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## Synthesis and Evaluation of Orexin-1 Receptor Antagonists with Improved Solubility and CNS Permeability

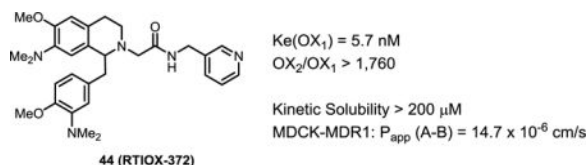
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### Abstract

Orexins are hypothalamic neuropeptides playing important roles in many functions including the motivation of addictive behaviors. Blockade of the orexin-1 receptor has been suggested as a potential strategy for the treatment of drug addiction. We have previously reported OX<sub>1</sub> receptor antagonists based on the tetrahydroisoquinoline scaffold with excellent OX<sub>1</sub> potency and selectivity; however, these compounds had high lipophilicity (clogP > 5) and low to moderate solubility. In an effort to improve their properties, we have designed and synthesized a series of analogs where the 7-position substituents known to favor OX<sub>1</sub> potency and selectivity were retained, and groups of different nature were introduced at the 1-position where substitution was generally tolerated as demonstrated in previous studies. Compound **44** with lower lipophilicity (clogP = 3.07) displayed excellent OX<sub>1</sub> potency (K<sub>e</sub> = 5.7 nM) and selectivity (> 1,760-fold over OX<sub>2</sub>) in calcium mobilization assays. In preliminary ADME studies, **44** showed excellent kinetic solubility (> 200 μM), good CNS permeability (P<sub>app</sub> = 14.7 × 10<sup>-6</sup> cm/sec in MDCK assay), and low drug efflux (efflux ratio = 3.3).

### TOC image



### Keywords

orexin; antagonist; selective; tetrahydroisoquinoline; ADME

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

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### Author Contributions

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

### Notes

The authors declare no competing financial interest.

## Introduction

Orexin-A and -B, also known as hypocretin-1 and -2, are two neuropeptides synthesized by neurons in the lateral hypothalamic areas, that activate two G protein-coupled receptors (GPCRs), the orexin-1 (OX<sub>1</sub>) and -2 (OX<sub>2</sub>) receptors. Orexins, the orexin receptors and the hypocretin genes were first discovered in 1998 by two research groups,<sup>1, 2</sup> and the system has been widely studied since.<sup>3, 4</sup> Initially, orexins were named for their appetite-enhancing effects as they were found to play a role in feeding behavior and energy expenditure. The orexin system was later shown to also be a key regulator of arousal and sleep/wake cycles. Hence, the orexin system is a promising target in the development of medications for the treatment of sleep disorders. A number of dual orexin receptor antagonists (DORAs) have been developed for this purpose, such as almorexant (**1**) and suvorexant (**2**) (Figure 1).<sup>5-9</sup> In particular, **2** developed by Merck & Co became the first orexin antagonist approved by the FDA for the treatment of insomnia in 2014 and is currently marketed under the brand name Belsomra.<sup>10</sup>

More recently, the orexins have been implicated in a range of motivation and reward processes, including drug addiction.<sup>11-14</sup> Accumulating evidence has confirmed the involvement of the orexin system, particularly the OX<sub>1</sub> receptor, in different stages of the addiction process to several drugs of abuse.<sup>15, 16</sup> In conditioned place preference (CPP) experiments, the widely used animal model measuring drug rewarding effects, the orexin system showed a role in acquisition, expression and reinstatement of morphine CPP.<sup>16, 17</sup> Blockade of the OX<sub>1</sub> receptor by systemically or intra-VTA (ventral tegmental area) administered SB334867 (**3**, Fig. 1), an OX<sub>1</sub> antagonist, attenuated motivated drug seeking behaviors of cocaine.<sup>18, 19</sup> Administration of **3** also attenuated cue- and stress-induced reinstatement of extinguished cocaine seeking in animals.<sup>19</sup> In addition, ethanol and nicotine self-administration and reinstatement can also be decreased by administration of **3**.<sup>20-22</sup>

Compound **3** was the first reported OX<sub>1</sub> selective antagonist and is still widely used in the orexin research community.<sup>23</sup> However, **3** suffers from several limitations, including moderate selectivity over OX<sub>2</sub> (~50×), off-target interactions with several receptors (serotonin, adenosine), and instability of the hydrochloride salt.<sup>24, 25</sup> Several other OX<sub>1</sub> selective antagonists have been since described (e.g. ACT-335827, **4**, Fig. 1), but most of them still have certain OX<sub>2</sub> activities.<sup>26-29</sup> While blockade of both orexin receptors has been shown to be effective in some addiction models in a limited number of studies, selective OX<sub>1</sub> antagonists provide the benefit of minimized sedation arising from OX<sub>2</sub> antagonism.<sup>30, 31</sup> In addition, the majority of *in vivo* studies so far for OX<sub>1</sub>-specific pathways were done with **3**. OX<sub>1</sub> antagonists with improved selectivity will help to further elucidate and validate the *in vivo* role and biology of the OX<sub>1</sub> receptors.

Our group has previously reported a series of OX<sub>1</sub> selective antagonists based on the tetrahydroisoquinoline (THIQ) scaffold.<sup>32-35</sup> In these studies, we explored the structure-activity relationships (SARs) at several locations, and have identified structural features that enhanced the potency and selectivity of OX<sub>1</sub> over OX<sub>2</sub>. As a result, several highly potent and selective OX<sub>1</sub> antagonists have been identified, including RTIOX-276 (**5**) and RTIOX-251 (**6**). These compounds attenuated the development of conditioned place preference for

cocaine,<sup>32</sup> or blocked development of locomotor sensitization to cocaine in rats.<sup>34</sup> In addition, at doses that attenuated the motivation for cocaine, **5** reduced spontaneous dopamine transient amplitude and cue-evoked dopamine release, and also attenuated cocaine-induced dopamine uptake inhibition at the level of dopamine terminals, confirming its *in vivo* efficacy.<sup>36</sup>

These THIQ-based OX<sub>1</sub> antagonists, despite the excellent potency and selectivity, have high lipophilicity (clogP > 5). The logP value of a compound is a well-established measure of a compound's lipophilicity; high lipophilicity, or low hydrophilicity, causes lower solubility and poor absorption, thus affecting amount of drug reaching its site of action. In general, substituents with increased polarity and/or ionizability (e.g. protonable amino groups) at physiological pH lead to lower lipophilicity.<sup>37</sup> Therefore, we aimed to introduce substituents at several positions of the THIQ scaffold that would retain OX<sub>1</sub> potency while leading to improved pharmacokinetic properties. Since the 7-position has been demonstrated as a key factor in determining the OX<sub>1</sub> potency and selectivity,<sup>32</sup> and substituents such as propoxy, trifluoroethoxy, methylsulfonate and dimethylamino groups led to excellent OX<sub>1</sub> potency and selectivity, these favorable 7-position substituents were retained (R<sub>1</sub>, Fig. 2). In addition, the 1-position has been shown to tolerate a variety of substituents, and therefore groups of different nature were introduced at the 1-position (R<sub>2</sub>, Fig. 2). Among these substituents at the 1- and 7-positions that have been shown to lead to good OX<sub>1</sub> potency and selectivity, several groups were either polar (e.g. trifluoroethoxy, methylsulfonate) or ionizable (e.g. dimethylamino), and are expected to have reduced lipophilicity and increased solubility. In addition, replacing the benzyl group at the acetamide position with groups such as pyridyl may also reduce lipophilicity. We herein describe the design, synthesis, and evaluation of the OX<sub>1</sub> potency and selectivity, as well as preliminary ADME properties, including aqueous solubility and CNS permeability, for these new analogs.

## Results and Discussion

### Chemistry

The general approach to this series of THIQ derivatives is shown in Scheme 1, starting from phenylacetic acids **8a-f**. Most of these phenylacetic acids were commercially available, except for **8f** which was synthesized by O-alkylation of 4-hydroxy-3-methoxyphenylacetic acid methyl ester (**7**) and hydrolysis under basic conditions. Acids **8a-f** were first coupled with 4-hydroxy-3-methoxyphenylethylamine to give the amides **9a-f**, which were then cyclized via a Bischler-Napieralski reaction using phosphorus oxychloride in toluene to form the dihydroisoquinolines, followed by reduction to tetrahydroisoquinolines **10a-f** using sodium borohydride. N-Alkylation was achieved using N-benzyl bromoacetamide in the presence of base to give intermediates **11a-f**. Finally, the phenol was alkylated using 1-iodopropane in the presence of potassium carbonate to afford the target compounds **12a-e,g**. The 3-dimethylamino derivative **12f** was obtained from the 3-nitro analog **12e** via reduction to the aniline using Raney nickel, then reductive amination with formaldehyde and sodium triacetoxyborohydride. An alternate approach was attempted for both **12d** and **12g**, where O-alkylation was performed at the amide stage (**9**) prior to Bischler-Napieralski reaction. While

this approach generally gave better yields in the following steps, it limited diversification in the later synthesis and was thus not further pursued.

7-Trifluoroethoxy derivatives **15a-b** were made via a similar approach (Scheme 2). The tetrahydroisoquinolines **10a-b** were N-alkylated with ethyl bromoacetate to give ester **13a-b**. Ester hydrolysis gave the acid, followed by amide coupling with 3-aminomethylpyridine to give **14a-b**. O-Alkylation using 1-iodo-2,2,2-trifluoroethane and cesium carbonate gave the desired analogs **15a-b**. 1-Pyridylmethyl derivatives **19a-c** were synthesized in analogous fashion using the general approach outlined above, starting from the appropriate 2-, 3- or 4-pyridylacetic acid (**16a-c**) (Scheme 2).

The 7-methylsulfonate derivatives **25a-b** (Scheme 3) were prepared from 4-hydroxy-3-methoxyphenylacetic acid **20**. Protection of the phenolic hydroxyl group as its benzyl ether gave intermediate **21**. Acid **21** was then coupled with 4-hydroxy-3-methoxyphenethylamine to give amide **22**, followed by sulfonylation of the phenol group with methanesulfonyl chloride to afford the sulfonate **23**. After cyclization to the tetrahydroisoquinoline **24** and N-alkylation as described above, the benzyl group of **25a** was removed under acidic conditions and the resulting hydroxyl group was converted to the butyl ether upon treatment with 1-bromobutane to give **25b**.

The 7-dimethylamino-6-methoxytetrahydroisoquinoline derivatives required synthesis of the phenethylamine **28**, which was prepared from 3-methoxyphenylacetonitrile **26** (Scheme 4), by nitration using tetrabutylammonium nitrate in the presence of trifluoroacetic anhydride and 18-crown-6 to give **27**, followed by reduction of the nitrile using borane-THF complex at 70 °C. The amine **28** was then coupled with 3,4-dimethoxyphenylacetic acid to give amide **29**. The presence of a strong electron withdrawing group such as a nitro group on the phenethylamine portion retards the reactivity of the aromatic system and makes the Bischler-Napieralski cyclization sluggish, so the amide **29** was reduced using Raney nickel to the aniline **30** then protected as the methyl carbamate using methyl chloroformate and diisopropylethylamine to give **31**. Bischler-Napieralski cyclization and reduction to the tetrahydroisoquinoline followed by N-alkylation with the acetamide component gave the acetamide **32** and removal of the carbamate using 2N sodium hydroxide solution in methanol provided amine **33**. This amine could then be derivatized via sulfonylation, reductive amination or acylation to give a series of derivatives **34a-e**.

The bis-dimethylamino derivatives **39** and **42** were made in analogous fashion to the other 7-amino derivatives (Scheme 5). For **39**, the phenethylamine **28** was coupled to 4-hydroxy-3-nitrophenylacetic acid, then the phenol was converted to the methyl ether using iodomethane to afford **35**. Reduction of both nitro groups with Raney nickel was followed by formation of the bis-methyl carbamate using methyl chloroformate to form **36**. Cyclization and then reduction gave the tetrahydroisoquinoline **37** then N-alkylation as before gave **38**. Both methyl carbamates were removed using sodium hydroxide and reductive amination provided the bis-dimethylamino product **39**. For **42**, amine **28** was first coupled with 3-nitrophenylacetic acid to afford amide **40** and both nitro groups were reduced with Raney nickel. Reductive amination gave the bis-dimethylamino amide **41**, which was then subjected to Bischler-Napieralski conditions, reduced and N-alkylated to afford the final

product **42**. Finally, the 1-(3-pyridylmethyl)benzyl analog **44** was prepared from intermediate **37**, which underwent alkylation using ethyl bromoacetate, ester hydrolysis, and coupling with 3-aminomethylpyridine to give **43**. The final sequence of carbamate removal and reductive amination with formaldehyde afforded the desired **44**.

### Pharmacological Evaluation

Activity of the target compounds at the OX<sub>1</sub> and OX<sub>2</sub> receptors was evaluated in a calcium mobilization based functional assay. The apparent dissociation constant K<sub>e</sub> was calculated from compound-mediated inhibition of orexin A activity as previously described.<sup>32, 34, 35, 38</sup> Briefly, EC<sub>50</sub> curves of the agonist, orexin A, were obtained alone and together with the test compound, respectively, and the right-shift of the agonist curve was measured. K<sub>e</sub> values were then calculated using the equation  $K_e = [L] / ((EC_{50}^+ / EC_{50}^-) - 1)$ , where [L] is the test compound concentration, EC<sub>50</sub><sup>+</sup> is the EC<sub>50</sub> of orexin A in the presence of test compound, and EC<sub>50</sub><sup>-</sup> is the EC<sub>50</sub> of orexin A alone. In these assays, the EC<sub>50</sub> for orexin A at OX<sub>1</sub> and OX<sub>2</sub> is 0.13 ± 0.02 nM and 4.2 ± 0.2 nM, respectively. All the compounds that had OX<sub>1</sub> K<sub>e</sub> values < 1 μM were also tested for agonist activity at 10 μM final concentration at the OX<sub>1</sub> receptor; none of them showed any agonist activity.

We previously reported SAR studies at three different locations of the THIQ core, namely the 7-position, the 1-position and the acetamide, and had identified structural features that led to enhanced potency and OX<sub>1</sub> selectivity at these positions.<sup>32, 34, 35</sup> At the 7-position, it was discovered that a modest increase in the chain length, from methoxy to propoxy or trifluoroethoxy groups, led to increased OX<sub>1</sub> potency and selectivity.<sup>32</sup> Similarly, methylsulfonate and dimethylamino groups also led to excellent potency and selectivity. At the 1-position of the THIQ core, a series of aromatic systems provided similar or slightly improved potency than the initial 3,4-dimethoxybenzyl group.<sup>34</sup> For example, we found that pyridylmethyl groups were as potent as the benzyl group.<sup>32</sup> In this study, we examined the effects of combining these favorable structural modifications on the OX<sub>1</sub> potency and selectivity. Given the tolerance for substitution at the 1-position, aromatic groups of different nature were introduced at this position in an effort to improve the PK properties of these compounds.

We first examined a series of 7-propoxy analogs with different substituents at the 1-benzyl position. At the 1-position, several groups that have previously been demonstrated to be tolerated were introduced. As expected, the naphthyl (**12a**), 3,4-dimethylphenyl (**12b**), and 4-isopropylphenyl (**12c**) all showed good OX<sub>1</sub> potency, consistent with our previous findings.<sup>34</sup> The introduction of a nitrogen atom into the structure (**12d, f**) did not significantly change the potency, but reduced the lipophilicity of these compounds from **12c** (clogP 7.4 vs. 6.17). The 3-dimethylamino analog **12f** was the most potent of the series with a K<sub>e</sub> value of 21 nM. When a pyridinylmethyl group was introduced at the 4-position (**12g**), the clogP was further lowered (5.96), the potency remained good (K<sub>e</sub> = 96.4 nM), and the selectivity was high (>100-fold). Overall, these results show that substitution at the 1-benzyl position results in compounds with good selectivity for the OX<sub>1</sub> receptor over the OX<sub>2</sub> receptor, although clogP remained high.

Previously reported compound **5**, with a trifluoroethoxy substitution at the 7-position, is a highly potent and selective OX<sub>1</sub> antagonist.<sup>32</sup> Both the naphthyl analog **15a** and 3,4-dimethyl analog **15b** showed excellent potency, comparable to the propoxy series (**12a-b**). The presence of the trifluoroethyl led to lower clogP than the propyl (**12b**: 6.98 vs. **15b**: 5.39). To further reduce clogP, we synthesized 3 different pyridinyl derivatives (**19a-c**) at the 1-position. Although they have lower clogP (4.47), all three compounds showed significantly lower potency at the OX<sub>1</sub> receptor and also displayed insurmountable antagonism in the curve shift assays. As previously reported by us,<sup>35</sup> increasing the receptor-test compound incubation period can help to elucidate whether this type of antagonism is due to an allosteric mechanism or an orthosteric antagonist with a slow dissociation rate. For derivatives **19a-c**, we found that increasing the incubation time led to activity profiles consistent with competitive antagonism.

