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Matthew P. Epplin **Date**

The Design, Synthesis, and Biological Evaluation of Subunit-Selective Modulators of the *N*-Methyl-D-Aspartate Receptor

By

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Doctor of Philosophy

Chemistry

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By

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B.S. and B.ChE., University of Minnesota, 2014

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An abstract of

A dissertation submitted to the Faculty of the James T. Laney of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry

2019

Abstract

The Design, Synthesis, and Biological Evaluation of Subunit-Selective Modulators of the *N*-Methyl-D-Aspartate Receptor

By: Matthew P. Epplin

The *N*-Methyl-D-Aspartate receptor (NMDAR) is an ion channel responsible for mediating the slow, Ca^{2+}-permeable component of glutamatergic synaptic transmission in the central nervous system (CNS). NMDARs are known to play a significant role in basic neurological functions and their dysfunction has been implicated in several CNS disorders. Four isoforms of the NMDAR, GluN2A-D, exhibit unique expression patterns in the brain and display different functional properties depending on the subunit makeup. Previous molecules targeting the receptor display a wide range of neurological side effects *in vivo*, perhaps due to engaging NMDAR subunits irrelevant to the targeted disease. This has led to the hypothesis that developing subunit-biased modulators could maintain efficacy while limiting the observed off-target effects. For this reason, our lab previously identified CIQ, a tetrahydroisoquinoline-based GluN2C- and GluN2D-selective positive allosteric modulator (PAM) for the receptor. Structural modifications resulted in IPQ2, a GluN2B-preferring PAM, albeit with modest potency and high lipophilicity. High affinity and low lipophilicity (i.e. high lipophilic efficiency) are highly desired in drug development to achieve low-dose compounds for patients. Chapter One of this thesis outlines efforts to improve the lipophilic efficiency of the series targeting the GluN2B subunit. This work resulted in the most potent small molecule positive modulator for GluN2B known at a pEC_{50} of 6.5. Although CIQ has made a significant impact as a first-in-class *in vitro* tool compound, it exhibits several liabilities limiting its use *in vivo*, including modest potency, modest potentiation, low aqueous solubility, and high lipophilicity. Chapters Two and Three of this thesis outline core changes from the tetrahydroisoquinoline scaffold of CIQ to two novel scaffolds for the receptor targeting these liabilities. Chapter Two describes a change to a dihydroisoquinolinone core that improved doubling concentrations 5-fold on average. These substrates also maintained selectivity for GluN2C- and GluN2D-containing receptors across a wider range of substrates without increasing compound lipophilicity. Chapter Three of this thesis describes the discovery of a second core change to a pyrrolopyrazinone scaffold that addresses each of potency, efficacy, and lipophilicity. The prototypical compound, **1180-453**, shows roughly order of magnitude improvements in doubling concentration, lipophilic efficiency, aqueous solubility, and an order of magnitude decrease in cLogP compared to CIQ. Separation of the enantiomers via chiral HPLC resulted in compounds such as ***R*-(+)-1180-450** with doubling concentrations up to 0.4 μM and a solubility to doubling concentration ratio of >100:1. This work has resulted in second-generation GluN2C- and GluN2D-selective PAMs of the NMDAR showing improved affinity, efficacy, and ADME properties over their predecessors. These compounds are a promising step towards the first useful *in vivo* tools to study positive modulation of GluN2C- and GluN2D-containing NMDA receptors.

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List of Schemes

List of Abbreviations

ABD: agonist binding domain

ACN: acetonitrile

ADHD: attention deficit hyperactivity disorder

ADME: absorption, distribution, metabolism, and excretion

ATD: amino terminal domain

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AMPAR: AMPA receptor

BHK: baby hamster kidney cells

Bn: benzyl

CI: confidence interval

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

*c*Hex: cyclohexyl

CNS: central nervous system

CO_2: carbon dioxide

*c*Pent: cyclopentyl

Cryo-EM: single-particle electron cryomicroscopy

CTD: carboxy terminal domain

DC: doubling concentration

DCM: dichloromethane

DMAP: dimethylamino pyridine

DMSO: dimethylsulfoxide

EC_{50}: half-maximal effective concentration

EDCI: *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride

ee: enantiomeric excess

FDA: Food and Drug Administration

GPCR: G-protein-coupled receptor

HPLC: high-performance liquid chromatography

*i*Bu: isobutyl

ID: indeterminable

*i*Pr: isopropyl

iGluR: ionotropic glutamate receptor

IP: intraperitoneal

IV: intravenous

LCMS: liquid chromatography-mass spectrometry

Me: methyl

MDD: major depressive disorder

mGluR: metabotropic glutamate receptor

µw: microwave

NAM: negative allosteric modulator

NHP5G: *N*-hydroxypyrazol-5-yl glycine

NMDA: *N*-methyl-D-aspartic acid

NMDAR: NMDA receptor

NMR: nuclear magnetic resonance

NRG1: neuregulin-1

OCD: obsessive-compulsive disorder

PAM: positive allosteric modulator

PAS: 20-oxo-5β-pregnan-3α-yl sulfate

PFC: pre-frontal cortex

PS: pregnenolone sulfate

PTSD: post-traumatic stress disorder

PYD: pyrrolidinone

SAR: structure activity relationship

SEM: standard error of the mean

TEVC: two-electrode voltage clamp

THF: tetrahydrofuran

TIQ: tetrahydroisoquinoline

TMD: transmembrane domain

TMS: trimethylsilyl ether

TRD: treatment-resistant depression

Chapter 1: The Design, Synthesis, and Biological Evaluation of GluN2B-Preferring Positive Allosteric Modulators of the N-Methyl-D-Aspartate Receptor

1.1 Statement of Purpose

The *N*-Methyl-D-Aspartate receptor is an ion channel in the brain responsible for mediating the slow, Ca^{2+}-permeable component of glutamatergic synaptic transmission in the central nervous system.[1] NMDARs are known to play a role in learning,[2, 3] memory,[4] brain development,[5] and synaptic plasticity[6, 7] and have been implicated in numerous neurological conditions.[8-19] Four isoforms of the receptor, GluN2A-D, are uniquely expressed both spatially and temporally in the brain[20-22] and endow the receptor with unique pharmacological properties[23-28]. Therefore, there is interest in manipulating specific circuits in the brain via subtype-selective modulators due to each subtype's unique role at different synapses.

There is ample evidence suggesting positive modulation of GluN2B-containing receptors could improve memory formation,[2, 6, 29-42] but there are few literature precedents for small, drug-like molecules selective for this subtype. A high-throughput screen run in the lab of Dr. Stephen Traynelis previously identified a tetrahydroisoquinoline (TIQ)-based scaffold of PAMs selective for GluN2C- and GluN2D-containing receptors.[43] Through significant medicinal chemistry efforts in our lab, an isopropoxy-containing TIQ scaffold evolved with preference for GluN2B-containing receptors. Additional structure-activity relationship (SAR) studies improved potency while identifying GluN2B-selective, GluN2B/C-selective, GluN2B/C/D-selective, and non-selective PAMs.[44]

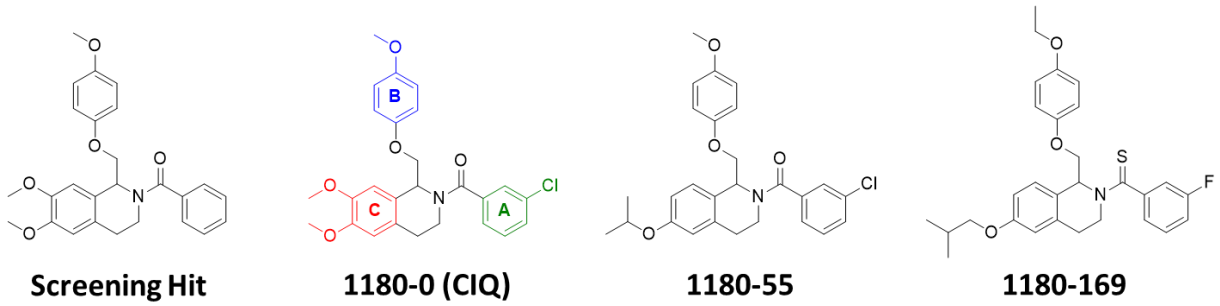


Figure 1. Prototypical compounds previously developed in 1180 series.

The goal of this research was to expand on the previously established SAR to identify more potent GluN2B-selective derivatives and improve the absorption, distribution, metabolism, and excretion (ADME) properties of the series, as most derivatives are poorly soluble due to high lipophilicity. This was accomplished through changes to the A-ring, A-ring linker, and B-ring substitution that had not been previously covered and was executed in the following manner:

1.) Design TIQ-based derivatives likely to exhibit improved potency and ADME properties (e.g. solubility) while maintaining selectivity for the GluN2B subunit based on previously established SAR trends and standard medicinal chemistry principles.

2.) Synthesize the strategically designed derivatives and test for their biological activity at GluN2A-D receptors via an *in vitro* two-electrode voltage clamp (TEVC) assay in *Xenopus laevis* oocytes, completed in the lab of collaborator Dr. Stephen Traynelis.

1.2 Introduction and Background

1.2.1 NMDAR structure, function and localization

Glutamate is the major excitatory neurotransmitter in the mammalian CNS, acting as an agonist for both metabotropic glutamate receptors (mGluRs) of the G-protein-coupled receptor (GPCR) family and ionotropic glutamate receptors (iGluRs) of the ligand-gated ion channel family. There are four subtypes of iGluRs, so named for the synthetic glutamate mimic that each selectively

binds: *N*-methyl-D-asparate (**i**) receptors (NMDARs), 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (**ii**) receptors (AMPARs), (2S,3S,4S)-3-(carboxymethyl)-4-prop-1-en-2-ylpyrrolidine-2-carboxylic acid (**iii**) (kainate) receptors, and the less-understood class of delta receptors (**Figure *2***).[1] NMDARs have been of particular interest to the scientific community as their dysfunction has been implicated in several neurological diseases including schizophrenia,[8, 9] Parkinson's disease,[10] Alzheimer's disease,[19] Huntington's chorea,[11] epilepsy,[12] neuropathic pain,[13] ischemic brain injury,[14-16] and depression,[17, 18] among others. This has led to the suggestion that selective modulation of the receptor may have positive clinical outcomes in humans and significant research into NMDAR assembly, functional properties, and modulator behavior.

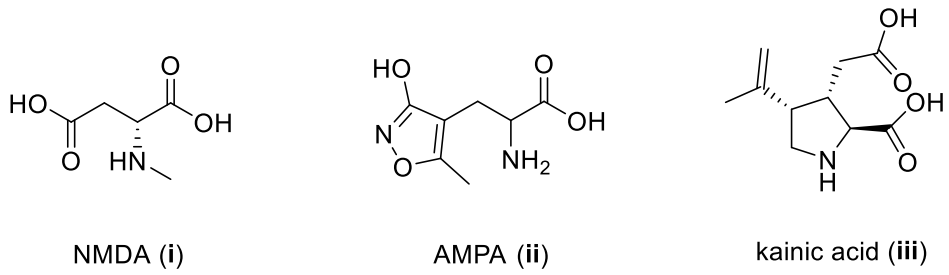


Figure 2. Synthetic ligands selective for the three main classes of glutamate receptors.

Structurally, NMDARs are large (>1000 amino acids per subunit) integral membrane proteins that assemble as tetrameric heterodimers.[1] Functional receptors consist of two obligatory glycine-binding GluN1 subunits and either two glutamate-binding GluN2 subunits, two glycine-binding GluN3 subunits, or one of each.[35, 45-49] While a single gene encodes for the GluN1 subunit, there are four isoforms of the GluN2 subunit, GluN2A-D, and two isoforms of GluN3, GluN3A-B. (There are also eight splice variants of GluN1, GluN1-1a–GluN1-4a and GluN1-1b–GluN1-4b.) NMDARs can assemble as both diheteromeric receptors and triheteromeric receptors.[29, 50] Diheteromers contain only one type of GluN2 or GluN3 subunit (e.g. two GluN1 subunits and two GluN2B subunits) while triheteromers can contain two different GluN2 or GluN3 subunits (e.g.

two GluN1 subunits, one GluN2A subunit, and one GluN3B subunit). Less is known regarding diheteromeric GluN3-containing receptors and triheteromeric receptors, but their effect on receptor properties has recently begun to come into focus.[51]

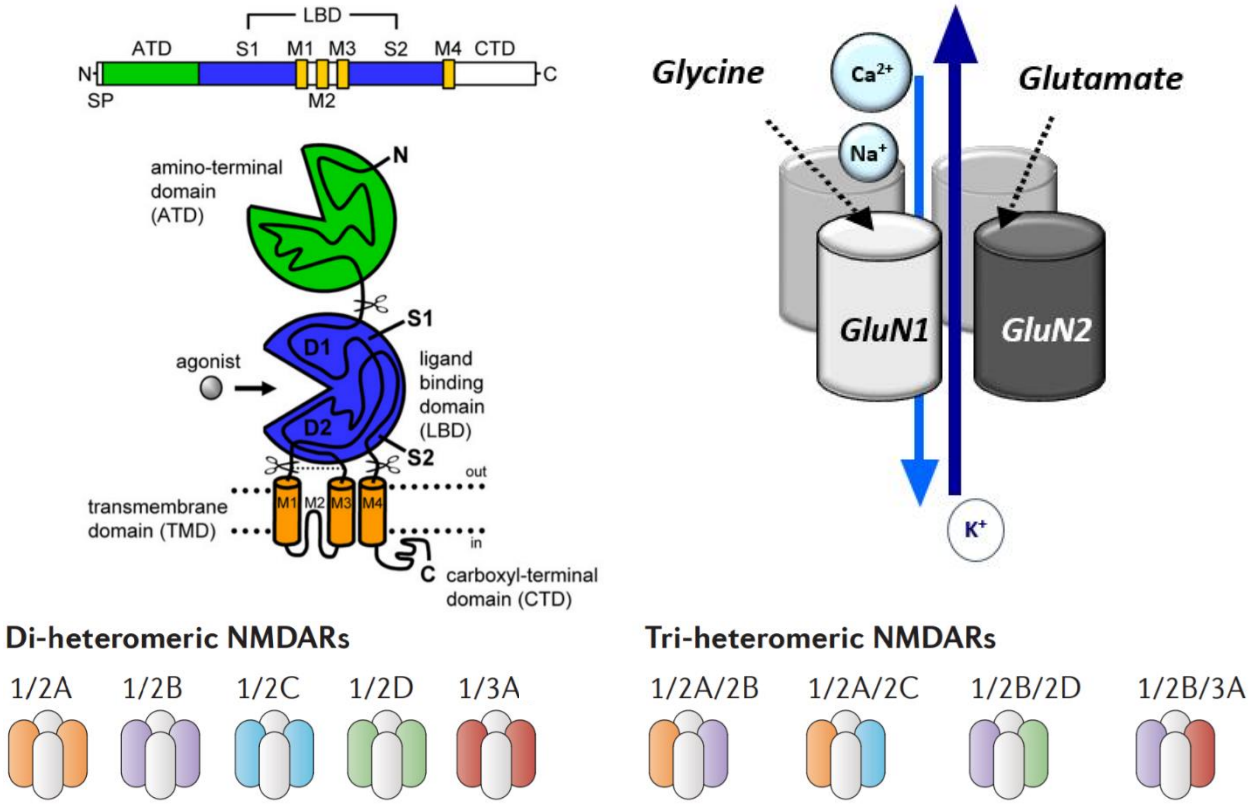


Figure 3. Linear glutamate receptor sequence and flat representation of a singular subunit showing the four semiautonomous domains (left).[1] Cartoon depiction of NMDAR heterotetramer, binding by co-agonists glutamate and glycine, and subsequent ion flow in and out of the cell (right). Subunit makeup of several diheteromeric and triheteromeric NMDARs (bottom).[35]

Significantly more is known regarding the structure and function of diheteromeric GluN2-containing receptors. All glutamate receptors contain four semiautonomous domains: an amino-terminal domain (ATD), an agonist-binding domain (ABD), a pore-containing transmembrane domain (TMD), and intracellular carboxyl terminal domain (CTD). Several crystal structures and single-particle electron cryomicroscopy (cryo-EM) images of the glutamate receptors have been recently solved leading to a deeper understanding of the relationship between structure and function.[45, 52, 53] The ATD forms in a clamshell-like fashion consisting of two halves, R1 and R2.

The cleft is further partitioned into three parts based on their chemical and functional properties. First, a hydrophilic pocket containing His127 and Glu284 that has been shown to be involved in Zn^{2+} binding.[54, 55] Second, a hydrophobic pocket in the inner core of the clamshell containing residues affecting binding of ifenprodil, a GluN2B-selective negative allosteric modulator (**Section 1.2.3**).[56] Then finally, a third ion-binding site located between the first two pockets that accommodates Na^{+} and Cl^{-} ions, present in both the zinc bound and unbound states. Allosteric modulators that bind the ATD are known to alter the properties of agonist binding to the LBD.[57] This is believed to be a result of tighter packing of the two domains in NMDARs (3107 Å^2) compared to other glutamate receptors such as AMPARs (1470 Å^2).[45]

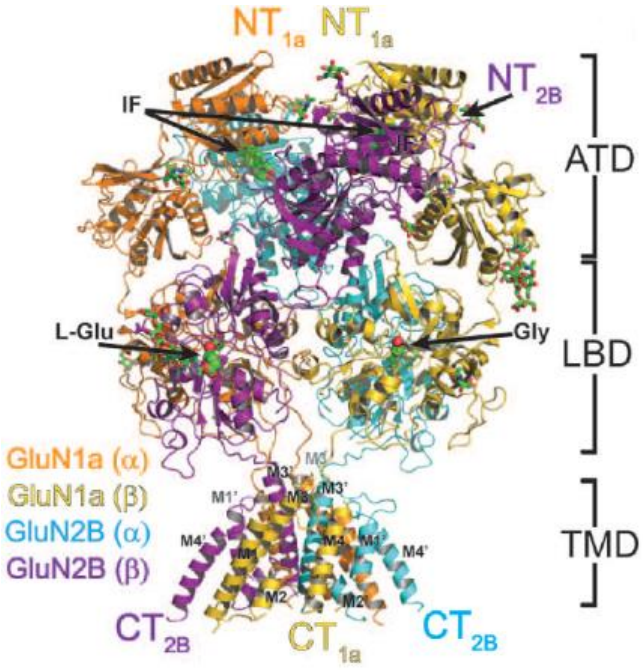


Figure 4. Recent crystal structure of the NMDAR with the GluN2B-selective negative allosteric modulator ifenprodil and co-agonists glutamate and glycine bound.[45]

The LBD also adopts a clamshell conformation consisting of two halves, S1 and S2, that each form one half of the clamshell, D1 and D2, respectively.[58] This section of the receptor is highly conserved across glutamate receptors and the agonist binding interactions are identical across each of the GluN2 subtypes.[27, 59-62] Binding of the co-agonists to the LBD begins the gating process for

the receptor. Upon activation via glutamate and glycine, the D2 lobe raises toward the D1 lobe, pulling the section of S2 connected to M3 in the TMD into an open arrangement allowing for ion flow through the receptor.[63-65]

The TMD forms the glutamate receptor ion pore and is conserved across the family. Consisting of three transmembrane helices (M1, M3, and M4) and a short reentrant loop (M2), the TMD contains residues associated with voltage-dependent NMDAR Mg^{2+} block[66] and the binding of uncompetitive antagonists.[9, 67] The M2 reentrant loop and M3 helix line the inner and outer portion of the pore, respectively, while M1 and M4 lie externally in relation, resulting in an ion pore with 4-fold symmetry upon assembly of the full tetramer. The M4 helix is attached to the intracellular CTD, which is the least conserved of the domains and is non-vital to NMDAR function. It acts in a regulatory fashion, influencing post-translational modifications, membrane targeting, and protein degradation among others.[1]

Over the past half-decade, X-ray crystallography and cryo-EM have provided insight into the quaternary structure of both the apo and activated states of NMDARs. Crystal structures of heterotetrameric GluN1-GluN2B NMDARs were recently solved with allosteric inhibitors, partial agonists, and the uncompetitive antagonists (**Figure 4**).[45, 68] These ligand-bound states revealed a 1-2-1-2 subunit arrangement with a two-fold symmetry axis throughout the receptor and a more tightly bound ATD-LBD interface compared to AMPARs. Then in 2016, Tajima *et al*. used cryo-EM to show that in the absence of ifenprodil (or other inhibitor), activation occurs through opening of the bi-lobed GluN2B ATD, reorientation of the GluN1-GluN2 ATD heterodimeric interface, and finally dilation of the gating ring.[53]

Our understanding of the functional properties and localization of the NMDAR has also advanced significantly in recent decades alongside the structural details. The GluN1 subunit is encoded by a

single gene, expressed widely throughout the CNS, and ubiquitously from the embryonic stage of development through adulthood. However, there are four isoforms of the GluN2 subunit, GluN2A-D, that are expressed with different spatiotemporal patterns in the brain and impart the receptor with unique pharmacological properties (**Figure *5***).[20, 21, 29] For example, GluN2A expression begins in young childhood, increasing throughout life to be expressed widely throughout the CNS in adulthood. GluN2B is one of only two subtypes (along with GluN2D) to be expressed in the pre-natal brain, with expression peaking one week after birth, and continuing in the forebrain throughout life. GluN2C expression is constrained almost completely to the cerebellum and olfactory and appears much later in life (postnatal day 10) compared to the other subunits. Finally, GluN2D drops off substantially post-birth and is expressed in only low levels in the diencephalon and mesencephalon during adulthood. Such strong embryonic GluN2B and GluN2D expression strongly suggests these receptor subtypes are important for synapse formation and maturation[69] while the predominance of GluN2A and GluN2B in the adult brain is suggestive of these subunits' important role in synaptic plasticity and function.[20-22]

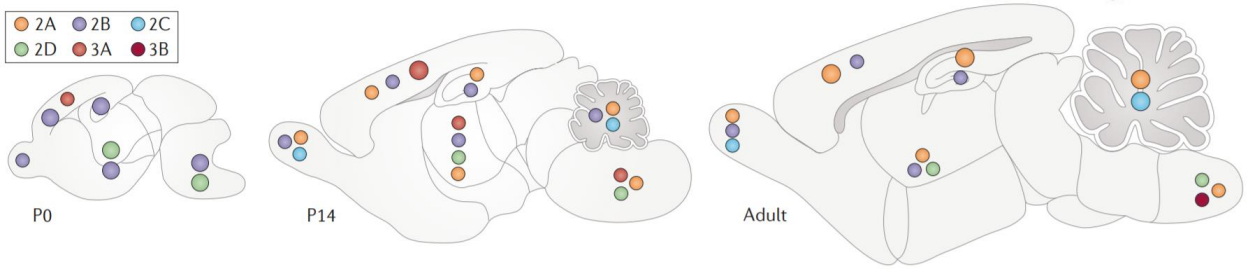


Figure 5. NMDAR subunit expression patterns in a mouse brain at P0, P14, and adulthood.[35]

Along with different expression patterns in the brain, the subunit makeup of the NMDAR also determines permeation and gating properties such as Ca^{2+} permeability, Mg^{2+} block, single-channel conductance,[1, 70, 71] agonist potency,[27] open probability,[23-26] and deactivation time.[28] For example, GluN2A- and GluN2B-containing receptors exhibit higher permeability to calcium,

higher Mg^{2+} sensitivity, and higher conductance compared to their GluN2C- and GluN2D-containing counterparts, all controlled by a single residue in the GluN2 M3 helix.[72] Also, open probability decreases, co-agonist sensitivity increases, and deactivation time increases in order from GluN2A-containing receptors to GluN2D-containing receptors.[1, 35, 70]

1.2.2 Therapeutic Rationale for NMDAR Positive Modulators

These unique subunit expression patterns and functional properties are vital for normal brain development, but present numerous opportunities for dysfunction that can lead to neuropsychiatric disease. NMDAR hypoactivity has been linked to numerous CNS disease states, for some of which the pathophysiology is quite well understood including epilepsy, Alzheimer's disease, and schizophrenia. Genetic studies of epilepsy patients have identified common NMDAR mutations between them that have been shown to result in loss-of-function phenotypes for the receptor.[73-76] Deterioration of synaptic function has also been observed in animal models of Alzheimer's disease.[77] Substantial evidence has accumulated linking NMDAR dysfunction to schizophrenia resulting in the glutamate hypofunction hypothesis of the disease.[78] In the early 1990's, it was reported that the use of uncompetitive antagonists PCP and ketamine induced the positive and negative symptoms of schizophrenia.[79, 80] Additionally, post-mortem studies of schizophrenia patients revealed reduced GluN2A expression in parvalbumin-expressing interneurons.[81, 82] Transgenic mice expressing only 5% of normal GluN1 levels display increased motor activity and stereotypy as well as abnormal social behaviors, consistent with schizophrenia animal models.[83] Further implicating interneuron dysfunction in schizophrenia, it was demonstrated that many of the above behaviors could be reproduced through GluN1 deletion in only corticolimbic interneurons.[84] Post-mortem schizophrenia brains have also shown decreased parvalbumin levels,

which has also been shown to occur upon NMDAR inhibition, suggesting a strong link between the two.[85]

GluN2B hypofunction has also been implicated in numerous processes related to memory in the adult brain. The NMDAR uncompetitive antagonists MK-801 and ketamine negatively affect memory performance in a rat model of attention deficit hyperactivity disorder (ADHD). GluN2B-containing NMDARs are highly expressed in the pre-frontal cortex (PFC), where these uncompetitive antagonists impart their inhibitory activity.[29, 30, 86] There is also evidence decreased GluN2B expression levels during aging may play a part in age-dependent cognitive decline.[6, 29, 38-41] Similarly, GluN2B overexpression has been shown to improve memory function in certain cases. Overexpression of GluN2B in the PFC of rats has been shown to lead to increased long-term potentiation, which was reversed with a GluN2B-selective antagonist.[31] Overexpression of GluN2B NMDARs in the forebrain of mice also led to enhanced NMDAR response to stimuli, which was connected to improved long-term memory, spatial performance, and cued and contextual fear conditioning.[2] This evidence highlights the clinical potential of a potent, GluN2B-selective PAM as a treatment for age-related memory loss in the adult population.

1.2.3 Classes of NMDAR modulators

The established connection between NMDAR dysfunction and disease has led to the question of if modulators of the receptor could alleviate the symptoms of the above neuropsychiatric conditions. Both endogenous and exogenous small-molecules acting on the NMDAR have been identified over the past few decades. The NMDARs are distinct from AMPARs and kainate receptors in that they require activation by glycine (**iv**, **Figure *6***) as well as by glutamate. Similarly to AMPARs and kainate receptors, glycine has been shown to bind between the D1 and D2 domains of the GluN1 dimer with potencies of 1.1 μM for GluN1/GluN2A heterodimers, 0.72 μM

for GluN1/GluN2B, 0.34 μM for GluN1/GluN2C, and 0.13 μM for GluN1/GluN2D. L-glutamate (**v**, **Figure *6***) shows lower potency for the GluN2 dimer than glycine for GluN1 with 3.3 μM for GluN2A, 2.9 μM for GluN2B, 1.7 μM for GluN2C, 0.51 μM for GluN2D.[87, 88] The selectivity of glutamate for GluN2 arises from Tyr730 in the GluN2 LBD that is stabilized upon contact with the carboxylate chain of glutamate.[66] The GluN2 LBD also contains a threonine where GluN1 contains a valine, which allows for a hydrogen bond to be formed between the threonine and the aforementioned glutamate carboxylate chain. The preference of glycine for GluN1 is due to hydrogen bonds formed between the carboxylate end of glycine and Arg522, Thr518, and Ser688 residues in the GluN1 LBD as well as interactions between the amino end of glycine and Pro516, Thr518, and Asp732 residues.[56]

Several of these compounds also show selectivity for the NMDA receptor over the other glutamate receptors. Glutamate itself exhibits moderate selectivity for NMDA, showing activities near the nanomolar region at NMDARs compared to micromolar and millimolar affinities for AMPA and kainate receptors.[1] It is thought that the replacement of a glutamate residue in AMPA and kainate receptors with Asp731 in NMDA receptors is the cause of this selectivity. The side carboxylate chain of the agonist glutamate is unable to interact with the aspartate residue due to its smaller carboxylate side chain in comparison to glutamate, and instead forms hydrogen bonds with Glu413 and Try761.[66] NMDA is also selective for NMDA receptors over other glutamate receptors, although it shows only moderate micromolar range affinities for the receptor. The selectivity is thought to derive from the methylated amino group that occupies the open space created by the shorter aspartate residue in the binding pocket. This methyl group is also sterically hindered by a methionine in the LBD of all AMPA receptors, resulting in a lack of affinity for all GluA subunits.[59]

There exist relatively few agonists for either the GluN1 or GluN2 dimers that are selective for a GluN2 subtype. D-cycloserine (**vi**, **Figure *6***), a GluN1 partial agonist, does show increased efficacy for GluN2C-containing NMDA receptors over GluN2A-, GluN2B-, or GluN2D-containing receptors.[89] In terms of GluN2, a series of *N*-hydroxypyrazol-5-yl glycine (NHP5G) (**vii**, **Figure *6***) derivatives have shown GluN2 subunit specificity along with selectivity for both NMDARs over AMPARs and kainate receptors. It was shown that certain NHP5G derivatives act as agonists at GluN2A-containing receptors and antagonists in GluN2D-containing receptors.[90] For example, propyl derivatives of NHP5G, Pr-NHP5G, showed antagonistic activity at GluN2A (no activity observed) while acting as an agonist at GluN2D with a potency of 153 μM. Significant differences in other pharmacological properties are also seen between GluN2A and GluN2D upon exposure to Pr-NHP5G. For example, the mean open time for GluN2D-containing receptors was nearly double that for GluN2A-containing receptors, at 0.34 ms and 0.172 ms, respectively.[91] Along with the NHP5G series, SYM2081 (**viii**, **Figure *6***) shows nearly 50-fold selectivity for GluN1/GluN2D receptors over GluN1/GluN2A receptors. This is likely due to an additional methyl substituent interacting sterically with Tyr730 in the LBD of GluN2A, while forming a hydrogen bond with a glutamate residue in GluN2D-containing receptors.[27]

The main class of pan-antagonists for the NMDAR is the (*R*)-2-amino-5-phosphonopentanoate (**ix**, **Figure *6***) GluN2 competitive antagonist class that shows affinities in the low micromolar range with equilibrium constants ranging between 0.28 μM and 17 μM.[92] Two small peptides, conantokin-R and conantokin-T, act as both competitive and noncompetitive antagonists while exhibiting pan-antagonist behavior in the low-micromolar region.[93] One set of GluN1-selective competitive antagonists is the kynurenic acids (**x**, **Figure *6***), which exhibit high affinity for GluN1/GluN2A and GluN1/GluN2B receptors with equilibrium dissociation constants at 0.03-0.6

μM and 0.05-0.2 μM, respectively. The kynureic acid derivatives bind within the D1 domain of the GluN1 LBD. The amino end interacts with Pro516 in the binding pocket, the carboxylate end interacts with an Arg523 and forms a hydrogen bond with Thr518, and the chlorine substituents interact with the two aromatic rings of Phe408 and Trp731.[56] Along with extensive positive protein interactions, it also prevents two residue interactions seen in agonist binding, ultimately resulting in a substantial decrease in the closure of the clamshell domain upon binding. Xenon gas is another proposed GluN1 competitive antagonist, binding in the same pocket as glycine causing similar anesthetic effects to ketamine.[56]

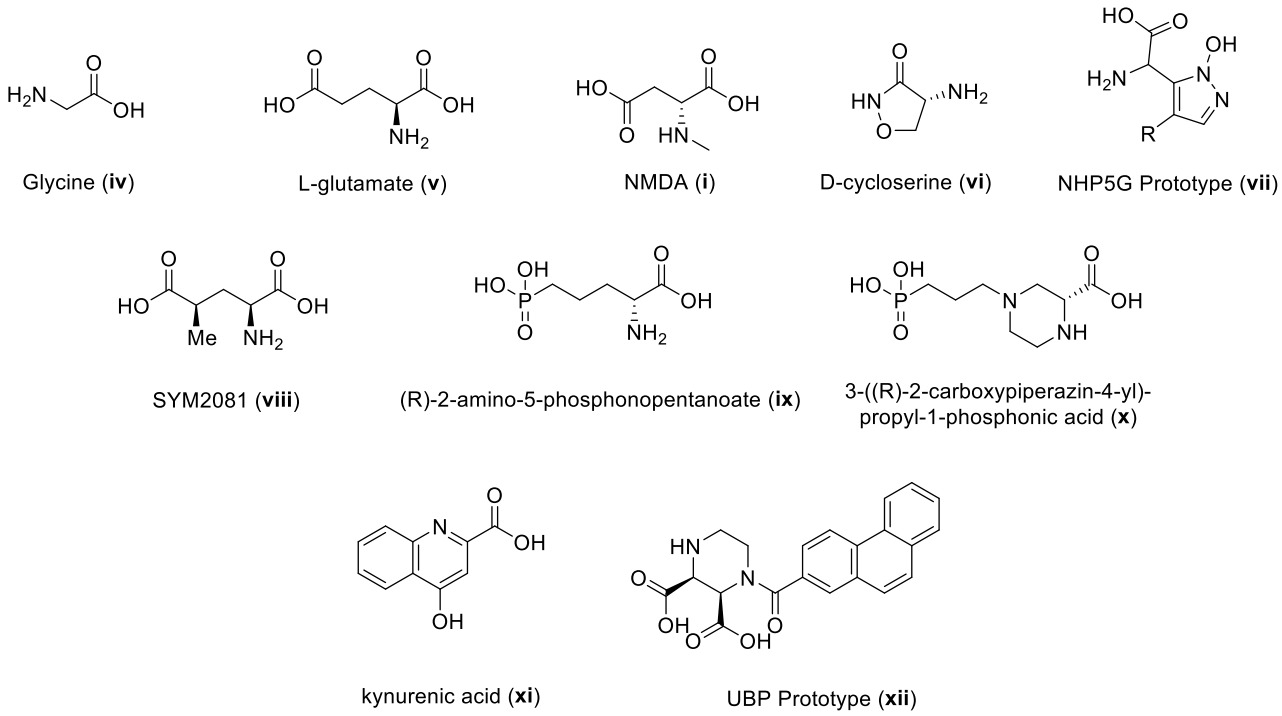


Figure 6. Classes of NMDAR modulators.

The number of subunit-selective GluN2 competitive antagonists is considerably smaller, perhaps due to the high sequence homology between the LBD of the GluN2 subunits. For example, each of the residues known to be associated with the binding of glutamate are conserved across the family.[60, 66] There are, however, certain compounds and classes that do show moderate subunit-

selective activity. A phenanthrene-piperazine dicarboxylic acid series (UBP) (**xi**, **Figure *6***) has shown modest 10-fold selectivity for GluN2C- and GluN2D-containing receptors over GluN2A- and GluN2B-containing ones.[92, 94-96] Another compound, 3-((*R*)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (**xii**, **Figure *6***), shows 50-fold selectivity for GluN2A over GluN2D, but still shows sub-micromolar activity at GluN2B and GluN2C and thus has limited use as a tool compound.[92, 97, 98] Other peptides such as conantokin-G show 20-fold selectivity for GluN2A- and GluN2B over GluN2C and GluN2D via interaction with Met739, which is located outside the D2 domain and only exists in the GluN2C and GluN2D subunits.[93]

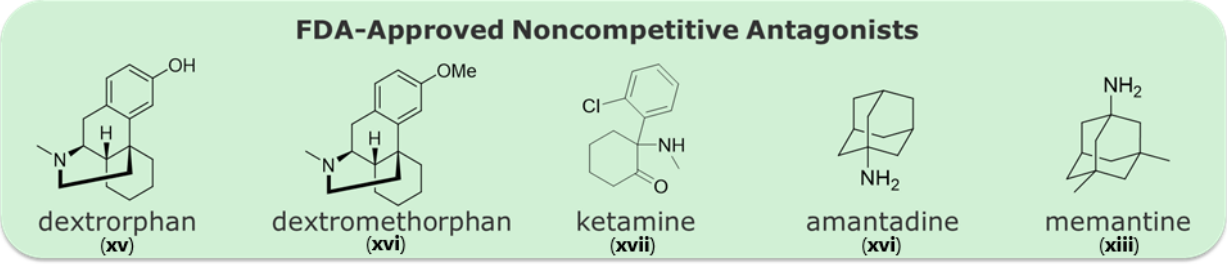


Figure 7. Structures of FDA-approved uncompetitive antagonists of the NMDAR.

The reported NMDAR uncompetitive antagonists (also known as channel blockers) exhibit wide chemical diversity, consisting of single-atom ions such as Mg^{2+}, polyamines, cage-like adamantine derivatives such as memantine (**xiii**) and amantadine (**xiv**), along with drug-like small molecules such as dextrorphan (**xv**), dextromethorphan (**xvi**), MK-801, and ketamine (**xvii**) (**Figure *7***). These antagonists bind deep in the ion pore and require NMDAR activation prior to binding.[99] Ketamine is FDA approved for use as an anesthetic in certain subpopulations and is prescribed off-label for treatment-resistant depression (TRD) and major depressive disorder (MDD).[100, 101] It has also been examined clinically for post-traumatic stress disorder (PTSD)[102] and obsessive-compulsive disorder (OCD),[103] although the mechanism of action for these indications is not well understood. Memantine and amantadine are also FDA approved to treat moderate to severe cases of

Alzheimer's disease and Parkinson's disease, respectively.[19, 104-107] MK-801, another caged amine, acts via channel block and shows roughly 10-fold selectivity for GluN2A- and GluN2B-containing receptors over GluN2C- and GluN2D-containing ones.[108, 109] Other polyamines such as *N*-dansyl-spermine and TB-3-4 show 40-fold selectivity for GluN2A and GluN2D, but other NMDAR uncompetitive antagonists range from poorly selective to completely non-selective, potentially leading to the observed neuropsychiatric side effects.[110, 111] These channel blockers bind to the M2 reentrant loop, similar to the AMPA uncompetitive antagonists, but also contain structural determinants in the pre-M1 pore-forming region as well. The conserved sequence homology between the subunits in the pore-forming region may inhibit the future development of subunit-selective NMDA uncompetitive antagonists.[112-115]

The pharmacology of NMDAR negative allosteric modulators (NAMs) is rich due to the depth of knowledge regarding ifenprodil (**xviii**), the first subunit-selective modulator of the receptor (**Figure *8***). It is a noncompetitive antagonist at GluN2B-containing receptors, showing 200-400-fold selectivity over GluN2A-, GluN2C-, and GluN2D-containing receptors.[116] It is thought to act via the GluN2B ATD and facilitate agonist binding, but significantly decreases the open probability resulting in its antagonistic effects overall. Ifenprodil and its derivatives have been extensively examined clinically for traumatic brain injury, neuropathic pain, and TRD.[117-121] However, these compounds have significant off-target activity at α1-adrenergic receptors and calcium channels and result in PCP-like side effects in rats and rhesus monkeys,[122] suggesting possible abuse potential that has slowed commercial application.

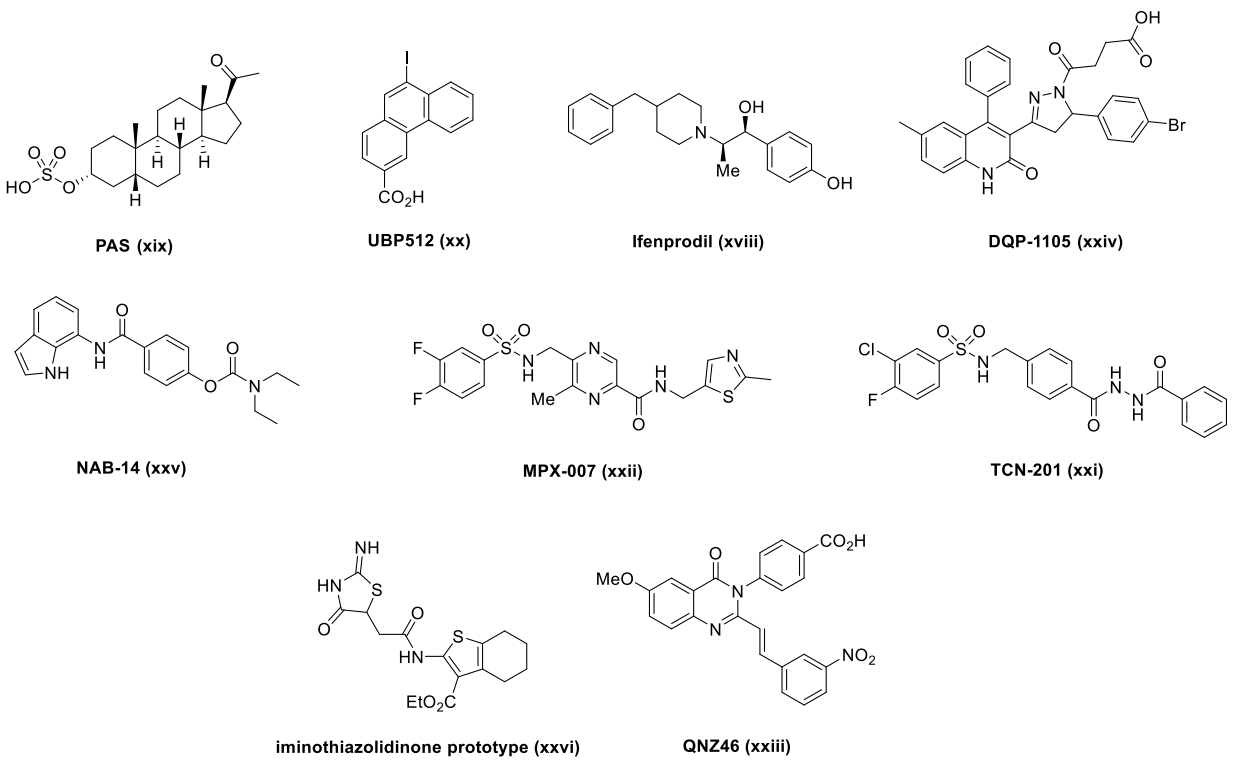
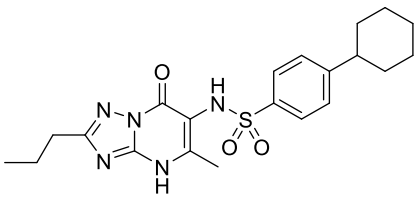


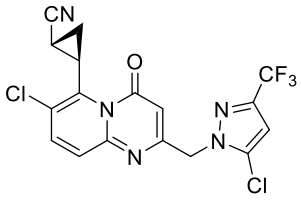
Figure 8. Negative allosteric modulators of the NMDAR.

Since the discovery of ifenprodil, numerous other NAMs of the NMDAR have been identified (**Figure *8***). The neurosteroid 20-oxo-5β-pregnan-3α-yl sulfate (PAS) (**xix**) acts non-selectively on NMDARs with potencies in the double-digit micromolar range. Mutation studies suggest binding may occur at the M3/S2 interface.[123] Several bi- and tri-aryl derivatives of a phenanthrene-3-carboxylic acid (UBP) compound display modest inhibition (~50 μM for the prototype UBP512 (**xx**)) of GluN2C/D-containing receptors. A GluN2A-selective series of sulfonamides (known as the TCN class (**xxi**)) was identified by Bettini *et al*. These compounds bind at the LBD GluN1/GluN2 dimer interface with an IC_{50} of roughly 100 nM and show >300-fold selectivity over GluN2B-, GluN2C-, and GluN2D-containing NMDARs.[67, 124, 125] Despite loss of activity in the presence of high glycine concentrations, Schild analysis suggests the series acts noncompetitively by reducing glycine and D-serine affinity.[67, 124, 126] Recently, two pyrazine derivatives of the series, MPX-004 and MPX-007 (**xxii**), were identified as more potent (27-79

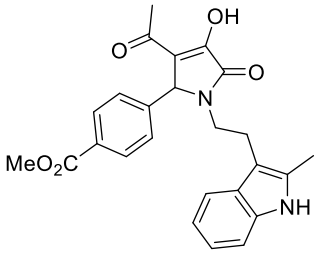
nM at GluN2A), selective, and soluble second-generation sulfonamide derivatives.[127] A quinazoline-4-one (QNZ) (**xxiii**) series of GluN2C/D-selective NAMS shows low-micromolar affinity for the receptor and likely binds in the S2 domain at the LBD/TMD interface.[128, 129] The series is believed to inhibit NMDARs in a mechanistically distinct fashion from the GluN2A-selective sulfonamides. It is thought that binding to S2 prevents the S2-M3 linker from moving in response to glutamate-induced LBD cleft closure, maintaining channel closure.[129] Another series of GluN2C/D-selective NAMS is the pyrazoline-based DQP (**xxiv**) series that displays 100-500 nM potency and 50-200-fold selectivity over GluN2A- and GluN2B-containing receptors.[130] This series shares similar structural determinants to the QNZ series and therefore likely shares similar binding sites and mechanism of action.[129, 131] An *N*-arylbenzamides-based series (prototype NAB-14 (**xxv**)) of GluN2C/D-selective NAMS also hit NMDARs in the 1-3 μM range with >400-fold selectivity over GluN2A/B.[132] Finally, a series of iminothiazolidinones (**xxvi**) was also found to be modestly (~10-fold) selective for GluN2C/D-containing receptors over GluN2A/B-containing ones in the low-micromolar range.[133]



GNE-9278 (xxvii)



GNE-5729 (xxviii)



PYD-106 (xxix)

Figure 9. Subunit-selective positive allosteric modulators of the NMDAR.

By mitigating the effects of NMDAR hypofunction, NMDAR positive allosteric modulators (PAMs) could be useful in conditions associated with reduced NMDAR activity, including schizophrenia,[78, 134, 135] autism spectrum disorders,[136, 137] anti-NMDAR encephalitis,[138-140] and age-related memory loss (**Figure *9***).[2, 71, 141, 142] Several non-selective and subunit-selective PAMs have

been revealed recently. Wang *et al*. published GNE-9278 (**xxvii**), a non-selective benzenesulfonamide-based PAM that hits each of the GluN1/GluN2 NMDARs in the low-micromolar (3-16 μM) range.[143] Structural determinants place binding near the GluN1 pre-M1 helix and it was shown to potentiate the receptor by increasing co-agonist affinity, increasing receptor response at saturating co-agonist concentrations, and slowing deactivation after glutamate removal. Genentech also published a GluN2A-selective series of thiazole derivatives that binds in a similar pocket to the TCN class of NAMs described above. This compound potentiates via stabilization of the agonist-bound state.[144, 145] Significant optimization resulted in GNE-5729 (**xxviii**), a 37 nM compound at GluN2A showing improved AMPAR selectivity and unbound clearance and an excellent secondary profile.[146] The only known series of compounds able to distinguish between GluN2C- and GluN2D-containing receptors is the series of pyrrolidinone-based (prototype PYD-106 (**xxix**)) GluN2C-selective PAMs.[147, 148] Appearing to increase mean open time and open probability via actions on the ATD and S1, further elucidation of the binding site could lead to further development of GluN2C- or GluN2D-selective compounds.

1.2.4 Discovery and structure-activity relationship of a tetrahydroisoquinoline class of NMDAR positive allosteric modulators

In 2007, a collaborator (Stephen Traynelis, Pharmacology) screened roughly 100,000 compounds in a high-throughput Ca^{2+}-flux assay in baby hamster kidney cells (BHK), filtering for selectivity for GluN2C- and GluN2D-containing receptors. From this, 839 compounds altered the response more than 40% from baseline and 516 of the 839 were purchased. A secondary two-electrode voltage clamp assay in *Xenopus laevis* oocytes expressing recombinant GluN1/GluN2D receptors was then run on the 516 purchased compounds, resulting in only 54 compounds that showed more than a 25% in activity from baseline at 10 μM of drug. Upon confirmation of the activity via a full dose-response curve at each of GluN2A-, GluN2B-, GluN2C-, and GluN2D-containing receptors, 5 compounds were found to selectively potentiate the response at saturating concentrations of glutamate (100 μM) and glycine (30 μM). One of these 5 compounds was a tetrahydroisoquinoline based compound (**Figure 11**) that became to be known as compound **1180**.[149] This compound showed EC_{50} values of 12.3 μM (181%) and 11.4 μM (162%) at GluN2C and GluN2D, respectively, while showing no activity at GluN2A, GluN2B, GluN1, AMPA or kainite receptors. Initial SAR studies were performed on the tetrahydroisoquinoline core and upon the addition of a chlorine to the *meta*-position of the A-ring, EC_{50} values were improved to 2.9 μM (197%) and 2.8 μM (211%) at GluN2C and GluN2D, respectively, and the compound was named **1180-0**, or CIQ (**Figure 10**).[43]

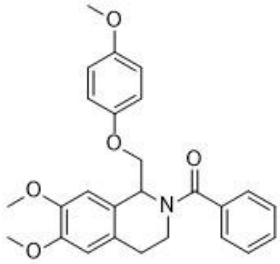


Figure 11. High-throughput screening hit.

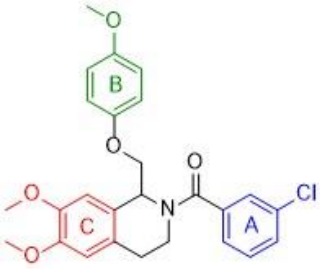
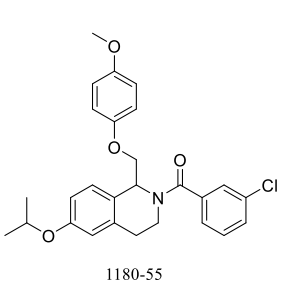
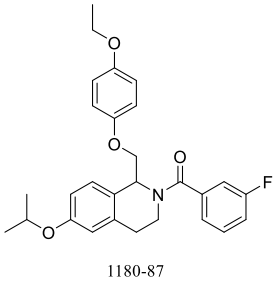


Figure 10. CIQ and ring-labeling convention.

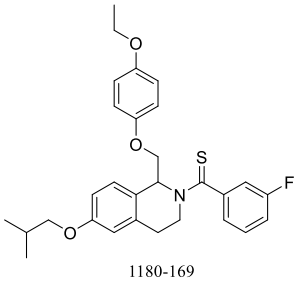
Table 1. Structures and activities of 1180-55, 1180-87, and 1180-169.



1180-55



1180-87



1180-169

Compound Number	GluN2A EC_{50} (μM)/Max %	GluN2B EC_{50} (μM)/Max %	GluN2C EC_{50} (μM)/Max %	GluN2D EC_{50} (μM)/Max %
1180-55*	NE	5.0/220	1.9/255	3.5/332
1180-87*	NE	7.0/152	NE	NE
1180-169*	NE	0.85/398	0.36/315	0.20/564

*Synthesized by Dr. Katie Strong
NE indicates less than 20% potentiation

Substantial synthetic efforts resulted in replacement of the dimethoxy substitution on the C-ring of CIQ with a single isopropoxy group to give **1180-55** (**Table *1***), which tuned in activity at GluN2B while maintaining activity at GluN2C and GluN2D. This was intriguing as there were few reports of small, drug-like GluN2B-selective PAMs in the literature. Efforts to optimize for GluN2B-selectivity led to **1180-87**, which contained an ethoxy substitution on the B-ring and fluoro substitution on the A-ring. This compound tuned out all GluN2C/D activity to give the only GluN2B-selective potentiator in the series at a modest 7 μM and 152% potentiation **(Table *1***). Improving potency was another objective alongside developing GluN2B-selective compounds. One important development in this area was the conversion of the amide C-ring linker to its thioamide counterpart. These thioamides were not selective for GluN2B-containing receptors, but in cases such as **1180-169** (**Table *1***), the EC_{50} values were improved nearly 50-fold over CIQ.[44] Detailed summaries of the previous SAR can be seen in the figures below (**Figure *12***).

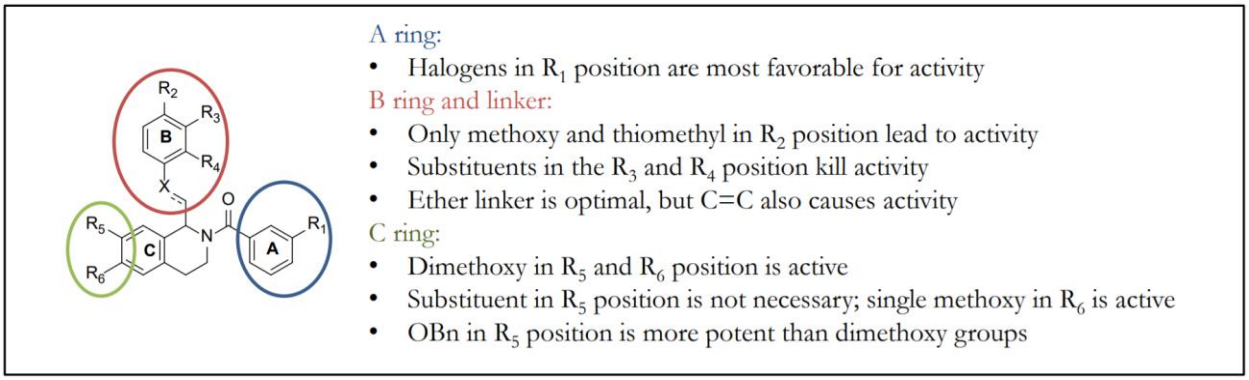
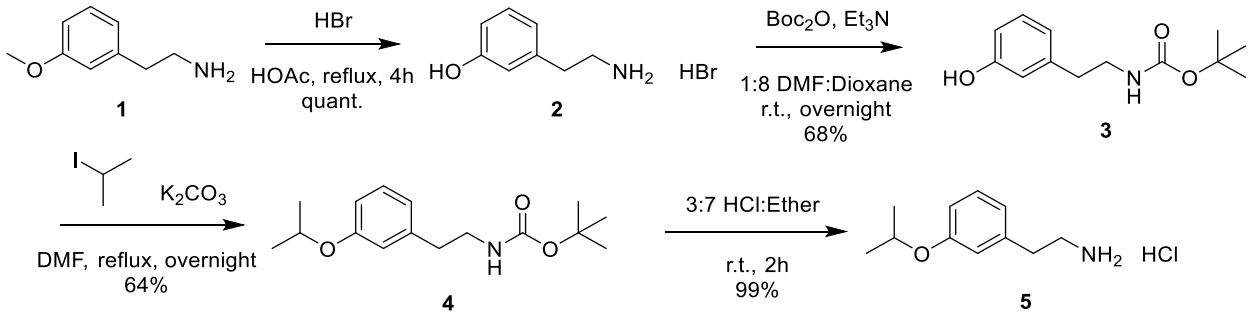


Figure 12. Summary of previous SAR in the 1180 series.[150, 151]

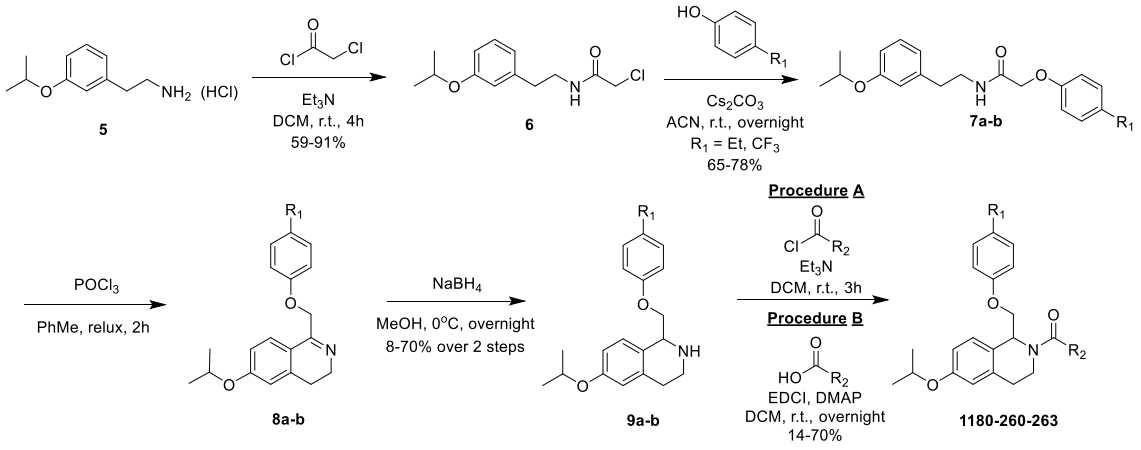
1.3 Synthesis, Rationale, Results, and Discussion of GluN2B-Selective Positive Modulators

Although the isoproxy-containing **1180-55** core has been extensively explored over the last few years, the series still exhibits several liabilities including modest activity, high lipophilicity, poor solubility, and high plasma protein binding *in vivo*.[44] These attributes can lead to negative outcomes such as a lack of pharmacological response, poor bioavailability, low free fraction *in vivo*, and poor receptor occupancy in the brain. Modifications to the both the A- and B-rings were proposed to address these liabilities. First, the lipophilic phenyl-based A-ring would be replaced with hydrophilic substituents such as a thiazole and a crontonic acid derivative to decrease lipophilicity and increase solubility. Second, the alkyl *para*-substituent on the B-ring would be replaced with a trifluoromethoxy group to improve potency as precedence indicated the binding pocket tolerated a number of large substituents.[44] The isopropoxy starting material common to all target products was synthesized from the commercially available methoxy derivative. The synthesis began with a demethylation of phenethylamine **1** using conc. hydrobromic acid and acetic acid to give phenol **2** in quantitative yield, which was then protected using boc anhydride to give boc-protected phenol **3**. An alkylation using 2-iodopropane was done to set the C-ring and give **4**, which was deprotected with ether/hydrochloric acid to give the hydrochloride salt of the primary amine starting material **5** (**Scheme *1***).



Scheme 1. Synthesis of 1180-55 scaffold starting material.

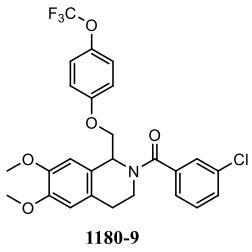
The amine hydrochloride salt was then acylated with chloroacetyl chloride to form amide **6**, which was then alkylated with the appropriate commercially available *para*-substituted phenol to give biaryl compounds **7a-b**. These were then cyclized under Bischler-Napieralski conditions using phosphorous oxychloride in toluene to give imines **8a-b**, which were reduced without purification to secondary amines **9a-b** using sodium borohydride. Next, the secondary amines underwent either an acylation using the appropriate acyl chloride or an amide coupling using the appropriate carboxylic acid and EDCI/DMAP to give the final compounds (**Scheme *2***).



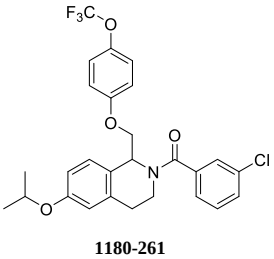
Scheme 2. Synthesis of 1180-55 scaffold derivatives.

Neither thiazole **1180-260** nor linear trifluoromethyl compound **1180-263** were tolerated at any GluN2 subunit. However, compounds **1180-261** and **1180-262** containing the *para*-substituted trifluoromethyl group on the B-ring were active at GluN2B/GluN2C/GluN2D (pEC_{50} = 5.4-5.9), showing that activity can be revived with this substitution once the C-ring is changed from the dimethoxy CIQ scaffold (**1180-9**) to the isopropoxy group (**1180-261**) (**Table *2*** and **Figure 13**).

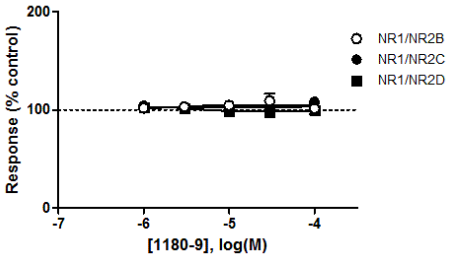
Figure 13. Structure and dose response curve comparison between trifluoromethyl substituted CIQ scaffold and 1180-55 scaffold.



1180-9



1180-261



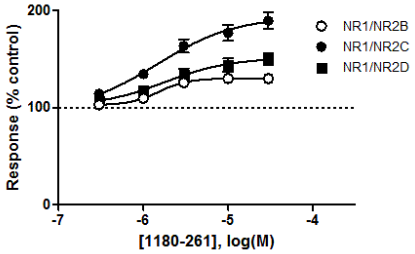
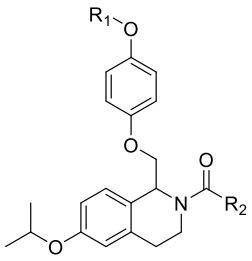
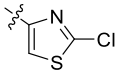
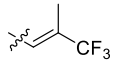
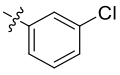
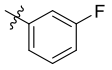


Table 2. SAR of 1180-55 derivatives with modifications to the A- and B-rings.



Compound Number	R_1	R_2	X	GluN2A pEC_{50} (max) (%)	GluN2B pEC_{50} (max) (%)	GluN2C pEC_{50} (max) (%)	GluN2D pEC_{50} (max) (%)
1180-260	OEt		O	NE	NE	NE	NE
1180-263	OEt		O	NE	NE	NE	NE
1180-261	OCF_3		O	NE	5.8 (129)	5.8 (180)	5.9 (143)
1180-262	OCF_3		O	NE	5.5 (123)	5.6 (159)	5.4 (138)

NE indicates less than 20% potentiation

As mentioned previously, an observed trend in the series was the retention of activity at GluN2B, GluN2C, and GluN2D upon the addition of large substituents at the *para*-position of the B-ring (**Figure *14***). Each of the methoxy (**1180-55**), ethoxy (**1180-83**), and isopropoxy (**1180-264**) derivatives were active and interestingly, **1180-83** and **1180-264** were selective for GluN2B/C

over GluN2D. It was hypothesized that additionally increasing substituent size would further improve selectivity while maintaining potency. Accordingly, several *p*-cyclopentyl, *p*-isobutyl, and *p*-3-pentyl derivatives were synthesized in a similar fashion to the previous **1180-55** derivatives (**Figure *14***). The phenol starting materials were not commercially available, however, and were synthesized in one step through an alkylation of hydroquinone using the appropriate alkyl halide to give phenols **10a-c** (**Scheme *3***).

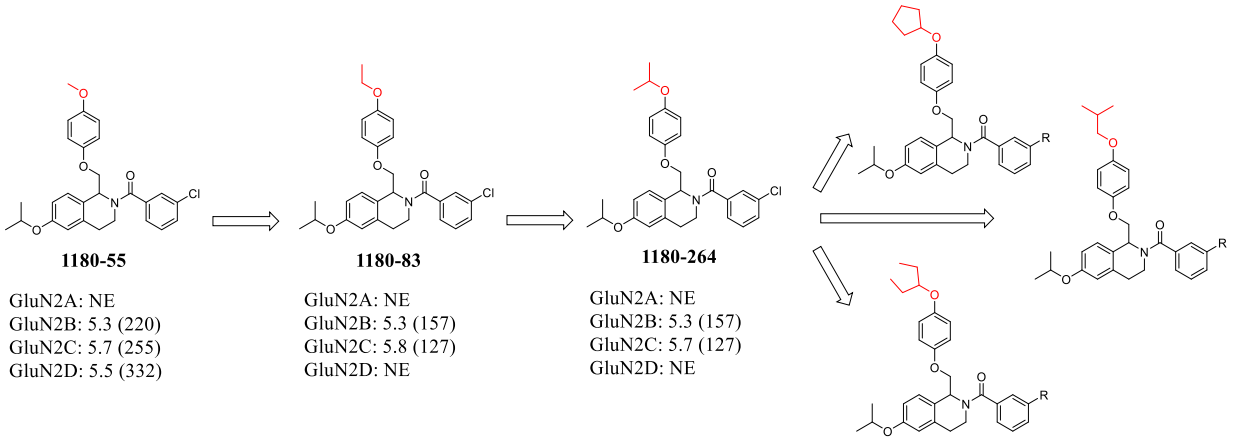
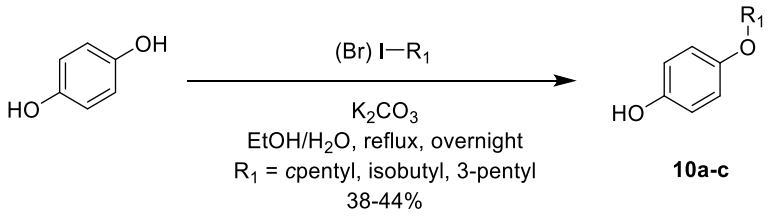
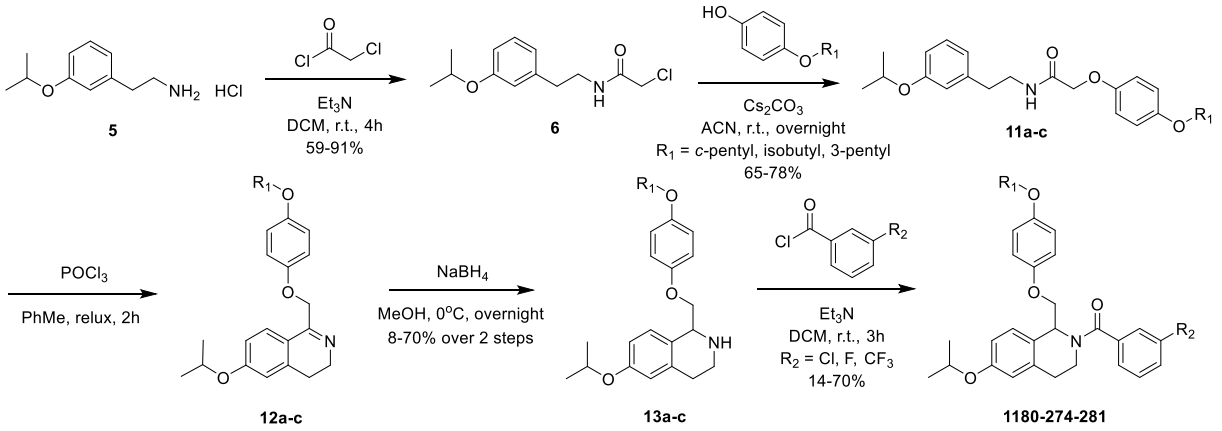


Figure 14. Proposed derivatives based on increasing alkyl substituent size on the B-ring. Affinities are reported as pEC_{50}s and (max).

