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Rose M. Santangelo Date

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

By

Rose Mary Santangelo
Doctor of Philosophy

Chemistry

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Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

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Date

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

By

Rose M. Santangelo

B.S., Juniata College, 2006

Advisor: Dennis C. Liotta, Ph.D.

An abstract of

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

2012

Abstract

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

*Chapter 1: Design, Synthesis, and Biological Evaluation of GluN1/GluN2B Selective NMDA Receptor Antagonists for the Potential Treatment of Neurodegenerative Diseases*

*Chapter 2: Design, Synthesis, and Biological Evaluation of First-in-Class GluN2C/2D-Selective NMDA Receptor Potentiators*

By: Rose M. Santangelo

Chapter 1: N-methyl-D-aspartate (NMDA) receptors are ligand gated members of the ionotropic glutamate receptor family which mediate a slow $Ca^{2+}$-permeable component of excitatory synaptic transmission within the central nervous system. Each NMDA receptor is a tetrameric complex composed of two glycine-binding GluN1 subunits and two glutamate binding GluN2 subunits. The GluN2 subunits are divided into four distinct subtypes labeled GluN2A, GluN2B, GluN2C, and GluN2D; each receptor subtype endows the receptor with unique pharmacological properties. Overactivation of NMDA receptors has been implicated in a number of neurodegenerative diseases including traumatic brain injury (TBI), Alzheimer's disease, stroke, and neuropathic pain. In the search for treatments for these neurological conditions, a number of NMDA receptor antagonists have been developed that target the receptor under a variety of mechanisms of action.

Towards this treatment goal, our lab developed a small library of ethanolamines which selectively target GluN2B-containing NMDA receptors. Unfortunately, the compounds displayed

significant off-target effects which would prevent their use in the clinic. A structurally related class was developed with the goal to decrease off-target effects while maintaining potency. Specifically, these compounds were aimed to decrease binding to the hERG (human ether-a-go-go) channel in the heart, a phenomenon which has been linked to drug related cardiotoxicity. In Chapter 1, a subset of compounds is described which sought to increase potency and efficacy by incorporating functionality from potent compounds in both series. These compounds were also designed to decrease hERG binding compared to the earlier class of compounds. The compounds described have been evaluated against the GluN1/GluN2B subunit of the NMDA receptor for both potency ($IC_{50}$) and pH sensitivity (fold shift). The fold shift refers to the ratio between the $IC_{50}$ measured at a more acidic pH (6.9) compared to that measured at physiological pH (7.4). An observed increase in potency at more acidic pH is hypothesized to have a beneficial therapeutic effect under ischemic conditions.

Chapter 2: Unlike the large body of work surrounding GluN2B-containing NMDA receptors, very little work has been described specific to GluN2C- and GluN2D-containing receptors. The published work around subunit-selective modulators of NMDA receptors has mostly focused on NMDA receptor antagonists. A few endogenous compounds, such as the polyamines and neurosteroids have shown some subunit-selective potentiation of the NMDA receptor complex, but no therapeutically useful subunit-selective potentiators have been described to date. Based on well-documented experimental evidence, NMDA receptor potentiators may have therapeutic potential in the treatment of schizophrenia and related diseases of psychosis, as well as in anxiety disorders or the enhancement of learning and memory.

Based on a screening hit from a fluorescence based high-throughput screen, a library of novel compounds has been developed. Herein, we describe the synthesis and biological evaluation of this new class of subunit-selective potentiators of NMDA receptors containing a tetrahydroisoquinoline core. Through structural modifications, the potency of the series was improved 40-fold over the original screening hit. Additionally, a structurally related compound was discovered with potentiation at all four GluN2-subunits of NMDA, suggesting that a binding site exists on all four subunits. One compound from the series was evaluated for pharmacokinetic properties as well as in an animal model of fear extinction. The results show a preliminary proof of concept for the treatment of anxiety disorders using NMDA-receptor potentiators.

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Chapter 1:



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**List of Abbreviations**

**α1:** α-adrenergic receptors (α1 subtype)

**Ac:** Acyl ($C(O)CH_3$)

**$Ac_2O$:** Acetic anhydride

**AcOH:** Acetic acid

**aLQTS:** acquired Long QT Syndrome

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

**Ar:** Aryl

**ATD:** Amino Terminal Domain

**Boc:** *tert*-Butyloxycarbonyl

**Bn:** Benzyl

**CNS:** Central Nervous System

**CS:** Conditioned Stimulus

**CSF:** Cerebrospinal fluid

**Cys**: cysteine

**DCM:** Dichloromethane (methylene chloride, $CH_2Cl_2$)

**DCS**: D-cycloserine

**de:** Diastereomeric Excess

**DIAD:** Diisopropyl azodicarboxylate

**DIPEA:** *N*,*N*-diisopropylethylamine

**DMAP:** 4-(Dimethylamino)pyridine

**DMF:** *N*,*N*,-dimethylformamide

**DMSO:** Dimethyl Sulfoxide

**dr:** Diastereomeric Ratio

**$EC_{50}$:** Half-Maximal Effective Concentration

**EDCI:** 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

***ee:*** Enantiomeric Excess

**Et**: Ethyl ($CH_2CH_3$)

**EtOAc:** Ethyl Acetate

**EtOH:** Ethanol

**FDA:** Food and Drug Administration

**hERG:** human Ether-a-go-go Related Gene

**HPLC:** High Performance Liquid Chromatography

**GABA**: ϒ-aminobutyric acid

**$IC_{50}$:** Half-Maximal Inhibitory Concentration

**iGluR:** Ionotropic Glutamate Receptor

**IP:** Intraperitoneal

**IV**: Intravenous

**Ki:** Inhibitory Constant

**LBD:** Ligand Binding Domain

**LCMS:** Liquid Chromatography-Mass Spectrometry

**Me**: Methyl ($CH_3$)

**MeCN**: Acetonitrile

**mGluR:** Metabotropic Glutamate Receptor

**Ms:** Mesyl, Mesylate ($SO_2CH_3$)

**MsCl:** Methanesulfonyl chloride

**NAAG:** *N*-acetylaspartylglutamate

**NMDA:** N-Methyl-D-Aspartate

**NMO**: *N*-methyl-morpholine *N*-oxide

**NMR:** Nuclear Magnetic Resonance

**OCD**: Obsessive Compulsive Disorder

**OMe**: Methoxy ($OCH_3$)

**PCC:** Pyridinium Chlorochromate

**PCP:** Phenylcyclidine

**PD:** Parkinson's Disease

**Ph:** phenyl

**PK:** Pharmacokinetics

***p*TSA:** *para*-Toluenesulfonic acid

**PTSD:** Post-Traumatic Stress Disorder

**Pyr**: Pyridine

**rt:** room temperature

**SAR:** Structure Activity Relationship

**SFC:** Supercritical Fluid Chromatography

**SSRI**: Selective Serotonin Reuptake Inhibitor

**$T_{1/2}$:** Half-life

**TdP:** Torsades de Pointes

**TFA:** Trifluoroacetic acid

**THF:** Tetrahydrofuran

**TBI:** Traumatic Brain Injury

**TLC:** Thin Layer Chromatography

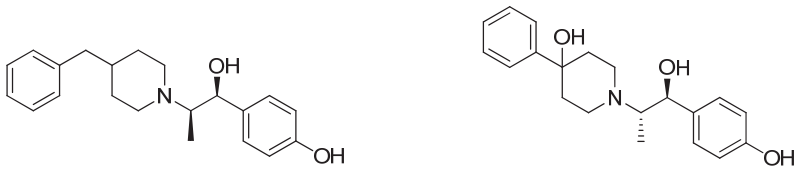
**TPAP:** Tetrapropylammonium perruthenate

**US:** Unconditioned Stimulus

# *Chapter 1: Design, Synthesis and Biological Evaluation of GluN1/GluN2B Selective NMDA Receptor Antagonists for the Potential Treatment of Neurodegenerative Diseases*

## 1.1 STATEMENT OF PURPOSE

Our research group is interested in the preparation of pH-sensitive antagonists of GluN2B-containing *N*-methyl-D-aspartate (NMDA) receptors for the treatment of neurological conditions. Overactivation, or hypofunction, of NMDA receptors is thought to contribute to the development and progression of many common neurological disorders which involve ischemia and/or neuronal cell death. Excessive stimulation of the receptors occurs during hypoxia[1-3], brain[4,5], and spinal cord injury[6-8], Parkinson's disease[9,10], and neuropathic pain, among others. Data also suggests that overactivation of NMDA receptors may contribute to neurodegenerative diseases such as Alzheimer's disease and Huntington's chorea. During all of the aforementioned conditions, acidification of the pH of the brain is observed.[11-13] This decrease in pH largely affects the normal biochemistry of the brain, particularly glutamate receptor function.[14-16]

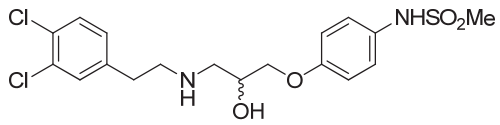



ifenprodil (1) traxoprodil (CP-101,606)

**Figure 1. Structures of example GluN2B-selective NMDA antagonists, ifenprodil and traxoprodil (CP-101,606)**

At physiological pH (7.4), protons tonically inhibit NMDA receptor function.[15] The small molecule antagonists, ifenprodil (**1**) and traxoprodil (**CP-101-606**), both specific to GluN2B-containing NMDA receptors, show enhanced inhibition of NMDA receptor function under acidic conditions.[16] However, these compounds show severe adverse events in both animal models and in humans, and these are thought to be attributed to non-specific drug binding. GluN2B-

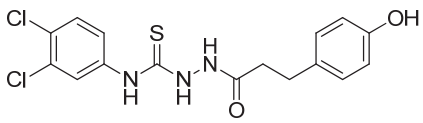
selective compounds which show greater inhibition under the acidic conditions associated with hypoxia than under physiological conditions represent a potential target for improved neuroprotection with an improved side effect profile.




**AM-92016 (2)**

**Figure 2. Structure of screening hit on which 93-series of ethanolamines was based**

Previous work has been done in our research group around enantiomeric propanolamines as pH-sensitive GluN2B-selective NMDA receptor antagonists, exemplified by the screening hit (AM-92016, **2**) on which the propanolamine series was based.[17] This class, also called the 93-series, contained highly potent compounds selective for GluN2B-containing receptors over GluN2A-, GluN2C-, and GluN2D-containing receptors, as well as over the other ionotropic glutamate receptors, AMPA and kainate. These compounds also had the desired effect of increased inhibition at acidic pH compared to physiological pH, a phenomenon referred to as fold shift. Unfortunately, this class of compounds showed significant off-target activity at the hERG channel, a similar ion channel located in the heart, limiting the potential of the class to produce a viable drug candidate.




**211**

**Figure 3. Structure of screening hit on which the 96-series of NMDAR antagonists was based**

The Traynelis lab discovered a compound in a primary screen (**211**) with some structural similarities to the previously developed 93-series with inhibitory activity against GluN2B-containing NMDA receptors. This compound contained a thiosemicarbazide backbone which was hypothesized to have decreased affinity for the hERG ion channel. Our lab developed a structure activity relationship (SAR) around this compound, later called the 96-series; a subset of compounds which contributed to this SAR is described here. The goal of this research was to decrease the off-target effects observed in the previous GluN2B-selective series while maintaining the biological activity. The compounds described herein were synthesized to test the combination of functionalities which had shown the highest degree of potency and fold shift within both series of GluN2B-selective antagonists. The goals of this project were achieved using the following strategy:

1. Development of a structure activity relationship (SAR) to design analogues which were potent and selective for GluN2B-containing NMDA receptors, had significant fold shift but with decreased off-target effects.
2. Novel compounds based on this SAR were synthesized.
3. The analogues were tested *in vitro* against GluN1/GluN2B-containing NMDA receptors for inhibitory activity at both pH 7.6 and pH 6.9. The biological evaluation of the compounds within this series was carried out in the laboratory of Dr. Stephen Traynelis in the Department of Pharmacology within Emory University's School of Medicine.

## 1.2 INTRODUCTION AND BACKGROUND

### *1.2.1 NMDA Receptor structure, function, and localization*

Glutamate is the major excitatory neurotransmitter within the central nervous system (CNS). The glutamate family of receptors can be subdivided into two distinct classes: metabotropic and ionotropic. Metabotropic glutamate receptors (mGluRs) are members of the group C family of G-protein coupled receptors (GPCRs). This class is comprised of 8 receptor types (mGluR1 through mGluR8) which are further categorized into three groups (Group I, II and III) based on receptor structure and physiological activity.[18] Ionotropic glutamate receptors (iGluRs) are cell surface ion channels which require glutamate binding for normal function. The ionotropic glutamate receptors are subdivided into 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid (AMPA, **3**), *N*-methyl-D-aspartate (NMDA, **4**), and kainate (**5**) receptors based on amino acid sequence homology, structure and pharmacology.[19] The three iGluR families get their names from the synthetic glutamate mimic which binds specifically and selectively to each respective receptor (Figure 4).

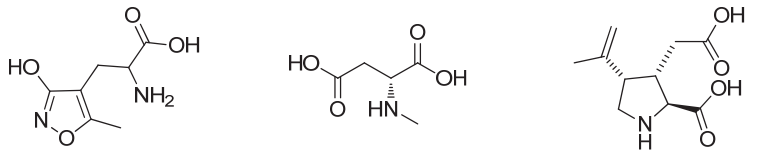



**Figure 4. Synthetic glutamate mimics which bind selectively to respective iGluRs**

NMDA receptors are ligand-gated tetrameric ion channels which mediate a slow $Ca^{2+}$-permeable component of excitatory synaptic transmission in the central nervous system. Each NMDA receptor is a heterooligomeric assembly of two GluN1 subunits and two GluN2 subunits (Figure 5). The GluN1 subunit consists of 8 functional isoforms (a-h) arising from a single gene

while the GluN2 subunit is divided into four distinct variants (labeled A-D) encoded by GluN2 genes.

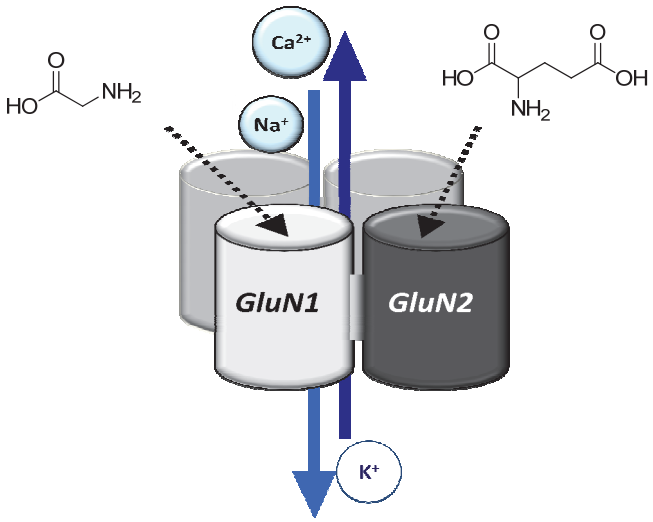



**Figure 5. NMDA Receptor Subunit Arrangement**

The subunits arrange to form an ion conduction pore which allows for cation permeability. Each receptor subunit, either GluN1 or GluN2, consists of three semiautonomous domains: an amino-terminal domain (ATD), a ligand-binding domain (LBD), and a transmembrane domain (TMD) (Figure 6). The co-agonists glycine and glutamate bind in the LBD of GluN1 and GluN2, respectively (Figure 5).[20]

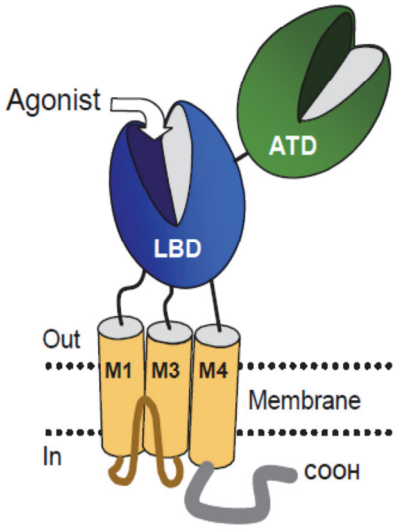



**Figure 6. Cartoon Depiction of NMDA Receptor Subunit Architechture**

NMDA is unique among the iGluRs as it requires the binding of both glycine and glutamate for NMDA receptor activation. Co-agonist binding followed by membrane depolarization causes a conformational shift which leads to the removal of the magnesium ion block located in the ion conduction pore at membrane resting potential. This sequence of events causes the ion channel to open and allows for the flow of calcium ions into the cell. This process is an important component of neuron to neuron synaptic transmission.[14]

Each of the four GluN2 subunits (A-D) endows the receptor with unique pharmacological properties. The receptor's open probability, single channel conductance, deactivation time course and agonist sensitivity all vary based on subunit composition.[21] In addition, the four GluN2 subunits are differentially expressed throughout the brain with changes in expression over a lifetime. As depicted in Figure 7, the GluN1 subunit is ubiquitously expressed throughout the brain during the developmental period from postnatal day 1 to postnatal day 14 as well as into adulthood. Both the GluN2A and GluN2C mRNA expression increases over the lifetime of the rat with little to no expression observed at postnatal day 1 to much larger concentrations

observed in adult rat. In contrast, GluN2B and GluN2D receptor mRNA expression gradually increase from postnatal day 1 to postnatal day 11 with marked decrease in expression after day 14.[22]

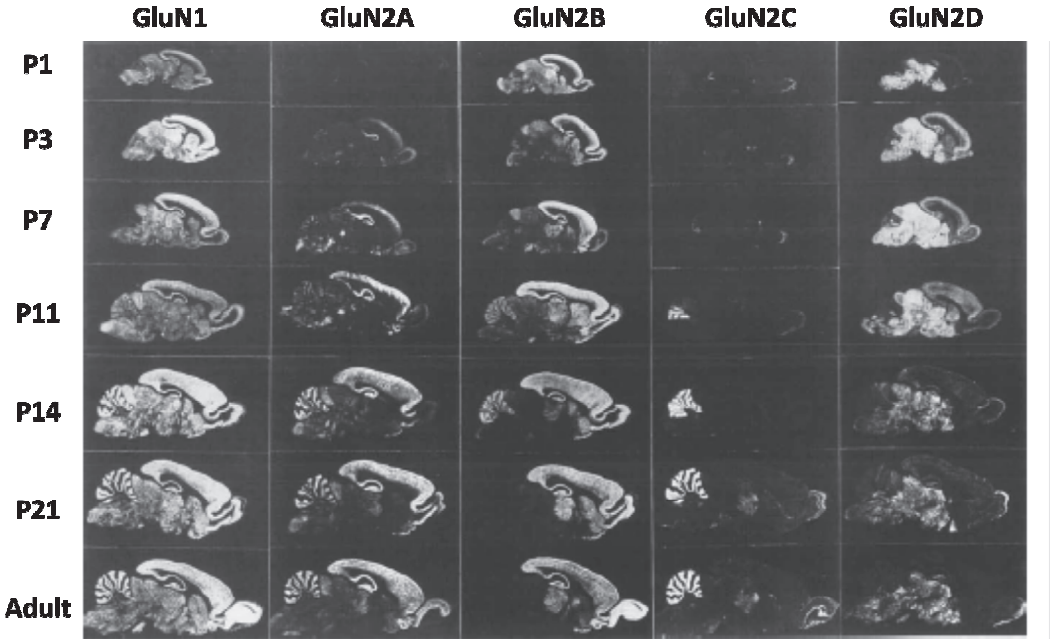



**Figure 7. NMDA subunit expression in rat brain from post-natal day 1 to adult generated via *in situ* hybridization**

In addition to the changes in expression during development, each receptor subunit has distinct localization in different regions of the brain. In the brain of an adult rat, the GluN1 subunit mRNA is expressed in virtually all regions of the brain whereas the four GluN2 subunits are differentially expressed. The GluN2A subunit mRNA is highly expressed in the cerebral cortex and in the hippocampus, the GluN2B mRNA is prominently expressed in the telencephalic regions and the thalamus, the GluN2C mRNA is concentrated in the cerebellum, and GluN2D mRNA expression is most prominent in the brainstem.[22]

Because of the differential expression of each of the four GluN2 subunits and the varied pharmacological properties, it seems likely that the physiological function of each NMDA receptor may differ based upon the identity of the GluN2 subunit.

### *1.2.2 Classes of NMDA Receptor Antagonists*

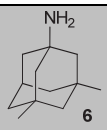
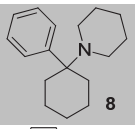
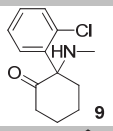
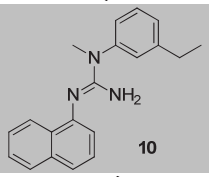
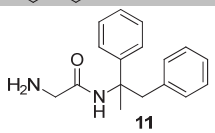
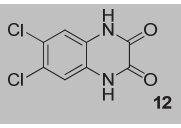
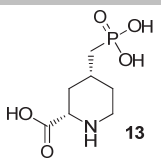
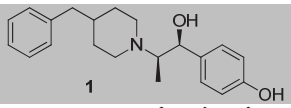
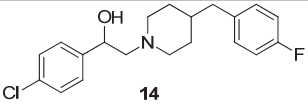
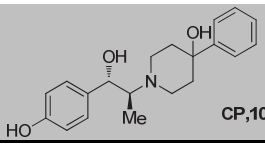
Significant interest has been directed towards the study and modulation of NMDA receptors due to the important role the receptor plays in synaptic plasticity[23], neuronal development[24], and essential higher level processes such as learning and memory[25]. A number of NMDA receptor antagonists have been described in the literature and can mostly be categorized into three distinct classes: channel blockers, competitive antagonists, and allosteric modulators (Table 1). Channel blockers are voltage-dependent because they bind within the ion conduction pore and block the flow of calcium into the cell, thereby, reducing neuronal toxicity. Examples of NMDA channel blockers include memantine (Namenda®, **6**) which is FDA approved for the treatment of moderate to severe Alzheimer's disease, amantadine (Symmetrel®, **7**) which is FDA-approved for use in Parkinson's disease, and phencyclidine (PCP, **8**) which was used early on as an anesthetic but has since been pulled from the market due to its hallucinogenic and psychomimetic effects.[26] Although some NMDA channel blockers have shown promise in the clinic and memantine and amantadine have achieved FDA approval, they typically cause negative side effects due to significant selectivity issues, limiting their use for chronic therapies.[27,28] Memantine is unique among the channel blockers because of its low-affinity binding and fast off-rate kinetics, which allow the channel to close and for subsequent agonist unbinding.[29,30] The high-affinity binding and slow dissociation rate of other channel blockers does not allow for channel closure; factors which contribute to their low tolerability in the clinic.[30,31] Other examples of non-competitive antagonists are shown in Table 1 and include ketamine (**9**), aptiganel (**10**) and remacemide (**11**).

Competitive antagonists can be further grouped into two categories based on their binding site. Antagonists which compete for either the glycine binding site on GluN1 or the glutamate binding site on GluN2 have been described. Examples of these include licostinel (**12**)

which binds in the glycine site on GluN1 and selfotel (**13**) which competes with glutamate for its binding site on GluN2. Although licostinel is highly potent against NMDA receptors with an $IC_{50}$ of 5.9 nM, it also has activity against related ionotropic glutamate receptors such as AMPA ($IC_{50}$ = 2 μM).[32] In addition to the lack of selectivity, blood brain barrier permeation is an issue due to the charged nature of the compound. Clinical trials with licostinel have indicated that the drug is safe, however, crystals found in urine of patients suggested poor aqueous solubility and metabolism.[33]

The final class of NMDA receptor antagonists, allosteric modulators, is typified by ifenprodil (**1**) but a large number of structurally related compounds have been identified including eliprodil (**14**) and traxoprodil (**CP-101,606**). The compounds in this class which have been described to date are non-competitive, GluN2B-selective allosteric inhibitors of NMDA receptor function. Many of the GluN2B-selective inhibitor libraries described in the literature, including those described herein, have been templated based on ifenprodil. The ideal compound in this category would be a GluN2B-selective, non-competitive, allosteric inhibitor with a reduced side effect profile compared to the failed clinical candidates.

**Table 1. Classes of NMDA receptor antagonists with example compounds from each class**

| Compound Name | Structure | Mechanism of Action | Indication |
|---|---|---|---|
| **Memantine** |  | Non-competitive antagonist | Alzheimer's Disease |
| **Amantadine** |  | Non-competitive antagonist | Parkinson's Disease |
| **Phencyclidine** |  | Non-competitive antagonist | Anesthesia |
| **Ketamine** |  | Non-competitive antagonist | Anesthesia |
| **Aptiganel** |  | Non-competitive antagonist | Stroke |
| **Remacemide** |  | Non-competitive antagonist | Stroke, Epilepsy, Huntington's Disease, Parkinson's Disease |
| **Licostinel** |  | Competitive glycine antagonist | Stroke |
| **Selfotel** |  | Competitive glutamate antagonist | Stroke, Head Injury |
| **Ifenprodil** |  | Allosteric GluN2B-selective antagonist | Depression, Stroke, TBI |
| **Eliprodil** |  | Allosteric GluN2B-selective antagonist | Stroke, Epilepsy |
| **Traxoprodil** |  | Allosteric GluN2B-selective antagonist | Head Injury |

### *1.2.3 Therapeutic Rationale for NMDA Antagonists*

The NMDA receptor has been strongly implicated in the acute neuronal death caused by cerebral ischemia and traumatic brain injury (TBI).[28] In multiple preclinical models, glycine and glutamate site antagonists, channel blockers and GluN2B-selective allosteric antagonists have all shown neuroprotective effects.[5,34] Unfortunately, the observed neuroprotective effects have not yet translated into clinical trials. The failure of these NMDA-modulators in stroke and TBI clinical trials can be attributed to several factors and in some cases these factors correlate to the nature of the compound class.[19] For example, both the channel blockers and the glutamate site antagonists have significant adverse events associated with them due to the large concentration required for neuroprotection. At such high levels, these compounds have also been shown to alter cardiovascular function, disrupt cognition and lead to psychomimetic effects.[35] As a result, a major contributor to the failure of NMDA antagonists in TBI trials may be the narrow treatment window within which these antagonists have been shown to be effective. Literature suggests that NMDA receptor antagonists have efficacy in TBI treatment for up to 2 hours after injury, which is a difficult timing window to achieve in practice. Therefore, treatment windows were extended in clinical trials which likely significantly reduced the neuroprotective effect.[19,36]

In addition to TBI and related ischemic conditions, NMDA receptor antagonists have shown efficacy in a number of neurodegenerative disease states. For example, the NMDA receptor channel blocker memantine is FDA approved for the treatment of moderate to severe Alzheimer's disease.[37,38] Although not approved for these uses, memantine has also shown positive effects in dementia patients[39] as well as in dementia associated with Parkinson's disease.[40] Memantine is unique among the channel blockers because it does not exhibit many of the typical side effects associated with the non-specific binding of this class of compounds. Other NMDA receptor channel blockers such as phencyclidine (PCP), ketamine, and MK-801

have shown significant cognitive disruption, inducing side effects such as hallucinations, loss of coordination, acute anxiety, and paranoia.[26,41] The different side effect profile of memantine compared to other channel blockers can be attributed to its lower binding affinity, faster dissociation kinetics and distinct binding mechanism.[42]

There is significant literature precedent suggesting that NMDA receptor inhibition can either prevent or reduce neuropathic pain.[43] As a proof of principle, the known NMDA channel blocker ketamine has shown efficacy in the short-term treatment of pain related to surgery, cancer, peripheral nerve disease, and spinal cord injury.[44-46] Unfortunately, ketamine has negative side effects associated with its use and has a relatively short half-life reducing its clinical usefulness.[41] These negative effects observed in the clinic can be attributed not only to the off-rate kinetics and binding affinity of the channel blockers but also to their non-selective nature. NMDA receptor inhibitors with increased selectivity may then achieve the desired result in the treatment of neuropathic pain while avoiding the negative side effects. Preclinical data indicates that targeting GluN2B-containing NMDA receptors specifically may lead to an effective and more clinically useful drug for the treatment of neuropathic pain.[47,48]

### *1.2.4 GluN2B-Subunit Selective Antagonists*

GluN2B-containing NMDA receptors have been the focus of a large number of pharmacological studies. Evidence has indicated that selective inhibition of NMDA receptors containing the GluN2B-subtype could have therapeutic potential for conditions such as cerebral ischemia[49], epilepsy[50], Parkinson's disease[51], depression, and Alzheimer's disease[52]. In transgenic mice with an overexpression of GluN2B-containing NMDA receptors, increased sensitivity to pain was observed. In addition, GluN2B-selective antagonists have been shown to be antinociceptive in certain pain models.[47,53,54] As shown in Figure 4, GluN2B-containing

receptors are primarily found in the forebrain, dorsal root ganglion, striatum, and spinal cord and are notably absent in the cerebellum. Due to their distribution, the hypothesis follows that a selective antagonist may not cause the psychomimetic symptoms that are commonly associated with administration of channel blockers and glutamate site antagonists.

A large number of GluN2B-selective NMDA receptor antagonists have been reported in the literature. Since these antagonists are allosteric modulators, the inhibition they induce cannot be overcome by saturating the receptors with excess glutamate or glycine. These compounds are typically thought to bind within the amino terminal domain (ATD) of the GluN2B subunit, like ifenprodil. Although ifenprodil has long been known to bind selectively to the ATD of GluN2B-containing receptors, the recently published crystal structure shows the compound binding to a site located at the GluN1-GluN2B heterodimer ATD interface.[55] The structural similarities between many of the published classes and ifenprodil suggest that they likely share this binding site.

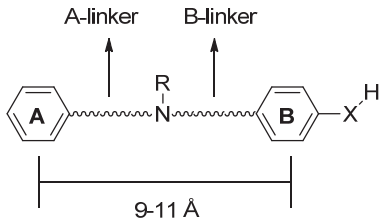
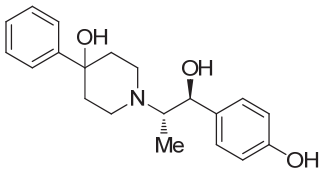



**Figure 8. The GluN2B-selective antagonist pharmacophore**

Structurally, many of the most well studied GluN2B-selective antagonists resemble ifenprodil. The pharmacophore can be described as a non-polar aryl A-ring, a 9-11 Å linker which typically contains a basic amine, and an aryl B-ring which contains a hydrogen bond donor substituent (Figure 8). A number of ifenprodil-like analogues have been described with improved pharmacokinetic and pharmacodynamic properties.




Traxoprodil (CP-101,606)

**Figure 9. Structure of Traxoprodil (CP-101,606), a GluN2B-selective antagonist**

A promising analogue reported by a medicinal chemistry group at Pfizer, Traxoprodil (**CP-101,606**) was found to be highly selective for GluN2B containing NMDA receptors.[56] Traxoprodil was well-tolerated in safety studies and was shown to be effective in treating mild to moderate traumatic brain injury.[57] Unfortunately, an animal study in rats and rhesus monkeys showed that inhibition of GluN2B may play a role in addiction or substance abuse as both species preferentially self-administered traxoprodil to phencyclidine (PCP).[58]

### *1.2.5 Brain pH acidification*

There are a number of regulatory sites within NMDA receptor which play a role in gating and overall NMDA receptor function. One of these regulatory sites is a proton sensor. NMDA receptors are inhibited by protons with an $IC_{50}$ value that corresponds to a pH of 7.3.[59,60,61] Therefore, at physiological pH (7.4), the receptors are tonically inhibited by protons. This means that small changes in the interstitial pH could have an effect on NMDA receptor function.[16]

During normal synaptic transmission, interstitial pH undergoes multiphasic changes, in part, regulating the release of glutamate by the synapses. During ischemic conditions, lactic acid production increases which causes the pH surrounding the receptor to decrease by 0.2 to more than 1.0 pH units.[13,62] During seizures and ischemia, neuronal death and injury is associated with an increase in extracellular glutamate and subsequent NMDA receptor overactivation. Assuming that these acidic conditions persist during the time when glutamate levels are

elevated, acidification of the extracellular space during ischemic conditions may have a slight neuroprotective effect by limiting the extent of neurotoxicity and inhibiting NMDA receptor activation. [16,63,64] Prevention of glutamate-induced excitotoxicity is a treatment target for a number of associated neurological conditions.

The hypothesis follows that a compound could be developed which effectively prevents neuronal cell death attributed to excess glutamate and overactivation of NMDA receptors through selective inhibition of NMDA receptors during ischemic conditions. The ideal compound would have no activity at physiologic pH but be very potent under ischemic conditions. Such a compound could potentially be used as prophylactic or as a neuroprotectant therapy in patients who are at risk or have a history of ischemic events. We have quantified this differential activity by a measure of its fold shift. The fold shift of a compound is a ratio of the $IC_{50}$ at pH 7.6 and 6.9. Fold shift is calculated using the following formula:

$$IC_{50}\ (pH\ 7.6)/IC_{50}\ (pH\ 6.9) = \text{fold shift}$$

The more potent a compound is at acidic pH, the higher its fold shift. A high fold shift corresponds to decreased side effects associated with NMDA receptor inhibition during normal physiologic function at a more alkaline pH. Ideally, a compound would have a large fold shift corresponding to very little activity at physiologic pH as to not disrupt normal NMDA function.

### *1.2.6 Phenethanolamines*

One of the first classes of subunit-selective NMDA antagonists was the phenethanolamines and is typically exemplified by ifenprodil. A wide range of analogues of ifenprodil have been reported in the literature including the benzylpiperidines, eliprodil (**14**), traxoprodil (**CP-101,606**), and Ro-25-6981 (**15**, Figure 10). Other classes of GluN2B-selective antagonists have been described including oxamides (**22**)[65], 5-substituted benzimidazoles (**16**,

**19**)[66], indole-2-carboxamides (**20**)[67], benzyl cinnamamidines (**18**)[68], and other biaryl analogues (**17**, **21**, **23**).

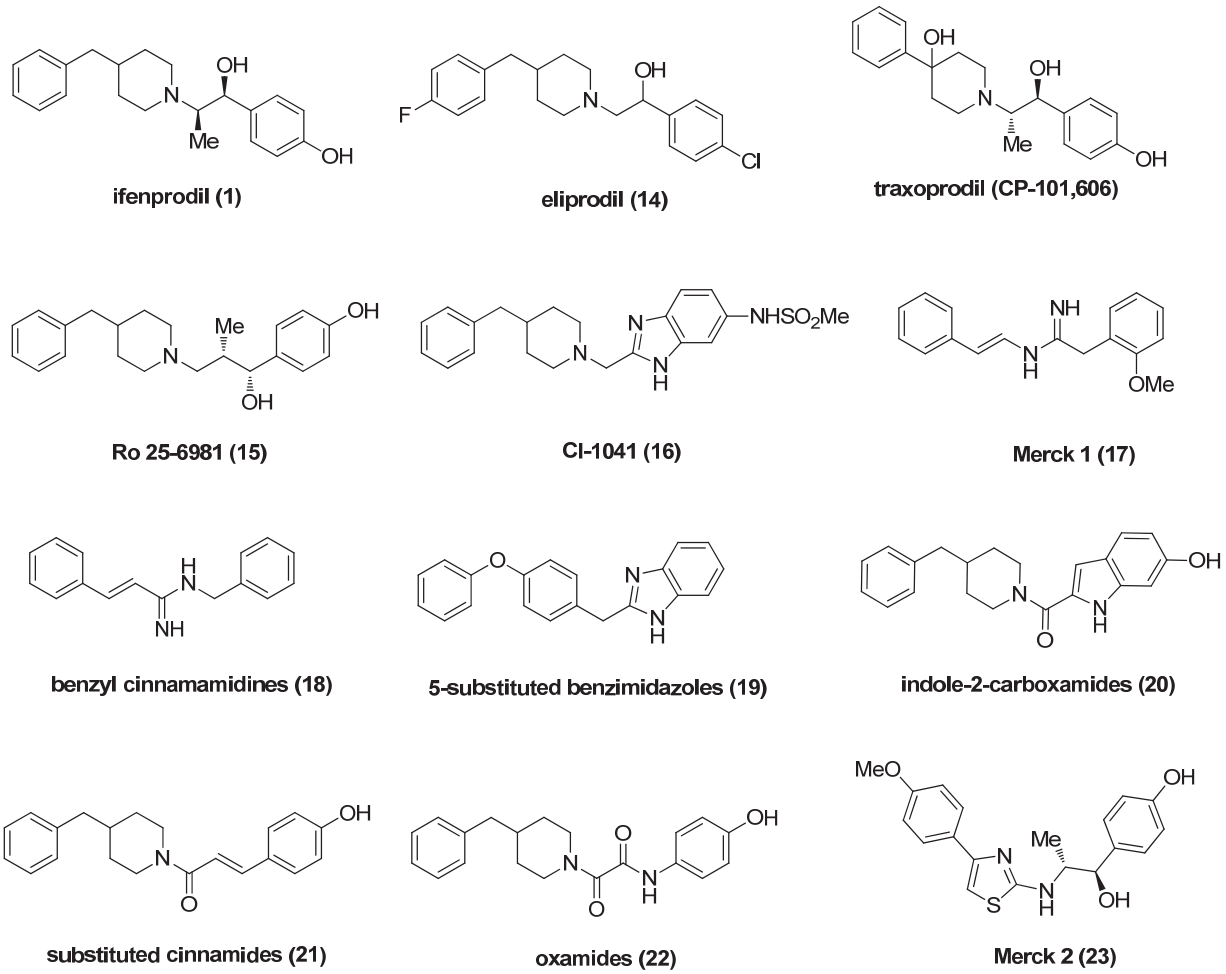
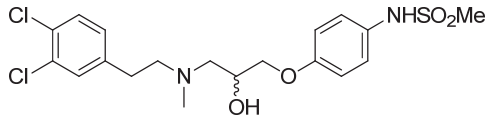



**Figure 10. Structures of known GluN2B-selective NMDA receptor antagonists**

Due to the potency and activity of ifenprodil and related compounds, the Liotta lab undertook a research project to develop a structure activity relationship (SAR) around a screening hit discovered by the Traynelis lab called **AM-92016** (Figure 11). A few structural features were found to consistently correspond to a more potent compound. A 7-atom linker length was found to be optimal which corresponds to a length of about 9-11 Å. In addition, a 3,4-dichloro substitution pattern on the A-ring was present in the most potent analogues with 3-

chloro-4-fluoro- and 4-chloro-substitution giving similar activities. Finally, a *para*-methanesulfonamide substituent on the B-ring was found to yield the most potent compounds.[17]

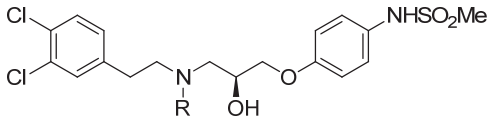



**AM-92016**

**Figure 11. Structure of screening hit on which the 93-series was based**

Although these changes to the A-ring, B-ring, and linker did have an effect on the fold shift associated with a particular compound, the most prounounced changes occurred with substitution on the central nitrogen within the linker region. In fact, the fold shift increased with increasing chain length, following the trend *N*-methyl < *N*-ethyl < *N*-propyl < *N*-butyl > *N*-pentyl (Table 2).[17] This trend seems to indicate that there is some space, while limited, within the binding pocket where these alkyl chains interact with the protein. Interestingly, the chirality of the alcohol on the linker also had an effect on the compounds' activity. The *S*-enantiomer was consistently more potent than the *R*-enantiomer in rat NMDA receptors whereas in human NMDA receptors, the oppostive effect was observed.

**Table 2. Correlation between chain length and fold shift for the 93-series**




| Compound ID | R | $IC_{50}$ pH 6.9 (nM)† | $IC_{50}$ pH 7.6 (nM)† | Fold Shift |
|---|---|---|---|---|
| **93-4** | H | 18 | 37 | 2 |
| **93-1** | Methyl | 39 | 259 | 7 |
| **93-5** | Ethyl | 11 | 89 | 8 |
| **93-6** | Propyl | 50 | 496 | 10 |
| **93-31** | Butyl | 27 | 454 | 17 |
| **93-87** | Pentyl | 141 | 653 | 5 |

†The $IC_{50}$ value was determined from two electrode voltage clamp recordings of rat NR1/NR2B receptor function, fitted as described in the experimental section. For all experiments, data are the fitted $IC_{50}$ value for the mean composite averaged from between 16 and 29 oocytes from 3 or more different frogs.

### *1.2.7 The human-ether-a-go-go related gene (hERG) ion channel*

The hERG channel is an ion channel located in the heart which plays a role in the electrical impulses that control the beating of the heart. In recent years, many drugs have been pulled off the market or been subject to significant restrictions due to hERG binding.[69-71] Withdrawal of marketed drugs like sertindole[72,73], grepafloxacin[74,75] and terfenadine[76-79] is attributed to prolongation of the length of time between the start of the Q wave and the end of the T wave on an electrocardiogram (QT interval). The majority of the drugs withdrawn for prolonging the QT interval and causing torsades de pointes (TdP) were later discovered to interact preferentially with a product of the human ether-a-go-go related gene (hERG), the $\alpha$-subunit of IKr channels responsible for the rapid component of the delayed rectifier potassium current in the heart.[80]

Blockade of the hERG channel has become a significant barrier to medicinal chemists in the hit-to-lead and lead optimization processes. Drug interactions with the hERG channel can cause drug-induced or acquired long-QT syndrome (aLQTS) which can lead to sudden death. As a result, the Food and Drug Administration (FDA) now requires drug candidates to undergo preclinical cardiac safety assessment to evaluate the potential for hERG binding. As a result of the FDA guidelines, the compounds in this class were evaluated for their binding affinity for the hERG channel.

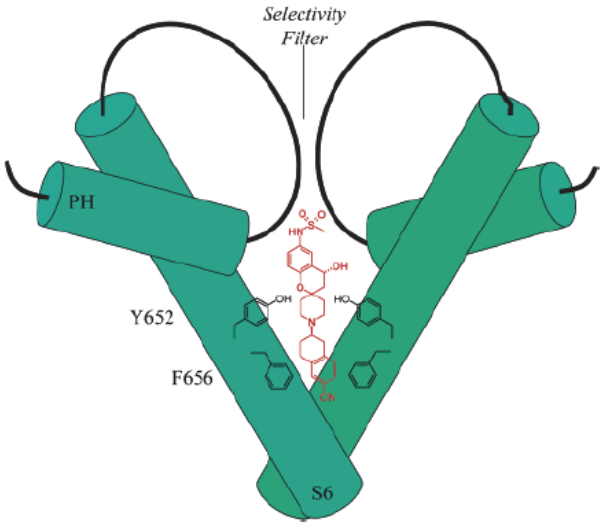



**Figure 12. Interactions of MK-499 with the hERG channel based on homology model.[81]**

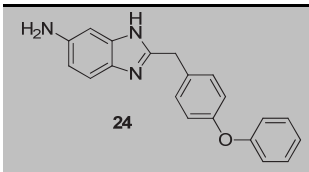
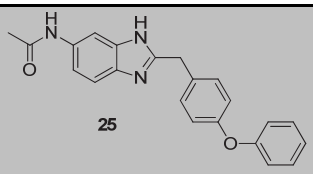
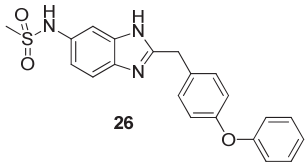
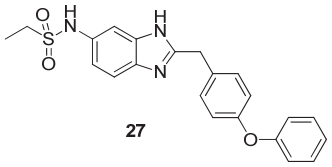
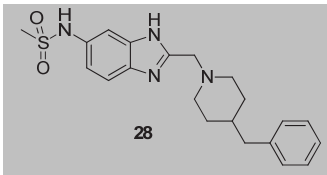
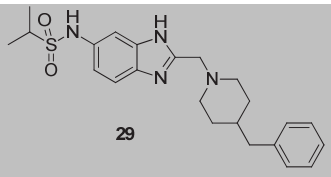
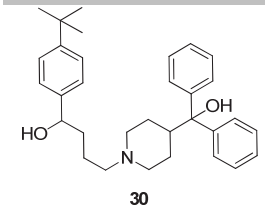
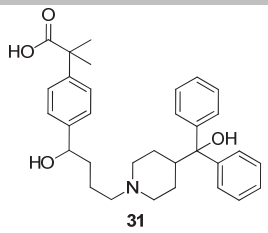
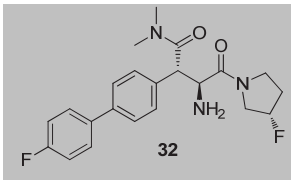
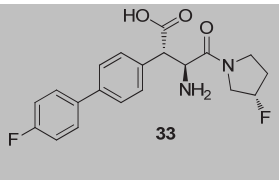
Medicinal chemists have developed a number of strategies to eliminate drug interactions at the hERG channel. These methods include discrete structural modification, formation of zwitterions, control of logP, and attenuation of pKa.[81] Although in many cases, one or more of these methods has proven effective, there is by no means a gold standard for detuning hERG activity. In many cases where hERG binding is observed, more than one of these tactics is employed to diminish the undesired effect.

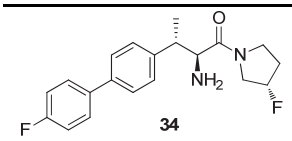
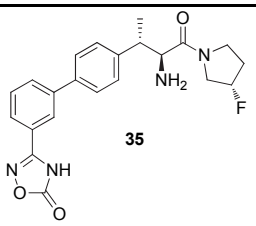
Often peripheral modifications to a drug molecule can have a pronounced effect on hERG activity. Mutagenesis studies and homology modeling on the open and closed states of the hERG channel have suggested that major determinants of hERG-drug interactions are π-stacking and hydrophobic interactions between aromatic residues (i.e. F656 and Y652) and aromatic moieties suitably positioned in a drug molecule.[81,82,83] Figure 12 shows a spiropiperidine-based antiarrythmic agent (**MK-499**) and its interactions with the hERG channel based on homology modeling.[82]

Modification of these structural features which interact with residues within the hERG channel could potentially disrupt said interactions and attenuate the affinity for the hERG channel. Strategies which have been utilized are not restricted to modifications to the distal aryl rings but have also included the introduction of constraint, stereochemical variation, and increases in lipophilicity. Several groups have reported using these approaches to successfully remove hERG activity. One example from a medicinal chemistry group at Merck involved the optimization of a benzimidazole series of GluN2B-containing NMDA receptor antagonists.[66] Compound **24** was derived from a screening hit and had a high affinity for the GluN2B channel with a $K_i$ of 180 nM. Unfortunately, it also showed high hERG affinity in the MK-499 binding assay (IP = 0.12 μM). This was a surprising discovery since these compounds lack a basic amine which is often perceived to be a key determinant of hERG binding activity. Acetylation of the benzimidazole amine substituent to give compound **25** resulted in an almost 22-fold decrease in hERG affinity (IP = 2.6 μM) while slightly increasing affinity for GluN2B-containing NMDA receptors ($K_i$ = 93 nM). Similarly, the simple change from a methylsulfonamide (**26**) to an ethylsulfonamide (**27**) resulted in a 13-fold decrease in hERG binding affinity. In a similar series of sulfonamide containing benzimidazoles, the isopropylsulfonamide containing analogue (**29**) showed a 10-fold reduction in affinity compared to the corresponding methylsulfonamide (**28**).

In all three of these examples, the reduction of hERG affinity was achieved through structural modifications to the periphery of the molecules. This phenomenon suggests that specific changes may partially disrupt the interactions that are occurring between the aromatic ring and aromatic residues within the hERG channel binding site.

