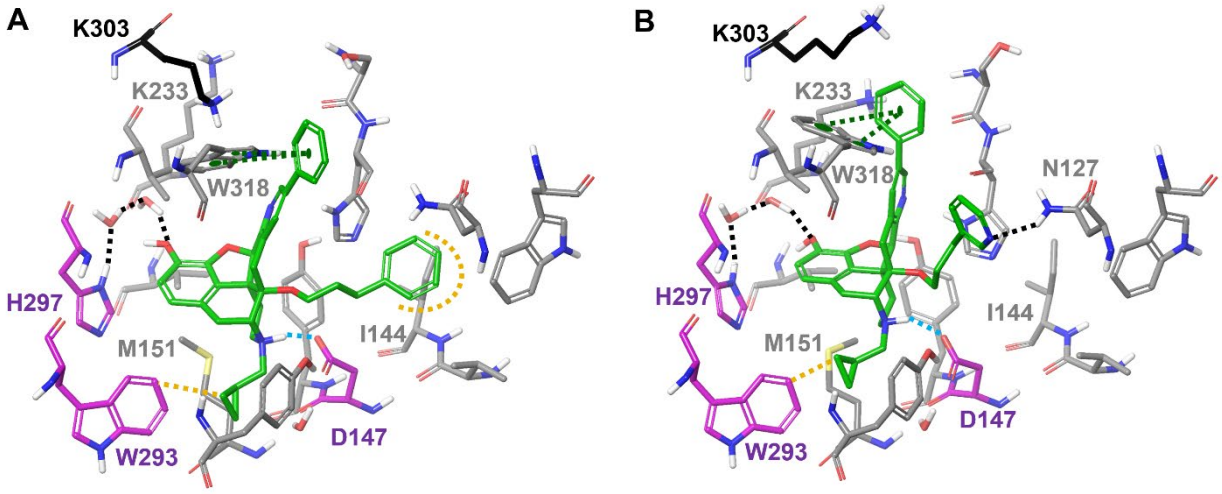


Figure 2. Docking poses at MOR (PDB ID 5C1M). (A) Compound **8** and (B) Compound **46**. Compounds are colored green. Hydrogen bond, salt bridge, hydrophobic contact, and π-π stacking are indicated by black, cyan, yellow, and dark green dashed lines, respectively. All residue numbers are based on MOR crystal structure 5C1M. Extracellular side is facing top.

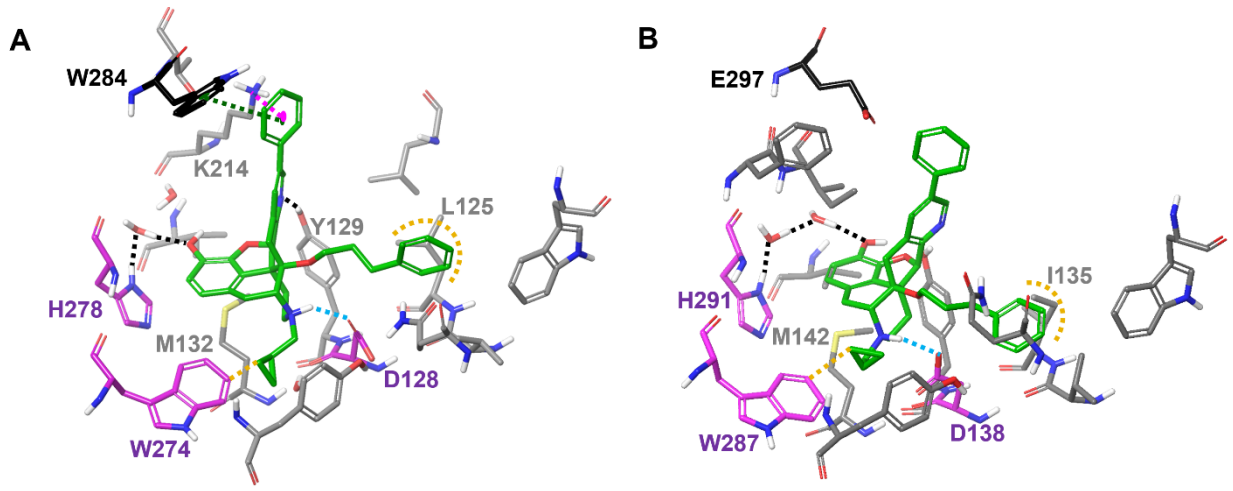


Figure 3. Docking poses of compound **8** at (A) DOR (PDB ID 4N6H) and (B) KOR (PDB ID 4DJH). Compounds are colored green. Hydrogen bond, salt bridge, hydrophobic contact, π-π stacking, and π-cation interaction are indicated by black, cyan, yellow, dark green, and purple dashed lines, respectively. Extracellular side is facing top. W274$^{6.48}$, H278$^{6.52}$, D128$^{3.32}$ in DOR and W287$^{6.48}$, H291$^{6.52}$, and D138$^{3.32}$ in KOR correspond to conserved residues W293$^{6.48}$, H297$^{6.52}$, and D147$^{3.32}$ in MOR.

Antinociceptive Studies in Mice. The antinociceptive potency and efficacy of select compounds was evaluated in male CD1 mice using the 55°C warm water tail-flick assay. Previous studies with compound **6** were performed via icv administration. In the current study, we selected 16 compounds that displayed promising in vitro binding and functional activity profiles and evaluated them following icv or intravenous (iv) administration. Tail withdrawal latencies were assessed at various time-points for up to five hours post-dose and were compared to vehicle. Due to variability in aqueous solubility of the test compounds, three different vehicles were used: saline (icv and iv), 100% DMSO (icv), and 10:10:80 DMSO:Tween 80:saline (icv, iv). When 100% DMSO was used as a vehicle for icv injections, the tail-flick latency was significantly increased over saline or 10:10:80 for the first hour of evaluation (p=0.001=0.05); data collected with 100% DMSO was

excluded based upon solubility limitations and confounding effects on behavior. No statistically significant differences were seen among vehicles for iv administration (p=0.97), therefore, data points were combined. The observed antinociceptive profile of the evaluated compounds is presented in Table 4. Compounds **9**, **16**, **21**, **48**, and **50** showed poor antinociceptive activity by the icv route of administration and were not advanced to systemic evaluation. All other compounds were evaluated after iv dosing.

Table 4. Antinociceptive Activity of Selected Compounds in Warm Water Tail-Flick Assay.[a]

compd	Route	Dose	MPE ± SEM (n)	Time of Effect Onset (min)	Time of Peak Effect (min)	Duration of Effect (min)
9	icv	10 nmol	75 ± 22 (5)	10	30	10-45
14	iv	10 mg/kg	100 ± 0 (4)	15	45	15-180
15	iv	10 mg/kg	100 ± 0 (5)	15	15	15-240
16	icv	10 nmol	65 ± 18 (5)	10	10	10
19	iv	10 mg/kg	100 ± 0 (4)	15	15	15-240
20	iv	10 mg/kg	100 ± 0 (5)	15	30-180	15-300
21	icv	10 nmol	86 ± 14 (5)	10	10	15-300
25	iv	10 mg/kg	100 ± 0 (4)	15	15	15-300
30	iv	10 mg/kg	99 ± 0.5 (5)	15	45	15-180
34	iv	10 mg/kg	100 ± 0 (5)	15	30	15-120
39	iv	10 mg/kg	75 ± 14 (5)	15	15	15-60
41	iv	10 mg/kg	100 ± 0 (4)	15	15	15-120
42	iv	10mg/kg	100 ± 0 (5)	15	30	15-180
48	icv	10 nmol	80 ± 13 (5)	15	15	15-45
49	iv	10 mg/kg	100 ± 0 (3)	30	60	30-180
50	icv	10 nmol	77 ± 22 (4)	10	45	10-60

[a]Tail-flick latencies were determined as described in the experimental section. Time of effect onset is listed when the antinociceptive effect was first observed to be >30%. Duration of effect is given as the total time antinociception remained above 30% maximum possible effect (MPE).

Based on an MPE duration of >2 hrs, and lack of respiratory depression, aggression, and related side effects via qualitative observation, two compounds **20** and **42** were chosen for further evaluation. These two compounds produced dose-dependent antinociception following iv administration of 1 mg/kg, 3 mg/kg, and 10 mg/kg doses. Maximal effects were observed following all three doses of **20** starting 15 min after injections that persisted through 90 min. The highest dose tested, 10 mg/kg, retained >50% antinociceptive effects that were significantly higher than vehicle-treated values for four hours after administration (Figure 4A). Administration of **42** dose-dependently mitigated heat evoked nociception beginning 15 min after injection. In contrast to **20**, which displayed a threshold antinociceptive effect (100 ± 0%) for 15-180 min, the maximal peak effect (80 ± 20%) of **42** occurred at 45 min (Figure 4B). Relative to morphine (10 mg/kg, iv),[47] compound **20** produced potent, maximal antinociception despite modest MOR/DOR binding affinity (91 and 48 nM, respectively, Table 1). One potential explanation is that while **20** had modest binding affinity, it showed a strong in vitro functional potency and efficacy (MOR agonist EC_{50} = 13 nM and DOR antagonist IC_{50} = 2.4 nM, Table 1). This difference suggests that **20** has strong intrinsic efficacy, whereby modest binding could still produce potent, efficient receptor activation.[48] In addition, blood brain barrier permeability, P-gp efflux, and favorable pharmacokinetic properties could underlie the potency and efficacy of **20** in producing antinociception as well as for its ability to produce antinociception by systemic administration compared with compound **6**.

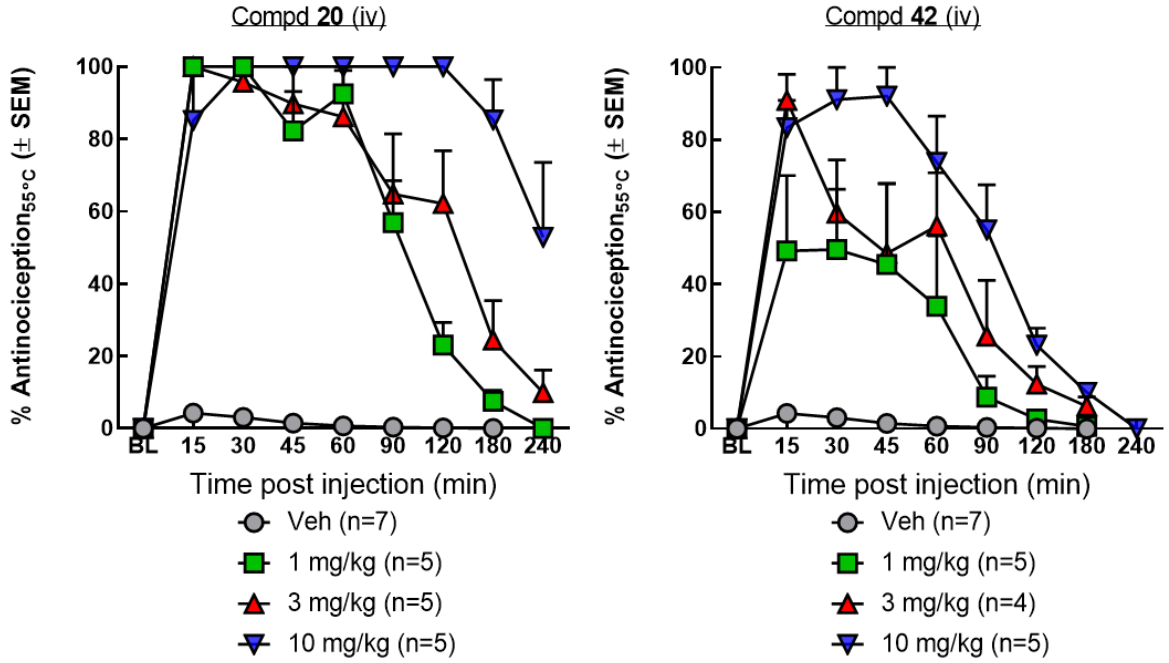


Figure 4. Antinociceptive dose– and time–response curves for **20** (panel A) and **42** (panel B) in the 55°C warm water tail-flick assay following iv administration to naïve male CD-1 mice. Compounds were evaluated in a minimum of two groups with the tester blinded to treatment (sample sizes per group noted within the graph). Two-way repeated measure (RM) ANOVA, Bonferroni post-hoc was used for statistical analysis.

Since compound **20** showed a longer duration and maximal antinociception compared to **42** and morphine (10 mg/kg) following iv administration, additional in vivo characterization was pursued with compound **20** (designated SRI-39067). We evaluated compound **20** by subcutaneous (sc) administration of 3.2, 10, 18, and 32 mg/kg doses as compared to morphine. Importantly, compound **20** produced significant dose-dependent antinociception following subcutaneous administration ($F(36,190) = 4.436$, $p<0.0001$) with a longer duration than morphine[49,50] (Figure

5). The calculated A_{50} value at the 60 min time point after administration was 20.8 mg/kg and the A_{90} was 21.1 mg/kg (Figure 5A). Compound **20** was also evaluated after oral administration at doses of 1, 10, and 32 mg/kg. The 10 mg/kg dose produced ≤ 16% effect over five hours while the 32 mg/kg resulted in 100 % effect in 1/6 animals and < 30% in 5/6 animals; there was no significant difference between the doses (2-way ANOVA Interaction p=0.18). The time of peak effect was 90 min (Figure 5B).

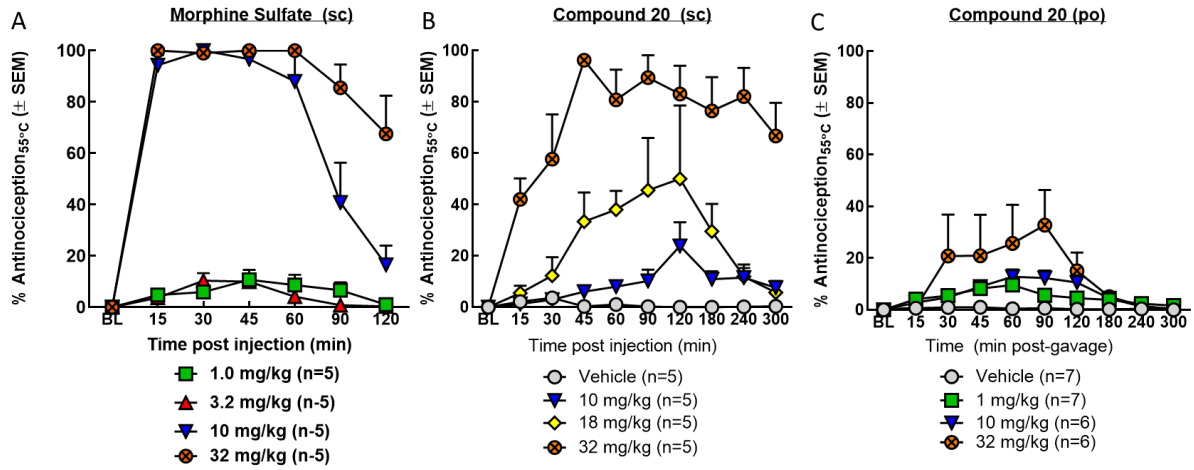


Figure 5. Antinociceptive dose– and time–response curve for morphine sulfate (A, sc) and compound **20** administered subcutaneously (sc: panel B) and oral gavage (po: panel C) in the 55 °C warm water tail-flick assay using naïve male CD1 mice. Compound **20** was evaluated in a minimum of 2 groups for a total of n=5-7 per condition. Two-way RM ANVOA, Bonferroni post-hoc was used for statistical analysis.

We next evaluated the sensitivity of antinociceptive effects of **20** to naloxone. While the compound displayed potent antinociceptive effects in naïve mice (Figure 5), in mice pretreated with naloxone

(10 mg/kg, ip; t = -10 min) the antinociceptive effects of compound **20** (32 mg/kg, sc) were completely blocked (Figure 6). The vehicle controls in the presence or absence of naloxone did not display any significant differences in tail-flick latency across the duration of evaluation. These data suggest that compound **20** elicits antinociceptive effects via its agonist activity at opioid receptors in vivo.

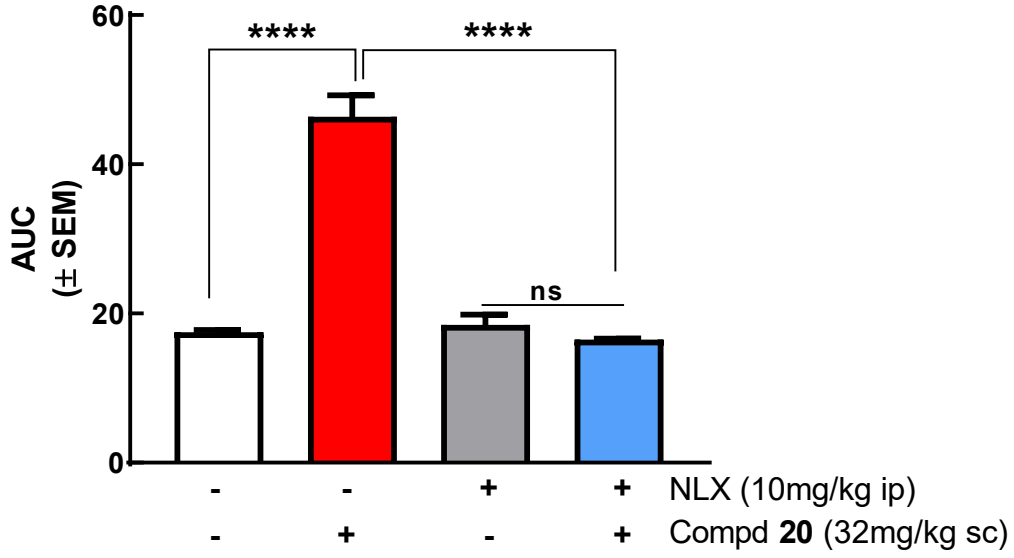


Figure 6. Blockade of antinociceptive efficacy of compound **20** by pretreatment with naloxone. Pharmacological blockade of opioid receptors with the non-selective antagonist naloxone (10 mg/kg ip) prevented the antinociception observed after subcutaneous administration of **20** alone (32 mg/kg, sc) over a duration of four hours as in Figure 5A (n=5-6 male CD1 mice per treatment). Data represented as the mean ± SEM of Areas under the curve (AUC) for each condition. One-way ANOVA, Bonferroni post-hoc was used for statistical analysis. n.s.= not statistically significant, ****$p < 0.0001$.

Antinociceptive Tolerance. Antinociceptive dose response curves for compound **20** and morphine sulfate (MS) were generated using male CD1 mice in the warm water tail-flick assay on Day 1 of dosing. On three subsequent days, animals were injected (sc) with the A_{90} dose of either compound **20** (21 mg/kg, determined in Fig 5A) or morphine sulfate[51] (10 mg/kg) twice a day (9 a.m. and 5 p.m.). The antinociceptive dose response curves were again generated on Day 5 (Figure 7). Whereas the repeated administration of morphine produced a 3.3-fold right-ward shift of ED_{50} from 6.4 mg/kg to 21.7 mg/kg, compound **20** displayed only 1.2-fold shift in ED_{50} from 20.8 mg/kg to 25.4 mg/kg. This suggests that compound **20** produced significantly less tolerance development than morphine (Figure 7).

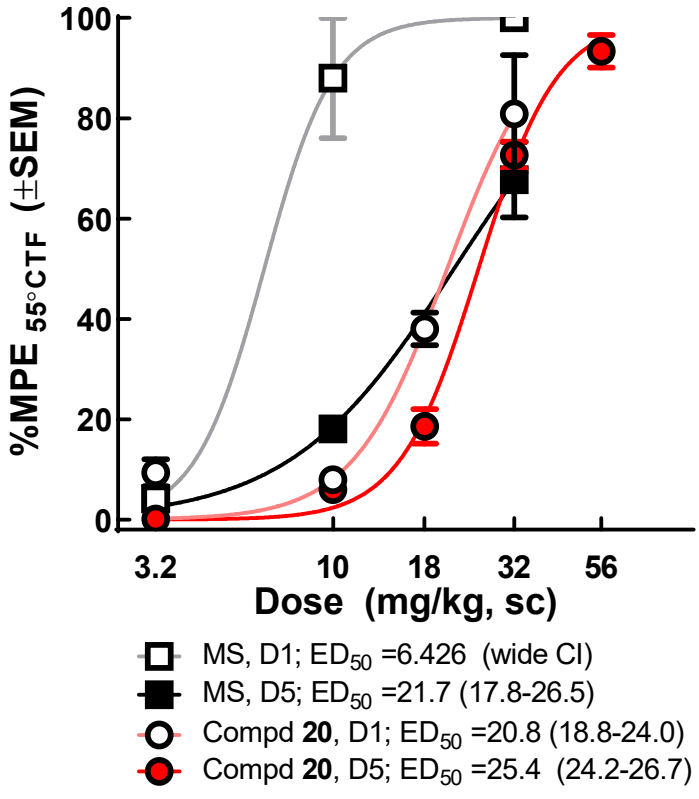


Figure 7. Repeated administration of compound **20** produces less antinociceptive tolerance. Dose response curves were generated in naïve male CD1 mice on Day 1. Subsequently, mice were dosed twice a day with 21 mg/kg of **20**, the calculated A_{90}, or 10 mg/kg of morphine sulfate (MS) for four days. On Day 5, the dose response curve was re-generated from data collected 45 min after drug administration. Non-linear regression. ED_{50} values were compared between days 1 and 5 to determine the development of antinociceptive tolerance (95% Confidence Interval). N=5-8/group.

Physical Dependence and Precipitated Withdrawal. Physical dependence was determined using a precipitated withdrawal approach.[52] Mice were dosed for four days with vehicle, morphine sulfate (10 mg/kg, ip) or compound **20** (21 mg/kg = A_{90}, sc). Prior to naloxone administration, mice were evaluated for evidence of spontaneous withdrawal over 30 min as a baseline; no symptoms of spontaneous withdrawal were observed. Naloxone (10 mg/kg ip) was then administered. Body weight, fecal output, urination, and stereotypical withdrawal behaviors (i.e. jumping, paw tremors, wet-dog shakes, backward steps, etc.) were recorded. Changes in the number of steps and wet-dog shakes were not observed in this cohort and thus not included in overall calculations. Within all treatment groups, the number of animals displaying diarrhea and jumping behavior were increased. Both morphine and compound **20** significantly increased urinary output over vehicle, whereas only compound **20** significantly increased the number of fecal pellets excreted (Figure 8A-B). Though urination and diarrhea are important features of precipitated opioid withdrawal, the literature suggests that jumping behaviors elicited by opioid antagonists are the most robust somatic predictor of physical dependence.[53,54] Mice dosed with morphine jumped significantly more than vehicle or compound **20** exposed mice; compound **20** did not elicit a significant increase when compared with vehicle treatment, suggesting at least some markers of

dependence and withdrawal are reduced for **20** (Fig 8C). Calculation of the overall withdrawal score was performed then normalized to vehicle condition. Under these conditions, both morphine and compound **20** induced significant physical dependence and withdrawal compared to vehicle. (Figure 8D; p=0.002 and p=0.05, respectively One-way ANOVA F=7.786, Tukey post-hoc, outliers identified n=2 compound 20, n=2 vehicle, n=0 morphine).

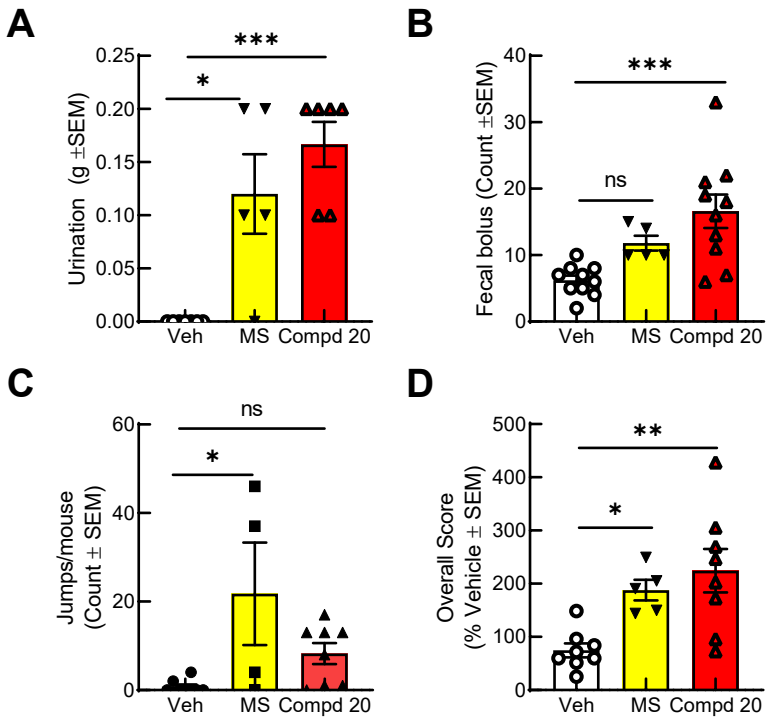


Figure 8. Physical dependence of mice injected repeatedly with A_{90} doses of **20** (red) or morphine sulfate (10 mg/kg ip; yellow). Mice were dosed with compound **20** as in Figure 7. On Day 5, four hours after the final dose of drug or vehicle (white), mice were evaluated for behaviors indicative of withdrawal (spontaneous) for 30 min; no behaviors indicating spontaneous withdrawal were observed. Mice were then dosed with the opioid antagonist naloxone (10 mg/kg, ip) to precipitate withdrawal. Behaviors were re-assessed for 30 min post-dosing. Behaviors included are amount of urine expelled onto a filter paper (A), number of fecal pellets (B), and number of jumps (C)

Overall withdrawal scores were calculated then normalized to vehicle controls (D). One-way ANOVA/behavior, Tukey post-hoc was used for statistical analysis. n.s. = not statistically significant; *p < 0.05, **p < 0.01, ***p < 0.001; N=6-10 included/group.

Respiratory Depression. Respiratory depression was assessed using whole body plethysmography.[55] Morphine significantly reduced respiratory rate at 40 min and 45 min of observation (p=0.01 and 0.02, respectively) whereas tidal volume was reduced at min 42 and 45 of data collection (p=0.04 and 0.008, respectively). Morphine-exposed mice did present with a significant reduction in minute ventilation as compared to saline control mice during the full duration of 5% CO_2 challenge from 41-45 min (p=.0004 to 0.004). In contrast, mice receiving compound **20** did not show a reduction in any respiratory measures across the duration of the experiment. However, the tidal volume appeared to increase with escalating doses (up to 32 mg/kg) during the 5% CO_2 challenge (Figure 9 and Figure S1 in Supplementary Information). These data suggest that compound **20** at > A_{90} dose does not induce respiratory depression acutely.