From there, the synthesis proceeded as before as amine **5** was acylated with chloroacetyl chloride to give amide **6** before alkylation with the appropriate phenol to give biaryl compounds **11a-c**. These were then cyclized under Bischler-Napieralski conditions with phosphorous oxychloride to give imines **12a-c**, reduced with sodium borohydride to give secondary amines **13a-c**, and acylated with the appropriate acid chloride to give the final compounds (**Scheme *4***).

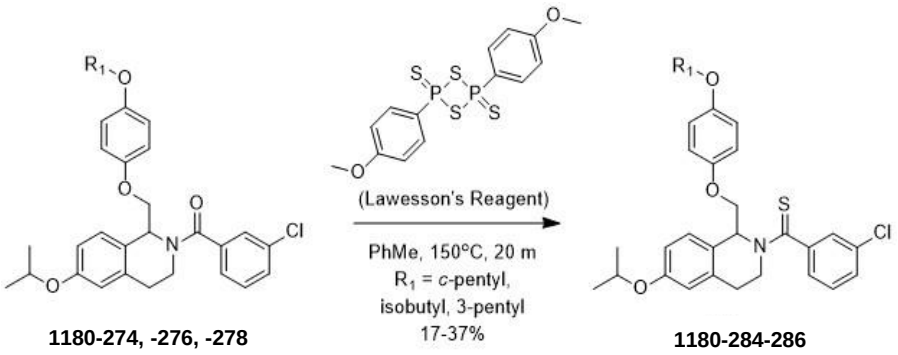


Scheme 3. Synthesis of alkylated phenols.



Scheme 4. Synthesis of 1180-55 derivatives with increased alkyl steric bulk on the B-ring.

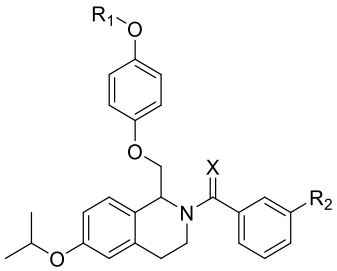
None of the eight compounds (**1180-274-281**) showed potentiation above 130% at any GluN2 subunit, but several exhibited potentiation in the 110-129% range, suggesting weak but real receptor activation. Therefore, compounds **1180-274**, **1180-276**, and **1180-278** were each converted to the thioamide using Lawesson's reagent to give compounds **1180-284-286** (**Scheme 5**). Conversion to the thioamide has previously been shown to improve ligand affinity for GluN2B-containing receptors[44] so we postulated this may increase potentiation levels. Each of these compounds increased potentiation at GluN2B-containing receptors upon conversion to the thioamide while the cyclopentyl (**1180-285**) and 3-pentyl (**1180-286**) derivatives also maintained activity at GluN2C-containing receptors. These derivatives showed improved potency (pEC_{50} = 5.9-6.5 at GluN2B) and similar max potentiation (136-163% at GluN2B) in comparison to **1180-**



Scheme 5. Synthesis of thioamide compounds.

55, **-83**, and **-264** (pEC_{50} = 5.3 and 157-220% at GluN2B) which is consistent with the trend (**Table *3***). These results are an excellent starting point for the development of additional compounds that are both potent and selective towards the GluN2B subunit.

Table 3. SAR of compounds with increased alkyl bulk on the B-ring.



#	R_1	R_2	X	GluN2A pEC_{50} (max) (%)	GluN2B pEC_{50} (max) (%)	GluN2C pEC_{50} (max) (%)	GluN2D pEC_{50} (max) (%)
55*	Me	Cl	O	NE	5.3 (220)	5.7 (255)	5.5 (332)
83*	Et	Cl	O	NE	5.3 (157)	5.8 (127)	NE
264*	*i*-Pr	Cl	O	NE	5.3 (157)	5.7 (127)	NE
274	*i*-Bu	Cl	O	NE	NE	NE	NE
275	*i*-Bu	F	O	NE	NE	NE	NE
276	*c*-Pent	Cl	O	NE	NE	NE	NE
277	*c*-Pent	F	O	NE	NE	NE	NE
280	*c*-Pent	CF_3	O	NE	NE	NE	NE
278	3-Pent	Cl	O	NE	NE	NE	NE
281	3-Pent	F	O	NE	NE	NE	NE
279	3-Pent	CF_3	O	NE	NE	NE	NE
284	*i*-Bu	Cl	S	NE	6.1 (136)	NE	NE
285	*c*-Pent	Cl	S	NE	6.5 (157)	6.2 (145)	NE
286	3-Pent	Cl	S	NE	5.9 (163)	6.1 (156)	NE

*Synthesized by Dr. Katie Strong; NE indicates less than 20% potentiation

1.4 Conclusions

Substantial SAR was performed on the 1180 series to improve affinity, decrease lipophilicity, and increase selectivity for GluN2B-containing receptors. Placement of a trifluoromethyl group in the *para* position of the B-ring on the **1180-55** scaffold (**1180-261-262**) recovered activity at GluN2B, GluN2C, and GluN2D compared to the CIQ scaffold where it showed no activity at any subunits. However, attempts to decrease lipophilicity via replacement of the A-ring with hydrophilic substituents (**1180-260**, **263**) resulted in exclusively inactive compounds. Addition of alkyl

substituents in the *para* position of the B-ring (**1180-274-281**) was also not tolerated, but conversion of the amide of select derivatives to the thioamide (**1180-284-286**) recovered potent (pEC_{50} = 5.9-6.5) and selective activity for GluN2B. Compound **1180-285** is the most potent PAM known at the GluN2B subunit with an EC_{50} value of 0.3 μM. This trend is consistent with previously observed data for the methyl, ethyl, and isopropyl derivatives and sets an excellent starting point for the further optimization of GluN2B-selective PAMs of the NMDAR.

1.5 Experimental Details

1.5.1 Chemistry experimental procedures

General Experimental: All starting materials were purchased from commercial sources and used directly without further purification. Purification by flash column chromatography was done using a Teledyne ISCO Combiflash Companion instrument using Teledyne Redisep normal phase columns. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury-300, VNMR-400, INOVA-400, or INOVA-600 NMR spectrometer. Chemical shifts were reported in parts per million and referenced to the residual deuterated solvent. Reactions were monitored by thin layer chromatography on precoated aluminum plates (silica gel 60 F254, 0.25 mm) or LCMS on an Agilent Technologies 1200 series instrument. High resolution mass spectra were recorded on a VG 70-S Nier Johnson or JEOL instrument by the Emory University Mass Spectroscopy Center. Purity was established via LCMS (Varian) in at least two solvent systems (MeOH:water/ACN:water or MeOH:water/MeOH:water) unless otherwise noted. The conditions were determined individually for each compound in which purity was established via LCMS and the retention times in both solvent systems are given.

General Procedure for Alpha-Chloro Amides (Procedure I): Hydrochloride salt or free amine (1 equiv) was dissolved in dry DCM and triethylamine (2 equiv) was added. The solution was

brought to 0°C, 2-chloroacetyl chloride (1.2 equiv) was added, and the mixture was reacted at room temperature for 4 hours, when deemed complete by TLC. The reaction was then quenched with 1 M HCl, extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Biaryl Linear Compounds (Procedure II): Phenol (1.2 equiv) was dissolved in acetonitrile and cesium carbonate (4 equiv) was added. This mixture was stirred at room temperature for 2 hours before alpha-chloro amide (1 equiv) in acetonitrile was added and allowed to react at room temperature overnight. The reaction was then quenched with saturated ammonium chloride and the product extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Bischler-Napieralksi Cyclizations (Procedure III): Acetamide (1 equiv) was dissolved in dry toluene and heated to reflux before phosphoryl trichloride (3 equiv) was added. This was reacted at reflux for 2 hours when the reaction was deemed complete via TLC. The reaction was cooled to room temperature and saturated ammonium hydroxide was added. This was stirred at room temperature overnight after which the product was extracted in DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated to afford the crude compound.

General Procedure for Secondary Amines (Procedure IV): Imine (1 equiv) was dissolved in dry MeOH and cooled to 0°C before sodium borohydride (3 equiv) was added in ~100 mg portions. The mixture was stirred at room temperature overnight. The reaction was then concentrated and quenched with 1 M HCl. The product was extracted into DCM, washed with brine (3x), dried over

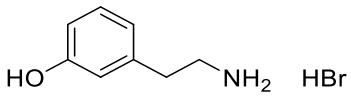
$MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Final CIQ Compounds (Procedure V-A): Secondary amine (1 equiv) was dissolved in dry DCM and triethylamine (2 equiv) and acid chloride (1.2 equiv) were added. The mixture was stirred at room temperature for 3 hours. The reaction was then quenched with 1 M HCl and the organic layer was extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

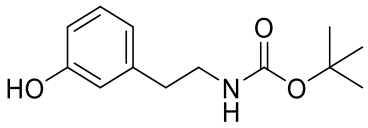
General Procedure for Final CIQ Compounds (Procedure V-B): Carboxylic acid (1.1 equiv) was dissolved in dry DCM and cooled to 0 ^oC. EDCI (1.2 equiv) and DMAP (1.2 equiv) were then added and allowed to stir for 2 hours before the secondary amine (1 equiv) was added and the mixture stirred at room temperature overnight. The reaction was then quenched with deionized water and the organic layer was extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Alkylated Phenols (Procedure VI): Hydroquinone (1.5 equiv) and an alkyl halide (1 equiv) were dissolved in ethanol and potassium hydroxide (1.5 equiv) in water was added. The mixture was heated to reflux and allowed to react overnight. The reaction was then quenched with 1 M HCl and the organic layer was extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated. The product was then triturated with DCM and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Thioamides (Procedure VII): Amide (1 equiv) in a microwave vial was dissolved in toluene and Lawesson's Reagent (1.5 equiv) was added. This mixture was reacted in a microwave at 150°C for 20 minutes. The reaction was then diluted with DCM, washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

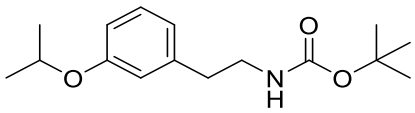


3-(2-aminoethyl)phenol hydrobromide (2). 2-(3-methoxyphenyl)ethan-1-amine (6.90 mL, 47.4 mmol) was dissolved in a 1:1 solution of acetic acid (70 mL) and 48% hydrobromic acid (70 mL). The solution was heated to reflux and allowed to react for 4 hours. Upon reaction completion, the reaction flask was removed from heat and allowed to cool to room temperature. The solution was concentrated *in vacuo* to afford the title compound as a green solid. (10.3 g, quant.). R_f (1:10 MeOH:DCM): 0.10; ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.21 – 7.09 (m, 1H), 6.77 – 6.66 (m, 3H), 3.22 – 3.10 (m, 2H), 2.96 – 2.84 (t, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, Methanol-d_4) δ 157.54, 137.92, 129.63, 119.46, 115.22, 113.77, 40.58, 33.06.

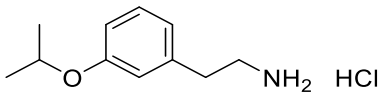


tert-butyl (3-hydroxyphenethyl)carbamate (3). Compound **2** (10.3 g, 47.4 mmol) was dissolved in a 1:8 ratio of DMF (17 mL) and dioxane (140 mL) and triethylamine (6.60 mL, 47.4 mmol) was added dropwise. The solution was allowed to stir for 15 minutes before di-tert-butyl dicarbonate (10.3 g, 47.4 mmol) was added and the resulting mixture was stirred at room temperature overnight. Upon reaction completion, the mixture was concentrated *in vacuo*, extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product

was purified via flash column chromatography (ISCO, Redisep 40 g column, 20-80% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (7.65 g, 68%). R_f (1:10 EtOAc:Hex): 0.20; 1H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.10 (m, 1H), 6.77 – 6.65 (m, 3H), 6.02 (s, 1H), 3.44 – 3.31 (m, 2H), 2.73 (t, *J* = 6.9 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, cdcl3) δ 166.21, 156.12, 140.62, 129.71, 120.86, 115.66, 113.47, 41.57, 35.99, 28.38.

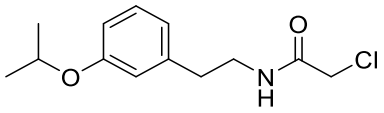


tert-butyl (3-isopropoxyphenethyl)carbamate (4). Compound **3** (7.65 g, 32.3 mmol) was dissolved in dry DMF (100 mL) and potassium carbonate (17.8 g, 129 mmol) was added. This was stirred at room temperature for 2 hours before 2-iodopropane (6.44 mL, 64.5 mmol) was added. The resulting mixture was allowed to react at 60^{o}C overnight, after which the reaction was deemed complete via TLC. The product was then extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil (5.73 g, 64%). Rf (1:10 EtOAC:Hex): 0.78; 1H NMR (400 MHz, Chloroform-d) δ 7.22 – 7.15 (m, 1H), 6.79 – 6.69 (m, 3H), 4.60 – 4.50 (m, 2H), 3.42 – 3.32 (m, 2H), 2.75 (t, J = 6.9 Hz, 2H), 1.43 (s, 9H), 1.33 (d, J = 6.1 Hz, 6H). 13C NMR (101 MHz, cdcl3) δ 158.00, 155.81, 140.54, 129.52, 120.90, 116.38, 113.60, 69.67, 41.60, 36.20, 28.38, 22.06.

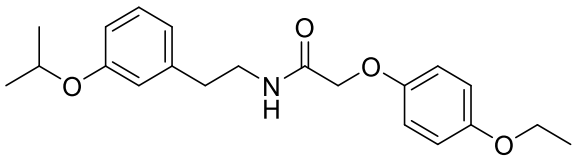


2-(3-isopropoxyphenyl)ethan-1-amine hydrochloride (5). Compound **4** (5.73 g, 20.5 mmol) was dissolved in a 2:5 ratio of conc. HCl (12 mL) and Et_2O (30 mL) and stirred at room temperature for 2 hours while monitored by TLC. Upon reaction completion, the product was concentrated afford the title compound as a white solid (4.38 g, 99%). R_f (1:10 MeOH:DCM): 0.21 ^{1}H NMR

(400 MHz, Methanol-d4) δ 7.27 – 7.17 (m, 1H), 6.84 – 6.77 (m, 3H), 4.64 – 4.53 (m, 1H), 3.18 – 3.09 (m, 2H), 2.89 (t, J = 8.3 Hz 2H), 1.28 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, cd3od) δ 158.32, 137.92, 129.61, 120.34, 116.09, 113.94, 69.36, 40.47, 33.14, 20.89.

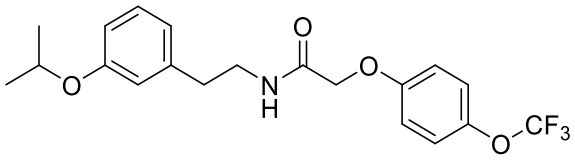


2-chloro-N-(3-isopropoxyphenethyl)acetamide (6). General procedure I was followed using compound **5** (3.17 g, 17.7 mmol), triethylamine (4.93 mL, 35.4 mmol), and 2-chloroacetyl chloride (1.70 mL, 21.2 mmol) in dry DCM (65 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.66 g, 59%). R_f (1:1 EtOAc:Hex): 0.63; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.25 – 7.16 (m, 1H), 6.82 – 6.70 (m, 3H), 4.62 – 4.47 (m, 1H), 4.03 (s, 2H), 3.63 – 3.49 (m, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 1.32 (s, 6H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 165.77, 158.17, 139.87, 129.73, 120.82, 116.36, 113.90, 69.76, 42.66, 40.85, 35.48, 22.07. HRMS calcd. for $C_{13}H_{17}O_2NCl$, 254.09423 $[M + H]^+$; found 254.09421 $[M + H]^+$.

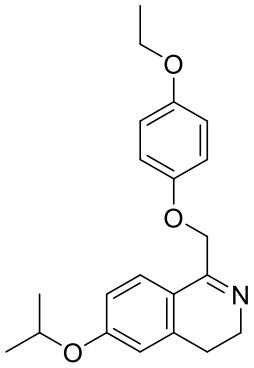


2-(4-ethoxyphenoxy)-N-(3-isopropoxyphenethyl)acetamide (7a): General procedure II was followed using 4-ethoxyphenol (0.87 g, 6.3 mmol), cesium carbonate (6.83 g, 21.0 mmol), and compound **6** (1.34 g, 5.24 mmol) in acetonitrile (25 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a clear oil (1.35 g, 72%). R_f (1:1 EtOAC:Hex): 0.37; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 – 7.15 (m, 1H), 6.88 – 6.64 (m, 8H), 4.61 – 4.48 (m, 1H), 4.41 (s, 2H), 3.99 (q, J = 6.9 Hz, 2H), 3.66 – 3.53 (m, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.32 (d,

J = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.52, 158.13, 155.54, 140.01, 129.70, 122.72, 120.83, 116.45, 115.52, 113.62, 69.66, 67.67, 39.94, 35.61, 22.03. HRMS calcd. for $C_{21}H_{28}O_4N$, 358.20128 $[M + H]^+$; found 358.20140 $[M + H]^+$.

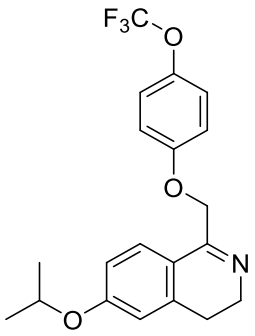


N-(3-isopropoxyphenethyl)-2-(4-(trifluoromethoxy)phenoxy)acetamide (7b). General procedure II was followed using 4-(trifluoromethoxy)phenol (0.79 mL, 6.1 mmol) in acetonitrile (15 mL), cesium carbonate (6.62 g, 20.3 mmol), and compound **6** (1.30 g, 5.08 mmol) in acetonitrile (10 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a clear oil (1.58 g, 78%). R_f (1:1 EtOAc:Hex): 0.32; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 – 7.11 (m, 3H), 6.88 – 6.68 (m, 5H), 4.67 – 4.49 (m, 1H), 4.45 (s, 2H), 3.67 – 3.54 (m, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 1.32 (d, *J* = 6.1 Hz, 6H). HRMS calcd. for $C_{20}H_{23}O_4NF_3$, 398.15737 $[M + H]^+$; found 398.15737 $[M + H]^+$.

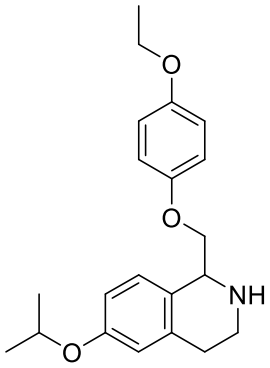


1-((4-ethoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinoline (8a): General procedure III was followed using compound **7a** (1.35 g, 3.78 mmol) and phosphoryl trichloride (1.06 mL, 11.3 mmol) in toluene (20 mL) to give the crude compound as a green solid. The crude material

was carried forward without further purification. HRMS calcd. for $C_{21}H_{26}O_3N$, 340.19072 $[M + H]^+$; found 340.19054 $[M + H]^+$.

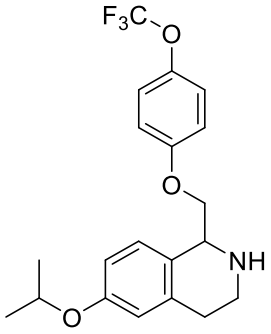


6-isopropoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-3,4-dihydroisoquinoline (8b): General procedure III was followed using compound **7b** (1.58 g, 3.98 mmol) and phosphoryl trichloride (1.12 mL, 11.9 mmol) in toluene (20 mL) to give the crude compound as a green solid. The crude material was carried forward without further purification. HRMS calcd. for $C_{20}H_{21}O_3NF_3$, 380.14680 $[M + H]^+$; found 380.14716 $[M + H]^+$.

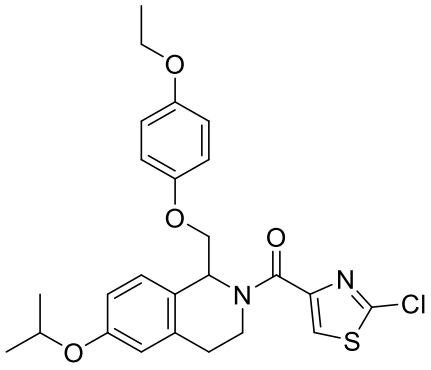


1-((4-ethoxyphenoxy)methyl)-6-isopropoxy-1,2,3,4-tetrahydroisoquinoline (9a): General procedure IV was followed using compound **8a** (0.73 g, 2.2 mmol) and sodium borohydride (245 mg, 6.47 mmol) in methanol (15 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% MeOH/DCM gradient) to afford the title compound as a yellow solid (0.24 g, 18% over two steps). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.10 – 7.05 (m, 1H), 6.89 – 6.79 (m, 4H), 6.75 – 6.62 (m, 3H), 5.30 (s, 1H), 4.59 – 4.45 (m, 1H),

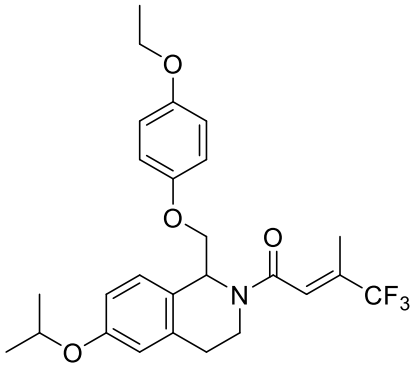
4.36 (dd, J = 9.2, 3.6 Hz, 1H), 4.15 – 4.04 (m, 2H), 3.98 (q, J = 6.9 Hz, 2H), 3.29 – 3.14 (m, 1H), 3.10 – 2.95 (m, 1H), 2.82 (t, J = 6.3 Hz, 2H), 1.39 (t, J = 7.0 Hz, 4H), 1.32 (d, J = 6.1 Hz, 6H). HRMS calcd. for $C_{21}H_{28}O_3N$, 342.20637 $[M + H]^+$; found 342.20613 $[M + H]^+$.



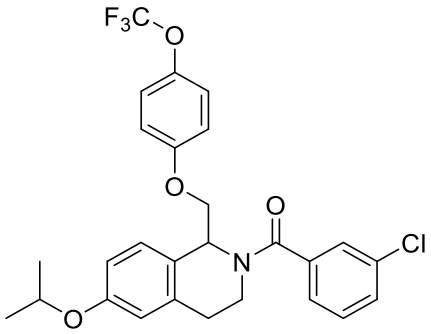
6-isopropoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (9b): General procedure IV was followed using dihydroisoquinoline **8b** (1.33 g, 3.51 mmol) and sodium borohydride (0.40 g, 11 mmol) in methanol (20 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% MeOH/DCM gradient) to afford the title compound as a yellow solid (0.30 g, 19% over two steps). R_f (1:1 EtOAc:Hex): 0.26; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.16 – 7.04 (m, 5H), 6.97 – 6.87 (m, 2H), 6.76 – 6.65 (m, 3H), 4.60 – 4.45 (m, 1H), 4.39 (dd, J = 9.0, 3.5 Hz, 1H), 4.22 – 4.03 (m, 2H), 3.29 – 3.14 (m, 1H), 3.11 – 2.97 (m, 1H), 2.82 (t, J = 5.5 Hz, 2H), 1.33 (d, J = 6.1 Hz, 5H). HRMS calcd. for $C_{20}H_{23}O_3NF_3$, 382.16245 $[M + H]^+$; found 382.16235 $[M + H]^+$.



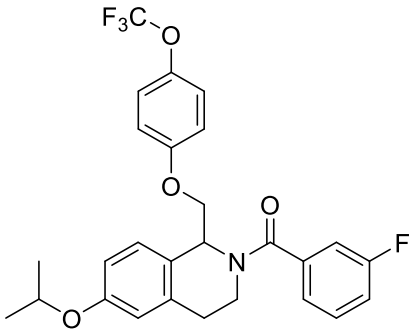
(2-chlorothiazol-4-yl)(1-((4-ethoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-260): General procedure V-A was followed using compound **9a** (117 mg, 0.343 mmol), triethylamine (0.096 mL, 0.69 mmol), and 2-chlorothiazole-4-carbonyl chloride (0.075 mL, 0.41 mmol) in DCM (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a red solid (23 mg, 14%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.93 – 7.81 (m, 1H), 7.25 – 7.04 (m, 1H), 7.23 – 6.46 (m, 9H), 6.07 (dd, *J* = 8.6, 4.0 Hz, 0.5H), 5.89 (t, *J* = 5.1 Hz, 0.5H), 4.80 (dd, *J* = 13.1, 5.2 Hz, 0.5H), 4.60 – 4.40 (m, 2H), 4.38 – 4.07 (m, 2.5H), 4.00 – 3.76 (m, 3H), 3.39 – 3.23 (m, 0.5H), 3.14 – 3.02 (m, 1H), 2.89 – 2.76 (m, 1H), 1.48 – 1.26 (m, 12H); ^{13}C NMR (75 MHz, cdcl$_3$) δ 162.62, 161.98, 157.33, 157.05, 156.76, 153.35, 153.26, 152.76, 152.29, 149.27, 136.27, 136.00, 128.57, 128.32, 126.38, 125.27, 124.44, 115.77, 115.72, 115.54, 115.33, 115.29, 114.34, 114.24, 71.10, 70.76, 69.86, 69.82, 55.85, 52.63, 42.42, 36.34, 29.84, 28.56, 22.10, 22.04, 14.94; HRMS calcd. for $C_{25}H_{28}O_4N_2ClS$, 487.14528 $[M + H]^+$; found 487.14506 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.38 min). Method 2: 85% isocratic ACN in water over 3 min at 1 mL/min (retention time 1.69 min).



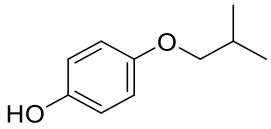
(E)-1-(1-((4-ethoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)-4,4,4-trifluoro-3-methylbut-2-en-1-one (1180-263): General procedure V-B was followed using (E)-4,4,4-trifluoro-3-methylbut-2-enoic acid (0.044 mL, 0.38 mmol), EDCI (64 mg, 0.41 mmol), N,N-dimethylpyridin-4-amine (50 mg, 0.41 mmol), and compound **9a** (117 mg, 0.343 mmol) in DCM (1.4 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a red oil (78 mg, 48%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 – 7.06 (m, 1H), 6.95 – 6.56 (m, 8H), 5.87 (t, *J* = 5.4 Hz, 0.5H), 5.12 (dd, *J* = 8.2, 5.1 Hz, 0.5H), 4.78 (dd, *J* = 12.2, 5.0 Hz, 0.5H), 4.61 – 4.45 (m, 1H), 4.29 – 4.19 (m, 0.5H), 4.14 – 4.04 (m, 1H), 4.04 – 3.89 (m, 2H), 3.84 – 3.46 (m, 1H), 3.20 – 2.72 (m, 2.5H), 1.97 (d, *J* = 4.6, 2H), 1.42 – 1.25 (m, 10H). HRMS calcd. for $C_{26}H_{31}O_4NF_3$, 478.21997 $[M + H]^+$; found 478.21943 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 6 min at 1 mL/min (retention time = 5.90 min). Method 2: 85% isocratic ACN in water over min at 1 mL/min (retention time 1.76 min).



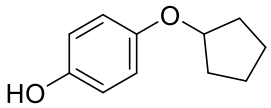
(3-chlorophenyl)(6-isopropoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-261): General procedure V-A was followed using compound **9b** (145 mg, 0.380 mmol), triethylamine (0.106 mL, 0.760 mmol), and 3-chlorobenzoyl chloride (0.058 mL, 0.46 mmol) in DCM (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (89 mg, 45%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.61 – 7.32 (m, 3H), 7.22 – 7.01 (m, 3H), 6.97 – 6.48 (m, 5H), 5.99 (t, *J* = 5.2 Hz, 0.5H), 5.16 (dd, *J* = 9.9, 3.1 Hz, 0.5H), 4.86 (dd, *J* = 11.5, 4.8 Hz, 0.5H), 4.61 – 4.47 (m, 1H), 4.38 (d, *J* = 5.1 Hz, 1H), 4.18 (t, *J* = 10.0 Hz, 0.5H), 3.95 (dd, *J* = 10.0, 3.6 Hz, 0.5H), 3.79 – 3.62 (m, 1H), 3.40 – 3.02 (m, 1H), 2.99 – 2.66 (m, 1.5H), 1.34 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, cdcl$_3$) δ 164.47, 133.42, 130.13, 130.04, 129.84, 129.73, 128.49, 128.06, 127.91, 126.79, 124.61, 122.60, 122.51, 116.01, 115.66, 115.46, 115.09, 114.55, 114.31, 77.45, 77.03, 76.60, 70.70, 69.89, 69.67, 56.84, 51.57, 42.73, 35.27, 29.69, 28.28, 22.05, 22.01; HRMS calcd. for $C_{27}H_{26}O_4NClF_3$, 520.14970 [M + H]$^+$; found 520.14947 [M + H]$^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.89 min). Method 2: 85% ACN in water over 3 min at 1 mL/min (retention time 2.34 min).



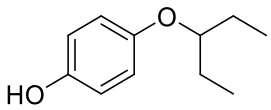
(3-fluorophenyl)(6-isopropoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-262): General procedure V-A was followed using tetrahydroisoquinoline **9b** (145 mg, 0.380 mmol), triethylamine (0.106 mL, 0.760 mmol), and 3-fluorobenzoyl chloride (0.055 mL, 0.46 mmol) in DCM (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (0.10 g, 53%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.44 – 7.31 (m, 1H), 7.23 – 6.52 (m, 10H), 5.99 (t, *J* = 4.9 Hz, 0.5H), 5.18 (dd, *J* = 9.7, 3.2 Hz, 0.5H), 4.87 (dd, *J* = 6.7, 4.6 Hz, 0.5H), 4.61 – 4.47 (m, 1H), 4.38 (d, *J* = 4.9 Hz, 1H), 4.18 (t, *J* = 10.0 Hz, 0.5H), 3.96 (dd, *J* = 10.2, 3.4 Hz, 0.5H), 3.84 – 3.56 (m, 1H), 3.37 – 3.04 (m, 1H), 3.00 – 2.69 (m, 1.5H), 1.34 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $cdcl_3$) δ 157.12, 136.40, 135.40, 130.53, 130.43, 130.18, 130.02, 128.48, 128.02, 125.75, 124.60, 123.09, 122.57, 122.49, 122.21, 118.81, 116.84, 116.57, 116.02, 115.67, 115.45, 115.10, 114.78, 114.53, 114.29, 114.05, 113.75, 109.99, 77.46, 77.04, 76.61, 70.70, 69.89, 69.66, 56.78, 51.55, 42.66, 35.26, 29.70, 28.30, 22.04, 22.01; HRMS calcd. for $C_{27}H_{26}O_4NF_4$, 504.17925 $[M + H]^+$; found 504.17909 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.54 min). Method 2: 85% isocratic ACN in water over 3 min at 1 mL/min (retention time 1.89 min).



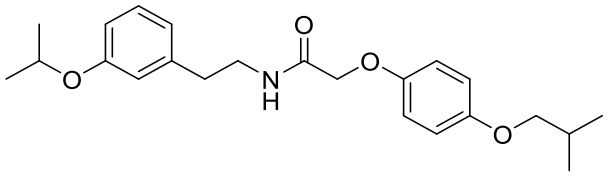
4-isobutoxyphenol (10a): General procedure VI was followed using hydroquinone (5.00 g, 45.4 mmol) and 1-bromo-2-methylpropane (3.29 mL, 30.3 mmol) in ethanol (100 mL) and potassium hydroxide (2.55 g, 45.4 mmol) in water (10 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 5-35% EtOAc/hexanes gradient) to afford the title compound as a red oil (2.24 g, 44%). R_f (1:10 EtOAc:Hex): 0.59; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.84 – 6.70 (d, J = 4.7 Hz, 4H), 3.66 (d, *J* = 6.6 Hz, 2H), 2.15 – 1.98 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, cdcl3) δ 153.34, 149.28, 116.05, 115.73, 75.36, 28.28, 19.28. HRMS calcd. for $C_{10}H_{13}O_2$, 165.09210 $[M + H]^+$; found 165.09280 $[M + H]^+$.



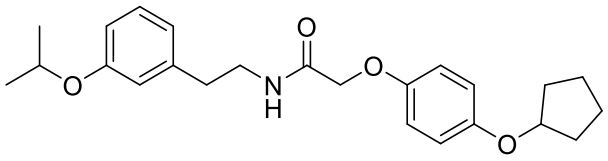
4-(cyclopentyloxy)phenol (10b): General procedure VI was followed using hydroquinone (1.00 g, 9.08 mmol) and iodocyclopentane (0.70 mL, 6.1 mmol) in ethanol (20 mL) and potassium hydroxide (0.51 g, 9.1 mmol) in water (2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 5-35% EtOAc/hexanes gradient) to afford the title compound as a red oil (0.42 g, 39%). R_f (1:4 EtOAc:Hex): 0.77; ^{1}H NMR (300 MHz, Chloroform-d) δ 6.75 (d, J = 1.1 Hz, 4H), 4.72 – 4.60 (m, 1H), 1.96 – 1.69 (m, 6H), 1.70 – 1.53 (m, 2H). ^{13}C NMR (101 MHz, cdcl3) δ 152.12, 149.15, 116.75, 115.91, 79.85, 32.73, 23.91. HRMS calcd. for $C_{11}H_{14}O_2$, 178.09883 $[M + H]^+$; found 178.09870 $[M + H]^+$.



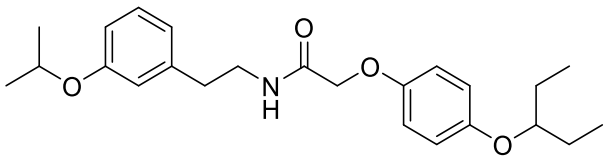
4-(pentan-3-yloxy)phenol (10c): General procedure VI was followed using hydroquinone (5.00 g, 45.4 mmol) and 3-bromopentane (7.25 mL, 30.3 mmol) in ethanol (100 mL) and potassium hydroxide (2.55 g, 45.4 mmol) in water (10 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 5-35% EtOAc/hexanes gradient) to afford the title compound as a orange oil (2.08 g, 38%). R_f (1:1 EtOAC:Hex): 0.47; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.85 – 6.69 (m, 4H), 3.96 (p, *J* = 5.8 Hz, 1H), 1.63 (qd, *J* = 7.4, 5.8 Hz, 4H), 0.95 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 152.28, 149.74, 118.18, 116.26, 82.50, 26.00, 9.62. HRMS calcd. for $C_{11}H_{15}O_2$, 179.10666 $[M + H]^+$; found 179.10657 $[M + H]^+$.



2-(4-isobutoxyphenoxy)-N-(3-isopropoxyphenethyl)acetamide (11a): General procedure II was followed using compound **10a** (1.25 g, 7.51 mmol), cesium carbonate (4.83 g, 25.0 mmol), and compound **6** (1.60 g, 6.26 mmol) in acetonitrile (20 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a pink oil (1.57 g, 65%). R_f (1:1 EtOAC:Hex): 0.92; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 – 7.13 (m, 1H), 6.86 – 6.66 (m, 8H), 4.59 – 4.43 (m, 1H), 4.38 (s, 2H), 3.65 (d, *J* = 6.5 Hz, 2H), 3.62 – 3.50 (m, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 2.13 – 1.94 (m, 1H), 1.31 (d, *J* = 6.1 Hz, 6H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 168.37, 158.11, 154.35, 151.22, 140.19, 129.65, 120.85, 116.36, 115.61, 113.71, 74.94, 69.59, 68.17, 39.99, 35.71, 28.30, 22.07, 19.28. HRMS calcd. for $C_{23}H_{32}O_4N$, 386.23258 $[M + H]^+$; found 386.23304 $[M + H]^+$.

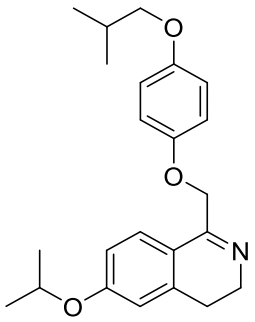


2-(4-(cyclopentyloxy)phenoxy)-N-(3-isopropoxyphenethyl)acetamide (11b): General procedure II was followed using phenol **10b** (1.11 g, 6.23 mmol), cesium carbonate (4.00 g, 20.8 mmol), and compound **6** (1.33 g, 5.19 mmol) in acetonitrile (15 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a red solid (1.47 g, 71). R_f (1:1 EtOAC:Hex): 0.20; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.22 – 7.11 (m, 1H), 6.83 – 6.66 (m, 8H), 4.70 – 4.59 (m, 1H), 4.58 – 4.44 (m, 1H), 4.37 (s, 2H), 3.63 – 3.46 (m, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 1.93 – 1.44 (m, 7H), 1.30 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 168.39, 158.10, 153.08, 151.09, 140.18, 129.65, 120.85, 116.58, 116.35, 115.60, 113.70, 79.65, 69.59, 68.14, 39.99, 35.71, 32.75, 23.97, 22.06. HRMS calcd. for $C_{24}H_{32}O_4N$, 398.23258 $[M + H]^+$; found 398.23231 $[M + H]^+$.

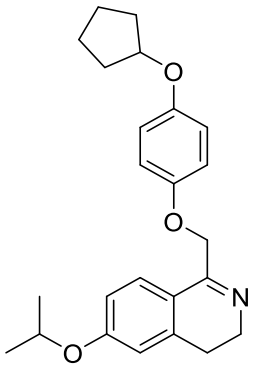


N-(3-isopropoxyphenethyl)-2-(4-(pentan-3-yloxy)phenoxy)acetamide (11c): General procedure II was followed using phenol **10c** (1.52 g, 8.41 mmol), cesium carbonate (5.41 g, 28.0 mmol), and compound **6** (1.79 g, 7.01 mmol) in acetonitrile (20 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a red oil (1.92 g, 69%). R_f (1:4 EtOAC:Hex): 0.28; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.14 (m, 1H), 6.86 – 6.68 (m, 8H), 4.58 – 4.47 (m, 1H), 4.39 (s, 2H), 3.99 (p, *J* = 5.8 Hz, 1H), 3.63 – 3.53 (m, 2H), 2.79 (t, *J* = 7.0 Hz, 2H), 1.77 – 1.57 (m, 4H), 1.31 (d, *J* = 6.1 Hz, 6H), 0.95 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 168.32,

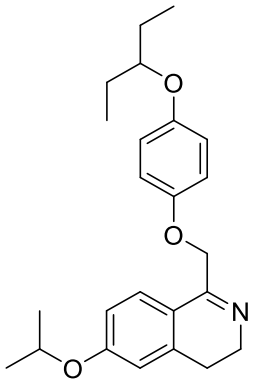
158.07, 153.68, 151.19, 140.12, 129.60, 120.81, 117.30, 116.30, 115.58, 113.66, 81.10, 69.56, 68.08, 39.94, 35.66, 25.96, 22.01, 9.56. HRMS calcd. for $C_{24}H_{34}O_4N$, 400.24824 $[M + H]^+$; found 400.24800 $[M + H]^+$.



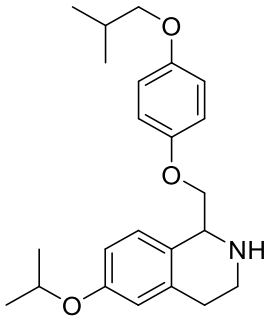
1-((4-isobutoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinoline (12a): General procedure III was followed using compound **11a** (1.57 g, 4.07 mmol) and phosphoryl trichloride (1.14 mL, 12.2 mmol) in toluene (20 mL) to give the crude compound as a green oil. The crude material was carried forward without further purification. HRMS calcd. for $C_{23}H_{31}O_2N_2$, 367.23800 $[M + H]^+$; found 367.23767 $[M + H]^+$.



1-((4-(cyclopentyloxy)phenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinoline (12b): General procedure III was followed using compound **11b** (1.47 g, 3.70 mmol) and phosphoryl trichloride (1.03 mL, 11.1 mmol) in toluene (20 mL) to give the crude compound as a green/white/black solid. The crude material was carried forward without further purification. HRMS calcd. for $C_{24}H_{30}O_3N$, 380.22280 $[M + H]^+$; found 380.22266 $[M + H]^+$.

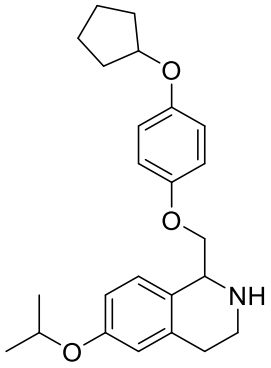


6-isopropoxy-1-((4-(pentan-3-yloxy)phenoxy)methyl)-3,4-dihydroisoquinoline (12c): General procedure III was followed using compound **11c** (1.92 g, 4.81 mmol) and phosphoryl trichloride (1.34 mL, 14.4 mmol) in toluene (25 mL) to give the crude compound as a red oil. The crude material was carried forward without further purification. HRMS calcd. for $C_{24}H_{32}O_3N$, 382.23767 $[M + H]^+$; found 382.23707 $[M + H]^+$.

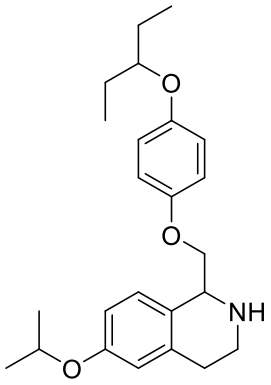


1-((4-isobutoxyphenoxy)methyl)-6-isopropoxy-1,2,3,4-tetrahydroisoquinoline (13a): General procedure IV was followed using compound **12a** (1.25 g, 3.40 mmol) and sodium borohydride (386 mg, 10.2 mmol) in methanol (20 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% MeOH/DCM gradient) to afford the title compound as a green foam (380 mg, 30% over two steps). R_f (1:1 EtOAC:Hex): 0.63; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.07 – 6.90 (m, 2H), 6.84 – 6.62 (m, 5H), 4.59 – 4.11 (m, 4H), 3.65 (d, J = 6.6 Hz, 2H), 3.51 – 3.36 (m, 1H), 3.28 – 3.12 (m, 1H), 3.09 – 2.88 (m, 1H), 2.15 – 1.95 (m,

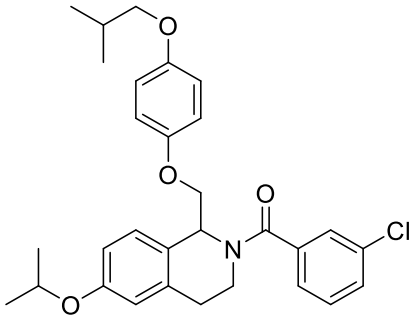
1H), 1.32 (d, J = 6.1 Hz, 5H), 1.01 (d, J = 6.7 Hz, 6H). HRMS calcd. for $C_{23}H_{32}O_3N$, 370.23767 $[M + H]^+$; found 370.23706 $[M + H]^+$.



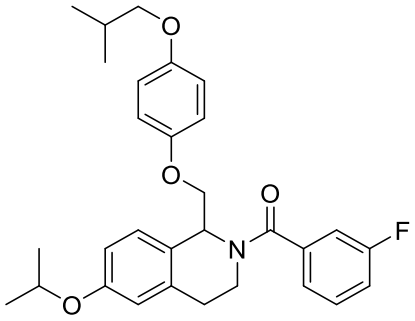
1-((4-(cyclopentyloxy)phenoxy)methyl)-6-isopropoxy-1,2,3,4-tetrahydroisoquinoline (13b): General procedure IV was followed using compound **12b** (1.40 g, 3.69 mmol) and sodium borohydride (419 mg, 11.1 mmol) in methanol (20 mL). The crude product was a green foam and was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% MeOH/DCM gradient) to afford the title compound as a green solid (990 mg, 70% over two steps). R_f (1:1 EtOAC:Hex): 0.54; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.02 (d, *J* = 8.7 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.78 – 6.69 (m, 3H), 6.62 (d, *J* = 2.5 Hz, 1H), 4.62 (ddd, *J* = 17.0, 6.4, 3.1 Hz, 2H), 4.50 (p, *J* = 6.1 Hz, 1H), 4.44 – 4.27 (m, 2H), 3.55 – 3.44 (m, 1H), 3.27 – 3.08 (m, 2H), 3.02 – 2.90 (m, 1H), 1.92 – 1.73 (m, 6H), 1.64 – 1.54 (m, 2H), 1.31 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 157.42, 152.83, 151.64, 134.31, 127.24, 120.54, 116.41, 115.64, 115.03, 69.85, 69.13, 54.03, 39.58, 32.74, 26.27, 23.94, 21.98. HRMS calcd. for $C_{24}H_{32}O_3N$, 382.23767 $[M + H]^+$; found 382.23658 $[M + H]^+$.



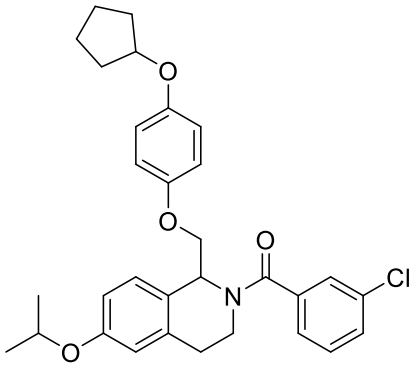
6-isopropoxy-1-((4-(pentan-3-yloxy)phenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (13c): General procedure IV was followed using compound **12c** (1.83 g, 4.80 mmol) and sodium borohydride (544 mg, 14.4 mmol) in methanol (25 mL). The crude product was a green foam and was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% MeOH/DCM gradient) to afford the title compound as a green foam (1.07 g, 60% over two steps). R_f (1:1 EtOAC:Hex): 0.47; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.02 (d, J = 8.7 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.83 – 6.70 (m, 3H), 6.63 (d, *J* = 2.6 Hz, 1H), 4.61 (dd, *J* = 7.5, 3.8 Hz, 1H), 4.51 (p, *J* = 6.1 Hz, 1H), 4.45 – 4.29 (m, 2H), 3.96 (p, *J* = 5.7 Hz, 1H), 3.55 – 3.45 (m, 1H), 3.29 – 3.07 (m, 2H), 3.04 – 2.93 (m, 1H), 1.67 – 1.57 (m, 4H), 1.31 (d, *J* = 6.1 Hz, 6H), 0.93 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 157.46, 153.49, 151.76, 134.25, 127.22, 120.41, 117.21, 116.17, 115.65, 115.08, 81.17, 69.87, 69.01, 54.03, 39.54, 26.22, 26.00, 21.97, 9.60. HRMS calcd. for $C_{24}H_{34}O_3N$, 384.25332 $[M + H]^+$; found 384.25226 $[M + H]^+$.



(3-chlorophenyl)(1-((4-isobutoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-274): General procedure V-A was followed using compound **13a** (150 mg, 0.406 mmol), triethylamine (0.113 mL, 0.812 mmol), and 3-chlorobenzoyl chloride (0.062 mL, 0.49 mmol) in DCM (6 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a red foam (0.10 g, 50%). R_f (1:4 EtOAC:Hex): 0.57; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 6.64 (m, 11H), 5.99 (t, *J* = 5.0 Hz, 0.5H), 5.14 (dd, *J* = 9.4, 3.3 Hz, 0.5H), 4.86 (dd, *J* = 12.7, 5.2 Hz, 0.5H), 4.61 – 4.47 (m, 1H), 4.39 – 4.32 (m, 0.5H), 4.19 – 4.07 (m, 1H), 3.93 (dd, *J* = 10.2, 3.8 Hz, 0.5H), 3.81 – 3.69 (m, 1H), 3.67 (d, *J* = 6.6 Hz, 2H), 3.33 – 3.07 (m, 1.5H), 2.95 – 2.69 (m, 2H), 2.13 – 1.98 (m, 1H), 1.34 (d, *J* = 6.0 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 171.14, 170.18, 169.39, 157.31, 156.81, 153.85, 153.72, 152.69, 152.19, 138.14, 137.98, 136.33, 135.31, 134.61, 134.27, 129.98, 129.67, 129.55, 128.49, 128.09, 127.98, 126.79, 125.62, 124.94, 124.64, 123.87, 115.94, 115.62, 115.46, 115.35, 115.27, 115.18, 115.02, 114.50, 114.18, 75.04, 71.03, 69.95, 69.83, 60.39, 57.09, 51.74, 42.56, 35.23, 29.71, 28.30, 22.07, 21.06, 19.29, 14.21. HRMS calcd. for $C_{30}H_{35}O_4NCl$, 508.22491 $[M + H]^+$; found 508.22485 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.76 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 4.17 min).

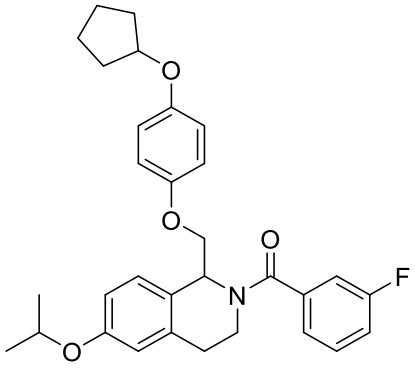


(3-fluorophenyl)(1-((4-isobutoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-275): General procedure V-A was followed using compound **13a** (150 mg, 0.406 mmol), triethylamine (0.113 mL, 0.812 mmol), and 3-fluorobenzoyl chloride (0.059 mL, 0.49 mmol) in DCM (6 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a red foam (0.11 g, 53%). R_f (1:4 EtOAC:Hex): 0.63; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.62 (s, 1H), 7.44 – 7.11 (m, 5H), 6.96 – 6.63 (m, 9H), 5.99 (t, J = 5.0 Hz, 0.5H), 5.14 (dd, J = 9.4, 3.3 Hz, 0.5H), 4.86 (dd, J = 12.7, 5.2 Hz, 0.5H), 4.61 – 4.47 (m, 1H), 4.39 – 4.32 (m, 1H), 4.19 – 4.07 (m, 0.5H), 3.93 (dd, J = 10.2, 3.8 Hz, 0.5H), 3.81 – 3.69 (m, 1H), 3.67 (d, J = 6.6 Hz, 2H), 3.33 – 3.07 (m, 1.5H), 2.95 – 2.69 (m, 2H), 2.13 – 1.98 (m, 1H), 1.34 (d, J = 6.0 Hz, 6H), 1.02 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 170.27, 169.52, 157.30, 156.78, 153.87, 153.72, 152.70, 152.21, 136.32, 135.32, 130.45, 130.37, 130.06, 129.98, 128.48, 128.05, 125.68, 124.96, 123.91, 123.19, 122.23, 116.68, 116.57, 116.46, 116.36, 115.95, 115.61, 115.45, 115.36, 115.29, 115.21, 115.17, 115.06, 114.93, 114.48, 114.17, 114.02, 113.80, 110.37, 109.99, 75.06, 71.06, 69.98, 69.84, 57.04, 51.71, 42.52, 35.22, 32.87, 29.72, 28.29, 22.02, 19.27. HRMS calcd. for $C_{30}H_{35}O_4NF$, 492.25446 $[M + H]^+$; found 492.25421 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 4.80 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 3.65 min).



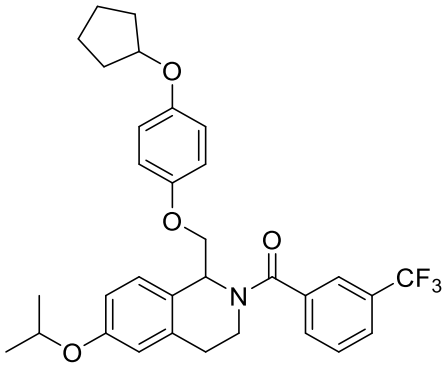
(3-chlorophenyl)(1-((4-(cyclopentyloxy)phenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-276): General procedure V-A was followed using compound **13b** (198 mg, 0.519 mmol), triethylamine (0.145 mL, 1.04 mmol), and 3-chlorobenzoyl chloride (0.080 mL, 0.62 mmol) in DCM (8 mL). The crude product was a green oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a red foam (0.19 g, 69%). R_f (1:4 EtOAC:Hex): 0.33; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 – 7.46 (m, 1H), 7.44 – 7.18 (m, 4H), 6.94 – 6.66 (m, 6H), 6.03 – 5.95 (m, 0.5H), 5.14 (dd, J = 6.1, 3.5 Hz, 0.5H), 4.86 (dd, J = 12.8, 5.4 Hz, 0.5H), 4.70 – 4.63 (m, 1H), 4.59 – 4.48 (m, 1H), 4.39 – 4.32 (m, 1H), 4.19 – 4.09 (m, 0.5H), 3.93 (dd, J = 10.2, 3.8 Hz, 0.5H), 3.81 – 3.63 (m, 1H), 3.33 – 3.08 (m, 1.5H), 2.97 – 2.70 (m, 2H), 1.93 – 1.52 (m, 8H), 1.34 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 170.21, 169.42, 167.35, 158.60, 157.31, 156.80, 152.58, 152.44, 152.11, 138.14, 137.97, 136.34, 135.32, 134.63, 134.28, 132.89, 132.09, 130.00, 129.68, 129.65, 129.60, 129.57, 128.51, 128.10, 128.06, 127.98, 126.81, 125.65, 124.97, 124.66, 123.88, 116.65, 116.52, 116.45, 115.95, 115.61, 115.18, 114.52, 114.20, 79.71, 71.03, 69.94, 69.84, 57.11, 51.77, 42.61, 35.26, 32.76, 29.72, 28.31, 23.97, 22.04. HRMS calcd. for $C_{31}H_{35}O_4NCl$, 520.22491 $[M + H]^+$; found 520.22521 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5

μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.76 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 4.21 min).



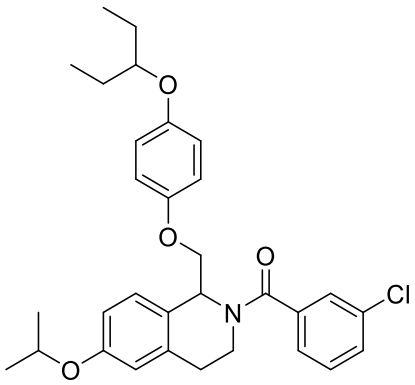
(1-((4-(cyclopentyloxy)phenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-fluorophenyl)methanone (1180-277): General procedure V-A was followed using compound **13b** (198 mg, 0.519 mmol), triethylamine (0.145 mL, 1.04 mmol), and 3-fluorobenzoyl chloride (0.076 mL, 0.62 mmol) in DCM (8 mL). The crude product was a green oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a red foam (0.19 g, 70%). R_f (1:4 EtOAC:Hex): 0.34; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.01 (m, 6H), 6.96 – 6.63 (m, 5H), 5.99 (t, J = 4.8 Hz, 1H), 5.16 (dd, J = 5.8, 3.7 Hz, 0.5H), 4.86 (dd, J = 6.9, 5.4 Hz, 0.5H), 4.71 – 4.64 (m, 1H), 4.59 – 4.45 (m, 1H), 4.39 – 4.32 (m, 1H), 4.17 – 4.09 (m, 0.5H), 3.94 (dd, J = 6.2, 3.9 Hz, 0.5H), 3.82 – 3.62 (m, 1H), 3.33 – 3.08 (m, 1.5H), 2.97 – 2.70 (m, 2H), 1.94 – 1.46 (m, 8H), 1.34 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 170.22, 169.43, 163.79, 163.61, 161.84, 161.32, 161.15, 157.31, 156.80, 152.61, 152.58, 152.43, 152.13, 138.49, 136.34, 135.37, 130.47, 130.39, 130.07, 129.99, 128.51, 128.08, 125.02, 123.96, 123.22, 122.25, 116.63, 116.53, 116.46, 116.33, 115.96, 115.61, 115.22, 115.07, 114.94, 114.49, 114.18, 114.02, 113.81, 79.73, 71.04, 69.97, 69.83, 57.05, 51.72, 42.54, 35.22, 32.75, 29.73, 28.31, 23.96, 22.03. HRMS calcd. for $C_{31}H_{35}O_4NF$, 504.25446 $[M + H]^+$; found 504.25450 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18

column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 4.83 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 3.67 min).



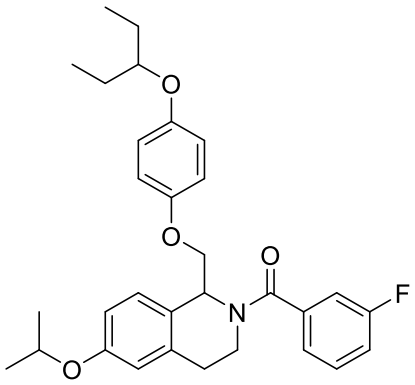
(1-((4-(cyclopentyloxy)phenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-280): General procedure V-A was followed using compound **13b** (198 mg, 0.519 mmol), triethylamine (0.145 mL, 1.04 mmol), and 3-(trifluoromethyl)benzoyl chloride (0.094 mL, 0.62 mmol) in DCM (8 mL). The crude product was a green oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a red oil (0.18 mg, 62%). R_f (1:4 EtOAC:Hex): 0.23; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.92 (s, 1H), 7.75 – 7.49 (m, 3H), 7.25 – 7.15 (m, 1H), 6.95 – 6.66 (m, 6H), 6.11 – 5.90 (m, 0.5H), 5.11 (dd, J = 6.5, 3.1 Hz, 0.5H), 4.89 (dd, J = 12.9, 5.5 Hz, 0.5H), 4.71 – 4.63 (m, 1H), 4.62 – 4.48 (m, 1H), 4.41 – 4.34 (m, 1H), 4.25 – 4.03 (m, 1H), 3.94 (dd, J = 6.5, 3.6 Hz, 0.5H), 3.80 – 3.64 (m, 1H), 3.36 – 3.11 (m, 1.5H), 2.96 – 2.72 (m, 2H), 1.94 – 1.47 (m, 8H), 1.35 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 170.18, 169.39, 157.39, 156.86, 152.63, 152.58, 152.48, 152.05, 137.29, 137.14, 136.32, 135.25, 130.91, 129.90, 129.21, 128.83, 128.51, 128.04, 126.32, 126.28, 126.21, 124.92, 123.74, 123.66, 116.61, 116.52, 115.98, 115.61, 115.14, 114.57, 114.22, 79.72, 71.05, 69.85, 57.22, 51.87, 42.67, 35.22, 32.75, 29.68, 28.26, 23.95, 22.01. HRMS calcd. for $C_{32}H_{35}O_4NF_3$, 554.25127 $[M + H]^+$; found

554.25169 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.40 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 4.15 min).



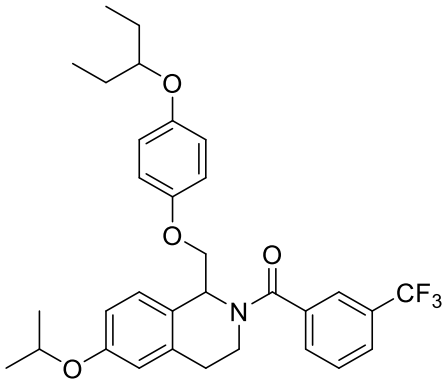
(3-chlorophenyl)(6-isopropoxy-1-((4-(pentan-3-yloxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-278): General procedure V-A was followed using compound **13c** (214 mg, 0.558 mmol), triethylamine (0.156 mL, 1.12 mmol), and 3-chlorobenzoyl chloride (0.086 mL, 0.67 mmol) in DCM (9 mL). The crude product was a green oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a yellow foam (0.16 g, 56%). R_f (1:4 EtOAC:Hex): 0.43; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.62 (s, 0H), 7.45 – 7.18 (m, 4H), 6.96 – 6.66 (m, 6H), 5.99 (t, J = 5.0 Hz, 1H), 5.14 (dd, J = 6.0, 3.5 Hz, 0.5H), 4.86 (dd, J = 7.6, 4.8 Hz, 0.5H), 4.61 – 4.47 (m, 1H), 4.39 – 4.32 (m, 1H), 4.20 – 4.09 (m, 1H), 4.03 – 3.85 (m, 2H), 3.80 – 3.64 (m, 1H), 3.33 – 3.08 (m, 1.5H), 2.98 – 2.68 (m, 2H), 1.77 – 1.52 (m, 4H), 1.34 (d, J = 6.0 Hz, 6H), 0.96 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 170.14, 169.35, 157.31, 156.80, 153.21, 153.05, 152.88, 152.77, 152.28, 138.21, 138.03, 136.35, 135.34, 134.63, 134.27, 129.66, 129.63, 129.53, 128.50, 128.10, 127.99, 126.81, 125.64, 124.99, 124.65, 123.89, 117.46, 117.34, 117.18, 115.95, 115.60, 115.19, 115.03, 114.51, 114.19, 81.31, 81.24, 71.01, 69.93, 69.83, 57.08, 51.73,

42.60, 35.22, 29.73, 28.31, 26.04, 22.04, 19.83, 18.81, 14.12, 9.63. HRMS calcd. for $C_{31}H_{37}O_4NCl$, 522.24056 $[M + H]^+$; found 522.24083 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 6.12 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 4.47 min).



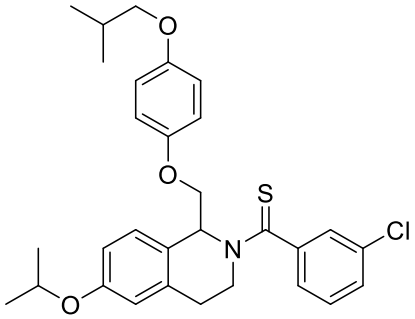
(3-fluorophenyl)(6-isopropoxy-1-((4-(pentan-3-yloxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-281): General procedure V-A was followed using compound **13c** (214 mg, 0.558 mmol), triethylamine (0.156 mL, 1.12 mmol), and 3-fluorobenzoyl chloride (0.081 mL, 0.67 mmol) in DCM (9 mL). The crude product was a green oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a yellow foam (0.16 g, 55%). R_f (1:4 EtOAC:Hex): 0.45; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.05 (m, 5H), 6.96 – 6.66 (m, 6H), 5.99 (t, J = 5.0 Hz, 0.5H), 5.16 (dd, J = 6.1, 3.3 Hz, 0.5H), 4.86 (dd, J = 7.4, 5.4 Hz, 0.5H), 4.61 – 4.47 (m, 1H), 4.39 – 4.29 (m, 1H), 4.19 – 4.05 (m, 1H), 3.97 (m, 1.5H), 3.82 – 3.63 (m, 1H), 3.33 – 3.08 (m, 1.5H), 2.96 – 2.70 (m, 2H), 1.76 – 1.53 (m, 4H), 1.34 (d, J = 6.0 Hz, 6H), 0.96 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 170.22, 169.47, 163.79, 163.59, 161.32, 161.14, 157.31, 156.80, 153.23, 153.05, 152.78, 152.28, 138.54, 138.47, 138.36, 138.30, 136.34, 135.36, 130.47, 130.38, 130.06, 129.98, 128.50, 128.07, 125.02, 123.93, 123.22, 123.19, 122.24,

122.21, 117.45, 117.33, 117.18, 116.66, 116.53, 116.44, 116.32, 115.96, 115.60, 115.22, 115.04, 114.94, 114.49, 114.17, 114.02, 113.80, 81.31, 81.25, 71.00, 69.95, 69.82, 57.03, 51.71, 42.56, 35.21, 29.73, 28.31, 26.03, 22.07, 22.03, 21.04, 19.79, 18.80, 15.62, 14.10, 9.62. HRMS calcd. for $C_{31}H_{37}O_4NF$, 506.27011 $[M + H]^+$; found 506.27028 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.13 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 3.94 min).