Another group that provided satisfactory results in previous SAR studies was the 7-methylsulfonate. Again, these methylsulfonate analogs (**25a, b**) showed excellent OX<sub>1</sub> potency and selectivity. However, both compounds had clogP in the 5-6 range.

All these structural alterations discussed thus far have resulted in potent and selective OX<sub>1</sub> antagonists that continue to have high lipophilicity (clogP > 5). Thus, a series of 7-amino compounds were prepared and their potency against OX<sub>1</sub> and OX<sub>2</sub> receptors was assayed (Table 2). It was expected that the introduction of the amino groups not only would reduce clogP or lipophilicity, but would also facilitate the formation of more soluble ammonium salts.

As can be seen from Table 2, all the compounds in the 7-amino series were generally tolerated for OX<sub>1</sub> activity. The unsubstituted aniline **33** was active with a K<sub>e</sub> of 494 nM, but showed little selectivity. Dimethylation of the amino group (**34a**) significantly improved the OX<sub>1</sub> potency (494 nM vs. 31.2 nM). The benzylamino analog (**34b**) was less potent, showing a K<sub>e</sub> value of 352 nM, suggesting larger groups may not be well tolerated. When the amino group was acylated (**34c**, 116 nM) or mesylated (**34d**, 128 nM), the resulting compounds had good potency and selectivity, as well as lower clogP (< 4). When the acyl group was elongated, the butyric analog (**34e**) was less potent (K<sub>e</sub> = 689 nM), consistent with the limited tolerance for bulk at this position. The methylcarbamate (**38**) was inactive, and showed increased OX<sub>2</sub> activity as well. The fact that **34a** (-NMe<sub>2</sub>) was more potent than all the NH containing analogs suggests that the presence of an hydrogen bond donor at this position may be unfavorable for OX<sub>1</sub> activity. Alternatively, the NH group may be forming an intramolecular hydrogen bond with the methoxy group at the 6-position, thus limiting the rotational freedom and ability of R<sub>1</sub> group to engage in favorable interactions with the receptor.

Given the encouraging results with the 3-dimethylamino analog (**34a**), we synthesized several additional analogs with amino groups also on the 1-benzyl position. While the 3-dimethylamino analog (**42**) had a K<sub>e</sub> of 148 nM, the corresponding 3-dimethylamino-4-methoxy derivative (**39**) was more potent (K<sub>e</sub> = 7.6 nM). Finally, when the benzylacetamide was replaced with the 3-pyridyl group, a potent and more selective OX<sub>1</sub> antagonist (**44**) was

obtained. Importantly, the clogP value of this compound was 3.07 and PSA was 70, implying that this modification could enhance solubility.

## Physicochemical Properties and Preliminary ADME Studies

Compound **44**, in general, appeared to have favorable physicochemical properties which would suggest good solubility and blood-brain barrier (BBB) permeability required for successful CNS agents (Table 3, calculated in ACD Labs).<sup>39, 40</sup> The lower clogP values suggested **44** (3.07) might have improved solubility over **5** (4.21). When the kinetic solubility was assessed at pH 7.4, **5** showed a solubility of  $77.8 \pm 4.1 \mu\text{M}$  (mean  $\pm$  %CV). Compound **44** was more soluble in aqueous solutions, displaying a kinetic solubility greater than  $200 \mu\text{M}$ .

We also determined the CNS permeability of **5** and **44**. CNS permeability is an important property for CNS targeting agents, and is generally determined by two factors: the ability to passively permeate through the BBB and efflux by the transport proteins such as the P-glycoprotein.<sup>37</sup> The apparent permeability of the compounds through MDCK-MDR1 monolayers were determined in both the apical-to-basolateral (A-to-B) and basolateral-to-apical (B-to-A) directions. Both compounds showed good apparent permeability ( $P_{\text{app}} > 10 \times 10^{-6} \text{ cm/sec}$ ). In general, efflux ratios  $> 2.5$  indicate drug efflux occurring.<sup>37</sup> Compounds **5** and **44** had efflux ratios of 3.0 and 3.3, respectively, suggesting efflux is present for both compounds, albeit relatively weak. Since these MDR1-transfected cells also express endogenous transporters,<sup>41</sup> the observed drug efflux may indicate these compound are P-gp substrates, but the effects could also be mediated by the endogenous transporters.

## Conclusions

The orexin system has been implicated in several important functions, including addiction. With the growing interest in the role of the orexin system on the reward pathway and the potential for orexin-1 antagonists as therapeutics in the treatment of drug addiction, there is a need for the development of orexin-1 selective antagonists. Our group has previously reported a series of tetrahydroisoquinoline-based antagonists. While some of the compounds showed high potency and selectivity, they had high lipophilicity and moderate or low solubility. In this study, we aimed to improve the ADME properties of the compounds by introducing structural elements that may lead to more optimal properties. In particular, groups such as propoxy, trifluoroethoxy, methylsulfonate and dimethylamino at the 7-position that had been previously demonstrated to be critical for OX<sub>1</sub> potency and selectivity have been retained, whereas groups of different nature were introduced at the 1-position which has been shown to tolerate a variety of substituents. These structural alterations resulted in several compounds with reduced lipophilicity as evidenced by the lower clogP and excellent OX<sub>1</sub> potency and selectivity, such as **44** (clogP = 3.07), which had a dimethylamino groups at the 7-position and on the 1-benzyl group, respectively.

Similar to the previously reported **5** which showed efficacy in several *in vivo* models, **44** displayed high OX<sub>1</sub> potency ( $K_e$  5.7 nM vs. 8.5 nM) and excellent selectivity (both  $>1,000$ -fold over OX<sub>2</sub>). These values also represent significant improvement from the commonly

used OX<sub>1</sub> antagonist SB334867 (IC<sub>50</sub> = 40 nM, 50× over OX<sub>2</sub>). Moreover, **44** showed greater kinetic solubility (>200 μM) than **5** (77.8 μM) and good BBB permeability. Finally, **44** possessed little Pgp activity with an efflux ratio of 3.3. Given its high OX<sub>1</sub> potency and selectivity, as well as good ADME properties, **44** may serve as an improved molecular tool in the elucidation and validation of the *in vivo* roles of the OX<sub>1</sub> receptor in many orexin related disorders.

## 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, 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. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in chloroform-d or methanol-d<sub>4</sub> with tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference. Chemical shifts are reported in ppm relative to the reference signal, and coupling constant (*J*) values are reported in Hz. TLC was done on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or iodine staining. Low resolution mass spectra were obtained using a Waters Alliance HT/Micromass ZQ system (ESI). All test compounds were greater than 95% pure as determined by HPLC on an Agilent 1100 system using an Agilent Zorbax SB-Phenyl, 2.1 mm × 150 mm, 5 μm column with gradient elution using the mobile phases (A) H<sub>2</sub>O containing 0.1% CF<sub>3</sub>COOH and (B) MeCN, with a flow rate of 1.0 mL/min. For ADME analysis, samples were analyzed by LC-MS/MS using a CTC PAL autosampler, Thermo Accela UPLC and a Thermo Quantum Ultra triple quadrupole mass spectrometer. The [M+H]<sup>+</sup> adducts of the test compounds and internal standard were monitored using positive mode electrospray ionization in multiple reaction monitoring (MRM) mode. The analytes were injected onto a C18 column and chromatographed using a reverse phase gradient with 0.1% formic acid in water and 0.1% formic acid in 20/80 isopropyl alcohol/acetonitrile mobile phases. Peak integrations were performed using Thermo Xcalibur (v 2.4) software.

### Methyl (4-hydroxy-3-methoxyphenyl)acetate (7)

To a solution of 4-hydroxy-3-methoxyphenylacetic acid (2.50 g, 13.72 mmol) in anhydrous methanol (60 mL) was added concentrated sulfuric acid (2.02 g, 1.1 mL, 20.59 mmol) and the reaction heated to reflux for 3 hr. The reaction was cooled, the solvent was removed under reduced pressure and NaHCO<sub>3</sub> solution was added. The aqueous solution was extracted three times with dichloromethane and the combined extracts were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give the methyl ester as a yellow oil (2.69 g, 100%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 6.84 - 6.90 (m, 1H),



6.80 (d,  $J = 1.70$  Hz, 1H), 6.73 - 6.78 (m, 1H), 5.57 (s, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.55 (s, 2H).

### 2-[3-Methoxy-4-(pyridin-2-ylmethoxy)phenyl]acetic acid (**8f**)

Phenol **7** (1.0 g, 5.10 mmol), 2-(bromomethyl)-pyridine hydrobromide (1.93 g, 7.65 mmol), potassium carbonate (2.82 g, 20.4 mmol) and tetrabutylammonium iodide (0.38 g, 1.02 mmol) were combined in anhydrous dimethylformamide (50 mL) and heated to 50 °C overnight. The reaction was cooled, diluted with EtOAc, washed twice with water and with brine, dried over  $MgSO_4$  and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-60% EtOAc in hexane) to give the desired ether as an orange oil (0.49 g, 34%).  $^1H$  NMR (300 MHz, CHLOROFORM- $d$ )  $\delta$  8.58 (d,  $J = 4.62$  Hz, 1H), 7.69 (dt,  $J = 1.65, 7.70$  Hz, 1H), 7.51 - 7.60 (m, 1H), 7.16 - 7.25 (m, 1H), 6.82 - 6.88 (m, 1H), 6.81 (s, 1H), 6.71 - 6.78 (m, 1H), 5.27 (s, 2H), 3.91 (s, 3H), 3.69 (s, 3H), 3.56 (s, 2H).

To the solution of ester (0.49 g, 1.71 mmol) in methanol (15 mL) was added 2N sodium hydroxide solution (3.4 mL, 6.82 mmol) and the reaction stirred at RT overnight. The pH was adjusted to between 8 and 9 with 2N HCl then all the solvents were removed under reduced pressure. The crude was dissolved in methanol as far as possible, the solids were removed by filtration then the solvent was removed under reduced pressure to give the acid as a yellow solid (0.47 g, 100%).  $^1H$  NMR (300 MHz, METHANOL- $d_4$ )  $\delta$  8.47 - 8.54 (m, 1H), 7.84 (dt,  $J = 1.70, 7.72$  Hz, 1H), 7.62 (d,  $J = 7.91$  Hz, 1H), 7.30 - 7.39 (m, 1H), 7.01 (d,  $J = 1.88$  Hz, 1H), 6.83 - 6.90 (m, 1H), 6.74 - 6.83 (m, 1H), 5.15 (s, 2H), 3.86 (s, 3H), 3.41 (s, 2H).

### N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(naphthalen-2-yl)acetamide (**9a**)

To 2-naphthylacetic acid (**8a**) (0.74 g, 3.97 mmol), 4-hydroxy-3-methoxyphenethylamine hydrochloride (0.81 g, 3.97 mmol) and HATU (1.66 g, 4.37 mmol) in anhydrous dimethylformamide (20 mL) was added diisopropylethylamine (2.06 g, 2.8 mL, 15.90 mmol) and the reaction stirred at RT under  $N_2$  overnight. The reaction was diluted with EtOAc, washed with 2N aqueous HCl solution,  $NaHCO_3$  solution and brine, dried over  $MgSO_4$  and the solvent was removed under reduced pressure to give the amide as a white solid (1.33 g, 100%).  $^1H$  NMR (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.74 - 7.87 (m, 3H), 7.62 (s, 1H), 7.47 - 7.54 (m, 2H), 7.24 - 7.29 (m, 2H), 6.61 (d,  $J = 7.91$  Hz, 1H), 6.52 (d,  $J = 1.88$  Hz, 1H), 6.40 (dd,  $J = 1.88, 7.91$  Hz, 1H), 5.38 (br. s., 1H), 3.71 (s, 3H), 3.70 (s, 2H), 3.43 (q,  $J = 6.78$  Hz, 2H), 2.63 (t,  $J = 6.88$  Hz, 2H).

### 2-(3,4-Dimethylphenyl)-N-[2-(4-hydroxy-3-methoxyphenyl)ethyl]acetamide (**9b**)

This was made by the same method as **9a**, using 3,4-dimethylphenylacetic acid (**8b**). Colorless film. Yield 100%.  $^1H$  NMR (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.25 - 7.29 (m, 1H), 7.06 (d,  $J = 7.54$  Hz, 1H), 6.83 - 6.96 (m, 2H), 6.72 - 6.79 (m, 1H), 6.59 (d,  $J = 1.51$  Hz, 1H), 6.48 (d,  $J = 7.91$  Hz, 1H), 5.39 (br. s., 1H), 3.83 (s, 3H), 3.46 (s, 2H), 3.42 (q,  $J = 6.78$  Hz, 2H), 2.65 (t,  $J = 6.88$  Hz, 2H), 2.25 (s, 3H), 2.22 (s, 3H).

**N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-[4-(propan-2-yl)phenyl]acetamide (9c)**

This was made by the same method as **9a** using 4-isopropylphenylacetic acid (**8c**). Colorless film. Yield 71%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.14 - 7.21 (m, 2H), 7.05 - 7.12 (m, 2H), 6.76 (d, *J* = 8.10 Hz, 1H), 6.61 (d, *J* = 1.51 Hz, 1H), 6.48 (dd, *J* = 1.60, 8.01 Hz, 1H), 5.53 (s, 1H), 5.40 (br. s., 1H), 3.84 (s, 3H), 3.50 (s, 2H), 3.43 (q, *J* = 6.78 Hz, 2H), 2.84 - 2.95 (m, 1H), 2.66 (t, *J* = 6.97 Hz, 2H), 1.25 (d, *J* = 6.97 Hz, 6H).

**2-[4-(Dimethylamino)phenyl]-N-[2-(4-hydroxy-3-methoxyphenyl)ethyl]acetamide (9d)**

This was made by the same method as **9a** using 4-dimethylaminophenylacetic acid (**8d**). White sticky solid. Yield 99%. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.70 (s, 1H), 7.89 (t, *J* = 5.42 Hz, 1H), 7.03 (d, *J* = 8.57 Hz, 2H), 6.72 (d, *J* = 1.60 Hz, 1H), 6.61 - 6.68 (m, 3H), 6.53 (dd, *J* = 1.65, 7.96 Hz, 1H), 3.71 (s, 3H), 3.15 - 3.27 (m, 4H), 2.85 (s, 6H), 2.57 (t, *J* = 7.30 Hz, 2H).

**N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(3-nitrophenyl)acetamide (9e)**

This was made by the same method as **9a** using 3-nitrophenylacetic acid (**8e**). White sticky solid. Yield 100%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.13 (d, *J* = 8.10 Hz, 1H), 8.08 (s, 1H), 7.44 - 7.59 (m, 2H), 6.79 (d, *J* = 8.10 Hz, 1H), 6.62 (d, *J* = 1.51 Hz, 1H), 6.56 (dd, *J* = 1.70, 8.10 Hz, 1H), 5.57 (s, 1H), 5.51 (br. s., 1H), 3.84 (s, 3H), 3.58 (s, 2H), 3.50 (q, *J* = 6.66 Hz, 2H), 2.72 (t, *J* = 6.88 Hz, 2H).

**N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-[3-methoxy-4-(pyridin-2-ylmethoxy)phenyl]acetamide (9f)**

This was made by the same method as **9a** using acid **8f**. Yellow sticky solid. Yield 69%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.63 (d, *J* = 4.14 Hz, 1H), 7.71 - 7.81 (m, 1H), 7.59 (d, *J* = 7.82 Hz, 1H), 7.27 - 7.32 (m, 1H), 6.67 - 6.81 (m, 3H), 6.58 (dd, *J* = 1.98, 8.10 Hz, 1H), 6.55 (d, *J* = 1.88 Hz, 1H), 6.37 (dd, *J* = 1.88, 8.01 Hz, 1H), 5.32 (br. s., 1H), 5.23 (s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.46 (s, 2H), 3.37 - 3.44 (m, 2H), 2.64 (t, *J* = 6.64 Hz, 2H).

**6-Methoxy-1-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (10a)**

Amide **9a** (1.37 g, 4.09 mmol) was suspended in anhydrous toluene (20 mL) and phosphorus oxychloride (3.13 g, 1.9 mL, 20.42 mmol) was added slowly. The mixture was heated to 90 °C for 2 hr, then cooled to RT and quenched cautiously with water. The reaction was heated for 15 min until the oil formed went into solution. The reaction was again cooled to RT, the toluene layer was removed and the aqueous layer was adjusted to pH 8-9 using 2N aqueous sodium hydroxide solution. It was then extracted 3 times with DCM, the combined extracts were dried over MgSO<sub>4</sub> and the solvents were removed under reduced pressure to give the crude dihydroisoquinoline as an orange viscous oil, which was used in the next step without further purification.