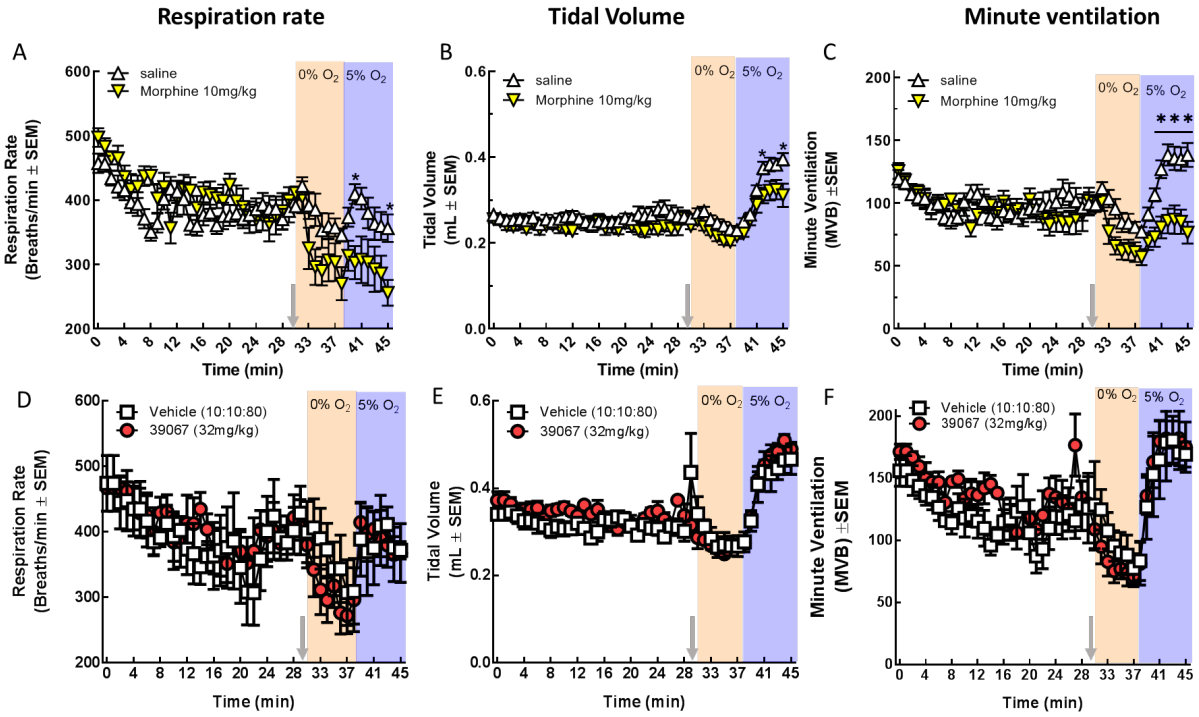


Figure 9. Respiratory measures of naïve mice and mice injected acutely with morphine (Top, yellow) or **20** (Bottom, red). An acute bolus of morphine (10 mg/kg) reduced respiratory rate, followed by tidal volume and minute ventilation indicating the induction of respiratory depression as measured by whole body plethysmograph (n=6-8) in the first 45 min after drug administration. Mice receiving compound **20** (32 mg/kg) did not deviate from the baseline respiratory rate, tidal volume, or minute ventilation nor were those values different from vehicle treated mice suggesting a lack of respiratory depression over the 45 min observation period. Two-way RM ANOVA, Bonferroni post-hoc was used for statistical analysis. *p<0.05; ***p<0.001.

Conditioned Place Preference/Aversion. Conditioned place preference (CPP) was defined as a >50 s increase over baseline (BL) values. Conditioned place aversion (CPA) was defined as a decrease from BL greater than 50 s. Neutral responses occurred when Test values were within 50

s of BL. The number of mice exhibiting CPP or CPA for saline, vehicle, morphine in saline, morphine in vehicle, and compound **20** are shown in Figure 10 A–E. Comparison of difference scores between treatments for animals showing CPA, CPP, or no preferences showed no difference between treatment groups (Figure 10F). Since difference scores capture before and after differences that may be masked by time in neutral chambers when using a three-chamber system, the total amount of time per chamber was also determined (Figure 10G). These data suggest that animals treated with morphine in vehicle and compound **20** spend equal amounts of time in each of the three chambers after conditioning whereas morphine and vehicle paired mice spend significantly more time in the drug-paired and counter-paired chamber, respectively (n=10-15/group, $^{**}p<0.01$). Together, these results indicate that compound **20** induced CPP in fewer animals than morphine and that the preference occurs to a lesser degree.

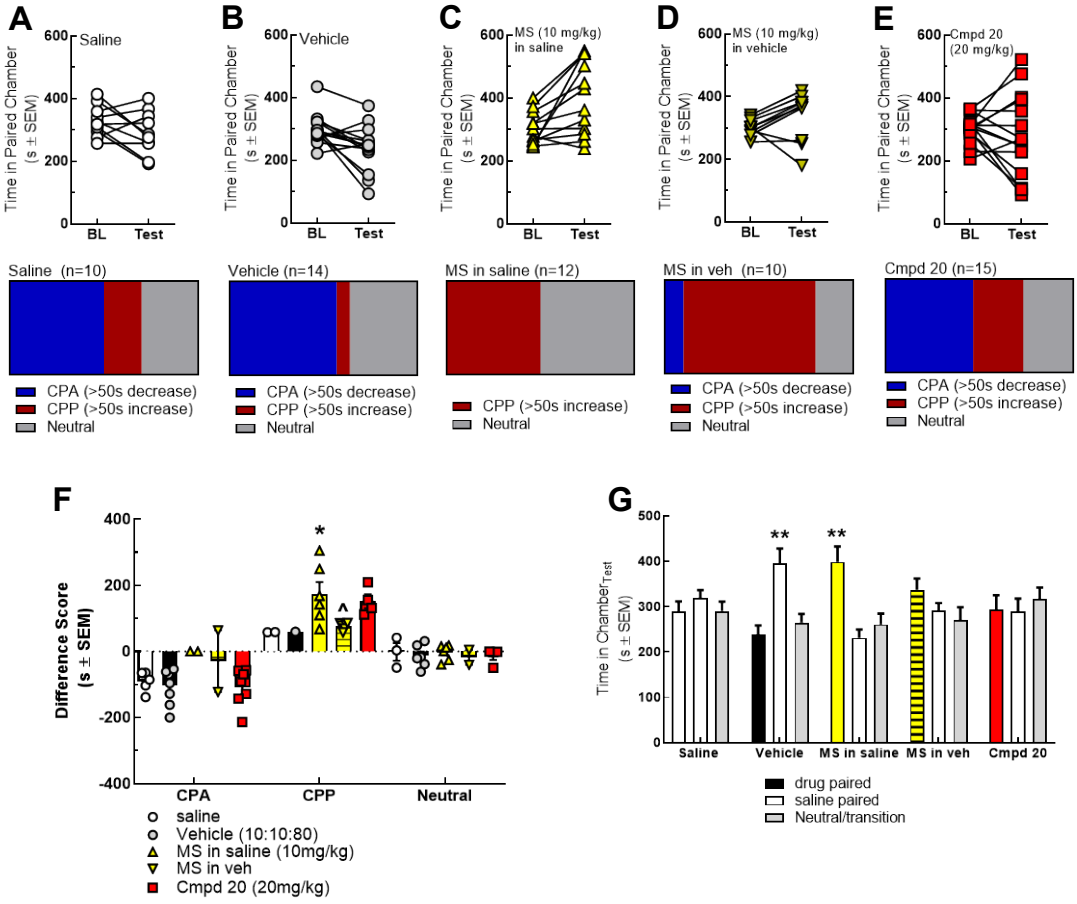


Figure 10. Reward liability as measured by conditioned place preference/aversion (CPP/CPA) of naïve male CD1 and male CD1 mice injected repeatedly with compound **20** or morphine. The same approximate numbers of mice displayed CPP, CPA, and neutrality after saline (A) or the vehicle of 10% DMSO, 10% Tween80, 80% saline (B). Morphine prepared in saline (C) or vehicle (D) induced significant place preference (F), regardless of preparation; ^p=0.05, *p=0.01 (One-way ANOVA, Bonferroni post-hoc). Five days of administration of compound **20** led to even numbers of CPA and CPP (E) but the degree of aversion or preference was not different from saline or vehicle. These findings were not confounded by the use of a three-chamber system (G). (One-way ANOVA, Bonferroni post-hoc). N=10-15/condition.

CONCLUSIONS

In this present effort, the influence of various aryl and heteroaryl substituents at the 5′-position of the 14-phenylpropoxy-pyridomorphinan scaffold on opioid receptor binding, functional activity, and ADME properties were explored. Subtle changes in the 5′-phenyl group had significant influence on binding affinity, agonist potency and efficacy at MOR. The binding affinity at MOR was not always reflective of the agonist potency and efficacy at MOR. For example, compounds **13, 15,** and **18** displayed poor binding affinity but displayed good agonist potency and efficacy at MOR, suggesting that these compounds have high intrinsic efficacy. At DOR, most of the 5′-aryl compounds retained antagonist potency and efficacy. Potent DOR antagonist activity was also displayed by most of the compounds bearing a 5′-heteroaryl group. However, compounds such as **32, 36–38** possessing a six-membered heteroaryl ring lost their ability to function as agonists at MOR. Similarly, replacement of the pendant phenyl ring of the 14-*O*-phenylpropyl group by pyridine rings (**43**, **46**, and **47**) also led to loss of agonist activity at MOR. Thus, in this pyridomorphinan series MOR activation was more sensitive to the nature of the substituents than DOR inhibition. None of the compounds evaluated produced any significant agonist activity at KOR.

Using in vivo antinociception and side effect profiling, we narrowed the selection of MOR agonist/DOR antagonist compounds to one 5′-aryl compound **20** and one 5′-heteroaryl compound **42**. Of these two compounds, the 5′-(3-methoxyphenyl) compound **20** displayed potent antinociceptive activity by the systemic, subcutaneous route of administration. Of significant interest is our finding that unlike morphine, compound **20** displayed diminished propensity to produce analgesic tolerance on repeated administration and produced no apparent respiratory depression and rewarding effect. These results encourage further pursuit of ligands possessing

mixed MOR agonist/DOR antagonist activity in the efforts toward identification of novel opioid analgesics with diminished side effects.

EXPERIMENTAL SECTION

Chemical Synthesis. *General Methods***.** All solvents and reagents were used as purchased without further purification. Unless otherwise stated, reactions were carried out under nitrogen atmosphere. Reaction conditions and yields were not optimized. The progress of all reactions was monitored by thin-layer chromatography (TLC) on pre-coated silica gel (60F254) aluminium plates (0.25 mm) from E. Merck and visualized using UV light (254 nm). Microwave reactions were performed using CEM discover Labmate System with Intelligent Technology for Focused Microwave Synthesizer (Explorer 48) or Biotage Initiator Robot 8 Microwave Synthesizer. Purification of compounds was performed on an Isco Teledyne Combiflash Rf200 with four channels to carryout sequential purification. Universal RediSep solid sample loading pre-packed cartridges (5.0 g silica) were used to absorb crude product and purified on 12 g silica RediSep Rf Gold Silica (20–40 μm spherical silica) columns using appropriate solvent gradients. Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus or SRS OptiMelt automated melting point system and are uncorrected. High resolution mass spectrometry (HRMS) analysis was performed with an Agilent 1100 LC-MS TOF instrument using electrospray ionization (ESI). ^{1}H NMR spectra were recorded at 400 MHz on Agilent/Varian MR-400 spectrometer and ^{13}C NMR spectra were recorded on Agilent/Varian MR-400 spectrometer or on Bruker Avance III-HD 600 MHz or 850 MHZ Spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and referenced according to deuterated solvent for ^{1}H spectra ($CDCl_3$, 7.26, DMSO-d_6, 2.50, or TMS 0.0) and ^{13}C spectra ($CDCl_3$, 77.2 or DMSO-d_6, 39.5). Purity of final compounds was checked by analytical HPLC using an Agilent 1100 LC

system equipped with phenomenex Kinetex C18 column (5 μm, 4.6 x 150 mm) and a diode array detector (DAD) using the solvent system: Solvent A: H_2O/0.1% trifluoroacetic acid, solvent B: CH_3CN/0.1% trifluoroacetic acid, 0-95% B over 22 min, flow rate 1 mL/min, λ 254 nm and λ 280 nm (System 1) or using a Waters HPLC system equipped with Sunfire C18 column (5 μm, 4.6 x 150 mm) and a Waters 2998 photodiode array detector using the solvent system: Solvent A: H_2O/0.1% formic acid, solvent B: CH_3CN/0.1% formic acid, 10-90% B over 20 min, flow rate 2 mL/min, λ 254 nm (System 2) or using an Agilent 1200 LC system equipped with phenomenex Kinetex Phenyl-Hexyl column (2.6 μm, 4.6 x 50 mm) and a diode array detector (DAD) using the solvent system: Solvent A: H_2O/0.1% formic acid, solvent B: CH_3CN/0.1% formic acid, 0-95% B over 4.5 min, flow rate 2 mL/min, λ 254 nm (System 3). On the basis of NMR, HPLC-DAD, HRMS (mass error less than 5 ppm) all final compounds were ≥95% pure.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-phenyl-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (8). *Step 1*. To a stirred solution of (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-11-phenyl-5,6,7,8,9,13b-hexahydro-8a*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline-1,8a-diol **54**[29] (0.5 g, 1.0 mmol) in DMF (10 mL) was added sodium hydride (0.2 g, 6.0 mmol, 60% dispersion in mineral oil) at 0 °C. After the mixture was stirred for 40 min, 3-phenylpropyl bromide (0.4 g, 2.2 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature and stirred for 4 h. Excess of sodium hydride was decomposed with drops of ice-cold water, the mixture was then diluted with water and extracted with $CHCl_3$ (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The solvent was removed under reduced pressure. The residue was purified by chromatography over a column of silica gel using hexanes/EtOAc (40:60) as the eluent to obtain (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-11-

phenyl-1,8a-bis(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-g]quinoline (0.24 g, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 2.2 Hz, 1H), 7.72 (s, 1H), 7.64 (dq, J = 6.4, 1.3 Hz, 2H), 7.52 – 7.41 (m, 2H), 7.44 – 7.34 (m, 1H), 7.30 – 6.98 (m, 8H), 6.91 (dt, J = 8.2, 1.4 Hz, 2H), 6.66 (dd, J = 8.2, 1.2 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 5.73 (d, J = 1.1 Hz, 4H), 5.42 (d, J = 1.1 Hz, 1H), 4.43 (td, J = 5.2, 1.4 Hz, 0H), 4.00 – 3.88 (m, 1H), 3.65 (t, J = 7.2 Hz, 2H), 3.38 (tdd, J = 6.5, 5.1, 1.2 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.14 (d, J = 18.6 Hz, 1H), 2.99 (d, J = 16.9 Hz, 1H), 2.70 – 2.44 (m, 5H), 2.35 (td, J = 16.9, 16.0, 8.1 Hz, 3H), 2.15 (t, J = 11.2 Hz, 1H), 1.92 – 1.78 (m, 2H), 1.75 – 1.54 (m, 3H), 1.48 (d, J = 11.5 Hz, 1H), 0.73 (s, 1H), 0.42 (d, J = 7.7 Hz, 2H), 0.11 (d, J = 10.3 Hz, 1H), 0.06 (s, 1H); ESI MS m/z 689.4 $[M + H]^+$.

Step 2. A solution of the above intermediate (0.22 g, 0.3 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to −78 °C. Boron tribromide (1.7 mL, 1.7 mmol, 1 M in CH_2Cl_2) was added dropwise, and the mixture was stirred for 1 h at 0 °C. The mixture was then allowed to come to room temperature, and the reaction was quenched by addition of drops of ice-cold water. The mixture was diluted with water and extracted with $CHCl_3$ (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) to obtain 0.06 g (32%) of the desired product **8** as a white solid; Mp: 110–112 °C; TLC (7.5% MeOH/CH_2Cl_2): Rf = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J = 2.3, 0.8 Hz, 1H), 7.52 – 7.36 (m, 7H), 7.17 – 7.10 (m, 2H), 7.10 – 7.04 (m, 1H), 7.00 – 6.95 (m, 2H), 6.67 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 5.62 (s, 1H), 3.71 (dt, J = 8.1, 5.9 Hz, 1H), 3.65 (d, J = 5.8 Hz, 1H), 3.29 – 3.18 (m, 2H), 2.84 (d, J = 16.6 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.58 – 2.41 (m, 5H), 2.38 – 2.26 (m, 2H), 1.80 – 1.64 (m, 3H), 0.88 – 0.71 (m, 1H), 0.61 – 0.33 (m, 2H), 0.20 – 0.03 (m, 2H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 152.4, 146.8, 143.5, 142.3, 139.0, 137.5, 136.3, 135.8, 131.1, 131.0, 129.2, 128.5, 128.3, 128.2, 127.3, 126.1, 125.6, 119.1, 116.9, 91.2, 59.9, 59.4, 55.6, 47.9, 44.7, 32.5, 31.6, 31.5, 30.6, 23.6, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{38}H_{39}N_2O_3$ $[M + H]^+$: 571.29552, found: 571.29556; HPLC (system 2) t_R = 6.29 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-11-(4-Bromophenyl)-7-(cyclopropylmethyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (9).

Step 1. Following the procedure described in Step 1 for the preparation of **8**, the 4-bromophenyl compound **55**[31] (0.6 g, 1.1 mmol) was reacted with 3-phenylpropyl bromide (0.7 g, 3.4 mmol) in the presence of sodium hydride (0.3 g, 6.8 mmol, 60% dispersion in mineral oil) to obtain (4b*S*,8*R*,8a*S*,13b*R*)-11-(4-bromophenyl)-7-(cyclopropylmethyl)-1,8a-bis(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (0.3 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.40 – 7.34 (m, 3H), 7.24 – 7.18 (m, 2H), 7.18 – 7.06 (m, 6H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.64 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.59 – 6.53 (m, 1H), 5.58 (d, *J* = 2.9 Hz, 1H), 4.15 – 4.06 (m, 1H), 4.03 – 3.95 (m, 1H), 3.72 (d, *J* = 7.1 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.19 (m, 2H), 2.84 (d, *J* = 16.5 Hz, 1H), 2.73 (q, *J* = 9.4, 7.2 Hz, 4H), 2.57 (d, *J* = 16.5 Hz, 1H), 2.52 – 2.42 (m, 4H), 2.38 – 2.25 (m, 2H), 2.02 – 1.93 (m, 2H), 1.72 (s, 3H), 0.81 (s, 1H), 0.55 – 0.45 (m, 2H), 0.13 (s, 2H); ESI MS *m*/*z* 767.3 $[M + H]^+$.

Step 2. The above intermediate (0.3 g, 0.4 mmol) was reacted with boron tribromide (2.4 mL, 2.4 mmol, 1 M in CH_2Cl_2) as described in Step 2 for the preparation of **8** to give the desired product **9** (0.08 g, 30%) as a white solid; Mp: 120–121 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.16 – 7.06 (m, 3H), 6.99 – 6.95 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 3.76 – 3.68 (m, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.18 (m, 2H), 2.88 – 2.80 (m, 1H), 2.80

– 2.66 (m, 2H), 2.59 – 2.51 (m, 1H), 2.51 – 2.40 (m, 4H), 2.37 – 2.25 (m, 2H), 1.77 – 1.67 (m, 4H), 0.84 – 0.76 (m, 1H), 0.53 – 0.45 (m, 2H), 0.14 – 0.11 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.9, 146.4, 143.5, 142.3, 139.0, 136.4, 135.6, 135.1, 132.3, 131.1, 131.1, 128.8, 128.5, 128.2, 126.0, 125.7, 122.7, 119.1, 116.9, 91.0, 59.9, 59.4, 55.5, 47.9, 44.6, 32.5, 31.6, 31.4, 30.6, 29.8, 23.5, 9.4, 4.2; HRMS (ESI) *m/z* calcd for $C_{38}H_{38}BrN_2O_3$ $[M + H]^+$: 649.20603, found: 649.20460; HPLC (system 1) t_R = 15.86 min, purity = 98.6%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(4-fluorophenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinolin-1-ol (10). *Step 1*. The 4-fluorophenyl compound **56**[31] (1.0 g, 2.1 mmol) was reacted with 3-phenylpropyl bromide (1.3 g, 1.0 mmol) in the presence of sodium hydride (0.5 g, 12.8 mmol, 60% dispersion in mineral oil) as described in Step 1 for the preparation of **8**, to obtain (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-11-(4-fluorophenyl)-1,8a-bis(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (0.84 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.2 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.16 – 7.07 (m, 8H), 7.01 – 6.94 (m, 2H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.58 (s, 1H), 4.11 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.99 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.71 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.65 (d, *J* = 5.9 Hz, 1H), 3.29 – 3.18 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.75 – 2.67 (m, 4H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.51 – 2.41 (m, 4H), 2.37 – 2.24 (m, 2H), 2.01 – 1.92 (m, 2H), 1.78 – 1.64 (m, 3H), 0.80 (q, *J* = 6.6 Hz, 1H), 0.49 (dtd, *J* = 7.8, 4.9, 3.5 Hz, 2H), 0.18 – 0.07 (m, 2H); ESI MS *m*/*z* 707.3 $[M + H]^+$.

Step 2. The above intermediate (0.4 g, 0.6 mmol) was reacted with boron tribromide (3.4 mL, 3.4 mmol, 1 M in CH_2Cl_2) as described in Step 2 for the preparation of **8** to give 0.03 g (9%) of the title compound **10** as a yellow solid; Mp: 160–161 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.2 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.18 – 7.05 (m, 5H), 6.97 (d, *J* = 6.6 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.61 (s, 1H), 3.72 (dt, *J* = 8.3, 6.0 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.18 (m, 2H), 2.83 (d, *J* = 16.6 Hz, 1H), 2.78 – 2.65 (m, 2H), 2.58 – 2.40 (m, 5H), 2.37 – 2.25 (m, 2H), 1.77 – 1.65 (m, 4H), 0.81 (dd, *J* = 12.5, 6.7 Hz, 1H), 0.49 (m, 2H), 0.20 – 0.06 (m, *J* = 5.4, 4.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9 (d, $J_{C\text{-}F}$ = 248 Hz, 1C), 152.4, 146.5, 143.3, 142.2, 138.7, 135.6, 135.3, 133.5, 130.9 (d, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9 Hz, 1C), 128.9, 128.8, 128.4, 128.1, 126.0, 125.5, 119.0, 116.6, 116.1 (d, $J_{C\text{-}C\text{-}F}$ = 22 Hz, 1C), 91.1, 59.7, 59.3, 55.4, 47.8, 44.5, 32.4, 31.5, 31.3, 30.4, 29.7, 23.4, 9.3, 4.1, 3.5.; HRMS (ESI) *m/z* calcd for $C_{38}H_{38}FN_2O_3$ $[M + H]^+$: 589.28610, found: 589.28665; HPLC (system 2) t_R = 5.58 min, purity = 97.7%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2,4-difluorophenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (11). *Step 1*. (4b*S*,8*R*,8a*S*,13b*R*)-11-Bromo-7-(cyclopropylmethyl)-5,6,7,8,9,13b-hexahydro-8a*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline-1,8a-diol (**59**)[30] (0.30 g, 0.7 mmol) in DMF (10 mL) was added sodium hydride (0.16 g, 4 mmol, 60% dispersion in mineral oil) at 0–5 °C. After the mixture was stirred for 40 min, 3-phenylpropyl bromide (0.29 g, 1.5 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature and stirred for 4 h. Excess of sodium hydride was decomposed with drops of ice-cold water, the mixture was then diluted with water and extracted with $CHCl_3$ (3 × 20 mL). Organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The solvent was removed under reduced pressure. The residue was purified by chromatography over a column of silica gel using Hexanes/EtOAc (40:60) as the eluent to obtain (4bS,8R,8aS,13bR)-11-Bromo-7-(cyclopropylmethyl)-1,8a-bis(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5H-4,8-

methanobenzofuro[3,2-h]pyrido[3,4-g]quinoline (**60**) (0.14 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.08 (m, 11H), 7.14 – 7.02 (m, 2H), 6.75 – 6.58 (m, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.08 (d, *J* = 1.4 Hz, 1H), 3.97 (dddt, *J* = 60.4, 32.4, 9.2, 6.3 Hz, 4H), 3.05 (d, *J* = 18.5 Hz, 1H), 2.84 – 2.57 (m, 5H), 2.56 – 1.84 (m, 11H), 1.65 (dd, *J* = 9.8, 3.1 Hz, 1H), 1.57 (dddd, *J* = 22.5, 13.1, 6.4, 2.8 Hz, 1H), 0.84 (s, 1H), 0.61 – 0.44 (m, 2H), 0.22 – 0.05 (m, 2H); ESI MS *m*/*z* 691.2 $(MH)^+$.

Step 2. Under argon atmosphere, the above intermediate **60** (0.25 g, 0.4 mmol), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.17 g, 0.7 mmol), potassium carbonate (0.15 mg, 1.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.04 mmol) were added to 5.5 mL of 10:1 DMF/H_2O. The resulting mixture was heated in microwave at 100 °C for 1 h. The mixture was allowed to cool down to room temperature and water was added. Aqueous layer was extracted with ethyl acetate (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) to obtain (4bS,8R,8aS,13bR)-7-(cyclopropylmethyl)-11-(2,4-difluorophenyl)-1,8a-bis(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinolone (**61**) (0.21 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (q, *J* = 1.2, 0.8 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.50 – 7.44 (m, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.33 (td, *J* = 8.6, 6.3 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.18 – 7.10 (m, 4H), 7.03 – 6.97 (m, 2H), 6.97 – 6.88 (m, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.58 (s, 1H), 4.11 (dt, *J* = 9.6, 6.3 Hz, 1H), 4.00 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.73 (dt, *J* = 8.2, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.18 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.65 (m, 4H), 2.57 (d, *J* = 16.5 Hz, 1H), 2.52 – 2.41 (m, 4H), 2.32 (ddd, *J* = 13.6, 10.8, 7.5 Hz, 2H), 2.04 – 1.92 (m, 2H), 1.79 – 1.66 (m, 3H), 0.87 – 0.75 (m, 1H), 0.56 – 0.44 (m, 2H), 0.19 – 0.06 (m, 2H); ESI MS *m*/*z* 725.3 $[M + H]^+$.

Step 3. The above intermediate **61** (0.21 g, 0.3 mmol) was reacted with boron tribromide (1.8 mL, 1.8 mmol, 1 M in CH_2Cl_2) as described in Step 2 for the preparation of **8** to obtain 0.08 g (43%) of the title compound **11** as a pale red solid; Mp: 210–211 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.41 (s, 1H), 7.32 (td, *J* = 8.6, 6.3 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.12 – 7.06 (m, 1H), 7.02 – 6.98 (m, 2H), 6.98 – 6.88 (m, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.60 (s, 1H), 3.73 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.18 (m, 2H), 2.83 (d, *J* = 16.6 Hz, 1H), 2.79 – 2.65 (m, 2H), 2.55 (d, *J* = 16.4 Hz, 1H), 2.51 – 2.40 (m, 5H), 2.38 – 2.26 (m, 2H), 1.79 – 1.64 (m, 3H), 0.85 – 0.76 (m, 1H), 0.50 (tt, *J* = 7.5, 4.1 Hz, 2H), 0.16 – 0.12 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.50 (p, *J* = 7.8 Hz), -113.00 (q, *J* = 8.9 Hz); HRMS (ESI) *m/z* calcd for $C_{38}H_{37}F_2N_2O_3$ $[M + H]^+$: 607.27668, found: 607.27678; HPLC (system 2) t_R = 7.22 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(3,4-difluorophenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (12). *Step 1*. The bromo compound **60** (0.22 g, 0.3 mmol) was reacted with 2-(3,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.15 g, 0.6 mmol) in the presence of potassium carbonate (0.13 g, 1.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol) as described in Step 2 for the preparation of **11** to give (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-11-(3,4-difluorophenyl)-1,8a-bis(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolone (**62**) (0.12 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.2 Hz, 1H), 7.67 (ddd, *J* = 12.0, 8.3, 1.4 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.34 (d, *J* = 2.2 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.25 – 7.06 (m, 8H), 7.01 – 6.96 (m, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.58 (s, 1H), 4.11 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.99 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.18 (m, 2H), 2.98

– 2.79 (m, 2H), 2.79 – 2.66 (m, 4H), 2.56 (d, *J* = 16.5 Hz, 1H), 2.51 – 2.41 (m, 3H), 2.38 – 2.24 (m, 2H), 2.03 – 1.92 (m, 2H), 1.72 (td, *J* = 14.0, 5.7 Hz, 3H), 0.81 (s, 1H), 0.50 (td, *J* = 8.0, 4.8 Hz, 2H), 0.17 – 0.08 (m, 2H); ESI MS *m*/*z* 725.3 $[M + H]^+$.