**Table 3. Medicinal chemistry optimizations on structural classes for hERG binding**

| hERG active | hERG (μM) | $IC_{50}$ (nM) | hERG Optimized | hERG (μM) | $IC_{50}$ (nM) |
|---|---|---|---|---|---|
|  24 | 0.12 | 180 |  25 | 2.6 | 96 |
|  26 | 0.12 | 0.68 |  27 | 1.6 | 3 |
|  28 | 0.34 | 0.99 |  29 | 3.3 | 240 |
|  30 | 0.056 | 1 |  31 | 23 | 15 |
|  32 | 4.6 | 12 |  33 | 76 | 6.6 |

| | | | | | |
|---|---|---|---|---|---|
|  **34** | 1.1 | 64 |  **35** | 28 | 3 |

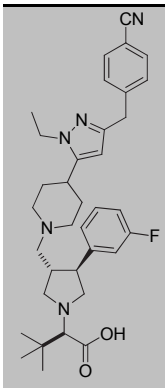
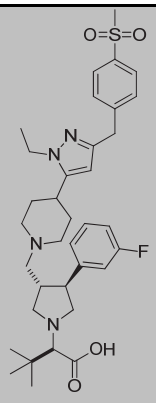
Terfenadine (**30**) is an antihistamine which was the first compound in its series to achieve FDA approval in 1982. Unfortunately, an analysis sometime after approval indicated that the drug was associated with a number of TdP-related incidents. In addition, when terfenadine was used in combination with drugs or foods that inhibit CYP3A4, the drug was found to prolong the QT interval due to elevated plasma levels.[84] Due to the cardiac issues with the drug, the FDA initially issued a black box warning. However, the cardiac arrhythmia events continued causing the removal of the drug from market in 1997. It was later discovered that an active metabolite of terfenadine, (**31**), was responsible for the therapeutic effect observed with the parent drug in the clinic. This carboxylic acid containing metabolite had significantly reduced hERG affinity and no effect on the QT interval.[85] The metabolite was later marketed under the name fexofadine. The low hERG affinity associated with fexofadine could be attributed to the poor cell membrane permeability of the compound which would limit its access to the intracellular lumen of the channel, which is thought to be critical for hERG channel blockade.

A series of biaryl-B-methylphenylalanine DPPIV inhibitors also reported using this method to reduce hERG binding affinity.[86] Conversion of the dimethylamide in compound **32** to the corresponding carboxylic acid (**33**), reduced the hERG affinity 16-fold with almost no effect on the potency at DPPIV. However, this modification was not without penalty altogether as the zwitterionic species had reduced oral bioavailability (**33,** *F*= 16% versus **32**, *F* = 67%). Incorporation of an acid bioisostere has also resulted in enhanced selectivity over hERG (**34** compared to **35**). Unfortunately, these compounds also showed a reduction in bioavailability

with the increased selectivity. This observation represents a significant possible limitation to the zwitterion formation approach.

During their optimization of a series of CCR5 antagonists, Shu and co-workers[87] incorporated hydrogen-bonding groups into their substrates in order to control log *P*. They effectively removed hERG activity by swapping the cyano-substituent on the distal aromatic ring for a methylsulfone. Although the methylsulfone-containing compound displayed suitable selectivity for CCR5 over hERG, it was accompanied by sub-optimal DMPK properties (i.e. – **36**, Clp (dog) = 22 mL/min kg; **37**, Clp = 108 mL/min kg). As with the previous approach, to achieve optimal hERG properties, other important characteristics, such as DMPK parameters in this case, are compromised.

**Table 4. Medicinal chemistry efforts to optimize hERG binding**

| hERG active | hERG (μM) | $IC_{50}$ (nM) | cLogP | hERG optimized | hERG (μM) | $IC_{50}$ (nM) | cLogP |
|---|---|---|---|---|---|---|---|
|  **36** | 1 | 1 | 3.56 |  **37** | inactive | 1.6 | 2.48 |

Many of the early GluN2B-selective antagonists resembling the ifenprodil pharmacophore contained a 4-benzylpiperidine or 4-phenylpiperidine moiety as well as the phenolic B-rings as is observed in ifenprodil. However, these ifenprodil-like compounds had undesirable off-target activity at the hERG and α1 adrenergic receptors.[81] A widely used

solution to the off-target issues has been to replace the phenol substituent with an alternate hydrogen bond donor. To this end, acyclic N-methylsulfonamides and ureas[66], heterocyclic phenolic isosteres such as benzimidazoles[66], benzimidazolones, benzoxalones, benzothiazoles, and benzoxazinones[65] have been reported as effective GluN2B-selective antagonists. Alternatively, the basicity of the central nitrogen could be masked to reduce off-target effects. The incorporation of amide linkages has effectively reduced off-target effects.

### *1.2.8 Previous Research/SAR Development of GluN2B-selective pH dependent antagonists*

The similarities between the propanolamines that were developed in the Liotta lab and the hERG pharmacophore were cause for concern. Because the screening hit AM-92016 (**2**) was a known antiarrythmic agent and the 93-series of GluN2B-selective antagonists developed in our lab were structurally very similar to the original hit, there was a high likelihood that these compounds would have significant hERG binding. Significant chemistry efforts in SAR development of the 93-series of GluN2B-selective antagonists resulted in a library of compounds with the best potencies in the 50-100 nM range. A subset of compounds in the 93-series was chosen for off-target testing against hERG and $\alpha$1 adrenergic receptors. Many of the selected compounds were shown to have affinities for the hERG channel with $IC_{50}$'s ranging from 70 nM to 2 $\mu$M. Affinities for the $\alpha$1 adrenergic receptor were significantly less pronounced but with a few of the compounds having $IC_{50}$'s in the low micromolar range.[17]

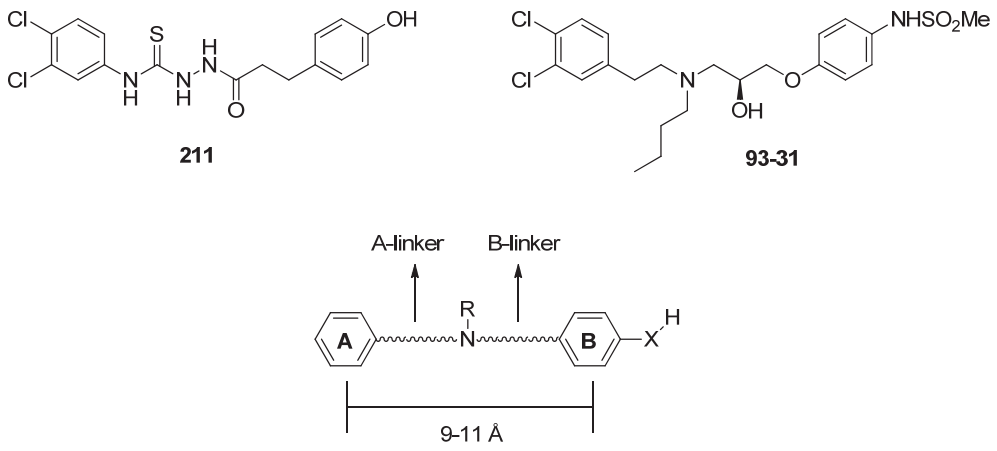



**Figure 13. Structures of screening hit, most potent compound from 93-series and the pharmacophore describing their relationship.**

From an additional screen, the Traynelis lab discovered compound **211** with a thiosemicarbazide backbone which showed inhibitory activity against GluN2B-containing NMDA receptors. This hit compound shared some structural features with the lead compounds from the previously developed 93-series (Figure 13). Specific shared structural features include a 3,4-dichlorophenyl A ring, a 7 atom linker between the A-ring and the B-ring which spans a distance of 9-11 Å, and a nitrogen atom in the third position on the linker. Both compounds also contained an aromatic B-ring with a hydrogen bond donor in the *para*-position.

These shared structural features led to the hypothesis that development of an SAR around **211** may lead to an optimized GluN2B-selective antagonist. We also hypothesized that compounds developed in relation to **211** may have reduced hERG binding due to the lack of the central basic amine which would be protonated at physiologic pH. Compound **211** showed inhibitory activity at GluN2B-containing NMDA receptors with an $IC_{50}$ of 320 nM at pH 6.9 and 600 nM at 7.6 giving a fold shift of 1.9. Although some of the compounds in the 93-series were more potent than this screening hit, **211** represented a good starting point for optimization using medicinal chemistry and SAR development.

Initial compounds synthesized in modification of **211** incorporated either semicarbazide or hydrazide functionalities into the backbone, keeping the overall rigidity of the original screening hit. Although these compounds did have decreased hERG binding, initial data suggested that the series would have a very flat SAR with little enhancement of potency, likely due to the lack of flexibility and free rotation. In addition, the hydrophilic nature of **211** and related analogues, containing multiple sites for hydrogen bonding, would likely make passive diffusion across the blood-brain barrier very unlikely. As a result of these early observations, the 96-series SAR development took a new direction to increase flexibility and free rotation by incorporating amide linkages within the linker region as compared to the 93-series. Compounds of this type would have decreased rigidity compared to **211** and related compounds and enhanced hydrophobicity; both properties were hypothesized to increase the likelihood of blood-brain barrier penetration as well as enhance SAR development with a more diverse range of modifications and resulting data.

Because of the structural similarities between the 93- and 96-series, some of the planned modifications in the 96-series were based upon a combination of data collected from both series. We probed the effects of combining modifications from both datasets which enhanced the biological activity profile. For example, since data from the 93-series suggested that a butyl chain in the 4-position of the linker enhanced potency and selectivity (Table 2), similar modifications were planned to the most potent compounds within the 96-series. The compounds chosen from the 96-series to incorporate this modification into were **96-13**, **96-22**, **96-20**, and **96-25** (Figure 14).

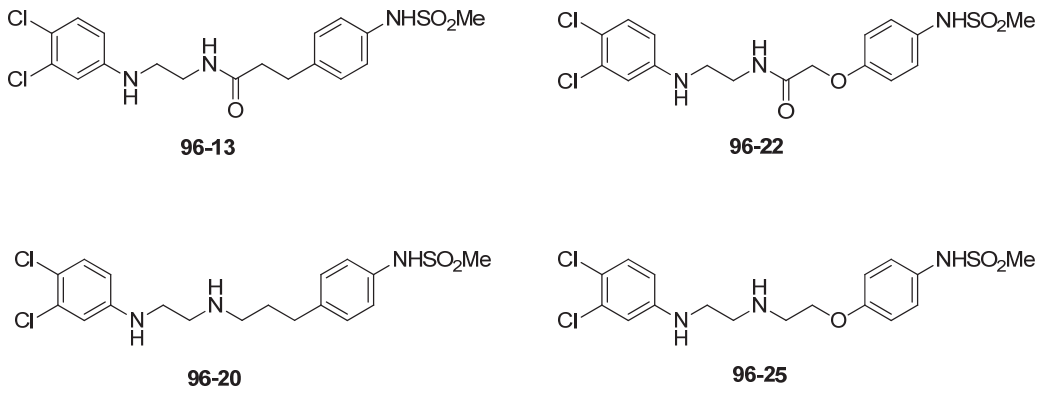


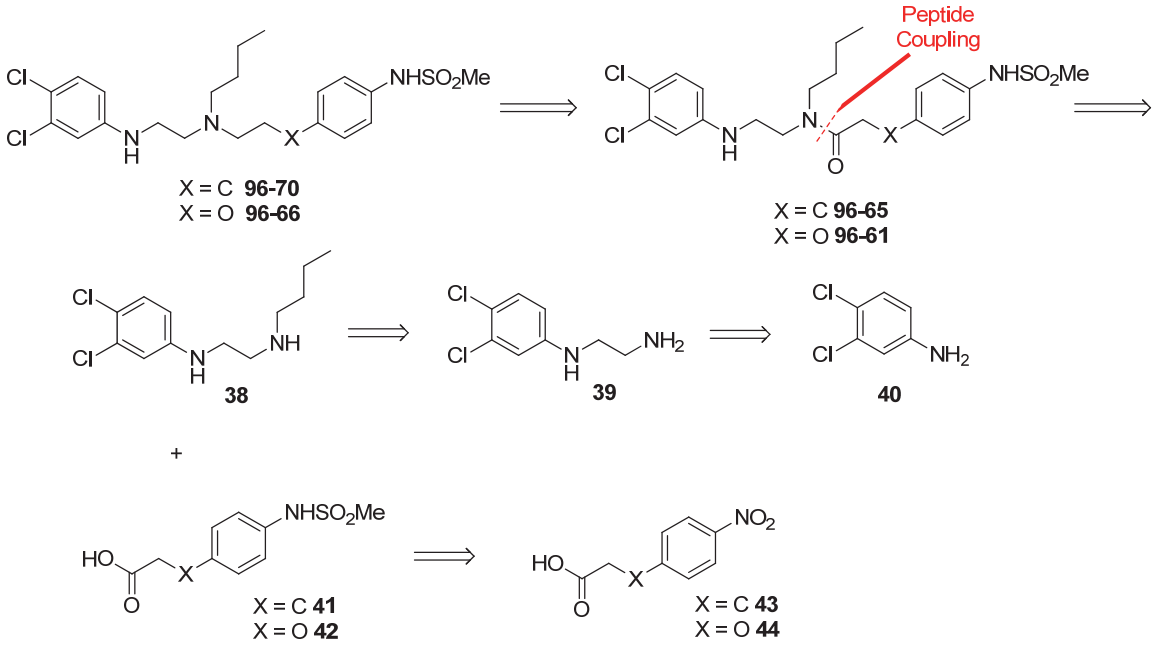

**Figure 14. Structures of 96-series compounds chosen for further modification.**

One commonly used method to decrease hERG binding is decreasing pKa through structural modifications. Some of the compounds in the 96-series (**96-20** and **96-25**) were likely to bind to hERG due to the central basic nitrogen which is protonated at physiological pH and can make cation-π interactions with key residues within the hERG ion channel. Two similar compounds with good potency and potentially decreased hERG binding were **96-22** and **96-13**; both of which have significantly decreased basicity of the central nitrogen through the introduction of an amide linkage. We hypothesized that the placement of the carbonyl into the linker was allowing for similar interactions to those observed within the 93-series when an enantiomeric alcohol is placed in the 5-position in the linker. We planned to test this hypothesis by moving the carbonyl to the 2-position in the linker thereby removing any important interactions with an oxygen attached in the 5-position. This compound still contains an amide linkage within the linker but keeps the basicity of the central nitrogen intact.

### 1.3 SYNTHESIS OF GLUN2B-SELECTIVE ANALOGUES

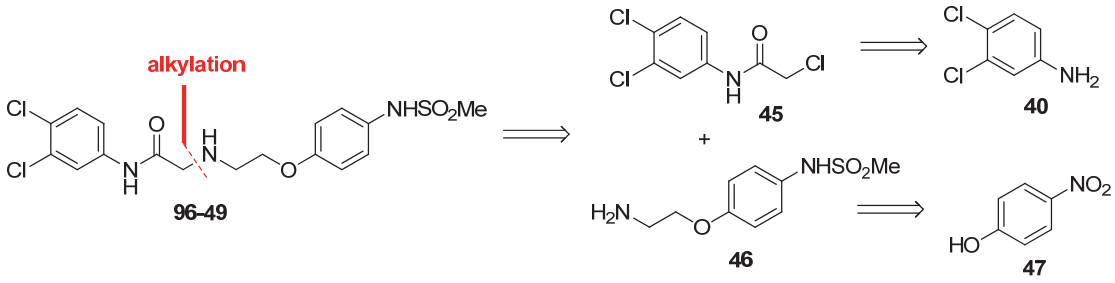
Retrosynthesis of compounds **96-66**, **96-70**, **96-61** and **96-65** is shown in Scheme 1 with a peptide coupling highlighting the final key step in the synthesis. The peptide coupling could be

performed using the carboxylic acid **41** or **42** and secondary amine **38**. The secondary amine could be synthesized in a few steps from the ethyldiamine (**39**) which is easily synthesized in one step from the commercially available aniline (**40**).



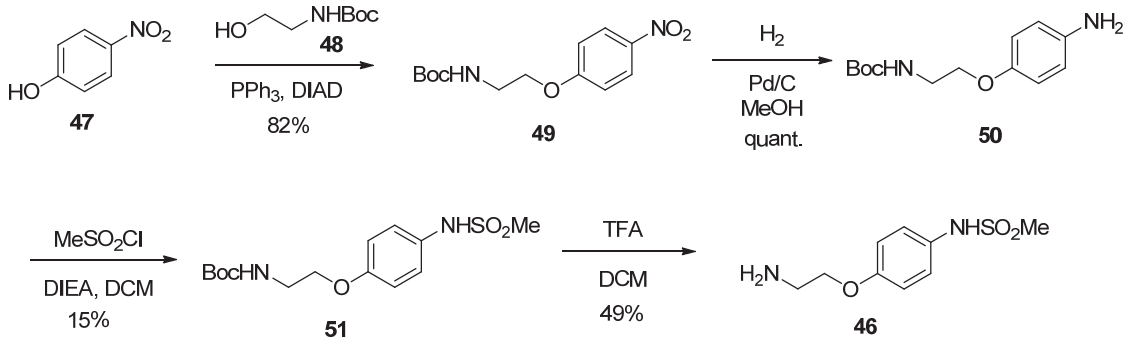

**Scheme 1. Retrosynthesis of 96-series GluN2B-selective antagonists**

Retrosynthesis of **96-49** is shown in Scheme 2. The central secondary amine could be constructed by a simple substitution reaction between the corresponding α-chloroamide (**45**) and primary amine (**46**). The α-chloroamide (**45**) could be easily prepared from commercially available 3,4-dichloroaniline (**40**). The primary amine (**46**) could be synthesized in a few steps from the commercially available 4-nitrophenol (**47**).

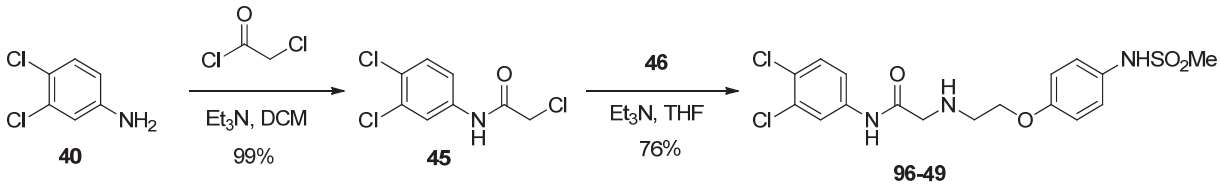



**Scheme 2. Retrosynthetic analysis of 96-49, a 96-series analogue**

Compound **96-49** was synthesized in a convergent fashion, starting from the commercially available 4-nitrophenol (**47**) which was alkylated under Mitsunobu conditions to afford the Boc-protected amine **49**. Hydrogenolysis of the nitro group afforded the aniline **50** in excellent yield, and this was subsequently reacted with methanesulfonyl chloride to afford the methyl sulfonamide, **51**. Finally, removal of the Boc-protecting group with trifluoroacetic acid afforded the primary amine **46** (Scheme 3). The commercially available 3,4-dichloroaniline (**40**) was acylated with chloroacetyl chloride to afford **45** which was then combined with **46** to afford the final compound, **96-49** (Scheme 4).

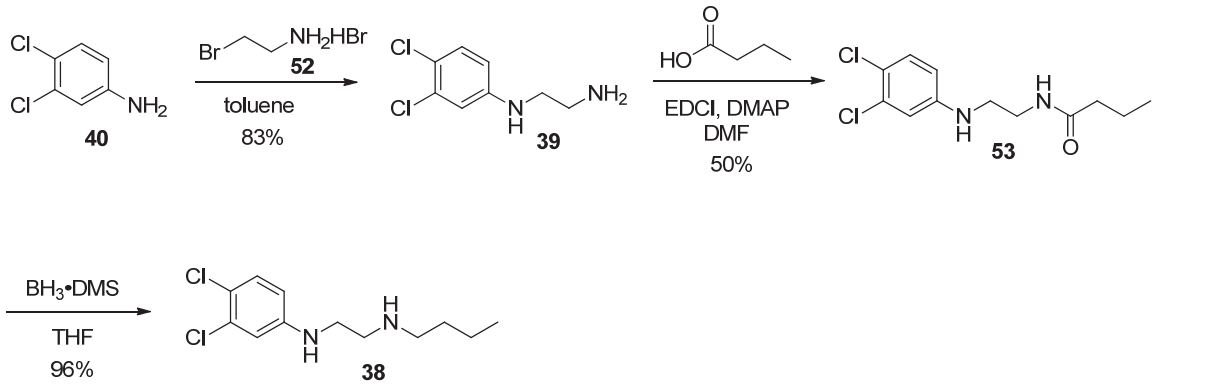



**Scheme 3. Construction of the fragment, 46, towards the synthesis of 96-49.**




**Scheme 4. Completion of the synthesis of 96-49**

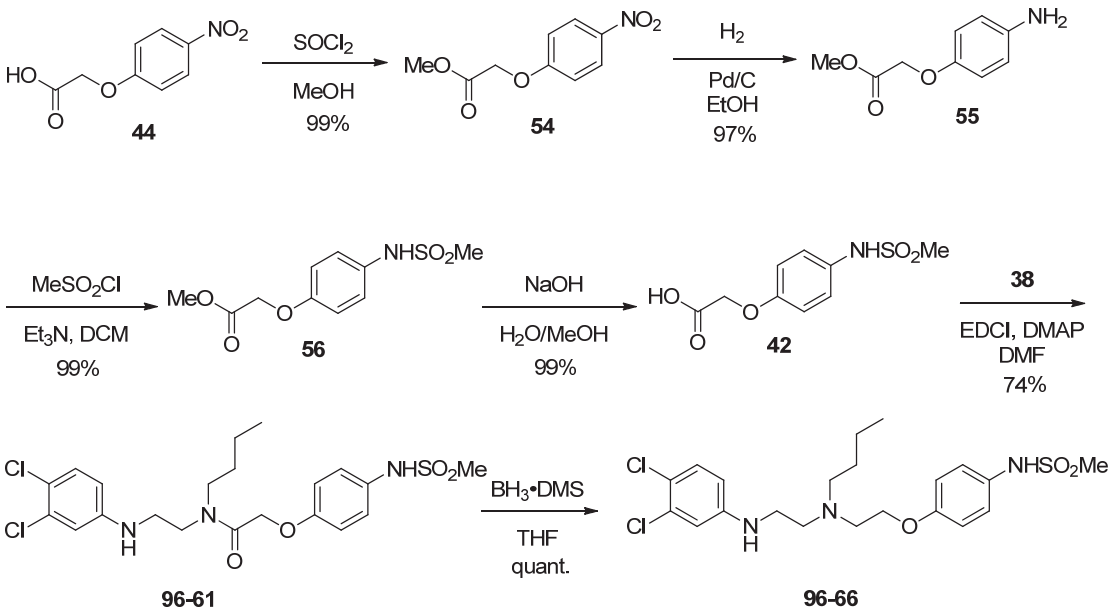
Compounds **96-61** and **96-66** were both synthesized from the commercially available materials, 3,4-dichloroaniline (**40**) and 4-nitrophenoxyacetic acid (**44**). Alkylation of aniline **40** with 2-bromoethylamine (**52**) provided the diamine **39** which then underwent an EDCI-mediated coupling with butyric acid to afford the amide **53**. Reduction of the resulting amide with borane dimethylsulfide complex cleanly provided the amine **38** (Scheme 5).




**Scheme 5. Construction of the diamine building block required for the synthesis of four 96-series analogues.**

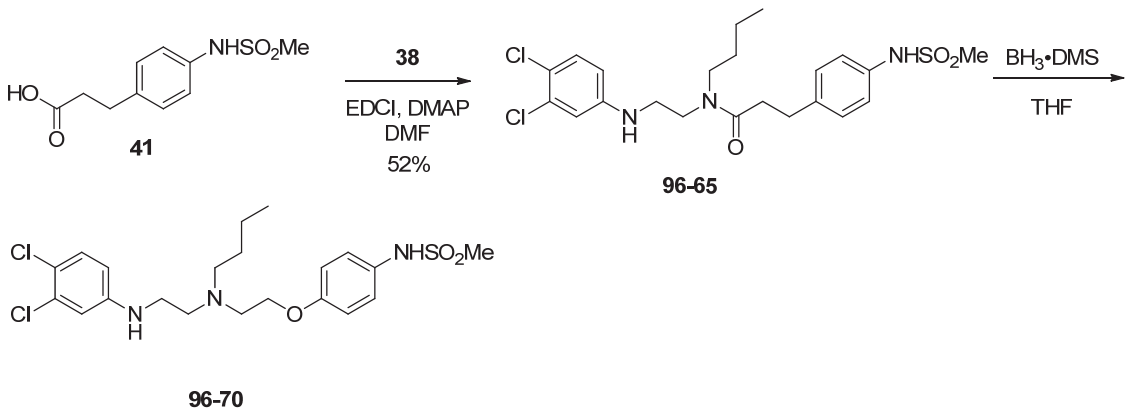
Esterification of **44** was carried out using thionyl chloride and methanol to afford the methyl ester **54**. The nitro group was hydrogenolized in the presence of palladium on carbon to afford the aniline **55**, which was subjected to methanesulfonyl chloride to afford the sulfonamide **56**. Upon saponification of the ester, the resulting carboxylic acid (**42**) was subjected to EDCI coupling conditions with the secondary amine **38** to afford the tertiary amide

**96-61** as the final product. Final compound **96-66** was synthesized by reduction in one step from **96-61**.




**Scheme 6. Completion of the synthesis of 96-61 and 96-66 using the previously synthesized diamine building block.**

Compound **96-65** was synthesized in one step from an EDCI coupling between **38** and carboxylic acid **41** which was previously prepared. Reduction of the amide with borane dimethylsulfide complex afforded the tertiary amine containing analogue **96-70**.

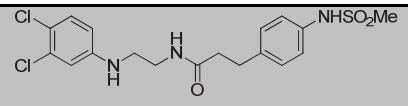
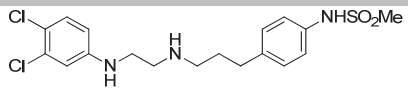
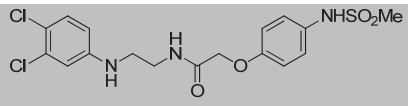
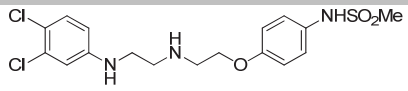
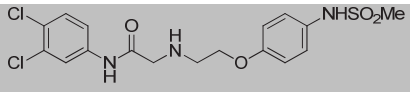
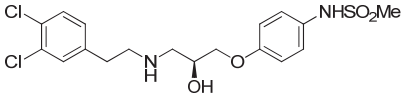
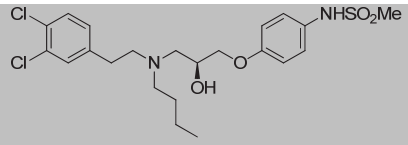
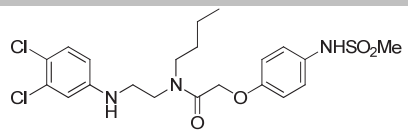
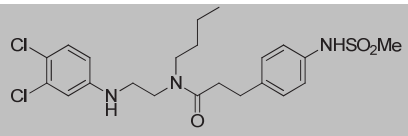
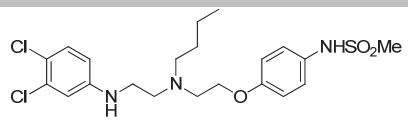
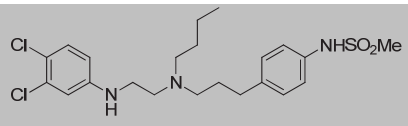



**Scheme 7. Completion of the synthesis of 96-65 and 96-70** .

## 1.4 RESULTS AND DISCUSSION

Biological data obtained for each of the compounds described herein is shown in Table 5. For comparison, the previously synthesized compounds **96-13**, **96-20**, **96-22**, and **96-25** are also shown in this table. The incorporation of an amide linkage in the linker in position 2, while maintaining the basicity of the central nitrogen, did not prove to be a productive modification as the potency and fold shift of **96-49** both show a marked decrease compared to **96-22** and **96-25**. This suggests that the interactions between the protein and this portion of the linker may be disturbed from the incorporation of the carbonyl. Alternatively, the large gap in potency observed may be explained by the increased rigidity in this portion of the linker. This would severely restrict the allowed free rotation and consequently disallow the preferred binding conformation of the compound. Key binding interactions may be disrupted by the forced binding conformation which would cause decreased binding affinity and efficacy.

**Table 5. Summary of 96-series compounds and associated biological data**

| Compound ID | Structure | $IC_{50}$ (μM) [¥] pH 7.6 | $IC_{50}$ (μM) [¥] pH 6.9 | Fold Shift |
|---|---|---|---|---|
| **96-13**[‡] |  | 0.065 | 0.03 | 2.1 |
| **96-20**[‡] |  | 0.019 | 0.0019 | 10 |
| **96-22**[‡] |  | 0.065 | 0.015 | 4.3 |
| **96-25**[‡] |  | 0.039 | 0.011 | 3.5 |
| **96-49** |  | 1.16 | 0.78 | 1.5 |
| **93-4*** |  | 0.037 | 0.018 | 2 |
| **93-31*** |  | 0.454 | 0.027 | 17 |
| **96-61** |  | 1.97 | 1.23 | 1.6 |
| **96-65** |  | 6.37 | 4.28 | 1.5 |
| **96-66** |  | 5.2 | 10.8 | 0.5 |
| **96-70** |  | 0.69 | NT | NT |

[‡] Synthesized by Dr. Cara Mosley *Synthesized by Dr. Yesim Tahirovic [¥] The $IC_{50}$ value was determined from two electrode voltage clamp recordings of rat NR1/NR2B receptor function, fitted as described in the experimental section. For all experiments, data are the fitted $IC_{50}$ value for the mean composite averaged from between 16 and 29 oocytes from 3 or more different frogs. NT = Not tested

During the SAR development of the 93-series of phenethanolamines, it was observed that a butyl chain incorporated at the central nitrogen on the linker yielded the optimal biological profile in terms of both potency and fold shift. This phenomenon is highlighted by a comparison between the two analogues **93-4** and **93-31**. The secondary-amide containing analogue (**93-4**) was highly potent with $IC_{50}$'s in the nanomolar region (37 nM at pH 7.6; 18 nM at pH 6.9) but only had a fold shift of 2. While the analogue containing an *n*-butyl chain (**93-31**) had comparable potency at pH 6.9 (27 nM), it was much less active at pH 7.6 (454 nM), for a fold shift of 17. The observation of such a large fold shift made **93-31** a much more attractive compound for potential use in ischemic conditions.

Compounds **96-61**, **96-65**, **96-66**, and **96-70** were all synthesized to test whether the results from the 93-series were transferable to the SAR development around the 96-series. A butyl chain was incorporated onto the central nitrogen of four of the most active compounds in the series, **96-13**, **96-20**, **96-22**, and **96-25**. A comparison between analogues **96-13** and **96-65** shows that the addition of the butyl chain gives a marked decrease in potency at both pH 7.6 and 6.9 without a large effect on the fold shift of the compounds. In contrast, **96-66** had an effect opposite of the desired result with a higher potency observed at physiological pH (pH 7.6) than at the more acidic conditions associated with ischemia (pH 6.9). The *n*-butyl analogue **96-66** also displayed significantly less overall potency compared to the related analogue **96-25**. Similar to the results observed with the previous compounds, a comparison between **96-61** and **96-22** also suggests that the 96-series does not follow the trend observed in the 93-series. The *n*-butyl analogue, **96-61**, is less potent and has a smaller fold shift than the corresponding secondary amide **96-22**. This suggests that the compounds in the 96-series, while structurally very similar to the 93-series, do not adopt the same binding mode as those compounds within the 93-series or do not share a binding site. It is possible that even a slight change in binding

conformation may cause steric interactions to occur within the binding pocket and result in decreased potency.

As one of the goals of this project was to reduce off-target activity, the most potent compound described herein was chosen for further off-target testing against hERG and α1 adrenergic receptors. As shown in Table 5, **96-49** was the only compound with a potency below 1 μM at either pH. Determination of hERG binding was performed in HEK293 cells by average displacement of [$^3$H]-astemizole. Determination of α1-binding was determined by the average displacement of [$^3$H]-prazosin from Wistar rat brain membranes. The results of this assay are shown in Table 6 along with the off-target data for synthetic analogue **96-22** which is shown for comparison. Unfortunately, the modification of amide location within the linker had a detrimental effect on the selectivity and off-target profile. Based on the hERG pharmacophore discussed in Section 1.1.6, it is not surprising that **96-49** had some affinity for the hERG channel. Although **96-49** did have a slightly better off-target profile than the amine compound **96-25**, it exhibited enough hERG and α1 binding to be a therapeutic concern. As a result, **96-49** was not developed or studied further as a result of its associated off-target data and reduced on-target efficacy.

**Table 6. Off-target data for a selection of 96-series compounds**

| Compound ID | GluN2B $IC_{50}$ (nM) | hERG (% displacement at 10 μM) | α1-Adrenergic (% displacement at 3 μM) |
|---|---|---|---|
| **96-22**‡ | 54 | 43 | <1 |
| **96-25**‡ | 39 | 97 | 49 |
| **96-49** | 1110 | 67 | 21 |

‡ Synthesized by Dr. Cara Mosley

In addition, the other synthesized compounds described herein (**96-61**, **96-65**, **96-66**, **96-71**) were not studied further due to their reduced efficacy compared to the earlier synthesized 96-series analogues (**96-13**, **96-20**, **96-22**, **96-25**). The entire 96-series of compounds was evaluated and the most potent and promising compounds were chosen for a brain penetration model study (MDR1-MDCK permeability). Unfortunately, this model study indicated that the most promising compound from this series **96-22** was likely a substrate for the P-glycoprotein (Pgp) efflux with an efflux ratio of 35 (Table 7).

**Table 7. MDR1-MDCK Permeability**

| Compound ID | $P_{app}$ (A-B)[a] | $P_{app}$ (B-A) | Efflux ratio |
|---|---|---|---|
| **96-22** | 1.80 | 63.2 | 35 |

[a] $P_{app}$ is the apparent permeability for the apical to basal (A–B) and the basal to apical (B–A) direction across MDR1-MDCK cell monolayers in Transwell® wells. $P_{app}$ units are x $10^{-6}$ cm/s.
[b] Efflux ratio = $P_{app}$ (A–B)/$P_{app}$ (B–A).

## 1.5 CONCLUSIONS

Although significant work has been done in the area of GluN2B-selective antagonists, the clinical use of such compounds has been limited by the associated significant adverse events and off-target effects. The contribution of our lab to this research included a class of novel enantiomeric propanolamines which afforded a promising compound in terms of both potency and fold shift, **93-31**. Unfortunately, this compound was also shown to bind to the hERG channel, an attribute which is known to contribute to acquired long QT syndrome and is a red flag for FDA approval. Our lab then undertook significant chemistry efforts to search for a GluN2B-selective antagonist which would have reduced off-target effects.

Using the screening hit **211** as a starting point, a number of structurally related compounds were synthesized with no distinct changes in potency or fold shift. By increasing the

flexibility of the linker while keeping the central amide functionality, the potency and the fold shift of this series was effectually increased. Four compounds were chosen to go forward with further modification with hopes to improve the fold shift of these compounds. Based on the trends observed in the 93-series, the incorporation of a butyl chain on the central amide caused a dramatic increase in the fold shift. These same modifications were performed on **96-22**, **96-25**, **96-13**, and **96-20**.

From the data associated with the structurally modified compounds described, it is clear that the trends observed in the 93-series do not fully translate into the 96-series. The incorporation of a butyl side chain, which enhanced potency and fold shift significantly in the 93-series, had a deleterious effect on the potency and fold shift of the 96-series.

Based on **211** and the most potent compounds in the 96-series, a compound with a similar structure to **96-22** was synthesized with the amide linkage moved to a different location in the linker. This may allow some of the same contacts to occur within the binding site while increasing the flexibility of the central portion of the linker. However, the biological data suggests that the movement of the central amide linkage to an earlier position in the linker has a negative effect on potency and fold shift.

The goal of this research was to decrease off-target effects associated with the 93-series while keeping the potency and fold shift. Unfortunately, the compounds described here were not as potent as the compounds in the 93-series and were not among the most potent in the 96-series. As a result, only **96-49** was tested for hERG affinity. The central amide placement likely decreases the hERG binding affinity of these compounds as **96-22** had a slightly better hERG profile than **96-49**.

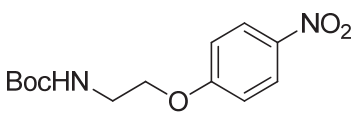
A few compounds in the 96-series were also evaluated in a model Pgp efflux study to determine blood-brain penetration. Unfortunately, while many of the compounds within the

96-series showed promise in the *in vitro* voltage clamp assays, their binding affinities for the Pgp efflux limits their ability to be effective neurological treatments.

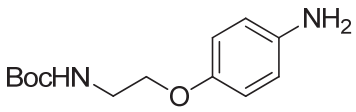
## 1.6 CHEMISTRY EXPERIMENTAL DETAIL

All reagents were obtained from commercial suppliers and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) on precoated aluminum backed plates (silica gel 60 F254, 0.25 mm thickness) or by LCMS (Varian). Flash chromatography was carried out by hand on silica gel 60 (230-400 mesh) or performed on a Teldyne ISCO CombiFlash Companion System with Teledyne RediSep or Silicycle normal phase columns with prepacked silica gel. $^{1}H$ and $^{13}C$ NMR spectra were recorded on an INOVA-400 (400 MHz), VNMRS-400 (400 MHz), INOVA-600 (600 MHz), or Mercury 300 Vx (300 MHz) instrument. The spectra obtained were referenced to the residual solvent peak. Chemical shifts are reported in parts per million and coupling constants in Hertz (Hz). Mass spectra were performed by the Emory University Mass Spectrometry center on either a VG 70-S Nier Johnson or JEOL instrument. Elemental analyses were performed by Atlantic Microlab, Inc (Norcross, GA). C, H, N agreed with proposed structures within ±0.4 of theoretical values. Purity of some compounds was determined by HPLC (Varian or Agilent). The conditions and column used for purity determination are noted for each individual compound.

### *1.6.1 Chemistry Experimental Procedures*

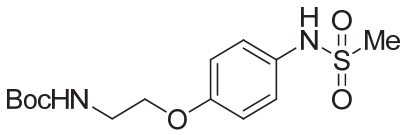


***Tert*-butyl *N*-2-(4-nitrophenoxy)ethylcarbamate (49)**. 4-nitrophenol (**47**, 1.9 g, 14 mmol, 1.1 equiv), *tert*-butyl *N*-2-hydroxyethylcarbamate (**48**, 2.0 mL, 13 mmol, 1.0 equiv) and triphenylphosphine (4.5 g, 18 mmol, 1.4 equiv) were dissolved dry THF (60 mL) at room temperature. The reaction mixture was then cooled to 0$^{o}$C in an ice bath followed by dropwise addition of diisopropylazodicarboxylate (DIAD, 3.6 mL, 18 mmol, 1.4 equiv). Once the addition was complete, the reaction was allowed to warm to room temperature and stirred there for 16 hours with TLC monitoring. Upon complete consumption of starting material, the solvent was removed *in vacuo.* The resulting yellow-orange residue was dissolved in EtOAc, and treated with 1 N NaOH. The organics were separated and the resulting aqueous phase was extracted 2x with EtOAc. The combined organics were washed with deionized water and brine, dried over $MgSO_4$, filtered and volatiles were removed *in vacuo*. The yellow residue was purified by silica gel chromatography (2:1 EtOAc/hexanes) to give the title compound as a yellow solid (3.0 g ,82%). $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, *J* = 9.3 Hz, 2H), 6.96 (d, *J* = 9.3 Hz, 2H), 4.95 (s, 1H, broad), 4.11 (t, *J* = 5.4 Hz, 2H), 3.56 (t, *J* = 5.4 Hz, 2H), 1.45 (s, 9H). 13C NMR (100 MHz, CDCl3) δ: 163.8, 156.1, 141.9, 126.2, 114.7, 70.2, 68.1, 40.0, 28.6.

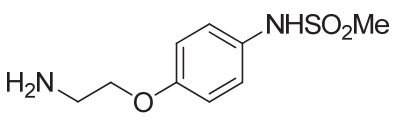



***Tert*-butyl *N*-2-(4-aminophenoxy)ethylcarbamate (50).** Compound **49** (3.0 g, 11 mmol, 1.0 equiv) was dissolved in dry MeOH (20 mL). Activated palladium on carbon (wet) (0.6 g, 5 mmol, 0.5 equiv) was added to the reaction mixture. The reaction flask was fitted with a hydrogen balloon and a rubber septum. The reaction mixture was purged with hydrogen under vacuum (3x) before stirring for 18 hours at room temperature. The reaction mixture was filtered over a pad of Celite and washed with DCM, EtOAc, and MeOH. The volatiles were removed *in vacuo* to

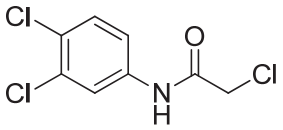
give the title compound as a brown-red oil (2.7 g, 100%) which was used in the next step without purification or further characterization. $^{1}$H (300 MHz, $CD_3OD$) 6.88-6.85 (m, 4H), 3.90 (t, *J* = 5.7 Hz, 2H), 3.36 (t, *J* = 5.7 Hz, 2H), 1.41 (s, 9H).




***Tert*-butyl *N*-2-(4-(methylsulfonamido)phenoxy)ethylcarbamate (51).** Compound **50** (2.5 g, 10 mmol, 1.0 equiv) was suspended in DCM (30 mL). Diisopropylethylamine (2 mL,12 mmol, 1.2 equiv) was added to the reaction mixture and allowed to stir for 15 minutes. The reaction mixture was cooled to 0$^{o}$C and methanesulfonyl chloride (0.9 mL, 11 mmol, 1.1 equiv) was added dropwise to the solution. The reaction was allowed to warm to room temperature and stirred for 10 hours with TLC monitoring. The reaction was quenched with water and extracted with DCM (3x). The organic layers were combined and washed with brine and water and dried over $MgSO_4$. The resulting brown residue was purified by silica gel chromatography (1:1 EtOAc/hexanes) to afford the title compound as an off-white solid (0.5 g, 15%). $^{1}$H NMR (300 MHz, $CD_3OD$) δ: 7.17 (d, *J* = 6.9 Hz, 2H), 6.89 (d, *J* = 6.9 Hz, 2H), 3.96 (t, *J* = 5.4 Hz, 2H), 3.39 (t, *J* = 3.5 Hz, 2H), 2.85 (s, 3H), 1.42 (s, 9H). $^{13}$C NMR (75 MHz, $CD_3OD$) δ: 156.0, 145.6, 124.0, 115.1, 67.0, 41.7, 39.8, 37.4, 27.5. HRMS calc'd for $C_{14}H_{23}N_2O_5S$, 331.13277; found 331.13245 $[M+H]^+$.

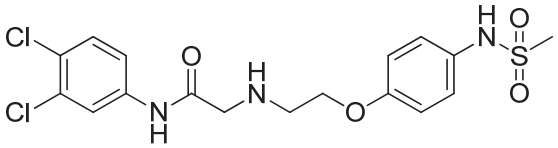


***N*-(4-(2-aminoethoxy)phenyl)methanesulfonamide hydrochloride (46).** Compound **51** (0.5 g, 2 mmol, 1 equiv), was dissolved in DCM (10 mL). Trifluoroacetic acid (5 mL) was added to the solution and the reaction mixture was allowed to stir for 3 hours with TLC monitoring. The reaction was quenched with water and extracted with DCM (2x). The organics were washed with brine and then dried over $MgSO_4$. Volatiles were removed *in vacuo* to yield a crude brown oil (0.17 g). The residue was dissolved in EtOAc and converted to the HCl salt by bubbling HCl gas through the solution. The resulting precipitate was filtered to afford the title compound as a purple solid (0.2 g, 49%). $^1$H NMR (300 MHz, $CD_3OD$) δ: 7.13 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.12 (t, *J* = 4.8 Hz, 2H), 3.28 (t, *J* = 3.6 Hz, 2H). $^3$C NMR (75 MHz, $CD_3OD$) δ: 145.3, 132.6, 124.0, 115.1, 67.0, 41.7, 39.8.

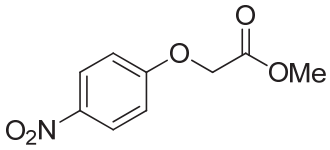



**2-chloro-*N*-(3,4-dichlorophenyl)acetamide (45).** 3,4-dichloroaniline (**40**, 2.0 g, 12 mmol, 1.0 equiv) and triethylamine (6.8 mL, 49 mmol, 4 equiv) were suspended in DCM (50 mL) and cooled to 0$^o$C in an ice bath. Chloroacetyl chloride (1.0 mL, 12 mmol, 1 equiv) was added dropwise to the reaction mixture before allowing the reaction to warm to room temperature and stir for 2 hours with TLC monitoring. Upon complete consumption of the starting material, the reaction was quenched with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with DCM (2x). The organics were combined and dried over $MgSO_4$. The volatiles were removed *in vacuo* to give the title compound as an off-white solid (2.9 g, 99%). $^1$H NMR (300 MHz, CDCl3) δ: 8.28 (s, 1H, broad), 7.81 (s, 1H), 7.41 (m, 2H), 4.21 (s, 2H). $^{13}$C (75 MHz,

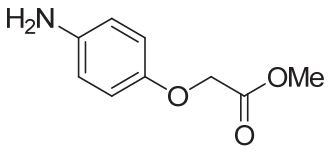
$CDCl_3$) δ: 165.2, 137.5, 132.1, 130.9, 129.6, 122.0, 119.5, 43.0. HRMS calc'd for $C_8H_7NOCl_3$, 237.95877; found 237.95886 $[M+H]^+$.



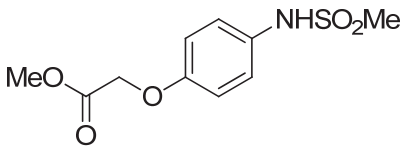
***N*-(3,4-dichlorophenyl)-2-(2-(4-(methylsulfonamido)phenoxy)ethylamino) acetamide (96-49).** Compound **46** (0.26 g, 1.0 mmol, 1.9 equiv) was suspended in 20 mL of THF. Triethylamine (0.2 mL, 1.0 mmol, 2.0 equiv) was added and the resulting mixture was allowed to stir for 10 minutes. Compound **45** (0.15 g, 0.6 mmol, 1.0 equiv) was added and the reaction was heated to reflux and allowed to stir for 16 hours. When TLC indicated complete conversion, the reaction mixture was basified with $NaHCO_3$ and extracted with DCM (2x). The combined organics were washed with water and brine, and then dried over $MgSO_4$. The resulting residue was dissolved in EtOAc and converted to the HCl salt by bubbling HCl gas through the solution. The volatiles were removed *in vacuo* to give the title compound as an orange amorphous solid (0.2 g, 76%). $^1$H NMR (300 MHz, $CD_3OD$)δ: 7.85 (d, *J* = 2.4 Hz, 1H), 7.43 (m, 1H), 7.38 (m, 1H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.40 (m, 2H), 3.93 (s, 2H), 3.20 (t, *J* = 3.6 Hz, 2H) 2.87 (s, 3H). $^{13}$C NMR (100 MHz, $CD_3OD$) δ: 165.8, 155.9, 137.5, 132.1, 131.8, 130.5, 127.2, 123.8, 123.3, 121.3, 115.2, 67.4, 54.7, 39.1, 37.6. HRMS calc'd for $C_{17}H_{20}N_3O_4SCl_2$, 432.05516; found 432.05423 $[M+H]^+$. Anal ($C_{17}H_{19}N_3O_4SCl_2$): C, H, N.



