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The Effect of 1-Substitution on Tetrahydroisoquinolines as Selective Antagonists for the Orexin-1 Receptor

David A. Perrey,[†] Nadezhda A. German,[†] Ann M. Decker,[†] David Thorn,[‡] Jun-Xu Li,[‡] Brian P. Gilmour,[†] Brian F. Thomas,[†] Danni L. Harris,[†] Scott P. Runyon,[†] and Yanan Zhang,[†,]*

[†]Research Triangle Institute, Research Triangle Park, North Carolina 27709, United States

[‡]Department of Pharmacology and Toxicology, University at Buffalo, the State University of New York, Buffalo, New York 14214, United States

KEYWORDS: Orexin, antagonist, selective, tetrahydroisoquinoline

ABSTRACT: Selective blockade of the Orexin-1 receptor has been suggested as a potential approach to drug addiction therapy because of its role in modulating the brain's reward system. We have recently reported a series of tetrahydroisoquinoline-based OX_1 selective antagonists. Aimed at elucidating SAR requirements in other regions of the molecule and further enhancing OX_1 potency and selectivity, we have designed and synthesized a series of analogs bearing a variety of substituents at the 1-position of the tetrahydroisoquinoline. The results show that an optimally substituted benzyl group is required for activity at the OX_1 receptor. Several compounds with improved potency and/or selectivity have been identified. When combined with

structural modifications that were previously found to improve selectivity, we have identified compound **73** (RTIOX-251) with an apparent dissociation constant (Ke) of 16.1 nM at the OX_1 receptor and >620-fold selectivity over the OX_2 receptor. In vivo, compound **73** was shown to block the development of locomotor sensitization to cocaine in rats.

Introduction

Orexins (hypocretins), including orexin A and orexin B, are neuropeptides exclusively produced in hypothalamic neurons arising in the dorsomedial hypothalamus (DMH), perifornical area (PFA), and lateral hypothalamus (LH).[1, 2] The orexin-producing neurons in the hypothalamus project widely to key areas of the central nervous system (CNS) that are commonly thought to control sleep–wake states, modulation of food intake, panic, anxiety, reward and addictive behaviors, suggesting diverse roles for these peptides.[3-5] Orexin A and B bind and activate two G protein-coupled receptors (GPCRs), orexin-1 (OX_1) and orexin-2 (OX_2), with OX_1 signaling via G_q proteins and OX_2 signaling via G_q or $G_{i/o}$ proteins.[6, 7] The OX_1 receptor has 10-fold higher affinity for orexin A than for orexin B; whereas OX_2 has equal affinity for both peptides. Interestingly, these receptors are differentially distributed throughout the brain, suggesting different physiological roles for each receptor.[1, 8, 9] Originally known for regulation of metabolic, circadian and stress systems, the orexin system has recently been associated with drug addiction.[10-13] The fact that orexin neurons project to the ventral tegmental area (VTA) and other brain regions involved in reward processing supports this notion. Selective blockade of the OX_1 receptor has been shown to attenuate stress- and cue-induced reinstatement of previously extinguished cocaine-, morphine-, and alcohol-seeking behavior.[14-18] Together, these findings suggest that OX_1 antagonists may have therapeutic utility for the treatment of drug addiction.

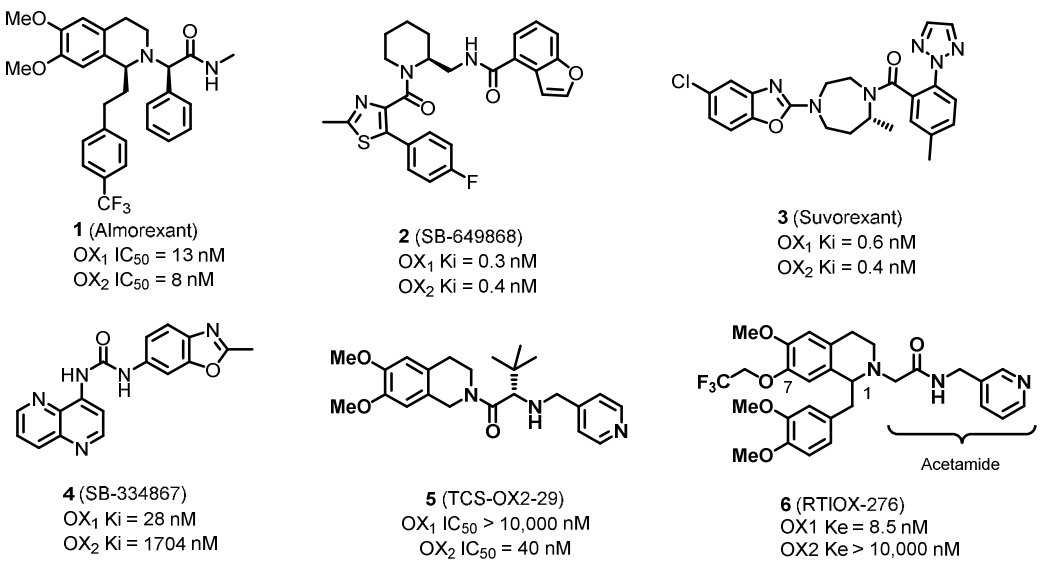


Figure 1. Orexin Antagonists

In order to elucidate the physiological role of the orexin receptors and explore the potential of orexin receptor antagonists as therapeutics, a number of groups, mostly from the pharmaceutical industry, have developed orexin receptor antagonists.[19-23] In these endeavors, the majority of research has focused on dual orexin receptor antagonists for new sleep medications development.[24, 25] Several dual antagonists, including almorexant (**1**) and SB-649828 (**2**), have been advanced into clinical trials, but their development was later halted because of tolerability and toxicity concerns, respectively. The most success was seen with suvorexant (**3**), a dual orexin antagonist developed by Merck. Recently, suvorexant was approved at a lower dose (20 mg) than initially proposed for the treatment of insomnia, and is currently marketed under the trade name Belsomra.[26] Several OX_1 receptor selective antagonists have also been developed to probe the importance of this receptor.[27] Among these, the OX_1 antagonist SB-334867 (**4**) was the first OX_1 selective antagonist reported and has been extensively studied because it has favorable preclinical pharmacokinetics.[28] Its affinity for OX_1 is ~50-fold higher than for OX_2, but some *in vivo* studies using high doses should be viewed cautiously because those doses may block both

receptors. Additionally, Rottapharm Madaus has reported a series of azaspiro compounds as selective OX_1 antagonists, and identified the spiro moiety as a key structural feature for OX_1 receptor selectivity.[29, 30] Several other OX_1 selective antagonists have also been reported, including GSK-1059865 and its analogs, as well as ACT-335827, although these compounds mostly retained a significant amount of OX_2 activity.[31-33]

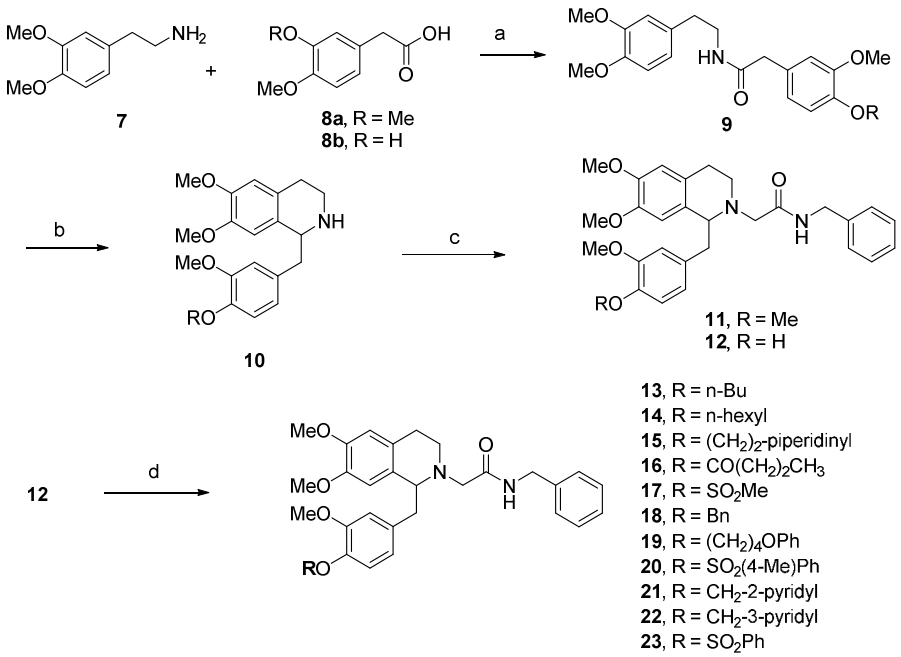
Our group has been developing OX_1 selective antagonists for the potential treatment of drug addiction and related disorders.[34-36] We recently described our progress toward selective OX antagonists based on the tetrahydroisoquinoline scaffold, which is found both in **1** and the OX_2 receptor selective antagonist TCS-OX2-29 (**5**).[37] The structural modifications focused on the 7-position of the tetrahydroisoquinoline ring and the acetamide positions, resulting in several potent and selective OX_1 antagonists. In particular, RTIOX-276 (**6**) showed excellent OX_1 potency and selectivity, and attenuated cocaine-induced conditioned place preference (CPP) in rats.[34] However, the structure-activity relationship (SAR) requirements in other regions of the structure have yet to be explored. Interestingly, at the 1-position of the tetrahydroisoquinoline, the dual orexin antagonist **1** has a 4-trifluoromethylphenylethyl group, whereas the OX_2 selective antagonist **5** does not bear any substitution, suggesting that this position may play an important role in receptor subtype selectivity. Therefore, we have examined a series of analogs bearing a variety of modifications at the 1-position of the tetrahydroisoquinoline. Herein, we report our effort in the design, synthesis, and *in vitro* and *in vivo* characterization of these 1-substituted analogs.

Results and Discussion

Chemistry. The overall approach to the synthesis followed methods detailed in our earlier work (Scheme 1).[34, 36] Briefly, commercially available 3,4-dimethoxyphenethylamine (**7**) and

phenylacetic acid **8a** were coupled using HBTU or BOP to give the amide **9**. Cyclization of **9** via the Bischler-Napieralski reaction using phosphorus oxychloride in toluene afforded the dihydroisoquinoline, which was readily reduced to the tetrahydroisoquinoline **10** with sodium borohydride. The nitrogen was alkylated using N-benzyl bromoacetamide with diisopropylethylamine as base to give final product **11**. Similarly, compound **12** was synthesized from **8b** (R = H). Elaboration of the phenol **12** was achieved by alkylation using the appropriate alkyl bromide in the presence of K_2CO_3, esterification via BOP-mediated coupling, or by sulfonylation using the sulfonyl chloride with triethylamine as base, to afford target compounds **13-23**.

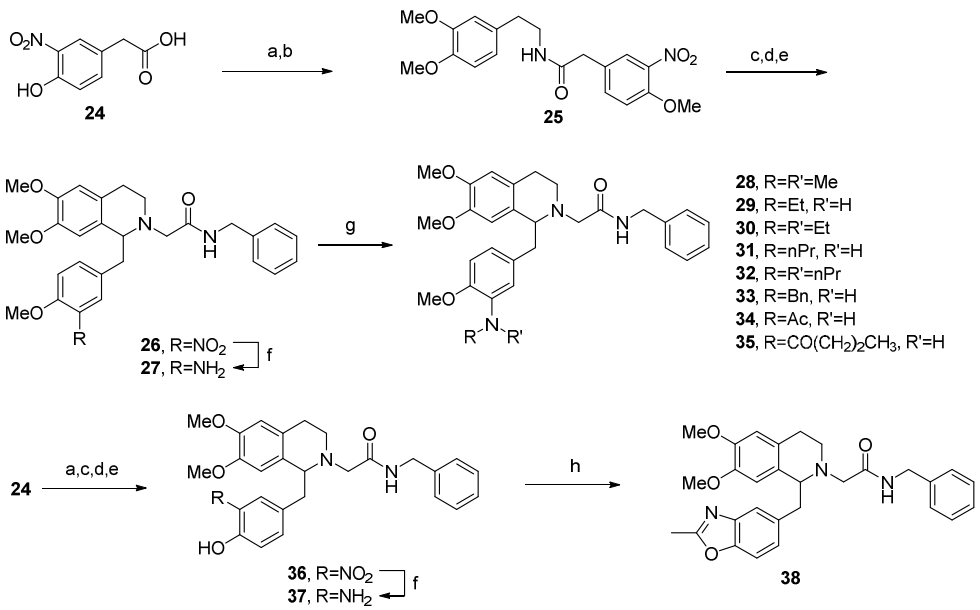
Scheme 1. Synthesis of 1-substituted tetrahydroisoquinolines **11-23**[a]



[a]Reagents and Conditions: (a) HBTU or BOP, iPr_2EtN, DMF; (b) (i) $POCl_3$, toluene; (ii) $NaBH_4$, MeOH; (c) $BrCH_2CONHCH_2Ph$, iPr_2EtN, Bu_4NI, DMF; (d) R'-Br, K_2CO_3, DMF or $CH_3(CH_2)_2COOH$, BOP, iPr_2EtN, CH_2Cl_2 or $R'SO_2Cl$, Et_3N, CH_2Cl_2.

Aniline derivatives were synthesized following a similar route (Scheme 2). Amide coupling of **24** with the amine **7** followed by alkylation of the hydroxyl group afforded intermediate **25**, which was converted to **27** via Bischler-Napieralski reaction, alkylation of the nitrogen and reduction of the nitro group**.** The free aniline in **27** was then modified by reductive amination using sodium triacetoxyborohydride or sodium cyanoborohydride, alkylation via an alkyl bromide or by amide coupling using BOP in DMF to provide final compounds **28-35**. Similarly, the benzoxazole **38** was prepared from **24** via the 4-hydroxy-3-amino intermediate **37** by condensation with ethyl acetimidate. In addition to the 3,4-disubstituted, several monosubstituted analogs were prepared in analogous fashion (Scheme 3), starting from acid **39**, via the tetrahydroisoquinoline **40** with further elaboration at phenol or aniline. Urea **50** was prepared by reaction with n-hexyl isocyanate in toluene.