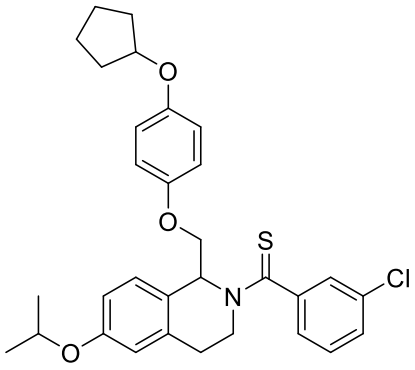
(6-isopropoxy-1-((4-(pentan-3-yloxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-279): General procedure V-A was followed using compound **13c** (214 mg, 0.558 mmol), triethylamine (0.156 mL, 1.12 mmol), and 3-(trifluoromethyl)benzoyl chloride (0.101 mL, 0.670 mmol) in DCM (9 mL). The crude product was a green oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as an orange oil (179 mg, 58%). R_f (1:4 EtOAC:Hex): 0.41; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 (s, 1H), 7.75 – 7.49 (m, 3H), 7.29 – 7.14 (m, 1H), 6.95 – 6.68 (m, 6H), 6.02 (t, J = 4.9 Hz, 0.5H), 5.12 (dd, J = 6.4, 3.0 Hz, 0.5H), 4.89 (dd, J = 12.9, 5.6 Hz, 0.5H), 4.62 – 4.48 (m, 1H), 4.42 – 4.32 (m, 1H), 4.21 – 4.08 (m, 1H), 4.04 – 3.90 (m, 1.5H), 3.76 – 3.70 (m, 1H), 3.36 – 3.11 (m, 1.5H), 2.97 – 2.73 (m, 2H), 1.82 – 1.53 (m, 4H), 1.35 (d, J = 6.1 Hz, 6H), 0.96 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ

170.17, 169.39, 157.39, 156.86, 153.28, 153.09, 152.75, 152.22, 137.29, 137.14, 136.32, 135.24, 130.91, 129.91, 129.20, 128.82, 128.51, 128.05, 126.28, 126.20, 126.16, 124.92, 124.89, 123.73, 123.70, 123.65, 117.44, 117.34, 117.16, 115.99, 115.60, 115.15, 115.04, 114.56, 114.22, 81.28, 81.27, 71.03, 69.84, 57.21, 51.87, 42.69, 38.67, 35.22, 29.68, 28.27, 26.02, 22.01, 19.77, 18.79, 14.08, 9.59. HRMS calcd. For $C_{32}H_{37}O_4NF_3$, 556.26692 $[M + H]^+$; found 556.26606 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 5.89 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 4.44 min).



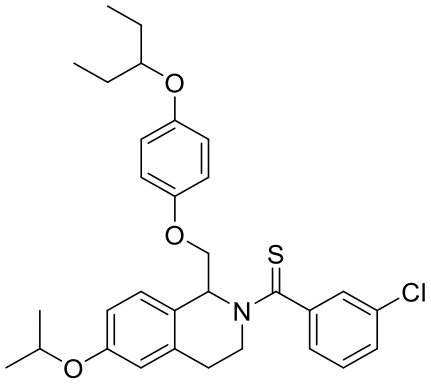
(3-chlorophenyl)(1-((4-isobutoxyphenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanethione (1180-284): General procedure VII was followed using compound **1180-274** (76.1 mg, 0.150 mmol) and Lawesson's Reagent (91 mg, 0.23 mmol) in toluene (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (14 mg, 17%). R_f (1:2 EtOAC:Hex): 0.97; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 – 6.92 (m, 5H), 6.90 – 6.66 (m, 6H), 5.72 (dd, J = 13.2, 6.1 Hz, 0.5H), 5.38 (dd, J = 9.5, 4.0 Hz, 0.5H), 4.67 (dd, J = 10.1, 4.2 Hz, 0.5H), 4.60 – 4.50 (m, 1H), 4.46 (dd, J = 10.1, 4.5 Hz, 0.5H), 4.24 – 4.10 (m, 0.5H), 4.06 – 3.84 (m, 1.5H), 3.66 (d, J = 6.5 Hz, 2H), 3.38 – 3.24 (m, 0.5H), 2.97 – 2.75 (m, 1.5H), 2.13 – 1.97 (m, 1H), 1.34 (d, J = 6.1 Hz, 6H), 1.01 (d, J = 6.8 Hz, 5H). ^{13}C NMR (101 MHz, cdcl3) δ 200.09, 198.71, 175.61, 157.59, 156.84, 154.00, 153.85, 152.51, 151.96, 144.79, 144.49, 135.94,

134.66, 134.50, 129.89, 128.49, 128.36, 128.23, 127.85, 124.69, 123.27, 115.75, 115.64, 115.63, 115.46, 115.40, 115.39, 115.35, 115.34, 115.27, 115.24, 114.82, 114.39, 75.06, 70.63, 69.90, 61.24, 58.17, 47.85, 42.45, 29.84, 28.28, 27.81, 22.05, 22.01, 21.98, 19.24. HRMS calcd. For $C_{30}H_{35}O_3NClS$, 524.20207 $[M + H]^+$; found 524.20182 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 7.37 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 5.54 min).



(3-chlorophenyl)(1-((4-(cyclopentyloxy)phenoxy)methyl)-6-isopropoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanethione (1180-285): General procedure VII was followed using compound **1180-276** (160 mg, 0.308 mmol) and Lawesson's Reagent (187 mg, 0.461 mmol) in toluene (3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (60 mg, 36%). R_f (1:2 EtOAC:Hex): 0.79; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.76 – 7.40 (m, 1H), 7.35 – 6.92 (m, 5H), 6.91 – 6.66 (m, 6H), 5.72 (dd, J = 13.3, 5.2 Hz, 0.5H), 5.38 (dd, J = 9.5, 4.1 Hz, 0.5H), 4.72 – 4.63 (m, 1H), 4.60 – 4.50 (m, 1H), 4.46 (dd, J = 10.1, 4.5 Hz, 0.5H), 4.19 (t, J = 9.6 Hz, 0.5H), 4.07 – 3.85 (m, 1.5H), 3.73 – 3.60 (m, 0.5H), 3.38 – 3.24 (m, 0.5H), 3.00 – 2.87 (m, 1H), 2.85 – 2.75 (m, 1H), 1.93 – 1.47 (m, 7H), 1.34 (d, J = 6.3 Hz, 5H). ^{13}C NMR (101 MHz, cdcl3) δ 200.06, 198.67, 157.59, 156.85, 152.72, 152.56, 152.41, 152.10, 151.87,

146.10, 145.01, 144.82, 144.50, 135.95, 134.68, 134.50, 129.93, 128.51, 128.37, 128.25, 127.87, 124.70, 123.27, 116.64, 116.51, 115.75, 115.61, 115.39, 115.25, 114.83, 114.41, 79.73, 70.59, 69.88, 61.25, 60.39, 58.19, 47.89, 42.45, 32.74, 31.58, 29.86, 27.83, 23.95, 22.65, 22.07, 22.04, 22.00, 21.06, 14.20, 14.14. HRMS calcd. For $C_{31}H_{35}O_3NClS$, 536.20207 $[M + H]^+$; found 536.20235 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 8 min at 1 mL/min (retention time = 7.97 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 5.38 min).



(3-chlorophenyl)(6-isopropoxy-1-((4-(pentan-3-yloxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanethione (1180-286): General procedure VII was followed using compound **1180-278** (138 mg, 0.265 mmol) and Lawesson's Reagent (161 mg, 0.397 mmol) in toluene (2.5 mL). The crude product was a yellow oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (53 mg, 37%). R_f (1:4 EtOAC:Hex): 0.40; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.17 (m, 3H), 7.16 – 7.08 (m, 1H), 7.00 – 6.66 (m, 7H), 5.72 (dd, J = 13.3, 4.7 Hz, 0.5H), 5.38 (dd, J = 9.6, 4.2 Hz, 0.5H), 4.68 (dd, J = 10.1, 4.2 Hz, 0.5H), 4.60 – 4.50 (m, 1H), 4.47 (dd, J = 10.1, 4.5 Hz, 0.5H), 4.28 – 4.16 (m, 0.5H), 4.07 – 3.85 (m, 2.5H), 3.72 – 3.61 (m, 0.5H), 3.37 – 3.26 (m, 0.5H), 3.05 – 2.88 (m, 1H), 2.85 – 2.75 (m, 1H), 1.77 – 1.58 (m, 4H),

1.45 – 1.29 (m, 6H), 1.02 – 0.82 (m, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 200.09, 198.68, 159.30, 157.60, 156.85, 153.37, 153.19, 152.58, 152.04, 144.81, 144.50, 134.69, 129.93, 128.52, 128.37, 128.24, 127.88, 124.70, 123.27, 117.45, 117.32, 115.76, 115.62, 115.60, 115.40, 115.26, 114.84, 114.41, 81.32, 70.56, 69.91, 69.89, 61.25, 58.18, 47.92, 42.46, 31.58, 29.86, 27.84, 26.02, 22.08, 22.03, 22.00, 21.06, 14.20, 14.14, 14.09, 9.60. HRMS calcd. For $C_{31}H_{37}O_3NClS$, 538.21772 $[M + H]^+$; found 538.21771 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 10 min at 1 mL/min (retention time = 9.05 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 5.87 min).

1.5.2 In vitro analysis of 1180 series analogs

Protocols utilizing *Xenopus laevis* oocytes were approved by the Emory University Institutional Animal Care and Use Committee. *Xenopus laevis* oocytes were purchased unfertilized from Ecocyte (Austin, TX). The oocytes were injected with mRNA to express recombinant rat GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D and two-electrode voltage clamp (TEVC) recordings were performed. Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (Univeristy of Heidelberg) provided the cDNAs for rat GluN1-1a (GenBank accession numbers U11418 and U08261, referred to as GluN1 henceforth), GluN2A (D13211), GluN2B (U11419), GluN2C (M91563), and GluN2D (D13213). GluN2C and GluN2D were altered according to literature precedent.[20] Isolation of oocytes, synthesis of cRNA, and injections of cRNA were each done according to literature precedent.[108] Oocytes were placed in perfusion chamber and continuously washed during TEVC recordings with a solution consisting of the following (in mM): 90 NaCl, 0.5 BaCl, 0.005 EDTA, 1.0 KCl, and 10 HEPES at pH 7.4 and 23 ℃. Glass electrodes were pulled from thin-walled glass capillaries (tip

resistance 0.5-2.5 MΩ) and filled with 0.3-3.0 M KCl while the oocyte membrane potential was held constant at -40 mV via an OC-725C amplifier (Warner Instrument Co.). Each compound was brought up in 20 mM DMSO and diluted with recording solution containing 30 μM glycine and 100 μM glutamate to the target concentration. To prevent the current increase typically seen during experiments with oocytes expressing GluN1/GluN2A receptors, the oocytes were either injected with 20 nL of 100 mM K-BAPTA (potassium 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid) or pretreated with 50 μM BAPTA-AM (1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid tetraacetoxymethyl ester) for 10 minutes. Compounds that potentiated GluN2A-containing receptors were not studied further. For test compounds with potentiation that exceeded 125% at 30 μM, an EC_{50} value (the half-maximal effective concentration of potentiator) was determined by fitting the following equation:

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

to the mean composite concentration−response data normalized to the current in the absence of the potentiator (100%) where N equals the Hill slope and max is the maximal response predicted for saturating concentration of potentiator.

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Chapter 2: Discovery of a 1,4-dihydroisoquinolin-3(2H)-one core that selectively potentiates the GluN2C and GluN2D subunits of the N-methyl-ᴅ-aspartate (NMDA) receptor with improved doubling concentrations

2.1 Statement of Purpose

Our lab has previously reported the first GluN2C/D-selective PAM of the NMDAR in CIQ (**Section 1.2.4**) (**Figure *1***).[1] Despite significant recent interest in subunit-selective modulators of the receptor, there exists relatively few literature examples of small, drug-like PAMs selective for GluN2C/D. Although CIQ is a useful, first-in-class *in vitro* tool compound, several compound characteristics prevent both its further use as an *in vivo* tool as well as its clinical development. Significant previous SAR succeeded in improving potency for GluN2C- and GluN2D-containing receptors but did so largely via hydrophobic effects and at the expense of compound lipophilicity. The lipophilicity of a small molecule drug has drastic effects on its off-target behavior, aqueous solubility, plasma protein binding, and *in vivo* free fraction, among others. These properties are important for drug absorption, oral bioavailability, and achieving receptor occupation in the brain (**Section 3.2.1**). For example, CIQ's *in vivo* free fraction was found to be only 0.1%, likely due at least in part to its high lipophilicity.[2] This prevents achievement of high concentrations of drug and receptor occupancy in the brain, exacerbated by CIQ's micromolar potency. If receptor occupancy cannot be achieved *in vivo*, the compound is useless as a *in vivo* tool compound to study its receptor target. Therefore, we were interested in developing new strategies to improve without harming the ADME properties of the series, using CIQ as a starting point.

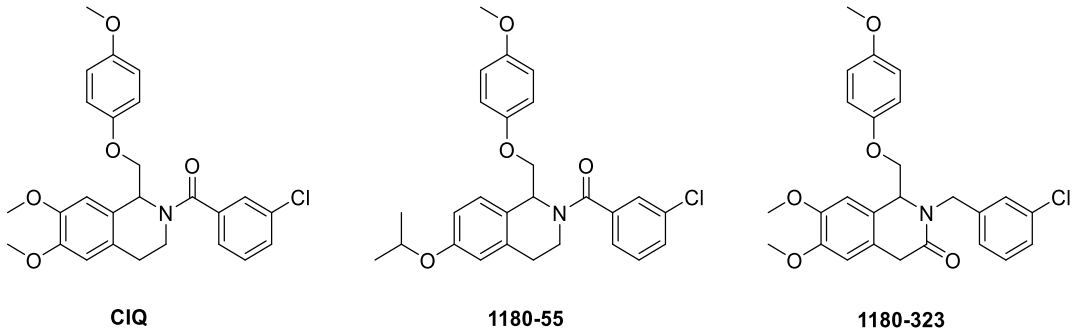


Figure 1. Scaffold of GluN2C/D-selective CIQ (left), GluN2B/C/D-preferring isopropoxy derivative (middle), and GluN2C/D-selective 1,4-dihydroisoquinolin-3(2H)-one that is the subject of this work (right).

Previous work on the TIQ-core largely involved the altering of substitution around the three main phenyl rings (the A-, B-, and C-rings). Little to no changes had been made to the TIQ-core itself, providing a unique opportunity to explore core changes that may improve potency while maintaining or improving the ADME properties discussed above. The goals of this project were achieved via the following strategy:

1.) Design core changes to the 1180 series likely to exhibit improved potency and ADME properties (e.g. solubility) while maintaining selectivity for GluN2C- and GluN2D-containing receptors based on previously established SAR trends and standard medicinal chemistry principles.

2.) Synthesize the strategically designed cores (and derivatives if active) and test for their biological activity at GluN2A-D receptors via an *in vitro* two-electrode voltage clamp (TEVC) assay in *Xenopus laevis* oocytes, completed in the lab of collaborator Dr. Stephen Traynelis.

2.2 Introduction and Background

2.2.1 Therapeutic rationale for GluN2C- and GluN2D-selective positive allosteric modulators of the NMDAR

We have previously described a dimethoxy-substituted TIQ class of PAMs, typified by CIQ, that are selective for GluN2C- and GluN2D-containing receptors over GluN2A- and GluN2B-containing receptors (**Chapter 1**).[1, 3] There are several lines of evidence suggesting positive therapeutic outcomes could be achieved with the development of potent, GluN2C/D-selective PAMs. One hypothesis is that the hypofunction of GluN2C- and GluN2D-containing receptors plays a role in schizophrenic symptoms[4] and thus GluN2C- and GluN2D-selective PAMs could have therapeutically relevant actions.[5] Furthermore, post-mortem examinations of schizophrenic patients with a specific *NRG1* gene polymorphism revealed reduced GluN2C expression in the right cerebellum.[6] There is also some evidence to suggest decreased inhibitory drive can lead to hyperactivity of principal cells and enhanced dopamine release.[5] Expression of GluN2D in interneurons[7-9] suggests that selective enhancement of GluN2C/D-containing receptor function could potentially rectify this hypothesized circuit imbalance. Finally, potentiation of GluN2C/D-containing receptors by CIQ has recently been shown to recover striatal synaptic plasticity deficit in a murine Parkinson's model[10] as well as facilitate the retention of fear and extinction learning in mice,[11] suggesting the clinical potential of a potent, GluN2C/D-selective PAM.

2.2.2 Photocrosslinking

Alongside improvements in affinity and ADME properties, we were interested in determining the binding site of these compounds on the receptor to potentially guide future discovery efforts. Extensive site-directed mutagenesis studies have previously been performed on 1180-series compounds to determine their binding location within the binding pocket.[12] However, this method

is not definitive for determining the binding location as the change in receptor behavior may be a result of intolerance to residue change at that location, rather than binding of the small molecule. One method to supplement the determination of the amino acids involved in binding is photocrosslinking, or photoaffinity labeling. Photocrosslinking works by attaching a photoreactive substituent to a ligand, which then forms a non-reversible covalent bond with residues in the binding pocket. Upon protein purification and proteolysis, the peptide fragment containing the ligand can be identified via LCMS-MS (**Figure *2***).[13, 14]

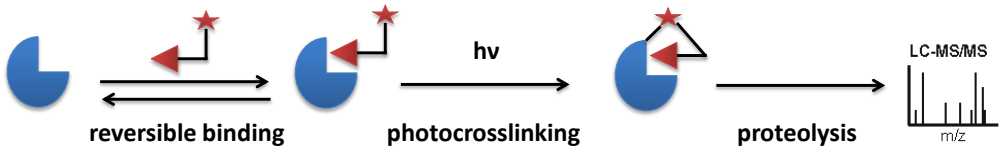


Figure 2. Process for photoaffinity labeling.[15]

Molecules dressed for photoaffinity labeling typically contain a photoreactive substituent (benzophenone, azide, diazirine, etc.) and a group that acts as a handle during SDS-page purification (biotin, etc.). Azides are advantageous photoreactive substituents since they require short wavelengths of light for activation, potentially limiting non-specific protein labeling.[13] They are also substantially smaller and more hydrophilic than benzophenone, for example, and therefore will more closely imitate the binding pose of the parent ligand while also limiting assay complications from lack of aqueous solubility. Upon binding to the protein, a pull-down handle is required for protein purification. An azide-labeled biotin tag is a common handle due to its ease of installation via click chemistry to an alkyne substituent located on the ligand.[13] This is also advantageous due to the small size of the alkyne moiety and robust nature of the cycloaddition chemistry required to set the handle in place.[16-18]

Therefore, the experiment would proceed as follows: First, an 1180 derivative would be synthesized with an azide and alkyne group strategically placed to produce a potent compound for

the receptor. HEK cells expressing NMDARs would then be incubated with the drug and irradiated at ultraviolet wavelengths (<300 nm) to facilitate covalent binding to the NMDARs. Then after centrifugation, the pellets would be subjected to biontinylation via an azide-labeled biotin molecule and copper-catalyzed click chemistry conditions. Finally, after protein purification, the peptide segment bound to the ligand could be determined via LCMS-MS analysis. (**Figure *3***).[19]

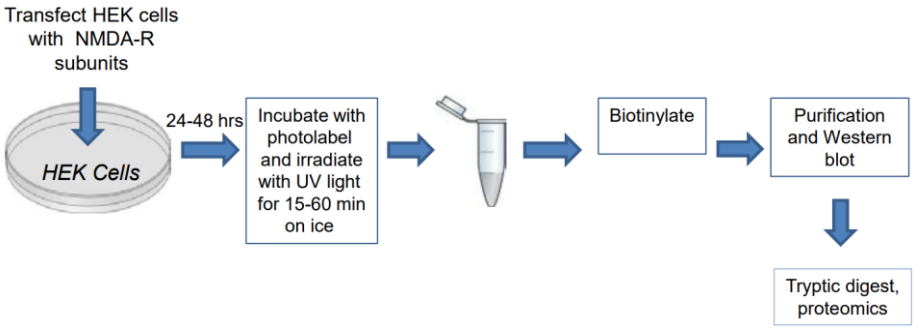


Figure 3. Detailed NMDAR photoaffinity assay.[15]

2.2.3 The identification of a 1,4-dihydroisoquinolin-3(2H)-one scaffold that maintains selectivity for GluN2C- and GluN2D-containing receptors

Previous computational work on a CIQ analog suggested that potency could be improved if the A-ring could be directed to adopt a *trans* conformation within the binding site, with *cis*/*trans* defined by the orientation of the amide carbonyl with respect to the stereocenter.[2] To investigate this hypothesis, a novel 1,4-dihydroisoquinolin-3(2*H*)-one scaffold was designed. We predicted that the translocation of the carbonyl onto the TIQ ring would provide enough steric influence to favor the *trans* conformation, and ultimately increase the fraction of drug in the predicted more active pose (**Figure *4***).

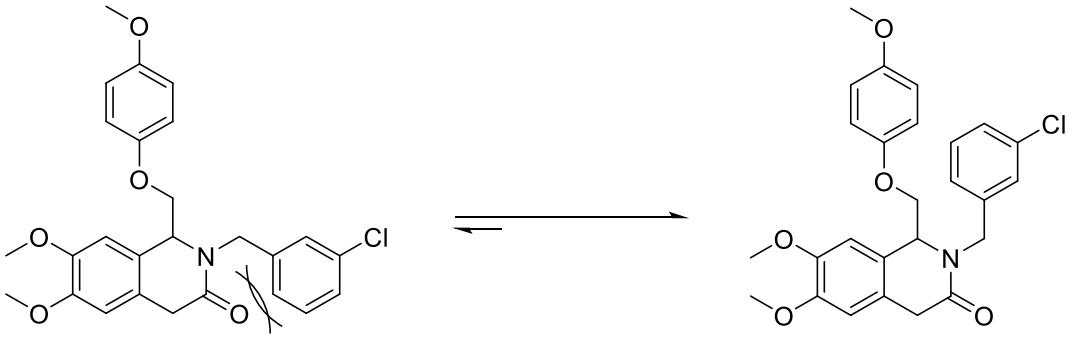


Figure 4. Model of the steric encumbrance upon translocation of the carbonyl in the 1,4-dihydroisoquinolin-3(2H)-one series. The "*cis*" conformation was hypothesized to create steric clash between the carbonyl and A-ring, creating preference for the more active "*trans*" conformation.

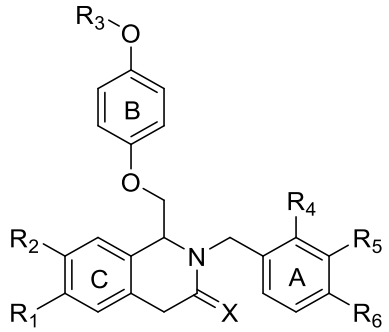
As predicted, compound **1180-323** showed improved potentiation (271-337%) of GluN2C/D-containing NMDAR responses to saturating co-agonists compared to CIQ (215-233%). Compound **1180-323** also exhibited similar potency (pEC_{50} = 5.0-5.3 at GluN2C/D) and subunit-selectivity (no activity at GluN2A/B) to CIQ (pEC_{50} = 5.3), resulting in improved doubling concentrations (pDC from 5.1 to 4.5-4.9). Selectivity for GluN2C and GluN2D was also maintained upon application of **1180-323** and subsaturating levels of co-agonists glutamate and glycine (**Table *1***). Previous studies revealed that a single methoxy substitution on the C-ring was favorable for activity.[1] We therefore synthesized compound **1180-297** and developed a structure-activity relationship around this analogue.

Table 1. Potentiation of GluN2A-D upon co-application of compound 323 and subsaturating concentrations of glutamate and glycine.

	$I_{10\ \mu M}/I_{control}$ (mean ± SEM, %) [Glu/Gly conc. (μM)][a]			
Compound	**GluN2A**	**GluN2B**	**GluN2C**	**GluN2D**
323	96 ± 5 [1.9/0.8]	88 ± 4 [0.8/0.5]	450 ± 12 [0.9/0.2]	400 ± 30 [0.3/0.1]

[a]Data are from between 4 and 8 oocytes from 1 frog for each compound and receptor tested.

Figure 5. Labeled 1,4-dihydroisoquinolin-3(2H)-one to distinguish between the A-, B-, and C-rings.

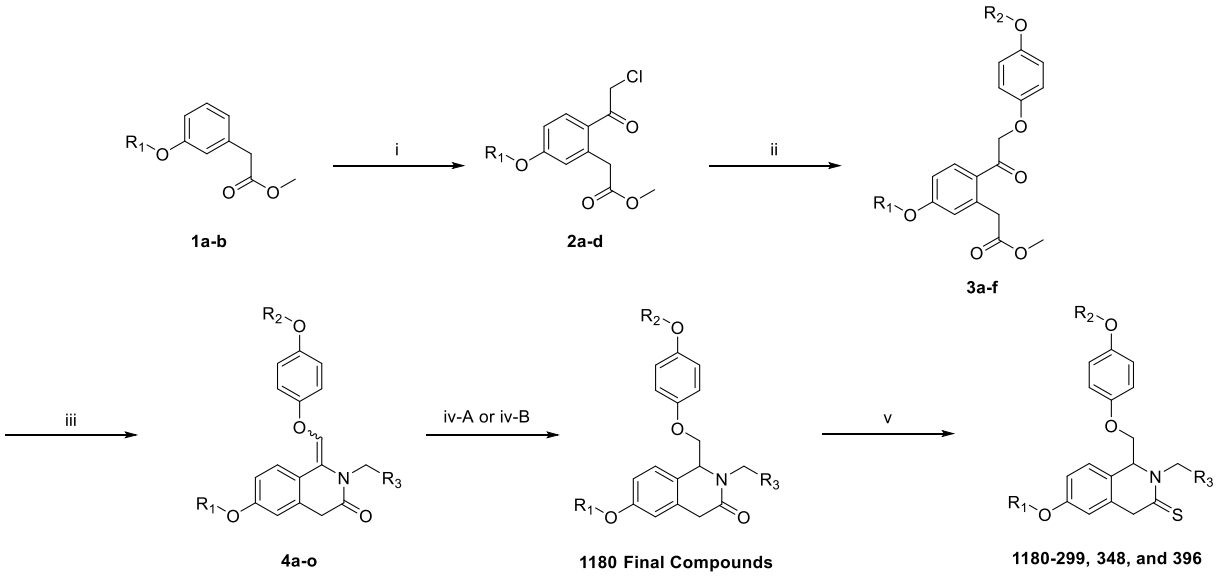


2.3 Synthesis, Rationale, Results, and Discussion of GluN2C/D-Selective 1,4-dihydroisoquinolin-3(2*H*)-one-Based Positive Allosteric Modulators

2.3.1 Synthesis of 1,4-dihydroisoquinolin-3(2H)-ones

The synthesis of 1,4-dihydroisoquinolin-3(2*H*)-one analogues is shown in **Scheme *1***. Methyl esters **1a** and **1b** were prepared according to modified literature procedures[2] while all others were commercially available. *Alpha*-chloro ketones **2a-2d** were prepared via Friedel-Crafts acylation of the appropriate methyl esters with chloroacetyl chloride and stannic(IV) chloride in dichloromethane. The resulting *α*-chloroamide was then reacted with the appropriate phenol and potassium iodide to give ketones **3a-3f**, which were cyclized in a microwave reactor using the appropriate amine, titanium(IV) isopropoxide, and sodium triacetoxyborohydride to afford the penultimate olefin intermediates **4a-4o** as mixtures of their *E* and *Z* isomers. Each olefin could then either be reduced via hydrogenation at 50 psi using palladium on carbon or in cases with aryl chlorides, hydrogenated with platinum oxide at 1 atm to give the final 1,4-dihydroisoquinolin-3(2*H*)-one compounds. Finally, select 1,4-dihydroisoquinolin-3(2H)-ones were treated with Lawesson's reagent under microwave conditions to give dihydroisoquinolinthione analogs **1180-299**, **1180-348**, and **1180-396**.

Scheme 1. Synthesis of dihydroisoquinolinones.



Scheme 1. i) chloroacetyl chloride, tin(IV) chloride, DCE, reflux, 90 m (33-48%) (procedure I); ii) substituted phenols, KI, K_2CO_3, reflux, 4 h (36-67%) (procedure II); iii) substituted primary amines, titanium(IV) isopropoxide, sodium triacetoxyborohydride, DCE, 120°C, µw, 20 m (17-73%) (procedure III); iv) a) platinum(IV) oxide, H_2 (1 atm), EtOH, rt, 10 h (10-56%) (procedure IV-A), b) Pd/C, H_2 (50 psi), EtOH, rt, 24 h (25-70%) (procedure IV-B); v) Lawesson's reagent, PhMe, 150 °C µw, 2 h (18-51%) (procedure V)

Compounds **1180-332**, **1180-348**, and **1180-396** were each separated via chiral semi-preparative HPLC using a ChiralPakAD-H column. Compound ***R*-(+)-1180-332** was demethylated with boron tribromide and bis-acylated with 4-nitrobenzoyl chloride to give **1180-434**, for which the absolute configuration was determined to be the *R*-(+)-enantiomer via X-ray crystallography (**Figure *6***) and allowed for absolute stereochemical assignment of the enantiomers.

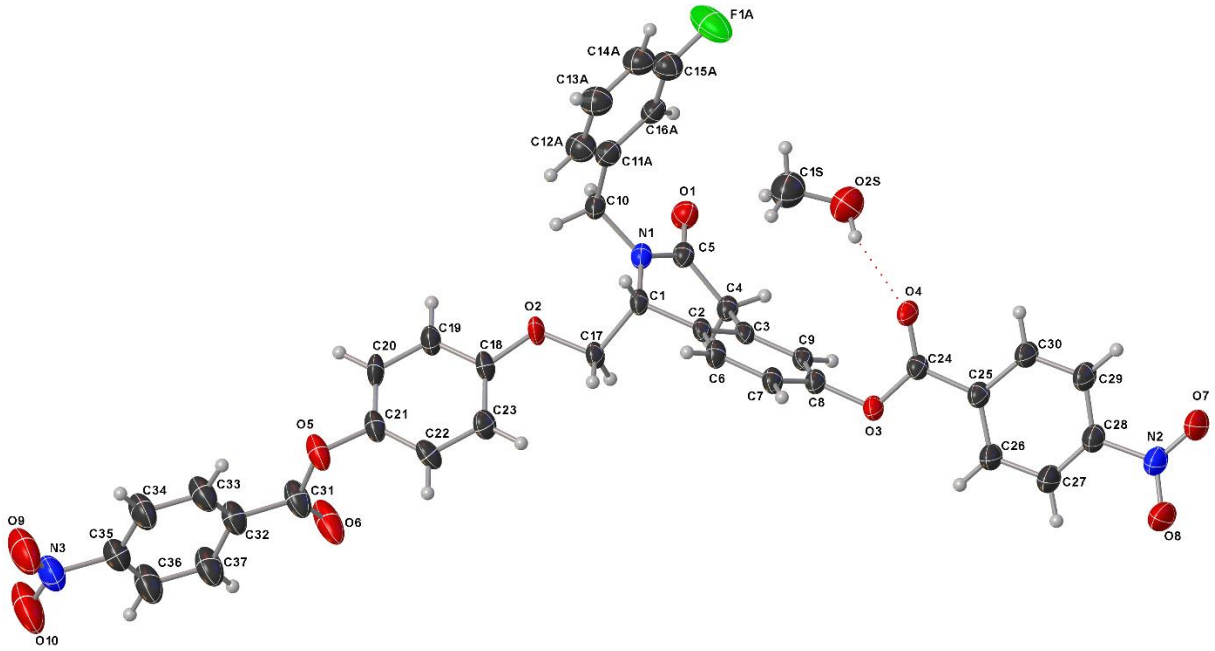


Figure 6. Crystal structure of bis-acylated *R*-(+)-1180-332 or 1180-434.

2.3.2 Potentiation of NMDARs by a 1,4-dihydroisoquinolin-3(2H)-one series

All compounds synthesized were evaluated via two-electrode voltage-clamp recordings of *Xenopus laevis* oocytes expressing four recombinant NMDA subtypes: GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D. Each compound was co-applied at 30 μM with saturating concentrations of glutamate (100 μM) and glycine (30 μM). When the mean potentiation exceeded 125%, concentration-effect curves were generated by co-applying increasing concentrations of compound with saturating agonist. We determined the pEC_{50} value and maximal degree of potentiation by fitting the concentration-effect curves to the equation in **Section 2.5.3**. Each concentration-effect curve was generated with data from 7-19 oocytes from 2-3 frogs; all inactive compounds were tested in 4-10 oocytes from 2-3 frogs. **Tables 1-8** summarize the mean pEC_{50} value with 95% confidence interval, average maximum potentiation (max), and negative log of the doubling concentration (pDC) (**Section 2.5.3**) for each active compound at GluN1/GluN2C and GluN1/GluN2D receptors. For compounds in which a pEC_{50} value was not

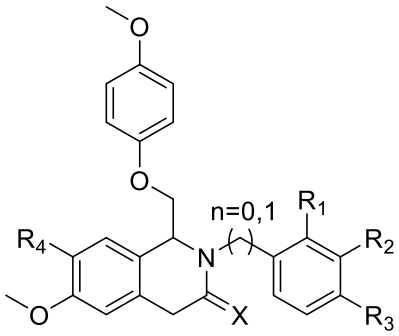
determined (ND), the maximum potentiation is reported as the average percent potentiation at 30 μM drug. The average percent potentiation is defined as the mean ratio of current upon application of drug at the stated concentration to the current response in its absence. The doubling concentration is defined as the concentration of test compound at which the response to maximally effective concentration of coapplied glutamate and glycine is increased 2-fold over the response to glutamate and glycine alone. Table **9** compares doubling concentrations of select compounds reported here to previously reported compounds. All compounds were also tested at GluN1/GluN2A and GluN1/GluN2B receptors at 10 or 30 μM and were typically found to have no effect (4-14 oocytes from 2-3 frogs). Only three compounds (**1180-324**, **1180-349**, and **1180-350**) exhibited potentiation above 130% at GluN2A- or GluN2B-containing receptors and only one exceeded 200% at 10 μM (**1180-350** at 204% potentiation; see **Table *4***).

2.3.3 Effect of modifying the A-ring, A-ring linker and amide

Structural modifications were performed on the A-ring and A-ring linker and recordings made using *Xenopus* oocytes to determine their effect on potency, efficacy, and selectivity for each of the GluN2 subunits (**Table 2**). These modifications revealed a similar SAR as in Santangelo-Freel *et al*. for the new dihydroisoquinolinone core in this portion of the molecule,[1] maintaining selectivity for GluN2C- and GluN2D-containing receptors and improving potency in accordance with increased lipophilicity. First, we examined the effect of 'walking' the halogen around the A-ring to produce compounds **1180-302** and **1180-307**, the ortho- and para- substituted derivatives, respectively, of **1180-297**. While **1180-307** maintained similar doubling concentrations (pDC = 5.5) to **1180-297** (pDC = 5.6-5.7), we exclusively focused on *meta*-substituted derivatives due to its slight superiority here and in previously observed structure-activity studies.[1, 2] Both the unsubstituted benzyl analog, **1180-329**, and the extended A-ring linker derivative, **1180-303**, also

showed substantial drops in doubling concentrations (pDCs ≤ 5.3) so we focused on the synthesis of other *meta*-substituted benzyl analogs, including the fluoro- and trifluoromethyl-substituted derivatives, compounds **1180-332** and **1180-340**, respectively. While compound **1180-332** showed a slight increase in potentiation (max = 352-376%) and similar doubling concentrations (pDC = 5.5-5.6) relative to **1180-297** (max = 271-337%, pDC = 5.6-5.7), the trifluoromethyl compound **1180-340** was the first compound to show doubling concentration gains (pDC = 5.7-6.0). Compound **1180-340** improved the pEC_{50} to 6.0 and 5.9 at GluN2C and GluN2D, respectively, while maintaining similar efficacy (max = 254-320%) to **1180-297** (max = 271-337%). Conversion of the amide to the thioamide produced analog **1180-299**, which also improved potencies into the nanomolar range (pEC_{50} = 6.0). However, it is likely the gains were due in large part to hydrophobic effects as thioamide substitution has been shown to increase cLogP roughly an order of magnitude on average in this series, driving binding.[2] Still, this does show that the 1,4-dihydroisoquinolin-3(2*H*)-one scaffold can recover activity that was lost within the CIQ series since thioamide incorporation on the CIQ scaffold rendered the compound completely inactive.

Table 2. Optimization of potency based on identity of A-ring and A-ring linker.



#	R_1	R_2	R_3	R_4	n	X	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)
							GluN2C	GluN2D	
CIQ[b]							5.3 (233)	5.3 (215)	4.9/4.5
323	H	Cl	H	OMe	1	O	5.3 [5.1-5.4] (271)	5.0 [4.9-5.1] (337)	5.1/5.1
297	H	Cl	H	H	1	O	5.7 [5.6-5.8] (272)	5.6 [5.5-5.8] (326)	5.6/5.7
302	Cl	H	H	H	1	O	5.2 [5.1-5.3] (231)	5.0 [4.9-5.1] (249)	4.7/4.7
307	H	H	Cl	H	1	O	5.6 [5.5-5.7] (284)	5.3 [5.2-5.4] (357)	5.5/5.5
303	H	Cl	H	H	2	O	4.7 [4.5-5.0] (207)	5.0 [5.0-5.0] (155)	<4.5/ID
329	H	H	H	H	1	O	5.2 [5.0-5.4] (236)	5.2 [5.1-5.3] (330)	4.7/5.3
332	H	F	H	H	1	O	5.4 [5.3-5.4] (352)	5.4 [5.3-5.5] (376)	5.5/5.6
340	H	CF_3	H	H	1	O	6.0 [5.9-6.1] (254)	5.9 [5.8-6.1] (320)	5.7/6.0
299	H	Cl	H	H	1	S	6.0 [5.9-6.1] (147)	6.0 [5.9-6.1] (127)	ID/ID

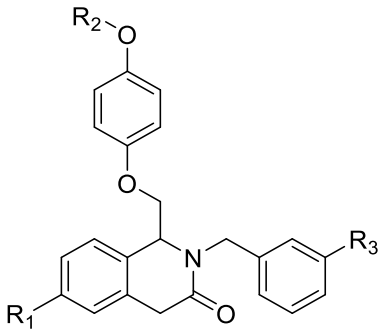
[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 6 and 19 oocytes from 2-3 frogs for each compound and receptor. [b]Previously published[1] data for **CIQ** were included for comparison. ID = indeterminable

2.3.4 Investigating GluN2B-preferring substitution on the dihydroisoquinolinone scaffold

Previous publications from our group have shown that alkyl functionalization on the C-ring controls the GluN2-subunit selectivity within the TIQ series.[2] Therefore, we converted the

methoxy substitution at R_1 to an isopropoxy group (**1180-327**), which has been shown to bring in activity at GluN2B (**Table 3**). Surprisingly, **1180-327** maintained selectivity exclusively for GluN2C and GluN2D and interestingly showed nearly an order of magnitude improvement in doubling concentrations (pDC = 6.5-6.6) in relation to compound **1180-297** (pDC = 5.6-5.7). This shows the 1,4-dihydroisoquinolin-3(2H)-one series maintains activity at GluN2C and GluN2D across a broader scope of A-ring substitution than the original TIQ series and these substitutions can produce notable affinities in choice cases. Notably, the isobutyl derivative, **1180-324**, displayed potentiation at GluN2A/B receptors in addition to GluN2C/D (**Table 4**), showing the selectivity of the series can still be tuned with select structural modifications. Previous publications from our lab have also shown that replacement of the methoxy group on the B-ring with large alkyl groups, such as ethoxy, can push selectivity away from GluN2C and GluN2D, especially in the case of fluoro-substitution on the A-ring.[2] In this case, however, ethoxy substitution (compounds **1180-339** and **1180-356**) at this position is not tolerated across all subtypes (max = 112-116% at GluN2C and 101-121% at GluN2D). Therefore, para-methoxy substitution was maintained throughout the series.

Table 3. Optimization of potency and selectivity based on identity of C- and B-rings.



#	R_1	R_2	R_3	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)
				GluN2C	GluN2D	
297[b]	OMe	Me	Cl	5.7 [5.6-5.8] (272)	5.6 [5.5-5.8] (326)	5.6/5.7
327	OiPr	Me	Cl	6.4 [6.3-6.5] (353)	6.3 [6.1-6.6] (366)	6.5/6.6
324	OiBut	Me	Cl	6.4 [6.3-6.4] (275)	6.2 [6.1-6.3] (369)	6.2/6.4
339	OMe	Et	F	ND (116)	ND (112)	-
356	OiPr	Et	F	ND (121)	ND (107)	-

[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 6 and 19 oocytes from 2-3 frogs for each compound and receptor. Data for GluN1/GluN2A and GluN1/GluN2B are given in ***Table 4***. [b]Compound **1180-297** was shown in a previous table and was included here for comparison.

2.3.5 Revisiting the A-ring

Excited by the activity boosts observed with **1180-327** and **1180-324**, a focused SAR of substitution known to be well-tolerated (**Section 2.3.3**) was pursued around the A-ring and A-ring linker. The substitution on the C- and B-rings was held to isopropoxy or isobutoxy, and para-methoxy, respectively, due to the trends observed in **Section 2.3.4** (**Table 5**). In general, the trends were maintained from the initial probing of the A-ring and produced an extremely potent

GluN2C/D-selective PAM in **1180-396**. First, the trifluoromethyl analog of compound **1180-327**, compound **1180-372**, maintained the excellent doubling concentrations (pDC = 6.3) observed with its chloro-substituted counterpart (pDC = 6.5-6.6) while the fluoro-substituted analog, **1180-349**, lost activity (pDC = 5.8-6.0) likely due to a decrease in lipophilicity.[2] This trend continued for isobutyl analogs as conversion from chloro-substituted analog **1180-324** (pDC = 6.2-6.4) to fluoro-substituted **1180-350** resulted in slightly decreased doubling concentrations (pDC = 6.0-6.1). Compounds **1180-349** and **1180-350** are also interesting due to their selectivity profile. They are the only compounds within the 1,4-dihydroisoquinolin-3(2H)-one series that bring in activity at GluN2B. This is consistent with the observation from previous studies indicating A-ring fluoro-substitution directs activity towards the GluN2B subunit (**Table 4**).[2]

Table 4. Potentiation of GluN2A and GluN2B-containing receptors.

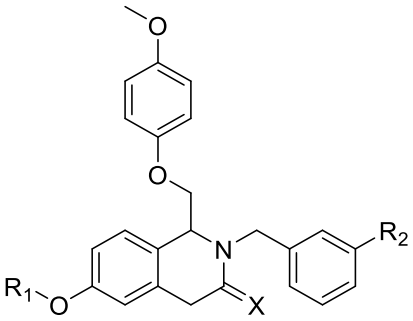
#	GluN1/GluN2A $I_{10\ \mu M}/I_{control}$ (mean ± SEM, %)[a]	GluN1/GluN2B $I_{10\ \mu M}/I_{control}$ (mean ± SEM, %)[a]
324	137 ± 7	193 ± 12
349	109 ± 3[a]	134 ± 7
350	102 ± 2[a]	204 ± 11

[a]The ratio of the current response to 100 μM glutamate and 30 μM glycine with test compound to the response to glutamate and glycine alone is shown for oocytes expressing either GluN1/GluN2A- or GluN1/GluN2B-containing receptors. Data are from 7-13 oocytes from 2-3 frogs. [a]Current ratio reported for 30 μM.

Activities were also improved upon conversion of compounds **1180-327** and **1180-372** to their thioamide counterparts, compounds **1180-348** and **1180-396** (**Table *5***). Despite an increase in lipophilicity, these compounds maintained selectivity for GluN2C and GluN2D and provided the

most potent racemic compound (**1180-396**) in the class at pEC_{50} values of 6.7 at GluN2C and 6.6 at GluN2D.

Table 5. Optimization of potency and selectivity based on identity of A-ring and amide carbonyl.



#	R_1	R_2	X	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)
				GluN2C	GluN2D	
327[b]	*i*Pr	Cl	O	6.4 [6.3-6.5] (353)	6.3 [6.1-6.6] (366)	6.5/6.6
372	*i*Pr	CF_3	O	6.4 [6.2-6.6] (276)	6.2 [6.2-6.3] (313)	6.3/6.3
349	*i*Pr	F	O	6.0 [5.9-6.0] (317)	5.7 [5.6-5.8] (332)	6.0/5.8
324[b]	*i*But	Cl	O	6.4 [6.3-6.4] (275)	6.2 [6.1-6.3] (369)	6.2/6.4
350	*i*But	F	O	6.0 [6.0-6.1] (324)	5.8 [5.7-5.8] (385)	6.1/6.0
348	*i*Pr	Cl	S	6.3 [6.1-6.6] (158)	6.3 [6.2-6.4] (150)	ID/ID
396	*i*Pr	CF_3	S	6.7 [6.7-6.8] (154)	6.6 [6.6-6.7] (148)	ID/ID

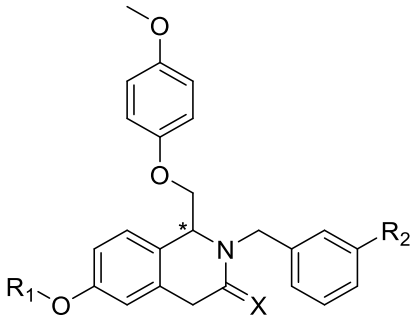
[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 8 and 16 oocytes from 2-3 frogs for each compound and receptor. Data for GluN1/GluN2B are given in ***Table 4***. [b]Compounds **1180-327** and **1180-324** were shown in a previous table and were included here for comparison. ID = indeterminable

2.3.6 Enantiomers

To this point, all analogs were synthesized and tested as racemic mixtures. Three of the racemates (**1180-332**, **1180-348**, and **1180-396**) were chosen for separation via normal phase chiral semi-preparatory HPLC (**Table 6**). The determination of the absolute configuration of these three compounds via X-ray crystallography proved fruitless even upon exhaustive crystallization efforts. Therefore, **(+)-332** (the active enantiomer) was converted to **1180-434** to facilitate crystal growth. Diffraction-quality crystals of **1180-434** were produced from hot methanol and the absolute configuration was determined to be the *R*-(+) enantiomer by X-ray crystallography (**Table 9**).

The activity of the enantiomers was found to be subunit-selective and stereodependent. The *R*-enantiomer significantly potentiated GluN2C- and GluN2D-containing receptors over GluN2A- and GluN2B-containing receptors in each case while the currents at 30 μM of *S*-enantiomer showed little to no difference in comparison to the control current with glutamate and glycine alone. This is noteworthy as the *S*-enantiomer of previous isopropoxy-substituted TIQs have shown non-selective potentiation of the NMDAR.[2] As expected, potency appeared to be maintained or improve in each case for the enantiopure material in comparison to racemic mixtures. Notably, separation of compound **1180-396** provided the best-in-class ***R*-(-)-1180-396**, which potentiated the GluN2C and GluN2D subunits selectively with pEC_{50} values of 6.7-6.8.

Table 6. Stereodependence of 1,4-dihydroisoquinolin-3(2H)-one series.



#	R_1	R_2	X	pEC_{50} [95% CI] (max) (%)[a]				pDC (GluN2C/2D)
				GluN2A	GluN2B	GluN2C	GluN2D	
***S*-(—)-332**	Me	F	O	ND (97)	ND (94)	ND (98)	ND (96)	-
***R*-(+)-332**	Me	F	O	ND (102)	ND (107)	5.8 [5.7-5.9] (289)	5.5 [5.4-5.6] (490)	5.8/6.0
***S*-(+)-348**	*i*Pr	Cl	S	ND (96)	ND (104)	ND (105)	ND (106)	-
***R*-(—)-348**	*i*Pr	Cl	S	ND (98)	ND (104)	6.6 [6.2-6.9] (211)	6.5 [6.2-6.7] (216)	5.6/5.7
***S*-(+)-396**	*i*Pr	CF_3	S	ND (95)	ND (84)	ND (98)	ND (100)	-
***R*-(—)-396**	*i*Pr	CF_3	S	ND (94)	ND (94)	6.7 [6.6-6.8] (233)	6.8 [6.7-6.8] (203)	6.2/5.2

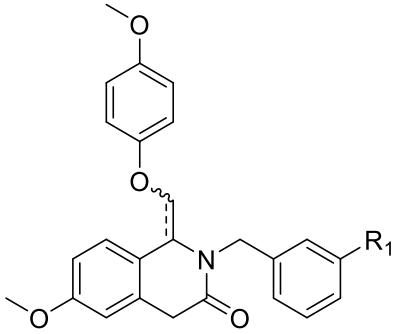
[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 6 and 16 oocytes from 2-3 frogs for each compound and receptor. ID = indeterminable

2.3.7 Olefins

Representative olefinic 1,4-dihydroisoquinolin-3(2*H*)-one precursor **1180-298** was also tested under saturating glutamate and glycine conditions and showed a slight decrease in doubling concentrations (pDC = 4.7-5.1) compared to the 1,4-dihydroisoquinolin-3(2*H*)-one counterpart **1180-297** (pDC = 5.6-5.7). The *E* and *Z* isomers of the precursors to compound **1180-332** were then separated on silica to observe if the activity was isomer-dependent. One isomer (**1180-369**) showed selective activity for GluN2C and GluN2D (pEC_{50} = 5.0-5.1, pDC = 4.6) while the other

isomer was not tolerated (max = 96-102%) at all subunits. This suggests conformational restriction of the B-ring into the same pose as the active isomer could result in improved potency for the target. (**Table *7***)

Table 7. Activity and selectivity profile of olefinic 1,4-dihydroisoquinolin-3(2H)-one precursors.



#	R_1	Alkene?	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)
			GluN2C	GluN2D	
297[b]	Cl	No	5.7 [5.6-5.8] (272)	5.6 [5.5-5.8] (326)	5.6/5.7
298 (mixture of cis and trans)	Cl	Yes	5.6 [5.4-5.7] (234)	5.4 [5.2-5.7] (220)	5.1/4.7
369 (*Z* isomer)	F	Yes	5.1 [5.0-5.2] (232)	5.0 [4.9-5.1] (244)	4.6/4.6
370 (*E* isomer, ~70% pure)	F	Yes	ND (102)	ND (96)	-

[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 6 and 12 oocytes from 2-3 frogs for each compound and receptor. [b]Compound **1180-297** was shown in a previous table and was included here for comparison.

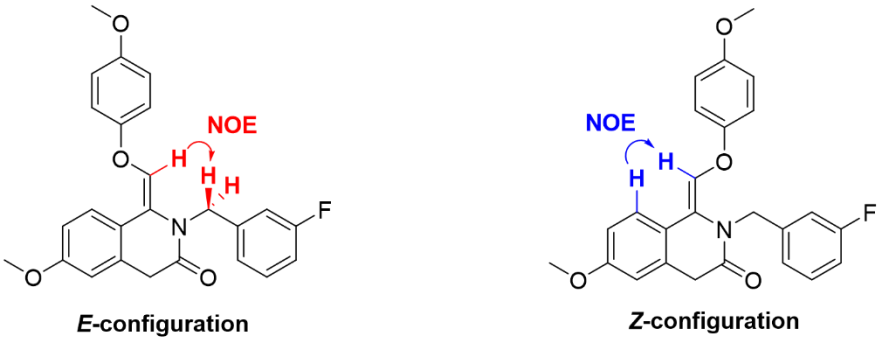


Figure 7. Expected NOEs for the E- and Z- configurations of 1180-369.

To investigate the identity of the active isomer, **1180-369**, a 2D NOESY experiment was performed using this compound. We anticipated an observed NOE between the alkene proton and the northern C-ring proton if it was in the *Z*-configuration and an NOE between the alkene proton and the benzyl methylene protons of the A-ring linker if it was in the *E*-configuration (**Figure *7***). The results of the NOESY experiment can be seen in **Figure *8*** and **Error! Reference source not found.**. There is a clear NOE between the C-ring aryl proton of active **1180-369** and the alkene proton in **Figure *8***, strongly suggesting the configuration of the active compound **1180-369** is the *Z*-configuration. Compounds are currently being designed and synthesized to imitate this configuration and potentially increase affinity for the receptor.

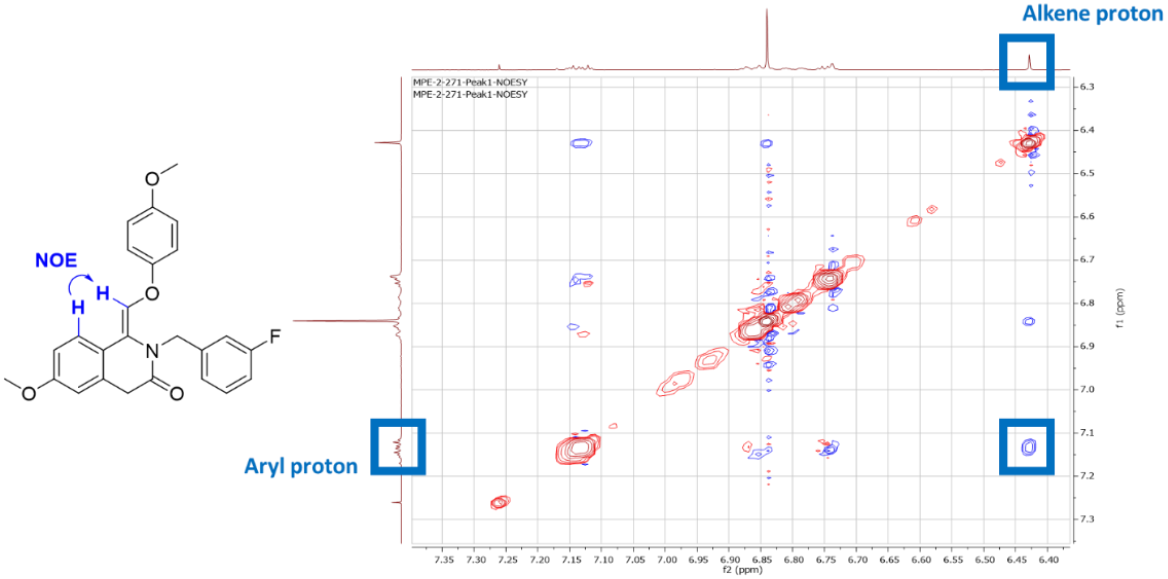
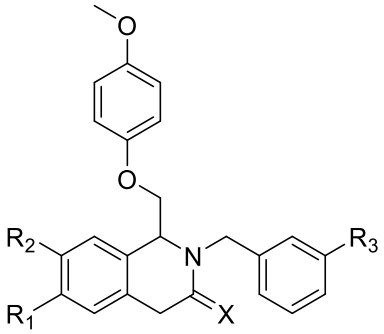


Figure 8. Aromatic region of the NOE spectrum of the active isomer, 1180-369.

2.3.8 1,4-dihydroisoquinolin-3(2H)-one compounds show improved doubling concentrations over their TIQ counterparts

We calculated the doubling concentration using the equation in **Section 2.5.3** for all 1,4-dihydroisoquinolin-3(2H)-ones and corresponding TIQs[1, 2] to demonstrate the trend of improved activity for 1,4-dihydroisoquinolin-3(2H)-one analogs (**Table 8**). The doubling concentration at GluN2C or GluN2D was improved in the 1,4-dihydroisoquinolin-3(2H)-one scaffold in 81% (13/16) of cases. Of the three cases in which the doubling concentration was not improved, two (compare **1180-348** and **1180-138** at GluN2C and GluN2D) were due to insufficient potentiation (max < 200%) and the third (compare **1180-324** and **1180-88** at GluN2C) showed only a 2-fold decrease. The average doubling concentration improvement was 5-fold across all calculable ratios (excluding **1180-329** and **1180-348** due to lower than 200% potentiation). This data demonstrates the ability of the 1,4-dihydroisoquinolin-3(2H)-one series to improve activity over literature precedent.

Table 8. Doubling concentrations of 1,4-dihydroisoquinolin-3(2H)-one compounds and their TIQ counterparts.



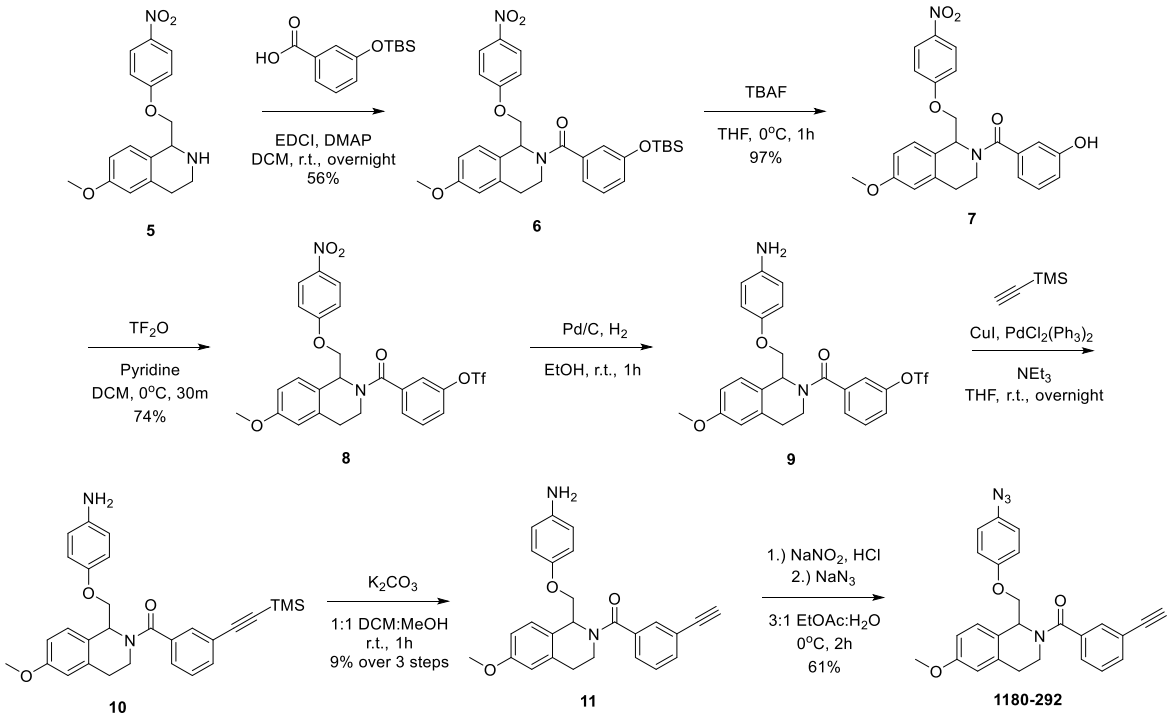
#	R_1	R_2	R_3	X	pDC[a]		ΔLLE	
					GluN2C	GluN2D	GluN2C	GluN2D
CIQ[c]	OMe	OMe	Cl	O	4.9	4.5	0.1	0.5
323[b]					5.1	5.1		
117[c]	OMe	H	Cl	O	5.5	5.3	0.1	0.4
297[b]					5.6	5.7		
116[c]	OMe	H	H	O	-	-	-	-
329[b]					4.7	5.3		
2[c]	OiPr	H	Cl	O	5.3	5.2	1.2	1.3
327[b]					6.6	6.6		
88[c]	OiBut	H	Cl	O	6.4	6.3	-0.3	0.0
324[b]					6.2	6.4		
127[c]	OiPr	H	CF_3	O	6.0	5.8	0.3	0.5
372[b]					6.3	6.3		
114[c]	OiPr	H	F	O	5.4	5.5	0.5	0.2
349[b]					6.0	5.8		
138[c]	OiPr	H	Cl	S	5.8	5.8	-	-
348[b]					-	-		

[a]The negative log of the concentration of test compound coapplied at which the response to maximally effective concentration of coapplied glutamate and glycine is increased 2-fold over the response to glutamate and glycine alone. [b]Compounds **1180-323**, **1180-297**, **1180-329**, **1180-327**, **1180-324**, **1180-372**, **1180-349**, and **1180-348** were shown in a previous table and were included here for comparison. [c]Previously published[1, 2] data for compounds **CIQ**, **1180-117**, **1180-116**, **1180-2**, **1180-88**, **1180-127**, **1180-114**, and **1180-138** were included for comparison.

2.3.9 Photocrosslinking

Compound **1180-292** (**Scheme *2***) was designed for photoaffinity labeling experiments with the NMDAR. The alkyne handle was placed on the A-ring as it has been shown to be tolerant to a

wide range of lipophilic substituents at the 3-position. In a similar fashion, the photoreactive azide was placed on the 4-position of B-ring due to its tolerance to several large substituents previously.[1, 2] The synthesis began with an EDCI coupling of tetrahydroisoquinoline **5** (synthesized per literature precedent)[1] and 3-((tert-butyldimethylsilyl)oxy)benzoic acid to give TBS protected phenol **6**. This was then deprotected with tetrabutylammonium fluoride to give phenol **7**, which was transformed to the triflate using triflic anhydride to give compound **8**. The nitro group could then be reduced via hydrogenation to give aniline **9**. A Sonogashira coupling was then utilized using trimethylsilylacetylene, copper(I) iodide, and bis(triphenylphosphine)palladium(II) dichloride to give aryl alkyne **10**. This was then deprotected with potassium carbonate to give alkyne **11,** and the aniline converted to the aryl azide using sodium nitrate and sodium azide resulting in the proposed photoaffinity linker **1180-292** (**Scheme *2***).



Scheme 2. Synthesis of 1180-292 for photoaffinity linking.

Unfortunately, this molecule was inactive at all GluN2 subunits, rendering it useless in terms of photoaffinity labeling. However, other 1180 series derivatives with azide and alkyne functionality have since shown activity at GluN2B-, GluN2C-, and GluN2D-containing receptors, leaving open the possibility for successful photoaffinity labeling with the series in the future.[15]

2.4 Conclusions

The GluN2C/GluN2D selective NMDAR PAM CIQ has seen extensive use as an *in vitro* tool compound since its discovery, but modest affinity and high lipophilicity has created a need for improved *in vivo* pharmacological tools. The novel 1,4-dihydroisoquinolin-3(2*H*)-one core and its derivatives described here are an important step in this direction, showing a 5-fold improvement in doubling concentrations across a wide range of derivatives with the most potent compound in the series potentiating GluN2C- and GluN2D-containing receptors 2-fold with pEC_{50} values in the 6.7-6.8 range. This improvement in activity is particularly noteworthy as the change in lipophilicity between the scaffolds is likely minimal due to their isomeric nature. This results in improved lipophilic efficiency for the NMDAR for the first time in the series.[1] It was discovered the activity can be tuned towards GluN2A and GluN2B upon simple structural changes, leading to the potential for future analogues with unique selectivity profiles. Moreover, separation of the enantiomers revealed activity resides exclusively in one enantiomer, which was revealed to be the *R*-(+) enantiomer by X-ray crystallography. This work begins the exploration of second-generation core scaffolds based on CIQ that could provide impactful clinical candidates and pharmacological tools in the future.

