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Substituted Tetrahydroisoquinolines as Selective Antagonists for the Orexin 1 Receptor

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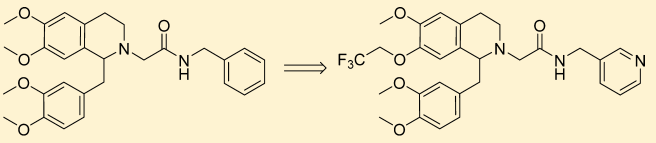
Supporting Information

ABSTRACT: Increasing evidence implicates the orexin 1 (OX_1) receptor in reward processes, suggesting OX_1 antagonism could be therapeutic in drug addiction. In a program to develop an OX_1 selective antagonist, we designed and synthesized a series of substituted tetrahydroisoquinolines and determined their potency in OX_1 and OX_2 calcium mobilization assays. Structure−activity relationship (SAR) studies revealed limited steric tolerance and a preference for electron deficiency at the 7-position. Pyridylmethyl groups were shown to be optimal for activity at the acetamide position. Computational studies resulted in a pharmacophore model and confirmed the SAR results. Compound **72** significantly attenuated the development of place preference for cocaine in rats.



6
Ke (OX_1) = 199 nM
Ke (OX_2) > 10000 nM

72
Ke (OX_1) = 8.5 nM
Ke (OX_2) > 10000 nM

INTRODUCTION

Orexin A and B, also known as hypocretin 1 and 2, are hypothalamic neuropeptides independently discovered by two groups in 1998.[1,2] They are the endogenous ligands for two G protein-coupled receptors (GPCRs), orexin 1 (OX_1) and orexin 2 (OX_2).[3,4] Orexin-expressing neurons are located predominantly in a small area of the hypothalamus.[2,5−7] However, the nerve fibers of orexin neurons project throughout the central nervous system (CNS).[1,7−9] Interestingly, orexin receptors have different patterns of expression: Some brain regions express predominantly OX_1, whereas others express predominantly OX_2,[2,10,11] suggesting that these receptors might modulate many unrelated functions, as also suggested by antagonist and knockout mouse studies.[3,4,12] The orexin system has been shown to play a role in a variety of important biological processes, including sleep/wake cycle,[13,14] feeding,[2] and energy homeostasis.[2]

Recently, the orexin system, particularly the OX_1 receptor, was implicated in drug reward, reinstatement of drug seeking, and psychomotor sensitization.[15−18] This is consistent with the findings that orexin neurons have a prominent input to the basal ganglia and forebrain structures (central amygdala, ventral bed nucleus of the stria terminalis, nucleus accumbens shell, ventral pallidum, and ventral tegmental area) that underlie motivation, reward, stress, and addiction-related behaviors.[19] Orexinergic signaling seems to be involved in the rewarding effects of natural rewards and some drugs. Mice lacking orexins not only have reduced appetite but also show much less addiction-like sequelae associated with exposure to morphine and amphetamines.[20,21] Chemical activation of lateral hypothalamus (LH) neurons reinstates extinguished morphine seeking in rats, and the effect is blocked by the selective OX_1 antagonist SB334867 (**1**).[16] Blockade of orexin A transmission also decreases alcohol self-administration and cue-induced reinstatement of extinguished alcohol and cocaine seeking,[22,23] and it attenuates the stress-induced reinstatement of extinguished cocaine and alcohol seeking.[19,24] Moreover, antagonism of orexin A transmission at the OX_1 receptor decreases nicotine self-administration in rats and the motivation to obtain the drug.[25]

Early efforts to modulate the orexin system have been focused on the blockade of both receptors, or OX_2 selectively, because of their well-recognized implications in the pathophysiology of sleep disorders. As a result, several structural classes of dual OX_1/OX_2 antagonists and OX_2-selective antagonists were developed (Figure 1).[12,26−29] The dual antagonists almorexant (**2**), SB-649868 (**3**), and suvorexant (**4**) entered clinical trials for insomnia.[27,28] However, relatively few OX_1-selective antagonists have been reported to date. Compound **1**, developed by GlaxoSmithKline, was the first selective OX_1 antagonist described.[30,31] It has a potency of ∼40 nM at OX_1 and is at least 50-fold selective for OX_1 over OX_2. Structure−activity relationship (SAR) studies have resulted in analogs with improved OX_1 selectivity,[32] but **1** remains an important tool to probe the pharmacology and function of OX_1. Despite its wide application, **1** has limitations including a less than desirable pharmacokinetic profile and a recently discovered hydrolytic instability in which the 2-methylbenzoxazole undergoes ring-opening under acidic conditions.[31,33] Other antagonists with

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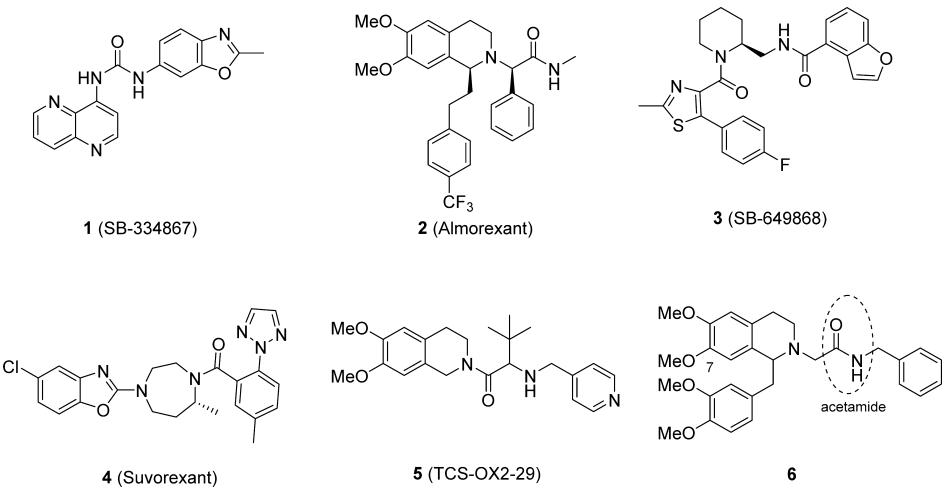
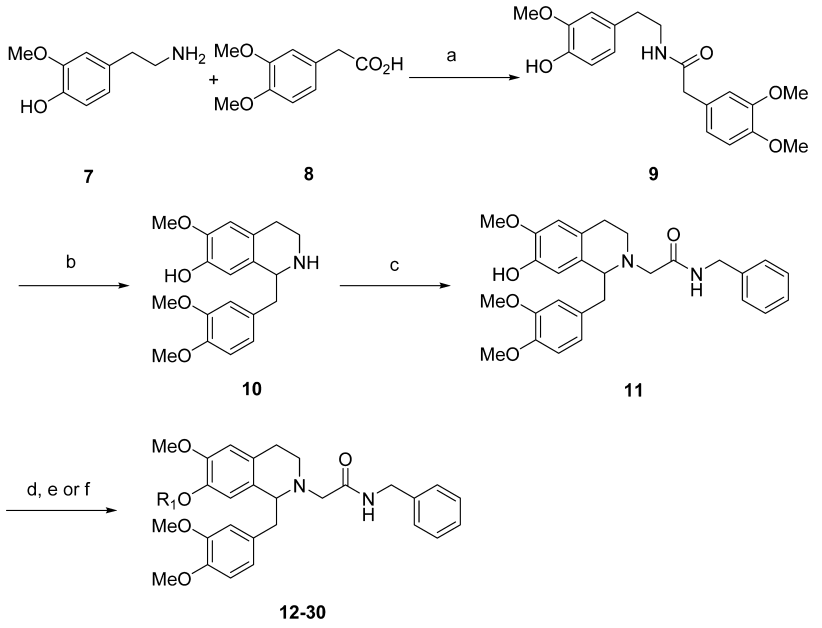


Figure 1. Orexin antagonists.

Scheme 1. Synthesis of 6-Methoxy-7-alkoxy-*N*-benzylacetamidotetrahydroisoquinolines[a]



[a]Reagents and conditions: (a) HBTU, *i*-Pr_2EtN, DMF; (b) (i) $POCl_3$, toluene, 90 °C, (ii) $NaBH_4$, MeOH; (c) $BrCH_2CONHBn$, *i*-Pr_2EtN, Bu_4NI, DMF; (d) R_1-Br, K_2CO_3, Bu_4NI, DMF; (e) R_1-I, Cs_2CO_3, DMF, 50 °C; (f) R-SO_2Cl, Et_3N, CH_2Cl_2 (R_1=R-SO_2).

OX_1 selectivity or preference are pyrrolidine-based SB674042 and disubstituted piperidines based on the structure of **3**.[34,35] Two compounds of the latter series showed OX_1 selectivity or preference, although significant OX_2 activity remains for most.[35] A similar approach by Rottapharm resulted in a number of spiro-piperidines and spiro-pyrrolidines with reasonable OX_1 potency and selectivity.[36] During the preparation of this manuscript, a phenylglycine-amide-substituted tetrahydroisoquinoline derivative (ACT-335827) was reported by Actelion that was potent and OX_1 selective; however, some OX_2 activity remained (IC_{50} OX_1 = 6 nM and OX_2 = 417 nM).[37]

Here, we report our efforts in developing OX_1-selective antagonists based on a tetrahydroisoquinoline scaffold as present in both **2** and TCS-OX2-29 (**5**), a selective OX_2 antagonist.[38] Compound **6**, identified in a high-throughput screening campaign by Actelion that led to the discovery of **2**, showed reasonable OX_1 activity and selectivity (IC_{50} OX_1 = 119 nM and OX_2 = 8100 nM).[39] Initial SAR studies by the same group identified several positions that could be modified to improve OX_1 activity. For example, replacement of the methoxy group at the 7-position with larger groups such as ethoxy or propoxy further increased OX_1 potency, whereas little OX_2 activity was observed. The present work further examines SARs within the tetrahydroisoquinoline series with the aim to improve their potency and selectivity over OX_2 and to identify a viable tool compound for pharmacological studies. Our investigation looked specifically at the structural requirement at the 7-position of the tetrahydroisoquinoline as well as the substitution pattern at the acetamide.

RESULTS AND DISCUSSION

Chemistry. 7-Alkoxytetrahydroisoquinolines were synthesized according to Scheme 1. Thus, amide coupling between amine **7** and acid **8** using HBTU yielded **9.** Bischler–

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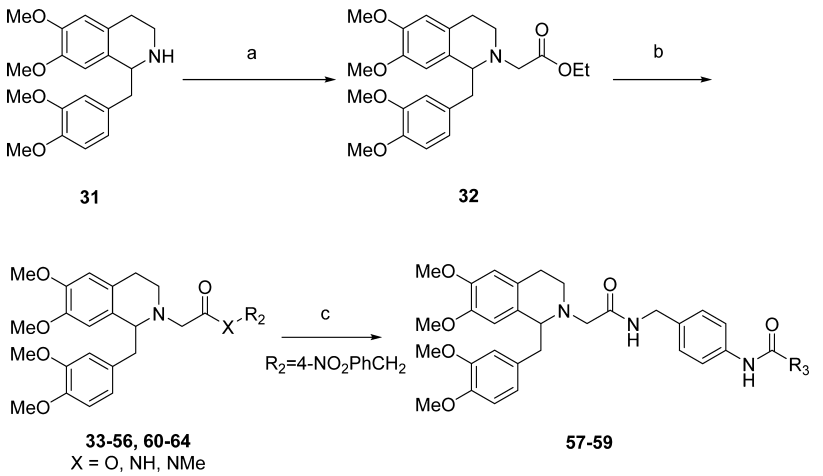
Scheme 2. Synthesis of *N*-Acetamidotetrahydroisoquinolines[a]



[a]Reagents and conditions: (a) $BrCH_2-CO_2Et$, *i*-Pr_2EtN, Bu_4NI, DMF; (b) (i) 2N NaOH, EtOH, (ii) R_2-NH_2 (or R_2-NHMe), BOP, *i*-Pr_2EtN, DMF or BnBr, K_2CO_3, Bu_4NI, DMF; (c) (i) Raney nickel, $NH_2NH_2{\cdot}H_2O$, EtOH, (ii) R_3-CO_2H and BOP, *i*-Pr_2EtN, CH_2Cl_2 or R_3CO_2O, *i*-Pr_2EtN, CH_2Cl_2 or R_3NCO, toluene.

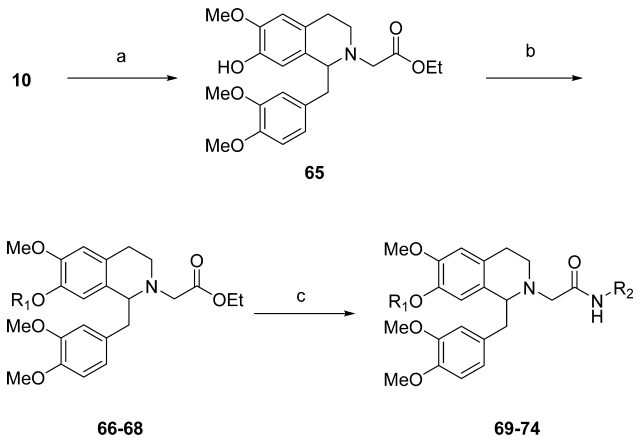
Napieralski reaction of **9** with phosphorus oxychloride in toluene at 90 °C gave the intermediate dihydroisoquinoline,[40] which was readily reduced to tetrahydroisoquinoline **10** using sodium borohydride. N-Alkylation with α-bromo-benzylacetoamide gave desired tetrahydroisoquinoline derivative **11**.[41,42] The 7-position could then be alkylated as desired using potassium carbonate as base and the addition of tetrabutylammonium iodide as appropriate. For trifluoroethyl analog **24**, better results were obtained using cesium carbonate at 50 °C. Sulfonates (**22**, **23**, **25**, and **26**) were prepared using the appropriate sulfonyl chloride in dichloromethane with triethylamine as base.