The crude material was dissolved in methanol (40 mL) and cooled in an ice bath. Sodium borohydride (0.78 g, 20.4 mmol) was added portionwise then the reaction was allowed to warm slowly to RT overnight. The reaction was quenched with water then the methanol was removed under reduced pressure. The reaction mixture was diluted with water and then

extracted 3 times with DCM. The combined extracts were dried over MgSO<sub>4</sub> and the solvents were removed under reduced pressure to give the product as a frothy yellow solid (0.41 g, 31%).

**N-Benzyl-2-[7-hydroxy-6-methoxy-1-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (11a)**

Amine **10a** (32 mg, 0.100 mmol), N-benzyl bromoacetamide (34 mg, 0.150 mmol) and tetrabutylammonium iodide (7 mg, 0.020 mmol) were combined in anhydrous DMF (1 mL), then diisopropylethylamine (32 mg, 44 mL, 0.250 mmol) was added. The reaction was stirred at RT overnight. The reaction was diluted with EtOAc and washed with NaHCO<sub>3</sub> solution and brine, then dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude material was purified by chromatography on silica (0-75% EtOAc/hexane) to give the desired product as a yellow viscous oil (20 mg, 43%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.76 (ddd, *J* = 3.49, 6.08, 11.73 Hz, 2H), 7.65 - 7.71 (m, 2H), 7.44 - 7.51 (m, 2H), 7.35 (dd, *J* = 1.70, 8.29 Hz, 1H), 7.08 - 7.16 (m, 3H), 6.75 (s, 1H), 6.55 - 6.65 (m, 4H), 5.52 (s, 1H), 4.13 (dd, *J* = 8.48, 14.69 Hz, 1H), 3.89 (s, 3H), 3.69 - 3.76 (m, 1H), 3.44 - 3.58 (m, 1H), 3.03 - 3.27 (m, 4H), 2.75 - 2.99 (m, 3H), 2.43 - 2.53 (m, 1H). MS (ESI) *m/z* 467 (M+H).

**N-Benzyl-2-{1-[(3,4-dimethylphenyl)methyl]-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (11b)**

This was made using the methods outlined for **10a** and **11a**, starting from **9b** to give **11b** as an off-white sticky solid in 4% overall yield. MS (ESI) *m/z* 445 (M+H).

**N-Benzyl-2-(7-hydroxy-6-methoxy-1-[[4-(propan-2-yl)phenyl]methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (11c)**

This was made using the methods outlined for **10a** and **11a**, starting from **9c** to give **11c** as an off-white sticky solid in 12% overall yield. MS (ESI) *m/z* 459 (M+H).

**N-Benzyl-2-{7-hydroxy-6-methoxy-1-[(3-nitrophenyl)methyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (11e)**

This was made using the methods outlined for **10a** and **11a**, starting from **9e** to give **11e** as an off-white sticky solid in 8% overall yield. MS (ESI) *m/z* 462 (M+H).

**N-Benzyl-2-[6-methoxy-1-(naphthalen-2-ylmethyl)-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (12a)**

To phenol **11a** (20 mg, 0.043 mmol) and potassium carbonate (18 mg, 0.129 mmol) in dimethylformamide (0.5 mL) was added 1-iodopropane (11 mg, 6 μL, 0.064 mmol) then the reaction was stirred at RT overnight. The reaction was diluted with EtOAc, washed with NaHCO<sub>3</sub> solution, water and brine, dried over MgSO<sub>4</sub> 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 product as a yellow solid (17 mg, 77%). m.p. 46-49 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.68 - 7.83 (m, 3H), 7.65 (s, 1H), 7.43 - 7.52 (m, 2H), 7.34 (dd, *J* = 1.51, 8.29 Hz, 1H), 7.15 (dd, *J* = 1.70, 4.90 Hz, 3H), 6.64 - 6.80 (m, 3H), 6.60

(s, 1H), 6.48 (s, 1H), 4.19 (dd,  $J = 8.19, 14.79$  Hz, 1H), 3.85 (s, 3H), 3.68 - 3.83 (m, 3H), 3.44 - 3.59 (m, 1H), 3.05 - 3.32 (m, 4H), 2.83 - 3.05 (m, 3H), 2.44 - 2.57 (m, 1H), 1.72 - 1.88 (m, 2H), 0.98 (t,  $J = 7.44$  Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>33</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 509.2799,  $m/z$  found 509.2817.

**N-Benzyl-2- $\{1-[(3,4\text{-dimethylphenyl)methyl]-6\text{-methoxy-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}\}$ acetamide (12b). Prepared as 12a**

White solid. Yield 70%. m.p. 105-106 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.19 - 7.37 (m, 4H), 6.86 - 7.08 (m, 5H), 6.59 (s, 1H), 6.48 (s, 1H), 4.44 (dd,  $J = 8.19, 14.98$  Hz, 1H), 3.89 (t,  $J = 6.88$  Hz, 2H), 3.82 - 3.86 (m, 3H), 3.37 - 3.68 (m, 3H), 3.06 - 3.33 (m, 2H), 2.78 - 3.01 (m, 4H), 2.43 - 2.55 (m, 1H), 2.13 (s, 6H), 1.76 - 1.93 (m, 2H), 1.04 (t,  $J = 7.44$  Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>31</sub>H<sub>39</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 487.2955,  $m/z$  found 487.2964.

**N-Benzyl-2-(6-methoxy-1- $\{4\text{-}(propan\text{-}2\text{-yl})phenyl\}$ methyl)-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (12c)**

Prepared as **12a**. Pale yellow solid. Yield 59%. m.p. 80-81 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.20 - 7.36 (m, 3H), 7.03 - 7.14 (m, 7H), 6.58 (s, 1H), 6.41 (s, 1H), 4.37 (dd,  $J = 7.63, 15.16$  Hz, 1H), 3.84 (s, 3H), 3.79 - 3.89 (m, 1H), 3.60 - 3.77 (m, 2H), 3.38 - 3.52 (m, 1H), 3.09 - 3.34 (m, 2H), 2.74 - 3.02 (m, 5H), 2.42 - 2.58 (m, 1H), 1.75 - 1.90 (m, 3H), 1.18 (dd,  $J = 4.90, 6.78$  Hz, 6H), 1.03 (t,  $J = 7.44$  Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>32</sub>H<sub>41</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 501.3112,  $m/z$  found 501.3121.

**N-Benzyl-2-(1- $\{4\text{-}(dimethylamino)phenyl\}$ methyl)-6-methoxy-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (12d)**

To a solution of amide **9d** (3.26 g, 9.93 mmol), potassium carbonate (3.43 g, 24.82 mmol) and tetrabutylammonium iodide (0.73 g, 1.99 mmol) in anhydrous DMF (50 mL) was added 1-bromopropane (1.83 g, 1.35 mL, 14.89 mmol) and the reaction stirred at rt under N<sub>2</sub> overnight. An additional aliquot of 1-bromopropane (0.95 g, 0.70 mL, 7.71 mmol) was added and stirring continued for an additional 24 hr. The reaction was diluted with EtOAc, washed with NaHCO<sub>3</sub> solution, water and brine, then dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give the desired intermediate as a white solid (3.17 g, 86%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.89 (t,  $J = 5.32$  Hz, 1H), 7.02 (d,  $J = 8.57$  Hz, 2H), 6.82 (d,  $J = 8.19$  Hz, 1H), 6.76 (s, 1H), 6.59 - 6.68 (m, 3H), 3.85 (t,  $J = 6.59$  Hz, 2H), 3.71 (s, 3H), 3.18 - 3.28 (m, 4H), 2.85 (s, 3H), 2.85 (s, 3H), 2.61 (t,  $J = 7.16$  Hz, 2H), 1.70 (sxt,  $J = 7.06$  Hz, 2H), 0.96 (t,  $J = 7.35$  Hz, 3H).

This intermediate was used in the preparation of **12d** using the methods outlined for **10a** and **11a** as a white solid in 30% overall yield. m.p. 135-138 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.17 - 7.33 (m, 3H), 7.02 - 7.13 (m, 4H), 6.92 - 7.01 (m, 1H), 6.54 - 6.65 (m, 3H), 6.49 (s, 1H), 4.46 (dd,  $J = 8.10, 14.98$  Hz, 1H), 3.90 (t,  $J = 6.88$  Hz, 2H), 3.84 (s, 3H), 3.50 - 3.65 (m, 2H), 3.39 - 3.50 (m, 1H), 3.08 - 3.32 (m, 2H), 2.75 - 2.99 (m, 10H), 2.39 - 2.54 (m, 1H), 1.76 - 1.94 (m, 2H), 1.04 (t,  $J = 7.44$  Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>31</sub>H<sub>40</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 502.3064,  $m/z$  found 502.3074.

**N-Benzyl-2-{6-methoxy-1-[(3-nitrophenyl)methyl]-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (12e)**

This was prepared using the method for **12a** starting from **11e**. Colorless film. Yield 68%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.02 (s, 1H), 7.87 (dd, *J* = 1.22, 8.19 Hz, 1H), 7.43 (d, *J* = 7.54 Hz, 1H), 7.17 - 7.34 (m, 4H), 6.97 - 7.07 (m, 2H), 6.73 (br. s., 1H), 6.60 (s, 1H), 6.44 (s, 1H), 4.33 (dd, *J* = 7.06, 14.98 Hz, 1H), 3.85 (s, 3H), 3.81 - 3.95 (m, 2H), 3.71 (dd, *J* = 5.37, 9.14 Hz, 1H), 3.11 - 3.47 (m, 4H), 2.84 - 3.10 (m, 4H), 2.43 - 2.57 (m, 1H), 1.76 - 1.93 (m, 2H), 0.97 - 1.09 (m, 3H). MS (ESI) *m/z* 504 (M+H).

**N-Benzyl-2-(1-[[3-(dimethylamino)phenyl]methyl]-6-methoxy-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (12f)**

To the nitro derivative **12e** (15 mg, 0.03 mmol) in ethanol (0.5 mL) was added hydrazine monohydrate (15 mg, 14 μL, 0.298 mmol) and the reaction warmed to 50 °C. Raney nickel (2800 type, as a slurry in water, 5 mg) was added and the reaction stirred at 50 °C for 1 hr, filtered through Celite and the solvent was removed under reduced pressure to give the amine as a colorless film (7 mg, 50%).

To the amine (7 mg, 0.015 mmol) in 1,2-dichloroethane (0.5 mL) was added formaldehyde (37% solution in water, 6 mg, 6 μL, 0.074 mmol) then sodium triacetoxyborohydride (16 mg, 0.074 mmol) and the reaction stirred at RT overnight. The solvent was removed under reduced pressure and redissolved in EtOAc, washed with NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> 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 a white solid (5 mg, 71%). mp 48-51 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.17 - 7.33 (m, 3H), 6.99 - 7.14 (m, 4H), 6.48 - 6.63 (m, 5H), 4.45 (dd, *J* = 8.19, 14.98 Hz, 1H), 3.90 (t, *J* = 6.88 Hz, 2H), 3.85 (s, 3H), 3.54 - 3.70 (m, 2H), 3.38 - 3.53 (m, 1H), 3.08 - 3.32 (m, 2H), 2.79 - 2.99 (m, 10H), 2.41 - 2.53 (m, 1H), 1.78 - 1.92 (m, 2H), 1.04 (t, *J* = 7.35 Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>31</sub>H<sub>40</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 502.3064, *m/z* found 502.3087.

**N-Benzyl-2-(6-methoxy-1-[[3-methoxy-4-(pyridin-2-ylmethoxy)phenyl]methyl]-7-propoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamide (12g)**

To a mixture of phenol **9f** (0.66 g, 1.56 mmol), potassium carbonate (0.65 g, 4.69 mmol) and tetrabutylammonium iodide (0.12 g, 0.31 mmol) in dimethylformamide (10 mL) was added 1-bromopropane (0.29 g, 0.21 mL, 2.34 mmol) and the reaction stirred at RT under N<sub>2</sub> overnight. The reaction was diluted with EtOAc, washed with NaHCO<sub>3</sub> solution, water and brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-20% CMA-80 in EtOAc) to give the desired propoxy derivative as an off-white solid (0.38 g, 53%). m.p. 117-119 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.59 (td, *J* = 0.84, 4.83 Hz, 1H), 7.71 (dt, *J* = 1.13, 7.68 Hz, 1H), 7.56 (d, *J* = 7.82 Hz, 1H), 7.17 - 7.26 (m, 1H), 6.83 (d, *J* = 8.01 Hz, 1H), 6.69 - 6.76 (m, 2H), 6.60 - 6.68 (m, 2H), 6.50 (dd, *J* = 1.51, 8.10 Hz, 1H), 5.43 (br. s., 1H), 5.27 (s, 2H), 3.94 (t, *J* = 6.78 Hz, 2H), 3.86 (d, *J* = 0.47 Hz, 3H), 3.81 (d, *J* = 0.47 Hz, 3H), 3.37 - 3.50 (m, 4H), 2.67 (t, *J* = 6.88 Hz, 2H), 1.84 (sxt, *J* = 7.18 Hz, 2H), 1.02 (t, *J* = 7.44 Hz, 3H).

This intermediate was used in the preparation of **12g** using the methods outlined for **10a** and **11a** as a yellow sticky solid in 58% overall yield. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.58 (d, *J* = 4.80 Hz, 1H), 7.60 - 7.71 (m, 1H), 7.49 - 7.56 (m, 1H), 7.16 - 7.33 (m, 4H), 7.06 - 7.13 (m, 2H), 6.99 (dd, *J* = 5.18, 7.72 Hz, 1H), 6.62 - 6.75 (m, 3H), 6.58 (s, 1H), 6.47 (s, 1H), 5.14 (s, 2H), 4.45 (dd, *J* = 7.91, 14.98 Hz, 1H), 3.89 (t, *J* = 6.83 Hz, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.58 - 3.69 (m, 2H), 3.09 - 3.50 (m, 3H), 2.78 - 2.99 (m, 4H), 2.41 - 2.54 (m, 1H), 1.76 - 1.92 (m, 2H), 1.04 (t, *J* = 7.44 Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>36</sub>H<sub>42</sub>N<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 596.3119, *m/z* found 596.3130.

### Ethyl 2-[7-hydroxy-6-methoxy-1-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetate (**13a**)

Tetrahydroisoquinoline **10a** (0.37 g, 1.158 mmol), ethyl bromoacetate (0.29 g, 0.19 mL, 1.738 mmol) and tetrabutylammonium iodide (86 mg, 0.232 mmol) were combined in anhydrous DMF (12 mL). Diisopropylethylamine (0.37 g, 0.50 mL, 2.896 mmol) was added and the reaction was stirred at RT overnight. The reaction was diluted with water and extracted twice with EtOAc. The combined extracts were washed twice with brine, dried over MgSO<sub>4</sub> and then the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica (0-40% EtOAc/hexane) to give the desired acetate as a yellow oil (0.21 g, 44%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.70 - 7.82 (m, 3H), 7.60 (s, 1H), 7.37 - 7.47 (m, 2H), 7.33 (dd, *J* = 1.60, 8.38 Hz, 1H), 6.53 (s, 1H), 6.44 (s, 1H), 5.38 (s, 1H), 3.96 - 4.14 (m, 3H), 3.85 (s, 3H), 3.32 - 3.48 (m, 2H), 3.19 - 3.31 (m, 2H), 3.04 - 3.13 (m, 1H), 2.97 (td, *J* = 4.76, 12.72 Hz, 1H), 2.69 - 2.84 (m, 1H), 2.43 - 2.54 (m, 1H), 1.12 (t, *J* = 7.06 Hz, 3H). MS (ESI) *m/z* 406 (M+H).

### Ethyl 2-{1-[(3,4-dimethylphenyl)methyl]-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetate (**13b**)

This was made by the same method as **13a** using **10b**. Yellow oil. Yield 24%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 6.99 - 7.03 (m, 1H), 6.94 (s, 1H), 6.85 - 6.91 (m, 1H), 6.54 (s, 1H), 6.35 (s, 1H), 5.38 (br. s., 1H), 4.11 (quin, *J* = 7.06 Hz, 2H), 3.92 (t, *J* = 6.31 Hz, 1H), 3.85 (s, 3H), 3.22 - 3.46 (m, 3H), 2.91 - 3.10 (m, 2H), 2.74 - 2.86 (m, 2H), 2.47 - 2.57 (m, 1H), 2.22 (s, 6H), 1.20 (t, *J* = 7.16 Hz, 3H). MS (ESI) *m/z* 384 (M+H).

### 2-[6-Methoxy-1-(naphthalen-2-ylmethyl)-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]-N-(pyridin-3-ylmethyl)acetamide (**14a**)

2N Sodium hydroxide solution (1.02 mL, 2.04 mmol) was added to a solution of ester **13a** (207 mg, 0.51 mmol) in ethanol (5 mL) and stirred at RT overnight. The pH was adjusted to 7-8 using 2N HCl, then all solvents were removed under reduced pressure. The residue was dissolved as far as possible in methanol, filtered and the solvent was removed under reduced pressure to give the crude acid as a white solid which was used without further purification.