2.5 Experimental Details

2.5.1 Chemistry experimental procedures

General Experimental: All starting materials were purchased from commercial sources and used directly without further purification. All reactions were run under a nitrogen atmosphere unless otherwise noted. Purification by flash column chromatography was done using a Teledyne ISCO Combiflash Companion instrument using Teledyne Redisep normal phase columns. ^{1}H and ^{13}C NMR spectra were recorded on a VNMR-400 (400 MHz), INOVA-400 (400 MHz), or INOVA-500 (500 MHz) NMR spectrometer. Chemical shifts were reported in parts per million and referenced to the residual deuterated solvent. Reactions were monitored by thin layer chromatography on precoated aluminum plates (silica gel 60 F254, 0.25 mm) or LCMS on an Agilent Technologies 1200 series instrument. High resolution mass spectra were recorded on a VG 70-S Nier Johnson or JEOL instrument by the Emory University Mass Spectroscopy Center. Purity was established via LCMS (Varian) in at least two solvent systems (MeOH:water/ACN:water or MeOH:water/MeOH:water) unless otherwise noted. The conditions were determined individually for each compound in which purity was established via LCMS and the retention times in both solvent systems are given. Two compounds (**1180-303** and **1180-382**) were not greater than 95% pure by LCMS but were greater than 79% and specific details for each compound are given below. Optical rotations were established using a PerkinElmer 314 instrument.

General Procedure for Alpha-Chloro Ketones (Procedure I): Methyl ester (1 equiv) was dissolved in DCE (1.0 M) and 1 M tin(IV) chloride in DCM (5 equiv) was added dropwise and for 10 minutes at room temperature. 2-chloroacetyl chloride (4 equiv) was then added at room temperature and the resulting mixture was heated to reflux for 90 minutes. Upon completion, the

reaction was cooled to room temperature and quenched carefully with 1 M HCl. The organic layer was extracted with DCM, washed with saturated $NaHCO_3$ (2x), brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Biaryl Ketones (Procedure II): To a suspension of potassium iodide (1.2 equiv) and potassium carbonate (2 equiv) in acetone (0.17 M) was added alpha-chloro ketone (1 equiv) and phenol (1.2 equiv). The resulting mixture was then heated open to atmosphere at reflux for 4 hours. Upon completion, the reaction was cooled to room temperature and solvent removed *in vacuo*. The resulting residue was then dissolved in EtOAc and washed with water. The organic layer was then extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Tertiary Olefins (Procedure III): An appropriate microwave vial was charged with ketone (1 equiv), primary amine (1.2 equiv), tetraisopropoxytitanium (3 equiv), and DCE (0.2 M) and the solution was stirred for 10 minutes before sodium triacetoxyborohydride (3 equiv) was added and the mixture was irradiated at 120 ^{o}C for 30 min. Upon completion, the reaction was cooled to room temperature, diluted with DCM and washed with 1 M HCl. The organic layer was extracted with DCM, washed with $NaHCO_3$, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound as a mixture of E/Z isomers, the mass confirmed via LCMS, and carried forward without further characterization.

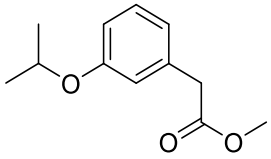
General Procedure for Final 1,4-dihydroisoquinolin-3(2H)-one Compounds (Procedure IV-A): A 10 mL microwave vial was charged with olefin (1 equiv), platinum (IV) oxide (10 mol%), and ethanol. The vial was then purged with hydrogen and evacuated (3x) and reacted at room

temperature under hydrogen for 6-24 hours, monitoring via LCMS to ensure no dehalogenation occurred. Upon first sight of dehaolgenation via LCMS, the reaction was diluted with MeOH, filtered through a plug of celite washing with MeOH, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

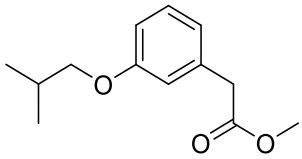
General Procedure for Final 1,4-dihydroisoquinolin-3(2H)-one Compounds (Procedure IV-B): Olefin (1 equiv) was dissolved in ethanol and 10% Pd/C (0.15 equiv) was added and the mixture was hydrogenated at 50 psi overnight. The reaction mixture was filtered through a pad of celite, washing with methanol, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Thioamides (Procedure V): Amide (1 equiv) in a microwave vial was dissolved in toluene and Lawesson's Reagent (1.5 equiv) was added. This mixture reacted in a microwave at 150^{o}C for 20 minutes. The reaction was then diluted with DCM, washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Final CIQ Compounds (Procedure VI): Carboxylic acid (1.1 equiv) was dissolved in dry DCM and cooled to 0^{o}C. EDCI (1.2 equiv) and DMAP (1.2 equiv) were then added and allowed to stir for 2 hours before the tetrahydroisoquinoline (1 equiv) was added and the mixture allowed to stir at room temperature overnight. The reaction was then quenched with deionized water and the organic layer was extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

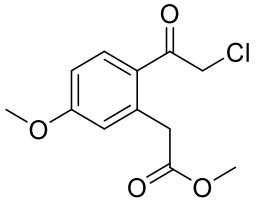


Methyl 2-(3-isopropoxyphenyl)acetate (1a). Methyl 2-(3-hydroxyphenyl)acetate (7.83 g, 47.1 mmol) was dissolved in THF (196 mL) and isopropanol (5.40 mL, 70.7 mmol), triphenylphosphine (18.5 g, 70.7 mmol) and 40% diethyl azodicarboxylate in toluene (32.2 mL, 70.7 mmol) was added and allowed to react overnight at room temperature. The crude product was purified via flash column chromatography (ISCO, Redisep 120 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a clear oil (8.19 g, 83%). R_f (1:1 EtOAC:Hex): 0.88; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 (t, J = 8.1 Hz, 1H), 6.88 – 6.76 (m, 3H), 4.55 (hept, J = 6.1 Hz, 1H), 3.69 (s, 3H), 3.59 (s, 2H), 1.34 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 171.90, 157.98, 135.34, 129.52, 121.31, 116.79, 114.34, 69.67, 52.00, 41.20, 22.02. HRMS calcd. for $C_{12}H_{17}O_3$, 209.11722 $[M + H]^+$; found 209.11720 $[M + H]^+$.

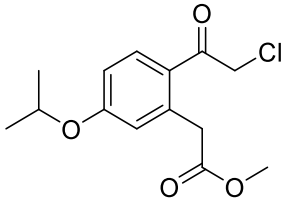


Methyl 2-(3-isobutoxyphenyl)acetate (1b). Methyl 2-(3-hydroxyphenyl)acetate (2.50 g, 15.0 mmol) was dissolved in dry DMF (46 mL) and potassium carbonate (8.32 g, 60.2 mmol) was added. This was stirred at room temperature for 2 hours before 1-iodo-2-methylpropane (3.70 mL, 30.1 mmol) was added. The resulting mixture was allowed to react at 60ºC overnight, after which the reaction was deemed complete via TLC. The product was then extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-20% EtOAc/hexanes gradient) to afford the title compound as a clear oil (1.64 g, 49%). Rf (1:1 EtOAC:Hex): 0.91; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.20 (m, 1H), 6.88 – 6.77 (m, 3H), 3.72 (d, *J* = 6.5 Hz, 2H), 3.70 (s,

3H), 3.60 (s, 2H), 2.16 – 2.01 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 171.95, 159.37, 135.26, 129.47, 121.31, 115.45, 113.15, 74.27, 52.05, 41.22, 28.28, 19.27. HRMS calcd. for $C_{13}H_{19}O_3$, 223.13287 $[M + H]^+$; found 223.13264 $[M + H]^+$.

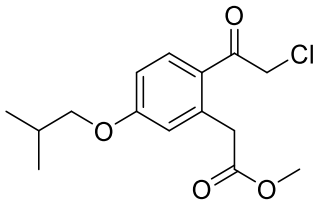


Methyl 2-(2-(2-chloroacetyl)-5-methoxyphenyl)acetate (2a). General procedure I was followed using methyl 2-(3-methoxyphenyl)acetate (2.23 mL, 13.9 mmol), 1 M tin(IV) chloride in DCM (69.4 mL, 69.4 mmol), and 2-chloroacetyl chloride (4.45 mL, 55.5 mmol) in DCE (14 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.65 g, 46%). R_f (1:1 EtOAC:Hex): 0.66; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.75 (d, J = 8.7 Hz, 1H), 6.86 (dd, J = 8.7, 2.6 Hz, 1H), 6.78 (d, J = 2.6 Hz, 1H), 4.63 (s, 2H), 3.92 (s, 2H), 3.85 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, cdcl3) δ 191.80, 171.51, 162.84, 138.55, 132.11, 126.56, 119.12, 112.02, 55.49, 51.92, 47.07, 40.55. HRMS calcd. for $C_{12}H_{14}O_4Cl$, 257.05751 $[M + H]^+$; found 257.05751 $[M + H]^+$.

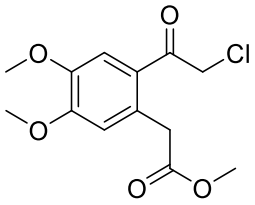


Methyl 2-(2-(2-chloroacetyl)-5-isopropoxyphenyl)acetate (2b). General procedure I was followed using **1a** (8.10 g, 38.9 mmol), 1 M tin(IV) chloride in DCM (194 mL, 194 mmol), and 2-chloroacetyl chloride (12.5 mL, 156 mmol) in DCE (39 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 80 g column, 0-30% EtOAc/hexanes gradient)

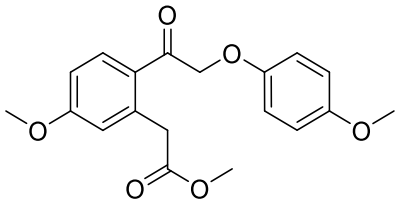
to afford the title compound as a white solid (5.20 g, 47%). R_f (1:1 EtOAC:Hex): 0.81; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.74 (d, J = 8.7 Hz, 1H), 6.82 (dd, J = 8.7, 2.6 Hz, 1H), 6.75 (d, J = 2.6 Hz, 1H), 4.63 (hept, J = 5.8 Hz, 3H), 4.63 (s, 2H), 3.91 (s, 2H), 3.68 (s, 3H), 1.35 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 191.60, 171.61, 161.43, 138.62, 132.26, 125.90, 120.51, 113.06, 70.24, 51.95, 47.15, 40.66, 21.86. HRMS calcd. for $C_{14}H_{18}O_4Cl$, 285.08881 $[M + H]^+$; found 285.08867 $[M + H]^+$.



Methyl 2-(2-(2-chloroacetyl)-5-isobutoxyphenyl)acetate (2c). General procedure I was followed using **1b** (1.08 g, 4.86 mmol), 1 M tin(IV) chloride in DCM (24.3 mL, 24.3 mmol), and 2-chloroacetyl chloride (1.56 mL, 19.4 mmol) in DCE (4.9 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 80 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.70 g, 48%). R_f (1:1 EtOAC:Hex): 0.88; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.74 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 8.7, 2.6 Hz, 1H), 6.79 (d, J = 2.6 Hz, 1H), 4.63 (s, 2H), 3.92 (s, 2H), 3.77 (d, J = 6.5 Hz, 2H), 3.69 (s, 3H), 2.08 (hept, J = 6.7 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 191.66, 171.62, 162.60, 138.54, 132.19, 126.14, 119.63, 112.42, 74.54, 51.96, 47.17, 40.66, 28.14, 19.13. HRMS calcd. for $C_{15}H_{20}O_4Cl$, 299.10446 $[M + H]^+$; found 299.10431 $[M + H]^+$.

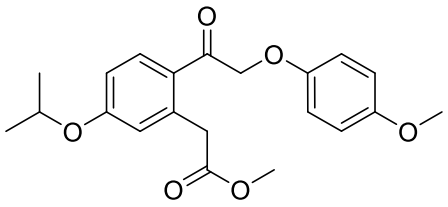


Methyl 2-(2-(2-chloroacetyl)-4,5-dimethoxyphenyl)acetate (2d). General procedure I was followed using methyl 2-(3,4-dimethoxyphenyl)acetate (2.50 g, 11.9 mmol), 1 M tin(IV) chloride in DCM (59.5 mL, 59.5 mmol), and 2-chloroacetyl chloride (3.81 mL, 47.6 mmol) in DCE (12 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-55% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.13 g, 33%). R_f (1:1 EtOAC:Hex): 0.45; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 (s, 1H), 6.74 (s, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.88 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 191.92, 171.81, 152.44, 147.41, 130.46, 126.04, 115.55, 112.67, 56.23, 56.04, 51.99, 47.22, 40.00. HRMS calcd. for $C_{13}H_{16}O_5Cl$, 287.06808 $[M + H]^+$; found 287.06795 $[M + H]^+$.

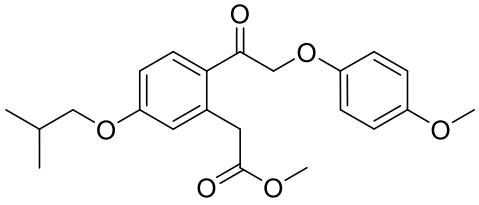


Methyl 2-(5-methoxy-2-(2-(4-methoxyphenoxy)acetyl)phenyl)acetate (3a). General procedure II was followed using **2a** (10.2 g, 39.7 mmol), potassium iodide (7.92 g, 47.7 mmol), 4-methoxyphenol (5.92 g, 47.7 mmol), and potassium carbonate (11.0 g, 79.0 mmol) in acetone (238 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 120 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white solid (7.23 g, 53%). R_f (1:1 EtOAC:Hex): 0.59; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.83 (d, J = 8.7 Hz, 1H), 6.88 – 6.77 (m, 6H), 5.10 (s, 2H), 3.94 (s, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 195.62, 171.70, 162.66, 154.26, 152.20, 138.22, 131.74, 126.76, 118.98,

115.83, 114.56, 111.98, 71.99, 55.64, 55.46, 51.94, 40.45. HRMS calcd. for $C_{19}H_{21}O_6$, 345.13326 $[M + H]^+$; found 345.13321 $[M + H]^+$.

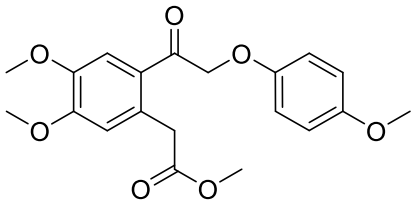


Methyl 2-(5-isopropoxy-2-(2-(4-methoxyphenoxy)acetyl)phenyl)acetate (3b). General procedure II was followed using **2b** (332 mg, 1.17 mmol), potassium iodide (232 mg, 1.40 mmol), 4-methoxyphenol (174 mg, 1.40 mmol), and potassium carbonate (322 mg, 2.33 mmol) in acetone (7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (289 mg, 67%). R_f (1:1 EtOAC:Hex): 0.73; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.83 (d, J = 8.7 Hz, 1H), 6.92 – 6.74 (m, 6H), 5.11 (s, 2H), 4.65 (hept, J = 6.0 Hz, 1H), 3.94 (s, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 1.36 (d, J = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, cdcl3) δ 195.49, 171.77, 161.27, 154.30, 152.30, 138.32, 131.81, 126.33, 120.39, 115.88, 114.61, 113.10, 76.78, 72.06, 70.19, 55.72, 51.98, 40.50, 21.92. HRMS calcd. for $C_{21}H_{25}O_6$, 373.17043 $[M + H]^+$; found 373.17143 $[M + H]^+$.

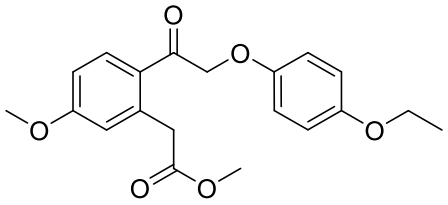


Methyl 2-(5-isobutoxy-2-(2-(4-methoxyphenoxy)acetyl)phenyl)acetate (3c). General procedure II was followed using **2c** (700 mg, 2.34 mmol), potassium iodide (467 mg, 2.81 mmol), 4-methoxyphenol (349 mg, 2.81 mmol), and potassium carbonate (648 mg, 4.69 mmol) in acetone (14 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a white solid (469 mg,

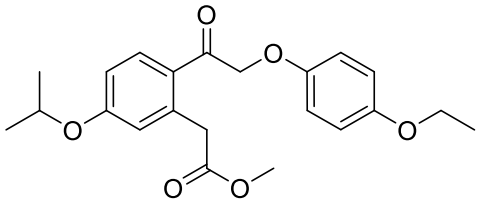
52%). R_f (1:1 EtOAC:Hex): 0.90; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.83 (d, J = 8.7 Hz, 1H), 6.90 – 6.73 (m, 6H), 5.11 (s, 2H), 3.94 (s, 2H), 3.78 (d, J = 6.6 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 2.10 (hept, J = 6.5 Hz, 1H), 1.03 (d, J = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, cdcl3) δ 195.60, 171.80, 162.47, 154.30, 152.28, 138.25, 131.77, 126.53, 119.50, 114.62, 112.42, 74.55, 72.09, 55.72, 52.00, 40.51, 28.20, 19.19. HRMS calcd. for $C_{22}H_{27}O_6$, 387.18022 $[M + H]^+$; found 387.18013 $[M + H]^+$.



Methyl 2-(4,5-dimethoxy-2-(2-(4-methoxyphenoxy)acetyl)phenyl)acetate (3d). General procedure II was followed using **3d** (1.08 g, 3.77 mmol), potassium iodide (750 mg, 4.52 mmol), 4-methoxyphenol (561 mg, 4.52 mmol), and potassium carbonate (1.04 g, 7.53 mmol) in acetone (23 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 20-90% EtOAc/hexanes gradient) to afford the title compound as a white solid (503 mg, 36%). R_f (1:1 EtOAC:Hex): 0.45; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 (s, 1H), 6.89 – 6.78 (m, 4H), 6.75 (s, 1H), 5.08 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.90 (s, 2H), 3.75 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 196.11, 171.98, 154.40, 152.30, 152.15, 147.40, 130.15, 126.42, 115.89, 115.48, 114.66, 112.60, 72.55, 56.27, 56.06, 55.71, 52.01, 39.89. HRMS calcd. for $C_{20}H_{23}O_7$, 375.14383 $[M + H]^+$; found 375.14387 $[M + H]^+$.

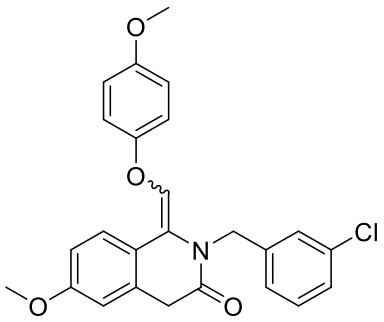


Methyl 2-(2-(2-(4-ethoxyphenoxy)acetyl)-5-methoxyphenyl)acetate (3e). General procedure II was followed using **2a** (500 mg, 1.95 mmol), potassium iodide (288 mg, 2.34 mmol), 4-methoxyphenol (323 mg, 2.34 mmol), and potassium carbonate (538 mg, 3.90 mmol) in acetone (12 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (352 mg, 50%). R_f (1:1 EtOAC:Hex): 0.74; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.84 (d, J = 8.7 Hz, 1H), 6.91 – 6.77 (m, 6H), 5.10 (s, 2H), 3.96 (q, J = 6.1 Hz, 2H), 3.95 (s, 2H), 3.86 (s, 3H), 3.67 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 195.76, 171.69, 162.68, 153.68, 152.21, 138.26, 131.76, 126.91, 118.97, 115.88, 115.36, 112.01, 72.15, 63.96, 55.48, 51.96, 40.44, 14.92. HRMS cal. for $C_{20}H_{23}O_6$, 359.14891 $[M + H]^+$; found 359.14863 $[M + H]^+$.

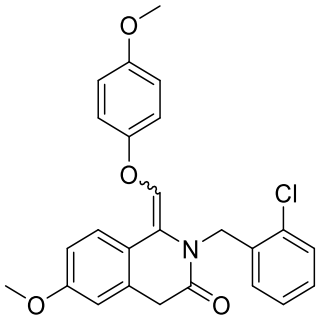


Methyl 2-(2-(2-(4-ethoxyphenoxy)acetyl)-5-isopropoxyphenyl)acetate (3f). General procedure II was followed using **2b** (730 mg, 2.56 mmol), potassium iodide (511 mg, 3.08 mmol), 4-methoxyphenol (425 mg, 3.08 mmol), and potassium carbonate (709 mg, 5.13 mmol) in acetone (15 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (547 mg, 55%). R_f (1:1 EtOAC:Hex): 0.77; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.82 (d, J = 8.7 Hz, 1H), 6.88 – 6.73 (m, 6H), 5.10 (s, 2H), 4.64 (hept, J = 6.2 Hz, 1H), 3.96 (q, J = 6.8 Hz, 2H), 3.93 (s,

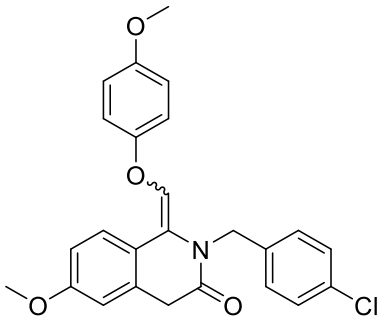
2H), 3.66 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H), 1.36 (d, J = 5.8 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 195.47, 171.76, 161.23, 153.58, 152.16, 138.27, 131.79, 126.25, 120.35, 115.80, 115.27, 113.05, 71.99, 70.15, 63.89, 51.93, 40.49, 21.88, 14.90. HRMS cal. for $C_{22}H_{27}O_6$, 387.18022 $[M + H]^+$; found 387.18023 $[M + H]^+$.



(E/Z)-2-(3-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4a). General procedure III was followed using compound **3a** (100 mg, 0.290 mmol), 3-chlorobenzylamine (43 μL, 0.35 mmol), tetraisopropoxytitanium (260 μL, 0.87 mmol), and sodium triacetoxyborohydride (185 mg, 0.871 mmol) in DCE (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a ~1:2 mixture of E/Z isomers and an orange oil (74 mg, 59%). HRMS calcd. for $C_{25}H_{23}O_4NCl$, 436.13101 $[M + H]^+$; found 436.13017 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.68 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.32 min).

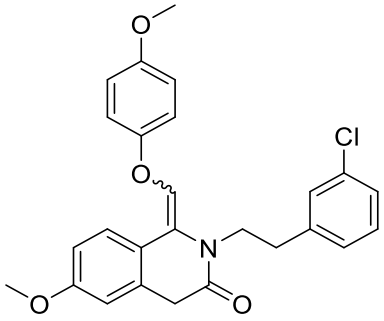


(E/Z)-2-(2-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,2-dihydroisoquinolin-3(4H)-one (4b). General procedure III was followed using compound **3a** (50 mg, 0.15 mmol), 2-chlorobenzylamine (21 μL, 0.17 mmol), tetraisopropoxytitanium (0.13 mL, 0.44 mmol), and sodium triacetoxyborohydride (92 mg, 0.44 mmol) in DCE (0.7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (39 mg, 62%). HRMS calcd. for $C_{25}H_{23}O_4NCl$, 436.13101 $[M + H]^+$; found 436.13005 $[M + H]^+$.

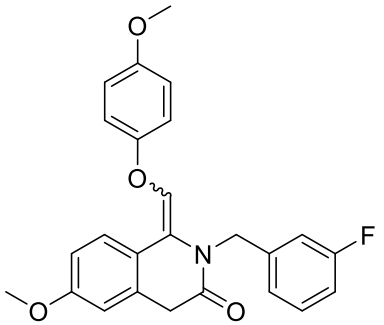


(E/Z)-2-(4-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,2-dihydroisoquinolin-3(4H)-one (4c). General procedure III was followed using compound **3a** (50 mg, 0.15 mmol), 4-chlorobezylamine (21 μL, 0.17 mmol), tetraisopropoxytitanium (0.13 mL, 0.44 mmol), and sodium triacetoxyborohydride (92 mg, 0.44 mmol) in DCE (0.7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange

oil (38 mg, 60%). HRMS calcd. for $C_{25}H_{23}O_4NCl$, 436.13101 $[M + H]^+$; found 436.13013 $[M + H]^+$.

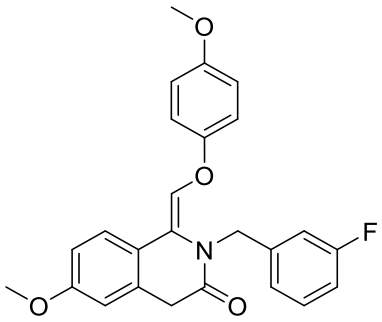


(E/Z)-2-(3-chlorophenethyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,2-dihydroisoquinolin-3(4H)-one (4d). General procedure III was followed using compound **3a** (100 mg, 0.290 mmol), 2-(3-chlorophenyl)-ethanamine (48 μL, 0.35 mmol), tetraisopropoxytitanium (0.26 mL, 0.87 mmol), and sodium triacetoxyborohydride (185 mg, 0.871 mmol) in DCE (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (22 mg, 17%). HRMS calcd. for $C_{26}H_{25}O_4NCl$, 450.14666 $[M + H]^+$; found 450.14673 $[M + H]^+$.

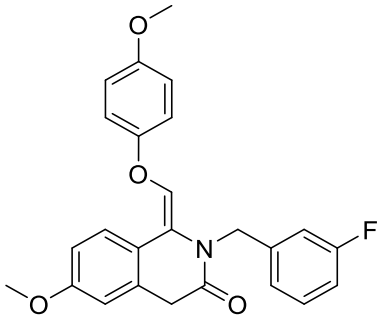


(E/Z)-2-(3-fluorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4e). General procedure III was followed using compound **3a** (300 mg, 0.871 mmol), 3-fluorobenzylamine (119 μL, 1.05 mmol), tetraisopropoxytitanium (793 μL,

2.61 mmol), and sodium triacetoxyborohydride (554 mg, 2.61 mmol) in DCE (4.4 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (250 mg, 68%). HRMS calcd. for $C_{25}H_{23}O_4NF$, 420.16056 $[M + H]^+$; found 420.15970 $[M + H]^+$.

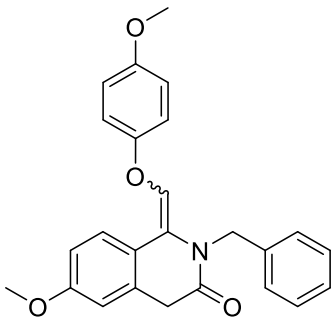


(Z)-2-(3-fluorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (1180-369). Compound **4e** (51 mg, 0.15 mmol) was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil (19 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 – 7.10 (m, 2H), 6.89 – 6.85 (m, 2H), 6.84 (s, 4H), 6.82 – 6.77 (m, 1H), 6.77 – 6.72 (m, 2H), 6.43 (s, 1H), 5.26 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.72 (s, 2H).

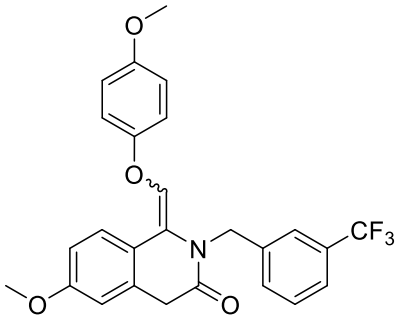


(Z)-2-(3-fluorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (1180-370). Compound **4e** (51 mg, 0.15 mmol) was purified via

flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as an impure (~70%) red oil (12 mg).

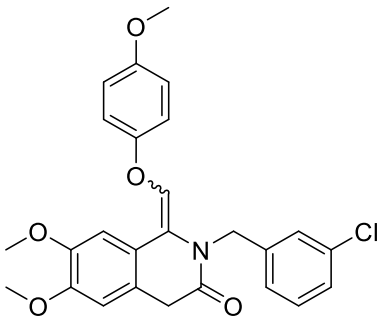


(E/Z)-2-benzyl-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4f). General procedure III was followed using compound **3a** (198 mg, 0.575 mmol), benzylamine (78 μL, 0.69 mmol), tetraisopropoxytitanium (523 μL, 1.73 mmol), and sodium triacetoxyborohydride (366 mg, 1.73 mmol) in DCE (2.9 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (0.10 g, 43%). HRMS calcd. for $C_{25}H_{24}O_4N$, 402.16998 $[M + H]^+$; found 402.17019 $[M + H]^+$.

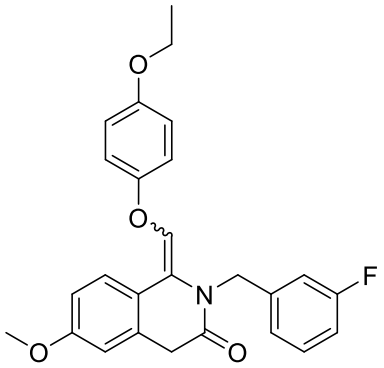


(E/Z)-6-methoxy-1-((4-methoxyphenoxy)methylene)-2-(3-(trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one (4g). General procedure III was followed using compound **3a** (75 mg, 0.22 mmol), 3-trifluoromethylbenzylamine (37 μL, 0.26 mmol), tetraisopropoxytitanium (198 μL, 0.653 mmol), and sodium triacetoxyborohydride (138 mg, 0.653 mmol) in DCE (1.1 mL). The

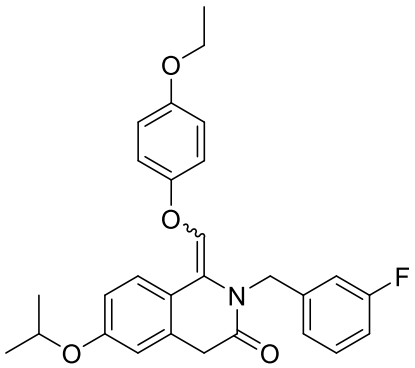
crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a yellow oil (58 mg, 57%). HRMS calcd. for $C_{26}H_{23}O_4NF_3$, 470.15737 $[M + H]^+$; found 470.15782 $[M + H]^+$.



(E/Z)-2-(3-chlorobenzyl)-6,7-dimethoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4h). General procedure III was followed using compound **3d** (200 mg, 0.534 mmol), 3-chlorobenzylamine (78 μL, 0.64 mmol), tetraisopropoxytitanium (486 μL, 1.60 mmol), and sodium triacetoxyborohydride (340 mg, 1.60 mmol) in DCE (2.7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a white solid (150 mg, 59%). HRMS calcd. for $C_{26}H_{25}O_5NCl$, 466.14158 $[M + H]^+$; found 466.14082 $[M + H]^+$.

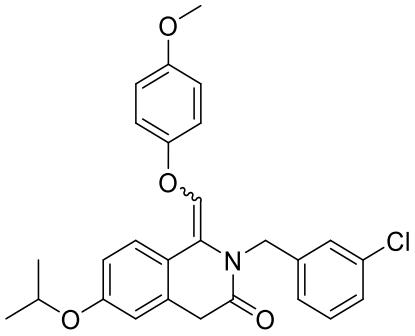


1-((4-ethoxyphenoxy)methylene)-2-(3-fluorobenzyl)-6-methoxy-1,4-dihydroisoquinolin-3(2H)-one (4i). General procedure III was followed using compound **3e** (75 mg, 0.21 mmol), 3-fluorobenzylamine (28 μL, 0.25 mmol), tetraisopropoxytitanium (0.19 mL, 0.63 mmol), and sodium triacetoxyborohydride (0.13 g, 0.63 mmol) in DCE (1.0 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a orange oil (40 mg, 44%). HRMS calcd. for $C_{26}H_{25}O_4NF$, 434.17621 $[M + H]^+$; found 434.17626 $[M + H]^+$.

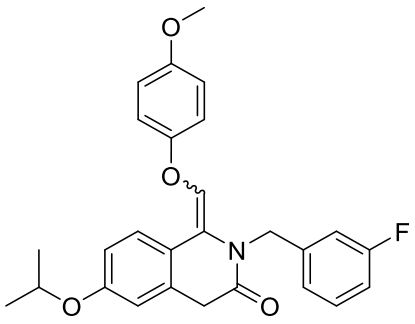


(E/Z)-1-((4-ethoxyphenoxy)methylene)-2-(3-fluorobenzyl)-6-isopropoxy-1,4-dihydroisoquinolin-3(2H)-one (4j). General procedure III was followed using compound **3f** (75 mg, 0.19 mmol), 3-fluorobenzylamine (27 μL, 0.23 mmol), tetraisopropoxytitanium (177 μL, 0.582 mmol), and sodium triacetoxyborohydride (123 mg, 0.582 mmol) in DCE (1.0 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35%

EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a clear oil (36 mg, 40%). HRMS calcd. for $C_{28}H_{29}O_4NF$, 462.20751 $[M + H]^+$; found 462.20740 $[M + H]^+$.

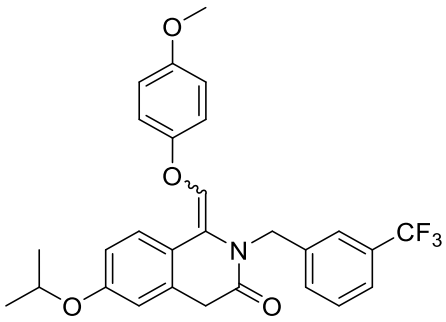


(E/Z)-2-(3-chlorobenzyl)-6-isopropoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4k). General procedure III was followed using compound **3b** (148 mg, 0.397 mmol), 3-chlorobenzylamine (58 μL, 0.48 mmol), tetraisopropoxytitanium (362 μL, 1.19 mmol), and sodium triacetoxyborohydride (253 mg, 1.19 mmol) in DCE (2.0 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (130 mg, 71%). HRMS calcd. for $C_{27}H_{27}O_4NCl$, 464.16231 $[M + H]^+$; found 464.16224 $[M + H]^+$.

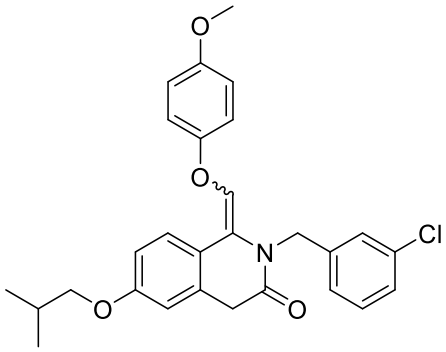


(E/Z)-2-(3-fluorobenzyl)-6-isopropoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4l). General procedure III was followed using compound **3b** (50 mg, 0.13 mmol), 3-fluorobenzylamine (18 μL, 0.16 mmol), tetraisopropoxytitanium (122 μL, 0.403 mmol), and sodium triacetoxyborohydride (85 mg, 0.40 mmol) in DCE (0.7 mL). The crude

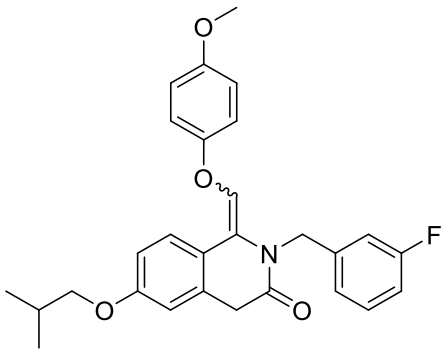
product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (35 mg, 58%). HRMS calcd. for $C_{27}H_{27}O_4NF$, 448.19186 $[M + H]^+$; found 448.19096 $[M + H]^+$.



(E/Z)-6-isopropoxy-1-((4-methoxyphenoxy)methylene)-2-(3-(trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one (4m). General procedure III was followed using compound **3b** (75 mg, 0.22 mmol), 3-(trifluoromethyl)benzylamine (37 μL, 0.26 mmol), tetraisopropoxytitanium (198 μL, 0.653 mmol), and sodium triacetoxyborohydride (138 mg, 0.653 mmol) in DCE (1.1 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a yellow oil (58 mg, 57%). HRMS calcd. for $C_{28}H_{29}O_4NF_3$, 500.20432 $[M + H]^+$; found 500.20464 $[M + H]^+$.

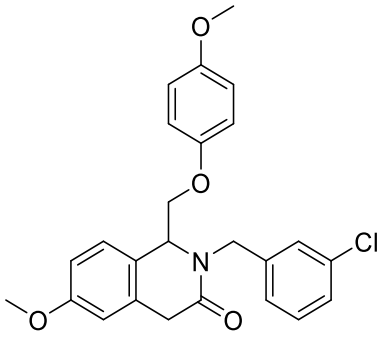


(E/Z)-2-(3-chlorobenzyl)-6-isobutoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4n). General procedure III was followed using compound **3c** (500 mg, 1.29 mmol), 3-chlorobenzylamine (190 μL, 1.55 mmol), tetraisopropoxytitanium (1.18 mL, 3.88 mmol), and sodium triacetoxyborohydride (823 mg, 3.88 mmol) in DCE (6.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-25% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (450 mg, 73%). HRMS calcd. for $C_{28}H_{29}O_4NCl$, 478.17796 $[M + H]^+$; found 478.17837 $[M + H]^+$.

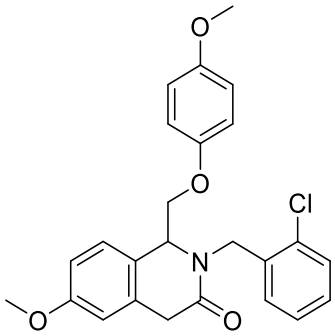


(E/Z)-2-(3-fluorobenzyl)-6-isobutoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4o). General procedure III was followed using compound **3c** (235 mg, 0.608 mmol), 3-fluorobenzylamine (83 μL, 0.73 mmol), tetraisopropoxytitanium (553 μL, 1.82 mmol), and sodium triacetoxyborohydride (387 mg, 1.82 mmol) in DCE (3.0 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35%

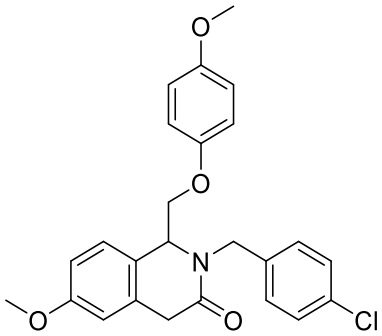
EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (0.16 g, 58%). HRMS calcd. for $C_{28}H_{29}O_4NF$, 462.20822 $[M + H]^+$; found 462.20798 $[M + H]^+$.



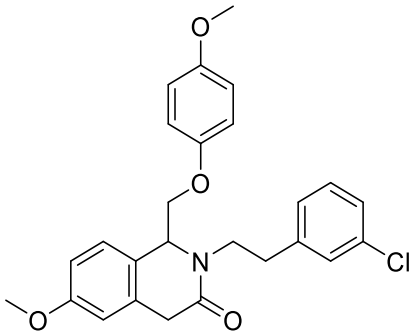
2-(3-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one (1180-297). General procedure IV-A was followed using compound **4a** (113 mg, 0.259 mmol) and platinum(IV) oxide (8.4 mg, 0.037 mmol) in ethanol (2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (63 mg, 56%). R_f (1:1 EtOAc:Hex): 0.59; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 – 7.11 (m, 3H), 7.09 – 7.02 (m, 2H), 6.82 – 6.67 (m, 6H), 5.44 (d, J = 15.5 Hz, 1H), 4.62 (t, J = 5.0 Hz, 1H), 4.37 (d, J = 15.5 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.94 (d, J = 19.1 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.66 (d, J = 19.2 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 169.64, 159.42, 154.21, 152.14, 139.15, 134.44, 134.11, 129.94, 127.85, 127.58, 127.06, 125.73, 124.55, 115.39, 114.64, 112.82, 112.33, 71.54, 59.90, 55.65, 55.33, 48.57, 37.63. HRMS calcd. for $C_{25}H_{25}O_4NCl$, 438.14666 $[M + H]^+$; found 438.14644 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.83 min).



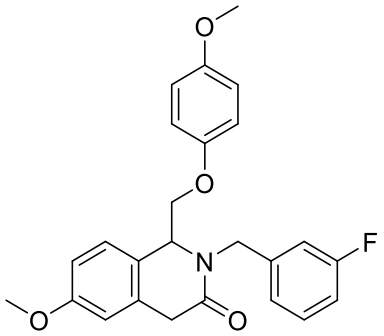
2-(2-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one (1180-302). General procedure IV-A was followed using compound **4b** (105 mg, 0.241 mmol) and platinum(IV) oxide (7.8 mg, 0.034 mmol) in ethanol (2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (49 mg, 46%). R_f (1:1 EtOAc:Hex): 0.65; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 (d, J = 7.7 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.13 – 7.06 (m, 3H), 6.83 – 6.68 (m, 6H), 5.45 (d, J = 16.2 Hz, 1H), 4.71 – 4.62 (m, 2H), 4.15 – 4.04 (m, 2H), 3.98 (d, J = 19.2 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.68 (d, J = 19.2 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 169.86, 159.42, 154.17, 152.25, 134.25, 133.31, 129.49, 128.47, 128.44, 127.12, 127.10, 124.71, 115.38, 114.61, 112.82, 112.33, 71.43, 60.51, 55.68, 55.35, 46.71, 37.72. HRMS calcd. for $C_{25}H_{25}O_4NCl$, 438.14666 $[M + H]^+$; found 438.14638 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.98 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.11 min).



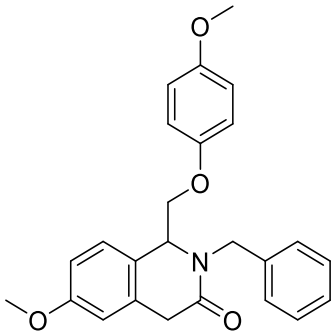
2-(4-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one (1180-307). General procedure IV-A was followed using compound **4c** (38 mg, 0.087 mmol) and platinum(IV) oxide (6.6 mg, 0.029 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (18 mg, 47%). Rf (1:1 EtOAc:Hex): 0.47; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.82 – 6.67 (m, 6H), 5.46 (d, J = 15.4 Hz, 1H), 4.60 (t, J = 5.1 Hz, 1H), 4.35 (d, J = 15.4 Hz, 1H), 4.09 – 3.97 (m, 2H), 3.93 (d, J = 19.2 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.66 (d, J = 19.2 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 169.60, 159.43, 154.21, 152.16, 135.47, 134.12, 133.14, 129.06, 128.77, 127.05, 124.59, 115.36, 114.63, 112.78, 112.33, 71.51, 59.74, 55.68, 55.34, 48.40, 37.65. HRMS calcd. for $C_{25}H_{25}O_4NCl$, 438.14666 $[M + H]^+$; found 438.14656 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.87 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.02 min).



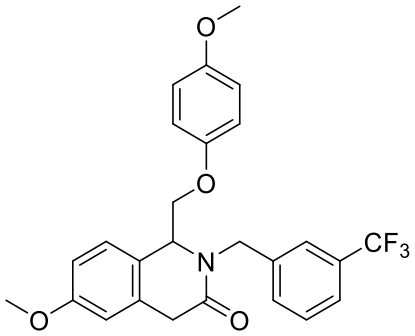
2-(3-chlorophenethyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one (1180-303). General procedure IV-A was followed using compound **4d** (100 mg, 0.290 mmol), 2-(3-chlorophenyl)-ethanamine (48 μL, 0.35 mmol), tetraisopropoxytitanium (260 μL, 0.87 mmol), and sodium triacetoxyborohydride (185 mg, 0.871 mmol) in DCE (1.5 mL) then platinum(IV) oxide (6.6 mg, 0.029 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (35 mg, 44%). R_f (1:1 EtOAc:Hex): 0.58; ^{1}H NMR (600 MHz, Chloroform-d) δ 7.22 – 7.09 (m, 3H), 7.01 (d, J = 7.4 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.81 – 6.67 (m, 6H), 4.38 – 4.29 (m, 2H), 4.00 – 3.90 (m, 2H), 3.81 (s, 3H), 3.80 (m, 1H), 3.73 (s, 3H), 3.57 (d, J = 19.1 Hz, 1H), 3.38 – 3.30 (m, 1H), 2.93 – 2.83 (m, 2H). ^{13}C NMR (151 MHz, cdcl3) δ 169.24, 159.40, 154.20, 152.35, 152.19, 141.19, 134.18, 134.10, 129.67, 128.97, 127.10, 126.48, 124.60, 115.38, 114.65, 112.71, 112.27, 71.52, 62.01, 55.66, 55.35, 49.04, 37.77, 33.86. HRMS calcd. for $C_{26}H_{27}O_4NCl$, 452.16231 $[M + H]^+$; found 452.16219 $[M + H]^+$. Purity was established to be 79% pure using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.44 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.18 min).



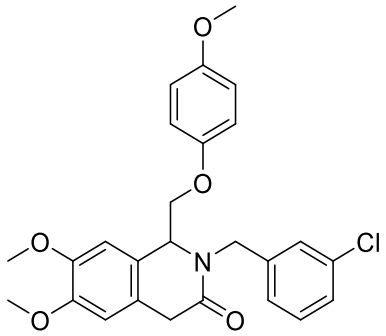
2-(3-fluorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-332). General procedure IV-B was followed using compound **4e** (44 mg, 0.11 mmol) and 10% Pd/C (17 mg, 0.016 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (11 mg, 25%). R_f (1:1 EtOAc:Hex): 0.47; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.24 – 7.19 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.91 (t, J = 10.1 Hz, 2H), 6.81 – 6.69 (m, 6H), 5.49 (d, J = 15.5 Hz, 1H), 4.63 (t, J = 5.1 Hz, 1H), 4.38 (d, J = 15.5 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.94 (d, J = 19.2 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.67 (d, J = 19.3 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 169.62, 163.02 (d, J = 246.5 Hz, ^1J), 159.48, 154.28, 152.22, 139.65 (d, J = 7.0 Hz, ^3J), 134.16, 130.18 (d, J = 8.2 Hz, ^3J), 127.10, 124.62, 123.18 (d, J = 2.8 Hz, ^4J), 115.44, 114.69, 114.57 (d, J = 21.9 Hz, ^2J), 114.33 (d, J = 21.2 Hz, ^2J), 112.87, 112.38, 71.61, 59.94, 55.72, 55.38, 48.64, 37.67. HRMS calcd. for $C_{25}H_{25}O_4NF$, 422.17621 $[M + H]^+$; found 422.17602 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.90 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.07 min).



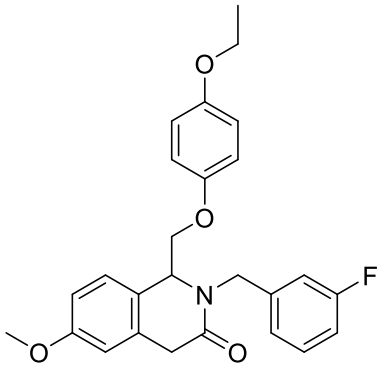
2-benzyl-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-329). General procedure IV-B was followed using compound **4f** (50 mg, 0.13 mmol) and 10% Pd/C (20 mg, 0.019 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (14 mg, 28%). R_f (1:1 EtOAc:Hex): 0.45; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.28 – 7.17 (m, 5H), 7.03 (d, J = 8.4 Hz, 1H), 6.80 – 6.68 (m, 6H), 5.52 (d, J = 15.3 Hz, 1H), 4.62 (t, J = 5.0 Hz, 1H), 4.37 (d, J = 15.3 Hz, 1H), 4.07 – 3.98 (m, 2H), 3.94 (d, J = 19.2 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.67 (d, J = 19.3 Hz, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 169.63, 159.40, 154.22, 152.33, 136.90, 134.30, 128.67, 127.71, 127.38, 127.12, 124.92, 115.48, 114.67, 112.74, 112.30, 71.45, 59.61, 55.72, 55.36, 48.85, 37.74. HRMS calcd. for $C_{25}H_{26}O_4N$, 404.18563 $[M + H]^+$; found 404.18552 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 3.66 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.29 min).



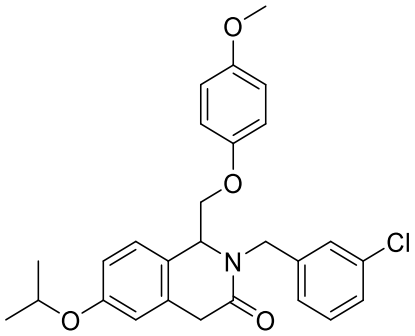
6-methoxy-1-((4-methoxyphenoxy)methyl)-2-(3-(trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-340). General procedure IV-B was followed using compound **41g** (58 mg, 0.12 mmol) and 10% Pd/C (20 mg, 0.019 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (41 mg, 70%). R_f (1:1 EtOAc:Hex): 0.50; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.51 – 7.45 (m, 2H), 7.36 (m, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.80 – 6.76 (m, 3H), 6.74 – 6.69 (m, 3H), 5.52 (d, J = 15.5 Hz, 1H), 4.63 (t, J = 5.6 Hz, 1H), 4.48 (d, J = 15.6 Hz, 1H), 4.09 – 4.01 (m, 2H), 3.95 (d, J = 19.2 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.68 (d, J = 19.2 Hz, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 169.76, 159.53, 154.31, 152.13, 138.16, 134.10, 130.90 (q, J = 32.1 Hz, ^2J), 130.86, 129.23, 127.06, 124.48, 124.48 (q, J = 3.8 Hz, ^3J), 124.49 (q, J = 3.8 Hz, ^3J), 123.97 (q, J = 272.3 Hz, ^1J), 115.40, 114.70, 112.90, 112.43, 71.65, 60.13, 55.70, 55.38, 48.88, 37.67. HRMS calcd. for $C_{26}H_{25}O_4NF_3$, 472.17302 $[M + H]^+$; found 472.17339 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.64 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.93 min).



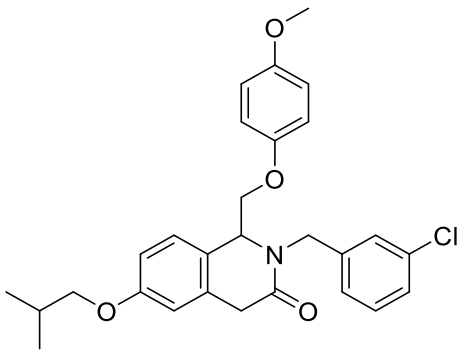
2-(3-chlorobenzyl)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-323). General procedure IV-A was followed using compound **4h** (136 mg, 0.292 mmol) and PtO_2 (17 mg, 0.041 mmol) in ethanol (2.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (30 mg, 22%). R_f (1:1 EtOAc:Hex): 0.28; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.24 – 7.16 (m, 3H), 7.12 – 7.06 (m, 1H), 6.82 – 6.63 (m, 6H), 5.49 (d, J = 15.5 Hz, 1H), 4.59 (t, J = 5.1 Hz, 1H), 4.37 (d, J = 15.5 Hz, 1H), 4.08 – 4.03 (m, 2H), 3.97 – 3.92 (m, 1H), 3.90 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.73 – 3.59 (m, 2H). ^{13}C NMR (75 MHz, cdcl3) δ 169.83, 154.27, 152.15, 148.99, 147.83, 139.16, 134.49, 129.99, 127.91, 127.62, 125.77, 124.72, 124.18, 115.39, 114.68, 110.20, 109.00, 71.50, 60.12, 56.09, 56.01, 55.70, 48.48, 36.88. HRMS calcd. for $C_{26}H_{27}O_5NCl$, 468.15723 $[M + H]^+$; found 468.15734 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.45 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 1.34 min).



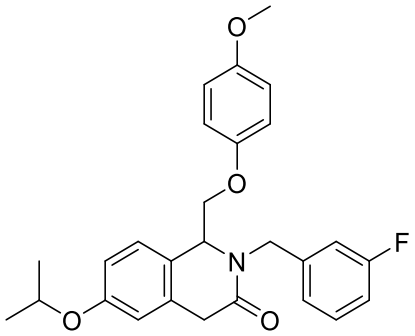
1-((4-ethoxyphenoxy)methyl)-2-(3-fluorobenzyl)-6-methoxy-1,4-dihydroisoquinolin-3(2H)-one (1180-339). General procedure IV-B was followed using compound **4i** (39 mg, 0.090 mmol) and 10% Pd/C (14 mg, 0.013 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (18 mg, 46%). R_f (1:1 EtOAc:Hex): 0.40; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.24 – 7.19 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.81 – 6.75 (m, 3H), 6.74 – 6.68 (m, 3H), 5.49 (d, J = 15.5 Hz, 1H), 4.63 (t, J = 5.1 Hz, 1H), 4.38 (d, J = 15.5 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.96 (q, J= 6.9 Hz, 2H), 3.94 (d, J = 19.2 Hz, 1H), 3.80 (s, 3H), 3.67 (d, J = 19.3 Hz, 1H), 1.38 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 169.61, 163.02 (d, J = 246.5 Hz, ^1J), 159.48, 153.61, 152.15, 139.67 (d, J = 6.9 Hz, ^3J), 134.17, 130.17 (d, J = 8.2 Hz, ^3J), 127.10, 124.64, 123.18 (d, J = 2.7 Hz, ^4J), 115.43, 114.57 (d, J = 21.6 Hz, ^2J), 114.32 (d, J = 21.1 Hz, ^2J), 112.86, 112.39, 71.59, 63.99, 59.95, 55.38, 48.64, 37.67, 14.90. HRMS calcd. for $C_{26}H_{26}O_4NFNa$, 458.17381 $[M + Na]^+$; found 458.17390 $[M + Na]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 3.14 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.54 min).



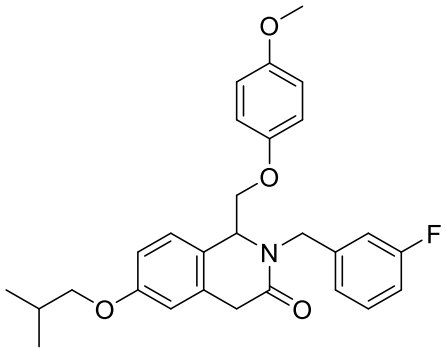
2-(3-chlorobenzyl)-6-isopropoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-327). General procedure IV-A was followed using compound **4k** (150 mg, 0.323 mmol) and PtO_2 (19 mg, 0.046 mmol) in ethanol (2.6 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as an orange oil. (15 mg, 10%). R_f (1:1 EtOAc:Hex): 0.59; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.22 – 7.15 (m, 3H), 7.09 – 7.05 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.81 – 6.69 (m, 6H), 5.46 (d, J = 15.4 Hz, 1H), 4.63 – 4.59 (m, 1H), 4.54 (hept, J = 6.1 Hz, 1H), 4.37 (d, J = 15.4 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.91 (d, J = 19.3 Hz, 1H), 3.75 (s, 3H), 3.64 (d, J = 19.3 Hz, 1H), 1.33 (d, J = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, cdcl3) δ 169.69, 157.82, 154.28, 152.21, 139.19, 134.49, 134.08, 129.95, 127.95, 127.61, 127.09, 125.81, 124.30, 115.44, 114.70, 114.42, 114.25, 71.68, 70.00, 59.93, 55.72, 48.64, 37.66, 22.05. HRMS calcd. for $C_{27}H_{29}O_4NCl$, 466.17796 $[M + H]^+$; found 466.17791 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 90-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.56 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 3.00 min).



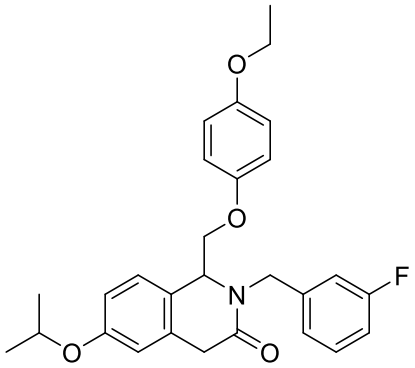
2-(3-chlorobenzyl)-6-isobutoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-324). General procedure IV-A was followed using compound **4n** (200 mg, 0.418 mmol) and PtO_2 (24 mg, 0.059 mmol) in ethanol (3.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a red foam. (82 mg, 54%). R_f (1:1 EtOAc:Hex): 0.76; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 – 7.14 (m, 3H), 7.09 – 7.03 (m, 2H), 6.81 – 6.69 (m, 6H), 5.46 (d, J = 15.5 Hz, 1H), 4.62 (t, J = 5.0 Hz, 1H), 4.37 (d, J = 15.5 Hz, 1H), 4.09 – 3.99 (m, 2H), 3.94 (d, J = 19.3 Hz, 1H), 3.75 (s, 3H), 3.71 (d, J = 6.5 Hz, 2H), 3.66 (d, J = 19.3 Hz, 1H), 2.08 (hept, J = 6.9 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, cdcl3) δ 169.69, 159.13, 154.22, 152.16, 139.16, 134.45, 134.02, 129.94, 127.87, 127.57, 127.00, 125.73, 124.27, 115.39, 114.65, 113.28, 112.96, 74.47, 71.59, 59.89, 55.67, 48.58, 37.62, 28.24, 19.24. HRMS calcd. for $C_{28}H_{31}O_4NCl$, 480.19361 $[M + H]^+$; found 480.19404 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.05 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.86 min).



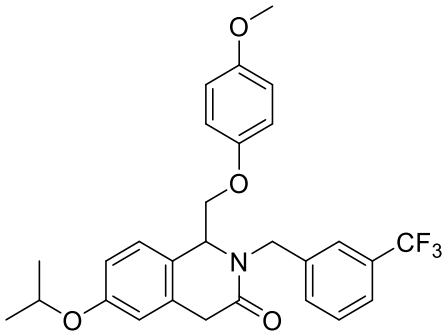
2-(3-fluorobenzyl)-6-isopropoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-349). General procedure IV-B was followed using compound **4l** (104 mg, 0.232 mmol) and 10% Pd/C (37 mg, 0.035 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (67 mg, 64%). R_f (1:1 EtOAc:Hex): 0.57; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.19 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.81 – 6.69 (m, 6H), 5.49 (d, J = 15.5 Hz, 1H), 4.65 – 4.60 (m, 1H), 4.54 (hept, J = 6.0 Hz, 1H), 4.39 (d, J = 15.5 Hz, 1H), 4.10 – 3.99 (m, 2H), 3.92 (d, J = 19.2 Hz, 1H), 3.75 (s, 3H), 3.65 (d, J = 19.3 Hz, 1H), 1.34 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.68, 162.98 (d, J = 246.5 Hz, ^1J), 157.77, 154.20, 152.19, 139.65 (d, J = 7.0 Hz, ^3J), 134.07, 130.14 (d, J = 8.2 Hz, ^3J), 127.08, 124.26, 123.17 (d, J = 2.8 Hz, ^4J), 115.38, 114.63, 114.55 (d, J = 21.6 Hz, ^2J), 114.35, 114.28 (d, J = 21.3 Hz, ^2J), 114.18, 71.59, 69.93, 59.91, 55.67, 48.63, 37.63, 22.03. HRMS calcd. for $C_{27}H_{29}O_4NF$, 450.20751 $[M + H]^+$; found 450.20731 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 90-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.54 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 1.01 min).



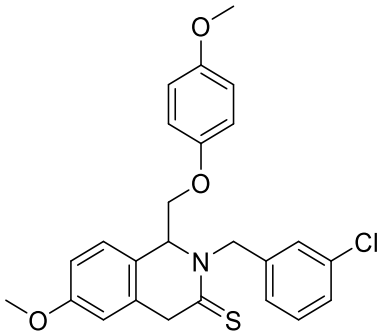
2-(3-fluorobenzyl)-6-isobutoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-350). General procedure IV-B was followed using compound **4o** (163 mg, 0.353 mmol) and 10% Pd/C (56 mg, 0.053 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (90 mg, 55%). R_f (1:1 EtOAc:Hex): 0.62; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.18 (m, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.82 – 6.69 (m, 6H), 5.50 (d, J = 15.5 Hz, 1H), 4.66 – 4.60 (m, 1H), 4.39 (d, J = 15.5 Hz, 1H), 4.10 – 3.99 (m, 2H), 3.93 (d, J = 19.2 Hz, 1H), 3.75 (s, 3H), 3.71 (d, J = 6.5 Hz, 2H), 3.66 (d, J = 19.3 Hz, 1H), 2.07 (hept, J = 6.7 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.68, 162.98 (d, J = 246.4 Hz, ^1J), 159.14, 154.20, 152.19, 139.64 (d, J = 7.0 Hz, ^3J), 134.03, 130.15 (d, J = 8.2 Hz, ^3J), 127.01, 124.28, 123.13 (d, J = 2.8 Hz, ^4J), 115.38, 114.63, 114.52 (d, J = 22.1 Hz, ^2J), 114.29 (d, J = 21.2 Hz, ^2J), 113.28, 112.95, 74.47, 71.57, 59.90, 55.67, 48.59, 37.62, 28.24, 19.24. HRMS calcd. for $C_{27}H_{29}O_4NF$, 450.20751 $[M + H]^+$; found 450.20731 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 90-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.20 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 1.21 min).



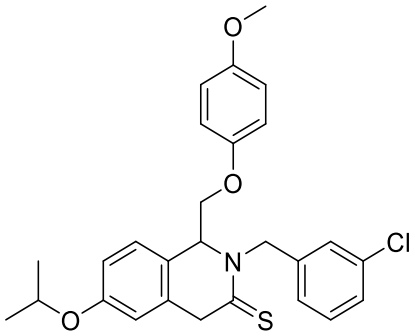
1-((4-ethoxyphenoxy)methyl)-2-(3-fluorobenzyl)-6-isopropoxy-1,4-dihydroisoquinolin-3(2H)-one (1180-356). General procedure IV-B was followed using compound **4j** (36 mg, 0.078 mmol) and 10% Pd/C (12 mg, 0.012 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as an orange oil. (20 mg, 55%). R_f (1:1 EtOAc:Hex): 0.66; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.18 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.81 – 6.64 (m, 6H), 5.49 (d, J = 15.5 Hz, 1H), 4.64 – 4.59 (m, 1H), 4.54 (hept, J = 6.1 Hz, 1H), 4.38 (d, J = 15.5 Hz, 1H), 4.09 – 4.00 (m, 2H), 3.97 (q, J = 6.9 Hz, 2H), 3.91 (d, J = 19.4 Hz, 1H), 3.64 (d, J = 19.3 Hz, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.33 (d, J = 6.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-d) δ 169.67, 162.98 (d, J = 246.4 Hz, ^1J), 157.76, 153.53, 152.10, 139.63, (d, J = 6.9 Hz, ^3J), 134.05, 130.13 (d, J = 8.3 Hz, ^3J), 127.07, 124.25, 123.17 (d, J = 2.8 Hz, ^4J), 115.36, 115.34, 114.55 (d, J = 21.7 Hz, ^2J), 114.35, 114.30 (d, J = 21.4 Hz, ^2J), 114.16, 71.56, 69.93, 63.94, 59.88, 48.60, 37.63, 22.00, 14.88. HRMS calcd. for $C_{28}H_{31}O_4NF$, 464.22316 $[M + H]^+$; found 464.22318 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 90-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.40 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 1.27 min).



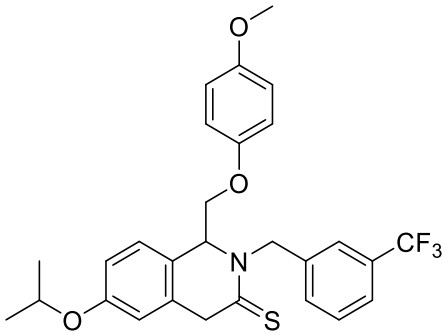
6-isopropoxy-1-((4-methoxyphenoxy)methyl)-2-(3-(trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-372). General procedure IV-B was followed using compound **4m** (45 mg, 0.090 mmol) and 10% Pd/C (14 mg, 0.014 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (32 mg, 71%). R_f (1:1 EtOAc:Hex): 0.65; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.51 – 7.44 (m, 2H), 7.39 – 7.34 (m, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.82 – 6.77 (m, 2H), 6.76 – 6.73 (m, 1H), 6.73 – 6.66 (m, 3H), 5.52 (d, J = 15.6 Hz, 1H), 4.65 – 4.59 (m, 1H), 4.58 – 4.51 (m, 1H), 4.48 (d, J = 15.5 Hz, 1H), 4.10 – 4.00 (m, 2H), 3.93 (d, J = 19.2 Hz, 1H), 3.75 (s, 3H), 3.66 (d, J = 19.3 Hz, 1H), 1.33 (d, J = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, cdcl3) δ 169.80, 157.86, 154.29, 152.14, 138.19, 134.04, 130.89, 130.89 (q, J = 32.0 Hz, ^2J), 129.22, 127.06, 124.50 (q, J = 3.8 Hz, ^3J), 124.27 (q, J = 3.9 Hz, ^3J), 124.19, 123.98 (q, J = 272.5 Hz, ^1J), 115.39, 114.69, 114.46, 114.31, 71.69, 70.01, 60.14, 55.71, 48.91, 37.67, 22.02. HRMS calcd. for $C_{28}H_{29}O_4NF_3$, 500.20432 $[M + H]^+$; found 500.20333 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 3.54 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 1.05 min).



