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Synthesis and Structure Activity Relationship of Tetrahydroisoquinoline-based Potentiators of GluN2C and GluN2D Containing N-Methyl-D-Aspartate Receptors

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Abstract

We describe here the synthesis and evaluation of a series of tetrahydroisoquinolines that show subunit-selective potentiation of NMDA receptors containing the GluN2C or GluN2D subunits. Bischler-Napieralski conditions were employed in the key step for the conversion of acyclic amides to the corresponding tetrahydroisoquinoline containing analogs. Compounds were evaluated using both two electrode voltage clamp recordings from *Xenopus laevis* oocytes and imaging of mammalian BHK cells loaded with Ca^{2+} -sensitive dyes. The most potent analogues had EC_{50} values of 300 nM and showed over 2-fold potentiation of the response to maximally effective concentrations of glutamate and glycine, but had no effect on responses from NMDA receptors containing the GluN2A or GluN2B subunits, AMPA, kainate, GABA, or glycine receptors or a variety of other potential targets. These compounds represent a potent class of small molecule subunit-selective potentiators of NMDA receptors.

Introduction

The ionotropic family of glutamate receptors comprises N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptor subtypes, subdivided on the basis of amino acid sequence homology, structure homology, and pharmacology. The NMDA receptor mediates a slow, Ca^{2+} -permeable component of excitatory synaptic transmission in the central nervous system, and plays a prominent role in normal brain processes such as learning, memory, synaptic plasticity, and neuronal development.¹⁻⁸ In addition, dysfunction of NMDA receptors, either overactivation or hypofunction, has been implicated as a contributing factor to a wide range of neurological disorders including schizophrenia⁹⁻¹¹, Alzheimer's disease¹², Parkinson's disease¹³, Huntington's chorea¹⁴, depression^{15, 16}, epilepsy⁶, neuropathic pain¹⁷, and acute brain injury following ischemia¹⁸⁻²⁰, hypoxia or trauma.^{8, 21}

NMDA receptors are ligand-gated cation channels that are tetramers of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits. There are four different GluN2 subunits (GluN2A-D), each of which endows the receptor with unique open probability, single channel conductance, and deactivation time course.^{22, 23} For example, GluN2C- and GluN2D-containing NMDA receptors have a lower open probability,²⁴⁻²⁶ decreased

sensitivity to block by Mg^{2+} ,²⁷ and can be activated by lower concentrations of glycine and glutamate than GluN2A- and GluN2B-containing receptors.^{28, 29} The four different subunits are differentially expressed throughout the brain, with particularly prominent GluN2C and GluN2D expression in the cerebellum, basal ganglia, and cortical and hippocampal interneurons.³⁰⁻³² The distinct localized expression and the unique functional properties of each of the four subunits, along with the potential involvement of NMDA receptors in disease states and injuries, creates a compelling rationale for development of subunit-selective modulators with potential use in a variety of neuropathological conditions. Compounds that increase the strength of glutamatergic synapses have been hypothesized to be therapeutically useful in treating schizophrenia.³³⁻³⁵ For examples, agonists at the GluN1 subunit, e.g. glycine and D-serine, have received attention as potential therapies for schizophrenia³⁶; however, these molecules will increase the activity of all NMDA receptor subtypes to a similar degree and have activity at other cell-surface receptors expressed in the CNS.³⁷ By contrast, small molecules directly potentiating the NMDA receptor at regions other than the agonist binding site might exhibit advantageous subunit-selectivity and be more selective for the NMDA receptor over other receptors.³⁸ Moreover the GluN2C and GluN2D subunits are particularly interesting targets in this context because they are expressed on hippocampal and cortical interneurons,²⁷ whose hypofunction is thought to cause disinhibition of pyramidal cells leading to excessive drive of the dopaminergic system.^{35, 39, 40}

Each NMDA receptor subunit contains four semi-autonomous domains: an extracellular amino-terminal domain (ATD), an extracellular ligand binding domain (LBD), a transmembrane domain that contributes to the ion conduction pore, and an intracellular carboxy-terminus. The binding sites for at least six classes of antagonists of the NMDA receptor are known. Voltage-dependent channel blockers, typically rigid organic cations such as phencyclidine (PCP), bind deep within the ion conduction pore in a voltage-dependent fashion.⁴¹⁻⁴³ Two additional classes of NMDA receptor antagonists include competitive antagonists that bind with high affinity to either the glycine site on the GluN1 subunit or the glutamate site on the GluN2 subunit.⁴⁴⁻⁴⁷ A fourth class of non-competitive antagonists, which includes quinazoline-4-ones and dihydroquinoline-pyrazolines, act at the membrane-proximal portion of the ligand binding domain and are more potent after glutamate but not glycine binding.⁴⁸⁻⁵⁰ A fifth class of NMDA receptor antagonists binds to the weakly conserved ATD, and is highly selective for the GluN2B subunit.⁵¹ Antagonists in this class, which include ifenprodil and a wide range of related structures, show well over 200-fold

selectivity for GluN2B over GluN2A, GluN2C and GluN2D. Finally, a sixth class of antagonists selectively inhibits GluN2A-containing receptors through actions at the dimer interface between the GluN1 and GluN2 ligand binding domains. These compounds, typified by TCN201, are allosteric regulators of glycine binding.^{52, 53} In addition to these six classes, several phenanthroic acid and naphthoic acid analogues are noncompetitive antagonists that act outside the ATD.^{54, 55}

In contrast to NMDA receptor antagonists, relatively few compounds have been shown to potentiate NMDA receptor function. Polyamines (e.g. spermine)⁵⁶⁻⁵⁸, aminoglycosides⁵⁹, and sulfated neurosteroids⁶⁰ can enhance the function of GluN2B-containing NMDA receptors with EC₅₀ values in range of 40-130 μ M. Phenanthroic acid and naphthoic acid derivatives increase the current response of GluN2A- and GluN2B-containing receptors at concentrations around 100 μ M.^{61, 62} In addition, D-cycloserine binds the GluN1 subunit and is a partial agonist at GluN2A, GluN2B, or GluN2D receptors, but can activate GluN2C-containing receptors to a greater extent than glycine.^{63, 64} Thus, the few potentiators that are known show strong GluN2 subunit dependence, suggesting potentiation of NMDA receptors is mediated by less conserved portions of the receptor.

To identify small drug-like subunit-selective modulators of NMDA receptors, we previously employed a reverse chemical genetics approach utilizing a fluorescence Ca²⁺ imaging-based screen of a diversity library containing 100,000 compounds on BHK cell lines expressing GluN1/GluN2C or GluN1/GluN2D receptors.^{65, 66} We identified an NMDA receptor potentiator with micromolar potency that selectively enhanced the function of both GluN2C- and GluN2D-containing NMDA receptors, but was without action on GluN2A- and GluN2B-containing receptors. This compound, (6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(*1H*)-yl)(phenyl)methanone), had a tetrahydroisoquinoline backbone (**1**). Compound **1** enhanced the response of GluN2C/D-containing NMDA receptors by 1.5-fold in the presence of maximally effective concentrations of co-agonists glutamate and glycine with an EC₅₀ value estimated to be 12 μ M, but the solubility limit prevented accurate determination of the maximal effect. Compound **1** and related analogues had no agonist activity on their own. We recently described the mechanism and site of action of a related compound, 3-chlorophenyl(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(*1H*)-yl)methanone (**2**, also referred to as CIQ), which had a reported EC₅₀ value of 3 μ M and enhanced receptor responses less than 2-fold.⁶⁶

In this study, we report synthetic efforts towards the optimization of substituents on the core structure of **2** that have led to the development of a structure-activity relationship (SAR) for this class of compounds.⁶⁷ The active compounds in this class selectively potentiated current response from GluN2C- and GluN2D-containing receptors. While the core backbone of these compounds is similar to that of the previously identified GluN2B-selective antagonist, HON0001 (**3**, Figure 1)⁶⁸, none of the compounds studied here inhibit GluN2B at relevant concentrations. Moreover, this class of compounds did not affect responses from GluN2A-containing receptors nor from GluA1 AMPA receptors and GluK2 kainate receptors, suggesting this class of compounds shows strong subunit selectivity.

Results

Chemistry. To explore the SAR of the tetrahydroisoquinoline compound class as positive allosteric modulators of GluN2C/2D-containing NMDA receptors, a series of derivatives were synthesized. For SAR development, the core tetrahydroisoquinoline was divided into 3 modifiable rings (A, B, and C) and 2 modifiable linker regions (Linker-A and Linker-B) (Figure 2). Compounds **5**, **6**, and **7** were synthesized from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**4**) and the corresponding benzoyl chloride (Scheme 1). All other synthetically derived analogues were generated via one of three pathways, each starting with substituted phenethylamines. 2-(3-(benzyloxy)phenyl)ethanamine (**12**) was prepared from 3-methoxyphenethylamine (**8**) in the sequence shown in Scheme 2. The starting material (**8**) was demethylated in a refluxing mixture of acetic acid and hydrobromic acid to form the phenol **9**. The primary amine was then Boc-protected to form **10** followed by an alkylation of the phenol with benzyl bromide to give **11**. The Boc group was removed under acidic conditions to give the phenethylamine **12**.

The synthetic scheme employed for the preparation of each analogue was dependent upon the identity of the linker between the tetrahydroisoquinoline core and the B ring (Figure 2). For compounds containing an ether or thioether linker, an appropriately substituted phenethylamine (**8**, **12-18**) was acylated with chloroacetyl chloride to afford the α -chloroamide-containing compounds **19-26**. Displacement of the chlorine with a phenol or thiophenol in the presence of base afforded **27-42** and **43**, respectively. The amides **27-43** were then subjected to Bischler-Napieralski conditions to form the dihydroisoquinolines (**45-62**). The nitro-containing amide compound **42** was

1 subjected to hydrogenolysis, followed by a reductive amination to afford the dimethylamino-containing intermediate
2 which was then cyclized using Bischler-Napieralski conditions to give the dihydroisoquinoline **44**. The
3 dihydroisoquinolines were subsequently reduced with sodium borohydride (NaBH_4) to afford the racemic
4 tetrahydroisoquinolines **63-80**. Acylation of **63-80** with a substituted benzoyl chloride afforded analogues **2** and **81-127**
5 (Scheme 3). Nitro-containing analogues **128-130** were reduced to the corresponding anilines (**131-133**) with tin
6 (II) chloride dehydrate.⁶⁹ The anilines (**131-133**) were then subjected to reductive amination conditions to give the
7 methylamino-containing analogues **134** and **135**.^{69, 70} Although the A-ring in each of the compounds described above
8 is a substituted phenyl ring, a number of compounds were synthesized with various aromatic or heterocyclic moieties
9 in place of the phenyl. These compounds were synthesized in one step from tetrahydroisoquinoline **63** in an
10 acylation reaction with an aryl chloride or 4-morpholinyl chloride (Scheme 4). In addition, tetrahydroisoquinoline **63**
11 was acylated with chloroacetyl chloride followed by chlorine displacement with morpholine to afford **23**, with a
12 modified A-ring and linker A. Tetrahydroisoquinoline **63** was also subjected to alkylation conditions to form the
13 tertiary amine **141** (Scheme 4).
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31 Additionally, compounds with either a saturated or an unsaturated carbon linker, a substituted cinnamic acid
32 or phenylpropionic acid underwent standard EDC-coupling conditions with a substituted phenethylamine (**8** or **13**) to
33 afford amides **142-145**. Amides **142-145** were then subjected to Bischler-Napieralski conditions in refluxing POCl_3
34 to afford the corresponding dihydroisoquinolines (**146-149**), which were subsequently reduced with NaBH_4 to afford
35 the tetrahydroisoquinolines **150-153**. Acylation of **150-153** with a series of substituted benzoyl chlorides afforded
36 the final analogues **154-162** (Scheme 5). Compounds with a shorter linker than those described above were
37 synthesized according to the procedure shown in Scheme 6. The commercially available phenylacetic acids (**163** and
38 **164**) were each treated with thionyl chloride to form the corresponding acid chlorides, which were subsequently
39 reacted with 3,4-dimethoxyphenethylamine (**13**) to give amides **165** and **166**. The amides were then subjected to
40 Bischler-Napieralski reaction conditions to form the dihydroisoquinoline intermediates (**167** and **168**), which were
41 further reduced to the tetrahydroisoquinolines (**169** and **170**) with sodium borohydride. The core was then acylated
42 with an appropriately substituted benzoyl chloride to afford final compounds **171-175**.
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58 Stereoselective synthesis of compound **2**

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The stereoisomers for **2** were synthesized according to the procedure shown in Scheme 7. Either enantiomer of the commercially available chiral amine (**177**) was subjected to acylation conditions with 3,4-dimethoxyphenylacetyl chloride (**176**), to give the secondary amide **178**. Reduction of the amide with borane dimethylsulfide complex and boron trifluoride etherate gave the corresponding amine (**179**) in excellent yields.⁷¹ Acylation with chloroacetyl chloride followed by halogen displacement with 4-methoxyphenol afforded the tertiary amide (**181**). Treatment of amide **181** with phosphorus oxychloride afforded the chiral iminium intermediate, which was subsequently reduced to the tetrahydroisoquinoline (**182**) with sodium borohydride. Although crystallographic data will be needed to confirm the assignment, the stereochemistry of the reduction has been assigned based on the model shown in Figure 3 and on literature precedent for the use of this chiral directing group in similar reductions⁷²⁻⁷⁴. Tetrahydroisoquinoline **182** was subjected to hydrogenolysis to remove the chiral directing group, followed by acylation with 3-chlorobenzoyl chloride, to give the assigned *R*-(+) and *S*-(-) enantiomers of **2**.

Potential of NMDA Receptors

All of the compounds synthesized in addition to 33 commercially available analogues (**184-217**) were evaluated using two electrode voltage clamp recordings of currents from four recombinant NMDA receptor subtypes: GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D. We initially evaluated the conditions under which to best assess compound activity. At low concentrations of agonist (0.3 μ M glutamate, 0.1 μ M glycine), compound **2** produced strong potentiation (353 \pm 36% of control at 10 μ M for GluN2D), but full concentration-effect curves could not be fitted with the Hill equation, limiting our ability to obtain EC₅₀ values with which to compare analogues. By contrast, concentration-effect curves for compound **2** recorded in response to maximally-effective concentrations of glutamate (100 μ M) and glycine (30 μ M) were well-fitted by the Hill equation (maximum 228 \pm 8.8% of control for GluN2D). For all subsequent experiments, concentration-response curves for each compound were generated by co-applying increasing concentrations of compound with maximally effective concentrations of glutamate and glycine. Each compound was tested in at least 5 oocytes from two different frogs. The mean degree of potentiation measured at 10 μ M for each compound at GluN1/GluN2C and GluN1/GluN2D is presented in Tables 1-9. For compounds exhibiting more than 115% potentiation at 10 μ M, the EC₅₀ values were determined by fitting composite concentration-response curves to equation 1 (Table 1-9). None of the compounds

tested potentiated responses from receptors comprised of GluN1/GluN2A or GluN1/GluN2B, and thus these data are not shown. A small subset of compounds produced weak inhibition (70% of the control response at 100 μ M) of GluN1/GluN2A (compounds **7**, **84**, **110**, **186**) or GluN1/GluN2B (compounds **1**, **96**, **100**, **101**, **109**, **139**, **192**, **206**); these inhibitory effects were not studied further.

In addition, several active compounds were tested against a representative member of the AMPA-selective class of glutamate receptors (GluA1) and of the kainate-selective glutamate receptor class (GluK2). Compounds **1**, **2**, **5**, **87**, **96**, **98**, **111**, **117**, **118**, **138**, **140**, **155**, **157**, **158**, **159**, **161**, **162**, **190**, **197** co-applied with 100 μ M glutamate had no effects on homomeric GluA1 responses recorded under two electrode voltage clamp. Compounds **1**, **2**, **190**, and **197** were co-applied with 100 μ M glutamate to GluK2 expressing oocytes and had no effect on GluK2-mediated currents. Compound **83** was tested on an additional 19 receptors (e.g., AMPA, GABA, glycine, nicotinic acetylcholine, purinergic) using the oocyte expression system (see below). Together, these results suggest strong GluN2C/D-selectivity for this series of compounds.

Effect of removing Linker-B and the B-ring.

In order to determine the importance of each portion of the compound for potency, fragments of the lead compound **1** and two lead compounds **2**, **192** were synthesized and tested. Compounds **5**, **6**, and **7** correspond to compounds **1**, **2**, and **190** without the Linker-B and the B-ring (Figure 4). All three of these compounds were inactive against all recombinant NMDA receptors ($n=6-10$ oocytes for GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, GluN1/GluN2D, data not shown). Reducing the length of the linker to a single methylene also removed all activity (**171-175** in Figure 4; data not shown). Thus, the B-ring and the two atom linker are essential for activity in this series.

Optimization of A- and B-Ring Substituent Position.

We evaluated the optimal placement of substituents on the A-ring (Table 1). Substituents in the 3-position, (R_3 in Table 1) showed the strongest potentiation compared to substitution in the 2- (R_4) or 4- (R_2) position. This is evident when comparing potentiation associated with the methyl-containing analogues **184**, **185**, and **186**. For this subset of compounds, **185**, with a methyl in the 3-position (R_3 , Table 1), is the most effective and potentiates

GluN2C- and GluN2D-containing receptors to a greater extent. When a chlorine substituent was placed on the A-ring, as in compounds **187**, **2**, and **188**, the 3-chloro analogue (**2**) showed greater potentiation compared to the 2- and 4-chloro derivatives (**187**, **188**; Table 1). Analogues with dichloro (**86**, **85**, **194**, **87**) or 3-chloro-4-fluoro (**88**) substitutions on the A-ring showed EC₅₀ values (when active) ranging from 1.4-21 μM on GluN2C and 1.9-24 μM on GluN2D (Table 1).

We also evaluated the positional effects of B-ring substitutions. Data in Table 2 show that the *para*-position (R₂, Table 2) on the B-ring is the only position that affords any detectable activity for methoxy substituents. When a methoxy substituent is placed in either the *ortho*- or *meta*-position, all activity is lost (Table 2).

Optimization of Substituent Identity on A- and B-Rings.

Since substitution in the *meta*-position on the A-ring yielded the most potent and effective potentiators, a number of modifications were made to this position (R₁ in Table 3). Substitution on the A-ring with 3-bromo (**190**), 3-iodo (**93**), and 3-trifluoromethyl (**198**) gave strong potentiation with potencies similar to compound **2**⁶⁶. All other substitutions on the 3-position on the A-ring showed either decreased potency or decreased maximum degree of potentiation. These data suggest that the binding pocket has both size and electronic requirements. Since **2** and **190** show similar potencies and maximal effects, and they are more active than the 3-fluoro (**197**) analogue, it was expected that the 3-iodo (**93**) analogue would be active. While not as potent as the 3-bromo (**190**) derivative, the 3-iodo (**93**) analogue showed enhanced maximal potentiation. Interestingly, addition of a similarly large phenyl (**94**) ring shows reasonable potency but a diminished degree of potentiation. In addition, when R₃ is an electron-withdrawing group, such as nitro (**84**), the compounds are less potent but more efficacious (Table 3). Figure 5A summarizes optimal substitutions on the A ring. We subsequently evaluated a range of different ring systems in place of Ring-A (Table 4). Only 2-thiophene (**203**) showed weak activity at GluN2C-containing receptors with no or minimal potentiating effects at GluN2D-containing receptors. The weak selectivity of this ring system for GluN2C suggests a possible starting point from which to develop future compounds with selectivity for GluN2C over GluN2D.

As shown in Table 2, only compounds with a *para*-substitution pattern around the B-ring have detectable potentiation on recombinant GluN2C/GluN2D receptors. Several modifications were made to the *para*-position substituent on the B-ring to test for the optimal functionality in this position (R_2 in Table 5). When a thiomethyl is placed in the 4-position, there is potentiation if the analogue also contains a 3-chloro on the A-ring (**104**), but not a hydrogen (**103**). The potency of **104** is similar to the 4-methoxy containing analogue (**2**), but the degree of potentiation is reduced. The 4-ethyl analogue is weakly active at GluN2C (**207**; Table 5). A 4-dimethylamino substituent shows potentiation preferentially of GluN2C if the analogue also contains a 3-chloro or 3-bromo on Ring-A (**107** and **108**, respectively), but not a hydrogen (**106**). Substitution with ethoxy (**100**, **101**), benzyloxy (**109**), amino (**133**, **132**, **131**), or nitro (**129**, **130**, **128**) led to compounds with no detectable activity on recombinant GluN2C- or GluN2D-containing receptors. These results suggest that the methyl ether is important for binding. Moreover, steric effects may explain the lack of efficacy for the larger substituents such as benzyloxy (**109**; Table 5).

Optimization of C-Ring Substitutions

All of the compounds described above contain a dimethoxy substitution pattern on the C-ring (R_3 and R_4 , Table 6). Substitution of methyl groups in place of both methoxy substituents results in modestly enhanced potency ($\sim 1 \mu\text{M EC}_{50}$) and increased maximal potentiation (compare **122** and **123** to **2** and **190**). When a dioxolane is fused at these two positions (**110**, **111**, **112**), the potency is decreased when compared to the dimethoxy analogues (**1**, **2**, **190**). When the R_3 -methoxy is removed and a R_2 -methoxy is installed (Table 6), the resulting compounds show modest changes in either potency or maximal effect. Compounds with dimethoxy substitutions at R_4 and R_5 (**120** and **121**; Table 6) are inactive. This suggests that substitution at the R_5 position introduces unfavorable steric interactions within the binding pocket. In addition, the decrease in potency associated with a non-hydrogen substituent at R_2 may be explained by steric interactions between linker-B and the substituent at R_2 on the C-ring.

Interestingly, when a single methoxy is placed at R_4 on the C-ring, as in compounds **116** and **117**, potency is increased when compared to the dimethoxy counterparts (Table 6). While compound **118** does not show increased potency compared to its dimethoxy analog, it does exhibit a greater maximum potentiation, further suggesting that a single substitution at R_4 on the C-ring is optimal for activity. This trend of increased effectiveness also appears to hold for the methyl-substituted C ring. Compounds **122** and **123** show increased potency compared to **2** and **190**, and

when a single methyl is placed at R₄ on the C-ring as in compounds **124**, **125**, and **126** the maximal effect is slightly increased. Interestingly, introduction of O-benzyl substitutions at the R₄ position results in the most potent compounds tested. Compounds **82** and **83** show submicromolar EC₅₀ values (0.3-0.4 μM) with strong potentiation of 254-257% at GluN2C and 198-219% at GluN2D, suggesting that space exists within the binding pocket that can be exploited to enhance potency. Figure 5B summarizes optimal substitutions on the C ring.

Optimization of Linker-A and Linker-B.

There are two regions on the backbone that link the 3 rings together: linker-A and linker-B (Figure 2). In both the original screening hit (**1**) and **2**, linker-A is an amide linkage. As shown in Table 7, extension of this linker into a urea (**211**, **212**) or thiourea (**211**, **212**, **213**, **214**, and **215**) leads to a loss of activity for all but one analogue (**215**), which retained only weak potentiating activity (Table 7). Substitution of the amide with a sulfonamide (**216**, **217**) eliminated all activity on GluN1/GluN2C and GluN1/GluN2D receptors (Table 8), as did reduction of the amide linkage to a tertiary amine (**141**; Table 8). These data suggest that both the potency and maximal degree of potentiation of this series is dependent on the amide linkage.

All of the compounds described thus far contained an ether linkage in linker-B. Table 9 shows modifications to this linker region. When the linker is aliphatic, as in **154**, **160**, **161**, **162**, the compounds either show a significant reduction in potency or are inactive. Similarly, replacing the linkage with a thioether (**127**) eliminated activity of the compounds. When the compounds contain unsaturation within linker-B, the compounds appear less soluble and show varying effects. For example, **156**, **158**, and **159** all showed increased potency compared to the related compounds containing an ether linkage (**2**, **117**, and **118**, respectively). By contrast, **155** shows decreased potency compared to **1**. Analogues with a single methoxy on the C-ring (**158** and **159**) were similarly potent as analogs with a dimethoxy (**156** and **157**), indicating two different changes (single methoxy, removal of ether) did not have additive effects. These data suggest modest enhancements in potency can be gained through alterations in the composition of this linker.

Off-Target Testing

We subsequently tested the most potent analogue (**83**) against a variety of other targets. We used two electrode voltage clamp recordings to assess the ability of 3 μ M **83** (10 times the EC_{50}) to inhibit GABA, glycine, serotonin, nicotinic acetylcholine, AMPA, kainate, and purinergic receptors. Although compound **83** had a statistically significant effect on seven of the receptors tested (Table 10), it showed less than 10% inhibition or 5% potentiation, suggesting compound **83** shows approximately 100-fold selectivity for GluN2C or GluN2D compared to these receptors. Compound **83** was also submitted to the National Institute of Mental Health Psychoactive Drug Screening Program (PDSP, <http://pdsp.med.unc.edu/>) for further off-target profiling (Supplementary Table S1). In the PDSP assays less than 50% inhibition of ligand binding was observed with 5 μ M compound **83** at serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT_{5A}, 5-HT₆, 5-HT₇), adrenergic receptors (α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , α_{2C} , β_2 , β_3), brain and peripheral benzodiazepine sites, dopamine receptors (D₁, D₂, D₃, D₄, D₅), opioid receptors (δ and μ), histamine receptors (H₁, H₂, H₃), acetylcholine muscarinic receptors (M₁, M₂, M₃, M₄, M₅), sigma receptors (σ_1 , σ_2), as well as serotonin, dopamine, and norepinephrine transporters (n=4 for each). The initial screen determined significant inhibition at the κ opioid receptors, which was studied further. Compound **83** inhibited antagonist binding to kappa opioid with a K_i greater than 5 μ M, 15-fold higher than the EC_{50} for NMDA receptor potentiation. The combined data from these off-target screens highlights the remarkable selectivity of this series for GluN2C- and GluN2D-containing receptors.

Potency of Stereoisomers.

All compounds in this series thus far have been synthesized and tested as racemic mixtures. We studied the stereoisomers of compound **2** by first separating the two enantiomers using chiral supercritical fluid chromatography (SFC; see *Methods*). We assessed the activity of each enantiomer in BHK cells that stably express GluN1/GluN2C or GluN1/GluN2D using the Ca^{2+} sensitive dye Fluo4 and in oocytes expressing GluN1/GluN2C or GluN1/GluN2D using two electrode voltage clamp recordings. The activity determined in these two assays suggested that one enantiomer potentiates the response of GluN1/GluN2C and GluN1/GluN2D receptors to a far greater extent than the other. In Ca^{2+} -imaging experiments with BHK cells, the active SFC peak potentiated GluN2C and GluN2D responses with EC_{50} values of 7.1 and 6.6 μ M, respectively (N=4). We therefore carried out stereoselective-synthesis of the two enantiomers of compound **2** and directly compared the activity of these two enantiomers using two

electrode voltage clamp recordings. The results suggested that the *S*-(-)-enantiomer (>98% ee) of compound **2** (with stereochemistry assigned based on literature precedent⁷²⁻⁷⁴) potentiates the response of GluN2C and GluN2D by 304% and 294% with estimated EC₅₀ values of 9.0 and 8.0 μM, respectively. Like the racemic form, **2-S**-(-) had no effect on GluN2A- or GluN2B-containing receptors. By contrast, the *R*-(+)-enantiomer (90% ee) possessed minimal activity, which was indistinguishable from that predicted for the 5% residual *S*-(-)-enantiomer (Fig 5C). These data suggest that the binding pocket preferentially accommodates one enantiomer, and this stereoselectivity may provide a means to further enhance the selectivity of this compound class over other central nervous system targets. Given the limited solubility of compound **2**, we attribute the slightly reduced potency of the purified enantiomer (8-9 μM) compared to the racemic mixture (4.6-5.0 μM) to the greater amount of active species in solution for the purified enantiomer compared to racemic mixture at concentrations near the limit of solubility. The larger amount of the active enantiomer in solution before the solubility limit allows a better estimate of the maximum potentiation, which was higher for the *S*-(-)-isomer (304% and 294% for GluN2C and GluN2D) than for racemic **2** (233% and 215% for GluN2C and GluN2D). The higher potentiation led to increases in EC₅₀ values compared to racemic mixture.