The crude acid was combined with 3-pyridylmethylamine (54 mg, 0.50 mmol) and HATU (230 mg, 0.60 mmol) in anhydrous DMF (5 mL), then diisopropylethylamine (195 mg, 0.26 mmol, 1.51 mmol) was added. The reaction was stirred at RT overnight. The reaction was diluted with EtOAc, then washed with aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude material was

purified by chromatography on silica (0-30% CMA-80/EtOAc) to give the desired amide as a white solid (106 mg, 45% over 2 steps). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.34 - 8.43 (m, 1H), 7.63 - 7.85 (m, 5H), 7.44 - 7.54 (m, 2H), 7.32 - 7.44 (m, 1H), 6.99 - 7.07 (m, 1H), 6.89 - 6.99 (m, 1H), 6.79 (s, 1H), 6.60 (s, 1H), 6.46 - 6.55 (m, 1H), 3.99 (dd, *J* = 8.38, 15.16 Hz, 1H), 3.89 (s, 3H), 3.79 - 3.87 (m, 1H), 3.61 - 3.73 (m, 2H), 3.02 - 3.28 (m, 4H), 2.83 - 3.01 (m, 2H), 2.67 (dd, *J* = 4.71, 15.07 Hz, 1H), 2.43 - 2.55 (m, 1H).

**2-{1-[(3,4-Dimethylphenyl)methyl]-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-3-ylmethyl)acetamide (14b)**

This was prepared by the same method as **14a** from **13b**. White solid. Yield 27% over 2 steps. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.45 - 8.51 (m, 1H), 8.24 (s, 1H), 7.35 (d, *J* = 8.10 Hz, 1H), 7.21 (dd, *J* = 4.99, 7.63 Hz, 1H), 6.95 - 7.06 (m, 3H), 6.76 - 6.85 (m, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 4.33 (dd, *J* = 8.19, 15.35 Hz, 1H), 3.88 (s, 3H), 3.38 - 3.59 (m, 3H), 3.04 - 3.29 (m, 2H), 2.82 - 2.99 (m, 4H), 2.41 - 2.52 (m, 1H), 2.13 (s, 6H).

**2-[6-Methoxy-1-(naphthalen-2-ylmethyl)-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]-N-(pyridin-3-ylmethyl)acetamide (15a)**

In a sealed tube, tetrahydroisoquinoline **14a** (30 mg, 0.064 mmol) was combined with cesium carbonate (42 mg, 0.128 mmol) in anhydrous DMF (0.75 mL), then 2,2,2-trifluoroiodoethane (20 mg, 10 μL, 0.096 mmol) was added. The vessel was sealed and heated to 100 °C for 2 hr. The reaction was cooled and diluted with water. The mixture was extracted twice with EtOAc and the combined extracts were washed with brine, dried over MgSO<sub>4</sub> and the solvents were removed under reduced pressure. The crude was purified by chromatography on silica (10-30% CMA-80/EtOAc) to give the desired product as a yellow sticky solid (16 mg, 46%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.40 (dd, *J* = 1.70, 4.71 Hz, 1H), 7.66 - 7.86 (m, 5H), 7.44 - 7.54 (m, 2H), 7.38 (dd, *J* = 1.51, 8.29 Hz, 1H), 7.00 - 7.08 (m, 1H), 6.90 - 7.00 (m, 1H), 6.78 (s, 1H), 6.67 (s, 1H), 6.52 (d, *J* = 7.35 Hz, 1H), 4.26 - 4.42 (m, 2H), 4.01 (dd, *J* = 8.38, 14.98 Hz, 1H), 3.82 - 3.91 (m, 3H), 3.48 - 3.77 (m, 2H), 3.04 - 3.28 (m, 4H), 2.85 - 3.02 (m, 2H), 2.70 - 2.81 (m, 1H), 2.49 - 2.63 (m, 1H). <sup>19</sup>F NMR (282 MHz, CHLOROFORM-d) δ -74.1 (t, *J* = 8.8 Hz). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>31</sub>H<sub>31</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 550.2312, *m/z* found 550.2339.

**2-{1-[(3,4-Dimethylphenyl)methyl]-6-methoxy-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-(pyridin-3-ylmethyl)acetamide (15b)**

This was prepared by the same method as **15a** using **14b**. White solid. Yield 56%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.49 (d, *J* = 4.71 Hz, 1H), 8.26 (s, 1H), 7.37 (d, *J* = 7.91 Hz, 1H), 7.15 - 7.30 (m, 1H), 6.93 - 7.04 (m, 3H), 6.75 - 6.87 (m, 1H), 6.69 (s, 1H), 6.64 (s, 1H), 4.26 - 4.44 (m, 3H), 3.86 (s, 3H), 3.42 - 3.65 (m, 3H), 3.04 - 3.30 (m, 2H), 2.76 - 3.00 (m, 4H), 2.47 - 2.59 (m, 1H), 2.14 (s, 6H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>29</sub>H<sub>33</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 528.2469, *m/z* found 528.2490.

**N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(pyridin-2-yl)acetamide (17a)**

2-Pyridylacetic acid hydrochloride (**16a**) (1.0 g, 5.76 mmol), DCC (1.43 g, 6.91 mmol) and HOBT monohydrate (0.93 g, 6.91 mmol) were combined in anhydrous THF (40 mL) and

stirred at RT under N<sub>2</sub> for 2 hr. A solution of 4-hydroxy-3-methoxyphenethylamine hydrochloride (1.29 g, 6.34 mmol) and triethylamine (2.91 g, 4.0 mL, 28.80 mmol) in THF (20 mL) was added and the resulting mixture stirred at RT overnight. The reaction was diluted with EtOAc and filtered, then the filtrate was washed with brine and dried over MgSO<sub>4</sub>, then the solvent was removed under reduced pressure. The crude material was purified by chromatography on silica (0-10% MeOH/DCM) to give the desired amide as an yellow oil (0.57 g, 35%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.40 - 8.45 (m, 1H), 7.65 (dt, *J* = 1.79, 7.68 Hz, 1H), 7.29 - 7.38 (m, 1H), 7.15 - 7.26 (m, 2H), 6.73 - 6.82 (m, 1H), 6.54 - 6.70 (m, 2H), 5.78 (br. s., 1H), 3.82 (s, 3H), 3.69 (s, 2H), 3.43 - 3.54 (m, 2H), 2.71 (t, *J* = 6.97 Hz, 2H).

#### N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(pyridin-3-yl)acetamide (17b)

4-Hydroxy-3-methoxyphenethylamine hydrochloride (1.17 g, 5.76 mmol), 3-pyridylacetic acid hydrochloride (**16b**) (1.0 g, 5.76 mmol) and HBTU (2.40 g, 6.34 mmol) were combined in anhydrous DMF (30 mL). Diisopropylethylamine (2.98 g, 4.0 mL, 23.04 mmol) was added and the reaction stirred at RT under N<sub>2</sub> overnight. The reaction was diluted with EtOAc, the solution was washed with aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-10% MeOH/DCM) to give the desired amide as a yellow oil (0.52 g, 32%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.52 (dd, *J* = 1.51, 4.71 Hz, 1H), 8.44 (d, *J* = 1.70 Hz, 1H), 7.53 - 7.60 (m, 1H), 7.22 - 7.30 (m, 2H), 6.80 (d, *J* = 7.91 Hz, 1H), 6.61 (d, *J* = 1.70 Hz, 1H), 6.55 (dd, *J* = 1.88, 7.91 Hz, 1H), 5.51 (br. s., 1H), 3.84 (s, 3H), 3.43 - 3.54 (m, 4H), 2.70 (t, *J* = 6.97 Hz, 2H).

#### N-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-2-(pyridin-4-yl)acetamide (17c)

This was prepared by the method used for **17b** using 4-pyridylacetic acid hydrochloride (**16c**). Yellow oil. Yield 35%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.51 - 8.57 (m, 2H), 7.13 (d, *J* = 5.84 Hz, 2H), 6.82 (d, *J* = 8.10 Hz, 1H), 6.61 (d, *J* = 1.70 Hz, 1H), 6.55 (dd, *J* = 1.60, 8.01 Hz, 1H), 5.59 (br. s., 1H), 5.37 (br. s., 1H), 3.83 (s, 3H), 3.44 - 3.54 (m, 4H), 2.71 (t, *J* = 6.88 Hz, 2H).

#### 6-Methoxy-1-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (18a)

Amide **17a** (0.56 g, 1.96 mmol) was dissolved in anhydrous acetonitrile (10 mL) with warming. Phosphorus oxychloride (1.92 g, 1.2 mL, 12.52 mmol) was added and the reaction heated at reflux for 1 hr. The reaction was cooled and all solvents removed under reduced pressure. The crude was suspended in water and then heated until fully dissolved. The solution was cooled and the pH was adjusted to 8 with conc. ammonium hydroxide solution, then extracted 3 times with DCM. The combined extracts were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give an orange viscous oil.

The crude dihydroisoquinoline was dissolved in anhydrous methanol (10 mL) and cooled in an ice bath under N<sub>2</sub>. Sodium borohydride (0.15 g, 3.91 mmol) was added portionwise, the mixture was stirred in ice for 30 min then at RT overnight. The reaction was quenched with water, the methanol was removed under reduced pressure, then the mixture was diluted further with water and extracted 3 times with DCM. The combined extracts were dried over



MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-10% MeOH/DCM) to give the desired tetrahydroisoquinoline as an orange solid (0.36 g, 68%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.57 (dd, *J*= 0.85, 4.80 Hz, 1H), 7.61 (dt, *J*= 1.79, 7.68 Hz, 1H), 7.11 - 7.21 (m, 2H), 6.73 (s, 1H), 6.55 (s, 1H), 4.39 (dd, *J*= 3.20, 9.98 Hz, 1H), 3.82 (s, 3H), 3.25 - 3.33 (m, 1H), 3.21 (dd, *J*= 5.75, 11.96 Hz, 1H), 3.06 (dd, *J*= 10.08, 14.03 Hz, 1H), 2.95 (td, *J*= 5.91, 12.10 Hz, 1H), 2.67 - 2.77 (m, 2H).

#### **6-Methoxy-1-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (18b)**

This was prepared using the method for **18a** using **17b**. Orange oil. Yield 50%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.44 - 8.52 (m, 2H), 7.57 (d, *J*= 7.72 Hz, 1H), 7.20 - 7.29 (m, 1H), 6.75 (s, 1H), 6.56 (s, 1H), 4.11 (dd, *J*= 3.49, 9.51 Hz, 1H), 3.81 (s, 3H), 3.09 - 3.22 (m, 2H), 2.83 - 2.97 (m, 2H), 2.60 - 2.79 (m, 2H).

#### **6-Methoxy-1-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (18c)**

This was prepared using the method for **18a** using **17c**. Orange oil. Yield 27%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.50 - 8.55 (m, 2H), 7.19 (d, *J*= 6.03 Hz, 2H), 6.78 (s, 1H), 6.58 (s, 1H), 4.16 (dd, *J*= 3.49, 9.70 Hz, 1H), 3.86 (s, 3H), 3.12 - 3.23 (m, 2H), 2.60 - 2.98 (m, 4H).

#### **N-Benzyl-2-[6-methoxy-1-(pyridin-2-ylmethyl)-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (19a)**

This was prepared by the methods used for **11a** and **16a**, starting from **18a**. Orange sticky solid. Yield 20% over 2 steps. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.19 - 8.30 (m, 1H), 7.53 - 7.69 (m, 1H), 7.23 - 7.45 (m, 4H), 7.13 - 7.22 (m, 2H), 6.88 - 7.01 (m, 2H), 6.57 - 6.76 (m, 2H), 4.41 - 4.53 (m, 1H), 4.23 - 4.39 (m, 2H), 4.02 - 4.17 (m, 2H), 3.80 - 3.88 (m, 3H), 3.15 - 3.40 (m, 3H), 3.11 (d, *J*= 6.97 Hz, 2H), 2.73 - 2.91 (m, 2H), 2.35 - 2.48 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>27</sub>H<sub>29</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 500.2156, *m/z* found 500.2173.

#### **N-Benzyl-2-[6-methoxy-1-(pyridin-3-ylmethyl)-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (19b)**

This was prepared by the methods used for **11a** and **16a**, starting from **18b**. Yellow solid. Yield 9% over 2 steps. m.p. 49-50 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.43 (br. s., 1H), 8.37 (d, *J*= 3.58 Hz, 1H), 7.36 - 7.46 (m, 1H), 7.23 - 7.36 (m, 3H), 7.11 (d, *J*= 6.78 Hz, 2H), 7.01 (dd, *J*= 4.52, 7.72 Hz, 1H), 6.66 - 6.75 (m, 1H), 6.64 (s, 1H), 6.61 (s, 1H), 4.25 - 4.46 (m, 3H), 3.86 (s, 3H), 3.81 - 3.93 (m, 1H), 3.60 - 3.73 (m, 1H), 3.07 - 3.45 (m, 3H), 2.81 - 3.03 (m, 4H), 2.46 - 2.61 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>27</sub>H<sub>29</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 500.2156, *m/z* found 500.2181.

#### **N-Benzyl-2-[6-methoxy-1-(pyridin-4-ylmethyl)-7-(2,2,2-trifluoroethoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (19c)**

This was prepared by the methods used for **11a** and **16a**, starting from **18c**. Yellow solid. Yield 17% over 2 steps. m.p. 56-58 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.40 (d,

$J = 5.84$  Hz, 1H), 7.24 - 7.39 (m, 4H), 7.10 - 7.20 (m, 2H), 7.01 - 7.07 (m, 2H), 6.61 - 6.79 (m, 3H), 4.23 - 4.46 (m, 3H), 3.86 (s, 3H), 3.64 - 3.84 (m, 2H), 3.06 - 3.42 (m, 3H), 2.78 - 3.03 (m, 4H), 2.44 - 2.61 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>27</sub>H<sub>29</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M + H]<sup>+</sup> 500.2156,  $m/z$  found 500.2180.

### 2-[4-(Benzyloxy)-3-methoxyphenyl]acetic acid (21)

Sodium metal (0.76 g, 32.94 mmol) was added portionwise to anhydrous methanol (17 mL) under N<sub>2</sub> at RT. When dissolution was complete, acid **20** (3.0 g, 16.47 mmol) was added in one portion and the mixture warmed until all solids had dissolved. Benzyl bromide (5.63 g, 3.9 mL, 32.94 mmol) was added and the reaction heated to reflux for 5 hr then allowed to stand at RT overnight. The reaction was diluted with ether and the solids collected by filtration. These were rinsed with EtOAc, dissolved in 1N HCl as far as possible and the solids collected by filtration to give the benzyl ether as a white solid (3.22 g, 72%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.23 - 7.47 (m, 5H), 6.79 - 6.86 (m, 2H), 6.70 - 6.77 (m, 1H), 5.13 (s, 2H), 3.88 (s, 3H), 3.57 (s, 2H).

### 2-[4-(Benzyloxy)-3-methoxyphenyl]-N-[2-(4-hydroxy-3-methoxyphenyl)ethyl]acetamide (22)

This was prepared by the method used for **9a**, starting from acid **21** and 4-hydroxy-3-methoxyphenethylamine, with HBTU as coupling agent. White sticky solid. Yield 96%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.42 - 7.48 (m, 2H), 7.28 - 7.41 (m, 3H), 6.78 (dd,  $J = 8.05, 12.10$  Hz, 2H), 6.70 (d,  $J = 1.98$  Hz, 1H), 6.57 - 6.64 (m, 2H), 6.48 (dd,  $J = 1.88, 8.01$  Hz, 1H), 5.57 (s, 1H), 5.41 (br. s., 1H), 5.15 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.45 (s, 2H), 3.38 - 3.44 (m, 2H), 2.66 (t,  $J = 6.92$  Hz, 2H).

### 4-(2-{2-[4-(Benzyloxy)-3-methoxyphenyl]acetamido}ethyl)-2-methoxyphenyl methanesulfonate (23)

To a solution of amide **22** (0.67 g, 1.58 mmol) in dichloromethane (2 mL) cooled in an ice bath under N<sub>2</sub> was added triethylamine (0.24 g, 0.33 mL, 2.37 mmol) then slowly methanesulfonyl chloride (0.22 g, 0.15 mL, 1.90 mmol). The reaction was stirred in an ice bath for 4 hr, quenched by the addition of water then the layers separated. The aqueous portion was extracted twice with dichloromethane and the combined organic fractions were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-100% EtOAc in hexane) to give the sulfonate as a white solid (0.51 g, 65%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.41 - 7.48 (m, 2H), 7.28 - 7.41 (m, 3H), 7.13 (d,  $J = 8.19$  Hz, 1H), 6.83 (d,  $J = 8.10$  Hz, 1H), 6.74 (dd,  $J = 1.84, 4.10$  Hz, 2H), 6.56 - 6.64 (m, 2H), 5.53 (t,  $J = 5.37$  Hz, 1H), 5.14 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.40 - 3.50 (m, 4H), 3.14 (s, 3H), 2.73 (t,  $J = 7.02$  Hz, 2H).