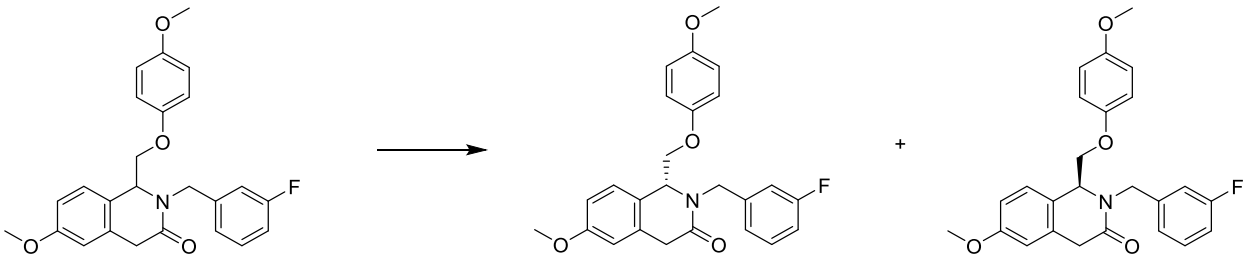
2-(3-chlorobenzyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2-dihydroisoquinoline-3(4H)-thione (1180-299). General procedure V was followed using compound **1180-297** (58 mg, 0.13 mmol) and Lawesson's Reagent (80 mg, 0.20 mmol) in toluene (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-40% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (11 mg, 18%). R_f (1:1 EtOAc:Hex): 0.77; ^{1}H NMR (600 MHz, Chloroform-d) δ 7.24 – 7.15 (m, 3H), 7.06 – 7.01 (m, 2H), 6.83 – 6.77 (m, 3H), 6.76 – 6.71 (m, 3H), 6.49 (d, J = 15.2 Hz, 1H), 4.91 (dd, J = 6.9, 4.7 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.53 (d, J = 19.6 Hz, 1H), 4.28 (d, J = 19.6 Hz, 1H), 4.11 – 4.03 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 199.43, 159.91, 154.43, 151.83, 137.15, 134.57, 133.42, 130.05, 127.90, 127.74, 126.65, 125.47, 123.14, 115.45, 114.72, 113.30, 111.58, 70.64, 62.71, 56.22, 55.69, 55.39, 47.73. HRMS calcd. HRMS calcd. for $C_{25}H_{25}O_3NClS$, 454.12382 $[M + H]^+$; found 454.12380 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.74 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 2.85 min).



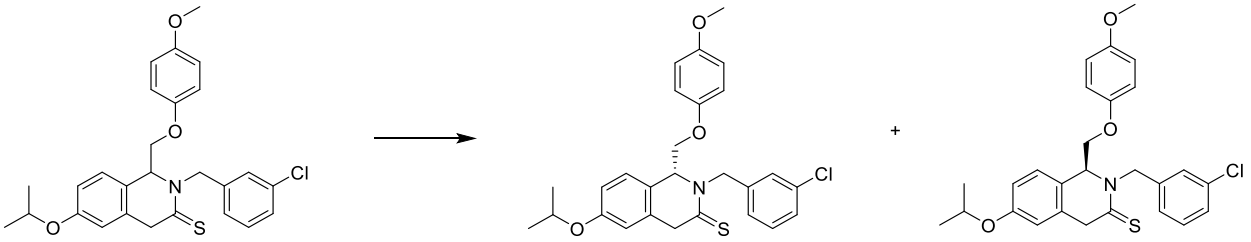
2-(3-chlorobenzyl)-6-isopropoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinoline-3(2H)-thione (1180-348). General procedure V was followed using compound **1180-327** (102 mg, 0.219 mmol) and Lawesson's Reagent (133 mg, 0.328 mmol) in toluene (2.2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-15% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (39 mg, 37%). R_f (1:1 EtOAc:Hex): 0.84; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.26 – 7.17 (m, 3H), 7.07 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.83 – 6.73 (m, 6H), 6.51 (d, J = 15.3 Hz, 1H), 4.95 – 4.89 (m, 1H), 4.84 (d, J = 15.3 Hz, 1H), 4.60 – 4.50 (m, 2H), 4.29 (d, J = 19.6 Hz, 1H), 4.12 – 4.04 (m, 2H), 3.78 (s, 4H), 1.36 (d, J = 6.1 Hz, 6H).^{13}C NMR (126 MHz, cdcl3) δ 199.53, 158.31, 154.47, 151.89, 137.24, 134.59, 133.39, 130.08, 127.92, 127.81, 126.69, 125.55, 122.86, 115.50, 114.87, 114.77, 113.42, 70.75, 70.07, 62.77, 56.28, 55.73, 47.77, 22.06. HRMS calcd. for $C_{27}H_{29}O_3NClS$, 482.15563 $[M + H]^+$; found 482.15563 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.91 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.83 min).



6-isopropoxy-1-((4-methoxyphenoxy)methyl)-2-(3-(trifluoromethyl)benzyl)-1,4-dihydroisoquinoline-3(2H)-thione (1180-396). General procedure V was followed using compound **1180-372** (57 mg, 0.11 mmol) and Lawesson's Reagent (69 mg, 0.17 mmol) in toluene (1.1 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-20% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (30 mg, 51%). R_f (1:1 EtOAc:Hex): 0.68; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.50 (d, J = 7.4 Hz, 1H), 7.44 (s, 1H), 7.40 – 7.30 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.79 – 6.71 (m, 4H), 6.55 (d, J = 15.4 Hz, 1H), 4.96 – 4.88 (m, 2H), 4.60 – 4.48 (m, 2H), 4.28 (d, J = 19.6 Hz, 1H), 4.15 – 4.03 (m, 2H), 3.76 (s, 3H), 1.34 (d, J = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, cdcl3) δ 199.71, 158.36, 154.50, 151.84, 136.24, 133.38, 131.03 (q, J = 32.2 Hz, ^2J), 130.54, 129.32, 126.63, 124.52 (q, J = 3.9 Hz, ^3J), 124.40 (q, J = 3.8 Hz, ^3J), 123.89 (q, J = 272.4 Hz, ^1J), 122.76, 115.47, 114.91, 114.78, 113.53, 70.72, 70.11, 63.02, 56.47, 55.71, 47.79, 22.02. HRMS calcd. for $C_{28}H_{29}O_3NF3S$, 516.18148 $[M + H]^+$; found 516.18108 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.86 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.77 min).

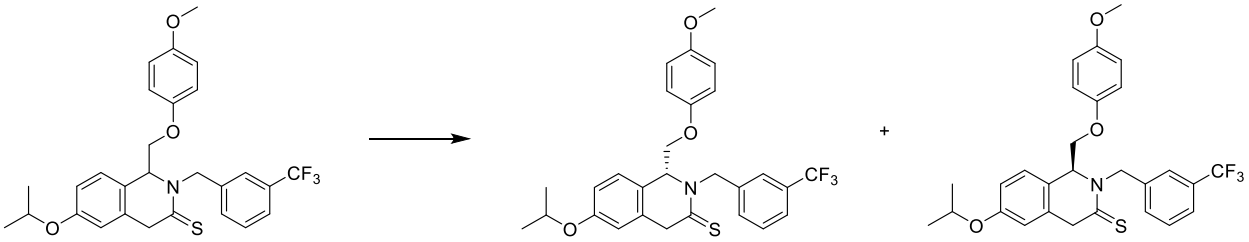


*Separation of **1180-332** Enantiomers*. Semipreparative separation of **1180-332** enantiomers from racemic **1180-332** (0.020 g) was done using a ChiralPak AD-H (30 mm × 250 mm) with the following conditions: 20 mL/min flow rate, 10 mL injection volume (2 mg/1 mL), 85% hexanes/15% IPA over 90 min to afford ***S*-(−)-1180-332**, t_R 54.4 min; ***R*-(+)-1180-332**, t_R 75.3 min. The enantiomeric excess (ee) was determined using an Agilent pump on a ChiralPak AD-H column (4.6 mm × 150 mm, 5 μm) with the following conditions: 1 mL/min flow rate, 10 μL injection volume, 85% hexanes/15% IPA. *S*-(−)-**1180-332**: t_R 17.8 min; >99% ee; [α]D20 = −24 (c 0.10, dry $CHCl_3$). *R*-(+)-**1180-332**: t_R 24.5 min, >99% ee; [α]D20 = +23 (c 0.10, dry $CHCl_3$). The proton spectrum for each enantiomer was identical to that of the racemic mixture.

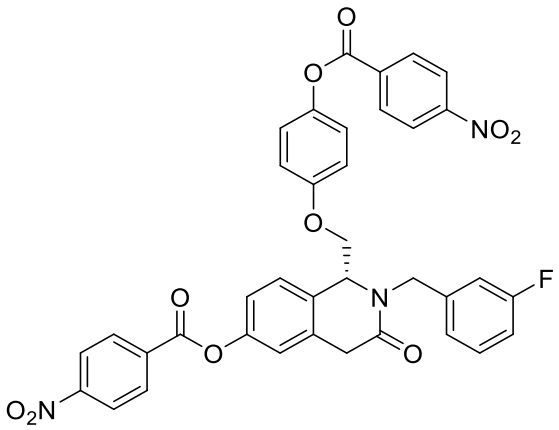


*Separation of **1180-348** Enantiomers*. Semipreparative separation of **1180-348** enantiomers from racemic **1180-348** (0.020 g) was done using a ChiralPak AD-H (30 mm × 250 mm) with the following conditions: 20 mL/min flow rate, 10 mL injection volume (2 mg/1 mL), 95% hexanes/5% IPA over 90 min to afford ***S*-(−)-1180-348**, t_R 47.9 min; ***R*-(+)-1180-348**, t_R 65.0 min. The enantiomeric excess (ee) was determined using an Agilent pump on a ChiralPak AD-H column (4.6 mm × 150 mm, 5 μm) with the following conditions: 1 mL/min flow rate, 10 μL injection volume, 95% hexanes/5% IPA. ***S*-(−)-1180-348**: t_R 14.6 min; >99% ee; [α]D20 = −51 (c 0.10, dry

$CHCl_3$). ***R*-(+)-1180-348**: t_R 19.6 min, >99% ee; [α]D20 = +50 (c 0.10, dry $CHCl_3$). The proton spectrum for each enantiomer was identical to that of the racemic mixture.



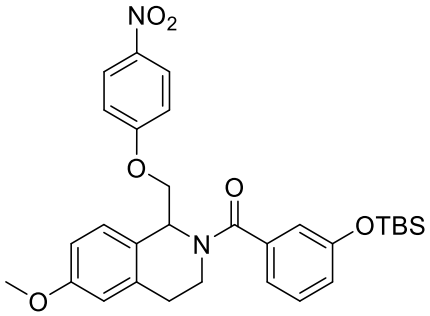
*Separation of **1180-396** Enantiomers*. Semipreparative separation of **1180-396** enantiomers from racemic **1180-396** (0.020 g) was done using a ChiralPak AD-H (30 mm × 250 mm) with the following conditions: 20 mL/min flow rate, 10 mL injection volume (2 mg/1 mL), 95% hexanes/5% IPA over 60 min to afford ***R*-(+)-1180-396**, t_R 29.3 min; ***S*-(−)-1180-396**, t_R 44.6 min. The enantiomeric excess (ee) was determined using an Agilent pump on a ChiralPak AD-H column (4.6 mm × 150 mm, 5 μm) with the following conditions: 1 mL/min flow rate, 10 μL injection volume, 95% hexanes/5% IPA. ***R*-(+)-1180-396**: t_R 17.8 min; >99% ee; [α]D20 = +14 (c 0.10, dry $CHCl_3$). ***S*-(—)-1180-396**: t_R 25.2 min, >99% ee; [α]D20 = -15 (c 0.10, dry $CHCl_3$). The proton spectrum for each enantiomer was identical to that of the racemic mixture.



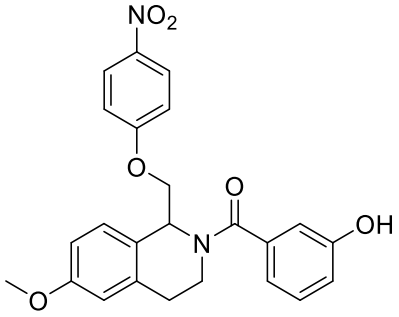
(*R*)-2-(3-fluorobenzyl)-1-((4-((4-nitrobenzoyl)oxy)phenoxy)methyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl 4-nitrobenzoate (1180-434). Compound ***R*-(+)-1180-332** (31 mg,

0.074 mmol) was dissolved in DCM (2 mL) and cooled to 0 ^{o}C before 1 M boron tribromide in DCM (0.26 mL, 0.26 mmol, 3.5 equiv) was added. The reaction mixture was then stirred at 0 ^{o}C for 1 hour before being warmed to room temperature and stirred an additional hour. After completion, the reaction mixture was cooled to 0 ^{o}C, diluted with DCM, and quenched with water. The organic layer was then extracted with DCM, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a clear oil that was carried forward without further characterization. (29 mg, quant.). The crude material (29 mg, 0.074 mmol, 1 equiv) was dissolved in DCM (1.2 mL) and triethylamine (41 µL, 0.30 mmol, 4 equiv) was added followed by 4-nitrolbenzoyl chloride (34 mg, 0.18 mmol, 2.5 equiv). The reaction mixture was stirred for 1 hour at room temperature. Upon reaction completion, the mixture was diluted with DCM and quenched with 1 M HCl. The organic layer was then extracted with DCM, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow foam. (46 mg, 90%). R_f (1:1 EtOAc:Hex): 0.50; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.37 (s, 4H), 8.35 (s, 4H), 7.28 – 7.22 (m, 2H), 7.16 – 7.10 (m, 4H), 7.02 (d, J = 7.8 Hz, 1H), 7.00 – 6.92 (m, 2H), 6.88 – 6.81 (m, 2H), 5.48 (d, J = 15.4 Hz, 1H), 4.77 (t, J = 4.8 Hz, 1H), 4.44 (d, J = 15.4 Hz, 1H), 4.23 – 4.13 (m, 2H), 4.04 (d, J = 19.4 Hz, 1H), 3.78 (d, J = 19.6 Hz, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 169.11, 163.51, 163.20, 163.05 (d, J = 247.0 Hz, ^{1}J), 155.94, 151.02, 150.90, 150.34, 144.65, 139.22 (d, J = 6.9 Hz, ^{3}J), 134.86, 134.70, 134.55, 131.32, 131.24, 130.48, 130.37 (d, J = 8.3 Hz, ^{3}J), 127.38, 123.78, 123.70, 123.30 (d, J = 3.0 Hz, ^{4}J), 122.45, 120.57, 120.09, 115.30, 114.81 (d, J = 21.9 Hz, ^{2}J), 114.64 (d, J = 21.0 Hz, ^{2}J), 70.89, 59.98, 48.65, 37.35. HRMS calcd. for $C_{37}H_{27}O_{10}N_3F$, 692.16750, $[M + H]^+$; found 692.16781 [M

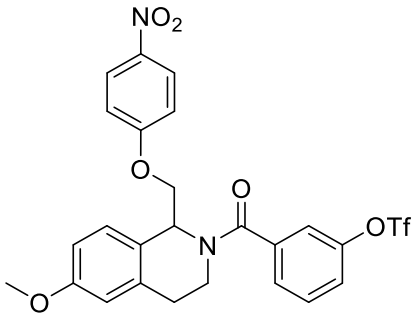
+ H]$^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 µm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.31 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.65 min).



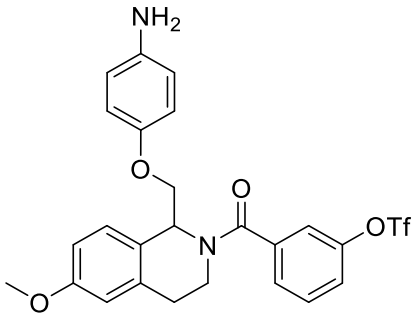
(3-((tert-butyldimethylsilyl)oxy)phenyl)(6-methoxy-1-((4-nitrophenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (6): General procedure VI was followed using compound **5** (0.54 g, 1.7 mmol), EDCI (0.32 g, 2.1 mmol), DMAP (0.25 g, 2.1 mmol), and 3-((tert-butyldimethylsilyl)oxy)benzoic acid (0.71 g, 1.9 mmol) in DCM (70 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a white foam (0.53 g, 56%). R_f (1:1 EtOAC:Hex): 0.82; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.22 – 8.14 (m, 2H), 7.05 – 6.66 (m, 9H), 6.00 (t, J = 5.1 Hz, 1H), 5.34 – 5.24 (m, 0.5H), 4.95 – 4.82 (m, 0.5H), 4.48 (d, J = 5.3 Hz, 2H), 3.81 (s, 3H), 3.67 – 3.54 (m, 1H), 3.31 – 3.10 (m, 1.5H), 2.99 – 2.73 (m, 2.5H), 0.97 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (75 MHz, cdcl3) δ 171.17, 170.87, 163.58, 158.71, 155.81, 141.70, 137.39, 135.72, 129.91, 128.53, 125.93, 124.67, 121.47, 119.34, 118.15, 114.67, 114.40, 113.64, 112.95, 70.80, 60.40, 55.29, 51.18, 42.79, 35.29, 29.75, 25.60, 21.06, 18.15, 14.20, -4.41. HRMS calcd. For $C_{30}H_{37}O_6N_2Si$, 549.24154 [M + H]$^+$; found 549.24163 [M + H]$^+$.



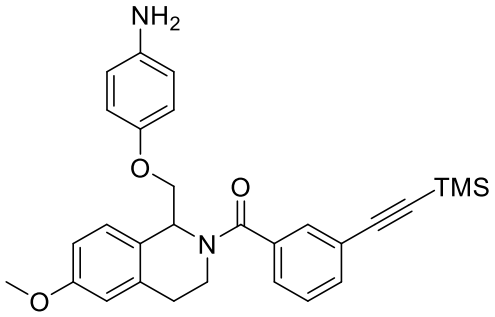
(3-hydroxyphenyl)(6-methoxy-1-((4-nitrophenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (7): Compound **6** (0.53 g, 0.97 mmol) was dissolved in THF (6 mL) and cooled to 0°C before 1 M tetrabutylammonium fluoride in THF (1.93 mL, 1.93 mmol) was added and allowed to react at room temperature for 1 hour. The reaction mixture was then quenched with 1 M HCl, the organic phase was extracted with EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated to give the title compound as a white foam (0.41 g, 97%). R_f (1:1 EtOAC:Hex): 0.27; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (d, J = 9.2 Hz, 2H), 8.04 (d, J = 9.1 Hz, 1H), 7.24 – 7.05 (m, 3H), 6.97 – 6.87 (m, 3H), 6.83 – 6.79 (m, 6H), 6.77 – 6.73 (m, 1H), 6.70 – 6.66 (m, 1H), 6.00 (t, J = 5.4 Hz, 1H), 5.35 (dd, J = 9.1, 3.7 Hz, 0.5H), 4.84 (dd, J = 13.2, 5.8 Hz, 0.5H), 4.43 (d, J = 5.6 Hz, 1H), 3.78 (s, 3H), 3.64 – 3.52 (m, 1H), 3.34 – 3.06 (m, 1.5H), 2.90 (td, J = 14.6, 12.1, 6.3 Hz, 1H), 2.74 (d, J = 16.3 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 176.57, 172.50, 171.89, 171.50, 163.44, 159.16, 158.74, 157.01, 141.64, 136.28, 135.53, 129.83, 128.45, 125.88, 125.83, 124.18, 117.92, 117.51, 117.41, 114.63, 114.33, 114.05, 113.89, 113.67, 113.01, 112.94, 70.61, 69.65, 60.53, 56.58, 55.32, 55.28, 51.40, 42.69, 35.60, 29.59, 28.34, 25.58, 21.05, 20.77, 17.94, 14.14, -3.70. HRMS calcd. For $C_{24}H_{23}O_6N_2$, 435.15506 $[M + H]^+$; found 435.15509 $[M + H]^+$.



3-(6-methoxy-1-((4-nitrophenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl trifluoromethanesulfonate (8): Compound **7** (0.41 g, 0.93 mmol) was dissolved in DCM (3.5 mL) and pyridine (0.15 mL) was added before the solution was brought to 0^oC and trifluoromethanesulfonic anhydride (0.19 mL, 1.1 mmol) was added. This mixture was allowed to warm to room temperature and reacted for 30 minutes. The reaction was then diluted with DCM, quenched with 1 M HCl, washed with saturated $NaHCO_3$, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a clear oil (0.39 g, 74%). R_f (1:1 EtOAC:Hex): 0.52; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.19 (d, J = 9.0 Hz, 2H), 7.60 – 7.30 (m, 4H), 7.03 – 6.70 (m, 5H), 5.99 (t, J = 5.0 Hz, 0.5H), 5.27 – 5.18 (m, 0.5H), 4.87 (dd, J = 12.3, 5.0 Hz, 0.5H), 4.48 (d, J = 5.2 Hz, 1H), 3.81 (s, 3H), 3.78 – 3.60 (m, 1H), 3.37 – 3.11 (m, 1H), 2.98 – 2.77 (m, 2H). ^{13}C NMR (101 MHz, cdcl3) δ 187.01, 163.39, 158.84, 149.28, 138.32, 137.29, 136.31, 135.32, 130.89, 128.46, 126.73, 125.95, 124.18, 122.71, 119.93, 114.61, 114.34, 114.19, 113.66, 113.17, 70.68, 56.66, 55.31, 51.55, 42.89, 35.34, 29.54, 28.13. HRMS calcd. For $C_{25}H_{22}O_8N_2F_3S$, 567.10435 $[M + H]^+$; found 567.10435 $[M + H]^+$.

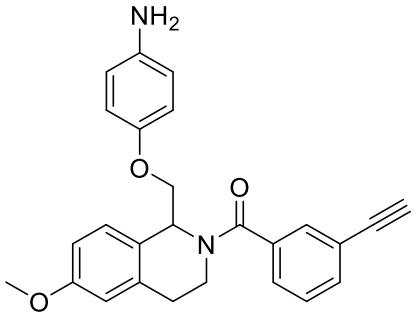


3-(1-((4-aminophenoxy)methyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl trifluoromethanesulfonate (9): Compound **8** (0.39 g, 0.69 mmol) was dissolved in ethanol (10 mL) and 10% Pd/C (0.11 g, 0.10 mmol) was added and the mixture was hydrogenated at 40 psi for 1 hour. The reaction mixture was filtered through a pad of celite, washing with methanol, and concentrated *in vacuo*. The crude product was confirmed via LCMS and carried forward without further purification.

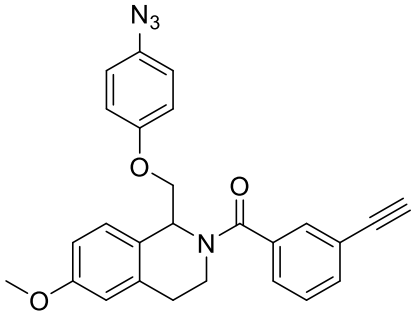


(1-((4-aminophenoxy)methyl)-6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-((trimethylsilyl)ethynyl)phenyl)methanone (10): Compound **9** (0.30 g, 0.56 mmol), bis(triphenylphospine)palladium(II) dichloride (18 mg, 0.027 mmol) and copper(I) iodide (10. mg, 0.055 mmol) were charged to a 10 mL microwave vial. The vial was capped, purged with argon and evacuated three times, and triethylamine (2.30 mL, 16.5 mmol), ethynyltrimethylsilane (70. mg, 0.72 mmol), and THF (3 mL) were added. The mixture was then reacted at room temperature overnight. Upon completion, the reaction was cooled to room temperature, filtered through a pad

of celite washing with EtOAc, and concentrated *in vacuo*. The crude product was confirmed via LCMS and carried forward without further purification.

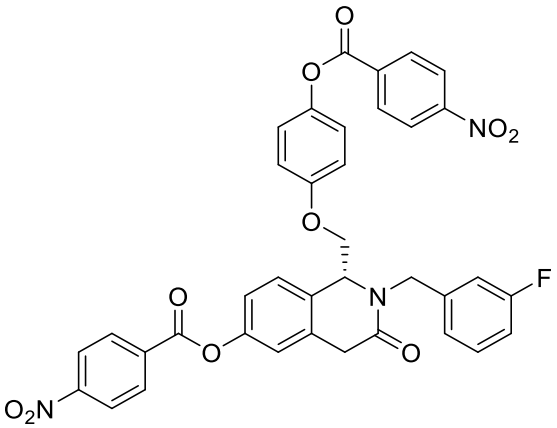


(1-((4-aminophenoxy)methyl)-6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-ethynylphenyl)methanone (11): To compound **10** (0.22 g, 0.45 mmol) dissolved in DCM (3.5 mL) was added potassium carbonate (0.20 g, 1.5 mmol) and MeOH (3.5 mL) and the solution was allowed to react at room temperature for 1 hour. The reaction mixture was then quenched with water, the organic phased extracted into DCM, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was a yellow oil and was purified via flash column chromatography (ISCO, Redisep 12 g column, 1-2% MeOH/DCM gradient) to afford the title compound as a clear oil (16 mg, 5% over 3 steps). R_f (1:1 EtOAC:Hex): 0.45; ^{1}H 1H NMR (400 MHz, Chloroform-d) δ 7.73 – 7.30 (m, 4H), 7.23 (d, J = 8.5 Hz, 1H), 6.94 – 6.58 (m, 6H), 5.97 (t, J = 4.9 Hz, 0.5H), 5.11 (dd, J = 9.4, 3.4 Hz, 0.5H), 4.86 (dd, J = 12.7, 5.6 Hz, 0.5H), 3.79 (s, 3H), 3.44 (s, 2H), 3.32 – 3.13 (m, 1H), 3.10 (d, J = 9.5 Hz, 1H), 2.96 – 2.70 (m, 2H).



(1-((4-azidophenoxy)methyl)-6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-ethynylphenyl)methanone (1180-292): Compound **11** (16 mg, 0.040 mmol) was dissolved in EtOAc (133 µL) and water (16 µL) and cooled to 0° before conc. HCl (40 µL) was added and allowed to react for 10 minutes. Sodium nitrite (4.6 mg, 0.066 mmol) in water (24 µL) was then added and allowed to react for 1 hour. Sodium azide (4.3 mg, 0.066 mmol) in water (24 µL) was then added dropwise and allowed to react for 1 hour. Upon reaction completion, the reaction mixture was diluted with water and the organic layer extracted into EtOAc, washed with 1 M NaOH, brine (3x), dried over $MgSO_4$, and concentrated to give the title compound as a red oil. (11 mg, 60%). R_f (1:1 EtOAC:Hex): 0.39; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.58 – 7.30 (m, 4H), 7.23 (d, J = 8.4 Hz, 1H), 6.98 – 6.67 (m, 6H), 5.99 (t, J = 5.0 Hz, 0.5H), 5.16 (dd, J = 9.5, 3.6 Hz, 0.5H), 4.87 (dd, J = 12.8, 5.4 Hz, 0.5H), 4.37 (d, J = 5.0 Hz, 1H), 3.80 (s, 3H), 3.72 – 3.59 (m, 1H), 3.33 – 3.14 (m, 1H), 3.12 (s, 1H), 2.99 – 2.71 (m, 2H). ^{13}C NMR (101 MHz, cdcl3) δ 159.03, 158.55, 155.98, 155.45, 136.55, 136.47, 136.41, 135.43, 133.17, 133.05, 132.71, 132.38, 131.21, 130.87, 130.07, 128.77, 128.75, 128.49, 128.41, 128.40, 128.07, 127.69, 126.84, 124.98, 122.67, 122.37, 120.05, 120.01, 115.98, 115.55, 113.99, 113.54, 112.90, 112.79, 82.84, 82.62, 78.28, 78.11, 77.21, 70.70, 69.61, 68.12, 56.84, 55.30, 51.49, 42.67, 38.67, 35.19, 31.91, 30.31, 29.74, 29.68, 29.35, 28.89, 28.32, 23.70, 22.97, 22.68, 14.13, 14.06, 10.95. HRMS calcd. for $C_{26}H_{23}O_3N_4$, 439.17647 $[M + H]^+$; found 439.17685 $[M + H]^+$.

2.5.2 Crystal structure data and experimental



Single colorless needle-shaped crystals of **1180-434** were crystallized from hot methanol. A suitable crystal (0.33×0.07×0.05 mm^3) was selected and mounted on a loop with paratone oil on an XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was cooled to T = 100(2) K during data collection. The structure was solved with the ShelXT (Sheldrick, 2015) structure solution program using the Intrinsic Phasing solution method and by using Olex2 (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2014/7 of ShelXL-2014 (Sheldrick, 2015) using Least Squares minimization. Crystal data: $C_{38}H_{30}FN_3O_{11}$, M_r = 723.65, hexagonal, $P6_5$ (No. 170), a = 31.1273(7) Å, b = 31.1273(7) Å, c = 7.70440(10) Å, α = 90°, β = 90°, γ = 120°, V = 6464.8(3) $Å^3$, T = 100(2) K, Z = 6, Z' = 1, μ(CuKα) = 0.724 mm^{-1}, 36033 reflections measured, and of these 7907 were unique (R_{int} = 0.0655) which were used in all calculations. The final wR_2 was 0.2147 (all data) and R_1 was 0.0745 (I > 2σ(I)). Crystals grown and data collected and analyzed by John Bacsa, PhD at the Emory X-crystallography core facility. Crystallographic data is summarized in ***Table 9***.

Table 9. Crystal data and structure refinement for 1180-434.

Formula	$C_{38}H_{30}FN_3O_{11}$
$D_{calc.}$/ g cm^{-3}	1.115
μ/mm^{-1}	0.724

Formula Weight	723.65
Colour	colourless
Shape	needle
Size/mm^3	0.33×0.07×0.05
T/K	100(2)
Crystal System	hexagonal
Flack Parameter	-0.06(11)
Hooft Parameter	-0.08(10)
Space Group	$P6_5$
a/Å	31.1273(7)
b/Å	31.1273(7)
c/Å	7.70440(10)
α/°	90
β/°	90
γ/°	120
V/Å^3	6464.8(3)
Z	6
Z'	1
Wavelength/Å	1.54184
Radiation type	CuK_α
Θ_{min}/°	2.839
Θ_{max}/°	69.941
Measured Refl.	36033
Independent Refl.	7907
Reflections with I > 2σ(I)	6775
R_{int}	0.0655
Parameters	544
Restraints	454
Largest Peak	0.562
Deepest Hole	-0.471
GooF	1.061
wR_2 (all data)	0.2147
wR_2	0.2031
R_1 (all data)	0.0846
R_1	0.0745

2.5.3 In vitro analysis of 1180 series analogs

Protocols utilizing *Xenopus laevis* oocytes were approved by the Emory University Institutional Animal Care and Use Committee. *Xenopus laevis* oocytes were purchased unfertilized from Ecocyte (Austin, TX). The oocytes were injected with mRNA to express recombinant rat

GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D and two-electrode voltage clamp (TEVC) recordings were performed. Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (Univeristy of Heidelberg) provided the cDNAs for rat GluN1-1a (GenBank accession numbers U11418 and U08261, referred to as GluN1 henceforth), GluN2A (D13211), GluN2B (U11419), GluN2C (M91563), and GluN2D (D13213). GluN2C and GluN2D were altered according to literature precedent.[7] Isolation of oocytes, synthesis of cRNA, and injections of cRNA were each done according to literature precedent.[20] Oocytes were placed in perfusion chamber and continuously washed during TEVC recordings with a solution consisting of the following (in mM): 90 NaCl, 0.5 BaCl, 0.005 EDTA, 1.0 KCl, and 10 HEPES at pH 7.4 and 23 ℃. Glass electrodes were pulled from thin-walled glass capillaries (tip resistance 0.5-2.5 MΩ) and filled with 0.3-3.0 M KCl while the oocyte membrane potential was held constant at -40 mV via an OC-725C amplifier (Warner Instrument Co.). Each compound was brought up in 20 mM DMSO and diluted with recording solution containing 30 μM glycine and 100 μM glutamate to the target concentration. To prevent the current increase typically seen during experiments with oocytes expressing GluN1/GluN2A receptors, the oocytes were either injected with 20 nL of 100 mM K-BAPTA (potassium 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid) or pretreated with 50 μM BAPTA-AM (1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid tetraacetoxymethyl ester) for 10 minutes. Compounds that potentiated GluN2A- and GluN2B-containing receptors were not studied further.

Every test compound was recorded at 5−7 concentrations in 7-19 oocytes from 2-3 frogs; all inactive compounds were tested in 4-10 oocytes from 2-3 frogs. For test compounds with potentiation that exceeded 125% at 30 μM, an EC_{50} value (the half-maximal effective concentration of potentiator) was determined by fitting the following equation

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

to the mean composite concentration−response data normalized to the current in the absence of the potentiator (100%) where *N* equals the Hill slope and max is the maximal response predicted for saturating concentration of potentiator.

The concentration that gave a 2-fold increase in the current response was determined by rearranging eq 1 to yield

$$doubling\ concentration = EC_{50}\ ((100 - max) / (200 - max) - 1)^{1/N}$$

in which the Hill slope was held constant at 1.

2.6 References

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Chapter 3: Discovery of GluN2C- and GluN2D-selective N-methyl-D-aspartate (NMDA) receptor positive allosteric modulators showing improved potency, efficacy, and decreased lipophilicity

3.1 Statement of Purpose

As discussed previously (**Chapter 1 and Chapter 2**), CIQ was a first-in-class GluN2C/D-selective NMDAR PAM that has seen extensive use as an *in vitro* pharmacological tool in the years since its publication. However, it is not a perfect tool compound, exhibiting modest potency, modest potentiation, low aqueous solubility, and high plasma protein binding leading to a low free fraction *in vivo*. Through the changes described in **Chapter 2**, we were able to address the modest potency and efficacy by instituting a core change from a TIQ to a dihydroisoquinolinone that ultimately resulted in a 5-fold improvement in doubling concentrations. However, there remained room to optimize the ADME properties (solubility, protein binding, etc.) of the series. Many of the ADME liabilities are likely due to the highly lipophilic nature of the series, exhibiting cLogP values near 6 (and >8 for the most potent analogues) and aqueous solubilities in the single-digit micromolar range (<10 μM for CIQ). Significant previous efforts on the series have resulted in a deep understanding of the effects of different substitutions on the three phenyl rings of CIQ, but very few core changes or hydrophilic replacements have been explored. We thought one strategy for addressing the high lipophilicity may be to replace the three phenyl substituents of CIQ with more hydrophilic heterocycles and substituents. Our hypothesis was that we could maintain (or even improve) affinity for the target, while developing more drug-like, less lipophilic derivatives of the series. If achieved, we believed we could drive receptor occupancy *in vivo* and potentially develop the first GluN2C/D-selective compounds useful for *in vivo* experiments. The goals of this project were achieved via the following strategy:

1.) Design hydrophilic aryl replacements to the 1180 series likely to exhibit improved ADME properties (e.g. solubility) while maintaining or improving affinity for GluN2C- and GluN2D-containing receptors based on previously established SAR trends and standard medicinal chemistry principles.

2.) Synthesize the strategically designed cores (and derivatives if active) and test for their biological activity at GluN2A-D receptors via an *in vitro* two-electrode voltage clamp (TEVC) assay in *Xenopus laevis* oocytes, completed in the lab of collaborator Dr. Stephen Traynelis.

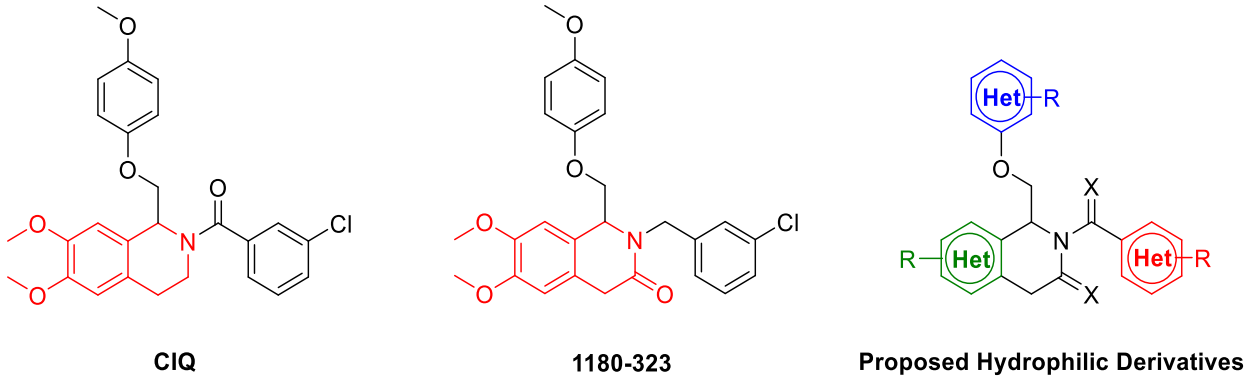


Figure 1. Development of the 1180 series from the tetrahydroisoquinoline core of CIQ (left), to the dihydroisoquinolinone core (middle) discussed in Chapter 2, to the hydrophilic derivatives (right) discussed in this chapter.

3.2 Introduction and Background

3.2.1 The absorption, distribution, metabolism, and excretion (ADME) and safety profile of a small molecule drug is impacted by its lipophilicity

The lipophilicity of a small molecule is an important physiochemical property that has substantial implications on the ADME properties of that substance.[1-3] A substance's lipophilicity is the sum of three terms: hydrophobicity, polarity, and ionic interactions.[4] The hydrophobic term accounts for the van der Waals forces, the polarity term for hydrogen bonding and inductive effects, and the ionic interaction term for charge attraction and repulsion. The lipophilicity of a compound can be

controlled by balancing the ratio of hydrophobic substituents to polar/ionic substituents. This is important in drug discovery as it is the hydrophobic effect that drives the binding of ligands to their protein targets. Most protein binding sites contain at least one hydrophobic pocket and therefore the binding of a lipophilic ligand creates more favorable interactions than the interactions between the protein and solvating water molecules.[5] This is also explained via a decrease in the Gibbs free energy of the system, seen in eq 1 below:

$$-RT[\ln(K)] = \Delta G = \Delta H - T\Delta S \quad (1)$$

Upon binding, entropy (ΔS) increases due to the increased degrees of freedom for the waters expelled from the solvation shell and enthalpy (ΔH) decreases upon increased ligand lipophilicity. This leads to an increased released of Gibbs free energy (ΔG) and ultimately a favorable influence on the equilibrium constant (K).[6, 7]

Traditionally, *in vitro* potency has been overemphasized in drug discovery programs,[8] but optimizing the ADME properties of a drug is vitally important to providing low-dose compounds for patients. Lower dose drugs are easier to formulate, decrease patient pill burden, increase patient compliance, and decrease the risk for idiosyncratic toxicities.[9-12] There is substantial evidence the lipophilicity of a molecule affects its ADME properties and safety profile. Highly lipophilic compounds have been associated with increased risk for drug-induced liver injury.[9] An analysis of ~45,000 Pfizer compounds revealed a direct relationship between lipophilicity and *in vitro* clearance,[13] a factor in determining the dose of a drug.[1] This is likely due to the preference of metabolizing proteins and increased hepatocyte permeability for more lipophilic compounds. There is also evidence renal clearance increases for compounds with extremely hydrophilic profiles,[14, 15] suggesting the odds of producing a compound with acceptable *in vivo* clearance may be highest in the 0-3 log*D* range. Adequate aqueous solubility is another important factor for low

dosing as sufficient dissolution is required for the crossing of lipid membranes. An analysis of ~45,000 GSK compounds demonstrated the probability of achieving high solubility decreases significantly at logP > 3,[16] and a study of 711 drug-like compounds concluded only 1% of molecules with logP > 3 were soluble (> 250 μg/mL).[17] This is theoretically consistent in that the solubility of a compound is determined by its activity coefficient, which is impacted by its hydrophobicity.[18] Passive membrane permeability is also affected as highly lipophilic compounds may be trapped in hydrophobic cell membranes[4] while polar compounds exhibit decreased affinity for the phospholipid bilayer and incur a severe water desolvation energy penalty pre-permeation.[14] Since bioavailability is a summation of the above-discussed parameters, it could be assumed that a balance of lipophilicity may be optimal to achieve orally available drugs. Topliss *et al*. examined a set of 232 structurally diverse drugs and demonstrated that out of the subset of those 232 that exhibit >80% bioavailability, 99% fell in the -2 – 3 log*D* range.[19] Finally, lipophilicity has been demonstrated to have a strong effect on plasma protein binding,[20] and therefore also unbound plasma drug concentration. Since the unbound concentration is the concentration of active drug available to the body, it is a major determiner of efficacy and thus plays large role in the required dose.

There is also ample evidence suggesting lipophilicity plays a role in the safety profile of a compound. Since increased lipophilicity promotes binding in general, it is expected that highly lipophilic compounds will bind more promiscuously than their hydrophilic counterparts, perhaps ultimately binding a target with toxic pharmacology.[6] One analysis of ~2,100 compounds from the Cerep Bioprint database concluded promiscuity increases substantially for compounds with logP > 3[21] while another of 213 Roche compounds showed promiscuity increases for logP > 2.[22]

Relatedly, the chance of drug-induced phospholipidosis,[23, 24] CYP inhibition,[16] and hERG liability[16, 25, 26] increase dramatically with increasing lipophilicity.

This body of evidence strongly suggests the lipophilicity of a given compound has profound effects on its behavior in the body and is an important consideration in the development of a drug. Of course, it must also be optimized in conjunction with potency and the identification of scaffolds or substitution that improve potency while decreasing lipophilicity (i.e. logP) is vital to a successful drug discovery program.[27] One metric to measure this progress is the ligand-lipophilic efficiency (LLE), calculated as below:

$$LLE = pEC_{50} - cLogP \quad (2)$$

This equation highlights that progress can be made in discovery programs by improving potency *or* decreasing lipophilicity, which acted as the guide for the work described below.[21, 28, 29]

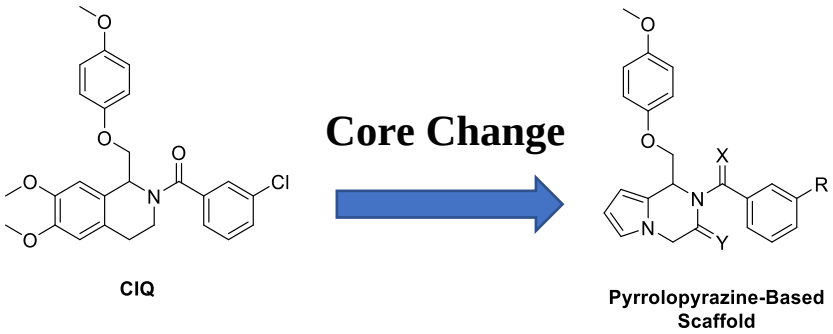
3.2.2 Core changes to a tetrahydroisoquinoline class of GluN2C/D-selective NMDAR PAMs resulted in a second-generation pyrrolopyrazine class with improved ADME properties

Despite extensive development of a structure-activity relationship (SAR) around the 1180 series, there has been little progress in terms of lipophilic efficiency (i.e LLE) towards the target. Previously in Santangelo *et al*., potency was improved 1.5 orders of magnitude from the screening hit, but ultimately at the expense of 3 orders of magnitude of cLogP. Although useful for understanding the SAR of the series, this ultimately decreased the LLE 1.5 orders of magnitude and made development of compounds with clinically relevant ADME profiles that could be useful *in vivo* difficult. This was especially harmful for this series due to the relatively lipophilic nature of the screening hit already (cLogP ~ 5), likely leading to poor aqueous solubility of the prototypical compound CIQ (<10 μM). The highly lipophilic nature of CIQ is also likely the cause of its low free fraction *in vivo* that will limit its concentrations in the brain and receptor

occupancy.[30] As discussed in **Section 3.2.1**, highly lipophilic compounds also typically exhibit numerous liabilities including high clearance, low aqueous solubility, low membrane permeability, low oral bioavailability, and a higher likelihood of idiosyncratic toxicity, making optimization of this property vital in medicinal chemistry efforts.

There have been scattered previous attempts at decreasing the lipophilicity of the series,[31] but in nearly each case this led to a complete loss in potency. Herein, we describe a series of hydrophilic-focused changes to the three rings of CIQ that resulted in a pyrrolopyrazine-based scaffold with dramatically improved lipophilic efficiency for the NMDAR. Prototypical compounds also show a roughly order of magnitude improvement aqueous solubility, a relatively clean off-target profile, improved ease of analysis due to elimination of rotamers observed with CIQ, and less metabolically labile aryl methoxy substituents compared with CIQ.

Figure 2. A series of core changes to the TIQ-based CIQ lead to a pyrrolopyrazine-based scaffold.

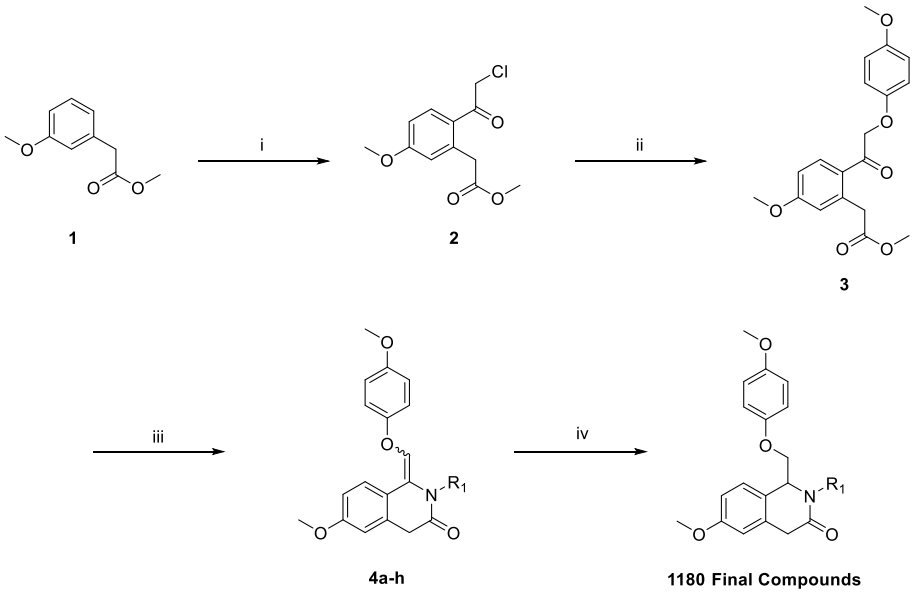


3.3 Synthesis, Rationale, Results, and Discussion of Hydrophilic GluN2C/D-Selective Positive Allosteric Modulators

3.3.1 Synthesis of alternative A-, B-, and C-rings to the phenyl rings of CIQ

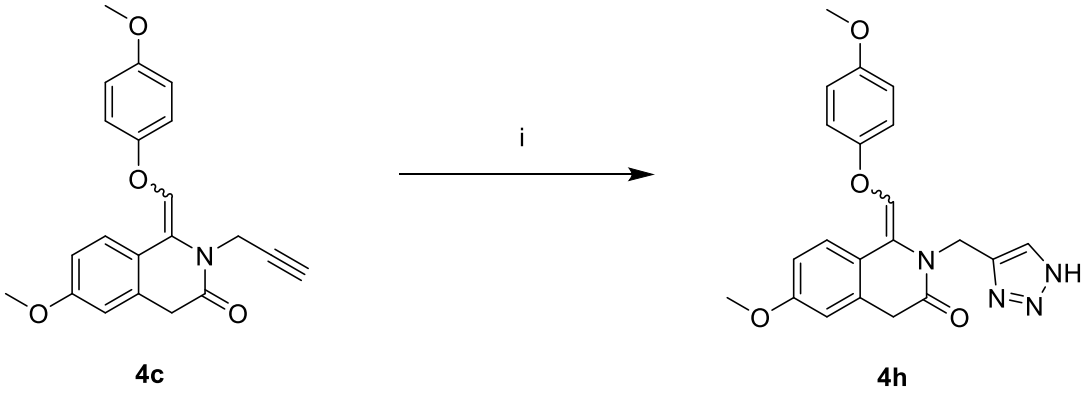
The synthesis of the changes to the A-ring was completed according to **Scheme *1*** in **Section 2.3.1** and is outlined in **Scheme *1*** below. Formation of triazole **4h** was completed via copper-catalyzed click chemistry of alkyne **4c** and is outlined in **Scheme *2***.

Scheme 1. Synthesis of dihydroisoquinolinones.



Scheme 1. i) chloroacetyl chloride, tin(IV) chloride, DCE, reflux, 90 m (46%) (procedure I); ii) substituted phenols, KI, K_2CO_3, reflux, 4 h (53%) (procedure II); iii) substituted primary amines, titanium(IV) isopropoxide, sodium triacetoxyborohydride, DCE, 120°C, μw, 20 m (19-80%) (procedure III); iv) Pd/C, H_2 (50 psi), EtOH, rt, 24 h (23-83%) (procedure IV)

Scheme 2. Synthesis of A-ring triazole intermediate.

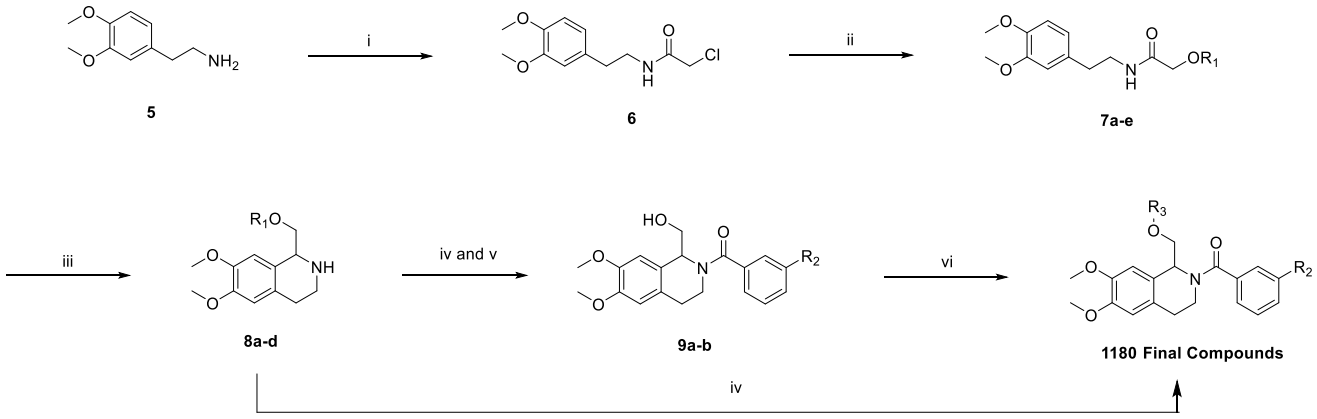


Scheme 2. i) sodium azide, 37% CH_2O in H_2O, cat. sodium ascorbate, cat. aq. $CuSO_4$, AcOH, THF, rt, overnight (29%)

The synthesis of B-ring derivatives is outlined in **Scheme *3***, beginning with commercially available 3,4-dimethoxyphenethylamine. First, the primary amine was acylated via chloroacetyl chloride to give *alpha*-chloro amide **6**, which could then be alkylated with primary alcohols and

sodium hydride to give *alpha*-hydroxy amides **7a-e**. These compounds could then be cyclized to the imine under modified Bischler-Napieralski conditions and subsequently reduced via sodium borohydride or hydrogenation to yield secondary amines **8a-d**. Finally, the secondary amines were acylated using either 3-(trifluoromethyl)benzoyl chloride or 3-chlorobenzoyl chloride and deprotected to the respective primary alcohols **9a-b**, which were functionalized using Buchwald or S_NAr conditions to the final 1180 compounds. Alternatively, in cases where B-ring substitution was installed in step ii, such as in cases **8a-c**, the secondary amines could be directly acylated with acid chloride the the final compounds.

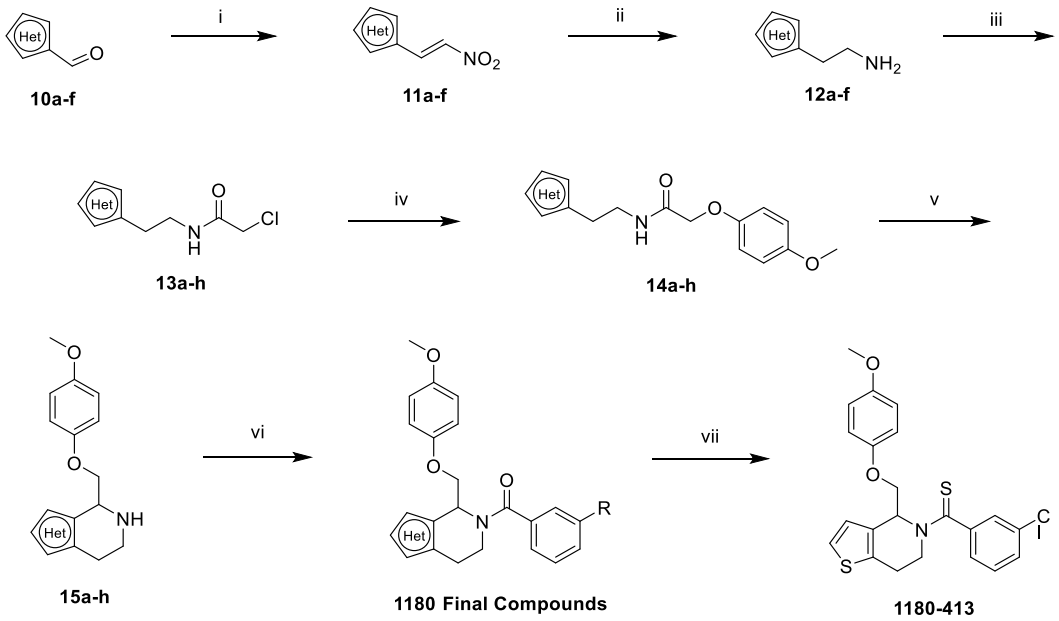
Scheme 3. Synthesis of B-ring derivatives.



Scheme 3. i) chloroacetyl chloride, Et_3N, DCM, 0 °C, 30 m, 74% (procedure V); ii) R_1OH, NaH or Cs_2CO_3, 54-74% (procedures VI or VII); iii) $POCl_3$, ACN, reflux then $NaBH_4$, MeOH, 0 °C, 10 m, 16-62% (procedure VIII); iv) acid chloride, Et_3N, DCM, rt, 1 h, 44-100% (procedure IX); v) methane sulfonic acid, DCM, rt, 6h, 44% OR Pd/C, H_2 (50 psi), MeOH, o/n, 8% over 3 steps vi) Het-F, NaH, THF, reflux, o/n, 27-47% (procedure X) OR Het-I, 1,10-Phen, CuI, Cs_2CO_3, PhMe, 80 °C, o/n, 21%

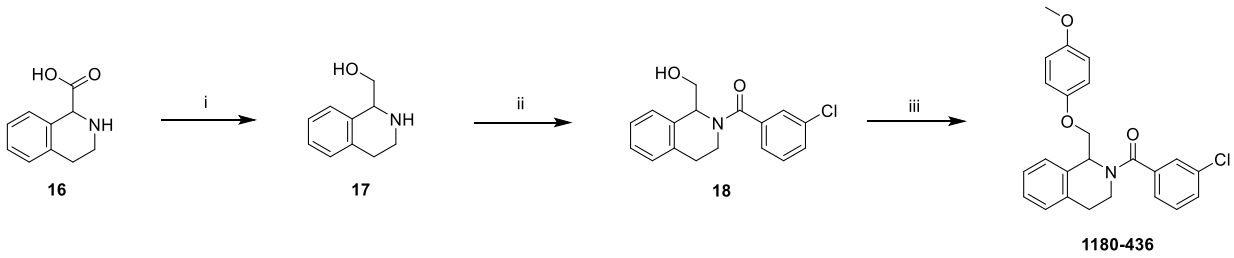
The synthesis of the C-ring core changes is described in **Scheme 4** and were done according to modified literature precedent[31] beginning from the ethylamine starting material. Certain ethylamines (**12a-f**) were not commercially available and were thus synthesized from the corresponding aldehyde through a Henry-type nitroalkenylation and subsequent reduction via in situ generated alane (**Scheme 4, steps i and ii**). 2-methoxy-5-formylthiophene was not commercially available and was synthesized according to literature precedent.[32] Compound **1180-436** was synthesized beginning with the commercially available cyclic amino acid 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (Compound **16**). This was first reduced to the amino alcohol **17** via borane-dimethylsulfide complex, N-acylated using 3-chlorobenzoyl chloride to give **18**, and finally coupled under copper-catalyzed Buchwald conditions to yield the final compound, **1180-436** (**Scheme 5**). Dihydropyrrolopyrazinone derivatives were also synthesized according to precedent (**Section 2.3.1**) with slight modifications (**Scheme 6**). The methyl ester starting material **20** was synthesized from glycine methyl ester hydrochloride (**19**) using 2,5-dimethoxytetrahydrofuran in refluxing acid. Other modifications included replacement of $SnCl_4$ with $AlCl_3$ at milder temperatures in step ii and the addition of KI also at milder temperatures in step iii. Compounds **1180-420**, **-447**, and **-450** were separated via normal phase preparatory chiral HPLC using a ChiralPakAD-H column and the activities of the enantiomers tested individually.

Scheme 4. Synthesis of heterocyclic core scaffolds.



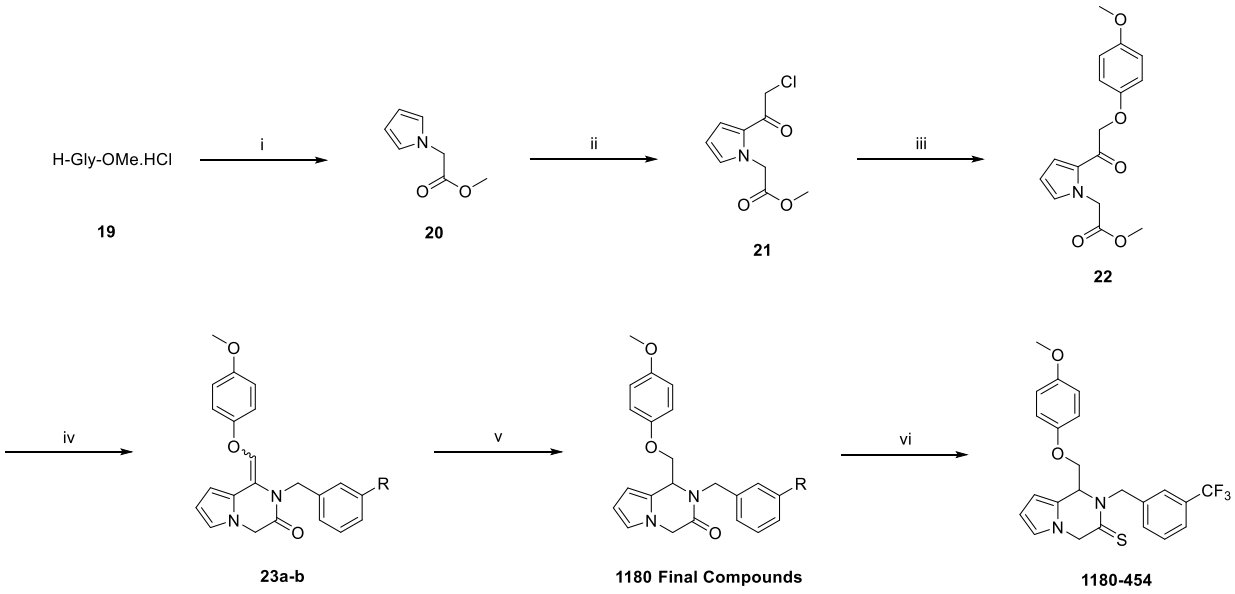
Scheme 4. i) cat. butylamine, cat. AcOH, 4 Å MS, $MeNO_2$, reflux, 30 m, 31-100% (procedure XI); ii) $LiAlH_4/H_2SO_4$, THF, 0 °C to reflux, 5 m (procedure XII); iii) chloroacetyl chloride, Et_3N, DCM, 0 °C, 30 m, 5-61% over 2 steps or 82-100% over 1 step (procedure V); iv) substituted phenols, Cs_2CO_3, overnight, 47-93% (procedure VI); v) $POCl_3$, ACN, reflux, overnight then $NaBH_4$, MeOH, 0 °C, 10 m, 9-74% (procedure VIII); vi) acid chloride, Et_3N, DCM, rt, 1 h, 33-96% (procedure IX) OR carboxylic acid, EDCI, DMAP, rt, o/n, 26-33% (procedure XIII); vii) Lawesson's reagent, PhMe, 150 °C μw, 2 h, 18% (procedure XIV)

Scheme 5. Synthesis of phenyl-based 1180-436.



Scheme 5. i) BH_3-DMS complex, THF, rt, overnight, 64%; ii) 3-chlorobenzoyl chloride, Et_3N, DCM, rt, 1 h, 17% (procedure IX; iii) 4-iodoanisole, CuI, Me_4-phenanthroline, Cs_2CO_3, PhMe, 110 °C, 48 h, 52%

Scheme 6. Synthesis of dihydropyrrolopyrazinones.



Scheme 6. i) 2,5-dimethoxytetrahydrofuran, NaOAc, 2:1 v/v AcOH:water, reflux, 4 h, 68%; ii) chloroacetyl chloride, $AlCl_3$, DCM, 0 °C, 1 h, 22% (procedure XV); iii) 4-methoxyphenol, KI, K_2CO_3, acetone, rt, overnight, 52% (procedure XVI); iv) substituted primary amines, $Ti(OiPr)_4$, STAB, DCE, 120 °C, µw, 2 h, 32-38% (procedure XVII); v) Pd/C, H_2 (1 atm), EtOAc, rt, overnight, 36-58% (procedure XVII); vi) Lawesson's reagent, PhMe, 150 °C, µw, 2 h, 32% (procedure XIV)

3.3.2 Potentiation of NMDARs by a novel series of PAMs

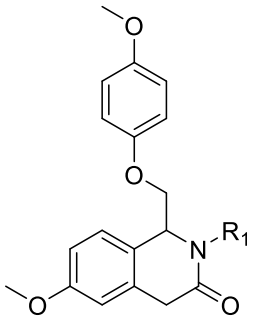
All compounds synthesized were evaluated via two-electrode voltage-clamp recordings of *Xenopus laevis* oocytes expressing four recombinant NMDA subtypes: GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D. Each compound was tested using 4-15 oocytes from 1-2 frogs. Concentration effect curves were generated by co-applying increasing concentrations of compound with saturating concentrations of glutamate (100 μM) and glycine (30 μM) and if the mean potentiation exceeded 125%, a pEC_{50} value was calculated by fitting the dose-response curves to the equation in **Section 3.4.2**. **Tables 1-6** show the mean pEC_{50} value, 95% confidence interval, average maximum potentiation (max), and negative log of the doubling concentration (pDC) for each compound active at GluN1/GluN2C and GluN1/GluND2 receptors. The doubling concentration is defined as the concentration of test compound at which the response

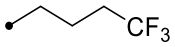
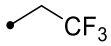
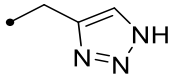
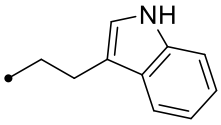
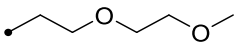
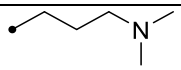
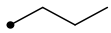
to maximally effective concentration of coapplied glutamate and glycine is increased 2-fold over the response to glutamate and glycine alone. The cLogP (calculated from CambridgeSoft's ChemDraw suite) is also given for all compounds, along with the solubility (sol.) and LLE for each compound it was determined. All compounds were also tested at GluN1/GluN2A and GluN1/GluN2B receptors at 30 μM and were typically found to have no effect (~4 oocytes from 1 frog). Any effects seen were not investigated further.