Conclusion

Introduction of a single of O-benzyl substitution at the R₄ position of the tetrahydroisoquinoline of compound **2** provided compound **83**, a GluN2C- and GluN2D-selective potentiator with 300 nM potency. Moreover, the majority of the activity attributed to the compounds in this class of tetrahydroisoquinoline potentiators appears to arise from a single enantiomer, tentatively assigned with *S*-stereochemistry. This class of potentiators also demonstrates strong selectivity for GluN2C and GluN2D receptors with the most potent analogue showing no activity at over 65 receptors, channels, and transporters expressed in the central nervous system. Additionally, compounds **107**, **108**, **205** and **203** may represent potential starting point for developing GluN2C-selective modulators.

Biology Experimentals.

Two-electrode voltage-clamp recordings were performed on *Xenopus laevis* oocytes expressing recombinant rat GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, GluN1/GluN2D, GluA1, or GluK2 receptors. cDNAs for rat GluN1-1a (GenBank accession numbers U11418 and U08261; hereafter GluN1), GluN2A (D13211), GluN2B (U11419), GluN2C (M91563), GluN2D (L31611), GluA1 (X17184), GluK2 (Z11548) were provided by Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (University of Heidelberg). Oocyte isolation, RNA synthesis, and RNA injection were completed as described in detail elsewhere⁷⁵; all protocols involving *Xenopus laevis* were approved by the Emory University Institutional Animal Care and Use Committee. During two-electrode voltage-clamp recordings, oocytes were placed into a perfusion chamber and continually washed with recording solution containing (in mM) 90 NaCl, 1.0 KCl, 0.5 BaCl₂, 0.005 EDTA, and 10 HEPES at pH 7.4 (23°C). Glass electrodes with a tip resistance of 0.3-1.0 MΩ were pulled from thin-walled glass capillary tubes and filled with 3.0 M KCl. An OC-725C amplifier (Warner Instruments) was used to hold the membrane potential of the oocytes at -40 mV during current recording. All compounds were made as 20 mM stock solutions in DMSO, and dissolved to reach the desired final concentration in recording solution containing 100 μM glutamate and 30 μM glycine for use on oocytes expressing NMDA receptors. Final DMSO content was 0.05-0.5% (vol/vol). Oocytes expressing GluK2 receptors were pre-treated with 10 μM concanavalin A for 10 minutes. Recombinant GluA1 and GluK2 receptors were activated by 100 μM glutamate. In order to prevent a gradual increase in current response over the course of the experiment, which is a common feature of GluN1/GluN2A receptor responses in oocytes, some oocytes expressing GluN1/GluN2A were either pretreated for 10 minutes with 50 μM BAPTA-AM (1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetrakis(acetoxymethyl ester)) or injected with 50 nl of 2 mM K-BAPTA (potassium 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid). For every test compound, we recorded 5-7 concentrations in at least 5 oocytes obtained from two different frogs. We subsequently determined mean potentiation at 10 μM (±SEM), and when potentiation exceeded 115% of control we determined the EC₅₀ (half-maximally effective concentration of potentiator) by fitting the equation

$$Response = maximum + (100 - maximum) / (1 + ([concentration] / EC_{50})^N) \quad (1)$$

to the average composite concentration-response data normalized to the current in the absence of potentiator (100%). N is the Hill slope, which ranged between 1 and 2 and is not reported; *maximum* is the maximal response predicted for saturating concentration of potentiator. A few compounds produced modest inhibition (70% of controls at 100 μ M); these inhibitory actions were not studied further.

For off-target data, GABA_C ($\rho 1$), glycine ($\alpha 1$), serotonin (5-HT_{3A}), nicotinic acetylcholine (nAChR, $\alpha 1\beta 1\delta\gamma$, $\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 9\alpha 10$, $\alpha 7$), and purinergic (P2_{X2} rat, P2_{X2} human) receptors were expressed in *Xenopus* oocytes. cRNA encoding the receptor subunits was synthesized from linear template cDNA using the mMessage mMachine kit (Ambion). Oocytes were injected with 1-5 ng cRNA in a 50 nL volume and incubated in Barth's solution at 15°C for 2-5 days prior to recording. $\alpha 1\beta 1\delta\gamma$ nAChR subunits were injected at a 1:1:1:1 ratio while $\alpha 4\beta 2$, $\alpha 3\beta 4$, and $\alpha 9\alpha 10$ nAChR subunits were injected at a 1:1 ratio. The cDNAs encoding GABA_C, glycine, and serotonin subunits were provided by Dr. D. Weiss (University of Texas Health Science Center at San Antonio). cDNAs encoding nicotinic acetylcholine receptor subunits were provided by Drs. R. Papke (University of Florida) and S. Heinemann (Salk Institute). cDNAs encoding the purinergic receptors were provided by Dr. R. Hume (University of Michigan). GABA_C receptors were activated by 2 μ M GABA. Acetylcholine was used at the indicated concentrations (in μ M) to activate the nicotinic acetylcholine receptors: $\alpha 1\beta 1\delta\gamma$ (1), $\alpha 4\beta 2$ (10), $\alpha 3\beta 4$ (10), $\alpha 9\alpha 10$ (1), $\alpha 7$ (300). 50 μ M glycine was used to activate the glycine receptor, 100 μ M serotonin was used to activate 5-HT_{3A} receptor, and 9 μ M ATP was used to activate the purinergic receptors. K_i determinations and receptor binding profiles were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. For experimental details please refer to the PDSP web site <http://pdsp.med.unc.edu/>

Ca²⁺ imaging experiments were performed as described previously⁷⁶ with the following modifications. One day prior to the experiment, the cells were seeded in 20 μ l media at 600,000 cells/ml in black clear bottom 384 well plates (Corning CellBind). On the day of the experiment, the media was aspirated and replaced with Flou-4 NW (Invitrogen) dissolved in HEPES-buffered saline (HBSS, Gibco #14175-053) comprised of (in mM) 5.33 KCl, 0.441

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2 KH₂PO₄, 4.17 NaHCO₃, 137.9 NaCl, 0.338 Na₂HPO₄, 5.56 D-glucose, 2 CaCl₂, and 20 HEPES (pH 7.4), with 2.5
3 mM (1%) Probenecid, and 30 μM 7-chlorokynurenic acid for 60 minutes at 37° C in the dark. Cells were then gently
4 washed with 30 μl/well using the same buffer without the Fluo-4 dye, and placed in 20 μl/well buffer. Using a
5 FDSS7000 instrument (Hamamatsu) real time recordings of changes in Fluo-4 emission was performed (excitation
6 480 nm and emission 540 nm) at room temperature (20-22° C). After 10 seconds of baseline recordings, 10 μl/well of
7 3x concentrated test compound, controls, or assay buffer in HBSS (pH 7.4) and 1 mM glycine (final concentration)
8 were added. After 2 minutes, an additional 10 μl/well were added containing a 4x concentrated solutions of NMDA
9 (GluN2C: 1000 μM and GluN2D: 300 μM). Changes in fluorescence were recorded for subsequent 2 minutes. For
10 determination of the concentration-response relationships, test compounds were serial diluted 3-fold over 10
11 concentration steps. Responses (fluorescence units, FU) were normalized to the first recording and expressed as
12 percent of maximally effective concentration of NMDA (see above). The EC₅₀ value was determined by non-linear
13 least squares fitting of equation 1 to the data.
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28 The maximum solubility (20 μM) was determined for compound **2** using a BMG Labtech Nephelostar
29 nephelometer (Offenburg, Germany), according to manufacturer's instructions. Only responses for concentrations
30 below the experimentally determined limit of solubility were measured; whenever visual evidence of precipitation at
31 higher concentrations was observed, experiments were repeated with 1-10 mM 2-hydroxypropyl-β-cyclodextrin
32 added to the recording solution to ensure that the compounds remained in solution. 2-hydroxypropyl-β-cyclodextrin
33 had no detectable effect on NMDA receptor response amplitude (data not shown). We also evaluated the stability of
34 potentiator activity by making a solution of 10 μM **2** and continuously agitating it. After increasing periods of time,
35 some of the solution was filtered (0.2 μm nylon filter) and used to measure potentiation of GluN1/GluN2D receptors
36 expressed in *X. laevis* oocytes. Similarly, we tested the concentration-response effects of **2** on maximal responses
37 induced by NMDA on GluN1/GluN2C in BHK cells by measuring changes in fluorescence of Fluo-4 at different
38 time points after making the compound solutions. Activity (potency and efficacy) was retained without loss until 6
39 hours, whereas no activity was seen after 24 hours. Results from these two experiments suggested that compound **2**
40 remains active in solution up to 2-3 hours, with activity decreasing thereafter until by 24 hours there is no detectable
41 activity.
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2 The enantiomers of **2** were obtained by supercritical fluid chromatography on a Berger Multigram II
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4 operating at 50 ml/min at 35 °C and 100 bar backpressure. The column was a Phenomenex Lux 5u Cellulose-1 (250
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6 x 21.2 mm). The eluent was CO₂ (60 %) and methanol + 0.1 % diethylamine (40%). 15 mg were dissolved in
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8 methanol and 200 stacked injections of 0.4 ml were performed. Enantiomeric excess was determined on an Aurora
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10 Fusion A5 SFC system operating at 3 ml/min at 40 °C and 100 bar backpressure. The column was a Phenomenex
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12 Lux 3u Cellulose-1 (150 x 4.6 mm). The eluent was CO₂ (70 %) and ethanol + 0.1 % diethylamine (30%). EE of
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14 peak 1 (rt 1.584 min) determined at 220 nM 98.3 %. Peak 2 (rt 2.708 min) 98.2 %.
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Chemistry Experimentals. Compounds not described were purchased from either Life Chemicals (Compounds 184, 187, 189-194, 196-197, 200-201, 203-206, 208, 210-217) or Chem Div (Compounds 2, 185-186, 188, 195, 198, 127, 207, 209)). All purchased compounds were greater than 90% pure, as determined by the suppliers, by HPLC or NMR.

All reagents for synthesis were obtained from commercial suppliers and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) on precoated aluminum plates (silica gel 60 F254, 0.25 mm). Proton and carbon NMR spectra were recorded on an INOVA-400 (400 MHz) or VNMRs 400 (400 MHz). The spectra obtained were referenced to the residual solvent peak. Mass spectra were performed by the Emory University Mass Spectroscopy Center on either a VG 70-S Nier Johnson or JEOL instrument. Elemental analyses were performed by Atlantic Microlab Inc. Purity was established using HPLC, unless indicated by combustion analysis, and were found to be $\geq 95\%$. C, H, N agreed with proposed structures $\pm 0.4\%$ of theoretical values unless indicated. Optical activity was measured at 20°C with a Perkin-Elmer model 341 polarimeter. Flash chromatography was performed on a Teldyne ISCO CombiFlash Companion System with prepackaged Teldyne RediSep or Silicycle normal phase columns with silica gel.

General preparation for 1,2,3,4-tetrahydroisoquinoline compounds (Procedure I). 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (1.0 g, 4.4 mmol) was dissolved in DCM (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The biphasic reaction mixture was cooled to 0 °C in an ice bath and benzoyl chloride (3 equiv) was added dropwise. After complete addition, the reaction was warmed to room temperature and stirred for an additional 2 hours, when TLC indicated complete conversion. The organics were separated and the aqueous phase was extracted with DCM (2x). The organics were combined, washed with brine and water, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was subjected to flash column chromatography.

General preparation for 2-chloro-N-phenethylacetamide compounds (Procedure II). A solution of a phenethylamine (1.0 equiv) in DCM was cooled to 0 °C in an ice bath. To this solution, Et₃N (3.0 equiv) was added followed by dropwise addition of an acid chloride (1.2 equiv). Upon complete addition, the reaction was warmed to room temperature and stirred for 2 hours. When TLC indicated complete conversion, the reaction mixture was

concentrated *in vacuo*. The resulting residue was taken up into DCM and washed with a saturated solution of NH_4Cl and brine. The aqueous layer was then extracted with DCM (2x). The organic layers were combined, washed with water, dried over MgSO_4 and filtered. The solvent was removed *in vacuo*. The resulting solid was subjected to flash column chromatography.

General preparation for *N*-(phenethyl)-2-(phenoxy)acetamide and *N*-(phenethyl)-2-(phenylthio)acetamide compounds (Procedure III). To a solution of phenol or thiophenol (7.3 mmol) in MeCN (15 mL) was added Cs_2CO_3 (3.0 equiv.) at room temperature and the reaction mixture was allowed to stir for 2 hours. A solution of the α -chloroamide (1.2 equiv.) dissolved in dry MeCN (15 mL) was added and the resulting reaction mixture was stirred for 18 h under an argon atmosphere. After TLC indicated complete conversion, the volatiles were removed *in vacuo* and the resulting residue was treated with NH_4Cl and extracted into EtOAc (2x). The resulting organic layer was washed with brine and water, dried over MgSO_4 , filtered, and concentrated *in vacuo*. The resulting solid was subjected to flash column chromatography.

General preparation for 3,4-dihydroisoquinoline compounds (Procedure IV). To a solution of **3** (3.5 mmol) suspended in toluene (40 mL) was added POCl_3 (3.0 equiv.), dropwise. The reaction mixture was brought to reflux and allowed to stir for 90 minutes before cooling to room temperature. The resulting precipitate was filtered and carried on without further purification.

General preparation for 3,4-dihydroisoquinoline compounds (Procedure V). The amide (1.0 equiv) was dissolved in dry toluene (30 mL) and brought to reflux. Phosphorus pentoxide (7.0 equiv) was added to the refluxing solution over about 15 minutes. The reaction was refluxed for an additional 30 minutes. The toluene was decanted and the remaining residue was dissolved in water and washed with ether (2x). The aqueous solution was treated with NH_4OH and extracted into DCM (3x). The organic layer was separated, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was taken on without further purification.

General preparation for 1,2,3,4-tetrahydroisoquinoline compounds (Procedure VI). The dihydroisoquinoline **4** (4.0 mmol) was suspended in anhydrous MeOH (40 mL). The reaction mixture was cooled to 0 °C in an ice bath.

NaBH₄ (3.0-4.0 equiv.) was added slowly to the reaction mixture under an argon atmosphere. It was then allowed to warm to room temperature and stirred for 6 hours to overnight, until TLC indicated complete conversion. Volatiles were removed *in vacuo*. The resulting residue was dissolved in DCM and washed with 1 N HCl, water, and brine. The aqueous layer was extracted with DCM (2x). The organic layers were combined, dried over MgSO₄ and filtered. Volatiles were removed *in vacuo*. The crude residue was subjected to flash column chromatography.

General preparation for 3,4-dihydroisoquinolin-2(1H)-ylmethanone compounds (Procedure VII). The tetrahydroisoquinoline **5** (1 mmol) was dissolved in anhydrous DCM (10 mL). The solution was cooled to 0 °C in an ice bath. Triethylamine (3.0 equiv.) was added to the cooled solution followed by dropwise addition of a benzoyl chloride (1.2 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for an additional 90 minutes. Volatiles were removed *in vacuo*. The resulting residue was treated with NH₄Cl saturated solution followed by extraction with DCM (2x). The organic phase was washed with brine and water, dried over MgSO₄, filtered, and concentrated to yield a residue. The resulting residue was subjected to column chromatography to afford the final products as a mixture of two rotamers.

General preparation for 3,4-dihydroisoquinolin-2(1H)-ylmethanone compounds (Procedure VIII). Benzoic acid (1.0-1.3 equiv) was dissolved in dry DCM (15 mL) and cooled to 0 °C in an ice bath. DMAP (1.2 equiv) and EDC (1.2 equiv) were added and the reaction was stirred at 0 °C for 2 hours. Tetrahydroisoquinoline (1.0 equiv) dissolved in DCM (10 mL) was added to the cooled reaction and it was warmed to room temperature and stirred for an additional 18 hours. When TLC indicated complete conversion, 1M HCl was added and the aqueous phase was extracted with DCM (2x). The organics were combined and washed with brine and water, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting residue was subjected to column chromatography to afford the final products as a mixture of two rotamers.

General preparation of N-(phenethyl)-3-phenylpropanamide and (E)-N-(phenethyl)-3-(phenyl)acrylamide compounds (Procedure IX). Phenylpropionic acid (6.7 mmol, 1.0 equiv) or cinnamic acid (5.6 mmol, 1.0 equiv) was dissolved in dry DCM (20 mL) and DMF (10 mL) and the reaction mixture was brought to 0 °C in an ice bath. EDC (1.3 equiv) and DMAP (1.1 equiv) were added and the reaction mixture was stirred at 0 °C for 2 hours. 3,4-

dimethoxyphenethylamine (6.7 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred overnight. After TLC indicated complete conversion, 1M HCl was added and the reaction mixture was extracted into DCM (3x). The organics were combined, washed with brine and water, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solid was subjected to flash column chromatography.

(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (5). Compound **5** was prepared according to Procedure I using benzoyl chloride (1.5 mL, 13 mmol, 3.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.9 g, 67%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.45-7.39 (m, 7H), 6.62-6.38 (m, 1H), 4.81 (m, 1H), 3.97 (m, 1H), 3.86 (s, 6H), 3.76 (m, 1H), 3.60 (m, 1H), 2.81 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ: 171.1, 170.6, 147.9, 136.4, 129.9, 128.7, 127.4, 127.0, 125.8, 125.0, 111.5, 109.6, 108.8, 56.2, 56.1, 49.8, 45.6, 44.7, 29.3, 28.1. HRMS calcd. for C₁₈H₂₀NO₃, 298.14377 [M + H]⁺; found, 298.14362 [M + H]⁺.

(3-chlorophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (6). Compound **6** was prepared according to Procedure I using 3-chlorobenzoyl chloride (1.7 mL, 13 mmol, 3.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 1.1 g, 76%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.51-7.31 (m, 4H), 6.65-6.39 (m, 2H), 4.80 (s, 1H), 3.96 (m, 1H), 3.84 (s, 6H), 3.77 (m, 1H), 3.60 (m, 1H), 2.88 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ: 169.6, 169.2, 148.2, 137.9, 134.8, 133.2, 130.5, 129.9, 127.3, 125.6, 125.2, 124.7, 111.6, 109.5, 108.8, 56.2, 56.1, 49.7, 45.6, 44.7, 29.3, 27.9. HRMS calcd. for C₁₈H₁₉NO₃Cl, 332.10480 [M + H]⁺; found, 332.10483 [M + H]⁺.

(3-bromophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (7). Compound **7** was prepared according to Procedure I using 3-bromobenzoyl chloride (1.7 mL, 13 mmol, 3.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.4 g, 85%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.56-7.52 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.29-7.24 (m, 1H), 6.63-6.68 (m, 2H), 4.76 (m, 1H), 4.45 (m, 1H), 3.93 (m, 1H), 3.82 (s, 6H), 3.75 (m, 1H), 3.57 (m, 1H), 2.81 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ: 169.4, 148.2, 138.2, 133.1, 130.4, 130.2, 126.6, 125.9,

125.6, 124.7, 124.4, 122.9, 111.7, 109.5, 56.2, 56.1, 54.1, 49.7, 45.6, 44.7, 29.2, 28.1. HRMS calcd. for $C_{18}H_{19}NO_3Br$, 376.05428 $[M + H]^+$; found, 376.05471 $[M + H]^+$.

(6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (81).

Compound **81** was prepared according to Procedure VII using tetrahydroisoquinoline **63** (0.2 g, 0.53 mmol) and benzoyl chloride (0.09 g, 0.07 mL, 0.64 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.18 g, 71%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.52-7.22 (m, 10H), 6.93-6.71 (m, 7H), 1H [6.01, 5.19 (t, $J = 4.4$ Hz; dd, $J_I = 3.8$ Hz, $J_2 = 8.6$ Hz)], 5.05 (s, 2H), 1H [4.88, 4.10 (dd, $J_I = 5.4$ Hz, $J_2 = 13$ Hz; t, $J = 9.6$ Hz)], 4.36 (d, $J = 4.4$ Hz, 1H), 3.93-3.66 (m, 4H), 3.27-3.15 (m, 1H), 3.93-2.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 172.0, 171.3, 158.4, 157.9, 154.2, 153.1, 152.7, 137.0, 136.8, 136.7, 136.6, 135.9, 129.8, 129.7, 128.9, 128.6, 128.3, 127.7, 126.8, 126.5, 126.1, 125.1, 115.9, 115.6, 115.4, 115.2, 114.9, 113.8, 113.6, 96.1, 71.4, 70.4, 70.2, 57.2, 56.0, 51.8, 42.9, 35.4, 30.1, 28.7. HRMS calcd. for $C_{31}H_{30}NO_4$, 480.21694 $[M + H]^+$; found, 480.21792 $[M + H]^+$.

(6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-chlorophenyl)methanone (82).

Compound **82** was prepared according to Procedure VII using tetrahydroisoquinoline **63** (0.2 g, 0.53 mmol) and 3-chlorobenzoyl chloride (0.1 g, 0.08 mL, 0.64 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.20 g, 70%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.59-7.21 (m, 9H), 6.93-6.76 (m, 7H), 1H [5.98, 5.14 (t, $J = 4.8$ Hz; dd, $J_I = 4.4$ Hz, $J_2 = 9.2$ Hz)], 5.04 (s, 2H), 1H [4.85, 4.13 (dd, $J_I = 5.2$ Hz, $J_2 = 13$ Hz; m)], 4.35 (m, 1H), 3.94-3.67 (m, 4H), 3.26-2.73 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.5, 169.7, 168.5, 158.5, 158.0, 154.4, 153.0, 152.6, 138.3, 137.1, 137.0, 136.7, 135.7, 134.9, 134.6, 133.4, 130.3, 129.9, 128.9, 128.4, 127.7, 127.1, 125.8, 125.7, 124.9, 124.7, 115.9, 115.5, 115.3, 114.9, 113.9, 113.7, 71.3, 70.2, 57.3, 56.0, 52.0, 42.9, 35.5, 30.0, 28.6. HRMS calcd. for $C_{31}H_{29}NO_4Cl$, 514.17796 $[M + H]^+$; found, 514.17923 $[M + H]^+$.

(6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-bromophenyl)methanone (83).

Compound **83** was prepared according to Procedure VII using tetrahydroisoquinoline **63** (0.2 g, 0.53 mmol)

and 3-bromobenzoyl chloride (0.1 g, 0.08 mL, 0.64 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.21 g, 71%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.56-7.21 (m, 9H), 6.94-6.76 (m, 7H), 1H [5.98, 5.13 (t, $J = 4.7$ Hz; dd, $J_1 = 2.6$ Hz, $J_2 = 9.4$ Hz)], 5.05 (s, 2H), 1H [4.85, 4.13 (m, m)], 4.34 (m, 1H), 3.93-3.67 (m, 4H), 3.26-2.72 (m, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.3, 169.6, 158.5, 158.0, 154.4, 153.1, 152.6, 138.6, 138.4, 136.9, 136.7, 135.7, 132.9, 132.8, 131.1, 130.5, 130.2, 129.9, 129.0, 128.9, 128.3, 127.7, 126.3, 125.7, 125.3, 124.7, 123.0, 122.7, 115.9, 115.5, 115.3, 115.0, 114.9, 114.0, 113.7, 71.3, 70.2, 57.3, 56.0, 52.0, 42.9, 35.5, 30.0, 29.0. HRMS calcd. for $\text{C}_{31}\text{H}_{29}\text{NO}_4\text{Br}$, 558.12745 $[\text{M} + \text{H}]^+$; found, 558.12878 $[\text{M} + \text{H}]^+$.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-nitrophenyl)methanone

(84). Compound **84** was prepared according to Procedure VII using **63** (0.2 g, 0.6 mmol, 1.0 equiv) and 3-nitrobenzoyl chloride (0.1 g, 0.6 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as a white amorphous solid (0.1, 33%, mixture of rotamers). ^1H NMR (CDCl_3 , 400 MHz) δ : 1H [8.57, 8.30 (s, s)], 8.28 (d, $J = 7.6$ Hz, 1H), 1H [7.86, 7.74 (d, $J = 8.0$ Hz; d, $J = 7.2$ Hz), 7.64-7.57 (m, 1H), 6.89 (d, $J = 8.8$ Hz, 1H), 6.86-6.81 (m, 3H), 1H [6.70, 6.65 (s, s)], 1H [6.46, 5.98 (s, m)], 1H [5.04, 4.90 (dd, $J_1 = 3.4$ Hz, $J_2 = 9.8$ Hz; dd, $J_1 = 5.6$ Hz, $J_2 = 13.2$ Hz)], 4.39 (d, $J = 5.2$ Hz, 1H), 4.23-3.97 (m, 1H), 3.88-3.74 (m, 9H), 3.74-3.72 (m, 1H), 3.30-3.12 (m, 1H), 2.91-2.71 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 169.3, 168.5, 154.5, 152.9, 152.3, 149.0, 148.6, 148.2, 147.9, 138.1, 133.9, 133.0, 130.2, 129.8, 127.2, 126.0, 124.9, 124.5, 123.5, 122.1, 115.9, 115.4, 115.0, 112.1, 111.5, 110.3, 109.8, 71.0, 69.9, 57.7, 56.3, 56.2, 55.9, 52.2, 43.1, 35.7, 29.2, 27.7. HRMS calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_7$, 479.18128 $[\text{M} + \text{H}]^+$; found, 479.18062 $[\text{M} + \text{H}]^+$.

(3,4-dichlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (85). Compound **85** was prepared according to Procedure VII using **64** (0.2 g, 0.6 mmol) and 3,4-dichlorobenzoyl chloride (0.2 g, 0.7 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.2 g, 67%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.74-7.44 (m, 2H), 7.37-7.20 (m, 1H), 6.86-6.77 (m, 4H), 1H [6.66, 6.60 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.07, 5.05 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 6.0$

Hz, $J_2 = 13$ Hz)], 4.34 (d, $J = 4.0$ Hz, 1H), 1H [4.16, 3.96 (t, $J = 10.0$ Hz; dd, $J_1 = 4.0$ Hz, $J_2 = 10.0$ Hz)], 3.86-3.74 (m, 10H), 1H [td, $J_1 = 4.0$ Hz, $J_2 = 13$ Hz; td, $J_1 = 5.2$ Hz, $J_2 = 10.0$ Hz), 2.92-2.66 (m, 2H). ^{13}C NMR (CDCl_3 , 400 MHz) δ : 169.6, 154.5, 154.3, 152.9, 152.4, 149.0, 148.5, 148.1, 136.3, 134.0, 132.9, 131.0, 130.7, 130.2, 127.2, 126.1, 125.0, 123.8, 115.9, 115.5, 114.9, 112.0, 111.5, 109.8, 96.8, 57.6, 56.3, 56.2, 56.0, 43.0, 35.8, 29.2, 27.7. HRMS calcd. for $\text{C}_{26}\text{H}_{26}\text{NO}_5\text{Cl}_2$, 502.11826 $[\text{M} + \text{H}]^+$; found, 502.11841 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{25}\text{NO}_5\text{Cl}_2$): C, H, N.