Step 2. The above intermediate **62** (0.21 g, 0.3 mmol) was reacted with boron tribromide (1.0 mL, 1.0 mmol, 1 M in CH_2Cl_2) as described in Step 2 for the preparation of **8** to give (0.07 g, 64%) of the desired compound **12** as a pale red solid; Mp: 181–182 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.2 Hz, 1H), 7.34 (d, *J* = 2.2 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.25 – 7.18 (m, 2H), 7.17 – 7.06 (m, 3H), 6.98 (d, *J* = 6.7 Hz, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.60 (s, 1H), 3.77 – 3.68 (m, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.17 (m, 2H), 2.83 (d, *J* = 16.6 Hz, 1H), 2.79 – 2.65 (m, 2H), 2.54 (d, *J* = 16.6 Hz, 1H), 2.46 (dt, *J* = 15.6, 6.8 Hz, 4H), 2.39 – 2.24 (m, 3H), 1.79 – 1.63 (m, 3H), 0.80 (p, *J* = 7.2, 6.8 Hz, 1H), 0.56 – 0.44 (m, 2H), 0.13 (d, *J* = 2.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -136.56 (ddd, *J* = 21.2, 11.0, 6.6 Hz), -138.36 (dt, *J* = 18.8, 9.3 Hz); HRMS (ESI) *m/z* calcd for $C_{38}H_{37}F_2N_2O_3$ $[M + H]^+$: 607.27668, found: 607.27660; HPLC (system 2) t_R = 7.27 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(*o*-tolyl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (13). *Step 1*. The bromo compound **60** (0.22 g, 0.3 mmol) was 0.25 g, 0.4 mmol) was reacted with 4,4,5,5-tetramethyl-2-(*o*-tolyl)-1,3,2-dioxaborolane (0.08 g, 0.4 mmol) in the presence of potassium carbonate (0.15 g, 1.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.04 mmol) as described in Step 2 for the preparation of **11** to give (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-1,8a-bis(3-phenylpropoxy)-11-(*o*-tolyl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (**63**) (0.22 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.26 – 7.19 (m, 6H), 7.13 – 7.08 (m, 2H), 7.05 – 7.00 (m, 2H),

6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 1H), 4.14 (dt, *J* = 9.7, 6.3 Hz, 1H), 4.03 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.75 (dt, *J* = 8.3, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.20 (m, 2H), 2.86 – 2.65 (m, 6H), 2.62 – 2.41 (m, 6H), 2.37 – 2.26 (m, 2H), 2.18 (s, 3H), 2.05 – 1.94 (m, 2H), 1.78 – 1.67 (m, 3H), 1.62 (d, *J* = 5.7 Hz, 3H), 0.86 – 0.76 (m, 1H), 0.50 (dtd, *J* = 7.8, 4.5, 3.2 Hz, 2H), 0.15 – 0.11 (m, 2H); ESI MS *m*/*z* 703.4 $[M + H]^+$.

Step 2. The above intermediate **63** (0.22 g, 0.3 mmol) was reacted with boron tribromide (1.9 mL, 1.9 mmol, 1 M in CH_2Cl_2) to give 0.06 g (30%) of the desired compound **13** as a white solid; Mp: 110–111 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.26 – 7.20 (m, 3H), 7.17 (dd, *J* = 8.1, 6.5 Hz, 2H), 7.14 – 7.08 (m, 2H), 7.04 – 7.00 (m, 2H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 3.75 (dt, *J* = 8.3, 5.8 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.32 – 3.19 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.73 (td, *J* = 13.1, 12.0, 6.0 Hz, 2H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.52 – 2.40 (m, 4H), 2.32 (dt, *J* = 11.8, 6.5 Hz, 2H), 2.19 (s, 3H), 1.98 (s, 1H), 1.78 – 1.66 (m, 3H), 0.87 – 0.74 (m, 1H), 0.50 (dq, *J* = 7.9, 4.0 Hz, 2H), 0.13 (t, *J* = 3.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.0, 148.4, 143.6, 142.4, 138.9, 138.0, 137.8, 137.2, 135.8, 131.2, 130.7, 130.5, 130.0, 128.5, 128.3, 128.3, 126.2, 125.7, 119.1, 116.8, 91.4, 59.8, 59.7, 55.6, 48.0, 44.7, 32.9, 31.9, 31.5, 30.6, 29.8, 23.5, 20.5, 9.4, 4.3, 3.6 ; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_3$ $[M + H]^+$: 585.31117, found: 585.31002; HPLC (system 1) t_R = 15.17 min, purity 99.0%.

(4b*S*,8*R*,8a*S*,13bR)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(*m*-tolyl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (14). This compound was prepared by the two step procedure described for the preparation of **11**. In step 1, the bromo compound **60** was reacted with 4,4,5,5-tetramethyl-2-(*m*-tolyl)-1,3,2-dioxaborolane to obtain intermediate **64**. Yield: 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 – 8.76

(m, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.24 – 7.18 (m, 3H), 7.16 – 7.08 (m, 6H), 7.01 – 6.96 (m, 2H), 6.64 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.59 (d, *J* = 1.1 Hz, 1H), 4.16 – 4.06 (m, 1H), 4.00 (dt, *J* = 9.9, 6.4 Hz, 1H), 3.76 – 3.60 (m, 2H), 3.30 – 3.19 (m, 2H), 2.84 (d, *J* = 16.5 Hz, 1H), 2.78 – 2.67 (m, 4H), 2.57 (d, *J* = 16.5 Hz, 1H), 2.52 – 2.42 (m, 4H), 2.41 (s, 3H), 2.37 – 2.28 (m, 2H), 2.01 – 1.91 (m, 2H), 1.78 – 1.65 (m, 3H), 0.85 – 0.71 (m, 1H), 0.49 (ddd, *J* = 8.0, 4.7, 3.6 Hz, 2H), 0.17 – 0.06 (m, 2H); ESI MS *m*/*z* 703.3 $[M + H]^+$. In step 2, this intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain the title compound **14**. Yield = 67%; white solid; Mp: 78–80 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 2.1 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.23 – 7.18 (m, 1H), 7.17 – 7.11 (m, 2H), 7.11 – 7.05 (m, 1H), 7.02 – 6.96 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.61 (s, 1H), 3.72 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.64 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.13 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.65 (m, 2H), 2.58 – 2.42 (m, 6H), 2.40 (s, 3H), 2.36 – 2.26 (m, 2H), 1.71 (dq, *J* = 20.9, 6.4, 4.7 Hz, 3H), 0.86 – 0.76 (m, 1H), 0.56 – 0.36 (m, 2H), 0.13 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.3, 146.7, 143.5, 142.4, 139.0, 138.8, 137.5, 136.5, 135.9, 131.1, 130.9, 129.1, 128.5, 128.3, 128.2, 128.0, 126.0, 125.6, 124.4, 119.1, 116.9, 100.1, 91.1, 59.9, 59.4, 55.6, 47.9, 44.7, 32.5, 31.6, 31.5, 29.8, 23.5, 21.6, 9.4, 4.2; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_3$ $[M + H]^+$: 585.31117, found: 585.31153; HPLC (system 1) t_R = 15.30 min, purity = 100%.

(4b*S*,8R,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(*p*-tolyl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (15). This compound was prepared following the same procedure described for **11**. The bromo compound **60** was reacted with 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane to obtain intermediate **65**. Yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.2 Hz, 1H), 7.41 (dd, *J*

= 8.5, 2.0 Hz, 3H), 7.28 – 7.18 (m, 4H), 7.17 – 7.05 (m, 6H), 7.01 – 6.96 (m, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.11 (dt, *J* = 9.7, 6.4 Hz, 1H), 4.00 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.71 (dt, *J* = 8.4, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.16 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.67 (m, 4H), 2.57 (d, *J* = 16.4 Hz, 1H), 2.52 – 2.42 (m, 4H), 2.40 (s, 3H), 2.31 (ddd, *J* = 17.7, 13.0, 6.4 Hz, 2H), 2.03 – 1.92 (m, 2H), 1.77 – 1.68 (m, 3H), 0.86 – 0.75 (m, 1H), 0.50 (dtd, *J* = 7.8, 5.1, 3.5 Hz, 2H), 0.18 – 0.07 (m, 2H); ESI MS *m*/*z* 703.4 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain the desired compound **15**. Yield = 19%; white solid; Mp: 185–186 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.2 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.24 (s, 1H), 7.14 (dd, *J* = 8.0, 6.2 Hz, 2H), 7.11 – 7.04 (m, 1H), 7.01 – 6.95 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 3.71 (q, *J* = 6.5 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.23 (dd, *J* = 16.1, 7.8 Hz, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.58 – 2.41 (m, 6H), 2.40 (s, 3H), 2.36 – 2.24 (m, 2H), 1.70 (s, 4H), 0.80 (d, *J* = 9.6 Hz, 1H), 0.49 (dd, *J* = 8.1, 3.5 Hz, 2H), 0.12 (d, *J* = 3.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.0, 146.5, 143.5, 142.3, 139.1, 138.2, 136.2, 135.6, 134.5, 131.1, 130.9, 129.9, 128.5, 128.2, 127.1, 125.6, 119.1, 117.0, 91.0, 59.8, 59.4, 55.6, 47.9, 44.7, 32.5, 31.6, 30.5, 29.8, 23.5, 21.3, 14.3, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_3$ $[M + H]^+$: 585.31117, found: 585.31098; HPLC (system 1) t_R = 15.16 min, purity = 97.1%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(4-fluoro-2-methylphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-h]pyrido[3,4-*g*]quinolin-1-ol (16). This compound was prepared by the same procedure described for **11**. The bromo compound **60** was reacted with 2-(4-fluoro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane to obtain **66**. Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.58 – 7.52 (m, 1H), 7.50 – 7.43 (m, 1H), 7.25 – 7.19 (m, 2H), 7.18 –

7.08 (m, 6H), 7.07 – 6.99 (m, 3H), 6.98 – 6.88 (m, 2H), 6.66 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.13 (dt, *J* = 9.7, 6.3 Hz, 1H), 4.02 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.75 (dt, *J* = 8.3, 5.8 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.19 (m, 2H), 2.81 (d, *J* = 16.4 Hz, 1H), 2.78 – 2.70 (m, 3H), 2.57 (d, *J* = 16.3 Hz, 1H), 2.46 (dt, *J* = 15.3, 6.9 Hz, 4H), 2.37 – 2.26 (m, 2H), 2.16 (s, 2H), 2.04 – 1.94 (m, 2H), 1.77 – 1.67 (m, 3H), 0.81 (q, *J* = 6.7 Hz, 1H), 0.50 (dtd, *J* = 7.8, 4.5, 3.2 Hz, 2H), 0.13 (dq, *J* = 5.0, 1.3 Hz, 2H); ESI MS *m*/*z* 721.4 $[M + H]^+$. Phenolic-*O*-dealkylation of this intermediate with boron tribromide in CH_2Cl_2 gave **16** as a white solid in 44% yield. Mp: 106–107 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.22 – 7.15 (m, 3H), 7.14 – 7.05 (m, 2H), 7.04 – 6.99 (m, 2H), 6.99 – 6.89 (m, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 5.27 (s, 1H), 3.76 (dt, *J* = 8.3, 5.8 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.18 (m, 2H), 2.86 – 2.66 (m, 3H), 2.55 (d, *J* = 16.5 Hz, 1H), 2.45 (tdd, *J* = 9.0, 6.1, 3.1 Hz, 4H), 2.37 – 2.26 (m, 2H), 2.17 (s, 3H), 1.79 – 1.69 (m, 2H), 1.25 (s, 1H), 0.90 – 0.74 (m, 1H), 0.50 (dtd, *J* = 7.6, 4.4, 3.2 Hz, 2H), 0.13 (td, *J* = 3.1, 2.4, 1.3 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.3, 148.5, 143.5, 142.4, 138.9, 138.1, 136.3, 133.8, 131.6, 131.5, 131.1, 130.6, 128.5, 128.3, 126.2, 125.7, 119.2, 117.3, 117.2, 116.8, 113.1, 113.0, 91.3, 59.8, 59.7, 55.6, 48.0, 44.7, 32.9, 31.9, 31.4, 29.9, 23.5, 20.7, 4.3, 3.6; HRMS (ESI) *m/z* calcd for $C_{39}H_{40}FN_2O_3$ $[M + H]^+$: 603.30175, found: 603.30150; HPLC (system 2) t_R = 7.40 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2-cyclopropylphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (17). This compound was prepared by the same procedure described for **11**. The bromo compound **60** was reacted with 2-(2-cyclopropylphenyl)boronic acid to obtain **67**. Yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.29

(dd, *J* = 7.5, 1.5 Hz, 1H), 7.25 – 7.07 (m, 9H), 7.03 – 6.99 (m, 2H), 6.92 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 4.14 (dt, *J* = 9.7, 6.3 Hz, 1H), 4.02 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.75 (dt, *J* = 8.3, 5.8 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.18 (m, 2H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.73 (tt, *J* = 12.1, 7.2 Hz, 4H), 2.58 (d, *J* = 16.4 Hz, 1H), 2.52 – 2.39 (m, 4H), 2.37 – 2.25 (m, 2H), 2.05 – 1.94 (m, 2H), 1.72 (qd, *J* = 6.5, 6.0, 3.8 Hz, 4H), 1.26 (s, 1H), 0.87 – 0.77 (m, 1H), 0.75 – 0.60 (m, 4H), 0.56 – 0.44 (m, 2H), 0.13 (ddt, *J* = 4.0, 2.8, 1.6 Hz, 2H); ESI MS *m*/*z* 729.5 $[M + H]^+$. Reaction of this intermediate with boron tribromide in CH_2Cl_2 gave the desired compound **17**. Yield = 53%; white solid; Mp: 114–115 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.29 (td, *J* = 7.6, 1.6 Hz, 1H), 7.22 – 7.14 (m, 3H), 7.14 – 7.08 (m, 2H), 7.04 – 6.99 (m, 2H), 6.92 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.63 (s, 1H), 3.76 (dt, *J* = 8.3, 5.8 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.19 (m, 2H), 2.84 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.68 (m, 2H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.51 – 2.39 (m, 4H), 2.37 – 2.27 (m, 2H), 1.75 – 1.67 (m, 6H), 0.77 – 0.71 (m, 2H), 0.69 – 0.64 (m, 2H), 0.54 – 0.45 (m, 2H), 0.13 (ddt, *J* = 3.7, 2.5, 1.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 148.8, 143.6, 142.4, 141.3, 138.9, 138.3, 138.2, 137.2, 131.2, 130.4, 129.9, 128.5, 128.3, 126.2, 125.7, 125.6, 124.0, 119.1, 116.7, 91.5, 59.8, 59.8, 55.6, 48.0, 44.7, 32.9, 32.0, 31.5, 30.7, 29.9, 23.5, 13.6, 10.0, 9.7, 9.4, 4.3, 3.5; HRMS (ESI) *m/z* calcd for $C_{41}H_{43}N_2O_3$ $[M + H]^+$: 611.32682, found: 611.32525; HPLC (system 2) t_R = 8.06 min, purity = 98.5%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2,6-dimethylphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (18). This compound was prepared by the same procedure described for **11**. The bromo compound **60** was reacted with 2-(2,6-dimethylphenyl)boronic acid to obtain **68**. Yield:

70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.0 Hz, 1H), 7.25 – 7.11 (m, 8H), 7.11 – 7.03 (m, 5H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.60 (s, 1H), 4.14 (dt, *J* = 9.7, 6.4 Hz, 1H), 4.03 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.75 (dt, *J* = 8.3, 6.0 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.20 (m, 2H), 2.84 – 2.66 (m, 5H), 2.59 (d, *J* = 16.3 Hz, 1H), 2.51 – 2.41 (m, 4H), 2.37 – 2.26 (m, 2H), 2.05 – 1.96 (m, 5H), 1.88 (s, 3H), 1.69 (ddt, *J* = 9.7, 5.6, 2.3 Hz, 3H), 1.26 (s, 1H), 0.83 (tt, *J* = 13.1, 7.0 Hz, 1H), 0.56 – 0.44 (m, 2H), 0.13 (ddd, *J* = 4.7, 2.7, 1.6 Hz, 2H); ESI MS *m*/*z* 717.4 [M + H]$^+$. Reaction of this intermediate with boron tribromide in CH_2Cl_2 gave **18** as a white solid. Yield = 34%; Mp: 111–112 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 2.1, 0.8 Hz, 1H), 7.24 – 7.03 (m, 10H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 5.63 (s, 1H), 3.77 (dt, *J* = 8.3, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.32 – 3.18 (m, 2H), 2.86 – 2.66 (m, 3H), 2.57 (d, *J* = 16.3 Hz, 1H), 2.52 – 2.39 (m, 4H), 2.37 – 2.27 (m, 2H), 2.01 (s, 3H), 1.88 (s, 3H), 1.74 – 1.64 (m, 3H), 0.81 (s, 1H), 0.50 (dd, *J* = 8.5, 5.4 Hz, 2H), 0.13 (d, *J* = 3.6 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.1, 148.5, 143.7, 142.4, 139.0, 138.2, 137.5, 136.6, 136.4, 130.9, 128.5, 128.3, 128.0, 127.7, 127.6, 126.1, 125.7, 119.1, 116.8, 91.4, 60.0, 59.8, 55.6, 48.0, 44.7, 33.1, 32.2, 31.5, 29.9, 21.3, 21.0, 9.4, 4.3, 3.6; HRMS (ESI) *m/z* calcd for $C_{40}H_{43}N_2O_3$ [M + H]$^+$: 599.32682, found: 599.32604; HPLC (system 1) t_R = 15.56 min, purity 96.2%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2-methoxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (19). *Step 1*. To a stirred solution of (4b*S*,8*R*,8a*S*,13b*R*)-11-bromo-7-(cyclopropylmethyl)-5,6,7,8,9,13b-hexahydro-8a*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline-1,8a-diol (**59**)[30] (1.59 g, 3.5 mmol) in acetone (50 mL) were added potassium carbonate (1.45 g, 10.5 mmol) and benzyl bromide (1.4 mL, 4.2 mmol). The reaction mixture was heated at reflux for 3 h.

Reaction mixture was cooled to room temperature and filtered. The inorganic solids were washed several times with acetone (3 × 40 mL). The solvent was removed under reduced pressure. The residue was purified by chromatography over a column of silica gel using $CHCl_3$/MeOH (95:5) as the eluent to obtain (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-11-bromo-7-(cyclopropylmethyl)-5,6,7,8,9,13b-hexahydro-8a*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-8a-ol (0.66 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.32 – 7.21 (m, 5H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.49 (s, 1H), 5.19 – 5.07 (m, 2H), 4.91 (s, 1H), 3.28 (d, *J* = 6.5 Hz, 1H), 3.14 (d, *J* = 18.7 Hz, 1H), 2.74 (q, *J* = 5.3, 4.5 Hz, 1H), 2.70 (d, *J* = 2.6 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.56 (d, *J* = 16.2 Hz, 1H), 2.48 – 2.36 (m, 3H), 2.36 – 2.27 (m, 1H), 1.81 (d, *J* = 10.8 Hz, 1H), 0.88 (ddt, *J* = 9.2, 7.5, 2.9 Hz, 1H), 0.62 – 0.50 (m, 2H), 0.19 – 0.08 (m, 2H); ESI MS *m*/*z* 545.1 $[M + H]^+$.

Step 2. The above intermediate (2.0 g, 3.7 mmol) was reacted with 3-phenylpropyl bromide (2.2 g, 11.0 mmol) in the presence of sodium hydride (0.6 g, 14.7 mmol, 60% dispersion in mineral oil) to obtain (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-11-bromo-7-(cyclopropylmethyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (**85**) (0.78 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.2 Hz, 1H), 7.40 (d, *J* = 2.2 Hz, 1H), 7.29 (tt, *J* = 6.2, 3.0 Hz, 2H), 7.26 – 7.20 (m, 5H), 7.17 – 7.12 (m, 1H), 7.04 – 6.99 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.51 (s, 1H), 5.19 – 5.05 (m, 2H), 3.69 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.61 (d, *J* = 5.8 Hz, 1H), 3.24 – 3.14 (m, 2H), 2.78 – 2.62 (m, 3H), 2.54 – 2.46 (m, 3H), 2.41 (td, *J* = 12.0, 6.0 Hz, 2H), 2.34 – 2.21 (m, 2H), 1.75 (dtd, *J* = 10.4, 7.4, 4.4 Hz, 2H), 1.66 (dd, *J* = 11.6, 3.4 Hz, 1H), 0.84 – 0.72 (m, 1H), 0.48 (dq, *J* = 7.5, 4.2 Hz, 2H), 0.16 – 0.06 (m, 2H); ESI MS *m*/*z* 663.2 $(MH)^+$.

Step 3. Under an atmosphere of argon, the above intermediate **85** (0.20 g, 0.3 mmol), 2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.07 g, 0.3 mmol), potassium carbonate (0.13 g, 0.9 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol) was added to 10:1 DMF/H_2O (5.5 mL). The resulting mixture was heated in microwave at 100 °C for 1 h. The mixture was then allowed to cool to room temperature and the mixture was diluted with water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) to obtain (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-(2-methoxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline **86** (0.17 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.1 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.26 – 7.20 (m, 4H), 7.15 (td, *J* = 6.8, 1.2 Hz, 2H), 7.11 – 7.06 (m, 1H), 7.05 – 6.96 (m, 4H), 6.68 – 6.64 (m, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 5.24 – 5.10 (m, 2H), 3.74 (s, 3H), 3.73 – 3.69 (m, 1H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.30 – 3.16 (m, 2H), 2.81 (d, *J* = 16.4 Hz, 1H), 2.72 (td, *J* = 11.8, 10.6, 5.9 Hz, 2H), 2.45 (q, *J* = 10.7, 10.0 Hz, 4H), 2.29 (ddd, *J* = 18.2, 12.7, 6.5 Hz, 2H), 1.77 – 1.67 (m, 3H), 0.85 – 0.76 (m, 1H), 0.49 (dq, *J* = 7.7, 4.0 Hz, 2H), 0.13 – 0.11 (m, 2H); ESI MS *m*/*z* 691.4 $[M + H]^+$.

Step 4. To a solution of the above intermediate **86** (0.16 g 0.2 mmol) in a mixture of CH_2Cl_2 (7 mL) and MeOH (7 mL) under argon atmosphere was added 10% of palladium(II) carbon (16.0 mg, 10 wt%). The reaction mixture was evacuated under vacuum and flushed with hydrogen (H_2; 3 cycles) and was continued to stir under H_2 atmosphere at room temperature for 20 h. The reaction mixture was filtered through a pad of celite followed by rinsing with EtOH. The solvent was removed under reduced pressure. The residue was purified by chromatography

over a column of silica gel using $CHCl_3$/MeOH (95:5) as the eluent to obtain the title compound **19** (0.1 g). Yield = 68%; white solid; Mp: 200–201 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.80; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 2.1, 0.7 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.35 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.11 – 7.06 (m, 1H), 7.04 – 6.95 (m, 4H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 3.73 (s, 3H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.18 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.55 (d, *J* = 16.5 Hz, 1H), 2.46 (td, *J* = 10.1, 9.4, 5.6 Hz, 5H), 2.39 – 2.26 (m, 3H), 1.78 – 1.66 (m, 3H), 0.81 (p, *J* = 7.0, 6.3 Hz, 1H), 0.53 – 0.46 (m, 2H), 0.14 – 0.12 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 151.7, 148.7, 143.6, 142.4, 139.0, 138.2, 133.9, 131.2, 130.8, 130.3, 129.7, 128.5, 128.2, 126.7, 125.6, 121.1, 119.0, 116.8, 111.3, 91.3, 59.8, 59.6, 55.6, 47.9, 44.7, 32.7, 32.1, 31.7, 31.5, 30.6, 29.8, 23.5, 9.4, 4.3, 3.6; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_4$ [M + H]$^+$: 601.30608, found: 601.30498; HPLC (system 1) t_R = 14.56 min, purity = 97.8%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(3-methoxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (20). *Step 1*. The bromo compound **85** (0.20 g, 0.3 mmol) was reacted with 2-(3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.07 g, 0.3 mmol) in the presence of potassium carbonate (0.13 g, 0.9 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol) as described in Step 3 for the preparation of **19** to give **87** (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-(3-methoxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (**87**) (0.05 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 4H), 7.17 – 7.12 (m, 3H), 7.12 – 7.09 (m, 1H), 7.09 – 7.05 (m, 1H), 7.01 – 6.96 (m, 2H), 6.93 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.66 (d, *J* =

8.1 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 5.20 – 5.10 (m, 2H), 3.84 (s, 3H), 3.75 – 3.68 (m, 1H), 3.65 (d, *J* = 5.9 Hz, 1H), 3.22 (d, *J* = 6.5 Hz, 2H), 2.77 – 2.70 (m, 2H), 2.55 (d, *J* = 16.8 Hz, 1H), 2.49 – 2.33 (m, 6H), 1.76 – 1.68 (m, 3H), 0.80 (s, 1H), 0.50 – 0.47 (m, 2H), 0.11 (d, *J* = 7.0 Hz, 2H); ESI MS *m*/*z* 691.3 $[M + H]^+$.

Step 2. A solution of the above intermediate **87** (0.05 g, 0.08 mmol) in 2,2,2-trifluoroacetic acid (5 mL) was heated at refluxed for 1.5 h. The mixture was cooled to room temperature and the 2,2,2-trifluoroacetic acid was removed under reduced pressure. The residue was dissolved in water and neutralized by aqueous NH_4OH. The resulting suspension was extracted with EtOAc (3 × 10 mL) and washed with water (10 mL). The extract was dried, and the solvent was removed under reduced pressure. The residue was purified by chromatography over a column of silica gel using $CHCl_3$/MeOH (95:5) as the eluent to obtain 25.0 mg (54%) of the desired product **20** as a white solid. Mp: 107–108 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.35 (dd, *J* = 17.9, 9.8 Hz, 2H), 7.15 – 7.02 (m, 4H), 7.01 – 6.90 (m, 4H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.60 (s, 1H), 3.83 (s, 3H), 3.67 (d, *J* = 20.8 Hz, 2H), 3.24 (dq, *J* = 11.4, 5.3, 4.6 Hz, 2H), 2.90 – 2.63 (m, 3H), 2.57 – 2.28 (m, 8H), 1.71 (d, *J* = 19.5 Hz, 3H), 0.81 (s, 1H), 0.50 (s, 2H), 0.13 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.2, 146.8, 143.5, 142.3, 139.0, 136.2, 135.9, 131.1, 130.2, 128.5, 128.2, 125.6, 119.7, 119.1, 116.9, 113.7, 113.1, 91.1, 59.8, 59.4, 55.5, 47.9, 44.7, 33.6, 32.5, 32.1, 31.5, 29.8, 29.8, 29.5, 23.3, 22.8, 18.0, 14.3, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_4$ $[M + H]^+$: 601.30608, found: 601.30498; HPLC (system 1) t_R = 14.85 min, purity = 98.2%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(4-methoxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (21). *Step 1*. The bromo compound **85** (0.20 g, 0.3 mmol) was reacted with 2-

(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.07 g, 0.3 mmol) in the presence of potassium carbonate (0.13 g, 0.9 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol) as described in Step 3 for the preparation of **19** to obtain (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-(4-methoxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (**88**) (0.16 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 7.17 – 7.11 (m, 2H), 7.11 – 7.05 (m, 1H), 7.01 – 6.96 (m, 4H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 5.21 – 5.09 (m, 2H), 3.85 (s, 3H), 3.74 – 3.67 (m, 1H), 3.64 (d, *J* = 5.8 Hz, 1H), 3.22 (dd, *J* = 16.7, 11.0 Hz, 2H), 2.82 (d, *J* = 16.5 Hz, 1H), 2.78 – 2.65 (m, 2H), 2.58 – 2.40 (m, 5H), 2.36 – 2.23 (m, 2H), 1.72 (ddd, *J* = 23.9, 12.6, 6.9 Hz, 3H), 0.85 – 0.75 (m, 1H), 0.49 (dq, *J* = 7.8, 4.3 Hz, 2H), 0.17 – 0.09 (m, 2H); ESI MS *m*/*z* 691.3 $[M + H]^+$.