3.3.3 Evaluation of hydrophilic A-ring replacements

First, hydrophilic replacements of the A-ring were investigated on the dihydroisoquinolinone scaffold. Of the alternative substituents examined, only alkyl trifluoromethyl derivatives **1180-300** (pDC = 5.0-5.1) and **1180-301** (pDC < 4.5) (**Table *1***) were tolerated suggesting hydrophobic effects play a large role in this receptor pocket. Despite lowering cLogP values nearly 2 orders of magnitude, these trifluoromethyl derivatives still showed doubling concentrations in the double-digit micromolar range. Although below acceptable potency ranges, these substitutions may be useful for future potent derivatives to tune ADME properties. Derivatives with shorter chains such as compound **1180-338** show no activity, likely due in large part to decreased hydrophobic effects in comparison to aryl and longer alkyl substituents. Heterocycles such as triazole **1180-360** (max = 98-111%) or tryptamine derivative **1180-364** (max = 85%) showed little-to-no potentiation as did other linear functionalization such as the 2-methoxyethoxy ethyl compound **1180-373** (max = 98-102%) or the dimethylaminopropyl compound **1180-382** (max = 96-114%). This provides further evidence hydrophobic effects dominate receptor-ligand interactions in this portion of the molecule and therefore exclusively *meta*-substituted benzyl derivatives were synthesized from this point forward, as they provided the most promising combination of activity and lipophilic efficiency.

Table 1. Hydrophilic A-ring substitutions.



#	R_1	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)	cLogP	LLE
		GluN2C	GluN2D			
297[b]	3-chlorobenzyl	5.7 [5.6-5.8] (272)	5.6 [5.5-5.8] (326)	5.6/5.7	5.9	-0.2/-0.3
300		5.1 [4.9-5.3] (286)	4.7 [4.5-4.9] (451)	5.0/5.1	4.1	1.0/0.6
301		<4.5 (328)	<4.5 (163)	<4.5/ID	4.1	-
360		ND (111)	ND (98)	-	2.9	-
364		ND (85)	ND (85)	-	5.1	-
373		ND (98)	ND (102)	-	3.1	-
382		ND (114)	ND (96)	-	3.6	-
338		ND (97)	ND (94)	-	4.0	-

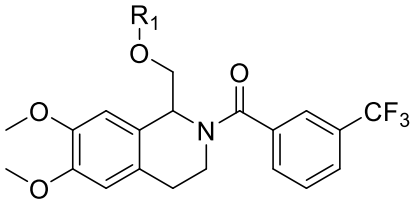
[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 6 and 11 oocytes from 2 frogs for each compound and receptor. [b]Compound **1180-297** was shown in a previous table and was included here for comparison. ID = indeterminable

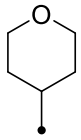
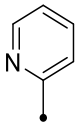
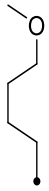
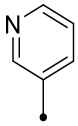
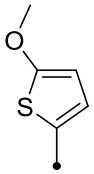
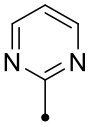
3.3.4 Evaluation of hydrophilic B-ring replacements

Second, while maintaining the A-ring to 3-(trifluoromethyl)benzoyl substitution, hydrophilic derivatives were examined in place of the B-ring (**Table 2**). However, none of the heterocyclic,

ethereal, or thiophene-based derivatives were tolerated at any GluN2 subtype. Nitrogen heterocycles such the 1-pyridinyl (**1180-431**), 2-pyridinyl (**1180-430**), and 2-pyrimidinyl (**1180-429**) all showed between only 88-97% potentiation of GluN2C- and GluN2D-containing receptors. Neither the tetrahydropyran (**1180-433**) nor methoxybutyl (**1180-437**) showed above 106% potentiation and bioisosteric replacement with thiophene (**1180-287**) was also not tolerated, despite previous success with thiophene-based compounds in place of the A-ring.[31] However, initial experiments have revealed compounds **1180-433** and **1180-437** show GluN1/GluN3A-selective activity, opening the possibility these derivatives could be useful despite their lack of activity at GluN2-containing receptors.

Table 2. Hydrophilic B-ring substitutions.



#	R_1	pEC_{50} (max) (%)[a]		cLogP	#	R_1	pEC_{50} (max) (%)[a]		cLogP
		GluN2C	GluN2D				GluN2C	GluN2D	
1426[b]	4-methoxy-phenyl	5.6 (201)	5.6 (218)	5.8	**433**		ND (100)	ND (95)	3.4
431		ND (96)	ND (97)	5.2	**437**		ND (106)	ND (99)	4.1
430		ND (90)	ND (88)	4.8	**287**		ND (103)	ND (112)	5.6
429		ND (97)	ND (95)	4.3					

[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from 4 oocytes from 1 frog for each compound and receptor. [b]Compound **1426** was purchased and was included here for comparison.

3.3.5 Effect of bioisosteric replacement of the C-ring

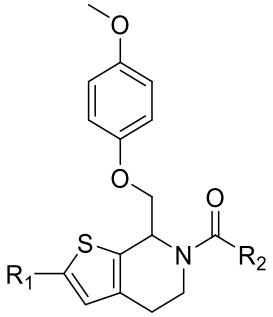
Although derivatization of the three rings of CIQ has led to numerous useful tool compounds (see references, **Chapter 1**, and **Chapter 2**),[30, 31] wholesale changes to the C-ring and TIQ core itself have been minimal. We viewed this as an underdeveloped area of the SAR in which opportunities

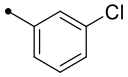
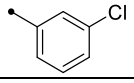
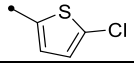
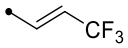
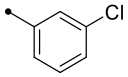
for decreasing lipophilicity and improving affinity for the target could emerge, assuming appropriate choice of hydrophilic core. Due to thiophene's known use as a classical phenyl isostere, tetrahydrothienopyridine **1180-400** was synthesized and its activity against each of the GluN2 subunits (**Table *3***) was examined via two-electrode voltage clamp recordings of *Xenopus laevis* oocytes. To our delight, **1180-400** showed improved maximum potentiation (275%-349%) while maintaining similar potency (pEC_{50} = 5.4) and selectivity (no activity at GluN2A/B) to CIQ. Due to the improved potentiation, **1180-400** showed improved doubling concentrations (pDC = 5.3-5.6) in comparison to CIQ (pDC = 4.5-4.9). This exemplified changes to the TIQ core were tolerated and we hypothesized other more hydrophilic substitution would follow a similar trend.

3.3.6 SAR of additional TIQ core changes

Using this result as a starting point, several tetrahydrothienopyridine-based derivatives were subsequently explored (**Table *3***). First, bioisosteric 2-chlorothiophene replacement of the A-ring provided compound **1180-404**, which was similarly tolerated (pDC = 5.3-5.6) to **1180-400**. The trifluorocrotonic acid derivative **1180-405** suffered a loss in potency (pEC_{50} = 4.8-4.9) compared to CIQ, but ultimately resulted in a large improvement in LLE (ΔLLE ~ 1.5-1.6) due to its notable decrease in cLogP (5.6 to 3.6). This may be an attractive substitution for tuning the ADME properties of more potent future derivatives but rendered this compound outside the range of acceptable potency. Finally, methoxy substitution on the thiophene (**1180-423**) was examined due to previous SAR trends (**Chapter 2**).[30, 31] This compound showed no advantages in terms of LLE over CIQ and therefore unsubstituted heterocycles were the focus of the remaining synthetic efforts.

Table 3. Optimization of A-ring functionality for thiophene core.



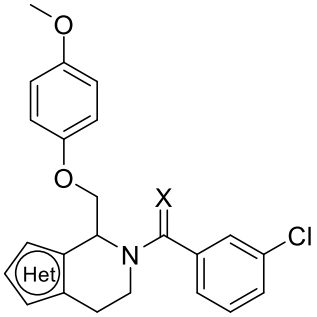
#	R_1	R_2	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)	sol. (μM)	cLogP	LLE (GluN2C/2D)
			GluN2C	GluN2D				
CIQ[b] (TIQ core)			5.3 (233)	5.3 (215)	4.9/4.5	8	5.6	-0.3/-0.3
400	H		5.4 [5.3-5.5] (275)	5.4 [5.3-5.5] (349)	5.3/5.6	46	5.6	-0.2/-0.2
404	H		5.3 [5.3-5.3] (293)	5.3 [5.2-5.4] (395)	5.3/5.6	-	5.4	-0.1/0.1
405	H		4.9 [4.8-5.0] (286)	4.8 [4.6-4.9] (334)	4.8/4.9	-	3.6	1.3/1.2
423	OMe		5.3 [5.2-5.4] (223)	5.2 [5.1-5.2] (222)	4.6/4.5	-	5.7	-0.4/-0.5

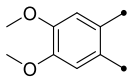
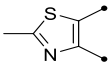
[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 10 and 12 oocytes from 2 frogs for each compound and receptor. [b]Previously published data for **CIQ** were included for comparison.

A regioisomer of **1180-400**, **1180-401**, also showed improved doubling concentrations (pDC = 5.4-5.5) over CIQ but was unlikely to offer a lipophilicity advantage over **1180-400** and therefore additional hydrophilic core changes were designed (**Table 4**). The furan derivative, **1180-403**, was the first to show a substantial improvement in LLE compared to CIQ (ΔLLE = 0.3-0.4) without catastrophically harming potency or efficacy, maintaining good doubling concentrations (pDC = 5.4-5.5) while lowering cLogP (5.6 to 5.1). However, other more hydrophilic derivatives such as the 2-methylthizole **1180-402**, N-methylimidazole **1180-407**, and isothiazole **1180-411** were each

not tolerated. One particularly interesting derivative was pyrrolopyrazine **1180-420**, which exhibited the best doubling concentrations (pDC = 5.8-5.9) of any hydrophilic derivative while also lowering cLogP by 0.7 log units compared to CIQ (5.6 to 4.9). Consistent with the decreased cLogP, compound **1180-420** also showed a 4.5-fold improvement in solubility over CIQ at 36 µM. Although not a heterocycle, phenyl derivative **1180-436** was interesting as no unsubstituted TIQ-based derivative had been previously synthesized,[30, 31] but was actually harmful to LLE (LLE = -0.9) in this case. Replacement of the A-ring amide linker with a thioamide has previously been shown to improve potency >10-fold in some cases.[30] However, it was not tolerated on compound **1180-413** containing the tetrahydrothienopyridine scaffold. Nonetheless, compound **1180-420** was an exciting development towards compounds with improved lipophilic efficiencies and therefore other derivatives with this same pyrrolopyrazine core were developed.

Table 4. Optimization of the heterocyclic core.



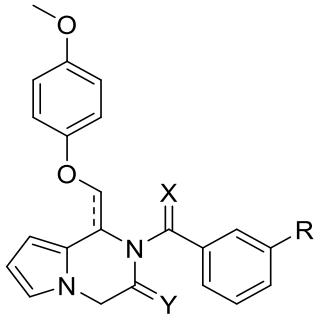
#	Core	X	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)	sol. (μM)	cLogP	LLE (GluN2C/2D)
			GluN2C	GluN2D				
CIQ[b]		O	5.3 (233)	5.3 (215)	4.9/4.5	8	5.6	-0.3/-0.3
401		O	5.4 [5.3-5.4] (325)	5.3 [5.2-5.3] (339)	5.5/5.4	-	5.6	-0.2/-0.3
402		O	ND (102)	ND (100)	-	-	4.8	-
403		O	5.2 [5.1-5.3] (337)	5.1 [5.0-5.3] (474)	5.4/5.5	-	5.1	0.1/0.0
407		O	< 4.5 (207)	< 4.5 (216)	-	-	4.2	-
411		O	4.8 [4.7-4.9] (243)	4.8 [4.7-4.9] (256)	4.5/4.5	-	5.0	-0.2/-0.2
420		O	5.6 [5.5-5.7] (372)	5.5 [5.4-5.7] (369)	5.9/5.8	36	4.9	0.7/0.6
436		O	5.2 [5.1-5.3] (257)	5.1 [4.9-5.2] (296)	5.0/5.0	-	6.0	-0.8/-0.9
413		S	ND (97)	ND (94)	-	-	6.0	-

[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 7 and 15 oocytes from 2 frogs for each compound and receptor for which an EC_{50} value was determined and between 4 and 9 oocytes from 1-2 frogs for all others. [b]Previously published data for **CIQ** were included for comparison.

3.3.7 Pyrrolopyrazine- and pyrrolopyrazinone-based analogues

Based on previously established SAR within the series, a targeted sample of derivatives was designed and synthesized keeping the pyrrolopyrazine core consistent throughout (**Table *5***). First, based on a potency boost seen in **Chapter 2** and Santangelo *et al.*,[31] the chlorine of compound **1180-420** was substituted for a trifluoromethyl substituent to give compound **1180-450**. This compound pushed the doubling concentration at GluN2C into the nanomolar region (pDC = 6.1) while also displaying the highest solubility (58 μM) of any derivative tested, over 7-fold higher than CIQ. Translocation of the carbonyl, analogous to the core change described in **Chapter 2**, resulted in **1180-447** that also displayed similar doubling concentrations (pDC = 5.9-6.1) and solubility (57 μM) to **1180-450**. Fluorine was also tolerated (**1180-453**) in place of the trifluoromethyl group and although a slight affinity drop was observed (pEC_{50} = 5.5), excitingly it showed roughly order of magnitude improvements in LLE (ΔLLE = 0.9-1.0), doubling concentration (ΔpDC = 0.8-1.1), solubility (8 to 74 μM), and cLogP (ΔcLogP = 1.1). The amide of **1180-447** was converted to the thioamide to give **1180-454**, but this resulted in a complete loss of activity on the pyrrolopyrazinone core like the tetrahydrothienopyridine core above. Finally, one alkene precursor isomer exhibited GluN2C/D-selective activity in the work described in **Chapter 2**, but neither isomer (compounds **1180-448** and **1180-449**) was tolerated on the pyrrolopyrazinone core.

Table 5. Optimization of potency and solubility for pyrrolopyrazine-and pyrrolopyrazinone-based derivatives.



#	X	Y	Olefin	R	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)	sol. (μM)	cLogP	LLE (GluN2C/2D)
					GluN2C	GluN2D				
CIQ[b] (TIQ core)				Cl	5.3 (233)	5.3 (215)	4.9/4.5	8	5.6	-0.3/-0.3
450	O	-	No	CF_3	5.8 [5.7-5.9] (381)	5.7 [5.5-5.9] (288)	6.1/5.6	58	5.1	0.7/0.6
447	-	O	No	CF_3	5.9 [5.7-6.0] (298)	5.8 [5.6-6.0] (396)	5.9/6.1	57	5.2	0.7/0.6
453	-	O	No	F	5.5 [5.4-5.6] (348)	5.5 [5.4-5.6] (334)	5.7/5.6	74	4.5	1.0/1.0
454	-	S	No	CF_3	ND (115)	ND (113)	-	-	5.4	-
448	-	O	Yes	CF_3	ND (91)	ND (89)	-	-	5.3	-
449	-	O	Yes	CF_3	ND (100)	ND (99)	-	-	5.3	-

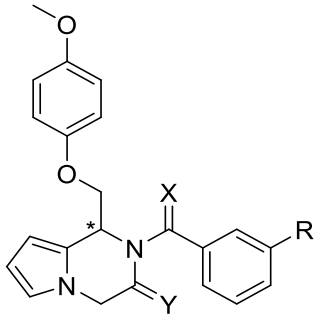
[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 7 and 15 oocytes from 2 frogs for each compound and receptor. [b]Previously published data for **CIQ** were included for comparison.

3.3.8 Enantiomers

Three compounds with promising profiles (**1180-420**, **1180-447**, and **1180-450**) were selected for separation via chiral HPLC to examine the behavior of the individual enantiomers (**Table *6***). Consistent with CIQ and its derivatives, the *R*-(+)-enantiomer held all activity while the *S*-(–)-enantiomer was inactive in each case. This produced the compound (***R*-(+)-1180-450**) with

attractive doubling concentrations (pDC = 6.3-6.4) and solubility (58 μM), exhibiting a ~50:1 solubility to potency ratio and >100:1 solubility to doubling concentration ratio, compared to ~2:1 and <1:1 for CIQ, respectively.

Table 6. Stereodependence of select pyrrolopyrazine cores.



#	X	Y	R	pEC_{50} [95% CI] (max) (%)[a]		pDC (GluN2C/2D)	sol. (μM)[c]	cLogP	LLE (GluN2C/2D)
				GluN2C	GluN2D				
CIQ[b] (TIQ core)			Cl	5.3 (233)	5.3 (215)	4.9/4.5	8	5.6	-0.3/-0.3
***S*-(—)-447**	-	O	CF_3	ND (84)	ND (88)	-	57	5.2	-
***R*-(+)-447**	-	O	CF_3	6.1 [6.0-6.3] (276)	6.1 [6.0-6.2] (332)	6.0/6.2	57	5.2	0.9/0.9
***S*-(—)-420**	O	-	Cl	ND (98)	ND (99)	-	36	4.9	-
***R*-(+)-420**	O	-	Cl	5.7 [5.7-5.8] (408)	5.7 [5.7-5.8] (453)	6.1/6.2	36	4.9	0.8/0.8
***S*-(—)-450**	O	-	CF_3	ND (99)	ND (98)	-	58	5.1	-
***R*-(+)-450**	O	-	CF_3	5.9 [5.8-6.0] (464)	5.9 [5.8-5.9] (542)	6.3/6.4	58	5.1	0.8/0.8

[a]Fitted pEC_{50} values are shown to two significant figures when potentiation at 30 μM exceeded 125%; values in brackets are the 95% confidence interval for the corresponding log fitted pEC_{50} value and values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. For compounds in which a pEC_{50} was not determined, max potentiation is reported as percent potentiation at 30 μM drug. Data are from between 6 and 13 oocytes from 2 frogs for each compound and receptor. [b]Previously published data for **CIQ** were included for comparison. [c]Solubilities reported from racemic mixtures.

3.3.9 Off-target activity

Compounds **1180-447** and **1180-420** were further examined for their behavior against common off-target receptors. First, their specificity against other ion channels in the brain were examined

via two-electrode voltage clamp recordings of *Xenopus* oocytes expressing AMPA, nicotinic acetylcholine, serotonin, GABA, and glycine receptors (**Table *7***). Current responses were tested with saturating concentrations of glutamate (100 μM) and glycine (30 μM) in both the absence of drug and presence of 10 μM **1180-447** and **1180-420** (~10-times the EC_{50}). Neither compound exhibited >50% inhibition or potentiation at any of the receptors tested and only showed >25% inhibition or potentiation at the $\alpha4\beta2$ nicotinic acetylcholine receptor. Compounds **1180-447** and **1180-420** were also submitted to the National Institute of Mental Health Psychoactive Drug Screening Program (PDSP, https://pdsp.unc.edu/ims/investigator/web/) to examine the activity of both the pyrrolopyrazine and pyrrolopyrazinone cores at additional off-target receptors (**Table *8*** and **Table *9***). The primary binding screen examined inhibition of ligand binding at 10 μM **1180-447** or **1180-420** and if the drug exhibited >50% inhibition, a secondary binding screen was run to determine K_i. Compounds **1180-447** and **1180-420** showed >50% inhibition at only 4 and 3, respectively, of the 44 off-target receptors examined, and all K_i values were in the micromolar range, suggesting reasonable selectivity for the GluN2C and GluN2D subtypes.

Table 7. Off-target actions of 1180-447 and 1180-420 at ligand-gated ion channels.

Receptor	% control response (10 μM 1180-447)[a]	% control response (10 μM 1180-420)[a]
GluA1	96.8 ± 13.3	98.9 ± 13.7
GluA2	99.3 ± 2.9	101.6 ± 1.3
$\alpha4\beta2$-nACh	52.7 ± 6.3	56.4 ± 5.3
$\alpha1\beta2\gamma\delta$-nACh	78.5 ± 4.5	93.4 ± 15.5
5-HT_{3A}	98.1 ± 10.4	ND
$\alpha1\beta2\gamma2$-$GABA_A$	81.7 ± 7.5	81.4 ± 8.5
$\alpha1$-Glycine	ND	77.6 ± 4.9

[a]The mean responses to agonist with 10 μM **1180-420** and **1180-447** and the standard error of the mean are given for each compound and receptor tested.

Table 8. Off-target actions of compound 1180-447.

Receptor	Radioligand binding in 10 μM XX (% control)	pK_i values from non-linear regression of radioligand competition binding isotherms
5-HT_{1A}	101	-
5-HT_{1B}	109	-
5-HT_{1D}	115	-
5-HT_{1E}	80	-
5-HT_{2A}	49	5.7 ± 0.1
5-HT_{2B}	78	-
5-HT_{2C}	32	<5
5-HT_3	68	-
5-HT_{5A}	92	-
5-HT_6	85	-
5-HT_7	83	-
D_1	87	-
D_2	101	-
D_3	93	-
D_4	101	-
D_5	67	-
serotonin transporter	91	-
norepinephrine transporter	70	-
dopamine transporter	76	-
μ-opioid receptor	99	-
δ-opioid receptor	93	-
κ-opioid receptor	47	5.8 ± 0.1
GABAA	118	-
H_1	86	-
H_2	103	-
H_3	79	-
H_4	107	-
α_{1A}	97	-
α_{1B}	102	-
α_{1D}	79	-
α_{2A}	98	-
α_{2B}	94	-
α_{2C}	85	-
β_1	80	-
β_3	73	-
M_1	88	-
M_2	90	-
M_3	87	-
M_4	100	-

M_5	108	-
benzodiazapine rat brain site	88	-
translocator protein (peripheral benzodiazepine site)	84	-
hERG binding	70	-
σ_1	76	-
σ_2	32	5.8 ± 0.1

Receptor binding profiles of compound **1180-447** were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. Radioligand binding was measured in the presence of 10 μM **1180-447**. A K_i value was determined for each receptor at which compound **1180-447** showed >50% inhibition. For experimental details please refer to the PDSP web site https://pdsp.unc.edu/ims/investigator/web/.

Table 9. Off-target actions of compound 1180-420.

Receptor	Radioligand binding in 10 μM XX (% control)	pK_i values from non-linear regression of radioligand competition binding isotherms
5-HT_{1A}	110	-
5-HT_{1B}	95	-
5-HT_{1D}	112	-
5-HT_{1E}	78	-
5-HT_{2A}	69	-
5-HT_{2B}	97	-
5-HT_{2C}	113	-
5-HT_3	116	-
5-HT_{5A}	95	-
5-HT_6	75	-
5-HT_7	115	-
D_1	59	-
D_2	87	-
D_3	71	-
D_4	90	-
D_5	37	5.9 ± 0.2
serotonin transporter	86	-
norepinephrine transporter	75	-
dopamine transporter	98	-
μ-opioid receptor	104	-
δ-opioid receptor	89	-

κ-opioid receptor	32	5.8 ± 0.1
GABAA	110	-
H_1	74	-
H_2	75	-
H_3	99	-
H_4	90	-
α_{1A}	91	-
α_{1B}	100	-
α_{1D}	79	-
α_{2A}	79	-
α_{2B}	93	-
α_{2C}	83	-
β_1	98	-
β_3	74	-
M_1	90	-
M_2	110	-
M_3	69	-
M_4	84	-
M_5	101	-
benzodiazapine rat brain site	71	-
translocator protein (peripheral benzodiazepine site)	67	-
hERG binding	73	-
σ_1	76	-
σ_2	48	5.8 ± 0.1

Receptor binding profiles of compound **1180-420** were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. Radioligand binding was measured in the presence of 10 μM **1180-420**. A K_i value was determined for each receptor at which compound **1180-420** showed >50% inhibition. For experimental details please refer to the PDSP web site https://pdsp.unc.edu/ims/investigator/web/.

3.3.10 Conclusions

Although CIQ is a useful *in vitro* tool compound for the study of GluN2C- and GluN2D-containing receptors, its *in vivo* use is limited due to modest potency and potentiation, low solubility, and high lipophilicity. We have developed second-generation GluN2C- and GluN2D-selective PAMs that address each of these concerns. For example, compound **1180-453** is a 3 μM potentiator that shows

order of magnitude improvements in lipophilic efficiency (ΔLLE = 1.3), doubling concentration (ΔpDC = 0.8-1.1), solubility (8 to 74 μM), and an order of magnitude decrease in cLogP (ΔcLogP = 1.1) compared to CIQ. Compound ***R*-(+)-1180-450** is a 1 μM potentiator with doubling concentrations in the 400-450 nM range resulting from >4.5-fold potentiation and a doubling concentration to solubility ratio of >100:1. These derivatives show minimal off-target activity and have been submitted for pharmacokinetic evaluation. If acceptable half-lives and brain penetration are observed, these compounds are excellent candidates for *in vivo* pain and schizophrenia animal models in the future. Overall, these compounds show dramatic improvements in potency, efficacy, and ADME properties over their predecessors and are a promising step towards the first useful *in vivo* tools to study positive modulation of GluN2C- and GluN2D-containing NMDA receptors.

3.4 Experimental Details

3.4.1 Chemistry experimental procedures

General Experimental: All starting materials were purchased from commercial sources and used directly without further purification. Purification by flash column chromatography was done using a Teledyne ISCO Combiflash Companion instrument using Teledyne Redisep normal phase columns. ^{1}H and ^{13}C NMR spectra were recorded on a Mercury-300, VNMR-400, INOVA-400, or INOVA-600 NMR spectrometer. Chemical shifts were reported in ppm and referenced to the residual deuterated solvent. Reactions were monitored by thin layer chromatography on precoated aluminum plates (silica gel 60 F254, 0.25 mm) or LCMS on an Agilent Technologies 1200 series instrument. High resolution mass spectra were recorded on a VG 70-S Nier Johnson or JEOL instrument by the Emory University Mass Spectroscopy Center. Purity was established via LCMS (Varian) in at least two solvent systems (MeOH:water/ACN:water or MeOH:water/MeOH:water) unless otherwise noted. The conditions were determined individually for each compound in which

purity was established via LCMS and the retention times in both solvent systems are given. Optical rotations were established using a PerkinElmer 314 instrument.

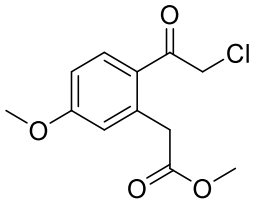
General Procedure for Alpha-Chloro Ketones (Procedure I): Methyl ester (1 equiv) was dissolved in DCE (1.0 M) and 1 M tin(IV) chloride in DCM (5 equiv) was added dropwise and for 10 minutes at room temperature. 2-chloroacetyl chloride (4 equiv) was then added at room temperature and the resulting mixture was heated to reflux for 90 minutes. Upon completion, the reaction was cooled to room temperature and quenched carefully with 1 M HCl. The organic layer was extracted with DCM, washed with saturated $NaHCO_3$ (2x), brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Biaryl Ketones (Procedure II): To a suspension of potassium iodide (1.2 equiv) and potassium carbonate (2 equiv) in acetone (0.17 M) was added alpha-chloro ketone (1 equiv) and phenol (1.2 equiv). The resulting mixture was then heated open to atmosphere at reflux for 4 hours. Upon completion, the reaction was cooled to room temperature and solvent removed *in vacuo*. The resulting residue was then dissolved in EtOAc and washed with water. The organic layer was then extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

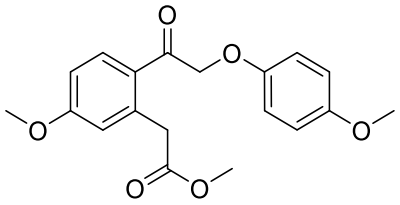
General Procedure for Tertiary Olefins (Procedure III): An appropriate microwave vial was charged with ketone (1 equiv), primary amine (1.2 equiv), tetraisopropoxytitanium (3 equiv), and DCE (0.2 M) and the solution was stirred for 10 minutes before sodium triacetoxyborohydride (3 equiv) was added and the mixture was irradiated at 120 ^oC for 30 min. Upon completion, the reaction was cooled to room temperature, diluted with DCM and washed with 1 M HCl. The organic layer was extracted with DCM, washed with $NaHCO_3$, washed with brine (3x), dried over

$MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound as a mixture of E/Z isomers, the mass confirmed via LCMS, and carried forward without further characterization.

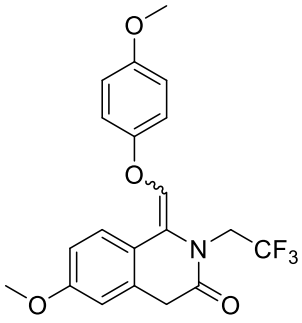
General Procedure for Final 1,4-dihydroisoquinolin-3(2H)-one Compounds (Procedure IV): Olefin (1 equiv) was dissolved in ethanol and 10% Pd/C (0.15 equiv) was added and the mixture was hydrogenated at 50 psi overnight. The reaction mixture was filtered through a pad of celite, washing with methanol, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.



Methyl 2-(2-(2-chloroacetyl)-5-methoxyphenyl)acetate (2). General procedure I was followed using methyl 2-(3-methoxyphenyl)acetate (**1**) (2.23 mL, 13.9 mmol), 1 M tin(IV) chloride in DCM (69.4 mL, 69.4 mmol), and 2-chloroacetyl chloride (4.45 mL, 55.5 mmol) in DCE (14 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.65 g, 46%). R_f (1:1 EtOAC:Hex): 0.66; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.75 (d, J = 8.7 Hz, 1H), 6.86 (dd, J = 8.7, 2.6 Hz, 1H), 6.78 (d, J = 2.6 Hz, 1H), 4.63 (s, 2H), 3.92 (s, 2H), 3.85 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, cdcl3) δ 191.80, 171.51, 162.84, 138.55, 132.11, 126.56, 119.12, 112.02, 55.49, 51.92, 47.07, 40.55. HRMS calcd. for $C_{12}H_{14}O_4Cl$, 257.05751 $[M + H]^+$; found 257.05751 $[M + H]^+$.

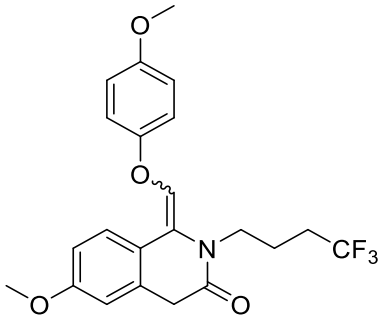


Methyl 2-(5-methoxy-2-(2-(4-methoxyphenoxy)acetyl)phenyl)acetate (3). General procedure II was followed using **2** (10.2 g, 39.7 mmol), potassium iodide (7.92 g, 47.7 mmol), 4-methoxyphenol (5.92 g, 47.7 mmol), and potassium carbonate (11.0 g, 79.0 mmol) in acetone (238 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 120 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white solid (7.23 g, 53%). R_f (1:1 EtOAC:Hex): 0.59; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.83 (d, J = 8.7 Hz, 1H), 6.88 – 6.77 (m, 6H), 5.10 (s, 2H), 3.94 (s, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 195.62, 171.70, 162.66, 154.26, 152.20, 138.22, 131.74, 126.76, 118.98, 115.83, 114.56, 111.98, 71.99, 55.64, 55.46, 51.94, 40.45. HRMS calcd. for $C_{19}H_{21}O_6$, 345.13326 $[M + H]^+$; found 345.13321 $[M + H]^+$.

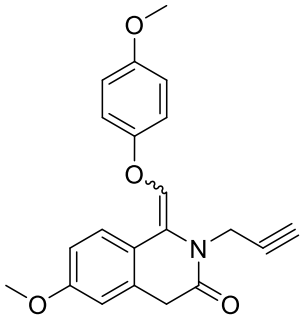


(E/Z)-6-methoxy-1-((4-methoxyphenoxy)methylene)-2-(2,2,2-trifluoroethyl)-1,2-dihydroisoquinolin-3(4H)-one (4a). General procedure III was followed using compound **3** (150 mg, 0.436 mmol), 2,2,2-trifluoroethanamine (69 μL, 0.87 mmol, 2 equiv), tetraisopropoxytitanium (400 μL, 1.3 mmol), and sodium triacetoxyborohydride (277 mg, 1.31 mmol) in DCE (2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30%

EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a yellow oil (33 mg, 19%). HRMS calcd. for $C_{20}H_{19}O_4NF_3$, 394.12607 $[M + H]^+$; found 394.12617 $[M + H]^+$.

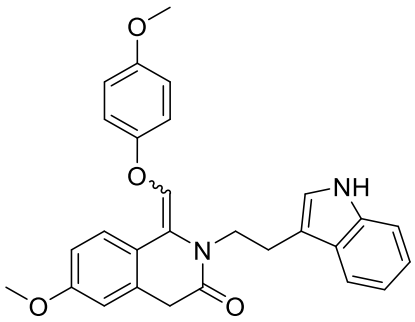


(E/Z)-6-methoxy-1-((4-methoxyphenoxy)methylene)-2-(4,4,4-trifluorobutyl)-1,2-dihydroisoquinolin-3(4H)-one (4b). General procedure III was followed using compound **3** (100 mg, 0.290 mmol), 4,4,4-trifluorobutan-1-amine (44 mg, 0.35 mmol), tetraisopropoxytitanium (260 μL, 0.87 mmol), and sodium triacetoxyborohydride (185 mg, 0.871 mmol) in DCE (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and an orange oil (42 mg, 34%). HRMS calcd. for $C_{22}H_{23}O_4NF_3$, 422.15737 $[M + H]^+$; found 422.15750 $[M + H]^+$.

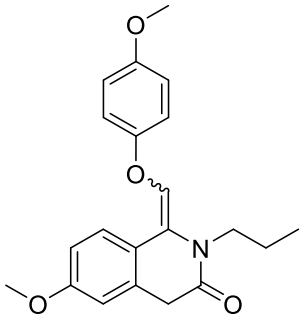


(E/Z)-6-methoxy-1-((4-methoxyphenoxy)methylene)-2-(prop-2-yn-1-yl)-1,4-dihydroisoquinolin-3(2H)-one (4c). General procedure III was followed using compound **3** (200 mg, 0.581 mmol), propargylamine (112 μL, 1.74 mmol), tetraisopropoxytitanium (495 μL, 1.74

mmol), and sodium triacetoxyborohydride (369 mg, 1.74 mmol) in DCE (3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as single E/Z isomer and a white solid (160 mg, 80%). HRMS calcd. for $C_{21}H_{20}O_4N$, 350.13868 $[M + H]^+$; found 350.13837 $[M + H]^+$.

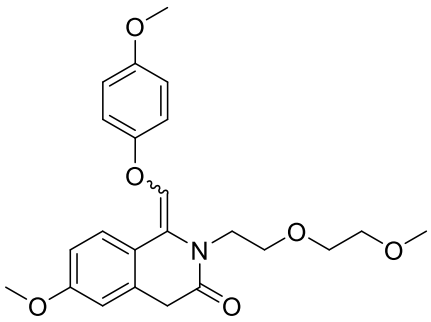


(E/Z)-2-(2-(1H-indol-3-yl)ethyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4d). General procedure III was followed using compound **3** (75 mg, 0.22 mmol), tryptamine (42 mg, 0.26 mmol), tetraisopropoxytitanium (198 μL, 0.653 mmol), and sodium triacetoxyborohydride (138 mg, 0.653 mmol) in DCE (1.1 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a red oil (20 mg, 40%). HRMS calcd. for $C_{28}H_{27}O_4N_2$, 455.19653 $[M + H]^+$; found 455.19586 $[M + H]^+$.

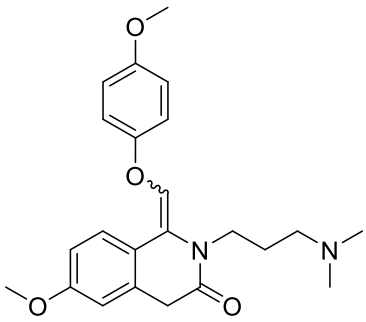


(E/Z)-6-methoxy-1-((4-methoxyphenoxy)methylene)-2-propyl-1,4-dihydroisoquinolin-3(2H)-one (4e). General procedure III was followed using compound **3** (75 mg, 0.22 mmol), propylamine (21 μL, 0.26 mmol), tetraisopropoxytitanium (198 μL, 0.653 mmol), and sodium

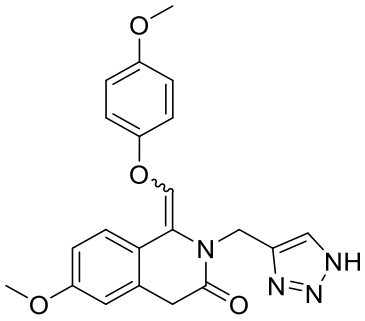
triacetoxyborohydride (138 mg, 0.653 mmol) in DCE (1.1 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-40% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a brown oil (31 mg, 40%). HRMS calcd. for $C_{21}H_{28}O_4N$, 358.20128 $[M + H]^+$; found 358.20118 $[M + H]^+$.



(E/Z)-6-methoxy-2-(2-(2-methoxyethoxy)ethyl)-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4f). General procedure III was followed using compound **3** (60 mg, 0.18 mmol), 2-(2-methoxyethoxy)ethanamine (25 mg, 0.21 mmol), tetraisopropoxytitanium (159 μL, 0.524 mmol), and sodium triacetoxyborohydride (111 mg, 0.524 mmol) in DCE (0.9 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a red oil (14 mg, 19%). HRMS calcd. for $C_{23}H_{28}O_6N$, 414.19111 $[M + H]^+$; found 414.19038 $[M + H]^+$.

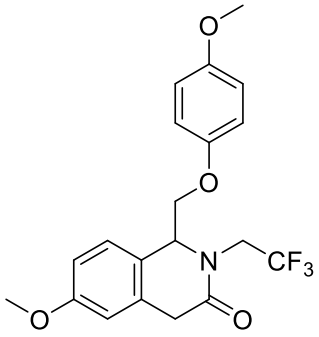


(E/Z)-2-(3-(dimethylamino)propyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4g). General procedure III was followed using compound **3** (50 mg, 0.15 mmol), 3-(dimethylamino)-1-propylamine (37 μL, 0.29 mmol, 2 equiv), tetraisopropoxytitanium (132 μL, 0.436 mmol), and sodium triacetoxyborohydride (92 mg, 0.44 mmol) in DCE (0.7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-10% DCM/(1% NH_4OH in MeOH) gradient) to afford the title compound as a mixture of E/Z isomers and a red oil (13 mg, 23%). HRMS calcd. for $C_{23}H_{29}O_4N_2$, 397.21218 $[M + H]^+$; found 397.21243 $[M + H]^+$.



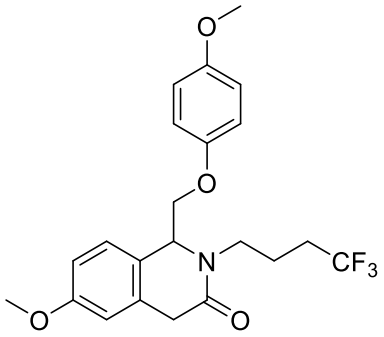
2-((1H-1,2,3-triazol-4-yl)methyl)-6-methoxy-1-((4-methoxyphenoxy)methylene)-1,4-dihydroisoquinolin-3(2H)-one (4h). 37% Formaldehyde in H_2O (0.17 mL, 2.2 mmol, 10 equiv) acetic acid (0.018 mL, 0.32 mmol, 1.5 equiv) were dissolved in THF (0.2 mL) and stirred for 15 minutes. Sodium azide (21 mg, 0.32 mmol, 1.5 equiv) and **3** (75 mg, 0.22 mmol, 1 equiv) dissolved in THF (0.2 mL) were then added in succession and stirred for 10 minutes. Then sodium ascorbate (9.0 mg, 0.045 mmol, 0.2 equiv) was added, followed by an aqueous $CuSO_4$ solution (200 mg/mL, 0.05 equiv) and the reaction was stirred at room temperature for 24 hours. The reaction was then concentrated before being dissolved in EtOAc and washed with 1 M NaOH. The organic layer was extracted with EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-10% DCM/(1% NH_4OH in MeOH) gradient) to afford the title compound as a single E/Z isomer and a

yellow oil (24 mg, 29%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.46; ^1H NMR (399 MHz, Chloroform-d) δ 7.51 (s, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.88 – 6.83 (m, 3H), 6.75 (dd, J = 8.5, 2.6 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.53 (s, 1H), 5.23 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.68 (s, 2H). ^{13}C NMR (100 MHz, cdcl3) δ 169.47, 159.54, 156.01, 150.66, 132.14, 130.80, 130.79, 123.75, 123.67, 121.91, 117.80, 114.91, 114.77, 113.21, 112.13, 55.70, 55.40, 40.04, 39.03. HRMS calcd. for $C_{21}H_{21}O_4N_4$, 393.15573 $[M + H]^+$; found 393.15487 $[M + H]^+$.

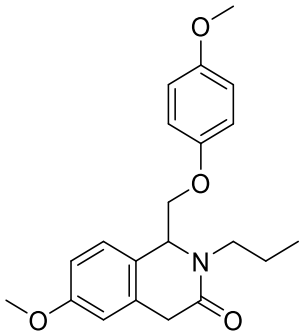


6-methoxy-1-((4-methoxyphenoxy)methyl)-2-(2,2,2-trifluoroethyl)-1,2-dihydroisoquinolin-3(4H)-one (1180-301). General procedure IV was followed using compound **4a** (33 mg, 0.084 mmol) and 10% Pd/C (13 mg, 0.013 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (8.8 mg, 27%). Rf (1:1 EtOAc:Hex): 0.60; ^1H NMR (400 MHz, Chloroform-d) δ 7.19 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 8.6, 2.8 Hz, 1H), 6.81 – 6.72 (m, 4H), 6.72 (d, J = 2.3 Hz, 1H), 5.07 – 4.96 (m, 1H), 4.94 (dd, J = 7.6, 4.0 Hz, 1H), 4.09 (dd, J = 9.7, 3.8 Hz, 1H), 3.99 (dd, J = 9.7, 7.8 Hz, 1H), 3.96 – 3.82 (m, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.68 (d, J = 19.6 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 169.94, 159.72, 154.39, 151.92, 133.63, 127.25, 126.69 (q, J = 273.5 Hz, ^1J), 123.64, 115.32, 114.70, 113.06, 112.61, 72.08, 61.32, 55.67, 55.39, 46.33 (q, J = 33.6 Hz, ^2J), 37.37. HRMS calcd. for $C_{20}H_{21}O_4NF_3$, 396.14172 $[M + H]^+$; found 396.14143 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column

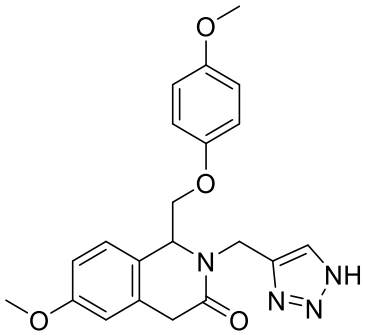
(4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 10 min at 1 mL/min (retention time = 1.21 min). Method 2: 75-95% MeOH in water over 6 min at 1 mL/min (retention time 3.78 min).



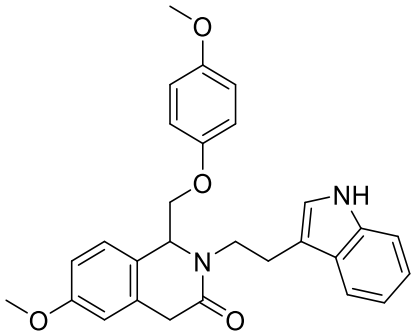
6-methoxy-1-((4-methoxyphenoxy)methyl)-2-(4,4,4-trifluorobutyl)-1,2-dihydroisoquinolin-3(4H)-one (1180-300). General procedure IV was followed using compound **4b** (79 mg, 0.19 mmol) and 10% Pd/C (30 mg, 0.028 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-30% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (18 mg, 23%). R_f (1:1 EtOAc:Hex): 0.47; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 2.6 Hz, 1H), 6.82 – 6.69 (m, 5H), 4.68 (t, J = 5.4 Hz, 1H), 4.09 – 3.98 (m, 2H), 3.81 (d, J = 19.3 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.56 (d, J = 19.3 Hz, 1H), 3.37 – 3.26 (m, 2H), 2.18 – 2.05 (m, 2H), 1.94 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 169.45, 159.55, 154.31, 152.19, 134.18, 127.12, 126.95 (q, J = 276.2 Hz, ^1J), 124.58, 115.39, 114.71, 112.86, 112.43, 71.71, 61.17, 55.70, 55.38, 45.69, 37.67, 31.34 (q, J = 29.1 Hz, ^2J), 20.45 (q, J = 2.6 Hz, ^3J). HRMS calcd. for $C_{22}H_{25}O_4NF_3$, 424.17302 $[M + H]^+$; found 424.17256 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 6 min at 1 mL/min (retention time = 4.69 min). Method 2: 85-95% ACN in water over 6 min at 1 mL/min (retention time 1.48 min).



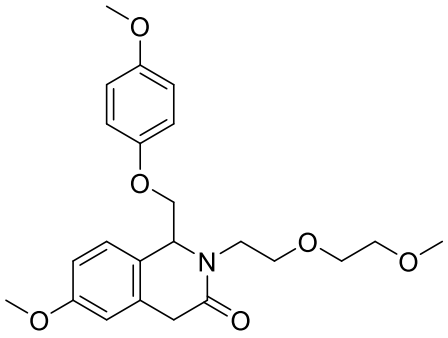
6-methoxy-1-((4-methoxyphenoxy)methyl)-2-propyl-1,4-dihydroisoquinolin-3(2H)-one (1180-338). General procedure IV was followed using compound **4e** (31 mg, 0.088 mmol) and 10% Pd/C (14 mg, 0.013 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (15 mg, 48%). R_f (1:1 EtOAc:Hex): 0.28; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.19 (d, J = 8.4 Hz, 1H), 6.83 – 6.68 (m, 6H), 4.68 (t, J = 5.3 Hz, 1H), 4.16 – 4.00 (m, 3H), 3.84 (d, J = 19.2 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.56 (d, J = 19.2 Hz, 1H), 3.14 – 3.06 (m, 1H), 1.70 – 1.55 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 169.16, 159.38, 154.20, 152.39, 134.51, 127.19, 125.12, 115.45, 114.66, 112.65, 112.28, 71.43, 60.86, 55.70, 55.37, 48.26, 37.78, 20.95, 11.37.NMR (126 MHz, cdcl3) δ 169.29, 159.38, 154.21, 152.34, 134.28, 127.13, 124.56, 115.44, 114.67, 112.79, 112.23, 71.46, 63.11, 55.71, 55.37, 37.31, 34.69. HRMS calcd. for $C_{21}H_{26}O_4N$, 356.18563 $[M + H]^+$; found 356.18553 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.35 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 0.81 min).



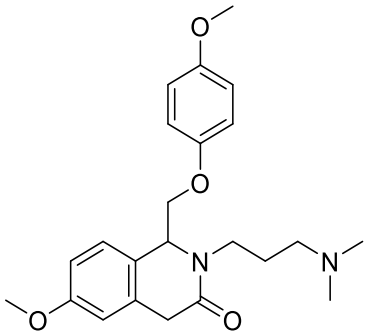
2-((1H-1,2,3-triazol-4-yl)methyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-360). A modified version of general procedure IV was followed using compound **4h** (22 mg, 0.056 mmol), 10% Pd/C (8.9 mg, 0.0083 mmol), and AcOH (catalytic) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (15 mg, 68%). R_f (9:1 DCM:MeOH): 0.43; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.66 (s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.80 – 6.65 (m, 6H), 5.27 (d, J = 15.3 Hz, 1H), 4.87 (t, J = 4.8 Hz, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.16 – 4.00 (m, 2H), 3.91 (d, J = 19.3 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.60 (d, J = 19.4 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 170.08, 159.39, 154.17, 152.15, 133.72, 127.10, 124.33, 115.38, 114.61, 112.93, 112.23, 71.62, 61.11, 55.67, 55.35, 41.05, 37.45. HRMS calcd. for $C_{21}H_{23}O_4N_4$, 395.17138 $[M + H]^+$; found 395.17077 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 6 min at 1 mL/min (retention time = 1.78 min). Method 2: 75-95% MeOH in water over 3 min at 1 mL/min (retention time 1.53 min).



2-(2-(1H-indol-3-yl)ethyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-364). A modified version of general procedure IV was followed using compound **4d** (21 mg, 0.046 mmol), 10% Pd/C (7.3 mg, 0.0069 mmol) and AcOH (catalytic) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (10 mg, 45%). R_f (1:1 EtOAc:Hex): 0.17; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.88 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.78 – 6.62 (m, 6H), 4.42 – 4.33 (m, 2H), 3.94 – 3.89 (m, 2H), 3.84 (d, J = 19.2 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.58 (d, J = 19.0 Hz, 1H), 3.53 – 3.43 (m, 1H), 3.08 (t, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 169.28, 159.28, 154.12, 152.33, 136.21, 134.39, 127.25, 126.97, 125.15, 122.20, 122.04, 119.43, 118.80, 115.41, 114.62, 113.10, 112.56, 112.13, 111.10, 71.39, 61.88, 55.70, 55.38, 47.99, 37.94, 23.73. HRMS calcd. for $C_{28}H_{29}O_4N_2$, 457.21218 $[M + H]^+$; found 457.21230 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 2.29 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.94 min).



6-methoxy-2-(2-(2-methoxyethoxy)ethyl)-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-373). General procedure IV was followed using compound **4f** (16 mg, 0.039 mmol) and 10% Pd/C (6.2 mg, 0.0059 mmol) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a red oil. (10 mg, 83%). R_f (1:1 EtOAc:Hex): 0.44; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.16 (d, J = 8.4 Hz, 1H), 6.83 – 6.66 (m, 6H), 4.93 (t, J = 5.0 Hz, 1H), 4.18 – 4.01 (m, 3H), 3.84 (d, J = 18.2 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.73 – 3.68 (m, 1H), 3.65 – 3.59 (m, 1H), 3.59 – 3.51 (m, 3H), 3.51 – 3.45 (m, 1H), 3.44 – 3.40 (m, 2H), 3.31 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 169.62, 159.29, 154.10, 152.50, 134.39, 127.16, 125.40, 115.42, 114.62, 112.64, 112.21, 71.78, 71.43, 70.40, 69.95, 62.31, 58.97, 55.71, 55.36, 46.85, 37.84. HRMS calcd. for $C_{23}H_{30}O_6N$, 416.20676 $[M + H]^+$; found 416.20700 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 6 min at 1 mL/min (retention time = 3.58 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.86 min).



2-(3-(dimethylamino)propyl)-6-methoxy-1-((4-methoxyphenoxy)methyl)-1,4-dihydroisoquinolin-3(2H)-one (1180-382). A modified version of general procedure IV was followed using compound **4g** (16 mg, 0.039 mmol), 10% Pd/C (6.2 mg, 0.0059 mmol), and AcOH (catalytic) in ethanol (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a red oil. (10 mg, 83%). R_f (1:1 EtOAc:Hex): 0.40; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.16 (d, J = 8.4 Hz, 1H), 6.83 – 6.66 (m, 6H), 4.93 (t, J = 5.0 Hz, 1H), 4.18 – 4.01 (m, 3H), 3.84 (d, J = 18.2 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.73 – 3.68 (m, 1H), 3.65 – 3.59 (m, 1H), 3.59 – 3.51 (m, 3H), 3.51 – 3.45 (m, 1H), 3.44 – 3.40 (m, 2H), 3.31 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 169.62, 159.29, 154.10, 152.50, 134.39, 127.16, 125.40, 115.42, 114.62, 112.64, 112.21, 71.78, 71.43, 70.40, 69.95, 62.31, 58.97, 55.71, 55.36, 46.85, 37.84. HRMS calcd. for $C_{23}H_{31}O_4N_2$, 399.22783 $[M + H]^+$; found 399.22743 $[M + H]^+$. Purity was established to be 85% pure using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 50-95% MeOH in water over 6 min at 1 mL/min (retention time = 5.56 min). Method 2: 75-95% MeOH in water over 6 min at 1 mL/min (retention time 1.18 min).

B-Ring Derivatives

General Procedure for Alpha-Chloro Amides (Procedure V): Primary amine (1 equiv) was dissolved in dry DCM and triethylamine (2 equiv) was added. The solution was brought to 0 ℃, 2-chloroacetyl chloride (1.2 equiv) was added, and the mixture was reacted at room temperature for 1 hour, when deemed complete by LCMS. The reaction was then quenched with 1 M HCl, extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

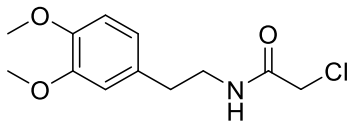
General Procedure for Alkylation of Alkyl Halide Using Cesium Carbonate (Procedure VI): Phenol (1.2 equiv) was dissolved in acetonitrile and cesium carbonate (4 equiv) was added. This mixture was stirred at room temperature for 2 hours before alpha-chloro amide (1 equiv) in acetonitrile was added and allowed to react at room temperature overnight. The reaction was then quenched with saturated ammonium chloride and the product extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Alkylation of Alkyl Halide Using Sodium Hydride (Procedure VII): 60% sodium hydride dispersion in mineral oil (1.4-3 equiv) was added to a solution of alcohol (1.2 equiv) in dry THF or DMF (~0.4-0.8 M) at 0 ℃ under argon. After 30 minutes, alkyl halide in dry THF (~0.4-0.8M) was added dropwise, and the mixture was stirred at room temperature overnight. Upon reaction completion, excess sodium hydride was quenched with water, poured over ice, and 1 M HCl was added. The organic layer was extracted with ethyl acetate (3x) and the organic layers combined, washed with brine (1x), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

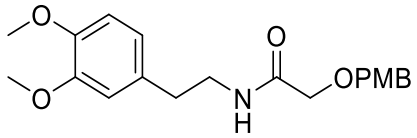
General Procedure for Bischler-Napieralksi Cyclizations (Procedure VIII): Acetamide (1 equiv) was dissolved in dry acetonitrile (~0.05 M) and $POCl_3$ (3 equiv) was added. This was reacted at reflux overnight when the reaction was deemed complete via TLC. The reaction was cooled to room temperature and concentrated *in vacuo* to afford the crude compound. The crude imine was dissolved in dry MeOH and cooled to 0 ℃ before sodium borohydride (3 equiv) was added in ~100 mg portions. The mixture stirred at room temperature for 10 minutes. The reaction was then concentrated and subsequently partitioned between EtOAc and H_2O. The product was then extracted into EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Tetrahydroisoquinolines (Procedure IX): Secondary amine (1 equiv) was dissolved in dry DCM, triethylamine (2 equiv) was added and the solution was brought to 0 ℃ before acid chloride (1.2 equiv) was added dropwise. The mixture was stirred at room temperature for 1 hours. The reaction was then quenched with 1 M HCl and the organic layer was extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for S_NAr Reactions (Procedure X): Primary alcohol (1 equiv) was dissolved in dry THF or DMF (~0.2 M) and 60% sodium hydride dispersion in mineral oil (2-3 equiv) was added. This was stirred for 30 minutes at room temperature before heteroaryl halide (1.5 equiv) was added. The reaction was stirred at 70 ℃ overnight. The reaction was then cooled to room temperature, quenched carefully with water, and diluted with both EtOAc and water. The aqueous layer was extracted with EtOAc, the organic layers combined, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

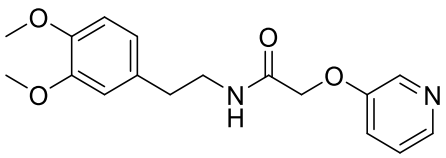


2-(3,4-dimethoxyphenyl)ethanamine (6): General procedure V was followed using compound 3,4-dimethoxyphenethylamine (**5**) (5.59 mL, 33.1 mmol), triethylamine (9.23 mL, 66.2 mmol), and 2-chloroacetyl chloride (3.16 mL, 39.7 mmol) in dry DCM (120 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-80% EtOAc/hexanes gradient) to afford the title compound as a white solid (6.32 g, 74%). R_f (1:1 EtOAc:Hex): 0.56; ^{1}H NMR (300 MHz, Chloroform-d) δ 6.82 (d, J = 8.0 Hz, 1H), 6.77 – 6.69 (m, 2H), 6.64 (s, 0H), 4.02 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.53 (q, J = 6.9 Hz, 2H), 2.78 (t, J = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, cdcl3) δ 165.74, 149.01, 147.76, 130.78, 120.63, 111.75, 111.33, 55.89, 42.67, 41.07, 35.06. HRMS calcd. for $C_{12}H_{17}O_3NCl$, 258.08915 $[M + H]^+$; found 258.08876 $[M + H]^+$.

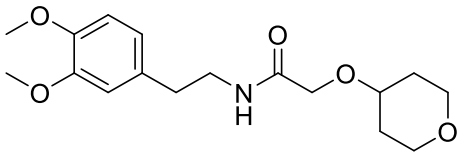


N-(3,4-dimethoxyphenethyl)-2-((4-methoxybenzyl)oxy)acetamide (7a): General procedure VII was followed using compound **6** (18.8 g, 73.0 mmol), 4-methoxybenzyl alcohol (12.1 g, 87.5 mmol), and 60% sodium hydride dispersion in mineral oil (4.38 g, 110. mmol) in THF (196 mL). The crude material was purified via flash column chromatography (ISCO, Redisep 320 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as an orange solid (20.1 g, 74%). R_f (1:1 EtOAc:Hex): 0.67; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.22 (t, J = 7.8 Hz, 1H), 7.19 – 7.13 (m, 2H), 6.91 – 6.84 (m, 2H), 6.81 – 6.73 (m, 3H), 6.65 (s, 1H), 4.43 (s, 2H), 3.94 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.54 (q, J = 7.0 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 169.61, 159.85, 159.59, 140.33, 129.63, 129.54, 128.92, 121.05, 114.37, 113.96, 111.98,

73.17, 69.28, 55.30, 55.15, 39.78, 35.71. HRMS calcd. for $C_{20}H_{26}O_5N$, 360.18055 $[M + H]^+$; found 360.18023 $[M + H]^+$.

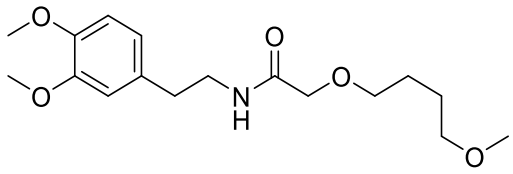


N-(3,4-dimethoxyphenethyl)-2-(pyridin-3-yloxy)acetamide (7b): General procedure VI was followed using compound **6** (0.20 g, 0.78 mmol), 3-hydroxypyridine (89 mg, 0.93 mmol), and cesium carbonate (1.0 g, 3.1 mmol) in acetonitrile (4.6 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.15 g, 60%). R_f (9:1 DCM:MeOH): 0.49; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.28 – 8.23 (m, 2H), 7.24 – 7.18 (m, 1H), 7.14 – 7.08 (m, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.70 – 6.63 (m, 3H), 4.47 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.57 (q, J = 6.9 Hz, 2H), 2.78 (t, J = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 167.19, 153.44, 149.11, 147.82, 143.42, 138.30, 130.85, 124.00, 120.93, 120.65, 111.81, 111.35, 67.47, 55.91, 55.83, 40.22, 35.16. HRMS calcd. for $C_{17}H_{21}O_4N_2$, 317.14958 $[M + H]^+$; found 317.14920 $[M + H]^+$.

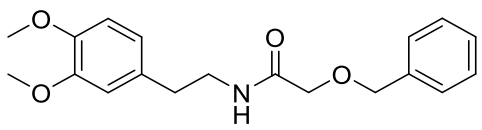


N-(3,4-dimethoxyphenethyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)acetamide (7c): General procedure VII was followed using compound **6** (0.20 g, 0.78 mmol), 4-hydroxytetrahydropyran (95 mg, 0.93 mmol), and 60% sodium hydride dispersion in mineral oil (43 mg, 1.1 mmol) in THF (3.9 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.19 g, 75%). R_f (9:1 DCM:MeOH): 0.62; ^{1}H NMR (500 MHz, Chloroform-d) δ 6.79 (d, J = 7.9 Hz, 1H), 6.75

– 6.70 (m, 2H), 6.62 (s, 1H), 3.93 (s, 2H), 3.90 – 3.83 (m, 8H), 3.53 (q, J = 6.9 Hz, 2H), 3.47 (tt, J = 8.7, 4.0 Hz, 1H), 3.39 (ddd, J = 12.0, 9.7, 2.7 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.56 – 1.45 (m, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 169.73, 149.08, 147.76, 131.14, 120.64, 111.83, 111.29, 74.97, 67.26, 65.33, 55.92, 55.85, 39.92, 35.19, 32.13. HRMS calcd. for $C_{17}H_{26}O_5N$, 324.18055 $[M + H]^+$; found 324.18056 $[M + H]^+$.

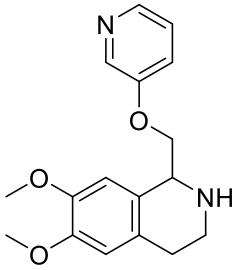


N-(3,4-dimethoxyphenethyl)-2-(4-methoxybutoxy)acetamide (7d): General procedure VII was followed using compound **6** (0.10 g, 0.39 mmol), 4-methoxy-1-butanol (49 mg, 0.47 mmol), and 60% sodium hydride dispersion in mineral oil (22 mg, 0.54 mmol) in THF (1.0 mL). The crude material was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a clear oil (68 mg, 54%). R_f (9:1 DCM:MeOH): 0.58; ^{1}H NMR (399 MHz, Chloroform-d) δ 6.77 (d, J = 8.1 Hz, 1H), 6.74 – 6.67 (m, 2H), 6.61 (bs, 1H), 3.86 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.49 (q, J = 7.0 Hz, 2H), 3.42 (t, J = 6.1 Hz, 2H), 3.32 (t, J = 6.1 Hz, 2H), 3.28 (s, 3H), 2.74 (t, J = 7.1 Hz, 2H), 1.63 – 1.43 (m, 4H). ^{13}C NMR (100 MHz, cdcl3) δ 169.71, 148.98, 147.64, 131.19, 120.59, 111.80, 111.28, 72.28, 71.39, 70.15, 58.52, 55.83, 55.77, 39.95, 35.25, 26.29, 26.12. HRMS calcd. for $C_{17}H_{28}O_5N$, 326.19620 $[M + H]^+$; found 326.19579 $[M + H]^+$.



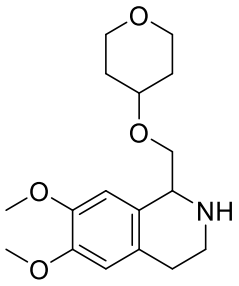
2-(benzyloxy)-N-(3,4-dimethoxyphenethyl)acetamide (7e): Compound **6** (2.97 g, 11.5 mmol) was dissolved in dry THF (14 mL) and cooled to 0°C under argon and sodium hydride (0.61 g, 15

mmol) was added. This mixture was stirred for 30 min before benzyl alcohol (1.41 g, 13.0 mmol) in THF (14 mL) was added dropwise and allowed to react at room temperature overnight. The reaction was then cooled to 0°C and quenched with water. It was then poured over ice and 1 M HCl was added, after which the organic layer was extracted in EtOAc, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 30-100% EtOAc/hexanes gradient) to afford the title compound as a yellow oil (2.7 g, 70%). R_f (1:1 EtOAC:Hex): 0.19; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.20 (m, 4H), 6.85 – 6.65 (m, 4H), 4.49 (s, 2H), 3.97 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.54 (q, J = 6.8 Hz, 2H), 2.78 (t, J = 7.0 Hz, 2H).^{13}C NMR (101 MHz, cdcl3) δ 171.08, 169.37, 148.95, 147.61, 136.76, 131.14, 128.52, 128.14, 127.75, 120.58, 111.74, 111.23, 73.40, 69.54, 55.75, 39.95, 35.20. HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16998 $[M + H]^+$; found 330.16945 $[M + H]^+$.

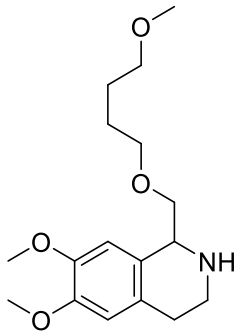


6,7-dimethoxy-1-((pyridin-3-yloxy)methyl)-1,2,3,4-tetrahydroisoquinoline (8a): General procedure VIII was followed using compound **7b** (0.20 g, 0.64 mmol), phosphorous oxychloride (0.30 mL, 3.2 mmol), and sodium borohydride (72 mg, 1.9 mmol) in acetonitrile (7.4 mL) and MeOH (1.9 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a white solid (0.12 g, 60%). R_f (8:2 DCM:MeOH): 0.66; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.34 (dd, J = 2.6, 0.9 Hz, 1H), 8.21 (dd, J = 4.1, 1.9 Hz, 1H), 7.25 – 7.16 (m, 2H), 6.65 (s, 1H), 6.61 (s, 1H), 4.36

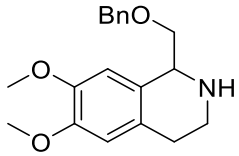
(dd, J = 7.9, 4.6 Hz, 1H), 4.21 – 4.12 (m, 2H), 3.84 (s, 4H), 3.82 (s, 3H), 3.19 (ddd, J = 12.2, 6.8, 5.4 Hz, 1H), 3.03 (dt, J = 12.1, 5.5 Hz, 1H), 2.75 (q, J = 5.3 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 148.03, 147.30, 142.42, 138.05, 128.25, 125.95, 123.85, 121.19, 112.08, 109.52, 71.16, 56.06, 55.84, 54.60, 39.82, 29.21. HRMS calcd. for $C_{17}H_{21}O_3N_2$, 301.15467 $[M + H]^+$; found 301.15442 $[M + H]^+$.