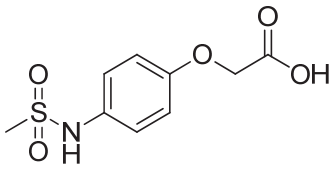
**Methyl 2-(4-nitrophenoxy)acetate (54).** Thionyl chloride (9.8 mL, 134 mmol, 3.3 equiv) was added dropwise to a solution of dry methanol (39 mL, 974 mmol, 24 equiv) at -10 $^{o}$C. After stirring for 10 minutes, 4-nitrophenoxyacetic acid (**44**, 8.0 g, 41 mmol) was added to give a white precipitate in an orange solution. The mixture was stirred for an additional hour before slowly warming to room temperature. The resulting solution was concentrated *in vacuo* to give an off-white solid. The solid was dissolved in EtOAc and a $NaHCO_3$ (sat'd) solution was added. The organic layer was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the title compound as a white solid (8.6 g, 99%). $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 9.2 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 2H), 4.75 (s, 2H), 3.84 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 168.4, 162.7, 142.5, 126.2, 114.9, 65.5, 52.8.




**Methyl 2-(4-aminophenoxy)acetate (55).** Compound **54** (14.0 g, 66 mmol) was dissolved in dry methanol (100 mL) and 5% palladium on activated carbon (2.8 g, 10 wt%) was added. The suspension was hydrogenolyzed under atmospheric pressure for 12 hours. The mixture was filtered over a pad of Celite and washed with EtOAc and MeOH. The resulting solution was concentrated in vacuo to give a light pink oil which solidified upon trituration with chloroform. The crude material was purified by silica gel chromatography (1:2 EtOAc/hexanes) to give a light pink solid (11.7 g, 97%). 1H NMR (400 MHz, CDCl3) δ: 6.74 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.6 Hz, 2H), 4.53 (s, 2H), 3.76 (s, 3H), 3.51 (s, 2H, broad). $^{13}$C NMR (100 MHz, CDCl3) d: 170.1, 151.1, 141.4, 116.5, 116.2, 66.5, 52.4. HRMS calc'd for $C_9H_{12}NO_3$, 182.08117; found 182.08110 $[M+H]^+$

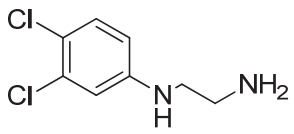



**Methyl 2-(4-(methylsulfonamido)phenoxy)acetate (56).** Aniline **55** (11.0 g, 61 mmol) was dissolved in dry DCM (50 mL) and cooled to 0 $^{o}$C. Diisopropylethylamine (11 mL, 61 mmol, 1.0 equiv) was added and the solution was allowed to stir for 10 minutes. Methanesulfonyl chloride (4.8 mL, 61 mmol, 1.0 equiv) was added dropwise and the reaction was warmed to room temperature. The resulting mixture was allowed to stir for 20 hours with TLC monitoring. After TLC indicated complete conversion of the starting material, the reaction was quenched by addition of water and diluted with DCM. The organics were separated and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to. The crude material was purified by silica gel chromatography (1:1 EtOAc/hexanes) to give the title compound as a white solid (15.7 g, 99%). 1H NMR (400 MHz, $CDCl_3$) $\delta$: 7.20 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.65 (s, 2H), 3.83 (s, 3H), 2.96 (s, 3H). 13C NMR (75 MHz, CDCl3) $\delta$: 169.5, 155.8, 130.6, 124.2, 115.6, 65.5, 52.5, 38.7.

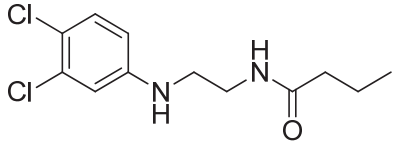



**2-(4-(methylsulfonamido)phenoxy)acetic acid (41).** The sulfonamide ester **56** (15.7 g, 61 mmol) was dissolved in MeOH (100 mL). To this solution, 1.0 N NaOH (230 mL) was added. The mixture was stirred at room temperature for 18 hours. The pH of the solution was adjusted to pH 3 with aqueous HCl. The volume of MeOH was reduced by rotary evaporation, upon which the product crashed out of solution. The pink crystals were collected by filtration and dried *in*

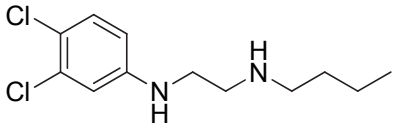
*vacuo* (11 g, 74%). 1H NMR (400 MHz, $CD_3OD$) δ: 7.17 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 4.63 (s, 2H), 2.86 (s, 3H). $^{13}C$ NMR (75 MHz, $CD_3OD$) δ: 172.7, 157.3, 132.8, 125.0, 116.5, 66.2, 38.8. HRMS calc'd for $C_9H_{10}NO_5S$, 244.02852; found 244.02864 $[M+H]^+$.



***N*[1]-(3,4-dichlorophenyl)ethane-1,2-diamine (39).** Bromoethylamine hydrobromide (**52**, 6.0 g, 29 mmol) was suspended in toluene (10 mL) and 3,4-dichloroaniline (**40**, 33 g, 201 mmol, 7.0 equiv) was added. The dark brown solution was heated to reflux for 1 h. The resulting mixture was cooled to room temperature to afford a brown precipitate which was filtered and washed with toluene. The solid was treated with 20% w/v NaOH (100 mL) and extracted with DCM (2x). The organics were washed with an acetic acid/sodium acetate buffer solution (300 mL of 0.1 M, pH 5.5). The aqueous layer was then basified with 20% w/v NaOH (100 mL) and extracted with DCM (2x). The combined organics were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude brown oil. The crude material was purified by silica gel chromatography (0-10% MeOH in DCM + 1% $Et_3N$ gradient) to give the title compound as a brown residue (5.0 g, 83%). $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 8.6 Hz, 1H), 6.69 (s, 1H), 6.46 (d, *J* = 8.6 Hz, 1H), 4.25 (s, 1H, broad), 3.13 (t, *J* = 5.1 Hz, 2H), 2.96 (t, *J* = 5.1 Hz, 2H), 1.41 (s, 2H, broad). $^{13}C$ NMR (150 MHz, $CDCl_3$) δ: 148.1, 133.0, 131.8, 114.0, 113.0, 46.2, 40.9. HRMS calc'd for $C_8H_{11}N_2Cl_2$, 205.02993; found 205.02914 $[M+H]^+$.

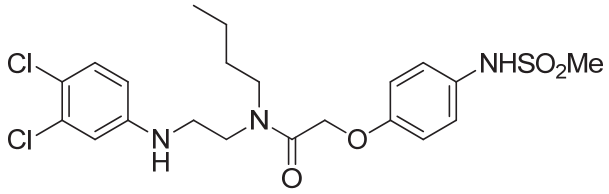


***N*-(2-((3,4-dichlorophenyl)amino)ethyl)butyramide (53).** Butyric acid (0.8 g, 8.8 mmol) was dissolved in DMF (10 mL) and cooled to 0 $^{o}$C. DMAP (1.2 g, 9.7 mmol, 1.1 equiv) and EDCI (1.9 g, 9.7 mmol, 1.1 equiv) were added successively. The mixture was allowed to stir for 1 hour at which time all reactants were completely dissolved. Compound **39** (1.8 g, 8.8 mmol) in DMF (10 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred there for 24 hours. The reaction was quenched with 1 M HCl and extracted with EtOAc (3x). The organics were combined, washed with brine (2x), and dried over $MgSO_4$. The volatiles were removed *in vacuo* to afford a crude brown residue. The crude material was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.2 g, 50%). $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.11 (d, $J$ = 9.2 Hz, 1H), 6.58 (d, $J$ = 2.8 Hz, 1H), 6.36 (dd, $J_1$ = 2.8 Hz, $J_2$ = 9.2 Hz, 1H) 6.28 (s, 1H, broad), 4.49 (s, 1H, broad), 3.43 (q, $J$ = 5.8 Hz, 2H), 3.15 (m, 2H), 2.12 (t, $J$ = 7.4 Hz, 2H), 1.60 (m, 2H), 0.88 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl3) $\delta$: 174.7, 147.9, 132.9, 130.8, 119.6, 113.6, 112.6, 44.6, 39.0, 38.7, 19.3, 14.0. HRMS calc'd for $C_{12}H_{17}N_2OCl_2$, 275.07125; found 275.07123 $[M+H]^+$



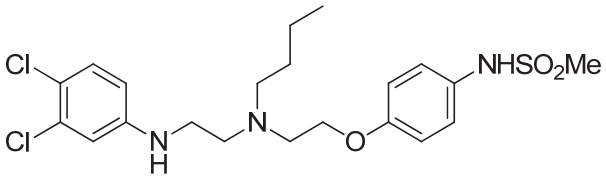

***N*$^1$-butyl-*N*$^2$-(3,4-dichlorophenyl)ethane-1,2-diamine (38).** Amide **53** (1.0 g, 3.6 mmol) was dissolved in dry THF (15 mL). Borane dimethylsulfide complex (1.0 mL, 11 mmol, 3.0 equiv) was added to the solution and the reaction was heated to reflux for 18 hours. The reaction was then cooled to room temperature. Deionized water and 1.0 M HCl were added to quench and the resulting mixture was partitioned with EtOAc. The organics were separated and the aqueous phase was extracted with EtOAc (1x). The combined organics were dried over MgSO4, filtered

and concentrated *in vacuo* to afford the title compound as a white solid (0.91 g, 96%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, *J* = 8.6 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 6.52 (dd, $J_1$ = 2.6 Hz, $J_2$ = 8.6 Hz, 1H) 3.53 (q, *J* = 4.8 Hz, 2H), 3.15 (m, 2H), 2.89 (m, 2H), 1.78 (m, 2H), 1.34 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H). HRMS calc'd for $C_{12}H_{19}N_2Cl_2$, 261.09198; found 261.09195 $[M+H]^+$

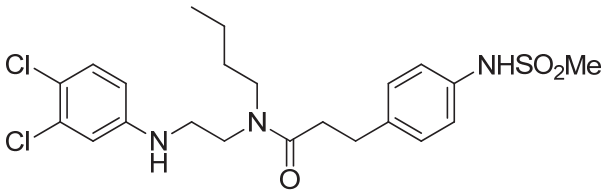



***N*-butyl-*N*-(2-((3,4-dichlorophenyl)amino)ethyl)-2-(4-(methylsulfonamido)phenoxy)acetamide (96-61).** The carboxylic acid **41** (0.21 g, 0.86 mmol) was dissolved in dry DMF (20 mL) and cooled in an ice bath to 0 °C. EDCI (0.18 g, 0.94 mmol, 1.1 equiv) was added followed by DMAP (0.12 g, 0.94 mmol, 1.1 equiv). The resulting reaction mixture was allowed to stir for 1 hour. Compound **38** (0.22 g, 0.86 mmol) was dissolved in dry THF (5 mL) and then added to the reaction mixture. The resulting solution was allowed to slowly warm to room temperature and was stirred at room temperature for 24 hours. The reaction was quenched with the addition of deionized water and 1M HCl. The solution was then extracted with EtOAc (3x). The organics were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude off-clear oil was purified by silica gel chromatography (5:4 EtOAc/hexanes) to afford the title compound as a white solid (0.36 g, 84%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.44 (s, 1H, broad), 7.17-7.07 (m, 2H), 6.81 (d, *J* = 9.2 Hz, 2H), 6.68-6.65 (m, 1H), 6.61 (d, *J* = 2.8 Hz, 1H), 6.43-6.39 (m, 1H), 4.71 (s, 2H), 3.63 (t, *J* = 5.6 Hz, 2H), 3.39-3.26 (m, 4H), 2.91 (s, 3H), 1.62-1.50 (m, 2H), 1.38-1.24 (m, 2H), 0.97-0.88 (m, 3H). $^{13}$C NMR (100 MHz, CDCl3) δ: 169.3, 156.3, 147.8, 132.9, 130.8, 130.7, 124.6, 119.5, 115.6, 113.4, 112.6, 67.0, 47.9, 45.4, 42.5, 39.0, 31.2, 30.3, 14.0. HRMS

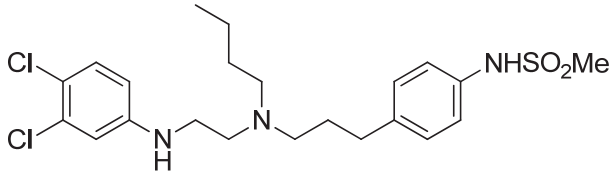
calc'd for $C_{21}H_{28}N_3O_4SCl_2$, 448.11721; found 448.11752 $[M+H]^+$. HPLC: Reverse Phase $C_8$ column. Method 1: 75% MeOH/25% water/0.1% formic acid to 95% MeOH/Water/0.1 % formic acid gradient over 3 minutes at 1 mL/min; 99% purity (retention time = 1.396 minutes). Method 2: 85% MeCN/5% water/0.1% formic acid isocratic over 3 minutes at 1 mL/min; 100% purity (retention time = 0.641 minutes). Anal ($C_{21}H_{27}Cl_2N_3O_4S$): C, H, N.




***N*-(4-(2-(butyl(2-((3,4-dichlorophenyl)amino)ethyl)amino)ethoxy)phenyl)methanesulfonamide (96-66).** Compound **96-61** (0.40 g, 0.82 mmol) was dissolved in dry THF (20 mL). Borane dimethylsulfide complex (1.0 M in THF, 0.19 g, 2.5 mmol, 3.0 equiv) was added dropwise to the resulting solution. Upon complete addition, the reaction was heated to reflux and allowed to stir at reflux for 8 hours. Upon cooling to room temperature, water was carefully added to the reaction followed by a small amount of 1M HCl. The resulting mixture was extracted with EtOAc (2x), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude solid was purified by silica gel chromatography (2:1 EtOAc/hexanes) to afford the title compound as a white solid (0.39 g, 100%). $^1$H ($CDCl_3$, 400 MHz) δ: 7.18-7.10 (m, 3H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.38 (m, 1H), 4.06-3.95 (m, 2H), 3.63 (m, 2H), 3.18-3.03 (m, 2H), 3.01-2.81 (m, 5H), 2.67-2.51 (m, 2H), 1.67-0.81 (m, 7H). $^{13}$C ($CDCl_3$, 400 MHz) δ: 142.3, 138.5, 135.2, 132.8, 131.1, 130.0, 129.7, 121.5, 120.3, 113.3, 112.5, 56.2, 48.9, 45.8, 43.1, 39.3, 35.1, 31.2, 31.0, 27.3, 20.2, 14.2. HRMS calc'd for $C_{21}H_{30}N_3O_3SCl_2$, 474.13795; found 474.13796 $[M+H]^+$. Anal ($C_{21}H_{29}Cl_2N_3O_3S$): C (53.16, 53.82), H (6.16, 6.08), N (8.86, 8.72).




***N*-butyl-*N*-(2-((3,4-dichlorophenyl)amino)ethyl)-3-(4-(methylsulfonamido)phenyl)propanamide (96-65).** The carboxylic acid **41** (0.21 g, 0.86 mmol) was dissolved in dry DMF (20 mL) and cooled in an ice bath to 0 $^{o}$C. EDCI (0.18 g, 0.94 mmol, 1.1 equiv) was added followed by DMAP (0.12 g, 0.94 mmol, 1.1 equiv). The resulting reaction mixture was allowed to stir for 1 hour. Diamine **38** (0.22 g, 0.86 mmol) was dissolved in dry THF (5 mL) and then added to the reaction mixture. The resulting solution was allowed to slowly warm to room temperature and was stirred at room temperature for 24 hours. The reaction was quenched with the addition of deionized water and 1M HCl. The solution was then extracted with EtOAc (3x). The organics were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude brown residue was purified by silica gel chromatography (ISCO, Redisep, 4 g column, 30-100% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.22 g, 52%). $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.64-7.62 (m, 1H), 7.14-6.96 (m, 5H), 6.60-6.57 (m, 1H), 6.39-6.36 (m, 1H), 3.55 (t, *J* =6.0 Hz, 2H), 3.19-3.11 (m, 4H), 2.92-2.81 (m, 4H), 2.57 (t, *J* = 8.0 Hz, 2H), 1.48-1.41 (m, 2H), 1.28-1.17 (m, 3H), 0.91-0.82 (m, 3H). $^{13}$C NMR (100 MHz, CDCl3) $\delta$: 173.8, 148.0, 138.5, 135.4, 132.8, 130.8, 129.8, 129.6, 121.6, 119.2, 113.3, 112.5, 48.7, 45.6, 43.1, 39.3, 34.9, 31.2, 31.0, 20.2, 14.0. Anal ($C_{22}H_{29}Cl_2N_3O_3S$): C, H, N. HPLC: Reverse Phase $C_8$ column. Method 1: 75% MeOH/25% water/0.1% formic acid to 95% MeOH/Water/0.1 % formic acid gradient over 3 minutes at 1 mL/min; 100% purity (retention time = 1.726 minutes). Method 2: 85% MeCN/5% water/0.1% formic acid isocratic over 3 minutes at 1 mL/min; 100% purity (retention time = 0.926 minutes).




**N-(4-(3-(butyl(2-((3,4-dichlorophenyl)amino)ethyl)amino)propyl)phenyl)methanesulfonamide (96-70).** Compound **96-65** (0.30 g, 0.62 mmol) was dissolved in dry THF (10 mL). Borane dimethylsulfide complex (1.0 M in THF, 1.9 mL, 1.9 mmol, 3.0 equiv) was added dropwise to the resulting solution. Upon complete addition, the reaction was heated to reflux and allowed to stir at reflux for 8 hours. Upon cooling to room temperature, water was carefully added to the reaction followed by a small amount of 1M HCl. The resulting mixture was extracted with EtOAc (2x), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude solid was purified by silica gel chromatography (2:1 EtOAc/hexanes) to afford the title compound as a white solid (0.12 g, 41%). $^1$H ($CDCl_3$, 400 MHz) δ: 7.24 (m, 1H), 7.17-7.13 (m, 2H), 7.07-7.04 (m, 2H), 6.64 (m, 1H), 6.48 (m, 1H), 3.29 (m, 2H), 3.20-2.93 (m, 5H), 2.86-2.72 (m, 4H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.98-1.87 (m, 2H), 1.85-1.81 (m, 2H), 1.59-1.48 (m, 2H), 0.92-0.83 (m, 3H). $^{13}$C ($CDCl_3$, 400 MHz) δ: 142.6, 138.3, 135.1, 132.8, 131.0, 130.0, 129.6, 121.5, 119.2, 113.3, 112.5, 56.2, 48.9, 45.8, 43.1, 39.3, 35.1, 31.2, 31.0, 20.2, 14.2. HRMS calc'd for $C_{21}H_{30}N_3O_3SCl_2$, 474.13795; found 474.13796 $[M+H]^+$. Anal ($C_{22}H_{31}Cl_2N_3O_2S$): C, H, N.

*1.6.2 Combustion Analysis (Atlantic Microlab, Norcross, GA)*

| Compound ID | Molecular Formula | Theoretical | Experimental |
|---|---|---|---|
| **96-49** | $C_{17}H_{19}Cl_2N_3O_4S$ | C: 47.23, H: 4.43, N: 9.72 | C: 47.52, H: 4.59, N: 9.78 |
| **96-61** | $C_{21}H_{27}Cl_2N_3O_4S$ | C: 51.64, H: 5.57, N: 8.60 | C: 52.03, H: 5.54, N: 8.62 |
| **96-65** | $C_{22}H_{29}Cl_2N_3O_3S$ | C: 54.32, H: 6.01, N: 8.64 | C: 54.41, H: 6.03, N: 8.64 |
| **96-66**‡ | $C_{21}H_{29}Cl_2N_3O_3S$ | C: 53.16, H: 6.16, N: 8.86 | C: 53.82, H: 6.08, N: 8.72 |
| **96-70** | $C_{22}H_{31}Cl_2N_3O_2S$ | C: 55.93, H: 6.61, N: 8.89 | C: 56.21, H: 6.63, N: 8.90 |

‡Value did not fall within ±0.4

## 1.7 BIOLOGY EXPERIMENTAL DETAIL

### *1.7.1 In vitro assay: NMDA receptor antagonism (Dr. Stephen Traynelis)*

Biological experiments described below were performed in the laboratory of Dr. Stephen Traynelis in the Department of Pharmacology at Emory University's School of Medicine.

*Expression of glutamate receptors in Xenopus laevis oocytes.*

All protocols involving the use of animals were approved by the Emory University IACUC. cRNA was synthesized from linearized template cDNA for rat glutamate receptor subunits according to manufacturer specifications (Ambion). Quality of synthesized cRNA was assessed by gel electrophoresis, and quantity was estimated by spectroscopy and gel electrophoresis. Stage V and VI oocytes were surgically removed from the ovaries of large, well-fed and healthy *Xenopus laevis* anesthetized with 3-amino-benzoic acid ethyl ester (1-3 gm/l) as previously described.[88] Clusters of isolated oocytes were incubated with 292 U/ml Worthington (Freehold, NJ) type IV collagenase or 1.3 mg/ml collagenase (Life Technologies, Gaithersburg, MD; 17018–029) for 2 hr in $Ca^{2+}$-free solution comprised of (in mM) 89 NaCl, 1 KCl, 2.4 $NaHCO_3$, 0.82 $MgSO_4$, 10 HEPES, with slow agitation to remove the follicular cell layer. Oocytes were then washed extensively in the same solution and maintained in Barth's solution comprised of (in mM) 88 NaCl, 1 KCl, 2.4 $NaHCO_3$, 10 HEPES, 0.82 $MgSO_4$, 0.33 $Ca(NO_3)_2$, and 0.91 $CaCl_2$ and supplemented with 100 µg/ml gentamycin, 10 µg/ml streptomycin, and 10 µg/ml penicillin. Oocytes were manually defolliculated and injected within 24 hrs of isolation with 3-5 ng of GluN1-1a (hereafter GluN1) subunit and 7-10 ng of GluN2 subunit in a 50 nl volume, or 5-10 ng in 50 nl of AMPA or kainate receptor cRNAs, and incubated in Barth's 248 solution at 15°C for 1–7 d. Glass injection pipettes had tip sizes ranging from 10-20 microns, and were backfilled with mineral oil.

*Two electrode voltage clamp recording from Xenopus laevis oocytes.*

Two electrode voltage-clamp recordings were made 2–7 days post-injection as previously described.[88] Oocytes were placed in a dual-track plexiglass recording chamber with a single perfusion line that splits in a Y-configuration to perfuse two oocytes. Dual recordings were made at room temperature (23 $^{o}$C) using two Warner OC725B or OC725C two-electrode voltage clamp amplifiers, arranged as recommended by the manufacturer. Glass microelectrodes (1-10 MΩ) were filled with 300 mM KCl (voltage electrode) or 3 M KCl (current electrode). The bath clamps communicated across silver chloride wires placed into each side of the recording chamber, both of which were assumed to be at a reference potential of 0 mV. Oocytes were perfused with a solution comprised of (in mM) 90 NaCl, 1 KCl, 10 HEPES, and 0.5 $BaCl_2$; pH was adjusted to 7.4 or 7.6 by addition of 1 M NaOH. Oocytes expressing GluN1/GluN2A were pre-incubated before recording in recording solution supplemented with 50 μM BAPTA-AM at room temperature. Oocytes were recorded under voltage clamp at -40 mV. Final concentrations for control application of glutamate (50-100 μM) plus glycine (30 μM) to oocytes expressing NMDA receptors were achieved by dilution from 100 and 30-100 mM stock solutions, respectively. In addition, 10 μM final EDTA was obtained by adding a 1:1000 dilution of 10 mM EDTA, in order to chelate contaminant divalent ions such as extracellular $Zn^{2+}$. Homomeric GluR1 AMPA receptors were activated by 100 μM glutamate. Homomeric GluR6 kainate receptors were incubated in concanavalin A (10 μM) for 5 minutes, and activated by 100 μM glutamate. Concentration-response curves for experimental compounds acting on NMDA receptors were obtained by applying in successive fashion a maximally effective concentration of glutamate/glycine, followed by glutamate/glycine plus variable concentrations of experimental compounds. Concentration-response curves consisting of 5 to 8 concentrations were obtained in this manner. The baseline leak current at -40 mV was measured before and after recording, and the

full recording linearly corrected for any change in leak current. Oocytes with glutamate-evoked responses smaller than 50 nA were not included in the analysis. The level of inhibition produced by experimental compounds was expressed as a percent of the initial glutamate response, and averaged together across oocytes from a single frog. Each experiment consisted of recordings from 3 to 10 oocytes obtained from a single frog. Results from >3 experiments using oocytes from 3 different frogs were pooled, and the percent responses at antagonist concentrations for each oocyte were fitted by the equation,

$$Percent\ Response = (100 - minimum) / (1 + ([conc] / IC50)nH ) + minimum$$

where *minimum* is the residual percent response in saturating concentration of the experimental compounds, $IC_{50}$ is the concentration of antagonist that causes half of the achievable inhibition, and *nH* is a slope factor describing steepness of the inhibition curve. *Minimum* was constrained to be greater than or equal to 0.

*1.7.2 In vitro binding studies for off-target effects (MDS Pharma, Inc.)*

Compounds were evaluated for binding to the human ether-a-go-go potassium channel (hERG) expressed in HEK293 cells by displacement of $^{3}$[H]-astemizole according to the methods by Finlayson et al.[89] Compounds were incubated at 10 μM, in duplicate, and the amount of $^{3}$[H]-astemizole determined by liquid scintillation counting. In some cases, a seven concentration (each concentration in duplicate) displacement curve was generated to determine $IC_{50}$. Ki values for human hERG channels determined by displacement of 1.5 nM $^{3}$[H]-astemizole from HEK-293 cell membranes transfected with human recombinant hERG channels (MDS Pharma). Data from multipoint displacement curves were fit by a nonlinear, least squares regression analysis and the Ki calculated using the Cheng and Prusoff equation.

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# *Chapter 2: Design, Synthesis, and Biological Evaluation of First-in-Class GluN2C/GluN2D-Selective NMDA Receptor Potentiators*

## 2.1 STATEMENT OF PURPOSE

Ifenprodil (**1**) was the first small molecule identified which showed subunit selective inhibition at NMDA receptors. Specifically, ifenprodil selectively inhibits GluN2B-containing receptors over GluN2A-, GluN2C-, and GluN2D-containing NMDA receptors.[1] Since the discovery of ifenprodil, many other structurally related compounds have been identified which also selectively target GluN2B-containing receptors (*Section 1.2.4*). However, no compounds have been identified, prior to the recent work from our lab[2-4], which selectively target GluN2A-, GluN2C-, or GluN2D-containing NMDA receptors. As a result of the lack of literature in this area, very little is known about the individual receptor subunits and their distinct physiological functions.

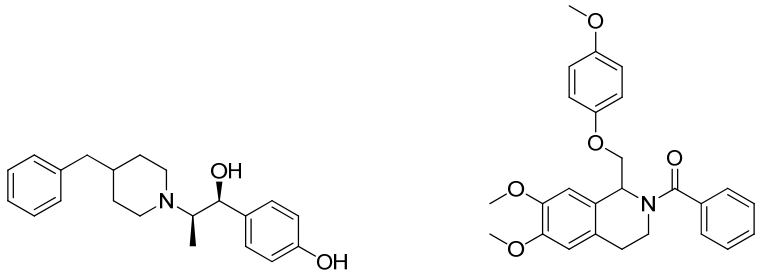



**Figure 1. Structure of ifenprodil, the classical GluN2B-selective antagonist and 1180, the screening hit on which this work is based**

The Traynelis lab has undertaken a substantial effort to search for non-competitive allosteric modulators of GluN2C- and GluN2D-containing NMDA receptors. Discovery of such compounds would allow the study of receptor function and the role GluN2C- and GluN2D-containing receptors play in brain function. Due to the important role the NMDA receptor plays in the central nervous system (CNS), subunit-selective compounds also have potential to treat a

number of CNS-related disease states. The Traynelis lab performed a fluorescence-based primary screen of almost 100,000 compounds and discovered a small number of hits. Of these hits, one showed potentiation of NMDA-related current and was chosen for further study (1180 series, Figure 1, **1180**). This compound was selective for GluN2C- and GluN2D-containing NMDA receptors over GluN2A- and GluN2B-containing receptors. The goal of this project was to generate a structure activity relationship in collaboration with the Traynelis laboratory. We sought to increase potency of this series of compounds which would selectively potentiate GluN2C- and GluN2D-containing NMDA receptor function. The goals of this project were achieved using the following strategy:

1. Design and synthesis of novel 1180 series analogues with an emphasis on improving potency.
2. Determination of the important binding interactions within GluN1/GluN2D-containing NMDA receptors *in vitro*.
3. Determination of preliminary *in vivo* pharmacokinetic properties of 1180-series.
4. Evaluation of efficacy of 1180-series analogues in an animal model for fear extinction.

## 2.2 INTRODUCTION AND BACKGROUND

### *2.2.1 Subunit-Selective Modulators of NMDA function*

Prior to our work in this area, there were no synthetic subunit selective positive allosteric modulators reported in the literature. However, there have been several endogenous compounds reported, such as the polyamines and neurosteroids, that positively modulate NMDA receptors. For example, the polyamines spermine and spermidine selectively potentiate GluN2B-containing receptors with partial inhibition observed at other subunits.[5,6] In addition,

the neurosteroid pregnenolone sulfate potentiates GluN2A- and GluN2B-containing NMDA receptors with slight inhibition observed at GluN2C- and GluN2D-containing NMDA receptors.[7]

Although there was a lack of references in the literature to subunit selective potentiators of NMDA when we undertook this study, there were a large number of subunit selective antagonists reported. However, the literature was mostly limited to GluN2B-selective antagonists, such as ifenprodil (**1**) and related compounds, with other subunit-selective antagonists markedly absent from the literature. Since the primary screen performed by the Traynelis lab in the search for new subunit selective modulators, our lab has reported a number of NMDA receptor antagonists selective for GluN2C- and GluN2D-containing receptors.[3,2] In addition, in recent years the Monaghan group has published a series of subunit-selective modulators; some of which show modest potentiation.[8] Despite the ongoing work in this area, there is still a lack of selective modulators for the GluN2A-, GluN2C-, and GluN2D-containing NMDA receptors. Due to the differential expression discussed in Chapter 1 (*1.2.1*), it is hypothesized that each of the subunits may contribute to distinct physiological functions and may also be involved in the pathophysiology of different disease states.[9] However, due to the lack of subunit selective modulators, very little is known about the specific biological action of each of the individual receptor subtypes. Selective positive or negative allosteric modulators of the individual subunits of NMDA receptors would be useful tools to study the normal function of each of the receptors and their individual role in brain development and function.

### *2.2.2 Therapeutic Rationale for GluN2D-selective potentiators*

During ischemic conditions, NMDA receptors are overactivated leading to glutamate-induced toxicity and neuronal death. In these conditions, an NMDA antagonist would be ideal to balance the overactivation and prevent cell death.[10] However, in certain disease states, such

as schizophrenia and related diseases of psychosis, the hypofunction of NMDA receptors seems to play a role in the negative symptoms associated with the disease.[11]

Genetic risk prediction studies have identified schizophrenia risk genes which affect NMDA receptor function or glutamatergic neurotransmission.[12-15] In addition, placebo-controlled trials with glycine site activators have shown a reduction in negative symptoms, improved cognition, and in some cases, reduction in positive symptoms of schizophrenic patients receiving concurrent antipsychotic medications.[16-19] The NMDA agonist D-serine also has shown positive effects on the symptoms of schizophrenia when given in conjunction with current antipsychotic medications.[20]

Studies have also shown modified NMDA receptor levels in the brain of schizophrenic patients. Akbarian and coworkers reported a regional deficit in NMDA receptor subunit density in post-mortem brain tissue of schizophrenic patients.[21] The expression patterns of GluN1 and each GluN2 subunit were measured in prefrontal, parieto-temporal, and cerebellar cortical tissue of 15 schizophrenic patients. A significant increase in GluN2D subunit mRNA levels was observed in the prefrontal tissue with no significant changes observed in the expression of the other NMDA receptor subunits. The authors hypothesize that the observed increase in GluN2D mRNA expression could reflect a compensatory response to decreased function in the prefrontal cortical regions of the schizophrenic brain.

*2.2.3 Glutamate Hypofunction Hypothesis*

Schizophrenia remains a very disabling illness, despite years of antipsychotic research and several generations of approved antipsychotic medications. Currently, antipsychotics are the gold standard for schizophrenia treatment. However, approximately one third of schizophrenic patients either does not respond or has a negative response to antipsychotic

treatment.[22] There remains a need for more effective approaches to treatment for schizophrenia. Although much research has gone into studying the mechanism and underlying physiology of schizophrenia, a thorough understanding of the disease remains elusive. The glutamate hypofunction hypothesis emerged in 1980 from the seminal paper which reported decreased glutamate concentrations in cerebrospinal fluid (CSF) of schizophrenic patients.[23] However, despite significant attempts, the findings reported in this paper have not been successfully replicated.[24-26] Even many years later when more sophisticated instrumentation was available, no difference was observed in the CSF glutamate levels of schizophrenic patients. However, significant reductions in γ-glutamylglutamine, a compound thought to be involved with glutamate uptake and/or glutamate release, were observed.[27]

Data from post-mortem studies in schizophrenic patients have suggested that hypofunction of glutamatergic processes may play a role in schizophrenic etiology. Changes in neuropeptides and related enzymes are often used as indicators of glutamatergic activity. *N*-acetylaspartylglutamate (NAAG) is a neuropeptide found in high concentrations in glutamatergic neurons. NAAG serves as a biological precursor or a storage form for glutamate and is thought to act as a glutamate antagonist in competition for the NMDA receptor glutamate site.[28] When NAAG is present in high levels, it is associated with hypofunction of the glutamatergic system. Post-mortem studies in schizophrenic patients showed an increase in NAAG levels in the prefrontal and hippocampal regions compared to controls.

In the late 1950's, it was reported that the administration of PCP, a non-competitive NMDA receptor antagonist, to normal human subjects induced some of the primary symptoms observed in schizophrenic patients.[29] In addition, NMDA channel blockers such as PCP and ketamine have been shown to profoundly exacerbate both positive and negative symptoms in schizophrenic patients.[29-32] To better study diseases of psychosis, research was directed towards

the development of an animal model. The hypothesis followed that the availability of psychomimetic compounds which could induce psychotic behavior would accelerate the research process and therefore more quickly lead to the development of an effective therapeutic. Since the original observation of these effects upon administration of PCP, the use of psychomimetic drugs in both humans and animals has become the most widely accepted and utilized class of schizophrenia models.[33]

Since typical antipsychotics are not sufficiently effective on either the negative or positive symptoms of psychosis, researchers have been studying novel pharmacological targets and new treatment strategies. Augmentation is a strategy widely utilized to improve the antipsychotic therapies. This strategy involves the modulation of neurotransmission systems, other than dopaminergic and serotoninergic systems, in order to potentiate the action of traditional antipsychotic drugs.[34] The glutamatergic system has widely been hypothesized to play a role in the psychosis pathophysiology with a large collection of data supporting the theory.[11,35-40]

The glutamate system is highly complex and there are several possible targets for modulation. Recent augmentation strategies have involved targeting either modulation of receptor activity or glutamate release inhibition.[38] Activation of the NMDA receptor occurs through the binding of glutamate and glycine to their respective binding sites. Opening of the channel cannot occur without the binding of glycine, which occurs after glutamate is bound. Direct stimulation of NMDA receptors by excess glutamate can trigger neuronal excitotoxicity. However, stimulation of the glycine binding site may potentiate NMDA receptor-mediated neurotransmission without significant risk of neuroexcitotoxicity.[41] Stimulation of the glycine site could be achieved through the use of direct glycine agonists such as glycine, D-serine, and

D-cycloserine (DCS), or by blocking glycine re-uptake and increasing synaptic glycine levels through the use of glycine transporter inhibitors.

Abnormal glutamatergic signaling has been thought to contribute to negative and cognitive symptoms of psychosis.[40] Mice mutated to reduce NMDA receptor glycine affinity, as well as mice treated with NMDA competitive glycine site antagonists, were shown to have cognitive and social behavior impairments. In most cases, dysfunctions were reverted by exposure to either D-serine, a direct glycine agonist, or clozapine, an atypical antipsychotic which is believed to act on the NMDA glycine site.[42,43] In addition, high doses of glycine administered to schizophrenic patients in conjunction with antipsychotic medications showed improved negative symptoms.[18] Although these results are promising in small scale clinical trials, they have not been confirmed in larger multi-center trials. It is not clear whether the co-administration of glycine and antipsychotics is more efficacious than clozapine alone. The need exists for additional methods to increase the glutamatergic signaling through the enhancement of NMDA function.

*2.2.4 Enhancement of Learning and Memory*

The activation of NMDA-receptors also has potential for the enhancement of learning and memory. Several studies have shown that transgenic mice with increased expression of GluN2B-containing NMDA receptors exhibit superior learning and memory in behavioral models.[44,45] This serves as a proof of concept for the potential of drug-induced potentiation of NMDA receptor function to produce in humans the same effectual increased learning and memory observed in genetically modified mice.

Other evidence exists supporting the potential for positive modulators of NMDA receptor function to enhance learning and memory. Many NMDAR antagonists have shown

impairment of the learning process. Acute and chronic administration of SDZ EAA 494, a potent NMDAR competitive antagonist showed considerable impairment of verbal and nonverbal memory performance without significantly affecting reaction time or spatial-memory tests.[46,47] Ketamine, a known NMDA channel blocker, has been shown to impair spatial and verbal learning in healthy human subjects but retrieval of information learned prior to administration was not affected.[48] In a different study in healthy human volunteers, ketamine produced a dose-dependent impairment of episodic and working memory as well as impairment of recognition memory and procedural learning.[49] These data combined with the observations in transgenic mice suggest that NMDA plays a significant role in learning and memory and represents a potential target for enhancement of these processes.

*2.2.5 Extinction of Fear*

Anxiety disorders are among the most commonly diagnosed disorders in the developed world. Current treatments for anxiety disorders include both pharmacotherapy and psychotherapy techniques. Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed as treatment for anxiety. In some cases, benzodiazepines may also be used for treatment but these are typically only given for a short time period in order to avoid issues such as dependence or tolerance.[50] Many of the current psychotherapies involve controlled exposure to the feared stimulus with the end goal of extinction of fear. Although both of these techniques have proven effective, they have not shown an additive effect when used in combination.[51,52]

Some anxiety disorders, such as post-traumatic stress disorder (PTSD) and phobias, are thought to be attributed to strong associative learning as is observed in Pavlovian fear conditioning.[53-56] This means that the psychotherapeutic approaches such as exposure therapy

can be compared to the experimentally-induced fear extinction used in animal models. If anxiety disorders are closely related to a conditioned fear response, then pharmacological agents with an effect on the fear memory in animal models, especially an effect of improved extinction of fear, may be an effective treatment for anxiety disorders in humans as well.[57,58]

NMDA receptors have long been known to play a crucial role in the processes of learning and memory. These NMDA-related processes include those of the acquisition[59,60], consolidation[61,62], reconsolidation[63], and extinction[64,65] of fear memories. As a result, several studies have been published attempting to enhance the effects of psychotherapy through modulation of the NMDA receptor. The partial glycine-site agonist, DCS, has been commonly used in these combination protocols and has been reported to improve the effects of psychotherapy upon administration.[66] DCS is a partial agonist at GluN2A-, GluN2B-, and GluN2D-containing NMDA receptors but shows potentiation at GluN2C-containing NMDA receptors. In addition, a recent report has shown that GluN2C knockout mice have impaired acquisition of conditioned fear learning.[67] These data suggest that the activity associated with DCS may be attributed to its potentiating effects on GluN2C-containing receptors. DCS has shown marked improvements in a number of anxiety disorders including phobias[68], social anxiety[69], and obsessive compulsive disorder (OCD).[70,71]

Many of the studies involving fear extinction use an animal model based on Pavlovian fear conditioning. In these model studies, an animal is exposed to pairings of a neutral conditioned stimulus (CS, e.g. – light or tone) with a naturally aversive unconditioned stimulus (US, e.g. –shock). After being exposed to these stimuli, the presence of the CS will elicit behaviors that are typically associated with a fear response (e.g. – tachycardia, elevated blood pressure, potentiated startle response). This is attributed to a learned fear response. Upon

repeated presentation of the CS on its own, the learned fear response can be reduced effectually extinguishing the fear response.

Although the study of fear extinction is procedurally simple, it is very complicated conceptually and still not fully understood. As a result, a number of theories exist to explain the process of fear extinction. Although some have suggested that extinction arises from "unlearning" the association between the conditioned stimulus and the unconditioned stimulus (Rescorla-Wagner model, 1972), some of the common observations from fear extinction models do not align with this perspective. A number of studies show that extinction requires exposure to the conditioned stimulus apart from the aversive event rather than just the passage of time. This suggests a more complicated process than the Rescorla-Wagner model. Two other perspectives have been suggested which help to explain this discrepancy: the devaluation of the unconditioned stimulus[72] and the learning of a competing association[73] that interferes with the original conditioned-unconditioned stimuli association. These both account for the common observation of the return of fear after extinction.[74] Although the "unlearning" theory does not explain some of the common findings associated with conditioned fear response and fear extinction, it is possible that extinction involves unlearning in combination with other processes. This is an ongoing area of research and it may require hybrid models of extinction to fully explain the observed phenomena.[75] It is clear from these data, however, that the processes of learning and memory are also involved in the extinction of fear. The implications of the NMDA receptor in fear conditioning and fear extinction make it a viable target for modulation of the fear response and a potential treatment path for anxiety disorders.

*2.2.6 Rationale for 1180-Series Analogues*

After the initial screen for NMDA-receptor modulators, **1180** was chosen for further chemical modification and SAR development. The Traynelis laboratory ordered a small library of structurally related compounds to obtain more biological information. Almost 40 compounds were tested in this initial phase of the 1180-series and trends began to emerge from this selection of compounds. Structural modifications to the original screening hit (**1180**) based on plans for development of an SAR are summarized in the general structure (**2**) shown in Figure 2.

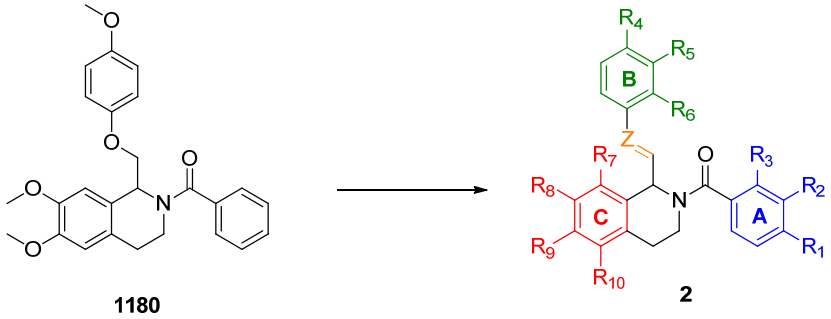
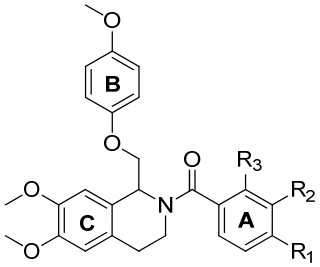



**Figure 2. Generic structure illustrating the planned modifications to the screening hit (1180) for SAR development**

Many of the purchased compounds incorporated substituents in various positions on the A-ring, shown in blue in Figure 2. All of the biological data shown in the following tables was collected by the Traynelis laboratory. Preliminary data suggested that substitution at the $R_2$ position on the A-ring was well tolerated and may even result in an increase in potency. For example, as shown in Table 1 both **1390** and **1425** with substituents in the $R_2$ position showed increased potency compared to **1180**. Substitution at $R_1$ seemed to be tolerated with **1371, 1368**, and **1393** but the potencies were slightly better when, by comparison, the same functionality was placed in the $R_2$ position. In fact, a marked improvement in potency is observed between the bromine- and methoxy-containing analogues when either of these

substituents is placed at $R_2$ instead of $R_1$. Substitution at $R_3$ does not appear to be tolerated on the A-ring.

**Table 1. Effect of A-ring substituent placement on potency of 1180-series**



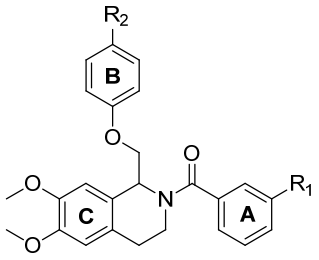

| | | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|---|
| **Compound ID** | **$R_1$** | **$R_2$** | **$R_3$** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | H | H | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1371** | Me | H | H | 106 ± 5.1 | 108 ± 2.7 | -- | -- |
| **1425** | H | Me | H | 171 ± 11 | 135 ± 9.4 | 6.2 (211%) | 5.5 (174%) |
| **1263** | H | H | Me | 108 ± 2.0 | 101 ± 2.4 | -- | -- |
| **1368** | Cl | H | H | 128 ± 3.2 | 111 ± 4.1 | 4.1 (135%) | -- |
| **1390** | H | Cl | H | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1409** | H | H | Cl | 112 ± 10 | 101 ± 8.9 | -- | -- |
| **1393** | Br | H | H | 107 ± 2.9 | 108 ± 3.1 | -- | -- |
| **1391** | H | Br | H | 183 ± 11 | 178 ± 6.6 | 0.9 (195%) | 2.2 (188%) |
| **1364** | OMe | H | H | 101 ± 1.1 | 96 ± 1.9 | -- | -- |
| **1392** | H | OMe | H | 147 ± 12 | 132 ± 10.5 | 5.8 (181%) | 12 (179%) |
| **1370** | $NO_2$ | H | H | 96 ± 1.4 | 102 ± 1.8 | -- | -- |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No significant effect was observed at GluN2A- or GluN2B-containing receptors (data not shown).

Preliminary assessment of substitution on the B-ring indicates that the *para*-methoxy group ($R_4$) is important for activity (Table 2). Only a few changes were made to the substitution

on this ring and although the *para*-ethyl containing analogue was weakly active at GluN2C- and GluN2D-containing receptors and the *para*-methylester containing analogues both showed weak potentiation at GluN2C-containing receptors, all compounds showed either a reduction or complete loss of activity upon replacement of the *p*-methoxy.

**Table 2. Effect of B-ring substituent type on potency and potentiation of 1180-series**




| | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|
| **Compound ID** | **$R_1$** | **$R_2$** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | OMe | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** | Cl | OMe | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1366** | H | Et | 120 ± 2.4 | 108 ± 2.4 | 23 (160%) | -- |
| **1444** | Cl | $CO_2Me$ | 104 ± 2.4 | 107 ± 1.7 | -- | -- |
| **1410** | Br | $CO_2Me$ | 107 ± 4.0 | 102 ± 0.8 | -- | -- |
| **2029** | Cl | $NO_2$ | 90 ± 0.7 | 93 ± 0.8 | -- | -- |
| **1394** | F | F | 85 ± 1.3 | 86 ± 1.2 | -- | -- |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No significant effect was observed at GluN2A- or GluN2B-containing receptors (data not shown).