To prepare compounds varying in the N-acetamide (Scheme 2), the base tetramethoxy-tetrahydroisoquinoline (**31**) was made according to literature procedures and then N-alkylated by ethyl bromoacetate to give ester **32**.[39] The ester could then be hydrolyzed and the acid converted to the amide using BOP and the corresponding amine. Further elaboration of the 4-nitrophenyl derivative gave a series of acylated anilines, **57**–**59**. Benzyl ester **40** was also made by alkylation on the acid with benzyl bromide.

To prepare the 7-alkoxy derivatives with a greater variety in the acetamide, a series of compounds were synthesized via Scheme 3. Phenol **10** was alkylated with ethyl bromoacetate to give the tetrahydroisoquinoline acetate **65** in good yield. The phenol was then alkylated with the appropriate alkyl halide, with either potassium or cesium carbonate as base. Hydrolysis of ester **66**–**68** with aqueous sodium hydroxide in ethanol gave the acid, which could then be coupled with the desired amine using BOP as the coupling agent.

The activity of the target compounds at the OX_1 and OX_2 receptors was evaluated in a calcium mobilization-based functional assay. The apparent dissociation constant, K_e, was calculated from the compound-mediated inhibition of orexin A activity as previously described.[32] Briefly, EC_{50} curves of the agonist, orexin A, were obtained alone and together with the test compound, respectively, and the right-shift of the agonist curve was measured. The K_e values were then calculated using the equation $K_e = [L]/((EC_{50}^{-}/EC_{50}^{+}) - 1)$, where [L] is the test compound concentration, EC_{50}^{-} is the EC_{50} of orexin A alone, and EC_{50}^{+} is the EC_{50} of orexin A in the presence of the

Scheme 3. Synthesis of Tetrahydroisoquinoline Derivatives Varied at Both Acetamide and 7 Positions[a]



[a]Reagents and conditions: (a) $BrCH_2CO_2Et$, *i*-Pr_2EtN, Bu_4NI, DMF; (b) R_1-X, K_2CO_3 or Cs_2CO_3, Bu_4NI (for X = Br), DMF; (c) (i) 2N NaOH, EtOH, (ii) R_2-NH_2, BOP, *i*-Pr_2EtN, DMF.

test compound. In these assays, the EC_{50} for orexin A at OX_1 and OX_2 is 0.13 ± 0.02 and 4.2 ± 0.2 nM, respectively. All of the compounds that had OX_1 K_e values <1 μM were also tested alone at 10 μM as agonists at the OX_1 receptor. None of them showed any agonist activity. Because of the lack of commercially available radioligands, binding studies were not performed on these compounds.

Our studies on this series focused on two primary areas of the molecule: the 7-position of the tetrahydroisoquinoline moiety and the acetamide side chain. Table 1 shows the changes at the 7-position. Unsubstituted 7-hydroxy analog **11** showed micromolar potency at both OX_1 and OX_2. The OX_1 potency increased as the size of the alkoxy group increased (**6**, **12**, and **13**), in agreement with the literature.[39] However, the potency started to drop as the chain length further increased (**14** and **15**), and the isopentyl (**16**) was equipotent with hexyl (**15**). Finally, compound **17**, with the space-demanding cyclohexylmethyl group, had no OX_1 activity up to 10 μM, suggesting a limited bulk tolerance at this position. In an

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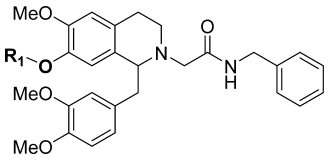
Table 1. Effect of the 7-Position Substitution on OX Antagonism



no.	R_1	K_e (OX_1, nM)[b]	K_e (OX_2, nM)[c]	OX_2/OX_1
11	H	1530 ± 530	5740 ± 96	3.8
6	methyl	199 ± 47	>10 000	>50.3
12	ethyl	30.0 ± 9.0	>10 000	>333
13	*n*-propyl	17.3 ± 3.1	>10 000	>578
14	*n*-butyl	54.7 ± 23	1890 ± 480	34.6
15	*n*-hexyl	315 ± 81	>10 000	>31.7
16	isopentyl	326 ± 46	3920 ± 1200	12.0
17	cyclohexylCH_2	>10 000	[a]	
18	Me_2N-CH_2CH_2	4740 ± 440	[a]	
19	Me_2N-$(CH_2)_4$	5740 ± 3600	[a]	
20	*N*-piperidinyl-CH_2CH_2	8040 ± 5400	[a]	
21	benzyl	402 ± 58	[a]	
22	2-pyridine-CH_2	101 ± 56	[a]	
23	3-pyridine-CH_2	277 ± 75	[a]	
24	PhO-$(CH_2)_4$	43.5 ± 9.2	>10 000	>230
25	$CH_3CH_2CH_2CO$	78.5 ± 24	>10 000	>127
26	CH_3SO_2	7.3 ± 2.7	2170 ± 790	297
27	CF_3SO_2	10.0 ± 2.8	>10 000	>1000
28	CF_3CH_2	9.4 ± 1.7	>10 000	>1060
29	$PhSO_2$	30.5 ± 9.1	2900 ± 191	95.1
30	4-Me$PhSO_2$	118 ± 54	[a]	

[a]Demonstrated <30% inhibition at 10 μM. [b]These values are the mean of at least three independent experiments performed in duplicate. [c]These values are the mean of at least two independent experiments performed in duplicate; for compounds with K_e < 100 nM at OX_1, at least three independent experiments in duplicate were performed.

attempt to probe possible hydrogen-bonding effects, heteroatoms as H acceptors were introduced on the alkyl chain, and this resulted in a significant decrease in potency (**18**, **19**, and **20**). Aromatic substituents were then examined. Although the benzyl (**21**) was similar in potency to the hexyl (**15**), the two pyridylmethyl analogs (**22** and **23**) showed a modest increase in potency over benzyl **21**. Interestingly, when a phenoxybutyl group was introduced, **24** displayed equipotency to the butyl analog. This may suggest additional aromatic-stacking interaction in this region, which is probably farther away from the tetrahydroisoquinoline core.

The electronic properties at the 7-position were also investigated. Butyryl analog **25** showed similar OX_1 activity as that of butyl compound **14**, suggesting that electron-withdrawing groups are tolerated. Interestingly, two highly electron-withdrawing sulfonate analogs (**26** and **27**) showed excellent potency, further confirming the preference of electronegativity at this position. Trifluoroethyl (**28**), a group that can be considered a bioisostere for acetyl or mesylate because of its electron-deficient character and similar size, gave a low nanomolar potency and an over 1000-fold selectivity over the OX_2 receptor. This also suggests that the observed high potency is a result of the electronic properties other than potential hydrogen-bonding interactions with the presence of the additional oxygen atoms. Finally, the phenyl (**29**) and tolyl (**30**) sulfonates both had higher potency than the benzyl analog.

At the acetamide position (Table 2), extending the benzyl to a phenethyl (**33**) or phenylpropyl (**34**) lowered the potency at OX_1. Conformational restriction of the aromatic group led to analogs such as tetrahydroisoquinoline **35**, piperidines **36** and **37**, and piperazine **38**, but none of these compounds showed any appreciable OX_1 activity. It was posited that the NH group might be required for potency, and, indeed, its importance was highlighted by *N*-methyl **39** and benzyl ester **40**, which both had a low potency at OX_1. None of these compounds showed any activity at OX_2.

Several fused aromatic or biphenyl systems were examined where the second aromatic ring occupies a similar position as that in the benzyl group but in a planar conformation. Naphthalene **41** had a K_e value of 732 nM, which is around 3.6-fold less potent than the benzyl compound. Heteroatom-containing aromatic systems such as quinolines **42** and **43** gave a further reduction in potency, suggesting a preference for a nonplanar conformation for the aromatic ring. We next examined a series of biphenyl analogs, **44**–**46**, with each acting as a phenyl spacer to the second aromatic ring. However, only 2-biphenyl **44** showed submicromolar OX_1 potency, with some activity at OX_2. These results suggest that a nonaromatic spacer is preferred for OX_1 potency. Indeed, the tetrahydronaphthalene (**47**) gave a K_e value of 41 nM, significantly more potent than naphthalene **41**. Interestingly, tetrahydroquinoline **48** was inactive, which shows that hydrophobic interactions might be preferred in this region of the molecule.

With the chiral center at the 1-position of the tetrahydroisoquinoline, substitution with a methyl at the α-position of the benzyl group (*S*-α-methylbenzyl) gave two diastereomers, which were separated by HPLC into compounds **49** and **50**. Although **50** showed good OX_1 potency and selectivity, **49** was inactive at 10 μM at both receptors. This is consistent with previous findings that the S conformation at the 1-position of the tetrahydroisoquinoline is required in **2** and its analogs.[28,43]

Substituents on the phenyl ring were generally well tolerated, with chloride **51** and fluoride **52** being about equipotent with the benzyl (**6**), suggesting that electron-withdrawing groups are tolerated. Among the pyridylmethyl analogs, the 3-pyridyl (**54**) showed a similar potency as the 2-analog (**53**), of which both were more potent than the 4-analog (**55**). Interestingly, the electron-rich dimethylamino (**56**) showed limited OX_1 potency in the micromolar range. To determine whether this activity loss is due to electronic or steric reasons, substituents, including amides and ureas, were introduced onto the nitrogen. Surprisingly, the acetyl group (**57**) resulted in a total loss of OX_1 activity. Large amide **58** and urea **59** showed no or little potency, suggesting limited or no tolerance for size at the 4-position of the benzyl group.

Finally, the requirement for aromaticity was investigated at the acetamide position. Straight-chain heptyl analog **60** showed a modest potency at 500 nM, although it was poorly selective over OX_2. Attempts to introduce heteroatoms or polar groups (**61**–**64**) all resulted in a dramatic loss of OX_1 potency. Taken together, these findings suggest that an aromatic group is generally needed for OX_1 potency and selectivity.

Although none of the acetamide substituents gave a significant improvement in potency from that of parent benzyl compound **6**, pyridylmethyl analogs **54** and **55** showed the most promise given their improved physicochemical properties because of the possibility of salt formation. Thus, several

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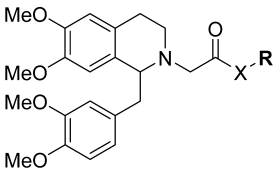
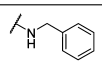
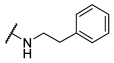
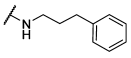
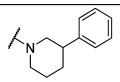
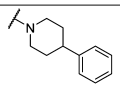
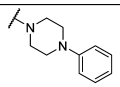
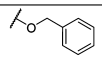
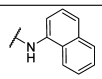
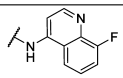
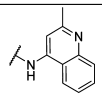
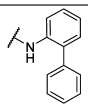
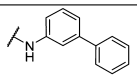
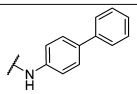
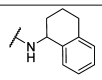
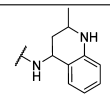
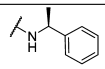
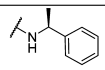
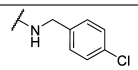
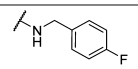
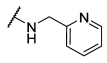
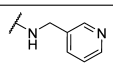
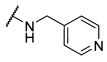
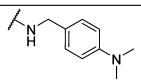
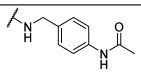
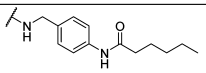
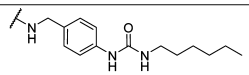
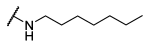
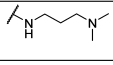
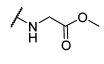
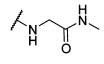
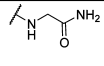
Table 2. Effect of N-Alkylation on OX Antagonism



No.	X-R	Ke (OX_1, nM)[b]	Ke (OX_2, nM)[c]	OX_2/OX_1
6		199 ±47	>10000	>50.3
33		3250 ±230	[a]	
34		2370 ±240	[a]	
35		3030 ±170	9000 ±760	3.0
36		3530 ±650	9030 ±3800	2.6
37		>10000	[a]	
38		>10000	[a]	
39		2090 ±330	>10000	>4.8
40		>10000	[a]	
41		732 ±250	[a]	
42		4220 ±1100	[a]	
43		4510 ±430	[a]	
44		944 ±160	1760 ±370	1.9
45		8980 ±2200	[a]	
46		2240 ±110	[a]	
47		41.1 ±6.0	655 ±190	15.9

No.	X-R	Ke (OX_1, nM)[b]	Ke (OX_2, nM)[c]	OX_2/OX_1
48		7170 ±390	[a]	
49	 (diastereomer 1)	>10000	[a]	
50	 (diastereomer 2)	80.0 ±12	>10000	>125
51		162 ±16	2270 ±110	14.0
52		279 ±81	3460 ±1000	12.4
53		261 ±120	>10000	>38.3
54		152 ±41	>10000	>65.8
55		1010 ±160	[a]	
56		3230 ±1300	>10000	>3.1
57		>10000	[a]	
58		>10000	3790 ±670	<0.4
59		3680 ±1800	2440 ±670	0.7
60		589 ±230	2310 ±540	3.9
61		>10000	[a]	
62		6630 ±350	[a]	
63		7640 ±1100	[a]	
64		>10000	[a]	

[a]Demonstrated <30% inhibition at 10 μM. [b]These values are the mean of at least three independent experiments performed in duplicate. [c]These values are the mean of at least two independent experiments performed in duplicate; for compounds with K_e < 100 nM at OX_1, at least three independent experiments in duplicate were performed.

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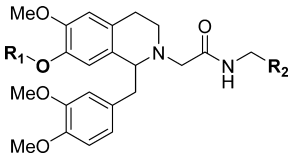
pyridylmethyl analogs were studied in conjunction with the more potent 7-position substituents (Table 3). Such analogs include 2- and 3-pyridines combined with the 7-ethoxy, propoxy, and trifluoroethoxy derivatives (**69**–**74**). All compounds showed good to excellent OX_1 potency (8–87 nM) and high selectivity over OX_2, with none of the compounds showing any activity at 10 μM.