### 1-[[4-(Benzyloxy)-3-methoxyphenyl]methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl methanesulfonate (24)

This was prepared using the method shown for **10a** using amide **23** to give **24** as a frothy white solid in 89% yield over 2 steps. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-*d*)  $\delta$  7.41 - 7.48 (m, 2H), 7.28 - 7.40 (m, 3H), 7.18 (br. s., 1H), 6.79 - 6.87 (m, 1H), 6.67 - 6.78 (m, 3H),

5.14 (s, 2H), 4.12 (dd,  $J = 2.45, 9.23$  Hz, 1H), 3.86 (s, 6H), 3.17 (s, 3H), 3.11 - 3.26 (m, 1H), 2.67 - 2.97 (m, 5H).

### 2-[(Benzyloxycarbonyl)methyl]-1-[[4-(benzyloxy)-3-methoxyphenyl]methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl methanesulfonate (25a)

This was prepared using the method shown for **11a** starting from **24** to give **25a** as a clear film in 65% yield.  $^1\text{H}$  NMR (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.36 - 7.43 (m, 2H), 7.35 (s, 1H), 7.19 - 7.33 (m, 4H), 7.09 (d,  $J = 6.59$  Hz, 2H), 7.05 (s, 1H), 6.83 - 6.92 (m, 1H), 6.61 - 6.76 (m, 5H), 4.97 (s, 2H), 4.42 (dd,  $J = 8.10, 14.98$  Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.54 - 3.73 (m, 2H), 3.32 - 3.48 (m, 1H), 3.17 (s, 3H), 3.06 - 3.32 (m, 2H), 2.80 - 3.02 (m, 4H), 2.48 - 2.59 (m, 1H). HRMS (ESI,  $\text{CH}_3\text{OH}$ )  $m/z$  calcd for  $\text{C}_{35}\text{H}_{39}\text{N}_2\text{O}_7\text{S}$   $[\text{M} + \text{H}]^+$  631.2472,  $m/z$  found 631.2475.

### 2-[(Benzyloxycarbonyl)methyl]-1-[[4-(butoxy)-3-methoxyphenyl]methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl methanesulfonate (25b)

To a solution of benzyl ether (0.16 g, 0.25 mmol) in methanol (5 mL) was added concentrated HCl (2.5 mL) and the reaction heated to reflux overnight. Methanol was removed under reduced pressure then the acid was carefully poured into  $\text{NaHCO}_3$  solution and then extracted three times with EtOAc. The combined extracts were dried over  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-100% EtOAc in hexane) to give the phenol as a colorless film (27 mg, 20%).

The phenol (40 mg, 0.074 mmol), potassium carbonate (26 mg, 0.185 mmol) and tetrabutylammonium iodide (6 mg, 0.015 mmol) were combined in dry dimethylformamide (1 mL) and 1-bromobutane (15 mg, 12  $\mu\text{L}$ , 0.111 mmol) was added. The reaction was heated to 50  $^\circ\text{C}$  overnight, then diluted with EtOAc, washed with  $\text{NaHCO}_3$  solution and brine, dried over  $\text{MgSO}_4$  and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-80% EtOAc in hexane) to give the desired ether as a clear film (39 mg, 91%).  $^1\text{H}$  NMR (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.18 - 7.34 (m, 3H), 7.04 - 7.14 (m, 3H), 6.82 - 6.93 (m, 1H), 6.60 - 6.76 (m, 4H), 4.47 (dd,  $J = 8.15, 14.93$  Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.84 (td,  $J = 3.33, 6.81$  Hz, 2H), 3.53 - 3.74 (m, 2H), 3.34 - 3.48 (m, 1H), 3.18 (s, 3H), 3.07 - 3.32 (m, 2H), 2.81 - 3.02 (m, 4H), 2.45 - 2.61 (m, 1H), 1.72 - 1.87 (m, 2H), 1.40 - 1.55 (m, 2H), 0.97 (t,  $J = 7.35$  Hz, 3H).  $m/z$  597 (M+H). HRMS (ESI,  $\text{CH}_3\text{OH}$ )  $m/z$  calcd for  $\text{C}_{32}\text{H}_{41}\text{N}_2\text{O}_7\text{S}$   $[\text{M} + \text{H}]^+$  597.2629,  $m/z$  found 597.2643.

### (3-Methoxy-4-nitrophenyl)acetonitrile (27)

To a solution of tetrabutylammonium nitrate (7.86 g, 25.82 mmol) and 18-crown-6 (0.11 g, 0.41 mmol) in dry dichloromethane (150 mL) cooled in an ice bath under  $\text{N}_2$  was added dropwise trifluoroacetic anhydride (13.13 g, 8.8 mL, 62.5 mmol). The solution was stirred in ice for 30 min, then transferred to an addition funnel and slowly added to a solution of 3-methoxyphenylacetonitrile (**26**) (4.0 g, 3.8 mL, 27.18 mmol) in dichloromethane (300 mL). The resulting mixture was stirred at RT overnight and washed with  $\text{NaHCO}_3$  solution. The aqueous layer was extracted once with  $\text{CH}_2\text{Cl}_2$ , then the combined organic fractions were dried over  $\text{MgSO}_4$  and solvent was removed under reduced pressure. The crude was purified

by chromatography on silica (0-40% EtOAc in hexane) to give the desired 4-nitro derivative as a viscous orange oil (2.71 g, 56%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.89 (d, *J* = 8.29 Hz, 1H), 7.05 - 7.12 (m, 1H), 7.00 (td, *J* = 0.80, 8.29 Hz, 1H), 4.01 (s, 3H), 3.84 (s, 2H).

### 2-(3-Methoxy-4-nitrophenyl)ethanamine (28)

To a solution of nitrile **27** (2.7 g, 14.05 mmol) in anhydrous tetrahydrofuran (75 mL) cooled in an ice bath under N<sub>2</sub> was slowly added a solution of borane-THF complex (1M solution in THF, 56 mL). Upon completion of addition, the reaction was warmed to RT then heated to 70 °C for 2 hr. The reaction was cooled then 2N HCl (7 mL) was carefully added to quench the reaction, then the solution made basic with 2N NaOH solution. It was extracted twice with EtOAc, then the combined extracts were dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure to give the phenylethanamine (2.7 g, 97%) as a dark orange oil. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.83 (d, *J* = 8.19 Hz, 1H), 6.83 - 6.97 (m, 2H), 3.96 (s, 3H), 3.02 (t, *J* = 6.78 Hz, 2H), 2.81 (t, *J* = 6.97 Hz, 2H).

### 2-(3,4-Dimethoxyphenyl)-N-[2-(3-methoxy-4-nitrophenyl)ethyl]acetamide (29)

3,4-Dimethoxyphenylacetic acid (0.53 g, 2.70 mmol) and amine **28** (0.53 g, 2.70 mmol) were combined in anhydrous DMF (15 mL), then BOP (1.20 g, 2.70 mmol) was added, followed by diisopropylethylamine (0.87 g, 1.2 mL, 6.75 mmol), then the reaction stirred at RT under N<sub>2</sub> overnight. The reaction was diluted with EtOAc, then washed with 2N HCl, NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> then the solvent was removed under reduced pressure to give the desired amide as an orange oil (1.01 g, 100%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.75 (d, *J* = 8.19 Hz, 1H), 6.64 - 6.85 (m, 5H), 5.50 (br. s., 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.44 - 3.57 (m, 4H), 2.82 (t, *J* = 6.97 Hz, 2H)

### N-[2-(4-Amino-3-methoxyphenyl)ethyl]-2-(3,4-dimethoxyphenyl)acetamide (30)

To a solution of amide **29** (1.02 g, 2.72 mmol) in ethanol was added hydrazine monohydrate (1.36 g, 1.32 mL, 27.2 mmol) then Raney nickel (as a slurry in water, 0.20 g) was added. The reaction was heated at 50 °C for 1 hr, cooled to RT then filtered through Celite, rinsing with ethanol. The solvent was removed under reduced pressure to give the aniline as an orange oil (0.94 g, 100%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 6.75 - 6.84 (m, 2H), 6.60 - 6.74 (m, 3H), 6.56 (d, *J* = 7.72 Hz, 1H), 6.51 (d, *J* = 1.51 Hz, 1H), 6.40 (dd, *J* = 1.65, 7.77 Hz, 1H), 5.42 (br. s., 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.47 (s, 2H), 3.42 (q, *J* = 6.72 Hz, 2H), 2.63 (t, *J* = 6.83 Hz, 2H).

### Methyl N-(4-{2-[2-(3,4-dimethoxyphenyl)acetamido]ethyl}-2-methoxyphenyl)carbamate (31)

To a solution of aniline **30** (0.94 g, 2.72 mmol) in DCM (15 mL) cooled in ice under N<sub>2</sub> was added diisopropylethylamine (0.88 g, 1.18 mL, 6.80 mmol) then methyl chloroformate (0.51 g, 0.42 mL, 5.44 mmol). The reaction was allowed to warm slowly to RT overnight. The reaction was quenched with methanol, then the solvents were removed under reduced pressure. The crude was purified by chromatography on silica (0-3% MeOH/DCM) to give the carbamate as a yellow oil (0.44 g, 40%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.93 (d, *J* = 7.35 Hz, 1H), 7.16 (br. s., 1H), 6.77 - 6.84 (m, 1H), 6.57 - 6.72 (m, 4H), 5.45 (br.

s., 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.76 - 3.79 (m, 3H), 3.40 - 3.51 (m, 4H), 2.70 (t,  $J = 6.88$  Hz, 2H).

**Methyl N-{2-[(benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl}carbamate (32)**

This was prepared using the methods used to make **10a** and **11a** sequentially, starting from **31**. Yellow oil. Yield 55% over 3 steps.  $^1\text{H NMR}$  (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.92 (br. s., 1H), 7.17 - 7.33 (m, 4H), 7.06 (d,  $J = 6.88$  Hz, 2H), 6.78 - 6.86 (m, 1H), 6.71 - 6.77 (m, 2H), 6.56 - 6.63 (m, 2H), 4.47 (dd,  $J = 8.38, 15.07$  Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 3.67 (dd,  $J = 4.19, 11.07$  Hz, 1H), 3.53 (dd,  $J = 4.66, 15.12$  Hz, 1H), 3.38 - 3.48 (m, 1H), 3.05 - 3.32 (m, 2H), 2.78 - 3.03 (m, 4H), 2.47 (dd,  $J = 4.62, 16.20$  Hz, 1H).

**2-{7-Amino-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}-N-benzylacetamide (33)**

To a solution of carbamate **32** (0.36 g, 0.67 mmol) in methanol (30 mL) was added sodium hydroxide solution (2N, 3.35 mL, 6.70 mmol) and the reaction heated at 50 °C for 48 hr. The reaction was cooled and the methanol removed under reduced pressure. It was further diluted with water and extracted 3 times with EtOAc. The combined extracts were dried over  $\text{MgSO}_4$  and the solvent removed under reduced pressure. The crude material was purified by chromatography on silica (0-100% EtOAc/hexane) to give the free aniline as a white solid (0.19 g, 59%). m.p. 65-67 °C.  $^1\text{H NMR}$  (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.17 - 7.34 (m, 4H), 7.08 (d,  $J = 6.97$  Hz, 2H), 6.93 (dd,  $J = 4.85, 7.30$  Hz, 1H), 6.56 - 6.77 (m, 4H), 6.50 (s, 1H), 6.44 (s, 1H), 4.47 (dd,  $J = 8.24, 15.12$  Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.52 - 3.63 (m, 2H), 3.33 - 3.49 (m, 1H), 3.09 - 3.32 (m, 2H), 2.78 - 2.97 (m, 4H), 2.37 - 2.50 (m, 1H). HRMS (ESI,  $\text{CH}_3\text{OH}$ )  $m/z$  calcd for  $\text{C}_{28}\text{H}_{34}\text{N}_3\text{O}_4$  [ $\text{M} + \text{H}$ ] $^+$  476.2544,  $m/z$  found 476.2546.

**N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-(dimethylamino)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (34a)**

To amine **33** (7 mg, 0.015 mmol) in 1,2-dichloroethane (0.5 mL) was added formaldehyde (37% solution in water, 6 mg, 6  $\mu\text{L}$ , 0.074 mmol) then sodium triacetoxyborohydride (16 mg, 0.074 mmol) and the reaction stirred at RT overnight. The solvent was removed under reduced pressure and redissolved in EtOAc, washed with  $\text{NaHCO}_3$  solution and brine, dried over  $\text{MgSO}_4$  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 a white solid (5 mg, 71%). m.p. 128-130 °C.  $^1\text{H NMR}$  (300 MHz, CHLOROFORM- $d$ )  $\delta$  7.18 - 7.34 (m, 3H), 7.07 - 7.15 (m, 2H), 7.00 (dd,  $J = 5.13, 7.30$  Hz, 1H), 6.60 - 6.74 (m, 3H), 6.56 (s, 1H), 6.51 (s, 1H), 4.50 (dd,  $J = 8.01, 14.98$  Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.66 (dd,  $J = 4.99, 15.07$  Hz, 2H), 3.34 - 3.48 (m, 1H), 3.13 - 3.34 (m, 2H), 2.79 - 2.99 (m, 4H), 2.73 (s, 6H), 2.42 - 2.57 (m, 1H). HRMS (ESI,  $\text{CH}_3\text{OH}$ )  $m/z$  calcd for  $\text{C}_{30}\text{H}_{38}\text{N}_3\text{O}_4$  [ $\text{M} + \text{H}$ ] $^+$  504.2857,  $m/z$  found 504.2867.

**N-Benzyl-2-[7-(benzylamino)-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (34b)**

Aniline **33** (30 mg, 0.063 mmol) was combined with sodium bicarbonate (2 mg, 0.025 mmol) and benzaldehyde (7 mg, 7  $\mu$ L, 0.069 mmol) in anhydrous methanol (0.5 mL) and heated to 40 °C for 1 hour. The reaction was then cooled in an ice bath and sodium borohydride (2 mg, 0.041 mmol) was added. The reaction was allowed to warm to RT slowly overnight. The solvent was removed under reduced pressure and the crude purified by chromatography on silica (0-100% EtOAc/hexane) to give the benzylamine as a clear film (3 mg, 8%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d)  $\delta$  7.32 - 7.44 (m, 4H), 7.18 - 7.31 (m, 5H), 7.08 (d,  $J$  = 6.59 Hz, 2H), 6.92 - 7.00 (m, 1H), 6.57 - 6.73 (m, 3H), 6.48 (s, 1H), 6.21 (s, 1H), 4.48 (dd,  $J$  = 8.05, 14.93 Hz, 1H), 4.30 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.50 - 3.63 (m, 2H), 3.33 - 3.47 (m, 1H), 3.10 - 3.32 (m, 2H), 2.70 - 2.98 (m, 4H), 2.38 - 2.49 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>35</sub>H<sub>40</sub>N<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup> 566.3013,  $m/z$  found 566.3031.

**N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-acetamido-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (34c)**

To a solution of aniline **33** (30 mg, 0.063 mmol) and diisopropylethylamine (20 mg, 27  $\mu$ L, 0.158 mmol) in anhydrous DCM (0.5 mL) was added acetic anhydride (13 mg, 12  $\mu$ L, 0.126 mmol) and the reaction stirred at RT overnight. The reaction mixture was applied directly to chromatography on silica (0-100% EtOAc/hexane) to give the desired amide as a white solid (24 mg, 73%). m.p. 81-84 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d)  $\delta$  8.23 (s, 1H), 7.75 (s, 1H), 7.17 - 7.34 (m, 3H), 7.06 (d,  $J$  = 6.97 Hz, 2H), 6.69 - 6.88 (m, 3H), 6.55 - 6.65 (m, 2H), 4.47 (dd,  $J$  = 8.38, 15.07 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.62 - 3.70 (m, 1H), 3.37 - 3.58 (m, 2H), 3.05 - 3.31 (m, 2H), 2.78 - 3.03 (m, 4H), 2.48 (dd,  $J$  = 4.52, 16.29 Hz, 1H), 2.22 (s, 3H). HRMS (ESI, CH<sub>3</sub>OH)  $m/z$  calcd for C<sub>30</sub>H<sub>36</sub>N<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 518.2649,  $m/z$  found 518.2658.