### *2.2.7 Cysteine Reactive Groups*

A common practice used to probe binding sites is the use of covalent modification of the protein through reaction of a ligand with a natural or unnatural residue within the protein. Limitations with this method lie in the reactivity of both the reactive group on the ligand and the

nucleophilic residue. In order for this method to be maximally effective, the reactive group chosen for the ligand should be selective for the targeted residue. It also must react in conditions that will not denature the protein in question so requires reactivity in aqueous media, low to ambient temperature and at or near neutral pH.[76] In addition, the electrophilic group must be sufficiently reactive to bind to the protein rapidly during the relatively short time period associated with the experiments. Taking all of these limitations into account, the ligand must also not alter the biological system in any way other than intended. These represent significant chemical challenges for this technique.

For the purpose of probing the binding site, mutants are made with nucleophilic residues placed in deliberate and specific locations where ligand binding is expected. An electrophilic group is then placed onto a ligand known to act at the receptor. If the ligand binds within an area where a mutation has been made, the nucleophilic residue will react with the electrophile, causing a covalent modification of the protein. Cysteine is commonly used for this purpose due to the strongly nucleophilic nature of the sulfhydryl side chain. In addition, cysteine has a relatively low natural abundance[77] which decreases the likelihood of reaction between the ligand and other natural cysteine residues within the protein.

Commonly used functional groups for this purpose are summarized in Figure 3 and include isothiocyanates, $\alpha$-chlorocarbonyl, among other electrophilic groups.[78] The nucleophilic cysteine residues are strategically placed into areas which are thought to participate in ligand binding. Therefore, some information about the potential binding interactions is required prior to using this strategy.

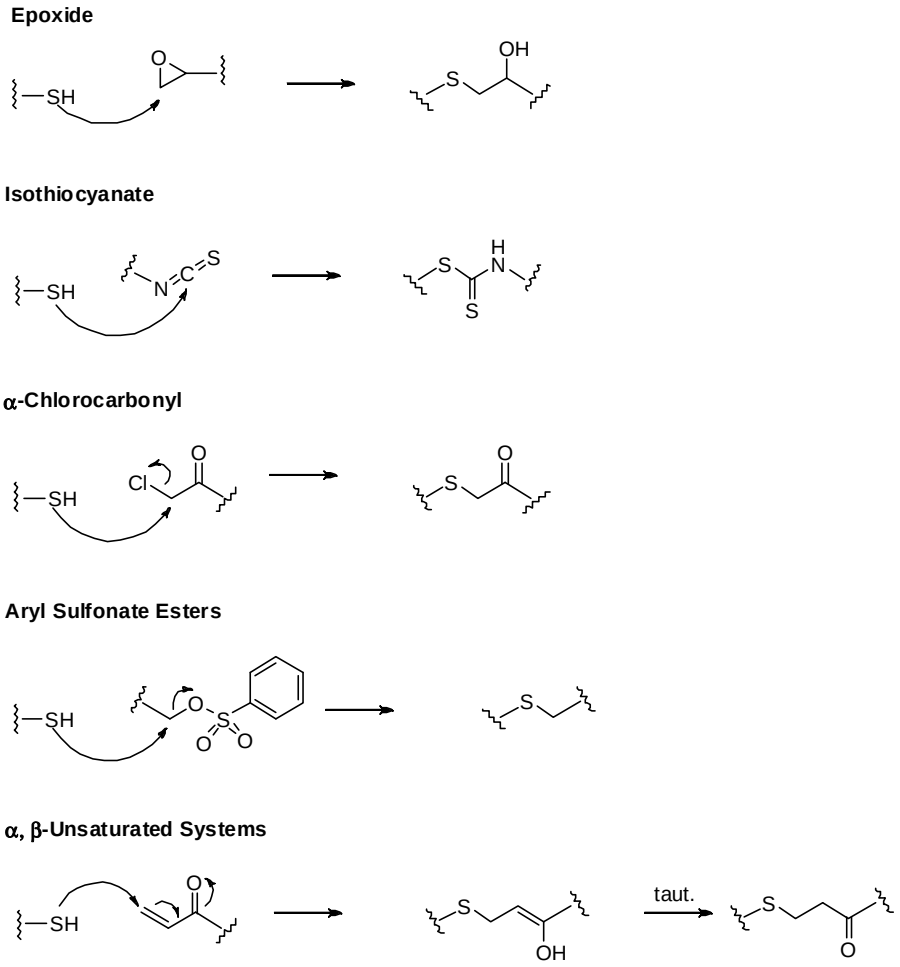



**Figure 3. Commonly used functional groups for the covalent modification of nucleophilic residues in proteins.**

In order to further probe the binding site of the 1180-series, analogues with strategic structural modifications based on those summarized in Figure 3 were planned for an experiment of this type. The Traynelis lab performed site directed mutagenesis on native GluN2D-containing NMDA receptors to incorporate a Cys-residue in predetermined sites. Synthesis of potentially reactive 1180-analogues was performed in order to fully test these mutants.

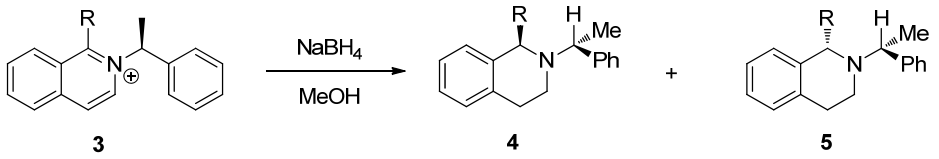
*2.2.8 Literature Precedent for Chiral Synthesis*

A number of strategies exist for the stereoselective synthesis of enantiomeric tetrahydroisoquinolines. A commonly used strategy to obtain a single enantiomer involves the use of chiral salts to selectively crystallize one enantiomer out of a racemic mixture. This requires the presence of a basic moiety, such as an amine, to co-crystallize with a chiral acid (or vice-versa) in order for the crystallization to occur. Often this route requires multiple crystallizations to resolve the two enantiomers fully. Tartaric acid and its analogues are among the most common chiral salts used for the resolution of racemic amines. Other chiral acids such as camphorsulfonic acid have also been used with success.[79]

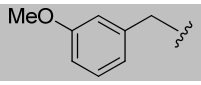
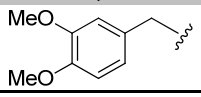
A number of stereoselective synthetic strategies have also been utilized to achieve chirally pure materials. These routes have an advantage in that no mass is lost due to the presence of fifty percent of the other enantiomer. For the synthesis of tetrahydroisoquinolines, an asymmetric reduction of the corresponding dihydroisoquinoline is often used to achieve a stereoselective compound. This route often requires the use of metals such as iridium[80,81], rhodium[82], or ruthenium[83,84] and a chiral ligand to direct the chirality of the hydrogen addition. From a drug development standpoint, this is undesirable due to FDA restrictions on heavy metal contaminants in administered drugs. In addition, these reagents tend to be costly and not amenable to the large scale synthesis required for production.

Other synthetic strategies involve the use of chiral directing groups. For example, in the course of the synthesis of (-)-argemonine, a model study was performed on a number of substituted tetrahydroisoquinolines (Table 3)[85]. Using a single enantiomer of methylbenzylamine as a directing group, the investigators achieved high yields and between 74-84% diasteromeric excess from the reduction of the iminium species.

**Table 3. Results of model study in the synthesis of chiral tetrahydroisoquinolines using methylbenzylamine as a directing group.**



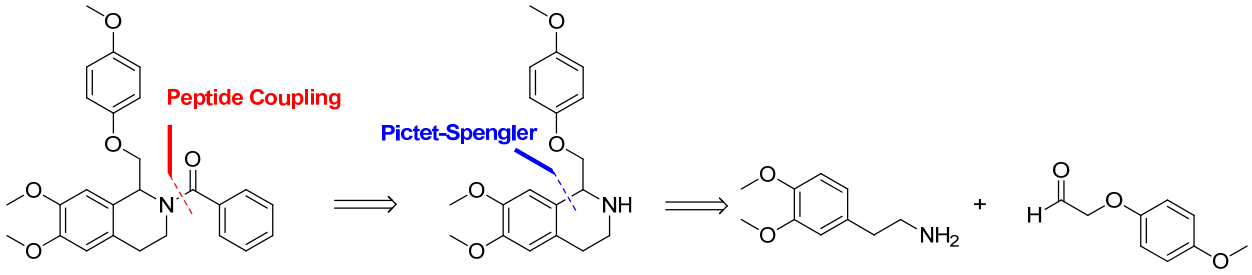

3 4 5

| R | Total Yield (4 + 5) | d.e. |
|---|---|---|
| Me | 77 | 74 |
| Ph | 97 | 74 |
|  | 95 | 82 |
|  | 92 | 84 |

## 2.3 SYNTHESIS OF 1180-SERIES ANALOGUES

### *2.3.1 Synthesis of tetrahydroisoquinoline analogues*

Retrosynthetic analysis of the 1180-series is shown in Scheme 1. The first disconnection was the amide bond linkage which could be formed using standard amide coupling or acylation conditions. The tetrahydroisoquinoline core (**6**) was envisioned to arise from the Pictet-Spengler reaction upon combination of the corresponding aldehyde (**8**) and primary amine (**7**).

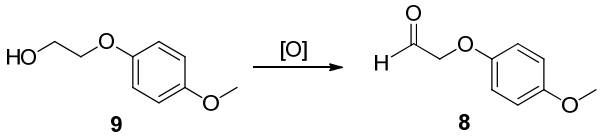



1180 6 7 8

**Scheme 1. Retrosynthetic analysis of 1180-series with Pictet-Spengler reaction employed as key step**

Although many phenethylamine building blocks are readily available, the phenoxyacetylaldehydes (**8**) required for formation of the imine are not available commercially. Starting from the commercially available alcohol (**9**), two different oxidation conditions were attempted to form the desired aldehyde (Table 4). Unfortunately, although consumption of the starting material occurred, none of the desired product was observed.

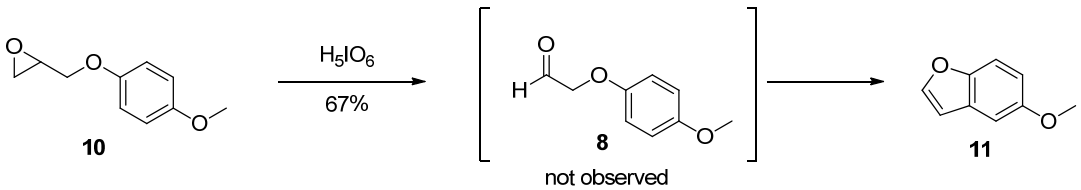
**Table 4. Oxidation conditions attempted for the conversion of the primary alcohol to the desired aldehyde building block**




**9** **8**

| Oxidation Conditions | Solvent | Time | Yield |
|---|---|---|---|
| PCC | DCM | 18 hr | 0% |
| TPAP, NMO | DCM | 18 hr | 0% |

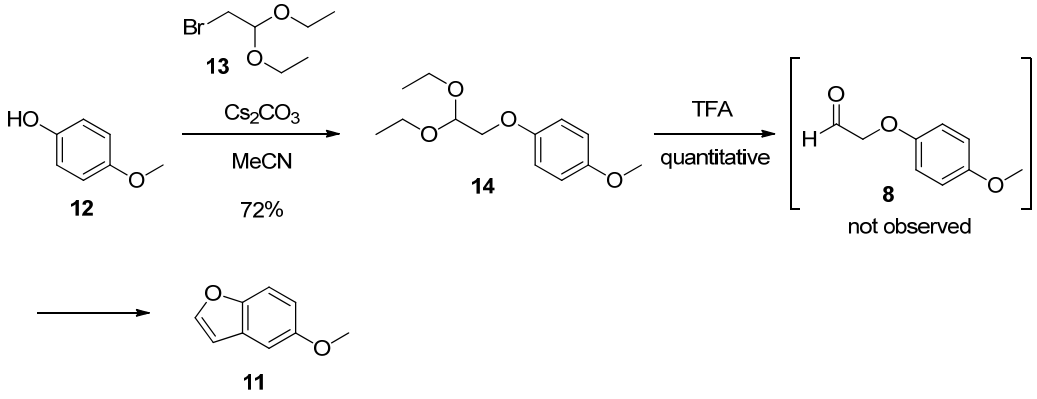
A new route was chosen in an attempt to synthesize the desired aldehyde from alternate starting materials. The commercially available epoxide (**10**) was treated with periodic acid following the Feiser procedure for epoxide cleavage. Although the starting material was consumed, the aldehyde (**8**) was not isolated. Instead, the corresponding benzofuran (**11**) was isolated in 67% yield (Scheme 2).




**10** **8** not observed **11**

**Scheme 2. Cleavage of the epoxide to the benzofuran instead of the desired aldehyde building block**

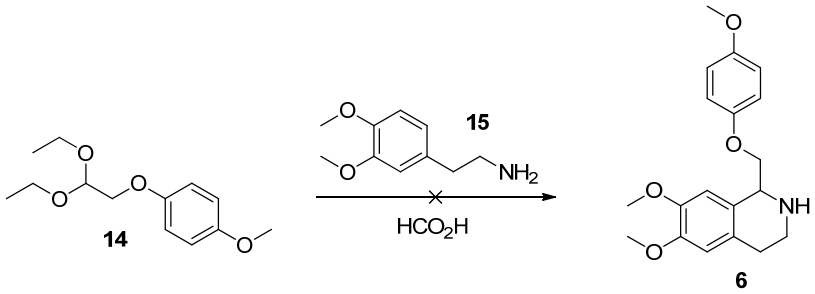
As an alternative route to the desired aldehyde, a diethylacetal was installed as a masked aldehyde. The milder conditions used in the deprotection of the acetal were thought to allow a successful transformation to the desired aldehyde that was impossible with the harsh conditions attempted previously. Alkylation of 4-methoxyphenol (**12**) with 2-bromo-1,1-diethoxyethane (**13**) was achieved in good yields to afford the masked aldehyde (**14**). Unfortunately, upon treatment with acidic conditions the desired aldehyde (**8**) was again not observed and instead the corresponding benzofuran (**11**) was isolated in quantitative yields (Scheme 3).




**Scheme 3. Use of a masked aldehyde to attempt the formation of desired aldehyde**

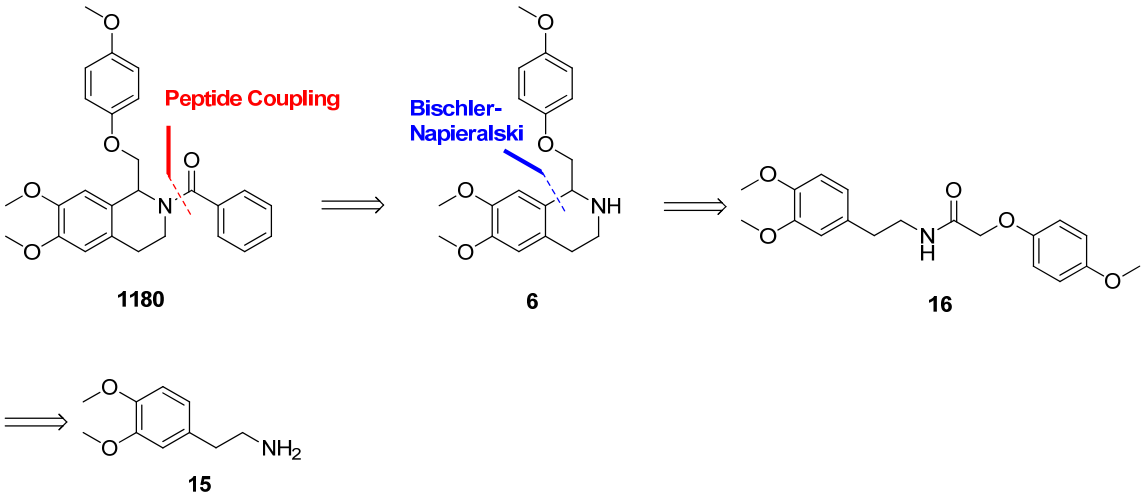
The intramolecular cyclization onto the newly synthesized aldehyde was facilitated by the electron-rich nature of the aromatic system. In order to prevent the cyclization to the benzofuran, a one-pot procedure was attempted with deprotection of the diethyl acetal (**14**) and subsequent formation of the imine with 3,4-dimethoxyphenethylamine (**6**) for the Pictet-

Spengler cyclization to the tetrahydroisoquinoline (**6**, Scheme 4). Unfortunately, this method also proved unsuccessful as a complex mixture was observed.



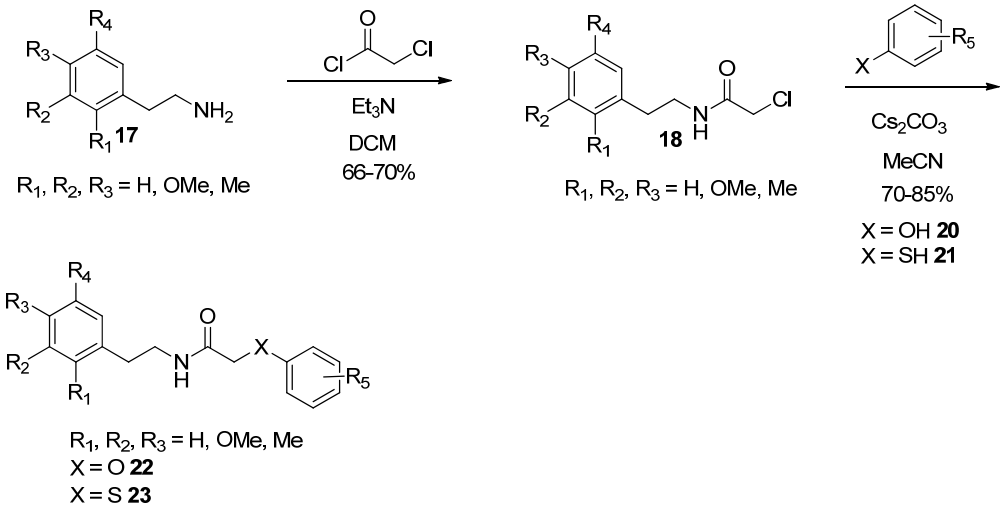

**Scheme 4. Attempted one-pot Pictet-Spengler from masked aldehyde**

After several unsuccessful attempts to make the aldehyde building block, an alternative retrosynthetic analysis was performed (Scheme 5). In this route, the tetrahydroisoquinoline core (**6**) would be achieved in two steps from a Bischler-Napieralski cyclization and reduction sequence. The acyclic amide precursor (**16**) could be synthesized in just a few steps from a commercially available phenethylamine (**15**). Although this route increased the total step count with the addition of the required reduction after the cyclization, it avoided the need for the unstable phenoxyacetylaldehydes required for the Pictet-Spenger reaction.

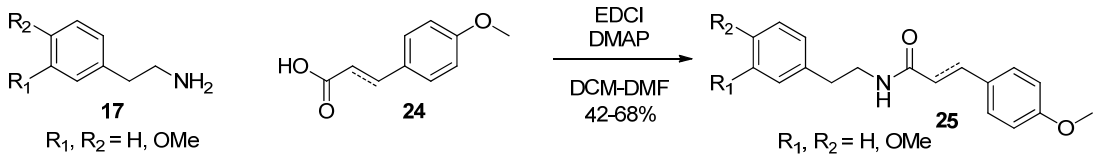



**Scheme 5. Retrosynthetic analysis incorporating a Bischler-Napieralski cyclization as the key step**

This route required the synthesis of the acyclic amide (**16**) which was performed starting from appropriately substituted phenethylamines. The synthetic route to obtain these amide-based intermediates was highly dependent upon the identity of the linker. For the ether and thioether linkage, commercially available phenethylamines (**17**) with the desired substitution pattern were acylated with chloroacetyl chloride to afford the α-chloro amides (**18**) in good yields (Scheme 6). The chloride was then displaced in a substitution reaction with an appropriately substituted phenol (**20**) or thiophenol (**21**) to afford the acyclic amides with the ether (**22**) and thioether (**23**) linkages, respectively. For both the unsaturated and saturated carbon-based linkers, the amide linkage was formed from a standard EDCI peptide coupling reaction between the commercially available phenethylamines (**24**) and carboxylic acids (**25**)(Scheme 7). The starting materials and intermediates described by the generic structures are detailed in Tables 5-12.

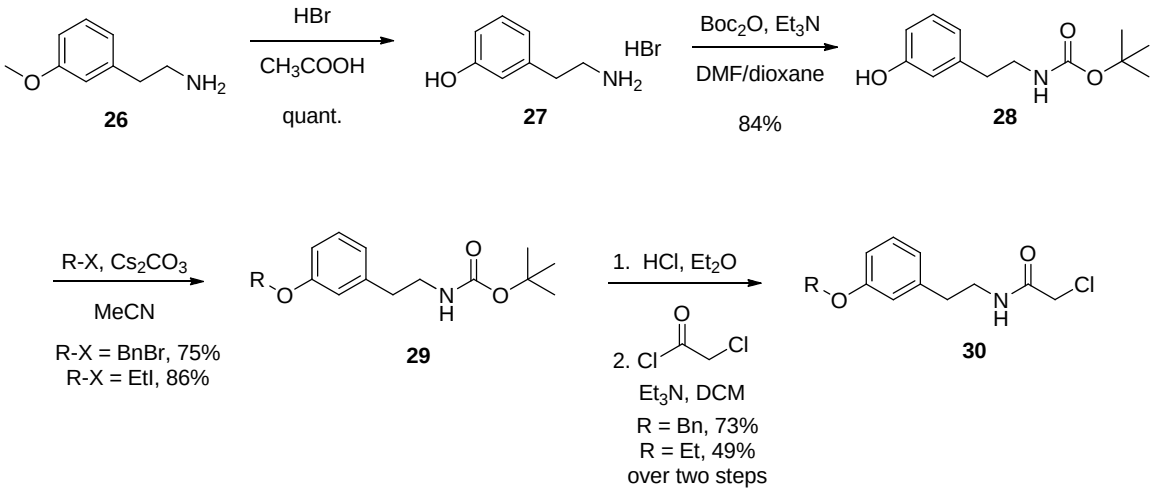



**Scheme 6. Generalized synthesis of amide with an ether (22) or thioether (23) linker**



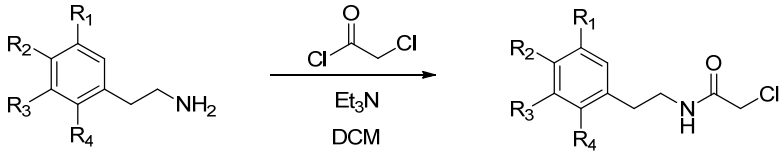

**Scheme 7. Generalized synthesis of amide 25 with a saturated or unsaturated carbon linker**

For phenethylamines that were not commercially available, the synthesis was performed following the synthesis in Scheme 8.




**Scheme 8. Synthesis of phenethylamines**

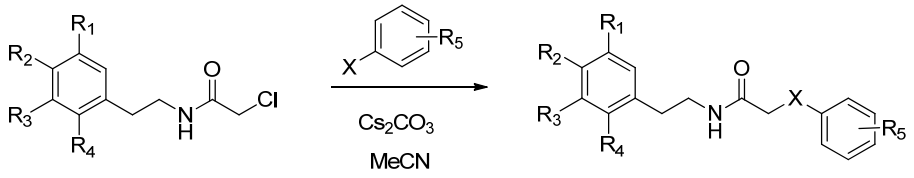
**Table 5. Summary of phenethylamines subjected to acylation conditions**




| Starting Material ID | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Product ID |
|---|---|---|---|---|---|
| **17a** | H | H | O*i*Pr | H | **18a** |
| **15** | H | OMe | OMe | H | **18b** |
| **17b** | H | O-$CH_2$-O | | H | **18c** |
| **17c** | OMe | H | OMe | H | **18d** |
| **26** | H | H | OMe | H | **18e** |
| **17d** | H | Me | Me | H | **18f** |
| **17e** | H | H | Me | H | **18g** |
| **17f** | H | H | OMe | OMe | **18h** |

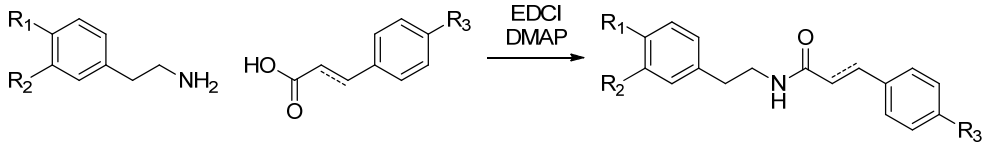
The commercially available 3-methoxyphenethylamine (**26**) was treated with refluxing HBr and acetic acid to form the phenolic compound, **27**. The resulting salt was free based and protected with Boc-anhydride in a one pot procedure to afford the Boc-protected amine (**28**). The phenol (**28**) was alkylated with an appropriate alkyl halide to give the ether-containing compounds (**29**). Removal of the protecting group followed by acylation with 2-chloroacetyl chloride afforded the $\alpha$-chloro amide compounds (**30**)**.** These compounds were then subjected to the conditions shown in Scheme 6 to complete the synthesis.

**Table 6. Summary of α-chloroamides subjected to alkylation conditions**



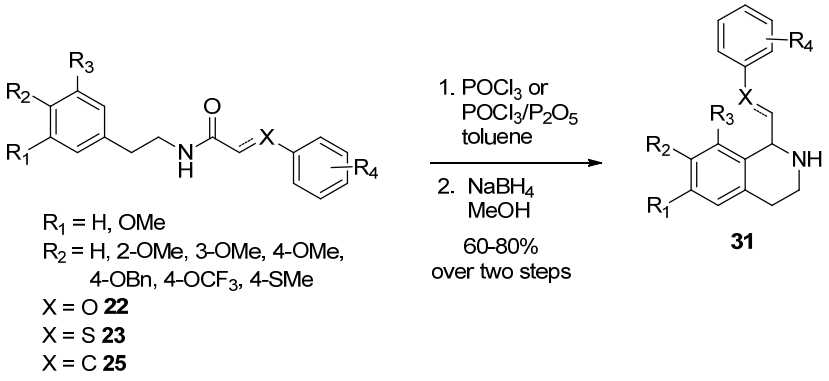

| Starting Material ID | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Product ID |
|---|---|---|---|---|---|---|---|
| **18a** | H | H | O*i*Pr | H | *p*-OMe | O | **22b** |
| **18b** | H | OMe | OMe | H | *p*-OMe | O | **16** |
| **18b** | H | OMe | OMe | H | H | O | **22d** |
| **18b** | H | OMe | OMe | H | *m*-OMe | O | **22e** |
| **18b** | H | OMe | OMe | H | *o*-OMe | O | **22f** |
| **18b** | H | OMe | OMe | H | *p*-OBn | O | **22l** |
| **18b** | H | OMe | OMe | H | *p*-SMe | O | **22m** |
| **18b** | H | OMe | OMe | H | *p*-$OCF_3$ | O | **22n** |
| **18b** | H | OMe | OMe | H | *p*-OEt | O | **22o** |
| **18b** | H | OMe | OMe | H | *p*-OMe | S | **23a** |
| **18c** | H | O-$CH_2$-O | | H | *p*-OMe | O | **22g** |
| **18d** | OMe | H | OMe | H | *p*-OMe | O | **22h** |
| **18e** | H | H | OMe | H | *p*-OMe | O | **22i** |
| **18f** | H | Me | Me | H | *p*-OMe | O | **22j** |
| **18g** | H | H | Me | H | *p*-OMe | O | **22k** |
| **18h** | H | H | OMe | OMe | *p*-OMe | O | **22p** |
| **30a** | H | H | OBn | H | *p*-OMe | O | **22a** |
| **30b** | H | H | OEt | H | *p*-OMe | O | **22c** |

**Table 7. Summary of phenethylamines subjected to EDCI coupling conditions**



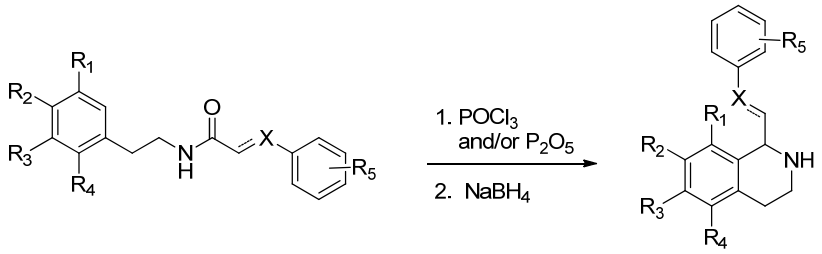

| Amine ID | Acid ID | Double Bond? (Y/N) | $R_1$ | $R_2$ | $R_3$ | Product ID |
|---|---|---|---|---|---|---|
| **15** | **24a** | N | OMe | OMe | OMe | **25a** |
| **15** | **24b** | Y | OMe | OMe | OMe | **25b** |
| **26** | **24b** | Y | H | OMe | OMe | **25c** |
| **15** | **24c** | N | OMe | OMe | H | **25d** |

All of the acyclic amide intermediates (**22**, **23**, and **25**) were then subjected to Bischler-Napieralski conditions using phosphorus oxychloride or phosphorus pentoxide or a mixture of both. These conditions afforded the dihydroisoquinoline which was subsequently reduced with sodium borohydride to give the tetrahydroisoquinoline (**31**) core (Scheme 9). The final step for amide-containing analogues was either a standard EDCI coupling reaction or an acid chloride acylation to afford the final products (**1180-X**) (Scheme 10). Alternatively, the tetrahydroisoquinoline core (**31**) was alkyated with benzyl bromide to afford the benzyl analogue **1180-17**. From **1180-22**, the benzyl group was removed using methanesulfonic acid to afford the phenolic compound **1180-65** (Scheme 11).

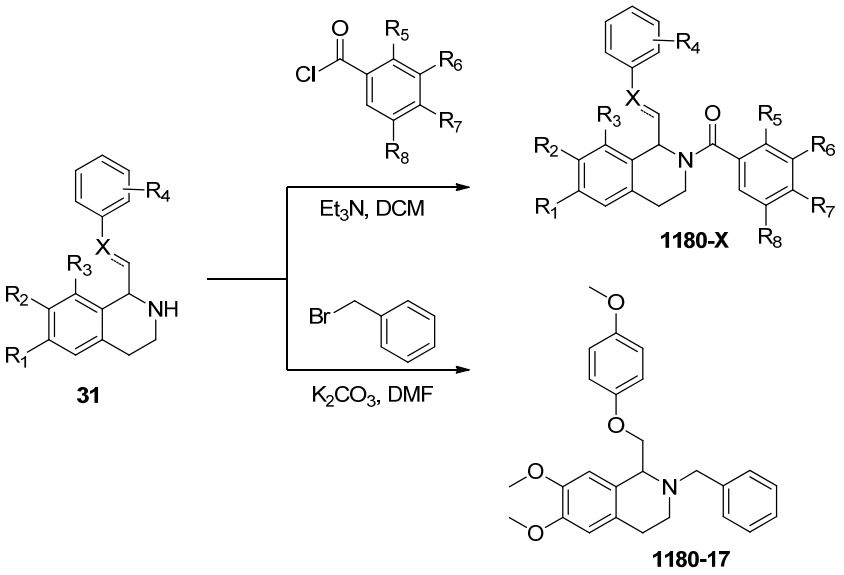



**Scheme 9. Synthesis of the tetrahydroisoquinoline core**

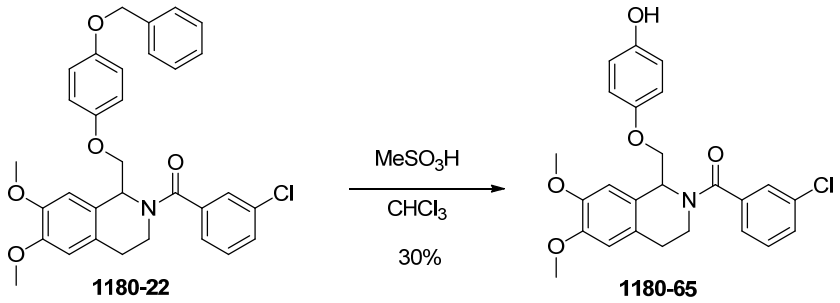
**Table 8. Summary of acyclic amides subjected to Bischler-Napieralski conditions to form the tetrahydroisoquinoline core**




| Starting Material ID | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Double bond? (Y/N) | Product ID |
|---|---|---|---|---|---|---|---|---|
| **22a** | H | H | OMe | H | *p*-OMe | O | N | **31a** |
| **22b** | H | H | O*i*Pr | H | *p*-OMe | O | N | **31b** |
| **22c** | H | H | OEt | H | *p*-OMe | O | N | **31c** |
| **16** | H | OMe | OMe | H | *p*-OMe | O | N | **6** |
| **22d** | H | OMe | OMe | H | H | O | N | **31d** |
| **22e** | H | OMe | OMe | H | *m*-OMe | O | N | **31e** |
| **22f** | H | OMe | OMe | H | *o*-OMe | O | N | **31f** |
| **22g** | H | O-$CH_2$-O | | H | *p*-OMe | O | N | **31g** |
| **22h** | OMe | H | OMe | H | *p*-OMe | O | N | **31h** |
| **22i** | H | H | OMe | H | *p*-OMe | O | N | **31i** |
| **22j** | H | Me | Me | H | *p*-OMe | O | N | **31j** |
| **22k** | H | H | Me | H | *p*-OMe | O | N | **31k** |
| **22l** | H | OMe | OMe | H | *p*-OBn | O | N | **31l** |
| **22m** | H | OMe | OMe | H | *p*-SMe | O | N | **31m** |
| **22n** | H | OMe | OMe | H | *p*-$OCF_3$ | O | N | **31n** |
| **22o** | H | OMe | OMe | H | *p*-OEt | O | N | **31o** |
| **22p** | H | H | OMe | OMe | *p*-OMe | O | N | **31p** |
| **23a** | H | OMe | OMe | H | *p*-OMe | S | N | **31q** |
| **25a** | H | OMe | OMe | H | *p*-OMe | C | N | **31r** |
| **25b** | H | OMe | OMe | H | *p*-OMe | C | Y | **31s** |
| **25d** | H | OMe | OMe | H | H | C | N | **31t** |



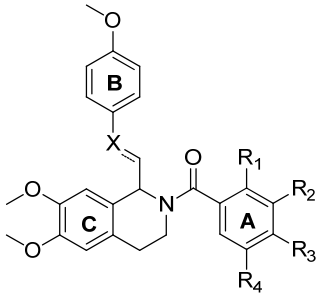

**Scheme 10. Final step in the synthesis of 1180-series analogues**




**Scheme 11. Formation of 1180-65 from a debenzylation of 1180-22**

Based on the original screening hit, a number of compounds were synthesized keeping the dimethoxy moiety on the C-ring and the *para*-methoxy moiety on the B-ring constant (Table 9). These compounds were varied in the type, placement and number of substituents on the A-ring or in the identity of the linker between the tetrahydroisoquinoline core and the B-ring. The A-ring and linker was also completely removed and replaced with alternate moieties which are summarized in Table 10.

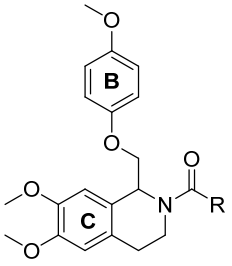
**Table 9. Summary of 1180-series analogues with modified A-ring substitution**




**1180-X**

| 1180-X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Double bond? (Y/N) |
|---|---|---|---|---|---|---|
| **1390** | H | Cl | H | H | O | N |
| **1180-11** | H | I | H | H | O | N |
| **1180-16** | H | $NO_2$ | H | H | O | N |
| **1180-3** | H | OH | H | H | O | N |
| **1180-18** | H | Cl | F | H | O | N |
| **1180-10** | H | Cl | Cl | H | O | N |
| **1180-12** | Cl | Cl | H | H | O | N |
| **1180-34** | H | Cl | H | Cl | O | N |
| **1180-36** | H | $CH_2Cl$ | H | H | O | N |
| **1180-52** | H | $CHCl_2$ | H | H | O | N |
| **1180-37** | H | CN | H | H | O | N |
| **1180-57** | H | Ph | H | H | O | N |
| **1180-58** | H | C(O)Me | H | H | O | N |
| **1180-66** | H | $C(O)CH_2Cl$ | H | H | O | N |
| **1180-51** | H | H | H | H | S | N |
| **1180-42** | H | H | H | H | C | N |
| **1180-40** | H | Cl | H | H | C | N |
| **1180-41** | H | Br | H | H | C | N |
| **1180-33** | H | H | H | H | C | Y |
| **1180-31** | H | Cl | H | H | C | Y |
| **1180-32** | H | Br | H | H | C | Y |

**Table 10. Summary of 1180-series analogues with modified A-ring**

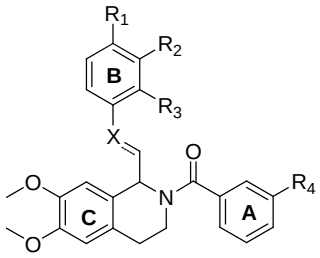



**1180-X**

| 1180-X | R |
|---|---|
| **1180-68** | $CH_2Cl$ |
| **1180-4** | 2-furan |
| **1180-5** | 5-isoxazole |
| **1180-35** | 2-naphthyl |
| **1180-23** | *N*-morpholine |
| **1180-24** | $CH_2$-*N*-morpholine |

After the ideal substitution pattern on the A-ring was identified, modifications were made to the B-ring substituent type and placement while keeping the dimethoxy moiety on the C-ring constant. For these compounds, the substituent identity and placement in the *meta*-position of the A-ring was strategic based on the results of biological data (Table 11). Finally, compounds were synthesized with changes to the substitution around the C-ring, keeping the substitution around the B-ring and A-ring constant based upon the results of biological evaluation. The compounds synthesized with modifications to the C-ring are summarized in Table 12.

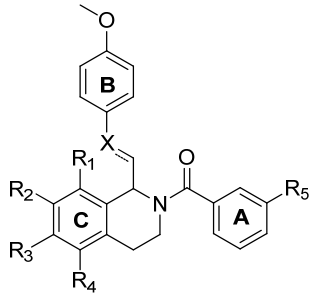
**Table 11. Summary of 1180-series analogues with modified substitution around B-ring**




**1180-X**

| 1180-X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | X | Double Bond? (Y/N) |
|---|---|---|---|---|---|---|
| **1180-2** | H | H | H | H | O | N |
| **1180-7** | H | OMe | H | H | O | N |
| **1180-6** | H | OMe | H | Cl | O | N |
| **1180-8** | H | H | OMe | Cl | O | N |
| **1180-22** | OBn | H | H | Cl | O | N |
| **1180-65** | OH | H | H | Cl | O | N |
| **1180-14** | SMe | H | H | H | O | N |
| **1180-13** | SMe | H | H | Cl | O | N |
| **1180-9** | $OCF_3$ | H | H | Cl | O | N |
| **1180-53** | OEt | H | H | Cl | O | N |
| **1180-54** | OEt | H | H | Br | O | N |
| **1180-1** | H | H | H | F | C | N |

**Table 12. Summary of 1180-series analogues with modifications to C-ring substitution**

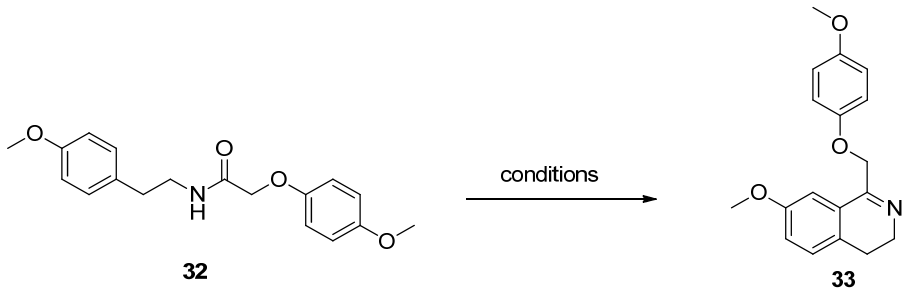



**1180-X**

| 1180-X | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | X | Double Bond? (Y/N) |
|---|---|---|---|---|---|---|---|
| **1180-99** | H | H | OBn | H | H | O | N |
| **1180-97** | H | H | OBn | H | Cl | O | N |
| **1180-98** | H | H | OBn | H | Br | O | N |
| **1180-55** | H | H | O*i*Pr | H | Cl | O | N |
| **1180-93** | H | H | OEt | H | Cl | O | N |
| **1180-94** | H | H | OEt | H | Br | O | N |
| **1180-95** | H | H | OEt | H | H | O | N |
| **1180-96** | H | H | OEt | H | $CF_3$ | O | N |
| **1180-47** | H | O-$CH_2$-O | | H | H | O | N |
| **1180-25** | H | O-$CH_2$-O | | H | Cl | O | N |
| **1180-48** | H | O-$CH_2$-O | | H | Br | O | N |
| **1180-19** | OMe | H | OMe | H | H | O | N |
| **1180-20** | OMe | H | OMe | H | Cl | O | N |
| **1180-21** | OMe | H | OMe | H | Br | O | N |
| **1180-46** | H | H | OMe | H | H | O | N |
| **1180-26** | H | H | OMe | H | Cl | O | N |
| **1180-27** | H | H | OMe | H | Br | O | N |
| **1180-67** | H | H | OMe | H | C(O)Me | O | N |
| **1180-38** | H | H | OMe | H | Cl | C | Y |
| **1180-39** | H | H | OMe | H | Br | C | Y |
| **1180-44** | H | Me | Me | H | Cl | O | N |
| **1180-45** | H | Me | Me | H | Br | O | N |
| **1180-69** | H | H | Me | H | H | O | N |
| **1180-70** | H | H | Me | H | Cl | O | N |
| **1180-71** | H | H | Me | H | Br | O | N |
| **1180-49** | H | H | OMe | OMe | Cl | O | N |
| **1180-50** | H | H | OMe | OMe | Br | O | N |

Multiple strategies were attempted to afford compounds with a single methoxy on the C-ring as in **33** (Table 13). Unfortunately, although the ring is electron-rich and the Bischler-Napieralski reaction typically favors cyclization onto an electron-rich ring, the 4-methoxy substituent (**32**) does not contribute to the cyclization due to the unfavorable electronics. Even at high temperatures or with phosphorus pentoxide added as a dessicant, the energy barrier could not be overcome.

**Table 13. Conditions attempted for the Bischler-Napieralski onto the 4-methoxy substituted ring**

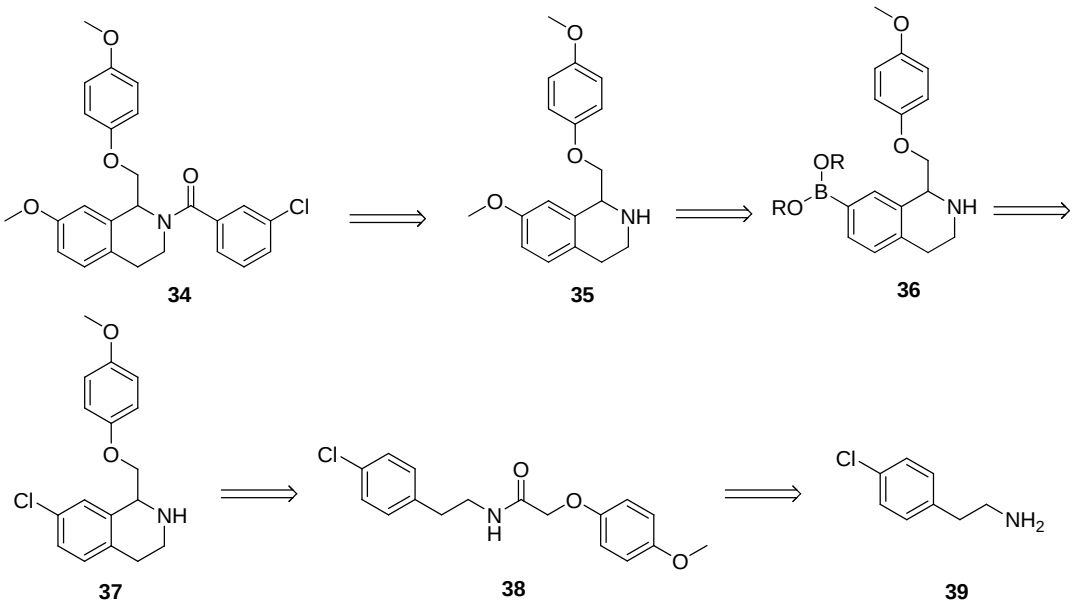



**32** **33**

| Reagents | Equivalents | Solvent | Temperature | Time | Yield |
|---|---|---|---|---|---|
| $POCl_3$ | 3.0 | toluene | Reflux | 2 hr | 0% |
| $POCl_3$ | 3.0 | toluene | Reflux | 24 hr | 0% |
| $POCl_3$ | 2.5 | MeCN | Reflux | 24 hr | 0% |
| $POCl_3/P_2O_5$ | 3.0/2.0 | toluene | Reflux | 2 hr | 0% |

Due to the difficulties encountered during the attempted synthesis of compounds with a single methoxy in the *para*-position on the C-ring, an alternative method was attempted for synthesis of compounds that would introduce this functionality later in the synthesis. The retrosynthesis detailing this route is shown in Scheme 12. The final compound (**34**) could be synthesized as done previously from the acylation of the corresponding tetrahydroisoquinoline (**35**). The methoxy substituent was envisioned to come from a coupling reaction or from cleavage of the corresponding boronic acid or ester (**36**) which could be synthesized from the

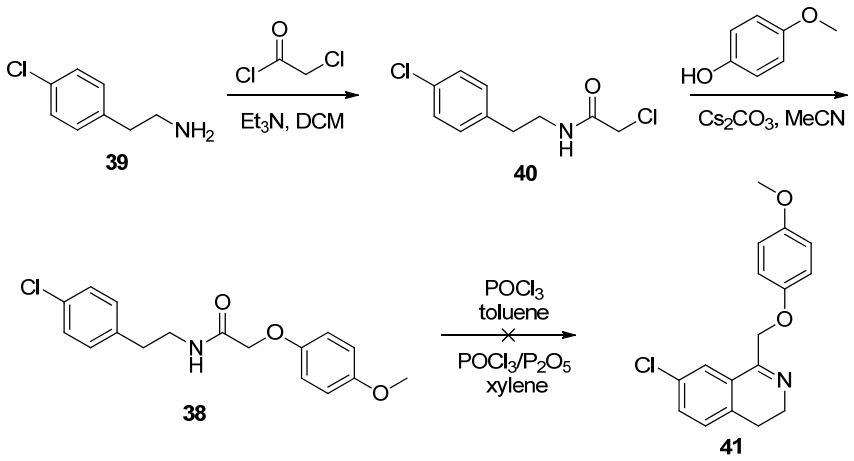
corresponding aryl chloride (**37**). The tetrahydroisoquinoline core was thought to arise from the Bischler-Napieralski on the acyclic amide (**38**) as had been done in the synthesis of previous analogues. Although the deactivating nature of the chlorine would likely disfavor cyclization, literature precedent exists for the successful Bischler-Napieralski cyclization onto a ring with the same substitution.[86] Based on this precedent, the acyclic amide (**38**) could be synthesized in a few steps from the commercially available 4-chlorophenethylamine (**39**).