Table 3. Effect of Multiple Changes on OX Antagonism



no.	R_1	R_2	K_e (OX_1, nM)[a]	K_e (OX_2, nM)[a]	OX_2/OX_1
69	*n*-propyl	2-pyridyl	20.6 ± 5.5	>10 000	>485
70	*n*-propyl	3-pyridyl	41.9 ± 16	>10 000	>239
71	CF_3CH_2	2-pyridyl	22.5 ± 2.7	>10 000	>444
72	CF_3CH_2	3-pyridyl	8.5 ± 1.0	>10 000	>1180
73	ethyl	2-pyridyl	87.4 ± 12	>10 000	>114
74	ethyl	3-pyridyl	15.7 ± 1.7	>10 000	>637

[a]These values are the mean of at least three independent experiments performed in duplicate.

Computational Analysis. A comprehensive 3D pharmacophore for the orexin antagonists evaluated in this study was developed. The pharmacophore was initiated by generating conformational libraries for each analog in this class. This included computation of the 3D distance metrics between four candidate pharmacophore points (variable substituents off the 7-position, the two centroids for each of the aromatic ring substituents, and the nitrogen on the tetrahydroisoquinoline core) and the determination of the conformations of each ligand giving rise to a common 3D display (Figure 2A,B). Superposition of all ligands in the training set with these four pharmacophore points allowed us to investigate a series of substituent properties that proved to be important for OX_1 potency. Twenty-one properties, including stereochemical (Verloop parameters,[44,45] volume, area, and globularity), electrostatic (positions of electrostatic minima and maxima), polar (polar surface area), electronic (E-HOMO, E-LUMO, and polarizability), thermodynamic (vibrational and rotational heat capacity and entropies at 300 K), and atom-based hydrophobicity (clogP) were evaluated for ligand conformations that complied with a 3D pharmacophore overlap rule.[46] In addition, the same subset of properties was computed for substituents (fragments) alone without the tetrahydroisoquinoline core compliant pharmacophoric region. This dual approach was chosen to allow the addition of substituent-independent properties to the QSAR analysis.

Three properties were found to correlate the structural modification at the 7-position with alterations in OX1 potency using a three-variable QSAR analysis. The Sterimol parameters, including the spatial extent of the substituent at position 7 and particularly the width (Verloop B1) relative to the long axis, logP of the substituent, and energy of the lowest unoccupied molecular orbital (E-LUMO), demonstrated statistically significant correlations with changes in OX_1 potency (R^2 = 0.69) (Figure 2C). It is apparent from the 3D QSAR model (Figure 2D) and the functional activity data that the size of the substituent at the 7-position plays a considerable role in determining potency. OX_1 potency increases monotonically from 1530 to 17 nM for compounds **11** (−OH), **6** ($-OCH_3$), **12** ($-OCH_2CH_3$), and **13** ($-OCH_2CH_2CH_3$), respectively, at which point the trend begins to reverse. This indicates that substituents of a particular size are required for activity.

Although steric properties at the 7-position play a main role in determining potency, the QSAR analysis also highlights the importance of other nonobservable factors, such as LUMO energy, on antagonist potency. Figure 2E depicts the spatial distribution of the LUMO density on compound **6**. Position 7 is on the aromatic ring most associated with LUMO electron density. Naturally, substitutions at that position would modulate the energy of the LUMO orbital and charge-density transfer, a facet plausibly having a role in stabilization of the receptor bound ligand configuration.

Figure 3 depicts a similar 3D QSAR and COMFA analysis for substituent variation corresponding to the N-alkylation variations summarized in Table 2. Figure 3B illustrates results from a COMFA analysis of the training set superposition shown in Figure 3A. Both steric and electrostatic variations in the ligand substituents contributed relatively equally to the underlying rationale for the $K_e(OX_1)$ variations. This was independently verified in the 2D QSAR analysis shown in Figure 3D, where coefficients of the B1 Verloop parameter and the polar surface area made significant contributions along with the energy of the HOMO and led to a model predictive of ln $K_e(OX_1)$. Analogous to our identification of the E(LUMO) term for position 7 variations, the atomic centers containing the highest occupied molecular orbital were found on the ring system directly attached to the position 2 substitutions. The results from these studies highlight the manner in which substitutions can be rationalized in terms of underlying physical properties keyed to the molecular interactions and binding free energies, and they provide a basis for a comprehensive 3D pharmacophore.

Through the establishment of this 3D pharmacophore model, a basic understanding of the impact that specific substitutions have on receptor potency and selectivity has been achieved. This information will be important to guide the selection of scaffold modifications to favorably alter receptor potency, subtype selectivity, or ADM. Alternatively, establishing quantitative pharmacophore models allows us to transfer the information from the 3D display of physiochemical properties to new scaffolds with an understanding of those that are critical for activity.

Conditioned Place Preference. Given the well-established activity of OX_1 antagonists in attenuating the rewarding and reinforcing the effects of drugs, compound **72** was studied in conditioned place preference (CPP). As shown in Figure 4, the vehicle did not produce significant CPP. Cocaine at 10 mg/kg induced a robust and significant CPP. Compound **72** at 20 mg/kg did not produce CPP or place aversion but significantly attenuated the development of place preference induced by cocaine.

CONCLUSIONS

To develop OX_1-selective antagonists, we synthesized and evaluated a series of tetrahydroisoquinolines, a core structure that is present in both dual OX_1/OX_2 antagonist **2** and OX_2-selective antagonist **5**. SAR studies suggested a preference for steric bulk at the 7-position; however, this tolerance is limited, as the potency decreases with the further size increase of the substituents. Electron-deficient groups are also well tolerated at

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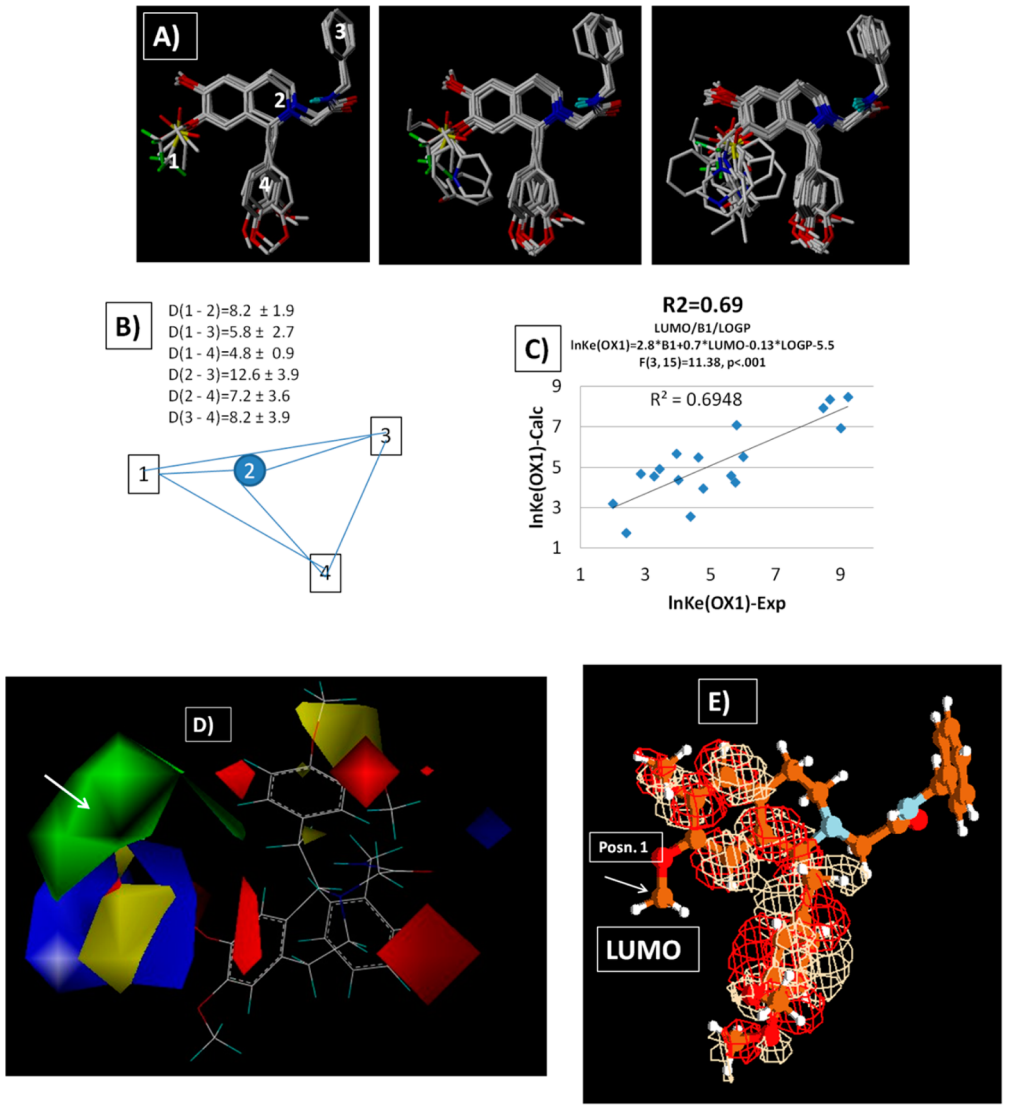

Figure 2. (A) Ligands superimposed at 3D pharmacophore points defined by (B) the abstract pharmacophore representation computed from 21 ligands in Table 1. (C) Plot of the predicted ln $K_e(OX_1)$ vs experimental for a fragment (2D) QSAR illustrating that contributions from the width (Verloop Sterimol "B1"), polar surface area, clogP, and lowest unoccupied (LUMO) energy of the substituent give a robust analysis (R^2 = 0.7/F = 8.2 (n1 = 4, n2 = 18), p = 0.001/2.8B1 + 0.7×E(LUMO) − 0.13logP −5.5). (D) 3D COMFA/QSAR illustrating that the increased steric-bulk contributions region of the substituent variation highlighted by green correlate with low K_e values with minor modulation because of electrostatic contributions. (E) Depiction of the location of the LUMO density on compound **6**.

this position. At the acetamide position, an aromatic system was generally preferred, and the pyridylmethyl groups gave the best potency. The pharmacophore model obtained through computational analysis confirmed the steric and electronic requirement at the 7-position. This model also suggests that steric and electrostatic variations in the ligand substituents contributed equally to the underlying rationale for the $K_e(OX_1)$ variations at the acetamide position. In the CPP paradigm, compound **72**, which had excellent OX_1 potency and selectivity over OX_2 in the calcium assay, significantly attenuated cocaine CPP. In summary, several compounds with excellent potency at and selectivity for the OX_1 receptor have been identified, and they will serve as probes to investigate further the pharmacology and function of the OX_1 receptor and the orexin system. Modifications at other positions are ongoing and will be reported in due course.

EXPERIMENTAL SECTION

Chemistry. All solvents and chemicals were reagent grade. Unless otherwise mentioned, all solvents and chemicals were purchased from commercial vendors and used as received. Flash column chromatography was done with a Teledyne ISCO CombiFlash Rf system using prepacked columns. The solvents used were hexane, ethyl acetate (EtOAc), dichloromethane, methanol and chloroform/methanol/ammonium hydroxide (80:18:2) (CMA-80). The purity and characterization of the compounds was established by a combination of high-pressure liquid chromatography (HPLC), thin-layer chromatography (TLC), mass spectrometry (MS), and nuclear magnetic resonance (NMR) analysis. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in chloroform-d or methanol-d_4 with tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Chemical shifts are reported in ppm relative to the reference signal, and coupling constant (J) values are reported in Hz. TLC was done on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or iodine staining. Low-resolution mass spectra were obtained using a Waters Alliance HT/Micromass ZQ system (ESI). All test compounds were

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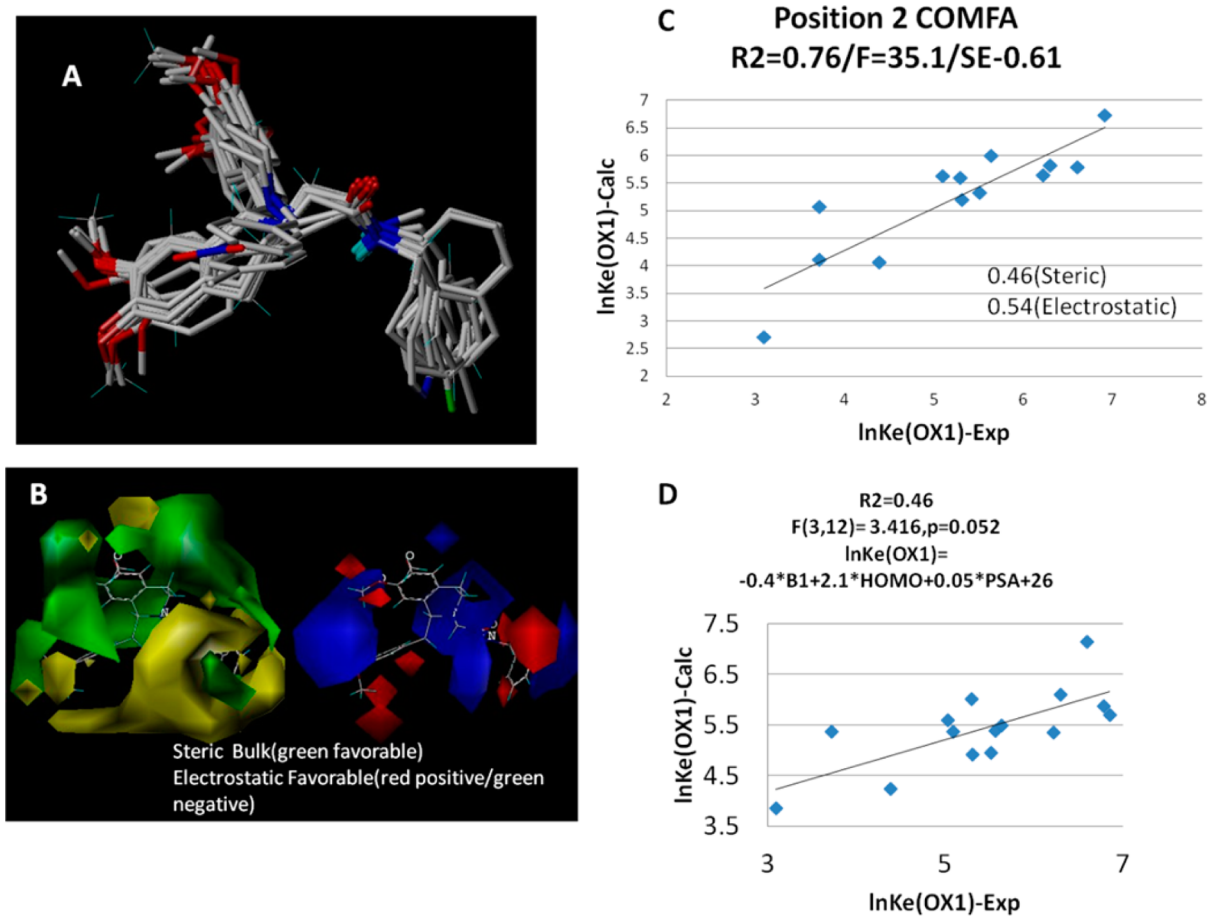

Figure 3. Depiction of COMFA steric (left) and electrostatic fields (right) about compound **6** derived from the analysis of **6**, **20**, **21**, **23**, **30**, **41**, **44**, **47**, **50**, **51**, **52**, **55**, and **60**. The analysis (R^2 = 0.761/F[n1 = 1, n2 = 11]) 35.108, SE = 0.61) for ln $K_e(OX_1)$ using the 3D pharmacophore quaternion least-squares superposition of the pharmacophore points illustrated in Figure 2.