**N-Benzyl-2-{1-[(3,4-dimethoxyphenyl)methyl]-7-methanesulfonamido-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}acetamide (34d)**

To a solution of aniline **33** (50 mg, 0.105 mmol) in DCM (0.5 mL) cooled in ice was added triethylamine (43 mg, 59  $\mu$ L, 0.420 mmol) then methanesulfonyl chloride (36 mg, 24  $\mu$ L, 0.315 mmol). The reaction was allowed to warm slowly to RT overnight. The crude reaction was directly applied to chromatography on silica (0-100% EtOAc/hexane) to give a mixture of mono- and bis-sulfonamides (mono 17 mg, 29%; bis 23 mg, 35%). The bis-sulfonamide was suspended in aqueous sodium hydroxide (3N, 1 mL) and heated to 80 °C overnight. The reaction was cooled and the pH adjusted to 7 with 2N HCl, forming a precipitate. The mixture was extracted 3 times with EtOAc, the combined extracts were then dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give the mono-sulfonamide as a clear oil (17 mg, 85%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d)  $\delta$  7.18 - 7.35 (m, 3H), 7.07 (d,  $J$  = 7.44 Hz, 2H), 6.77 - 6.85 (m, 1H), 6.58 - 6.76 (m, 5H), 4.49 (dd,  $J$  = 8.24, 15.02 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.75 - 3.90 (m, 1H), 3.73 (s, 3H), 3.62 - 3.71 (m, 1H), 3.37 - 3.60 (m, 2H), 3.07 - 3.34 (m, 2H), 2.94 (s, 3H), 2.79 - 3.04 (m, 4H), 2.47 - 2.59 (m,

1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>29</sub>H<sub>36</sub>N<sub>3</sub>O<sub>6</sub>S [M + H]<sup>+</sup> 554.2319, *m/z* found 554.2341.

**N-{2-[(Benzylcarbamoyl)methyl]-1-[(3,4-dimethoxyphenyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl}butanamide (34e)**

To a solution of aniline **33** (30 mg, 0.063 mmol), butyric acid (6 mg, 6 μL, 0.063 mmol) and BOP (33 mg, 0.076 mmol) in anhydrous DCM (0.5 mL) was added diisopropylethylamine (24 mg, 33 μL, 0.189 mmol) and the reaction was stirred at RT overnight. The solution was applied directly to chromatography on silica (0-100% EtOAc/hexane) to give the desired amide as a yellow solid (28 mg, 82%). m.p. 101-103 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.28 (s, 1H), 7.75 (s, 1H), 7.17 - 7.33 (m, 3H), 7.06 (d, *J* = 6.88 Hz, 2H), 6.70 - 6.86 (m, 3H), 6.55 - 6.63 (m, 2H), 4.46 (dd, *J* = 8.38, 15.07 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.62 - 3.75 (m, 1H), 3.38 - 3.58 (m, 2H), 3.03 - 3.31 (m, 2H), 2.77 - 3.03 (m, 4H), 2.48 (dd, *J* = 4.52, 16.48 Hz, 1H), 2.39 (t, *J* = 7.39 Hz, 2H), 1.71 - 1.86 (m, 2H), 1.03 (t, *J* = 7.35 Hz, 3H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>32</sub>H<sub>40</sub>N<sub>3</sub>O<sub>5</sub> [M + H]<sup>+</sup> 546.2962, *m/z* found 546.2974.

**2-(4-Methoxy-3-nitrophenyl)-N-[2-(3-methoxy-4-nitrophenyl)ethyl]acetamide (35)**

To a solution of 4-hydroxy-3-nitrophenylacetic acid (1.97 g, 10 mmol), amine **28** (1.96 g, 10 mmol) and HBTU (4.17 g, 11 mmol) in dimethylformamide (50 mL) was added diisopropylethylamine (3.23 g, 4.4 mL, 25 mmol) and the reaction stirred at RT under N<sub>2</sub> overnight. It was diluted with EtOAc, washed with 2N HCl, NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was absorbed onto Celite and purified by chromatography on silica (0-100% EtOAc in hexane) to give the amide (2.35 g, 63%) as a dark orange oil. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.00 (s, 1H), 7.96 (d, *J* = 1.98 Hz, 1H), 7.78 (d, *J* = 8.29 Hz, 1H), 7.47 (dd, *J* = 2.12, 8.62 Hz, 1H), 6.88 (s, 1H), 6.78 (dd, *J* = 1.37, 8.34 Hz, 1H), 5.81 (br. s., 1H), 3.92 (s, 3H), 3.56 (d, *J* = 6.78 Hz, 2H), 3.49 (s, 2H), 2.83 - 2.92 (m, 2H).

To the phenol (2.35 g, 6.26 mmol) and potassium carbonate (1.30 g, 9.39 mmol) in dimethylformamide (30 mL) cooled in ice under N<sub>2</sub> was added iodomethane (1.07 g, 0.47 mL, 7.51 mmol) and the reaction stirred in ice for 1 hr, then additional aliquots of potassium carbonate (1.30 g) and iodomethane (0.47 mL) were added and the reaction heated at 60 °C for 1 hr. The reaction was cooled and diluted with EtOAc. It was washed with water and brine, dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure to give the desired amide (2.38 g, 98%) as a dark orange oil. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.76 (d, *J* = 8.29 Hz, 1H), 7.72 (d, *J* = 2.17 Hz, 1H), 7.38 (dd, *J* = 2.31, 8.71 Hz, 1H), 7.04 (d, *J* = 8.57 Hz, 1H), 6.86 (s, 1H), 6.77 (dd, *J* = 1.22, 8.29 Hz, 1H), 5.87 (br. s., 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.55 (q, *J* = 6.78 Hz, 2H), 3.48 (s, 2H), 2.87 (t, *J* = 6.88 Hz, 2H).

**N-{2-Methoxy-4-[2-(2-{4-methoxy-3-[(methoxycarbonyl)amino]phenyl}acetamido)ethyl]phenyl}carbamate (36)**

To the nitro derivative **35** (2.38 g, 6.11 mmol) in ethanol (60 mL) was added hydrazine monohydrate (3.06 g, 3.0 mL, 61.1 mmol) then Raney nickel (2800 type as a slurry in water, 0.48 g). The reaction was heated to 50 °C for 90 min, cooled then filtered through Celite,

rinsing thoroughly with ethanol. The solvent was removed under reduced pressure to give the aniline as a yellow oil which was used in the next step without further purification (1.98 g, 99%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 6.62 - 6.76 (m, 2H), 6.56 - 6.62 (m, 1H), 6.51 - 6.56 (m, 1H), 6.40 - 6.51 (m, 2H), 5.52 (br. s., 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.35 - 3.42 (m, 4H), 2.63 (t, *J* = 6.88 Hz, 2H).

To a mixture of the aniline (1.98 g, 6.01 mmol) and diisopropylethylamine (3.11 g, 4.2 mL, 24.04 mmol) in dichloromethane (30 mL) cooled in an ice bath under N<sub>2</sub> was added slowly methyl chloroformate (1.70 g, 1.4 mL, 18.03 mmol). The reaction was allowed to warm to RT overnight, then quenched with NaHCO<sub>3</sub> solution. The layers were separated, the aqueous extracted once with dichloromethane, then the combined extracts were dried over MgSO<sub>4</sub> and the solvents removed under reduced pressure. The crude was absorbed onto Celite and purified by chromatography on silica (0-3% methanol in dichloromethane) to give the bis-carbamate as a yellow oil (1.61 g, 60%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.79 - 7.95 (m, 1H), 7.14 (br. s., 1H), 6.78 (s, 2H), 6.50 - 6.62 (m, 2H), 5.42 (br. s., 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 3.38 - 3.52 (m, 4H), 2.67 (t, *J* = 6.83 Hz, 2H).

#### **Methyl N-[6-Methoxy-1-({4-methoxy-3-[(methoxycarbonyl)amino]phenyl)methyl}-1,2,3,4-tetrahydroisoquinolin-7-yl]carbamate (37)**

To amide **36** (1.61 g, 3.61 mmol) suspended in anhydrous toluene (20 mL) was added phosphorus oxychloride (2.77 g, 1.7 mL, 18.1 mmol) and the reaction heated to 90 °C for 2 hr. The reaction was cooled and poured carefully into water and stirred vigorously for 15 min. The layers were separated then the aqueous layer was adjusted to pH 8-9 with NaHCO<sub>3</sub> solution and extracted three times with dichloromethane. The combined extracts were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give a viscous orange oil.

The crude was dissolved in methanol (40 mL) and cooled in an ice bath under N<sub>2</sub>. Sodium borohydride (0.69 g, 18.1 mmol) was added portionwise and the reaction allowed to warm slowly to RT overnight. The reaction was quenched with water, the methanol was removed under reduced pressure and the aqueous solution was extracted three times with dichloromethane. The combined extracts were dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure to give the desired tetrahydroisoquinoline (1.41 g, 91%) as a frothy solid. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.00 (br. s., 1H), 7.20 (d, *J* = 15.16 Hz, 1H), 6.87 - 6.96 (m, 1H), 6.77 - 6.85 (m, 1H), 6.57 (s, 1H), 4.14 (dd, *J* = 3.20, 10.55 Hz, 1H), 3.69 - 3.92 (m, 13H), 3.15 - 3.32 (m, 2H), 2.67 - 2.98 (m, 4H).

#### **Methyl N-[2-[(Benzylcarbamoyl)methyl]-6-methoxy-1-({4-methoxy-3-[(methoxycarbonyl)amino]phenyl)methyl}-1,2,3,4-tetrahydroisoquinolin-7-yl]carbamate (38)**

To amine **37** (0.94 g, 2.19 mmol), N-benzyl bromoacetamide (0.75 g, 3.28 mmol) and tetrabutylammonium iodide (0.16 g, 0.44 mmol) in dimethylformamide (22 mL) was added diisopropylethylamine (0.71 g, 0.95 mL, 5.47 mmol) and the reaction stirred under N<sub>2</sub> at RT overnight. The reaction was diluted with EtOAc, washed with NaHCO<sub>3</sub> solution, water and brine, dried over MgSO<sub>4</sub> 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 (0.74 g, 59%) as a frothy orange solid. m.p. 88-90 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.99 (br. s., 1H), 7.88 (br. s., 1H), 7.12 - 7.32 (m, 5H), 6.92 - 7.06 (m, 3H), 6.81 - 6.91 (m, 1H), 6.50 - 6.67 (m, 2H), 4.27 - 4.46 (m, 1H), 3.58 - 3.91 (m, 14H), 3.41 - 3.55 (m, 1H), 3.19 - 3.35 (m, 1H), 2.76 - 3.13 (m, 5H), 2.38 - 2.55 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>31</sub>H<sub>37</sub>N<sub>4</sub>O<sub>7</sub> [M + H]<sup>+</sup> 577.2657, *m/z* found 577.2668.

#### **N-Benzyl-2-[7-(dimethylamino)-1-[[3-(dimethylamino)-4-methoxyphenyl]methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (39)**

To a solution of carbamate **38** (0.73 g, 1.26 mmol) in methanol (15 mL) was added sodium hydroxide solution (2N, 8 mL, 16 mmol) and the cloudy reaction heated to 50 °C overnight. The reaction was cooled, the methanol was removed under reduced pressure and the reaction was diluted with water. It was extracted three times with EtOAc then the combined extracts were dried over MgSO<sub>4</sub> 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 amine as a light yellow oil (0.47 g, 81%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.34 (m, 4H), 7.06 - 7.12 (m, 2H), 6.95 - 7.04 (m, 1H), 6.56 (dd, *J* = 1.74, 6.55 Hz, 2H), 6.50 (s, 1H), 6.45 (s, 1H), 4.48 (dd, *J* = 8.29, 15.16 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.34 - 3.61 (m, 3H), 3.05 - 3.31 (m, 2H), 2.74 - 2.99 (m, 4H), 2.37 - 2.50 (m, 1H).

To a solution of the intermediate amine (50 mg, 0.11 mmol) and formaldehyde (37% aqueous, 81 μL, 1.09 mmol) in 1,2-dichloroethane (1 mL) was added portionwise sodium triacetoxyborohydride (230 mg, 1.09 mmol) and the reaction stirred at RT overnight. The reaction was diluted with EtOAc, washed with NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-5% methanol in dichloromethane) to give the desired product as a yellow solid (33 mg, 58%). m.p. 127-129 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.18 - 7.34 (m, 3H), 7.03 - 7.15 (m, 3H), 6.70 - 6.79 (m, 2H), 6.58 - 6.64 (m, 1H), 6.55 (s, 1H), 6.50 (s, 1H), 4.48 (dd, *J* = 7.91, 15.07 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.61 - 3.72 (m, 2H), 3.35 - 3.50 (m, 1H), 3.13 - 3.34 (m, 2H), 2.79 - 3.00 (m, 4H), 2.75 (s, 6H), 2.73 (s, 6H), 2.44 - 2.57 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>31</sub>H<sub>41</sub>N<sub>4</sub>O<sub>3</sub> [M + H]<sup>+</sup> 517.3173, *m/z* found 517.3178.

#### **N-[2-(3-Methoxy-4-nitrophenyl)ethyl]-2-(3-nitrophenyl)acetamide (40)**

To a solution of 3-nitrophenylacetic acid (0.25 g, 1.38 mmol), amine **28** (0.27 g, 1.38 mmol) and BOP (0.67 g, 1.52 mmol) in dimethylformamide (7 mL) was added diisopropylethylamine (0.45 g, 0.6 mL, 3.45 mmol) and the reaction stirred at RT under N<sub>2</sub> overnight. It was diluted with EtOAc, washed with 2N HCl, NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude was purified by chromatography on silica (0-100% EtOAc in hexane) to give the amide as an orange solid (0.28 g, 56%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.06 - 8.18 (m, 2H), 7.78 (s, 1H), 7.56 - 7.64 (m, 1H), 7.47 - 7.54 (m, 1H), 6.87 (d, *J* = 1.32 Hz, 1H), 6.78 (dd, *J* = 1.51, 8.29 Hz, 1H), 5.73 (br. s., 1H), 3.91 (s, 3H), 3.61 (s, 2H), 3.52 - 3.59 (m, 2H), 2.83 - 2.92 (m, 2H).

**N-{2-[4-(Dimethylamino)-3-methoxyphenyl]ethyl}-2-[3-(dimethylamino)phenyl]acetamide (41)**

To amide **40** (0.28 g, 0.78 mmol) in ethanol (10 mL) was added hydrazine monohydrate (0.39 g, 0.38 mL, 7.79 mmol) then Raney nickel (2800 type as a slurry in water, 56 mg). The reaction was heated to 50 °C for 60 min, cooled then filtered through Celite, rinsing thoroughly with ethanol. The solvent was removed under reduced pressure to give the aniline as a light yellow oil which was used in the next step without further purification (0.21 g, 91%). <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.00 - 7.14 (m, 1H), 6.33 - 6.74 (m, 6H), 5.55 (br. s., 1H), 3.79 (s, 3H), 3.31 - 3.48 (m, 4H), 2.55 - 2.70 (m, 2H).

The aniline intermediate was converted to **41**, using the method for **39**. Orange oil. Yield 68%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.17 (t, *J* = 7.86 Hz, 1H), 6.78 (d, *J* = 7.91 Hz, 1H), 6.47 - 6.68 (m, 5H), 5.58 (br. s., 1H), 3.82 (s, 3H), 3.50 (s, 2H), 3.43 (q, *J* = 6.72 Hz, 2H), 2.93 (s, 6H), 2.75 (s, 6H), 2.67 (t, *J* = 6.92 Hz, 2H).

**N-Benzyl-2-[7-(dimethylamino)-1-[[3-(dimethylamino)phenyl]methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]acetamide (42)**

This was prepared from **41** using the procedures described for **37** and **38** to give **42** as a white solid in 4% overall yield. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 7.16 - 7.38 (m, 4H), 7.00 - 7.15 (m, 3H), 6.47 - 6.65 (m, 5H), 4.38 - 4.54 (m, 1H), 3.80 - 3.89 (m, 3H), 3.38 - 3.73 (m, 3H), 3.07 - 3.33 (m, 2H), 2.87 (s, 6H), 2.78 - 3.00 (m, 3H), 2.74 (s, 6H), 2.68 (dd, *J* = 3.81, 10.60 Hz, 1H), 2.41 - 2.55 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>30</sub>H<sub>39</sub>N<sub>4</sub>O<sub>2</sub> [M + H]<sup>+</sup> 487.3068, *m/z* found 487.3092.

**Methyl N-[6-methoxy-1-({4-methoxy-3-[(methoxycarbonyl)amino]phenyl)methyl}-2-[[pyridin-3-ylmethyl]carbamoyl]methyl)-1,2,3,4-tetrahydroisoquinolin-7-yl]carbamate (43)**

This was prepared using the methods for **13a** and **14a** starting from **37**. Yellow oil. Yield 39%. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.36 - 8.55 (m, 2H), 7.91 (br. s., 1H), 7.01 - 7.23 (m, 4H), 6.85 - 6.97 (m, 1H), 6.63 - 6.73 (m, 1H), 6.59 (d, *J* = 4.52 Hz, 2H), 6.56 (s, 1H), 4.05 - 4.36 (m, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.64 - 3.72 (m, 1H), 3.23 - 3.38 (m, 2H), 2.74 - 3.18 (m, 4H), 2.42 - 2.64 (m, 1H).