**Scheme 12. Retrosynthesis of 1180-analogue with single methoxy on C-ring**

Commercially available 4-chlorophenethylamine (**39**) was acylated with chloroacetyl chloride to give the α-chloroamide **40**, followed by displacement of the chlorine with 4-methoxyphenol. The amide (**38**) was then subjected to Bischler-Napieralski conditions using a mixture of phosphorus oxychloride and phosphorous pentoxide in refluxing xylene or phosphorus oxychloride on its own in refluxing toluene (Scheme 13). Unfortunately, neither of these conditions was successful in performing the desired transformation. The deactivating

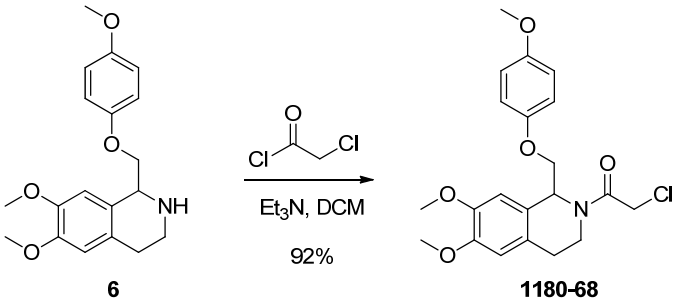
nature of the chlorine decreases the nucleophilicity of the ring and as a result does not allow the cyclization to occur.




**Scheme 13. Attempted Bischler-Napieralski onto chlorine-substituted aromatic ring**

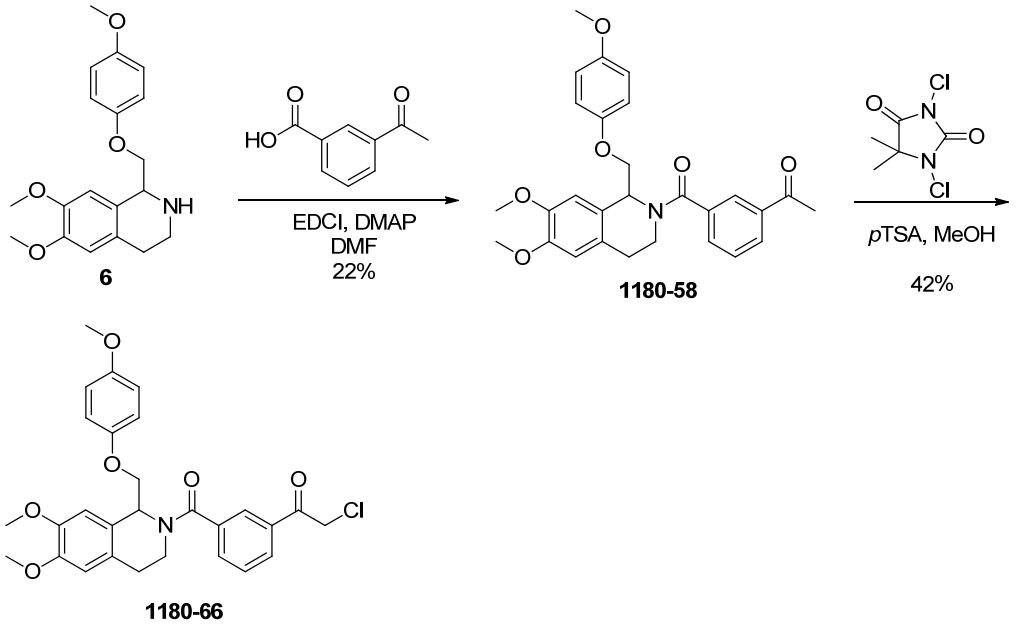
*2.3.2 Synthesis of potential Cysteine-reactive analogues*

From the literature on commonly utilized reactive functionality, a few compounds were selected to be synthesized for biological evaluation with the Cys-mutant GluN2D NMDA receptors (*Section 2.2.7*). The first analogue chosen for synthesis and further testing was **1180-68**. Synthesis of this compound proceeded as in the previous section (*2.3.1*) with a Bischler-Napieralski reaction and subsequent reduction employed for the construction of the tetrahydroisoquinoline core (Scheme 9). The racemic tetrahydroisoquinoline (**6**) was then acylated with chloroacetyl chloride to afford **1180-68** containing an $\alpha$-chloroketone as the reactive moiety (Scheme 14).




**Scheme 14. Synthesis of potential Cys-reactive analogue 1180-68**

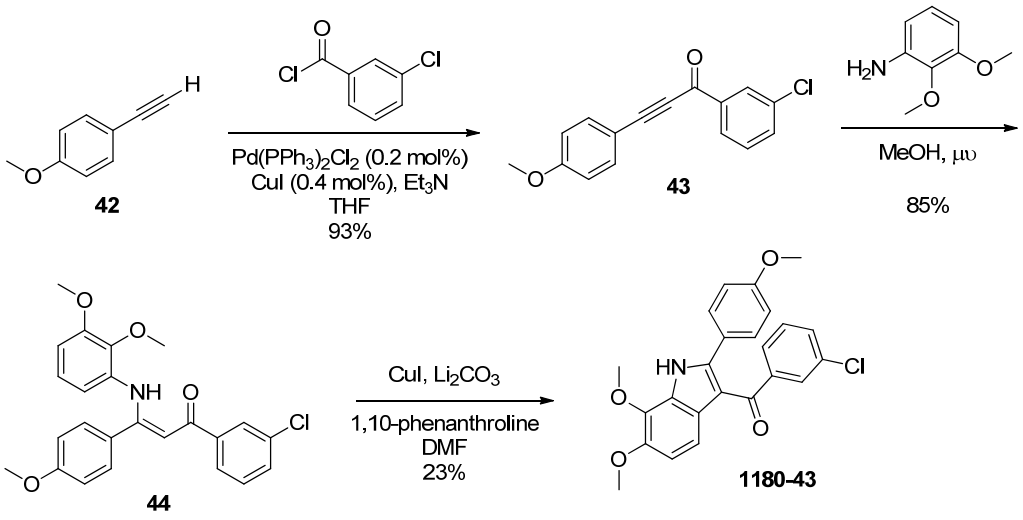
The second analogue chosen for synthesis and testing against the Cys-mutants was **1180-66**. The tetrahydroisoquinoline core (**6**) of this compound was synthesized as described previously utilizing a Bischler-Napieralski reaction as the key step. The amide bond was formed via standard EDCI peptide coupling conditions with 3-acetylbenzoic acid to afford **1180-58**. Chlorination of this compound in the α-position was performed using the N,N'-dichlorohydantoin reagent 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione[87] which afforded the desired analogue **1180-66** (Scheme 15).




**Scheme 15. Synthesis of potential Cys-reactive analogue, 1180-66**

*2.3.3 Synthesis of indole-containing compound*

The indole analogue was synthesized according to Scheme 16. In a modified Sonogashira reaction[88], the commercially available aryl alkyne (**42**) was reacted with 3-chlorobenzoyl chloride to form the ynone (**43**). Under microwave irradiation, the ynone (**43**) was treated with 2,3-dimethoxyaniline to form the enamine (**44)**. The yield of this enamine intermediate was based upon LCMS and NMR because it was afforded as a 3:1 mixture of product to starting material that was inseparable by column chromatography or crystallization. Using copper catalyzed C-H functionalization, the enamine (**44**) was cyclized to give the final indole compound (**1180-43**) in low yields.[89]

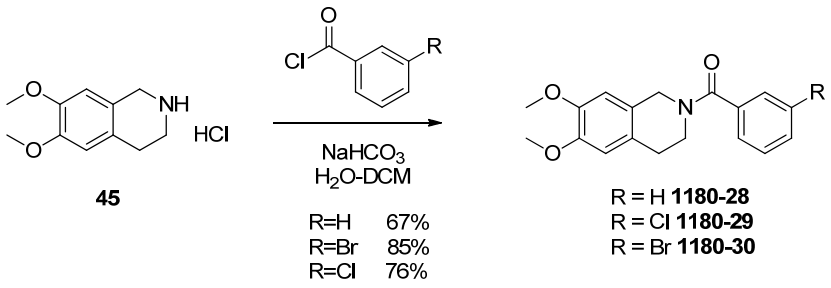



**Scheme 16. Synthesis of indole-containing analogue of 1180-series**

*2.3.4 Synthesis of the enantiomers of 1390*

Since the purchased compounds were tested as the racemic mixture, it was necessary to test whether the enantiomers had different degrees of potency. Before synthesizing the enantiomers individually, modifications were made to the compounds to test whether the

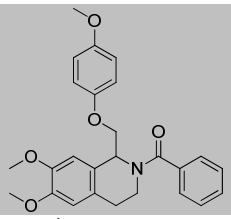
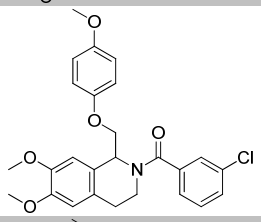
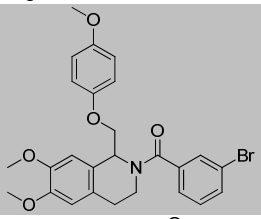
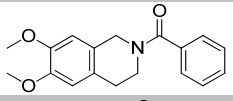
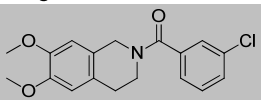
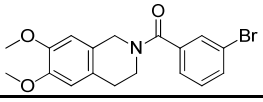
portion of the molecule attached at the stereocenter was even required for activity. In order to do this, three compounds were synthesized to compare to the commercially available analogues **1180**, **1390**, and **1391**.




**Scheme 17. Synthesis of compounds without the B-ring and linker B**

Commercially available 6,7-dimethoxytetrahydroisoquinoline hydrochloride (**45**) was free-based and acylated with an appropriately substituted benzoyl chloride in a one-pot procedure to form the final compounds, **1180-28**, **1180-29**, **1180-30** (Scheme 17). All three compounds (**1180-28**, **1180-29**, **1180-30**) were inactive against all recombinant NMDA receptor subunits *in vitro* (Table 14). At 100 μM, **1180-28**, **1180-29**, and **1180-30** showed slight inhibition at all four subunits (GluN2A-D) in the order **1180-30** > **1180-29** > **1180-28**. Since the compounds without the B-ring and linker B were not active, this suggests that this portion of the compound is important for activity. Since linker B is attached to the tetrahydroisoquinoline core at the stereocenter, this increased the possibility that the individual enantiomers would result in differential activity.

**Table 14. Comparison of biological activity between 1180-series compounds with and without B ring and linker B**

| Compound ID | Structure | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %) | |
|---|---|---|---|---|---|
| | | GluN2C | GluN2D | GluN2C | GluN2D |
| **1180** |  | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** |  | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1391** |  | 183 ± 11 | 178 ± 6.6 | 0.9 (195%) | 2.2 (188%) |
| **1180-28** |  | 95 ± 1.6 | 96 ± 2.1 | -- | -- |
| **1180-29** |  | 99 ± 1.8 | 98 ± 3.9 | -- | -- |
| **1180-30** |  | 85 ± 2.7 | 89 ± 4.9 | -- | -- |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No significant effect was observed at GluN2A- or GluN2B-containing receptors (data not shown).

The enantiomers of 1390 were separated by H. Lundbeck A/S using supercritical fluid chromatography (SFC). Using an analytical chiral HPLC column, the racemic mixture was separated into two peaks showing a 50:50 mixture of the two enantiomers is present in the

racemic mixture. Both of these enantiomers were evaluated by two-electrode voltage clamp analysis in *Xenopus* oocytes. The results are shown in Table 15 and clearly show activity for one enantiomer and little to no activity for the other enantiomer.

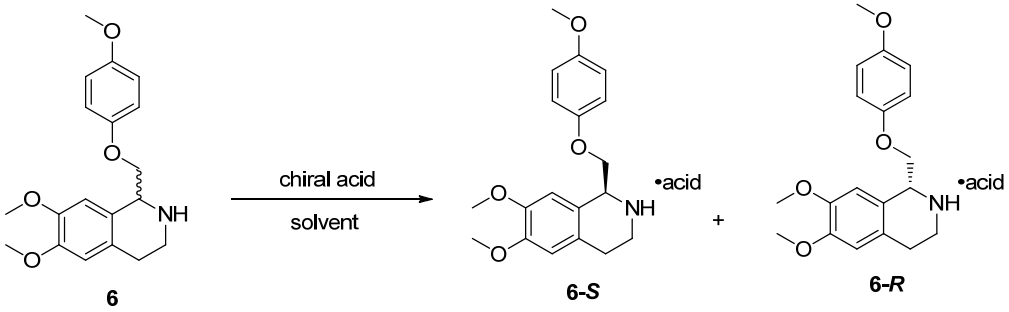
**Table 15. HPLC and biological data from enantiomers of 1390 as separated by supercritical fluid chromatography (SFC)**

| Peak | Retention Time[b] | $I_{10\mu M}/I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (max potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|
| | | GluN2C | GluN2D | GluN2C | GluN2D |
| **1** | 8.080 min | 113 ± 4.2 | 105 ± 1.0 | 9.5 (335%) | 6.1 (243%) |
| **2** | 9.138 min | 158 ± 7.3 | 148 ± 10 | -- | -- |

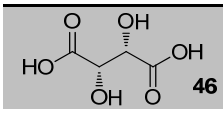
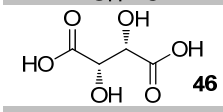
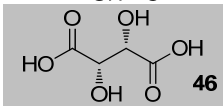
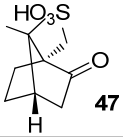
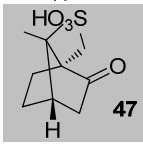
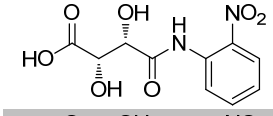
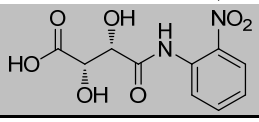
[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A or GluN2B receptors.
[b] Retention time was obtained on an Agilent HPLC using an OD-RH column. Mobile phase was 75% isocratic MeCN with 0.1% formic acid over 20 minutes.

In order to determine the stereochemical configuration of each of the enantiomers of 1390, the precursor (**6**) was synthesized in a gram quantity in order to attempt a chiral resolution with a chiral acid. (*S*,*S*)-Tartaric acid (**46**) combined with the tetrahydroisoquinoline (**6**) did not afford any solid material. Camphorsulfonic acid (CSA, **47**) did afford some solid material but unfortunately did not resolve the enantiomers when used in a 1:1 ratio or in 1:0.5 ratio. Like CSA, (2*S,* 3*S*)-2'-nitrotartranilic acid (**48**) did not afford any resolution, although some solid was obtained (Table 16).

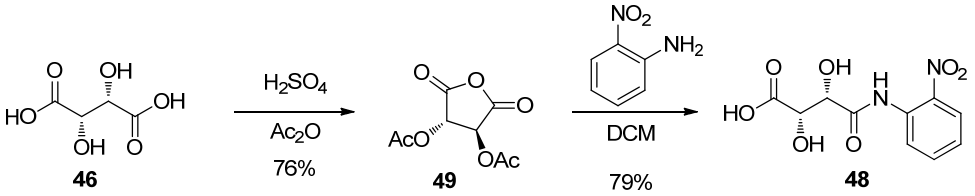
**Table 16. Attempted crystallization conditions for the resolution of the racemic tetrahydroisoquinoline intermediate**




**6** **6-*S*** **6-*R***

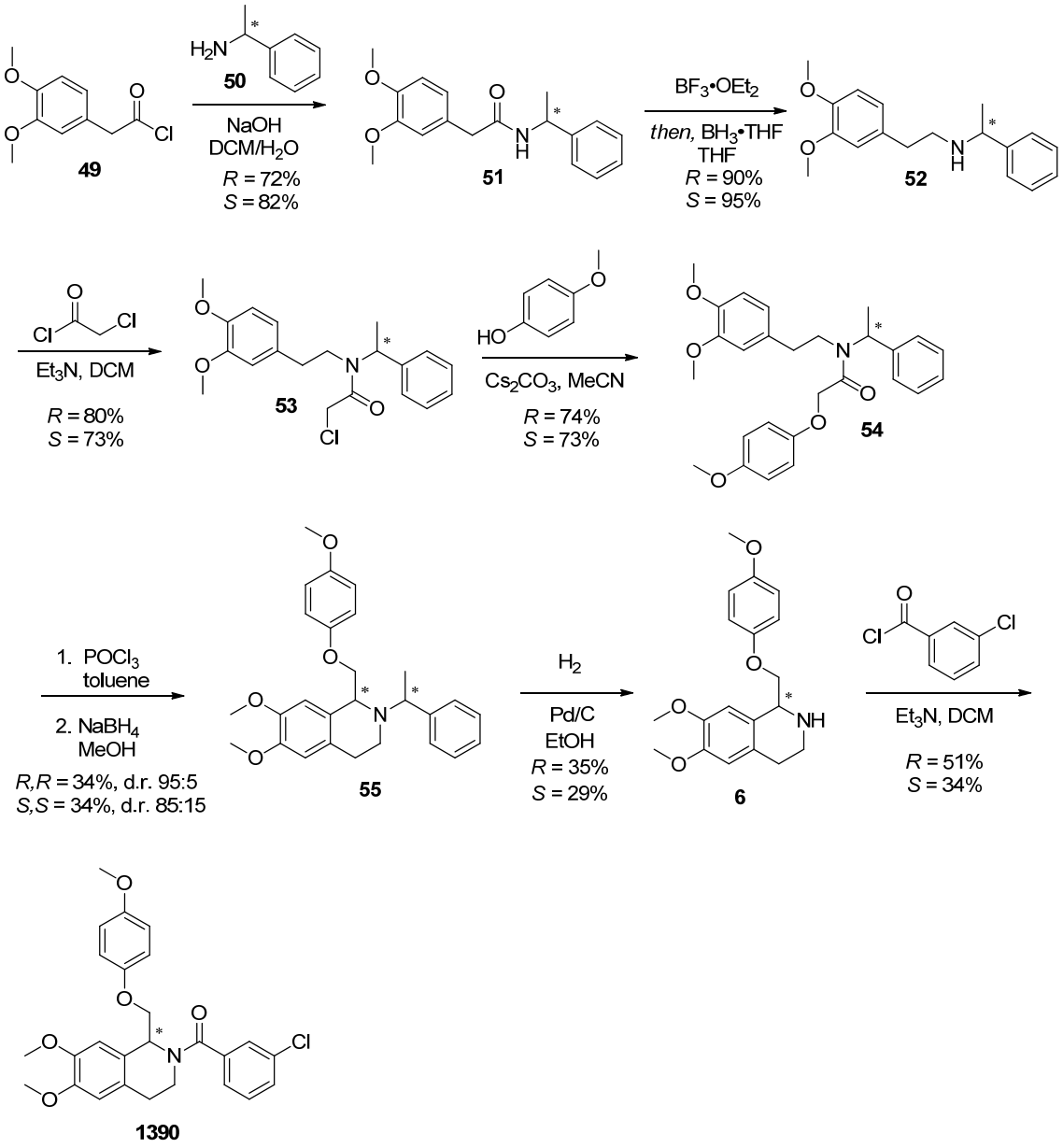
| Acid | Solvent | Equivalents | Results |
|---|---|---|---|
|  **46** | EtOH | 1.0 | Oiled out, no solid obtained |
|  **46** | DCM/ether | 1.0 | Oiled out, no solid obtained |
|  **46** | EtOH | 0.5 | Oiled out of solution, no solid obtained |
|  **47** | EtOH | 1.0 | Solid white powder, no resolution after 3 crystallizations |
|  **47** | EtOH | 0.5 | Solid white powder, no resolution after 2 crystallizations |
|  **48** | EtOH | 0.5 | Solid yellow powder obtained; no resolution after 2 crystallizations |
|  **48** | EtOH/$H_2O$ | 0.5 | Solid yellow powder obtained; no resolution after 2 crystallizations |

The (2*S,* 3*S*)-2'-nitrotartranilic acid (**48**) was not commercially available and was synthesized according to the procedure in Scheme 18.[90] Commercially available (*S*, *S*)-tartaric acid (**46**) was treated with sulfuric acid in acetic anhydride to form the succinic anhydride derivative (**49**). The succinic anhydride (**49**) was then opened with 2-nitroaniline to afford the nitrotartranilic acid **48**.



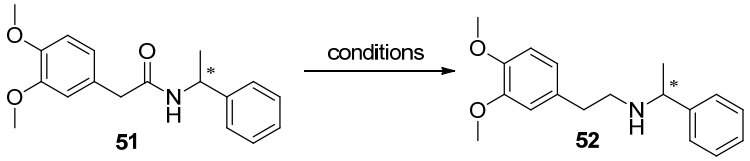

**Scheme 18. Synthesis of nitrotartanilic acid for chiral resolution**

Due to the lack of success with the chiral resolution, a new route was developed using chiral directing groups to synthesize the enantiomers individually. Both *R*-methylbenzylamine and *S*-methylbenzylamine were taken forward independently to synthesize each enantiomer (Scheme 19). The commercially available 3,4-dimethoxyphenylacetyl chloride (**49**) and the commercially available chiral methylbenzylamine (**50-*R*, 50-*S***) were combined to form the amide **51**.[91] Although structurally simple, amide **51** proved very difficult to reduce. A number of conditions were attempted and are summarized in Table 17. Literature precedent for the combination of boron trifluoride etherate with borane tetrahydrofuran complex was ultimately the successful conditions used for the transformation from **51** to **52**.[92]




**Scheme 19. Synthesis of enantiomers of 1390**

**Table 17. Conditions attempted for the reduction of amide 51.**




| Conditions | Additive | Equiv. | Time | Temperature | Yield |
|---|---|---|---|---|---|
| $BH_3$·DMS | None | 3.0 | 24 h | Reflux | 0 |
| $BH_3$·DMS | None | 3.0 | 48 h | Reflux | 0 |
| $LiAlH_4$ | None | 3.0 | 24 h | Ambient | 0 |
| $LiAlH_4$ | None | 3.0 | 24 h | Reflux | 0 |
| $BH_3$·THF | None | 3.0 | 24 h | Reflux | 0 |
| $BH_3$·THF | None | 3.0 | 5 d | Reflux | 30% |
| $BH_3$·THF | $BF_3$·$Et_2O$ | 2.0/1.3 | 2 h | Reflux | 95% |

The amine **52** was then acylated with 2-chloroacetyl chloride to afford the tertiary amide **53**. The chlorine was displaced with 4-methoxyphenol to afford **54**. The amide **54** was then subjected to Bischler-Napieralski conditions in phosphorous oxychloride followed by subsequent reduction of the iminium with sodium borohydride to afford the diastereomeric compound **55**. The diastereomeric ratio (dr) for this product was determined by HPLC. The chiral directing group was then removed with hydrogenolysis with palladium on carbon. The resulting tetrahydroisoquinoline (**6**) was acylated with 3-chlorobenzoyl chloride to afford the chiral final products **1390-*R*** and **1390-*S*** (Scheme 19). Although significant attempts were made to crystallize the individual enantiomers of **1390**, a crystal structure has not yet been obtained for these compounds. Enantiomeric excess of the final compounds was determined by HPLC. The stereochemistry was tentatively assigned based on the model shown in Figure 4. Based on

this model, greater than 99% *ee* was obtained for the synthesis of the *S*-enantiomer using this sequence. For the *R*-enantiomer, an 90% *ee* was obtained with a ratio of 95% *R* to 5% *S*.

Both synthesized enantiomers were then compared by HPLC analysis to the enantiomers separated by H. Lundbeck A/S and were subjected to biological testing. The results are shown in Table 18. The stereochemistry of the enantiomers separated by Lundbeck was assigned based on these results and the tentative assignment of the synthetic enantiomers.

**Table 18. HPLC and biological data for synthesized enantiomers of 1390**

| Peak | Retention Time[b] | $I_{10\mu M}/I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (max potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|
| | | GluN2C | GluN2D | GluN2C | GluN2D |
| ***S*** | 8.140 min | 208 ± 11 | 204 ± 6.0 | 8.1 (293%) | 10.6 (314%) |
| ***R*** | 9.170 min | 121 ± 6.0 | 116 ± 4.9 | No Effect | No Effect |
| ***R + S*** | -- | 197 ± 11 | 179 ± 6.9 | 6.5 (290%) | 7.2 (252%) |

[a] Fitted $EC_{50}$ values are shown to two significant digits; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% overall potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A or GluN2B receptors.
[b] Retention time was obtained on an Agilent HPLC using an OD-RH column. Mobile phase was 75% isocratic MeCN, 25% water with 0.1% formic acid over 20 minutes.

The stereochemical model used to assign the stereochemistry of the reduction of the iminium formed by the Bischler-Napieralksi cyclization is shown in Figure 4 using the *S*-enantiomer of compound **56** as an example. The presence of the iminium ion creates a flat molecule which is now subject to $A_{1,3}$ strain if the methyl group is in the plane. This strain makes it very unlikely for *Re* face attack to occur due to the higher energy of this conformation. However, if the hydrogen is in the plane, this strain is no longer present and this conformation is much more energetically favored. The hydride would then attack from the *Si* face that is

opposite to the large phenyl group. The opposite would be observed for the *R*-enantiomer, giving the enantiomer with the *R*-stereochemistry.

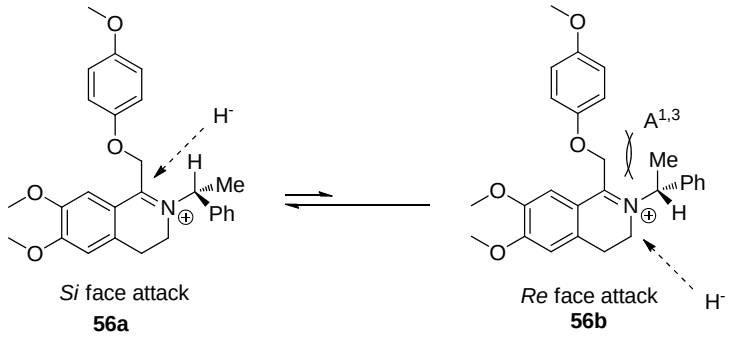



**Figure 4. Proposed rationale for observed stereoselectivity in the reduction of the iminium ion (56)**

The biological data associated with the enantiomers clearly shows that the enantiomer assigned with S-stereochemistry is the active enantiomer. Interestingly, the active enantiomer also potentiates GluN2D-containing receptors to a higher maximum than the racemic form.

## 2.4 RESULTS AND DISCUSSION

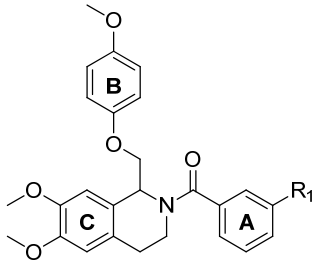
### *2.4.1 Structure Activity Relationship of 1180-series – A-Ring Modifications*

Although some information could be gleaned from the commercially available analogues of 1180 about the substitution on both the A- and B-rings, all of the purchased compounds were disubstituted on the C-ring with methoxy substituents. Analogues with additional modifications to the A- and B-ring were also necessary in order to develop a full and informative SAR.

From the purchased compounds, it was already becoming clear that the *meta*-position on the A ring was best for activity. However, it was not clear what substituent type would afford the best activity. A number of analogues were synthesized with varied substituent type in the

*meta*-position ($R_2$) and are summarized in Table 19. At this point, the most potent compounds were the chlorine- (**1390**), bromine- (**1391**), and trifluoromethyl- (**1426**) containing analogues. Although **1390** and **1391** showed similar activity against GluN2C- and GluN2D-containing NMDA receptors, the fluorine- and iodine-containing analogues (**1369** and **1180-11**, respectively) were slightly less active although not markedly so. Interestingly, all four of these compounds potentiated to a similar degree with maximum effects in the upper 100's for **1369** and **1391** and in the low to mid 200's for **1390** and **1180-11**. It was expected that, due to the large disparity in both size and electronegativity between the four halogens, a trend would emerge from the biological data around these four compounds. However, no general trend emerged, suggesting that the binding of these compounds is tolerant of large substituents and is not affected by the electronegativity of the substituents. However, the analogues containing an electron-withdrawing substituent such as nitro (**1180-16**), cyano (**1180-37**), keto (**1180-58)** and trifluoromethyl (**1426**) had different activities and maximum effects associated with them, following no obvious trend. Electron-donating substituents such as methoxy (**1392**) and methyl (**1425**) did seem to have a consistent effect, except with the phenolic analogue (**1180-3**) which, in contrast to the other two analogues containing electron-donating substituents, showed no biological effect.

**Table 19. Effect of A ring substituent identity on potency and max potentiation of 1180 analogues**



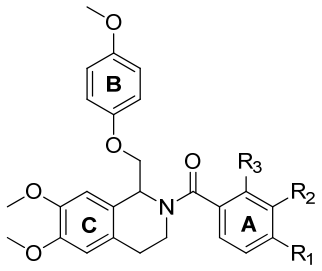

| | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|
| **Compound ID** | **$R_1$** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1425** | Me | 171 ± 11 | 135 ± 9.4 | 6.2 (211%) | 5.5 (174%) |
| **1392** | OMe | 147 ± 12 | 132 ± 10.5 | 5.8 (181%) | 12 (179%) |
| **1391** | Br | 183 ± 11 | 178 ± 6.6 | 0.9 (195%) | 2.2 (188%) |
| **1390** | Cl | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1369** | F | 154 ± 7.0 | 142 ± 4.5 | 7.2 (184%) | 7.0 (169%) |
| **1180-11** | I | 209 ± 9.8 | 163 ± 13 | 4.0 (251%) | 4.9 (239%) |
| **1180-16** | $NO_2$ | 160 ± 7.4 | 151 ± 6.3 | 11 (250%) | 13 (261%) |
| **1426** | $CF_3$ | 187 ± 12 | 202 ± 7.0 | 2.4 (201%) | 2.4 (218%) |
| **1180-3** | OH | 96 ± 0.8 | 96 ± 2.3 | -- | -- |
| **1180-36** | $CH_2Cl$ | 138 ± 2.7 | 115 ± 2.2 | -- | -- |
| **1180-37** | CN | 119 ± 4.2 | 139 ± 5.8 | 29 (164%) | 7.7 (166%) |
| **1180-58** | C(O)Me | 105 ± 2.4 | 104 ± 1.2 | -- | -- |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No significant effect was observed for GluN2A and GluN2B containing receptors (data not shown).

Although a large number of single modifications were tested on the A-ring, it remained to be seen if the receptor would tolerate disubstitution on the A-ring. A subset of compounds was synthesized with two substituents on the A-ring (Table 20). For many of these compounds, chlorine substituents were chosen due to the high potency observed in the mono-chlorine substituted compound **1390**. As was observed previously, substituents in $R_3$ on the A-ring were not well tolerated, as in **2009** which was inactive. The disubstituted analogue **1180-12** showed

reduced efficacy compared to **1390**, which aligned well with the observations early on in this work where **1409,** with a single chlorine at $R_3$, was completely inactive.

**Table 20. Effect of A ring disubstitution on potency and max potentiation of 1180 series analogues**



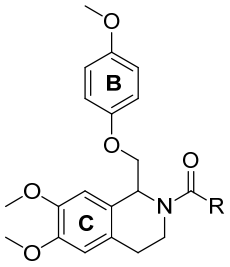

| | | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|---|
| **Compound ID** | **$R_1$** | **$R_2$** | **$R_3$** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | H | H | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** | H | Cl | H | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1180-10** | Cl | Cl | H | 126 ± 5.2 | 136 ± 5.2 | 21 (178%) | 24 (220%) |
| **1180-12** | H | Cl | Cl | 120 ± 3.1 | 109 ± 8.4 | 1.4 (127%) | -- |
| **2009** | Cl | H | Cl | 112 ± 5.0 | 99 ± 3.1 | -- | -- |
| **1180-34** | H | 3,5-diCl | H | 149 ± 8.0 | 138 ±8.2 | 4.8 (201%) | 1.9 (159%) |
| **1180-18** | F | Cl | H | 183 ± 13 | 168 ± 10 | 5.3 (232%) | 5.3 (206%) |
| **1408** | O-$CH_2$-O | | H | 106 ± 3.6 | 99 ± 1.5 | -- | -- |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No significant effect was observed for GluN2A and GluN2B containing receptors (data not shown).

A few of the commercially supplied compounds replaced the A-ring entirely with a heteroaromatic ring such as pyridine or thiophene or with an alkyl substituent in the case of *t*-butyl. A number of synthetic analogues were prepared to fully test the isosteric replacement of the A-ring. For all of the compounds tested, either a reduction or complete loss of potency was observed (Table 21). The thiophene analogue, **1486**, retained some activity at GluN2C-

containing NMDA receptors ($EC_{50}$ = 9.0 μM) but had decreased max effect. The 2-napthyl analogue, **1180-35**, also showed weak potentiation at GluN2C-containing NMDA receptors but, like the thiophene analogue, had a low maximum effect. Since aqueous solubility remains to be an issue for this series, two analogues were synthesized with the goal of increasing solubility by incorporating a morpholine into the analogue. These two compounds (**1180-23**, **1180-24**) were unfortunately met with a loss of potency.

**Table 21. Effect of replacing A-ring on potency and max potentiation**



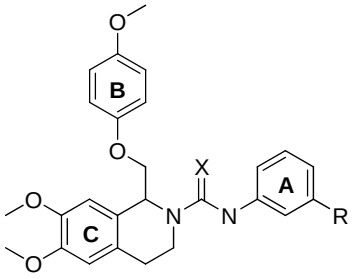

| | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|
| **Compound ID** | **R** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | Phenyl | 116 ± 2.9 | 123 ± 2.3 | 12/ 145% | 11 / 156% |
| **1180-68** | $CH_2Cl$ | 95 ± 1.6 | 95 ± 2.8 | -- | -- |
| **2013** | *t*-butyl | 90 ± 3.6 | 95 ± 1.4 | -- | -- |
| **1484** | 2-pyridine | 87 ± 4.3 | 99 ± 2.4 | -- | -- |
| **1485** | 3-pyridine | 98 ± 1.5 | 94 ± 1.7 | -- | -- |
| **1510** | 4-pyridine | 100 ± 1.3 | 97 ± 1.8 | -- | -- |
| **1486** | 2-thiophene | 117 ± 2.1 | 105 ± 1.6 | 9.0 (134%) | -- |
| **1180-4** | 2-furan | 102 ± 1.3 | 100 ± 1.4 | -- | -- |
| **1180-5** | 5-isoxazole | 93 ± 2.3 | 97 ± 2.4 | -- | -- |
| **2008** | 1-napthyl | 97 ± 2.8 | 96 ± 0.6 | -- | -- |
| **1180-35** | 2-napthyl | 113 ± 2.8 | 106 ± 1.5 | 23 (151%) | -- |
| **1180-23** | *N*-morpholine | 95 ± 1.9 | 96 ± 2.0 | -- | -- |
| **1180-24** | $CH_2$-*N*-morpholine | 92 ± 2.7 | 94 ± 0.5 | -- | -- |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No significant effect was observed at GluN2A- or GluN2B-containing receptors (data not shown).

*2.4.2 Structure Activity Relationship of 1180-series – Linker A modifications*

Use of compounds from the 1180-series in biological systems was hindered early on in the project due to significant aqueous solubility issues. In an attempt to circumvent these solubility issues, a number of compounds were purchased with increased linker length between the tetrahydroisoquinoline core and the A-ring. The hypothesis was that increasing this linker length may decrease the π-stacking that could be occurring and thus, contribute to the lack of solubility. The introduction of additional heteroatoms may also improve solubility by increasing dipole-dipole and/or hydrogen bonding interactions. Unfortunately, all of the compounds with increased linker length were met with a complete loss of potency (Table 22).

**Table 22. Effect of increasing length of linker A on potency of 1180-series**

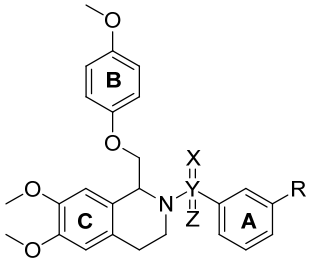



| | | | $I_{10\ \mu M} / I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|
| **Compound ID** | **R** | **X** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1407** | H | O | 99 ± 3.7 | 99 ± 1.5 | -- | -- |
| **1411** | Cl | O | 93 ± 1.9 | 90 ± 2.0 | -- | -- |
| **1412** | H | S | 94 ± 1.4 | 89 ± 1.2 | -- | -- |
| **1415** | Cl | S | 99 ± 1.1 | 98 ± 1.5 | -- | -- |
| **1414** | F | S | 98 ± 1.9 | 103 ± 2.0 | -- | -- |
| **1416** | Br | S | 95 ± 1.9 | 124 ± 6.4 | -- | -- |
| **1413** | Me | S | 116 ± 2.0 | 126 ± 6.6 | 5.2 (126%) | 4.9 (130%) |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. Some compounds induced mild inhibition for which the half-maximally effective concentration of compound was >100 μM. Data are from between 5-14 oocytes from between 2-3 frogs for each compound and receptor tested. No significant effect was observed at GluN2A and GluN2B containing receptors (data not shown).

In addition, to decrease the stacking that may be a cause of poor aqueous solubility, modifications were made to linker A. A common modification during SAR development to enhance solubility is the incorporation of a sulfonamide. In the case of the 1180-series, the amide bond was replaced with a sulfonamide (**1487**, **1511**) in an attempt to enhance solubility, although these analogues were inactive (Table 23).

**Table 23. Effect of linker A on potency of 1180-series**




| | | | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|---|---|
| Compound ID | **R** | **X** | **Y** | **Z** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | O | C | - | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** | Cl | O | C | - | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1487** | H | O | S | O | 92 ± 1.5 | 98 ± 0.6 | -- | -- |
| **1180-17** | H | - | $CH_2$ | - | 102 ± 3.4 | 92 ± 2.4 | -- | -- |
| **1511** | Cl | O | S | O | 97 ± 1.8 | 96 ± 0.5 | -- | -- |

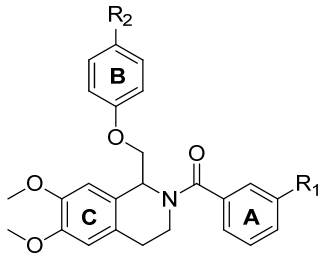
[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. NE indicates less than 10% potentiation. Compounds 1180 and 1390 from preceding Tables are included here for comparison. Data are from between 6-18 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed against GluN2A- or GluN2B-containing NMDA receptors (data not shown).

*2.4.3 Structure Activity Relationship of 1180-series – B-Ring Modifications*

Apparent from the commercially supplied compounds was that the *para*-methoxy substituent on the B-ring was necessary for activity as a number of other substituents in this position were inactive. However, the substituent placement had yet to be explored. After making modifications to the substituent placement on the B-ring, it became quickly apparent that the *para*-position on the B-ring was the only position that would afford any activity (Table 24). Additional substituents such as trifluoromethoxy (**1180-9**), thiomethyl (**1180-13** & **1180-14**), hydroxy (**1180-65**) and benzyloxy (**1180-22**) were introduced into the *para*-position in place

of the methoxy. These moieties were chosen because they should allow for similar interactions as the methoxy substituent. Although the thiomethyl (**1180-13**) showed some activity, its potency was significantly reduced from structurally related methoxy-containing compound **1390**.

**Table 24. Effect of varied B-ring substitution on potency and max potentiation**




| | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|
| **Compound ID** | **$R_1$** | **$R_2$** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | OMe | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** | Cl | OMe | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1180-14** | H | SMe | 102 ± 5.3 | 100 ± 1.9 | -- | -- |
| **1180-13** | Cl | SMe | 164 ± 6.7 | 141 ± 6.3 | 7.9 (202%) | 7.7 (174%) |
| **1180-9** | Cl | $OCF_3$ | 102 ± 1.1 | 93 ± 0.9 | -- | -- |
| **1180-22** | Cl | OBn | 93 ± 1.6 | 99 ± 0.9 | -- | -- |
| **1180-65** | Cl | OH | 105 ± 1.9 | 98 ± 0.8 | -- | -- |

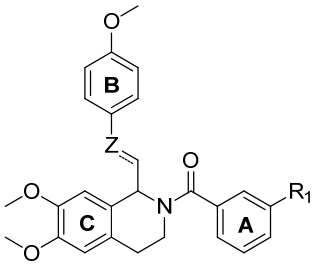
[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A- or GluN2B-containing NMDA receptors (data not shown).

*2.4.4 Structure Activity Relationship of 1180-series – Linker B Modifications*

To this point, all compounds contained an ether linkage between the tetrahydroisoquinoline core and the B-ring. It remained to be determined whether this oxygen could be replaced and have the compounds maintain activity. A number of compounds were synthesized which replaced this oxygen in the linker with varied biological results (Table 25).

When the oxygen was replaced with a sulfur as in **1180-51**, the compound lost activity altogether. In a similar fashion, when the oxygen was replaced with a methylene (**1180-42**, **1180-40**, **1180-41**) the compounds had significantly reduced or a complete loss of activity compared to the comparable oxygen-containing compounds (**1180**, **1390**, **1391**, respectively). Interestingly, when a carbon-carbon double bond was incorporated into the linker, these compounds showed good activity. In the case of **1180-31** and **1180-32**, the olefin-containing compounds had comparable activity to the ether-containing compound **1390**.

**Table 25. Effect of modifications to Linker B on potency and max potentiation**



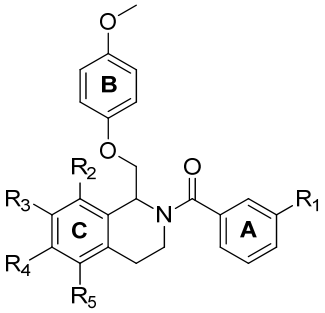

| | | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|---|
| **Compound ID** | **$R_1$** | **Z** | **C=C** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | O | No | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** | Cl | O | No | 204 ± 9.5 | 182 ± 7.7 | 4.1 (245%) | 4.1 (213%) |
| **1391** | Br | O | No | 183 ± 11 | 178 ± 6.6 | 0.9 (195%) | 2.2 (188%) |
| **1180-51** | H | S | No | 103 ± 4.3 | 94 ± 1.0 | -- | -- |
| **1180-1** | F | C | No | 92 ± 1.7 | 95 ± 2.3 | -- | -- |
| **1180-42** | H | C | No | 102 ± 3.4 | 108 ± 2.0 | -- | -- |
| **1180-40** | Cl | C | No | 114 ± 2.6 | 108 ± 2.0 | 19 (143%) | 27 (135%) |
| **1180-41** | Br | C | No | 128 ± 5.2 | 134 ± 7.4 | 11 (129%) | 15 (128%) |
| **1180-33** | H | C | Yes | 122 ± 4.4 | 127 ± 5.1 | 35 (192%) | 35 (199%) |
| **1180-31** | Cl | C | Yes | 169 ± 6.9 | 155 ± 6.4 | 1.1 (172%) | 1.3 (157%) |
| **1180-32** | Br | C | Yes | 181 ± 17 | 169 ± 7.3 | 2.8 (188%) | 2.8 (174%) |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A- or GluN2B-containing NMDA receptors (data not shown).

*2.4.5 Structure Activity Relationship of 1180-series – C-Ring Modifications*

All of the purchased compounds were disubstituted on the C ring with the same dimethoxy substitution pattern. It remained to be tested whether the binding site could tolerate varied substitution on this ring. The two methoxy substituents were replaced with a dioxolane ring (**1180-25**, **1180-48**, **1180-47**) in order to keep the placement of the oxygen atoms consistent but to force them into a fixed conformation. These compounds were less active than the comparable dimethoxy-containing compounds (**1180**, **1390**, and **1391**), suggesting that the free rotation may allow the methyl groups to adopt an optimal conformation (Table 26).

**Table 26. Effect of varied C ring substitution on potency and potentiation**




| | | | | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (max potentiation) (μM, %)[a] | |
|---|---|---|---|---|---|---|---|---|---|
| **ID** | **$R_1$** | **$R_2$** | **$R_3$** | **$R_4$** | **$R_5$** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | H | H | OMe | OMe | H | 116 ± 2.9 | 123 ± 2.3 | 12 (145%) | 11 (156%) |
| **1390** | Cl | H | OMe | OMe | H | 204 ± 9.5 | 182 ± 7.7 | 4.2 (245%) | 4.1 (213%) |
| **1391** | Br | H | OMe | OMe | H | 183 ± 11 | 178 ± 6.6 | 0.9 (195%) | 2.2 (188%) |
| **1180-25** | Cl | H | O-$CH_2$-O | | H | 126 ± 4.3 | 134 ± 6.6 | 16 (200%) | 7.4 (186%) |
| **1180-48**‡ | Br | H | O-$CH_2$-O | | H | 170 ± 9.9 | 136 ± 6.8 | 3.2 (177%) | 3.4 (138%) |
| **1180-47**‡ | H | H | O-$CH_2$-O | | H | 99 ± 2.7 | 99 ± 1.9 | -- | -- |
| **1180-19** | H | OMe | H | OMe | H | 143 ± 5.0 | 141 ± 9.0 | 10 (182%) | 14 (190%) |
| **1180-20** | Cl | OMe | H | OMe | H | 178 ± 21 | 166 ± 7.0 | 6.1 (234%) | 9.2 (233%) |
| **1180-21** | Br | OMe | H | OMe | H | 178 ± 8.6 | 166 ± 4.3 | 9.0 (261%) | 7.8 (228%) |
| **1180-46** | H | H | H | OMe | H | 136 ± 13 | 144 ± 6.5 | 7.5 (174%) | 5.7 (167%) |
| **1180-26** | Cl | H | H | OMe | H | 210 ± 12 | 216 ± 18 | 1.3 (240%) | 1.0 (219%) |
| **1180-27** | Br | H | H | OMe | H | 263 ± 24 | 281 ± 24 | 2.0 (294%) | 3.4 (459%) |
| **1180-67** | C(O)Me | H | H | OMe | H | 140 ± 4.1 | 124 ± 2.9 | 21 (241%) | 32 (242%) |
| **1180-49** | Cl | H | H | OMe | OMe | 96 ± 3.4 | 93 ± 0.6 | -- | -- |
| **1180-50** | Br | H | H | OMe | OMe | 98 ± 2.1 | 95 ± 0.9 | -- | -- |
| **1180-44** | Cl | H | Me | Me | H | 238 ± 11 | 179 ± 8.2 | 1.4 (244%) | 1.5 (180%) |
| **1180-45** | Br | H | Me | Me | H | 195 ± 14 | 211 ± 0.9 | 0.9 (197%) | 1.1 (211%) |

‡Synthesized by Kathryn Chepiga

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A- or GluN2B-containing NMDA receptors (data not shown).

Interestingly, when a halogen substituent was introduced onto the A-ring of **1180** as in **1390** (chlorine) and **1391** (bromine), the potency increased compared to the original screening hit. However, this trend did not follow into the series of three compounds with a modified C-ring substitution. In the case of **1180-19**, **1180-20**, and **1180-21**, very little change was observed

when a halogen was introduced on the A-ring for these compounds (Table 26). This observation may be attributed to the preferred binding mode of these compounds. As shown in Figure 5, although multiple rotational isomers exist, the placement of the methoxy in the $R_7$ position increases steric interactions between the lone pairs on the methoxy oxygen and the oxygen in the ether linkage; an interaction that is not present in **1180**, **1390** and **1391**. If the preferred binding conformation places the ether linkage towards the C-ring, the steric interactions would prevent the compound from obtaining the most stable conformation and therefore disallow binding.