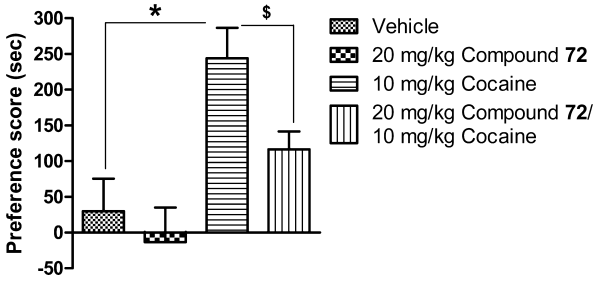

Figure 4. Effects of compound **72** on cocaine-induced conditioned place preference in rats (n = 8 to 9). The data are presented as the mean ± SEM. * P < 0.05 as compared to vehicle-treated rats. $ P < 0.05 as compared to 10 mg/kg cocaine-treated rats.

greater than 95% pure (except where noted), as determined by HPLC on an Agilent 1100 system using an Agilent Zorbax SB-Phenyl, 2.1 × 150 mm^2, 5 μm column with gradient elution using mobile phases (A) H_2O containing 0.1% CF_3COOH and (B) MeCN, with a flow rate of 1.0 mL/min.

*2-(3,4-Dimethoxyphenyl)-N-[2-(4-hydroxy-3-methoxyphenyl)-ethyl]acetamide (**9**).* 3,4-Dimethoxyphenylacetic acid (0.45 g, 2.29 mmol), 4-hydroxy-3-methoxyphenethylamine hydrochloride (0.47 g, 2.29 mmol), and HBTU (0.96 g, 2.52 mmol) were combined in dry dimethylformamide (20 mL) at rt under N_2. Diisopropylethylamine (1.19 g, 1.6 mL, 9.17 mmol) was added, and the reaction was stirred at rt overnight. The reaction was diluted with ethyl acetate, washed with 2N hydrochloric acid, sodium bicarbonate solution, and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the desired amide as a yellow oil that solidified upon standing (0.72 g, 91%). ^{1}H NMR (300 MHz, chloroform-d) δ 2.67 (t, J = 6.88 Hz, 2H), 3.36−3.43 (m, 2H), 3.45 (s, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 6.04 (br s, 1H), 6.44−6.53 (m, 1H), 6.61 (d, J = 1.70 Hz, 1H), 6.66−6.77 (m, 3H), 6.78−6.86 (m, 1H), 7.97 (s, 1H).

*General Procedure for the Bischler−Napieralski Reaction/Sodium Borohydride Reduction. 1-[(3,4-Dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (**10**).* Amide **9** (0.39 g, 0.91 mmol) was suspended in anhydrous toluene (5 mL), and phosphorus oxychloride (0.70 g, 0.4 mL, 4.56 mmol) was added slowly. The reaction was heated at 90 °C for 2 h. The reaction was cooled, quenched by the slow addition of the reaction mixture to water, and stirred vigorously at room temperature for 15 min. A sodium hydroxide solution (2N) was added until pH was 8 to 9, and the solution was then extracted three times with dichloromethane. The combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure.

The crude dihydroisoquinoline was dissolved in methanol (5 mL) and cooled in an ice bath under N_2. Sodium borohydride (0.17 g, 4.52 mmol) was added portionwise, and the reaction was allowed to warm slowly to rt overnight. The reaction was quenched with water, and the methanol was removed under reduced pressure. The aqueous solution was extracted three times with dichloromethane, the combined extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to give desired tetrahydroisoquinoline **10** as a frothy solid (0.26 g, 67%). ^{1}H NMR (300 MHz, chloroform-d) δ 2.59−2.93 (m, 5H), 3.11−3.24 (m, 1H), 3.34−3.58 (m, 2H), 3.79−3.92 (m, 9H), 4.08 (dd, J = 9.42, 3.20 Hz, 1H), 6.57 (s, 1H), 6.60−6.71 (m, 1H), 6.72−6.88 (m, 3H).

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*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**11**).* Amine **10** (3.65 g, 11.08 mmol), *N*-benzyl-2-bromoacetamide (3.77 g, 16.62 mmol), and tetrabutylammounium iodide (0.82 g, 2.21 mmol) were combined in dry DMF (110 mL), and diisopropylethylamine (3.58 g, 4.8 mL, 27.70 mmol) was added. The reaction was stirred at rt overnight under N_2. The reaction was diluted with EtOAc, washed with a $NaHCO_3$ solution, water, and brine (×2), and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica (0−100% EtOAc in hexane) to obtain the desired product as a frothy white solid (2.98 g, 56%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.15−7.36 (m, 3H), 7.07 (d, *J* = 7.06 Hz, 2H), 6.89 (br s, 1H), 6.65−6.77 (m, 4H), 6.52−6.64 (m, 3H), 5.51 (s, 1H), 4.48 (dd, *J* = 8.24, 15.02 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.33−3.68 (m, 3H), 3.06−3.32 (m, 2H), 2.78−2.99 (m, 4H), 2.46 (d, *J* = 15.82 Hz, 1H). *m*/*z* 477 (M + H).

*General Procedure for O-Alkylation. N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**12**).* Phenol **11** (25 mg, 0.025 mmol) and potassium carbonate (22 mg, 0.157 mmol) were combined in dry dimethylformamide, 1-bromoethane (12 mg, 6 μL, 0.079 mmol) was added, and the reaction was stirred at rt under N_2 overnight. The reaction mixture was diluted with ethyl acetate, washed with a sodium bicarbonate solution and brine, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−75% EtOAc in hexane) to obtain the desired product as a pale-yellow solid (19 mg, 73%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.19−7.34 (m, 3H), 7.07−7.14 (m, 1H), 6.94−7.01 (m, 1H), 6.56−6.74 (m, 5H), 6.48 (s, 1H), 4.49 (dd, *J* = 8.05, 14.93 Hz, 1H), 4.02 (q, *J* = 6.97 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.57−3.70 (m, 2H), 3.34−3.48 (m, 1H), 3.12−3.34 (m, 2H), 2.79−2.99 (m, 4H), 2.41−2.54 (m, 1H), 1.45 (t, *J* = 6.97 Hz, 3H). *m*/*z* 505 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**6**).* Prepared in 51% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.18−7.35 (m, 2H), 7.07−7.14 (m, 2H), 6.98 (dd, *J* = 4.94, 7.58 Hz, 1H), 6.62−6.74 (m, 3H), 6.59 (s, 1H), 6.45 (s, 1H), 4.50 (dd, *J* = 8.05, 14.93 Hz, 1H), 3.84−3.89 (m, 3H), 3.81 (d, *J* = 1.88 Hz, 6H), 3.78−3.83 (m, 6H), 3.75 (s, 3H), 3.59−3.71 (m, 2H), 3.35−3.48 (m, 1H), 3.11−3.35 (m, 2H), 2.80−3.00 (m, 4H), 2.41−2.55 (m, 1H). *m*/*z* 491 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**13**).* Prepared in 48% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.20−7.34 (m, 3H), 7.07−7.14 (m, 2H), 6.98 (dd, *J* = 4.95, 7.77 Hz, 1H), 6.61−6.75 (m, 3H), 6.59 (s, 1H), 6.47 (s, 1H), 4.50 (dd, *J* = 8.10, 14.98 Hz, 1H), 3.89 (t, *J* = 6.88 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.58−3.70 (m, 2H), 3.34−3.48 (m, 1H), 3.11−3.34 (m, 2H), 2.79−2.99 (m, 4H), 2.49 (d, *J* = 15.92 Hz, 1H), 1.77−1.92 (m, 2H), 1.00−1.09 (m, 3H). *m*/*z* 519 (M + H).

*N-Benzyl-2-{7-butoxy-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**14**).* Prepared in 75% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.19−7.35 (m, 3H), 7.10 (d, *J* = 6.78 Hz, 2H), 6.93−7.02 (m, 1H), 6.61−6.75 (m, 3H), 6.58 (s, 1H), 6.47 (s, 1H), 4.50 (dd, *J* = 8.10, 14.98 Hz, 1H), 3.89−3.97 (m, 2H), 3.83−3.87 (m, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.58−3.71 (m, 2H), 3.34−3.48 (m, 1H), 3.11−3.34 (m, 2H), 2.80−2.98 (m, 4H), 2.42−2.54 (m, 1H), 1.75−1.88 (m, 2H), 1.42−1.55 (m, 2H), 0.98 (t, *J* = 7.30 Hz, 3H). *m*/*z* 533 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-(hexyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**15**).* Prepared in 64% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.18−7.35 (m, 3H), 7.10 (d, *J* = 6.69 Hz, 2H), 6.97 (dd, *J* = 4.99, 7.44 Hz, 1H), 6.61−6.76 (m, 3H), 6.58 (s, 1H), 6.48 (s, 1H), 4.50 (dd, *J* = 8.10, 14.98 Hz, 1H), 3.92 (t, *J* = 6.83 Hz, 2H), 3.82−3.87 (m, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.58−3.69 (m, 2H), 3.34−3.49 (m, 1H), 3.11−3.34 (m, 2H), 2.80−2.99 (m, 4H), 2.41−2.54 (m, 1H), 1.75−1.89 (m, 2H), 1.30−1.53 (m, 6H), 0.91 (t, *J* = 6.90 Hz, 3H). *m*/*z* 561 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-(3-methylbutoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**16**).* Prepared in 88% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.20−7.36 (m, 3H), 7.11 (d, *J* = 6.97 Hz, 2H), 6.95−7.04 (m, 1H), 6.62−6.76 (m, 3H), 6.59 (s, 1H), 6.48 (s, 1H), 4.51 (dd, *J* = 8.01, 14.98 Hz, 1H), 3.95 (t, *J* = 6.88 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.60−3.71 (m, 2H), 3.35−3.49 (m, 1H), 3.13−3.34 (m, 2H), 2.78−2.99 (m, 4H), 2.49 (d, *J* = 15.73 Hz, 1H), 1.84 (td, *J* = 6.62, 13.33 Hz, 1H), 1.71−1.77 (m, 2H), 0.98 (d, *J* = 6.50 Hz, 6H). *m*/*z* 547 (M + H).

*N-Benzyl-2-[7-(cyclohexylmethoxy)-1-[(3,4-dimethoxyphenyl)-methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (**17**).* Prepared in 33% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.19−7.34 (m, 3H), 7.10 (d, *J* = 6.78 Hz, 2H), 7.01 (d, *J* = 6.97 Hz, 1H), 6.61−6.76 (m, 3H), 6.58 (s, 1H), 6.45 (s, 1H), 4.49 (dd, *J* = 8.01, 14.98 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.59−3.72 (m, 4H), 3.34−3.47 (m, 1H), 3.12−3.34 (m, 2H), 2.79−2.95 (m, 4H), 2.48 (d, *J* = 16.01 Hz, 1H), 1.61−1.97 (m, 6H), 0.92−1.40 (m, 5H). *m*/*z* 573 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-[2-(dimethylamino)ethoxy]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**18**).* Prepared in 46% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.19−7.34 (m, 3H), 7.07−7.14 (m, 2H), 6.95 (dd, *J* = 4.76, 7.77 Hz, 1H), 6.68−6.75 (m, 2H), 6.61−6.67 (m, 1H), 6.59 (s, 1H), 6.56 (s, 1H), 4.50 (dd, *J* = 8.19, 14.98 Hz, 1H), 4.01−4.12 (m, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.57−3.68 (m, 2H), 3.36−3.50 (m, 1H), 3.12−3.34 (m, 2H), 2.83−2.99 (m, 4H), 2.75−2.82 (m, 2H), 2.44−2.54 (m, 1H), 2.38 (s, 6H). *m*/*z* 548 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-[4-(dimethylamino)butoxy]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**19**).* Phenol **11** (0.30 g, 0.63 mmol) and potassium carbonate (0.35 g, 1.26 mmol) were combined in dimethylformamide (6 mL), and 1-bromo-4-chlorobutane (0.22 g, 0.15 mL, 1.26 mmol) was added. The reaction was heated at 50 °C overnight. The reaction was cooled, diluted with water, and extracted twice with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was then purified by chromatography on silica (0−80% EtOAc in hexane) to obtain the desired chloride (0.22 g, 61%) for use in the following reaction. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.20−7.35 (m, 3H), 7.11 (d, *J* = 7.16 Hz, 2H), 6.93−7.01 (m, 1H), 6.62−6.75 (m, 3H), 6.60 (s, 1H), 6.48 (s, 1H), 4.50 (dd, *J* = 14.93, 8.05 Hz, 1H), 3.97 (t, *J* = 5.51 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.58−3.70 (m, 4H), 3.36−3.55 (m, 1H), 3.12−3.34 (m, 2H), 2.79−2.98 (m, 4H), 2.42−2.56 (m, 1H), 1.94−2.03 (m, 4H).