Step 2. The above intermediate **88** (0.16 g, 0.2 mmol) was debenzylated with 10% of palladium(II) carbon (16.0 mg, 10 wt%) under H_2 atmosphere as described in Step 4 in the preparation of **19** to obtain 0.05 g (33%) of the desired compound **21** as a white solid. Mp: 100–101 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.39 – 7.30 (m, 3H), 7.10 (dq, *J* = 14.2, 7.3 Hz, 3H), 7.00 – 6.91 (m, 4H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.59 (s, 1H), 3.84 (s, 3H), 3.74 – 3.59 (m, 2H), 3.32 – 3.15 (m, 2H), 2.82 – 2.66 (m, 3H), 2.46 (q, *J* = 13.1, 10.5 Hz, 6H), 2.38 – 2.22 (m, 2H), 1.83 – 1.62 (m, 3H), 0.80 (s, 1H), 0.54 – 0.43 (m, 2H), 0.13 (d, *J* = 0.9 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.9, 151.7, 146.3, 143.5, 142.3, 135.9, 135.3, 131.2, 130.9, 129.8, 128.5, 128.3, 128.2, 126.0, 125.6, 119.1, 116.9, 114.6, 91.1, 59.9, 59.4, 55.6, 55.5, 47.9, 44.7, 33.6, 32.5, 32.1, 31.6, 29.9, 29.5,

23.3, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_4$ $[M + H]^+$: 601.30608, found: 601.30432; HPLC (system 1) t_R = 14.54 min, purity = 99%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(3-hydroxyphenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (22). This compound was prepared by same procedure described for **11**. The bromo compound **60** was reacted with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol to obtain **69**. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 2.1 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.03 (m, 8H), 7.02 – 6.94 (m, 6H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.63 (s, 1H), 4.05 (dt, *J* = 9.5, 6.2 Hz, 1H), 3.93 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.75 – 3.60 (m, 2H), 3.30 – 3.16 (m, 2H), 2.84 – 2.67 (m, 3H), 2.60 – 2.39 (m, 7H), 2.31 (ddd, *J* = 19.7, 12.3, 7.5 Hz, 2H), 1.89 – 1.66 (m, 5H), 0.84 – 0.71 (m, 1H), 0.50 (ddt, *J* = 7.9, 5.3, 2.7 Hz, 2H), 0.14 – 0.12 (m, 2H); ESI MS *m/z* 705.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **22** as a white solid. Yield = 58%; white solid; Mp: 155–157 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.23 (s, 1H), 7.10 – 6.95 (m, 4H), 6.95 – 6.86 (m, 2H), 6.77 (t, *J* = 5.9 Hz, 2H), 6.63 (t, *J* = 5.8 Hz, 2H), 6.34 (s, 1H), 5.55 (s, 1H), 3.65 (dt, *J* = 10.8, 5.8 Hz, 2H), 3.27 – 3.16 (m, 2H), 2.83 – 2.60 (m, 4H), 2.55 – 2.25 (m, 8H), 1.73 – 1.56 (m, 3H), 0.77 (p, *J* = 6.6 Hz, 1H), 0.49 (dp, *J* = 9.5, 5.1 Hz, 2H), 0.27 – 0.03 (m, 2H); ^{13}C NMR (214 MHz, $CDCl_3$) δ 157.5, 151.5, 144.6, 143.4, 142.2, 139.9, 137.1, 136.4, 135.6, 131.7, 130.9, 129.9, 128.4, 128.2, 125.6, 125.5, 125.1, 119.3, 118.1, 117.6, 116.1, 113.8, 89.5, 59.8, 59.5, 55.6, 47.8, 44.7, 32.4, 31.5, 31.4, 30.4, 23.6, 9.4, 3.7; HRMS (ESI) *m/z* calcd for $C_{38}H_{39}N_2O_4$ $[M + H]^+$: 587.29043, found: 587.28972; HPLC (system 1) t_R = 13.61 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2-(dimethylamino)phenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (23). As described for the preparation of **11**, the bromo compound **60** was reacted with *N,N*-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline to obtain **70**. Yield: 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.26 – 7.09 (m, 10H), 7.06 – 7.01 (m, 3H), 6.99 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.58 (s, 1H), 4.12 (dt, *J* = 9.8, 6.3 Hz, 1H), 4.02 (dt, *J* = 9.7, 6.3 Hz, 1H), 3.73 (dt, *J* = 8.3, 6.1 Hz, 1H), 3.64 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.17 (m, 2H), 2.82 (d, *J* = 16.4 Hz, 1H), 2.77 – 2.68 (m, 4H), 2.59 – 2.53 (m, 1H), 2.49 – 2.45 (m, 3H), 2.44 (s, 6H), 2.36 – 2.27 (m, 2H), 2.03 – 1.93 (m, 2H), 1.70 (t, *J* = 7.7 Hz, 3H), 0.85 – 0.75 (m, 1H), 0.49 (td, *J* = 7.9, 4.7 Hz, 2H), 0.13 (s, 2H); ESI MS *m/z* 732.4 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **23** as a white solid. Yield = 43%. Mp: 102–104 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 1.9 Hz, 1H), 7.53 (d, *J* = 2.1 Hz, 1H), 7.29 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H), 7.21 – 7.15 (m, 2H), 7.12 (ddd, *J* = 5.9, 4.2, 2.4 Hz, 2H), 7.07 – 6.98 (m, 4H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 3.74 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.32 – 3.19 (m, 2H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.54 (d, *J* = 16.4 Hz, 1H), 2.48 (d, *J* = 8.3 Hz, 3H), 2.45 (s, 6H), 2.37 – 2.29 (m, 2H), 1.69 (ddd, *J* = 11.3, 8.4, 4.7 Hz, 3H), 1.26 (s, 2H), 0.80 (q, *J* = 6.6 Hz, 1H), 0.56 – 0.42 (m, 2H), 0.13 (dd, *J* = 4.6, 1.4 Hz, 2H); ^{13}C NMR (214 MHz, $CDCl_3$) δ 151.8, 151.6, 148.3, 143.6, 142.5, 138.8, 137.2, 137.1, 131.6, 131.2, 130.6, 129.1, 128.5, 128.3, 126.2, 125.7, 122.2, 119.0, 118.3, 116.6, 91.7, 59.9, 59.8, 55.6, 48.0, 44.7, 43.7, 32.9, 32.0, 30.7, 29.9, 29.5, 23.5, 9.4, 4.3, 3.6; HRMS (ESI) *m/z* calcd for $C_{40}H_{44}N_3O_3$ $[M + H]^+$: 614.33772, found: 614.33649; HPLC (system 1) t_R = 13.73 min, purity = 95.7%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(3-(dimethylamino)phenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (24). Following the procedure for the preparation of **11**, the bromo compound **60** was reacted with *N,N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline to obtain **71** in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 2.2 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.25 – 7.18 (m, 2H), 7.17 – 7.05 (m, 6H), 7.01 – 6.96 (m, 2H), 6.84 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H), 6.80 (t, *J* = 2.1 Hz, 1H), 6.76 (ddd, *J* = 8.4, 2.6, 0.9 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.11 (dt, *J* = 9.7, 6.4 Hz, 1H), 4.00 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.71 (dt, *J* = 8.0, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.19 (m, 2H), 2.97 (s, 6H), 2.85 (d, *J* = 16.5 Hz, 1H), 2.77 – 2.68 (m, 4H), 2.58 (d, *J* = 16.6 Hz, 1H), 2.47 (ddd, *J* = 12.5, 6.8, 3.3 Hz, 4H), 2.37 – 2.25 (m, 2H), 2.04 – 1.93 (m, 2H), 1.76 – 1.67 (m, 3H), 0.82 (q, *J* = 6.4 Hz, 1H), 0.54 – 0.44 (m, 2H), 0.20 – 0.05 (m, 2H); ESI MS *m*/*z* 732.3 [M + H]$^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **24** as a white solid. Yield = 63%. Mp: 140–142 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 2.3, 1.0 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.11 – 7.05 (m, 1H), 7.01 – 6.96 (m, 2H), 6.84 (ddd, *J* = 7.5, 1.7, 0.8 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 3.72 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.18 (m, 2H), 2.98 (s, 6H), 2.85 (d, *J* = 16.6 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.56 (d, *J* = 16.6 Hz, 1H), 2.51 – 2.41 (m, 4H), 2.37 – 2.26 (m, 2H), 1.76 – 1.68 (m, 4H), 0.80 (t, *J* = 6.4 Hz, 1H), 0.54 – 0.42 (m, 2H), 0.13 (ddt, *J* = 3.8, 2.6, 1.2 Hz, 2H); ^{13}C NMR (214 MHz, $CDCl_3$) δ 152.2, 151.1, 147.1, 143.5, 142.4, 138.8, 138.6, 137.4, 136.0, 131.2, 130.8, 129.8, 128.6, 128.5, 128.3, 126.2, 125.6, 119.0, 116.7, 115.7, 112.4, 111.4, 91.5, 59.9, 59.4, 55.6, 47.9, 44.7, 40.7, 32.6, 31.7, 30.6, 29.9, 23.6, 9.4, 4.2; HRMS (ESI)

m/z calcd for $C_{40}H_{44}N_3O_3$ $[M + H]^+$: 614.33772, found: 614.33714; HPLC (system 1) t_R = 12.66 min, purity = 98.8%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(4-(dimethylamino)phenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (25). This compound was prepared by the same procedure described for **11**. The bromo compound **60** was reacted with *N,N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline to obtain **72**. Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.17 – 7.05 (m, 7H), 7.01 – 6.97 (m, 2H), 6.81 – 6.76 (m, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 5.58 (s, 1H), 4.11 (dt, *J* = 9.6, 6.4 Hz, 1H), 4.00 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.74 – 3.61 (m, 2H), 3.30 – 3.16 (m, 2H), 3.00 (s, 6H), 2.87 – 2.78 (m, 1H), 2.78 – 2.66 (m, 5H), 2.56 (d, *J* = 16.4 Hz, 1H), 2.52 – 2.41 (m, 5H), 2.38 – 2.25 (m, 2H), 2.04 – 1.92 (m, 2H), 0.80 (q, *J* = 6.6 Hz, 1H), 0.56 – 0.43 (m, 2H), 0.19 – 0.07 (m, 2H); ESI MS *m/z* 732.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **25.** Yield = 26%; pale yellow solid; Mp: 128–130 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.0 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.18 – 7.07 (m, 3H), 7.00 – 6.96 (m, 2H), 6.80 – 6.76 (m, 2H), 6.66 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 3.70 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.64 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.17 (m, 2H), 3.00 (s, 6H), 2.86 – 2.66 (m, 3H), 2.58 – 2.40 (m, 6H), 2.37 – 2.25 (m, 2H), 1.80 – 1.64 (m, 3H), 0.87 – 0.77 (m, 1H), 0.55 – 0.44 (m, 2H), 0.17 – 0.09 (m, 2H); ^{13}C NMR (214 MHz, $CDCl_3$) δ 150.9, 150.6, 146.2, 143.5, 142.4, 138.9, 136.3, 134.6, 131.2, 130.7, 128.6, 128.3, 128.2, 127.9, 126.1, 125.6, 125.1, 119.0, 116.7, 112.9, 91.5, 91.5, 59.9, 59.4, 55.6, 47.9, 44.7, 40.6, 32.5, 31.6, 31.5, 30.6, 23.6, 9.4, 4.2,

3.6; HRMS (ESI) *m/z* calcd for $C_{40}H_{44}N_3O_3$ $[M + H]^+$: 614.33772, found: 614.33632; HPLC (system 1) t_R = 13.06 min, purity = 94.5%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2-((dimethylamino)methyl)phenyl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (26). The bromo compound **60** was reacted with *N,N*-dimethyl-1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine as described in Step 2 for the preparation of **11** to obtain **73** in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.49 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.35 (td, *J* = 7.5, 1.5 Hz, 1H), 7.29 (td, *J* = 7.5, 1.5 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.23 – 7.19 (m, 1H), 7.19 – 7.14 (m, 5H), 7.14 – 7.09 (m, 2H), 7.07 – 7.03 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.60 (s, 1H), 4.13 (dt, *J* = 9.7, 6.3 Hz, 1H), 4.03 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.19 (m, 4H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.78 – 2.67 (m, 4H), 2.57 (d, *J* = 16.4 Hz, 1H), 2.52 – 2.42 (m, 4H), 2.33 (dd, *J* = 12.6, 6.8 Hz, 2H), 2.08 (s, 6H), 2.05 – 1.96 (m, 2H), 1.72 (td, *J* = 12.7, 11.7, 5.4 Hz, 3H), 0.85 – 0.75 (m, 1H), 0.53 – 0.43 (m, 2H), 0.13 (td, *J* = 3.2, 1.3 Hz, 2H); ESI MS *m/z* 746.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **26** as a pale brown solid in 34% yield. Mp: 120–121 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.60 – 7.48 (m, 4H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.20 (dd, *J* = 12.4, 4.3 Hz, 3H), 7.10 (d, *J* = 7.5 Hz, 3H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 4.98 (d, *J* = 13.6 Hz, 1H), 4.86 (d, *J* = 13.8 Hz, 1H), 3.66 (dd, *J* = 24.6, 6.6 Hz, 2H), 3.33 – 3.13 (m, 2H), 2.85 (d, *J* = 16.8 Hz, 1H), 2.72 (d, *J* = 19.2 Hz, 5H), 2.56 (d, *J* = 8.1 Hz, 6H), 2.44 (dt, *J* = 18.8, 6.1 Hz, 2H), 2.32 (dd, *J* = 12.9, 7.4 Hz, 2H), 1.81 – 1.74 (m, 2H), 1.68 (d, *J* = 11.3 Hz, 1H), 0.82 – 0.71 (m, 1H), 0.51 – 0.45 (m, 2H), 0.12 – 0.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.4, 148.4, 143.3, 142.5,

141.8, 139.3, 138.4, 135.6, 134.6, 132.0, 130.9, 128.6, 128.3, 127.0, 125.6, 119.3, 117.2, 90.3, 59.8, 58.3, 55.5, 47.8, 45.5, 45.1, 44.6, 32.7, 31.9, 31.3, 30.4, 29.8, 29.5, 23.5, 22.8, 14.3, 9.3, 4.1, 3.7.; HRMS (ESI) *m/z* calcd for $C_{41}H_{46}N_3O_3$ $[M + H]^+$: 628.35337, found: 628.35178; HPLC (system 1) t_R = 16.33 min, purity = 95.7%.

***N*-(2-((4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-1-hydroxy-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-11-yl)phenyl)acetamide (27).** This compound was prepared by same procedure described for **11**. Reaction of the bromo compound **60** with *N*-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide gave **74** in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.39 (td, *J* = 8.3, 7.8, 1.7 Hz, 1H), 7.29 (d, *J* = 2.1 Hz, 1H), 7.25 – 7.08 (m, 11H), 7.02 – 6.98 (m, 2H), 6.77 (d, *J* = 6.2 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 1H), 4.13 (dt, *J* = 9.5, 6.3 Hz, 1H), 4.00 (dt, *J* = 9.5, 6.4 Hz, 1H), 3.73 (q, *J* = 6.5 Hz, 1H), 3.67 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.18 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.68 (m, 4H), 2.57 (d, *J* = 16.4 Hz, 1H), 2.51 – 2.41 (m, 4H), 2.37 – 2.26 (m, 2H), 2.05 – 1.96 (m, 2H), 1.84 (d, *J* = 1.2 Hz, 3H), 1.71 (d, *J* = 12.1 Hz, 2H), 0.85 – 0.75 (m, 1H), 0.57 – 0.44 (m, 2H), 0.13 (dq, *J* = 5.0, 1.4 Hz, 2H); ESI MS *m*/*z* 746.4 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **27** in 47% yield as a pale yellow solid. Mp: 214–215 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 9.06 (s, 1H), 8.50 (d, *J* = 2.1 Hz, 1H), 7.49 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.37 (td, *J* = 8.0, 7.4, 2.0 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.21 – 7.14 (m, 2H), 7.13 – 7.07 (m, 1H), 7.05 – 7.00 (m, 2H), 6.51 (s, 2H), 5.37 (s, 1H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.28 (t, *J* = 7.5 Hz, 1H), 3.12 (d, *J* = 18.5 Hz, 1H), 2.98 (d, *J* = 16.7 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.61 – 2.52 (m, 1H), 2.46 – 2.34 (m, 5H), 2.29 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.22 – 2.13 (m, 1H), 1.85 (s,

3H), 1.63 (p, *J* = 7.2 Hz, 2H), 1.47 (d, *J* = 11.5 Hz, 1H), 0.78 – 0.66 (m, 1H), 0.51 – 0.36 (m, 2H), 0.17 – 0.00 (m, 2H); ^{13}C NMR (214 MHz, DMSO) δ 168.8, 152.0, 147.2, 143.5, 142.0, 139.3, 137.2, 135.2, 134.2, 132.5, 131.0, 130.5, 130.3, 128.4, 128.2, 128.1, 127.3, 125.9, 125.5, 125.1, 118.5, 117.0, 89.9, 76.4, 59.0, 58.9, 54.6, 47.1, 44.0, 31.9, 31.4, 30.7, 30.5, 23.0, 22.8, 9.1, 3.9; HRMS (ESI) *m/z* calcd for $C_{40}H_{42}N_3O_4$ $[M + H]^+$: 628.31698, found: 628.31533; HPLC (system 1) t_R = 13.29 min, purity = 99.5%.

***N*-(3-((4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-1-hydroxy-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-11-yl)phenyl)acetamide (28).** The bromo compound **60** was reacted with *N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide as described in Step 2 for the preparation of **11** to obtain **75** in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.23 – 7.05 (m, 11H), 7.01 – 6.95 (m, 2H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 1H), 4.03 (t, *J* = 8.0 Hz, 1H), 3.90 (d, *J* = 6.6 Hz, 1H), 3.70 (dt, *J* = 8.1, 6.0 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.17 (m, 2H), 2.78 – 2.65 (m, 5H), 2.46 (h, *J* = 6.7, 5.9 Hz, 5H), 2.37 – 2.28 (m, 2H), 2.23 (s, 3H), 1.90 (d, *J* = 7.5 Hz, 2H), 1.77 – 1.65 (m, 3H), 0.86 – 0.76 (m, 1H), 0.50 (ddt, *J* = 8.1, 4.7, 2.4 Hz, 2H), 0.15 – 0.12 (m, 2H); ESI MS *m*/*z* 746.4 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **28** in 70% yield as a white solid. Mp: 165–166 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.25 – 6.99 (m, 6H), 6.93 (d, *J* = 7.3 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.56 (s, 1H), 3.74 – 3.54 (m, 2H), 3.31 – 2.92 (m, 3H), 2.68 (q, *J* = 17.8, 16.4 Hz, 3H), 2.51 – 2.23 (m, 7H), 2.19 (s, 3H), 1.80 – 1.56 (m, 3H), 0.78 (s, 1H), 0.48 (d, *J* = 7.8 Hz, 2H), 0.18 – 0.04 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 151.9, 145.6, 143.6, 142.3, 139.4, 138.4,

135.3, 131.2, 128.5, 128.2, 127.4, 125.8, 125.6, 120.4, 119.3, 117.4, 90.4, 76.5, 59.8, 59.4, 55.6, 47.8, 44.6, 32.5, 32.1, 31.5, 31.3, 30.5, 29.8, 24.7, 23.5, 9.4, 4.2, 3.7.; HRMS (ESI) *m/z* calcd for $C_{40}H_{42}N_3O_4$ $[M + H]^+$: 628.31698, found: 628.31612; HPLC (system 1) t_R = 13.31 min, purity = 96.5%.

***N*-(4-((4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-1-hydroxy-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-11-yl)phenyl)acetamide (29).** Reaction of the bromo compound **60** with *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide gave **76** in 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 – 8.72 (m, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.49 – 7.43 (m, 2H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.16 – 7.05 (m, 6H), 7.00 – 6.95 (m, 2H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.58 (s, 1H), 4.10 (ddd, *J* = 9.4, 6.9, 5.8 Hz, 1H), 3.98 (ddd, *J* = 9.2, 6.9, 5.9 Hz, 1H), 3.71 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.19 (m, 2H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.78 – 2.66 (m, 4H), 2.56 (d, *J* = 16.5 Hz, 1H), 2.46 (td, *J* = 9.2, 8.5, 5.9 Hz, 4H), 2.36 – 2.25 (m, 2H), 2.21 (s, 3H), 2.02 – 1.92 (m, 2H), 1.62 (dd, *J* = 7.5, 6.5 Hz, 4H), 0.85 – 0.74 (m, 1H), 0.49 (dtd, *J* = 7.9, 4.9, 3.5 Hz, 2H), 0.16 – 0.09 (m, 2H); ESI MS *m/z* 746.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **29** in 72% yield as a white solid. Mp: 173–174 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.13 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.25 – 6.99 (m, 6H), 6.93 (d, *J* = 7.3 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.56 (s, 1H), 3.74 – 3.54 (m, 2H), 3.31 – 2.92 (m, 3H), 2.68 (q, *J* = 17.8, 16.4 Hz, 3H), 2.51 – 2.23 (m, 7H), 2.19 (s, 3H), 1.80 – 1.56 (m, 3H), 0.78 (s, 1H), 0.48 (d, *J* = 7.8 Hz, 2H), 0.18 – 0.04 (m, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 151.9, 145.6, 143.6, 142.3, 139.4, 138.4, 135.3, 131.2, 128.5, 128.2, 127.4, 125.8, 125.6, 120.4, 119.3, 117.4, 90.4, 76.5, 59.8, 59.4, 55.6, 47.8, 44.6, 32.5, 32.1, 31.5, 31.3,

30.5, 29.8, 24.7, 23.5, 9.4, 4.2, 3.7; HRMS (ESI) *m/z* calcd for $C_{40}H_{42}N_3O_4$ $[M + H]^+$: 628.31698, found: 628.31682; HPLC (system 1) t_R = 13.05 min, purity = 98.1%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(1H-pyrrol-1-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (30). A mixture of the bromo compound **60** (0.25 g, 0.4 mmol), 1*H*-pyrrole (28 µL, 0.4 mmol), cesium carbonate (0.2 g, 0.6 mmol), $Pd_2(dba)_3$ (9.9 mg, 10.8 µmol) and tri-*tert*-butylphosphine (10.8 µL, 10.8 µmol) in a toluene (5 mL) was heated at 100 °C for 15 h under nitrogen atmosphere. The mixture was allowed to cool down to room temperature and diluted with water. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) to obtain (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-1,8a-bis(3-phenylpropoxy)-11-(1*H*-pyrrol-1-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (0.17 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.24 – 7.09 (m, 8H), 7.03 – 6.98 (m, 3H), 6.64 (dd, *J* = 8.1, 5.3 Hz, 1H), 6.58 – 6.53 (m, 1H), 6.38 – 6.35 (m, 1H), 5.56 (s, 1H), 4.09 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.99 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.74 – 3.67 (m, 1H), 3.64 (t, *J* = 5.8 Hz, 1H), 3.29 – 3.16 (m, 2H), 2.86 – 2.64 (m, 5H), 2.58 – 2.42 (m, 4H), 2.31 (ddd, *J* = 15.7, 12.2, 7.6 Hz, 2H), 2.03 – 1.90 (m, 2H), 1.80 – 1.64 (m, 3H), 1.57 (d, *J* = 2.1 Hz, 4H), 0.80 (t, *J* = 6.3 Hz, 1H), 0.54 – 0.43 (m, 2H), 0.16 – 0.09 (m, 2H); ESI MS *m*/*z* 678.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **30** in 32% yield as a white solid. Mp: 116–118 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.5 Hz, 1H), 7.17 – 7.05 (m, 4H), 7.01 – 6.96 (m, 2H), 6.91 (t, *J* = 2.2 Hz, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.37 – 6.27 (m, 2H), 5.58 (s, 1H), 3.74 – 3.58 (m, 2H), 3.28 – 3.13

(m, 2H), 2.82 – 2.63 (m, 3H), 2.55 – 2.38 (m, 5H), 2.38 – 2.23 (m, 2H), 1.79 – 1.62 (m, 3H), 0.87 – 0.69 (m, 1H), 0.55 – 0.41 (m, 2H), 0.18 – -0.04 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 143.5, 142.2, 139.6, 139.3, 136.2, 128.5, 128.5, 128.3, 128.2, 127.9, 125.7, 125.7, 119.2, 119.0, 117.3, 111.5, 90.4, 76.5, 59.8, 59.4, 55.5, 47.9, 44.6, 32.4, 31.5, 31.4, 30.5, 23.5, 9.4, 4.2; HRMS (ESI) *m/z* calcd for $C_{36}H_{38}N_3O_3$ $[M + H]^+$: 560.29077, found: 560.2902; HPLC (system 1) t_R = 14.85 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(pyridin-2-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (31). The bromo compound **60** was reacted with pyridin-2-ylboronic acid as described in Step 2 for the preparation of **11** to obtain **77** in 29% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.23 (ddt, *J* = 6.4, 5.5, 1.1 Hz, 4H), 7.19 – 7.10 (m, 5H), 7.04 – 6.96 (m, 2H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.48 (s, 1H), 4.07 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.98 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.69 (dt, *J* = 7.9, 6.0 Hz, 1H), 3.62 (d, *J* = 5.9 Hz, 1H), 3.25 – 3.15 (m, 2H), 2.81 – 2.58 (m, 6H), 2.55 – 2.38 (m, 6H), 2.29 (ddd, *J* = 19.3, 12.4, 7.6 Hz, 2H), 2.03 – 1.92 (m, 2H), 1.85 – 1.61 (m, 4H), 0.85 – 0.72 (m, 1H), 0.55 – 0.43 (m, 2H), 0.11 (dq, *J* = 5.0, 1.3 Hz, 2H); ESI MS *m*/*z* 691.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **31** in 26% yield as a white solid. Mp: 184–185 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.1 Hz, 1H), 8.71 – 8.66 (m, 1H), 7.96 (d, *J* = 2.1 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.26 (ddd, *J* = 7.2, 4.8, 1.3 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.10 – 7.03 (m, 1H), 7.02 – 6.97 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 3.70 (dt, *J* = 8.0, 6.1 Hz, 1H), 3.64 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.17 (m, 2H), 2.88 (d, *J* = 16.6 Hz, 1H), 2.72 (ddt, *J* = 17.1, 11.9, 5.2 Hz, 2H), 2.57 – 2.40 (m, 6H), 2.31 (ddd, *J* = 17.5, 12.8, 6.5 Hz, 2H), 1.71 (ddt, *J* = 18.1, 11.7, 5.5 Hz,