6,7-dimethoxy-1-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline (8b): General procedure VIII was followed using compound **7c** (187 mg, 0.578 mmol), phosphorous oxychloride (0.27 mL, 2.9 mmol), and sodium borohydride (66 mg, 1.7 mmol) in acetonitrile (9.2 mL) and MeOH (2.4 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a clear oil (29 mg, 16%). R_f (9:1 DCM:MeOH): 0.44; ^{1}H NMR (399 MHz, Chloroform-d) δ 6.62 (s, 1H), 6.58 (s, 1H), 4.08 (dd, J = 8.8, 3.9 Hz, 1H), 3.98 – 3.87 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.72 (dd, J = 9.2, 4.0 Hz, 1H), 3.63 – 3.49 (m, 2H), 3.48 – 3.37 (m, 2H), 3.18 (dt, J = 11.7, 5.7 Hz, 1H), 2.96 (dt, J = 11.8, 5.9 Hz, 1H), 2.73 (t, J = 5.8 Hz, 2H), 2.40 (s, 1H), 1.97 – 1.85 (m, 2H), 1.69 – 1.52 (m, 2H). ^{13}C NMR (100 MHz, cdcl3) δ 147.62, 147.02, 127.89, 127.18, 111.86, 109.30, 74.44, 70.86, 65.64, 56.00, 55.99, 55.79, 55.24, 40.17, 32.60, 32.27, 29.28. HRMS calcd. for $C_{17}H_{26}O_4N$, 308.18563 $[M + H]^+$; found 308.18552 $[M + H]^+$.

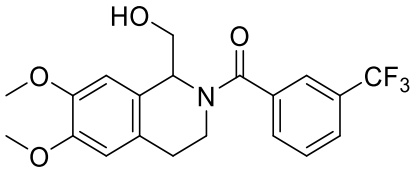


6,7-dimethoxy-1-((4-methoxybutoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (8c): General procedure VIII was followed using compound **7d** (68 mg, 0.21 mmol), phosphorous oxychloride (97 µL, 1.0 mmol), and sodium borohydride (24 mg, 0.63 mmol) in acetonitrile (3.1 mL) and MeOH (0.80 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a clear oil (26 mg, 40%). R_f (9:1 DCM:MeOH): 0.35; ^{1}H NMR (500 MHz, Chloroform-d) δ 6.62 (s, 1H), 6.58 (s, 1H), 4.10 (dd, J = 8.7, 3.6 Hz, 1H), 3.83 (s, 6H), 3.67 (dd, J = 9.5, 3.8 Hz, 1H), 3.61 – 3.45 (m, 4H), 3.41 – 3.35 (m, 2H), 3.32 (s, 3H), 3.19 (dt, J = 11.7, 5.7 Hz, 1H), 2.97 (dt, J = 11.8, 5.8 Hz, 1H), 2.74 (t, J = 5.7 Hz, 2H), 1.72 – 1.61 (m, 4H). ^{13}C NMR (126 MHz, cdcl3) δ 147.65, 147.12, 127.87, 127.17, 111.91, 109.37, 73.77, 72.53, 71.12, 58.53, 56.00, 55.81, 55.06, 40.17, 29.24, 26.40, 26.37. HRMS calcd. for $C_{17}H_{28}O_4N$, 310.20128 $[M + H]^+$; found 310.20110 $[M + H]^+$.



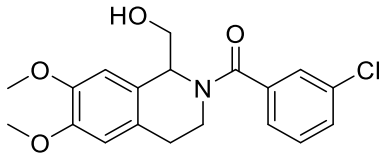
1-((benzyloxy)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8d): General procedure VIII was followed using compound **7e** (2.67 g, 8.11 mmol), phosphorous oxychloride (2.27 mL, 24.3 mmol), and sodium borohydride (0.64 g, 24 mmol) in acetonitrile (~40 mL) and MeOH (~10 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a white foam (1.6 g,

62% over two steps). R_f (1:1 EtOAC:Hex): 0.29; ^{1}H NMR (300 MHz, Chloroform-d) δ 7.38 – 7.26 (m, 5H), 6.58 (s, 2H), 4.68 – 4.50 (m, 2H), 4.17 (dd, J = 8.2, 3.9 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.75 – 3.62 (m, 2H), 3.25 – 3.10 (m, 1H), 3.04 – 2.90 (m, 1H), 2.74 (t, J = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, cdcl3) δ 147.62, 147.06, 138.03, 128.40, 127.79, 127.72, 127.66, 126.64, 111.76, 109.23, 73.29, 72.89, 55.92, 55.77, 54.99, 40.03, 28.95. HRMS calcd. for $C_{19}H_{24}O_3N$, 314.17507 $[M + H]^+$; found 314.17453 $[M + H]^+$.



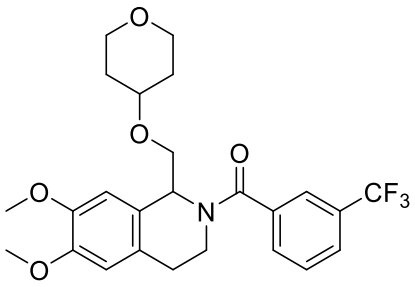
(1-(hydroxymethyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (9a): In step 1, a modified version of general procedure VIII was followed, in which the material was refluxed for only 1 h instead of overnight and only one equivalent of $POCl_3$ was used due to the loss of the PMB protecting group and conversion to the alkyl chloride upon continued heating. This proceeded using compound **7a** (11.1 g, 30.8 mmol), phosphorous oxychloride (2.87 mL, 30.8 mmol), and sodium borohydride (3.50 g, 92.5 mmol) in acetonitrile (493 mL) and MeOH (123 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-15% MeOH/DCM gradient) to afford impure 6,7-dimethoxy-1-(((4-methoxybenzyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinoline as a clear oil (4.71 g) that was carried forward without further characterization. General procedure IX was followed for step 2 using the above compound (4.71 g, 13.7 mmol), triethylamine (3.82 mL, 27.4 mmol), and 3-(trifluoromethyl)benzoyl chloride (2.48 mL, 16.4 mmol) in DCM (214 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 80 g column, 0-100% EtOAc/hexanes gradient) to afford impure (6,7-dimethoxy-1-(((4-methoxybenzyl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone as a clear oil (2.77 g) that

was carried forward without further characterization. Finally, the above compound (2.77 g, 5.37 mmol) was hydrogenated at 50 psi using 10% Pd/C (0.57 g, 0.54 mmol) in MeOH (32 mL) overnight. The reaction mixture was filtered through a pad of celite, washing with methanol, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white foam (1.01 g, 8% over 3 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 – 7.54 (m, 4H), 6.76 – 6.37 (m, 2H), 5.77 (dd, *J* = 8.8, 3.6 Hz, 0.8H), 4.88 – 4.71 (m, 0.2H), 4.14 – 4.07 (m, 1H), 4.02 – 3.93 (m, 1H), 3.88 (s, 2.5H), 3.86 (s, 3.5H), 3.79 – 3.70 (m, 2H), 3.64 – 3.55 (m, 0.8H), 3.31 – 3.21 (m, 0.2H), 3.09 (ddd, *J* = 17.7, 12.5, 6.5 Hz, 0.2H), 2.94 (ddd, *J* = 17.0, 11.9, 5.7 Hz, 0.8H), 2.74 – 2.66 (m, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 171.37, 148.40, 148.07, 136.65, 130.22, 129.30, 126.78, 125.75, 124.26, 123.89, 111.48, 110.11, 66.93, 56.08, 55.94, 55.53, 42.29, 28.73 (Unable to discern between fluorine splitting and minor peaks; only major peaks reported; major CF_3 peak not reported). HRMS calcd. for $C_{20}H_{21}O_4NF_3$, 396.14172 $[M + H]^+$; found 369.14133 $[M + H]^+$.



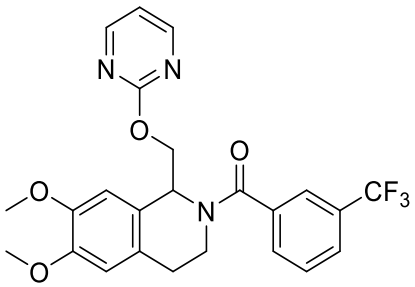
(3-chlorophenyl)(1-(hydroxymethyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (9b): General procedure IX was followed using compound **8d** (1.56 g, 4.98 mmol), triethylamine (1.39 mL, 9.96 mmol), and 3-chlorobenzoyl chloride (0.77 mL, 6.0 mmol) in DCM (80 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a white foam (1.4 g) that was carried forward without further characterization. This material (1.4 g, 3.0 mmol) was dissolved in a 2:3 mixture of chloroform (40 mL) and methanesulfonic acid (60 mL) and allowed to react at room temperature for 6 hours. The reaction was then poured over ice, dilute with EtOAc,

and quenched with saturated $NaHCO_3$. The organic layer was then washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a white foam (0.48 g, 44% over 2 steps). R_f (1:1 EtOAC:Hex): 0.07; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.60 – 6.97 (m, 4H), 6.78 – 6.38 (m, 2H), 5.75 (dd, J = 8.6, 3.7 Hz, 0.5H), 4.83 – 4.74 (m, 0.5H), 4.08 (dd, J = 11.6, 3.9 Hz, 1H), 3.93 (dd, J = 11.5, 8.9 Hz, 1H), 3.89 – 3.70 (m, 6H), 3.67 (dd, J = 11.8, 4.2 Hz, 0.5H), 3.57 (td, J = 13.5, 12.9, 4.0 Hz, 1H), 3.23 (td, J = 13.0, 4.2 Hz, 0.5H), 3.06 (td, J = 14.1, 12.2, 6.0 Hz, 0.5H), 2.92 (ddd, J = 17.1, 11.9, 5.8 Hz, 1H), 2.69 (t, J = 15.6 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 171.13, 170.44, 148.31, 148.18, 147.84, 147.40, 137.96, 137.55, 134.63, 134.29, 130.08, 130.03, 129.69, 129.63, 129.57, 128.39, 128.02, 127.81, 126.97, 126.61, 125.73, 125.71, 124.89, 124.41, 124.26, 111.67, 111.33, 110.04, 109.51, 66.54, 65.83, 64.58, 64.56, 59.61, 56.02, 55.95, 55.89, 55.23, 42.07, 35.49, 28.76, 27.64, 15.25. HRMS calcd. for $C_{19}H_{21}O_4NCl$, 362.11536 $[M + H]^+$; found 362.11479 $[M + H]^+$.



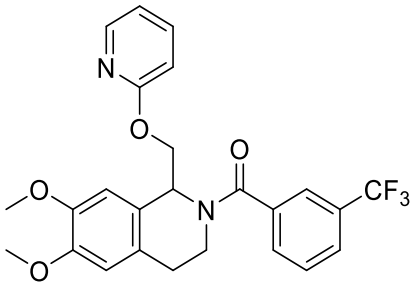
(6,7-dimethoxy-1-(((tetrahydro-2H-pyran-4-yl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-433): General procedure IX was followed using compound **8b** (29 mg, 0.094 mmol), triethylamine (26 µL, 0.19 mmol), and 3-(trifluoromethyl)benzoyl chloride (17 µL, 0.11 mmol) in DCM (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white foam (45 mg, quant.). R_f (1:1 EtOAC:Hex): 0.62;

^{1}H NMR (500 MHz, Chloroform-d) δ 7.85 (s, 0.5H), 7.71 – 7.45 (m, 3.5H), 6.79 (s, 0.5H), 6.64 (s, 0.5H), 6.60 (s, 0.5H), 6.41 (s, 0.5H), 5.77 (t, J = 5.5 Hz, 0.5H), 4.83 (ddd, J = 13.8, 11.3, 5.1 Hz, 1H), 3.95 – 3.83 (m, 7.5H), 3.77 (s, 1.5H), 3.74 – 3.53 (m, 2.5H), 3.51 – 3.36 (m, 2.5H), 3.22 (td, J = 12.7, 4.2 Hz, 0.5H), 3.09 (td, J = 14.4, 12.3, 6.2 Hz, 0.5H), 2.85 (ddd, J = 17.0, 11.7, 6.0 Hz, 0.5H), 2.75 (dd, J = 16.2, 3.4 Hz, 0.5H), 2.65 (d, J = 15.7 Hz, 0.5H), 1.93 – 1.82 (m, 2H), 1.65 – 1.49 (m, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 170.19, 169.12, 148.57, 148.16, 147.75, 147.50, 137.35, 137.25, 131.29, 131.02, 130.76, 130.51, 129.89, 129.25, 128.95, 128.75, 126.79, 126.29, 126.16, 126.13, 125.78, 125.73, 125.08, 125.06, 124.38, 123.60, 111.82, 111.35, 110.33, 109.76, 74.97, 73.95, 69.99, 69.57, 65.50, 65.44, 65.32, 57.86, 56.04, 55.90, 51.98, 42.60, 35.38, 32.39, 32.31, 32.05, 32.01, 28.97, 27.57. (Unable to discern between fluorine splitting and minor peaks, all peaks reported as seen). HRMS calcd. for $C_{25}H_{29}O_5NF_3$, 480.19923 $[M + H]^+$; found 480.19912 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 50-95% MeOH in water over 6 min at 1 mL/min (retention time = 3.62 min). Method 2: 75-95% MeOH in water over 3 min at 1 mL/min (retention time 0.88 min).



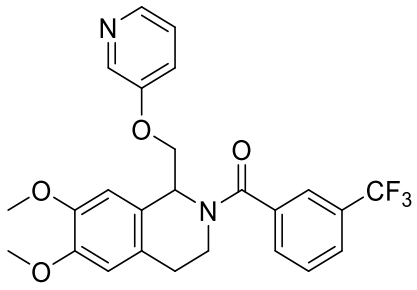
(6,7-dimethoxy-1-((pyrimidin-2-yloxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-429): General procedure X was followed using compound **9a** (25 mg, 0.063 mmol), 2-chloropyrimidine (11 mg, 0.095 mmol), and 60% sodium hydride dispersion in mineral oil (3.1 mg, 0.13 mmol) in DMF (0.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes

gradient) to afford the title compound as a clear oil (14 mg, 47%). R_f (9:1 DCM:MeOH): 0.67; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.45 (d, J = 4.5 Hz, 1H), 8.37 (d, J = 4.6 Hz, 1H), 7.66 – 7.29 (m, 4H), 6.90 – 6.82 (m, 1.5H), 6.62 (s, 0.5H), 6.54 (d, J = 7.0 Hz, 1H), 6.07 – 6.02 (m, 0.5H), 5.11 (dd, J = 9.2, 3.3 Hz, 0.5H), 4.87 (dd, J = 11.4, 4.2 Hz, 0.5H), 4.81 (dd, J = 13.1, 6.0 Hz, 0.5H), 4.71 (dd, J = 11.3, 6.8 Hz, 0.5H), 4.61 – 4.54 (m, 0.5H), 4.45 (dd, J = 11.8, 3.8 Hz, 0.5H), 3.84 (s, 1.5H), 3.82 (s, 1.5H), 3.79 (s, 1.5H), 3.76 (s, 1.5H), 3.72 – 3.67 (m, 1H), 3.34 – 3.27 (m, 0.5H), 3.06 (ddd, J = 17.5, 12.5, 6.3 Hz, 0.5H), 2.81 (ddd, J = 17.4, 10.8, 6.9 Hz, 0.5H), 2.77 – 2.71 (m, 0.5H), 2.65 (d, J = 16.1 Hz, 0.5H). ^{13}C NMR (151 MHz, CDCl3) δ 169.96, 169.40, 165.01, 164.63, 159.28, 148.79, 148.32, 147.92, 147.68, 137.15, 136.92, 131.19, 130.97, 130.86, 130.76, 130.66, 129.98, 129.18, 128.76, 127.19, 126.40, 126.33, 126.04, 125.94, 124.60, 124.48, 123.67, 123.54, 122.79, 120.98, 115.48, 115.33, 111.84, 111.42, 110.17, 109.80, 68.74, 67.94, 56.63, 56.11, 55.93, 51.18, 42.50, 35.63, 28.94, 27.65 (Unable to discern between fluorine splitting and minor peaks, all peaks reported as seen). HRMS calcd. for $C_{24}H_{23}O_4N_3F_3$, 474.16325 $[M + H]^+$; found 474.16477 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 50-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.84 min). Method 2: 75-95% MeOH in water over 3 min at 1 mL/min (retention time 0.82 min).



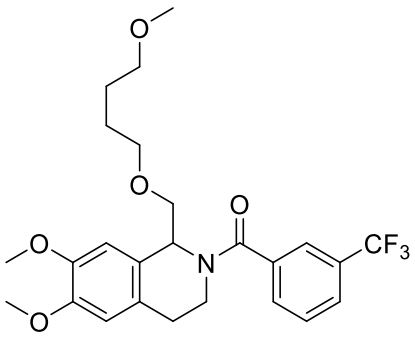
(6,7-dimethoxy-1-((pyridin-2-yloxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-431): General procedure X was followed using

compound **9a** (25 mg, 0.063 mmol), 2-fluoropyrimidine (8.2 µL, 0.095 mmol), and 60% sodium hydride dispersion in mineral oil (4.6 mg, 0.19 mmol) in THF (0.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white foam (8.0 mg, 27%). R_f (1:1 EtOAC:Hex): 0.40; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.08 (d, J = 3.7 Hz, 0.5H), 7.91 (d, J = 4.1 Hz, 0.5H), 7.67 (s, 0.5H), 7.59 (d, J = 7.6 Hz, 0.5H), 7.52 (t, J = 7.1 Hz, 1.5H), 7.45 (t, J = 8.4 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.33 (t, J = 7.6 Hz, 0.5H), 6.86 – 6.76 (m, 1.5H), 6.71 (d, J = 8.3 Hz, 0.5H), 6.66 (d, J = 8.3 Hz, 0.5H), 6.61 (s, 0.5H), 6.54 (s, 1H), 6.06 – 6.01 (m, 0.5H), 5.14 – 5.09 (m, 0.5H), 4.89 – 4.78 (m, 1H), 4.63 (dd, J = 11.2, 4.2 Hz, 0.5H), 4.50 (t, J = 10.8 Hz, 0.5H), 4.39 (dd, J = 11.8, 3.4 Hz, 0.5H), 3.83 (s, 1.5H), 3.81 (s, 1.5H), 3.79 (s, 1.5H), 3.75 (s, 1.5H), 3.71 – 3.63 (m, 0.5H), 3.63 – 3.57 (m, 0.5H), 3.29 (td, J = 12.9, 4.2 Hz, 0.5H), 3.06 (ddd, J = 17.7, 12.6, 6.2 Hz, 0.5H), 2.83 – 2.70 (m, 1H), 2.60 (d, J = 15.2 Hz, 0.5H). ^{13}C 13C NMR (151 MHz, CDCl3) δ 169.96, 169.32, 163.41, 162.86, 148.69, 148.31, 147.86, 147.64, 146.61, 146.50, 138.95, 137.27, 136.98, 131.15, 130.94, 130.85, 130.63, 130.46, 129.82, 129.17, 128.72, 127.04, 126.21, 126.06, 126.04, 125.84, 124.70, 124.67, 123.92, 123.52, 117.34, 117.24, 111.76, 111.43, 111.36, 111.08, 110.35, 109.82, 66.79, 66.62, 57.00, 56.05, 55.94, 51.70, 42.01, 35.50, 28.90, 27.65. (Unable to discern between fluorine splitting and minor peaks, all peaks reported as seen). HRMS calcd. for $C_{25}H_{24}O_4N_2F_3$, 473.16827 $[M + H]^+$; found 473.16871 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 50-95% MeOH in water over 6 min at 1 mL/min (retention time = 4.27 min). Method 2: 75-95% MeOH in water over 3 min at 1 mL/min (retention time 1.10 min).



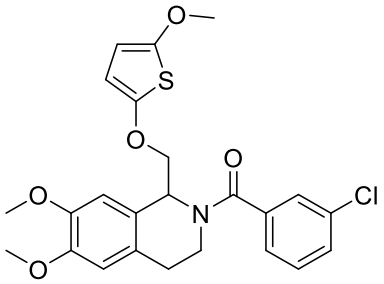
(6,7-dimethoxy-1-((pyridin-3-yloxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-430): General procedure IX was followed using compound **8a** (25 mg, 0.082 mmol), triethylamine (23 µL, 0.16 mmol), and 3-(trifluoromethyl)benzoyl chloride (15 µL, 0.10 mmol) in DCM (1.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white foam (17 mg, 44%). R_f (9:1 DCM:MeOH): 0.64; ^{1}H NMR (600 MHz, Chloroform-d) δ 8.08 (d, J = 3.7 Hz, 0.5H), 7.91 (d, J = 4.1 Hz, 0.5H), 7.67 (s, 0.5H), 7.59 (d, J = 7.6 Hz, 0.5H), 7.52 (t, J = 7.1 Hz, 1.5H), 7.45 (t, J = 8.4 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.33 (t, J = 7.6 Hz, 0.5H), 6.86 – 6.76 (m, 1.5H), 6.71 (d, J = 8.3 Hz, 0.5H), 6.66 (d, J = 8.3 Hz, 0.5H), 6.61 (s, 0.5H), 6.54 (s, 1H), 6.06 – 6.01 (m, 0.5H), 5.14 – 5.09 (m, 0.5H), 4.89 – 4.78 (m, 1H), 4.63 (dd, J = 11.2, 4.2 Hz, 0.5H), 4.50 (t, J = 10.8 Hz, 0.5H), 4.39 (dd, J = 11.8, 3.4 Hz, 0.5H), 3.83 (s, 1.5H), 3.81 (s, 1.5H), 3.79 (s, 1.5H), 3.75 (s, 1.5H), 3.71 – 3.63 (m, 0.5H), 3.63 – 3.57 (m, 0.5H), 3.29 (td, J = 12.9, 4.2 Hz, 0.5H), 3.06 (ddd, J = 17.7, 12.6, 6.2 Hz, 0.5H), 2.83 – 2.70 (m, 1H), 2.60 (d, J = 15.2 Hz, 0.5H). ^{13}C NMR (151 MHz, CDCl3) δ 169.96, 169.32, 163.41, 162.86, 148.69, 148.31, 147.86, 147.64, 146.61, 146.50, 138.95, 137.27, 136.98, 131.15, 130.94, 130.85, 130.63, 130.46, 129.82, 129.17, 128.72, 127.04, 126.21, 126.06, 126.04, 125.84, 124.70, 124.67, 123.92, 123.52, 117.34, 117.24, 111.76, 111.43, 111.36, 111.08, 110.35, 109.82, 66.79, 66.62, 57.00, 56.05, 55.94, 51.70, 42.01, 35.50, 28.90, 27.65. (Unable to discern between fluorine splitting and minor peaks, all peaks reported as seen). HRMS calcd. for $C_{26}H_{20}O_4N_2F_3$, 473.16827

$[M + H]^+$; found 473.16919 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 50-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.59 min). Method 2: 75-95% MeOH in water over 3 min at 1 mL/min (retention time 0.77 min).



(6,7-dimethoxy-1-((4-methoxybutoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-437): General procedure IX was followed using compound **8c** (26 mg, 0.084 mmol), triethylamine (23 µL, 0.17 mmol), and 3-(trifluoromethyl)benzoyl chloride (15 µL, 0.10 mmol) in DCM (1.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white foam (30 mg, 74%). R_f (1:1 EtOAC:Hex): 0.18; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.85 – 7.45 (m, 4H), 6.76 (s, 0.5H), 6.64 (s, 0.5H), 6.59 (s, 0.5H), 6.41 (s, 0.5H), 5.80 (t, J = 5.4 Hz, 0.5H), 4.82 (ddd, J = 13.8, 11.3, 5.0 Hz, 1H), 3.90 – 3.83 (m, 5.5H), 3.78 (s, 1.5H), 3.74 – 3.57 (m, 2H), 3.52 (dd, J = 10.3, 4.1 Hz, 0.5H), 3.48 – 3.21 (m, 7H), 3.09 (ddd, J = 18.1, 12.6, 6.3 Hz, 0.5H), 2.85 (ddd, J = 17.3, 12.0, 6.3 Hz, 0.5H), 2.75 (dd, J = 16.3, 3.4 Hz, 0.5H), 2.64 (d, J = 15.6 Hz, 0.5H), 1.74 – 1.55 (m, 4H).^{13}C NMR (126 MHz, cdcl3) δ 170.13, 169.08, 148.51, 148.12, 147.78, 147.49, 137.39, 137.28, 131.25, 131.05, 130.99, 130.78, 130.52, 129.92, 129.19, 128.97, 128.71, 126.81, 126.25, 126.11, 125.72, 125.06, 125.03, 124.46, 123.62, 111.77, 111.36, 110.20, 109.73, 73.23, 72.72, 72.42, 72.38, 71.46, 71.20, 58.51, 58.45,

57.85, 56.01, 55.89, 51.73, 42.41, 35.45, 28.95, 27.60, 26.38, 26.29, 26.26. (Unable to discern between fluorine splitting and minor peaks, all peaks reported as seen). HRMS calcd. for $C_{21}H_{28}O_4N$, 482.21488 $[M + H]^+$; found 482.21488 [M + Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 0.68 min). Method 2: 75-95% MeOH in water over 3 min at 1 mL/min (retention time 0.96 min).H]$^+$.



(3-chlorophenyl)(6,7-dimethoxy-1-(((5-methoxythiophen-2-yl)oxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-287): Compound **9b** (100 mg, 0.276 mmol), 2-iodo-5-methoxythiophene (73 mg, 0.30 mmol), 1,10-phenanthroline (10. mg, 0.055 mmol), copper(I) iodide (11 mg, 0.055 mmol), and cesium carbonate (0.18 g, 0.55 mmol) were charged to a 10 mL microwave vial. The vial was capped, purged with argon and evacuated three times, and toluene (0.5 mL) was added. The vial was heated to 80 ^{o}C and allowed to react for 24 hours. Upon completion, the reaction was cooled to room temperature, filtered through a pad of celite washing with EtOAc, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 10-90% EtOAc/hexanes gradient) to afford the title compound as a white foam (28 mg, 21%). R_f (1:1 EtOAC:Hex): 0.47; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.58 – 7.28 (m, 4H), 6.79 – 6.41 (m, 2H), 5.92 (dd, J = 13.0, 4.5 Hz, 1H), 5.77 (s, 1H), 5.05 (dd, J = 9.0, 3.2 Hz, 0.5H), 4.88 (dd, J = 13.1, 5.4 Hz, 0.5H), 4.38 (d, J = 5.1 Hz, 1H), 4.18 (t, J = 10.0 Hz, 0.5H) 4.01 (dd, J = 10.5, 4.0 Hz, 0.5H), 3.95 – 3.72 (m, 9H), 3.62 (td, J =

13.1, 3.6 Hz, 1H), 3.24 (td, J = 12.9, 3.7 Hz, 0.5H), 3.09 (td, J = 16.8, 5.9 Hz, 0.5H), 2.86 (ddd, J = 15.3, 13.1, 5.9 Hz, 0.5H), 2.76 (dd, J = 16.2, 3.0 Hz, 0.5H), 2.68 (d, J = 15.4 Hz, 0.5H). ^{13}C NMR (101 MHz, cdcl3) δ 170.10, 169.37, 168.44, 155.06, 154.95, 152.66, 152.02, 148.69, 148.47, 148.26, 147.94, 147.85, 147.58, 139.89, 137.88, 134.68, 134.64, 134.41, 130.04, 129.99, 129.86, 129.78, 129.75, 129.60, 127.69, 127.08, 126.83, 126.73, 126.08, 125.47, 124.70, 124.63, 124.27, 123.07, 116.36, 111.76, 111.38, 111.30, 109.90, 109.76, 109.51, 103.43, 102.79, 100.68, 77.21, 76.20, 74.84, 68.82, 65.85, 60.45, 60.36, 56.97, 56.04, 55.89, 51.83, 51.54, 51.05, 42.65, 42.15, 35.49, 28.92, 28.77, 27.55, 15.27. HRMS calcd. for $C_{24}H_{25}O_5NClS$, 474.11365 $[M + H]^+$; found 474.11362 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 85-95% MeOH in water over 5 min at 1 mL/min (retention time = 1.74 min). Method 2: 75-95% ACN in water over 5 min at 1 mL/min (retention time 3.56 min).

C-Ring Derivatives

General Procedure for Nitro Alkenes (Procedure XI): Aldehyde (1 equiv) was dissolved in dry nitromethane (~1 M) and butylamine (0.12 equiv), acetic acid (0.2 equiv), and 4 Å molecular sieves (~10 wt%) were added. The solution was brought to reflux for 30 minutes before the mixture was concentrated *in vacuo* and the crude material was purified via flash column chromatography to afford the title compound.

General Procedure for Ethylamines (Procedure XII): Sulfuric acid (2.23 equiv) was added dropwise to a solution of lithium aluminum hydride (4.46 equiv) in THF (~0.15 M) at 0 °C and allowed to stir for 20 minutes. Nitroalkene (1 equiv) dissolved in dry THF (~1.5 M) was then added dropwise at 0 °C and was stirred for 10 minutes. The mixture was then heated to reflux for

5 minutes, cooled to 0 °C, and quenched carefully with iPrOH (6 equiv) and NaOH (9 equiv). The resulting suspension was then filtered and concentrated *in vacuo* to afford the crude title compound that was carried forward without further purification.

General Procedure for Carboxylic Acid Coupling to Final 1180 Compounds (Procedure XIII): Carboxylic acid (1.1 equiv) was dissolved in dry DCM and cooled to 0 °C. EDCI (1.2 equiv) and DMAP (1.2 equiv) were then added and allowed to stir for 2 hours before the free amine (1 equiv) was added and the mixture allowed to stir at room temperature overnight. The reaction was then quenched with deionized water and the organic layer was extracted into DCM, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

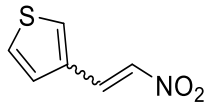
General Procedure for Thioamides (Procedure XIV): Amide (1 equiv) in a microwave vial was dissolved in toluene and Lawesson's Reagent (1.5 equiv) was added. This mixture was allowed to react in a microwave at 150°C for 20 minutes. The reaction was then diluted with DCM, washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Alpha-Chloro Ketones (Procedure XV): Methyl ester (1 equiv) was dissolved in dry DCM (0.5 M) and brought to 0 °C. Aluminum trichloride (1.1 eq) was added followed by chloroacetyl chloride (1.1 eq) and the mixture was warmed to room temperature and allowed to react for 1 hour. The reaction was then quenched by pouring into cold water and extracted with DCM. The organic layer was washed with 2 M NaOH (3x), brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

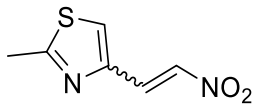
General Procedure for Biaryl Ketones (Procedure XVI): To a suspension of potassium iodide (1.2 equiv) and potassium carbonate (2 equiv) in acetone (0.3 M) was added alpha-chloro ketone (1 equiv) and phenol (1.2 equiv). The resulting mixture was then stirred open to atmosphere at room temperature overnight. Upon completion, the solvent was removed *in vacuo* and the resulting residue was dissolved in EtOAc and washed with water. The aqueous layer was then extracted with EtOAc and all organic layers combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.

General Procedure for Tertiary Olefins (Procedure XVII): An appropriate microwave vial was charged with ketone (1 equiv), primary amine (1.2 equiv), tetraisopropoxytitanium (3 equiv), and DCE (0.2 M) and the solution was stirred for 10 minutes before sodium triacetoxyborohydride (3 equiv) was added and the mixture was irradiated at 120 ℃ for 2 h. Upon completion, the reaction was cooled to room temperature, diluted with DCM and washed with 1 M HCl. The organic layer was extracted with DCM, washed with $NaHCO_3$, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound as a mixture of E/Z isomers, the mass confirmed via LCMS, and carried forward without further characterization.

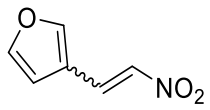
General Procedure for Final Pyrrolopyrazinone Compounds (Procedure XVIII): Olefin (1 equiv) was dissolved in EtOAc and 10% Pd/C (0.15 equiv) was added. The flask was purged with hydrogen from a balloon (3x) and the mixture was hydrogenated (1 atm) overnight. The reaction mixture was filtered through a pad of celite, washing with methanol, and concentrated *in vacuo*. The crude product was purified via flash column chromatography to afford the title compound.



3-(2-nitrovinyl)thiophene (11a). General procedure XI was followed using thiophene-3-carbaldehyde (3.00 g, 26.7 mmol), butylamine (0.32 mL, 3.2 mmol), acetic acid (0.31 mL, 5.4 mmol) and 4 Å molecular sieves (300 mg) in nitromethane (27 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow solid. (3.3 g, 79%). R_f (1:1 EtOAc:Hex): 0.58; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 (dd, J = 13.5, 0.5 Hz, 1H), 7.73 (ddd, J = 2.5, 1.3, 0.6 Hz, 1H), 7.49 (d, J = 13.5 Hz, 1H), 7.44 (ddd, J = 5.1, 2.9, 0.7 Hz, 1H), 7.28 (ddd, J = 5.1, 1.3, 0.5 Hz, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 136.73, 132.55, 132.46, 132.23, 128.16, 125.06. HRMS calcd. for $C_6H_6O_2NS$, 156.01138 $[M + H]^+$; found 156.01151 $[M + H]^+$.



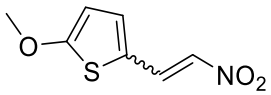
2-methyl-4-(2-nitrovinyl)thiazole (11b). General procedure XI was followed using 2-methylthiazole-4-carbaldehyde (1.00 g, 7.86 mmol), butylamine (93 μL, 0.94 mmol), acetic acid (90 μL, 1.6 mmol) and 4 Å molecular sieves (100 mg) in nitromethane (8 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-80% EtOAc/hexanes gradient) to afford the title compound as a yellow solid. (0.41 g, 31%). R_f (1:1 EtOAc:Hex): 0.70; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.85 (s, 1H), 7.85 (s, 1H), 7.54 (s, 1H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 167.93, 146.94, 139.11, 130.46, 126.18, 19.39. HRMS calcd. for $C_6H_7O_2N_2S$, 171.02227 $[M + H]^+$; found 171.02191 $[M + H]^+$.



3-(2-nitrovinyl)furan (11c). General procedure XI was followed using furan-3-carbaldehyde (1.80 mL, 20.8 mmol), butylamine (0.25 mL, 2.5 mmol), acetic acid (0.24 mL, 4.2 mmol) and 4 Å molecular sieves (200 mg) in nitromethane (21 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow solid. (2.9 g, quant.). R_f (1:1 EtOAc:Hex): 0.83; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 (d, J = 13.5 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.56 – 7.48 (m, 1H), 7.39 (d, J = 13.5 Hz, 1H), 6.59 – 6.55 (m, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 147.33, 145.34, 136.67, 129.56, 118.17, 107.20. No ionization observed by HRMS.

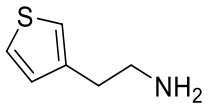
1-methyl-5-(2-nitrovinyl)-1H-pyrazole (11d). General procedure XI was followed using 1-methyl-1H-pyrazole-5-carbaldehyde (2.00 g, 18.2 mmol), butylamine (0.22 mL, 2.2 mmol), acetic acid (0.21 mL, 3.6 mmol) and 4 Å molecular sieves (200 mg) in nitromethane (18 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow solid. (1.7 g, 62%). R_f (1:1 EtOAc:Hex): 0.65; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.94 (d, J = 13.4 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.51 (d, J = 13.4 Hz, 1H), 6.66 (d, J = 2.2 Hz, 1H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 139.43, 137.59, 133.20, 124.35, 107.53, 37.30. HRMS calcd. for $C_6H_8O_2N_3$, 154.06110 $[M + H]^+$; found 154.06109 $[M + H]^+$.

5-(2-nitrovinyl)isothiazole (11e). General procedure XI was followed using isothiazole-5-carbaldehyde (1.00 g, 8.84 mmol), butylamine (0.105 mL, 1.06 mmol), acetic acid (0.101 mL, 1.77 mmol) and 4 Å molecular sieves (100 mg) in nitromethane (9 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as an orange solid. (0.82 g, 59%). R_f (1:1 EtOAc:Hex): 0.78; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.55 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 13.7 Hz, 1H), 7.56 (d, J = 13.7 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 158.60, 158.54, 155.19, 139.56, 126.59. HRMS calcd. for $C_5H_5O_2N_2S$, 157.00662 $[M + H]^+$; found 157.00649 $[M + H]^+$.

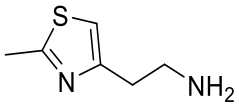


2-methoxy-5-(2-nitrovinyl)thiophene (11f). 2-methoxythiophene (1.06 g, 9.28 mmol) was dissolved in Et_2O (19 mL, 0.5 M) and n-butyllithium (5.57 mL, 13.9 mmol, 2.5 M in hexanes) was added dropwise under nitrogen at 0 ^{o}C. The mixture was then heated to reflux and allowed to react for 1 hour. The reaction was then cooled to 0 ^{o}C and quenched carefully via dropwise addition of water before the organic layer was extracted with Et_2O, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product as a yellow oil (1.32 g, 100%) that was carried forward without further purification. General procedure XI was then followed using the crude material (1.32 g, 9.28 mmol), butylamine (0.110 mL, 1.11 mmol), acetic acid (0.106 mL, 1.86 mmol) and 4 Å molecular sieves (132 mg) in nitromethane (19 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a red solid. (1.25 g over two steps, 73%). R_f (1:1 EtOAc:Hex): 0.66; ^{1}H NMR (399 MHz, Chloroform-d) δ 8.02 (d, J = 13.1 Hz, 1H), 7.24 (d, J =

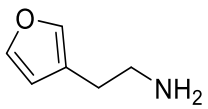
13.1 Hz, 2H), 7.18 (d, J = 4.2 Hz, 1H), 6.25 (d, J = 4.2 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 172.23, 136.21, 133.71, 131.86, 120.35, 106.35, 60.60. HRMS calcd. for $C_7H_8O_3NS$, 186.02194 $[M + H]^+$; found 186.02186 $[M + H]^+$.



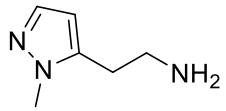
2-(thiophen-3-yl)ethan-1-amine (12a). General procedure XII was followed using compound **11a** (3.27 g, 21.1 mmol), sulfuric acid (2.51 mL, 47.0 mmol) and 2 M lithium aluminum hydride in THF (47.0 mL, 94.0 mmol) in THF (144 mL) to afford the title compound as a red oil (2.10 g). The crude material was confirmed via LCMS and carried forward without further purification.



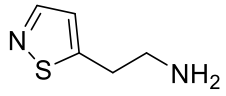
2-(2-methylthiazol-4-yl)ethan-1-amine (12b). General procedure XII was followed using compound **11b** (411 mg, 2.42 mmol), sulfuric acid (0.29 mL, 5.4 mmol) and 1 M lithium aluminum hydride in THF (10.8 mL, 10.8 mmol) in THF (17 mL) to afford the title compound as a red oil. (60 mg). The crude material was confirmed via LCMS and carried forward without further purification.



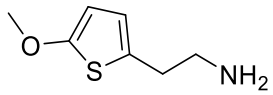
2-(furan-3-yl)ethan-1-amine (12c). General procedure XII was followed using compound **11c** (1.45 g, 10.4 mmol), sulfuric acid (1.24 mL, 23.2 mmol) and 2 M lithium aluminum hydride in THF (23.2 mL, 46.5 mmol) in THF (71 mL) to afford the title compound as a yellow oil (0.89 g). The crude material was confirmed via LCMS and carried forward without further purification.



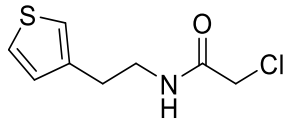
2-(1-methyl-1H-pyrazol-5-yl)ethan-1-amine (12d). General procedure XII was followed using compound **11d** (1.60 g, 10.5 mmol), sulfuric acid (1.24 mL, 23.3 mmol) and 2 M lithium aluminum hydride in THF (23.3 mL, 46.6 mmol) in THF (71 mL) to afford the title compound as a pale-yellow oil. (0.80 g). The crude material was confirmed via LCMS and carried forward without further purification.



2-(isothiazol-5-yl)ethan-1-amine (12e). General procedure XII was followed using compound **11e** (0.82 g, 5.3 mmol), sulfuric acid (0.62 mL, 12 mmol) and 2 M lithium aluminum hydride in THF (11.7 mL, 23.4 mmol) in THF (36 mL) to afford the title compound as an orange oil. (0.15 g). The crude material was confirmed via LCMS and carried forward without further purification.

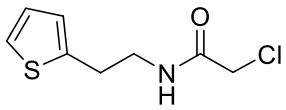


2-(5-methoxythiophen-2-yl)ethan-1-amine (12f). General procedure XII was followed using compound **11f** (1.19 g, 6.43 mmol), sulfuric acid (0.76 mL, 14 mmol) and 2 M lithium aluminum hydride in THF (14.3 mL, 28.7 mmol) in THF (39 mL) to afford the crude title compound as a pale-yellow oil. (1.01 g). The crude material was confirmed via LCMS and carried forward without further purification.

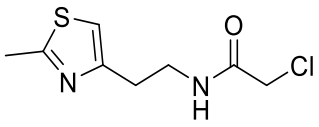


2-chloro-N-(2-(thiophen-3-yl)ethyl)acetamide (13a). General procedure V was followed using crude compound **12a** (2.10 g, 16.5 mmol), triethylamine (3.34 mL, 33.0 mmol) and 2-chloroacetyl

chloride (1.59 mL, 19.8 mmol) in DCM (60 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white solid. (2.20 g, 51% over 2 steps). R_f (1:1 EtOAc:Hex): 0.47; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.30 (dd, J = 4.9, 2.9 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.96 (dd, J = 4.9, 1.3 Hz, 1H), 6.65 (s, 1H), 4.02 (s, 2H), 3.56 (d, J = 6.1 Hz, 2H), 2.89 (t, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 165.82, 138.58, 127.93, 126.24, 121.61, 42.68, 40.24, 29.96. HRMS calcd. for $C_8H_{11}ONClS$, 204.02444 $[M + H]^+$; found 204.02490 $[M + H]^+$.

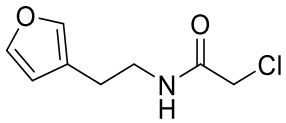


2-chloro-N-(2-(thiophen-2-yl)ethyl)acetamide (13b). General procedure V was followed using 2-(thiophen-2-yl)ethan-1-amine (2.00 g, 15.7 mmol), triethylamine (3.18 mL, 31.4 mmol) and 2-chloroacetyl chloride (1.51 mL, 18.9 mmol) in DCM (57 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a red oil. (2.64 g, 82%). R_f (1:1 EtOAc:Hex): 0.51; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.18 (dd, J = 5.2, 1.2 Hz, 1H), 6.95 (dd, J = 5.1, 3.4 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.75 (s, 1H), 4.03 (s, 2H), 3.58 (q, J = 6.7 Hz, 2H), 3.07 (t, J = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 165.92, 140.61, 127.16, 125.56, 124.20, 42.66, 41.11, 29.66. HRMS calcd. for $C_8H_{10}ONClNaS$, 226.00638 $[M + Na]^+$; found 226.00658 $[M + Na]^+$.

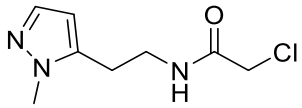


2-chloro-N-(2-(2-methylthiazol-4-yl)ethyl)acetamide (13c). General procedure V was followed using crude compound **12b** (60 mg, 0.42 mmol), triethylamine (0.12 mL, 0.84 mmol) and 2-chloroacetyl chloride (34 μL, 0.42 mmol) in DCM (1.5 mL). The crude product was purified via

flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (27 mg, 5% over 2 steps). R_f (1:1 EtOAc:Hex): 0.39; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.59 (s, 0H), 6.81 (s, 1H), 4.03 (s, 2H), 3.62 (q, J = 6.5 Hz, 2H), 2.93 (t, J = 6.3 Hz, 2H), 2.68 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 166.31, 165.94, 153.48, 113.97, 42.75, 39.31, 30.39. HRMS calcd. for $C_8H_{11}ON_2ClS$, 219.03534 $[M + H]^+$; found 219.03522 $[M + H]^+$.

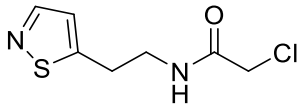


2-chloro-N-(2-(furan-3-yl)ethyl)acetamide (13d). General procedure V was followed using crude compound **12c** (0.860 g, 7.74 mmol), triethylamine (2.16 mL, 15.5 mmol) and 2-chloroacetyl chloride (0.74 mL, 9.3 mmol) in DCM (28 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a red oil. (0.84 g, 43% over 2 steps). R_f (1:1 EtOAc:Hex): 0.61; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 (t, J = 1.7 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.66 (s, 1H), 6.30 (dd, J = 1.8, 0.9 Hz, 1H), 4.03 (s, 2H), 3.50 (q, J = 6.2 Hz, 2H), 2.68 (t, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 165.82, 143.43, 139.65, 121.30, 110.70, 42.67, 39.84, 24.76. HRMS calcd. for $C_8H_{10}O_2NClNa$, 210.02923 $[M + H]^+$; found 210.02875 $[M + H]^+$.

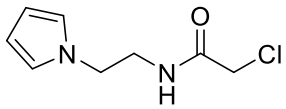


2-chloro-N-(2-(1-methyl-1H-pyrazol-5-yl)ethyl)acetamide (13e). General procedure V was followed using crude compound **12d** (0.78 g, 6.2 mmol), triethylamine (1.74 mL, 12.5 mmol) and 2-chloroacetyl chloride (0.60 mL, 7.5 mmol) in DCM (23 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-10% (1% NH_4OH in

MeOH)/DCM gradient) to afford the title compound as a yellow oil. (0.86 g, 41% over 2 steps). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.43; ^1H NMR (500 MHz, Chloroform-d) δ 7.40 (d, J = 1.9 Hz, 1H), 6.79 (bs, 1H), 6.07 (dt, J = 1.9, 0.6 Hz, 1H), 4.03 (s, 2H), 3.81 (s, 3H), 3.57 (dt, J = 7.1, 6.0 Hz, 3H), 2.88 (t, J = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 166.14, 138.95, 138.46, 104.76, 42.56, 38.54, 36.24, 25.54. HRMS calcd. for $C_8H_{13}ON_3Cl$, 202.07417 $[M + H]^+$; found 202.07392 $[M + H]^+$.

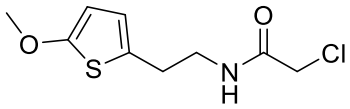


2-chloro-N-(2-(isothiazol-5-yl)ethyl)acetamide (13f). General procedure V was followed using crude compound **12e** (0.15 g, 1.2 mmol), triethylamine (0.33 mL, 2.3 mmol) and 2-chloroacetyl chloride (0.11 mL, 1.4 mmol) in DCM (4.2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (71 mg, 7% over 2 steps). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.50; ^1H NMR (500 MHz, Chloroform-d) δ 8.38 (d, J = 1.6 Hz, 1H), 7.07 – 7.02 (m, 1H), 6.92 (bs, 1H), 4.04 (s, 2H), 3.60 (q, J = 6.7 Hz, 2H), 3.20 (t, J = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 169.31, 166.52, 157.92, 122.93, 42.55, 40.43, 27.59. HRMS calcd. for $C_7H_{10}ON_2ClS$, 205.01969 $[M + H]^+$; found 205.01955 $[M + H]^+$.

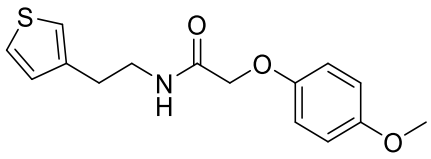


N-(2-(1H-pyrrol-1-yl)ethyl)-2-chloroacetamide (13g). General procedure V was followed using 2-(1H-pyrrol-1-yl)ethanamine (1.00 g, 9.08 mmol), triethylamine (2.53 mL, 18.2 mmol) and 2-chloroacetyl chloride (0.87 mL, 11 mmol) in DCM (33 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-100% (EtOAc/hexanes gradient) to

afford the title compound as an orange solid. (1.7 g, quant.). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.69; ^{1}H NMR (500 MHz, Chloroform-d) δ 6.66 (t, J = 2.0 Hz, 2H), 6.19 (t, J = 2.0 Hz, 2H), 4.05 (t, J = 5.9 Hz, 2H), 4.03 (s, 2H), 3.62 (q, J = 5.9 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 166.25, 120.60, 109.02, 48.56, 42.48, 41.26. HRMS calcd. for $C_8H_{12}ON_2Cl$, 187.06327 $[M + H]^+$; found 187.06360 $[M + H]^+$.

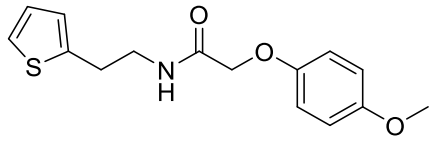


2-chloro-N-(2-(5-methoxythiophen-2-yl)ethyl)acetamide (13h). General procedure V was followed using crude compound **12f** (1.01 g, 6.43 mmol), triethylamine (1.79 mL, 12.9 mmol) and 2-chloroacetyl chloride (0.62 mL, 7.7 mmol) in DCM (23 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as an orange solid. (0.92 g, 61% over 2 steps). R_f (1:1 EtOAc:Hex): 0.43; ^{1}H NMR (400 MHz, Chloroform-d) δ 6.75 (s, 1H), 6.47 – 6.41 (m, 1H), 6.01 (d, J = 3.7 Hz, 1H), 4.04 (s, 2H), 3.85 (s, 3H), 3.51 (q, J = 6.5 Hz, 2H), 2.89 (t, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, cdcl3) δ 165.97, 164.95, 126.58, 122.80, 103.19, 60.18, 42.61, 40.93, 30.07. HRMS calcd. for $C_9H_{13}O_2NClS$, 234.03500 $[M + H]^+$; found 234.03492 $[M + H]^+$.

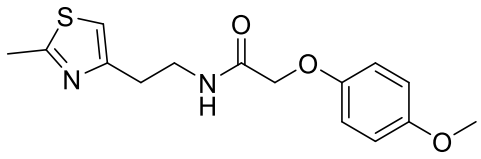


2-(4-methoxyphenoxy)-N-(2-(thiophen-3-yl)ethyl)acetamide (14a). General procedure VI was followed using compound **13a** (1.00 g, 4.91 mmol), 4-methoxyphenol (0.731 g, 5.89 mmol) and cesium carbonate (6.40 g, 19.6 mmol) in acetonitrile (15 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid. (1.20 g, 84%). R_f (1:1 EtOAc:Hex): 0.40; ^{1}H NMR (500

MHz, Chloroform-d) δ 7.28 (dd, J = 4.9, 3.0 Hz, 1H), 6.97 – 6.94 (m, 1H), 6.93 (dd, J = 4.9, 1.3 Hz, 1H), 6.87 – 6.77 (m, 4H), 6.66 (s, 1H), 4.42 (s, 2H), 3.77 (s, 3H), 3.60 (d, J = 6.1 Hz, 2H), 2.87 (t, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 168.40, 154.71, 151.31, 138.79, 127.98, 126.07, 121.55, 115.60, 114.85, 68.10, 55.71, 39.31, 30.19. HRMS calcd. for $C_{15}H_{18}O_3NS$, 292.10019 $[M + H]^+$; found 292.10028 $[M + H]^+$.

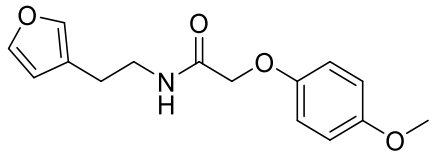


2-(4-methoxyphenoxy)-N-(2-(thiophen-2-yl)ethyl)acetamide (14b). General procedure VI was followed using compound **13b** (2.64 g, 13.0 mmol), 4-methoxyphenol (1.93 g, 15.6 mmol) and cesium carbonate (16.9 g, 51.8 mmol) in acetonitrile (39 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an orange solid. (3.26 g, 86%). R_f (1:1 EtOAc:Hex): 0.40; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.16 (dd, J = 5.1, 1.2 Hz, 1H), 6.93 (dd, J = 5.1, 3.4 Hz, 1H), 6.87 – 6.77 (m, 6H), 4.43 (s, 2H), 3.77 (s, 3H), 3.61 (q, J = 6.7 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 168.50, 154.71, 151.33, 140.85, 127.08, 125.49, 124.08, 115.65, 114.84, 68.14, 55.69, 40.26, 29.89. HRMS calcd. for $C_{30}H_{35}O_6N_2S_2$, 583.19361 $[2M + H]^+$; found 583.19343 $[2M + H]^+$.

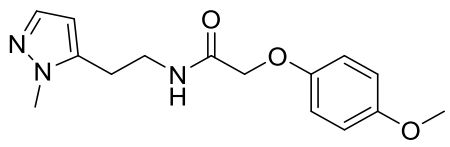


2-(4-methoxyphenoxy)-N-(2-(2-methylthiazol-4-yl)ethyl)acetamide (14c). General procedure VI was followed using compound **13c** (27 mg, 0.12 mmol), 4-methoxyphenol (18 mg, 0.15 mmol) and cesium carbonate (161 mg, 0.494 mmol) in acetonitrile (0.4 mL). The crude product was

purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (35 mg, 93%). R_f (1:1 EtOAc:Hex): 0.08; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.31 (s, 1H), 6.82 (s, 4H), 6.74 (s, 1H), 4.43 (s, 2H), 3.76 (s, 3H), 3.67 (q, J = 6.1 Hz, 2H), 2.93 (t, J = 6.8 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 168.47, 166.09, 154.62, 153.59, 151.51, 115.62, 114.80, 113.90, 68.18, 55.69, 38.34, 30.85, 19.16. HRMS calcd. for $C_{15}H_{19}O_3N_2S$, 307.11109 $[M + H]^+$; found 307.11127 $[M + H]^+$.

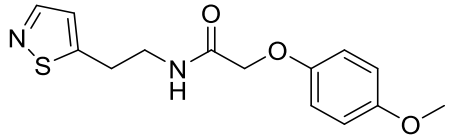


N-(2-(furan-3-yl)ethyl)-2-(4-methoxyphenoxy)acetamide (14d). General procedure VI was followed using compound **13d** (0.837 g, 4.46 mmol), 4-methoxyphenol (0.665 g, 5.35 mmol) and cesium carbonate (5.81 g, 17.8 mmol) in acetonitrile (13 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (1.07 g, 87%). R_f (1:1 EtOAc:Hex): 0.18; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 (t, J = 1.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 6.87 – 6.76 (m, 4H), 6.67 (bs, 0H), 6.27 (dd, J = 1.8, 0.9 Hz, 1H), 4.42 (s, 2H), 3.77 (s, 3H), 3.54 (q, J = 6.9 Hz, 2H), 2.66 (t, J = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 168.42, 154.72, 151.30, 143.26, 139.60, 121.46, 115.59, 114.84, 110.74, 68.12, 55.69, 38.94, 24.98. HRMS calcd. for $C_{15}H_{18}O_4N$, 276.12303 $[M + H]^+$; found 276.12303 $[M + H]^+$.

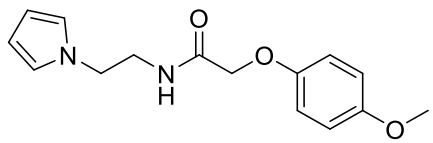


2-(4-methoxyphenoxy)-N-(2-(1-methyl-1H-pyrazol-5-yl)ethyl)acetamide (14e). General procedure VI was followed using compound **13e** (0.83 g, 4.1 mmol), 4-methoxyphenol (0.613 g,

4.94 mmol) and cesium carbonate (5.36 g, 16.5 mmol) in acetonitrile (24 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-10% EtOAc/hexanes gradient) to afford the title compound as a white solid. (1.0 g, 84%). R_f (1:1 EtOAc:Hex): 0.76; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.39 (d, J = 1.8 Hz, 1H), 6.87 – 6.76 (m, 5H), 6.03 (d, J = 1.9 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.61 (q, J = 6.9 Hz, 2H), 2.88 (t, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, cdcl3) δ 168.66, 154.76, 151.15, 139.10, 138.34, 115.59, 114.83, 104.66, 68.01, 55.67, 37.66, 36.22, 25.75. HRMS calcd. for $C_{15}H_{20}O_3N_3$, 290.14992 $[M + H]^+$; found 290.14994 $[M + H]^+$.

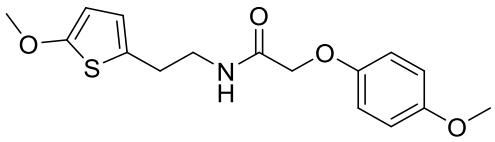


N-(2-(isothiazol-5-yl)ethyl)-2-(4-methoxyphenoxy)acetamide (14f). General procedure VI was followed using compound **13f** (0.071 g, 0.35 mmol), 4-methoxyphenol (0.052 g, 0.42 mmol) and cesium carbonate (0.45 g, 1.4 mmol) in acetonitrile (2.1 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (48 mg, 47%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.47; ^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 (s, 1H), 7.01 – 6.96 (m, 1H), 6.88 – 6.76 (m, 5H), 4.43 (s, 2H), 3.75 (s, 3H), 3.64 (q, J = 6.6 Hz, 2H), 3.19 (t, J = 6.8 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 168.80, 164.50, 157.82, 154.79, 151.18, 122.80, 115.61, 114.87, 68.08, 55.67, 39.54, 27.87. HRMS calcd. for $C_{14}H_{16}O_3N_2NaS$, 315.07738 $[M + Na]^+$; found 315.07712 $[M + Na]^+$.

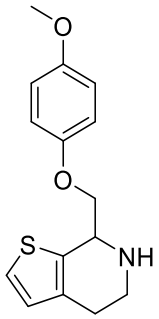


N-(2-(1H-pyrrol-1-yl)ethyl)-2-(4-methoxyphenoxy)acetamide (14g). General procedure VI was followed using compound **13g** (0.87 g, 4.7 mmol), 4-methoxyphenol (0.694 g, 5.59 mmol)

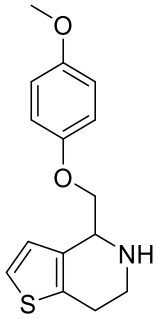
and cesium carbonate (6.08 g, 18.7 mmol) in acetonitrile (28 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (1.1 g, 89%). R_f (1:1 EtOAc:Hex): 0.30; ^{1}H NMR (500 MHz, Chloroform-d) δ 6.88 – 6.76 (m, 4H), 6.69 (s, 1H), 6.61 (t, J = 2.1 Hz, 2H), 6.17 (t, J = 2.1 Hz, 2H), 4.43 (s, 2H), 4.08 – 4.01 (m, 2H), 3.78 (s, 3H), 3.65 (q, J = 6.1 Hz, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 168.77, 154.77, 151.21, 120.62, 115.62, 114.84, 108.87, 67.99, 55.71, 48.86, 40.40. HRMS calcd. for $C_{15}H_{19}O_3N_2$, 275.13902 $[M + H]^+$; found 275.13913 $[M + H]^+$.



2-(4-methoxyphenoxy)-N-(2-(5-methoxythiophen-2-yl)ethyl)acetamide (14h). General procedure VI was followed using compound **13h** (0.89 g, 3.8 mmol), 4-methoxyphenol (0.57 g, 4.6 mmol) and cesium carbonate (4.96 g, 15.2 mmol) in acetonitrile (38 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white solid. (0.97 g, 79%). R_f (1:1 EtOAc:Hex): 0.41; ^{1}H NMR (400 MHz, Chloroform-d) δ 6.88 – 6.79 (m, 4H), 6.75 (bs, 1H), 6.37 (dt, J = 3.7, 0.8 Hz, 1H), 5.98 (d, J = 3.7 Hz, 1H), 4.43 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 3.55 (q, J = 6.6 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, cdcl3) δ 168.43, 164.86, 154.65, 151.29, 126.87, 122.68, 115.59, 114.78, 103.18, 68.08, 60.18, 55.67, 40.06, 30.32. HRMS calcd. for $C_{16}H_{20}O_4NS$, 322.11076 $[M + H]^+$; found 322.11032 $[M + H]^+$.

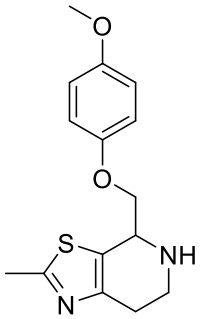


7-((4-methoxyphenoxy)methyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (15a). General procedure VIII was followed using compound **14a** (1.17 g, 4.02 mmol), $POCl_3$ (1.87 mL, 20.1 mmol) and sodium borohydride (0.456 g, 12.1 mmol) in acetonitrile (60 mL) and then methanol (17 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-10% (1% NH_4OH in MeOH)/DCM gradient) to afford the title compound as an orange oil. (0.120 g, 11%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.63; ^1H NMR (500 MHz, Chloroform-d) δ 7.16 (d, J = 5.1 Hz, 1H), 6.91 – 6.88 (m, 2H), 6.85 – 6.82 (m, 3H), 4.49 – 4.43 (m, 1H), 4.17 – 4.06 (m, 2H), 3.77 (s, 3H), 3.70 (dd, J = 20.3, 11.2 Hz, 1H), 3.31 (dt, J = 12.5, 4.8 Hz, 1H), 3.06 (ddd, J = 13.0, 8.4, 4.9 Hz, 1H), 2.80 – 2.63 (m, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 154.11, 152.71, 135.50, 133.88, 127.50, 123.03, 115.73, 114.64, 72.24, 55.70, 54.25, 41.74, 26.70. HRMS calcd. for $C_{15}H_{18}O_2NS$, 276.10528 $[M + H]^+$; found 276.10526 $[M + H]^+$.

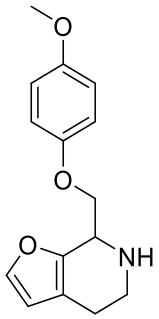


4-((4-methoxyphenoxy)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (15b). General procedure VIII was followed using compound **14b** (1.00 g, 3.43 mmol), $POCl_3$ (1.60 mL, 17.2 mmol) and sodium borohydride (0.390 g, 10.3 mmol) in acetonitrile (60 mL) and then methanol

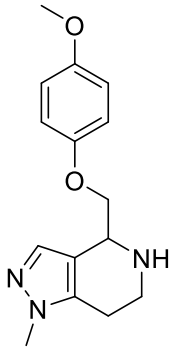
(17 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-10% (1% NH_4OH in MeOH)/DCM gradient) to afford the title compound as an orange oil. (371 mg, 39%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.86; ^1H NMR (500 MHz, Chloroform-d) δ 7.11 (d, J = 5.2 Hz, 1H), 6.91 – 6.80 (m, 5H), 4.39 – 4.33 (m, 1H), 4.19 (dd, J = 9.2, 3.8 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.77 (s, 3H), 3.70 (dd, J = 21.8, 11.2 Hz, 1H), 3.37 – 3.28 (m, 1H), 3.14 – 3.05 (m, 1H), 2.97 – 2.80 (m, 2H). ^{13}C NMR (126 MHz, cdcl3) δ 154.04, 152.87, 135.87, 133.68, 124.60, 122.44, 115.60, 114.65, 71.15, 55.71, 54.23, 41.28, 25.91. HRMS calcd. for $C_{15}H_{18}O_2NS$, 276.10528 $[M + H]^+$; found 276.10513 $[M + H]^+$.