(2,3-dichlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (86). Compound **86** was prepared according to Procedure VIII using **64** (0.2 g, 0.6 mmol, 1.0 equiv) and 2,3-dichlorobenzoic acid (0.1 g, 0.6 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Rediseq 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.1 g, 33%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.50-7.45 (m, 1H), 7.30-7.22 (m, 1H), 1H [7.19, 7.12 (dd, $J_1 = 1.6$ Hz, $J_2 = 5.2$ Hz; dd, $J_1 = 1.6$ Hz, $J_2 = 5.2$ Hz)], 6.87-6.83 (m, 1H), 6.83-6.70 (m, 3H), 6.67-6.60 (m, 1H), 6.50-5.92 (m, 1H), 1H [4.93, 4.76 (m, m)], 4.41-4.32 (m, 1H), 1H [4.08, 3.93 (t, $J_1 = 10.0$ Hz; dd, $J_1 = 4.2$ Hz, $J_2 = 10.0$ Hz), 3.86-3.72 (m, 9H), 3.60-3.44 (m, 1H), 3.27-2.96 (m, 1H), 2.84-2.64 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 174.1, 167.2, 166.8, 154.2, 152.8, 152.6, 148.4, 148.0, 147.8, 138.2, 133.8, 133.2, 130.9, 128.2, 127.2, 126.4, 126.2, 125.7, 125.1, 124.8, 124.0, 115.8, 115.4, 114.8, 111.9, 111.5, 109.9, 81.3, 70.9, 70.5, 56.3, 56.1, 55.9, 51.8, 42.4, 29.0, 28.0. HRMS calcd. for $\text{C}_{26}\text{H}_{26}\text{NO}_5\text{Cl}_2$, 502.11826 $[\text{M} + \text{H}]^+$; found, 502.11832 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{25}\text{NO}_5\text{Cl}_2$): C, H, N.

(3,5-dichlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (87). Compound **87** was prepared according to Procedure VII using **64** (0.11 g, 0.33 mmol) and 3,5-dichlorobenzoyl chloride (0.08 g, 0.37 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.06 g, 36%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.51 (s, 1H), 7.42 (s, 1H), 7.25 (m, 1H), 6.9-6.79 (m, 4H), 1H [6.68, 6.64 (s, s)], 1H [6.51, 5.94 (s, m)], 1H [5.06, 4.85 (dd, $J_1 = 2.8$ Hz, $J_2 = 9.6$ Hz; dd, $J_1 = 5.6$ Hz, $J_2 = 13.2$ Hz)], 4.36 (d, $J = 4.4$ Hz, 1H), 1H [4.21, 3.99 (t, $J = 10.0$ Hz; dd, $J_1 = 3.6$ Hz, $J_2 = 10.0$ Hz), 3.89-3.73 (m, 9H), 3.72-3.68 (m, 1H), 3.27-3.08 (m, 1H), 2.94-2.70 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 168.2, 154.5, 154.4, 149.0, 148.5, 148.1, 147.9, 139.2, 135.7, 135.3, 129.9, 129.8, 127.2, 126.5, 126.1, 125.3, 124.9,

123.7, 115.9, 115.4, 115.0, 114.9, 112.0, 111.5, 110.3, 109.8, 71.0, 70.1, 57.6, 56.3, 56.2, 55.9, 52.1, 42.9, 35.8, 29.2, 27.7. HRMS calcd. for $C_{26}H_{26}NO_5Cl_2$, 502.11826 $[M + H]^+$; found, 502.11748 $[M + H]^+$.

(3-chloro-4-fluorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (88). Compound **88** was prepared according to Procedure VIII using **64** (0.1 g, 0.3 mmol) and 3-chloro-4-fluorobenzoic acid (0.06 g, 0.4 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.10 g, 68%). 1H NMR ($CDCl_3$, 400 MHz) δ : 8.08-7.74 (m, 1H), 7.46-7.13 (m, 2H), 6.88-6.80 (m, 4H), 6.72-6.63 (m, 1H) 1H [6.50, 5.95 (s, m)], 1H [5.10, 4.84 (m, dd, $J_1 = 5.2$ Hz, $J_2 = 12$ Hz)], 4.36 (m, 1H), 4.22-3.97 (m, 1H), 3.87-3.76 (m, 9H), 3.73-3.66 (m, 1H), 3.30-3.07 (m, 1H), 2.88-2.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ : 169.7, 154.5, 152.9, 152.5, 148.9, 148.5, 148.1, 147.8, 133.5, 130.8, 127.3, 126.1, 125.1, 123.8, 115.9, 115.5, 114.9, 112.0, 109.8, 70.3, 57.7, 56.2, 56.1, 55.9, 43.0, 35.8, 29.9, 29.2, 27.7, 15.5. HRMS (m/z): $[M]^+$ calcd. for $C_{26}H_{26}NO_5ClF$, 486.14781; found, 486.14826. Anal. ($C_{26}H_{25}NO_5ClF$) C, H, N.

6,7-dimethoxy-1-(phenoxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl(phenyl)methanone (89). Compound **89** was prepared according to Procedure VII using **79** (0.6 g, 2 mmol) and benzoyl chloride (0.4 g, 0.3 mL, 3 mmol, 1.3 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, gradient 0-60% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.8 g, 99% yield). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.50 (m, 1H), 7.38 (m, 4H), 7.23 (m, 2H), 6.94-6.89 (m, 2H), 1H [6.81, 6.60 (s, s)], 1H [6.78, 6.66 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.16, 4.84 (dd, $J_1 = 4.0$ Hz, $J_2 = 9.0$ Hz; dd, $J_1 = 6.0$ Hz, $J_2 = 9.4$ Hz)], 4.39 (m, 1H), 1H [4.18, 3.99 (m, m)], 3.84-3.75 (m, 6H), 1H [3.78, 3.63 (m, m)], 3.28-3.02 (m, 1H), 2.91-2.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 171.9, 171.2, 158.9, 158.5, 148.8, 148.4, 148.0, 147.7, 136.6, 129.8, 128.8, 128.6, 127.7, 127.5, 126.8, 126.5, 125.4, 124.3, 121.5, 121.3, 114.9, 114.6, 112.1, 111.6, 110.5, 110.0, 70.3, 69.6, 57.2, 56.2, 56.1, 51.7, 43.0, 35.7, 29.3, 27.9. HRMS calcd. for $C_{25}H_{25}NO_4$, 404.18564 $[M + H]^+$; found, 404.18538 $[M + H]^+$. Anal. ($C_{25}H_{24}NO_4$): C, H, N.

(6,7-dimethoxy-1-((3-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (90). Compound **90** was prepared according to Procedure VII using **65** (0.2 g, 0.6 mmol, 1.0 equiv) and benzoyl chloride

(0.1 g, 0.7 mmol, 1.2 equiv, 0.08 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.18 g, 60%). ¹H NMR (CDCl₃, 400 MHz) δ: 8.06-7.12 (m, 6H), 6.80-5.98 (m, 4H), 1H [5.16, 4.89 (dd, *J*₁ = 4.0 Hz, *J*₂ = 8.8 Hz; dd, *J*₁ = 6.0 Hz, *J*₂ = 12 Hz)], 4.40-3.96 (m, 2H), 3.85-3.75 (m, 10H), 3.66-2.64 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ: 171.9, 171.3, 161.1, 160.1, 159.7, 148.8, 148.4, 147.9, 147.7, 136.5, 133.5, 130.3, 129.9, 128.8, 128.6, 127.7, 127.5, 126.9, 126.4, 125.3, 124.2, 112.0, 111.5, 110.4, 109.9, 107.0, 106.8, 101.3, 70.4, 69.7, 57.2, 56.2, 56.1, 55.6, 51.6, 43.0, 35.7, 29.3, 27.9. HRMS calcd. for C₂₆H₂₈NO₅, 434.19620 [M + H]⁺; found, 434.19602 [M + H]⁺. Anal. (C₂₆H₂₇NO₅): C, H, N.

(3-chlorophenyl)(6,7-dimethoxy-1-((3-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(91). Compound **91** was prepared according to Procedure VII using **65** (0.2 g, 0.6 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.1 g, 0.7 mmol, 1.2 equiv, 0.07 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.20 g, 67%). ¹H NMR (CDCl₃, 400 MHz) δ: 8.03-7.46 (m, 1H), 7.39-7.29 (m, 3H), 7.16 (t, *J* = 8.4 Hz, 1H), 1H [6.78, 6.66 (s, s)], 1H [6.61, 6.47 (s, s)], 6.52-5.95 (m, 3H), 1H [5.10, 4.86 (dd, *J*₁ = 3.0 Hz *J*₂ = 9.0 Hz; dd, *J*₁ = 5.6 Hz, *J*₂ = 13 Hz)], 4.38 (m, 1H), 1H [4.20, 3.98 (m, m)], 3.85-3.75 (m, 9H), 3.75-3.45 (m, 1H), 3.28-3.04 (m, 1H), 2.92-2.66 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.4, 169.6, 161.1, 160.0, 148.0, 147.8, 138.2, 134.6, 132.3, 130.3, 130.0, 128.2, 128.0, 127.3, 127.1, 125.7, 125.0, 123.8, 111.5, 110.3, 109.9, 107.3, 107.0, 106.5, 101.3, 101.0, 70.3, 57.4, 56.2, 56.1, 55.6, 42.9, 35.7, 29.2, 27.8. HRMS calcd. for C₂₆H₂₇NO₅Cl, 468.15723 [M + H]⁺; found, 468.15689 [M + H]⁺. Anal. (C₂₆H₂₆NO₅Cl): C, H, N.

(3-chlorophenyl)(6,7-dimethoxy-1-((2-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(92). Compound **92** was prepared according to Procedure VII using **66** (0.5 g, 2 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.3 g, 2 mmol, 1.2 equiv, 0.22 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.5 g, 70%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.81-7.23 (m, 4H), 6.98-6.72 (m, 5H), 1H [6.64, 6.59 (s, s)], 1H [6.48, 5.98 (s, m)], 1H [5.12, 4.84 (dd, *J*₁ = 4.0 Hz, *J*₂ = 9.6 Hz; dd, *J*₁ = 5.8 Hz, *J*₂ = 13 Hz)], 4.42-4.38 (m, 1H), 4.05-4.01 (m, 1H), 3.89-3.66 (m, 10H), 3.30-3.04 (m, 1H), 2.93-2.60 (m, 2H).

¹³C NMR (CDCl₃, 100 MHz) δ: 170.5, 169.6, 149.9, 149.7, 147.9, 147.7, 138.3, 138.2, 134.8, 134.6, 132.0, 130.2, 129.9, 128.3, 127.3, 127.1, 126.2, 126.1, 125.8, 125.2, 124.9, 124.1, 122.1, 121.1, 120.8, 114.2, 113.4, 112.3, 112.0, 111.8, 111.5, 110.6, 110.0, 71.1, 70.1, 57.5, 56.1, 56.0, 55.8, 51.7, 42.8, 35.6, 29.2, 27.7. HRMS calcd. for C₂₆H₂₇NO₅Cl, 468.15723 [M + H]⁺; found, 468.15685 [M + H]⁺. Anal. (C₂₆H₂₆NO₅Cl): C, H, N.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-iodophenyl)methanone

(93). Compound **93** was prepared according to Procedure VIII using **64** (0.2 g, 0.6 mmol, 1.0 equiv) and 3-iodobenzoic acid (0.2 g, 0.6 mmol, 1.0 equiv). The crude material was subjected to silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.2 g, 59%). ¹H NMR (CDCl₃, 400 MHz) δ: 1H [7.94, 7.70 (s, s)], 7.74 (d, *J* = 7.6 Hz, 1H), 1H [7.46, 7.33 (d, *J* = 8.0 Hz; d, *J* = 7.6 Hz)], 7.13 (q, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 9.6 Hz, 1H), 6.80 (m, 3H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.92 (s, m)], 1H [5.07, 4.83 (dd, *J*₁ = 3.8 Hz, *J*₂ = 9.8 Hz; dd, *J*₁ = 6.8 Hz, *J*₂ = 13 Hz)], 4.33 (m, 1H), 4.17-4.01 (m, 1H), 3.97-3.60 (m, 1H), 3.86-3.74 (m, 9H), 3.27-3.04 (m, 1H), 2.90-2.64 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.0, 169.3, 154.4, 154.3, 153.0, 152.5, 148.9, 148.4, 148.0, 147.8, 138.8, 138.6, 138.5, 136.7, 135.6, 130.3, 127.3, 126.8, 126.2, 125.2, 124.0, 115.9, 115.5, 114.9, 112.0, 111.5, 109.9, 94.5, 94.4, 71.1, 70.2, 57.5, 56.3, 56.1, 55.9, 43.0, 35.7, 29.2. HRMS calcd. for C₂₆H₂₇NO₅I, 560.09285 [M + H]⁺; found, 560.09224 [M + H]⁺. Anal. (C₂₆H₂₆NO₅I): C, H, N.

[1,1'-biphenyl]-3-yl(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (94). Compound **94** was prepared according to Procedure VIII using **64** (0.5 g, 1.5 mmol) and 3-phenylbenzoic acid (0.3 g, 1.5 mmol, 1.0 equiv) in DCM (10 mL) and DMF (2.0 mL). The crude yellow residue was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.26 g, 34%, mixture of rotamers). ¹H NMR (CDCl₃, 400 MHz) δ: 7.83-7.30 (m, 8H), 6.92-6.74 (m, 5H), 1H [6.68, 6.62 (s, s)], 1H [6.49, 6.01 (s, m)], 1H [5.21, 4.91 (dd, *J*₁ = 3.8 Hz, *J*₂ = 9.0 Hz; dd, *J*₁ = 5.6 Hz, *J*₂ = 12.8 Hz), 4.43-4.35 (m, 1H), 1H [4.22, 4.00 (m, m)], 3.90-3.72 (m, 9H), 1H [3.67, 3.26 (m, m)], 1H [3.15, 2.89 (m, m)], 2.78-2.65 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 171.8, 171.1, 154.4, 154.3, 153.1, 152.6, 148.8, 148.4, 148.0, 147.7, 141.8, 141.5, 140.6, 140.4, 137.2, 129.3, 129.1, 128.5, 128.4, 128.0, 127.9, 127.4, 126.6, 126.5 (2), 125.6, 125.5, 124.5, 115.9, 115.6, 114.9, 112.1, 111.6, 110.5, 110.0, 71.2, 70.5, 57.5, 56.3,

56.1, 55.9, 51.8, 43.0, 35.8, 29.3, 27.8. HRMS calcd. for $C_{32}H_{32}NO_5$, 510.22750 $[M + H]^+$; found, 510.22802 $[M + H]^+$. Anal. ($C_{32}H_{31}NO_5$): C, H, N.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-hydroxyphenyl)methanone

(95). Compound **95** was prepared according to Procedure VIII using **64** (0.16 g, 0.5 mmol) and 3-hydroxybenzoic acid (0.07 g, 0.5 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.09 g, 41%, mixture of rotamers). 1H NMR ($CDCl_3$, 400 MHz) δ : 8.14-8.02 (m, 1H), 7.72-7.40 (m, 3H), 7.34-7.04 (m, 2H), 6.84-6.74 (m, 2H), 6.65-5.98 (m, 2H), 1H [5.20, 4.83 (m, m)], 4.32 (m, 1H), 4.18-3.90 (m, 1H), 3.84-3.70 (m, 9H), 3.70-3.68 (m, 1H), 3.30-3.02 (m, 1H), 2.84-2.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 171.7, 157.1, 154.3, 153.0, 152.6, 148.4, 147.9, 137.0, 130.0, 126.4, 125.1, 117.9, 117.5, 117.1, 115.9, 115.6, 115.4, 114.9, 114.3, 112.0, 111.5, 110.4, 71.1, 67.7, 63.2, 56.2, 56.1, 55.9, 52.0, 42.9, 29.2, 27.9. HRMS calcd. for $C_{26}H_{28}NO_6$, 450.19111 $[M + H]^+$; found, 459.19206 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_6$) C, H, N.

(3-(chloromethyl)phenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (96). Compound **96** was prepared according to Procedure VII using **64** (0.8 g, 2.4 mmol) and 3-(chloromethyl)benzoyl chloride (0.5 g, 2.9 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-70% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.30 g, 26%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.57-7.34 (m, 3H), 6.92-6.77 (m, 4H), 6.69-6.62 (m, 2H), 1H [6.50, 5.98 (s, m)], 1H [5.15, 4.90 (m, dd, $J_1 = 5.6$ Hz, $J_2 = 13.2$ Hz)], 4.60 (m, 2H), 4.43-4.31 (m, 1H), 4.19-4.11 (m, 1H), 3.88-3.67 (m, 10H), 3.32-3.08 (m, 1H), 2.96-2.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.7, 169.6, 154.4, 154.3, 153.0, 152.6, 148.8, 148.4, 148.0, 138.3, 138.0, 137.0, 133.5, 130.8, 130.3, 130.2, 130.0, 129.3, 129.1, 128.1, 127.7, 127.3, 127.1, 126.8, 126.3, 125.3, 124.2, 115.9, 115.6, 114.9, 112.0, 111.5, 110.4, 109.9, 71.1, 70.3, 57.5, 56.2, 56.1, 55.9, 51.9, 46.0, 45.7, 43.0, 35.7, 29.2, 27.9. HRMS calcd. for $C_{27}H_{29}NO_5Cl$, 482.17288 $[M + H]^+$; found, 482.17250 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_5Cl$): C, H, N.

(3-(dichloromethyl)phenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (97). Compound **97** was prepared according to Procedure VII using **64** (0.2 g, 0.6 mmol) and 3-

(dichloromethyl)benzoyl chloride (0.16 g, 0.72 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as a white amorphous solid (0.07 g, 21%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.76-7.44 (m, 4H), 6.91-6.64 (m, 6H), 1H [6.50, 5.99 (s, m)], 1H [5.13, 4.90 (m, m)], 4.39 (m, 1H), 4.20-3.94 (m, 1H), 3.88-3.69 (m, 10H), 3.29-3.13 (m, 1H), 2.98-2.70 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.8, 170.1, 154.3, 153.0, 152.5, 148.9, 147.8, 141.1, 137.1, 129.4, 129.3, 128.3, 127.5, 125.8, 125.2, 124.8, 124.0, 115.5, 114.9, 71.2, 64.3, 57.5, 56.3, 56.2, 56.1, 55.9, 52.0, 43.0, 27.2. HRMS calcd. for C₂₇H₂₈NO₅Cl₂, 516.13391 [M + H]⁺; found, 516.13457 [M + H]⁺. Anal. (C₂₇H₂₇NO₅Cl₂): C, H, N.

3-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzonitrile (98).

Compound **98** was prepared according to Procedure VII using **64** (0.21 g, 0.63 mmol) and 3-cyanobenzoyl chloride (0.13 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Rediseq 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.28 g, 99%). ¹H NMR (CDCl₃, 400 MHz) δ: 8.00-7.44 (m, 4H), 6.98-6.75 (m, 4H), 1H [6.70, 6.62 (s, s)], 1H [6.48, 6.00 (s, m)], 1H [5.02, 4.88 (m, m)], 4.38 (m, 1H), 4.06-3.71 (m, 10H), 3.28 (m, 1H), 3.14 (m, 1H), 2.96-2.69 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 169.4, 168.6, 154.4, 154.2, 152.7, 152.2, 148.9, 148.4, 147.9, 147.7, 137.6, 134.5, 134.0, 133.1, 133.0, 132.0, 131.5, 131.0, 130.3, 129.7, 129.3, 127.1, 125.9, 124.7, 123.4, 118.2, 118.0, 115.7, 115.3, 114.9, 114.7, 113.0, 112.6, 111.4, 110.2, 109.7, 70.8, 70.0, 57.5, 56.1, 55.9, 55.7, 51.9, 43.0, 35.6, 29.0, 27.6. HRMS calcd. for C₂₇H₂₇N₂O₅, 459.19145 [M + H]⁺; found, 459.19087 [M + H]⁺. Anal. (C₂₇H₂₇N₂O₅): C, H, N.

1-(3-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-

carbonyl)phenyl)ethanone (99). Compound **99** was prepared according to Procedure VIII using **64** (1.0 g, 3.0 mmol) and 3-acetylbenzoic acid (0.5 g, 3.04 mmol, 1.0 equiv) in DCM (10 mL) and DMF (2.0 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.32 g, 22%, mixture of rotamers). ¹H NMR (CDCl₃, 400 MHz) δ: 8.15-7.97 (m, 2H), 7.72-7.46 (m, 2H), 6.87-6.78 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.43, 5.95 (s, m)], 1H [5.06, 4.87 (dd, *J*₁ = 3.6 Hz, *J*₂ = 9.2 Hz; dd, *J*₁ = 5.8 Hz, *J*₂ = 13 Hz)], 4.39-4.31 (m, 1H), 1H [4.14, 3.96 (m, m)], 3.84-3.72 (m, 9H), 1H [3.66, 3.25 (m, m)], 1H [3.12, 2.86 (m, m)], 2.77-2.61 (2H), 3H [2.58, 2.56 (s, s)]. ¹³C NMR (CDCl₃, 100 MHz) δ: 197.8, 197.6, 170.9, 170.2, 154.5, 154.3, 153.0, 152.5, 148.9, 148.4, 148.0, 137.6, 137.4,

137.1, 132.3, 131.3, 129.6, 129.4, 129.2, 128.9, 128.0, 127.3, 126.8, 126.2, 125.2, 124.0, 115.9, 115.6, 114.9 (2), 112.1, 111.5, 110.4, 109.8, 71.1, 70.3, 57.5, 56.2, 56.1, 55.9, 51.9, 43.1, 35.7, 29.2, 27.8, 27.0. HRMS calcd. for $C_{28}H_{30}NO_6$, 476.20676 $[M + H]^+$; found, 476.20717 $[M + H]^+$. Anal. ($C_{28}H_{29}NO_6$): C, H, N.

(3-chlorophenyl)(1-((4-ethoxyphenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(100). Compound **100** was prepared according to Procedure VII using **75** (0.14 g, 0.4 mmol) and 3-chlorobenzoyl chloride (0.08 g, 0.5 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.1 g, 47%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.60-7.24 (m, 4H), 6.86-6.76 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.07, 4.84 (, $J_1 = 3.8$ Hz, $J_2 = 9.4$ Hz; dd, $J_1 = 5.4$ Hz, $J_2 = 13$ Hz)], 4.33 (m, 1H), 4.18-3.93 (m, 3H), 3.86-3.73 (m, 7H), 1H [3.65, 3.23 (m, m)], 1H [3.09, 2.85 (m, m)], 2.77-2.65 (m, 1H), 1.37 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.3, 169.6, 153.6, 152.9, 152.5, 148.9, 148.0, 147.8, 138.3, 124.9, 134.5, 130.2, 130.0, 129.8, 128.2, 127.3, 127.1, 126.2, 125.9, 125.2, 124.9, 124.0, 115.9, 115.7, 115.6, 115.4, 112.0, 111.5, 110.4, 109.9, 71.1, 70.2, 64.2, 57.5, 56.2, 56.1, 51.9, 42.9, 35.7, 29.2, 27.8, 15.1. HRMS calcd. for $C_{27}H_{29}NO_5Cl$, 482.17288 $[M + H]^+$; found, 482.17324 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_5Cl$): C, H, N.

(3-bromophenyl)(1-((4-ethoxyphenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(101). Compound **101** was prepared according to Procedure VII using **75** (0.14 g, 0.4 mmol) and 3-bromobenzoyl chloride (0.10 g, 0.5 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.1 g, 51%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.76-7.50 (m, 2H), 7.44-7.23 (m, 2H), 6.86-6.79 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.07, 4.84 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 5.8$ Hz, $J_2 = 13$ Hz)], 4.33 (m, 1H), 4.18-3.92 (m, 3H), 3.85-3.73 (m, 7H), 1H [3.65, 3.23 (m, m)], 1H [3.09, 2.85 (m, m)], 2.76-2.65 (m, 1H), 1.36 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.2, 169.5, 153.8, 153.6, 152.9, 152.5, 148.9, 148.0, 147.8, 138.5, 132.9, 132.7, 131.0, 130.5, 130.2, 129.9, 127.3, 126.3, 125.4, 125.2, 124.0, 122.9, 122.7, 115.9, 115.7, 115.6, 115.4, 112.0, 111.5, 110.4, 109.8, 71.1, 70.2, 64.2, 57.5, 56.3, 56.2, 51.9, 42.9, 35.7, 29.2, 27.8, 15.2. HRMS calcd. for $C_{27}H_{29}NO_5Br$, 526.12236 $[M + H]^+$; found, 526.12256 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_5Br$): C, H, N.

(6,7-dimethoxy-1-((4-(methylthio)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (103).

Compound **103** was prepared according to Procedure VII using **73** (0.4 g, 1.2 mmol) and benzoyl chloride (0.8 g, 1.3 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of rotamers, 0.12 g, 23%). ¹H NMR (CDCl₃, 400 MHz) δ: 1H [7.93, 7.79 (m, m)], 7.67 (dd, *J*₁ = 1.4 Hz, *J*₂ = 8.2 Hz, 1H), 7.60-7.47 (m, 1H), 7.44-7.36 (m, 1H), 7.28 (m, 2H), 7.16-7.07 (m, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.67-6.59 (m, 2H), 5.08-4.92 (m, 1H), 4.31-4.23 (m, 1H), 4.12-4.02 (m, 1H), 3.97-3.79 (m, 8H), 3.49-3.35 (m, 1H), 2.62-2.67 (m, 1H), 2.39 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ: 169.8, 161.4, 161.3, 157.1, 148.6, 148.4, 147.6, 134.4, 133.6, 132.1, 130.7, 130.6, 130.1, 129.5, 128.7, 127.7, 126.9, 126.8, 125.0, 115.4, 112.0, 110.4, 70.2, 66.1, 56.2, 56.1, 54.4, 54.2, 38.4, 27.9, 18.0, 15.5. HRMS calcd. for C₂₆H₂₈NO₄S, 450.17336 [M + H]⁺; found, 450.17413 [M + H]⁺. Anal. (C₂₆H₂₇NO₄S): C, H, N.

(3-chlorophenyl)(6,7-dimethoxy-1-((4-(methylthio)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (104). Compound **104** was prepared according to Procedure VII using **73** (0.17 g, 0.5 mmol) and 3-chlorobenzoyl chloride (0.10 g, 0.6 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.16 g, 68%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.86-7.65 (m, 1H), 7.59-7.44 (m, 2H), 7.37-7.30 (m, 1H), 7.24-7.20 (m, 1H), 7.16-7.07 (m, 2H), 6.77-6.74 (m, 1H), 6.65-6.59 (m, 2H), 5.05-4.92 (m, 1H), 4.28-4.23 (m, 1H), 4.09-4.00 (m, 1H), 3.98-3.80 (m, 8H), 3.47-3.36 (m, 1H), 3.08-2.86 (m, 1H), 2.39 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.3, 169.7, 157.3, 156.8, 148.9, 148.5, 148.0, 147.8, 138.2, 134.9, 134.6, 130.3, 130.1, 129.9, 129.7, 128.2, 127.4, 127.0, 126.3, 125.8, 124.9, 123.8, 115.6, 115.2, 112.1, 111.6, 110.4, 109.9, 70.5, 69.7, 57.3, 56.3, 56.1, 51.8, 42.9, 35.7, 29.2, 27.8, 18.0, 17.9. HRMS (m/z): [M]⁺ calcd. for C₂₆H₂₇NO₄SCl, 484.13438 [M + H]⁺; found, 484.13530 [M + H]⁺. Anal. (C₂₆H₂₆NO₄SCl): C, H, N.