3H), 0.83 – 0.74 (m, 1H), 0.57 – 0.42 (m, 2H), 0.17 – 0.06 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.4, 154.0, 150.2, 146.4, 143.5, 142.4, 139.0, 137.1, 135.9, 134.4, 131.2, 131.1, 128.6, 128.2, 126.0, 125.6, 123.0, 120.8, 119.1, 116.9, 91.0, 59.9, 59.4, 55.6, 47.9, 44.6, 32.5, 31.6, 31.3, 30.5, 29.8, 23.5, 9.4, 4.2; HRMS (ESI) *m/z* calcd for $C_{37}H_{38}N_3O_3$ $[M + H]^+$: 572.29077, found: 572.29036; HPLC (system 2) t_R = 5.76 min, purity = 95.5%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(pyridin-3-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (32). Following the procedure for the preparation of **11**, the bromo compound **60** was reacted 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine to obtain **78** in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.76 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.80 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.38 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.18 – 7.06 (m, 6H), 7.01 – 6.97 (m, 2H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.11 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.99 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.73 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.19 (m, 2H), 2.86 (d, *J* = 16.5 Hz, 1H), 2.78 – 2.69 (m, 4H), 2.59 (d, *J* = 16.5 Hz, 1H), 2.53 – 2.41 (m, 4H), 2.39 – 2.26 (m, 2H), 2.03 – 1.92 (m, 2H), 1.73 (td, *J* = 13.6, 6.0 Hz, 3H), 0.85 – 0.77 (m, 1H), 0.65 – 0.56 (m, 2H), 0.49 (tt, *J* = 8.8, 5.0 Hz, 2H); ESI MS *m/z* 690.4 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **32** in 17% yield as a white solid. Mp: 219–220 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.85 (d, *J* = 2.2 Hz, 1H), 8.64 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.83 (ddd, *J* = 7.9, 2.4, 1.7 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.39 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 7.17 – 7.11 (m, 2H), 7.11 – 7.05 (m, 1H), 7.01 – 6.96 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.64 (s, 1H), 3.73 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.66 (d, *J* = 5.9 Hz, 1H), 3.30 – 3.19 (m, 2H), 2.87 (d, *J* = 16.6 Hz, 1H), 2.80

– 2.67 (m, 2H), 2.58 (d, *J* = 16.5 Hz, 1H), 2.47 (dt, *J* = 12.9, 6.8 Hz, 4H), 2.38 – 2.26 (m, 2H), 1.79 – 1.65 (m, 4H), 0.80 (q, *J* = 6.7 Hz, 1H), 0.58 – 0.42 (m, 2H), 0.23 – 0.07 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.7, 149.2, 148.2, 146.7, 143.6, 142.3, 139.2, 135.6, 134.6, 133.2, 132.9, 131.4, 131.0, 128.5, 128.3, 125.8, 125.7, 123.9, 119.2, 117.1, 91.0, 59.8, 59.4, 55.5, 47.9, 44.6, 32.5, 31.6, 31.5, 30.6, 23.5, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{37}H_{38}N_3O_3$ $[M + H]^+$: 572.29077, found: 572.28940; HPLC (system 2) t_R = 4.58 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(pyridin-4-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (33). A procedure similar to that employed for the preparation of **11** was used. Reaction of the bromo compound **60** with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine gave **79** in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.2 Hz, 1H), 8.70 – 8.66 (m, 2H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.24 – 7.17 (m, 2H), 7.17 – 7.05 (m, 6H), 7.01 – 6.94 (m, 2H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.10 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.99 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.73 (q, *J* = 6.3 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.18 (m, 2H), 2.86 (d, *J* = 16.6 Hz, 1H), 2.80 – 2.66 (m, 4H), 2.58 (d, *J* = 16.5 Hz, 1H), 2.54 – 2.41 (m, 4H), 2.38 – 2.26 (m, 1H), 2.03 – 1.92 (m, 2H), 1.79 – 1.70 (m, 2H), 1.25 (s, 2H), 0.81 (d, *J* = 7.3 Hz, 1H), 0.54 – 0.46 (m, 2H), 0.13 (d, *J* = 3.8 Hz, 2H).; ESI MS *m/z* 690.4 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **33** in 30% yield as a white solid. Mp: 233–234 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 2.0 Hz, 1H), 8.65 – 8.60 (m, 2H), 7.86 (d, *J* = 2.2 Hz, 1H), 7.73 – 7.69 (m, 2H), 7.11 – 7.05 (m, 2H), 7.04 – 6.98 (m, 1H), 6.96 – 6.87 (m, 2H), 6.56 (s, 2H), 5.47 (s, 1H), 3.81 (s, 1H), 3.75 (dt, *J* = 8.5, 5.9 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.29 – 3.22 (m, 1H), 3.08 (d, *J* = 17.0 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.62 – 2.30 (m, 8H), 1.81 – 1.59 (m, 3H), 0.92 – 0.77 (m, 1H), 0.61 –

0.42 (m, 2H), 0.26 – 0.10 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 150.6, 146.5, 144.9, 143.5, 142.2, 139.0, 135.8, 133.4, 131.5, 131.0, 128.5, 128.3, 126.0, 125.7, 121.7, 119.3, 117.0, 90.9, 59.8, 59.5, 55.5, 47.9, 44.6, 32.5, 31.6, 31.5, 30.6, 23.5, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{37}H_{38}N_3O_3$ $[M + H]^+$: 572.29077, found: 572.28991; HPLC (system 2) t_R = 3.81 min, purity 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2-methylpyridin-4-yl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (34). This compound was prepared by the same procedure described for **11**. The bromo compound **60** was reacted with 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine to obtain **80** in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.56 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.23 – 7.18 (m, 3H), 7.17 – 7.06 (m, 7H), 7.00 – 6.95 (m, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.11 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.99 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.73 (dt, *J* = 8.2, 5.9 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.17 (m, 2H), 2.85 (d, *J* = 16.6 Hz, 1H), 2.80 – 2.66 (m, 5H), 2.62 (s, 3H), 2.58 (d, *J* = 16.5 Hz, 1H), 2.51 – 2.41 (m, 5H), 2.39 – 2.25 (m, 2H), 2.02 – 1.92 (m, 2H), 0.80 (dd, *J* = 11.9, 6.8 Hz, 1H), 0.57 – 0.43 (m, 2H), 0.19 – 0.08 (m, 2H); ESI MS *m*/*z* 704.3 $[M + H]^+$. This intermediate was reacted with boron tribromide in CH_2Cl_2 to obtain **34** in 24% yield as a white solid. Mp: 198–200 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.2 Hz, 1H), 8.56 (dd, *J* = 5.3, 0.8 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.23 (dd, *J* = 5.4, 1.7 Hz, 1H), 7.17 – 7.07 (m, 3H), 6.99 – 6.95 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 3.73 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.24 (dt, *J* = 12.7, 5.6 Hz, 2H), 2.86 (d, *J* = 16.6 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.62 (s, 3H), 2.56 (d, *J* = 16.5 Hz, 1H), 2.51 – 2.42 (m, 4H), 2.32 (ddd, *J* =

13.5, 10.8, 7.5 Hz, 2H), 1.78 – 1.67 (m, 4H), 0.86 – 0.74 (m, 1H), 0.55 – 0.44 (m, 2H), 0.17 – 0.09 (m, 2H); ^{13}C NMR (214 MHz, $CDCl_3$) δ 159.4, 154.3, 150.0, 146.6, 143.5, 142.3, 138.9, 135.8, 133.7, 131.4, 131.0, 128.5, 128.5, 128.4, 128.3, 126.1, 125.7, 121.3, 119.2, 118.9, 117.0, 91.1, 59.9, 59.5, 55.6, 47.9, 44.6, 32.5, 31.6, 31.5, 30.6, 24.7, 23.6, 9.4, 4.2; HRMS (ESI) *m/z* calcd for $C_{38}H_{40}N_3O_3$ $[M + H]^+$: 586.30642, found: 586.30626; HPLC (system 1) t_R = 11.48 min, purity 96%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(2-methoxypyridin-4-yl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (35). This compound was prepared by using a procedure similar to that described for the preparation of **19**. The bromo compound **85** was reacted with 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine to obtain **89** in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.2 Hz, 1H), 8.23 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 3H), 7.18 – 7.12 (m, 2H), 7.11 – 7.06 (m, 1H), 7.04 (dd, *J* = 5.4, 1.5 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.90 (dd, *J* = 1.6, 0.7 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.61 (s, 1H), 5.20 – 5.08 (m, 2H), 3.98 (s, 3H), 3.76 – 3.67 (m, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.18 (m, 2H), 2.84 (d, *J* = 16.6 Hz, 1H), 2.73 (td, *J* = 13.0, 11.9, 5.9 Hz, 2H), 2.55 (d, *J* = 16.5 Hz, 1H), 2.46 (dt, *J* = 13.9, 6.8 Hz, 4H), 2.37 – 2.23 (m, 2H), 1.79 – 1.66 (m, 4H), 0.86 – 0.74 (m, 1H), 0.49 (pd, *J* = 8.9, 7.9, 4.1 Hz, 2H), 0.18 – 0.04 (m, 2H); ESI MS *m*/*z* 692.3 $[M + H]^+$. This intermediate was debenzylated by hydrogenation in the presence of 10% of palladium(II) carbon as in step 4 for the preparation of **19** to obtain the title compound **35** in 63% yield as a white solid. Mp: 120–122 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dq, *J* = 10.2, 3.0 Hz, 1H), 8.21 (dp, *J* = 4.7, 2.4 Hz, 1H), 7.42 (dd, *J* = 5.8, 3.0 Hz, 1H), 7.18 – 7.04 (m, 3H), 7.04 – 6.94 (m, 3H), 6.87 (dt, *J* = 4.1, 2.0 Hz, 1H), 6.67

(dt, *J* = 8.5, 3.0 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.61 (s, 1H), 3.98 (s, 3H), 3.72 (q, *J* = 6.6 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.15 (m, 2H), 2.84 (dd, *J* = 16.5, 3.8 Hz, 1H), 2.72 (tt, *J* = 16.1, 8.9 Hz, 2H), 2.54 (d, *J* = 15.8 Hz, 1H), 2.45 (dt, *J* = 12.8, 7.0 Hz, 4H), 2.38 – 2.23 (m, 2H), 1.71 (dq, *J* = 20.8, 12.6, 9.7 Hz, 3H), 0.87 – 0.71 (m, 1H), 0.55 – 0.42 (m, 2H), 0.12 (h, *J* = 5.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 154.3, 147.8, 147.6, 146.4, 143.6, 142.2, 139.1, 135.8, 133.4, 131.3, 131.0, 128.5, 128.2, 125.9, 125.7, 119.2, 117.1, 115.1, 108.7, 90.8, 59.8, 59.4, 55.5, 53.8, 47.9, 44.6, 32.5, 31.5, 31.5, 30.6, 23.5, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{38}H_{40}N_3O_4$ $[M + H]^+$: 602.30133, found: 602.30102; HPLC (system 1) t_R = 14.03 min, purity = 99.2%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(pyrimidin-4-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (36). This compound was prepared by the two step procedure similar to that described for the preparation of **8**. Thus, reaction of **57**[31] with 3-phenylpropyl bromide in the presence of sodium hydride gave (4bS,8R,8aS,13bR)-7-(cyclopropylmethyl)-1,8a-bis(3-phenylpropoxy)-11-(pyrimidin-4-yl)-6,7,8,8a,9,13b-hexahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinoline in 31% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 1.3 Hz, 1H), 9.16 (d, *J* = 1.6 Hz, 1H), 8.80 (d, *J* = 5.3 Hz, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 7.70 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.23 – 7.05 (m, 7H), 7.02 – 6.96 (m, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.59 (s, 1H), 4.09 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.98 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.72 (dt, *J* = 8.4, 6.1 Hz, 1H), 3.66 (d, *J* = 5.9 Hz, 1H), 3.30 – 3.19 (m, 2H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.80 – 2.66 (m, 4H), 2.58 (d, *J* = 16.6 Hz, 1H), 2.52 – 2.41 (m, 4H), 2.38 – 2.24 (m, 2H), 2.01 – 1.90 (m, 2H), 1.78 – 1.67 (m, 3H), 1.62 – 1.58 (m, 1H), 0.85 – 0.74 (m, 1H), 0.56 – 0.43 (m, 2H), 0.19 – 0.07 (m, 2H); ESI MS *m/z* 691.3 $[M + H]^+$. This intermediate was then reacted with boron tribromide

in CH_2Cl_2 to give **36**. Yield = 41%; white solid; Mp: 244–245 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 1.6 Hz, 2H), 9.06 (s, 1H), 8.92 (d, *J* = 5.4 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 8.15 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.14 – 7.07 (m, 2H), 7.06 – 6.99 (m, 1H), 6.95 – 6.89 (m, 2H), 6.51 (s, 2H), 5.42 (s, 1H), 3.65 (td, *J* = 8.3, 7.1, 4.6 Hz, 2H), 3.30 – 3.22 (m, 1H), 3.09 (dd, *J* = 32.2, 17.7 Hz, 2H), 2.68 (dd, *J* = 10.9, 5.1 Hz, 1H), 2.58 (td, *J* = 12.2, 5.2 Hz, 1H), 2.47 – 2.27 (m, 6H), 2.18 (td, *J* = 11.9, 3.6 Hz, 1H), 1.60 (h, *J* = 6.5 Hz, 2H), 1.49 (d, *J* = 11.7 Hz, 1H), 0.81 – 0.69 (m, 1H), 0.51 – 0.38 (m, 2H), 0.17 – 0.02 (m, 2H); ^{13}C NMR (214 MHz, DMSO) δ 160.5, 158.9, 158.4, 155.8, 146.4, 143.4, 141.8, 139.5, 135.9, 131.2, 131.2, 130.8, 128.2, 128.1, 128.1, 125.5, 125.0, 118.8, 117.8, 117.1, 89.5, 76.3, 59.0, 54.7, 47.1, 44.0, 31.7, 31.2, 30.7, 30.5, 9.2, 3.9, 3.4; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}N_4O_3$ [M + H]$^+$: 573.28602, found: 573.28417; HPLC (system 2) t_R = 4.99 min, purity 96.4%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(pyrimidin-5-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (37). This compound was prepared using the same procedure described for **11**. The bromo compound **60** (0.25 g, 0.4 mmol) was reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (0.15 g, 0.7 mmol) in the presence of potassium carbonate (0.15 g, 1.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.04 mmol) to give 0.18 g (71%) of **81**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.86 (s, 2H), 8.77 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.24 – 7.06 (m, 7H), 7.02 – 6.97 (m, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.59 (s, 1H), 4.11 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.99 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.74 (dt, *J* = 7.9, 6.1 Hz, 1H), 3.67 (d, *J* = 5.8 Hz, 1H), 3.29 – 3.21 (m, 2H), 2.88 (d, *J* = 16.6 Hz, 1H), 2.80 – 2.66 (m, 4H), 2.59 (d, *J* = 16.6 Hz, 1H), 2.52 – 2.41 (m, 4H), 2.38 – 2.25 (m, 2H), 2.01 – 1.92 (m, 2H), 1.79 – 1.67 (m, 3H), 1.31 (d, *J* = 4.7 Hz, 1H), 0.80 (q, *J* = 6.8 Hz, 1H), 0.55 – 0.45

(m, 2H), 0.14 (dd, *J* = 2.9, 1.6 Hz, 2H); ESI MS *m*/*z* 691.4 $[M + H]^+$. This intermediate (0.18 g, 0.3 mmol) was reacted with boron tribromide (1.5 mL, 1.5 mmol, 1 M in CH_2Cl_2) to obtain 0.04 g (26%) of **37** as a pale yellow solid. Mp: 153–154 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 9.10 (s, 1H), 9.01 (s, 2H), 7.49 (s, 1H), 7.19 – 7.04 (m, 3H), 6.98 (d, *J* = 7.3 Hz, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.64 (s, 1H), 3.79 – 3.59 (m, 2H), 3.31 – 3.19 (m, 2H), 2.89 (d, *J* = 16.6 Hz, 1H), 2.73 (d, *J* = 10.2 Hz, 2H), 2.61 (d, *J* = 16.7 Hz, 1H), 2.48 (t, *J* = 7.7 Hz, 4H), 2.33 (d, *J* = 12.7 Hz, 2H), 2.17 (s, 1H), 1.80 – 1.62 (m, 3H), 0.80 (s, 1H), 0.49 (d, *J* = 8.1 Hz, 2H), 0.21 – 0.06 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.1, 155.1, 146.5, 143.5, 142.2, 139.1, 135.5, 131.9, 131.2, 130.9, 129.6, 128.5, 128.3, 125.7, 119.4, 117.1, 90.8, 59.8, 59.5, 55.5, 48.0, 44.6, 32.5, 31.6, 30.7, 29.8, 29.5, 23.5, 14.3, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}N_4O_3$ $[M + H]^+$: 573.28602, found: 573.28623; HPLC(system 2) t_R = 4.83 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(pyrazin-2-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (38). This compound was prepared by the procedure similar to that described for the preparation of **8**. Reaction of **58**[31] with 3-phenylpropyl bromide in the presence of sodium hydride gave (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-1,8a-bis(3-phenylpropoxy)-11-(pyrazin-2-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline in 28% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.2 Hz, 1H), 8.99 (d, *J* = 1.6 Hz, 1H), 8.65 (dd, *J* = 2.5, 1.6 Hz, 1H), 8.56 (d, *J* = 2.5 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.22 – 7.05 (m, 8H), 7.02 – 6.97 (m, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.60 (s, 1H), 4.10 (dt, *J* = 9.7, 6.3 Hz, 1H), 3.99 (dt, *J* = 9.7, 6.3 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.22 (m, 2H), 2.98 – 2.86 (m, 1H), 2.78 – 2.68 (m, 4H), 2.59 (d, *J* = 16.6 Hz, 1H), 2.52 – 2.42

(m, 4H), 2.38 – 2.24 (m, 2H), 2.02 – 1.90 (m, 2H), 1.72 (td, *J* = 12.5, 11.3, 5.4 Hz, 3H), 0.85 – 0.75 (m, 1H), 0.56 – 0.44 (m, 2H), 0.19 – 0.08 (m, 2H); ESI MS *m*/*z* 691.3 $[M + H]^+$. This intermediate (0.35 g, 0.5 mmol) was reacted with boron tribromide (3.0 mL, 3.0 mmol, 1 M in CH_2Cl_2) to give 0.11 g (37%) of **38** as a white solid. Mp: 137–138 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* = 2.2 Hz, 1H), 9.11 (d, *J* = 1.6 Hz, 1H), 8.66 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.57 (d, *J* = 2.5 Hz, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.20 – 7.11 (m, 2H), 7.12 – 7.04 (m, 1H), 7.03 – 6.96 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.69 (s, 1H), 5.65 (s, 1H), 3.72 (dt, *J* = 8.1, 6.1 Hz, 1H), 3.66 (d, *J* = 5.8 Hz, 1H), 3.31 – 3.18 (m, 2H), 2.92 (d, *J* = 16.6 Hz, 1H), 2.58 (d, *J* = 16.6 Hz, 1H), 2.53 – 2.40 (m, 4H), 2.38 – 2.26 (m, 2H), 1.79 – 1.61 (m, 5H), 0.79 (q, *J* = 6.5 Hz, 1H), 0.56 – 0.43 (m, 2H), 0.19 – 0.06 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.7, 149.2, 148.2, 146.7, 143.6, 142.3, 139.2, 135.6, 134.6, 133.2, 132.9, 131.4, 131.0, 128.5, 128.3, 125.8, 125.7, 123.9, 119.2, 117.1, 91.0, 59.8, 59.4, 55.5, 47.9, 44.6, 32.5, 31.6, 31.5, 30.6, 23.5, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}N_4O_3$ $[M + H]^+$: 573.28602, found: 573.28543; HPLC (system 2) t_R = 5.19 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-phenylpropoxy)-11-(1H-pyrazol-4-yl)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (39). This compound was prepared using the procedure described for **11**. Reaction of *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate with the bromo compound **60** gave directly the pyrazole intermediate **82** in 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 0.6 Hz, 2H), 7.34 – 7.32 (m, 1H), 7.22 – 7.16 (m, 2H), 7.15 – 7.06 (m, 6H), 7.00 – 6.96 (m, 2H), 6.67 – 6.62 (m, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.56 (s, 1H), 4.10 (dt, *J* = 9.7, 6.3 Hz, 1H), 3.98 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.75 – 3.67 (m, 1H),

3.64 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.18 (m, 2H), 2.84 – 2.65 (m, 5H), 2.57 – 2.41 (m, 5H), 2.37 – 2.25 (m, 2H), 2.01 – 1.89 (m, 2H), 1.79 – 1.65 (m, 3H), 0.85 – 0.76 (m, 1H), 0.54 – 0.44 (m, 2H), 0.14 – 0.12 (m, 2H); ESI MS *m*/*z* 679.4 $[M + H]^+$. This intermediate was then reacted with boron tribromide in CH_2Cl_2 to give **39**. Yield = 50%; white solid; Mp: 223–224 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 9.00 (s, 1H), 8.79 (d, *J* = 2.1 Hz, 1H), 8.28 – 8.24 (m, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.08 – 7.03 (m, 1H), 6.96 – 6.91 (m, 2H), 6.50 (s, 2H), 5.34 (s, 1H), 3.68 – 3.59 (m, 2H), 3.23 (q, *J* = 6.9 Hz, 1H), 3.11 (d, *J* = 18.5 Hz, 1H), 2.89 (d, *J* = 16.8 Hz, 1H), 2.67 (dd, *J* = 11.4, 5.0 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.48 – 2.41 (m, 1H), 2.41 – 2.27 (m, 5H), 2.17 (td, *J* = 11.8, 3.6 Hz, 1H), 1.61 (dq, *J* = 13.8, 6.9 Hz, 2H), 1.46 (d, *J* = 11.3 Hz, 1H), 0.73 (dd, *J* = 11.9, 5.9 Hz, 1H), 0.51 – 0.36 (m, 2H), 0.09 (m, 2H); ^{13}C NMR (151 MHz, DMSO) δ 150.6, 144.7, 143.4, 141.9, 139.4, 136.5, 133.2, 131.0, 130.8, 128.4, 128.2, 128.1, 126.1, 125.5, 125.0, 118.4, 117.6, 117.0, 89.9, 76.3, 59.0, 58.7, 54.7, 46.9, 44.0, 31.7, 31.3, 30.7, 30.5, 22.9, 9.2, 3.8; HRMS (ESI) *m/z* calcd for $C_{35}H_{37}N_4O_3$ $[M + H]^+$: 561.28602, found: 561.28488; HPLC (system 1) t_R = 12.06 min, purity = 99.6%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(1-methyl-1H-pyrazol-4-yl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (40). This compound was prepared according to the procedure described for the preparation of **11**. The bromo compound **60** was reacted with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to obtain **83** in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.1 Hz, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 7.29 (d, *J* = 2.1 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.18 – 7.06 (m, 6H), 7.01 – 6.96 (m, 2H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 5.55 (s, 1H), 4.10 (dt, *J* = 9.6, 6.4 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.95 (s, 3H), 3.70 (dt, *J* = 8.0, 5.9

Hz, 1H), 3.64 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.17 (m, 2H), 2.82 – 2.67 (m, 5H), 2.56 – 2.41 (m, 5H), 2.38 – 2.24 (m, 2H), 2.02 – 1.92 (m, 2H), 1.79 – 1.69 (m, 2H), 1.26 (s, 1H), 0.85 – 0.75 (m, 1H), 0.56 – 0.44 (m, 2H), 0.12 (dq, *J* = 4.4, 1.3 Hz, 2H); ESI MS *m*/*z* 693.3 $[M + H]^+$. This intermediate was then reacted with boron tribromide in CH_2Cl_2 to obtain **40** in 37% yield as a pale yellow solid. Mp: 189–190 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 9.5 Hz, 1H), 7.68 (d, *J* = 3.9 Hz, 1H), 7.50 (d, *J* = 9.1 Hz, 1H), 7.23 (d, *J* = 5.3 Hz, 1H), 7.18 – 7.04 (m, 3H), 6.97 (d, *J* = 7.3 Hz, 2H), 6.68 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.57 (s, 1H), 3.92 (d, *J* = 3.5 Hz, 3H), 3.69 (q, *J* = 6.6 Hz, 1H), 3.62 (d, *J* = 5.8 Hz, 1H), 3.28 – 3.15 (m, 2H), 2.81 – 2.62 (m, 3H), 2.45 (dt, *J* = 12.9, 6.9 Hz, 6H), 2.36 – 2.26 (m, 2H), 1.80 – 1.61 (m, 3H), 0.86 – 0.72 (m, 1H), 0.48 (dp, *J* = 9.6, 5.0 Hz, 2H), 0.18 – 0.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 144.5, 143.7, 142.3, 139.6, 136.8, 133.6, 131.3, 131.0, 128.5, 128.2, 128.0, 127.2, 125.6, 125.4, 119.1, 119.0, 117.4, 90.4, 76.5, 59.8, 59.3, 55.5, 47.7, 44.6, 39.2, 32.4, 31.5, 31.1, 30.5, 23.5, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{36}H_{39}N_4O_3$ $[M + H]^+$: 575.30167, found: 575.30177; HPLC (system 2) t_R = 4.99 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(3-methylisoxazol-4-yl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (41). This compound was prepared by using a procedure similar to that described for the preparation of **11**. The bromo compound **60** was reacted with 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole to obtain **84** in 30% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.40 (s, 1H), 7.24 – 7.08 (m, 9H), 7.01 – 6.96 (m, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.56 (s, 1H), 4.11 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.99 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.74 (dt, *J* = 8.1, 5.9 Hz, 1H), 3.65 (d, *J* = 5.9 Hz, 1H), 3.30 – 3.17 (m, 2H), 2.82

(d, J = 16.5 Hz, 1H), 2.78 – 2.66 (m, 4H), 2.55 (d, J = 16.5 Hz, 1H), 2.45 (ddt, J = 9.8, 5.9, 3.3 Hz, 4H), 2.37 – 2.25 (m, 5H), 2.02 – 1.92 (m, 2H), 1.72 (td, J = 14.3, 6.5 Hz, 3H), 0.80 (q, J = 6.6 Hz, 1H), 0.50 (tt, J = 7.4, 4.0 Hz, 2H), 0.13 (dq, J = 4.0, 1.2 Hz, 2H); ESI MS m/z 694.4 $[M + H]^+$. This intermediate was then reacted with boron tribromide in CH_2Cl_2 to obtain **41** in 40% yield as a white solid. Mp: 191–192 °C; TLC (10% MeOH/CH_2Cl_2): Rf = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 2.1 Hz, 1H), 8.44 (s, 1H), 7.26 – 7.24 (m, 1H), 7.19 – 7.09 (m, 3H), 7.02 – 6.95 (m, 2H), 6.67 (dd, J = 8.1, 0.7 Hz, 1H), 6.60 – 6.55 (m, 1H), 5.59 (s, 1H), 3.74 (dt, J = 8.1, 5.8 Hz, 1H), 3.65 (d, J = 5.8 Hz, 1H), 3.29 – 3.17 (m, 2H), 2.86 – 2.66 (m, 3H), 2.54 (d, J = 16.6 Hz, 1H), 2.45 (dt, J = 11.6, 6.3 Hz, 4H), 2.37 – 2.28 (m, 5H), 1.80 – 1.65 (m, 4H), 0.87 – 0.69 (m, 1H), 0.49 (dp, J = 9.2, 4.9 Hz, 2H), 0.12 (t, J = 5.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.4, 155.7, 153.3, 147.1, 143.4, 142.3, 138.9, 136.5, 131.4, 131.0, 128.5, 128.3, 126.1, 125.8, 125.2, 119.3, 117.5, 116.9, 91.0, 59.8, 59.6, 55.5, 47.9, 44.6, 32.6, 31.7, 31.5, 30.6, 23.5, 10.9, 9.4, 4.2, 3.6; HRMS (ESI) m/z calcd for $C_{36}H_{38}N_3O_3$ $[M + H]^+$: 576.28568, found: 576.28601; HPLC (system 2) t_R = 6.28 min, purity = 96.8%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-(5-methyl-1,3,4-oxadiazol-2-yl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (42). *Step 1*. A mixture of 3-*O*-benzylnaltrexone[56] (10 g, 23.2 mmol), ethyl 2-formyl-3-oxopropanoate (4.0 g, 27.8 mmol) and ammonium acetate (5.4 g, 69.5 mmol) in glacial acetic acid (45 mL) was stirred under reflux at 110 °C for 18 h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue was suspended in water (40 mL), and the pH of the mixture was adjusted to 7 with concentrated aqueous NH_4OH. The resulting suspension was extracted with $CHCl_3$ (3 × 80 mL) and washed with water (160 mL). The extract was dried, and the solvent was removed under reduced pressure. The residue was purified by flash

chromatography over a column of silica using hexanes/EtOAc (40:60) as the eluent to yield **90** (0.9 g, 7.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.24 (m, 1H), 7.24 – 7.21 (m, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.56 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.56 (s, 1H), 5.17 – 5.07 (m, 2H), 4.38 (qd, *J* = 7.2, 0.7 Hz, 2H), 3.34 (s, 1H), 3.16 (d, *J* = 18.7 Hz, 1H), 2.81 – 2.64 (m, 4H), 2.57 – 2.16 (m, 5H), 1.88 – 1.79 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 1H), 0.61 – 0.53 (m, 2H), 0.17 (d, *J* = 5.1 Hz, 2H). ESI MS *m*/*z* 539.2 $[M + H]^+$.