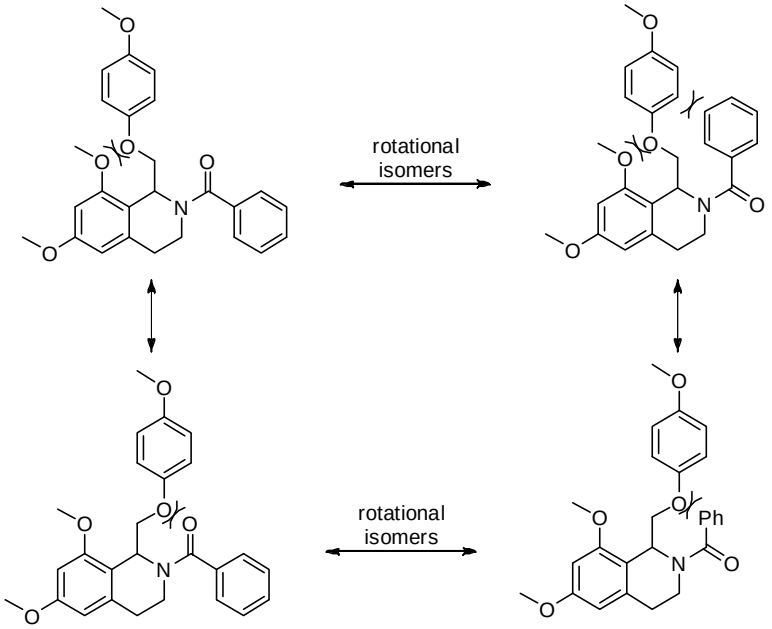
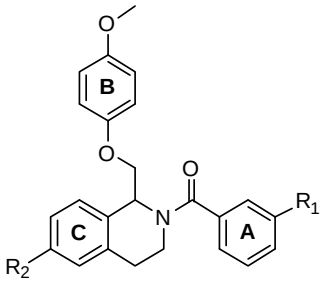



**Figure 5. Rotational isomers of 1180-series compounds depicting steric interactions which may be the cause of observed potency decrease.**

Interestingly, when a single methoxy group was placed on the C-ring as in **1180-46**, **1180-26**, and **1180-27**, the potency was similar to, if not slightly better than, that of the dimethoxy analogues **1180**, **1390**, and **1391**. This further supports the hypothesis shown in Figure 5 that the placement of the methoxy at the top of the C-ring causes steric interactions which disrupt binding.

In order to test the substituent type tolerated on the C-ring, dimethyl analogues (**1180-44** and **1180-45**) were synthesized. Both of these compounds were active in the low micromolar region, similar to the corresponding dimethoxy compounds (**1180**, **1390**, **1391**), suggesting that the oxygen atoms are not required for activity (Table 26). They do, however, help with solubility as the addition of β-cyclodextrin was required to get a full concentration-effect curve on these compounds. The trend observed with the methoxy-containing analogues did not translate into the methyl-containing analogues as a single methoxy substituent on the C-ring, as in **1180-69**, **1180-70**, and **1180-71**, showed decreased potency compared to the dimethoxy analogues (Table 27). These compounds also required β-cyclodextrin as they had significantly decreased solubility.

**Table 27. Effect of varied C ring single substitution on potency and max potentiation of 1180 series**




| | | | $I_{10\ \mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | | | |
|---|---|---|---|---|---|---|---|---|
| **ID** | **$R_1$** | **$R_2$** | **GluN2C** | **GluN2D** | **GluN2A** | **GluN2B** | **GluN2C** | **GluN2D** |
| **1180-69** | H | Me | 116 ± 3.9 | 109 ± 1.8 | -- | -- | 24 (182%) | -- |
| **1180-70** | Cl | Me | 207 ± 10 | 201 ± 11 | -- | -- | 5.0 (252%) | 4.7 (237%) |
| **1180-71** | Br | Me | 205 ± 12 | 230 ± 9.2 | -- | -- | 3.2 (227%) | 3.6 (257%) |
| **1180-99** | H | OBn | 212 ± 11 | 182 ± 9.1 | -- | -- | 0.7 (222%) | 2.3 (177%) |
| **1180-97** | Cl | OBn | 252 ± 13 | 195 ± 17 | -- | -- | 0.4 (254%) | 0.4 (198%) |
| **1180-98** | Br | OBn | 253 ± 23 | 219 ± 15 | -- | -- | 0.3 (257%) | 0.3 (219%) |
| **1180-55** | Cl | O$^i$Pr | 249 ± 31 | 228 ± 28 | 1.9 (130%) | 4.5 (193%) | 1.8 (266%) | 2.9 (243%) |
| **1180-95** | H | OEt | 165 ± 8.3 | 147 ± 5.6 | -- | 37 (159%) | 17 (301%) | 18 (259%) |
| **1180-93** | Cl | OEt | 266 ± 22 | 297 ± 16 | -- | 7.1 (165%) | 2.4 (294%) | 3.0 (345%) |
| **1180-94** | Br | OEt | 275 ± 15 | 312 ± 17 | -- | 5.1 (153%) | 1.9 (290%) | 2.3 (336%) |
| **1180-96** | $CF_3$ | OEt | 282 ± 17 | 236 ± 17 | -- | 8.2 (141%) | 1.5 (250%) | 2.3 (322%) |

[a] Fitted Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A- or GluN2B-containing NMDA receptors (data not shown). $EC_{50}$ values are shown to two significant digits; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested.

Due to the solubility issues, only analogues with an oxygen-containing substituent were synthesized after these data were obtained. Three analogues were synthesized with a benzyloxy substituent on the C-ring (**1180-97**, **1180-98**, and **1180-99**) in order to test the available space in the binding pocket. These compounds had increased potency compared to the comparable methoxy-analogues and were the most compounds synthesized during the course of the project.

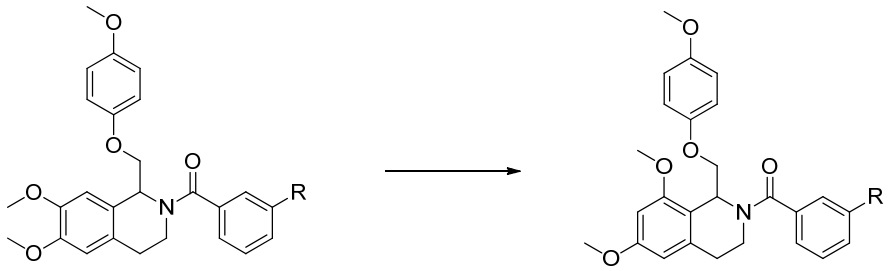
Interestingly, when an isopropoxy substituent was placed at $R_2$ on the C ring (**1180-55**, Table 27), the compound was no longer selective for GluN2C- and GluN2D-containing receptors. This suggested that there may be a binding pocket available on all four subunits for this series of compounds. This compound represented the first known potentiator of all four GluN2 subunits of NMDA. Both methyl groups of the isopropyl appear to be important for the observed potentiation, as when an ethoxy substituent was placed on this ring, the potentiation observed at GluN2A was diminished. These compounds represent an interesting new direction for this series. Since there are a number of modifications to the 1180-series which cause a complete loss of activity, it may be possible to tune out the activity observed at GluN2C- and GluN2D-containing receptors by making strategic structural modifications based on the SAR.

*2.4.6 Rationale and results for indole-containing compound*

In the course of the SAR development, a trend emerged from three compounds made with modifications to the substitution around the C-ring (**1180-19**, **1180-20**, and **1180-21**). In all three of these compounds, the methoxy group in the $R_8$ position in **1180**, **1390**, and **1391** was moved to $R_7$ (Table 26). In general, the addition of halogens onto the A-ring increased the activity of compounds within this series. Since this trend did not follow into the three compounds with a modified C-ring (Table 28), the hypothesis follows that the substitution

around the C-ring is responsible for the decreased potency observed. The movement of the methoxy group must have introduced steric interactions that disfavor the most energetically favored binding mode.

**Table 28. Comparison between the potency and max effect of isomeric 1180 analogues with varied C ring substitution pattern**



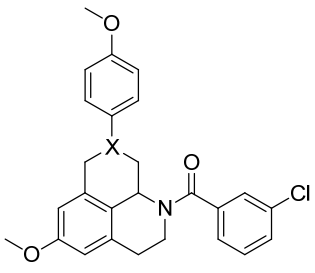
**1180** R = H
**1390** R = Cl
**1391** R = Br

**1180-19** R = H
**1180-20** R = Cl
**1180-21** R = Br

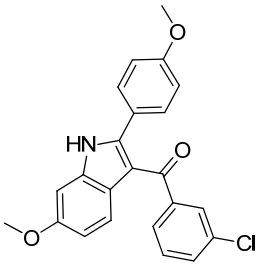
| | $I_{10\,\mu M}$ / $I_{CONTROL}$ (mean ± SEM, %) | | $EC_{50}$ (maximal potentiation) (μM, %)[a] | |
|---|---|---|---|---|
| **Compound ID** | **GluN2C** | **GluN2D** | **GluN2C** | **GluN2D** |
| **1180** | 116 ± 2.9 | 123 ± 2.3 | 12.3 (145%) | 11.4 (156%) |
| **1390** | 204 ± 9.5 | 182 ± 7.7 | 2.9 (215%) | 2.8 (205%) |
| **1391** | 183 ± 11 | 178 ± 6.6 | 0.9 (195%) | 2.2 (188%) |
| **1180-19** | 143 ± 5.0 | 141 ± 9.0 | 10 (182%) | 13.6 (190%) |
| **1180-20** | 178 ± 21 | 166 ± 7.0 | 6.1 (234%) | 9.2 (233%) |
| **1180-21** | 178 ± 8.6 | 166 ± 4.3 | 9.0 (261%) | 7.8 (228%) |

[a] Fitted $EC_{50}$ values are shown to two significant digits when potentiation at 10 μM test compound exceeds 115%; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested. No effect was observed at GluN2A- or GluN2B-containing NMDA receptors (data not shown).

If the binding conformation of the 1180-series compounds places the ether linkage preferentially towards the C-ring as this data suggests, then connecting the linker directly to the C-ring may lock the compound in the preferred binding mode resulting in a more active compound (**57**, Figure 6).




57




1180-43

**Figure 6. Structure of synthesized indole-containing compound based on the generic structure 57.**

Based on the structure shown in Figure 6, **57**, the indole-containing compound (**1180-43**) was selected to be synthesized. This compound was chosen based on its synthetic tractability. While not all of the portions of the 1180-series are intact, the functionalities which are known to be important for activity are all present. Unfortunately, this compound was completely inactive against all NMDA receptor subunits. This scaffold was abandoned due to lack of potency and efficacy.

*2.4.7 In vitro analysis of 1180-series mechanism of action and binding interactions*

Representative current recordings for **1390** at all four GluN2 subunits show the potentiation of current evoked by an 1180-series compound (Figure 7.A). Concentration-effect curves for **1390** administered *in vitro* to each individual GluN1/GluN2 receptor and at the related glutamate receptors AMPA (GluR1) and kainate (GluR6) are shown to highlight the subunit selectivity of this series (Figure 7.B).

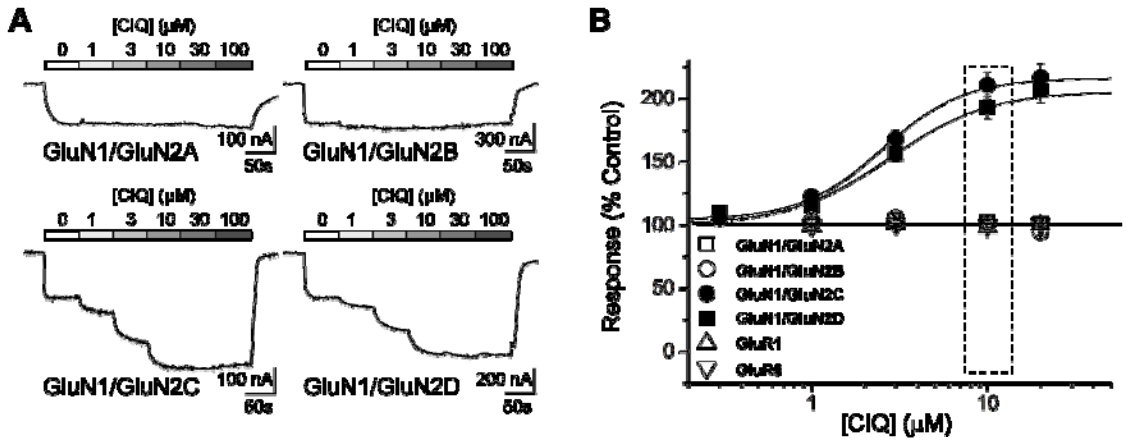



**Figure 7.** ***In vitro*** **analysis of 1180-series: Panel A: Representative current recordings from two-electrode voltage-clamp recordings of recombinant NMDA receptors expressed in** ***Xenopus*** **oocyte in response to 100 μM glutamate/30 μM glycine under increasing concentrations of 1390 (1-100 μM). Panel B: Composite concentration-effect curves for 1390 at GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, GluN1/GluN2D, AMPA (GluR1) and KA (GluR6) receptors.**

In order to gain insight into the binding site for the 1180-series, the Traynelis lab generated a number of chimeric receptors to find the molecular determinants of activity associated with 1390. These were identified by evaluating NMDA response to 1390 using GluN2A-GluN2D chimeric subunits (Figure 8).[4] Since **1390** potentiates GluN1/GluN2D receptors and not GluN1/GluN2A, portions of GluN2D could be inserted into GluN2A to evaluate gain of function.

Transfer of the linker between the ATD and S1 (L), S1, M1-M3 and S2 from GluN2D into GluN2A effectively conferred response to 1390. In fact, transfer of just the linker (L), S1 and M1 also effectively altered receptor sensitivity to 1390 administration. Data from the transfer of various combinations of smaller portions of these sections of GluN2D into GluN2A chimeras suggested that the molecular determinants for **1390** activity lie within the linker (L) in between the ATD and LBD and five residues (590-594) in the M1 transmembrane loop of GluN2D (Figure 9). In fact, the chimera GluN2A-(2D L + M1e) containing only these two regions from GluN2D showed potentiation in response to 10 μM **1390**. However, no activity was observed when **1390**

was applied to the chimeric receptors with the ATD-S1 linker of GluN2D or residues 590-594 transferred alone.

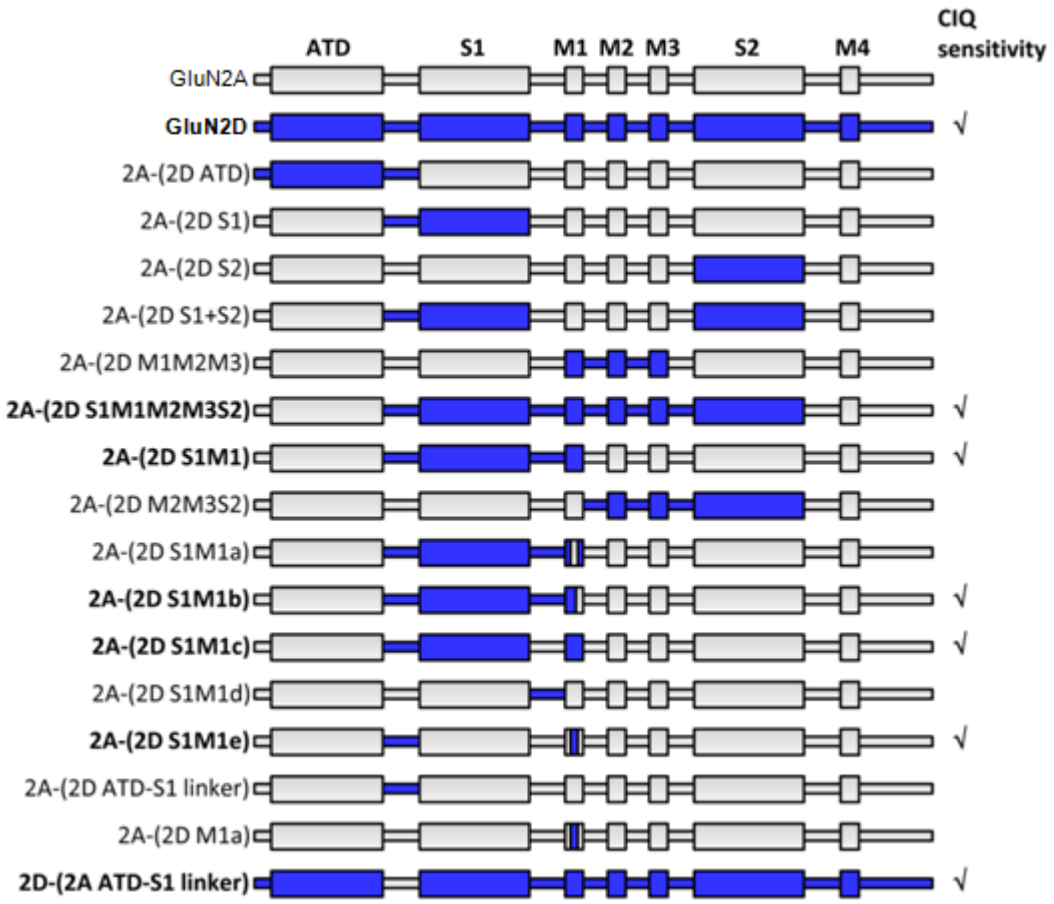



**Figure 8. Schematic representation of the GluN2 subunit polypeptide. Schematic representations of chimeras between the GluN2D subunit and the corresponding region in GluN2A with CIQ (1390) activity denoted by a check.**

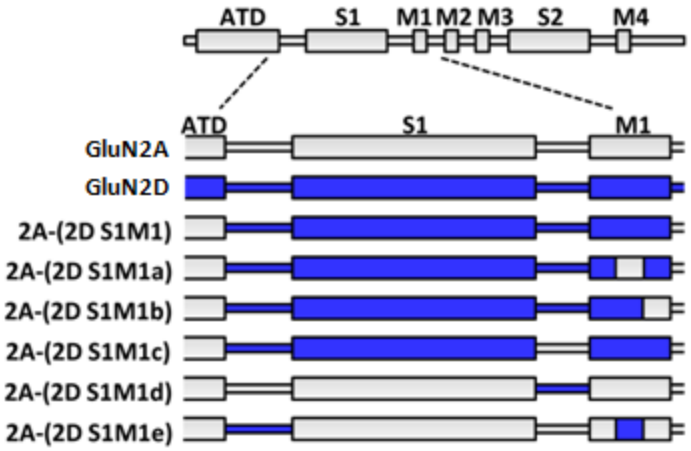



**Figure 9. Schematic representation of the GluN2 subunit polypeptide with chimeras shown between the GluN2D ATD-M1 region and the corresponding region in GluN2A.**

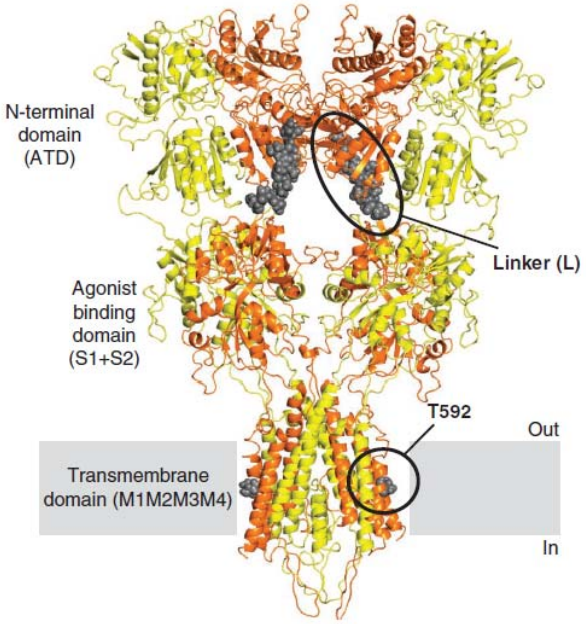



**Figure 10. Homology model of a GluN1/GluN2 heterodimer of the tetrameric NMDA receptor based on GluR2 receptor. Regions important for activity of 1390 shown in gray (T592 and ATD-S1 linker). GluN1 is shown in yellow and GluN2 is shown in orange.**

The linker region (L) between the ATD and binding domain of GluN2D has been previously shown to reduce the open probability of GluN2A when transferred into a GluN2A-

GluN2D chimera.[93] This, coupled with the gain of function mutant data, raises the possibility that the potentiation associated with **1390** binding may require a low open probability.

GluN2D loss of function mutants were also evaluated. Interestingly, transfer of the GluN2A ATD-S1 linker (L) into GluN2D did not significantly alter the activity of **1390** (Figure 9). However, chimeric receptors in which both the GluN2A ATD and ATD-S1 linker are placed into GluN2D are no longer potentiated. This observation suggests that some residues or secondary structure beyond the linker enhance the activity of **1390** on GluN2D-containing NMDA receptors.

Site-directed mutagenesis was performed on the M1 region of GluN2D which revealed a single residue (Thr592) conserved in GluN2C and GluN2D but different in GluN2A and GluN2B which was an important determinant of **1390** activity. Mutation of this residue to the corresponding residue in GluN2A (GluN2D T592I) completely eliminated **1390** potentiation. The corresponding reverse mutation (GluN2A I567T) combined with the linker (L) between GluN2D ATD and S1 caused receptor sensitivity to 10 μM 1390 (135 ± 5%). However, the combination of the linker and point mutation was not sufficient to transfer the full potentatiation observed in wild type GluN2D receptors to GluN2A. However, from this data, it is clear that the ATD and linker between ATD and S1 as well as residue Thr592 are important structural determinants of **1390** potentiation of GluN2D (Figure 10).

*2.4.8 Cysteine Mutants*

To further probe the binding site of the 1180-series, the Traynelis lab made cysteine point mutations to the GluN2D subunit. The specific mutation proposed for testing was T592C since the mutagenesis suggested this residue was important for the activity associated with **1390**. Only functional mutants were used in further experiments as not all mutants displayed

normal NMDA function *in vitro*. Synthetic analogues of 1180 containing electrophilic reactive sites were proposed for these further studies. The reactive moiety was incorporated into the portion of the molecule that had been observed to tolerate the most functionality; in this case the moiety was proposed to be incorporated onto the A-ring. The reactive moiety was chosen based on synthetically tractability. These compounds were tested against wild type NMDA-receptors to ensure activity prior to testing against the Cys-mutant NMDA receptors.

*2.4.9 Results of cysteine-reactive mutants*

Based on the chimeric studies which suggested that the molecular determinants of action of 1390 involve Thr592, a cysteine point mutation was made to this key residue (T592C). In addition, a cysteine which resides in this portion of the receptor on GluN2D was mutated to an alanine for a double mutant GluN2D receptor (C590A + T592C). Before these compounds were tested against the mutants, they were tested against wild type NMDA receptors to ensure their binding to the receptors. Although both synthesized compounds showed little to no potentiation at native GluN2C- and GluN2D-containing receptors, it was possible that a small amount of compound was still binding. When the compounds were applied to GluN2D (T592C) receptors, covalent modification would be observed if, after washout of 1180-66, the current elicited by application of glutamate and glycine were larger than prior to compound application. This would suggest persistent potentiation induced by the covalent modification of the protein. After washout, **1390** was then applied to measure any resulting change in current. If **1390** could no longer potentiate, it would suggest that the binding site was blocked by the covalently attached analogue.

The $\alpha$-chloroketone analogue, **1180-66**, did potentiate GluN2D (T592C) receptors but did not show any activity against GluN2D (C590A + T592C) (Figure 11). The current elicited by

glutamate and glycine was not altered by exposure to **1180-66** at GluN2D (T592). In addition, the response associated with the administration of 3 μM **1390** is not altered by the pre-application of **1180-66** (Figure 12). All of these data suggests that **1180-66** is not covalently modifying GluN2D-containing receptors. However, it is possible that ligands with other reactive functionalities may be effective in this experiment as the lack of covalent attachment observed may be due to the identity of the electrophilic group or the lack of potentiation associated with **1180-66** on wild type GluN2D-containing receptors. The α-chloroketone may not be reactive enough to modify the cysteine residue or a compound with the same group placed in a different location on the compound may provide a compound that can covalently modify the protein. The lack of covalent attachment could also be explained if the cysteine residues present were in their oxidized state. This would make the residue non-nucleophilic and therefore, prevent covalent attachment of the test compound.

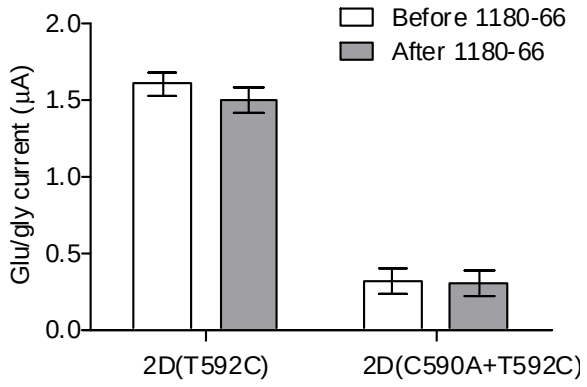



**Figure 11. Graphs depicting the current elicited by glutamate and glycine application both before and after administration of 1180-66.**

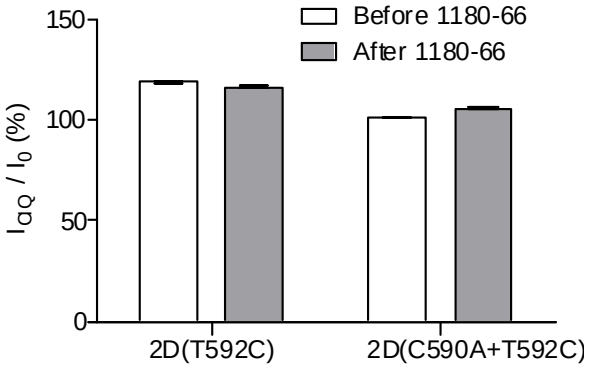



**Figure 12. Graphs depicting the current elicited by application of CIQ (1390) both before and after 1180-66 administration**

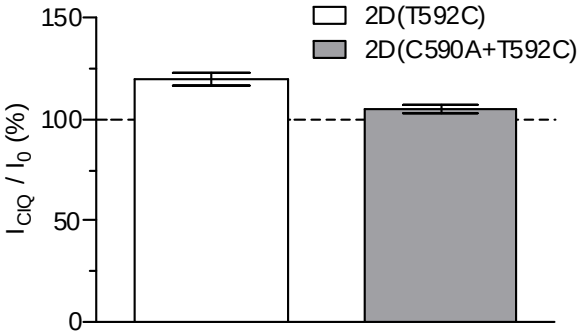



**Figure 13. Graph depicting the current elicited by application of CIQ (1390) to both cysteine-mutant GluN2D receptors**

*2.4.10 In vivo analysis for pharmacokinetic properties of 1390*

Pharmacokinetic properties of **1390** were assessed by the Traynelis lab. The analogue, **1390**, was assessed for blood-brain barrier penetration, half-life, and bioavailability. For these calculations, **1390** was injected intravenously (IV, 5 mg/kg) or intraperitoneally (IP, 20 mg/kg) to mice. The concentration of **1390** (CIQ) was measured in plasma and in the brain (Figure 14.A and B, respectively). From IV administration, **1390** had a half-life of 46 minutes and a half life of 81 minutes after IP injection. Brain concentrations of **1390** peaked 30 minutes after administration for both IV and IP routes and decreased following first-order kinetics. When

injected IP, the bioavailability of **1390** was 0.42 and the brain to plasma concentration ratio was 11.6 thirty minutes after injection.

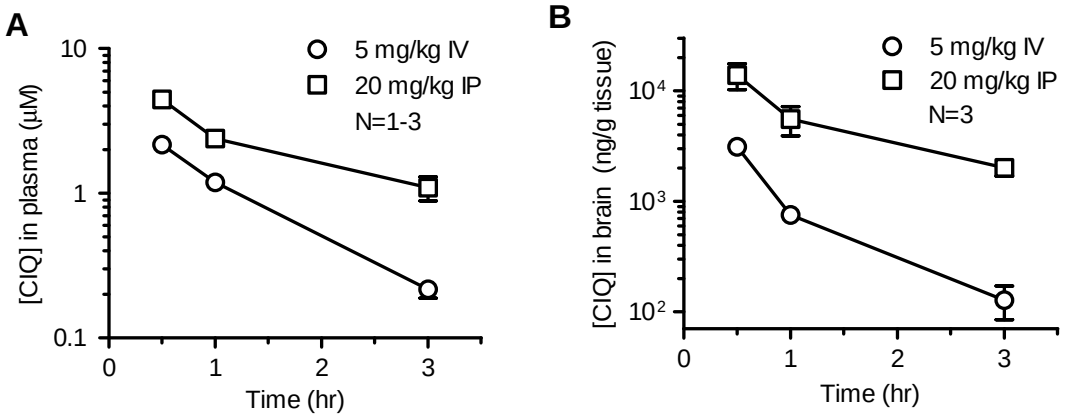



**Figure 14. Pharmacokinetics of 1390 (CIQ). Panel A: Plasma concentrations of 1390 (CIQ) after IV and IP administrations. Panel B: Brain concentrations of 1390 (CIQ) after IV and IP administrations.**

2.4.11 *In vitro analysis of selectivity of 1390*

The 1180-series analogue **1390** had no effect on currents from $GABA_A$, $GABA_C$, glycine, 5-$HT_3$ or nicotinic acetylcholine receptors. The analogue **1390** was also analyzed at 10 μM for activity at 63 receptors or pumps expressed in the CNS. Evaluation was based on the displacement of radioligand selective for the receptor or pump in question. From all of the receptors screened, **1390** had an effect on the displacement of radioligands in the κ opioid receptor, the 5-$HT_{2B}$ receptor, and the 5-$HT_6$ receptor. A secondary concentration-response binding assay was performed on those receptors which **1390** showed effect. An $IC_{50}$ was measured for **1390** against κ opioid receptors of 3.6 ± 0.6 μM. In an assay against 5-$HT_{2B}$ receptors, **1390** had an $IC_{50}$ of 2.8 ± 0.3 μM. Against 5-$HT_6$ receptors, **1390** had an $IC_{50}$ of 0.51 ± 0.04 μM. Although **1390** had off-target activity at these three receptors, **1390** appears to be fairly selective as it did not affect any of the other 60 tested targets.

*2.4.12 Evaluation of 1390 in fear extinction*

Subunit-selective NMDA receptor potentiators have a number of potential therapeutic uses. One of the compounds which showed a higher degree of potency and potentiation early on in this project was chosen for further testing in an animal model of fear extinction. A dose-response study was performed to compare the effects of varied concentrations of **1390** on retention of learned fear. Mice were trained using Pavlovian fear conditioning with an auditory cue as the conditioned stimulus (CS) paired with mild foot shocks as the unconditioned stimulus (US). Immediately following this training, the mice were infused with either **1390** or vehicle. Twenty-four hours later mice were assessed for cue-induced freezing in the absence of drug. A dose-dependent increase in percent freezing was observed for **1390** compared to vehicle for each of the tone-alone trials (Figure 15). In addition, a significant increase in freezing was observed in mice treated with **1390** (Figure 16).

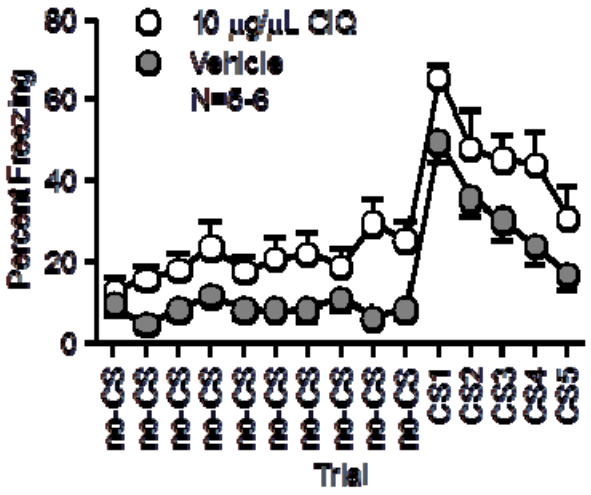



**Figure 15. Percent freezing in mice treated with 1390 (CIQ) or vehicle for the tone-alone trials**

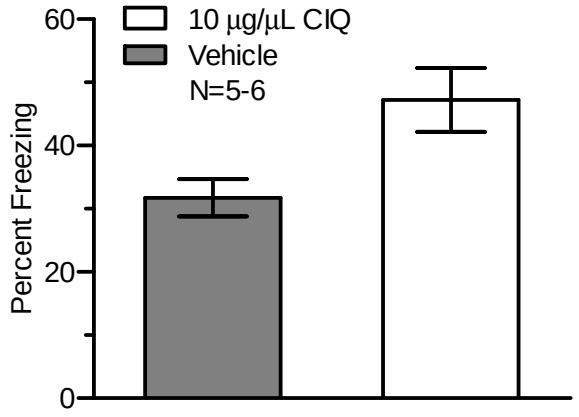



**Figure 16. Evaluation of percent freezing in mice treated with 1390 (CIQ) or vehicle during the tone-alone trials**

The effect of **1390** on the extinction of a previously learned fear was also evaluated. Mice were first subjected to fear conditioning and then placed into two groups based on expression of learned fear based on similar percent freezing. Twenty-four hours later, mice were given extinction training and were immediately treated with 10 µg **1390** or vehicle. Retention of the extinction training was evaluated 24 hours later in the absence of drug. The percent freezing observed at each of the tone-alone trials was decreased by **1390** administration which suggests that the treated mice had enhanced retention of extinction (Figure 17). As depicted in Figure 18, mice treated with CIQ (**1390**) displayed a smaller percent freezing compared to mice administered with vehicle.

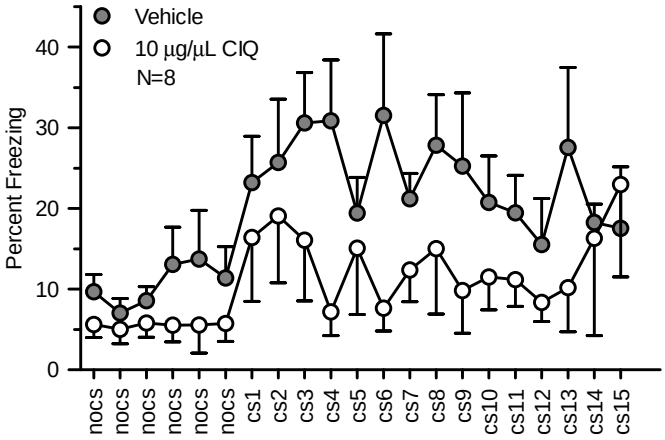



**Figure 17. Percent freezing in tone-alone trials following fear extinction training**

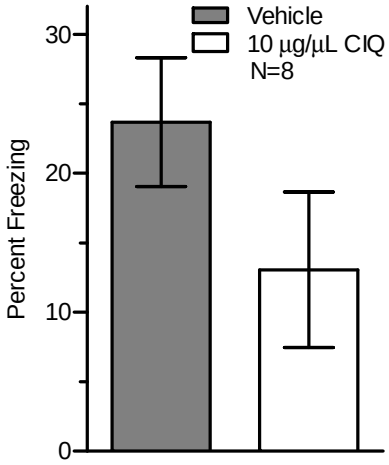



**Figure 18. Evaluation of percent freezing in response to conditioned stimuli (tone) for mice treated with CIQ (1390) and vehicle**

In addition, **1390** was tested on performance in the Morris water maze to evaluate the effect of **1390** on spatial memory and learning. For this experiment, **1390** was injected IP 30 minutes prior to training in the water maze. This number was chosen based on the half life and brain concentrations observed in the PK study. The treated mice performed similarly in this test to vehicle-treated mice with no differences observed in latency to mount the platform or

swimming the path length and both sets of mice appeared to learn the task over the course of the 5 days.

Since most of the compounds in the 1180-series have activity at GluN2C-containing NMDA receptors which are highly expressed in the cerebellum, **1390** was also evaluated for its effect on altering locomotor behavior or movement where it caused no detectable change in locomotor activity or time spent on the rotarod compared to vehicle.

## 2.5 CONCLUSIONS

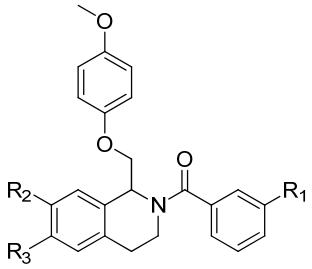
The positive modulation of NMDA receptor activity has long been hypothesized to have potential therapeutic benefit. Prior to this work, this hypothesis was unable to be tested as no selective positive allosteric modulators were known.

Using the screening hit **1180** as a starting point, a large number of structurally related compounds were synthesized. From these data, it was clear that potency of this series was highly dependent upon the substitution around each of the three aromatic rings. Modifications to either linker A (the amide linkage) or linker B (the ether linkage) did not increase potency, and in some cases resulted in a complete loss of activity. Substitution on the A-ring was well-tolerated but the most potent compounds contain a substituent in the *meta*-position. Specifically, this substitution is typically a chlorine or bromine. By contrast, substitution on the B-ring was not well-tolerated as the only compounds with significant potentiating effects contained a *para*-methoxy substituent on this ring. Changes made to the substitution around the C-ring had the largest positive effect on the potency of this series with the most potent analogues being the *O*-benzyl compounds **1180-97** and **1180-98**.

Interestingly, the enantiomers of **1390** had a differential effect on recombinant NMDA receptors with only the *S*-enantiomer having any detectable activity. Synthesis of the enantiomers was accomplished through the use of a chiral directing group and afforded both enantiomers in 99% *ee* for the active *S*-enantiomer and an 86% *ee* for the inactive *R*-enantiomer.

These data show that a previously unknown and novel pharmacophore exists in the M1 region of NMDA on the GluN2C- and GluN2D-subunits. A similar pharmacophore exists on GluN2A- and GluN2B-subunits as a few compounds in this class show potentiation at all four subunits. The most potency compounds in this series, **1180-97** and **1180-98** showed a significant improvement in potency of this series from the original screening hit with **1180-98** active at an $EC_{50}$ of 300 nM and potentiating to over 200% at both GluN2C- and GluN2D-containing NMDA receptors (Table 29).

**Table 29. Comparison between most potent compounds in the series with original screening hit**




| Compound ID | $R_1$ | $R_2$ | $R_3$ | GluN2C $EC_{50}$ (μM)[a] | GluN2D $EC_{50}$ (μM)[a] |
|---|---|---|---|---|---|
| **1180** | H | OMe | OMe | 12.3 (145%) | 11.4 (156%) |
| **1180-97** | Cl | H | OBn | 0.4 (254%) | 0.4 (198% |
| **1180-98** | Br | H | OBn | 0.3 (257%) | 0.3 (219%) |

[a] Fitted $EC_{50}$ values are shown to two significant digits; values in parentheses are the fitted maximum response as a percentage of the initial glutamate (100 μM) and glycine (30 μM) current. No Effect indicates less than 10% potentiation. Data are from between 4-17 oocytes from between 2-4 frogs for each compound and receptor tested.

Overall, this class of compounds portrayed generally poor aqueous solubility. As a result, undetectable precipitation during the biological evaluation may have occurred thereby reducing the actual concentration of compound in solution. As a consequence, the compounds discussed herein may be more potent than we have conservatively reported.

Evaluation of the pharmacokinetic properties of **1390** shows good blood-brain barrier penetration; a highly important factor for the therapeutic indications described. In addition, assessment of the efficacy of **1390** in an animal model of fear extinction showed enhanced retention of extinction of fear; a phenomenon which translates into a potential for compounds of this type in the treatment of anxiety. This also serves as a general proof of concept for the hypothesis that enhancement of NMDA function may have therapeutic benefit in anxiety disorders.

The compounds described herein represent the first-in-class subunit selective potentiators for GluN2C- and GluN2D-containing NMDA receptors. Further work is ongoing on this class of compounds to enhance the potency and explore the possibility of subunit selective potentiation at GluN2A- and GluN2B-containing NMDA receptors.

## 2.6 CHEMISTRY EXPERIMENTAL DETAIL

All reagents for synthesis were obtained from commercial suppliers and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) on precoated aluminum plates (silica gel 60 F254, 0.25 mm). Proton and carbon NMR spectra were recorded on an INOVA-400 (400 MHz) or VNMRS 400 (400 MHz). The spectra obtained were referenced to the residual solvent peak. Mass spectra were performed by the Emory University Mass Spectroscopy Center on either a VG 70-S Nier Johnson or JEOL instrument. Elemental analyses were performed by Atlantic Microlab Inc. Purity was established using HPLC for some compounds under the conditions listed. C, H, N agreed with proposed structures ±0.4% of theoretical values unless otherwise indicated. Flash chromatography was performed on a Teldyne ISCO CombiFlash Companion System with prepackaged Teledyne RediSep or Silicycle normal phase columns with silica gel.

### *2.6.1 Chemistry Experimental Detail for 1180-series*

**General preparation for 2-chloro-*N*-phenethylacetamide compounds (Procedure A).** A solution of a phenethylamine (1.0 equiv) in DCM was cooled to 0 $^{o}$C in an ice bath. To this solution, $Et_3N$ (3.0 equiv) was added followed by dropwise addition of an acid chloride (1.2 equiv). Upon complete addition, the reaction was warmed to room temperature and stirred for 2 hours. When TLC indicated complete conversion, the reaction mixture was concentrated *in vacuo*. The resulting residue was taken up into DCM and washed with a saturated solution of $NH_4Cl$ and brine. The aqueous layer was then extracted with DCM (2x). The organic layers were combined, washed with water, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The resulting solid was subjected to flash column chromatography.

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

**General preparation of *N*-(phenethyl)-3-phenylpropanamide and (*E*)-*N*-(phenethyl)-3-(phenyl)acrylamide compounds (Procedure C).** Phenylpropionic acid (6.7 mmol, 1.0 equiv) or cinnamic acid (5.6 mmol, 1.0 equiv) was dissolved in dry DCM (20 mL) and DMF (10 mL) and the reaction mixture was brought to 0 $^{o}$C in an ice bath. EDC (1.3 equiv) and DMAP (1.1 equiv) were added and the reaction mixture was stirred at 0 $^{o}$C for 2 hours. 3,4-dimethoxyphenethylamine (6.7 mmol, 1.0 equiv) was added dropwise. The solution was warmed to room temperature and stirred overnight. After TLC indicated complete conversion, 1M HCl was added and the reaction mixture was extracted into DCM (3x). The organics were combined, washed with brine and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting solid was subjected to flash column chromatography.

**General preparation for 3,4-dihydroisoquinoline compounds (Procedure D).** To a solution of **3** (3.5 mmol) suspended in toluene (40 mL) was added $POCl_3$ (3.0 equiv.), dropwise. The reaction

mixture was brought to reflux and allowed to stir for 90 minutes before cooling to room temperature. The resulting precipitate was filtered and carried on without further purification.

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

**General preparation for 1,2,3,4-tetrahydroisoquinoline compounds (Procedure F).** The dihydroisoquinoline **4** (4.0 mmol) was suspended in anhydrous MeOH (40 mL). The reaction mixture was cooled to 0 $^{o}$C in an ice bath. $NaBH_4$ (3.0-4.0 equiv.) was added slowly to the reaction mixture under an argon atmosphere. It was then allowed to warm to room temperature and stirred for 6 hours to overnight, until TLC indicated complete conversion. Volatiles were removed *in vacuo*. The resulting residue was dissolved in DCM and washed with 1 N HCl, water, and brine. The aqueous layer was extracted with DCM (2x). The organic layers were combined, dried over $MgSO_4$ and filtered. Volatiles were removed *in vacuo.* The crude residue was subjected to flash column chromatography.

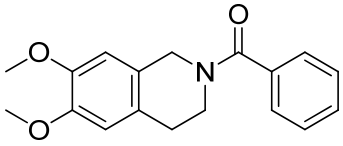
**General preparation for 1,2,3,4-tetrahydroisoquinoline compounds (Procedure G).** 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**45**, 1.0 g, 4.4 mmol) was dissolved in DCM (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The biphasic reaction mixture was cooled to 0 $^{o}$C in an ice bath and benzoyl chloride (3 equiv) was added dropwise. After complete addition, the reaction was warmed to room temperature and stirred

for an additional 2 hours, when TLC indicated complete conversion. The organics were separated and the aqueous phase was extracted with DCM (2x). The organics were combined, washed with brine and water, dried over MgSO4, filtered and concentrated *in vacuo*. The resulting residue was subjected to flash column chromatography.

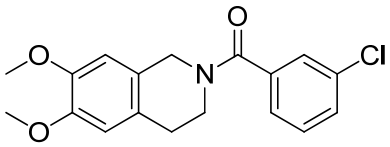
**General preparation for 3,4-dihydroisoquinolin-2(*1H*)-yl)methanone compounds (Procedure H).** The tetrahydroisoquinoline **5** (1 mmol) was dissolved in anhydrous DCM (10 mL). The solution was cooled to 0 $^{o}$C in an ice bath. Triethylamine (3.0 equiv.) was added to the cooled solution followed by dropwise addition of a benzoyl chloride (1.2 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for an additional 90 minutes. Volatiles were removed *in vacuo*. The resulting residue was treated with $NH_4Cl$ saturated solution followed by extraction with DCM (2x). The organic phase was washed with brine and water, dried over $MgSO_4$, filtered, and concentrated to yield a residue. The resulting residue was subjected to column chromatography to afford the final products as a mixture of two rotamers.

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

**Individual Procedures**

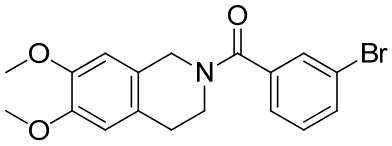


**(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-28).** Compound **1180-28** was prepared according to Procedure G using benzoyl chloride (1.5 mL, 13 mmol, 3.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.9 g, 67%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.45-7.39 (m, 7H), 6.62-6.38 (m, 1H), 4.81 (m, 1H), 3.97 (m, 1H), 3.86 (s, 6H), 3.76 (m, 1H), 3.60 (m, 1H), 2.81 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.1, 170.6, 147.9, 136.4, 129.9, 128.7, 127.4, 127.0, 125.8, 125.0, 111.5, 109.6, 108.8, 56.2, 56.1, 49.8, 45.6, 44.7, 29.3, 28.1. HRMS calcd. for $C_{18}H_{20}NO_3$, 298.14377 $[M + H]^+$; found, 298.14362 $[M + H]^+$. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 1.782 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 1.783 minutes).

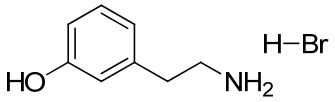


**(3-chlorophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-29).** Compound **1180-29** was prepared according to Procedure G using 3-chlorobenzoyl chloride (1.7 mL, 13 mmol, 3.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 1.1 g, 76%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.51-7.31 (m, 4H), 6.65-6.39

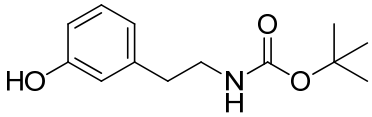
(m, 2H), 4.80 (s, 1H), 3.96 (m, 1H), 3.84 (s, 6H), 3.77 (m, 1H), 3.60 (m, 1H), 2.88 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.6, 169.2, 148.2, 137.9, 134.8, 133.2, 130.5, 129.9, 127.3, 125.6, 125.2, 124.7, 111.6, 109.5, 108.8, 56.2, 56.1, 49.7, 45.6, 44.7, 29.3, 27.9. HRMS calcd. for $C_{18}H_{19}NO_3Cl$, 332.10480 $[M + H]^+$; found, 332.10483 $[M + H]^+$. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 98% purity (retention time = 1.670 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 99% purity (retention time = 1.671 minutes).