Scheme 2. Synthesis of 1-aminobenzyl substituted tetrahydroisoquinolines **28-38**[a]

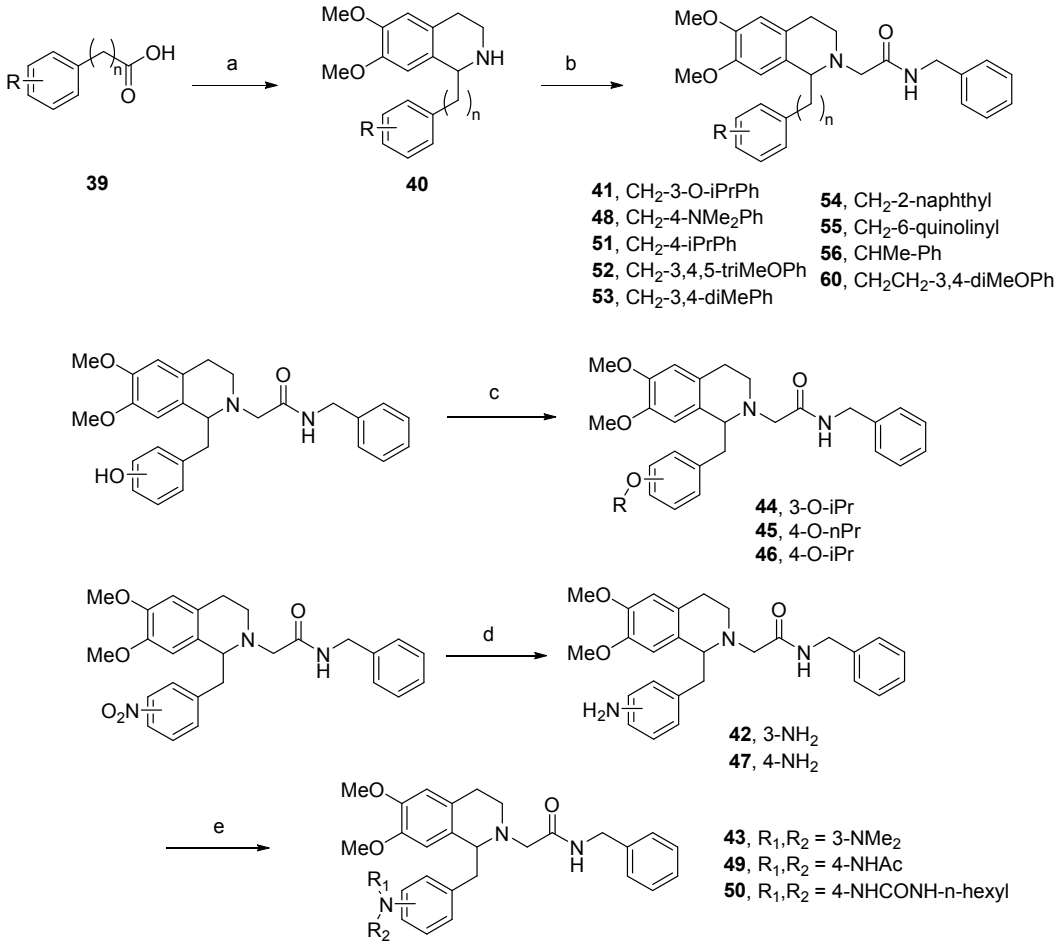


[a]Reagents and Conditions: (a) 3,4-dimethoxyphenethylamine (**7**), HBTU, iPr_2EtN, DMF; (b) Me-I, K_2CO_3, DMF; (c) $POCl_3$, toluene; (d) $NaBH_4$, MeOH; (e) $BrCH_2CONHCH_2Ph$, iPr_2EtN,

Bu_4NI, DMF; (f) Raney Ni, $NH_2NH_2.H_2O$, EtOH; (g) R-CHO, $Na(AcO)_3BH$, 1,2-DCE or R-CHO, $NaBH_3CN$, AcOH, MeOH or R-Br, iPr_2EtN, Bu_4NI, DMF or butyric acid, BOP, iPr_2EtN, DMF; (h) ethyl acetimidate HCl, $CHCl_3$.

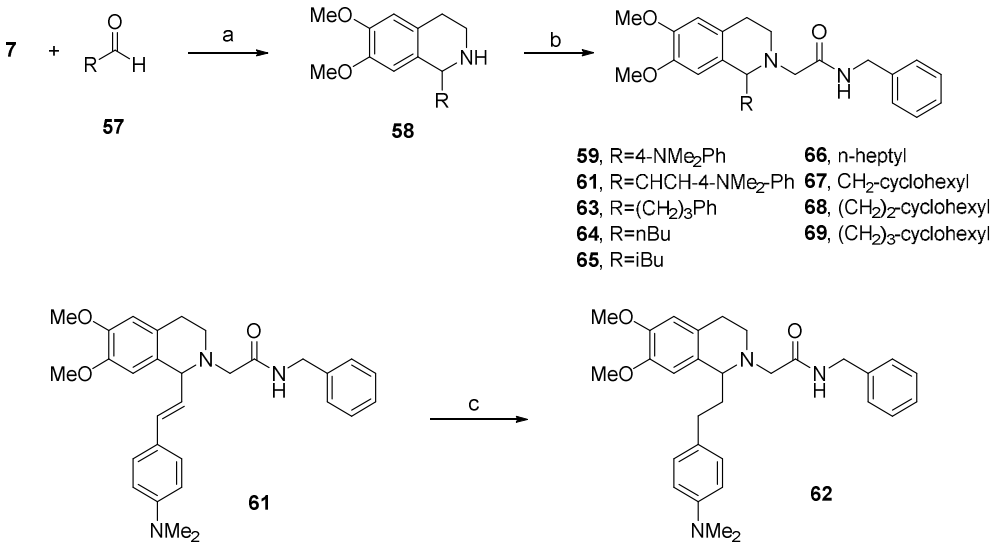
Compounds with substituents other than the benzyl group at the 1-position were made via Pictet-Spengler condensation between **7** and the corresponding aldehydes in toluene and trifluoroacetic acid at 140 °C for 30 minutes in the microwave, followed by N-alkylation as described above (Scheme 4). The olefin **61** was reduced by hydrogenation on Pd/C in ethanol to give the saturated analog **62**. Non-commercial aldehydes in the Pictet-Spengler reaction were prepared via pyridinium chlorochromate oxidation of the appropriate alcohols.

Scheme 3. Synthesis of 1-substituted tetrahydroisoquinolines **41-56**[a]



[a]Reagents and Conditions: (a) (i) **7**, HBTU, iPr_2EtN, DMF; (ii) $POCl_3$, toluene; (iii) $NaBH_4$, MeOH; (b) $BrCH_2CONHCH_2Ph$, iPr_2EtN, Bu_4NI, DMF; (c) R-Br, K_2CO_3, DMF; (d) Raney Ni, $NH_2NH_2.H_2O$, EtOH; (e) R-CHO, $Na(AcO)_3BH$, 1,2-DCE or Ac-Cl, iPr_2EtN, CH_2Cl_2 or n-hexyl isocyanate, toluene.

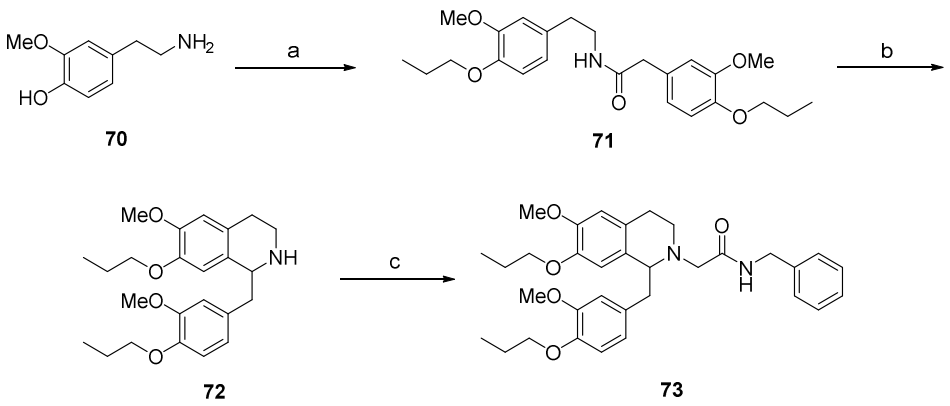
Scheme 4. Synthesis of 1-substituted tetrahydroisoquinolines **59-69**[a]



[a]Reagents and Conditions: (a) CF_3CO_2H, toluene; (b) $BrCH_2CONHCH_2Ph$, iPr_2EtN, Bu_4NI, DMF; (c) H_2, 10% Pd/C, EtOH.

The 7-propoxy derivative **73** was prepared in a similar fashion as described above (Scheme 5), starting from 4-hydroxy-3-methoxy-phenethylamine (**70**). Amide coupling between **70** and **8b**, followed by alkylation of the two hydroxyl groups afforded intermediate **71**. Cyclization followed by reduction provided amine **72** and then a final N-alkylation with the bromoacetamide gave **73**.

Scheme 5. Synthesis of 7-propoxy tetrahydroisoquinoline **73**.[a]



[a]Reagents and Conditions: (a) (i) **8b**, HBTU, iPr_2EtN, DMF; (ii) 1-iodopropane, K_2CO_3, DMF; (b) (i) $POCl_3$, toluene; (ii) $NaBH_4$, MeOH; (c) $BrCH_2CONHCH_2Ph$, K_2CO_3, DMF.

Biological Evaluation. Activity of the target compounds at the human OX_1 and OX_2 receptors was evaluated using Fluorescent Imaging Plate Reader technology (FLIPR^{TM}, Molecular Devices), which measures intracellular calcium mobilization in live cells. The apparent dissociation constant Ke was calculated from compound-mediated inhibition of orexin A activity as previously described.[34-36] In these assays, the EC_{50} for orexin A at OX_1 and OX_2 is 0.13 ± 0.02 nM and 4.2 ± 0.2 nM, respectively. All the compounds that had OX_1 Ke values < 1 μM were also tested for agonist activity at 10 μM; none of them were active.

Our studies aimed at mapping out the SAR requirements at the 1-positon based on both the steric and electronic considerations. An examination of several reported orexin antagonists based on the tetrahydroisoquinoline scaffold revealed the importance of the 1-postion. The dual orexin antagonist **1** has a 4-trifluoromethylphenylethyl group at the 1-position. Conversely, the OX_2 selective antagonist **5** does not bear any substitution at the 1-position. Compound **11**, the hit identified in a high-throughput screening campaign by Actelion, has a 3,4-dimethoxybenzyl group at the 1-position of the tetrahydroisoquinoline, and showed some selectivity for the OX_1 receptor (Table 1).[34, 38] The OX_1 receptor selective antagonist **6** developed in our lab also has the

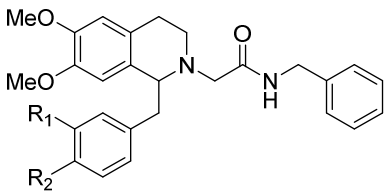
3,4-dimethoxy substitution. Taken together, these results suggest that the 1-position substituents may have differential effects on the activity of ligands at the two orexin receptors.

The small set of analogs of **11** reported by Actelion suggests that the substitution pattern on the 1-benzyl group may have a significant effect on the activity at the orexin receptors.[38] For instance, the corresponding phenyl analog which lacked the dimethoxy groups at the 3 and 4-positons, showed little activity at either receptor. Removing one of the methoxy groups also resulted in significant loss of activity at both receptors. Therefore, we first evaluated a series of 3,4-disubstituted benzyl analogs that retained the 3-methyoxy group but had different alkyl-substituted groups at the 4-position of the benzyl group (Table 1). All of the target compounds were prepared racemically, although the 1-position stereochemistry is undoubtedly important, as evidenced by both **1** and our own findings.[34, 39] While removing the methyl group at the 4-methoxy position gave a slight drop in potency in phenol **12**, the potency was regained and even increased by substituting with a larger alkyl group such as butyl **13** or hexyl **14**, with **13** having slightly higher potency. Further increasing the size to a piperidinylethyl group, which may provide improved drug-like properties due to the basic nitrogen, resulted in a total loss of activity, suggesting limited size tolerance at this site. Interestingly, the butyric ester **16** was equally potent to the butyl analog **13**, suggesting polar groups can be tolerated at this site. Analog **17** with a mesyl group, which has the size between a methyl (**11**) and butyl groups (**13**) but a high electron deficiency, had a Ke = 485 nM, only slightly less potent than **11**. These findings indicate that steric bulk may play a more prominent role at this position than electronic effects. A series of aromatic substituents at the 4-alkoxy position were then examined (**18-22**). The O-benzyl analog **18** was 2-fold less potent than **11**. Extending the phenyl group away from the ring system had no effect on potency (**19**). The corresponding sulfonyl analog (**20**) showed

no potency at the OX_1 receptor. The two pyridylmethyl derivatives **21** and **22** showed similar potency to compound **11**. Finally, the phenylsulfonyl analog (**23**) had a ~9-fold decrease in potency.

We next synthesized a series of compounds that had modifications at the 3-position of the 1-benzyl group, while retaining the 4-methoxy group (Table 1). Replacement of the oxygen moiety with a series of nitrogen-containing groups, with the aim of reducing logP and improving the drug-likeness, gave some interesting results. The 3-nitro analog (**26**) showed ~7-fold reduced potency, whereas dimethylamino analog **28** gave a significant improvement of potency at the OX_1 receptor (Ke = 13 nM) but also increased the OX_2 receptor potency. However, larger N-alkyl groups were not as well tolerated and the potency decreased with the increase of the size of the alkyl groups (**29-33**), with the benzyl analog (**33**) having no activity at concentrations up to 10 μM. Interestingly, while the acetyl derivatives **34** had a significant drop in potency, **35**, which had a larger acyl group, regained most of the potency. Finally, the corresponding 4-hydroxyl substituent had a significant potency reduction compared to its 4-methoxy analog (**36** vs. **26**). The benzoxazole **38** had a Ke in the micromolar range.