Step 2. A mixture of the above intermediate **90** (0.9 g, 1.7 mmol) and hydrazine hydrate (1.1 g, 16.9 mmol) in ethanol (10 mL) was heated at 80 °C for overnight. The solvent was evaporated to obtain (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-8a-hydroxy-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline-11-carbohydrazide ESI MS *m*/*z* 525.2 $[M + H]^+$. The crude product was used as such in the next step.

Step 3. The above intermediate (0.9 g, 1.7 mmol) and 1,1,1-triethoxyethane (0.8 g, 5.1 mmol) in acetic acid (15 mL) was heated at 150 °C for 3h. The reaction mixture was cooled down to room temperature and solvent was removed under vacuum. The residue was neutralized by NH_4OH and extracted with $CHCl_3$ (3 × 80 mL) and washed with water (20 mL). The extract was dried, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over a column of silica using hexanes/EtOAc (40:60) as the eluent to yield **91** (0.6 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.27 – 7.19 (m, 3H), 6.70 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.57 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.58 (d, *J* = 0.9 Hz, 1H), 5.31 – 4.98 (m, 2H), 3.17 (d, *J* = 18.8 Hz, 1H), 2.78 (d, *J* = 15.3 Hz, 3H), 2.63 (s, 3H), 2.41 (d, *J* = 33.9 Hz, 2H), 1.85 (d, *J* = 12.2 Hz, 1H), 1.59 (s, 4H), 0.92 (s, 1H), 0.59 (s, 2H), 0.19 (s, 2H). ESI MS *m*/*z* 549.2 $[M + H]^+$.

Step 4. The above intermediate **91** (0.5 g, 0.9 mmol) was reacted with 3-phenylpropyl bromide (0.5 g, 2.7 mmol) in the presence of sodium hydride (0.15 g, 3.7 mmol, 60% dispersion in mineral oil) to obtain (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-(5-methyl-1,3,4-oxadiazol-2-yl)-8a-(3-phenylpropoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (0.23 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 2.1 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.24 (dtt, *J* = 7.2, 5.0, 1.9 Hz, 3H), 7.20 – 7.15 (m, 2H), 7.13 – 7.05 (m, 1H), 7.03 – 6.97 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 1H), 5.58 (s, 1H), 5.16 – 5.03 (m, 2H), 3.76 – 3.57 (m, 2H), 3.26 – 3.11 (m, 2H), 2.99 – 2.82 (m, 1H), 2.78 – 2.21 (m, 11H), 1.77 – 1.65 (m, 2H), 1.63 (s, 2H), 0.85 – 0.73 (m, 1H), 0.49 (dq, *J* = 8.5, 4.4 Hz, 2H), 0.12 (p, *J* = 1.9 Hz, 2H); ESI MS *m/z* 667.3 $[M + H]^+$.

Step 5. The above intermediate (0.23 g, 0.3 mmol) was debenzylated with 10% of palladium(II) carbon (23 mg, 10 wt%) under H_2 atmosphere to give (0.13 g, 63%) of the desired compound **42** as a white solid. Mp: 128–130 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.60; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (dt, *J* = 4.7, 2.2 Hz, 1H), 7.95 (s, 1H), 7.17 (ddd, *J* = 7.5, 6.4, 1.4 Hz, 2H), 7.12 – 7.06 (m, 1H), 7.03 – 6.97 (m, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.57 (d, *J* = 1.8 Hz, 1H), 3.72 (dt, *J* = 8.3, 6.1 Hz, 1H), 3.65 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.18 (m, 2H), 2.87 (dd, *J* = 16.7, 2.0 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.64 (s, 3H), 2.57 – 2.39 (m, 5H), 2.39 – 2.21 (m, 2H), 1.70 (tdd, *J* = 11.7, 9.2, 5.0 Hz, 3H), 0.84 – 0.72 (m, 1H), 0.58 – 0.42 (m, 2H), 0.18 – 0.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 162.7, 156.9, 145.8, 142.2, 135.4, 131.8, 131.8, 130.8, 128.5, 128.3, 125.7, 119.8, 119.4, 117.3, 90.6, 76.5, 59.8, 59.5, 55.4, 47.9, 47.9, 44.6, 32.5, 31.6, 31.3, 30.5, 23.5, 11.3, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{35}H_{37}N_4O_4$ $[M + H]^+$: 577.28093, found: 577.27998; HPLC (system 1) t_R = 13.17 min, purity 98.6%.

(4b*S*,8*R*,8a*S*,13b*R*)-11-(4-Chlorophenyl)-7-(cyclopropylmethyl)-8a-(3-(pyridin-4-yl)propoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (43). *Step 1*. Compound **7**[29] (2 g, 4.1 mmol) was reacted with benzyl bromide (0.6 mL, 4.9 mmol) in the presence of potassium carbonate (1.1 g, 8.2 mmol) to obtain **92** (1.3 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (td, *J* = 7.0, 6.6, 2.2 Hz, 1H), 7.85 – 7.76 (m, 1H), 7.30 (dq, *J* = 6.1, 3.6, 3.2 Hz, 3H), 7.21 (dd, *J* = 16.3, 8.6 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 7.01 – 6.88 (m, 2H), 5.77 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 43.5 Hz, 2H), 3.81 (dt, *J* = 27.1, 6.1 Hz, 2H), 3.05 (t, *J* = 6.0 Hz, 1H), 2.88 (t, *J* = 6.2 Hz, 3H), 2.76 (t, *J* = 5.1 Hz, 2H), 1.68 (dp, *J* = 40.9, 5.6 Hz, 5H), 1.48 (d, *J* = 6.3 Hz, 1H); ESI MS *m*/*z* 577.2 $[M + H]^+$.

Step 2. The above intermediate **92** (7.0 g, 12.1 mmol) was reacted with 3-bromoprop-1-ene (2.9 g, 24.3 mmol) in the presence of sodium hydride (2.9 g, 72.8 mmol, 60% dispersion in mineral oil) to obtain **93** (3.6 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, *J* = 2.3 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.53 (dt, *J* = 9.0, 1.6 Hz, 1H), 7.25 (ddt, *J* = 5.1, 4.1, 1.3 Hz, 2H), 6.73 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.41 (s, 1H), 5.10 – 4.83 (m, 2H), 4.16 (dd, *J* = 13.0, 5.0 Hz, 1H), 3.87 (dd, *J* = 12.7, 5.1 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.46 – 3.33 (m, 1H), 3.39 – 3.19 (m, 2H), 3.32 (s, 9H), 3.21 – 2.96 (m, 1H), 2.66 (dd, *J* = 11.8, 4.2 Hz, 1H), 2.61 – 2.44 (m, 3H), 2.42 – 2.30 (m, 2H), 2.14 (dd, *J* = 12.5, 8.9 Hz, 1H), 1.47 (d, *J* = 12.0 Hz, 1H), 0.47 (t, *J* = 7.8 Hz, 1H), 0.11 (s, 1H).

Step 3. A mixture of the above intermediate **93** (0.28 g, 0.5 mmol), 4-bromopyridine hydrochloride (0.09 g, 0.54 mmol), potassium carbonate (0.14 g, 1.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.005 g, 0.005 mmol) and diacetoxypalladium (0.001 g, 0.005 mmol) in DMF (8 mL) was heated at 130 °C for 1 h under an atmosphere of argon. The mixture was allowed to cool down to room temperature and was diluted with water. The aqueous

layer was extracted with ethyl acetate (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) to obtain 0.19 g (59%) of **94**. The crude product was uses as such in the next step.

Step 4. The above intermediate **94** (0.16 g, 0.2 mmol) treated with 10% of palladium(II) carbon (16.0 mg, 10 wt%) under H_2 atmosphere at 40 psi to give **95** which was used for next step without purification.

Step 5. The above intermediate **95** (0.15 g, 0.2 mmol) was refluxed in 2,2,2-trifluoroacetic acid (3 mL). The mixture was cooled to room temperature and the acid was removed under reduced pressure. The residue was dissolved in water and neutralized by aqueous NH_4OH. The resulting suspension was extracted with EtOAc (3 × 10 mL) and washed with water (10 mL). The extract was dried, and the solvent was removed under reduced pressure. The residue was purified by chromatography over a column of silica gel using $CHCl_3$/MeOH (95:5) as the eluent to obtain 45 mg (35%) of **43** as a white solid. Mp: 150–154 °C; TLC (7.5% MeOH/$CHCl_3$): R*f* = 0.63; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.02 (s, 1H), 8.80 (d, *J* = 2.3 Hz, 1H), 8.33 – 8.22 (m, 2H), 7.76 – 7.65 (m, 3H), 7.62 – 7.42 (m, 2H), 6.95 – 6.88 (m, 2H), 6.49 (s, 2H), 5.36 (s, 1H), 3.61 (dd, *J* = 10.0, 5.6 Hz, 2H), 3.29 – 3.20 (m, 1H), 3.10 (d, *J* = 18.5 Hz, 1H), 2.97 (d, *J* = 16.9 Hz, 1H), 2.64 (dt, *J* = 16.6, 8.4 Hz, 1H), 2.59 – 2.23 (m, 6H), 2.15 (dd, *J* = 12.9, 9.4 Hz, 1H), 1.71 – 1.53 (m, 1H), 1.61 (s, 1H), 1.46 (d, *J* = 11.8 Hz, 1H), 0.82 (s, 1H), 0.42 (d, *J* = 7.9 Hz, 3H), 0.09 (t, *J* = 13.4 Hz, 3H); HRMS (ESI) *m/z* calcd for $C_{37}H_{37}ClN_3O_3$ $[M + H]^+$: 606.25180, found: 606.24893; HPLC (system 2) t_R = 3.73 min, purity 96.2%.

(4bS,8R,8aS,13bR)-11-(4-Chlorophenyl)-7-(cyclopropylmethyl)-8a-(2-phenoxyethoxy)-6,7,8,8a,9,13b-hexahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinolin-1-ol (44).

To a solution of 2-phenoxyethanol (2.0 g, 14.5 mmol) in CH_2Cl_2 (200 mL) and anhydrous triethylamine (2.2 g, 21.7 mmol) cooled to -30 °C under argon was added slowly trifluoromethanesulfonic anhydride (4.90 g, 17.37 mmol). The solution was stirred at -30 °C for 1 h. The solution was diluted with ethyl acetate and washed with 20% HCl, saturated aqueous $NaHCO_3$ and brine. Organic layers were collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain a red viscous oil. The crude 2-phenoxyethyl trifluoromethanesulfonate thus obtained (0.41 g, 1.5 mmol) was added to a solution of **7**[29] (0.3 g, 0.8 mmol) in nitromethane (2.5 mL). To the reaction mixture was added 1,2,2,6,6-pentamethylpiperidine (0.19 g, 1.2 mmol) and the reaction mixture was heated at 50 °C for 1.5 h. Solvent was removed under reduced pressure. The residue was treated with 10% HCl and then neutralized with aqueous NH_4OH. The mixture was diluted with water and extracted with $CHCl_3$ (3 × 20 mL). Organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) to obtain (0.35 g, 81%) of **96**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (d, J = 2.0 Hz, 1H), 8.74 (d, J = 1.9 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.74 – 7.64 (m, 2H), 7.30 – 7.18 (m, 4H), 7.00 – 6.80 (m, 8H), 6.78 (d, J = 8.3 Hz, 1H), 6.40 (s, 1H), 5.41 (td, J = 9.5, 8.9, 4.7 Hz, 1H), 5.29 (d, J = 14.2 Hz, 1H), 5.18 (s, 1H), 4.70 (s, 1H), 4.76 – 4.60 (m, 1H), 4.38 – 4.20 (m, 2H), 4.23 – 4.10 (m, 1H), 4.16 (s, 2H), 3.39 (d, J = 6.2 Hz, 1H), 3.19 (d, J = 19.0 Hz, 1H), 3.03 (d, J = 17.0 Hz, 1H), 2.82 – 2.65 (m, 3H), 2.43 (d, J = 6.5 Hz, 3H), 2.25 – 2.13 (m, 1H), 1.70 (d, J = 12.4 Hz, 1H), 0.51 (dd, J = 8.8, 6.7 Hz, 2H), 0.16 (d, J = 4.9 Hz, 2H); ESI MS m/z 727.3 $[M + H]^+$. Phenolic-O-delalkylation of this intermediate (0.20 g, 0.3 mmol) with boron tribromide (0.35 g, 1.4 mmol) and the usual workup gave 0.1 g (59%) of **44** as a white solid. Mp: 156–158 °C; TLC (7.5% MeOH/CH_2Cl_2): Rf = 0.14; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 1.9 Hz, 1H), 9.39 (s,

1H), 8.73 (d, *J* = 1.9 Hz, 1H), 7.96 – 7.84 (m, 2H), 7.74 – 7.62 (m, 2H), 7.33 – 7.22 (m, 2H), 6.99 – 6.88 (m, 3H), 6.61 (q, *J* = 8.1 Hz, 2H), 6.34 (s, 1H), 5.44 (ddd, *J* = 13.7, 9.2, 4.0 Hz, 1H), 5.30 (d, *J* = 14.1 Hz, 1H), 5.14 (s, 1H), 4.79 – 4.63 (m, 1H), 3.48 – 3.32 (m, 2H), 3.19 – 3.07 (m, 1H), 3.01 (d, *J* = 17.0 Hz, 1H), 2.75 (d, *J* = 16.5 Hz, 2H), 2.65 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.41 (d, *J* = 6.6 Hz, 3H), 2.25 – 2.13 (m, 1H), 1.68 (d, *J* = 11.9 Hz, 1H), 0.49 (q, *J* = 9.4, 8.6 Hz, 2H), 0.15 (d, *J* = 4.9 Hz, 2H); HRMS (ESI) *m/z* calcd for $C_{37}H_{36}ClN_2O_4$ $[M + H]^+$: 607.23581, found: 607.23475; HPLC (system 2) t_R = 3.74 min, purity 96.8%.

(4bS,8R,8aS,13bR)-11-(4-Chlorophenyl)-7-(cyclopropylmethyl)-8a-(quinolin-2-ylmethoxy)-6,7,8,8a,9,13b-hexahydro-5H-4,8-methanobenzofuro[3,2-h]pyrido[3,4-g]quinolin-1-ol (45). *Step 1*. Compound **7**[29] (0.29 g, 0.6 mmol) was reacted with 2-(chloromethyl)quinoline (0.22 g, 1.3 mmol) in the presence of sodium hydride (0.14 g, 3.4 mmol, 60% dispersion in mineral oil) to obtain 0.2 g (46%) of **97**. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.59 (s, 1H), 9.52 (s, 1H), 9.39 (s, 1H), 8.74 (s, 1H), 8.29 (d, *J* = 1.0 Hz, 0H), 8.00 – 7.91 (m, 1H), 7.94 – 7.84 (m, 2H), 7.77 – 7.60 (m, 2H), 7.27 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.06 – 6.84 (m, 4H), 6.62 (p, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 5.44 (dd, *J* = 13.1, 8.5 Hz, 1H), 5.31 (d, *J* = 14.6 Hz, 1H), 5.14 (s, 1H), 4.74 (s, 1H), 3.49 – 3.20 (m, 3H), 3.18 – 3.07 (m, 1H), 3.02 (dd, *J* = 18.2, 9.1 Hz, 1H), 2.75 (d, *J* = 16.6 Hz, 2H), 2.71 – 2.61 (m, 1H), 2.65 – 2.49 (m, 1H), 2.51 – 2.32 (m, 4H), 2.21 (d, *J* = 11.3 Hz, 1H), 1.68 (d, *J* = 12.3 Hz, 1H), 0.92 (s, 1H), 0.50 (t, *J* = 7.9 Hz, 2H), 0.15 (d, *J* = 5.0 Hz, 2H).; ESI MS *m*/*z* 769.3 $[M + H]^+$.

Step 2. The above intermediate **97** (0.28 g, 0.4 mmol) was reacted with boron tribromide (0.55 g, 2.2 mmol) and following the usual workup and purification 0.01 g (5%) of **45** was obtained as a white solid. Mp: 152–154 °C; TLC (7.5% MeOH/$CHCl_3$): R*f* = 0.37; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.05 (s, 1H), 8.75 (d, *J* = 2.2 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 7.83 (dd, *J* = 10.2,

8.5 Hz, 2H), 7.76 – 7.55 (m, 2H), 7.53 – 7.43 (m, 4H), 6.58 – 6.47 (m, 2H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.94 (d, *J* = 12.6 Hz, 1H), 4.57 (d, *J* = 12.6 Hz, 1H), 3.90 (d, *J* = 5.8 Hz, 1H), 3.30 – 3.09 (m, 3H), 2.80 (dd, *J* = 11.5, 4.9 Hz, 1H), 2.72 – 2.31 (m, 6H), 2.31 – 2.19 (m, 1H), 1.56 (d, *J* = 11.1 Hz, 1H), 0.84 (s, 1H), 0.49 – 0.38 (m, 1H), 0.42 (s, 1H), 0.17 – 0.03 (m, 2H).; HRMS (ESI) *m/z* calcd for $C_{39}H_{35}ClN_3O_3$ $[M + H]^+$: 629.23937, found: 629.23736; HPLC (system 3) t_R = 2.26 min, purity 95.9%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-phenyl-8a-(3-(pyridin-3-yl)propoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (46). This compound was prepared by a procedure similar to that employed for the preparation of **43**. *Step 1.* Compound **54**[29] (5 g, 11.1 mmol) was reacted with benzyl bromide (1.6 mL, 13.3 mmol) in the presence of potassium carbonate (3.1 g, 22.1 mmol) to obtain 1.7 g (29%) of **98**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 – 8.76 (m, 1H), 7.53 (d, *J* = 7.2 Hz, 3H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.35 (m, 1H), 7.33 – 7.28 (m, 2H), 7.27 – 7.20 (m, 3H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 5.62 (s, 1H), 5.23 – 5.09 (m, 2H), 4.95 (s, 1H), 3.32 (d, *J* = 6.4 Hz, 1H), 3.16 (d, *J* = 18.7 Hz, 1H), 2.85 – 2.63 (m, 4H), 2.52 – 2.30 (m, 4H), 1.85 (d, *J* = 12.6 Hz, 1H), 0.99 – 0.83 (m, 1H), 0.64 – 0.50 (m, 2H), 0.25 – 0.14 (m, 2H); ESI MS *m*/*z* 543.3 $[M + H]^+$.

Step 2. The above intermediate **98** (1.5 g, 2.8 mmol) was reacted with 3-bromoprop-1-ene (1.0 ml, 11.1 mmol) in the presence of sodium hydride (0.7 g, 16.6 mmol, 60% dispersion in mineral oil) to obtain (4b*S*,8*R*,8a*S*,13b*R*)-8a-(allyloxy)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-phenyl-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (1.6 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.1 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.40 – 7.29 (m, 2H), 7.27 – 7.16 (m, 3H), 6.68 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.85 – 5.71 (m, 1H), 5.65 (s, 1H), 5.24 – 5.09 (m, 2H), 5.05 (dt, *J* = 17.2, 1.9 Hz, 1H), 4.96

(dd, *J* = 10.4, 2.0 Hz, 1H), 4.31 – 4.22 (m, 1H), 3.95 – 3.86 (m, 1H), 3.71 (d, *J* = 5.7 Hz, 1H), 3.24 (d, *J* = 18.5 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.86 (d, *J* = 4.1 Hz, 1H), 2.73 (tt, *J* = 12.0, 5.1 Hz, 2H), 2.60 (d, *J* = 16.5 Hz, 1H), 2.49 (dt, *J* = 19.0, 6.5 Hz, 2H), 2.41 – 2.26 (m, 2H), 1.79 – 1.63 (m, 1H), 0.91 (q, *J* = 6.6 Hz, 1H), 0.55 (p, *J* = 9.1 Hz, 2H), 0.18 (d, *J* = 4.8 Hz, 2H); ESI MS *m*/*z* 583.3 $[M + H]^+$.

Step 3. The above intermediate (0.4 g, 0.7 mmol), was reacted with 3-bromopyridine (0.11 g, 0.7 mmol), potassium carbonate (0.1 g, 0.7 mmol), tetrakis(triphenylphosphine)palladium(0) (0.008 g, 0.007 mmol) and diacetoxypalladium (0.002 g, 0.007 mmol) in DMF (8 mL) at 130 °C for 1 h. Workup of the reaction mixture and purification by column chromatography on silica gel eluting with $CHCl_3$/MeOH (95:5) gave 0.10 g (22%) of (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-phenyl-8a-(((E)-3-(pyridin-3-yl)allyl)oxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.84 – 8.72 (m, 2H), 8.38 – 8.27 (m, 2H), 8.24 – 8.15 (m, 1H), 7.75 – 7.57 (m, 5H), 7.60 – 7.35 (m, 5H), 7.29 – 7.20 (m, 9H), 7.24 – 7.10 (m, 1H), 6.99 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.80 – 6.71 (m, 1H), 6.62 (dd, *J* = 8.2, 6.4 Hz, 1H), 6.56 – 6.48 (m, 1H), 5.53 (d, *J* = 3.1 Hz, 1H), 5.45 (s, 0H), 5.08 – 4.90 (m, 3H), 4.66 – 4.54 (m, 1H), 3.87 (d, *J* = 5.8 Hz, 1H), 3.80 (s, 1H), 3.25 – 3.12 (m, 3H), 3.08 – 2.91 (m, 2H), 2.69 (d, *J* = 12.7 Hz, 0H), 2.56 (s, 1H), 2.53 (d, *J* = 7.9 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.26 – 2.14 (m, 1H), 1.65 – 1.43 (m, 2H), 0.95 (s, 0H), 0.78 (s, 1H), 0.66 (d, *J* = 6.3 Hz, 0H), 0.50 – 0.37 (m, 2H), 0.11 (td, *J* = 9.2, 8.8, 4.6 Hz, 1H), 0.07 (s, 3H).

Step 4. The above intermediate (0.26 g, 0.4 mmol) treated with 10% of palladium(II) carbon (50.0 mg, 10 wt%) under H_2 atmosphere at 40 psi to 0.06 g (25%) of **46** as a white solid. Mp: 126–130 °C; TLC (7.5% MeOH/$CHCl_3$): R*f* = 0.47; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.02 (s, 1H), 8.78 (d, *J* = 2.2 Hz, 1H), 8.32 – 8.23 (m, 3H), 8.19 (d, *J* = 2.2 Hz, 1H), 7.71 (d, *J* = 2.2 Hz, 1H),

7.72 – 7.61 (m, 2H), 7.54 – 7.43 (m, 2H), 7.48 – 7.29 (m, 3H), 7.12 (ddd, *J* = 7.7, 4.7, 0.9 Hz, 1H), 6.48 (d, *J* = 7.7 Hz, 2H), 5.37 (s, 1H), 3.62 (t, *J* = 7.4 Hz, 2H), 3.10 (d, *J* = 18.5 Hz, 1H), 2.99 (d, *J* = 16.9 Hz, 1H), 2.65 (dd, *J* = 11.2, 5.1 Hz, 1H), 2.54 (td, *J* = 12.0, 5.0 Hz, 1H), 2.49 – 2.22 (m, 6H), 2.21 – 2.10 (m, 1H), 1.61 (dp, *J* = 13.4, 6.8 Hz, 2H), 1.45 (t, *J* = 11.4 Hz, 1H), 0.51 – 0.33 (m, 2H), 0.10 (dd, *J* = 10.1, 4.7 Hz, 0H); HRMS (ESI) *m/z* calcd for $C_{37}H_{38}N_3O_3$ $[M + H]^+$: 572.29077, found: 572.29104; HPLC (system 2) t_R = 3.51 min, purity 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-phenyl-8a-(3-(pyridin-4-yl)propoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (47). The allyloxy intermediate obtained in Step 2 in the preparation of **46** (0.4 g, 0.7 mmol) was reacted with 4-bromopyridine hydrochloride (0.13 g, 0.8 mmol) in the presence of potassium carbonate (0.29 g, 2.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.008 g, 0.007 mmol) and diacetoxypalladium (0.002 g, 0.007 mmol) in DMF (8 mL) to obtain 0.12 g (27%) of (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-phenyl-8a-(((*E*)-3-(pyridin-4-yl)allyl)oxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline. This intermediate 0.12 g, 0.2 mmol) was treated with 10% of palladium(II) carbon (20.0 mg, 10 wt%) under H_2 atmosphere at 40 psi to obtain 0.06 g (54%) of **47** as a white solid. Mp: 136–138 °C; TLC (7.5% MeOH/$CHCl_3$): R*f* = 0.30; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.02 (s, 1H), 8.80 (d, *J* = 2.2 Hz, 1H), 8.30 (d, *J* = 1.1 Hz, 1H), 8.29 – 8.22 (m, 2H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 5.6 Hz, 2H), 6.49 (s, 2H), 5.36 (s, 1H), 3.63 (d, *J* = 6.1 Hz, 2H), 3.11 (d, *J* = 18.5 Hz, 1H), 2.98 (d, *J* = 16.9 Hz, 1H), 2.65 (d, *J* = 11.6 Hz, 2H), 2.54 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.46 – 2.23 (m, 5H), 2.16 (dd, *J* = 12.9, 9.4 Hz, 1H), 1.61 (dt, *J* = 14.5, 7.4 Hz, 2H), 1.46 (d, *J* = 11.9 Hz, 1H), 1.21 (s, 1H), 0.42 (d, *J* =

8.2 Hz, 2H), 0.11 (d, *J* = 10.9 Hz, 1H), 0.05 (s, 1H); HRMS (ESI) *m/z* calcd for $C_{37}H_{38}N_3O_3$ [M + H]$^+$: 572.29077, found: 572.29104; HPLC (system 2) t_R = 2.97 min, purity 97%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-8a-(3-(4-fluorophenyl)propoxy)-11-phenyl-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (48). *Step 1*. Compound **54**[29] (0. 55 g, 1.22 mmol) was dissolved in anhydrous DMF (8 mL) under argon atmosphere and the mixture was cooled to 0 °C. Sodium hydride (0.292 g, 7.29 mmol) was added and the mixture was stirred at 0 °C for 5 min. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 20 min. Reaction mixture was cooled again to 0 ° C and 1-(3-bromopropyl)-4-fluorobenzene (1.055 g, 4.86 mmol) was added. Ice bath was removed and the reaction mixture was allowed to attain room temperature and stir for another 5 h. The reaction mixture was then quenched by adding ice-cold water and the mixture was extracted with CH_2Cl_2 (3 X 60 mL) and washed with brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexanes/EtOAc as eluent to obtain 0.175 g (19.9%) of (4b*S*,8*R*,8a*S*,13b*R*)-7-(cyclopropylmethyl)-1,8a-bis(3-(4-fluorophenyl)propoxy)-11-phenyl-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline. ESI-MS *m/z* 725.3 [M + H]$^+$.