**2-[7-(Dimethylamino)-1-[[3-(dimethylamino)-4-methoxyphenyl]methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]-N-(pyridin-3-ylmethyl)acetamide (44)**

This was prepared by the method used for **39** using **43**. Yellow solid. Yield 35%. m.p. 68-70 °C. <sup>1</sup>H NMR (300 MHz, CHLOROFORM-d) δ 8.48 (dd, *J* = 1.51, 4.71 Hz, 1H), 8.32 (d, *J* = 1.70 Hz, 1H), 7.40 - 7.47 (m, 1H), 7.21 (dd, *J* = 4.90, 7.35 Hz, 1H), 6.97 - 7.05 (m, 1H), 6.77 - 6.81 (m, 2H), 6.65 (d, *J* = 8.67 Hz, 1H), 6.57 (d, *J* = 1.88 Hz, 2H), 4.39 (dd, *J* = 7.91, 15.26 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.55 - 3.64 (m, 2H), 3.40 - 3.53 (m, 1H), 3.12 - 3.32 (m, 2H), 2.81 - 2.99 (m, 4H), 2.77 (s, 6H), 2.76 (s, 6H), 2.45 - 2.56 (m, 1H). HRMS (ESI, CH<sub>3</sub>OH) *m/z* calcd for C<sub>30</sub>H<sub>40</sub>N<sub>5</sub>O<sub>3</sub> [M + H]<sup>+</sup> 518.3126, *m/z* found 518.3141.

## Calcium Mobilization $K_e$ Assays

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 wall/clear bottom 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  $\mu\text{g}/\text{mL}$  normocin<sup>TM</sup>. The cells were incubated overnight at 37°C, 5%  $\text{CO}_2$ . 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  $\mu\text{L}$  of pre-warmed (37°C) assay buffer. The cells were incubated for 45 minutes at 37°C, 5%  $\text{CO}_2$  in 200  $\mu\text{L}$  of the diluted Calcium 5 dye. A single concentration of each test compound was prepared at 10 $\times$  the desired final concentration in 2.5% BSA/8% DMSO/assay buffer. Serial dilutions of orexin A were prepared at 10 $\times$  the desired final concentration in 0.25% BSA/1% DMSO/assay buffer, aliquoted into 96-well polypropylene plates, and warmed to 37°C for 15 min. After the dye-loading incubation period, the cells were pre-treated with 25  $\mu\text{L}$  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  $\mu\text{L}$  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  $\text{EC}_{50}$  values (GraphPad Prism, GraphPad Software, Inc., San Diego, CA). Apparent  $K_e$  values were calculated using the equation  $K_e = [L]/((\text{EC}_{50}^+/\text{EC}_{50}^-) - 1)$  where  $[L]$  is the concentration of test compound,  $\text{EC}_{50}^+$  is the  $\text{EC}_{50}$  of orexin A with test compound, and  $\text{EC}_{50}^-$  is the  $\text{EC}_{50}$  of orexin A alone.  $K_e$  values were considered valid when the  $\text{EC}_{50}^+/\text{EC}_{50}^-$  ratio was at least 4.

## Kinetic Solubility

The kinetic solubility of test compounds was measured in commercial PBS, pH 7.4 consisting of potassium phosphate monobasic 1 mM, sodium phosphate dibasic 3 mM and sodium chloride 155 mM.

A 10  $\mu\text{L}$  of test compound stock solution (10 mM DMSO) was combined with 490  $\mu\text{L}$  of PBS buffer. The solution was agitated on a VX-2500 multi-tube vortexer (VWR) for 2 hours at room temperature. Following agitation, the sample was filtrated on a glass-fiber filter (1  $\mu\text{m}$ ) and the eluate was diluted 200-fold with a mixture of acetonitrile: water (1:1). On each experimental occasion, nifedipine and imipramine were assessed as reference compounds for low and high solubility, respectively. All samples were assessed in triplicate and analyzed by LC-MS/MS using electrospray ionization against standards prepared in the same matrix.

## BBB Permeability

MCK-mdr1 cells at passage 5 were seeded onto permeable polycarbonate supports in 12-well Costar Transwell plates and allowed to grow and differentiate for 3 days. On day 3, culture medium (DMEM supplemented with 10% FBS) was removed from both sides of the transwell inserts and cells were rinsed with warm HBSS. After the rinse step, the chambers were filled with warm transport buffer (HBSS containing 10 mM HEPES, 0.25% BSA, pH 7.4) and the plates were incubated at 37 °C for 30 min prior to TEER (Trans Epithelial Electric Resistance) measurements.

The buffer in the donor chamber (apical side for A-to-B assay, basolateral side for B-to-A assay) was removed and replaced with the working solution (10 μM test article in transport buffer). The plates were then placed at 37 °C under light agitation. At designated time points (30, 60 and 90 min), an aliquot of transport buffer from the receiver chamber was removed and replenished with fresh transport buffer. Samples were quenched with ice-cold ACN containing internal standard and then centrifuged to pellet protein. Resulting supernatants are further diluted with 50/50 ACN/H<sub>2</sub>O (H<sub>2</sub>O only for Atenolol) and submitted for LC-MS/MS analysis. Reported apparent permeability ( $P_{app}$ ) values were calculated from single determination. Atenolol and propranolol were tested as low and moderate permeability references. Bidirectional transport of digoxin was assessed to demonstrate Pgp activity/expression.

The apparent permeability ( $P_{app}$ , measured in cm/s) of a compound is determined according to the following formula:

$$P_{app} = \frac{(dQ)/(dt)}{A \times C_i \times 60}$$

where  $dQ/dt$  is the net rate of appearance in the receiver compartment, A is the area of the Transwell measured in cm<sup>2</sup> (1.12 cm<sup>2</sup>),  $C_i$  is the initial concentration of compound added to the donor chamber and 60 is the conversion factor for minute to second.

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## ABBREVIATIONS

<b>BOP</b>	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
<b>HATU</b>	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
<b>HBTU</b>	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
<b>HPLC</b>	high performance liquid chromatography

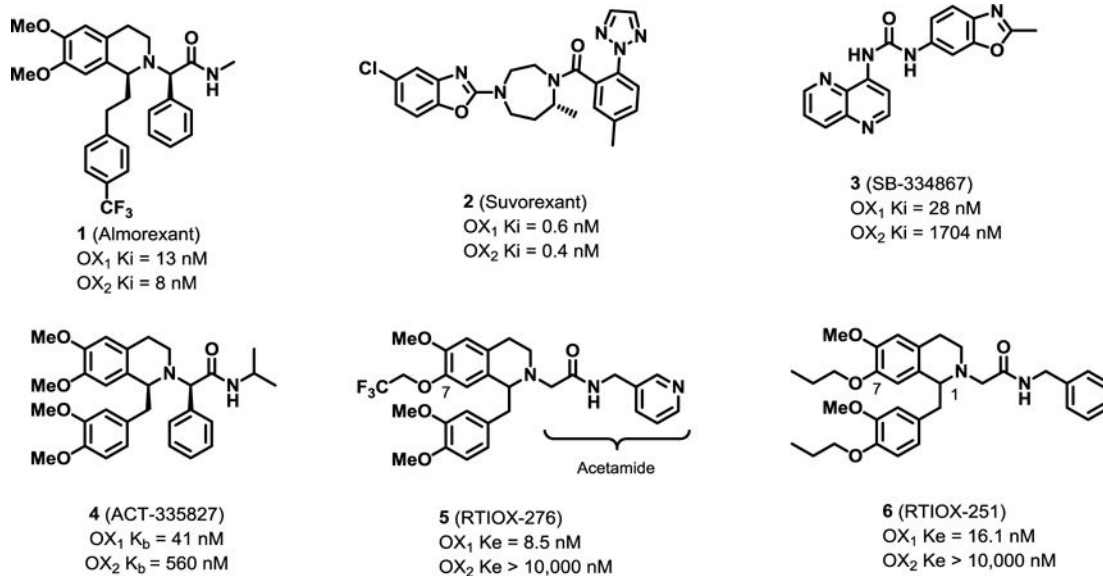
<b>OX<sub>1</sub></b>	orexin-1 receptor
<b>OX<sub>2</sub></b>	orexin-2 receptor
<b>SAR</b>	structure-activity relationship
<b>TLC</b>	thin layer chromatography
<b>m.p</b>	melting point
<b>MDCK</b>	Madin-Darby Canine Kidney
<b>ADME</b>	absorption, distribution, metabolism, and excretion

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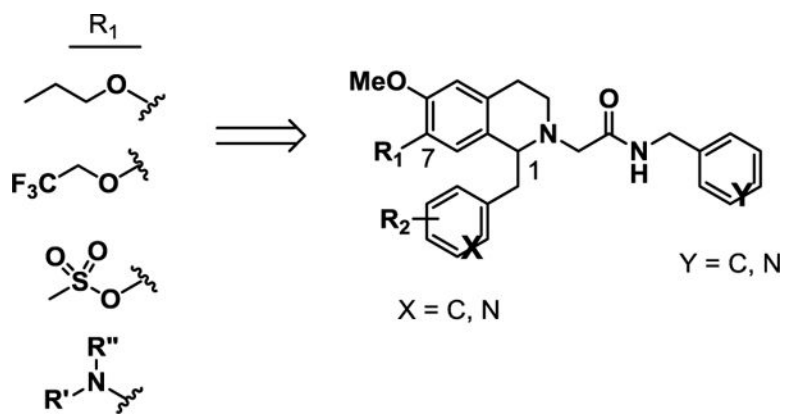
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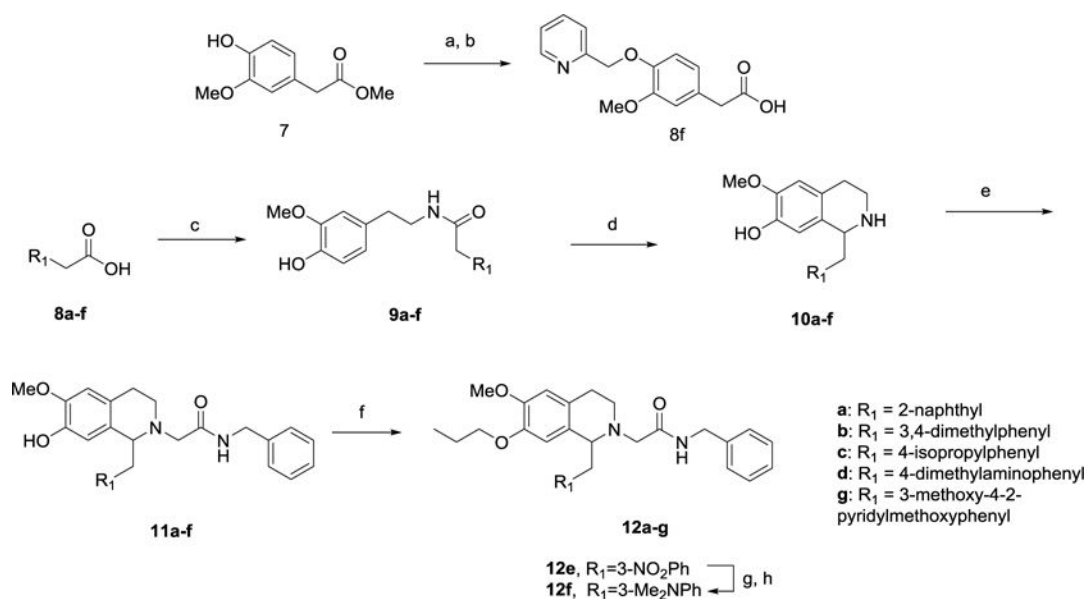


**Figure 1.**  
 Representative Orexin antagonists



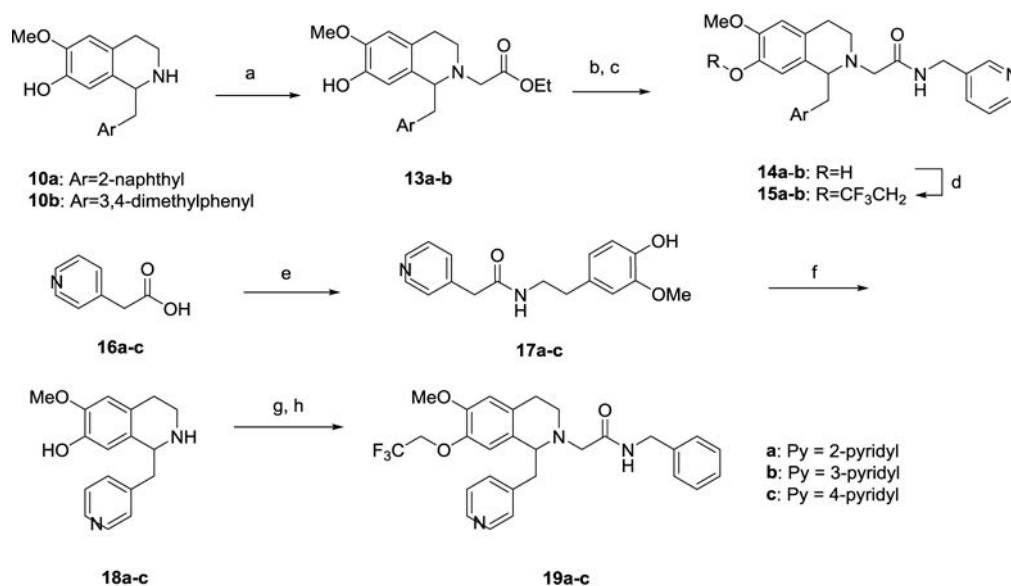


**Figure 2.**  
Structural modifications at the 7-, 1-, and acetamide positions

**Scheme 1.**

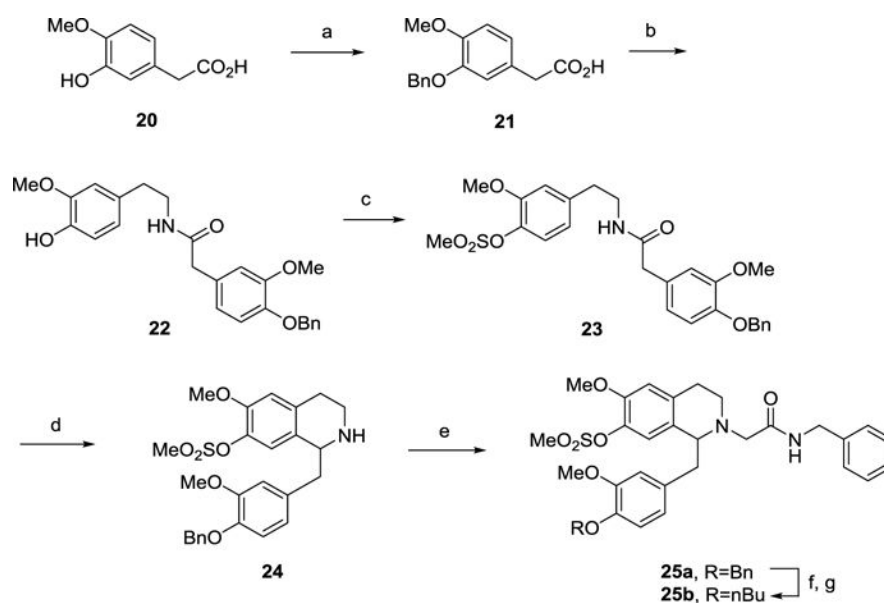
Synthesis of 7-propoxy-6-methoxy THIQ derivatives **12a-g**.<sup>a</sup>

<sup>a</sup>Reagents and Conditions: (a) 2-(bromomethyl)pyridine hydrobromide,  $\text{K}_2\text{CO}_3$ ,  $\text{Bu}_4\text{NI}$ , DMF, rt, 16 h; (b) 2N NaOH (aq), EtOH, rt, 16 h; (c) 4-Hydroxy-3-methoxyphenylethylamine, HBTU,  $i\text{Pr}_2\text{EtN}$ , DMF, rt, 16 h; (d) (i)  $\text{POCl}_3$ , toluene,  $90^\circ\text{C}$ , 2 h; (ii)  $\text{NaBH}_4$ , MeOH, rt, 16 h; (e)  $\text{BrCH}_2\text{CONHCH}_2\text{Ph}$ ,  $i\text{Pr}_2\text{EtN}$ ,  $\text{Bu}_4\text{NI}$ , DMF, rt, 16 h; (f) 1-iodopropane,  $\text{K}_2\text{CO}_3$ , DMF, rt, 16 h; (g) Raney Ni,  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ , EtOH,  $50^\circ\text{C}$ , 1 h; (h) HCHO,  $\text{NaBH}(\text{OAc})_3$ , 1,2-DCE, rt, 16 h.