Table 1. Effect of benzyl substitution on OX antagonism



Number	R_1	R_2	Ke (OX_1, nM)[b]	Ke (OX_2, nM)[c]	OX_2/OX_1
11	OMe	OMe	199 ± 47	>10,000	>50.3

12	OMe	OH	419 ± 64	>10,000	>24
13	OMe	O-n-Butyl	48 ± 27	2000 ± 860	42
14	OMe	O-n-Hexyl	120 ± 20	>10,000	>83
15	OMe	O-$(CH_2)_2$-piperidinyl	>10,000[d]	a	
16	OMe	$OCO(CH_2)_2CH_3$	43.5 ± 3.7	2080 ± 600	48
17	OMe	OSO_2Me	480 ± 180	a	
18	OMe	OBenzyl	399 ± 22	a	
19	OMe	O-$(CH_2)_4$-OPh	385 ± 96	a	
20	OMe	OSO_2(4-Me)Ph	> 10,000	a	
21	OMe	OCH_2-2-Pyridyl	153 ± 43	a	
22	OMe	OCH_2-3-Pyridyl	250 ± 120	a	
23	OMe	OSO_2Ph	1820 ± 680	a	
26	NO_2	OMe	1500 ± 230	a	
28	NMe_2	OMe	12.7 ± 2.8	970 ± 350	76.7
29	NHEt	OMe	309 ± 39	>10,000	>32
30	NEt_2	OMe	208 ± 38	>10,000	>48
31	NH-n-Propyl	OMe	920 ± 140	>10,000	>11
32	N(n-Propyl)$_2$	OMe	857 ± 380[d]	a	
33	NH-Benzyl	OMe	>10,000[d]	a	
34	NHAc	OMe	>10,000[d]	a	
35	$NHCO(CH_2)_2CH_3$	OMe	320± 30	a	
36	NO_2	OH	>10,000[d]	a	
37	NH_2	OH	>10,000[d]	a	
38	2-Methyl-5-benzoxazole		2620± 870[d]	a	

a. < 35% inhibition at 10 μM;

b. Values are the mean ± SEM of at least three independent experiments performed in duplicate;

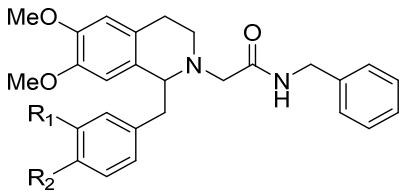
c. Values are the mean ± SEM of at least two independent experiments performed in duplicate; for compounds with Ke < 100 nM at OX_1 at least three independent experiments in duplicate were performed.

d. Values are the mean ± SEM of two independent experiments performed in duplicate.

All of the 1-benzyl analogs discussed thus far have a 3,4-substitution pattern. The relative importance of each of those positions was then examined by preparing a series of 3-substituted and 4-substituted analogs (Table 2). As previously reported, analogs singly substituted with a methoxyl group at either the 3- or 4-position had diminished activity at both OX_1 and OX_2 receptors.[38] Therefore, we have examined a series of analogs that bear substituents other than a methoxyl group at these positions. The 3-isopropoxyl analog (**41**) had a ~7-fold drop in OX_1 potency. In the 3-nitrogen containing analogs, the 3-nitro **42** showed activity only at OX_2 (1200 nM), whereas the aniline **43** showed modest potency at the OX_1 receptor and no activity at OX_2. Potency at the OX_1 receptor was further increased by dimethylation (**44**), which was the most potent mono-substituted compound in the series. However, **44** also showed significant potency at the OX_2 receptor (Ke = 660 nM). It appears that the 4-position may contribute more to the OX_1 potency as the 4-substituted mono isopropoxy derivative (**46)** showed increased potency compared to the corresponding 3-substituted derivative (**41**). The differences in OX_1 potency between the n-propyl **45** and the isopropyl **46** were modest and both were slightly less potent than **11**. In the 4-nitrogen series, the 4-aniline **47** showed no OX_1 activity and again this was restored with the 4-dimethylamino analog **48**, which had similar potency to compound **11** (253 v 199 nM). As with the disubstituted analogs, acylation as the acetamide **49** or the urea **50** caused a significant drop in potency. Finally, the isopropyl analog **51** had good potency, with a Ke of 85

nM, further reinforcing the idea that steric factors are the overriding factor in potency. The OX_2 selectivity of the nitro **42** indicates some preference for electron-withdrawing substituents for OX_2 potency and indeed a trifluoromethyl substituent may contribute to the OX_2 potency of **1**.

Table 2. Mono-substituted benzylic substituents at the 1-position and their effect on OX antagonism



Number	R_1	R_2	Ke (OX_1, nM)[b]	Ke (OX_2, nM)[c]	OX_2/OX_1
11	OMe	OMe	199± 47	>10,000	>50.3
41	O-Isopropyl	H	1470± 70	>10,000	>6.8
42	NO_2	H	>10,000	1200± 160	<0.12
43	NH_2	H	1310± 90	a	
44	NMe_2	H	75.3± 1.3	660±160	8.8
45	H	O-n-Propyl	370± 50	>10,000	>27
46	H	O-Isopropyl	489± 68	>10,000	>20
47	H	NH_2	>10,000[d]	a	
48	H	NMe_2	253± 85	>10,000	>40
49	H	NHAc	>10,000[d]	a	
50	H	NHCONH-n-hexyl	>10,000[d]	a	
51	H	Isopropyl	85± 21	>10,000	>118

a. < 35% inhibition at 10 μM;

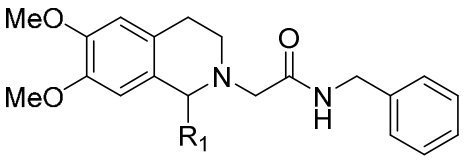
b. Values are the mean ± SEM of at least three independent experiments performed in duplicate;

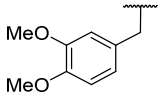
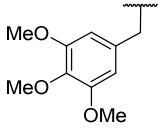
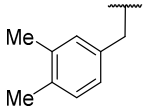
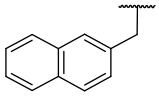
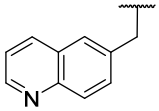
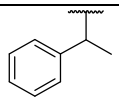
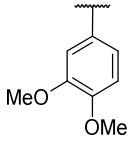
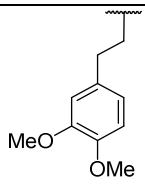
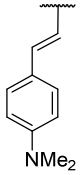
c. Values are the mean ± SEM of at least two independent experiments in performed duplicate; for compounds with Ke < 100 nM at OX_1 at least three independent experiments in duplicate were performed.

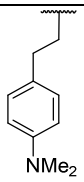
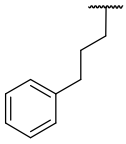
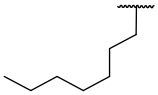
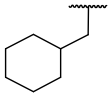
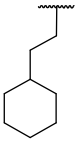
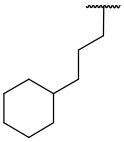
d. Values are the mean ± SEM of two independent experiments performed in duplicate.

We then investigated a series of alternate substituents, including differentially substituted benzylic and non-aromatic systems to further examine the SAR requirements at this position (Table 3). Surprisingly, the 3,4,5-trimethoxy analog **52** was mostly inactive at both receptors. This clearly shows that the 1-benzyl substituent is highly sensitive to substitutions, confirming the earlier observations. The 3,4-dimethylbenzyl analog **53** showed higher potency than **11**, further illustrating the importance of steric effects on potency. The naphthyl (**54**) and quinoline (**55**) analogs showed a modest reduction in potency compared to **11**. Interestingly, removing the methylene group resulted in a total loss of activity (**59** vs. **11**). Elongation of the methylene group (**60**, **62**, **63**) also led to significant loss of activity at the OX_1 receptor. This is somewhat surprising as the dual orexin antagonist **1** has a phenethyl group and has high potency at both receptors. Introduction of rigidity (**61**) led to diminished activity. The requirement for an aromatic system was then examined with the replacement of the 1-benzyl with nonaromatic systems (Table 3). A series of alkyl analogs were prepared and their OX potency evaluated; however, none of them (**64-69**) showed detectable antagonism in our assay at concentrations of 10 μM. Taken together, these findings clearly confirm that an optimally substituted benzyl group is required for OX_1 potency.

Table 3. Other substituents at the 1-position and their effect on OX antagonism



Number	R1	Ke (OX_1, nM)[b]	Ke (OX_2, nM)[c]	OX_2/OX_1
11		199 ± 47	>10,000	>50.3
52		>10,000[d]	>10,000	
53		94 ± 28	>10,000	>32
54		245 ± 40	1620 ± 230	6.6
55		432 ± 22	>10,000	>23
56		>10,000[d]	>10,000	
59		>10,000[d]	a	
60		>10,000[d]	>10,000	
61		>10,000[d]	a	

62		>10,000[d]	a	
63		>10,000[d]	a	
64		>10,000[d]	a	
65		>10,000[d]	a	
66		>10,000[d]	a	
67		>10,000[d]	a	
68		>10,000[d]	a	
69		>10,000[d]	a	

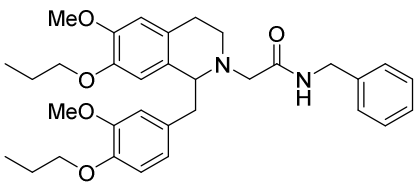
a. < 35% inhibition at 10 μM;

b. Values are the mean ± SEM of at least three independent experiments performed in duplicate;

c. Values are the mean ± SEM of at least two independent experiments in performed duplicate; for compounds with Ke < 100 nM at OX_1 at least three independent experiments in duplicate were performed.

d. Values are the mean ± SEM of two independent experiments performed in duplicate.

The structural modifications at the 1-position have led to the identification of several compounds that have improved OX_1 potency compared to the 3,4-dimethoxy analog **11**. Several compounds also showed improved OX_1 selectivity, greater than 50-fold (e.g. **16**, **28**, **51**), even though this improvement is only modest. As previously reported by our group, introducing larger alkyl groups such as a 7-propoxy at the 7-methoxy position led to improved potency and selectivity. Therefore, we synthesized a dipropoxy analog which has a propoxy group at the 7-position of the tetrahydroisoquinoline and the 4-position of the 1-benzyl group, respectively (**73**, RTIOX-251, Figure 2). Indeed, these modifications resulted in an analog that showed improvement in both OX_1 potency and selectivity (**73**). Compound **73** had a Ke of 16.1 nM (vs. 48 nM for the close analog **13**), but it was selectivity where the greatest improvement was seen in **73**, which increased to approximately >620-fold.



73
$Ke(OX_1)$ = 16.1 ± 3.6 nM
$Ke(OX_2)$ >10,000 nM
OX_2/OX_1 > 620

Figure 2. 7-Propoxy-1-(4-propoxy)benzyl tetrahydroisoquinoline derivative **73**.

Cocaine-induced Behavioral Sensitization. OX_1 receptor selective antagonist SB334867 has been reported to block the development of locomotor sensitization to cocaine when administrated i.p.[40] We next moved on to test one of the compounds that showed the highest potency and selectivity in this series of compounds, compound **73**, on the development of behavioral sensitization to cocaine in rats. As expected, acute cocaine treatment induced a dose-dependent hyperactivity (open circles, left panel, Fig. 3). Daily treatment with 15 mg/kg cocaine for 7 days

induced a significant locomotor sensitization, as demonstrated by a leftward shift of the cocaine dose-effect curve on day 15 as compared to day 1 (compare gray circles with open circles, right panel, Fig. 3). Two way ANOVA revealed significant main effects of repeated treatment ($F [2, 14] = 24.7$, $P < 0.0001$) and repeated treatment × cocaine dose interactions ($F [2, 14] = 35.2$, $P < 0.0001$). Post hoc analysis indicated that on day 15, the effects of 3.2 and 10 mg/kg cocaine were significantly increased while the effect of 32 mg/kg cocaine was significantly decreased. Although 10 mg/kg compound **73**, a dose that alone did not significantly alter the spontaneous activity in rats (data not shown), did not alter acute cocaine-induced hyperactivity when given acutely (left panel, Fig. 3), repeated treatment with compound **73** significantly blocked the development of cocaine sensitization (compare open circles with open squares, right panel, Fig. 3). Two way ANOVA revealed significant main effects of repeated treatment ($F [2, 14] = 7.2$, $P < 0.01$) and repeated treatment × cocaine dose interactions ($F [2, 14] = 10.5$, $P < 0.01$). Post hoc analysis indicated that on day 15, the effects of 10 mg/kg cocaine were significantly lower while the effect of 32 mg/kg cocaine was significantly higher in the compound **73** treated group as compared to control group, suggesting a significant blockade of cocaine sensitization.

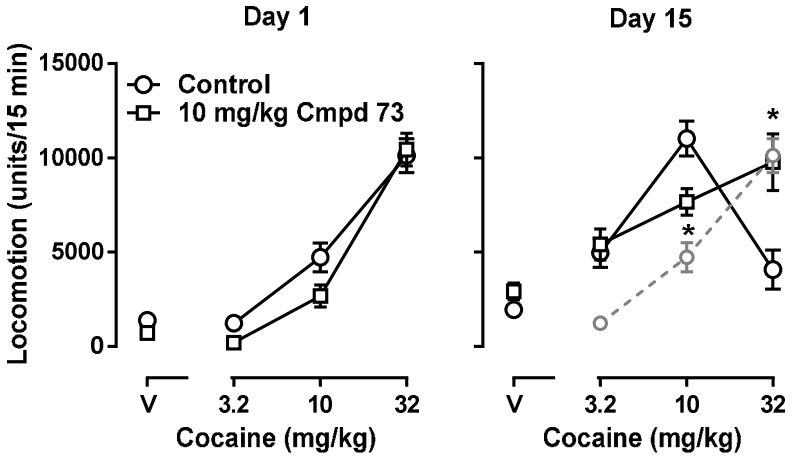


Figure 3. Compound **73** attenuated the development of cocaine-induced behavioral sensitization. Left: compound **73** did not significantly alter acute cocaine-induced hyperactivity (n=8/group). Right: compound **73** significantly reduced the development of cocaine sensitization during the challenge test (* $P < 0.05$ as compared with control group). Dashed line represents the replotted data of control group in Day 1 for comparison in Day 15. Data represent the mean ± SEM. The absence of error bars indicates that the variability is contained within the data point. V, vehicle.