The chloride (30 mg, 0.053 mmol), dimethylamine hydrochloride (7 mg, 0.079 mmol), potassium carbonate (18 mg, 0.132 mmol), and tetrabutylammonium iodide (4 mg, 0.011 mmol) were combined in dimethylformamide (0.5 mL) and heated at 50 °C overnight. The reaction was cooled, diluted with water, and extracted three times with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−50% CMA-80 in EtOAc) to give the desired product (6 mg, 19%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.19−7.35 (m, 3H), 7.07−7.15 (m, 2H), 6.91−7.00 (m, 1H), 6.62−6.76 (m, 3H), 6.59 (s, 1H), 6.51 (s, 1H), 4.50 (dd, *J* = 8.15, 15.02 Hz, 1H), 3.98 (t, *J* = 6.50 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.57−3.68 (m, 2H), 3.36−3.49 (m, 1H), 3.11−3.34 (m, 2H), 2.81−2.99 (m, 4H), 2.43−2.54 (m, 1H), 2.33−2.42 (m, 2H), 2.27 (s, 6H), 1.79−1.92 (m, 2H), 1.62−1.76 (m, 2H). *m*/*z* 576 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-[2-(piperidin-1-yl)ethoxy]-1,2,3,4-tetrahydroisoquinolin-2-yl}-acetamide (**20**).* Prepared in 24% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.20−7.35 (m, 3H), 7.10 (d, *J* = 7.06 Hz, 2H), 6.93 (dd, *J* = 4.71, 7.82 Hz, 1H), 6.68−6.76 (m, 2H), 6.61−6.66 (m, 1H), 6.59−6.61 (m, 1H), 6.58 (s, 1H), 4.49 (dd, *J* = 8.24, 15.02 Hz, 1H), 4.11 (t, *J* = 6.45 Hz, 2H), 3.85 (s, 3H), 3.81−3.84 (m, 3H), 3.74 (s, 3H), 3.55−3.65 (m, 2H), 3.36−3.51 (m, 1H), 3.11−3.33 (m, 2H), 2.75−2.98 (m, 6H), 2.41−2.61 (m, 5H), 1.56−1.71 (m, 4H), 1.48 (d, *J* = 4.99 Hz, 2H). *m*/*z* 588 (M + H).

*N-Benzyl-2-[7-(benzyloxy)-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (**21**).* Pre-

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pared in 78% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.39 (td, *J* = 7.11, 15.16 Hz, 3H), 7.19−7.33 (m, 4H), 7.10 (d, *J* = 6.69 Hz, 2H), 6.91−7.01 (m, 1H), 6.57−6.70 (m, 5H), 6.49 (s, 1H), 5.06 (s, 2H), 4.48 (dd, *J* = 8.05, 14.93 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.52−3.70 (m, 2H), 3.32−3.45 (m, 1H), 3.10−3.32 (m, 2H), 2.79−2.98 (m, 3H), 2.67−2.78 (m, 1H), 2.41−2.53 (m, 1H). *m*/*z* 567 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**22**).* Prepared in 61% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.60 (d, *J* = 4.71 Hz, 1H), 7.68−7.77 (m, 1H), 7.58 (d, *J* = 7.82 Hz, 1H), 7.17−7.35 (m, 5H), 7.08 (d, *J* = 7.06 Hz, 2H), 6.89 (br s, 1H), 6.56−6.75 (m, 4H), 5.27 (s, 2H), 4.48 (dd, *J* = 8.19, 14.98 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.50−3.62 (m, 2H), 3.33−3.48 (m, 1H), 3.08−3.31 (m, 2H), 2.68−3.00 (m, 4H), 2.48 (d, *J* = 15.64 Hz, 1H). *m*/*z* 568 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-(pyridin-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**23**).* Prepared in 47% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.68 (s, 1H), 8.58 (d, *J* = 4.71 Hz, 1H), 7.79 (d, *J* = 7.82 Hz, 1H), 7.18−7.37 (m, 4H), 7.11 (d, *J* = 7.06 Hz, 2H), 6.98 (br s, 1H), 6.57−6.73 (m, 4H), 6.50 (s, 1H), 5.05 (s, 2H), 4.49 (dd, *J* = 8.01, 14.98 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.54−3.71 (m, 2H), 3.34−3.48 (m, 1H), 3.10−3.33 (m, 2H), 2.72−3.01 (m, 4H), 2.43−2.57 (m, 1H). *m*/*z* 568 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-(4-phenoxybutoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**24**).* Prepared in 82% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.20−7.36 (m, 5H), 7.11 (d, *J* = 6.78 Hz, 2H), 6.87−7.01 (m, 4H), 6.62−6.76 (m, 3H), 6.60 (s, 1H), 6.51 (s, 1H), 4.51 (dd, *J* = 8.05, 14.93 Hz, 1H), 3.98−4.11 (m, 4H), 3.84 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.58−3.70 (m, 2H), 3.35−3.51 (m, 1H), 3.11−3.34 (m, 2H), 2.81−3.02 (m, 4H), 2.42−2.56 (m, 1H), 1.94−2.11 (m, 4H). *m*/*z* 624 (M + H).

*2-[(Benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl butanoate (**25**).* Phenol **11** (50 mg, 0.105 mmol), butyric acid (9 mg, 0.105 mmol), and BOP (46 mg, 0.105 mmol) were combined in dichloromethane (1 mL). Diisopropylethylamine (34 mg, 46 μL, 0.262 mmol) was added, and the reaction was stirred at rt under N_2 overnight. The reaction was diluted with EtOAc, washed with 2 M HCl, an $NaHCO_3$ solution, and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica (0−75% EtOAc in hexane) to give the desired product as a pale-yellow solid (54 mg, 95%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.18−7.34 (m, 4H), 7.10 (d, *J* = 6.69 Hz, 2H), 6.92 (d, *J* = 6.97 Hz, 1H), 6.74 (s, 1H), 6.56−6.71 (m, 4H), 4.47 (dd, *J* = 8.01, 15.07 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.59−3.70 (m, 2H), 3.11−3.44 (m, 3H), 2.77−3.01 (m, 4H), 2.55 (t, *J* = 7.00 Hz, 2H), 2.49 (d, *J* = 2.64 Hz, 1H), 1.72−1.87 (m, 2H), 1.05 (t, *J* = 7.39 Hz, 3H). *m*/*z* 547 (M + H).

*General Procedure for Sulfonate Formation: 2-[(Benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl Methanesulfonate (**26**).* To a solution of phenol **11** (30 mg, 0.063 mmol) in dichloromethane (0.5 mL) cooled in ice under N_2 was added triethylamine (16 mg, 22 μL, 0.157 mmol) and methanesulfonyl chloride (14 mg, 10 μL, 0.126 mmol). The reaction was allowed to warm slowly to rt overnight. The solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica (0−100% EtOAc in hexane) to give the desired product (35 mg, 54%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.20−7.36 (m, 3H), 7.03−7.12 (m, 3H), 6.86 (br s, 1H), 6.67−6.76 (m, 3H), 6.60−6.65 (m, 1H), 4.48 (dd, *J* = 8.10, 14.98 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.54−3.72 (m, 2H), 3.24−3.48 (m, 2H), 3.19 (s, 3H), 3.10−3.17 (m, 1H), 2.82−3.05 (m, 4H), 2.48−2.61 (m, 1H). *m*/*z* 555 (M + H).

*2-[(Benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl Trifluoromethanesulfonate (**27**).* Prepared in 18% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.21−7.36 (m, 4H), 7.10 (d, *J* = 8.01 Hz, 2H), 6.90 (s, 1H), 6.87 (br s, 1H), 6.75 (s, 1H), 6.59−6.72 (m, 2H), 4.49 (dd, *J* = 8.05, 15.02 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.60−3.73 (m, 2H), 3.33−3.45 (m, 1H), 3.11−3.33 (m, 2H), 2.77−3.04 (m, 4H), 2.56 (d, *J* = 18.46 Hz, 1H). ^{19}F NMR (282 MHz, chloroform-*d*) δ −73.7. *m*/*z* 609 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**28**).* Phenol **11** (100 mg, 0.24 mmol) and cesium carbonate (235 mg, 0.72 mmol) were combined in dry dimethylformamide (1.5 mL), and 2,2,2-trifluoroiodoethane (101 mg, 47 μL, 0.48 mmol) was added. The reaction was heated at 50 °C overnight until TLC (4:1 EtOAc/hexane) showed that all starting material was gone. The reaction was cooled, diluted with ethyl acetate, and washed with a sodium bicarbonate solution and brine. The solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−50% EtOAc in hexane) to obtain the desired product as a pale-yellow solid (86 mg, 72%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.19−7.34 (m, 3H), 7.09 (d, *J* = 6.69 Hz, 2H), 6.94 (d, *J* = 5.09 Hz, 1H), 6.59−6.75 (m, 5H), 4.48 (dd, *J* = 8.15, 15.02 Hz, 1H), 4.23−4.41 (m, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.57−3.68 (m, 2H), 3.34−3.50 (m, 1H), 3.09−3.34 (m, 2H), 2.76−3.00 (m, 4H), 2.44−2.57 (m, 1H). *m*/*z* 559 (M + H).

*2-[(Benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl Benzenesulfonate (**29**).* Prepared in 64% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.87−7.94 (m, 2H), 7.62−7.71 (m, 1H), 7.48−7.58 (m, 2H), 7.19−7.35 (m, 3H), 7.09 (d, *J* = 6.88 Hz, 2H), 6.96 (s, 1H), 6.83 (d, *J* = 2.83 Hz, 1H), 6.58−6.73 (m, 3H), 6.55 (s, 1H), 4.48 (dd, *J* = 8.24, 15.02 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.54−3.67 (m, 2H), 3.51 (s, 3H), 3.32−3.47 (m, 1H), 3.07−3.31 (m, 2H), 2.73−2.99 (m, 4H), 2.41−2.56 (m, 1H). *m*/*z* 617 (M + H).

*2-[(Benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl 4-Methylbenzene-1-sulfonate (**30**).* Prepared in 63% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.78 (d, *J* = 8.19 Hz, 2H), 7.19−7.37 (m, 5H), 7.08 (d, *J* = 6.97 Hz, 2H), 6.94 (s, 1H), 6.79−6.86 (m, 1H), 6.59−6.72 (m, 3H), 6.56 (s, 1H), 4.49 (dd, *J* = 8.19, 14.98 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.58−3.67 (m, 2H), 3.54 (s, 3H), 3.32−3.45 (m, 1H), 3.07−3.31 (m, 2H), 2.73−2.98 (m, 4H), 2.47−2.54 (m, 1H), 2.45 (s, 3H). *m*/*z* 631 (M + H).

*General Procedure for N-alkylation with Acetate: 2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetate (**32**).* Tetrahydroisoquinoline **31** (0.26 g, 0.63 mmol), ethyl bromoacetate (0.16 g, 0.11 mL, 0.95 mmol), and tetrabutylammonium iodide (47 mg, 0.13 mmol) were combined in anhydrous dimethylformamide (6 mL), and diisopropylethylamine (0.20 g, 0.28 mL, 1.58 mmol) was added. The reaction was stirred at rt under N_2 overnight. The reaction was diluted with ethyl acetate, washed with a sodium bicarbonate solution and brine, and dried over $MgSO_4$, and solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−50% EtOAc/hexane) to give the desired product as a frothy solid (0.17 g, 55%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.73−6.79 (m, 1H), 6.60−6.68 (m, 2H), 6.55 (s, 1H), 6.01 (s, 1H), 4.11−4.22 (m, 2H), 3.93 (dd, *J* = 7.39, 5.23 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.57 (s, 3H), 3.39−3.55 (m, 2H), 3.28 (ddd, *J* = 12.88, 9.68, 5.04 Hz, 1H), 3.14 (dd, *J* = 13.37, 4.99 Hz, 1H), 2.98 (dt, *J* = 12.60, 4.77 Hz, 1H), 2.73−2.87 (m, 2H), 2.45−2.59 (m, 1H), 1.26 (t, *J* = 7.11 Hz, 3H).

General Procedure for Ester Hydrolysis: 2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetic acid. Ester (80 mg, 0.16 mmol) was dissolved in ethanol (2 mL), and an aqueous sodium hydroxide solution (2N, 0.3 mL, 0.64 mmol) was added. The reaction was stirred at rt for 2 h. The pH of the solution was adjusted to between 8 and 9 with 2N HCl, and all solvents were removed under reduced pressure. The crude solid was redissolved as much as possible in methanol, the remaining solids were removed by filtration, and the filtrate was concentrated. The desired acid was obtained as a white solid (75 mg, 100%). ^{1}H NMR (300 MHz, methanol-d_4) δ 6.92 (d, *J* = 8.10 Hz, 1H), 6.82 (s, 1H), 6.68−6.78 (m, 2H), 5.96 (s, 1H), 4.67 (dd, *J* = 9.04, 5.09 Hz, 1H), 3.81−3.82 (m, 3H), 3.76 (s, 3H), 3.71−3.85 (m, 6H), 3.46 (s, 3H), 3.38−3.66 (m, 2H), 2.95−3.18 (m, 3H).