(3-chlorophenyl)(6,7-dimethoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (105). Compound **105** was prepared according to Procedure VII using **74** (0.33 g, 0.9 mmol) and 3-chlorobenzoyl chloride (0.2 g, 1.0 mmol, 1.3 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.3 g, 67%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.42-7.34 (m, 3H), 7.27-7.25 (m, 1H), 7.16-

7.13 (m, 2H), 6.95-6.79 (m, 2H), 6.69-6.64 (m, 1H), 1H [6.49, 5.98 (s, m)], 1H [5.14, 4.86 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.6$ Hz; dd, $J_1 = 5.4$ Hz, $J_2 = 12.6$ Hz)], 4.41-4.38 (m, 1H), 4.02-3.98 (m, 1H), 3.91-3.65 (m, 7H), 3.29-3.00 (m, 1H), 2.95-2.74 (2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.3, 169.7, 157.3, 156.8, 149.0, 148.6, 148.1, 147.9, 143.3, 138.1, 134.9, 134.6, 130.3, 130.1, 129.9, 128.1, 127.4, 127.0, 126.3, 125.8, 124.9, 124.8, 123.5, 122.8, 122.7, 122.0, 115.7, 115.3, 112.1, 11.6, 110.3, 109.8, 70.7, 69.9, 57.3, 56.2, 56.1, 51.8, 43.0, 35.7, 29.2, 27.7. HRMS calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_5\text{ClF}_3$, 522.12896 $[\text{M} + \text{H}]^+$; found, 522.12847 $[\text{M} + \text{H}]^+$.

(1-((4-(dimethylamino)phenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone

(106). Compound **106** was prepared according to Procedure VII using tetrahydroisoquinoline **78** (0.25 g, 0.73 mmol, 1.0 equiv) and benzoyl chloride (0.10 mL, 0.88 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Rediseq 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.17 g, 54%, mixture of rotamers) TLC (EtOAc: hexanes, 1:1, v/v) $R_f = 0.14$; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.53-7.51 (m, 1H), 7.39 (s, 4H), 6.88-6.81 (m, 1H), 6.76-6.60 (m, 4H), 1H [6.47, 5.96 (s, m) 1H [5.12, 4.87 (dd, $J_1 = 4.4$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 5.6$ Hz, $J_2 = 13$ Hz)], 4.39-4.31 (m, 1H), 4.15-3.94 (m, 1H), 3.85-3.77 (m, 7H), 3.68-3.61 (m, 1H), 3.33-3.08 (m, 1H), 2.84 (s, 6H), 2.83-2.64 (m, 2H). ^{13}C NMR (100 MHz) δ : 171.9, 171.2, 151.2, 150.8, 148.7, 148.3, 147.9, 147.6, 146.2, 136.7, 129.8, 128.6, 127.7, 127.4, 126.9, 126.4, 125.6, 124.6, 115.9, 115.6, 115.0, 114.9, 111.9, 111.5, 110.4, 110.0, 71.3, 70.6, 57.4, 56.2, 56.1, 51.7, 42.9, 41.9, 41.8, 35.7, 29.3, 27.9. HRMS calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_4$, 447.22783 $[\text{M} + \text{H}]^+$; found, 447.22759 $[\text{M} + \text{H}]^+$.

((3-chlorophenyl)(1-((4-(dimethylamino)phenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-

yl)methanone) (107). Compound **107** was prepared according to Procedure VII using tetrahydroisoquinoline **78** (0.25 g, 0.73 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.11 mL, 0.88 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Rediseq 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.33 g, 94%, mixture of rotamers). TLC (EtOAc: hexanes, 1:1, v/v) $R_f = 0.25$; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.61-7.25 (m, 4H), 6.87-6.84 (m, 1H), 6.80-6.78 (m, 1H), 6.72-6.68 (m, 2H), 1H [6.63, 6.60 (s,s)], 1H [6.47, 5.94 (s,m)], 1H [5.06, 4.85 (dd, $J_1 = 4.0$ Hz, $J_2 = 9.2$ Hz; dd $J_1 = 5.6$ Hz, $J_2 = 13$ Hz)], 4.37-4.33 (m, 1H), 4.17-3.92 (m, 1H), 3.86-3.62 (m, 7H), 3.74-3.62 (m, 1H), 3.27-3.02 (m, 1H), 2.85 (s, 6H), 2.83-2.64 (m, 1H). ^{13}C NMR (100 MHz) δ : 179.3, 169.6, 151.1, 148.8, 148.4, 147.9, 147.7, 146.4, 146.3, 138.3, 134.8,

134.5, 130.2, 129.9, 129.8, 128.2, 127.3, 127.1, 126.3, 125.9, 125.3, 124.9, 124.2, 115.9, 115.5, 114.8, 111.9, 111.5, 110.4, 109.9, 71.2, 70.4, 57.6, 56.2, 56.2, 51.9, 42.8, 41.9, 41.8, 35.6, 29.3, 27.8. HRMS calcd. for $C_{27}H_{30}N_2O_4Cl$, 481.18886 $[M + H]^+$; found, 481.18843 $[M + H]^+$; Anal. ($C_{27}H_{29}N_2O_4Cl$): C, H, N.

((3-bromophenyl)(1-((4-(dimethylamino)phenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone) (108). Compound **108** was prepared according to Procedure VII using tetrahydroisoquinoline **78** (0.25 g, 0.73 mmol, 1.0 equiv) and 3-bromobenzoyl chloride (0.12 mL, 0.88 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.25 g, 64%, mixture of rotamers). TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.25; 1H NMR ($CDCl_3$, 400 MHz) δ 7.78-7.43 (m, 2H), 7.31-7.23 (m, 2H), 6.87-6.79 (m, 2H), 6.71-6.69 (m, 2H), 1H [6.65-6.61 (s,s)], 1H [6.48, 5.93 (s, m)], 1H [5.06, 4.84 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 5.6$ Hz, $J_2 = 13$ Hz)], 4.37-4.30 (m, 1H), 4.18-3.92 (m, 1H), 3.86-3.78 (m, 7H), 3.74-3.62 (m, 1H), 3.27-3.01 (m, 1H), 2.85 (s, 6H), 2.83-2.64 (m, 2H). ^{13}C NMR (100 MHz) δ : 170.2, 169.4, 151.1, 150.7, 148.9, 148.4, 147.9, 147.8, 146.4, 146.2, 138.6, 132.8, 132.7, 131.1, 1330.4, 130.2, 129.9, 127.3, 126.3, 126.2, 125.4, 125.3, 124.2, 122.9, 122.6, 115.9, 115.5, 114.9, 111.9, 111.5, 110.4, 109.9, 71.2, 70.4, 57.6, 56.3, 56.2, 51.9, 42.9, 41.9, 41.8, 35.7, 29.2, 27.8. HRMS calcd. for $C_{27}H_{30}N_2O_4Br$, 252.13835 $[M + H]^+$; 525.13783 found, $[M + H]^+$; Anal. ($C_{27}H_{29}N_2O_4Br$): C, H, N.

(1-((4-(benzyloxy)phenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-chlorophenyl)methanone (109). Compound **109** was prepared according to Procedure VII using **72** (0.18 g, 0.44 mmol) and 3-chlorobenzoyl chloride (0.09 g, 0.5 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.13 g, 52%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.61-7.24 (m, 9H), 6.90-6.78 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.94 (s, m)], 1H [5.08, 4.85 (dd, $J_1 = 3.2$ Hz, $J_2 = 6.0$ Hz; dd, $J_1 = 5.4$ Hz, $J_2 = 13.0$ Hz)], 5.00 (s, 2H), 4.34 (m, 1H), 1H [4.16, 3.95 (m, m)], 3.85-3.78 (m, 6H), 3.75-3.64 (m, 1H), 3.28-3.05 (m, 1H), 2.92-2.64 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.4, 169.6, 153.5, 152.7, 148.9, 148.0, 147.8, 138.3, 137.4, 134.9, 134.6, 130.0, 128.8, 128.2, 127.7, 127.3, 127.1, 126.3, 126.0, 125.2, 124.0, 116.1, 115.5, 111.6, 109.9, 70.8, 57.5, 56.3, 56.2, 42.9, 29.2, 14.4. HRMS calcd. for $C_{32}H_{31}NO_5Cl$, 544.18853 $[M + H]^+$; found, 544.18945 $[M + H]^+$. Anal. ($C_{32}H_{30}NO_5Cl$): C, H, N.

(5-((4-methoxyphenoxy)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)(phenyl)methanone (110).

Compound **110** was prepared according to Procedure VII using **67** (0.14 g, 0.45 mmol) and benzoyl chloride (0.09 g, 0.68 mmol, 1.5 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4g column, 0-60% EtOAc/hexanes gradient) afforded the title compound as a white amorphous solid (mixture of rotamers, 0.14 g, 73%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.50-7.41 (m, 5H), 6.90-6.77 (m, 4H), 1H [6.66, 6.47 (s, s)], 6.61 (s, 1H), 5.91 (s, 2H), 1H [5.13, 5.85 (m, m)], 4.36 (m, 1H), 1H [4.12, 3.94 (m, m)], 3.81-3.71 (m, 4H), 1H [3.66, 3.26 (m, m)], 1H [3.09, 2.85 (m, m)], 2.78-2.64 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 172.1, 171.4, 154.5, 153.3, 152.9, 147.2, 146.9, 136.9, 130.1, 129.0, 128.8, 128.0, 127.9, 127.1, 126.8, 125.7, 116.1, 115.9, 115.1, 109.6, 108.9, 107.8, 107.3, 101.5, 71.6, 70.6, 57.8, 56.2, 52.4, 43.2, 35.8, 30.0, 28.6. HRMS calcd. for C₂₅H₂₄NO₅, 418.16490 [M + H]⁺; found, 418.16432 [M + H]⁺. Anal. (C₂₅H₂₃NO₅): C, H, N.

(3-chlorophenyl)(5-((4-methoxyphenoxy)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-

yl)methanone (111). Compound **111** was prepared according to Procedure VII using **67** (0.1 g, 0.3 mmol) and 3-chlorobenzoyl chloride (0.07 g, 0.05 mL, 0.4 mmol, 1.2 equiv.). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.08 g, 56%). ¹H NMR (CDCl₃, 400 MHz) δ: 8.05-7.5 (m, 1H), 7.41-7.28 (m, 3H), 6.89-6.48 (m, 6H), 5.95-5.90 (m, 2H), 1H [5.07, 4.84 (dd, *J*₁ = 3.4 Hz, *J*₂ = 9.4 Hz; dd, *J*₁ = 5.6 Hz, *J*₂ = 13 Hz)], 4.36-4.34 (m, 1H), 4.17-3.92 (m, 1H), 3.77 (s, 3H), 3.75-3.66 (m, 1H), 3.30-3.03 (m, 1H), 2.90-2.66 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.3, 169.6, 157.6, 154.3, 152.9, 152.5, 147.6, 147.1, 146.5, 138.1, 134.9, 134.6, 130.2, 129.9, 128.6, 128.1, 127.6, 127.0, 126.2, 125.8, 124.9, 115.9, 115.5, 114.9, 108.8, 107.4, 101.3, 71.2, 57.7, 56.0, 55.9, 52.3, 43.0, 35.6, 29.7, 28.2. HRMS calcd. for C₂₅H₂₃NO₅Cl, 452.12593 [M + H]⁺; found, 452.12608 [M + H]⁺. Anal. (C₂₅H₂₂NO₅Cl): C, H, N.

(3-bromophenyl)(5-((4-methoxyphenoxy)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-

yl)methanone (112). Compound **112** was prepared according to Procedure VII using **67** (0.14 g, 0.5 mmol) and 3-bromobenzoyl chloride (0.15 g, 0.68 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.08 g, 56%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.73-7.52 (m, 2H), 7.42-7.28 (m, 2H), 6.89-

6.81 (m, 4H), 1H [6.78, 6.61 (s, s)], 1H [6.67, 6.49 (s, s)], 5.96-5.91 (m, 2H), 1H [5.06, 4.83 (m, m)], 4.35 (d, $J = 4.4$ Hz, 1H), 4.16-3.93 (m, 1H), 3.77 (s, 3H), 3.75-3.63 (m, 1H), 3.28-3.04 (m, 1H), 2.90-2.66 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.4, 169.6, 154.6, 153.2, 147.3, 147.0, 138.7, 133.1, 133.0, 131.2, 130.7, 130.4, 130.1, 128.8, 127.8, 126.4, 125.6, 125.3, 123.2, 122.9, 116.1, 115.7, 115.2, 115.1, 109.6, 109.0, 107.7, 107.3, 101.6, 71.4, 70.4, 58.0, 56.2, 52.6, 43.2, 35.8, 29.9, 28.4. HRMS calcd. for $\text{C}_{25}\text{H}_{23}\text{NO}_5\text{Br}$, 496.07541 $[\text{M} + \text{H}]^+$; found, 496.07478 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{25}\text{H}_{22}\text{NO}_5\text{Br}$): C, H, N.

(6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (113).

Compound **113** was prepared according to Procedure VII using **68** (0.11 g, 0.3 mmol) and benzoyl chloride (0.06 g, 0.4 mmol, 1.2 equiv). The crude material was as a white solid (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.09 g, 62%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.48-7.29 (m, 5H), 6.88-6.78 (m, 4H), 6.36-6.24 (m, 2H), 1H [5.43, 4.88 (dd, $J_1 = 3.4$ Hz, $J_2 = 9.4$ Hz; dd, $J_1 = 6.0$ Hz, $J_2 = 13.2$ Hz)], 1H [4.47, 4.32 (dd, $J_1 = 3.2$ Hz, $J_2 = 10.4$ Hz; dd, $J = 7.4$ Hz, $J = 9.8$ Hz)], 4.09-3.99 (m, 1H), 3.84-3.71 (m, 10H), 3.35-3.10 (m, 1H), 2.89-2.69 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 172.1, 160.2, 157.0, 154.1, 153.5, 153.0, 137.7, 137.0, 136.5, 130.3, 129.6, 128.8, 128.3, 127.8, 126.8, 115.8, 115.5, 114.8, 114.0, 105.0, 96.9, 67.4, 56.0, 55.6, 53.4, 48.2, 42.0, 35.1, 29.8. HRMS calcd. for $\text{C}_{26}\text{H}_{28}\text{NO}_5$, 434.19620 $[\text{M} + \text{H}]^+$; found, 434.19690 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{27}\text{NO}_5$): C, H, N.

(3-chlorophenyl)(6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (114).

Compound **114** was prepared according to Procedure VII using **68** (0.11 g, 0.3 mmol) and 3-chlorobenzoyl chloride (0.07 g, 0.4 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.08 g, 51%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.52-7.22 (m, 4H), 6.88-6.79 (m, 4H), 6.37-6.22 (m, 2H), 1H [5.36, 4.85 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 6.2$ Hz, $J_2 = 13.4$ Hz)], 1H [4.46, 4.30 (dd, $J_1 = 2.8$ Hz, $J_2 = 10.0$ Hz; dd, $J_1 = 7.2$ Hz, $J_2 = 10.0$ Hz)], 4.10-3.95 (m, 1H), 3.84-3.74 (m, 9H), 3.75-3.70 (m, 1H), 3.36-3.08 (m, 1H), 2.72-2.87 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.4, 169.5, 160.3, 159.9, 157.0, 154.1, 153.3, 152.8, 138.9, 138.1, 137.5, 136.5, 134.4, 130.2, 129.6, 128.3, 125.8, 115.8, 115.3, 114.9, 114.3, 113.6, 105.0, 104.5, 96.9, 67.3, 56.0, 55.6, 53.5,

42.0, 35.1, 30.0. HRMS calcd. for $C_{26}H_{27}NO_5Cl$, 468.15723 $[M + H]^+$; found, 468.15753 $[M + H]^+$. Anal.

($C_{26}H_{27}NO_5Cl$): C, H, N.

(3-bromophenyl)(6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(115). Compound **115** was prepared according to Procedure VII using **68** (0.11 g, 0.3 mmol) and 3-bromobenzoyl chloride (0.09 g, 0.4 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.10 g, 58%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.70-7.13 (m, 4H), 6.86-6.76 (m, 4H), 6.34-6.18 (m, 2H), 1H [5.34, 4.82 (dd, $J_1 = 3.4$ Hz, $J_2 = 10.2$ Hz; dd, $J_1 = 6.4$ Hz, $J_2 = 13.2$ Hz)], 1H [4.43, 4.27 (dd, $J_1 = 3.4$ Hz, $J_2 = 10.2$ Hz; dd, $J_1 = 7.2$ Hz, $J_2 = 10.0$ Hz)], 4.10-3.92 (m, 2H), 3.81-3.69 (m, 9H), 3.33-3.06 (m, 1H), 2.84-2.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.3, 169.4, 160.3, 159.9, 157.0, 154.1, 152.8, 138.3, 137.5, 136.5, 132.6, 131.1, 129.9, 126.3, 122.5, 115.8, 115.3, 114.9, 113.6, 105.0, 104.5, 96.9, 67.2, 56.0, 55.6, 53.5, 42.0, 35.1, 28.5. HRMS calcd. for $C_{26}H_{27}NO_5Br$, 512.10671 $[M + H]^+$; found, 512.10713 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Br$): C, H, N.

(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (116).

Compound **116** was prepared according to Procedure VII using **69** (0.6 g, 2.0 mmol) and benzoyl chloride (0.34 g, 2.4 mmol, 1.2 equiv). The crude material was subjected to flash column chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.6 g, 74%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.52-7.22 (m, 5H), 6.92-6.00 (m, 7H), 1H [5.20, 4.87 (dd, $J_1 = 3.2$ Hz, $J_2 = 8.0$ Hz; dd, $J_1 = 5.2$ Hz, $J_2 = 12.0$ Hz)], 4.35 (m, 1H), 4.13-3.90 (m, 1H), 3.80-3.63 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.30-3.14 (m, 1H), 2.94-2.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 171.3, 159.2, 158.7, 154.4, 154.2, 153.2, 152.7, 136.8, 135.8, 129.8, 128.8, 128.6, 127.7, 126.8, 125.7, 124.8, 116.0, 115.6, 114.9, 113.7, 113.1, 71.4, 56.0, 55.9, 55.6, 51.8, 42.8, 35.4, 30.1, 28.7. HRMS calcd. for $C_{25}H_{26}NO_5$, 404.18564 $[M + H]^+$; found, 404.18527 $[M + H]^+$. Anal. ($C_{25}H_{25}NO_5$): C, H, N.

(3-chlorophenyl)(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(117). Compound **117** was prepared according to Procedure VII using **69** (0.25 g, 0.8 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep

4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.1 g, 27%).

^1H NMR (CDCl_3 , 400 MHz) δ : 7.61-6.94 (m, 5H), 6.89-5.98 (m, 6H), 1H [5.15, 4.87 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.6$ Hz; dd, $J_1 = 5.4$ Hz, $J_2 = 12.6$ Hz)], 4.36 (m, 1H), 1H [4.15, 3.94 (m, m)], 3.81 (s, 3H), 3.77 (s, 3H), 3.76-3.69 (m, 1H), 3.31-3.14 (m, 1H), 2.98-2.74 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.4, 169.7, 159.2, 158.8, 154.4, 153.0, 152.6, 138.4, 138.2, 136.6, 135.6, 134.9, 134.5, 130.2, 129.9, 128.7, 128.3, 128.2, 127.1, 125.8, 125.4, 124.9, 124.4, 115.9, 115.5, 115.0, 114.9, 114.2, 113.8, 113.2, 113.0, 71.3, 70.2, 57.3, 55.9, 55.5, 52.0, 42.8, 35.4, 35.4, 30.0, 28.5. HRMS calcd. for $\text{C}_{25}\text{H}_{24}\text{NO}_4\text{Cl}$, 438.14636 $[\text{M} + \text{H}]^+$; found, 438.14666 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{25}\text{H}_{23}\text{NO}_4\text{Cl}$): C, H, N.

(3-bromophenyl)(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(118). Compound **118** was prepared according to Procedure VII using **69** (0.25 g, 0.8 mmol) and 3-bromobenzoyl chloride (0.22 g, 1.0 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.22 g, 55%). ^1H NMR (CDCl_3 , 400 MHz) δ : 8.19-7.50 (m, 2H), 7.42-7.20 (m, 3H), 6.93-5.96 (6H), 1H [5.14, 5.12 (dd, $J = 3.4$ Hz, $J = 9.4$ Hz; dd, $J = 5.2$ Hz, 12.8 Hz)], 4.35-4.32 (m, 1H), 1H [4.12, 3.68 (m, m)], 3.98-3.84 (m, 1H), 3.30-3.08 (m, 1H), 2.94-2.72 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.3, 169.6, 158.8, 154.4, 153.1, 152.6, 138.5, 136.6, 136.3, 135.6, 133.2, 132.9, 131.0, 130.5, 130.1, 129.9, 128.8, 128.7, 128.3, 126.3, 125.3, 124.4, 122.7, 115.9, 115.5, 115.0, 114.9, 114.3, 113.8, 113.2, 113.0, 71.3, 70.2, 57.3, 55.9, 55.5, 52.0, 42.9, 35.5, 29.9, 28.5. HRMS calcd. for $\text{C}_{25}\text{H}_{25}\text{NO}_4\text{Br}$, 482.09615 $[\text{M} + \text{H}]^+$; found, 482.09600 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{25}\text{H}_{24}\text{NO}_4\text{Br}$): C, H, N.

1-(3-(6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)ethanone

(119). Compound **119** was prepared according to Procedure VIII using tetrahydroisoquinoline **69** (0.4 g, 1.3 mmol, 1.0 equiv) and 3-acetylbenzoic acid (0.22 g, 1.3 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (mixture of two rotamers, 0.3 g, 50%). ^1H NMR (CDCl_3 , 400 MHz) δ : 8.13-7.97 (m, 2H), 7.71-7.45 (m, 2H), 6.91-5.97 (m, 7H), 1H [5.10, 4.87 (dd, $J_1 = 3.4$ Hz, $J_2 = 9.4$ Hz; dd, $J_1 = 5.8$ Hz, $J_2 = 12.6$ Hz)], 4.36 (m, 1H), 4.13-3.91 (m, 1H), 3.77-3.69 (m, 8H), 3.31-2.73 (m, 2H), 2.62-2.51 (m, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 197.7, 171.0, 170.2, 159.3, 158.8, 154.5, 152.6, 137.6, 137.3, 137.1, 136.6, 132.2, 131.3, 129.4, 129.2, 128.9, 128.3, 128.0, 126.9, 115.9, 115.6, 114.9, 114.9, 114.3, 113.8, 113.2, 113.0, 71.4, 70.3, 57.4, 55.9, 55.5, 52.0,

43.0, 35.4, 30.0, 28.5, 27.0. HRMS calcd. for $C_{27}H_{28}NO_5$, 446.19620 $[M + H]^+$; found, 446.19649 $[M + H]^+$. Anal. ($C_{27}H_{27}NO_5$): C, H, N.

(3-chlorophenyl)(5,6-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(120). Compound **120** was prepared according to Procedure VII using **76** (0.20 g, 0.61 mmol) and 3-chlorobenzoyl chloride (0.12 g, 0.67 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.14 g, 49%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.58-7.24 (m, 4H), 7.03-5.97 (m, 6H), 1H [5.12, 4.87 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.4$ Hz; dd, $J_1 = 5.8$ Hz, $J_2 = 13$ Hz)], 4.33 (d, $J = 4.8$ Hz, 1H), 4.15-3.88 (m, 1H), 3.84-3.73 (m, 10H), 1H [3.60, 3.17 (m, m)], 3.08-2.68 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.3, 169.6, 154.4, 154.3, 153.0, 152.5, 152.1, 151.5, 147.0, 146.4, 138.2, 134.9, 134.5, 130.2, 129.8, 129.7, 128.8, 128.2, 127.1, 126.2, 125.9, 125.3, 124.9, 122.6, 115.9, 115.4, 114.9, 110.7, 71.2, 60.4, 57.2, 57.1, 56.1, 56.0, 55.9, 51.7, 42.4, 24.2, 22.9. HRMS calcd. for $C_{26}H_{27}NO_5Cl$, 468.15723 $[M + H]^+$; found, 468.15639 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N.

(3-bromophenyl)(5,6-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(121). Compound **121** was prepared according to Procedure VII using **76** (0.20 g, 0.61 mmol) and 3-bromobenzoyl chloride (0.15 g, 0.67 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes) to afford the title compound as a white amorphous solid (0.16 g, 51%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.73-7.50 (m, 2H), 7.43-7.21 (m, 2H), 6.89-5.96 (m, 6H), 1H [5.12, 4.87 (dd, $J_1 = 3.4$ Hz, $J_2 = 9.4$ Hz; dd, $J_1 = 5.8$ Hz, $J_2 = 13$ Hz)], 4.32 (d, $J = 4.4$ Hz, 1H), 4.15-3.88 (m, 1H), 3.84-3.73 (m, 10H), 1H [3.60, 3.17 (m, m)], 3.08-2.66 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.2, 169.5, 154.3, 153.0, 152.5, 152.0, 151.5, 146.4, 138.4, 132.9, 132.7, 131.0, 130.4, 129.9, 129.7, 128.8, 126.2, 125.3, 123.0, 122.7, 115.5, 114.8, 110.6, 71.2, 60.3, 57.2, 56.1, 56.0, 55.9, 51.7, 42.5, 35.1, 24.2, 22.9. HRMS calcd. for $C_{26}H_{27}NO_5Br$, 512.10671 $[M + H]^+$; found, 512.10571 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Br$): C, H, N.

(3-chlorophenyl)(1-((4-methoxyphenoxy)methyl)-6,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(122). Compound **122** was prepared according to Procedure VII using **70** (0.25 g, 0.8 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1.0 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO,

Redisep 4g column, 0-60% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.3 g, 82%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.61-7.25 (m, 4H), 7.07-5.97 (m, 6H), 1H [5.14, 4.87 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.4$ Hz; dd, $J_1 = 5.8$ Hz, $J_2 = 13.0$ Hz)], 4.38 (m, 1H), 1H [4.16, 3.96 (m, m)], 3.76 (s, 3H), 3.72-3.67 (m, 1H), 3.30-3.06 (m, 1H), 2.86-2.72 (m, 2H), 2.30-2.19 (m, 7H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.5, 169.7, 154.4, 153.1, 152.6, 138.3, 136.7, 136.0, 135.2, 135.0, 134.9, 134.5, 132.5, 131.6, 130.8, 130.3, 129.9, 129.8, 129.6, 128.2, 127.1, 125.9, 124.9, 115.9, 115.5, 114.9, 71.3, 57.5, 55.9, 55.9, 52.1, 43.1, 35.8, 27.8, 19.7. HRMS calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_3\text{Cl}$, 436.16740 $[\text{M} + \text{H}]^+$; found, 436.16736 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{26}\text{NO}_3\text{Cl}$): C, H, N.

(3-bromophenyl)(1-((4-methoxyphenoxy)methyl)-6,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

(123). Compound **123** was prepared according to Procedure VII using **70** (0.25 g, 0.8 mmol) and 3-bromobenzoyl chloride (0.22 g, 1.0 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes) to afford the title compound as a white amorphous solid (mixture of two rotamers, 0.3 g, 74%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.77-7.22 (m, 4H), 7.07-5.98 (6H), 1H [dd, $J_1 = 3.2$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 5.6$ Hz, $J_2 = 12.8$ Hz], 4.38 (m, 1H), 1H [4.15, 3.96 (m, m)], 3.76 (s, 3H), 3.74-3.64 (m, 1H), 3.30-3.05 (m, 1H), 2.9-2.68 (m, 2H), 2.25-2.21 (m, 6H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.3, 169.5, 154.4, 154.2, 153.1, 152.6, 138.7, 138.5, 136.7, 135.9, 135.2, 135.0, 132.8, 132.5, 131.6, 130.8, 130.5, 130.1, 129.9, 129.6, 128.5, 126.3, 125.4, 122.9, 122.7, 115.9, 115.5, 114.9, 76.8, 71.3, 70.2, 57.6, 56.0, 55.9, 52.1, 43.1, 35.8, 27.8, 19.8, 19.7. HRMS calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_3\text{Br}$, 480.11688 $[\text{M} + \text{H}]^+$; found, 480.11704 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{26}\text{NO}_3\text{Br}$): C, H, N.