Conclusions

Recently, the orexin system has been indicated to play an important role in the reward pathway and OX_1 receptor selective antagonists have been suggested to hold value for the treatment of addiction to a number of illicit drugs. While several OX_1 antagonists have been reported so far, they tend to retain some activity at the OX_2 receptor. In our continued effort to investigate the SAR on the tetrahydroisoquinoline scaffold and develop highly potent and selective OX_1 antagonists, we have designed and synthesized a series of compounds with a range of substituents at the 1-position. These compounds were then evaluated for the potency at the OX_1 and OX_2 receptors in FLPR-based calcium mobilization assays. The SAR results indicate that an optimally substituted benzyl group is required for activity at the OX_1 receptor. Shortening or elongation of the methylene unit in the benzyl group both led to dramatic decreases in OX_1 potency. Other nonaromatic systems including straight chain or cyclic alkyl groups were also not well tolerated. A number of analogs (e.g. **13**, **16** and **51**) showed improvement on potency at the OX_1 receptor compared with the dimethoxy substitution (**11**). In particular, the 3-dimethylamino-4-methyoxy substitution pattern **(28)** provided the best OX_1 potency (Ke = 12.7 nM) and reasonable selectivity (76.7-fold), although some activity at the OX_2 potency remains (Ke = 970 nM). When structural modifications at the 7-position of the tetrahydroisoquinoline that have

been shown to improve potency were introduced, OX_1 potency and selectivity were further enhanced. Compound **73** (RTIOX-251) is both a potent and highly selective OX_1 receptor antagonist. At 10 mg/kg **73** did not alter acute cocaine-induced hyperactivity when given acutely, but blocked the development of locomotor sensitization to cocaine in rats when repeatedly administrated.

Experimental Procedures

General. All solvents and chemicals were reagent grade. Unless otherwise mentioned, all were purchased from commercial vendors and used as received. Flash column chromatography was done on a Teledyne ISCO CombiFlash Rf system using prepacked columns. Solvents used were hexane, ethyl acetate (EtOAc), dichloromethane (DCM), methanol and chloroform:methanol:ammonium hydroxide (80:18:2) (CMA-80). Purity and characterization of 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-d4 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). High resolution mass spectra were obtained using an Agilent 6230 time-of-flight mass spectrometer. Melting points were determined using a Mel Temp II melting point apparatus and are uncorrected. All test compounds were greater than 95% pure as

determined by HPLC on an Agilent 1100 system using an Agilent Zorbax SB-Phenyl, 2.1 mm x 150 mm, 5 μm column with gradient elution using the mobile phases (A) H_2O containing 0.1% CF_3COOH and (B) MeCN, with a flow rate of 1.0 mL/min.

General procedures:

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(3-hydroxy-4-methoxyphenyl)acetamide (9). 3-Hydroxy-4-methoxyphenylacetic acid (1.0 g, 5.49 mmol), 3,4-dimethoxyphenethylamine (1.0 g, 0.93 mL, 5.49 mmol) and HBTU (2.08 g, 5.49 mmol) were combined in dry DMF (55 mL) at RT under N_2. Diisopropylethylamine (1.77 g, 2.4 mL, 13.72 mmol) was added and the reaction stirred at RT overnight. The reaction was diluted with EtOAc, washed with 2N HCl, $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure to give the desired amide as a yellow oil which solidified upon standing (1.50 g, 79%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.39 - 7.50 (m, 1H), 6.81 - 6.88 (m, 1H), 6.71 (d, *J* = 8.19 Hz, 1H), 6.57 - 6.67 (m, 3H), 6.50 (dd, *J* = 1.98, 8.10 Hz, 1H), 5.52 (br. s., 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.47 (s, 2H), 3.43 (t, *J* = 6.12 Hz, 2H), 2.67 (t, *J* = 6.83 Hz, 2H).

4-[(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]-2-methoxyphenol (10). Amide **9** (1.51 g, 4.37 mmol) was suspended in anhydrous toluene (22 mL) and phosphorous oxychloride (4.02 g, 2.45 mL, 26.23 mmol) added slowly. The reaction was heated to 90 °C for 2 hr, during which the solid went into solution, then a red oil separated. The reaction was cooled, then quenched by slow addition of the reaction mixture to water and heated until a solution formed. The toluene layer was removed, 2N sodium hydroxide solution was added until pH was 8-9, then the solution was extracted 3 times with DCM. The combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure.

The crude dihydroisoquinoline was dissolved in methanol (25 mL) and cooled in an ice bath under N_2. Sodium borohydride (0.83 g, 21.99 mmol) was added portionwise and the reaction allowed to warm slowly to RT overnight. The reaction was quenched with water then the methanol removed under reduced pressure. The aqueous solution was extracted 3 times with DCM and the combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give the desired tetrahydroisoquinoline as an off-white foam (0.73 g, 91%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 6.86 (d, *J* = 7.82 Hz, 1H), 6.70 - 6.79 (m, 2H), 6.66 (s, 1H), 6.60 (s, 1H), 4.13 (dd, *J* = 4.29, 9.18 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.11 - 3.27 (m, 2H), 2.83 - 2.98 (m, 4H), 2.63 - 2.79 (m, 2H).

N-Benzyl-2-{1-[(4-hydroxy-3-methoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (12). Amine **10** (0.20 g, 0.61 mmol), N-benzyl-2-bromoacetamide (0.152 g, 0.67 mmol) and tetrabutylammonium iodide (0.045 g, 0.12 mmol) were combined in dry DMF (6 mL) and diisopropylethylamine (0.196 g, 0.26 mL, 1.52 mmol) was added. The reaction was stirred at RT overnight under N_2. The reaction was diluted with EtOAc, washed with $NaHCO_3$ solution, water and brine (x2), then dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude was purified by chromatography on silica (0-60% EtOAc in hexane) to obtain the desired product as a pale yellow oil (0.097 g, 33%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.21 - 7.36 (m, 3H), 7.14 (d, *J* = 6.69 Hz, 2H), 6.93 - 7.04 (m, 1H), 6.76 - 6.84 (m, 1H), 6.66 - 6.73 (m, 1H), 6.64 (d, *J* = 1.51 Hz, 1H), 6.59 (s, 1H), 6.45 (s, 1H), 5.50 (s, 1H), 4.48 (dd, *J* = 8.01, 14.69 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.56 - 3.72 (m, 2H), 3.35 - 3.49 (m, 1H), 3.09 - 3.34 (m, 2H), 2.79 - 3.01 (m, 4H), 2.42 - 2.56 (m, 1H). *m/z* 477 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{28}H_{33}N_2O_5$ $[M+H]^+$ 477.2384, *m/z* found 477.2411.

N-Benzyl-2-{1-[(4-butoxy-3-methoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (13). Phenol **12** (50 mg, 0.105 mmol), potassium carbonate (29 mg, 0.210 mmol) and tetrabutylammonium iodide (8 mg, 0.021 mmol) were combined in DMF (1 mL) and 1-bromobutane (16 mg, 12 μL, 0.115 mmol) was added. The reaction was heated at 50 °C overnight. It was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude was purified by chromatography on silica (0-75% EtOAc in hexane) to give the desired product as a yellow glassy solid (47 mg, 84%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.34 (m, 3H), 7.11 (d, *J* = 6.50 Hz, 2H), 6.96 - 7.06 (m, 1H), 6.63 - 6.72 (m, 3H), 6.58 (s, 1H), 6.44 (s, 1H), 4.49 (dd, *J* = 8.05, 14.93 Hz, 1H), 3.83 - 3.91 (m, 5H), 3.81 (s, 3H), 3.79 (s, 3H), 3.58 - 3.71 (m, 2H), 3.34 - 3.51 (m, 1H), 3.10 - 3.34 (m, 2H), 2.78 - 3.00 (m, 4H), 2.41 - 2.56 (m, 1H), 1.72 - 1.87 (m, 2H), 1.39 - 1.53 (m, 2H), 0.97 (t, *J* = 7.35 Hz, 3H). *m/z* 533 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{32}H_{41}N_2O_5$ $[M+H]^+$ 533.3010, *m/z* found 533.3057.

N-Benzyl-2-(1-{[4-(hexyloxy)-3-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (14). This was made by the general procedure from phenol **12** in 73% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.19 - 7.34 (m, 3H), 7.08 - 7.16 (m, 2H), 7.01 (dd, *J* = 5.23, 7.49 Hz, 1H), 6.63 - 6.73 (m, 3H), 6.59 (s, 1H), 6.44 (s, 1H), 4.49 (dd, *J* = 8.01, 14.88 Hz, 1H), 3.84 - 3.90 (m, 5H), 3.81 (s, 3H), 3.79 (s, 3H), 3.58 - 3.71 (m, 2H), 3.34 - 3.49 (m, 1H), 3.10 - 3.34 (m, 2H), 2.79 - 2.99 (m, 4H), 2.41 - 2.56 (m, 1H), 1.74 - 1.88 (m, 2H), 1.29 - 1.51 (m, 6H), 0.91 (t, *J* = 6.78 Hz, 3H). *m/z* 561 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{34}H_{45}N_2O_5$ $[M+H]^+$ 561.3323, *m/z* found 561.3362.

N-Benzyl-2-[6,7-dimethoxy-1-({3-methoxy-4-[2-(piperidin-1-yl)ethoxy]phenyl}methyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (15). This was prepared from **12** using the

general procedure in 27% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.19 - 7.35 (m, 3H), 7.12 (d, *J* = 6.69 Hz, 2H), 7.03 (dd, *J* = 5.09, 7.44 Hz, 1H), 6.66 - 6.73 (m, 3H), 6.59 (s, 1H), 6.43 (s, 1H), 4.48 (dd, *J* = 7.96, 14.93 Hz, 1H), 4.02 (t, *J* = 6.31 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.59 - 3.72 (m, 2H), 3.34 - 3.48 (m, 1H), 3.11 - 3.34 (m, 2H), 2.83 - 2.99 (m, 4H), 2.76 - 2.82 (m, 2H), 2.42 - 2.56 (m, 5H), 1.61 (quin, *J* = 5.49 Hz, 4H), 1.40 - 1.51 (m, 2H). *m/z* 588 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{35}H_{46}N_3O_5$ $[M+H]^+$ 588.3432, *m/z* found 588.3489.

4-({2-[(Benzylcarbamoyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl}methyl)-2-methoxyphenyl butanoate (16). To a mixture of phenol **12** (50 mg, 0.105 mmol), butyric acid (9 mg, 10 μL, 0.105 mmol) and BOP (46 mg, 0.105 mmol) in DCM (1 mL) was added diisopropylethylamine (34 mg, 46 μL, 0.262 mmol) and the reaction stirred at RT under N_2 overnight. The reaction was diluted with EtOAc, washed with 2N HCl, $NaHCO_3$ solution and brine, then dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-75% EtOAc in hexane) to give the desired ester as a yellow oil (54 mg, 95%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.23 - 7.35 (m, 3H), 7.14 - 7.21 (m, 2H), 7.07 (t, *J* = 6.22 Hz, 1H), 6.78 - 6.85 (m, 1H), 6.66 - 6.74 (m, 2H), 6.58 (s, 1H), 6.36 (s, 1H), 4.40 - 4.50 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.63 - 3.95 (m, 2H), 3.11 - 3.47 (m, 3H), 2.78 - 3.04 (m, 4H), 2.42 - 2.63 (m, 3H), 1.73 - 1.89 (m, 2H), 1.07 (t, *J* = 7.39 Hz, 3H). *m/z* 547 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{32}H_{39}N_2O_6$ $[M+H]^+$ 547.2803, *m/z* found 547.2845.

4-({2-[(Benzylcarbamoyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl}methyl)-2-methoxyphenyl methanesulfonate (17). To a solution of phenol **12** (30 mg, 0.063 mmol) in DCM (0.5 mL) cooled in ice was added methanesulfonyl chloride (14 mg, 10 μL,

0.126 mmol) and triethylamine (16 mg, 22 μL, 0.157 mmol). The reaction was allowed to warm to RT overnight. The reaction mixture was applied directly to silica for chromatography (0-100% EtOAc in hexane) to give the desired sulfonate as a yellow oil (21 mg, 60%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.22 - 7.37 (m, 3H), 7.17 (d, *J* = 6.88 Hz, 2H), 7.09 (d, *J* = 8.29 Hz, 2H), 6.68 - 6.77 (m, 2H), 6.60 (s, 1H), 6.32 (s, 1H), 4.44 (dd, *J* = 7.25, 14.88 Hz, 1H), 3.95 (dd, *J* = 5.09, 14.98 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 6H), 3.66 - 3.74 (m, 1H), 3.28 - 3.42 (m, 2H), 3.22 (br. s., 1H), 3.14 (s, 3H), 2.81 - 3.06 (m, 4H), 2.53 (d, *J* = 16.20 Hz, 1H). *m/z* 555 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{35}N_2O_7S$ $[M+H]^+$ 555.2160, *m/z* found 555.2212.

N-Benzyl-2-(1-{[4-(benzyloxy)-3-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (18). This was prepared from phenol **12** by the general procedure in 15% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.19 - 7.45 (m, 8H), 7.12 (d, *J* = 6.78 Hz, 2H), 6.98 - 7.07 (m, 1H), 6.61 - 6.74 (m, 3H), 6.58 (s, 1H), 6.41 (s, 1H), 5.00 (s, 2H), 4.45 (dd, *J* = 8.01, 14.98 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.55 - 3.76 (m, 2H), 3.34 - 3.48 (m, 1H), 3.10 - 3.33 (m, 2H), 2.77 - 2.99 (m, 4H), 2.41 - 2.55 (m, 1H). *m/z* 567 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{35}H_{39}N_2O_5$ $[M+H]^+$ 567.2854, *m/z* found 567.2917.

N-Benzyl-2-(6,7-dimethoxy-1-{[3-methoxy-4-(4-phenoxybutoxy)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (19). This was prepared from **12** using the general procedure in 71% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.35 (m, 5H), 7.11 (d, *J* = 6.88 Hz, 2H), 7.02 (dd, *J* = 5.04, 7.39 Hz, 1H), 6.87 - 6.98 (m, 3H), 6.65 - 6.73 (m, 3H), 6.60 (s, 1H), 6.45 (s, 1H), 4.50 (dd, *J* = 8.01, 14.98 Hz, 1H), 4.04 (t, *J* = 5.89 Hz, 2H), 3.90 - 3.97 (m, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.60 - 3.73 (m, 2H), 3.36 - 3.51 (m, 1H), 3.11 - 3.35 (m, 2H), 2.80 - 3.01 (m, 4H), 2.44 - 2.57 (m, 1H), 1.91 - 2.04 (m, 4H). *m/z* 625 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{38}H_{45}N_2O_6$ $[M+H]^+$ 625.3272, *m/z* found 625.3335.