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*General Procedure for Final Coupling: 2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(2-phenylethyl)acetamide (**33**).* Acid (30 mg, 0.075 mmol), phenethylamine (9 mg, 9 μL, 0.075 mmol), and BOP (33 mg, 0.075 mmol) were combined in anhydrous dimethylformamide (1 mL), and diisopropylethylamine (24 mg, 33 μL, 0.187 mmol) was added. The reaction was stirred at rt under N_2 overnight. The reaction was diluted with ethyl acetate, washed with a sodium bicarbonate solution and brine, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−75% EtOAc/hexane) to give the desired product as a pale-yellow solid (10 mg, 26%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.18−7.33 (m, 3H), 7.11−7.18 (m, 2H), 6.66−6.83 (m, 4H), 6.58 (s, 1H), 6.41 (s, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 3.80 (s, 3H), 3.59 (dd, *J* = 5.56, 9.23 Hz, 1H), 3.28−3.47 (m, 2H), 3.03−3.28 (m, 2H), 2.73−2.99 (m, 5H), 2.39−2.67 (m, 3H). *m*/*z* 505 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(3-phenylpropyl)acetamide (**34**).* Prepared in 64% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.23−7.33 (m, 2H), 7.11−7.22 (m, 3H), 6.69−6.85 (m, 3H), 6.61−6.68 (m, 1H), 6.59 (s, 1H), 6.42 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.60 (dd, *J* = 5.37, 9.23 Hz, 1H), 3.01−3.50 (m, 4H), 2.78−3.00 (m, 4H), 2.60−2.78 (m, 1H), 2.42−2.57 (m, 3H), 1.45−1.69 (m, 2H). *m*/*z* 519 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-1-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethan-1-one (**35**).* Prepared in 32% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.01−7.24 (m, 3H), 6.53−6.90 (m, 5H), 6.27 (d, *J* = 11.87 Hz, 1H), 4.24−4.89 (m, 2H), 3.65−4.01 (m, 12H), 3.22−3.64 (m, 5H), 2.73−3.10 (m, 6H), 2.35−2.72 (m, 2H). *m*/*z* 517.4 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-1-(3-phenylpiperidin-1-yl)ethan-1-one (**36**).* Prepared in 42% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.13−7.41 (m, 6H), 6.88−7.10 (m, 1H), 6.52−6.83 (m, 3H), 4.64 (d, *J* = 7.72 Hz, 1H), 3.76−3.95 (m, 12H), 3.53−3.75 (m, 4H), 3.20−3.52 (m, 4H), 2.71−3.15 (m, 5H), 2.30−2.66 (m, 4H). *m*/*z* 545 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-1-(4-phenylpiperidin-1-yl)ethan-1-one (**37**).* Prepared in 52% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.02−7.40 (m, 5H), 6.63−6.83 (m, 3H), 6.59 (s, 1H), 6.31 (s, 1H), 4.53−4.85 (m, 1H), 3.77−3.91 (m, 9H), 3.72 (s, 3H), 3.62 (s, 1H), 3.21−3.55 (m, 4H), 2.75−3.18 (m, 5H), 2.36−2.72 (m, 4H), 1.86 (br s, 1H), 1.33−1.59 (m, 2H). *m*/*z* 545 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-1-(4-phenylpiperazin-1-yl)ethan-1-one (**38**).* Prepared in 42% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.18−7.39 (m, 3H), 6.89 (s, 2H), 6.71 (s, 3H), 6.59 (s, 1H), 6.33 (s, 1H), 3.77−3.94 (m, 9H), 3.73 (s, 3H), 3.47 (d, *J* = 12.81 Hz, 3H), 3.34 (d, *J* = 12.81 Hz, 5H), 2.70−3.07 (m, 8H), 2.47 (dd, *J* = 3.86, 16.48 Hz, 1H). *m*/*z* 546 (M + H).

*N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-methylacetamide (**39**).* Prepared in 47% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.17−7.37 (m, 4H), 7.01 (d, *J* = 7.16 Hz, 1H), 6.64−6.80 (m, 3H), 6.58 (d, *J* = 4.90 Hz, 1H), 6.18−6.34 (m, 1H), 4.40−4.74 (m, 1H), 3.89−4.33 (m, 2H), 3.78−3.88 (m, 9H), 3.65−3.76 (m, 3H), 3.28−3.58 (m, 3H), 2.83−3.15 (m, 4H), 2.70−2.82 (m, 3H), 2.39−2.60 (m, 1H). *m*/*z* 505 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetate (**40**).* Acid (30 mg, 0.075 mmol), potassium carbonate (26 mg, 0.187 mmol), and tetrabutylammonium iodide (6 mg, 0.015 mmol) were combined in dimethylformamide (1 mL), and benzyl bromide (19 mg, 13 μL, 0.112 mmol) was added. The reaction was heated at 50 °C under N_2 overnight. The reaction was cooled and diluted with EtOAc. The reaction was washed with an $NaHCO_3$ solution and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The material was purified by chromatography on silica (0−50% EtOAc in hexane) to give the desired ester (9 mg, 24%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.35 (s, 5H), 6.73 (d, *J* = 8.01 Hz, 1H), 6.57−6.66 (m, 2H), 6.55 (s, 1H), 6.00 (s, 1H), 5.16 (s, 2H), 3.90−4.03 (m, 1H), 3.84 (s, 6H), 3.78 (s, 3H), 3.45−3.65 (m, 5H), 3.22−3.36 (m, 1H), 3.09−3.20 (m, 1H), 2.94−3.08 (m, 1H), 2.71−2.90 (m, 2H), 2.53 (d, *J* = 16.39 Hz, 1H). *m*/*z* 492 (M + H). HPLC purity 91.0%.

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(naphthalen-1-yl)acetamide (**41**).* Prepared in 64% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.25 (s, 1H), 7.84 (d, *J* = 7.63 Hz, 2H), 7.66 (d, *J* = 8.10 Hz, 1H), 7.33−7.54 (m, 4H), 6.63−6.72 (m, 2H), 6.59 (s, 1H), 6.46 (s, 1H), 6.30 (d, *J* = 8.10 Hz, 1H), 3.87−3.92 (m, 3H), 3.90 (s, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.36−3.61 (m, 3H), 3.27 (s, 3H), 2.92−3.15 (m, 4H), 2.64 (d, *J* = 15.82 Hz, 1H). *m*/*z* 527 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(8-fluoroquinolin-4-yl)acetamide (**42**).* Prepared in 27% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.88 (d, *J* = 4.99 Hz, 1H), 8.31 (d, *J* = 4.99 Hz, 1H), 7.54 (dd, *J* = 1.60, 8.10 Hz, 1H), 7.28−7.46 (m, 2H), 6.87 (d, *J* = 8.38 Hz, 1H), 6.61−6.71 (m, 2H), 6.53 (d, *J* = 1.79 Hz, 1H), 6.43 (s, 1H), 6.37 (d, *J* = 8.10 Hz, 1H), 4.01 (t, *J* = 6.73 Hz, 1H), 3.90 (s, 3H), 3.75−3.81 (m, 3H), 3.68 (s, 3H), 3.39−3.55 (m, 6H), 2.89−3.20 (m, 4H), 2.62−2.76 (m, 1H). *m*/*z* 546 (M + H). HPLC purity 93.0%.

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(2-methylquinolin-4-yl)acetamide (**43**).* Prepared in 28% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.89 (s, 1H), 8.13 (s, 1H), 8.00 (d, *J* = 8.48 Hz, 1H), 7.66 (t, *J* = 7.30 Hz, 1H), 7.33 (t, *J* = 7.35 Hz, 1H), 7.11 (d, *J* = 8.38 Hz, 1H), 6.61−6.69 (m, 2H), 6.47−6.54 (m, 1H), 6.40 (s, 1H), 6.36 (d, *J* = 8.19 Hz, 1H), 3.99 (t, *J* = 6.64 Hz, 1H), 3.90 (s, 3H), 3.79−3.87 (m, 2H), 3.76 (s, 3H), 3.62−3.69 (m, 3H), 3.43−3.54 (m, 2H), 3.39 (s, 3H), 2.87−3.21 (m, 4H), 2.73 (s, 3H). *m*/*z* 542 (M + H). HPLC purity 93.0%.

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(2-phenylphenyl)acetamide (**44**).* Prepared in 40% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.41 (s, 1H), 8.35 (d, *J* = 8.29 Hz, 1H), 7.35−7.45 (m, 1H), 7.15−7.32 (m, 8H), 6.63 (d, *J* = 8.29 Hz, 1H), 6.51 (s, 1H), 6.36−6.45 (m, 2H), 5.85 (s, 1H), 3.87 (s, 3H), 3.73 (d, *J* = 11.68 Hz, 6H), 3.57−3.66 (m, 1H), 3.54 (s, 3H), 3.30−3.45 (m, 1H), 3.17−3.29 (m, 1H), 2.93−3.08 (m, 1H), 2.60 (d, *J* = 8.29 Hz, 4H), 2.27−2.39 (m, 1H). *m*/*z* 553 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(3-phenylphenyl)acetamide (**45**).* Prepared in 27% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.68 (s, 1H), 7.57 (d, *J* = 7.91 Hz, 2H), 7.39−7.53 (m, 3H), 7.29−7.37 (m, 1H), 7.23 (d, *J* = 8.29 Hz, 3H), 6.71 (d, *J* = 1.51 Hz, 3H), 6.63 (s, 1H), 6.48 (s, 1H), 3.89 (s, 3H), 3.81 (d, *J* = 6.40 Hz, 6H), 3.76 (s, 3H), 3.45−3.57 (m, 1H), 3.24−3.45 (m, 2H), 2.89−3.09 (m, 4H), 2.52−2.64 (m, 1H). *m*/*z* 553 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(4-phenylphenyl)acetamide (**46**).* Prepared in 16% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.74 (br s, 1H), 7.59 (d, *J* = 6.78 Hz, 3H), 7.28−7.51 (m, 4H), 7.06 (br s, 1H), 6.58−6.92 (m, 4H), 6.45 (s, 1H), 4.12 (q, *J* = 7.16 Hz, 1H), 3.77−3.97 (m, 6H), 3.56−3.76 (m, 6H), 3.23−3.54 (m, 4H), 2.85−3.13 (m, 3H), 2.58 (d, *J* = 15.82 Hz, 1H). *m*/*z* 553 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide (**47**).* Prepared in 63% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.06−7.22 (m, 4H), 6.53−6.63 (m, 2H), 6.18−6.49 (m, 3H), 5.00−5.21 (m, 1H), 3.79−3.88 (m, 3H), 3.74 (d, *J* = 6.03 Hz, 6H), 3.67 (s, 3H), 3.11−3.49 (m, 3H), 2.62−3.05 (m, 7H), 2.42−2.56 (m, 1H), 1.66−2.02 (m, 4H). *m*/*z* 531 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (**48**).* Quinoline **43** (20 mg, 0.037 mmol) and 10% palladium on carbon (20 mg) were combined in ethanol (5 mL) and chloroform (1 mL) and hydrogenated at 50 psi of H_2 in a Parr shaker for 3 days. The reaction was filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica (0−20% MMA-80 in EtOAc) to give the tetrahydroisoquinoline derivative (3 mg, 15%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.09 (s, 1H), 7.78 (s, 1H), 7.26 (s, 3H), 6.57−6.67 (m, 3H), 6.51 (s, 1H), 6.28 (s, 1H), 3.82−3.99 (m, 5H), 3.59−3.81

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(m, 10H), 3.27−3.54 (m, 4H), 3.04−3.19 (m, 1H), 2.79−3.03 (m, 5H), 2.58−2.70 (m, 1H), 2.48 (s, 3H). *m/z* 546 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-[(1S)-1-phenylethyl]acetamide (**49** and **50**).* Prepared from tetrahydroisoquinoline **11** and 2-bromo-*N*-[(1*S*)-1-phenylethyl]acetamide as above as a mixture of diastereomers in 54% yield. Diastereomers were separated by reverse-phase HPLC. The first to elute was **49** and the second, **50**. **49**: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.24 (br s, 1H), 7.20−7.37 (m, 5H), 6.74 (d, *J* = 8.10 Hz, 1H), 6.62 (s, 1H), 6.58 (s, 1H), 6.49 (d, *J* = 8.19 Hz, 1H), 5.86 (br s, 1H), 4.97−5.09 (m, 1H), 4.60−4.70 (m, 1H), 3.88−4.03 (m, 2H), 3.86 (s, 3H), 3.83−3.85 (m, 3H), 3.75 (s, 3H), 3.61 (dd, *J* = 11.73, 6.64 Hz, 2H), 3.53 (s, 3H), 3.45−3.50 (m, 1H), 3.19 (d, *J* = 10.83 Hz, 1H), 2.83−3.04 (m, 2H), 1.48 (d, *J* = 6.97 Hz, 3H). *m/z* 505 (M + H). **50**: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.49 (d, *J* = 7.63 Hz, 1H), 7.21−7.39 (m, 5H), 6.73 (d, *J* = 8.19 Hz, 1H), 6.62 (s, 1H), 6.54 (d, *J* = 1.70 Hz, 1H), 6.43 (d, *J* = 8.10 Hz, 1H), 5.78 (s, 1H), 5.05 (s, 1H), 4.52 (d, *J* = 6.31 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78−3.95 (m, 2H), 3.75 (s, 3H), 3.56−3.69 (m, 2H), 3.51−3.54 (m, 1H), 3.49 (s, 3H), 3.10−3.33 (m, 1H), 2.83−3.04 (m, 2H), 1.50 (d, *J* = 6.97 Hz, 3H). *m/z* 505 (M + H).