(1-((4-methoxyphenoxy)methyl)-6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (124).

Compound **124** was prepared according to Procedure VII using **71** (0.18 g, 0.64 mmol, 1.0 equiv) and benzoyl chloride (0.11 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white amorphous solid (mixture of two rotamers, 0.11 g, 45%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.50-6.02 (m, 12H), 1H [5.21, 4.88 (m, m)], 1H [4.38, 4.27 (m, m)], 3.92-3.46 (m, 6H), 3.27-2.70 (m, 2H), 2.39-2.25 (m, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 172.5, 171.3, 154.2, 138.4, 138.1, 137.0, 136.8, 134.4, 130.4, 129.8, 129.5, 128.8, 128.7, 128.6, 127.7, 127.6, 127.2, 126.8, 126.6, 126.0, 115.9, 115.6, 114.9, 71.5, 70.4, 67.1, 57.5, 56.0, 52.7, 52.0, 45.6, 43.0, 35.5, 34.0, 29.8, 28.3, 21.6, 21.3. HRMS calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_3$, 390.20637 $[\text{M} + \text{H}]^+$; found, 390.20671 $[\text{M} + \text{H}]^+$.

(3-chlorophenyl)(1-((4-methoxyphenoxy)methyl)-6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (125).

Compound **125** was prepared according to Procedure VII using **71** (0.18 g, 0.64 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.13 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white amorphous solid (mixture of two rotamers, 0.10 g, 37%). ¹H NMR (CDCl₃, 400 MHz) δ: 6.57-5.99 (m, 11H), 1H [5.14, 4.85 (m; dd, $J_1 = 5.6$ Hz, $J_2 = 13.2$ Hz)], 1H [4.36, 4.25 (m, m)], 4.20-3.56 (m, 6H), 3.48-2.71 (m, 3H), 2.33-2.26 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.9, 154.4, 138.2, 137.8, 134.6, 130.2, 129.8, 129.6, 128.8, 128.2, 127.7, 127.4, 127.0, 126.9, 126.1, 124.8, 115.9, 115.6, 115.5, 115.0, 70.2, 66.9, 57.6, 56.0, 52.6, 52.2, 45.5, 43.0, 35.6, 35.2, 29.7, 21.6, 21.3. HRMS calcd. for C₂₅H₂₅NO₃Cl, 422.15175 [M + H]⁺; found, 422.15201 [M + H]⁺.

(3-bromophenyl)(1-((4-methoxyphenoxy)methyl)-6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (126).

Compound **126** was prepared according to Procedure VII using **71** (0.18 g, 0.64 mmol, 1.0 equiv) and 3-bromobenzoyl chloride (0.17 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white amorphous solid (mixture of two rotamers, 0.11 g, 37%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.74-5.99 (11H), 1H [5.15, 4.85 (m; dd, $J_1 = 5.6$ Hz, $J_2 = 13.2$ Hz)], 1H [4.36, 4.26 (m, m)], 4.17-3.57 (m, 6H), 3.45-3.08 (m, 1H), 2.98-2.72 (m, 2H), 2.34-2.27 (m, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ: 170.7, 154.3, 152.6, 138.5, 137.8, 134.2, 132.8, 132.5, 130.3, 130.1, 129.8, 129.7, 128.8, 127.8, 127.5, 127.2, 126.1, 125.2, 122.6, 115.9, 115.5, 114.9, 71.3, 57.6, 55.9, 52.7, 45.5, 28.2, 21.6, 21.3. HRMS calcd. for C₂₅H₂₅NO₃Br, 466.10123 [M + H]⁺; found, 466.10158 [M + H]⁺.

(6,7-dimethoxy-1-(((4-methoxyphenyl)thio)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (127).

Compound **127** was prepared according to Procedure VII using **80** (0.2 g, 0.58 mmol) and benzoyl chloride (0.10 g, 0.70 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.10 g, 36%, mixture of rotamers). ¹H NMR (CDCl₃, 400 MHz) δ: 7.48 (d, $J = 8.8$ Hz, 2H), 7.43-7.37 (m, 5H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.62 (s, 1H), 6.57 (s, 1H), 5.86 (m, 1H), 1H [4.92, 4.75 (m, m)], 3.86-3.76 (m, 9H), 3.60-3.53 (m, 1H), 3.46-3.35 (m, 1H), 3.14-3.07 (m, 1H), 2.86-2.61 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ: 171.2, 159.3, 148.3, 147.8, 136.7, 133.6, 129.8, 128.8, 127.8, 127.5, 126.9, 126.7, 125.7, 114.9, 114.8, 111.5, 110.6, 56.3, 56.2, 56.0, 55.6, 55.5, 51.3, 42.3,

29.1. HRMS calcd. for $C_{26}H_{28}NO_4S$, 450.17336 $[M + H]^+$; found, 450.17354 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_4S$): C, H, N.

(6,7-dimethoxy-1-((4-nitrophenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (128).

Compound **128** was prepared according to Procedure VII using tetrahydroisoquinoline **77** (0.7 g, 2.1 mmol, 1.0 equiv) and benzoyl chloride (0.3 mL, 2.5 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow amorphous solid (0.86 g, 68%, mixture of rotamers). TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.44; 1H NMR ($CDCl_3$, 400 MHz) δ : 8.19-8.17 (m, 2H), 7.46-7.39 (m, 5H), 7.02-7.00 (m, 1H), 6.87-6.77 (m, 1H), 6.71-6.63 (m, 1H), 1H [6.46, 5.99 (s,m)], 1H [5.24, 4.89 (d, J = 5.2 Hz; d, J = 7.6)], 4.52-4.44 (m, 2H), 4.29-4.05 (m, 1H), 3.91-3.78 (m, 6H), 3.63-3.56 (m, 1H), 3.22-3.11 (m, 1H), 2.94-2.67 (m, 2H) ^{13}C NMR (100 MHz) δ : 171.8, 171.4, 163.8, 163.5, 149.1, 148.6, 148.1, 141.9, 136.2, 130.1, 128.9, 128.8, 127.6, 126.8, 126.6, 126.2, 124.6, 123.3, 114.9, 114.6, 112.1, 111.6, 110.4, 109.8, 106.5, 70.9, 70.2, 56.9, 56.3, 56.2, 53.7, 51.4, 43.1, 35.6, 29.2, 27.8. HRMS calcd. For $C_{25}H_{25}N_2O_6$, 449.17071 $[M + H]^+$; found, 449.17080 $[M + H]^+$; Anal. ($C_{25}H_{24}N_2O_6$): C, H, N.

(3-chlorophenyl)(6,7-dimethoxy-1-((4-nitrophenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (129).

Compound **129** was prepared according to Procedure VII using tetrahydroisoquinoline **77** (0.70 g, 2.0 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.3 mL, 2.5 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow amorphous solid (0.86 g, 86 %, mixture of rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.50; 1H NMR ($CDCl_3$, 400 MHz) δ : 8.17-8.15 (m, 2H), 7.55-7.33 (m, 2H), 7.26-7.24 (m, 1H), 7.00-6.98 (m, 1H), 6.92-6.76 (m, 1H), 6.67-6.63 (m, 1H), 1H [6.47, 5.97 (s, m)], 1H [5.16, 4.86 (d, J = 6.8 Hz; d, J = 7.6 Hz)], 4.47-4.27 (m, 2H), 4.09-4.06 (m, 1H), 3.85-3.79 (m, 6H), 3.65-3.58 (m, 1H), 3.22-3.10 (m, 1H), 2.92-2.70 (m, 2H); ^{13}C NMR (100 MHz) δ : 170.3, 169.8, 163.7, 163.1, 149.2, 148.7, 147.9, 142.0, 137.9, 134.9, 130.3, 130.2, 128.0, 127.5, 127.0, 126.4, 126.3, 125.6, 124.8, 124.3, 122.9, 114.9, 114.5, 112.1, 111.6, 110.3, 109.7, 70.8, 70.0, 60.6, 57.1, 56.3, 56.2, 53.7, 51.6, 49.6, 43.1, 35.7, 29.1, 27.7, 21.3. HRMS calcd. for $C_{25}H_{24}N_2O_6Cl$, 483.13174 $[M + H]^+$; found, 483.13178 $[M + H]^+$.

((3-bromophenyl)(6,7-dimethoxy-1-((4-nitrophenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone)

(130). Compound **130** was prepared according to Procedure VII using tetrahydroisoquinoline **77** (0.7 g, 2.1 mmol, 1.0 equiv) and 3-bromobenzoyl chloride (0.3 mL, 2.5 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow amorphous solid (0.86 g, 68%, mixture of rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.43; ^1H NMR (CDCl_3 , 400 MHz) δ : 8.18-8.14 (m, 2H), 7.71-7.49 (m, 2H), 7.38-7.24 (m, 2H), 7.00-6.98 (m, 1H), 6.93-6.76 (m, 1H), 6.67-6.63 (m, 1H), 1H [6.48, 5.96 (s, m)], 1H [5.17, 4.85 (d, J = 6.8 Hz; dd, J_1 = 4.8 Hz, J_2 = 13 Hz)], 4.50-4.42 (m, 1H), 4.32-4.00 (m, 1H), 3.84-3.79 (m, 6H), 3.65-3.57 (m, 1H), 3.22-3.09 (m, 1H), 2.92-2.69 (m, 2H); ^{13}C NMR (100 MHz) δ : 170.1, 169.7, 163.6, 163.1, 149.2, 148.7, 148.2, 147.9, 142.2, 142.1, 138.1, 133.1, 132.9, 130.9, 130.5, 130.3, 129.8, 127.5, 126.5, 125.3, 124.3, 123.0, 114.8, 114.6, 112.1, 111.6, 110.3, 109.7, 70.8, 69.9, 65.3, 64.2, 60.6, 57.1, 56.3, 56.2, 51.6, 43.1, 35.7, 29.1, 27.7, 21.3. HRMS calcd. For $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_6\text{Br}$, 527.08122 $[\text{M} + \text{H}]^+$; found, 527.08124 $[\text{M} + \text{H}]^+$.

((1-((4-aminophenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone) (131).

Compound **128** (0.30 g, 0.7 mmol, 1.0 equiv) and tin (II) chloride dihydrate (0.7 g, 3.3 mmol, 5.0 equiv) were suspended in EtOH (2.7 ml) and heated to 70 °C. The reaction mixture was allowed to stir for three hours. Upon completion, the reaction was basified to pH 9 with saturated NaHCO_3 . DCM was added and the mixture was filtered through a silica plug eluting with 10% MeOH/DCM. The organics were separated and washed with water and brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 25 g column, 10-80% EtOAc/hexanes gradient) to yield the title compound as a off-white amorphous solid (0.09 g, 33%, mixture of rotamers) TLC (MeOH/DCM, 1:10, v/v) R_f = 0.73; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.52-7.50 (m, 1H), 7.39 (s, 4H), 6.98-6.76 (m, 2H), 6.65-6.57 (m, 3H), 1H [6.46, 5.95 (s, m)], 1H [5.11, 4.87 (dd, J_1 = 4.4 Hz, J_2 = 8.8 Hz; dd, J_1 = 5.6, J_2 = 13)], 4.36-4.07 (m, 2H), 3.94-3.76 (m, 6H), 3.67-3.59 (m, 1H), 3.43 (s, 2H), 3.23-3.09 (m, 1H), 2.86-2.63 (m, 2H). ^{13}C NMR (100 MHz) δ : 171.9, 171.2, 152.1, 151.7, 148.7, 148.3, 147.9, 147.7, 140.6, 136.7, 129.8, 129.7, 128.7, 128.6, 127.8, 127.4, 126.9, 126.5, 125.7, 124.6, 116.5, 116.2, 115.8, 114.2, 112.0,

111.6, 110.1, 71.3, 70.6, 57.4, 56.2, 56.1, 53.7, 51.7, 42.9, 35.7, 29.9, 29.3, 27.9, 22.9. HRMS calcd. for $C_{25}H_{27}N_2O_4$, 419.19653 $[M + H]^+$; found, 419.19721 $[M + H]^+$.

((1-((4-aminophenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-chlorophenyl)methanone)

(132). Compound **129** (0.56 g, 1.1 mmol, 1.0 equiv) and tin (II) chloride dihydrate (1.2 g, 5.7 mmol, 5.0 equiv) were suspended in EtOH (5.8 ml) and heated to 70 °C. The reaction mixture was allowed to stir for three hours. Upon completion, the reaction was basified to pH 9 with saturated $NaHCO_3$. DCM was added and the mixture was filtered through a silica plug eluting with 10% MeOH/DCM. The organics were separated and washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.21 g, 42%, mixture of rotamers) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.64; 1H NMR ($CDCl_3$, 400 MHz) δ : 7.60-7.31 (m, 3H), 7.29-7.24 (m, 1H), 6.74-6.75 (m, 1H), 6.70-6.60 (m, 4H), 1H [6.46, 5.92 (s,m)], 1H [5.04, 4.84 (dd, J_1 = 3.6, J_2 = 9.2; dd, J_1 = 5.6, J_2 = 13)], 4.32-4.29 (m, 1H), 4.14-3.91 (m, 2H), 3.85-3.77 (m, 6H), 3.74-3.64 (m, 1H), 3.44 (s, 2H), 3.23-3.07 (m, 1H), 2.85-2.64 (m, 2H). ^{13}C NMR (100 MHz) δ : 170.3, 169.6, 151.9, 151.5, 148.8, 148.4, 147.9, 147.7, 140.8, 138.3, 138.1, 134.8, 134.5, 130.2, 129.9, 129.8, 128.2, 127.3, 127.1, 126.2, 125.9, 125.3, 124.9, 124.1, 116.5, 116.1, 115.6, 111.9, 111.5, 110.8, 110.4, 109.9, 104.4, 87.2, 81.2, 76.9, 71.2, 70.3, 65.6, 60.6, 57.5, 56.2, 56.1, 54.8, 51.9, 42.8, 35.7, 29.2, 27.8, 21.3. HRMS calcd. for $C_{25}H_{26}N_2O_4Cl$, 453.15756 $[M + H]^+$; found, 453.15723 $[M + H]^+$. Anal. ($C_{25}H_{26}N_2O_4Cl$): C, H, N.

((1-((4-aminophenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-bromophenyl)methanone)

(133). Compound **130** (0.20 g, 0.4 mmol, 1.0 equiv) and tin (II) chloride dihydrate (0.4 g, 1.9 mmol, 5.0 equiv) were suspended in EtOH (1.5 ml) and heated to 70 °C. The reaction mixture was allowed to stir for three hours. Upon completion, the reaction was basified to pH 9 with saturated $NaHCO_3$. DCM was added and the mixture was filtered through a silica plug eluting with 10% MeOH/DCM. The organics were separated and washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 25 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a brown amorphous solid (0.13 g, 66%, mixture of rotamers) TLC (MeOH:DCM, 1:10, v/v) R_f = 0.73; 1H NMR ($CDCl_3$, 400 MHz) δ : 7.54-7.42 (m, 3H), 7.29-7.25 (m, 3H), 6.78-6.75 (m, 1H), 6.71 (m, 1H), 6.65-6.61 (m, 3H), 1H [6.46, 5.92 (s,m)] 1H [5.04,

4.83 (dd, $J_1 = 3.5$, $J_2 = 9.1$; dd, $J_1 = 6.4$, $J_2 = 13$), 4.32-4.10 (m, 1H), 3.86-3.78 (m, 6H), 3.74-3.64 (m, 1H), 3.43 (s, 2H), 3.23-3.19 (m, 1H), 2.85-2.65 (m, 2H). ^{13}C NMR (100 MHz) δ : 170.2, 169.4, 151.9, 151.5, 148.9, 148.4, 148.0, 147.8, 140.9, 140.7, 138.6, 132.9, 132.7, 131.0, 130.5, 130.2, 129.9, 127.3, 126.3, 126.2, 125.4, 124.2, 122.9, 116.7, 116.1, 115.7, 112.0, 111.6, 109.9, 71.2, 70.3, 57.5, 56.3, 56.1, 53.7, 51.9, 42.8, 35.7, 29.2, 27.9. HRMS calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_4\text{Br}$, 497.10705 $[\text{M} + \text{H}]^+$; found, 497.10746 $[\text{M} + \text{H}]^+$.

(3-chlorophenyl)(6,7-dimethoxy-1-((4-(methylamino)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (134). Compound **132** (0.1 g, 0.2 mmol, 1 equiv.) and paraformaldehyde (0.03 g, 1.10 mmol, 5 equiv.) were suspended in dry methanol (2.8 ml) and sodium methoxide (0.05 ml, 0.2 mmol, 1 equiv.) was added dropwise at 0°C. After the addition was complete, the reaction was heated to reflux. After stirring at reflux for one hour the reaction was allowed to cool to room temperature. Sodium borohydride (0.04 g, 1.10 mmol, 5 equiv) was added and the reaction was heated to reflux for one additional hour. The reaction was allowed to cool to room temperature and 1M NaOH was added. The reaction mixture was extracted with DCM, washed with water and brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 20 g column, 0-80 % EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.07 g, 72 %). TLC (EtOAc: hexanes, 1:1, v/v) $R_f = 0.17$; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.61-7.27 (m, 4H), 6.82-7.78 (m, 1H), 6.76-6.73 (d, 1H, $J = 8.4$ Hz), 1H [6.65, 6.60 (s,s)], 6.56-6.54 (m, 2H), 1H [6.47, 5.93 (s, m)], 1H [5.05, 4.85 (dd, $J_1 = 3.6$ Hz, $J_2 = 9.2$ Hz; dd, $J_1 = 5.6$, $J_2 = 13$ Hz)], 4.33-4.31 (m, 1H), 4.16-3.93 (m, 1H), 3.86-3.78 (m, 6H), 3.73-3.65 (m, 1H), 3.24-3.08 (m, 1H), 2.85-2.81 (m, 1H), 2.78 (s, 3H), 2.77-2.65 (m, 1H). ^{13}C NMR (100 MHz) δ : 170.3, 169.7, 151.4, 150.9, 148.8, 148.4, 147.9, 147.7, 144.3, 114.1, 138.3, 134.9, 134.5, 130.2, 129.9, 129.8, 128.2, 127.3, 127.1, 126.2, 125.9, 125.3, 124.9, 121.4, 116.2, 115.8, 113.9, 111.9, 111.5, 110.4, 109.9, 71.3, 70.5, 66.1, 57.7, 56.3, 56.1, 52.5, 51.9, 42.8, 35.6, 31.9, 29.2, 27.8, 15.5. HRMS calcd. for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_4\text{Cl}$, 467.1732 $[\text{M} + \text{H}]^+$; found, 467.17265 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_4\text{Cl}$): C, H, N.

(3-bromophenyl)(6,7-dimethoxy-1-((4-(methylamino)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (135). Compound **133** (0.22 g, 0.44 mmol, 1 equiv.) and paraformaldehyde (0.066 g, 2.19 mmol, 5 equiv.) were suspended in dry methanol (5.5 ml) and sodium methoxide (0.10 ml, 0.44 mmol, 1 equiv.) was added dropwise at 0°C. After the addition was complete, the reaction was heated to reflux. After one hour at reflux, the

reaction was allowed to cool to room temperature. Sodium borohydride (0.083 g, 2.19 mmol, 5 equiv.) was added and the reaction was heated to reflux for one additional hour. The reaction was allowed to cool to room temperature and 1 M NaOH was added. The reaction mixture was extracted with DCM, washed with water and brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 20 g column, 0-80 % EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.15 g, 68%). TLC (MeOH:DCM, 1:10, v/v) R_f = 0.85; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.77-7.51 (m, 2H), 7.45-7.25 (m, 2H), 6.83-6.65 (m, 3H), 6.60-6.58 (m, 2H), 1H [6.47, 5.93 (s, m)], 1H [5.05, 4.84 (d, J = 5.2 Hz; dd, J_1 = 5.6 Hz, J_2 = 12.8 Hz)], 4.33-4.32 (m, 1H), 4.16-3.92 (m, 2H), 3.86-3.85 (m, 6H), 3.74-3.65 (m, 1H), 3.24-3.08 (m, 1H), 2.85-2.83 (m, 1H), 2.79 (s, 3H), 2.77-2.65 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.2, 169.4, 151.3, 150.8, 148.8, 148.4, 147.9, 147.7, 144.4, 138.5, 132.8, 131.7, 131.1, 130.4, 130.2, 129.9, 127.3, 126.3, 126.2, 125.4, 125.4, 124.2, 122.9, 233.6, 116.2, 115.8, 113.8, 111.9, 111.5, 110.4, 109.9, 71.3, 70.5, 57.6, 56.2, 56.2, 51.9, 42.9, 35.7, 32.1, 31.8, 30.8, 29.8, 29.6, 29.2, 27.8, 22.9, 14.4, 13.9. HRMS calcd. For $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_4\text{Cl}$, 467.1732 $[\text{M} + \text{H}]^+$; found, 467.17265 $[\text{M} + \text{H}]^+$.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(furan-2-yl)methanone (136).

Compound **136** was synthesized according to Procedure VII using **64** (0.1 g, 0.3 mmol) and 2-furoyl chloride (0.05 g, 0.4 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.1 g, 99%, mixture of rotamers). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.50-6.60 (m, 7H), 6.48 (m, 1H), 5.79 (t, J = 5.8 Hz, 1H), 4.73-4.20 (m, 3H), 3.85-3.83 (m, 6H), 3.73 (s, 3H), 3.25 (m, 1H), 3.09-2.99 (m, 1H), 2.88-2.71 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 164.1, 163.8, 158.6, 158.1, 154.4, 154.3, 152.7, 152.4, 151.0, 150.5, 148.2, 144.1, 126.9, 126.4, 123.5, 116.6, 115.9, 114.8, 111.4, 111.0, 110.2, 109.3, 108.4, 71.0, 70.4, 56.2, 56.1, 55.9, 42.2, 37.5, 29.1, 27.4. HRMS calcd. for $\text{C}_{24}\text{H}_{26}\text{NO}_6$, 424.17546 $[\text{M} + \text{H}]^+$; found, 424.17636 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{24}\text{H}_{25}\text{NO}_6$): C, H, N.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(isoxazol-5-yl)methanone

(137). Compound **137** was synthesized according to Procedure VII using **64** (0.1 g, 0.3 mmol) and isoxazole-5-carbonyl chloride (0.05 g, 0.4 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.1 g,

99%, mixture of rotamers). ^1H NMR (CDCl_3 , 400 MHz) δ : 1H [8.37, 8.34 (d, $J = 2\text{ Hz}$; dd, $J_1 = 3.6\text{ Hz}$, $J_2 = 1.6\text{ Hz}$)], 1H [6.99, 6.93 (d, $J = 2\text{ Hz}$; d, $J = 2\text{ Hz}$)], 6.96-6.67 (m, 6H), 1H [5.87, 5.65 (dd, $J_1 = 5.2\text{ Hz}$, $J_2 = 5.6\text{ Hz}$; dd, $J_1 = 4.4\text{ Hz}$, $J_2 = 8.8\text{ Hz}$)], 4.83-4.11 (m, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 3.36-2.79 (m, 3H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 164.1, 163.8, 158.6, 158.3, 158.1, 154.4, 154.3, 152.7, 152.4, 151.0, 150.5, 148.9, 148.6, 148.0, 126.9, 126.4, 124.6, 123.5, 115.9, 115.6, 114.9, 111.8, 111.5, 110.3, 110.0, 109.6, 108.1, 70.9, 70.6, 56.6, 56.3, 56.1, 55.9, 53.2, 42.6, 37.1, 29.3, 27.9. HRMS calcd. for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_6$, 425.17071 $[\text{M} + \text{H}]^+$; found, 425.17159 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_6$): C, H, N.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(naphthalen-2-yl)methanone (138). Compound **138** was prepared according to Procedure VII using **64** (0.13 g, 0.4 mmol) and 2-naphthoyl chloride (0.09 g, 0.5 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white amorphous solid (mixture of rotamers, 0.04 g, 21%). ^1H NMR (CDCl_3 , 400 MHz) δ : 8.07-7.83 (m, 4H), 7.66-7.49 (m, 3H), 6.95-6.84 (m, 2H), 6.80 (s, 2H), 1H [6.72, 6.65 (s, s)], 1H [6.45, 6.07 (s, m)], 1H [5.26, 4.97 (dd, $J_1 = 4.0\text{ Hz}$, $J_2 = 8.8\text{ Hz}$; dd, $J_1 = 5.4\text{ Hz}$, $J_2 = 13\text{ Hz}$)], 4.48-4.39 (m, 1H), 4.22-3.96 (m, 1H), 3.89-3.75 (m, 10H), 3.71-3.28 (m, 1H), 3.23-2.87 (m, 1H), 2.86-2.64 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 172.0, 171.2, 154.4, 153.1, 152.7, 148.8, 148.4, 147.9, 147.7, 133.9, 133.8, 133.0, 128.7, 128.0, 127.4, 127.3, 127.0, 126.5, 125.5, 125.4, 124.4, 124.2, 115.9, 115.4, 115.0, 110.5, 110.4, 110.0, 71.2, 56.2, 56.1, 51.8, 29.3. HRMS calcd. for $\text{C}_{30}\text{H}_{30}\text{NO}_5$, 484.21185 $[\text{M} + \text{H}]^+$; found, 484.21169 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{30}\text{H}_{29}\text{NO}_5$): C, H, N.

(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(morpholino)methanone (139). Compound **139** was synthesized according to Procedure VII using **64** (0.12 g, 0.36 mmol) and morpholine-4-carbonyl chloride (0.07 g, 0.44 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.05 g, 31%, mixture of rotamers). ^1H NMR (CDCl_3 , 400 MHz) δ : 6.82 (s, 4H), 6.72 (s, 1H), 6.62 (s, 1H), 5.23-5.20 (m, 1H), 4.24-4.19 (m, 1H), 4.13-4.09 (m, 1H), 3.86 (m, 7H), 3.76 (s, 3H), 3.69 (m, 4H), 3.50-3.24 (m, 5H), 3.30-2.95 (m, 1H), 2.68-2.62 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 154.2, 153.1, 148.1, 147.4, 128.2, 126.5,

115.8, 114.8, 112.1, 109.7, 71.5, 56.2, 56.0, 55.9, 54.9, 39.9, 29.3. HRMS calcd. for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$; found, 330.16968 $[M + H]^+$. Anal. ($C_{19}H_{24}NO_4$): C, H, N.