4-({2-[(Benzylcarbamoyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl}methyl)-2-methoxyphenyl 4-methylbenzene-1-sulfonate (20). This was prepared from **12** as sulfonate **17** above. Yield 80%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.76 (d, *J* = 8.29 Hz, 2H), 7.21 - 7.36 (m, 5H), 7.17 (d, *J* = 6.97 Hz, 2H), 7.05 (br. s., 1H), 6.91 (d, *J* = 8.10 Hz, 1H), 6.54 - 6.67 (m, 3H), 6.31 (s, 1H), 4.44 (dd, *J* = 7.30, 14.74 Hz, 1H), 3.92 (d, *J* = 4.90 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.62 - 3.71 (m, 1H), 3.49 (s, 3H), 3.10 - 3.39 (m, 3H), 2.75 - 3.03 (m, 4H), 2.49 - 2.57 (m, 1H), 2.46 (s, 3H). *m/z* 631 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{35}H_{39}N_2O_7S$ $[M+H]^+$ 631.2473, *m/z* found 631.2536.

N-Benzyl-2-(6,7-dimethoxy-1-{[3-methoxy-4-(pyridin-2-ylmethoxy)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (21). This was prepared from **12** using the general procedure in 92% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.59 (dd, *J* = 0.85, 4.05 Hz, 1H), 7.61 - 7.71 (m, 1H), 7.53 (d, *J* = 7.82 Hz, 1H), 7.17 - 7.32 (m, 4H), 7.10 (d, *J* = 6.59 Hz, 2H), 6.96 - 7.05 (m, 1H), 6.69 - 6.75 (m, 2H), 6.62 - 6.68 (m, 1H), 6.59 (s, 1H), 6.42 (s, 1H), 5.15 (s, 2H), 4.46 (dd, *J* = 7.86, 14.84 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.58 - 3.74 (m, 2H), 3.34 - 3.48 (m, 1H), 3.11 - 3.33 (m, 2H), 2.78 - 3.00 (m, 4H), 2.50 (d, *J* = 15.82 Hz, 1H). *m/z* 568 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{34}H_{38}N_3O_5$ $[M+H]^+$ 568.2806, *m/z* found 568.2869.

N-Benzyl-2-(6,7-dimethoxy-1-{[3-methoxy-4-(pyridin-3-ylmethoxy)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (22). This was prepared from **12** using the general procedure in 42% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.65 (d, *J* = 1.60 Hz, 1H), 8.57 (dd, *J* = 1.27, 4.76 Hz, 1H), 7.76 (d, *J* = 7.82 Hz, 1H), 7.18 - 7.34 (m, 4H), 7.12 (d, *J* = 6.59 Hz, 2H), 7.04 (br. s., 1H), 6.64 - 6.74 (m, 3H), 6.60 (s, 1H), 6.42 (s, 1H), 4.95 (s, 2H), 4.49 (dd, *J* = 7.91, 15.16 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.62 - 3.77 (m, 2H),

3.13 - 3.50 (m, 3H), 2.80 - 3.02 (m, 4H), 2.52 (d, *J* = 15.73 Hz, 1H). *m/z* 568 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{34}H_{38}N_3O_5$ $[M+H]^+$ 568.2806, *m/z* found 568.2869.

4-({2-[(Benzylcarbamoyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl}methyl)-2-methoxyphenyl benzenesulfonate (23). This was prepared from **12** as sulfonate **17** above. Yield 69%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.85 - 7.92 (m, 2H), 7.62 - 7.71 (m, 1H), 7.48 - 7.57 (m, 2H), 7.21 - 7.36 (m, 3H), 7.17 (d, *J* = 6.78 Hz, 2H), 7.04 (t, *J* = 5.93 Hz, 1H), 6.93 (d, *J* = 8.10 Hz, 1H), 6.64 (d, *J* = 8.19 Hz, 1H), 6.55 - 6.60 (m, 2H), 6.31 (s, 1H), 4.44 (dd, *J* = 7.39, 14.74 Hz, 1H), 3.86 (s, 3H), 3.84 - 3.96 (m, 1H), 3.76 (s, 3H), 3.63 - 3.72 (m, 1H), 3.45 (s, 3H), 3.11 - 3.38 (m, 3H), 2.76 - 3.03 (m, 4H), 2.41 - 2.55 (m, 1H). *m/z* 617 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{34}H_{37}N_2O_7S$ $[M+H]^+$ 617.2316, *m/z* found 617.2377.

N-Benzyl-2-{6,7-dimethoxy-1-[(4-methoxy-3-nitrophenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (26). Phenol **36** (40 mg, 0.08 mmol) and potassium carbonate (17 mg, 0.12 mmol) were combined in DMF (2 mL) and iodomethane (14 mg, 6 μL, 0.097 mmol) was added. The reaction was heated to 50 °C for 2 hr. The reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-100% EtOAc in hexane) to give the desired product (30 mg, 75%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.99 (s, 1H), 7.68 (d, *J* = 2.26 Hz, 1H), 7.28 - 7.39 (m, 4H), 7.02 - 7.14 (m, 1H), 6.75 (d, *J* = 8.29 Hz, 1H), 6.60 (s, 1H), 6.44 (s, 1H), 4.37 - 4.54 (m, 1H), 3.90 - 3.96 (m, 1H), 3.85 - 3.88 (m, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.65 (dd, *J* = 5.46, 9.23 Hz, 1H), 3.38 - 3.47 (m, 2H), 3.11 - 3.22 (m, 1H), 2.90 - 3.00 (m, 4H), 2.46 - 2.58 (m, 1H). m/z 506 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{28}H_{32}N_3O_6$ $[M+H]^+$ 506.2286, *m/z* found 506.2327.

2-{1-[(3-Amino-4-methoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-benzylacetamide (27). To the nitro derivative **26** (200 mg, 0.4 mmol) in ethanol (20 mL) was added hydrazine monohydrate (198 mg, 0.19 mL, 4.0 mmol) and then heated to 50 °C for 15 min. Raney nickel (2800 type as a slurry in water, 232 mg, 4.0 mmol) was added and heating continued for 1 hr. The reaction was filtered through Celite, rinsed with ethanol then the solvent was removed under reduced pressure to give the desired amine as a clear oil (100 mg, 53%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.68 (s, 2H), 7.20 - 7.35 (m, 5H), 7.09 (d, *J* = 6.78 Hz, 2H), 6.85 (br. s., 1H), 6.75 (d, *J* = 8.48 Hz, 1H), 6.59 (s, 1H), 6.43 (s, 1H), 4.47 (dd, *J* = 7.44, 15.16 Hz, 1H), 3.87 (s, 3H), 3.85 - 3.98 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 3.60 - 3.71 (m, 1H), 3.11 - 3.48 (m, 3H), 2.83 - 3.05 (m, 4H), 2.51 (d, *J* = 16.77 Hz, 1H). *m/z* 476 (M+H).

N-Benzyl-2-(1-{[3-(dimethylamino)-4-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (28). To a solution of amine **27** (50 mg, 0.10 mmol) in methanol (1 mL) was added formaldehyde (37% solution in water, 1 mL) and glacial acetic acid (21 mg, 20 μL, 0.35 mmol). To this was then added sodium cyanoborohydride (31 mg, 0.5 mmol) and the reaction stirred at RT for 2 hr. 1N HCl (0.1 mL) was added then the reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-50% EtOAc in hexane) to give the desired dimethylamine (26 mg, 52%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.34 (m, 3H), 7.01 - 7.14 (m, 3H), 6.70 - 6.78 (m, 2H), 6.55 - 6.65 (m, 2H), 6.41 (s, 1H), 4.48 (dd, *J* = 7.82, 14.98 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.59 - 3.72 (m, 2H), 3.37 - 3.51 (m, 1H), 3.13 - 3.35 (m, 2H), 2.79 - 3.00 (m, 4H), 2.75 (s, 6H), 2.44 - 2.56 (m, 1H). *m/z* 504 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{38}N_3O_4$ $[M+H]^+$ 504.2857, *m/z* found 504.2906.

N-Benzyl-2-(1-{[3-(ethylamino)-4-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (29). To amine **27** (30 mg, 0.06 mmol) in DMF (3 mL) was added 1-iodoethane (20 mg, 10 μL, 0.13 mmol) then diisopropylethylamine (20 mg, 26 μL, 0.16 mmol) and the reaction stirred at RT under N_2 overnight. The reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-15% methanol in DCM) to give the desired amine as a white solid (15 mg, 47%): mp 122-125 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.17 - 7.32 (m, 3H), 7.01 - 7.11 (m, 3H), 6.41 - 6.61 (m, 5H), 4.50 (dd, *J* = 8.29, 14.88 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H), 3.39 - 3.66 (m, 3H), 3.02 - 3.32 (m, 4H), 2.78 - 2.99 (m, 4H), 2.42 - 2.54 (m, 1H), 1.26 (t, *J* = 7.16 Hz, 3H). *m/z* 504 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{38}N_3O_4$ $[M+H]^+$ 504.2857, *m/z* found 504.2914.

N-Benzyl-2-(1-{[3-(diethylamino)-4-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (30). This was prepared as per **29** using 1-iodoethane (3 eq). Yield 76%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.16 - 7.37 (m, 3H), 7.08 (d, *J* = 7.54 Hz, 2H), 6.27 - 6.75 (m, 5H), 4.50 (dd, *J* = 8.38, 14.98 Hz, 1H), 3.85 (d, *J* = 6.03 Hz, 6H), 3.71 (s, 3H), 3.56 - 3.66 (m, 2H), 3.38 - 3.56 (m, 2H), 3.21 - 3.35 (m, 1H), 3.02 - 3.19 (m, 3H), 2.77 - 3.00 (m, 7H), 0.91 - 1.34 (m, 6H). *m/z* 532 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{32}H_{42}N_3O_4$ $[M+H]^+$ 532.3170, *m/z* found 532.3223.

N-Benzyl-2-(6,7-dimethoxy-1-{[4-methoxy-3-(propylamino)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (31). This was prepared as per **29** using 1-iodopropane (1 eq). Yield 15%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.16 - 7.34 (m, 3H), 6.99 - 7.12 (m, 3H), 6.40 - 6.64 (m, 5H), 4.51 (dd, *J* = 8.29, 15.07 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.70

(s, 3H), 3.38 - 3.67 (m, 4H), 3.09 - 3.32 (m, 2H), 2.98 - 3.08 (m, 1H), 2.77 - 2.93 (m, 4H), 2.42 - 2.57 (m, 1H), 1.60 - 1.72 (m, 2H), 1.01 (t, *J* = 7.44 Hz, 3H). *m/z* 518 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{31}H_{40}N_3O_4$ $[M+H]^+$ 518.3013, *m/z* found 518.3055.

N-Benzyl-2-(1-{[3-(dipropylamino)-4-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (32). This was prepared as per **29** using 1-iodopropane. Yield 51%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.17 - 7.40 (m, 2H), 6.91 - 7.15 (m, 3H), 6.67 - 6.78 (m, 1H), 6.34 - 6.65 (m, 4H), 4.37 - 4.58 (m, 1H), 3.74 - 3.93 (m, 6H), 3.70 (s, 3H), 3.56 - 3.66 (m, 1H), 3.36 - 3.55 (m, 1H), 3.09 - 3.35 (m, 2H), 2.76 - 3.08 (m, 9H), 2.50 (dd, *J* = 4.05, 15.92 Hz, 1H), 1.29 - 1.71 (m, 4H), 0.67 - 1.15 (m, 6H). *m/z* 560 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{34}H_{46}N_3O_4$ $[M+H]^+$ 560.3483, *m/z* found 560.3551.

N-Benzyl-2-(1-{[3-(benzylamino)-4-methoxyphenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (33). This was prepared as per **29** using benzyl bromide. Yield 82%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.06 - 7.34 (m, 10H), 6.93 (dd, *J* = 4.90, 7.91 Hz, 1H), 6.53 - 6.64 (m, 3H), 6.44 - 6.52 (m, 2H), 6.41 (d, *J* = 1.70 Hz, 1H), 4.51 (dd, *J* = 8.29, 15.07 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (d, *J* = 0.75 Hz, 2H), 3.73 (s, 3H), 3.47 - 3.62 (m, 2H), 3.25 - 3.40 (m, 1H), 3.01 - 3.24 (m, 2H), 2.58 - 2.96 (m, 4H), 2.42 (dd, *J* = 4.62, 16.86 Hz, 1H). *m/z* 566 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{35}H_{40}N_3O_4$ $[M+H]^+$ 566.3013, *m/z* found 566.3068.

N-Benzyl-2-{1-[(3-acetamido-4-methoxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (34). To a solution of amine **27** (50 mg, 0.10 mmol) and diisopropylethlamine (32 mg, 41 μL, 0.25 mmol) in DCM (3 mL) under N_2 cooled in an ice bath was added acetyl bromide (12 mg, 8 μL, 0.10 mmol). The reaction was stirred in ice for 10 min, then at RT for 3 hr. The reaction was diluted with $NaHCO_3$ solution and extracted 3 times with

EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude was purified by chromatography on silica (0-75% EtOAc in hexane) to give the desired amide as a yellow oil (32 mg, 62%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.34 (d, *J* = 1.51 Hz, 1H), 7.52 (s, 1H), 7.17 - 7.31 (m, 3H), 6.97 - 7.05 (m, 3H), 6.87 (dd, *J* = 1.70, 8.29 Hz, 1H), 6.66 (d, *J* = 8.29 Hz, 1H), 6.57 (d, *J* = 5.65 Hz, 2H), 4.42 (dd, *J* = 8.01, 15.35 Hz, 1H), 3.87 (s, 6H), 3.73 (s, 3H), 3.44 - 3.71 (m, 3H), 3.05 - 3.34 (m, 2H), 2.84 - 3.00 (m, 4H), 2.44 - 2.56 (m, 1H), 2.13 (s, 3H). *m/z* 518 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{36}N_3O_5$ $[M+H]^+$ 518.2650, *m/z* found 518.271.

N-[5-({2-[(Benzylcarbamoyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl}methyl)-2-methoxyphenyl]butanamide (35). To amine **27** (50 mg, 0.1 mmol) and BOP (44 mg, 0.1 mmol) in DMF (3 mL) was added butyric acid (9 mg, 9 μL, 0.1 mmol) then diisopropylethylamine (32 mg, 41 μL, 0.25 mmol) and the reaction stirred at RT under N_2 overnight. The reaction was diluted with EtOAc, washed with 1N HCl, 1N NaOH solution and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-15% methanol in DCM) to give the desired amide as a yellow oil (22 mg, 40%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.40 (d, *J* = 1.88 Hz, 1H), 7.58 (s, 1H), 7.17 - 7.33 (m, 3H), 7.01 (d, *J* = 6.40 Hz, 3H), 6.86 (dd, *J* = 2.07, 8.29 Hz, 1H), 6.64 (d, *J* = 8.29 Hz, 1H), 6.55 - 6.60 (m, 2H), 4.43 (dd, *J* = 8.10, 15.26 Hz, 1H), 3.86 (s, 6H), 3.72 (s, 4H), 3.41 - 3.69 (m, 2H), 3.05 - 3.34 (m, 2H), 2.77 - 3.02 (m, 4H), 2.42 - 2.55 (m, 1H), 2.32 (t, *J* = 7.44 Hz, 2H), 1.74 (qd, *J* = 7.43, 14.81 Hz, 2H), 1.01 (t, *J* = 7.35 Hz, 3H). *m/z* 546 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{32}H_{40}N_3O_5$ $[M+H]^+$ 546.2963, *m/z* found 546.3021.