**(3-bromophenyl)(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-30).** Compound **1180-30** was prepared according to Procedure G using 3-bromobenzoyl chloride (1.7 mL, 13 mmol, 3.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.4 g, 85%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.56-7.52 (m, 2H), 7.30 (d, *J*= 7.6 Hz, 1H), 7.29-7.24 (m, 1H), 6.63-6.68 (m, 2H), 4.76 (m, 1H), 4.45 (m, 1H), 3.93 (m, 1H), 3.82 (s, 6H), 3.75 (m, 1H), 3.57 (m, 1H), 2.81 (m, 1H).$^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.4, 148.2, 138.2, 133.1, 130.4, 130.2, 126.6, 125.9, 125.6, 124.7, 124.4, 122.9, 111.7, 109.5, 56.2, 56.1, 54.1, 49.7, 45.6, 44.7, 29.2, 28.1. HRMS calcd. for $C_{18}H_{19}NO_3Br$, 376.05428 $[M + H]^+$; found, 376.05471 $[M + H]^+$. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 98.5% purity (retention time = 1.751 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 99% purity (retention time = 1.750 minutes).

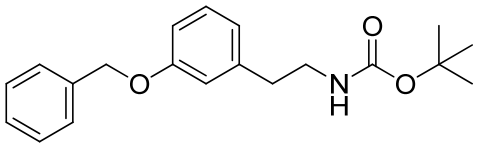



**3-(2-aminoethyl)phenol hydrobromide (27).** 3-methoxyphenethylamine (**26**, 1.0 g, 6.6 mmol) was dissolved in acetic acid (10 mL) and concentrated HBr (30 equiv, 11 mL) and heated to reflux. The solution was stirred at reflux for 4 hours and then cooled to room temperature. The volatiles were removed *in vacuo* using ethanol as an azeotrope to afford the title compound as a pale orange solid (1.4 g, 100%). $^{1}$H NMR (400 MHz, $CD_3OD$) δ: 7.13 (t, *J* = 7.8 Hz, 1H), 6.73-6.66 (m, 3H), 3.14 (t, *J* = 7.6 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CD_3OD$) δ: 157.8, 138.1, 129.8, 119.6, 115.4, 114.0, 40.8, 33.3. HRMS calcd. for $C_8H_{12}NO$, 138.09134 $[M + H]^+$; found, 138.09124 $[M + H]^+$.

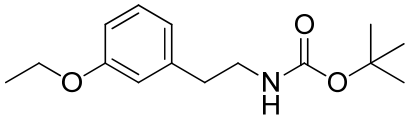



***tert*-butyl 3-hydroxyphenethylcarbamate (28).** Compound **27** (1.4 g, 6.6 mmol) was dissolved in DMF (2 mL) and dioxane (20 mL). Triethylamine (0.67 g, 6.6 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred for 15 minutes. Di-*tert*-butyl dicarbonate (1.4 g, 6.6 mmol, 1.0 equiv) was added to the suspension and the reaction was stirred at room temperature for 18 hours. The volatiles were removed *in vacuo* and the resulting residue was washed with water and extracted with EtOAc (3x). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. The crude oil was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.32 g, 84%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.16 (t, *J* = 7.8 Hz, 1H), 6.74-6.69 (m, 3H), 6.43 (s, 1H, broad), 4.65 (s, 1H, broad), 3.38 (q, *J* = 6.8 Hz, 2H), 2.74 (t, *J* =

6.8 Hz, 2H), 1.45 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 156.5, 140.6, 129.9, 120.8, 116.0, 113.8, 41.8, 36.3, 28.6. HRMS calcd. for $C_{13}H_{20}NO_3$ 238.14377 [M + H]; found 238.14385 [M + H].

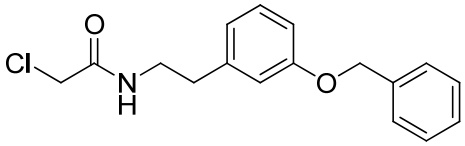


***tert*-butyl 3-(benzyloxy)phenethylcarbamate (29a).** Compound **28** (3.0 g, 12.6 mmol) was dissolved in dry MeCN (50 mL). Cesium carbonate (4.1 g, 12.6 mmol, 1.0 equiv) was added to the solution and the resulting mixture was allowed to stir for 30 minutes. Benzyl bromide (3.5 g, 20.2 mmol, 1.6 equiv) was added and the reaction was allowed to stir for 24 hours. When TLC indicated complete conversion, water was added and the aqueous phase was extracted with EtOAc (2x). The organics were combined and washed with brine (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a light orange oil (3.1 g, 75%). $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.45-7.32 (m, 5H), 7.34-7.20 (m, 1H), 6.86-6.79 (m, 3H), 5.05 (s, 2H), 4.68 (s, 1H, broad), 3.37 (q, *J* = 6.6 Hz, 2H), 2.77 (t, 2H, *J* = 6.6 Hz), 1.46 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 159.2, 156.1, 140.9, 137.2, 129.8, 128.8, 128.2, 127.8, 121.7, 115.7,112.9, 79.4, 70.1, 41.9, 36.5, 28.7. HRMS calcd. for $C_{20}H_{25}NO_3Na$, 350.17267 [M + Na]; found 350.17267 [M + Na].



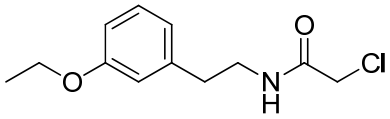
**tert-butyl 3-ethoxyphenethylcarbamate (29b).** Compound **29a** (3.0 g, 12.6 mmol) was dissolved in dry DMF (40 mL). Cesium carbonate (12.4 g, 38 mmol, 3.0 equiv) was added to the solution and the resulting mixture was allowed to stir for 30 minutes. Iodoethane (1.6 mL, 20.2

mmol, 1.6 equiv) was added and the reaction was allowed to stir for 24 hours. When TLC indicated complete conversion, water was added and the aqueous phase was extracted with EtOAc (2x). The organics were combined and washed with brine (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.9 g, 86%). $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.17 (t, *J*= 7.8 Hz, 1H), 6.74-6.70 (m, 3H), 4.61 (s, 1H, broad), 3.99 (q, *J* = 6.8 Hz, 2H), 3.34 (q, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 1.41 (s, 9H), 1.38 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 159.3, 156.1, 140.8, 129.7, 121.2, 115.2, 112.5, 79.4, 63.5, 41.9, 36.4, 28.6, 15.1. HRMS calcd. for $C_{15}H_{23}NO_3Na$, 288.15702 [M + Na]; found 288.15705 [M + Na].



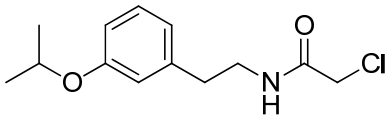

***N*-(3-(benzyloxy)phenethyl)-2-chloroacetamide (30a).** Compound **29a** (3.1 g, 9.5 mmol) was dissolved in diethyl ether (30 mL) and concentrated HCl (13 mL) and was allowed to stir at room temperature. After 2 hours, a white precipitate was present and TLC indicated complete consumption of starting material. The precipitate was filtered, washed with diethyl ether and carried on without purification. HRMS calcd. for $C_{15}H_{18}NO$, 228.13829 [M + H]; found 228.13807 [M + H]. The crude solid (2.5 g, 9.5 mmol)was dissolved in DCM (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). After 30 minutes of stirring at room temperature, chloroacetyl chloride (1.4 g, 12.3 mmol, 1.3 equiv) was added to the biphasic mixture. After 2 hours, TLC indicated complete conversion. The organic layer was removed and the aqueous phase extracted with DCM (2x). The organics were combined, washed with brine (2x), dried over MgSO4, filtered and concentrated *in vacuo*. The resulting solid was purified by silica gel chromatography (ISCO,

Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (2.09, 73%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.32 (m, 5H), 7.25-7.21 (m, 1H), 6.87-6.79 (m, 3H), 6.65 (s, 1H, broad), 5.05 (s, 2H), 4.00 (s, 2H), 3.54 (q, *J* = 7.0 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 166.1, 159.3, 140.2, 137.2, 130.0, 128.8, 128.2, 127.7, 121.6, 115.6, 113.2, 70.2, 42.9, 41.1, 35.7. HRMS calcd. for $C_{17}H_{19}NO_2Cl$, 304.10988 [M + H]; found 304.10954 [M + H].

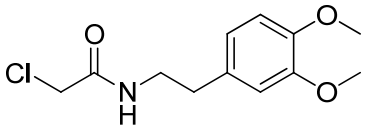



**2-chloro-N-(3-ethoxyphenethyl)acetamide (30b).** Compound **29b** (3.1 g, 9.5 mmol) was dissolved in diethyl ether (30 mL) and concentrated HCl (13 mL) and was allowed to stir at room temperature. After 2 hours, a white precipitate was present and TLC indicated complete consumption of starting material. The precipitate was filtered, washed with diethyl ether and carried on without purification. HRMS calcd. for $C_{10}H_{16}NO$, 166.12264 [M + H]; found 166.12241 [M + H]. The crude solid (2.2 g, 10.9 mmol) was dissolved in DCM (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). After 30 minutes of stirring at room temperature, chloroacetyl chloride (1.1 mL, 14.1 mmol, 1.3 equiv) was added to the biphasic mixture. After 2 hours, TLC indicated complete conversion. The organic layer was removed and the aqueous phase extracted with DCM (2x). The organics were combined, washed with brine (2x), dried over MgSO4, filtered and concentrated *in vacuo*. The resulting solid was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.3, 49%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.23 (t, *J* = 7.8 Hz, 1H), 6.80-6.74 (m, 3H), 6.65 (s, 1H, broad), 4.03 (m, 2H), 4.02 (s, 2H), 3.59 (q, *J* = 6.6 Hz, 2H), 2.82 (t, *J* = 6.6 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 166.0, 159.5, 140.1, 129.4,

121.1, 115.1, 112.9, 63.6, 42.9, 41.1, 35.7, 15.1. HRMS calcd. for $C_{12}H_{17}NO_2Cl$, 242.09423 [M + H]; found 242.09402 [M + H].

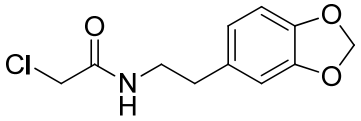


**2-chloro-N-(3-isopropoxyphenethyl)acetamide (18a).** 2-(3-isopropoxyphenyl)ethanamine hydrochloride (2.0 g, 9.3 mmol) was dissolved in a mixture of DCM (30 mL), $Et_3N$ (4 mL) and saturated aqueous $NaHCO_3$ (30 mL). The biphasic reaction mixture was cooled to 0 $^oC$ and chloroacetyl chloride (1.3 g, 11 mmol, 1.2 equiv) was added dropwise with stirring. Once the addition was complete, the reaction was warmed to room temperature and stirred for an additional 2 hours with TLC monitoring. After TLC indicated complete conversion, the organics were separated and the aqueous phase was extracted with DCM (2x). The combined organics were washed with brine and water, dried over MgSO4, filtered and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (ISCO, Silicycle 25 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.7 g, 72%). $^1H$ NMR ($CDCl_3$, 400 MHz) δ: 7.22 (t, *J* = 8 Hz, 1H), 6.77 (m, 3H), 6.65 (s, 1H, broad), 4.55 (sep., *J* = 6 Hz, 1H), 4.03 (s, 2H), 3.56 (q, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 1.34 (d, *J* = 6 Hz, 6H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ: 166.0, 158.4, 140.1, 129.9, 121.1, 116.7, 114.1, 70.0, 42.9, 41.1, 35.7, 22.3. HRMS calcd. for $C_{13}H_{19}O_2NCl$ , 256.10988 $[M + H]^+$; found, 256.10998 $[M + H]^+$.

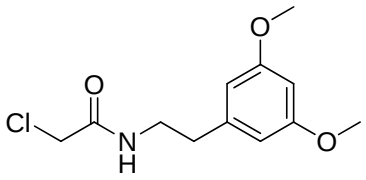


**2-chloro-*N*-(3,4-dimethoxyphenethyl)acetamide (18b)**. Compound **18b** was prepared according to Procedure A using 3,4-dimethoxyphenethylamine (2.0 g, 11 mmol, 1.0 equiv) and chloroacetyl chloride (1.5 g, 13 mmol, 1.2 equiv) in DCM (40 mL). The crude solid was purified

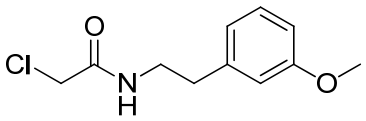
by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.0 g, 70%). TLC (EtOAc:hexanes, 1:1 v/v): $R_f$ = 0.43; $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.84 (s, 1H, broad), 6.67 (d, *J*= 20 Hz, 1H), 6.59 (m, 2H), 3.84 (s, 2H), 3.70 (s, 3H), 3.68(s, 3H), 3.37 (q, *J*= 6.4 Hz, 2H), 2.63 (t, *J*= 6.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 166.1, 149.0, 147.8, 131.2, 120.8, 112.3, 111.5, 55.9, 55.9, 42.8. 41.3, 35.1. HRMS calcd. for $C_{12}H_{17}NO_3Cl$, 258.08915 $[M + H]^+$; found, 258.08945 $[M + H]^+$.



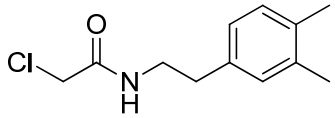

**N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-chloroacetamide (18c).** 2-(1,3-benzodioxol-5-yl)ethanamine hydrochloride (0.6 g, 3.0 mmol, 1.0 equiv) was dissolved in a mixture of DCM (20 mL) and saturated sodium bicarbonate solution (20 mL). The biphasic reaction mixture was cooled to 0 $^o$C and chloroacetyl chloride (0.4 g, 3.6 mmol, 1.2 equiv) was added dropwise with stirring. Once the addition was complete, the reaction was warmed to room temperature and stirred for an additional 2 hours. After TLC indicated complete conversion, the organics were separated and the aqueous phase was extracted with DCM (2x). The combined organics were washed with 1M HCl and brine, dried over MgSO4, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (0.54 g, 75%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.81 (s, 1H, broad), 6.69 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 2 Hz, 1H), 6.58 (dd, $J_1$ = 1.6 Hz, $J_2$ = 8 Hz, 1H), 5.86 (s, 2H), 3.94 (s, 2H), 3.44 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.2, 148.0, 146.5, 132.3, 121.8, 109.2, 108.6, 101.2, 42.9, 41.4, 35.3. HRMS calcd. For $C_{11}H_{13}NO_3Cl$, 242.05785 $[M + H]^+$; found 242.05823 $[M + H]^+$.



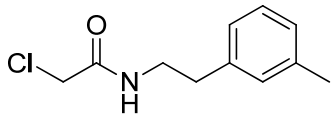
**2-chloro-N-(3,5-dimethoxyphenethyl)acetamide (18d).** Compound **18d** was prepared according to Procedure A using 3,5-dimethoxyphenethylamine (3.0 g, 16.6 mmol, 1.0 equiv) and chloroacetyl chloride (2.2 g, 19.8 mmol, 1.2 equiv) in DCM (40 mL). The crude product was purified by silica gel chromatography (0-70% EtOAc/hexanes) to afford the title compound as a white solid (2.9 g, 68%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.79 (s, 1H, broad), 6.32 (s, 3H), 3.98 (s, 2H), 3.73 (s, 6H), 3.50 (q, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.3, 161.2, 140.9, 106.8, 98.8, 55.5, 55.4, 42.8, 41.0, 35.9. HRMS calcd. for $C_{12}H_{17}NO_3Cl$, 258.08915 $[M + H]^+$; found, 258.08882 $[M + H]^+$.



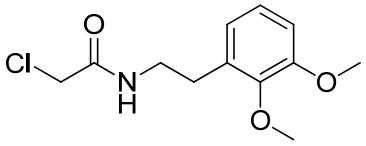
**2-chloro-N-(3-methoxyphenethyl)acetamide (18e).** Compound **18e** was prepared according to Procedure A using 3-methoxyphenethylamine (2.0 g, 13 mmol) and chloroacetyl chloride (1.5 g, 13 mmol, 1.0 equiv) in DCM (40 mL). The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.2 g, 73%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (t, *J* = 7.6 Hz, 1H), 6.79-6.73 (m, 4H), 3.99 (s, 3H), 3.78 (s, 2H), 3.54 (q, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 160.1, 140.2, 129.9. 121.2, 114.6, 112.3, 55.4, 42.9, 41.1, 35.7. HRMS calcd. for $C_{11}H_{15}NO_2Cl$, 228.07858 $[M + H]^+$; found 228.07848 $[M + H]^+$.



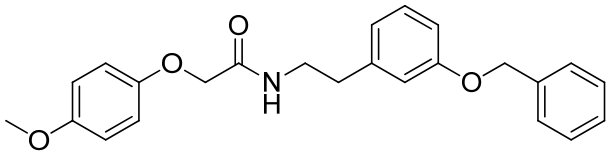
**2-chloro-N-(3,4-dimethylphenethyl)acetamide (18f).** Compound **18f** was prepared according to Procedure A using 3,4-dimethylphenethylamine (2.0 g, 13.4 mmol, 1.0 equiv) and chloroacetyl chloride (4.5 g, 40 mmol, 3.0 equiv) in DCM (40 mL). The crude material was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (2.5 g, 83%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.07 (d, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.89 (s, 1H, broad), 3.97 (s, 2H), 3.51 (q, *J* = 6.6 Hz, 2H), 2.78 (t, *J* = 6.6 Hz, 2H), 2.25 (s, 3H), 2.24 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.3, 137.1, 136.0, 135.0, 130.4, 130.3, 130.2, 126.3, 126.2, 42.9, 41.1, 35.2, 20.0, 19.6. HRMS calcd. for $C_{12}H_{17}NOCl$ , 226.09932 $[M + H]^+$; found, 226.09932 $[M + H]^+$.



**2-chloro-N-(3-methylphenethyl)acetamide (18g).** Compound **18g** was prepared according to Procedure A using 3-methylphenethylamine (2.0 g, 14.85 mmol, 1.0 equiv) and chloroacetyl chloride (2.0 g, 17.8 mmol, 1.2 equiv) in DCM (40 mL). The crude material was purified by silica gel chromatography (ISCO, RediSep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an orange oil (2.3 g, 74%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 7.6 Hz, 1H), 7.04-6.97 (m, 3H), 6.78 (s, 1H, broad), 3.97 (s, 2H), 3.51 (q, *J*= 7.2 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.2, 138.6, 129.8, 128.8, 127.6, 126.0, 42.9, 41.3, 35.6, 21.6. HRMS calcd. for $C_{11}H_{15}NOCl$ , 212.08367 $[M + H]^+$; found, 212.08299 $[M + H]^+$.

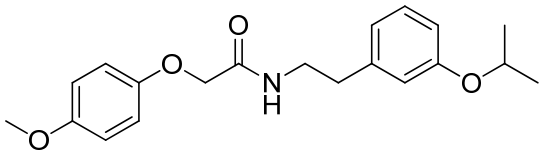


**2-chloro-*N*-(2,3-dimethoxyphenethyl)acetamide (18h).** Compound **18h** was prepared according to Procedure A using 2,3-dimethoxyphenethylamine (2.0 g, 11.0 mmol, 1.0 equiv) and chloroacetyl chloride (1.5 g, 13.2 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 25g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.88 g, 66%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.97 (t, $J$ = 7.6 Hz, 1H), 6.95 (s, 1H, broad), 6.80 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.0 Hz, 1H), 6.74 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.0 Hz, 1H), 3.96 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.49 (q, $J$ = 6.8 Hz, 2H), 2.84 (t, $J$ = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.3, 153.0, 147.3, 132.6, 124.5, 122.6, 111.5, 60.9, 56.0, 42.8, 41.1, 29.9. HRMS calcd. for $C_{12}H_{17}NO_3Cl$ , 258.08915 $[M + H]^+$; found, 258.08903 $[M + H]^+$.

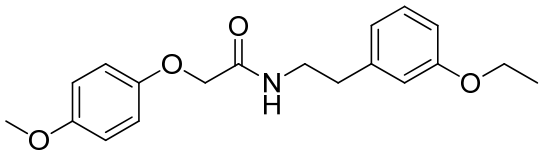


***N*-(3-(benzyloxy)phenethyl)-2-(4-methoxyphenoxy)acetamide (22a).** Compound **22a** was prepared according to Procedure B using **30a** (2.1 g, 6.9 mmol, 1.0 equiv) and 4-methoxyphenol (1.03 g, 8.3 mmol, 1.2 equiv) in MeCN (40 mL). The crude solid was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.1 g, 78%). TLC (EtOAc:hexanes, 1:2 v/v): $R_f$ = 0.41; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.31 (m, 5H), 7.21 (t, $J$ = 7.8 Hz, 1H), 6.87-6.76 (m, 7H), 6.70 (m, 1H, broad), 5.02 (s, 2H), 4.40 (s, 2H), 3.73 (s, 3H), 3.59 (q, $J$ = 6.8 Hz, 2H), 2.81 (t, $J$ = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.3, 154.9, 151.6, 140.5, 137.2, 130.0, 128.8, 128.2, 127.8, 121.6,

115.9, 115.6, 115.0, 113.1, 70.1, 68.4, 55.9, 55.9, 40.2, 35.9. HRMS calcd. for $C_{24}H_{26}NO_4$, 392.18564 $[M + H]^+$; found, 392.18551 $[M + H]^+$.

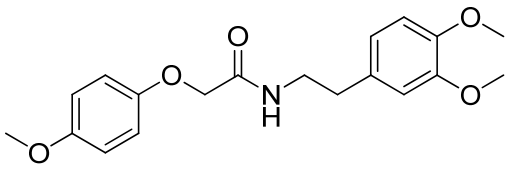


***N*-(3-isopropoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (22b).** Compound **22b** was prepared according to Procedure B using **18a** (1.6 g, 6.3 mmol) and 4-methoxyphenol (0.93 g, 7.5 mmol, 1.2 equiv) in dry MeCN (30 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.88 g, 87%). $^1$H NMR ($CDCl_3$, 400 MHz) δ : 7.20 (t, *J* = 8.4 Hz, 1H), 6.85-6.72 (m, 7H), 6.70 (s, 1H, broad), 4.54 (sep, *J* = 6 Hz, 1H), 4.42 (s, 2H), 3.78 (s, 3H), 3.60 (q, *J* = 6.4 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 1.33 (d, *J* = 5.6 Hz, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 158.4, 154.9, 151.5, 140.4, 129.8, 121.2, 116.7, 115.9, 115.0, 113.9, 69.8, 68.3, 56.0, 40.2, 35.9, 22.2. HRMS calcd. for $C_{20}H_{26}O_4N$, 344.18564 $[M + H]^+$; found, 344.18550 $[M + H]^+$.

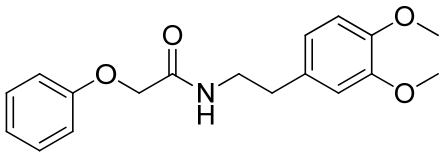


**N-(3-ethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (22c).** Compound **22c** was prepared according to Procedure B using **30b** (1.3 g, 5.4 mmol) and 4-methoxyphenol (0.80 g, 6.5 mmol, 1.2 equiv) in dry MeCN (30 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.5 g, 85%). $^1$H NMR ($CDCl_3$, 400 MHz) δ : 7.19 (t, *J* = 8.0 Hz, 1H), 6.81-6.70 (m, 7H), 4.37 (s, 2H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.56 (q, *J*= 6.8 Hz, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 1.37 (t, *J*= 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 159.4, 154.9, 151.6, 140.3,

129.9, 121.2, 115.9, 115.1, 115.0, 112.7, 68.4, 63.5, 55.9, 40.2, 35.9, 15.1. HRMS calcd. for $C_{19}H_{24}NO_4$ , 330.16999 $[M + H]^+$; found, 330.16956 $[M + H]^+$.

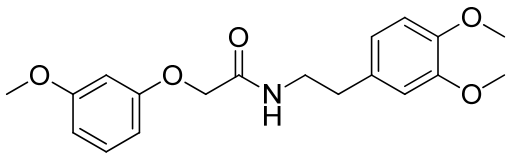


***N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (16).** Compound **16** was prepared according to Procedure B using **18b** (2.2 g, 8.7 mmol, 1.2 equiv.) and 4-methoxyphenol (0.90 g, 7.3 mmol) in MeCN (30 mL). The crude solid was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.0 g, 80%). TLC (EtOAc:hexanes, 1:2 v/v): $R_f$ = 0.34; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.68-6.84 (m, 8H), 4.42 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.58 (q, *J*= 6.4 Hz, 2H), 2.79 (t, *J*=7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 154.9, 151.5, 149.2, 147.9, 131.2, 120.9, 115.8, 115.0, 112.0, 111.5, 68.4, 56.1, 56.0, 55.9, 40.4, 35.5. HRMS calcd. for $C_{19}H_{24}NO_3$ , 346.16490 $[M + H]^+$; found, 346.16515 $[M + H]^+$.

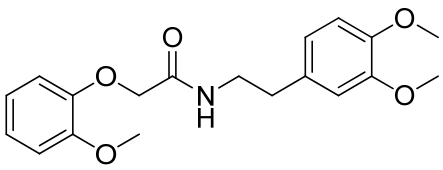


**N-(3,4-dimethoxyphenethyl)-2-phenoxyacetamide. (22d).** Compound **22d** was prepared according to Procedure A using 3,4-dimethoxyphenethylamine (1.0 g, 0.92 mL, 5.5 mmol, 1.0 equiv) and phenoxyacetyl chloride (1.2 g, 1.0 mL, 7.2 mmmol, 1.3 equiv). The crude solid was purified by silica gel chromatography (ISCO, Redisep 20-80% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.2 g, 69% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.24 (m, 2H), 7.00 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.68-6.65 (m, 2H), 6.63

(s, 1H, broad), 4.46 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.56 (q, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.3, 157.4, 149.3, 147.9, 131.2, 130.0, 122.3, 120.9, 114.8, 112.0, 111.5, 67.6, 56.1, 56.0, 40.4, 35.5.

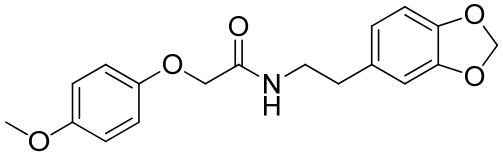


**N-(3,4-dimethoxyphenethyl)-2-(3-methoxyphenoxy)acetamide (22e).** Compound **22e** was prepared according to Procedure B using 3-methoxyphenol (0.6 g, 0.52 mL, 4.8 mmol, 1.0 equiv) and **18b** (1.5 g, 5.8 mmol, 1.2 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.5 g, 90% yield). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.70-6.66 (m, 3H), 6.57 (dd, $J_1$ = 1.4 Hz, $J_2$ = 8.4 Hz, 1H), 6.45-6.40 (m, 2H), 4.45 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.77 (s, 3H), 3.57 (q, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.2, 161.2, 158.5, 149.2, 147.9, 131.2, 130.5, 120.9, 112.0, 111.5, 107.8, 106.7, 101.5, 67.6, 56.1, 56.0, 55.5, 40.4, 35.5. HRMS calcd. for $C_{19}H_{24}NO_5$ , 346.16490 $[M + H]^+$; found, 346.16497 $[M + H]^+$.

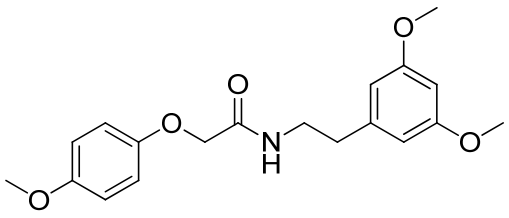


**N-(3,4-dimethoxyphenethyl)-2-(2-methoxyphenoxy)acetamide (22f).** Compound **22f** was prepared according to Procedure B using **18b** (1.5 g, 5.8 mmol, 1.2 equiv) and 2-methoxyphenol (0.6 g, 0.52 mL, 4.8 mmol, 1.0 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-60% EtOAc/hexanes gradient) to afford

the title compound as a white solid (1.1 g, 66%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.06 (s, 1H, broad), 6.95 (m, 1H), 6.86-6.77 (m, 3H), 6.73-6.70 (m, 1H), 6.66-6.63 (m, 2H), 4.46 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.53 (q, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H). $^{13}$C ($CDCl_3$, 100 MHz) δ: 168.7, 149.7, 149.1, 147.8, 147.3, 131.4, 123.2, 121.2, 120.8, 115.4, 112.1, 112.0, 111.5, 69.7, 56.0, 55.9, 55.8, 40.5, 35.5. HRMS calcd. for $C_{19}H_{24}NO_5$, 346.16490 $[M + H]^+$; found, 346.16484 $[M + H]^+$.

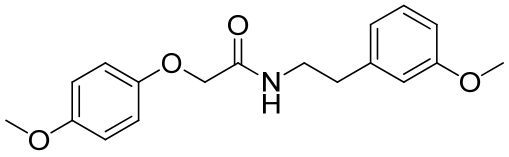


**N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-(4-methoxyphenoxy)acetamide (22g).** Compound **22g** was prepared according to Procedure B using **18c** (0.5 g, 2.2 mmol, 1.0 equiv) and 4-methoxyphenol (0.3 g, 2.5 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.56 g, 76%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.84 (d, *J* = 9.2 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.73-6.57 (m, 3H), 5.93 (s, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.54 (q, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.5, 148.1, 146.5, 132.5, 132.5, 121.9, 115.8, 115.0, 109.3, 108.6, 101.1, 68.3, 55.9, 40.4, 35.6. HRMS calcd. For $C_{18}H_{20}NO_5$, 330.13360 $[M + H]^+$; found 330.13387 $[M + H]^+$.

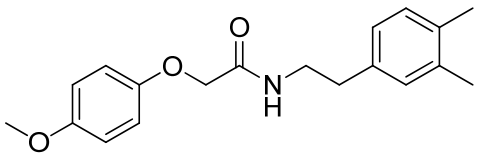


**N-(3,5-dimethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (22h).** Compound **22h** was prepared according to Procedure B using **18d** (1.0 g, 3.9 mmol, 1.0 equiv) and 4-methoxyphenol

(0.53, 4.3 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.9 g, 67%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.80-6.72 (m, 5H), 6.31 (s, 3H), 4.37 (s, 2H), 3.72 (s, 3H), 3.72 (s, 6H), 3.55 (q, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 161.2, 154.9, 151.6, 141.1, 115.8, 115.0, 106.9, 98.8, 68.4, 55.5, 40.1, 40.1, 36.1. HRMS calcd. for $C_{19}H_{24}NO_5$ , 346.16490 $[M + H]^+$; found, 346.16497 $[M + H]^+$.

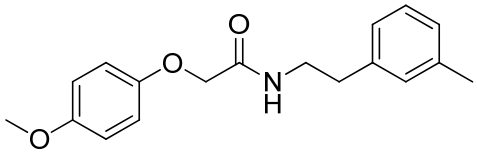


**N-(3-methoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (22i).** Compound **22i** was prepared according to Procedure B using **18e** (2.2 g, 10 mmol, 1.0 equiv) and 4-methoxyphenol (1.4 g, 12 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.5 g, 82%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 2H), 6.81-6.77 (m, 3H), 6.75-6.75 (m, 2H), 6.68 (s, 1H, broad), 4.42 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.61 (q, *J* = 6.8 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 160.1, 154.9, 151.5, 140.4, 129.9, 121.3, 115.8, 115.0, 114.5, 112.2, 55.9, 55.4, 55.3, 40.2, 35.9. HRMS calcd. For $C_{18}H_{22}NO_4$, 316.15433 $[M + H]^+$; found 316.15410 $[M + H]^+$.

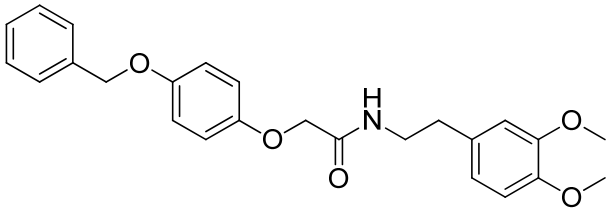


**N-(3,4-dimethylphenethyl)-2-(4-methoxyphenoxy)acetamide (22j).** Compound **22j** was prepared according to Procedure B using **18f** (2.5 g, 11.1 mmol, 1.0 equiv) and 4-methoxyphenol

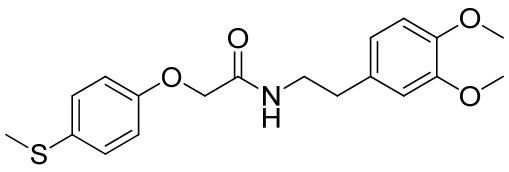
(1.65 g, 13.3 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 40g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.7g, 78%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.07 (d, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.71 (s, 1H, broad), 4.43 (s, 2H), 3.78 (s, 3H), 3.58 (q, *J* = 6.8 Hz, 2H), 2.79 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.6, 137.1, 136.2, 135.0, 130.3, 126.3, 115.8, 115.0, 68.4, 55.9, 55.8, 40.5, 35.4, 19.9, 19.6. HRMS calcd. For $C_{19}H_{23}NO_3$, 314.17507 $[M + H]^+$; found 314.17489 $[M + H]^+$.




**2-(4-methoxyphenoxy)-N-(3-methylphenethyl)acetamide (22k).** Compound **22k** was prepared according to Procedure B using **18g** (2.3 g, 10.9 mmol, 1.0 equiv) and 4-methoxyphenol (1.63 g, 13.1 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a pale orange solid (2.5 g, 77%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 7.2 Hz, 1H), 7.07-6.96 (m, 3H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.71 (s, 1H, broad), 4.43 (s, 2H), 3.78 (s, 3H), 3.60 (q, *J* = 6.6 Hz, 2H), 2.82 (t, *J* = 6.6 Hz, 2H), 2.33 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.9, 151.6, 138.7, 138.5, 129.8, 128.8, 127.6, 126.0, 115.8, 115.0, 68.4, 55.9, 40.3, 35.8, 21.6. HRMS calculated for $C_{18}H_{22}NO_3$, 300.15942 $[M + H]^+$, found 300.15920 $[M + H]^+$.

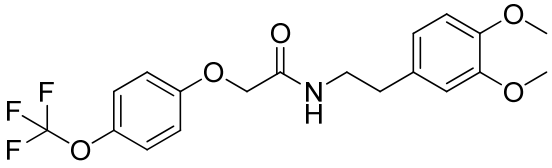


**2-(4-(benzyloxy)phenoxy)-N-(3,4-dimethoxyphenethyl)acetamide (22l).** Compound **22l** was prepared according to Procedure B using **18b** (0.9 g, 3.5 mmol, 1.0 equiv) and 4-(benzyloxy)phenol (0.84, 4.2 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 24g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (1.1 g, 75%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.30 (m, 5H), 6.92-6.90 (d, *J* = 9.2 Hz, 2H), 6.80-6.77 (m, 3H), 6.72-6.70 (m, 3H), 5.02 (s, 2H), 4.42 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.59 (q, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.6 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.1, 151.7, 149.2, 147.9, 137.2, 131.2, 128.8, 128.2, 127.7, 120.9, 116.2, 115.8, 112.0, 111.5, 70.8, 68.3, 56.1, 56.0, 40.4, 35.5. HRMS calcd. For $C_{25}H_{27}NO_5$, 422.19620 $[M + H]^+$; found 422.19572 $[M + H]^+$.

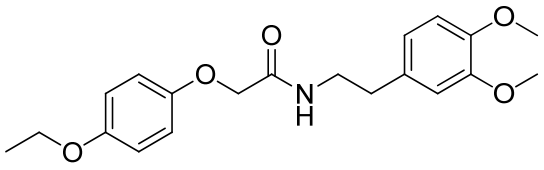


**N-(3,4-dimethoxyphenethyl)-2-(4-(methylthio)phenoxy)acetamide (22m).** Compound **22m** was prepared according to Procedure B using **18b** (1.2 g, 4.7 mmol) and 4-(methylmercapto)phenol (0.78 g, 5.6 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes) to afford the title compound as an off-white solid (1.2 g, 71%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, *J* = 8.8 Hz, 2H), 6.77-6.74 (m, 3H),6.69-6.67 (m, 2H), 6.61 (s, 1H, broad), 4.42 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.56 (q, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ:

168.2, 155.6, 149.2, 147.9, 131.1, 129.7, 120.9, 115.5, 111.9, 111.5, 67.7, 56.1, 56.0, 40.4, 35.5, 17.6. HRMS calcd. for $C_{19}H_{23}NO_4S$, 362.14206 $[M + H]^+$; found 362.14183 $[M + H]^+$.

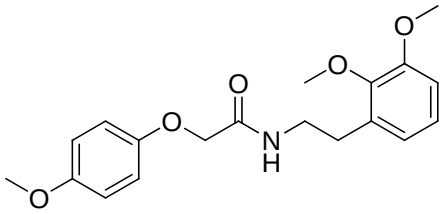


**N-(3,4-dimethoxyphenethyl)-2-(4-(trifluoromethoxy)phenoxy)acetamide (22n).** Compound **22n** was prepared according to Procedure B using **18b** (1.0 g, 4.4 mmol, 1.2 equiv) and 4-trifluoromethoxyphenol (0.6 g, 3.4 mmol, 1.0 equiv) in dry MeCN (40 mL). The crude solid was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.0 g, 74% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (d, *J* = 8.8 Hz, 2H), 6.83-6.58 (m, 6H), 4.43 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.58 (q, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 167.8, 155.8, 149.2, 147.9, 131.1, 122.9, 120.9, 115.7, 112.0, 111.4, 67.9, 56.1, 56.0, 40.4, 35.4. HRMS calcd. for $C_{19}H_{21}O_5NF_3$, 400.13663 $[M + H]^+$; found, 400.13633 $[M + H]^+$.

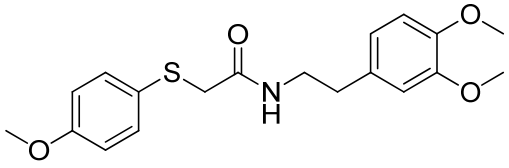


**N-(3,4-dimethoxyphenethyl)-2-(4-ethoxyphenoxy)acetamide (22o).** Compound **22o** was prepared according to Procedure B using **18b** (1.0 g, 3.9 mmol) and 4-ethoxyphenol (0.6 g, 4.7 mmol, 1.2 equiv) in dry MeCN (20 mL). The crude solid was purified by silica gel chromatography (ISCO, Silicycle 25 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (1.14 g, 82%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.80-6.65 (m, 7H),

6.64 (s, 1H, broad), 4.38 (s, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.54 (q, *J* = 6.8 Hz, 2H), 4.38 (s, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 154.3, 151.5, 149.3, 148.0, 131.3, 120.9, 115.8, 115.7, 112.1, 111.6, 68.4, 64.2, 56.1, 56.0, 40.4, 35.5, 15.1. HRMS calcd. for $C_{20}H_{26}O_5N$, 360.18055 $[M + H]^+$; found, 360.18092 $[M + H]^+$.

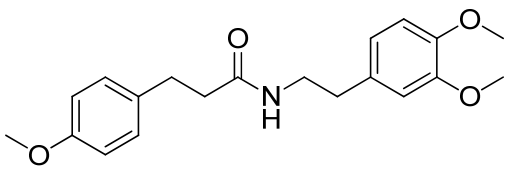


***N*-(2,3-dimethoxyphenethyl)-2-(4-methoxyphenoxy)acetamide (22p).** Compound **22p** was prepared according to Procedure B using **18h** (1.9 g, 7.3 mmol) and 4-methoxyphenol (1.1 g, 8.8 mmol, 1.2 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-clear oil (2.1 g, 84%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (m, 2H), 6.83 (m, 5H), 6.73 (m, 1H), 4.40 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.57 (q, *J* = 6.8 Hz, 2H), 2.87 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 154.8, 153.0, 151.7, 147.4, 132.7, 124.3, 122.4, 115.8, 115.0, 111.3, 68.3, 60.9, 55.9, 55.8, 40.1, 30.1. HRMS calcd. for $C_{19}H_{24}O_5N$, 346.16490 $[M + H]^+$; found, 346.16452 $[M + H]^+$.

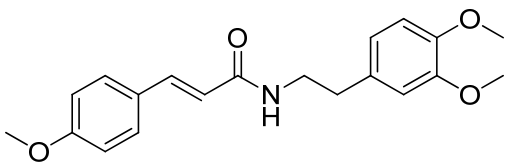


**N-(3,4-dimethoxyphenethyl)-2-((4-methoxyphenyl)thio)acetamide (23a).** Compound **23a** was prepared according to Procedure B using **18b** (2.0 g, 7.8 mmol) and 4-methoxybenzenethiol (1.3

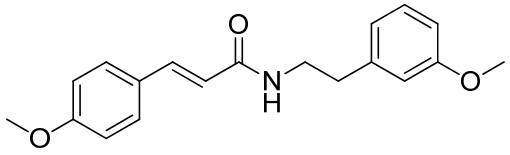
g, 9.3 mmol, 1.2 equiv) in dry MeCN (40 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 40 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a yellow solid (2.2 g, 71%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.13 (d, *J* = 9.2 Hz, 2H), 6.87 (s, 1H, broad), 6.80-6.76 (m, 3H), 6.69-6.65 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.50 (q, *J* = 7.2 Hz, 2H), 3.49 (s, 2H), 2.73 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.3, 159.4, 149.2, 147.9, 131.9, 131.2,125.0, 115.1, 115.0, 111.9, 111.8, 56.1, 55.6, 55.5, 41.1, 39.7, 35.2. HRMS calcd. for $C_{19}H_{24}O_4NS$ , 362.14206 $[M + H]^+$; found, 362.14165 $[M + H]^+$.




***N*-(3,4-dimethoxyphenethyl)-3-(4-methoxyphenyl)propanamide (25a).** Compound **25a** was prepared according to Procedure C using 3,4-dimethoxyphenethylamine ( 2.0 g, 11 mmol, 1.0 equiv) and 4-methoxyphenylpropionic acid (2.4 g, 13 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.5 g, 66%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.05 (d, *J* = 9.0 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 2 Hz, 1H), 6.58 (dd, $J_1$ = 2 Hz, $J_2$ = 8.2 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.41 (q, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.36 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.4, 158.2, 149.2, 147.8, 133.1, 131.6, 129.5, 120.8, 114.1, 112.0, 111.9, 111.5, 56.1, 56.0, 55.5, 55.4, 40.9, 39.0, 35.5, 31.0. HRMS calcd. for $C_{20}H_{25}NO_4$, 344.18564 $[M + H]^+$; found, 344.18531 $[M + H]^+$.

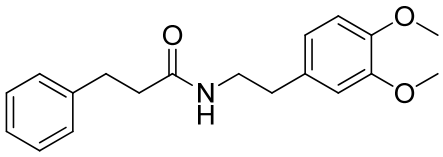


**(*E*)-*N*-(3,4-dimethoxyphenethyl)-3-(4-methoxyphenyl)acrylamide (25b).** Compound **25b** was prepared according to Procedure C using 3,4-dimethoxyphenethylamine (1.0 g, 5.6 mmol, 1.0 equiv) and 4-methoxycinnamic acid (1.2 g, 6.0 mmol, 1.1 equiv). The crude yellow residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.8 g, 42%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, *J* = 15.6 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.76-6.68 (m, 3H), 6.23 (d, *J* = 15.6 Hz, 1H), 6.09 (t, *J* = 5.6 Hz, 1H), 3.80 (s, 3H), 3.79 (d, 3H), 3.75 (s, 3H), 3.57 (q, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H).$^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 161.0,149.1, 147.8, 140.6, 131.7, 129.5, 127.7, 120.9, 118.6, 114.4, 112.1, 111.5, 56.1, 56.0, 55.6, 55.5, 41.2, 35.5. HRMS calcd. for $C_{20}H_{23}NO_4$, 342.16999 $[M + H]^+$; found, 342.16957 $[M + H]^+$.

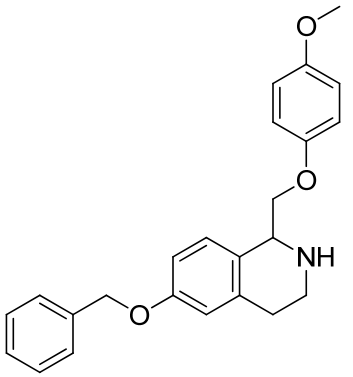


**(*E*)-*N*-(3-methoxyphenethyl)-3-(4-methoxyphenyl)acrylamide (25c).** Compound **25c** was prepared according to Procedure C using 3-methoxyphenethylamine (3.0 g, 20 mmol, 1.0 equiv) and 4-methoxycinnamic acid (3.5 g, 20 mmol, 1.0 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (4.1 g, 66%) $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, *J* = 16 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.82-6.74 (m, 3H), 6.20 (d, *J* = 15.2 Hz, 1H), 5.78 (t, *J* = 5.4 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.62 (q, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.5, 161.1, 160.0, 1408, 129.9, 139.6,

127.7, 121.3, 118.5, 114.4, 112.1, 55.6, 55.5, 55.4, 55.3, 40.9. 36.0. HRMS calcd. for $C_{19}H_{21}NO_3$, 312.15942 $[M + H]^+$; found, 312.15894 $[M + H]^+$.

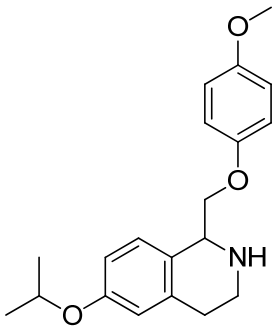


***N*-(3,4-dimethoxyphenethyl)-3-phenylpropanamide (25d).** Compound **(25d)** was prepared according to Procedure A using 3,4-dimethoxyphenethylamine (1.0 g, 5.5 mmol) and phenylpropionic acid chloride (1.2 g, 7.2 mmol, 1.2 equiv). The crude white solid was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-50% EtOAc/hexanes) to afford the title compound as a white solid (1.7 g, 99%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.17 (m, 5H), 6.77 (d, *J*= 7.6 Hz, 1H), 6.64 (m, 2H), 5.33 (s, 1H, broad), 3.86 (s, 3H), 3.85 (s, 3H), 3.46 (q, *J* = 6.2 Hz, 2H), 2.95 (t, *J* = 6 Hz, 2H), 2.69 (t, *J* = 6 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H). HRMS calcd. for $C_{19}H_{24}NO_3$, 314.17507 $[M + H]^+$; found, 314.17516 $[M + H]^+$.



**6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31a).** Compound **31a** was prepared using a one-pot procedure starting with Procedure D using **22a** (2.1 g, 5.4 mmol). The mixture was filtered to afford a tan solid (2.0 g). The crude material was

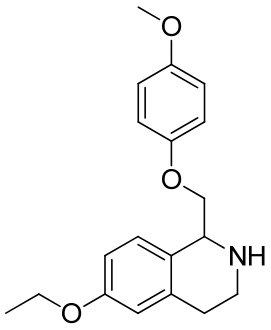
carried on without further purification. HRMS calcd. for $C_{24}H_{24}NO_3$, 374.17507 $[M + H]^+$; found, 374.17515 $[M + H]^+$. The crude dihydroisoquinoline (2.0 g, 5.4 mmol) was treated according to Procedure F. The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white foam (1.4 g, 70% over two steps). TLC (MeOH/DCM, 10:90 v/v): $R_f = 0.56$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ:7.41-7.28 (m, 5H), 7.07-6.71 (m, 7H), 4.99 (s, 2H), 4.66 (m, 1H), 4.44-4.29 (m, 1H), 3.85-3.51 (m, 5H), 3.28-2.96 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ: 158.6, 154.7, 152.1, 136.8, 134.4, 128.9, 128.3, 127.7, 127.6, 120.9, 115.6, 115.7, 115.0, 114.7, 70.2, 69.2, 55.9, 54.2, 39.8, 26.1. HRMS calcd. for $C_{24}H_{26}NO_3$, 379.19072 $[M + H]^+$; found, 379.19171 $[M + H]^+$.