4-((4-methoxyphenoxy)methyl)-2-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (15c). General procedure VIII was followed using compound **14c** (35 mg, 0.11 mmol), $POCl_3$ (53 μL, 0.57 mmol) and sodium borohydride (13 mg, 0.34 mmol) in acetonitrile (1.8 mL) and then methanol (0.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-10% (1% NH_4OH in MeOH)/DCM gradient) to afford the title compound as a clear oil. (3.6 mg, 9%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.40; ^1H NMR (500 MHz, Chloroform-d) δ 6.79 (s, 4H), 4.03 (t, J = 5.2 Hz, 2H), 3.73 (s, 3H), 3.12 – 2.92 (m, 6H), 2.65 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 165.78, 154.29, 153.94, 152.81, 115.53, 114.61, 113.44, 67.52, 55.68, 48.72, 48.53, 31.36, 19.11. HRMS calcd. for $C_{15}H_{19}O_2N_2S$, 291.11618 $[M + H]^+$; found 291.11615 $[M + H]^+$.

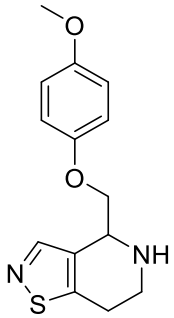


7-((4-methoxyphenoxy)methyl)-4,5,6,7-tetrahydrofuro[2,3-c]pyridine (15d). General procedure VIII was followed using compound **14d** (1.02 g, 3.71 mmol), $POCl_3$ (1.73 mL, 18.5 mmol) and sodium borohydride (0.421 g, 11.1 mmol) in acetonitrile (59 mL) and then methanol (15 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-20% (1% NH_4OH in MeOH)/DCM gradient) to afford the title compound as an orange oil. (0.570 g, 59%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.59; ^1H NMR (500 MHz, Chloroform-d) δ 7.31 – 7.26 (m, 1H), 6.91 – 6.79 (m, 4H), 6.26 (d, J = 1.9 Hz, 1H), 4.33 – 4.25 (m, 2H), 4.11 – 4.03 (m, 1H), 3.76 (s, 3H), 3.21 (dt, J = 12.7, 5.0 Hz, 1H), 2.98 (ddd, J = 12.6, 7.7, 4.9 Hz, 1H), 2.62 – 2.44 (m, 2H), 2.21 (bs, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 154.03, 152.90, 148.26, 141.06, 117.42, 115.73, 114.60, 110.37, 69.50, 55.69, 52.78, 41.62, 23.87. HRMS calcd. for $C_{15}H_{18}O_3N$, 260.12812 $[M + H]^+$; found 260.12799 $[M + H]^+$.

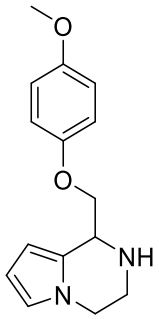


4-((4-methoxyphenoxy)methyl)-1-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (15e). General procedure VIII was followed using compound **14e** (0.70 g, 2.4 mmol), $POCl_3$ (1.13

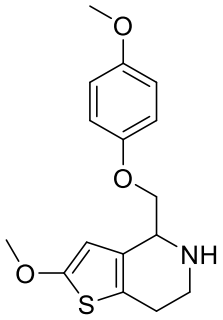
mL, 12.1 mmol) and sodium borohydride (0.275 g, 7.26 mmol) in acetonitrile (39 mL) and then methanol (10 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-10% (1% NH_4OH in MeOH)/DCM gradient) to afford the title compound as a clear oil. (0.25 g, 38%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.47; ^1H NMR (399 MHz, Chloroform-d) δ 7.33 (s, 1H), 6.92 – 6.78 (m, 4H), 4.28 (dd, J = 8.5, 4.0 Hz, 1H), 4.11 (dd, J = 9.1, 4.0 Hz, 1H), 3.92 (t, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.76 (s, 3H), 3.32 (dt, J = 12.3, 5.0 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.74 – 2.55 (m, 2H), 2.16 (bs, 1H). ^{13}C NMR (100 MHz, cdcl3) δ 153.96, 152.86, 137.49, 134.30, 115.55, 115.22, 114.61, 71.63, 55.68, 51.24, 40.91, 35.57, 22.70. HRMS calcd. HRMS calcd. for $C_{15}H_{20}O_2N_3$, 274.15500 $[M + H]^+$; found 274.15504 $[M + H]^+$.



4-((4-methoxyphenoxy)methyl)-4,5,6,7-tetrahydroisothiazolo[4,5-c]pyridine (15f). General procedure VIII was followed using compound **14f** (48 mg, 0.16 mmol), $POCl_3$ (0.077 mL, 0.82 mmol) and sodium borohydride (19 mg, 0.49 mmol) in acetonitrile (2.6 mL) and then methanol (0.7 mL). The crude product was carried forward without further purification.

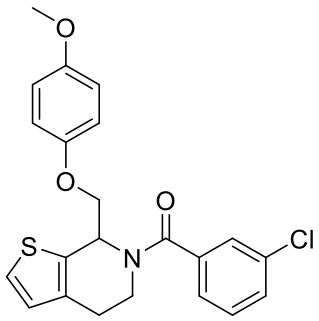


1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (15g). General procedure VIII was followed using compound **14g** (1.12 g, 4.08 mmol), $POCl_3$ (1.90 mL, 20.4 mmol) and sodium borohydride (0.463 g, 12.3 mmol) in acetonitrile (65 mL) and then methanol (16 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-10% (1% NH_4OH in MeOH)/DCM gradient) to afford the title compound as a white solid. (0.777 g, 74%). R_f (90:10:0.1 DCM:MeOH:NH_4OH): 0.58; ^1H NMR (500 MHz, Chloroform-d) δ 6.93 – 6.81 (m, 4H), 6.61 (t, J = 2.0 Hz, 1H), 6.18 (t, J = 3.0 Hz, 1H), 5.96 (dt, J = 3.3, 1.3 Hz, 1H), 4.46 (dd, J = 8.9, 3.3 Hz, 1H), 4.25 (dd, J = 9.2, 3.4 Hz, 1H), 4.06 – 3.93 (m, 3H), 3.78 (s, 3H), 3.37 (dt, J = 12.4, 4.0 Hz, 1H), 3.24 – 3.15 (m, 1H), 2.28 (s, 1H). ^{13}C NMR (126 MHz, cdcl3) δ 154.02, 152.83, 126.76, 119.48, 115.55, 114.65, 107.78, 102.75, 71.28, 55.72, 52.99, 45.55, 42.04. HRMS calcd. for $C_{15}H_{19}O_2N_2$, 259.14410 $[M + H]^+$; found 259.14418 $[M + H]^+$.



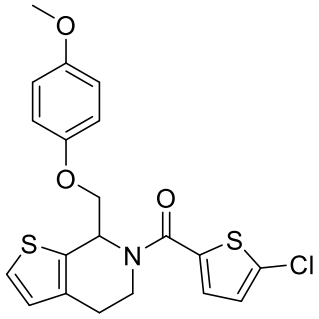
2-methoxy-4-((4-methoxyphenoxy)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (15h). General procedure VII was followed using compound **14h** (0.94 g, 2.9 mmol), $POCl_3$ (1.36 mL,

14.6 mmol) and sodium borohydride (0.33 g, 8.8 mmol) in acetonitrile (58 mL) and then methanol (15 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a red oil. (0.17 g, 19%). R_f (EtOAc): 0.17; ^{1}H NMR (500 MHz, Chloroform-d) δ 6.88 – 6.82 (m, 4H), 5.95 (s, 1H), 4.22 – 4.16 (m, 1H), 4.10 (dd, J = 9.2, 3.7 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.28 (dt, J = 12.1, 5.2 Hz, 1H), 3.07 (ddd, J = 12.2, 7.4, 4.9 Hz, 1H), 2.76 – 2.59 (m, 2H). ^{13}C NMR (151 MHz, CDCl3) δ 163.93, 154.03, 152.94, 130.71, 122.19, 115.61, 114.66, 101.30, 71.15, 60.28, 55.74, 54.09, 41.41, 25.38. HRMS calcd. for $C_{16}H_{20}O_3NS$, 306.11584 $[M + H]^+$; found 306.11537 $[M + H]^+$.



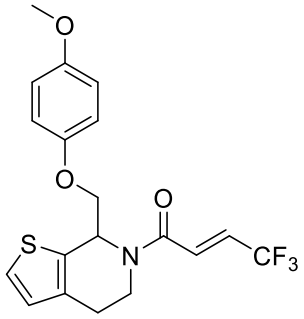
(3-chlorophenyl)(7-((4-methoxyphenoxy)methyl)-4,7-dihydrothieno[2,3-c]pyridin-6(5H)-yl)methanone (1180-400). General procedure IX was followed using compound **15a** (100 mg, 0.363 mmol), triethylamine (101 μL, 0.726 mmol) and 3-chlorobenzoyl chloride (56 μL, 0.44 mmol) in DCM (5.7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a white foam. (50 mg, 33%). R_f (1:1 EtOAc:Hex): 0.69; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 8.05 – 8.01 (m, 0.05H), 7.96 – 7.92 (m, 0.05H), 7.63 (bs, 0.3H), 7.57 – 7.52 (m, 0.5H), 7.45 – 7.32 (m, 3.3H), 7.32 – 7.23 (m, 2H), 6.95 – 6.78 (m, 5.2H), 6.09 (t, J = 5.4 Hz, 0.6H), 5.31 (dd, J = 9.1, 4.3 Hz, 0.4H), 4.92 (dd, J = 13.3, 5.6 Hz, 0.4H), 4.36 (dd, J = 9.3, 5.2 Hz, 0.6H), 4.28 (dd, J = 9.3, 6.1 Hz, 0.6H), 4.19 (t, J = 9.6 Hz, 0.4H), 3.98

(dd, J = 9.9, 4.4 Hz, 0.4H), 3.89 (dd, J = 13.7, 4.8 Hz, 0.6H), 3.77 (s, 3H), 3.63 – 3.54 (m, 0.6H), 3.26 – 3.15 (m, 0.4H), 2.99 (ddd, J = 17.1, 12.4, 5.7 Hz, 0.4H), 2.83 – 2.74 (m, 1H), 2.71 (dd, J = 15.9, 3.1 Hz, 0.6H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 170.51, 169.57, 153.87, 153.77, 152.30, 151.83, 137.55, 137.42, 136.03, 134.68, 134.38, 134.13, 132.11, 130.27, 130.11, 130.01, 129.97, 128.24, 127.84, 127.33, 126.83, 126.72, 125.50, 124.75, 124.70, 124.64, 124.32, 69.87, 69.63, 55.72, 55.63, 50.67, 43.15, 35.92, 26.45, 25.41. HRMS calcd. for $C_{22}H_{21}O_3NClS$, 414.09252 $[M + H]^+$; found 414.09298 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.42 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.702 min).



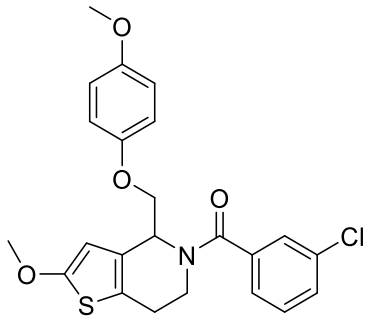
(5-chlorothiophen-2-yl)(7-((4-methoxyphenoxy)methyl)-4,7-dihydrothieno[2,3-c]pyridin-6(5H)-yl)methanone (1180-404). General procedure XIII was followed using compound **15a** (25 mg, 0.091 mmol), EDCI (17 mg, 0.11 mmol), DMAP (13 mg, 0.11 mmol) and 5-chlorothiophene-2-carboxylic acid (16 mg, 0.10 mmol) in DCM (0.4 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a clear oil. (10 mg, 26%). R_f (1:1 EtOAc:Hex): 0.90; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.41 (dd, J = 15.3, 1.8 Hz, 0.7H), 7.30 (d, J = 5.1 Hz, 0.7H), 7.24 (d, J = 5.1 Hz, 0.3H), 7.08 (dd, J = 15.3, 1.9 Hz, 0.3H), 6.89 – 6.73 (m, 6H), 6.02 (t, J = 5.2 Hz, 0.3H), 5.47 (dd, J = 8.9, 4.2 Hz, 0.7H), 4.91 (dd, J = 13.3, 4.7 Hz,

0.7H), 4.27 (dd, J = 9.4, 4.9 Hz, 0.3H), 4.22 – 4.15 (m, 2H), 4.12 (dd, J = 13.6, 4.3 Hz, 0.3H), 3.77 (s, 2H), 3.76 (s, 1H), 3.05 (td, J = 13.1, 4.3 Hz, 0.7H), 2.89 – 2.73 (m, 2H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 163.80, 162.90, 153.99, 153.78, 152.13, 151.57, 136.55, 134.06, 132.01, 130.04, 129.80, 129.65, 129.44, 129.42, 129.33, 129.30, 129.26, 129.22, 129.19, 128.96, 127.96, 127.29, 126.65, 124.98, 124.65, 123.54, 121.75, 115.35, 114.80, 114.55, 114.36, 69.89, 55.72, 55.69, 54.55, 51.01, 42.14, 36.11, 26.56, 25.40. HRMS calcd. for $C_{20}H_{19}O_3NClS_2$, 420.04894 $[M + H]^+$; found 420.04910 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.68 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.76 min).



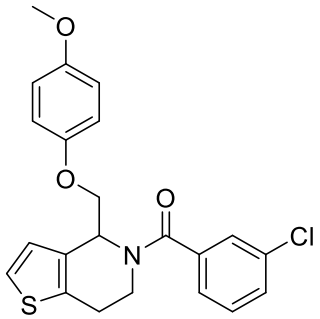
(E)-4,4,4-trifluoro-1-(7-((4-methoxyphenoxy)methyl)-4,7-dihydrothieno[2,3-c]pyridin-6(5H)-yl)but-2-en-1-one (1180-405). General procedure XIII was followed using compound **15a** (25 mg, 0.091 mmol), EDCI (17 mg, 0.11 mmol), DMAP (13 mg, 0.11 mmol) and (E)-4,4,4-trifluorobut-2-enoic acid (14 mg, 0.10 mmol) in DCM (0.4 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a yellow oil. (12 mg, 33%). R_f (1:1 EtOAc:Hex): 0.71; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.62 (d, J = 3.9 Hz, 0.5H), 7.28 – 7.24 (m, 1H), 7.15 (d, J = 3.8 Hz, 0.5H), 6.95 – 6.77 (m, 6H), 5.91 (t, J = 5.0 Hz, 0.5H), 5.81 (dd, J = 8.5, 5.0 Hz, 0.5H), 4.74 (dd, J = 13.4, 5.1 Hz, 0.5H), 4.47 (dd, J = 14.0, 4.8

Hz, 0.5H), 4.39 – 4.34 (m, 0.5H), 4.31 – 4.17 (m, 1.5H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.74 – 3.67 (m, 0.5H), 3.19 (td, J = 12.9, 3.5 Hz, 0.5H), 3.02 – 2.87 (m, 1H), 2.86 – 2.79 (m, 0.5H), 2.73 (dd, J = 16.4, 3.0 Hz, 0.5H). HRMS calcd. for $C_{19}H_{19}O_3NF_3S$, 398.10323 $[M + H]^+$; found 398.10325 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.00 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.64 min).



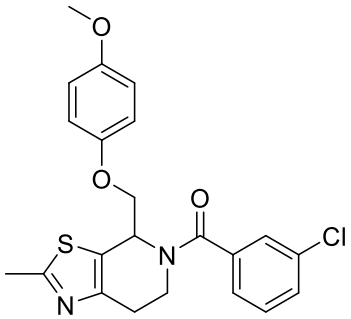
(3-chlorophenyl)(2-methoxy-4-((4-methoxyphenoxy)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone (1180-423). General procedure IX was followed using compound **15h** (25 mg, 0.082 mmol), triethylamine (23 μL, 0.16 mmol) and 3-chlorobenzoyl chloride (13 μL, 0.10 mmol) in DCM (1.3 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a micture of rotamers in solution and a yellow oil. (13 mg, 36%). R_f (1:1 EtOAc:Hex): 0.63; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.65 (bs, 0.5H), 7.44 – 7.32 (m, 3.5H), 7.29 – 7.24 (m, 0.5H), 6.90 – 6.76 (m, 4.5H), 6.01 (s, 0.5H), 5.79 (t, J = 4.6 Hz, 0.5H), 5.79 (s, 0.5H), 5.03 (dd, J = 9.5, 3.0 Hz, 0.5H), 4.94 (dd, J = 13.2, 5.6 Hz, 0.5H), 4.37 – 4.26 (m, 1H), 4.10 (t, J = 9.8 Hz, 0.5H), 3.94 – 3.86 (m, 1H), 3.86 (s, 1.5H), 3.81 (s, 1.5H), 3.77 (s, 3H), 3.73 – 3.67 (m, 0.5H), 3.24 (td, J = 12.8, 4.2 Hz, 0.5H), 3.06 – 2.97 (m, 0.5H), 2.85 – 2.76 (m, 0.5H), 2.68 (dd, J = 16.2, 3.6 Hz, 0.5H), 2.63 – 2.57 (m, 0.5H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 172.47, 170.55, 169.65, 164.48, 164.45, 153.77, 153.68, 152.48, 151.97,

137.66, 137.63, 134.65, 134.22, 130.25, 129.99, 129.90, 129.78, 129.14, 127.93, 127.71, 126.76, 125.69, 124.65, 121.90, 119.73, 115.29, 114.75, 114.49, 114.40, 101.00, 100.76, 69.37, 68.20, 60.13, 60.09, 56.07, 55.73, 55.72, 50.98, 43.51, 36.13, 25.24, 24.11. HRMS calcd. for $C_{23}H_{23}O_4NClS$, 444.10308 $[M + H]^+$; found 444.10290 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.33 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.69 min).



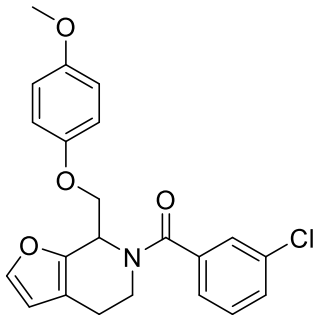
(3-chlorophenyl)(4-((4-methoxyphenoxy)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone (1180-401). General procedure IX was followed using compound **15b** (50 mg, 0.18 mmol), triethylamine (51 μL, 0.36 mmol) and 3-chlorobenzoyl chloride (28 μL, 0.22 mmol) in DCM (2.8 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a white foam. (49 mg, 65%). R_f (1:1 EtOAc:Hex): 0.77; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.67 (bs, 0.5H), 7.45 – 7.34 (m, 3H), 7.31 – 7.27 (m, 0.5H), 7.19 (dd, J = 16.2, 5.2 Hz, 1H), 6.99 (d, J = 5.2 Hz, 0.5H), 6.91 – 6.78 (m, 4H), 6.75 (d, J = 5.2 Hz, 0.5H), 5.99 (t, J = 4.8 Hz, 0.5H), 5.22 (dd, J = 9.6, 3.5 Hz, 0.5H), 4.99 (dd, J = 13.1, 5.4 Hz, 0.5H), 4.35 (qd, J = 9.8, 5.1 Hz, 1H), 4.11 (t, J = 9.8 Hz, 0.5H), 3.97 – 3.90 (m, 1H), 3.77 (s, 3H), 3.73 – 3.65 (m, 0.5H), 3.25 (td, J = 12.7, 4.0 Hz, 0.5H), 3.19 – 3.07 (m, 0.5H), 2.97 – 2.89 (m, 1H), 2.84 (dd, J = 16.0, 3.1 Hz, 0.5H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 170.67, 169.75, 153.80,

153.69, 152.46, 151.95, 137.71, 137.59, 136.30, 134.68, 134.25, 133.86, 132.25, 130.88, 130.29, 130.04, 129.93, 129.85, 127.98, 126.78, 125.71, 125.57, 125.04, 124.67, 123.91, 123.83, 69.52, 68.42, 56.18, 55.72, 51.08, 43.32, 36.05, 25.84, 24.76. HRMS calcd. for $C_{44}H_{40}O_6N_2Cl_2NaS_2$, 849.15970 $[2M + Na]^+$; found 849.16095 $[2M + Na]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.33 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.69 min).



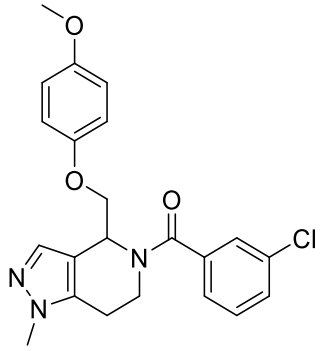
(3-chlorophenyl)(4-((4-methoxyphenoxy)methyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (1180-402). General procedure IX was followed using compound **15c** (5.0 mg, 0.014 mmol), triethylamine (3.8 μL, 0.028 mmol) and 3-chlorobenzoyl chloride (2.1 μL, 0.017 mmol) in DCM (0.2 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a yellow oil. (5.5 mg, 93%). R_f (1:1 EtOAc:Hex): 0.61; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.58 (s, 0.2H), 7.46 – 7.34 (m, 3H), 7.32 – 7.27 (m, 0.8H), 6.92 – 6.77 (m, 4H), 6.02 – 5.97 (m, 0.8H), 5.26 – 5.21 (m, 0.2H), 4.95 (dd, J = 13.3, 5.7 Hz, 0.2H), 4.34 (dd, J = 9.0, 4.6 Hz, 0.8H), 4.19 – 4.13 (m, 1H), 3.99 – 3.91 (m, 1H), 3.76 (s, 2H), 3.75 (s, 1H), 3.65 – 3.56 (m, 0.8H), 3.28 – 3.19 (m, 0.2H), 3.14 – 3.04 (m, 0.2H), 2.93 – 2.81 (m, 1.8H), 2.68 (s, 2H), 2.67 (s, 1H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 172.47, 170.39, 169.57, 165.82, 153.98, 153.87, 151.96, 151.60, 149.86, 147.99, 137.18, 137.11,

134.79, 134.54, 130.33, 130.30, 130.17, 130.16, 127.58, 126.95, 125.55, 125.23, 124.62, 123.69, 115.26, 114.90, 114.51, 114.46, 69.07, 68.88, 55.71, 54.39, 49.62, 43.37, 36.42, 27.63, 26.72, 19.48, 19.39. HRMS calcd. for $C_{22}H_{22}O_3N_2ClS$, 429.10342 $[M + H]^+$; found 429.10342 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.69 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.65 min).



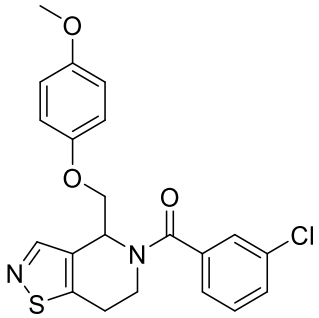
(3-chlorophenyl)(7-((4-methoxyphenoxy)methyl)-4,7-dihydrofuro[2,3-c]pyridin-6(5H)-yl)methanone (1180-403). General procedure IX was followed using compound **15d** (28 mg, 0.108 mmol), triethylamine (30 μL, 0.21 mmol) and 3-chlorobenzoyl chloride (17 μL, 0.13 mmol) in DCM (1.7 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a clear oil (19 mg, 44%). R_f (1:1 EtOAc:Hex): 0.44; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.62 (s, 0.3H), 7.44 – 7.32 (m, 4H), 7.28 – 7.24 (m, 0.7H), 6.86 – 6.77 (m, 4H), 6.35 – 6.30 (m, 1H), 5.86 (t, J = 4.1 Hz, 0.7H), 5.17 (dd, J = 8.8, 2.3 Hz, 0.3H), 4.89 (dd, J = 13.3, 5.3 Hz, 0.3H), 4.49 (dd, J = 10.1, 3.2 Hz, 0.7H), 4.40 (dd, J = 10.1, 4.2 Hz, 0.7H), 4.11 (t, J = 9.7 Hz, 0.3H), 4.05 (dd, J = 10.1, 3.2 Hz, 0.3H), 3.83 (dd, J = 13.7, 4.9 Hz, 0.7H), 3.77 (s, 1H), 3.77 (s, 2H), 3.75 – 3.68 (m, 0.7H), 3.25 – 3.13 (m, 0.3H), 2.88 – 2.78 (m, 0.3H), 2.67 – 2.58 (m, 0.7H), 2.58 – 2.45 (m, 1H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 170.89, 169.90, 153.79, 153.69, 152.46, 151.87, 145.67, 144.81, 142.63, 142.31, 137.67, 137.42, 134.62, 134.27,

130.21, 130.01, 129.90, 129.89, 127.84, 126.82, 125.56, 124.70, 118.52, 116.92, 115.32, 114.78, 114.47, 114.36, 110.47, 110.11, 68.48, 67.39, 55.73, 54.85, 50.14, 44.40, 36.70, 23.21, 21.95. HRMS calcd. for $C_{22}H_{21}O_4NCl$, 398.11536 $[M + H]^+$; found 398.11536 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.11 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.67 min).

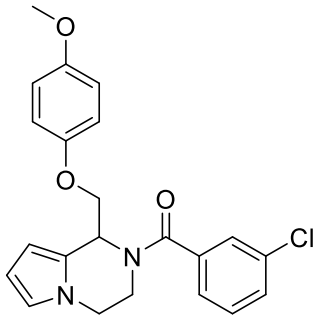


(3-chlorophenyl)(4-((4-methoxyphenoxy)methyl)-1-methyl-1,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)methanone (1180-407). General procedure IX was followed using compound **15e** (49 mg, 0.18 mmol), triethylamine (50 μL, 0.36 mmol) and 3-chlorobenzoyl chloride (28 μL, 0.38 mmol) in DCM (2.8 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a white solid. (71 mg, 96%). R_f (1:1 EtOAc:Hex): 0.64; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.62 (s, 0.5H), 7.47 (s, 0.5H), 7.44 – 7.31 (m, 3H), 7.29 – 7.23 (m, 0.5H), 7.18 (dd, J = 7.5, 3.9 Hz, 0.5H), 6.89 – 6.76 (m, 4H), 5.96 (d, J = 5.4 Hz, 0.5H), 5.18 (dd, J = 9.5, 4.0 Hz, 0.5H), 4.98 (dd, J = 13.4, 5.8 Hz, 0.5H), 4.26 (dd, J = 9.4, 5.4 Hz, 0.5H), 4.20 (dd, J = 9.4, 5.7 Hz, 0.5H), 4.04 (t, J = 9.8 Hz, 0.5H), 3.93 (dd, J = 13.9, 5.3 Hz, 0.5H), 3.84 (dd, J = 10.0, 4.1 Hz, 0.5H), 3.79 (s, 1.5H), 3.79 (s, 1.5H), 3.76 (s, 3H), 3.63 – 3.53 (m, 0.5H), 3.17 (td, J = 13.0, 4.3 Hz, 0.5H), 2.93 (ddd, J = 17.5, 12.0, 5.9 Hz, 0.5H), 2.79 –

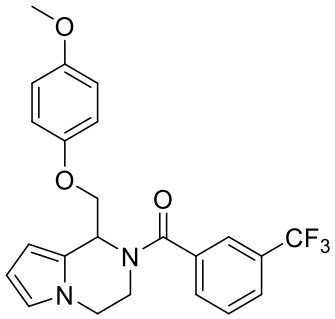
2.68 (m, 1H), 2.65 (dd, J = 15.5, 3.5 Hz, 0.5H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 170.97, 169.89, 153.79, 153.68, 152.41, 151.91, 137.75, 137.58, 137.45, 135.94, 135.55, 134.90, 134.72, 134.31, 130.32, 130.09, 129.98, 129.95, 129.14, 128.33, 127.81, 126.69, 125.53, 125.37, 124.59, 115.29, 114.76, 114.50, 114.40, 113.82, 112.83, 69.39, 68.74, 55.71, 53.01, 47.77, 42.36, 36.12, 35.13, 22.49, 21.70, 21.35. HRMS calcd. for $C_{22}H_{23}O_3N_3Cl$, 412.14225 $[M + H]^+$; found 412.14237 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.53 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 0.82 min).



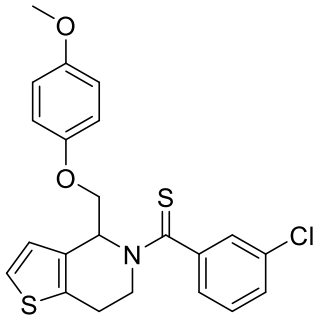
(3-chlorophenyl)(4-((4-methoxyphenoxy)methyl)-6,7-dihydroisothiazolo[4,5-c]pyridin-5(4H)-yl)methanone (1180-411). General procedure IX was followed using crude compound **15f** (45 mg, 0.16 mmol), triethylamine (45 μL, 0.33 mmol) and 3-chlorobenzoyl chloride (25 μL, 0.34 mmol) in DCM (2.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a yellow oil. (4.6 mg, 7% over three steps). R_f (1:1 EtOAc:Hex): 0.46; HRMS calcd. for $C_{21}H_{20}O_3N_2ClS$, 415.08777 $[M + H]^+$; found 415.08761 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.28 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.60 min).



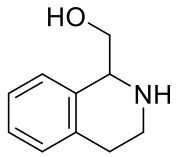
(3-chlorophenyl)(1-((4-methoxyphenoxy)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methanone (1180-420). General procedure IX was followed using compound **15g** (50 mg, 0.19 mmol), triethylamine (54 μL, 0.39 mmol) and 3-chlorobenzoyl chloride (30 μL, 0.23 mmol) in DCM (3.0 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a white foam. (67 mg, 87%). R_f (1:1 EtOAc:Hex): 0.58; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.69 (bs, 0.7H), 7.48 – 7.31 (m, 3H), 7.26 – 7.22 (m, 0.3H), 6.88 – 6.74 (m, 4H), 6.72 – 6.68 (m, 0.7H), 6.67 – 6.62 (m, 0.3H), 6.24 (t, J = 3.1 Hz, 0.3H), 6.21 (t, J = 3.1 Hz, 0.7H), 6.17 (t, J = 4.9 Hz, 0.3H), 6.12 (d, J = 3.4 Hz, 0.3H), 5.94 (d, J = 2.4 Hz, 0.7H), 5.44 (dd, J = 10.2, 3.8 Hz, 0.7H), 4.97 (dd, J = 13.7, 3.9 Hz, 0.7H), 4.40 (dd, J = 9.8, 4.2 Hz, 0.3H), 4.28 (dd, J = 9.8, 5.8 Hz, 0.3H), 4.20 – 4.07 (m, 2H), 4.04 – 3.84 (m, 2H), 3.77 (s, 3H), 3.51 – 3.42 (m, 0.7H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 170.73, 169.48, 153.79, 153.67, 152.48, 151.85, 137.16, 136.84, 134.79, 134.29, 130.36, 130.22, 130.14, 129.92, 128.12, 126.85, 125.93, 124.75, 124.61, 123.15, 120.23, 119.49, 115.35, 114.77, 114.49, 114.38, 108.82, 108.56, 105.04, 104.82, 70.21, 68.73, 55.72, 54.25, 49.39, 44.97, 44.30, 43.46, 35.85. HRMS calcd. for $C_{22}H_{22}O_3N_2Cl$, 397.13135 $[M + H]^+$; found 397.13144 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.87 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 0.96 min).



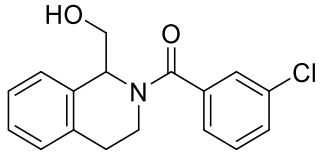
(1-((4-methoxyphenoxy)methyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-450). General procedure IX was followed using compound **15g** (100 mg, 0.387 mmol), triethylamine (108 μL, 0.774 mmol) and 3-chlorobenzoyl chloride (70 μL, 0.46 mmol) in DCM (6.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a white foam. (0.10 g, 62%). R_f (1:1 EtOAc:Hex): 0.60; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 8.01 (bs, 0.7H), 7.80 (d, J = 7.2 Hz, 0.7H), 7.72 (d, J = 7.6 Hz, 1H), 7.65 (s, 0.3H), 7.63 – 7.54 (m, 1.3H), 6.89 – 6.75 (m, 4H), 6.74 – 6.70 (m, 0.7H), 6.66 (m, 0.3H), 6.28 – 6.17 (m, 1H), 6.14 (d, J = 3.3 Hz, 0.3H), 5.95 (d, J = 2.5 Hz, 0.7H), 5.42 (dd, J = 10.4, 3.8 Hz, 0.7H), 5.00 (dd, J = 13.7, 4.0 Hz, 0.7H), 4.43 (dd, J = 9.9, 4.2 Hz, 0.3H), 4.34 – 4.29 (m, 0.3H), 4.23 – 4.09 (m, 2H), 4.06 – 3.95 (m, 1H), 3.89 (dd, J = 10.1, 4.0 Hz, 1H), 3.77 (s, 3H), 3.50 (td, J = 13.5, 4.1 Hz, 1H). ^{13}C NMR (151 MHz, cdcl3) δ 170.77, 169.52, 153.86, 153.74, 152.48, 151.79, 136.26, 135.97, 131.18, 130.81, 130.59, 130.01, 129.58, 129.10, 126.85, 125.14, 124.66, 124.56, 123.78, 123.01, 122.86, 120.31, 119.54, 115.35, 114.75, 114.50, 114.40, 108.88, 108.61, 105.10, 104.89, 70.24, 68.61, 55.70, 54.33, 49.54, 44.92, 44.27, 43.54, 35.85. HRMS calcd. for $C_{23}H_{22}O_3N_2F_3$, 431.15770 $[M + H]^+$; found 431.15762 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.90 min). Method 2: 95% MeOH in water over 3 min at 1 mL/min (retention time 0.90 min).



(3-chlorophenyl)(4-((4-methoxyphenoxy)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanethione (1180-413). General procedure XIV was followed using compound **1180-401** (48 mg, 0.12 mmol) and Lawesson's Reagent (80 mg, 0.20 mmol) in toluene (1.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-40% EtOAc/hexanes gradient) to afford the title compound as a clear oil. (11 mg, 18%). R_f (1:1 EtOAc:Hex): 0.77; ^{1}H NMR (600 MHz, Chloroform-d) δ 7.24 – 7.15 (m, 3H), 7.06 – 7.01 (m, 2H), 6.83 – 6.77 (m, 3H), 6.76 – 6.71 (m, 3H), 6.49 (d, J = 15.2 Hz, 1H), 4.91 (dd, J = 6.9, 4.7 Hz, 1H), 4.82 (d, J = 15.2 Hz, 1H), 4.53 (d, J = 19.6 Hz, 1H), 4.28 (d, J = 19.6 Hz, 1H), 4.11 – 4.03 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, cdcl3) δ 199.43, 159.91, 154.43, 151.83, 137.15, 134.57, 133.42, 130.05, 127.90, 127.74, 126.65, 125.47, 123.14, 115.45, 114.72, 113.30, 111.58, 70.64, 62.71, 56.22, 55.69, 55.39, 47.73. HRMS calcd. for $C_{25}H_{25}O_3NClS$, 454.12382 $[M + H]^+$; found 454.12380 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.84 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 1.41 min).

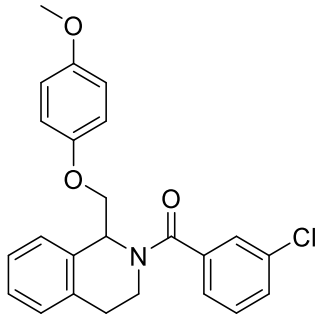


(1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (17). 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**16**) (1.00 g, 5.64 mmol) was dissolved in THF (56 mL) and borane dimethyl sulfide complex (1.88 mL, 19.8 mmol) was added dropwise via syringe pump at a rate of 0.1 mL per minute. The reaction was stirred overnight at room temperature before quenching with MeOH carefully at room temperature. 1M NaOH was added and the organic layer extracted with EtOAc before the combined organic layers were washed once more with 1M NaOH, washed with brine (3x), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as a white foam. (0.59 g, 64%). R_f (80:20:6 DCM:MeOH:NH_3): 0.71; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.19 – 7.04 (m, 4H), 4.04 (dd, J = 9.3, 4.3 Hz, 1H), 3.79 (dd, J = 10.9, 4.3 Hz, 1H), 3.65 (dd, J = 10.9, 9.3 Hz, 1H), 3.17 – 2.97 (m, 2H), 2.81 – 2.68 (m, 4H). ^{13}C NMR (100 MHz, cdcl3) δ 135.53, 135.23, 129.39, 126.51, 126.23, 126.02, 64.05, 56.35, 38.86, 29.59. HRMS calcd. for $C_{10}H_{14}ON$, 164.10699 $[M + H]^+$; found 164.10683 $[M + H]^+$.



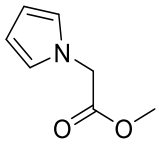
(3-chlorophenyl)(1-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (18). General procedure IX was followed using compound **17** (0.59 g, 3.6 mmol), triethylamine (1.00 mL, 7.23 mmol) and 3-chlorobenzoyl chloride (0.46 mL, 3.6 mmol) in DCM (56 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a mixture of rotamers in solution and a

clear foam. (0.18 g, 17%). R_f (90:10:2 DCM:MeOH:NH_3): 0.55; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.51 – 7.11 (m, 8H), 6.92 (d, J = 7.5 Hz, 0.2H), 5.84 (dd, J = 8.8, 3.9 Hz, 0.8H), 4.90 (dd, J = 8.7, 3.9 Hz, 0.2H), 4.82 (dd, J = 13.1, 5.8 Hz, 0.2H), 4.13 – 4.06 (m, 0.8H), 3.95 (dd, J = 11.5, 9.0 Hz, 0.8H), 3.89 – 3.75 (m, 1H), 3.74 – 3.54 (m, 1H), 3.35 – 3.21 (m, 0.2H), 3.20 – 3.07 (m, 0.2H), 3.07 – 2.93 (m, 0.8H), 2.89 – 2.74 (m, 1.8H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 171.56, 170.76, 137.57, 137.18, 134.66, 134.54, 134.33, 133.67, 132.29, 132.25, 130.39, 130.28, 129.90, 129.83, 129.49, 129.21, 127.85, 127.62, 127.58, 127.41, 127.03, 126.79, 126.28, 125.87, 124.98, 66.49, 64.37, 60.07, 55.47, 41.82, 35.20, 29.22, 28.22. HRMS calcd. for $C_{17}H_{17}O_2NCl$, 302.09423 $[M + H]^+$; found 302.09389 $[M + H]^+$.



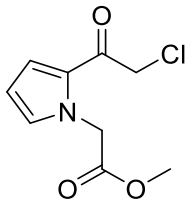
(3-chlorophenyl)(1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-436). An oven-dried microwave vial was charged with an oven-dried stir bar, compound **18** (100 mg, 0.331 mmol, 1 eq), copper(I) iodide (12 mg, 0.066 mmol, 0.2 eq), 3,4,7,8-tetramethyl-1,10-phenanthroline (16 mg, 0.066 mmol, 0.2 eq), 1-iodo-4-methoxybenzene (116 mg, 0.497 mmol, 1.5 eq), and cesium carbonate (162 mg, 0.497 mmol, 1.5 eq). The vessel was then capped and evacuated and back-filled with dry argon 3 times. Dry toluene (0.66 mL) was then added, the vial evacuated and back-filled with dry argon once more and the reaction stirred at 110 ^{o}C for 48 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc, and filtered through a plug of celite, washing with additional EtOAc. The crude material was then concentrated and purified via flash column chromatography (ISCO, Redisep 4 g column,

0-70% EtOAc/hexanes gradient) to afford the title compound as rotamers in solution and a white foam. (70 mg, 52%). R_f (1:1 EtOAc:Hex): 0.68; ^{1}H NMR (600 MHz, Chloroform-d, probe temp: -25 °C) δ 7.65 (bs, 0.5H), 7.46 – 7.17 (m, 7H), 7.04 (d, J = 7.6 Hz, 0.5H), 6.89 – 6.78 (m, 4H), 6.10 – 6.05 (m, 0.5H), 5.25 – 5.20 (m, 0.5H), 4.90 (dd, J = 13.0, 5.7 Hz, 0.5H), 4.45 – 4.35 (m, 1H), 4.17 (t, J = 10.2 Hz, 0.5H), 3.95 (dd, J = 10.1, 3.7 Hz, 0.5H), 3.85 – 3.79 (m, 0.5H), 3.77 (s, 1.5H), 3.77 (s, 1.5H), 3.72 (td, J = 13.5, 3.7 Hz, 0.5H), 3.27 (td, J = 12.8, 3.7 Hz, 0.5H), 3.18 (td, J = 14.6, 12.6, 5.9 Hz, 0.5H), 2.96 (ddd, J = 17.0, 12.1, 5.8 Hz, 0.5H), 2.92 – 2.87 (m, 0.5H), 2.81 (d, J = 16.0 Hz, 0.5H). ^{13}C NMR (151 MHz, cdcl3, probe temp: -25 °C) δ 170.37, 169.62, 153.81, 153.69, 152.51, 152.02, 137.80, 137.72, 135.12, 134.63, 134.29, 134.13, 132.71, 131.78, 129.90, 129.77, 129.15, 128.01, 127.37, 127.36, 127.23, 126.76, 126.75, 126.40, 125.69, 124.65, 115.32, 114.85, 114.50, 114.39, 70.64, 69.27, 57.39, 55.72, 51.92, 42.55, 35.13, 29.47, 28.08. HRMS calcd. for $C_{24}H_{23}O_3NCl$, 408.13610 $[M + H]^+$; found 408.13561 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.46 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 0.84 min).

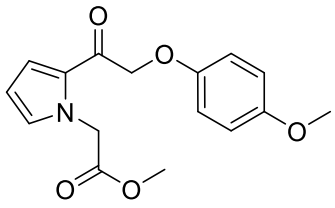


methyl 2-(1H-pyrrol-1-yl)acetate (20). Glycine methyl ester hydrochloride (**19**) (5.00 g, 39.8 mmol, 1 eq) and sodium acetate (4.90 g, 59.7 mmol, 1.5 eq) were dissolved in a 2:1 (v/v) mixture of acetic acid (50 mL) and water (25 mL). 2,5-dimethoxytetrahydrofuran (5.66 mL, 43.8 mmol, 1.1 eq) was then added and the resulting mixture was heated to 100 ^{o}C for 4 hours before cooling to room temperature. The crude mixture was poured into water, washed with EtOAc, and the aqueous phase neutralized with solid Na_2CO_3. This was then extracted with EtOAc, washed with

brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a clear oil (3.76 g, 68%). R_f (1:1 EtOAC:Hex): 0.68; ^{1}H NMR (399 MHz, Chloroform-d) δ 6.70 (t, J = 2.1 Hz, 2H), 6.24 (t, J = 2.1 Hz, 2H), 4.67 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, cdcl3) δ 169.29, 121.79, 109.07, 52.50, 50.65. HRMS calcd. for $C_7H_{10}O_2N$, 140.07061 $[M + H]^+$; found 140.07063 $[M + H]^+$.

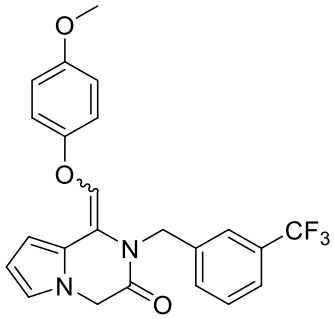


methyl 2-(2-(2-chloroacetyl)-1H-pyrrol-1-yl)acetate (21). General procedure XV was followed using **20** (2.00 g, 14.4 mmol), aluminum trichloride (2.11 g, 15.8 mmol), and 2-chloroacetyl chloride (1.27 mL, 15.8 mmol) in DCM (29 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 40 g column, 0-100% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.69 g, 22%). R_f (1:1 EtOAC:Hex): 0.60; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.06 (dd, J = 4.2, 1.6 Hz, 1H), 6.92 (dd, J = 2.4, 1.7 Hz, 1H), 6.26 (dd, J = 4.2, 2.6 Hz, 1H), 5.03 (s, 2H), 4.51 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 181.63, 168.77, 132.32, 127.73, 120.39, 109.52, 51.01, 45.52. HRMS calcd. for $C_9H_{13}O_3NCl$, 216.04220 $[M + H]^+$; found 216.04225 $[M + H]^+$.

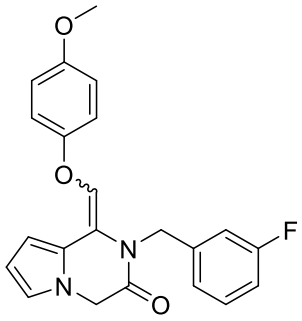


methyl 2-(2-(2-(4-methoxyphenoxy)acetyl)-1H-pyrrol-1-yl)acetate (22). General procedure XVI was followed using **21** (0.61 g, 2.8 mmol), potassium iodide (0.56 g, 3.4 mmol), 4-

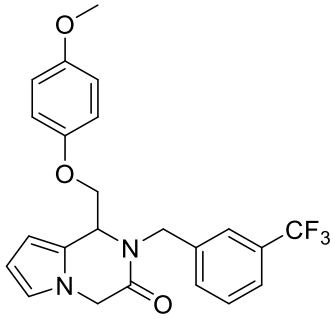
methoxyphenol (0.42 g, 3.4 mmol), and potassium carbonate (1.84 g, 5.66 mmol) in acetone (9.4 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a clear oil (0.45 g, 52%). R_f (1:1 EtOAC:Hex): 0.76; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.17 (dd, J = 4.1, 1.6 Hz, 1H), 6.90 (dd, J = 2.5, 1.5 Hz, 1H), 6.89 – 6.76 (m, 4H), 6.26 (dd, J = 4.2, 2.6 Hz, 1H), 5.05 (s, 2H), 5.00 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, cdcl3) δ 185.46, 168.89, 154.24, 152.31, 131.61, 127.78, 119.59, 115.69, 114.61, 109.37, 70.83, 55.66, 52.43, 51.02. HRMS calcd. for $C_{16}H_{18}O_5N$, 304.11795 $[M + H]^+$; found 304.11780 $[M + H]^+$.



1-((4-methoxyphenoxy)methylene)-2-(3-(trifluoromethyl)benzyl)-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-one (23a). General procedure XVII was followed using compound **22** (0.20 g, 0.66 mmol), 3-(trifluoromethyl)benzylamine (113 μL, 0.790 mmol), tetraisopropoxytitanium (0.58 mL, 2.0 mmol), and sodium triacetoxyborohydride (0.42 g, 2.0 mmol) in DCE (4.0 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 12 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a white solid (89 mg, 32%). HRMS calcd. for $C_{23}H_{20}O_3N_2F_3$, 429.14205 $[M + H]^+$; found 429.14178 $[M + H]^+$.

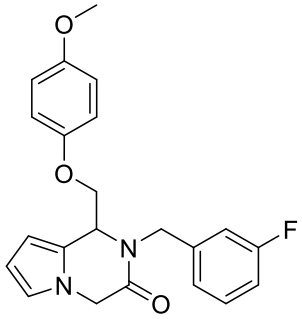


2-(3-fluorobenzyl)-1-((4-methoxyphenoxy)methylene)-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-one (23b). General procedure XVII was followed using compound **22** (50 mg, 0.16 mmol), 3-fluorobenzylamine (28 μL, 0.20 mmol), tetraisopropoxytitanium (0.15 mL, 0.49 mmol), and sodium triacetoxyborohydride (0.10 g, 0.49 mmol) in DCE (0.8 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a mixture of E/Z isomers and a white solid (24 mg, 38%). HRMS calcd. for $C_{22}H_{20}O_3N_2F$, 379.14525 $[M + H]^+$; found 379.14551 $[M + H]^+$.



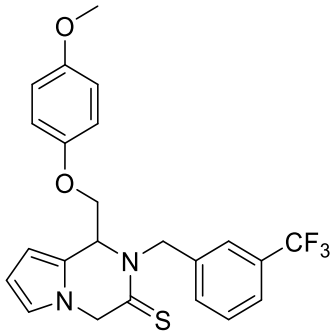
1-((4-methoxyphenoxy)methyl)-2-(3-(trifluoromethyl)benzyl)-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-one (1180-447). General procedure XVIII was followed using compound **23a** (55 mg, 0.13 mmol) and Pd/C (20 mg, 0.019 mmol) in EtOAc (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a white foam. (20 mg, 36%). R_f (1:1 EtOAc:Hex): 0.62; ^{1}H NMR (500 MHz, Chloroform-d) δ 7.54 – 7.50 (m, 2H), 7.45 (d, J = 7.7 Hz, 1H), 7.42 – 7.37 (m, 1H), 6.82 – 6.75 (m, 2H), 6.71 – 6.66 (m, 2H), 6.65 (dd, J = 2.7, 1.6 Hz, 1H), 6.22 (dd, J = 3.5,

2.8 Hz, 1H), 6.00 (dd, J = 3.5, 1.5 Hz, 1H), 5.44 (d, J = 15.4 Hz, 1H), 4.87 (d, J = 17.0 Hz, 1H), 4.83 (dd, J = 4.5, 3.3 Hz, 1H), 4.77 (d, J = 17.0 Hz, 1H), 4.49 (d, J = 15.4 Hz, 1H), 4.15 (dd, J = 9.7, 3.2 Hz, 1H), 4.04 (dd, J = 9.7, 4.7 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, cdcl3) δ 166.30, 154.46, 152.00, 137.41, 131.19, 131.11 (q, J = 31.7 Hz, ^{2}J), 129.35, 124.80 (q, J = 3.8 Hz, ^{3}J), 124.63 (q, J = 3.8 Hz, ^{3}J), 123.98, 123.9 (q, J = 272.5 Hz, ^{1}J), 118.89, 115.61, 114.70, 109.55, 103.94, 72.36, 55.68, 54.95, 49.03, 48.57. HRMS calcd. for $C_{23}H_{22}O_3N_2F_3$, 431.15770 $[M + H]^+$; found 431.15735 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.82 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 0.87 min).



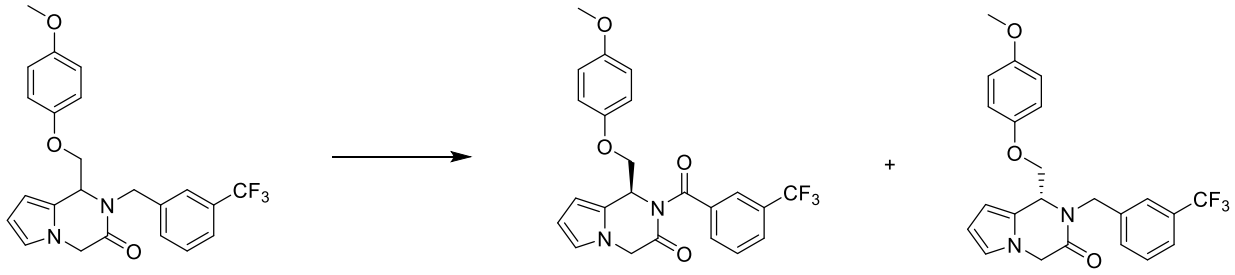
2-(3-fluorobenzyl)-1-((4-methoxyphenoxy)methyl)-1,2-dihydropyrrolo[1,2-a]pyrazin-3(4H)-one (1180-453). General procedure XVIII was followed using compound **23b** (24 mg, 0.063 mmol) and Pd/C (10 mg, 0.010 mmol) in EtOAc (5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-35% EtOAc/hexanes gradient) to afford the title compound as a white solid. (14 mg, 58%). R_f (1:1 EtOAc:Hex): 0.68; m.p. 87-88 ℃, ^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.20 (m, 1H), 7.03 (d, J = 7.9 Hz, 1H), 7.00 – 6.90 (m, 2H), 6.83 – 6.74 (m, 2H), 6.73 – 6.65 (m, 2H), 6.64 (dd, J = 2.7, 1.6 Hz, 1H), 6.22 (dd, J = 3.3, 2.8 Hz, 1H), 5.99 (dd, J = 3.5, 1.5 Hz, 1H), 5.43 (d, J = 15.4 Hz, 1H), 4.86 (d, J = 17.0 Hz, 1H), 4.82 (d, J = 3.7 Hz, 2H), 4.75 (d, J = 17.0 Hz, 1H), 4.37 (d, J = 15.4 Hz, 1H), 4.15 (dd, J = 9.7, 3.2 Hz,

1H), 4.02 (dd, J = 9.7, 4.5 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 166.24, 162.98 (d, J = 246.9 Hz, ^{1}J), 154.34, 152.03, 138.73 (d, J = 7.1 Hz, ^{3}J), 130.33 (d, J = 8.2 Hz, ^{3}J), 124.09, 123.48 (d, J = 2.9 Hz, ^{4}J), 118.82, 115.60, 114.93 (d, J = 21.9 Hz, ^{2}J), 114.93 (d, J = 21.2 Hz, ^{2}J), 114.62, 109.46, 103.83, 72.16, 55.68, 54.64, 49.02, 48.23. HRMS calcd. for $C_{22}H_{22}O_3N_2F$, 381.16090 $[M + H]^+$; found 381.16132 $[M + H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 1.41 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 0.80 min).

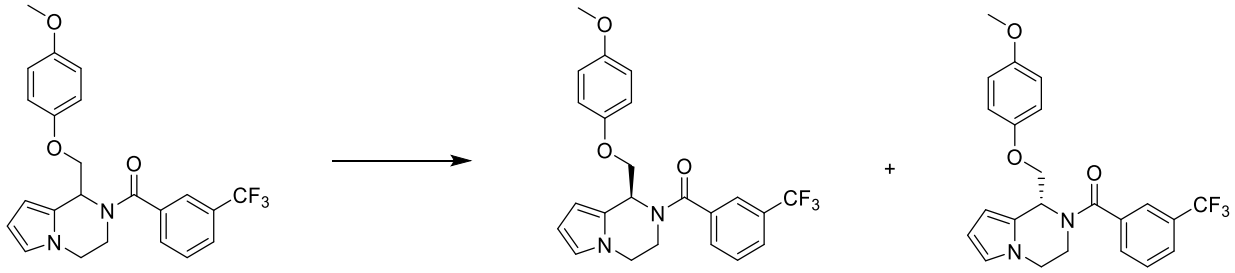


1-((4-methoxyphenoxy)methyl)-2-(3-(trifluoromethyl)benzyl)-1,2-dihydropyrrolo[1,2-a]pyrazine-3(4H)-thione (1180-454). General procedure XIV was followed using compound **1180-447** (13 mg, 0.030 mmol) and Lawesson's Reagent (18 mg, 0.045 mmol) in toluene (0.5 mL). The crude product was purified via flash column chromatography (ISCO, Redisep 4 g column, 0-20% EtOAc/hexanes gradient) to afford the title compound as a yellow oil. (4.3 mg, 32%). R_f (1:1 EtOAc:Hex): 0.83; ^{1}H NMR (399 MHz, Chloroform-d) δ 7.57 – 7.48 (m, 2H), 7.43 – 7.37 (m, 2H), 6.84 – 6.69 (m, 4H), 6.67 (dd, J = 2.7, 1.6 Hz, 1H), 6.40 (d, J = 15.3 Hz, 1H), 6.22 (dd, J = 3.5, 2.8 Hz, 1H), 6.00 (dd, J = 3.5, 1.4 Hz, 1H), 5.44 (d, J = 18.0 Hz, 1H), 5.15 (d, J = 18.0 Hz, 1H), 5.07 (dd, J = 6.0, 3.4 Hz, 1H), 4.93 (d, J = 15.3 Hz, 1H), 4.17 (dd, J = 10.0, 3.4 Hz, 1H), 4.10 (dd, J = 10.0, 6.1 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, cdcl3) δ 195.15, 154.58, 151.69,

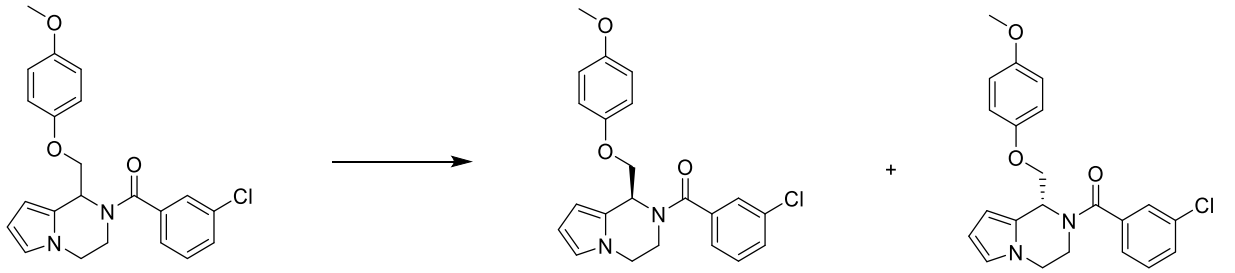
135.69, 131.15 (q, J = 32.5 Hz, ^{2}J), 130.77, 124.85 (q, J = 3.7 Hz, ^{3}J), 124.67 (q, J = 3.7 Hz, ^{3}J), 124.40 (q, J = 271.8 Hz, ^{1}J), 122.76, 118.70, 115.61, 114.73, 109.41, 104.06, 77.19, 72.04, 58.16, 56.61, 55.67. HRMS calcd. for $C_{23}H_{21}O_2N_2F_3S$, 445.12031 $[M - H]^+$; found 445.12034 $[M - H]^+$. Purity was established using an Agilent pump on a Zorbax XBD-C18 column (4.6 mm × 50 mm, 3.5 μm). Method 1: 75-95% MeOH in water over 3 min at 1 mL/min (retention time = 2.59 min). Method 2: 85-95% MeOH in water over 5 min at 1 mL/min (retention time 1.17 min).



*Separation of **1180-447** Enantiomers*. Semipreparative separation of **1180-447** enantiomers from racemic **1180-447** (0.020 g) was done using a ChiralPak AD-H (30 mm × 250 mm) with the following conditions: 20 mL/min flow rate, 10 mL injection volume (2 mg/1 mL), 90% hexanes/10% IPA over 60 min to afford ***S*-(—)-1180-447**, t_R 33.8 min; ***R*-(+)-1180-447**, t_R 47.2 min. The enantiomeric excess (ee) was determined using an Agilent pump on a ChiralPak OD-H column (4.6 mm × 150 mm, 5 μm) with the following conditions: 1 mL/min flow rate, 10 μL injection volume, 90% hexanes/10% IPA. ***S*-(—)-1180-447**: t_R 21.4 min; >99% ee; [α]D20 = −45 (c 0.10, dry $CHCl_3$). ***R*-(+)-1180-447**: t_R 30.1 min, >99% ee; [α]D20 = +45 (c 0.10, dry $CHCl_3$). The proton spectrum for each enantiomer was identical to that of the racemic mixture.



*Separation of **1180-450** Enantiomers*. Semipreparative separation of **1180-450** enantiomers from racemic **1180-450** (0.020 g) was done using a ChiralPak AD-H (30 mm × 250 mm) with the following conditions: 20 mL/min flow rate, 10 mL injection volume (2 mg/1 mL), 90% hexanes/10% IPA over 60 min to afford ***R*-(+)-1180-450**, t_R 41.4 min; ***S*-(—)-1180-450**, t_R 50.5 min. The enantiomeric excess (ee) was determined using an Agilent pump on a ChiralPak OD-H column (4.6 mm × 150 mm, 5 μm) with the following conditions: 1 mL/min flow rate, 10 μL injection volume, 90% hexanes/10% IPA. ***R*-(+)-1180-450**: t_R 27.1 min; >99% ee; [α]D20 = +148 (c 0.10, dry $CHCl_3$). ***S*-(—)-1180-450**: t_R 32.4 min, >99% ee; [α]D20 = −149 (c 0.10, dry $CHCl_3$). The proton spectrum for each enantiomer was identical to that of the racemic mixture.



*Separation of **1180-420** Enantiomers*. Semipreparative separation of **1180-420** enantiomers from racemic **1180-420** (0.020 g) was done using a ChiralPak AD-H (30 mm × 250 mm) with the following conditions: 20 mL/min flow rate, 10 mL injection volume (2 mg/1 mL), 90% hexanes/10% IPA over 90 min to afford ***R*-(+)-1180-420**, t_R 59.2 min; ***S*-(—)-1180-420**, t_R 70.7 min. The enantiomeric excess (ee) was determined using an Agilent pump on a ChiralPak OD-H column (4.6 mm × 150 mm, 5 μm) with the following conditions: 1 mL/min flow rate, 10 μL

injection volume, 90% hexanes/10% IPA. ***R*-(+)-1180-420**: t_R 31.5 min; >99% ee; [α]D20 = +172 (c 0.10, dry $CHCl_3$). ***S*-(—)-1180-420**: t_R 41.4 min, >99% ee; [α]D20 = −173 (c 0.10, dry $CHCl_3$). The proton spectrum for each enantiomer was identical to that of the racemic mixture.

3.4.2 In vitro analysis of 1180 series analogs

Protocols utilizing *Xenopus laevis* oocytes were approved by the Emory University Institutional Animal Care and Use Committee. *Xenopus laevis* oocytes were purchased unfertilized from Ecocyte (Austin, TX). The oocytes were injected with mRNA to express recombinant rat GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D and two-electrode voltage clamp (TEVC) recordings were performed. Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (Univeristy of Heidelberg) provided the cDNAs for rat GluN1-1a (GenBank accession numbers U11418 and U08261, referred to as GluN1 henceforth), GluN2A (D13211), GluN2B (U11419), GluN2C (M91563), and GluN2D (D13213). GluN2C and GluN2D were altered according to literature precedent.[33] Isolation of oocytes, synthesis of cRNA, and injections of cRNA were each done according to literature precedent.[34] Oocytes were placed in perfusion chamber and continuously washed during TEVC recordings with a solution consisting of the following (in mM): 90 NaCl, 0.5 BaCl, 0.005 EDTA, 1.0 KCl, and 10 HEPES at pH 7.4 and 23 ℃. Glass electrodes were pulled from thin-walled glass capillaries (tip resistance 0.5-2.5 MΩ) and filled with 0.3-3.0 M KCl while the oocyte membrane potential was held constant at -40 mV via an OC-725C amplifier (Warner Instrument Co.). Each compound was brought up in 20 mM DMSO and diluted with recording solution containing 30 μM glycine and 100 μM glutamate to the target concentration. To prevent the current increase typically seen during experiments with oocytes expressing GluN1/GluN2A receptors, the oocytes were either injected with 20 nL of 100 mM K-BAPTA (potassium 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-

tetraacetic acid) or pretreated with 50 μM BAPTA-AM (1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid tetraacetoxymethyl ester) for 10 minutes. Compounds that potentiated GluN2A- and GluN2B-containing receptors were not studied further.

Every test compound was recorded at 5−7 concentrations using 4-15 oocytes from 1-2 frogs. For test compounds with potentiation that exceeded 125% at 30 μM, an EC_{50} value (the half-maximal effective concentration of potentiator) was determined by fitting the following equation

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

to the mean composite concentration−response data normalized to the current in the absence of the potentiator (100%) where *N* equals the Hill slope and max is the maximal response predicted for saturating concentration of potentiator.

The concentration that gave a 2-fold increase in the current response was determined by rearranging eq 1 to yield

$$doubling\ concentration = EC_{50}\ ((100 - max) / (200 - max) - 1)^{1/N}$$

in which the Hill slope was held constant at 1.

3.4.3 Solubility determination

The maximum solubility for compounds **CIQ**, **1180-400**, **-420**, **-447**, **-450**, and **-453** was determined using a BMG Labtech Nephelostar nephelometer (Offenburg, Germany) according to manufacturer's instructions. Compound powder (1-3 mg) was taken up in DMSO (Sigma-Aldrich) to a 20 mM stock solution and serially diluted (~10 μL) to 15, 10, 5, 2.5 1.25, and 0.625 μM stock solutions. These, along with a DMSO blank, were distributed in triplicate to black, clear-bottom 96 well plates in 3 μL increments and subsequently diluted 100-fold using the oocyte recording solution described in **Section 3.4.2**. Each solution was shaken gently for 30 min before submission to the nephelometer.

3.4.4 In vitro analysis of off-target selectivity for 1180-420 and 1180-447

Receptor binding profiles, K_i determinations, and hERG activity of compounds **1180-420** and **1180-447** were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2013-00017-C (NIMH PDSP). The NIMH PDSP is Directed by Bryan L. Roth at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. Radioligand binding was measured in the presence of 10 μM **1180-420** and **1180-447**. A K_i value was determined for each receptor at which compound **1180-420** and **1180-447** showed >50% inhibition. For experimental details please refer to the PDSP web site https://pdsp.unc.edu/ims/investigator/web/. Both **1180-420** and **1180-447** were also tested at AMPA, nicotinic acetylcholine, serotonin, GABA, and glycine ion channels using a two-electrode voltage clamp assay.

3.5 References

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