N-Benzyl-2-{1-[(4-hydroxy-3-nitrophenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (36). This was made by the general procedure starting

from 4-hydroxy-3-nitrophenylacetic acid in 4 steps in 15% overall yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.85 (s, 1H), 7.21 - 7.40 (m, 4H), 7.05 (d, *J* = 7.06 Hz, 1H), 6.93 (d, *J* = 8.57 Hz, 1H), 6.85 (br. s., 1H), 6.60 (s, 1H), 6.44 (s, 1H), 4.37 (dd, *J* = 7.06, 15.07 Hz, 1H), 3.97 (dd, *J* = 5.18, 14.98 Hz, 1H), 3.85 (d, *J* = 11.68 Hz, 6H), 3.57 - 3.71 (m, 1H), 3.26 - 3.49 (m, 3H), 3.10 - 3.24 (m, 1H), 2.80 - 3.03 (m, 4H), 2.52 (d, *J* = 16.39 Hz, 1H). *m/z* 492 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{30}N_3O_6$ $[M+H]^+$ 492.2129, *m/z* found 492.2182.

2-{1-[(3-Amino-4-hydroxyphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-benzylacetamide (37). To the nitro derivative **36** (100 mg, 0.2 mmol) in ethanol (10 mL) was added hydrazine monohydrate (100 mg, 0.1 mL, 2 mmol) and the reaction warmed to 50 °C. Raney nickel (2800 type as a slurry in water, 20 mg) was added and the reaction stirred at 50 °C for 1 hr. The reaction was cooled, filtered through Celite and washed with ethanol. The solvent was removed under reduced pressure and the crude purified by chromatography on silica (0-10% methanol in DCM) to give the aminophenol (56 mg, 57%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.20 - 7.36 (m, 3H), 7.11 - 7.18 (m, 2H), 7.04 - 7.11 (m, 1H), 6.55 - 6.60 (m, 2H), 6.49 - 6.54 (m, 1H), 6.42 - 6.49 (m, 2H), 5.49 (br. s., 1H), 4.48 (dd, *J* = 8.01, 14.98 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (dd, *J* = 4.80, 14.98 Hz, 1H), 3.35 - 3.63 (m, 4H), 3.07 - 3.33 (m, 2H), 2.73 - 2.98 (m, 4H), 2.41 - 2.53 (m, 1H). *m/z* 462 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{32}N_3O_4$ $[M+H]^+$ 462.2387, *m/z* found 462.2384.

N-Benzyl-2-{6,7-dimethoxy-1-[(2-methyl-1,3-benzoxazol-5-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (38). To aminophenol **37** (56 mg, 0.12 mmol) in chloroform (10 mL) was added ethyl acetimidate hydrochloride (17 mg, 0.13 mmol). The reaction was heated to reflux for 16 hr. The solvent was removed under reduced pressure and the crude purified by chromatography on silica (0-10% MeOH in DCM) to give the desired

benzoxazole (29 mg, 50%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.49 (s, 1H), 7.19 - 7.29 (m, 4H), 7.11 (d, *J* = 8.29 Hz, 1H), 6.82 - 6.90 (m, 2H), 6.71 (br. s., 1H), 6.60 (s, 1H), 6.49 (s, 1H), 4.34 (dd, *J* = 7.91, 15.26 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.62 - 3.72 (m, 1H), 3.41 - 3.57 (m, 2H), 3.09 - 3.34 (m, 2H), 2.83 - 3.08 (m, 4H), 2.57 (s, 3H), 2.44 - 2.60 (m, 1H). *m/z* 486 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{32}N_3O_4$ $[M+H]^+$ 486.2387, *m/z* found 486.2435.

N-Benzyl-2-(6,7-dimethoxy-1-{[3-(propan-2-yloxy)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (41). This was made by the general procedure starting from 3-hydroxyphenylacetic acid to the phenol precursor in 4 steps in 6% overall yield. For the final step, the phenol (30 mg, 0.067 mmol), potassium carbonate (23 mg, 0.168 mmol) and tetrabutylammonium iodide (5 mg, 0.013 mmol) were combined in DMF (0.5 mL) and 2-bromopropane (12 mg, 9 μL, 0.101 mmol) was added and the reaction heated at 50 °C overnight. An additional 20 μL of 2-bromopropane was added and the reaction was heated at 50 °C for a further 24 hr. It was cooled, diluted with EtOAc, washed with $NaHCO_3$ solution, water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-70% EtOAc in hexane) to give the desired isoproxy derivative as an off-white solid (20 mg, 61%): mp 123-125 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.35 (m, 3H), 7.04 - 7.17 (m, 3H), 6.92 - 7.04 (m, 1H), 6.76 (d, *J* = 2.17 Hz, 2H), 6.60 - 6.73 (m, 1H), 6.58 (s, 1H), 6.43 (s, 1H), 4.38 - 4.54 (m, 2H), 3.83 - 3.89 (m, 3H), 3.76 - 3.82 (m, 3H), 3.60 - 3.71 (m, 2H), 3.34 - 3.52 (m, 1H), 3.07 - 3.32 (m, 2H), 2.79 - 3.03 (m, 4H), 2.42 - 2.55 (m, 1H), 1.26 - 1.32 (m, 6H). *m/z* 489 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$ 489.2748, *m/z* found 489.2802.

N-Benzyl-2-{6,7-dimethoxy-1-[(3-nitrophenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (42). This was made by the general procedure starting from 3-nitrophenylacetic

acid in 4 steps in 4% overall yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.03 (s, 1H), 7.86 (td, *J* = 0.99, 8.19 Hz, 1H), 7.43 (d, *J* = 7.35 Hz, 1H), 7.17 - 7.36 (m, 4H), 6.98 - 7.08 (m, 2H), 6.70 (t, *J* = 5.65 Hz, 1H), 6.60 (s, 1H), 6.43 (s, 1H), 4.33 (dd, *J* = 6.97, 14.88 Hz, 1H), 3.87 (s, 3H), 3.92 (d, *J* = 5.27 Hz, 0H), 3.81 (s, 3H), 3.71 (dd, *J* = 5.56, 9.32 Hz, 1H), 2.84 - 3.48 (m, 8H), 2.44 - 2.57 (m, 1H). *m/z* 476 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{30}N_3O_5$ $[M+H]^+$ 476.2180, *m/z* found 476.2229.

2-{1-[(3-Aminophenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-benzylacetamide (43). To the nitro derivative **42** (100 mg, 0.21 mmol) in ethanol (12 mL) was added hydrazine monohydrate (100 mg, 0.1 mL, 21 mmol) and the reaction warmed to 50 °C. Raney nickel (2800 type as a slurry in water, 50 mg) was added and the reaction stirred at 50 °C for 1 hr. The reaction was cooled, filtered through Celite and washed with ethanol. The solvent was removed under reduced pressure to give the amine (80 mg, 90%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.21 - 7.36 (m, 3H), 7.15 (d, *J* = 7.54 Hz, 2H), 6.94 - 7.10 (m, 2H), 6.56 - 6.65 (m, 2H), 6.43 - 6.54 (m, 3H), 4.47 (dd, *J* = 7.86, 14.93 Hz, 1H), 3.85 (d, *J* = 13.00 Hz, 6H), 3.76 (dd, *J* = 4.95, 14.93 Hz, 1H), 3.64 (dd, *J* = 5.89, 8.90 Hz, 1H), 3.36 - 3.54 (m, 3H), 3.23 - 3.35 (m, 1H), 3.06 - 3.19 (m, 1H), 2.76 - 3.00 (m, 4H), 2.43 - 2.55 (m, 1H). *m/z* 446 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{32}N_3O_3$ $[M+H]^+$ 446.2438, *m/z* found 446.2487.

N-Benzyl-2-(1-{[3-(dimethylamino)phenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (44). To a solution of amine **43** (80 mg, 0.18 mmol) in methanol (1 mL) was added formaldehyde (37% solution in water, 1.5 mL) and glacial acetic acid (39 mg, 37 μL, 0.65 mmol). To this was then added sodium cyanoborohydride (56 mg, 0.9 mmol) and the reaction stirred at RT for 2 hr. 1N HCl (0.1 mL) was added then the reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent

was removed under reduced pressure. The crude was purified by chromatography on silica (0-50% EtOAc in hexane) to give the desired dimethylamine as an off-white solid (30 mg, 35%): mp 101-103 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.17 - 7.33 (m, 4H), 7.06 - 7.14 (m, 3H), 6.98 - 7.06 (m, 1H), 6.45 - 6.62 (m, 4H), 4.46 (dd, *J* = 8.19, 14.98 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.55 - 3.71 (m, 2H), 3.39 - 3.53 (m, 1H), 3.08 - 3.33 (m, 2H), 2.86 - 2.88 (m, 6H), 2.78 - 3.00 (m, 4H), 2.42 - 2.55 (m, 1H). *m/z* 496 (M+Na), 474 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{36}N_3O_3$ $[M+H]^+$ 474.2751, *m/z* found 474.2803.

N-Benzyl-2-{6,7-dimethoxy-1-[(4-propoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (45). This was prepared as per **41** except using 1-bromopropane to give the desired product as a white solid. Yield of final step 39%: mp 126-127 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.20 - 7.34 (m, 3H), 7.06 - 7.15 (m, 4H), 6.84 - 6.94 (m, 1H), 6.76 (d, *J* = 8.57 Hz, 2H), 6.58 (s, 1H), 6.45 (s, 1H), 4.47 (dd, *J* = 8.10, 14.98 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.77 (dt, *J* = 2.35, 6.59 Hz, 2H), 3.54 - 3.66 (m, 2H), 3.37 - 3.52 (m, 1H), 3.08 - 3.32 (m, 2H), 2.80 - 2.99 (m, 4H), 2.42 - 2.55 (m, 1H), 1.72 - 1.86 (m, 2H), 1.03 (t, *J* = 7.44 Hz, 3H). *m/z* 489 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$ 489.2748, *m/z* found 489.2804.

N-Benzyl-2-(6,7-dimethoxy-1-{[4-(propan-2-yloxy)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (46). This was prepared as **41** starting from 4-hydroxyphenylacetic acid in 5 steps in 3% overall yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.19 - 7.34 (m, 3H), 7.14 (d, *J* = 7.63 Hz, 2H), 7.07 (d, *J* = 8.19 Hz, 2H), 6.94 - 7.03 (m, 1H), 6.76 (d, *J* = 8.10 Hz, 2H), 6.58 (s, 1H), 6.41 (s, 1H), 4.35 - 4.52 (m, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.54 - 3.72 (m, 2H), 3.33 - 3.52 (m, 1H), 3.07 - 3.32 (m, 2H), 2.78 - 2.99 (m, 4H), 2.42 -

2.54 (m, 1H), 1.31 (d, *J* = 6.03 Hz, 6H). *m/z* 489 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{37}N_2O_4$ $[M+H]^+$ 489.2748, *m/z* found 489.2807.

2-{1-[(4-Aminophenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-benzylacetamide (47). This was made by the general procedure starting from 4-nitrophenylacetic acid in 4 steps in 86% overall yield to give the 4-nitrophenyl derivative. The nitro compound (0.89 g, 1.87 mmol) was dissolved in ethanol (30 mL) and to it was added hydrazine monohydrate (1 mL), the solution warmed to 50 °C and Raney nickel (2800 type as a slurry in water, 0.25 g) was added. The reaction was stirred at 50 °C until gas evolution ceased (~ 1 hr) then it was filtered through Celite and the solvent was removed under reduced pressure to give the desired amine as an off-white solid (0.79 g, 95%): mp 145-147 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.21 - 7.37 (m, 3H), 7.17 (d, *J* = 6.78 Hz, 2H), 6.97 (d, *J* = 8.10 Hz, 3H), 6.58 (s, 1H), 6.50 (d, *J* = 8.01 Hz, 2H), 6.46 (s, 1H), 4.47 (dd, *J* = 7.96, 14.93 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.72 (dd, *J* = 4.99, 14.79 Hz, 1H), 3.36 - 3.61 (m, 4H), 3.05 - 3.33 (m, 2H), 2.74 - 3.01 (m, 4H), 2.40 - 2.55 (m, 1H). *m/z* 468 (M+Na), 446 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{32}N_3O_3$ $[M+H]^+$ 446.2438, *m/z* found 446.2476.

N-Benzyl-2-(1-{[4-(dimethylamino)phenyl]methyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (48). This was made by the general procedure starting from 4-dimethylaminophenylacetic acid in 4 steps in 15% overall yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.34 (m, 3H), 7.04 - 7.14 (m, 3H), 6.92 - 7.02 (m, 1H), 6.54 - 6.65 (m, 3H), 6.48 (s, 1H), 4.40 - 4.53 (m, 1H), 3.80 - 3.90 (m, 6H), 3.35 - 3.64 (m, 3H), 3.06 - 3.33 (m, 2H), 2.78 - 3.00 (m, 10H), 2.42 - 2.55 (m, 1H). *m/z* 474 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{36}N_3O_3$ $[M+H]^+$ 474.2751, *m/z* found 474.2746.

N-Benzyl-2-{1-[(4-acetamidophenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (49). To a solution of amine **47** (25 mg, 0.056 mmol) and diisopropylethlamine (18 mg, 24 μL, 0.140 mmol) in DCM (1 mL) under N_2 cooled in an ice bath was added acetyl chloride (9 mg, 8 μL, 0.112 mmol). The reaction was stirred in ice for 10 min, then at RT for 3 hr. The reaction was diluted with $NaHCO_3$ solution and extracted 3 times with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude was purified by chromatography on silica (0-75% EtOAc in hexane) to give the desired amide as an off-white solid (13 mg, 48%): mp 99-100 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.21 - 7.38 (m, 5H), 7.03 - 7.16 (m, 4H), 6.76 - 6.90 (m, 2H), 6.59 (s, 1H), 6.46 (s, 1H), 4.42 (dd, *J* = 7.77, 15.31 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.74 - 3.80 (m, 1H), 3.56 - 3.66 (m, 1H), 3.36 - 3.51 (m, 1H), 3.07 - 3.35 (m, 2H), 2.81 - 3.00 (m, 4H), 2.43 - 2.55 (m, 1H), 2.12 (s, 3H). *m/z* 488 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{34}N_3O_4$ $[M+H]^+$ 488.2544, *m/z* found 488.2597.