1-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-morpholinoethanone

(140). Compound **140** was prepared via a two step sequence. Tetrahydroisoquinoline **64** (0.7 g, 2.1 mmol) was dissolved in dry DCM (20 mL) and cooled to 0°C in an ice bath. Triethylamine (0.22 g, 2.1 mmol, 1.0 equiv) was added to the cooled mixture followed by dropwise addition of chloroacetyl chloride (0.24 g, 2.1 mmol, 1.0 equiv). The reaction was warmed to room temperature and stirred for an additional 2 hours. The reaction was quenched with 1M HCl and extracted into DCM (2x). The combined organics were washed with brine and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the α -chloro amide (0.67 g, 78%, mixture of rotamers) as a white amorphous solid. 1H NMR ($CDCl_3$, 400 MHz) δ : 6.85-6.78 (m, 4H), 1H [6.74, 6.71 (s, s)], 1H [6.66, 6.65 (s, s)], 1H [5.72, 4.26 (t, $J = 5.2$ Hz; m)], 1H [5.25, 4.74 (dd, $J_1 = 3.8$ Hz, $J_2 = 9.8$ Hz; m)], 1H [4.58, 4.34 (d, $J = 12.4$ Hz; d, $J = 12.4$ Hz)], 4.22-4.07 (m, 3H), 3.89-3.74 (m, 10H), 3.13-2.68 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 166.7, 166.0, 154.6, 154.3, 152.3, 148.9, 148.4, 148.0, 127.5, 126.4, 125.3, 123.2, 115.9, 115.6, 114.9, 114.8, 111.9, 111.3, 110.4, 110.0, 70.9, 70.7, 56.3, 56.2, 56.1, 55.9, 42.3, 42.0, 41.8, 31.8, 27.8, 22.9. HRMS calcd. for $C_{21}H_{25}NO_5Cl$, 406.14158 $[M + H]^+$; found, 406.14197 $[M + H]^+$. The α -chloro amide (0.20 g, 0.49 mmol, 1.0 equiv) was dissolved in absolute EtOH (10 mL). Morpholine (0.22 g, 0.22 mL, 2.5 mmol, 5.0 equiv) was added to this solution and the reaction was stirred at room temperature for 18 hours. After TLC indicated complete conversion, the volatiles were removed *in vacuo* and the crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient, dry load) to afford the title compound as a white amorphous solid (0.12 g, 53%). 1H NMR ($CDCl_3$, 400 MHz) δ : 6.84-6.77 (m, 4H), 1H [6.74, 6.71 (s, s)], 1H [6.64, 6.63 (s, s)], 1H [5.75, 5.63 (m, m)], 1H [4.74, 4.25 (dd, $J_1 = 4.4$ Hz, $J_2 = 13$ Hz; dd, $J_1 = 5.4$ Hz, $J_2 = 9.8$ Hz)], 4.18-4.06 (m, 2H), 3.91-3.82 (m, 6H), 3.75-3.35 (m, 9H), 3.32-3.23 (m, 1H), 3.09-2.78 (m, 2H), 2.70-2.46 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 168.9, 168.6, 154.4, 154.2, 152.9, 152.6, 148.7, 148.3, 147.8, 127.5, 126.7, 125.7, 124.6, 115.7, 115.5, 114.8, 111.9, 111.4, 110.5, 110.1, 70.9, 67.1, 62.3, 61.6, 56.2, 53.8, 51.7, 29.3, 28.0. HRMS calcd. for $C_{25}H_{33}N_2O_6$, 457.23331 $[M + H]^+$; found, 457.23263 $[M + H]^+$. Anal. ($C_{25}H_{33}N_2O_6$): C, H, N.

2-benzyl-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (141). The tetrahydroisoquinoline **64** (0.1 g, 0.30 mmol) was dissolved in dry THF (20 mL). Potassium carbonate (0.17 g, 1.2 mmol, 4.0 equiv) was added and the mixture was allowed to stir for 2 hours. Benzyl bromide (0.04 mL, 0.36 mmol, 1.2 mmol) was added and the reaction was allowed to stir at room temperature for 24 hours. Saturated aqueous NH_4Cl was added and the resulting mixture was extracted into EtOAc (2x). The organics were combined and washed with brine and water, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.05 g, 39%). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.51-7.24 (m, 5H), 6.86-6.60 (m, 6H), 4.38-4.24 (m, 1H), 4.12-3.98 (m, 1H), 3.97-3.74 (m, 12H), 3.29-3.15 (m, 1H), 2.98-2.82 (m, 2H), 2.65-2.50 (m, 1H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 158.2, 152.3, 148.2, 147.6, 146.2, 134.1, 129.6, 129.2, 127.6, 126.8, 125.2, 114.7, 114.5, 110.6, 78.5, 63.1, 56.3, 56.0, 55.6, 51.2, 42.2, 29.3. HRMS calcd. for $\text{C}_{26}\text{H}_{30}\text{NO}_4$, 420.21694 $[\text{M} + \text{H}]^+$; found, 420.21721 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{29}\text{NO}_4$): C, H, N.

(6,7-dimethoxy-1-phenethyl-3,4-dihydroisoquinolin-2(1H)-yl)(3-fluorophenyl)methanone (154). Compound **154** was prepared via Procedure VII using **153** (0.8 g, 3.0 mmol) and 3-fluorobenzoyl chloride (0.6 g, 3.0 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.8 g, 71%, mixture of rotamers). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.42-7.03 (m, 8H), 1H [6.64, 6.61 (s, s)], 1H [6.56, 6.34 (s, s)], 5.81 (m, 1H), 1H [4.82, 4.73 (m, m)], 3.85-3.78 (m, 6H), 3.73 (m, 1H), 3.50 (m, 1H), 1H [3.32, 3.09 (m, m)], 2.97 (m, 2H), 2.69-2.40 (m, 1H), 2.31-1.90 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 169.6, 164.1, 161.6, 148.1, 148.0, 141.9, 141.0, 138.9, 138.8, 130.8, 130.7, 129.4, 128.7, 128.5, 128.3, 126.4, 126.2, 125.9, 124.8, 122.8, 122.3, 116.9, 116.6, 114.1, 113.9, 112.0, 111.5, 110.3, 109.5, 58.0, 56.2, 56.1, 52.2, 41.2, 39.2, 38.5, 35.9, 33.1, 29.1, 27.8. HRMS calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_3\text{F}$, 420.19695 $[\text{M} + \text{H}]^+$; found, 420.19789 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{26}\text{H}_{26}\text{NO}_3\text{F}$): C, H, N.

(E)-(6,7-dimethoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (155). Compound **155** was prepared according to Procedure VII using **151** (0.15 g, 0.46 mmol) and benzoyl chloride (0.07 g, 0.55 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.10 g, 51%, mixture of rotamers). ^1H

NMR (CDCl₃, 400 MHz) δ : 7.48-7.36 (m, 5H), 7.30-7.15 (m, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.69-6.54 (m, 1H), 6.42-6.16 (m, 3H), 1H [5.29, 4.76 (m, m)], 3.86-3.76 (m, 10H), 3.48-3.20 (m, 1H), 3.15-2.86 (m, 1H), 2.80-2.56 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ : 171.3, 170.5, 159.6, 148.3, 147.8, 136.5, 132.8, 131.5, 130.4, 129.9, 129.5, 128.7, 128.0, 126.9, 126.0, 114.2, 111.4, 52.3, 56.2, 56.1, 55.6, 55.5, 41.5, 29.3, 19.2, 14.4. HRMS calcd. for C₂₇H₂₈NO₄, 430.20129 [M + H]⁺; found, 430.20090 [M + H]⁺. Anal. (C₂₇H₂₇NO₄): C, H, N.

(E)-(3-chlorophenyl)(6,7-dimethoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (156).

Compound **156** was prepared according to Procedure VII using **151** (0.15 g, 0.46 mmol) and 3-chlorobenzoyl chloride (0.10 g, 0.55 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Rediseq 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.12 g, 56%, mixture of rotamers). ¹H NMR (CDCl₃, 400 MHz) δ : 7.48-7.22 (m, 6H), 6.83 (d, J = 8.8 Hz, 2H), 6.67-6.54 (m, 1H), 6.43-6.33 (m, 1H), 6.30 (s, 1H), 6.19 (s, 1H), 1H [5.20, 4.73 (m, m)], 3.95-3.68 (m, 10H), 3.50-3.18 (m, 1H), 3.14-2.58 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz) δ : 168.9, 159.7, 148.4, 147.9, 138.2, 134.8, 133.1, 131.8, 130.2, 129.4, 128.9, 128.1, 127.2, 126.9, 126.5, 125.8, 125.0, 114.2, 111.5, 56.3, 56.2, 56.1, 55.6, 55.5, 54.1, 41.5, 37.1, 29.2. HRMS calcd. for C₂₇H₂₇NO₄Cl, 464.16231 [M + H]⁺; found, 464.16185 [M + H]⁺.

(E)-(3-bromophenyl)(6,7-dimethoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (157).

Compound **157** was prepared according to Procedure VII using **151** (0.15 g, 0.46 mmol) and 3-bromobenzoyl chloride (0.12 g, 0.55 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Rediseq 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.15 g, 64%, mixture of rotamers). ¹H NMR (CDCl₃, 400 MHz) δ : 7.62-7.21 (m, 6H), 6.83 (d, J = 8.4 Hz, 2H), 6.66-6.54 (m, 1H), 6.43-6.19 (m, 3H), 1H [5.19, 4.72 (m, m)], 3.86-3.67 (m, 10H), 3.56-3.42 (m, 1H), 3.12-2.84 (m, 1H), 2.80-2.61 (m, 1H). ¹³C NMR (CDCl₃, 100 MHz) δ : 168.8, 159.7, 148.4, 147.9, 138.4, 133.1, 131.8, 130.4, 129.4, 128.1, 126.5, 125.8, 125.4, 122.9, 114.2, 112.8, 111.2, 56.3, 56.2, 56.1, 55.6, 55.5, 54.2, 41.6, 29.1, 24.2, 19.9, 13.9. HRMS calcd. for C₂₇H₂₇NO₄Br, 508.11096 [M + H]⁺; found, 508.11132 [M + H]⁺.

(E)-(3-chlorophenyl)(6-methoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (158).

Compound **148** was prepared according to Procedure IV using **144** (4.1 g, 13 mmol, 1.0 equiv). The crude solid was

1 filtered and carried on without further purification. Compound **152** was prepared via Procedure VI using
2 dihydroisoquinoline **148** (3.0 g, 10.2 mmol). The crude residue was subjected to flash column chromatography
3 (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford **152** (0.6 g, 20%) in an impure form. The
4 impurities were inseparable by chromatography. The product was visible by LCMS and was carried on without
5 further purification. HRMS calcd. for $C_{19}H_{22}NO_2$, 296.16451 $[M + H]^+$; found, 269.16476 $[M + H]^+$. Compound
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13 **158** was prepared according to Procedure VII using **152** (0.3 g, 1.0 mmol) and 3-chlorobenzoyl chloride (0.21 g, 1.2
14 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 20-
15 70% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.37 g, 84%, mixture of
16 rotamers). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.44-7.24 (m, 6H), 7.14 (m, 1H), 6.96-6.81 (m, 3H), 6.69 (m, 1H), 6.32-
17 6.16 (m, 2H), 1H [5.25, 4.71 (m, m)], 3.80-3.75 (m, 6H), 1H [3.71, 3.48 (m, m)], 1H [3.45, 3.10 (m, m)], 2.96-2.69
18 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 168.9, 159.6, 158.7, 158.4, 158.1, 138.6, 138.2, 134.9, 133.9, 133.3, 132.7,
19 130.1, 129.8, 129.5, 128.8, 128.1, 127.2, 126.8, 125.0, 124.7, 114.2, 114.1, 113.1, 60.6, 55.5, 54.1, 52.2, 41.6, 41.2,
20 38.9, 32.1, 29.8, 28.7, 14.4. HRMS calcd. for $C_{26}H_{25}NO_3Cl$, 434.15175 $[M + H]^+$; found, 434.15147 $[M + H]^+$.
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31 **(E)-(3-bromophenyl)(6-methoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (159).**

32 Compound **148** was prepared according to Procedure IV using **144** (4.1 g, 13 mmol, 1.0 equiv). The crude solid was
33 filtered and carried on without further purification. Compound **152** was prepared via Procedure VI using
34 dihydroisoquinoline **148** (3.0 g, 10.2 mmol). The crude residue was subjected to flash column chromatography
35 (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford **152** (0.6 g, 20%) in an impure form. The
36 impurities were inseparable by chromatography. The product was visible by LCMS and was carried on without
37 further purification. HRMS calcd. for $C_{19}H_{22}NO_2$, 296.16451 $[M + H]^+$; found, 269.16476 $[M + H]^+$. Compound
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46 **159** was prepared according to Procedure VII with **152** (0.3 g, 1.0 mmol) and 3-bromobenzoyl chloride (0.27 g, 1.2
47 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 20-
48 70% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.30 g, 62%, mixture of
49 rotamers) as an off-white solid. 1H NMR ($CDCl_3$, 400 MHz) δ : 7.59-7.55 (m, 2H), 7.37-7.13 (m, 5H), 6.93-6.69 (m,
50 4H), 6.32-6.17 (m, 2H), 1H [5.24, 4.71 (m, m)], 3.78-3.68 (m, 7H), 3.48-2.69 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz)
51 δ : 168.4, 159.6, 158.6, 138.4, 133.5, 132.9, 130.4, 130.0, 129.4, 128.8, 128.1, 126.8, 125.4, 122.9, 115.8, 114.2,
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113.6, 113.1, 104.0, 55.5, 54.1, 41.6, 29.9, 28.7, 15.2. HRMS calcd. for $C_{26}H_{25}NO_3Br$, 478.10123 $[M + H]^+$; found, 478.10162 $[M + H]^+$.

(6,7-dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (160).

Compound **160** was prepared according to Procedure VII using **150** (0.20 g, 0.6 mmol) and benzoyl chloride (0.10 g, 0.73 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.10 g, 38%, mixture of rotamers). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.43-7.32 (m, 5H), 2H [7.18, 6.94 (d, $J = 5.5$ Hz; d, $J = 5.5$ Hz)], 2H [6.84, 6.76 (d, $J = 5.5$ Hz; d, $J = 5.5$ Hz)], 1H [6.65, 6.63 (s, s)], 1H [6.57, 6.32 (s, s)], 1H [5.83, 4.82 (dd, $J = 2.8$ Hz, $J = 6.4$ Hz; m)], 3.86-3.71 (m, 10H), 3.53-3.28 (m, 1H), 3.12-2.73 (m, 3H), 2.62-2.55 (m, 1H), 2.39-1.93 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 171.1, 158.1, 148.0, 137.0, 134.1, 129.7, 129.5, 129.3, 128.8, 127.2, 126.7, 125.0, 114.1, 112.0, 111.6, 110.5, 109.6, 57.9, 56.3, 56.1, 55.5, 52.0, 41.2, 39.6, 38.9, 35.7, 32.1, 29.2, 27.9. HRMS calcd. for $C_{27}H_{30}NO_4$, 432.21694 $[M + H]^+$; found, 432.21737 $[M + H]^+$. Anal. ($C_{27}H_{29}NO_4$): C, H, N.

(3-chlorophenyl)(6,7-dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (161).

Compound **161** was prepared according to Procedure VII using **150** (0.20 g, 0.6 mmol) and 3-chlorobenzoyl chloride (0.13 g, 0.73 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.21 g, 74%, mixture of rotamers). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.40-7.23 (m, 4H), 2H [7.16, 6.95 (d, $J = 8.4$ Hz; d, $J = 8.4$ Hz)], 2H (d, $J = 8.4$ Hz; d, $J = 8.4$ Hz), 1H [6.63, 6.59 (s, s)], 1H [6.55, 6.32 (s, s)], 1H [5.77, 4.73 (dd, $J_1 = 4.8$ Hz, $J_2 = 10$ Hz; m)], 3.88-3.70 (m, 10H), 1H [3.49, 3.31 (m, m)], 3.15-2.21 (m, 4H), 2.25-1.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 169.5, 158.1, 148.1, 147.9, 138.5, 134.9, 133.8, 130.3, 129.9, 129.4, 129.2, 126.9, 124.7, 114.1, 111.5, 110.3, 56.2, 56.1, 55.5, 52.2, 41.2, 38.7, 32.1, 29.0. HRMS calcd. for $C_{27}H_{29}NO_4Cl$, 466.17796 $[M + H]^+$; found, 466.17859 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_4Cl$): C, H, N.

(3-bromophenyl)(6,7-dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (162).

Compound **162** was prepared according to Procedure VII using **150** (0.20, 0.6 mmol) and 3-bromobenzoyl chloride

(0.16 g, 0.73 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.18 g, 58%, mixture of rotamers). ^1H NMR (CDCl_3 , 400 MHz) δ : 7.59-7.48 (m, 2H), 7.31-7.22 (m, 2H), 2H [7.18, 6.97 (d, J = 8.4 Hz, 2H; d, J = 8.4 Hz)], 2H [6.85, 6.78 (d, J = 8.8 Hz; d, J = 8.8 Hz)], 1H [6.66, 6.62 (s, s)], 1H [6.58, 6.35 (s, s)], 1H [4.82, 4.71 (m, m)], 3.87-3.76 (m, 10H), 3.54 (m, 1H), 2.93-2.80 (m, 2H), 2.80-2.70 (m, 1H), 2.68-2.53 (m, 1H), 2.21-2.59 (m, 2H). ^{13}C NMR (CDCl_3 , 400 MHz) δ : 169.3, 158.1, 148.1, 148.0, 147.7, 138.8, 138.6, 133.8, 132.9, 132.7, 130.5, 130.1, 129.7, 129.5, 129.2, 128.9, 125.9, 125.7, 125.2, 124.8, 123.0, 114.1, 112.0, 111.5, 110.4, 109.5, 56.2, 56.1, 55.5, 52.2, 41.2, 38.7, 32.1. 29.1. HRMS calcd. for $\text{C}_{27}\text{H}_{29}\text{NO}_4\text{Br}$, 510.12745 $[\text{M} + \text{H}]^+$; found, 510.12812 $[\text{M} + \text{H}]^+$. Anal. ($\text{C}_{27}\text{H}_{28}\text{NO}_4\text{Br}$): C, H, N.

((6,7-dimethoxy-1-(4-methoxybenzyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone) (171). Compound **167** was prepared via Procedure IV using **165** (1.2 g, 3.7 mmol, 1.0 equiv). The crude solid was filtered and carried on without further purification. Compound **171** was prepared via Procedure VI using dihydroisoquinoline **167** (0.88 g, 2.6 mmol, 1.0 equiv.). The crude residue was subjected to flash column chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford **169** (0.36 g, 41 %) in an impure form. The impurities were inseparable by chromatography. The product was visible by LCMS and was carried on without further purification. HRMS calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}_3$, 314.17507 $[\text{M} + \text{H}]^+$; found, 314.17543 $[\text{M} + \text{H}]^+$. Compound **171** was prepared via Procedure VII with tetrahydroisoquinoline **169** (0.18 g, 0.59 mmol, 1.0 equiv.) and benzoyl chloride (0.08 mL, 0.71 mmol, 1.2 equiv.). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 10 – 80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.13 g, 53 % mixture of two rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.67; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.41-7.34 (m, 2H), 7.29-6.25 (m, 3H) 7.15-7.13 (d, J = 8.8 Hz, 1H), 6.88-6.67 (m, 3H), 6.57-6.37 (m, 1H), 1H [6.10, 5.87 (s,m)], 1H [4.86, 4.75 (dd, J_1 = 5.6 Hz, J_2 = 13 Hz; t, J_1 = 7.2 Hz)], 3.85-3.64 (m, 10H), 3.36-3.25 (m, 1H), 3.16-3.03 (m, 2H), 2.86-2.49 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 171.3, 170.6, 158.8, 158.6, 148.3, 147.9, 147.3, 136.9, 131.1, 130.9, 130.2,

129.8, 129.5, 129.3, 128.7, 128.4, 128.1, 126.7, 126.7, 126.3, 125.5, 114.2, 113.9, 111.8, 111.3, 110.7, 110.1, 59.9, 56.1, 56.0, 55.9, 55.6, 55.5, 42.5, 41.9, 41.5, 35.7, 29.2, 28.1 HRMS calcd. for $C_{26}H_{28}NO_4$, 418.20179 $[M + H]^+$; found, 418.20165 $[M + H]^+$.

((3-chlorophenyl)(6,7-dimethoxy-1-(4-methoxybenzyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone) (172).

Compound **172** was prepared according to Procedure VII with tetrahydroisoquinoline **169** (0.18 g, 0.59 mmol, 1.0 equiv.) and 3-chlorobenzoyl chloride (0.09 mL, 0.71 mmol, 1.2 equiv.). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 10 – 80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.38 g, 64 % mixture of two rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.61; 1H NMR ($CDCl_3$, 400 MHz) δ : 7.34-7.08 (m, 4H), 6.86-6.80 (m, 3H), 6.85-6.36 (m, 2H), 1H [6.26, 5.81 (s, m)], 1H [4.85, 4.66 (dd, J_1 = 6.1 Hz, J_2 = 13 Hz; dd, J_1 = 4.9 Hz, J_2 = 9.5 Hz)], 3.84-3.69 (m, 9H), 3.61-3.56 (m, 1H), 3.37-3.28 (m, 1H), 3.14-3.12 (d, J = 6.8, 1H), 3.07-3.01 (m, 1H), 2.85-2.52 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 168.9, 158.9, 158.7, 148.0, 147.5, 138.5, 138.0, 134.7, 134.5, 131.0, 130.9, 130.2, 129.9, 129.7, 129.6, 129.5, 128.2, 127.9, 126.9, 126.2, 125.2, 124.8, 124.5, 114.4, 113.9, 111.8, 11.4, 110.6, 109.9, 60.2, 56.2, 56.1, 55.9, 55.5, 55.4, 42.4, 41.9, 41.5, 25.6, 29.1, 28.1. HRMS calcd. For $C_{26}H_{27}NO_4Cl$, 452.16231 $[M + H]^+$; found, 452.16270 $[M + H]^+$.

((6,7-dimethoxy-1-(3-methoxybenzyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone) (173). Compound **168** was prepared according to Procedure IV using **166** (2.0 g, 6.19 mmol, 1.0 equiv). The crude solid was filtered and carried on without further purification. Compound **170** was prepared according to Procedure VI using dihydroisoquinoline **168** (2.6 g, 8.4 mmol, 1.0 equiv.). The crude residue was subjected to flash column chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford **170** (0.5 g, 18 %) in an impure form. The impurities were inseparable by chromatography. The product was visible by LCMS and was carried on without further purification. HRMS calcd. for $C_{19}H_{23}NO_3$, 314.17507 $[M + H]^+$; found, 314.17484 $[M + H]^+$. Compound **173** was prepared according to Procedure VII using tetrahydroisoquinoline **171** (0.23 g, 0.74 mmol, 1.0 equiv.) and benzoyl chloride (0.10 mL, 0.89 mmol, 1.2 equiv.). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.12 g, 32 %, mixture of rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.63; 1H NMR ($CDCl_3$, 400 MHz) δ : 7.38 -7.32 (m, 2H), 7.26-7.24 (m, 3H), 7.21-7.12 (m, 1H), 6.88-6.76 (m, 2H), 6.64-6.34 (m,

2H), 1H [6.06, 5.89 (s,m)], 4.89-4.79 (m, 1H), 3.86-3.63 (m, 9H), 3.37-3.29 (m, 2H), 3.21-3.07 (m, 2H), 2.89-2.76 (m, 2H); ^{13}C NMR (100 MHz) δ : 171.2, 170.6, 160.0, 159.8, 148.3, 147.9, 147.4, 139.7, 139.2, 136.8, 136.5, 129.8, 129.6, 129.5, 129.3, 128.7, 128.4, 128.3, 127.9, 126.3, 125.3, 122.5, 122.3, 115.4, 115.1, 112.7, 112.6, 111.7, 111.3, 110.6, 110.0, 59.8, 56.1, 56.0, 55.9, 55.4, 43.5, 42.5, 41.9, 35.8, 29.1, 28.1. HRMS calcd. for $\text{C}_{26}\text{H}_{28}\text{NO}_4$, 418.20072 $[\text{M} + \text{H}]^+$; found, 418.20045 $[\text{M} + \text{H}]^+$.

((3-chlorophenyl)(6,7-dimethoxy-1-(3-methoxybenzyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone) (174).

Compound **174** was prepared according to Procedure VII using tetrahydroisoquinoline **170** (0.23 g, 0.740 mmol, 1.0 equiv.) and 3-chlorobenzoyl chloride (0.11 mL, 0.89 mmol, 1.2 equiv.). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.09 g, 31%, mixture of rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.59; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.36–7.09 (m, 4H), 6.84-6.77 (m, 2H), 6.70–6.62 (m, 1H), 6.55–6.37 (m, 2H), 1H [6.23, 5.87 (s,m)], 1H [4.87, 4.74 (dd, J_1 = 6.0 Hz, J_2 = 13 Hz; dd, J_1 = 5.2 Hz, J_2 = 8.8 Hz)], 3.86–3.69 (m, 9H), 3.64–3.59 (m, 1H), 3.42–3.30 (m, 1H), 3.17 (d, J = 6.8 Hz, 1H), 3.13–3.04 (m, 1H), 2.81–2.53 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 169.6, 169.1, 160.1, 159.8, 148.4, 148.1, 147.5, 139.0, 138.5, 137.9, 134.8, 134.5, 130.2, 129.9, 129.7, 129.6, 129.5, 128.1, 127.8, 126.9, 126.2, 125.1, 124.7, 124.6, 122.5, 122.3, 115.5, 115.4, 112.6, 112.5, 111.8, 111.3, 110.5, 109.8, 60.1, 56.1, 55.9, 55.4, 55.4, 43.4, 42.5, 41.9, 35.7, 29.1, 28.1. HRMS calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_4\text{Cl}$, 452.16165 $[\text{M} + \text{H}]^+$; found, 452.16148 $[\text{M} + \text{H}]^+$.

((3-bromophenyl)(6,7-dimethoxy-1-(3-methoxybenzyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone) (175).

Compound **175** was prepared according to Procedure VII using tetrahydroisoquinoline **170** (0.20 g, 0.62 mmol, 1.0 equiv) and 3-bromobenzoyl chloride (0.10 mL, 0.75 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.09 g, 31%, mixture of rotamers) TLC (EtOAc: hexanes, 1:1, v/v) R_f = 0.54; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.55-7.08 (m, 4H), 6.88-6.75 (m, 3H), 6.68-6.40 (m, 2H), 1H [6.24, 5.89 (s, m)], 1H [4.89, 4.77 (dd, J_1 = 6.1 Hz, J_2 = 13 Hz; dd, J_1 = 5.2, J_2 = 9.2)], 3.88-3.72 (m, 9H), 3.66-3.62 (m, 1H), 3.45-3.33 (m, 1H), 3.20 (d, J = 7.2 Hz, 1H), 3.19-3.08 (m, 1H), 2.91-2.57 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 169.5, 168.9, 160.1, 159.8, 148.5,

147.5, 147.5, 139.5, 139.5, 138.9, 138.7, 138.1, 132.7, 132.5, 130.4, 130.0, 129.8, 129.5, 129.3, 128.5, 128.1, 127.8, 126.2, 125.5, 125.2, 125.1, 122.9, 122.7, 122.5, 122.2, 115.5, 115.4, 112.6, 112.5, 111.8, 111.3, 110.5, 109.9, 76.9, 56.1, 55.9, 55.5, 43.4, 42.5, 41.9, 35.7, 29.1, 28.0. HRMS calcd. for $C_{26}H_{27}NO_4Br$, 496.11180 $[M + H]^+$; found, 496.11228 $[M + H]^+$.