**Scheme 2.**

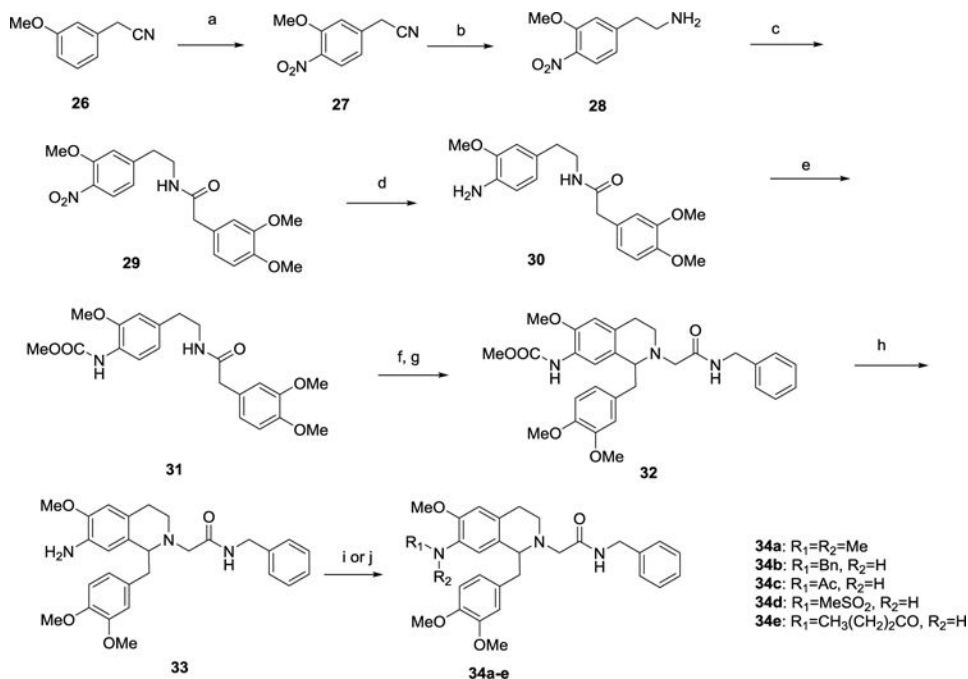
Synthesis of 7-trifluoroethoxy substituted THIQ derivatives **19a-c**.<sup>a</sup>

<sup>a</sup>Reagents and Conditions: (a) BrCH<sub>2</sub>CO<sub>2</sub>Et, iPr<sub>2</sub>EtN, Bu<sub>4</sub>NI, DMF, rt, 16 h; (b) 2N NaOH (aq), EtOH, rt, 16 h; (c) 3-aminomethylpyridine, HATU, iPr<sub>2</sub>EtN, DMF, rt, 16 h; (d) CF<sub>3</sub>CH<sub>2</sub>I, Cs<sub>2</sub>CO<sub>3</sub>, DMF, 100 °C, 2 h; (e) 4-Hydroxy-3-methoxyphenylethylamine, HBTU, iPr<sub>2</sub>EtN, DMF or DCC, HOBt, Et<sub>3</sub>N, THF, rt, 16 h; (f) (i) POCl<sub>3</sub>, CH<sub>3</sub>CN, reflux, 1 h; (ii) NaBH<sub>4</sub>, MeOH, 0 °C to rt, 16 h; (g) BrCH<sub>2</sub>CONHCH<sub>2</sub>Ph, iPr<sub>2</sub>EtN, Bu<sub>4</sub>NI, DMF, rt, 16 h; (h) CF<sub>3</sub>CH<sub>2</sub>I, Cs<sub>2</sub>CO<sub>3</sub>, DMF, 100 °C, 2 h.

**Scheme 3.**

Synthesis of 7-sulfonate substituted THIQ derivatives **25a-b**.<sup>a</sup>

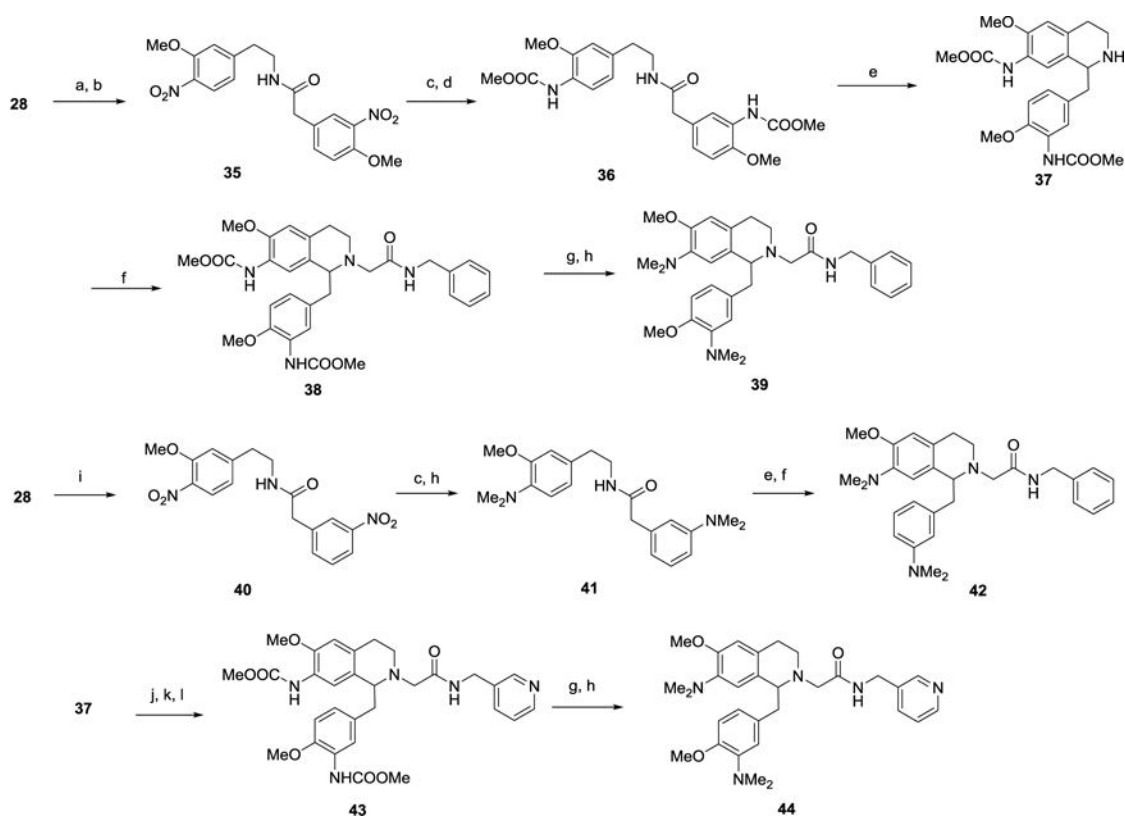
<sup>a</sup>Reagents and Conditions: (a) Na, BnBr, MeOH, reflux, 5 h; (b) 4-Hydroxy-3-methoxyphenylethylamine, HBTU, *i*Pr<sub>2</sub>EtN, DMF, rt, 16 h; (c) MeSO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 4 h; (d) (i) POCl<sub>3</sub>, toluene, 90 °C, 2 h; (ii) NaBH<sub>4</sub>, MeOH, rt, 16 h; (e) BrCH<sub>2</sub>CONHCH<sub>2</sub>Ph, *i*Pr<sub>2</sub>EtN, Bu<sub>4</sub>NI, DMF, rt, 16 h; (f) conc. HCl, MeOH, reflux, 16 h; (g) 1-bromobutane, K<sub>2</sub>CO<sub>3</sub>, Bu<sub>4</sub>NI, DMF, 50 °C, 16 h.



#### Scheme 4.

Synthesis of 7-dimethylamino substituted THIQ derivatives **34a-e**.<sup>a</sup>

<sup>a</sup>Reagents and Conditions: (a) Bu<sub>4</sub>NNO<sub>3</sub>, (CF<sub>3</sub>CO)<sub>2</sub>O, 18-crown-6, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 30 min; (b) BH<sub>3</sub>-THF, THF, 70 °C, 2 h; (c) 3,4-dimethoxyphenylacetic acid, HBTU, iPr<sub>2</sub>EtN, DMF, rt, 16 h; (d) Raney Ni, NH<sub>2</sub>NH<sub>2</sub>-H<sub>2</sub>O, EtOH, 50 °C, 1 h; (e) MeOCOCl, iPr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; (f) (i) POCl<sub>3</sub>, toluene, 90 °C, 2 h; (ii) NaBH<sub>4</sub>, MeOH, rt, 16 h; (g) BrCH<sub>2</sub>CONHCH<sub>2</sub>Ph, iPr<sub>2</sub>EtN, Bu<sub>4</sub>NI, DMF, rt, 16 h; (h) 2N NaOH, MeOH, 50 °C, 48 h; (i) **34a**: HCHO, NaBH(OAc)<sub>3</sub>, 1,2-DCE, rt, 16 h; **34b**: PhCHO, NaHCO<sub>3</sub>, MeOH, 40 °C, 1h, then NaBH<sub>4</sub>, rt, 16 h; (j) **34c**: Ac<sub>2</sub>O, iPr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; **34d**: MeSO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 16 h; then 3N NaOH, 80 °C, 16 h; **34e**: CH<sub>3</sub>(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H, BOP, iPr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h.

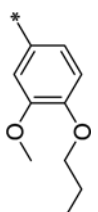

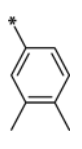
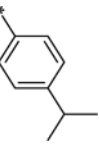
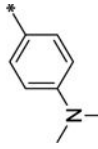
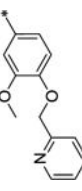
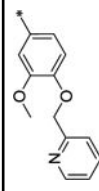
**Scheme 5.**

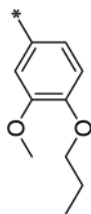
Synthesis of 7-dimethylamino substituted THIQ derivatives **39**, **42** and **44**.<sup>a</sup>

<sup>a</sup>Reagents and Conditions: (a) 4-hydroxy-3-nitrophenylacetic acid, HBTU, *i*Pr<sub>2</sub>EtN, DMF, rt, 16 h; (b) Me-I, K<sub>2</sub>CO<sub>3</sub>, DMF, 0-60 °C, 2 h; (c) Raney Ni, NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, EtOH, 50 °C, 90 min; (d) MeOCOC<sub>2</sub>Cl, *i*Pr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; (e) (i) POCl<sub>3</sub>, toluene, 90 °C, 2 h; (ii) NaBH<sub>4</sub>, MeOH, rt, 16 h; (f) BrCH<sub>2</sub>CONHCH<sub>2</sub>Ph, *i*Pr<sub>2</sub>EtN, Bu<sub>4</sub>NI, DMF, rt, 16 h; (g) 2N NaOH (aq), MeOH, 50 °C, 16 hr; (h) HCHO, NaBH(OAc)<sub>3</sub>, 1,2-DCE, rt, 16 h; (i) 3-nitrophenylacetic acid, HBTU, *i*Pr<sub>2</sub>EtN, DMF, rt, 16 h; (j) BrCH<sub>2</sub>CO<sub>2</sub>Et, *i*Pr<sub>2</sub>EtN, Bu<sub>4</sub>NI, DMF, rt, 16 h; (k) 2N NaOH, EtOH, rt, 16 h; (l) 3-aminomethylpyridine, HATU, *i*Pr<sub>2</sub>EtN, DMF, rt, 16 h.

Table 1

The effect of changes at the 7-position on OX antagonism incorporating the most active 1-position analogs

No.	R <sub>1</sub>	R <sub>2</sub>	Ar	Ke (OX <sub>1</sub> , nM) <sup>b</sup>	Ke (OX <sub>2</sub> , nM) <sup>c</sup>	OX <sub>2</sub> /OX <sub>1</sub>	clogP
6	Pr		Ph	16.1 ± 3.6	>10,000	>621	6.86
12a	Pr		Ph	121 ± 35	a	>82.6	7.29
12b	Pr		Ph	28.8 ± 4.4	a	>347	6.98
12c	Pr		Ph	141 ± 42	a	>70.9	7.40
12d	Pr		Ph	173 ± 5	>10,000	>58	6.17
12f	Pr		Ph	20.6 ± 2.8	a	>485	6.17
12g	Pr		Ph	96.4 ± 34	>10,000	>104	5.96



No.	R <sub>1</sub>	R <sub>2</sub>	Ar	K <sub>e</sub> (OX <sub>1</sub> , nM) <sup>b</sup>	K <sub>e</sub> (OX <sub>2</sub> , nM) <sup>c</sup>	OX <sub>2</sub> /OX <sub>1</sub>	clogP
<b>15a</b>	CF <sub>3</sub> CH <sub>2</sub>		3-Py	29.5 ± 2.2	1750 ± 230	59	5.70
<b>15b</b>	CF <sub>3</sub> CH <sub>2</sub>		3-Py	20.4 ± 2.9	1360 ± 150	67	5.39
<b>19a</b>	CF <sub>3</sub> CH <sub>2</sub>		Ph	884 ± 70 <sup>d</sup>	a	>11	4.47
<b>19b</b>	CF <sub>3</sub> CH <sub>2</sub>		Ph	>10,000 <sup>d</sup>	a	0	4.47
<b>19c</b>	CF <sub>3</sub> CH <sub>2</sub>		Ph	1,860 ± 140 <sup>d</sup>	a	>5.4	4.47
<b>25a</b>	MeSO <sub>2</sub>		Ph	43.0 ± 18	a	>232	5.25
<b>25b</b>	MeSO <sub>2</sub>		Ph	5.24 ± 1.0	1,200 ± 360	229	5.19

<sup>a</sup> < 50% inhibition at 10 μM final concentration;

<sup>b</sup> Values are the mean of at least three independent experiments in duplicate;

<sup>c</sup> Values are the mean of at least two independent experiments in duplicate; for compounds with K<sub>e</sub> < 100 nM at OX<sub>1</sub> at least three independent experiments in duplicate were performed.

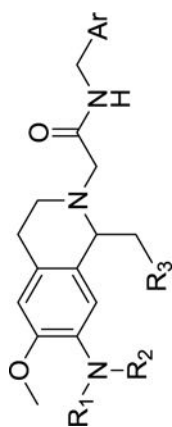
<sup>d</sup> Compound appeared insurmountable during standard assay procedure, so incubation was increased to 1 hour.



Table 2

7-Amino tetrahydroisoquinoline derivatives incorporating modifications at the 1-benzyl position.

No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Ar	Ke (OX <sub>1</sub> , nM) <sup>b</sup>	Ke (OX <sub>2</sub> , nM) <sup>c</sup>	OX <sub>2</sub> /OX <sub>1</sub>	clogP
33	H	H		Ph	494 ± 32	>10,000	>20	3.87
34a	Me	Me		Ph	31.2 ± 3.3	>10,000	>321	4.92
34b	Bn	H		Ph	352 ± 34	a	>28	6.13
34c	Ac	H		Ph	116 ± 44	>10,000	>86	3.76
34d	MeSO <sub>2</sub>	H		Ph	128 ± 13	>10,000	>78	3.63
34e	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> CO	H		Ph	689 ± 73	>10,000	>14.5	4.82
38	MeOCO	H		Ph	>10,000	592 ± 170	0.1	4.39



No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Ar	K <sub>e</sub> (OX <sub>1</sub> , nM) <sup>b</sup>	K <sub>e</sub> (OX <sub>2</sub> , nM) <sup>c</sup>	OX <sub>2</sub> /OX <sub>1</sub>	clogP
39	Me	Me		Ph	7.60 ± 2.8	857 ± 220	113	5.11
42	Me	Me		Ph	148 ± 36	1,360 ± 84	9.1	5.30
44	Me	Me		3-Py	5.7 ± 1.0	>10,000	>1,760	3.07

<sup>a</sup> < 35% inhibition at 10 μM final concentration;

<sup>b</sup> Values are the mean of at least three independent experiments in duplicate;

<sup>c</sup> Values are the mean of at least two independent experiments in duplicate; for compounds with K<sub>e</sub> < 100 nM at OX<sub>1</sub> at least three independent experiments in duplicate were performed.

**Table 3**Physicochemical and Preliminary ADME Properties of Compounds **6** and **44**

	<b>Desired value</b>	<b>5</b>	<b>44</b>
MW	< 500	559.6	517.7
ClogP	1 - 4	4.21	3.07
PSA	< 70	82.1	70.2
pKa	< 8	14.1, 5.4	14.2, 6.3
HBD	< 3	1	1
HBA	< 7	7	7
Solubility ( $\mu\text{M}$ )	> 60	$77.8 \pm 4.1$	> 200
$P_{\text{app}}$ ( $10^{-6}$ cm/sec) A-to-B	> 2	12.2	14.7
$P_{\text{app}}$ ( $10^{-6}$ cm/sec) B-to-A		36.2	47.8
Efflux ratio	< 2.5	3.0	3.3

HBD: H-bond donor; HBA: H-bond acceptor.

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