N-Benzyl-2-[1-({4-[(hexylcarbamoyl)amino]phenyl}methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (50). To the amine **47** (27 mg, 0.061 mmol) in toluene (1 mL) was added n-hexylisocyanate (8.5 mg, 10 μL, 0.067 mmol) and the reaction heated to 75 °C for 3 hr. The reaction was cooled and the solvents were removed under reduced pressure. The crude was purified by chromatography on silica (0-100% EtOAc in hexane) to give the desired urea as a white solid (33 mg, 94%): mp 81-84 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.22 - 7.35 (m, 4H), 7.05 - 7.13 (m, 5H), 6.82 - 6.93 (m, 1H), 6.59 (s, 1H), 6.45 (s, 1H), 5.97 (s, 1H), 4.55 (t, *J* = 5.56 Hz, 1H), 4.42 (dd, *J* = 7.77, 15.12 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.73 - 3.80 (m, 1H), 3.61 (dd, *J* = 5.79, 9.00 Hz, 1H), 3.35 - 3.50 (m, 1H), 3.08 - 3.34 (m, 4H), 2.80 - 3.01 (m, 4H), 2.42 - 2.56 (m, 1H), 1.44 - 1.55 (m, 2H), 1.22 - 1.39 (m, 6H), 0.85 - 0.93 (m, 3H).

m/z 573 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{34}H_{45}N_4O_4$ $[M+H]^+$ 573.3435, *m/z* found 573.3495.

N-Benzyl-2-(6,7-dimethoxy-1-{[4-(propan-2-yl)phenyl]methyl}-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (51). This was made by the general procedure starting from 4-isopropylphenylacetic acid in 4 steps to give the desired product as a white solid in 65% overall yield: mp 97-99 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.20 - 7.36 (m, 3H), 7.03 - 7.15 (m, 6H), 6.58 (s, 1H), 6.35 (s, 1H), 4.37 (dd, *J* = 7.54, 15.07 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.59 - 3.83 (m, 2H), 3.39 - 3.54 (m, 1H), 3.09 - 3.35 (m, 2H), 2.76 - 3.04 (m, 5H), 2.43 - 2.57 (m, 1H), 1.18 (dd, *J* = 5.18, 6.69 Hz, 6H). *m/z* 473 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{37}N_2O_3$ $[M+H]^+$ 473.2799, *m/z* found 473.2858.

N-Benzyl-2-{6,7-dimethoxy-1-[(3,4,5-trimethoxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (52). This was made by the general procedure starting from 3,4,5-trimethoxyphenylacetic acid in 4 steps to give the desired product as an orange solid in 7% overall yield: mp 127-128 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.10 - 7.39 (m, 6H), 6.59 (s, 1H), 6.32 - 6.41 (m, 3H), 4.46 - 4.57 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 3.77 (s, 6H), 3.81 (d, *J* = 2.26 Hz, 1H), 3.70 (dd, *J* = 5.84, 8.48 Hz, 1H), 3.12 - 3.45 (m, 3H), 2.78 - 3.04 (m, 4H), 2.45 - 2.59 (m, 1H). *m/z* 521 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{37}N_2O_6$ $[M+H]^+$ 521.2646, *m/z* found 521.2683.

N-Benzyl-2-{1-[(3,4-dimethylphenyl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (53). This was made by the general procedure starting from 3,4-dimethylphenylacetic acid in 4 steps to give the desired product as an off-white solid in 37% overall yield: mp 112-114 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.34 (m, 3H), 6.95 - 7.08 (m, 4H), 6.83 - 6.95 (m, 2H), 6.59 (s, 1H), 6.48 (s, 1H), 4.44 (dd, *J* = 8.15, 15.12

Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.40 - 3.67 (m, 3H), 3.06 - 3.32 (m, 2H), 2.80 - 3.01 (m, 4H), 2.43 - 2.55 (m, 1H), 2.13 (s, 6H). *m/z* 459 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$ 459.2642, *m/z* found 459.2695.

N-Benzyl-2-[6,7-dimethoxy-1-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (54). This was made by the general procedure starting from 2-naphthaleneacetic acid in 4 steps in 50% overall yield as an off-white: mp 69-72 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.68 - 7.84 (m, 3H), 7.66 (s, 1H), 7.41 - 7.53 (m, 2H), 7.35 (dd, *J* = 1.55, 8.34 Hz, 1H), 7.15 (dd, *J* = 1.79, 4.90 Hz, 2H), 6.64 - 6.76 (m, 3H), 6.61 (s, 1H), 6.49 (s, 1H), 4.13 - 4.25 (m, 1H), 3.87 (s, 3H), 3.70 - 3.81 (m, 4H), 3.45 - 3.60 (m, 1H), 3.05 - 3.32 (m, 4H), 2.83 - 3.03 (m, 3H), 2.45 - 2.58 (m, 1H). *m/z* 481 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{31}H_{33}N_2O_3$ $[M+H]^+$ 481.2486, *m/z* found 481.2493.

N-Benzyl-2-[6,7-dimethoxy-1-(quinolin-6-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (55). This was made by the general procedure starting from 2-(quinolin-6-yl)acetic acid in 4 steps in 48% overall yield as a yellow glassy solid. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 8.90 (dd, *J* = 1.60, 4.24 Hz, 1H), 8.01 (dd, *J* = 9.09, 12.76 Hz, 2H), 7.54 - 7.62 (m, 2H), 7.36 (dd, *J* = 4.24, 8.29 Hz, 1H), 7.13 - 7.20 (m, 2H), 6.69 - 6.81 (m, 3H), 6.61 (s, 1H), 6.43 (s, 1H), 4.23 (dd, *J* = 8.01, 14.79 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.69 - 3.84 (m, 1H), 3.42 - 3.58 (m, 1H), 3.06 - 3.35 (m, 4H), 2.84 - 3.02 (m, 3H), 2.46 - 2.60 (m, 1H). *m/z* 482 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{32}N_3O_3$ $[M+H]^+$ 482.2438, *m/z* found 482.2483.

N-Benzyl-2-[6,7-dimethoxy-1-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (56). This was made by the general procedure starting from 2-phenylpropionic acid in 4 steps in 29% overall yield as a yellow glassy solid. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.04 - 7.35 (m, 10H), 6.63 - 6.74 (m, 1H), 6.54 (s, 1H), 4.38 (dd, *J* = 7.63,

14.98 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.74 - 3.89 (m, 1H), 3.45 - 3.52 (m, 1H), 3.34 - 3.45 (m, 1H), 3.13 - 3.22 (m, 1H), 2.79 - 3.08 (m, 3H), 2.48 - 2.71 (m, 2H), 1.25 (d, *J* = 7.25 Hz, 1H). *m/z* 445 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{28}H_{33}N_2O_3$ $[M+H]^+$ 445.2486, *m/z* found 445.2496.

Pictet-Spengler route to 1-alkyl-tetrahydroisoquinolines. General procedure: **N-Benzyl-2-[1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (59).** 3,4-Dimethoxyphenethylamine (0.10 g, 93 μL, 0.55 mmol) and 3,4-dimethoxybenzaldehyde (0.11 g, 0.66 mmol) were combined in dry toluene (0.55 mL). Trifluoroacetic acid (0.50 g, 0.33 mL, 4.41 mmol) was added and the reaction heated in the microwave at 140 °C for 30 min. The reaction was cooled, the solvent was removed under reduced pressure and water was added. The pH was adjusted to 8-9 with 2N NaOH solution then extracted three times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield the tetrahydroisoquinoline which was used in the next step without further purification.

The crude tetrahydroisoquinoline was combined with N-benzyl bromoacetamide (0.19 g, 0.82 mmol) and tetrabutylammonium iodide (41 mg, 0.11 mmol) in DMF (6 mL), diisopropylethylamine (0.18 g, 0.24 mL, 1.37 mmol) was added then the reaction stirred at RT under N_2 overnight. The reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude was purified by chromatography on silica (0-75% EtOAc in hexane) to give the desired 1-phenyl derivative as an off-white solid (0.11 g, 41%): mp 140-141 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.47 - 7.58 (m, 1H), 7.25 - 7.38 (m, 3H), 7.21 (d, *J* = 7.44 Hz, 2H), 6.77 (s, 2H), 6.60 (d, *J* = 4.05 Hz, 2H), 6.14 (s, 1H), 4.35 - 4.55 (m, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.60 (s, 6H), 3.33 (d, *J* = 16.48 Hz, 1H), 3.12 (dd, *J* = 4.05, 11.11 Hz, 1H), 2.93 - 3.06 (m, 2H),

2.65 - 2.83 (m, 2H). *m/z* 477 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{28}H_{33}N_2O_5$ $[M+H]^+$ 477.2384, *m/z* found 477.2438.

N-Benzyl-2-{1-[2-(3,4-dimethoxyphenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (60). This was prepared via Bischler-Napieralski cyclization using the general procedures outlined for **12**. The compound was obtained in 45% yield over 4 steps as a yellow glassy solid. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.70 (br. t, *J* = 5.70 Hz, 1H), 7.22 - 7.40 (m, 5H), 6.74 (d, *J* = 8.01 Hz, 1H), 6.52 - 6.61 (m, 3H), 6.45 (s, 1H), 4.48 - 4.55 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 6H), 3.54 (dd, *J* = 4.90, 7.82 Hz, 1H), 3.15 - 3.40 (m, 3H), 2.74 - 2.95 (m, 2H), 2.41 - 2.72 (m, 3H), 1.84 - 2.12 (m, 2H). *m/z* 505 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{37}N_2O_5$ $[M+H]^+$ 505.2697, *m/z* found 505.2685.

N-Benzyl-2-{1-[(E)-2-[4-(dimethylamino)phenyl]ethenyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (61). Synthesized via Pictet-Spengler general method from 4-dimethylaminocinnamaldehyde. Yield 9%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.17 - 7.36 (m, 7H), 6.72 - 6.79 (m, 1H), 6.63 - 6.71 (m, 4H), 6.41 (d, *J* = 15.73 Hz, 1H), 5.66 (dd, *J* = 8.57, 15.73 Hz, 1H), 4.83 (d, *J* = 14.88 Hz, 1H), 4.31 (d, *J* = 8.67 Hz, 1H), 4.07 (d, *J* = 14.79 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.73 (d, *J* = 15.07 Hz, 1H), 3.19 (dd, *J* = 1.46, 14.27 Hz, 1H), 3.00 (s, 6H), 2.49 - 2.75 (m, 4H). *m/z* 486 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{36}N_3O_3$ $[M+H]^+$ 486.2751, *m/z* found 486.2817.

N-Benzyl-2-(1-{2-[4-(dimethylamino)phenyl]ethyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (62). The olefin **61** (20 mg, 0.041 mmol) and palladium on carbon (10%, 20 mg) in ethanol (5 mL) were stirred under an atmosphere of hydrogen (35 psi) on a Parr shaker for 1.5 hr. The reaction was filtered through Celite, rinsed with ethanol and the solvent was removed under reduced pressure. The crude was purified by chromatography on

silica (0-75% EtOAc in hexane) to give the saturated analog as a yellow oil (7 mg, 35%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.38 (m, 5H), 6.87 (d, *J* = 8.48 Hz, 2H), 6.76 - 6.82 (m, 1H), 6.64 - 6.75 (m, 5H), 5.00 (d, *J* = 14.98 Hz, 1H), 4.01 (br. s., 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 - 3.95 (m, 2H), 3.21 (d, *J* = 15.26 Hz, 1H), 2.92 (s, 6H), 2.81 - 2.88 (m, 1H), 2.59 - 2.72 (m, 2H), 2.24 - 2.56 (m, 2H), 1.79 (dt, *J* = 3.53, 8.08 Hz, 2H). *m/z* 488 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{30}H_{38}N_3O_3$ $[M+H]^+$ 488.2908, *m/z* found 488.2956.

N-Benzyl-2-[6,7-dimethoxy-1-(3-phenylpropyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (63). Synthesized via Pictet-Spengler general method from 4-phenylbutyraldehyde. Yield 69%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.70 (br. s., 1H), 7.15 - 7.38 (m, 8H), 7.05 (d, *J* = 7.72 Hz, 2H), 6.53 (s, 1H), 6.41 (s, 1H), 4.48 (d, *J* = 5.93 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.47 (d, *J* = 4.14 Hz, 1H), 3.17 - 3.34 (m, 2H), 3.07 - 3.17 (m, 1H), 2.69 - 2.89 (m, 2H), 2.43 - 2.64 (m, 3H), 1.53 - 1.80 (m, 4H). *m/z* 459 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{35}N_2O_3$ $[M+H]^+$ 459.2642, *m/z* found 459.269.

N-Benzyl-2-(1-butyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (64). Synthesized via Pictet-Spengler general method from valeraldehyde. Yield 68%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.76 (br. s., 1H), 7.28 - 7.41 (m, 5H), 6.55 (s, 1H), 6.48 (s, 1H), 4.51 (t, *J* = 5.70 Hz, 2H), 3.84 (s, 6H), 3.44 (dd, *J* = 4.85, 8.05 Hz, 1H), 3.12 - 3.36 (m, 3H), 2.71 - 2.92 (m, 2H), 2.44 - 2.57 (m, 1H), 1.51 - 1.75 (m, 2H), 1.14 - 1.34 (m, 4H), 0.80 (t, *J* = 6.78 Hz, 3H). *m/z* 397 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{24}H_{33}N_2O_3$ $[M+H]^+$ 397.2486, *m/z* found 397.253.

N-Benzyl-2-[6,7-dimethoxy-1-(2-methylpropyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (65). Synthesized via Pictet-Spengler general method from isovaleraldehyde. Yield 100% as an off-white solid: mp 92-94 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.75 (br.

s., 1H), 7.24 - 7.41 (m, 5H), 6.55 (s, 1H), 6.43 (s, 1H), 4.40 - 4.60 (m, 2H), 3.84 (s, 6H), 3.49 (dd, *J* = 4.57, 9.00 Hz, 1H), 3.09 - 3.41 (m, 3H), 2.73 - 2.99 (m, 2H), 2.45 (dd, *J* = 4.85, 16.44 Hz, 1H), 1.64 - 1.79 (m, 2H), 1.21 - 1.41 (m, 1H), 0.88 (dd, *J* = 2.07, 6.31 Hz, 6H). *m/z* 397 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{24}H_{33}N_2O_3$ $[M+H]^+$ 397.2486, *m/z* found 397.2544.