(R)-(3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (2-R). Compound **63-R** (0.10 g, 0.30 mmol) was dissolved in dry DCM (3 mL). Triethylamine (0.06 g, 0.08 mL, 0.6 mmol, 2.0 equiv) was added followed by dropwise addition of 3-chlorobenzoyl chloride (0.06 g, 0.04 mL, 0.33 mmol, 1.1 equiv). The reaction was allowed to stir at room temperature for 1 hour. Water was added to quench and the reaction was extracted with DCM (3x). The combined organics were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as a white amorphous solid (0.04 g, 28%). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.62-7.28 (m, 4H), 6.89-6.80 (m, 4H), 1H [6.68, 6.62 (s, s)], 6.48-5.96 (m, 1H), 1H [5.10, 4.87 (dd, $J_1 = 9.6$ Hz, $J_2 = 4$ Hz, dd, $J_1 = 9.6$ Hz, $J_2 = 4$ Hz)], 4.37-3.95 (m, 2H), 3.88-3.76 (m, 9H), 3.70-2.70 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 170.3, 169.6, 154.4, 154.3, 152.9, 152.5, 148.8, 148.4, 148.x0, 147.8, 138.3, 134.9, 134.5, 130.2, 129.9, 129.8, 128.2, 127.3, 127.0, 126.3, 125.9, 125.2, 124.9, 124.0, 115.9, 115.5, 115.0, 114.9, 112.0, 111.5, 110.4, 109.9, 71.1, 70.2, 57.4, 56.2, 56.1, 55.9, 51.9, 42.9, 35.7, 29.2, 27.8. HRMS calcd. for $C_{26}H_{27}NO_5Cl$, 468.15723 $[M + H]^+$; found, 468.15728 $[M + H]^+$; Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N. HPLC: Reverse Phase Chiral OD-RH column. Conditions: 75% MeCN/25% water plus 0.1% formic acid isocratic over 20 minutes, read at $\lambda_{max} = 285$ nm, RT = 9.192 minutes, 95%. (*S*-enantiomer, RT = 8.141 minutes, 5%). $[\alpha]_D^{20} = -88$ (c 0.1, dry DMSO).

(S)-(3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-

yl)methanone (2-S). Compound **2-S** was synthesized as described above with the crude material from **63-S** (0.4 g, 1.2 mmol). After purification, the title compound was obtained as a white amorphous solid (0.4 g, 70%, mixture of rotamers). 1H NMR ($CDCl_3$, 400 MHz) δ : 7.63-7.29 (m, 4H), 6.90-6.81 (m, 4H), 1H [6.69, 6.64 (s, s)], 6.50-5.96 (m, 1H), 1H [5.10, 4.88 (dd, $J_1 = 9.6$ Hz, $J_2 = 4$ Hz, dd, $J_1 = 9.6$ Hz, $J_2 = 4$ Hz)], 4.38-3.96 (m, 2H), 3.88-3.77 (m, 9H),

3.71-2.68 (m, 4H). ^{13}C NMR (CDCl_3 , 100 MHz) δ : 170.2, 169.8, 154.1, 154.3, 152.9, 152.5, 148.9, 148.4, 148.1, 147.8, 138.3, 135.1, 134.6, 130.2, 129.9, 129.9, 128.2, 127.2, 127.0, 126.4, 125.9, 125.2, 124.9, 123.8, 115.7, 115.5, 115.0, 114.9, 112.1, 111.7, 110.4, 110.0, 71.4, 70.1, 57.4, 56.2, 56.0, 55.8, 51.9, 42.7, 35.6, 29.2, 27.6. HRMS calcd. for $\text{C}_{26}\text{H}_{27}\text{NO}_5\text{Cl}$, 468.15723 $[\text{M} + \text{H}]^+$; found, 468.15857 $[\text{M} + \text{H}]^+$; Anal. ($\text{C}_{26}\text{H}_{26}\text{NO}_5\text{Cl}$): C, H, N. HPLC: Reverse Phase Chiral OD-RH column. Conditions: 75% MeCN/25% water plus 0.1% formic acid isocratic over 20 minutes, read at 254 nm, RT = 8.140 minutes, 100%. $[\alpha]_{\text{D}}^{20} = +121$ (c 0.1, dry DMSO).

Supporting Information Available: Supporting information including the experimental detail for the synthesis of all intermediates as well as off-target activity of compound **83** is available free of charge via the Internet at <http://pubs.acs.org>.

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Ancillary Information:

Abbreviations Used: ATD, amino-terminal domain; LBD, ligand-binding domain; PCP, phencyclidine; BHK, baby hamster kidney; BAPTA-AM, (1,2-bis(2-aminophenoxy)ethane- $\text{N},\text{N},\text{N}',\text{N}'$ -tetraacetic acid tetrakis(acetoxymethyl ester); K-BAPTA, potassium 1,2-bis(2-aminophenoxy)ethane- $\text{N},\text{N},\text{N}',\text{N}'$ -tetraacetic acid; SEM, standard error of the mean

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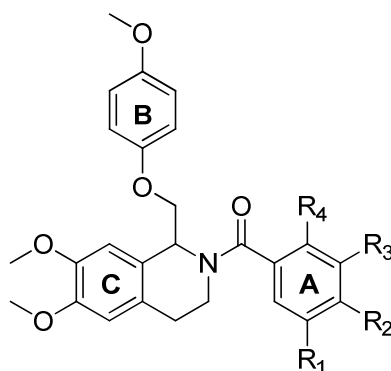
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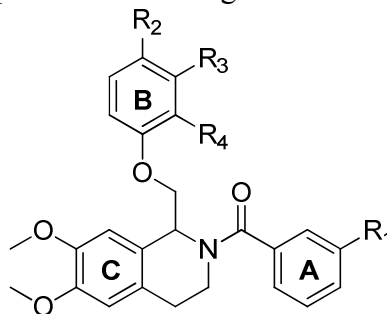
Table 1. Optimization of substituent placement on Ring A.



	R ₁	R ₂	R ₃	R ₄	I _{10 μM} / I _{CONTROL} (mean ± SEM, %)		EC ₅₀ (maximal potentiation) (μM, %) ^a	
					GluN2C	GluN2D	GluN2C	GluN2D
1	H	H	H	H	116 ± 2.9	123 ± 2.3	12 (145%)	11 (156%)
184	H	Me	H	H	106 ± 5.1	107 ± 2.4	--	--
185	H	H	Me	H	171 ± 11	132 ± 10	6.2 (211%)	5.5 (174%)
186	H	H	H	Me	108 ± 2.0	96 ± 1.7	--	--
187	H	Cl	H	H	128 ± 3.2	111 ± 4.1	4.1 (135%)	--
2	H	H	Cl	H	193 ± 7.3	179 ± 5.7	4.6 (233%)	5.0 (215%)
188	H	H	H	Cl	102 ± 7.1	101 ± 8.9	--	--
189	H	Br	H	H	107 ± 3.2	108 ± 3.1	--	--

190	H	H	Br	H	183 ± 11	178 ± 6.6	0.9 (195%)	2.2 (188%)
191	H	OMe	H	H	101 ± 1.1	96 ± 1.9	--	--
192	H	H	OMe	H	147 ± 12	132 ± 10.5	5.8 (181%)	12 (179%)
193	H	NO ₂	H	H	96 ± 1.4	102 ± 1.8	--	--
84	H	H	NO ₂	H	160 ± 7.4	151 ± 6.3	11 (250)	13 (261)
85	H	Cl	Cl	H	126 ± 5.2	136 ± 5.0	21 (178%)	24 (220%)
86	H	H	Cl	Cl	120 ± 3.1	109 ± 8.4	1.4 (127%)	--
194	H	Cl	H	Cl	112 ± 5.0	99 ± 3.1	--	--
87	Cl	H	Cl	H	149 ± 8.0	138 ± 8.2	4.8 (201%)	1.9 (159%)
88	H	F	Cl	H	183 ± 13	168 ± 10	5.3 (232%)	5.3 (206%)
195	H	O-CH ₂ -O		H	106 ± 3.6	99 ± 1.5	--	--

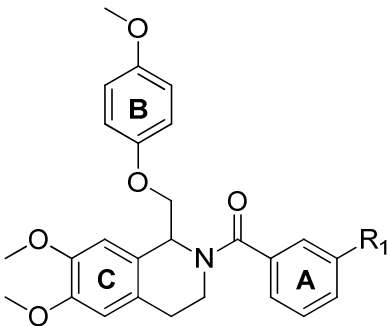
^a Fitted EC₅₀ values are shown to two significant digits when potentiation at 10 μM test compound exceeded 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data are from between 6-25 oocytes from 2-5 frogs for each compound and receptor tested.

Table 2. Optimization of substituent placement on Ring B.

	R_1	R_2	R_3	R_4	$I_{10\ \mu\text{M}} / I_{\text{CONTROL}}$ (mean \pm SEM, %)		EC_{50} (maximal potentiation) (μM , %) ^a	
					GluN2C	GluN2D	GluN2C	GluN2D
89	H	H	H	H	95 \pm 2.6	99 \pm 1.9	--	--
1	H	OMe	H	H	116 \pm 2.9	123 \pm 2.3	12 (145%)	11 (156%)
90	H	H	OMe	H	95 \pm 2.2	92 \pm 1.5	--	--
196	H	H	H	OMe	94 \pm 3.7	95 \pm 2.5	--	--
2	Cl	OMe	H	H	193 \pm 7.3	179 \pm 5.7	4.6 (233%)	5.0 (215%)
91	Cl	H	OMe	H	100 \pm 2.0	96 \pm 1.4	--	--
92	Cl	H	H	OMe	91 \pm 2.2	97 \pm 1.1	--	--

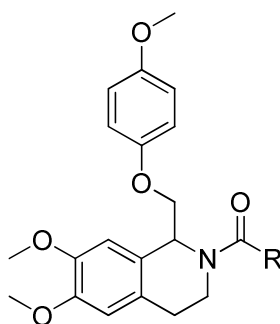
^a Fitted EC_{50} values are shown to two significant digits when potentiation at 10 μM test compound exceeded 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Compounds **1** and **2** were also shown in Table 1, and are included here for comparison. Data are from between 6-25 oocytes from between 2-4 frogs for each compound and receptor tested.

Table 3. Optimization of A Ring substituents



		$I_{10\ \mu\text{M}} / I_{\text{CONTROL}}$ (mean \pm SEM, %)		EC_{50} (maximal potentiation) (μM , %) ^a	
	R ₁	GluN2C	GluN2D	GluN2C	GluN2D
1	H	116 \pm 2.9	123 \pm 2.3	12 (145%)	11 (156%)
197	F	154 \pm 7.0	142 \pm 4.5	7.2 (184%)	7.0 (169%)
2	Cl	193 \pm 7.3	179 \pm 5.7	4.6 (233%)	5.0 (215%)
190	Br	183 \pm 11	178 \pm 6.6	0.9 (195%)	2.2 (188%)
93	I	209 \pm 9.8	163 \pm 13	4.0 (251%)	4.9 (239%)
185	Me	171 \pm 11	151 \pm 7.5	6.2 (211%)	5.5 (174%)
94	Ph	140 \pm 9.4	132 \pm 5.4	2.9 (142%)	3.6 (136%)
198	CF ₃	187 \pm 12	202 \pm 7.0	2.4 (201%)	2.4 (218%)
192	OMe	147 \pm 12	132 \pm 10	5.8 (181%)	12 (179%)
95	OH	96 \pm 0.8	96 \pm 2.3	--	--
84	NO ₂	160 \pm 7.4	151 \pm 6.3	11 (250%)	13 (261%)
96	CH ₂ Cl	138 \pm 2.7	115 \pm 2.2	17 (205%)	--
97	CHCl ₂	149 \pm 7.3	121 \pm 2.9	3.7 (161%)	5.4 (127%)
98	CN	119 \pm 4.2	139 \pm 5.8	29 (164%)	7.7 (166%)
99	C(O)Me	105 \pm 2.4	104 \pm 1.2	--	--

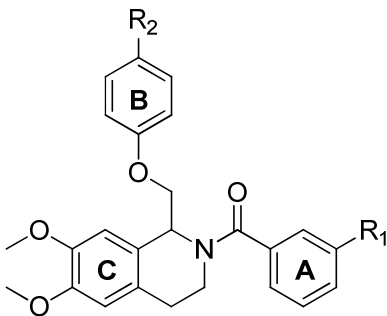
^a Fitted EC₅₀ values are shown to two significant digits when potentiation at 10 μM test compound exceeded 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Compounds **1**, **2**, **84**, **185**, **190**, **192** were also shown in preceding Tables, and are included here for comparison. Data are from between 6-25 oocytes from between 2-5 frogs for each compound and receptor tested.

Table 4. Replacement of Ring A

	R	$I_{10\ \mu\text{M}} / I_{\text{CONTROL}}$ (mean \pm SEM, %)		EC_{50} (maximal potentiation) (μM , %) ^a	
		GluN2C	GluN2D	GluN2C	GluN2D
1	phenyl	116 \pm 2.9	123 \pm 2.3	12 (145%)	11 (156%)
199	t-butyl	90 \pm 3.6	95 \pm 1.4	--	--
200	2-pyridine	87 \pm 4.3	99 \pm 2.4	--	--
201	3-pyridine	98 \pm 1.5	94 \pm 1.7	--	--
202	4-pyridine	100 \pm 1.3	97 \pm 1.8	--	--
203	2-thiophene	117 \pm 2.1	105 \pm 1.6	9.0 (134%)	--
136	2-furan	102 \pm 1.3	100 \pm 1.4	--	--
137	5-isoxazole	93 \pm 2.3	97 \pm 2.4	--	--
204	1-naphthyl	97 \pm 2.8	96 \pm 0.6	--	--
138	2-naphthyl ^b	113 \pm 2.8	106 \pm 1.5	--	--
139	N-morpholine	95 \pm 1.9	96 \pm 2.0	--	--
140	-CH ₂ -N-morpholine	92 \pm 2.7	94 \pm 0.5	--	--

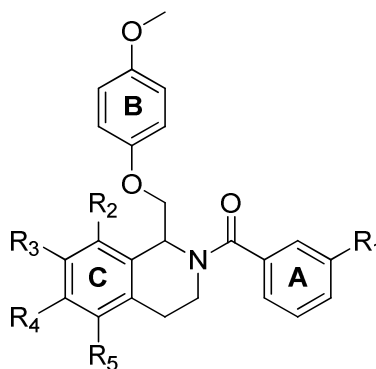
^a Fitted EC_{50} values are shown to two significant digits when potentiation at 10 μM test compound exceeded 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data are from between 5-20 oocytes from between 2-4 frogs for each compound and receptor tested. Compound **1** was included here for comparison. ^b In contrast to 1-naphthyl, higher concentrations of 2-naphthyl did show activity (136 \pm 5.5% potentiation of GluN2C at 100 μM).

Table 5. Optimization of B Ring substituents



	R ₁	R ₂	I ₁₀ μM / I _{CONTROL} (mean ± SEM, %)		EC ₅₀ (maximal potentiation) (μM, %) ^a	
			GluN2C	GluN2D	GluN2C	GluN2D
1	H	OMe	116 ± 2.9	123 ± 2.3	12 (145%)	11 (156%)
2	Cl	OMe	193 ± 7.3	179 ± 5.7	4.6 (233%)	5.0 (215%)
100	Cl	OEt	93 ± 5.5	92 ± 1.4	--	--
101	Br	OEt	99 ± 2.0	81 ± 1.7	--	--
102	Cl	OH	105 ± 1.9	98 ± 0.8	--	--
103	H	SMe	102 ± 5.3	100 ± 1.9	--	--
104	Cl	SMe	164 ± 6.7	143 ± 3.9	5.1 (191%)	5.3 (159%)
205	H	Et	120 ± 2.2	108 ± 2.6	23 (160%)	--
105	Cl	OCF ₃	102 ± 1.1	97 ± 1.5	--	--
131	H	NH ₂	102 ± 4.4	93 ± 0.9	--	--
132	Cl	NH ₂	97 ± 1.8	100 ± 1.1	--	--
133	Br	NH ₂	93 ± 0.8	95 ± 0.7	--	--
134	Cl	NHMe	97 ± 0.9	97 ± 1.7	--	--
135	Br	NHMe	108 ± 2.3	100 ± 1.1	--	--
106	H	NMe ₂	99 ± 2.0	97 ± 2.0	--	--
107	Cl	NMe ₂	120 ± 3.4	110 ± 1.3	35 (198%)	--
108	Br	NMe ₂	127 ± 4.1	108 ± 1.5	12 (167%)	--
206	Cl	CO ₂ Me	103 ± 2.3	107 ± 1.7	--	--
207	Br	CO ₂ Me	107 ± 4.0	102 ± 0.8	--	--
109	Cl	OBn	93 ± 1.6	93 ± 2.5	--	--
128	H	NO ₂	94 ± 2.0	91 ± 1.7	--	--
129	Cl	NO ₂	90 ± 0.7	93 ± 0.8	--	--
130	Br	NO ₂	95 ± 3.4	92 ± 2.6	--	--
208	F	F	85 ± 1.3	86 ± 1.2	--	--

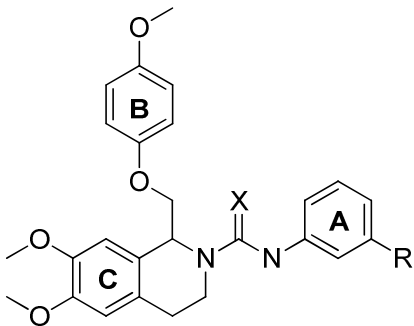
^a Fitted EC₅₀ values are shown to two significant digits when potentiation at 10 μM test compound exceeded 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data are from between 5-25 oocytes from 2-5 frogs for each compound. Compounds 1 and 2 were also shown in Tables 1-4, and are included here for comparison.

Table 6. Optimization of C ring substituents

	R_1	R_2	R_3	R_4	R_5	$I_{10\ \mu\text{M}} / I_{\text{CONTROL}}$ (mean \pm SEM, %)		EC_{50} (maximal potentiation) (μM , %) ^a	
						GluN2C	GluN2D	GluN2C	GluN2D
1	H	H	OMe	OMe	H	116 \pm 2.9	123 \pm 2.3	12 (145%)	11 (156%)
2	Cl	H	OMe	OMe	H	193 \pm 7.3	179 \pm 5.7	4.6 (233%)	5.0 (215%)
190	Br	H	OMe	OMe	H	183 \pm 11	178 \pm 6.6	0.9 (195%)	2.2 (188%)
110	H	H	O-CH ₂ -O		H	99 \pm 2.7	99 \pm 1.9	--	--
111	Cl	H	O-CH ₂ -O		H	126 \pm 4.3	134 \pm 6.6	16 (200%)	7.4 (186%)
112	Br	H	O-CH ₂ -O		H	170 \pm 9.9	136 \pm 6.8	3.2 (177%)	3.4 (138%)
113	H	OMe	H	OMe	H	143 \pm 5.0	141 \pm 9.0	10 (182%)	14 (190%)
114	Cl	OMe	H	OMe	H	178 \pm 21	166 \pm 7.0	6.1 (234%)	9.2 (233%)
115	Br	OMe	H	OMe	H	178 \pm 8.6	166 \pm 4.3	9.0 (261%)	7.8 (228%)
116	H	H	H	OMe	H	136 \pm 13	144 \pm 6.5	7.5 (174%)	5.7 (167%)
117	Cl	H	H	OMe	H	210 \pm 12	216 \pm 18	1.3 (240%)	1.0 (219%)
118	Br	H	H	OMe	H	263 \pm 24	281 \pm 24	2.0 (294%)	2.9 (373%)
119	C(O)Me	H	H	OMe	H	140 \pm 4.1	124 \pm 2.9	21 (241%)	32 (242%)
120	Cl	H	H	OMe	OMe	96 \pm 3.4	93 \pm 0.6	--	--
121	Br	H	H	OMe	OMe	98 \pm 2.1	95 \pm 0.9	--	--
122	Cl	H	Me	Me	H	238 \pm 11	179 \pm 8.2	1.4 (244%)	1.5 (180%)
123	Br	H	Me	Me	H	195 \pm 14	211 \pm 0.9	0.9 (197%)	1.1 (211%)
124	H	H	H	Me	H	116 \pm 3.9	109 \pm 1.8	24 (182%)	--
125	Cl	H	H	Me	H	207 \pm 10	201 \pm 11	5.0 (252%)	4.7 (237%)
126	Br	H	H	Me	H	205 \pm 12	230 \pm 9.2	3.2 (227%)	3.6 (257%)
81	H	H	H	OBn	H	212 \pm 11	182 \pm 9.1	0.7 (222%)	2.3 (177%)
82	Cl	H	H	OBn	H	252 \pm 13	195 \pm 17	0.4 (254%)	0.4 (198%)
83	Br	H	H	OBn	H	253 \pm 23	219 \pm 15	0.3 (257%)	0.3 (219%)

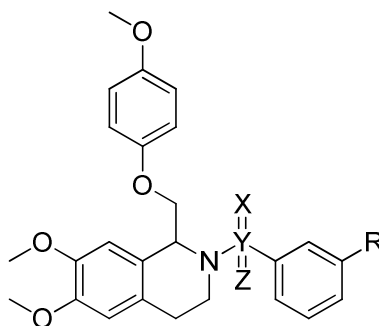
^a Fitted EC_{50} values are shown to two significant digits when potentiation at 10 μM test compound exceeded 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data are from between 5-25 oocytes from between 2-5 frogs for each compound and receptor tested. Compounds **1**, **2**, **190**, are also shown in preceding tables, and are included here for comparison.

Table 7. Optimization of linker A



	R	X	I ₁₀ μM / I _{CONTROL} (mean ± SEM, %)		EC ₅₀ (maximal potentiation) (μM, %) ^a	
			GluN2C	GluN2D	GluN2C	GluN2D
209	H	O	99 ± 3.7	99 ± 1.5	--	--
210	Cl	O	93 ± 1.9	90 ± 2.0	--	--
211	H	S	99 ± 2.6	89 ± 1.2	--	--
212	Cl	S	99 ± 1.1	98 ± 1.5	--	--
213	F	S	98 ± 1.9	103 ± 2.0	--	--
214	Br	S	99 ± 1.0	110 ± 6.0	--	--
215	Me	S	116 ± 2.0	126 ± 6.6	5.2 (126%)	4.9 (130%)

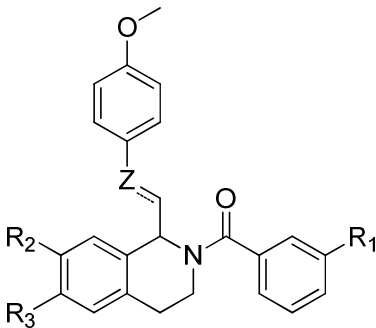
^a Fitted EC₅₀ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) response. Data are from between 8-14 oocytes from between 2-3 frogs for each compound and receptor tested.

Table 8. Optimization of linker A

	R	X	Y	Z	$I_{10\ \mu\text{M}} / I_{\text{CONTROL}}$ (mean \pm SEM, %)		EC ₅₀ (maximal potentiation) (μM , %) ^a	
					GluN2C	GluN2D	GluN2C	GluN2D
1	H	O	C	-	116 \pm 2.9	123 \pm 2.3	12 (145%)	11 (156%)
216	H	O	S	O	92 \pm 1.5	98 \pm 0.6	--	--
141	H	-	CH ₂	-	102 \pm 3.4	92 \pm 2.4	--	--
2	Cl	O	C	-	193 \pm 7.3	179 \pm 5.7	4.6 (233%)	5.0 (215%)
217	Cl	O	S	O	97 \pm 1.8	96 \pm 0.5	--	--

^a Fitted EC₅₀ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) responses. Compounds **1** and **2** from preceding Tables are included here for comparison. Data are from between 6-25 oocytes from between 2-5 frogs for each compound and receptor tested.

Table 9. Optimization of Linker B



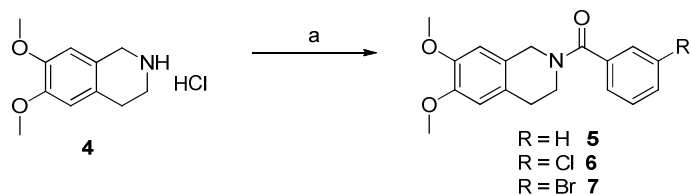
	R ₁	R ₂	R ₃	Z	C=C	I ₁₀ μM / I _{CONTROL} (mean ± SEM, %)		EC ₅₀ (maximal potentiation) (μM, %) ^a	
						GluN2C	GluN2D	GluN2C	GluN2D
1	H	OMe	OMe	O	No	116 ± 2.9	123 ± 2.3	12 (145%)	11 (156%)
2	Cl	OMe	OMe	O	No	193 ± 7.3	179 ± 5.7	4.6 (233%)	5.0 (215%)
190	Br	OMe	OMe	O	No	183 ± 11	178 ± 6.6	0.9 (195%)	2.2 (188%)
154	F	OMe	OMe	C	No	92 ± 1.7	95 ± 2.3	--	--
155	H	OMe	OMe	C	Yes	122 ± 4.4	127 ± 5.1	35 (192%)	35 (199%)
156	Cl	OMe	OMe	C	Yes	169 ± 6.9	155 ± 6.4	1.1 (172%)	1.3 (157%)
157	Br	OMe	OMe	C	Yes	181 ± 17	169 ± 7.3	2.8 (188%)	2.8 (174%)
158	Cl	H	OMe	C	Yes	184 ± 13	187 ± 15	1.0 (190%)	1.0 (192%)
159	Br	H	OMe	C	Yes	172 ± 21	164 ± 11	1.5 (176%)	1.7 (185%)
160	H	OMe	OMe	C	No	102 ± 3.4	100 ± 2.9	--	--
161	Cl	OMe	OMe	C	No	114 ± 2.6	108 ± 2.0	--	--
162	Br	OMe	OMe	C	No	128 ± 5.2	134 ± 7.4	11 (129%)	15 (128%)
127	H	OMe	OMe	S	No	103 ± 4.3	94 ± 1.0	--	--

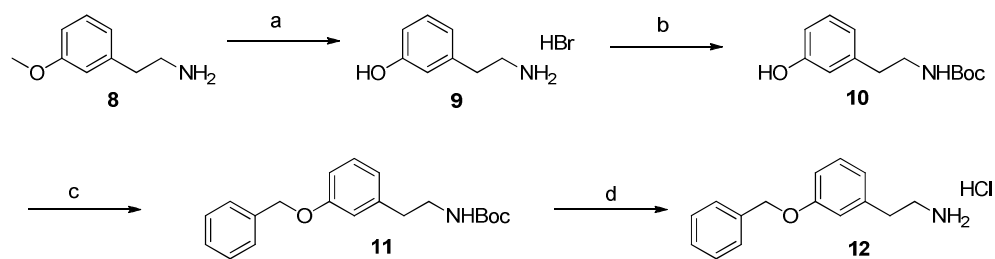
^a Fitted EC₅₀ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) responses. Data are from between 6-25 oocytes from between 2-5 frogs for each compound and receptor tested. Compounds **1**, **2**, **190** are also shown in preceding Tables, and are included here for comparison.