*N-[(4-Chlorophenyl)methyl]-2-{1-[(3,4-dimethoxyphenyl)-methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-acetamide (**51**).* Prepared in 60% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.21−7.29 (m, 2H), 7.03 (d, *J* = 8.38 Hz, 2H), 6.91 (t, *J* = 6.31 Hz, 1H), 6.63−6.78 (m, 3H), 6.59 (s, 1H), 6.48 (s, 1H), 4.41 (dd, *J* = 8.05, 15.02 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 3.52−3.65 (m, 2H), 3.36−3.51 (m, 1H), 3.09−3.34 (m, 2H), 2.80−3.01 (m, 4H), 2.42−2.55 (m, 1H). *m/z* 527, 525 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-[(4-fluorophenyl)methyl]acetamide (**52**).* Prepared in 64% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.02−7.11 (m, 2H), 6.87−7.02 (m, 3H), 6.64−6.78 (m, 3H), 6.59 (s, 1H), 6.47 (s, 1H), 4.42 (dd, *J* = 8.10, 14.79 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.52−3.66 (m, 2H), 3.36−3.51 (m, 1H), 3.09−3.34 (m, 2H), 2.80−3.00 (m, 4H), 2.42−2.56 (m, 1H). *m/z* 509 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-2-ylmethyl)acetamide (**53**).* Prepared in 57% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.52 (d, *J* = 4.52 Hz, 1H), 7.53−7.69 (m, 2H), 7.16 (dd, *J* = 5.18, 7.16 Hz, 1H), 7.09 (d, *J* = 7.82 Hz, 1H), 6.62−6.72 (m, 3H), 6.60 (s, 1H), 6.29 (s, 1H), 4.53 (dd, *J* = 6.55, 16.25 Hz, 1H), 4.17 (dd, *J* = 5.32, 16.25 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.67−3.75 (m, 7H), 3.17−3.51 (m, 3H), 2.82−3.11 (m, 4H), 2.45−2.60 (m, 1H). *m/z* 492 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-3-ylmethyl)acetamide (**54**).* Prepared in 49% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.50 (dd, *J* = 1.37, 4.76 Hz, 1H), 8.33 (d, *J* = 1.70 Hz, 1H), 7.43 (d, *J* = 7.82 Hz, 1H), 7.22 (dd, *J* = 4.80, 7.72 Hz, 1H), 6.89−6.98 (m, 1H), 6.64−6.79 (m, 3H), 6.60 (s, 1H), 6.51 (s, 1H), 4.41 (dd, *J* = 8.01, 15.26 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.56−3.70 (m, 2H), 3.38−3.54 (m, 1H), 3.09−3.34 (m, 2H), 2.82−3.02 (m, 4H), 2.43−2.57 (m, 1H). *m/z* 492 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-4-ylmethyl)acetamide (**55**).* Prepared in 89% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.48−8.56 (m, 2H), 6.96−7.02 (m, 2H), 6.92 (dd, *J* = 5.13, 7.68 Hz, 1H), 6.71−6.80 (m, 2H), 6.58−6.68 (m, 2H), 6.53 (s, 1H), 4.40 (dd, *J* = 8.10, 15.92 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H), 3.55−3.66 (m, 2H), 3.41−3.54 (m, 1H), 3.10−3.37 (m, 2H), 2.82−3.04 (m, 4H), 2.53 (d, *J* = 16.29 Hz, 1H). *m/z* 492 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-{[4-(dimethylamino)phenyl]methyl}-acetamide (**56**).* Prepared in 7% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.03 (d, *J* = 8.57 Hz, 2H), 6.92−6.99 (m, 1H), 6.62−6.73 (m, 5H), 6.58 (s, 1H), 6.38 (s, 1H), 4.38−4.49 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.52−3.69 (m, 2H), 3.31−3.45 (m, 1H), 3.21 (q, *J* = 16.80 Hz, 2H), 2.90−2.96 (m, 6H), 2.77−2.90 (m, 4H), 2.41−2.53 (m, 1H). *m/z* 534 (M + H).

2-Bromo-N-[(4-nitrophenyl)methyl]acetamide. To a solution of 4-nitrobenzylamine hydrochloride (1.89 g, 10 mmol) and triethylamine (1.01 g, 1.39 mL, 10 mmol) in dichloromethane (10 mL) cooled in an ice bath was added dropwise bromoacetyl bromide (1.01 g, 0.44 mL, 5 mmol). A precipitate formed immediately. The ice bath was removed, and the reaction was stirred at rt for 2 h. The precipitate was removed by filtration, and the solution was washed twice with 2N HCl and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the bromide as a white solid (1.4 g, 100%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.22 (d, *J* = 8.67 Hz, 2H), 7.47 (d, *J* = 8.48 Hz, 2H), 4.57−4.64 (m, 2H), 4.15 (s, 2H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-[(4-nitrophenyl)methyl]acetamide. Prepared as per the general alkylation procedure using 2-bromo-*N*-[(4-nitrophenyl)methyl]acetamide in 63% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.15 (d, *J* = 8.76 Hz, 2H), 7.23 (d, *J* = 8.67 Hz, 2H), 6.90−7.00 (m, 1H), 6.65−6.81 (m, 3H), 6.61 (s, 1H), 6.53 (s, 1H), 4.47 (dd, *J* = 8.01, 15.54 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.70−3.75 (m, 3H), 3.42−3.71 (m, 3H), 3.11−3.35 (m, 2H), 2.83−3.03 (m, 4H), 2.45−2.57 (m, 1H).

N-[(4-Aminophenyl)methyl]-2-{1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide. To a solution of nitrophenyl (197 mg, 0.37 mmol) and hydrazine monohydrate (0.15 mL) in ethanol (5 mL) warmed to 50 °C was added Raney nickel (2800, as a slurry in water, 25 mg), and the reaction was heated at 50 °C for 1 h. The reaction was cooled and filtered through Celite, and the solvent removed under reduced pressure to give the aniline (155 mg, 83%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.92 (d, *J* = 8.29 Hz, 2H), 6.70 (s, 2H), 6.56−6.68 (m, 4H), 6.40 (s, 1H), 4.39 (dd, *J* = 7.91, 14.51 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 6H), 3.79 (s, 3H), 3.51−3.67 (m, 3H), 3.32−3.44 (m, 1H), 3.10−3.31 (m, 2H), 2.78−2.98 (m, 4H), 2.42−2.53 (m, 1H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-[(4-acetamidophenyl)methyl]acetamide (**57**).* To the aniline (30 mg, 0.059 mmol) in dichloromethane (1 mL) was added acetic anhydride (12 mg, 11 μL, 0.119 mmol) and diisopropylethylamine (19 mg, 26 μL, 0.148 mmol), and the reaction was stirred at rt overnight. The reaction was diluted with EtOAc and washed with an $NaHCO_3$ solution. The aqueous phase was extracted once with EtOAc, and the combined organic phases were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−100% EtOAc in hexane) to give the amide (34 mg, 100%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.41 (d, *J* = 8.38 Hz, 2H), 7.23 (s, 1H), 7.05 (d, *J* = 8.38 Hz, 2H), 6.89−6.99 (m, 1H), 6.64−6.79 (m, 3H), 6.59 (s, 1H), 6.46 (s, 1H), 4.41 (dd, *J* = 7.91, 15.07 Hz, 1H), 3.87 (s, 3H), 3.81−3.84 (m, 6H), 3.78 (s, 3H), 3.54−3.67 (m, 2H), 3.35−3.50 (m, 1H), 3.09−3.33 (m, 2H), 2.78−2.99 (m, 4H), 2.42−2.56 (m, 1H), 2.17 (s, 3H). *m/z* 548 (M + H).

*N-{4-[(2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamido)methyl]phenyl}-hexanamide (**58**).* Aniline (23 mg, 0.046 mmol), hexanoic acid (5 mg, 0.046 mmol), and BOP (20 mg, 0.046 mmol) were combined in dichloromethane (1 mL), and diisopropylethylamine (12 mg, 16 μL, 0.091 mmol) was added. The reaction was stirred at rt overnight and diluted with EtOAc. The reaction was washed with an $NaHCO_3$ solution and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The compound was purified by chromatography on silica (0−100% EtOAc in hexane) to give the amide (30 mg, 100%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.43 (d, *J* = 8.29 Hz, 2H), 7.21−7.28 (m, 1H), 7.04 (d, *J* = 8.38 Hz, 2H), 6.94 (dd, *J* = 5.09, 7.72 Hz, 1H), 6.65−6.75 (m, 3H), 6.59 (s, 1H), 6.46 (s, 1H), 4.41 (dd, *J* = 8.05, 14.83 Hz, 1H), 3.86 (s, 3H), 3.81−3.84 (m, *J* = 0.80 Hz, 6H), 3.78 (s, 3H), 3.54−3.66 (m, 2H), 3.35−3.53 (m, 1H), 3.09−3.33 (m, 2H), 2.79−2.99 (m, 4H), 2.43−2.56 (m, 1H), 2.34 (t, *J* = 7.54 Hz, 2H), 1.64−1.79 (m, 2H), 1.31−1.39 (m, 4H), 0.87−0.95 (m, 3H). *m/z* 604 (M + H).

*2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-({4-[(hexylcarbamoyl)amino]phenyl}-methyl)acetamide (**59**).* To the aniline (40 mg, 0.079 mmol) in toluene (1 mL) was added *n*-hexyl isocyanate (11 mg, 13 μL, 0.087

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mmol), and the mixture was heated at 75 °C for 2 h. The reaction was cooled, the solvent was removed under reduced pressure, and the crude was purified by chromatography on silica (0−100% EtOAc in hexane) to give the urea (38 mg, 76%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.12 (d, *J* = 8.48 Hz, 2H), 7.00 (dd, *J* = 5.27, 7.72 Hz, 1H), 6.93 (d, *J* = 8.48 Hz, 2H), 6.87 (s, 1H), 6.66−6.77 (m, 3H), 6.60 (s, 1H), 6.49 (s, 1H), 5.29 (t, *J* = 5.56 Hz, 1H), 4.33 (dd, *J* = 7.82, 14.98 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.54−3.66 (m, 2H), 3.36−3.51 (m, 1H), 3.07−3.32 (m, 4H), 2.79−3.01 (m, 4H), 2.43−2.56 (m, 1H), 1.39−1.54 (m, 2H), 1.21−1.36 (m, 6H), 0.82−0.90 (m, 3H). *m*/*z* 633 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-heptylacetamide (**60**). Prepared in 63% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.67−6.91 (m, 3H), 6.59 (m, 2H), 6.42 (m, 1H), 3.74−3.96 (m, 12H), 3.62 (m, 1H), 3.33−3.49 (m, 1H), 3.03−3.30 (m, 3H), 2.78−3.02 (m, 4H), 2.62 (m, 1H), 2.51 (d, *J* = 16.29 Hz, 1H), 1.08−1.38 (m, 10H), 0.89 (m, 3H). *m*/*z* 499 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-[3-(dimethylamino)propyl]acetamide (**61**). Prepared in 57% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.86 (d, *J* = 8.10 Hz, 2H), 6.72−6.79 (m, 1H), 6.70 (d, *J* = 1.79 Hz, 1H), 6.59 (s, 1H), 6.35 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H), 3.58−3.65 (m, 1H), 3.32−3.46 (m, 1H), 3.05−3.31 (m, 3H), 2.78−3.03 (m, 4H), 2.59−2.74 (m, 1H), 2.44−2.58 (m, 1H), 2.12−2.22 (m, 6H), 2.10−2.24 (m, 2H), 1.35−1.53 (m, 2H). *m*/*z* 486 (M + H).

2-(2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamido)acetate (**62**). Prepared in 55% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.27 (d, *J* = 2.35 Hz, 1H), 6.94 (br s, 1H), 6.73−6.86 (m, 2H), 6.59 (d, *J* = 2.17 Hz, 1H), 6.41 (d, *J* = 2.07 Hz, 1H), 4.06 (s, 1H), 3.84−3.91 (m, 8H), 3.75−3.83 (m, 5H), 3.68−3.75 (m, 3H), 3.38−3.57 (m, 2H), 3.11−3.33 (m, 2H), 2.82−3.00 (m, 4H), 2.46−2.59 (m, 1H). *m*/*z* 473 (M + H).

2-(2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamido)acetic acid. Ester (60 mg, 0.127 mmol) was dissolved in methanol (5 mL), and a 2N sodium hydroxide solution (0.25 mL, 0.508 mmol) was added. The reaction was stirred at rt overnight. The pH was adjusted to 7 to 8 with 2N HCl, and all solvent was removed under reduced pressure. The solids were redissolved as much as possible in methanol, the solids were removed by decantation, and the solvents were removed under reduced pressure to give the acid as a white solid (93 mg, 100%). ^{1}H NMR (300 MHz, methanol-d_4) δ 6.78−6.96 (m, 3H), 6.69 (s, 1H), 6.51 (s, 1H), 3.77−3.86 (m, 9H), 3.63−3.77 (m, 6H), 3.46 (d, *J* = 5.18 Hz, 1H), 3.17−3.28 (m, 2H), 2.83−3.04 (m, 4H), 2.47−2.61 (m, 1H).

2-(2-{1-[(3,4-Dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamido)-N-methylacetamide (**63**). The acid (30 mg, 0.065 mmol), methylamine hydrochloride (9 mg, 0.131 mmol), and BOP (38 mg, 0.085 mmol) were combined in dry DMF (1 mL), and diisopropylethylamine (42 mg, 57 μL, 0.327 mmol) was added. The reaction was stirred at rt overnight and then diluted with EtOAc. The reaction was washed with an $NaHCO_3$ solution and brine and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The crude product was purified by chromatography on silica (0−50% CMA-80 in EtOAc) to give the desired amide (13 mg, 42%). ^{1}H NMR (300 MHz, methanol-d_4) δ 6.80−6.96 (m, 3H), 6.69 (s, 1H), 6.62 (s, 1H), 3.78−3.85 (m, 10H), 3.75 (s, 3H), 3.60−3.73 (m, 3H), 3.42−3.59 (m, 1H), 3.01−3.09 (m, 1H), 2.84−2.99 (m, 6H), 2.72 (s, 3H), 2.53 (dd, *J* = 5.09, 15.73 Hz, 1H). *m*/*z* 472 (M + H).