N-Benzyl-2-(1-heptyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (66). Synthesized via Pictet-Spengler general method from octyl aldehyde. Yield 89%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.76 (br. s., 1H), 7.21 - 7.42 (m, 5H), 6.55 (s, 1H), 6.47 (s, 1H), 4.51 (d, *J* = 5.84 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.44 (dd, *J* = 4.99, 8.10 Hz, 1H), 3.10 - 3.36 (m, 3H), 2.70 - 2.90 (m, 2H), 2.44 - 2.58 (m, 1H), 1.52 - 1.76 (m, 2H), 1.10 - 1.39 (m, 10H), 0.88 (t, *J* = 6.88 Hz, 3H). *m/z* 439 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{39}N_2O_3$ $[M+H]^+$ 439.2955, *m/z* found 439.3016.

N-Benzyl-2-[1-(cyclohexylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (67). Synthesized via Pictet-Spengler general method from 2-cyclohexylacetaldehyde. Yield 69%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.77 (br. s., 1H), 7.27 - 7.42 (m, 5H), 6.55 (s, 1H), 6.43 (s, 1H), 4.54 - 4.65 (m, 1H), 4.37 - 4.49 (m, 1H), 3.84 (s, 6H), 3.50 - 3.60 (m, 1H), 3.09 - 3.42 (m, 3H), 2.72 - 2.99 (m, 2H), 2.46 (dd, *J* = 4.99, 16.48 Hz, 1H), 1.55 - 1.85 (m, 5H), 1.32 - 1.52 (m, 2H), 0.82 - 1.20 (m, 6H). *m/z* 437 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{27}H_{37}N_2O_3$ $[M+H]^+$ 437.2799, *m/z* found 437.2855.

N-Benzyl-2-[1-(2-cyclohexylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (68). Synthesized via Pictet-Spengler general method from 3-cyclohexylpropionaldehyde. Yield 65%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.75 (t, *J* = 4.99 Hz, 1H), 7.28 - 7.41 (m, 5H), 6.54 (s, 1H), 6.47 (s, 1H), 4.41 - 4.58 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.41 (dd, *J* = 4.99, 7.91 Hz, 1H), 3.21 - 3.28 (m, 2H), 3.09 - 3.20 (m, 1H), 2.68 -

2.90 (m, 2H), 2.44 - 2.58 (m, 1H), 1.48 - 1.75 (m, 7H), 1.03 - 1.23 (m, 6H), 0.64 - 0.82 (m, 2H). *m/z* 451 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{28}H_{39}N_2O_3$ $[M+H]^+$ 451.2955, *m/z* found 451.301.

N-Benzyl-2-[1-(3-cyclohexylpropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (69). Synthesized via Pictet-Spengler general method from 4-cyclohexylbutyraldehyde. Yield 43%. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.76 (t, *J* = 5.60 Hz, 1H), 7.23 - 7.41 (m, 5H), 6.54 (s, 1H), 6.47 (s, 1H), 4.50 (d, *J* = 5.93 Hz, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.44 (dd, *J* = 4.85, 8.24 Hz, 1H), 3.11 - 3.35 (m, 3H), 2.70 - 2.91 (m, 2H), 2.43 - 2.57 (m, 1H), 1.48 - 1.75 (m, 9H), 1.02 - 1.20 (m, 6H), 0.68 - 0.86 (m, 2H). *m/z* 465 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{29}H_{41}N_2O_3$ $[M+H]^+$ 465.3112, *m/z* found 465.3171.

2-(3-Methoxy-4-propoxyphenyl)-N-[2-(3-methoxy-4-propoxyphenyl)ethyl]acetamide (71). To a solution of 4-hydroxy-3-methoxyphenethylamine hydrochloride **7** (2.24 g, 10.98 mmol), 4-hydroxy-3-methoxyphenylacetic acid (2.0 g, 10.98 mmol) and HBTU (4.58 g, 12.08 mmol) in dry DMF (60 mL) was added diisopropylethylamine (5.68 g, 7.7. mL, 43.92 mmol) and the reaction stirred under N_2 at RT overnight. The reaction was diluted with EtOAc, washed with 1N HCl, $NaHCO_3$ solution and saturated brine, then dried over $MgSO_4$ and the solvent removed under reduced pressure to give the amide.

To a solution of the amide in DMF (60 mL) was added potassium carbonate (9.08 g, 65.73 mmol) and 1-iodopropane (7.45 g, 4.3 mL, 43.82 mmol) and the reaction stirred at RT under N_2 overnight. The reaction was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the dipropoxy amide as a yellow oil which solidified on standing (3.69 g, 81%). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 6.80 (d, *J* = 8.67 Hz, 1H), 6.72 (d, *J* = 8.10 Hz, 1H), 6.61 - 6.69 (m, 3H),

6.49 (dd, *J* = 2.07, 8.10 Hz, 1H), 5.43 (br. t, *J* = 5.10 Hz, 1H), 3.96 (q, *J* = 6.78 Hz, 4H), 3.81 (s, 3H), 3.81 (s, 3H), 3.39 - 3.50 (m, 4H), 2.66 (t, *J* = 6.88 Hz, 2H), 1.79 - 1.92 (m, 4H), 1.01 - 1.08 (m, 6H).

6-Methoxy-1-[(3-methoxy-4-propoxyphenyl)methyl]-7-propoxy-1,2,3,4-tetrahydroisoquinoline (72). This was prepared by the method used for **10**, from amide **71**. Yield 28%. ^{1}H NMR (300 MHz, METHANOL-d$_4$) δ 6.83 - 6.89 (m, 1H), 6.71 - 6.82 (m, 2H), 6.66 (s, 1H), 6.56 (s, 1H), 4.09 (t, *J* = 6.78 Hz, 1H), 3.91 (t, *J* = 6.59 Hz, 2H), 3.71 - 3.81 (m, 8H), 3.04 - 3.22 (m, 2H), 2.80 - 2.92 (m, 2H), 2.71 (t, *J* = 5.75 Hz, 2H), 1.66 - 1.85 (m, 4H), 1.03 (t, *J* = 7.44 Hz, 3H), 0.99 (t, *J* = 7.54 Hz, 3H). *m/z* 400 (M+H).

N-Benzyl-2-{6-methoxy-1-[(3-methoxy-4-propoxyphenyl)methyl]-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (73). Amine **72** (0.85 g, 2.13 mmol), N-benzyl-2-bromoacetamide (0.58 g, 2.55 mmol) and potassium carbonate (0.59 g, 4.20 mmol) were combined in DMF (50 mL) and heated to 65 °C overnight. The reaction was cooled, diluted with water then extracted 3 times with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude material was purified by chromatography on silica (0-80% EtOAc in hexane) to give the desired product as a pale brown solid (0.67 g, 58%): mp 98-101 °C. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ 7.19 - 7.34 (m, 3H), 7.11 (d, *J* = 6.78 Hz, 2H), 6.96 - 7.06 (m, 1H), 6.62 - 6.73 (m, 3H), 6.58 (s, 1H), 6.47 (s, 1H), 4.49 (dd, *J* = 8.05, 14.93 Hz, 1H), 3.89 (t, *J* = 6.83 Hz, 2H), 3.84 (s, 3H), 3.76 - 3.83 (m, 5H), 3.57 - 3.70 (m, 2H), 3.34 - 3.48 (m, 1H), 3.11 - 3.33 (m, 2H), 2.79 - 2.98 (m, 4H), 2.42 - 2.54 (m, 1H), 1.76 - 1.92 (m, 4H), 1.04 (t, *J* = 7.39 Hz, 3H), 1.02 (t, *J* = 7.39 Hz, 3H). *m/z* 547 (M+H). HRMS (ESI, CH_3OH) *m/z* calcd for $C_{33}H_{43}N_2O_5$ $[M+H]^+$ 547.3167, *m/z* found 547.3231.

Calcium Mobilization Ke Assay for OX_1 and OX_2.

Two individual stable cell lines were created by over-expressing human OX_1 and OX_2 receptors in CHO-RD-HGA16 (Molecular Devices) cells. The day before the assay, cells were plated into 96-well black-walled assay plates at 25,000 cells/well in Ham's F12 supplemented with 10% fetal bovine serum, 100 units of penicillin and streptomycin, and 100 µg/mL normocin™. The cells were incubated overnight at 37°C, 5% CO_2. Prior to the assay, Calcium 5 dye (Molecular Devices) was reconstituted according to the manufacturer instructions. The reconstituted dye was diluted 1:40 in pre-warmed (37°C) assay buffer (1X HBSS, 20 mM HEPES, 2.5 mM probenecid, pH 7.4 at 37°C). Growth medium was removed and the cells were gently washed with 100 µL of pre-warmed (37°C) assay buffer. The cells were incubated for 45 minutes at 37°C, 5% CO_2 in 200 µL of the diluted Calcium 5 dye. A single concentration of each test compound was prepared at 10x the desired final concentration in 2.5% BSA/8% DMSO/assay buffer. Serial dilutions of orexin A were prepared at 10x the desired final concentration in 0.25% BSA/1% DMSO/assay buffer, aliquoted into 96-well polypropylene plates, and warmed to 37°C. After the dye-loading incubation period, the cells were pre-treated with 25 µL of the test compounds and incubated for 15 min at 37°C. After the pre-treatment incubation period, the plate was read with a FlexStation II (Molecular Devices). Calcium-mediated changes in fluorescence were monitored every 1.52 seconds over a 60 second time period, with the FlexStation II adding 25 µL of the orexin A serial dilutions at the 19 second time point (excitation at 485 nm, detection at 525 nm). Peak kinetic reduction (SoftMax, Molecular Devices) relative fluorescent units (RFU) were plotted against the log of compound concentration. Data were fit to a three-parameter logistic curve to generate EC_{50} values (Prism,

version 6.0, GraphPad Software, Inc., San Diego, CA). Ke values were calculated using the equation Ke = [L]/((EC_{50}^{+}/EC_{50}^{-}) – 1) where [L] is the concentration of test compound, EC_{50}^{+} is the EC_{50} of orexin A with test compound, and EC_{50}^{-} is the EC_{50} of orexin A alone.

Behavioral studies

Animals. Sixteen adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) (n = 8 per group) were housed individually on a 12/12-h light/dark cycle (behavioral experiments were conducted during the light period) with free access to water and food except during testing. Animals were maintained and experiments were approved by the Institutional Animal Care and Use Committee, University at Buffalo, the State University of New York, and with the *2011 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).

Drugs. Drugs used in this study included cocaine hydrochloride (Research Technology Branch, National Institute of Drug Abuse, Rockville, MD, USA) and compound **73**. Cocaine hydrochloride was dissolved in 0.9% physiological saline. Compound **73** was dissolved in a mixture of 1 part absolute ethanol, 1 part Emulphor-620 (Rhodia Inc.), and 18 parts physiologic saline. Doses were expressed as the weight of the forms listed above in milligrams per kilogram of body weight and drugs were administered intraperitoneally.

Experimental protocols. Locomotor activity was monitored by an infrared motor-sensor system (AccuScan Instruments, Columbus, OH) fitted outside clear acrylic chambers (40 × 40 × 30 cm) that were cleaned between test sessions. Locomotor activity (distance travelled) was analyzed with the Versa Max animal activity monitoring software (AccuScan Instruments, Columbus, OH).[41] The dose-effect curve of cocaine was determined by using a cumulative dosing procedure as previously described.[41, 42] For this experiment, vehicle or 10 mg/kg

compound **73** was administered immediately prior to the start of the test session and different doses of cocaine (cumulative doses of 3.2, 10, 32 mg/kg) were given at times 20 min, 40 min and 60 min. The locomotor effects of each dose of cocaine were recorded for 20 min but for each dose the data from the first 5 min immediately after the drug injection were discarded due to the brief hyperactivity associated with handling and injection. For behavioral sensitization study, a similar protocol was used as described in our previous reports.[41, 42] Briefly, an acute cocaine dose-effect curve with vehicle or 10 mg/kg compound **73** pretreatment was determined on day 1, which was followed by 7 days of daily 15 mg/kg cocaine in combination with vehicle or 10 mg/kg compound **73** and stayed in the test chambers for 1 hour. Thereafter, six days of drug-free period was implemented, which was followed by another cocaine dose-effect curve determination on day 15 during which no compound **73** was given.

Statistical analyses. The locomotion data were analyzed by two-way ANOVA (cocaine dose × compound **73** treatment) followed by *post hoc* Bonferroni's test. $P < 0.05$ was considered statistically significant.

ASSOCIATED CONTENT

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

AUTHOR INFORMATION

Corresponding Author

* Email: yzhang@rti.org; Tel: 919-541-1235; Fax: 919-541-6499

Author Contributions

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

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ABBREVIATIONS

BOP, (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; HBTU, O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate; HPLC, high performance liquid chromatography; OX_1, orexin 1 receptor; OX_2, orexin 2 receptor; SAR, structure-activity relationship; TLC, thin layer chromatography.

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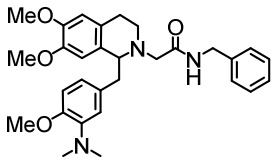
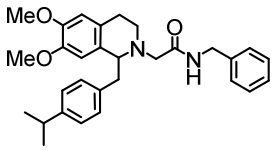
For Table of Contents Use Only

The Effect of 1-Substitution on Tetrahydroisoquinolines as Selective Antagonists for the Orexin-1 Receptor

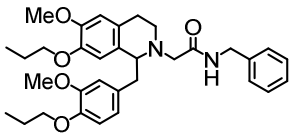
David A. Perrey,[†] Nadezhda A. German,[†] Ann M. Decker,[†] David Thorn,[‡] Jun-Xu Li,[‡] Brian P. Gilmour,[†] Brian F. Thomas,[†] Danni L. Harris,[†] Scott P. Runyon,[†] and Yanan Zhang,[†,]*



28
Ke (OX_1) = 12.7 nM
Ke (OX_2) = 970 nM



51
Ke (OX_1) = 85 nM
Ke (OX_2) > 10,000 nM



73
Ke(OX_1) = 16.1 nM
Ke(OX_2) >10,000 nM