Table 10. Off-target actions of compound **83**

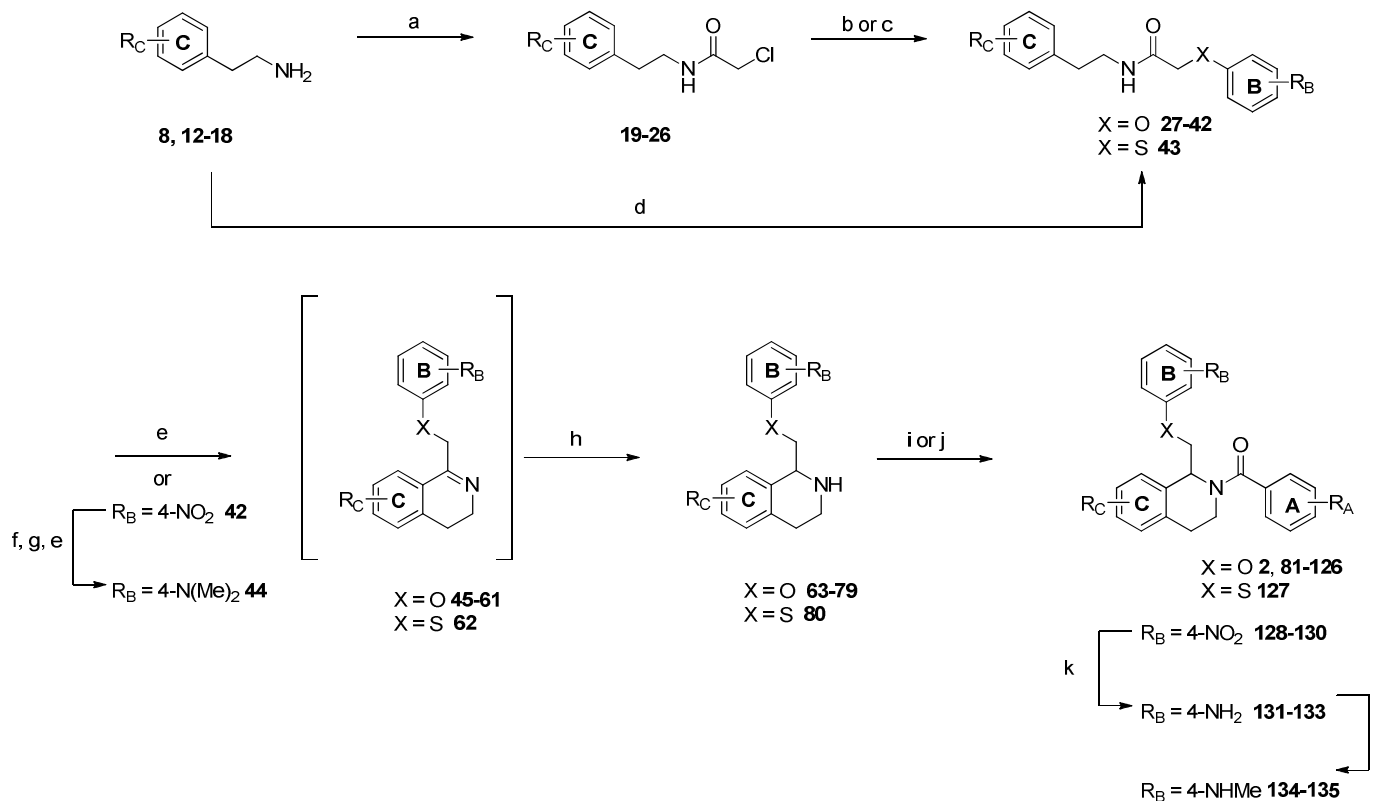
Receptor	Agonist (μM)	$I_{\text{TEST}} / I_{\text{CONTROL}}$ (mean \pm SEM, %)	n
GluN1/GluN2A	100 glutamate, 30 glycine	105 ± 2.3	7
GluN1/GluN2B	100 glutamate, 30 glycine	102 ± 4.0	4
GluN1/GluN2C	100 glutamate, 30 glycine	$247 \pm 20.1^*$	10
GluN1/GluN2D	100 glutamate, 30 glycine	$213 \pm 14.9^*$	8
GluA1	100 glutamate	100 ± 3.1	4
GluA2	100 glutamate	97 ± 1.5	4
GluA3	100 glutamate	99 ± 0.5	4
GluA4	100 glutamate	100 ± 1.0	4
GluK1	100 glutamate	101 ± 1.8	4
GluK2	100 glutamate	98 ± 1.3	4
GluK2/GluK5	100 glutamate	103 ± 1.1	4
Serotonin 5-HT_{3A}	100 serotonin	$93 \pm 0.8^*$	4
GABA_C ($\rho 1$)^(human)	2 GABA	99 ± 2.1	3
Glycine $\alpha 1$	50 glycine	91 ± 9.0	4
Nicotinic $\alpha 1\beta 1\gamma 8$^(mouse)	1 acetylcholine	$105 \pm 1.6^*$	9
Nicotinic $\alpha 4\beta 2$^(human)	10 acetylcholine	$91 \pm 1.5^*$	7
Nicotinic $\alpha 3\beta 4$^(human)	10 acetylcholine	$95 \pm 0.9^*$	5
Nicotinic $\alpha 7$^(human)	300 acetylcholine	90 ± 3.3	3
Nicotinic $\alpha 9\alpha 10$	1 acetylcholine	$92 \pm 1.4^*$	4
Purinergic P_{2X2}^(human)	9 ATP	$94 \pm 0.9^*$	4
Purinergic P_{2X2}	9 ATP	94 ± 2.5	4

Recombinant receptors were expressed in *Xenopus* oocytes and responses the agonists indicated were recorded under two electrode voltage clamp. All cDNAs encoded rat receptors unless otherwise indicated. Compound **83** tested at 3 μM (* $p < 0.05$, paired t-test).

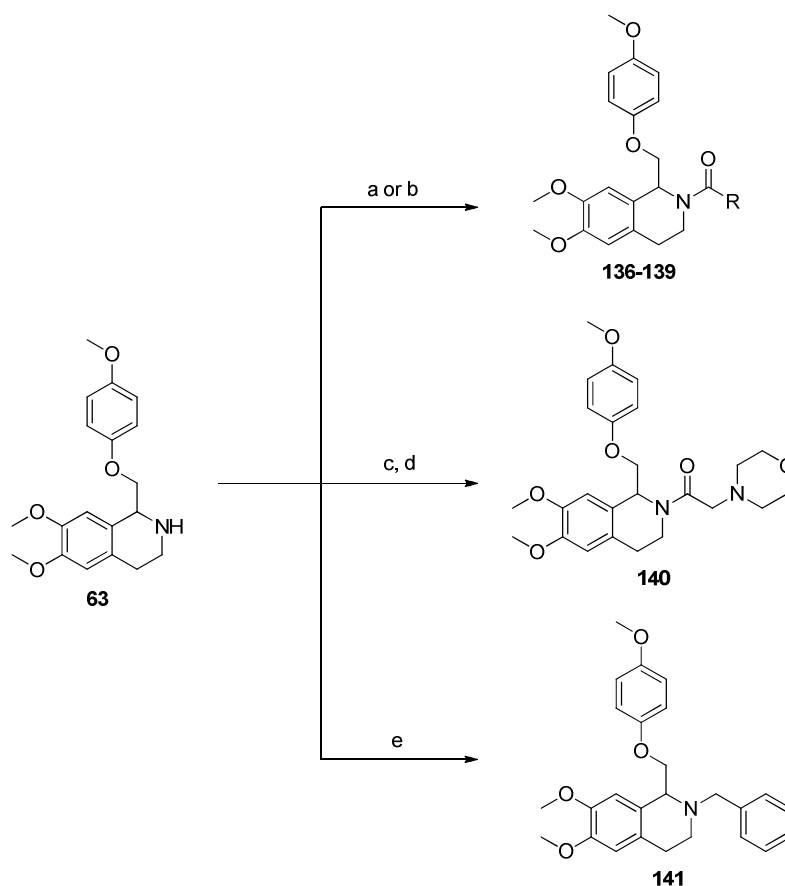
**Scheme 1.** a) substituted benzoyl chloride, NaHCO_3 , $\text{DCM}/\text{H}_2\text{O}$, 67-85% (*Procedure I*).



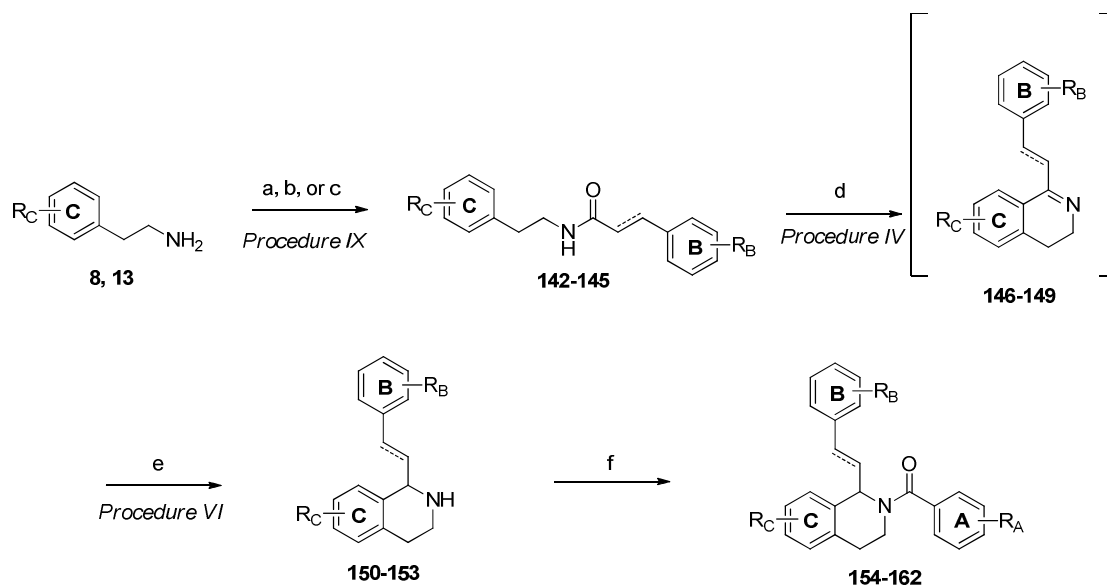
Scheme 2. a) HBr, AcOH, reflux, 4h, quant.; b) Et₃N, Boc₂O, DMF/dioxane, 18 h, 84%; c) Cs₂CO₃, BnBr, MeCN, 24 h, 75%; d) HCl, Et₂O.



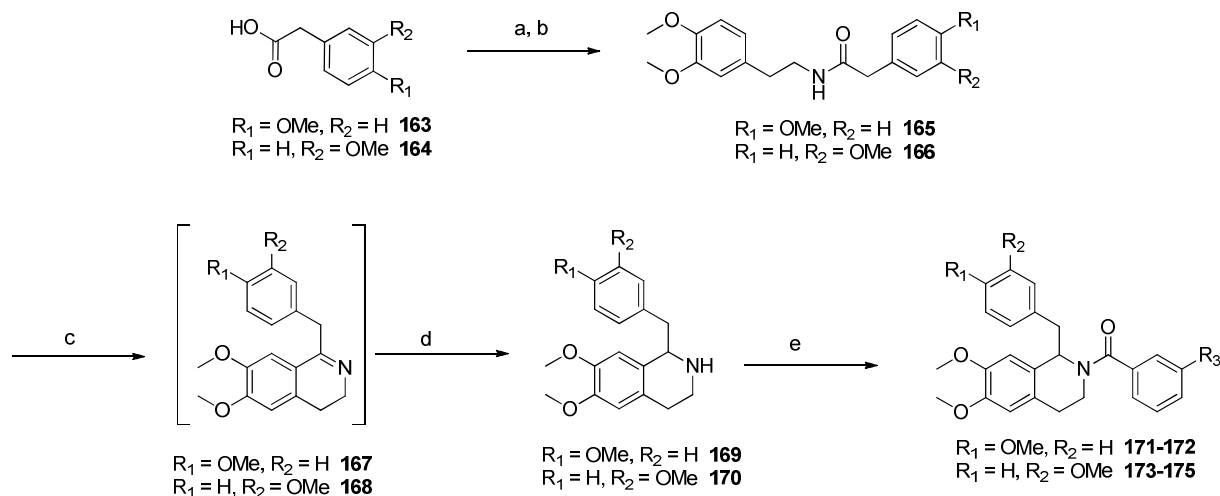
Scheme 3. a) chloroacetyl chloride, Et₃N, DCM, 0°C, 1.5-2h, 68-83% (*Procedure II*); b) substituted phenol, Cs₂CO₃, MeCN, 18h, 66-90% (*Procedure III*); c) 4-nitrophenol, CsF, DMF, 76%; d) phenoxyacetyl chloride, Et₃N, DCM, 0°C, 1.5-2h, 69%; e) POCl₃, toluene, reflux, 1.5-12 hrs (*Procedure IV*); f) Pd/C, H₂, MeOH, 97%; g) paraformaldehyde, NaCNBH₃, MeOH, 89%; h) NaBH₄, MeOH, 18h, 18-70% over two steps (*Procedure VI*); i) substituted benzoyl chloride, Et₃N, DCM, 0°C, 2h, 21-99% (*Procedure VII*); j) substituted benzoic acid, EDCI, DMAP, 18h, 22-68% (*Procedure VIII*); k) tin(II)chloride dihydrate, EtOH 33-66%; l) NaOMe, paraformaldehyde, sodium borohydride, MeOH, 68-72%.



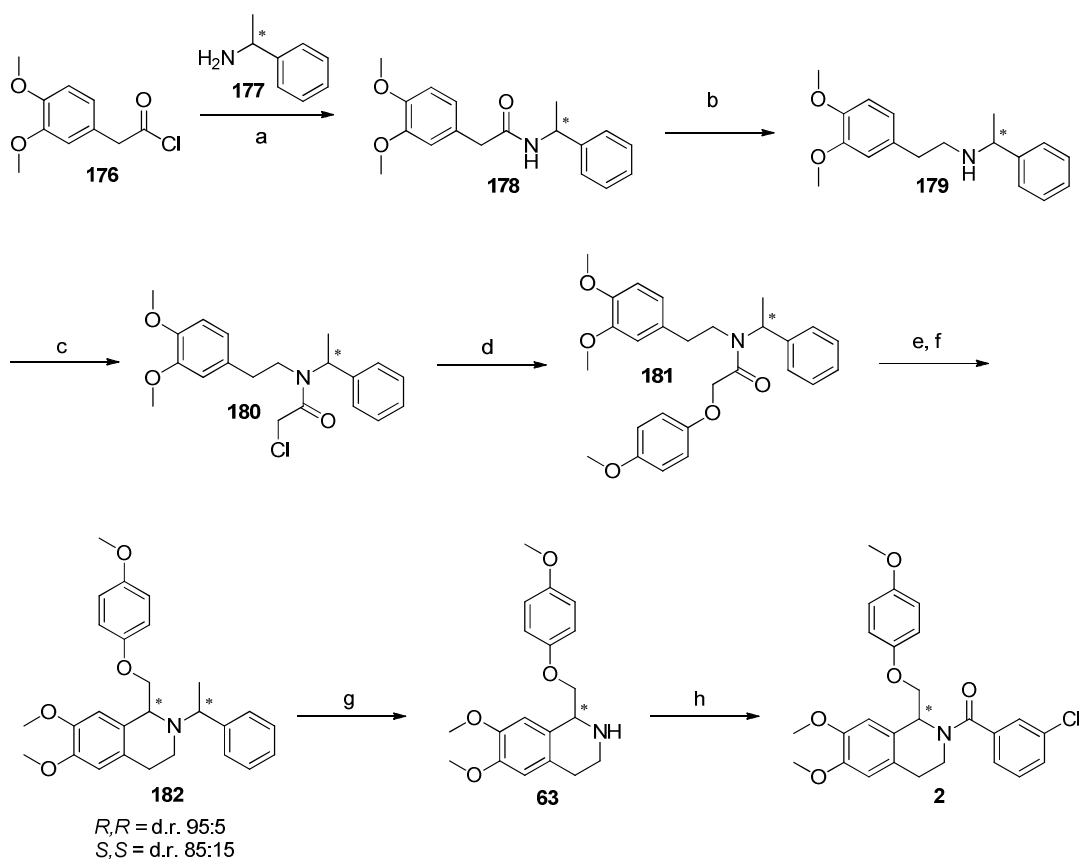
Scheme 4. a) aryl chloride, Et₃N, DCM, 0°C, 21-99% (*Procedure VII*); b) 4-morpholinecarbonyl chloride, Et₃N, DCM, 0°C, 31%; c) chloroacetyl chloride, Et₃N, DCM, 0°C, 78%; d) morpholine, EtOH, 53%; e) BnBr, K₂CO₃, DMF, 39%.



Scheme 5. a) 4-methoxycinnamic acid, EDC, DMAP, DMF/DCM, 18h, 42-66% (*Procedure IX*); b) 4-methoxyphenylpropionic acid, EDC, DMAP, DCM/DMF, 18h, 66% (*Procedure IX*); c) phenylpropionyl chloride, Et₃N, DCM, 99%; d) POCl₃, toluene, reflux, 1.5h (*Procedure VI*); e) NaBH₄, MeOH, 18h, 58-73% over two steps (*Procedure VI*); f) substituted benzoyl chloride, Et₃N, DCM, 0°C, 38-84% (*Procedure VII*).



Scheme 6. a) SOCl₂, DCM; b) 3,4-dimethoxyphenethylamine, Et₃N, DCM, 26-84% over two steps; c) POCl₃, toluene, reflux (*Procedure IV*); d) NaBH₄, MeOH, 18h, 26% over two steps (*Procedure VI*); e) substituted benzoyl chloride, Et₃N, DCM, 31-64% (*Procedure VII*).



Scheme 7. a) NaOH, DCM/H₂O, *R* = 72%, *S* = 82%; b) BF₃·OEt₂O, then BH₃·THF, THF, *R* = 90%, *S* = 95% c) 2-chloroacetyl chloride, Et₃N, DCM, *R* = 80%, *S* = 73%; d) 4-methoxyphenol, Cs₂CO₃, MeCN, *R* = 74%, *S* = 73%; e) POCl₃, toluene, reflux; f) NaBH₄, MeOH, -78 °C, *R*, *R* = 34%, *S*, *S* = 34%; g) H₂, Pd/C, EtOH; h) 3-chlorobenzoyl chloride, Et₃N, DCM, *R* = 51%, *S* = 34%.

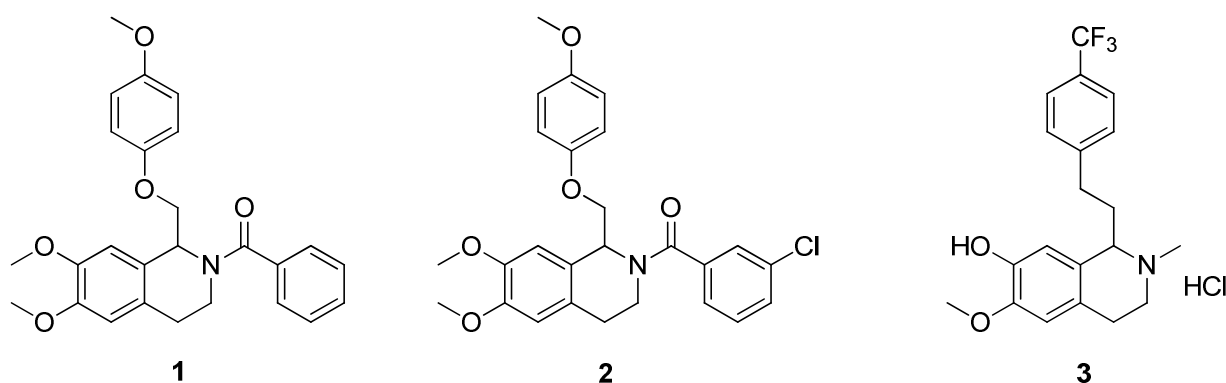


Figure 1. Structures for (6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1), CIQ (2) and HON0001 (3).

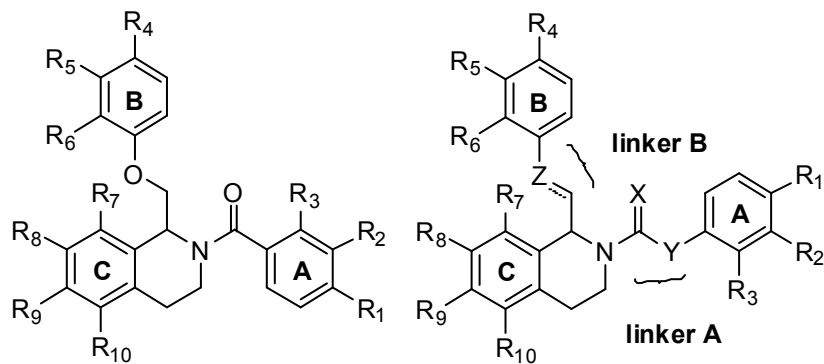


Figure 2. Generic structures showing A-,B-, and C-rings and A- and B-linkers for SAR development on the screening hit, 1180.

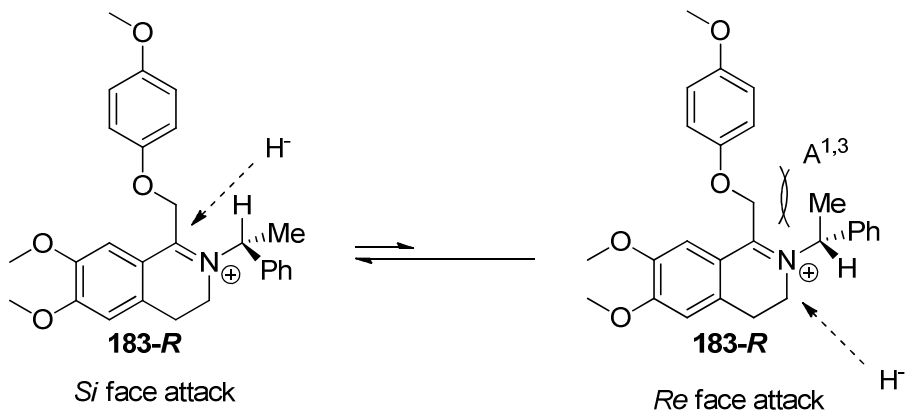


Figure 3. Proposed model to predict stereochemical outcome of the reduction of iminium 185-R

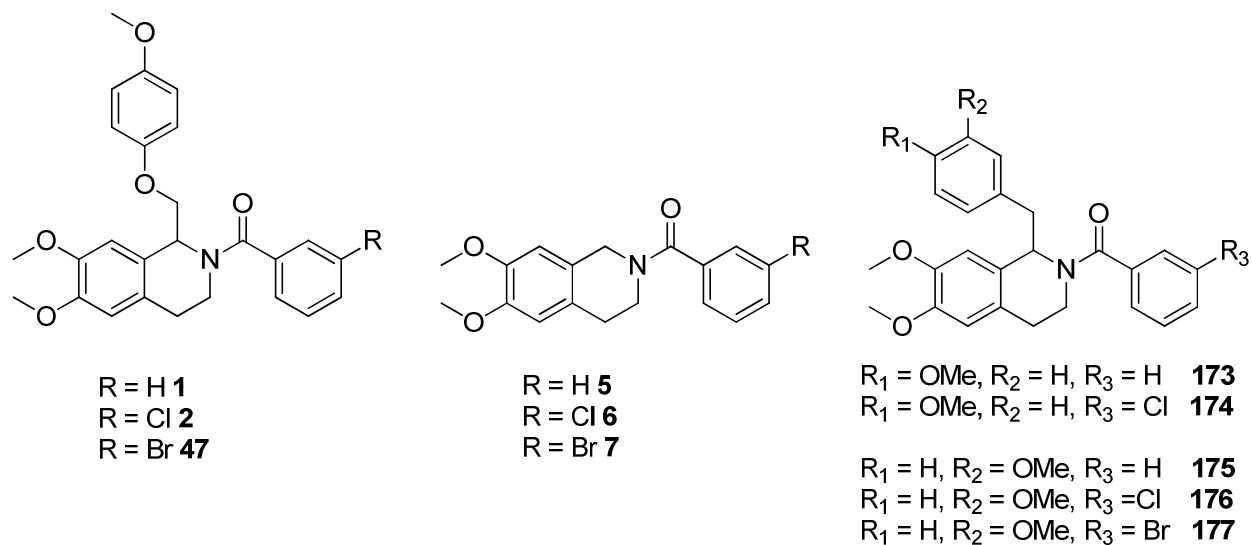


Figure 4. Structure of analogues with B-ring and linker B removed (5-7) and analogues with a one atom linker B (173-177)

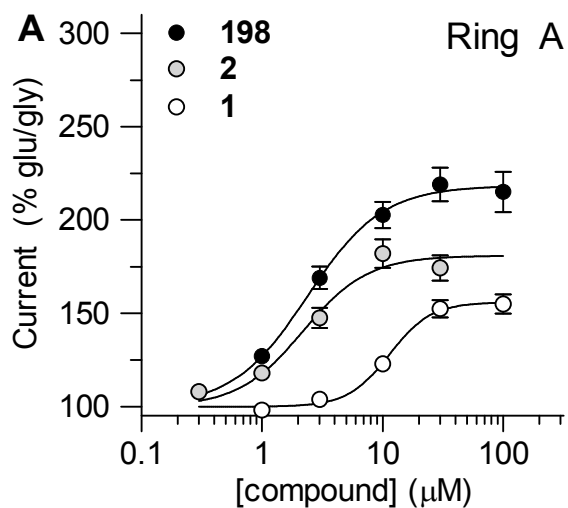


Figure 5. A, Composite concentration-effect data and fitted curves are shown for the initial screening hit (**1**), as well as for two modifications to Ring A that improve activity (**2**, or CIQ, and **198**). **B**. Composite concentration-effect data and fitted curves are shown for the initial screening hit (**1**), **2** or CIQ, and two analogues with Ring C modifications that yield more potent and efficacious potentiation. **C**. Composite concentration-effect data and fitted curves are shown for *R*-(-)-**2** (90% ee), and *S*-(+)-**2** (>98% ee). The broken line indicates predicted activity of 5% contaminant *S*-(+)-**2**. Data represent mean \pm SEM.

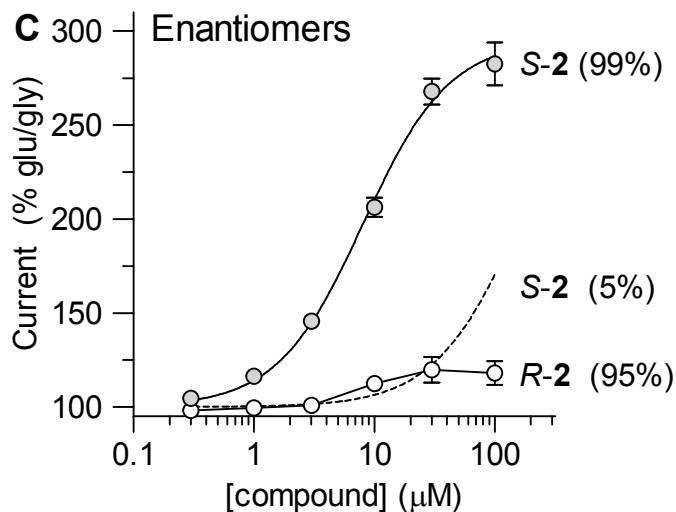
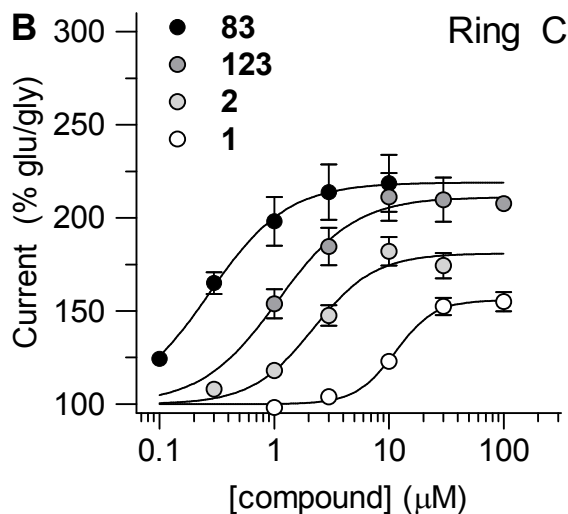


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