N-(Carbamoylmethyl)-2-{1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (**64**). Prepared from acid using ammonium chloride in 23% yield. ^{1}H NMR (300 MHz, methanol-d_4) δ 6.79−6.95 (m, 3H), 6.69 (s, 1H), 6.57−6.61 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.65−3.76 (m, 2H), 3.43−3.57 (m, 1H), 3.26−3.37 (m, 2H), 3.01−3.11 (m, 1H), 2.84−3.00 (m, 4H), 2.53 (dd, *J* = 5.04, 15.49 Hz, 1H). *m*/*z* 458 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6-methoxy-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-2-ylmethyl)-acetamide (**69**). Prepared in 52% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.52 (d, *J* = 4.80 Hz, 1H), 7.52−7.69 (m, 2H), 7.13−7.21 (m, 1H), 7.08 (d, *J* = 7.82 Hz, 1H), 6.62−6.74 (m, 3H), 6.59 (s, 1H), 6.33 (s, 1H), 4.53 (dd, *J* = 6.69, 16.20 Hz, 1H), 4.16 (dd, *J* = 5.27, 16.20 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.66−3.83 (m, 3H), 3.17−3.51 (m, 3H), 2.81−3.09 (m, 4H), 2.46−2.59 (m, 1H), 1.73−1.88 (m, 2H), 1.01 (t, *J* = 7.39 Hz, 3H). *m*/*z* 520 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6-methoxy-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-3-ylmethyl)-acetamide (**70**). Prepared in 43% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.45−8.52 (m, 1H), 8.33 (s, 1H), 7.43 (d, *J* = 7.82 Hz, 1H), 7.22 (dd, *J* = 4.85, 7.77 Hz, 1H), 6.89−6.99 (m, 1H), 6.63−6.78 (m, 3H), 6.59 (s, 1H), 6.53 (s, 1H), 4.40 (dd, *J* = 8.01, 15.26 Hz, 1H), 3.93 (t, *J* = 6.88 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.54−3.70 (m, 2H), 3.37−3.54 (m, 1H), 3.09−3.33 (m, 2H), 2.80−2.99 (m, 4H), 2.42−2.55 (m, 1H), 1.79−1.93 (m, 2H), 1.05 (t, *J* = 7.44 Hz, 3H). *m*/*z* 520 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6-methoxy-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-2-ylmethyl)-acetamide (**71**). Prepared in 31% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.52 (d, *J* = 3.96 Hz, 1H), 7.63 (t, *J* = 7.63 Hz, 1H), 7.51 (br s, 1H), 7.13−7.22 (m, 1H), 7.07 (d, *J* = 7.63 Hz, 1H), 6.55−6.73 (m, 4H), 6.50 (s, 1H), 4.50 (dd, *J* = 6.55, 15.97 Hz, 1H), 4.08−4.35 (m, 3H), 3.86 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.66−3.75 (m, 1H), 3.14−3.49 (m, 3H), 2.78−3.09 (m, 4H), 2.47−2.62 (m, 1H). *m*/*z* 560 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-6-methoxy-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-3-ylmethyl)-acetamide (**72**). Prepared in 29% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.49 (d, *J* = 4.71 Hz, 1H), 8.32 (s, 1H), 7.42 (d, *J* = 7.82 Hz, 1H), 7.22 (dd, *J* = 4.85, 7.68 Hz, 1H), 6.81−6.92 (m, 1H), 6.62−6.77 (m, 5H), 4.24−4.49 (m, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.54−3.66 (m, 2H), 3.38−3.53 (m, 1H), 3.07−3.34 (m, 2H), 2.77−3.02 (m, 4H), 2.45−2.61 (m, 1H). *m*/*z* 560 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-7-ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-2-ylmethyl)-acetamide (**73**). Prepared in 36% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.49−8.55 (m, 1H), 7.63 (dt, *J* = 1.84, 7.70 Hz, 1H), 7.55 (t, *J* = 5.79 Hz, 1H), 7.16 (dd, *J* = 5.32, 7.02 Hz, 1H), 7.08 (d, *J* = 7.82 Hz, 1H), 6.61−6.72 (m, 3H), 6.59 (s, 1H), 6.34 (s, 1H), 4.53 (dd, *J* = 6.69, 16.20 Hz, 1H), 4.14 (dd, *J* = 5.27, 16.20 Hz, 1H), 3.88−4.00 (m, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.65−3.70 (m, 1H), 3.17−3.48 (m, 3H), 2.81−3.08 (m, 4H), 2.46−2.57 (m, 1H), 1.41 (t, *J* = 6.97 Hz, 2H). *m*/*z* 506 (M + H).

2-{1-[(3,4-Dimethoxyphenyl)methyl]-7-ethoxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-3-ylmethyl)-acetamide (**74**). Prepared in 41% yield. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.49 (dd, *J* = 1.55, 4.76 Hz, 1H), 8.33 (d, *J* = 1.70 Hz, 1H), 7.43 (td, *J* = 1.93, 7.82 Hz, 1H), 7.18−7.25 (m, 1H), 6.93 (dd, *J* = 5.23, 7.58 Hz, 1H), 6.71−6.78 (m, 2H), 6.64−6.70 (m, 1H), 6.60 (s, 1H), 6.54 (s, 1H), 4.40 (dd, *J* = 8.01, 15.26 Hz, 1H), 4.06 (q, *J* = 7.00 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.55−3.68 (m, 2H), 3.38−3.54 (m, 1H), 3.10−3.33 (m, 2H), 2.77−3.01 (m, 4H), 2.43−2.56 (m, 1H), 1.47 (t, *J* = 6.97 Hz, 3H). *m*/*z* 506 (M + H).

Functional Determinations. The activity of the target compounds at the OX_1 and OX_2 receptors was assayed using RD-HGA16 cells (Molecular Devices), a CHO cell line stably overexpressing the promiscuous Gq-protein Ga16. Two individual cell lines were used that stably express either OX_1 or OX_2 receptors. Cells were cultured overnight in black, clear bottom, 96-well tissue culture plates at 25 000 cells per well in 100 μL/well of Ham's F12 medium supplemented with 10% FBS, 1× pen/strep, 0.1 μg/mL of normocin, 400 μg/mL of geneticin, and 200 μg/mL of hygromycin. The medium was then removed, and the cells were loaded with 200 μL/well of a calcium-sensitive fluorescent dye (calcium 5, Molecular Devices) in assay buffer (1× HBSS, 20 μM HEPES plus 2.7 mM probenecid) as per the manufacturer's instructions for 45 min at 37 °C. Cells were then pretreated by the addition of 25 μL/well of 10% DMSO (for intrinsic activity measurements) or 25 μL of 10% DMSO including a 10× final

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concentration of the test compound (for antagonist assays) for 15 min at 37 °C. Activity was then assayed on a FlexStation II at 37 °C. Baseline fluorescence was measured every 1.52 s for 19 s at which time 25 μL of 100 μM test compound (for intrinsic activity) or an 8-point half-log concentration curve of Orexin A (for antagonist activity) was added by the FlexStation II. Fluorescence was measured every 1.52 s for another 41 s. Activity was measured as the change in fluorescence intensity by setting the average baseline value of each well to 0 and measuring the peak fluorescence intensity following compound addition. EC_{50} values were calculated for orexin A (EC_{50}^{-}) and orexin A + test compound (EC_{50}^{+}), and these values were used to calculate the K_e value of the test compound. The concentration/response data were fit to a three-parameter logistic equation using GraphPad Prism (v5 for Windows; GraphPad Software, San Diego, CA) to calculate the EC_{50} values. For OX_1, at least two different concentrations of test compound were used for these experiments, and these were chosen such that they caused a 4-fold or greater rightward shift in the orexin A EC_{50}. For OX_2, test compounds were run at 10 μM because of the low potency of these compounds at OX_2. The K_e value was calculated from the formula $K_e = [L]/((EC_{50}^{-}/EC_{50}^{+}) - 1)$, where [L] equals the test compound concentration, EC_{50}^{-} equals the EC_{50} of orexin A alone, and EC_{50}^{+} equals the EC_{50} of orexin A in the presence of the test compound. The data represent the mean from at least three independent experiments.

Conformational Libraries and 3D Pharmacophores. The initial 3D geometries of the ligands were generated from SMILES strings using CORINA (Molecular Networks, Erlangen, Germany). Conformational libraries were generated using 12 genetic algorithm (GA) and energy minimization runs, each was based on a distinct random number seed, employing BALLOON as the GA engine.[47] An initial population size of 200 was employed for every GA run, each consisting of 200 generations. The energy (fitness) function was evaluated using the full MMFF94 force field and a continuum dielectric of 80 for dielectric response screening electrostatics. The GA runs for each ligand were then pooled and unique conformers retained. For the purposes of this study, a unique conformer was defined as any structure differing by less than 30 degrees for any torsion (excluding those terminating in hydrogens).

Three-dimensional pharmacophores were developed using MOLMOD.[48,49] This code takes as input (1) pharmacophore hypotheses, (2) conformational libraries for each of the ligands, (3) distance and tolerance criteria for each set of pharmacophore points defining pharmacophore metric compliance, and (4) an energy window for the consideration of conformations from each library. Given the relative homogeneity of the present study chemotype, the objective of the pharmacophore analysis was primarily the development of an overlap rule for those structural commonalities in the scaffold common to all ligands, enabling property evaluation and multivariate statistical analysis (2D and 3D QSAR) of the pharmacophore compliant conformations. Should one or more pharmacophores be found, MOLMOD outputs both distance metrics and a quaternion least-squares superposition of conformations of each of the ligands complying with the pharmacophore.

Property Evaluation: Properties of both whole ligand and fragments (substituents) were evaluated for each of the conformations complying with the pharmacophore(s) using semiempirical QM (MOPAC) models. Postcomputation analysis of the results was done with GRAPHA, a utility that extracts QM-energetic, electrostatic, hydrophobic, frontier-orbital energetic, Sterimol, shape, polar−nonpolar surface area, volume, and thermodynamic descriptors.[47]

Fragment/2D/3D QSAR: Properties compiled were analyzed to develop quantitative structure relationships in an effort to ascertain the key physiochemical properties modulating orexin K_e values as a function of substitution. Multivariate least-squares approaches embodied in the R PROJECT software for Statistical Computing (http://www.r-project.org/) and Tripos Sybyl were employed.

Conditioned Place Preference. *Subjects.* Adult Sprague−Dawley rats (Harlan, Indianapolis, IN) were housed individually on a 12/12 h light/dark cycle with free access to water and food except during experimental sessions. Testing occurred during the light period. Animal maintenance and experiments were done in accordance with the Institutional Animal Care and Use Committee, University at Buffalo, and the 2010 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, Washington, DC).

Apparatus. The standard experimental chamber for the automated assessment of CPP (LE890, Harvard Apparatus, Holliston, MA) consisted of two Perspex compartments of the same size (30 × 30 × 34 cm^3) interconnected by a central corridor (8 × 10 × 34 cm^3). Both side compartments were equipped with a gray Perspex guillotine door that separated the end compartment from the central gray corridor. Each compartment had distinct, yet neutral, visual and tactile cues: One had black walls and a white rough floor, the other had white walls and a black smooth floor. The corridor had gray walls and a gray floor. The time spent in each compartment was monitored by a video camera located on the ceiling that was controlled by video-tracking software (Smart Junior, Harvard Apparatus, Holliston, MA).

Procedure. Details were described previously.[50] Briefly, the experiment started with a 30 min pretest session during which rats had free access to both compartments to verify the absence of preference for either. Only the first 15 min (900 s) of the pretest session was recorded and analyzed. Rats spending more than 75% (>675 s) or less than 25% (<225 s) of the total time in a compartment were eliminated from further testing (only 1 rat was excluded from the studies). Although this was an unbiased set up, individual rats somewhat preferred one side over the other. On average, individual rats spent 58% of the total pretest time in one chamber and 38% in the other chamber, with the remaining 4% being spent in the central corridor. Following the pretest phase, the rats underwent place conditioning across 8 days, with alternating treatment-compartment pairings. The rats received a vehicle-compartment pairing on odd days and drug (cocaine, compound **72**, or cocaine + compound **72**)-compartment pairing on even days. For a conditioning session, vehicle or drug was administered, and the rat was placed immediately in the paired compartment with no access to the other compartment for 30 min. This conditioning time was chosen because it was used in other studies and was established in our laboratory.[50] The drug and compartment pairing were counterbalanced. On the test day (24 h after last conditioning session), the rats were randomly placed into one compartment without treatment and had access to both compartments during the 15 min observation period, and the time spent in each compartment was recorded. For the combination group, compound **72** was administered 10 min before cocaine. This pretreatment time was chosen because initial studies found that 10 min was adequate for compound **72** to be behaviorally active in a drug discrimination assay (data not shown).

Data Analyses. The magnitude of place preference was presented as the preference score, which was defined as the time spent in the drug-associated compartment on the test day minus the time spent in the drug-associated compartment on pretest day. The data were subjected to one-way analysis of variance with treatment (four groups) as the factor followed by Bonferroni's posthoc test. An effect was considered significant if $P < 0.05$.

Drugs. Cocaine hydrochloride (Research Technology Branch, National Institute on Drug Abuse, Rockville, MD) and compound **72** were dissolved in 0.9% physiological saline and administered i.p. The dose was expressed as milligrams of the form indicated above per kilogram of body weight (mg/kg). The injection volume was 1 mL/kg.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC analysis of target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ADME, absorption distribution metabolism excretion; BOP, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; COMFA, comparative molecular field analysis; CPP, conditioned place preference; HBTU, *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluoro-phosphate; HOMO, highest occupied molecular orbital; HPLC, high-performance liquid chromatography; LUMO, lowest unoccupied molecular orbital; OX_1, orexin 1 receptor; OX_2, orexin 2 receptor; QSAR, quantitative structure−activity relationship; SAR, structure−activity relationship; TLC, thin layer chromatography

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