Step 2. A solution of the above intermediate (0. 170 g, 0.23 mmol) in anhydrous CH_2Cl_2 (12 mL) was cooled to -78 °C and treated dropwise with 1 M solution of boron tribromide (2.35 mL, 2.35 mmol). The mixture was allowed to warm up to 0 °C and stir for 1 h. Workup of the reaction mixture gave 19 mg (14 %) of **48** as a light brown waxy solid. TLC (10% MeOH/CH_2Cl_2): R*f* = 0.25; ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 – 8.74 (m, 1H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.60 (t, *J* = 1.4 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.45 – 7.40 (m, 1H), 6.92 (dd, *J* = 8.6,

5.5 Hz, 2H), 6.83 – 6.77 (m, 2H), 6.59 (s, 2H), 5.49 (d, *J* = 9.5 Hz, 1H), 3.73 (d, *J* = 8.0 Hz, 1H), 3.07 (d, *J* = 17.6 Hz, 2H), 2.77 – 2.67 (m, 3H), 2.59 (d, *J* = 17.0 Hz, 2H), 2.42 (t, *J* = 7.7 Hz, 3H), 1.74 (d, *J* = 8.3 Hz, 4H), 1.25 (t, *J* = 7.2 Hz, 2H), 0.89 (d, *J* = 18.6 Hz, 2H), 0.55 (s, 2H), 0.22 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.9, 160.3, 150.0, 146.7, 143.5, 137.8, 137.3, 135.8, 134.7, 129.8, 129.7, 128.4, 127.2, 119.2, 116.9, 114.9, 114.8, 111.4, 91.1, 76.9, 59.8, 59.1, 55.5, 44.6, 31.6, 31.4, 29.8, 9.4, 4.2, 3.6; HRMS (ESI) *m/z* calcd for $C_{38}H_{38}FN_2O_3$ $[M + H]^+$: 589.2861, found: 589.28675; HPLC (system 2) t_R = 7.11 min, purity = 100 %.

(4b*S*,8*R*,8a*S*,13b*R*)-8a-(3-Cyclohexylpropoxy)-7-(cyclopropylmethyl)-11-phenyl-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (49). The benzyl compound **98** described in Step 1 in the preparation of **46** (0.580 g, 1.07 mmol) was reacted with (3-bromopropyl)cyclohexane (0.438 g, 2.14 mmol) in anhydrous DMF (8 mL) in the presence of sodium hydride (0.128 g, 3.21 mmol). Workup and purification as described Step 1 in the preparation of **48** gave 0.40 g (56 %) of (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-8a-(3-cyclohexylpropoxy)-7-(cyclopropylmethyl)-11-phenyl-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline (**99**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.77 (m, 1H), 7.58 – 7.49 (m, 1H), 7.50 – 7.33 (m, 3H), 7.34 – 7.15 (m, 4H), 6.66 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 5.60 (s, 1H), 5.23 – 5.07 (m, 1H), 3.67 (dd, J = 14.6, 7.1 Hz, 1H), 3.27 – 3.16 (m, 1H), 2.86 (d, J = 16.4 Hz, 1H), 2.79 – 2.62 (m, 1H), 2.60 – 2.22 (m, 3H), 1.63 – 1.45 (m, 4H), 1.54 (m, 7H), 1.38 (s, 1H), 1.10 – 1.02 (m, 4H), 0.98 – 0.85 (m, 1H), 0.90 (s, 1H), 0.73 – 0.62 (m, 1H), 0.53 (m, 1H), 0.21 – 0.02 (m, 6H), 0.02 – -0.14 (m, 4H); ESI-MS *m/z* 667.4 $[M + H]^+$. Reaction of this intermediate (0.36 g, 0.54 mmol) with boron tribromide (5.40 mL, 5.40 mmol) as described in Step 2 in the preparation of **48** gave 0.02 g (7 %) of **49** as a light yellow solid. Mp: 148–149 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.27; ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (d, *J* =

2.1 Hz, 1H), 7.77 (s, 1H), 7.63 – 7.59 (m, 2H), 7.50 – 7.44 (m, 2H), 7.43 – 7.38 (m, 1H), 6.63 (s, 2H), 3.69 (dt, *J* = 8.6, 5.5 Hz, 1H), 3.38 (d, *J* = 19.6 Hz, 2H), 3.17 (d, *J* = 17.2 Hz, 1H), 2.93 (s, 1H), 2.78 – 2.67 (m, 3H), 2.62 (d, *J* = 17.1 Hz, 2H), 1.76 (s, 2H), 1.52 (s, 3H), 1.42 (d, *J* = 9.0 Hz, 4H), 1.04 (m, 5H), 0.95 – 0.80 (m, 4H), 0.72 (m, 1H), 0.68 – 0.54 (m, 4H), 0.36 (m, 2H); HRMS (ESI) *m/z* calcd for $C_{38}H_{45}N_2O_3$ $[M + H]^+$: 577.34247, found: 577.34135; HPLC (system 2) t_R = 7.89 min, purity = 100 %.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-phenyl-8a-(3-(tetrahydro-2*H*-pyran-4-yl)propoxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (50). *Step 1*. Compound **98** (1.20 g, 2.21 mmol) was dissolved in anhydrous DMF (10 mL) and cooled at 0 °C. Sodium hydride (0.35 g, 8.85 mmol) was added and the reaction mixture was warmed up to room temperature and stirred for 15 min. Then 3-bromoprop-1-ene (0.60 mL, 6.63 mmol) was added dropwise and the reaction mixture was allowed to stir at rt for 3 h. Then water (250 mL) was added and the reaction mixture was extracted with EtOAc (3 X 100 mL). Organic extract was then washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Solvent was removed and crude product was purified by flash chromatography using hexanes/EtOAc as eluent to obtain 1.1 g (85%) of (4b*S*,8*R*,8a*S*,13b*R*)-8a-(allyloxy)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-phenyl-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, J = 2.3, 0.7 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.48 – 7.43 (m, 3H), 7.41 – 7.37 (m, 1H), 7.31 – 7.28 (m, 2H), 7.23 – 7.21 (m, 2H), 6.67 (d, J = 8.1 Hz, 1H), 6.53 (dd, J = 8.1, 0.8 Hz, 1H), 5.80 – 5.73 (m, 1H), 5.63 (s, 1H), 5.21 – 5.11 (m, 3H), 5.04 (dd, J = 17.3, 1.8 Hz, 1H), 4.95 (dd, J = 10.4, 1.7 Hz, 1H), 4.26 (ddd, J = 10.8, 3.4, 1.7 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.70 (d, J = 5.8 Hz, 1H), 3.24 (d, J = 18.5 Hz, 1H), 2.87 (d, J = 16.5 Hz, 1H), 2.77 – 2.70 (m, 2H), 2.64 – 2.58 (m, 1H), 2.52 – 2.45 (m,

2H), 2.38 – 2.28 (m, 2H), 1.72 – 1.68 (m, 1H), 0.95 – 0.88 (m, 1H), 0.57 – 0.51 (m, 2H), 0.17 (m, 2H); ESI-MS *m/z* 583.3 $[M + H]^+$.

Step 2. The above intermediate (1.10 g, 1.89 mmol), tetrakis triphenylphosphine palladium (0) (0.22 g, 0.19 mmol), diacetoxypalladium (0.04 g, 0.19 mmol), potassium carbonate (0.65 g, 4.72 mmol),4-bromo-3,6-dihydro-2*H*-pyran (0.46 g, 2.83 mmol) were added to anhydrous DMF (15 mL) at room temperature. The reaction mixture was then degassed for with Argon for 5 min and then the mixture was heated at 110 °C for 3 h. The reaction mixture was then filtered through a pad of celite and washed with EtOAc for several times. Water was added and the mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash chromatography using $CHCl_3$/MeOH as eluent yielded 0.4 g (32%) of (4b*S*,8*R*,8a*S*,13b*R*)-1-(benzyloxy)-7-(cyclopropylmethyl)-11-phenyl-8a-(((*E*)-3-(tetrahydro-2*H*-pyran-4-yl)allyl)oxy)-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinoline. ESI-MS *m/z* 665.3 $[M + H]^+$.

Step 3. The above intermediate (0.40 g, 0.60 mmol) was dissolved in MeOH (10 mL). 10 % palladium on carbon (35.6 mg, 0.03 mmol) was added and the reaction mixture was purged with hydrogen gas 3 time. The reaction vessel was fitted with a hydrogen gas filled balloon and the mixture was vigorously stirred at room temperature for 2 h. Workup of the reaction mixture gave 13 mg (3.8 %) of **50** as a colorless oil. TLC (10% MeOH/CH_2Cl_2): R*f* = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.54 – 7.41 (m, 5H), 6.79 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.68 (s, 1H), 4.35 (d, J = 6.3 Hz, 1H), 3.80 (d, J = 11.7 Hz, 2H), 3.63 (d, J = 6.9 Hz, 1H), 3.52 (dd, J = 13.5, 7.7 Hz, 1H), 3.35 (d, J = 19.5 Hz, 1H), 3.21 (dtd, J = 9.7, 6.9, 6.1, 3.4 Hz, 3H), 3.14 – 3.04 (m, 4H), 2.95 (d, J = 12.5 Hz, 2H), 2.77 (d, J = 16.5 Hz, 2H), 1.88 (d, J = 13.5 Hz, 1H), 1.62 – 1.53 (m, 2H), 1.38 – 1.30 (m, 3H), 1.18 (s, 1H), 1.00 (dq, J = 11.9, 6.2, 5.0

Hz, 2H), 0.89 – 0.79 (m, 3H), 0.70 (ddd, J = 18.0, 8.8, 5.1 Hz, 2H), 0.52 – 0.42 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 147.1, 143.7, 140.7, 137.6, 136.3, 135.9, 129.5, 129.1, 127.2, 120.5, 120.0, 118.9, 110.2, 89.2, 76.2, 68.1, 63.8, 58.3, 56.4, 46.7, 46.3, 34.6, 33.3, 33.1, 31.5, 29.9, 28.1, 25.9, 25.0, 5.9, 5.8, 3.2.; HRMS (ESI) *m/z* calcd for $C_{37}H_{43}N_2O_4$ $[M + H]^+$: 579.3217, found: 579.3208; HPLC (system 1) t_R = 13.49 min, purity = 99.7 %.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-phenyl-8a-(4-phenylbutoxy)-6,7,8,8a,9,13b-hexahydro-*5H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (51). *Step 1.* Compound **98** (1.05 g, 1.94 mmol) was reacted with sodium hydride (0.31 g, 7.74 mmol) and (4-bromobutyl)benzene (0.83 g, 3.87 mmol) in anhydrous DMF (10 mL). Workup and purification as described Step 1 in the preparation of **48** gave **100**. Yield = 0.4 g (30.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.77 (m, 1H), 7.47 – 7.45 (m, 2H), 7.44 – 7.42 (m, 2H), 7.40 – 7.36 (m, 2H), 7.31 – 7.28 (m, 2H), 7.22 (t, *J* = 1.3 Hz, 1H), 7.21 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.17 (d, *J* = 1.7 Hz, 1H), 7.16 – 7.15 (m, 1H), 7.14 – 7.13 (m, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.02 – 6.99 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.51 (s, 1H), 5.61 (s, 1H), 5.19 (d, *J* = 11.9 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 3.75 – 3.71 (m, 1H), 3.64 (d, *J* = 5.9 Hz, 1H), 3.24 (s, 2H), 2.86 (d, *J* = 16.5 Hz, 2H), 2.73 (s, 5H), 2.58 – 2.52 (m, 2H), 2.49 – 2.42 (m, 4H), 2.37 (d, *J* = 6.6 Hz, 2H), 0.88 – 0.83 (m, 1H), 0.53 – 0.49 (m, 2H), 0.15 (s, 2H); ESI-MS *m/z* 675.3 $[M + H]^+$.

Step 2. The above intermediate **100** (0.38 g, 0.56 mmol) was dissolved in 2,2,2-trifluoroacetic acid (8.0 mL, 105 mmol) and the mixture was heated at 70 °C for 2 h. Workup and purification gave 0.102 g (31 %) of **51** as a yellow foamy solid. Mp: 87–88 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.28; ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.49 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.40 – 7.37 (m, 1H), 7.27 – 7.13 (m, 2H), 7.09 – 7.03 (m, 2H), 7.03 – 6.95 (m, 2H), 6.93 – 6.88 (m, 2H), 6.56 (s, 2H),

3.78 (dd, *J* = 7.8, 4.8 Hz, 2H), 3.39 (dt, *J* = 8.3, 4.1 Hz, 1H), 3.25 (d, *J* = 18.6 Hz, 1H), 3.07 (d, *J* = 16.9 Hz, 1H), 2.74 – 2.64 (m, 3H), 2.56 – 2.48 (m, 3H), 2.46 (d, *J* = 6.2 Hz, 1H), 2.38 (t, *J* = 7.7 Hz, 3H), 2.34 – 2.30 (m, 1H), 0.91 (d, *J* = 4.8 Hz, 2H), 0.56 – 0.51 (m, 2H), 0.19 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.3, 146.6, 143.5, 142.7, 139.0, 137.4, 136.2, 135.7, 131.1, 131.0, 129.13, 128.34, 128.27, 128.19, 127.2, 125.9, 125.6, 119.1, 116.9, 91.1, 60.0, 59.9, 55.8, 47.8, 44.6, 35.6, 31.3, 30.5, 29.8, 29.7, 28.3, 23.5, 9.4, 4.1, 3.7; HRMS (ESI) *m/z* calcd for $C_{39}H_{41}N_2O_3$ $[M + H]^+$: 585.31117, found: 585.3103; HPLC (system 2) t_R = 7.36 min, purity = 100%.

(4b*S*,8*R*,8a*S*,13b*R*)-7-(Cyclopropylmethyl)-11-phenyl-8a-propoxy-6,7,8,8a,9,13b-hexahydro-5*H*-4,8-methanobenzofuro[3,2-*h*]pyrido[3,4-*g*]quinolin-1-ol (52). The allyloxy compound obtained in Step 1 in the preparation of compound **50** (0.15 g, 0.3 mmol) was treated with 10% of palladium(II) carbon (15.0 mg, 10 wt%) in mixture of CH_2Cl_2 (7 mL) and MeOH (7 mL). The reaction mixture was evacuated under vacuum and flushed with hydrogen 3 times. The mixture was allowed to stir under H_2 atmosphere at room temperature for 20 h. The reaction mixture was filtered through a pad of celite and rinsed with EtOH. The solvent was removed under reduced pressure. The residue was purified by chromatography over a column of silica gel using $CHCl_3$/MeOH (95:5) as the eluent to give 0.1 g (79%) of **52** as a white solid. Mp: 146–147 °C; TLC (10% MeOH/CH_2Cl_2): R*f* = 0.70; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (t, *J* = 2.1 Hz, 1H), 7.46 – 7.33 (m, 6H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 5.60 (s, 1H), 3.66 (dt, *J* = 7.5, 5.9 Hz, 2H), 3.28 – 3.13 (m, 2H), 2.84 (d, *J* = 16.5 Hz, 1H), 2.77 – 2.62 (m, 2H), 2.55 – 2.24 (m, 5H), 1.69 – 1.62 (m, 1H), 1.39 (dq, *J* = 11.3, 6.9 Hz, 2H), 1.26 (s, 1H), 0.94 – 0.84 (m, 1H), 0.66 (t, *J* = 7.4 Hz, 3H), 0.52 (dq, *J* = 7.6, 3.3 Hz, 2H), 0.21 – 0.11 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4, 146.7, 143.6, 136.2, 135.8, 131.2, 131.1, 129.2, 128.3, 127.3, 127.2, 119.1, 116.8, 76.6, 62.1, 59.9, 55.8, 47.9, 44.6, 31.4, 30.5, 29.8, 23.6, 23.4, 22.8, 11.1, 9.5, 4.2, 3.7; HRMS (ESI)

m/z calcd for $C_{32}H_{35}N_2O_3$ $[M + H]^+$: 495.26422, found: 495.26226; HPLC (system 2) t_R = 5.76 min, purity 100%.

Cell lines and Membrane Preparations. All in vitro molecular pharmacology evaluations were carried out in Chinese Hamster Ovary (CHO) cells stably expressing 3X-HA N-terminal tagged human MOR, DOR, or KOR constructs. The creation and evaluation of the cells, along with their established K_D values in response to ^{3}H-diprenorphine, are described in our previous work.[32,33,57-59] The cells were grown in 1:1 DMEM/F12 medium with 10% heat-inactivated fetal bovine serum and 1X penicillin/streptomycin additive, all Gibco brand (Thermo Fisher). Propagation cultures were further maintained with 500 μg/mL of G418 (Gibco/ThermoFisher). Cells were cultured for no more than 20 passages before bringing up a fresh stock. For experiments, cells were plated and grown to confluency in 3x15cm dishes, collected using 5 mM EDTA in dPBS (no calcium or magnesium), and the resulting cell pellets stored at -80°C until use. All cells were monitored for mycoplasma contamination by DAPI stain and imaging, and all cells used in this project were mycoplasma negative.

Radioligand Competition Binding Assay. Competition binding experiments were carried out versus a fixed concentration of ^{3}H-diprenorphine using a protocol previously reported in our published work.[32,33,58-60] The reactions were carried out using a fixed amount of membrane protein in each experiment (~25 μg/well), a fixed concentration of ^{3}H-diprenorphine (~1-2 nM), and concentration curves of experimental compound or positive control (naloxone for MOR and DOR, U50,488 for KOR) in a 200 μL reaction volume. Vehicle (100%, no competitor) and non-specific binding (NSB; 10 μM naloxone or U50,488) controls were included on each plate. Reactions were incubated at room temperature for 1 h. The resulting data was normalized to vehicle (100%) and NSB (0%) controls, and fitted with a 1 site non-linear regression competition binding curve using

GraphPad Prism 8.0. The affinity (K_i) was calculated for each drug using the previously measured K_D for ^{3}H-diprenorphine in each line (MOR = 5.4 nM; DOR = 1.7 nM; KOR = 1.2 nM),[61] and reported as the mean ± SEM of N ≥ 3 independent experiments.

In Vitro [^{35}S]-GTPγS Coupling Functional Assay. ^{35}S-GTPγS coupling experiments were performed as reported in our published work.[32,33] 15 μg/well of membrane protein was combined with 0.1 nM ^{35}S-GTPγS (PerkinElmer) and concentration curves of experimental compound or positive control agonist (MOR – DAMGO; DOR – SNC80; KOR – U50,488) in a 200 μL reaction volume. For DOR antagonist experiments, membrane protein was pre-incubated with concentration curves of experimental compound or naloxone positive control for 5 minutes prior to adding 100 nM SNC80. Vehicle treated controls were included on each plate. The reactions were incubated at 30°C for 1 h. The resulting data was normalized to the stimulation caused by positive control agonist (100%) or vehicle (0%) and fit with 3 variable non-linear regression curves using GraphPad Prism 8.0. These curves were used to calculate potency (EC_{50}/IC_{50}) and efficacy (E_{MAX}/I_{MAX}) of each compound. The efficacy values were calculated in relation to the positive control agonist or antagonist (100%). Each value was reported as the mean ± SEM of N ≥ 3 independent experiments.

Log *D* Determination. Distribution coefficient (log *D*) was determined by the method of Wilson et al.[62] A volume of 5 μL of DMSO solutions of the test compounds were added to a mixture of equal volumes of 50 mM phosphate buffer and 1-octanol and vortex mixed at 800 rpm for a period of 24 h. Subsequent to centrifugation at 14000 rpm for 30 min, 1 μL of each layer was analyzed by LC-MS/MS. LogD was determined using the peak areas obtained from each layer. The compounds were added at 50 nM concentration in order to limit the precipitation of the compound and have the mixture within the dynamic range of the LC-MS/MS instrumentation.

Aqueous Solubility. Aqueous solubility was determined by the method of Zhou et al.[63] using a miniaturized shake flask approach, under conditions of pH 6.8 and analyte concentration of 1.0 mM. Aqueous solutions of analyte were incubated at room temperature in the chamber of a Whatman (Piscataway, NJ) Mini-UniPrep syringeless filter for 24 h while shaking gently (600 rpm). Subsequent to incubation, filter plungers were pushed down to the bottom of the syringeless filter chamber assemblies, allowing filtrate to enter the plunger compartment. Following an additional 30 min incubation at room temperature, filtrates were diluted with 50:50 acetonitrile/water + 0.1% formic acid and analyzed by LC−MS/MS. Analyte concentrations were determined by the interpolation of peak area ratio from a calibration curve formed by matrix spiked with authentic reference material, over a calibration range of 0.05−12.5 μM (pH 6.8). The results are presented in Table S1.

In Vitro Mouse Liver Microsomal Stability. Metabolic stability of lead compounds was assessed in vitro by the method of Ackley et al.[64] Briefly, mouse liver microsome preparations (Corning Life Sciences, Woburn, MA) were isolated from CD-1 mice (male mice, 8−10 weeks of age). Assays were conducted using 0.123 mg/mL protein concentration (total protein concentration in the microsomal solution) and 1.0 μM drug concentration under incubation conditions of 37 °C. Metabolic stability was determined following 0, 5, 15, 30, and 60 min of incubation time. The samples were analyzed by reversed phase LC using a triple quadrupole mass spectrometer. Compound specific transitions of parent ion to product ion were monitored and percent remaining calculated based on peak area of 5−60 min time points (relative to time zero). Half-life calculations were determined using the formula $t_{1/2} = -\ln(2)/k$, where k (min^{-1}) is the turnover rate constant (the slope) estimated from a log−linear regression of the percentage compound remaining versus time.

In Vitro Human Liver Microsomal Stability. Metabolic stability of the compounds in human liver microsomes was determined by the method described above using pooled human liver microsome preparations from 20 male donors (Corning Life Sciences, Woburn, MA). Assays were conducted as described above and the calculated in vitro half-life of the compounds are presented in Table S1.

LC−MS/MS Analysis: LC−MS/MS analysis was conducted using an Agilent (Santa Clara, CA) 6460 triple quadrupole mass spectrometer coupled with an Agilent liquid chromatography (LC) system. The LC system consists of a binary pump, degasser, column heater, and autosampler. Chromatographic separation was performed on a Waters Atlantis T3 3µm 3.0 x 50 mm analytical column using a ballistic gradient of mobile phase consisting of 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) at a flow rate of 0.75 mL/min. Mobile phase was heated to a temperature of 45 °C.

Animals. Male CD-1 mice (25-35 g), purchased from Charles Rivers were housed in a climate-controlled room on a regular 12 h light/dark cycle with lights on at 7:00 am with food and water available *ad libitum*. Animals were initially housed 4-5 per cage. All procedures were performed during the 12-hour light cycle according to the policies/recommendations of the International Association for the Study of Pain and the NIH guidelines for laboratory animals, and with IACUC approval from the University of Arizona (17-223). All behaviors were evaluated in n=5-15 male mice by an observer blinded to the injection content with results compared to those of mice treated with vehicle (10% DMSO, 10% Tween80, 80% saline) or saline where appropriate.

Antinociception. Antinociceptive effects were evaluated using the tail-flick assay. Naïve mice were baselined in the 55 °C warm water tail-withdrawal test and the time to reflexively withdraw the distal third of the tail was recorded. Doses of morphine or the test compound were injected icv,

sc, iv, or po, and antinociception was assessed at 10, 15, 20, 30, 45, 60, 80, 120, and 180 min post-injection. Percent antinociception was calculated using equation 1

Eq. 1 %MPE (maximal possible effect) = 100 × (test − control)/(cutoff − control)

where control is the pre-drug latency, test is the post-drug latency, and cutoff is the maximal length of stimulus allowed 10 s for 55 °C tail-withdrawal). Antinociceptive A_{50} values and 95% confidence intervals were determined using linear regression software (GraphPad by Prism 7.0). Opioid activity of the test compounds was assessed by pretreating animals with naloxone (10 mg/kg intraperitoneal, −10 min) followed by a sc injection of the calculated A_{90} dose of test compound. If a compound did not produce a full agonist effect, then the dose that produced the greatest antinociceptive effect was used. Antinociception was assessed in the 55°C warm water tail-withdrawal test at the time of maximal percent effect. A positive response to a fixed dose of naloxone was indicated when greater than 80% reduction in the antinociceptive effect of the agonist was observed.

Tolerance Regimen. Mice were injected twice daily (8 a.m. and 5 p.m.) with an approximate A_{90} dose of morphine or A_{90} dose of Compound **20** for three days. Antinociceptive dose−response curves were generated on the morning of the fourth day using the procedures described above.

Physical Dependence/ Precipitated Withdrawal. Compound **20** was administered to male CD-1 mice at a dose of 32 mg/kg, sc, twice a day (9 a.m. and 5 p.m.) for three days. On the fourth day, four hours after the morning administration of compound **20**, the mice were given naloxone (30 mg/kg, ip) to precipitate withdrawal. Animals were immediately placed in clear acrylic cylinders and behaviors were monitored through video capture for forty minutes. Baseline behaviors for each animal were recorded forty minutes prior to naloxone administration. Monitored behaviors included urine output, presence/absence of diarrhea, paw tremor, and ptosis, as well as number of

droppings, vertical jumps, backward walking steps, and wet dog shakes to calculate an overall withdrawal score. All videos were observed as scored by an individual blinded to treatment.

Respiratory Depression. Respiratory depression was measured in freely moving, conscious male CD1 mice (25-30 g) average weight using whole body plethysmography chambers (Data Sciences International, St Paul, MN). Chambers were maintained at room temperature and flow and composition of the gas was set by mass flow controllers. Vehicle (10% DMSO, 10% Tween80, 80%; 10 mL/kg, sc), Saline (10mL/kg IP), morphine (10mg/kg, ip), or compound **20** (3.2, 10, 32 or 75 mg/kg, sc) was administered following a 30 min baseline. Mice remained in the chambers after injection for a 7-min room air reading (0% CO_2), followed by a 7-min 5% concentration of carbon dioxide/oxygen mixture challenge. Minute ventilation, tidal volume, and respiratory rate were recorded for each measure, baseline, room air, and 5% CO_2 concentration challenge. It should be noted that compound **20** was in solution for all of the doses except the 75 mg/kg dose; at the time of injection the compound had precipitated out of solution and was therefore administered as a suspension.

Conditioned Place Preference/Aversion (CPP/CPA). Basal time spent in each chamber (Panlab, Barcelona, Spain) was recorded for individual mice (CD-1, male, 25-35g) over 15 min. Any mouse spending more than 80% of the total time in any one chamber or less than 20% of the total time in the end chambers was excluded from further testing (n=0). Animals received injections both morning and afternoon and were placed and confined to one chamber or the other ten minutes following injection for a 15-minute duration such that all pairing combinations were executed. (e.g., if an animal received drug in the morning and was placed in the dotted chamber, then in the afternoon, the same animal received vehicle and was placed in the opposite (striped) chamber. Injections took place four hours apart as shown in Fig. 11. On Day 5, injections occurred in the

morning and testing was done in the afternoon. Mice were placed in the corridor with the doors to both chambers in place. Once the software was started the doors were lifted and the animals were allowed free access to all chambers for a 15-minute duration. Compound **20** was given at 20 mg/kg, morphine sulfate at 10 mg/kg; all injections were performed at 10 mL/kg (sc).

Statistical Analyses. Numbers of animals required for individual behavioral outcomes were determined in GPower3.1 to give 80% power to detect a 20% difference when alpha= 0.05. Results were statistically significant when $p \leq 0.05$. Individual assays were analyzed as follows: Tail Flick (Fig 4 and 5): Time x treatment, two-way RM ANOVA Bonferroni post-hoc; Tail Flick (Fig 6): one- way ANOVA, Bonferroni post-hoc; DRC (Fig 7) non-linear regression; PD (Fig 8): One-way ANOVA/ behavior; RD (Fig 9): Time x treatment Two-way RM ANOVA, Bonferroni post-hoc; CPP/CPA (Fig 10 F, G): One-way ANOVA/ behavior, Bonferroni post-hoc.

Computational Docking Study. Crystal structures of the agonist-bound mouse MOR (PDB ID 5C1M), antagonist-bound human DOR (PDB ID 4N6H), and antagonist bound human KOR (PDB ID 4DJH) were used in the docking studies. Protein structures were prepared using Schrödinger Small Molecule Drug Discovery Suite. Conserved water molecules were kept and modified residues in crystal structures were changed back to wildtype. The 3D structures of the compounds were generated using LigPrep in Schrödinger. Ligands in the crystals were used to define the binding site for docking. All compounds were docked to MOR, DOR, and KOR using induced fit docking protocol (flexible ligand and protein within 5 Å of ligand poses) implemented in Schrödinger.[65]

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Solubility, human liver microsomal stability, and computed values of compounds **8–52,** respiratory depression effect of compound **20**, and HPLC and HRMS data of compounds **20** and **42** (PDF)

3D coordinates of compound **8** docked into the active form of MOR (Figure 2A) (PDB)

3D coordinates of compound **46** docked into the active form of MOR (Figure 2B) (PDB)

3D coordinates of compound **8** docked into the inactive form of DOR (Figure 3A) (PDB)

3D coordinates of compound **8** docked into the inactive form of KOR (Figure 3B) (PDB)

Molecular formula strings with associated data (CSV)

AUTHOR INFORMATION

Corresponding Author

*Phone: (205) 581-2822. Fax: (205) 581-2726. E-mail: ananthan@southernresearch.org.

ORCID

Rakesh H. Vekariya: 0000-0001-8292-9793

Abhisek Ray: 0000-0002-0088-0576

John M. Streicher: 0000-0002-4173-7362

Subramaniam Ananthan: 0000-0002-4791-9116

Present Addresses

†For Rakesh H. Vekariya: Department of Biochemistry, Vanderbilt University, Nashville, Tennessee 37232, United States.

‡For Wei Lei: Department of Pharmaceutical and Administrative Sciences, Presbyterian College School of Pharmacy, 307 N. Broad St, Clinton, SC 29681.

†For Abhisek Ray: Nanosyn Inc., 3100 Central Expressway, Santa Clara, CA 95051, United States.

†For Surendra K. Saini: Department of Biotechnology, India Institute of Technology, Roorkee 247667, India.

Author Contributions

The manuscript was written through contributions of all authors. All authors have helped draft, review and then approve the final version of the manuscript.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Judith V. Hobrath for performing initial computational modeling studies. We thank Dr. Donghui Bao and Dr. Robert Deimler for their help with analytical and spectral data collection. We are grateful to Dr. Corinne E. Augelli-Szafran and Dr. Mark J. Suto for their encouragement, valuable comments and suggestions during the course of this work. This study was supported by a research grant from the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH) under Award Number R01DA038635. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ABBREVIATIONS

ADME, absorption, distribution, metabolism, and excretion; CHO, Chinese hamster ovary; CPA, conditioned place aversion; CPM, cyclopropylmethyl; CPP, conditioned place preference;

DADLE, [D-Ala^2,D-Leu^5]enkephalin; DAMGO, [D-Ala^2,Me-Phe,Gly-ol^5]enkephalin; DOR, δ opioid receptor; [^{35}S]GTP-γ-S, guanosine-5′-*O*-(3-[^{35}S]thio-triphosphate; KOR, κ opioid receptor; MOR, μ opioid receptor; MPE, maximum possible effect; MS, morphine sulfate; TLC, thin layer chromatography.

REFERENCES

1. Walsh, D. Pharmacological management of cancer pain. *Semin. Oncol.* **2000**, *27*, 45–63.

2. Benyamin, R.; Trescot, A. M.; Datta, S.; Buenaventura, R.; Adlaka, R.; Sehgal, N.; Glaser, S. E.; Vallejo, R. Opioid complications and side effects. *Pain Physician* **2008**, *11*, S105–120.

3. Swegle, J. M.; Logemann, C. Management of common opioid-induced adverse effects. *Am. Fam. Physician* **2006**, *74*, 1347–1354.

4. Pattinson, K. T. Opioids and the control of respiration. *Br. J. Anaesth.* **2008**, *100*, 747–758.

5. Dahan, A.; van der Schrier, R.; Smith, T.; Aarts, L.; van Velzen, M.; Niesters, M. Averting opioid-induced respiratory depression without affecting analgesia. *Anesthesiology* **2018**, *128*, 1027–1037.

6. Brock, C.; Olesen, S. S.; Olesen, A. E.; Frokjaer, J. B.; Andresen, T.; Drewes, A. M. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs* **2012**, *72*, 1847–1865.

7. Kiyatkin, E. A. Respiratory depression and brain hypoxia induced by opioid drugs: Morphine, oxycodone, heroin, and fentanyl. *Neuropharmacology* **2019**, *151*, 219–226.

8. Dhawan, B. N.; Cesselin, F.; Raghubir, R.; Reisine, T.; Bradley, P. B.; Portoghese, P. S.; Hamon, M. International Union of Pharmacology. XII. Classification of opioid receptors. *Pharmacol. Rev.* **1996**, *48*, 567–592.

9. Pasternak, G. W.; Pan, Y. X. Mu opioids and their receptors: evolution of a concept. *Pharmacol. Rev.* **2013**, *65*, 1257–1317.

10. Gunther, T.; Dasgupta, P.; Mann, A.; Miess, E.; Kliewer, A.; Fritzwanker, S.; Steinborn, R.; Schulz, S. Targeting multiple opioid receptors - improved analgesics with reduced side effects? *Br. J. Pharmacol.* **2017**, *175*, 2857–2868.

11. Cunningham, C. W.; Elballa, W. M.; Vold, S. U. Bifunctional opioid receptor ligands as novel analgesics. *Neuropharmacology* **2019**, *151*, 195–207.

12. Hruby, V. J. Multivalent peptide and peptidomimetic ligands for the treatment of pain without toxicities and addiction. *Peptides* **2019**, *116*, 63–67.

13. Schiller, P. W. Bi- or multifunctional opioid peptide drugs. *Life Sci.* **2010**, *86*, 598–603.

14. Bird, M. F.; Lambert, D. G. Simultaneous targeting of multiple opioid receptor types. *Curr. Opin. Support. Palliat. Care* **2015**, *9*, 98–102.

15. Ananthan, S. Opioid ligands with mixed mu/delta opioid receptor interactions: an emerging approach to novel analgesics. *AAPS J.* **2006**, *8*, E118–125.

16. Abdelhamid, E. E.; Sultana, M.; Portoghese, P. S.; Takemori, A. E. Selective blockage of delta opioid receptors prevents the development of morphine tolerance and dependence in mice. *J. Pharmacol. Exp. Ther.* **1991**, *258*, 299–303.

17. Fundytus, M. E.; Schiller, P. W.; Shapiro, M.; Weltrowska, G.; Coderre, T. J. Attenuation of morphine tolerance and dependence with the highly selective delta-opioid receptor antagonist TIPP[psi]. *Eur. J. Pharmacol.* **1995**, *286*, 105–108.

18. Hepburn, M. J.; Little, P. J.; Gingras, J.; Kuhn, C. M. Differential effects of naltrindole on morphine-induced tolerance and physical dependence in rats. *J. Pharmacol. Exp. Ther.* **1997**, *281*, 1350–1356.

19. Zhu, Y.; King, M. A.; Schuller, A. G.; Nitsche, J. F.; Reidl, M.; Elde, R. P.; Unterwald, E.; Pasternak, G. W.; Pintar, J. E. Retention of supraspinal delta-like analgesia and loss of morphine tolerance in δ opioid receptor knockout mice. *Neuron* **1999**, *24*, 243–252.

20. Ananthan, S.; Khare, N. K.; Saini, S. K.; Seitz, L. E.; Bartlett, J. L.; Davis, P.; Dersch, C. M.; Porreca, F.; Rothman, R. B.; Bilsky, E. J. Identification of opioid ligands possessing mixed μ agonist/δ antagonist activity among pyridomorphinans derived from naloxone, oxymorphone, and hydromorphone. *J. Med. Chem.* **2004**, *47*, 1400–1412.

21. Ananthan, S.; Saini, S. K.; Dersch, C. M.; Xu, H.; McGlinchey, N.; Giuvelis, D.; Bilsky, E. J.; Rothman, R. B. 14-Alkoxy- and 14-acyloxypyridomorphinans: μ agonist/δ antagonist opioid analgesics with diminished tolerance and dependence side effects. *J. Med. Chem.* **2012**, *55*, 8350–8363.

22. Schiller, P. W.; Fundytus, M. E.; Merovitz, L.; Weltrowska, G.; Nguyen, T. M.; Lemieux, C.; Chung, N. N.; Coderre, T. J. The opioid mu agonist/delta antagonist DIPP-NH(2)[Psi] produces a potent analgesic effect, no physical dependence, and less tolerance than morphine in rats. *J. Med. Chem.* **1999**, *42*, 3520–3526.

23. Anand, J. P.; Boyer, B. T.; Mosberg, H. I.; Jutkiewicz, E. M. The behavioral effects of a mixed efficacy antinociceptive peptide, VRP26, following chronic administration in mice. *Psychopharmacology (Berl)* **2016**, *233*, 2479–2487.

24. Anand, J. P.; Kochan, K. E.; Nastase, A. F.; Montgomery, D.; Griggs, N. W.; Traynor, J. R.; Mosberg, H. I.; Jutkiewicz, E. M. In vivo effects of μ-opioid receptor agonist/δ-opioid receptor antagonist peptidomimetics following acute and repeated administration. *Br. J. Pharmacol.* **2018**, *175*, 2013–2027.

25. Varadi, A.; Marrone, G. F.; Palmer, T. C.; Narayan, A.; Szabo, M. R.; Le Rouzic, V.; Grinnell, S. G.; Subrath, J. J.; Warner, E.; Kalra, S.; Hunkele, A.; Pagirsky, J.; Eans, S. O.; Medina, J. M.; Xu, J.; Pan, Y. X.; Borics, A.; Pasternak, G. W.; McLaughlin, J. P.; Majumdar, S. Mitragynine/Corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit beta-arrestin-2. *J. Med. Chem.* **2016**, *59*, 8381–8397.

26. Healy, J. R.; Bezawada, P.; Shim, J.; Jones, J. W.; Kane, M. A.; MacKerell, A. D., Jr.; Coop, A.; Matsumoto, R. R. Synthesis, modeling, and pharmacological evaluation of UMB 425, a mixed μ agonist/δ antagonist opioid analgesic with reduced tolerance liabilities. *ACS Chem. Neurosci.* **2013**, *4*, 1256–1266.

27. Imam, M. Z.; Kuo, A.; Ghassabian, S.; Cai, Y.; Qin, Y.; Li, T.; Smith, M. T. Intracerebroventricular administration of CYX-6, a potent μ-opioid receptor agonist, a δ- and κ-opioid receptor antagonist and a biased ligand at μ, δ & κ-opioid receptors, evokes antinociception with minimal constipation and respiratory depression in rats in contrast to morphine. *Eur. J. Pharmacol.* **2020**, *871*, 172918.

28. Henry, S.; Anand, J. P.; Twarozynski, J. J.; Brinkel, A. C.; Pogozheva, I. D.; Sears, B. F.; Jutkiewicz, E. M.; Traynor, J. R.; Mosberg, H. I. Aromatic-amine pendants produce highly potent and efficacious mixed efficacy μ-opioid receptor (MOR)/δ-opioid receptor (DOR) peptidomimetics with enhanced metabolic stability. *J. Med. Chem.* **2020**, *63*, 1671–1683.

29. Ananthan, S.; Kezar, H. S., 3rd; Carter, R. L.; Saini, S. K.; Rice, K. C.; Wells, J. L.; Davis, P.; Xu, H.; Dersch, C. M.; Bilsky, E. J.; Porreca, F.; Rothman, R. B. Synthesis, opioid receptor binding, and biological activities of naltrexone-derived pyrido- and pyrimidomorphinans. *J. Med. Chem.* **1999**, *42*, 3527–3538.

30. Ananthan, S.; Kezar, H. S., 3rd; Saini, S. K.; Khare, N. K.; Davis, P.; Dersch, C. M.; Porreca, F.; Rothman, R. B. Synthesis, opioid receptor binding, and functional activity of 5'-substituted 17-cyclopropylmethylpyrido[2',3':6,7]morphinans. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 529–532.

31. Ananthan, S.; Khare, N. K.; Saini, S. K.; Davis, P.; Dersch, C. M.; Porreca, F.; Rothman, R. B. Novel ligands for the opioid receptors: synthesis and structure-activity relationships among 5'-aryl and 5'-heteroaryl 17-cyclopropylmethyl-4,5 alpha-epoxypyrido[2',3':6,7]morphinans. *Bioorg. Med. Chem.* **2003**, *11*, 4143–4154.

32. Stefanucci, A.; Lei, W.; Hruby, V. J.; Macedonio, G.; Luisi, G.; Carradori, S.; Streicher, J. M.; Mollica, A. Fluorescent-labeled bioconjugates of the opioid peptides biphalin and DPDPE incorporating fluorescein-maleimide linkers. *Future Med. Chem.* **2017**, *9*, 859–869.

33. Olson, K. M.; Keresztes, A.; Tashiro, J. K.; Daconta, L. V.; Hruby, V. J.; Streicher, J. M. Synthesis and evaluation of a novel bivalent selective antagonist for the mu-delta opioid receptor heterodimer that reduces morphine withdrawal in mice. *J. Med. Chem.* **2018**, *61*, 6075–6086.

34. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3–26.

35. Leeson, P. D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* **2007**, *6*, 881–890.

36. Wager, T. T.; Chandrasekaran, R. Y.; Hou, X.; Troutman, M. D.; Verhoest, P. R.; Villalobos, A.; Will, Y. Defining desirable central nervous system drug space through the alignment of molecular properties, in vitro ADME, and safety attributes. *ACS Chem. Neurosci.* **2010**, *1*, 420–434.

37. Rankovic, Z. CNS drug design: balancing physicochemical properties for optimal brain exposure. *J. Med. Chem.* **2015**, *58*, 2584–2608.

38. Fichert, T.; Yazdanian, M.; Proudfoot, J. R. A structure-permeability study of small drug-like molecules. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 719–722.

39. Waring, M. J. Defining optimum lipophilicity and molecular weight ranges for drug candidates-Molecular weight dependent lower logD limits based on permeability. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2844–2851.

40. DeGoey, D. A.; Chen, H. J.; Cox, P. B.; Wendt, M. D. Beyond the rule of 5: lessons learned from AbbVie's drugs and compound collection. *J. Med. Chem.* **2018**, *61*, 2636–2651.

41. Huang, W.; Manglik, A.; Venkatakrishnan, A. J.; Laeremans, T.; Feinberg, E. N.; Sanborn, A. L.; Kato, H. E.; Livingston, K. E.; Thorsen, T. S.; Kling, R. C.; Granier, S.; Gmeiner, P.; Husbands, S. M.; Traynor, J. R.; Weis, W. I.; Steyaert, J.; Dror, R. O.; Kobilka, B. K. Structural insights into μ-opioid receptor activation. *Nature* **2015**, *524*, 315–321.

42. Fenalti, G.; Giguere, P. M.; Katritch, V.; Huang, X. P.; Thompson, A. A.; Cherezov, V.; Roth, B. L.; Stevens, R. C. Molecular control of δ-opioid receptor signalling. *Nature* **2014**, *506*, 191–196.

43. Wu, H.; Wacker, D.; Mileni, M.; Katritch, V.; Han, G. W.; Vardy, E.; Liu, W.; Thompson, A. A.; Huang, X. P.; Carroll, F. I.; Mascarella, S. W.; Westkaemper, R. B.; Mosier, P. D.; Roth, B. L.; Cherezov, V.; Stevens, R. C. Structure of the human κ-opioid receptor in complex with JDTic. *Nature* **2012**, *485*, 327–332.

44. Manglik, A.; Kruse, A. C.; Kobilka, T. S.; Thian, F. S.; Mathiesen, J. M.; Sunahara, R. K.; Pardo, L.; Weis, W. I.; Kobilka, B. K.; Granier, S. Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. *Nature* **2012**, *485*, 321–326.

45. Granier, S.; Manglik, A.; Kruse, A. C.; Kobilka, T. S.; Thian, F. S.; Weis, W. I.; Kobilka, B. K. Structure of the δ-opioid receptor bound to naltrindole. *Nature* **2012**, *485*, 400–404.

46. Claff, T.; Yu, J.; Blais, V.; Patel, N.; Martin, C.; Wu, L.; Han, G. W.; Holleran, B. J.; Van der Poorten, O.; White, K. L.; Hanson, M. A.; Sarret, P.; Gendron, L.; Cherezov, V.; Katritch, V.; Ballet, S.; Liu, Z. J.; Muller, C. E.; Stevens, R. C. Elucidating the active δ-opioid receptor crystal structure with peptide and small-molecule agonists. *Sci. Adv.* **2019**, *5*, eaax9115.

47. Elmagbari, N. O.; Egleton, R. D.; Palian, M. M.; Lowery, J. J.; Schmid, W. R.; Davis, P.; Navratilova, E.; Dhanasekaran, M.; Keyari, C. M.; Yamamura, H. I.; Porreca, F.; Hruby, V. J.; Polt, R.; Bilsky, E. J. Antinociceptive structure-activity studies with enkephalin-based opioid glycopeptides. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 290–297.

48. Black, J. W.; Leff, P. Operational models of pharmacological agonism. *Proc. R. Soc. Lond. B. Biol. Sci.* **1983**, *220*, 141–162.

49. Gades, N. M.; Danneman, P. J.; Wixson, S. K.; Tolley, E. A. The magnitude and duration of the analgesic effect of morphine, butorphanol, and buprenorphine in rats and mice. *Contemp. Top. Lab. Anim. Sci.* **2000**, *39*, 8–13.

50. Shu, H.; Wang, Z.; Ye, F.; Li, Q.; Dou, Y.; Lin, Y.; Huang, W.; Xiao, X. High-dose pentazocine antagonizes the antinociception induced by high-dose morphine. *Life Sci.* **2015**, *130*, 1–6.

51. Vanderah, T. W.; Suenaga, N. M.; Ossipov, M. H.; Malan, T. P., Jr.; Lai, J.; Porreca, F. Tonic descending facilitation from the rostral ventromedial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. *J. Neurosci.* **2001**, *21*, 279–286.

52. Wells, J. L.; Bartlett, J. L.; Ananthan, S.; Bilsky, E. J. In vivo pharmacological characterization of SoRI 9409, a nonpeptidic opioid μ-agonist/δ-antagonist that produces limited antinociceptive tolerance and attenuates morphine physical dependence. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 597–605.

53. Kest, B.; Palmese, C. A.; Hopkins, E.; Adler, M.; Juni, A.; Mogil, J. S. Naloxone-precipitated withdrawal jumping in 11 inbred mouse strains: evidence for common genetic mechanisms in acute and chronic morphine physical dependence. *Neuroscience* **2002**, *115*, 463–469.

54. Walker, E. A.; Sterious, S. N. Opioid antagonists differ according to negative intrinsic efficacy in a mouse model of acute dependence. *Br. J. Pharmacol.* **2005**, *145*, 975–983.

55. Lowery, J. J.; Raymond, T. J.; Giuvelis, D.; Bidlack, J. M.; Polt, R.; Bilsky, E. J. In vivo characterization of MMP-2200, a mixed δ/μ opioid agonist, in mice. *J. Pharmacol. Exp. Ther.* **2011**, *336*, 767–778.

56. Portoghese, P. S.; Sultana, M.; Moe, S. T.; Takemori, A. E. Synthesis of naltrexone-derived δ-opioid antagonists. Role of conformation of the δ address moiety. *J. Med. Chem.* **1994**, *37*, 579–585.

57. Lei, W.; Mullen, N.; McCarthy, S.; Brann, C.; Richard, P.; Cormier, J.; Edwards, K.; Bilsky, E. J.; Streicher, J. M. Heat-shock protein 90 (Hsp90) promotes opioid-induced

anti-nociception by an ERK mitogen-activated protein kinase (MAPK) mechanism in mouse brain. *J. Biol. Chem.* **2017**, *292*, 10414–10428.

58. Cai, S.; Bellampalli, S. S.; Yu, J.; Li, W.; Ji, Y.; Wijeratne, E. M. K.; Dorame, A.; Luo, S.; Shan, Z.; Khanna, M.; Moutal, A.; Streicher, J. M.; Gunatilaka, A. A. L.; Khanna, R. (-)-Hardwickiic acid and hautriwaic acid induce antinociception via blockade of tetrodotoxin-sensitive voltage-dependent sodium channels. *ACS Chem. Neurosci.* **2019**, *10*, 1716–1728.

59. Bellampalli, S. S.; Ji, Y.; Moutal, A.; Cai, S.; Wijeratne, E. M. K.; Gandini, M. A.; Yu, J.; Chefdeville, A.; Dorame, A.; Chew, L. A.; Madura, C. L.; Luo, S.; Molnar, G.; Khanna, M.; Streicher, J. M.; Zamponi, G. W.; Gunatilaka, A. A. L.; Khanna, R. Betulinic acid, derived from the desert lavender Hyptis emoryi, attenuates paclitaxel-, HIV-, and nerve injury-associated peripheral sensory neuropathy via block of N- and T-type calcium channels. *Pain* **2019**, *160*, 117–135.

60. Starnowska, J.; Costante, R.; Guillemyn, K.; Popiolek-Barczyk, K.; Chung, N. N.; Lemieux, C.; Keresztes, A.; Van Duppen, J.; Mollica, A.; Streicher, J. M.; Vanden Broeck, J.; Schiller, P. W.; Tourwe, D.; Mika, J.; Ballet, S.; Przewlocka, B. Analgesic properties of opioid/NK1 multitarget ligands with distinct in vitro profiles in naive and chronic constriction injury (CCI)-mice. *ACS Chem. Neurosci.* **2017**, *8*, 2315–2324.

61. Olson, K. M.; Duron, D. I.; Womer, D.; Fell, R.; Streicher, J. M. Comprehensive molecular pharmacology screening reveals potential new receptor interactions for clinically relevant opioids. *PLoS One* **2019**, *14*, e0217371.

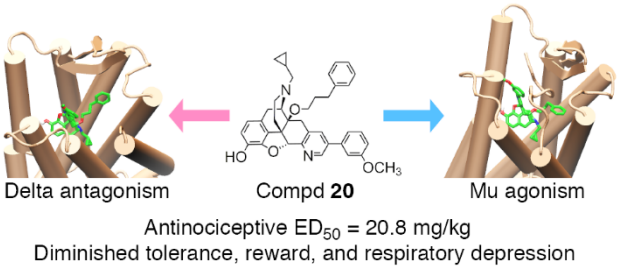
62. Wilson, D. M.; Wang, X.; Walsh, E.; Rourick, R. A. High throughput log D determination using liquid chromatography-mass spectrometry. *Comb. Chem. High Throughput Screen* **2001**, *4*, 511–519.

63. Zhou, L.; Yang, L.; Tilton, S.; Wang, J. Development of a high throughput equilibrium solubility assay using miniaturized shake-flask method in early drug discovery. *J. Pharm. Sci.* **2007**, *96*, 3052–3071.

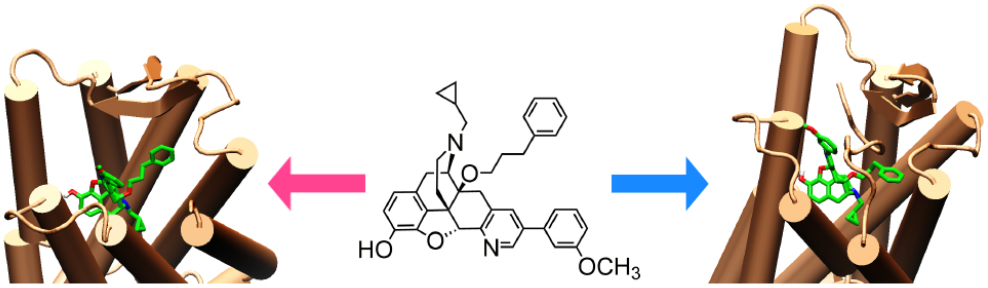
64. Ackley, D. C.; Rockich, K. T.; Baker, T. R., In Vitro Methods. In *Optimization in Drug Discovery*, Yan, Z.; Caldwell, G. W., Eds. Human Press: Totawa, NJ, 2004; p 151.

65. Sherman, W.; Day, T.; Jacobson, M. P.; Friesner, R. A.; Farid, R. Novel procedure for modeling ligand/receptor induced fit effects. *J. Med. Chem.* **2006**, *49*, 534–553.

Table of Contents graphic



Antinociceptive ED_{50} = 20.8 mg/kg
Diminished tolerance, reward, and respiratory depression



Antinociceptive ED_{50} = 20.8 mg/kg
Diminished tolerance, reward, and respiratory depression