**6-isopropoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31b).**

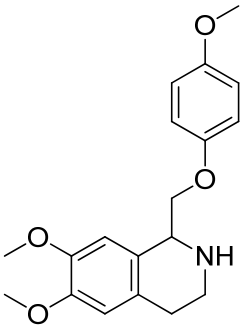
Compound **31b** was prepared using a one-pot procedure starting with Procedure D using **22b** (1.9 g, 5.5 mmol). The reaction was stirred at reflux for 6 hours. Upon cooling to room temperature, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with DCM (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was carried on without purification. HRMS calcd. for $C_{20}H_{24}NO_3$, 326.17507 $[M + H]^+$; found 326.17539 $[M + H]^+$. The crude dihydroisoquinoline (0.3 g, 0.83 mmol) was treated according to Procedure F. The crude off-white residue was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-10% MeOH/DCM gradient) to afford the title

compound as a white solid (0.08 g, 30%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.04 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.75 (dd, *J* = 2.6 Hz, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 4.63 (dd, *J* = 3.8 Hz, *J* = 7.0 Hz, 1H), 4.52 (m, 1H), 4.43 (dd, *J* = 3.8 Hz, *J* = 10.4 Hz, 1H), 4.35 (dd, *J* = 7.6 Hz, *J* = 10.4 Hz, 1H), 3.74 (s, 3H), 3.57-3.46 (m, 1H), 3.30-3.10 (m, 2H), 3.20-2.96 (m, 1H), 1.32 (d, *J* =6.4 Hz, 6H). $^{13}$C NMR ($CD_3OD$, 100 MHz) δ: 157.8, 154.7, 152.1, 134.4, 127.5, 120.4, 116.6, 116.5, 115.8, 114.7, 70.2, 69.2, 55.8, 54.2, 39.8, 26.3, 22.3. HRMS calcd. for $C_{20}H_{26}NO_3$ , 328.19072 $[M + H]^+$; found, 328.19108 $[M + H]^+$.

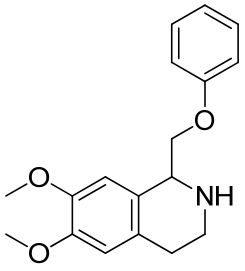



**6-ethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31c).** Compound **31c** was prepared using a one-pot procedure starting with Procedure D using **22c** (1.5 g, 4.6 mmol). The mixture was filtered to yield an off-white solid (1.4 g). The crude material was carried on without further purification. HRMS (m/z): $[M]^+$ calcd. for $C_{19}H_{22}NO_3$, 312.15942; found, 312.15914. The crude dihydroisoquinoline (1.4 g, 4.6 mmol) was treated according to Procedure F. The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.85 g, 60% over two steps). TLC (MeOH/DCM, 5:95 v/v): $R_f$ = 0.25; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.04 (d, *J* = 8.8 Hz, 1H), 7.00-6.97 (m, 2H), 6.81-6.66 (m, 4H), 4.67 (m, 1H), 4.45 (m, 1H), 4.36 (m,1H), 4.00 (q, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.60-3.03 (m, 4H), 1.41 (t, *J*= 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ:

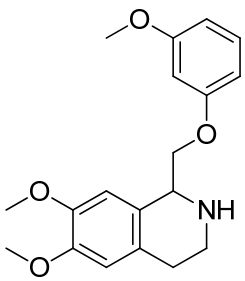
158.9, 154.9, 152.1, 134.3, 127.4, 120.3, 116.7, 116.6, 114.8, 114.5, 69.2, 63.2, 55.9, 54.2, 39.8, 26.2, 15.0. HRMS calcd. for $C_{19}H_{24}NO_3$, 314.17507 $[M + H]^+$; found, 314.17472 $[M + H]^+$.



**6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (6).** Compound **6** was prepared using a one-pot procedure starting with Procedure D using **16** (1.2 g, 3.5 mmol). The mixture was filtered to yield an off-white solid (1.1 g). The crude material was carried on without further purification. $^1$H NMR ($CD_3OD$, 400 MHz) δ: 7.40 (s, 1H), 7.15 (d, *J*= 8.8 Hz, 2H), 7.12 (s, 1H), 6.90 (d, *J*=9.2 Hz), 5.60 (s, 2H), 3.97 (s, 3H), 3.93 (m, 2H), 3.91 (s, 3H), 3.75 (s, 3H), 3.15 (t, *J*=8.4 Hz, 2H) $^{13}$C NMR ($CD_3OD$, 100 MHz) δ: 172.9, 157.7, 155.7, 151.0, 149.2, 134.5, 116.8, 115.0, 114.9, 111.4, 110.7, 66.7, 56.4, 55.4, 49.0, 41.3, 25.1. HRMS (m/z): $[M]^+$ calcd. for $C_{19}H_{22}NO_4$, 328.15433; found, 328.15416. The crude dihydroisoquinoline (1.8 g, 5.5 mmol) was treated according to Procedure F. The crude residue was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-20% MeOH/DCM gradient) to afford the title compound as an off-white solid (1.2 g, 64% over two steps). TLC (MeOH/DCM, 5:95 v/v): $R_f$ = 0.21; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.88 (d, *J*=9.2 Hz, 2H), 6.81 (d, *J*=9.2 Hz, 2H), 6.67 (s, 1H), 6.61 (s, 1H), 4.35 (t, *J*= 6 Hz, 1H), 4.13 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.22(m, 1H), 3.03 (m, 1H), 2.78 (q, *J*=5.2 Hz, 2H) $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 154.2, 153.1, 148.1, 147.4, 128.2, 126.5, 115.8, 114.8, 112.1, 109.7, 71.5, 56.2, 56.0, 55.9, 54.9, 39.9, 29.3. HRMS calcd. for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$; found, 330.16968 $[M + H]^+$.

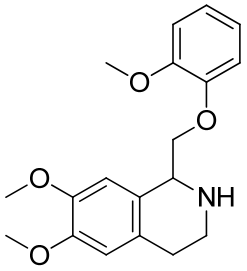


**6,7-dimethoxy-1-(phenoxymethyl)-1,2,3,4-tetrahydroisoquinoline (31d).** Compound **31d** was prepared using a one-pot procedure starting with Procedure D using **22d** (1.2 g, 3.5 mmol). The crude off-white solid (1.1 g) was carried on without further purification. HRMS (m/z): $[M]^+$ calcd. for $C_{18}H_{19}O_3N$ 298.14377; found 298.14369. The crude dihydroisoquinoline (1.1 g, 4.0 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0%-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.6 g, 54%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.26 (m, 2H), 6.97-6.94 (m, 3H), 6.68 (s, 1H), 6.61 (s, 1H), 4.37 (t, *J*= 5.6 Hz, 1H), 4.17 (d, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.26-3.19 (m, 1H), 3.06-3.00 (m, 1H), 2.80-2.76 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 158.9, 148.2, 147.5, 129.7, 128.1, 126.4, 121.3,114.8, 112.1, 109.7, 70.7, 56.2, 56.1, 54.8, 39.9, 29.1.



**6,7-dimethoxy-1-((3-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31e).** Compound **31e** was prepared using a one-pot procedure starting with Procedure D using **22e** (1.5 g, 4.3 mmol, 1.0 equiv). The crude solid was filtered and dried to afford an off-white solid

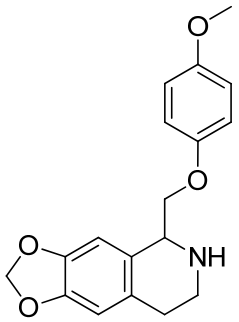
(1.4 g, 98% crude). The crude material was carried on without purification. The crude dihydroisoquinoline (1.4 g, 4.0 mmol, 1.0 equiv) was treated according to Procedure F. The crude solid was purified by silica gel chromatography (ISCO, Redisep 12 g column, gradient 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.42 g, 30%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.17 (m, 1H), 6.68 (s, 1H), 6.62 (s, 1H), 6.53 (m, 3H), 4.35 (t, *J*= 6.4 Hz, 1H), 4.13 (d, *J* = 6 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.20 (m, 1H), 3.02 (m, 1H), 2.76 (m, 2H). $^{13}$C NMR (100 MHz, CDCl3) δ: 160.9, 160.1, 147.9, 147.2, 130.0, 128.2, 126.4, 111.9, 109.5, 106.7, 106.6, 101.1, 70.7, 56.0, 55.8, 44.3, 54.7, 39.7, 29.2. HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16999 $[M + H]^+$; found, 330.17022 $[M + H]^+$.



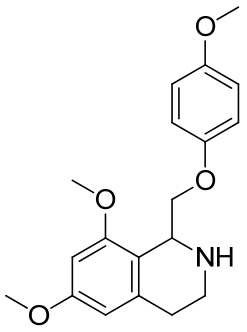

**6,7-dimethoxy-1-((2-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31f).**

Compound **31f** was prepared using a one-pot procedure starting with Procedure D using **22f** (1.1 g, 3.2 mmol, 1.0 equiv). The crude solid was filtered to afford an off-white solid (1.0 g). The crude material was carried on without purification. $^{1}$H NMR (400 MHz, $CD_3OD$) δ: 7.33 (s, 1H), 7.24-7.22 (m, 1H), 7.13-7.06 (m, 3H), 6.97-6.92 (m, 1H), 5.61 (s, 2H), 3.97-3.3.86 (m, 11H), 3.20-3.15 (m, 2H). The crude dihydroisoquinoline (1.0 g, 3.1 mmol, 1.0 equiv) was treated according to Procedure F. The crude solid was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.5 g, 63%) . $^{1}$H NMR (400 MHz, CDCl3) δ: 6.84 (m, 4H), 6.67 (s, 1H), 6.53 (s, 1H), 4.44 (t, *J*= 6 Hz), 4.22 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.27 (m, 1H), 3.09 (m, 1H), 2.80 (q, *J*= 5.6 Hz). $^{13}$C (100

MHz, CDCl3) δ: 149.9, 148.3, 148.1, 147.6, 127.2, 124.8, 122.3, 121.2, 115.1, 112.1, 111.9, 109.8, 71.9, 56.1, 16.0, 55.9, 54.3, 39.7, 28.0. HRMS calcd. for $C_{19}H_{24}O_4N$ , 330.16999 $[M + H]^+$; found, 330.17022 $[M + H]^+$.

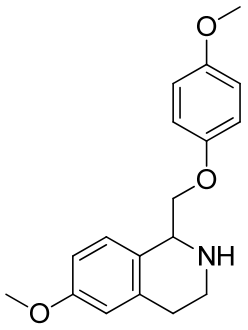



**5-((4-methoxyphenoxy)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (31g).** Compound **31g** was prepared using a one-pot procedure starting with Procedure D using **22g** (0.56 g, 1.7 mmol). The crude material was filtered off as an off-white solid (0.5 g). The crude solid was carried on without purification. The crude dihydroisoquinoline (0.5 g, 1.6 mmol, 1.0 equiv) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.10, 20% over 2 steps). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.97 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.58 (s, 2H), 5.94 (d, *J* = 4 Hz, 2H), 4.55 (s, 4.53, 1H), 4.43-4.31 (m, 2H), 3.74 (s, 3H), 3.72 (s, 1H, broad), 3.56-3.47 (m, 1H), 3.27 (m, 1H), 3.11-3.07 (m, 1H), 2.98-2.96 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 154.76, 152.0, 147.9, 147.2, 126.6, 121.4, 116.5, 144.8, 109.2, 106.0, 101.6, 69.2, 55.9, 55.8, 54.2, 39.7, 25.9. HRMS calcd. for $C_{18}H_{19}O_4N$ , 314.13868 $[M + H]^+$; found, 314.13848 $[M + H]^+$.

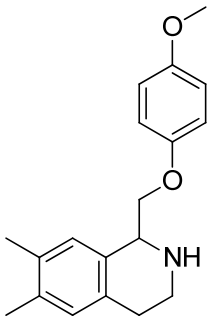


**6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31h).**

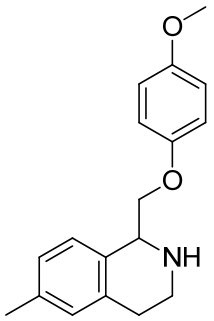
Compound **31h** was prepared using a one-pot procedure starting with Procedure D using **22h** (0.9 g, 2.6 mmol). The crude solid was filtered and carried on without further purification. HRMS calcd. for $C_{19}H_{22}NO_5$ $[M + H]^+$, 328.15433; found, 328.15450 $[M + H]^+$. The crude dihydroisoquinoline (0.84 g, 1.0 equiv) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.35 g, 41%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.96 (d, *J* = 9.4 Hz, 2H), 6.77 (d, *J* = 9.4 Hz, 2H), 6.32 (d, *J* = 2 Hz, 1H), 6.27 (d, *J* = 2 Hz, 1H), 4.93 (dd, $J_1$ = 2.8 Hz, $J_2$ = 6.2 Hz, 1H), 4.55 (dd, $J_1$ = 3.2 Hz, $J_2$ = 10.4 Hz, 1H), 4.15 (dd, $J_1$ = 8.4 Hz, $J_2$ = 10.6 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.80-3.73 (m, 1H), 3.74 (s, 3H), 3.48 (m, 2H), 3.30 (m, 1H), 2.98-2.91 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ:160.7, 157.5, 154.6, 152.2, 135.2, 116.6, 114.7, 109.4, 104.7, 97.6, 55.6, 50.5. HRMS calcd. for $C_{19}H_{24}O_4N$, 330.16999 $[M + H]^+$; found, 330.17026 $[M + H]^+$.



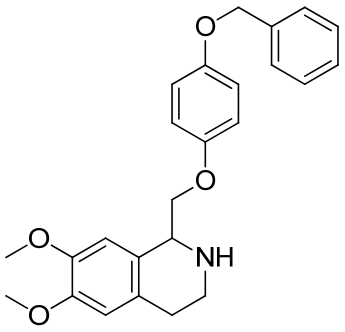
**6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31i).** Compound **31i** was synthesized using a one-pot procedure starting with Procedure D using **22i** (2.5 g, 8.0 mmol). The crude solid was filtered and characterized by HRMS and carried forward without further purification or characterization. HRMS calcd. for $[M + H]^+$ $C_{18}H_{20}NO_3$, 298.14377; found 298.14405 $[M + H]^+$. The crude dihydroisoquinoline (3.11 g, 10.5 mmol) was treated according to Procedure F. The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (1.9 g, 61% over 2 steps). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.11 (d, $J$ = 8.4 Hz, 1H), 6.89 (d, $J$ = 9.2 Hz, 2H), 6.84 (d, $J$ = 9.2 Hz, 2H), 6.75 (dd, $J_1$ = 2.4 Hz, $J_2$ = 8.4 Hz, 1H), 6.69 (d, $J$ = 2.4 Hz, 1H), 4.38 (dd, $J_1$ = 3.6 Hz, $J_2$ = 9.2 Hz, 1H), 4.16-4.05 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.26-3.21 (m, 1H), 3.10-3.08 (m, 1H), 2.85 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 158.4, 154.2, 153.1, 137.5, 127.7, 126.8, 115.8, 114.9, 114.2, 112.5, 71.4, 56.0, 55.9, 55.5, 54.9, 54.7, 39.8, 30.2. HRMS calcd. for $C_{18}H_{22}O_3N$, 300.15942 $[M + H]^+$; found, 300.15937 $[M + H]^+$.



**1-((4-methoxyphenoxy)methyl)-6,7-dimethyl-1,2,3,4-tetrahydroisoquinoline (31j).** Compound **31j** was synthesized using a one-pot procedure starting with Procedure D using **22j** (2.7 g, 8.6 mmol). The crude material was filtered off as an off-white solid and used without further purification. The crude dihydroisoquinoline (2.54 g, 8.6 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) and afforded the title compound as a white solid (0.5 g, 20% over two steps). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (d, $J$ = 9.0 Hz, 2H), 6.91 (s, 1H), 6.88 (s, 1H), 6.79 (d, $J$ = 9.0 Hz, 2H), 4.59 (dd, $J_1$ = 3.2 Hz, $J_2$ = 7.6 Hz, 1H), 4.41 (dd, $J_1$ = 4 Hz, $J_2$ = 10 Hz, 1H), 4.31 (dd, $J_1$ = 7.6 Hz, $J_2$ = 10 Hz, 1H), 3.75 (s, 3H), 3.49 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.94 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 154.6, 152.3, 136.8, 135.5, 130.6, 127.2, 126.7, 116.4, 114.8, 69.5, 55.9, 55.8, 54.4, 40.0, 26.0, 19.7, 19.6. HRMS calcd. for $C_{19}H_{23}NO_2$, 298.18016 $[M + H]^+$; found, 298.17992 $[M + H]^+$.

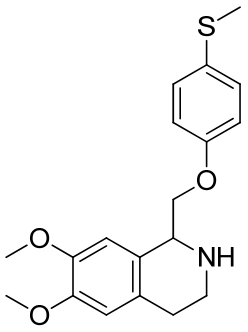



**1-((4-methoxyphenoxy)methyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline (31k).** Compound **31k** was synthesized using a one-pot procedure starting with Procedure D using **22k** (2.5 g, 8.4 mmol). The crude material was filtered off as an off-white solid, dried and used without further purification. The crude dihydroisoquinoline (1.4 g, 5.0 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) and afforded the title compound as a tan solid. (0.55 g, 23% over two steps). $^{1}$H NMR ($CD_3OD$, 400 MHz) δ: 7.25-7.18 (m, 1H), 7.12-7.05 (m, 3H), 6.97-6.91 (m, 2H), 6.87-6.84 (m, 2H), 4.54-4.18 (m, 2H), 3.72 (s, 3H), 3.62-3.38 (m, 3H), 3.13-2.96 (m, 2H), 2.31 (s, 3H). $^{13}$C NMR ($CD_3OD$, 100 MHz) δ: 154.9, 152.2, 138.6, 136.5, 132.2, 128.7, 126.2, 115.8, 115.5, 114.6, 68.5, 54.9, 39.3, 32.0, 25.3, 19.9. HRMS calcd. for $C_{18}H_{22}NO_2$, 284.16451 $[M + H]^+$; found, 284.16463 $[M + H]^+$.

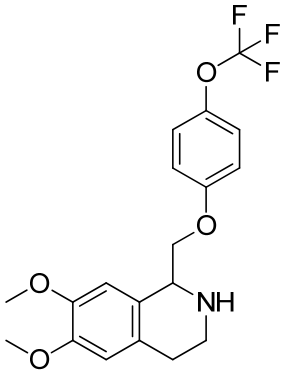


**1-((4-(benzyloxy)phenoxy)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (31l).**

Compound **31l** was synthesized using a one-pot procedure starting with Procedure D using **22l** (1.1 g, 2.6 mmol). The crude material was filtered off as an off-white solid and used without further purification. The crude dihydroisoquinoline (1.0 g, 2.48 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.18 g, 18% over two steps). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.29 (m, 5H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.61 (s, 2H), 4.99 (s, 2H), 4.64-4.61 (m, 1H), 4.46-4.35 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.53-3.47 (m, 1H), 3.28-3.22 (m, 1H), 3.13-3.07 (m, 1H), 3.03-2.97 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 153.9, 152.3, 149.3, 148.4, 137.3, 128.8, 128.2, 127.7, 125.3, 120.4, 116.5, 116.0, 108.9, 70.8, 56.4, 56.2, 54.2, 39.8, 25.6. HRMS calcd. for $C_{25}H_{28}NO_4$, 406.20129 $[M + H]^+$; found, 406.20148 $[M + H]^+$.

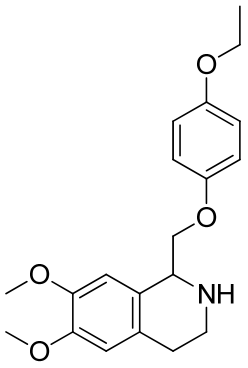


**6,7-dimethoxy-1-((4-(methylthio)phenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31m).** Compound **31m** was synthesized using a one-pot procedure starting with Procedure D using **22m** (1.2 g, 3.3 mmol). The crude material was filtered off as an off-white solid and used without further purification. The crude dihydroisoquinoline (1.4 g, 4.1 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.6 g, 43% over two steps). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.16 (m, 2H), 6.91-6.76 (m, 2H), 6.59-6.48 (m, 2H), 4.78-4.55 (m, 1H), 4.35 (m, 1H), 4.16-3.90 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.47-3.37 (m, 1H), 3.25-3.22 (m, 1H), 3.04-2.65 (m, 2H), 2.38 (s, 3H). HRMS calcd. for $C_{19}H_{24}NO_3S$, 346.14714 $[M + H]^+$; found, 346.14693 $[M + H]^+$.



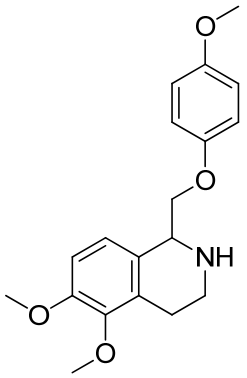
**6,7-dimethoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31n).** Compound **31n** was synthesized using a one-pot procedure starting with Procedure D using **22n**

(1.0 g, 2.4 mmol). The crude material was filtered off as a white solid and used without further purification. $^{1}$H NMR ($CD_3OD$, 400 MHz) δ: 7.44 (s, 1H), 7.31 (m, 4H), 7.14 (s, 1H), 5.72 (s, 2H), 3.98 (s, 3H), 3.93-3.89 (m, 5H), 3.19-3.15 (m, 2H). The crude dihydroisoquinoline (0.92 g, 2.4 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.33 g, 36% over two steps). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.11 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 6.63 (s, 1H), 6.60 (s, 1H), 4.65 (m, 1H), 4.50-4.42 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.49-3.38 (m, 2H), 3.28-3.18 (m, 1H), 3.11-3.04 (m, 1H), 2.98-2.90 (m, 1H). $^{13}$C NMR ($CDCl_3$, 400 MHz) δ: 156.4, 149.3, 148.3, 143.6, 125.4, 122.7, 120.4, 116.2, 111.8, 108.9, 69.0, 56.3, 56.1, 53.8, 39.7, 25.4.



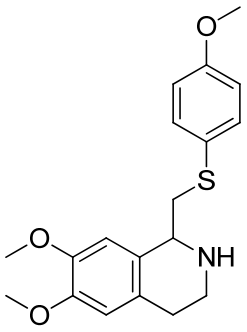

**1-((4-ethoxyphenoxy)methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (31o).** Compound **31o** was prepared using a one-pot procedure starting with Procedure D using **22o** (1.14 g, 3.2 mmol). The crude yellow solid was filtered and used without further purifications. HRMS calcd. for $C_{20}H_{24}NO_4$, 342.16999 $[M + H]^+$; found 342.17034 $[M + H]^+$. The crude dihydroisoquinoline (1.1 g, 3.2 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.27 g, 25%). $^{1}$H NMR ($CD_3OD$, 400 MHz) δ: 6.97 (d, *J* = 8.8 Hz), 6.77 (d, *J* = 9.2 Hz, 2H), 6.60 (s, 1H), 6.59 (s, 1H), 4.62 (m, 1H), 4.46-4.34 (m, 2H), 3.93 (q, *J* =

7.2 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80-3.74 (m, 1H), 3.54 (m, 1H), 3.34-3.26 (m, 1H), 3.16-2.98 (m, 2H), 1.37 (t, *J* = 7.2, 3H). HRMS calcd. for $C_{20}H_{26}NO_4$, 344.18564 $[M + H]^+$; found, 344.18599 $[M + H]^+$.

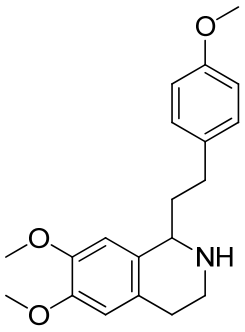


**5,6-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (31p).**

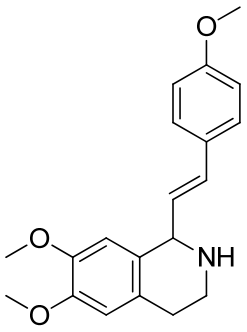
Compound **31p** was prepared using a one-pot procedure starting with Procedure D using **22p** (2.1 g, 6.2 mmol). The crude material was filtered as an off-white solid and used without further purification. HRMS calcd. for $C_{19}H_{22}NO_4$, 328.14533 $[M + H]^+$; found 328.15381 $[M + H]^+$. The crude dihydroisoquinoline (2.0 g, 6.2 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as an off-white solid (0.45 g, 22% over two steps). $^1$H NMR ($CD_3OD$, 400 MHz) δ: 7.11 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 9.6 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.86 (m, 1H), 4.51 (dd, *J* = 4.0 Hz, *J* = 10.4 Hz, 1H), 4.24 (dd, *J* = 9.2 Hz, *J* = 10.8 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 3.64-3.59 (m, 1H), 3.42-3.37 (m, 1H), 3.08 (t, *J* = 6.4 Hz, 2H). $^{13}$C NMR ($CD_3OD$, 100 MHz) δ: 155.1, 152.5, 152.0, 146.5, 126.4, 120.9, 115.8, 114.6, 111.8, 95.8, 65.2, 56.3, 55.4, 48.7, 42.0, 25.3. HRMS calcd. for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$; found, 330.16955 $[M + H]^+$.



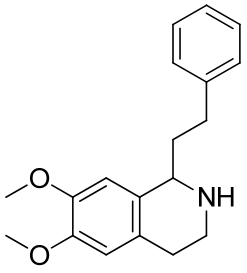
**6,7-dimethoxy-1-(((4-methoxyphenyl)thio)methyl)-1,2,3,4-tetrahydroisoquinoline (31q).** Compound **31q** was prepared using a one-pot procedure starting with Procedure D using **23a** (2.2 g, 6.1 mmol). The crude solid was filtered and carried on without further purification. HRMS calcd. for $C_{19}H_{22}NO_3S$, 344.13149 $[M + H]^+$; found 344.13095 $[M + H]^+$. The crude dihydroisoquinoline (2.1 g, 6.1 mmol) was treated according to Procedure F. The crude material was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.95 g, 45% over two steps). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 9.2 Hz, 2H), 6.53 (s, 1H), 6.47 (s, 1H), 4.34 (t, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.53-3.41 (m, 2H), 3.35-3.22 (m, 2H), 2.94 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 159.3, 148.6, 147.7, 134.3, 132.2, 125.8, 125.4, 114.9, 111.5, 109.9, 56.1, 55.6, 55.5, 53.2, 41.6, 26.4. HRMS calcd. for $C_{19}H_{23}NO_3S$, 346.14714 $[M + H]^+$; found, 346.14755 $[M + H]^+$.



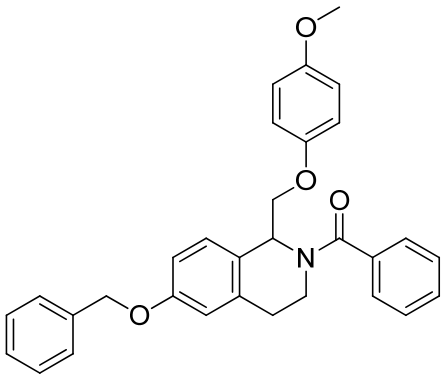
**6,7-dimethoxy-1-(4-methoxyphenethyl)-1,2,3,4-tetrahydroisoquinoline (31r).** Compound **31r** was prepared using a one-pot procedure starting with Procedure D using **25a** (2.5 g, 7.3 mmol, 1.0 equiv). The crude solid was filtered and carried on without further purification. HRMS calcd. for $C_{20}H_{23}NO_3$, 326.17507 $[M + H]^+$; found, 326.17475 $[M + H]^+$. The crude dihydroisoquinoline (3.0 g, 8.3 mmol, 1.0 equiv) was treated according to Procedure F. The crude residue was purified by silica gel chromatography (ISCO, Redisep 40 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (1.9 g, 70%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.18 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.75 (s, 1H), 6.43 (s, 1H), 4.56-4.49 (m, 1H), 4.37 (s, 1H, broad), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.63-3.51 (m, 1H), 3.23-3.08 (m, 1H), 2.92-2.78 (m, 2H), 2.45-2.21 (m, 2H), 2.04-1.83 (m, 2H). HRMS calcd. for $C_{20}H_{26}NO_3$, 328.19072 $[M + H]^+$; found, 328.19057 $[M + H]^+$.



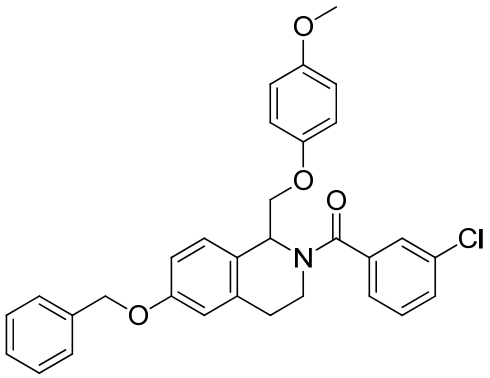
**(*E*)-6,7-dimethoxy-1-(4-methoxystyryl)-1,2,3,4-tetrahydroisoquinoline (31s).** Compound **31s** was prepared using a one-pot procedure starting with Procedure D using **25b** (0.8 g, 2.3 mmol, 1.0 equiv). The crude orange solid was filtered and carried on without further purification. $^{1}$H NMR ($CD_3OD$, 400 MHz) δ: 7.84-7.79 (m, 3H), 7.52 (s, 1H), 7.42 (d, *J* = 16 Hz, 1H), 7.12 (s, 1H), 7.04 (d, *J* = 9.2 Hz, 2H), 3.98 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.82 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.6 Hz, 2H). HRMS calcd. for $C_{20}H_{21}NO_3$, 324.15942 $[M + H]^+$; found, 324.15928 $[M + H]^+$. The crude dihydroisoquinoline (0.76 g, 2.4 mmol, 1.0 equiv) was treated according to Procedure F. The crude residue was subjected to flash column chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a yellow solid (0.44 g, 58%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (dd, $J_1$ = 2.2 Hz, $J_2$ = 8.8 Hz, 2H), 6.80 (dd, *J1* = 2.2 Hz, *J2* = 8.8 Hz, 2H), 6.59-6.55 (m, 2H), 6.44-6.37 (m, 2H), 4.97 (d, *J* = 6.8 Hz, 1H), 3.84-3.73 (m, 10H), 3.41 (m, 1H), 3.20 (m, 1H), 2.98 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 160.2, 149.1, 148.2, 138.0, 128.7, 128.3, 124.4, 122.4, 122.3, 114.3, 111.4, 110.3, 57.0, 56.2, 55.5, 55.4, 39.0, 25.2. ). HRMS calcd. for $C_{20}H_{24}NO_3$, 326.17507 $[M + H]^+$; found, 326.17493 $[M + H]^+$.



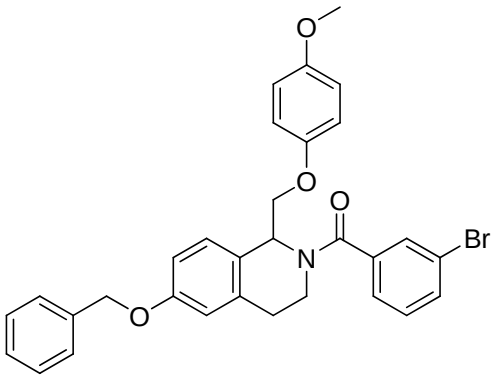

**6,7-dimethoxy-1-phenethyl-1,2,3,4-tetrahydroisoquinoline (31t).** Compound **31t** was prepared using a one-pot procedure starting with Procedure E using **25d** (1.1 g, 3.5 mmol, 1.0 equiv). The crude white solid (0.65 g, 63% crude) was taken on without further purification. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.29-7.15 (m, 5H), 6.93 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.97 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.1, 150.9, 147.7, 142.3, 131.7, 128.7, 126.2, 122.2, 110.5, 108.7, 56.4, 56.1, 47.2, 38.1, 33.4, 26.1. The crude dihydroisoquinoline (0.94 g, 3.0 mmol) was treated according to Procedure F. The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-10% MeOH/DCM gradient) to afford the title compound as a white solid (0.7 g, 73%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.28-7.14 (m, 5H), 6.56 (s, 1H), 6.54 (s, 1H), 3.98-3.86 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.26-3.16 (m, 1H), 2.91-3.01 (m, 1H), 2.86-2.58 (m, 4H), 1.97-2.16 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 147.5, 147.4, 142.6, 131.5, 128.7, 127.5, 126.1, 112.0, 109.3, 56.2, 56.0, 55.3, 53.7, 41.3, 38.5, 32.7, 29.7. HRMS calcd. for $C_{19}H_{24}NO_2$, 298.18016 $[M + H]^+$; found, 298.18005 $[M + H]^+$.



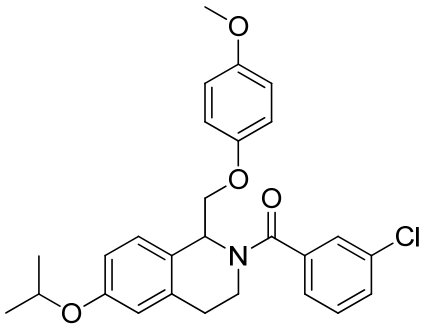
**(6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-99).** Compound **1180-99** was prepared according to Procedure H using tetrahydroisoquinoline **31a** (0.2 g, 0.53 mmol) and benzoyl chloride (0.09 g, 0.07 mL, 0.64 mmol, 1.2 equiv). The crude residue was purifed by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.18 g, 71%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.22 (m, 10H), 6.93-6.71 (m, 7H), 1H [6.01, 5.19 (t, $J$ = 4.4 Hz; dd, $J_1$ = 3.8 Hz, $J_2$ = 8.6 Hz)], 5.05 (s, 2H), 1H [4.88, 4.10 (dd, $J_1$ = 5.4 Hz, $J_2$ = 13 Hz; t, $J$ = 9.6 Hz), 4.36 (d, $J$ = 4.4 Hz, 1H), 3.93-3.66 (m, 4H), 3.27-3.15 (m, 1H), 3.93-2.70 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.0, 171.3, 158.4, 157.9, 154.2, 153.1, 152.7, 137.0, 136.8, 136.7, 136.6, 135.9, 129.8, 129.7, 128.9, 128.6, 128.3, 127.7, 126.8, 126.5, 126.1, 125.1, 115.9, 115.6, 115.4, 115.2, 114.9, 113.8, 113.6, 96.1, 71.4, 70.4, 70.2, 57.2, 56.0, 51.8, 42.9, 35.4. 30.1, 28.7. HRMS calcd. for $C_{31}H_{30}NO_4$, 480.21694 $[M + H]^+$; found,480.21792 $[M + H]^+$. Anal ($C_{31}H_{29}NO_4$): C, H, N.



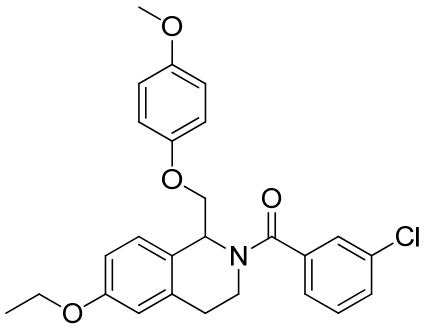

**(6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-chlorophenyl)methanone (1180-97).** Compound **1180-97** was prepared according to Procedure H using tetrahydroisoquinoline **31a** (0.2 g, 0.53 mmol) and 3-chlorobenzoyl chloride (0.1 g, 0.08 mL, 0.64 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off white amorphous solid (mixture of rotamers, 0.20 g, 70%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.59-7.21 (m, 9H), 6.93-6.76 (m, 7H), 1H [5.98, 5.14 (t, $J$ = 4.8 Hz; dd, $J_1$ = 4.4 Hz, $J_2$ = 9.2 Hz)], 5.04 (s, 2H), 1H [4.85, 4.13 (dd, $J_1$= 5.2 Hz, $J_2$ = 13 Hz; m)], 4.35 (m, 1H), 3.94-3.67 (m, 4H), 3.26-2.73 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.5, 169.7, 168.5, 158.5, 158.0, 154.4, 153.0, 152.6, 138.3, 137.1, 137.0, 136.7, 135.7, 134.9, 134.6, 133.4, 130.3, 129.9, 128.9, 128.4, 127.7, 127.1, 125.8, 125.7, 124.9, 124.7, 115.9, 115.5, 115.3, 114.9, 113.9, 113.7, 71.3, 70.2, 57.3, 56.0, 52.0, 42.9, 35.5, 30.0, 28.6. HRMS calcd. for $C_{31}H_{29}NO_4Cl$, 514.17796 $[M + H]^+$; found, 514.17923 $[M + H]^+$. Anal ($C_{31}H_{28}NO_4Cl$): C, H, N.



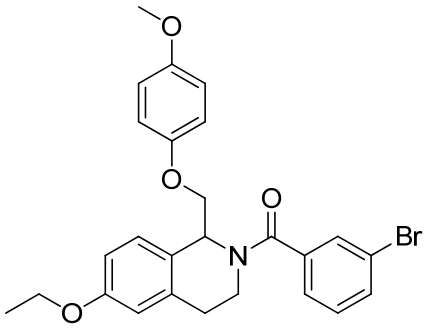

**(6-(benzyloxy)-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-bromophenyl)methanone (1180-98).** Compound **1180-98** was prepared according to Procedure H using tetrahydroisoquinoline **31a** (0.2 g, 0.53 mmol) and 3-bromobenzoyl chloride (0.1 g, 0.08 mL, 0.64 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.21 g, 71%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.56-7.21 (m, 9H), 6.94-6.76 (m, 7H), 1H [5.98, 5.13 (t, $J$ = 4.7 Hz; dd, $J_1$ = 2.6 Hz, $J_2$ = 9.4 Hz)], 5.05 (s, 2H), 1H [4.85, 4.13 (m, m)], 4.34 (m, 1H), 3.93-3.67 (m, 4H), 3.26-2.72 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 158.5, 158.0, 154.4, 153.1, 152.6, 138.6, 138.4, 136.9, 136.7, 135.7, 132.9, 132.8, 131.1, 130.5, 130.2, 129.9, 129.0, 128.9, 128.3, 127.7, 126.3, 125.7, 125.3, 124.7, 123.0, 122.7, 115.9, 115.5, 115.3, 115.0, 114.9, 114.0, 113.7, 71.3, 70.2, 57.3, 56.0, 52.0, 42.9, 35.5, 30.0, 29.0. HRMS calcd. for $C_{31}H_{29}NO_4Br$, 558.12745 $[M + H]^+$; found, 558.12878 $[M + H]^+$. Anal ($C_{31}H_{28}NO_4Br$): C, H, N.



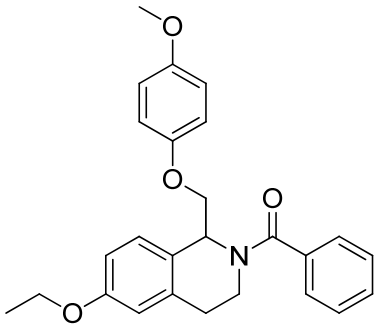

**(3-chlorophenyl)(6-isopropoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-55).** Compound **1180-55** was prepared according to Procedure H using tetrahydroisoquinoline **31b** (0.08 g, 0.24 mmol) and 3-chlorobenzoyl chloride (0.05 g, 0.04 mL, 0.29 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.08 g, 67%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.58-7.18 (m, 4H), 6.91-5.95 (m, 7H), 1H [5.11, 4.83 (dd, $J_1$ = 3.0 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.2 Hz, $J_2$ = 12.8 Hz], 4.51 (sept., $J$ = 6.4 Hz, 1H), 4.33 (m, 1H), 1H [4.12, 3.91 (t, $J$ = 10.2 Hz; dd, $J_1$ = 3.8 Hz, $J_2$ = 10.2 Hz)], 3.74 (s, 3H), 3.68 (m, 1H), 3.25-2.70 (m, 3H), 1.33 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.7, 157.6, 157.1, 154.4, 152.6, 138.4, 138.2, 136.6, 135.6, 134.9, 134.5, 130.2, 129.9, 128.7, 128.3, 128.2, 127.0, 125.9, 125.2, 124.9, 124.1, 116.2, 115.9, 115.5, 114.9, 114.8, 114.7, 114.4, 71.3, 70.2, 70.1, 57.3, 55.9, 52.0, 42.8, 35.5, 29.9, 28.5, 22.3, 22.2. HRMS calcd. for $C_{27}H_{29}NO_4Cl$, 466.17796 $[M + H]^+$; found, 466.17841 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_4Cl$): C, H, N. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 2.262 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 99% purity (retention time = 2.263 minutes).



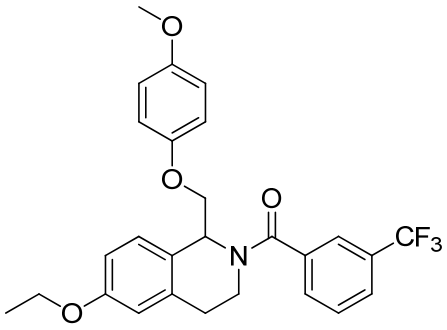
**(3-chlorophenyl)(6-ethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-93).** Compound **1180-93** was prepared according to Procedure H using tetrahydroisoquinoline **31c** (0.2 g, 0.64 mmol) and 3-chlorobenzoyl chloride (0.13 g, 0.10 mL, 0.77 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.18 g, 62%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.58-7.19 (m, 5H), 6.92-6.66 (m, 6H), 1H [5.96, 5.11 (t, *J* = 4.8 Hz; dd, *J* = 3.2 Hz, *J* = 9.6 Hz)], 1H [4.83, 4.12 (dd, *J* = 4.8 Hz, *J* = 12.8 Hz; m)], 4.33 (m, 1H), 4.00 (q, *J*= 6.8 Hz, 2H), 3.74 (s, 3H), 3.72-3.66 (m, 1H), 3.32-2.71 (m, 3H), 1.40 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.6, 158.6, 158.1, 154.3, 153.1, 152.6, 138.4, 138.2, 136.6, 135.5, 134.9, 134.5, 130.2, 129.8, 128.7, 128.3, 127.0, 125.8, 125.2, 124.8, 124.2, 118.3, 115.9, 115.4, 114.9, 114.8, 114.4, 113.6. 113.4, 79.1, 71.3, 70.2, 63.7, 57.3, 55.9, 51.9, 42.8, 35.5, 30.0, 28.5, 15.1. HRMS calcd. for $C_{26}H_{27}NO_4Cl$, 452.16231 $[M + H]^+$; found, 452.16349 $[M + H]^+$. Anal ($C_{26}H_{26}NO_4Cl$): C, H, N.



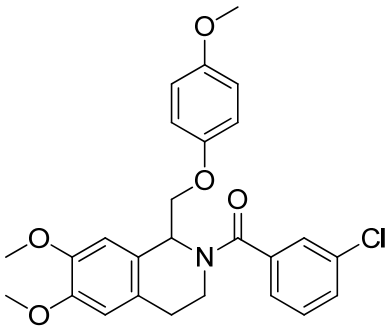
**(3-bromophenyl)(6-ethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-94).** Compound **1180-94** was prepared according to Procedure H using tetrahydroisoquinoline **31c** (0.2 g, 0.64 mmol) and 3-bromobenzoyl chloride (0.17 g, 0.10 mL, 0.77 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.24 g, 76%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1H [7.75, 7.54 (s, s)], 7.52-7.40 (m, 1H), 7.28-7.18 (m, 2H), 6.92-6.66 (m, 7H), 1H [5.9, 5.12 (m, m)], 4.83-4.09 (m, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 1H [3.92, 3.68 (m, m)], 3.73 (s, 3H), 3.27-3.10 (m, 1H), 2.91-2.71 (m, 2H), 1.39 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 169.4, 158.4, 158.1, 154.3, 153.2, 152.6, 138.5, 138.2, 136.8, 135.7, 134.9, 134.5, 130.2, 129.7, 128.8, 128.4, 127.0, 125.8, 125.0, 124.8, 124.1, 118.3, 116.2, 115.4, 114.9, 114.7, 114.5, 113.7. 113.4, 79.1, 71.3, 70.2, 63.8, 57.3, 55.7, 51.9, 43.1, 35.8, 30.2, 28.5, 15.4. HRMS calcd. for $C_{26}H_{27}NO_4Br$, 496.11180 $[M + H]^+$; found, 496.11298 $[M + H]^+$. Anal ($C_{26}H_{26}NO_4Br$): C, H, N.



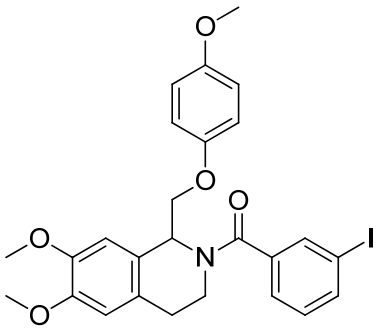
**(6-ethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-95).** Compound **1180-95** was prepared according to Procedure H using tetrahydroisoquinoline **31c** (0.2 g, 0.64 mmol) and benzoyl chloride (0.11 g, 0.09 mL, 0.77 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.20 g, 75%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.51-7.20 (m, 6H), 6.91-6.66 (m, 6H), 1H [5.99, 5.18 (t, *J* = 4.8 Hz; dd, $J_1$ = 3.6 Hz, $J_2$ =9.2 Hz)], 1H [4.86, 4.10 (dd, $J_1$ = 6.0 Hz, $J_2$ = 12.8 Hz; t, *J* = 9.2 Hz)], 4.35 (m, 1H), 4.00 (q, *J* = 6.8 Hz, 2H),3.93-3.78 (m, 1H), 3.73 (s, 3H), 3.69-3.65 (m, 1H), 3.34-3.12 (m, 1H), 2.95-2.68 (m, 1H), 1.39 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.2, 158.5, 158.1, 154.2, 153.2, 136.7, 135.8, 129.8, 128.8, 128.6, 127.7, 126.8, 125.6, 115.9, 115.6, 114.9, 114.4, 113.5, 113.3, 71.4, 70.3, 63.7, 57.2, 55.9, 51.8, 42.8, 35.4, 30.1, 28.7, 15.1. HRMS calcd. for $C_{26}H_{28}NO_4$, 418.20129 $[M + H]^+$; found, 418.20220. $[M + H]^+$. Anal ($C_{26}H_{27}NO_4$): C, H, N.



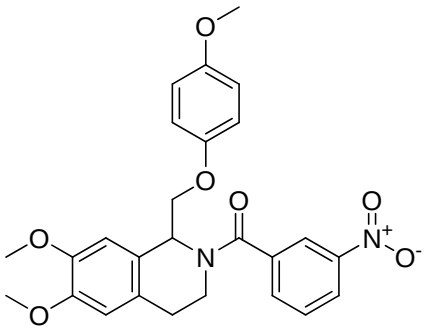
**(6-ethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-(trifluoromethyl)phenyl)methanone (1180-96).** Compound **1180-96** was prepared according to Procedure H using tetrahydroisoquinoline **31c** (0.17 g, 0.54 mmol) and 3-(trifluoromethyl)benzoyl chloride (0.14 g, 0.10 mL, 0.65 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound as an off-white amorphous solid (mixture of rotamers, 0.18 g, 68%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.85-7.54 (m, 4H), 7.52-7.21 (m, 1H), 6.91-6.77 (m, 6H), 1H [5.99, 5.09 (t, *J* = 4.8 Hz; m)], 1H [4.87, 4.13 (dd, $J_1$ = 5.6 Hz, $J_2$ = 12.8 Hz; m)], 4.37 (m, 1H), 4.01 (q, *J* = 6.8 Hz, 2H), 1H [3.92, 3.71 (m, m)], 3.74 (s, 3H), 3.61-2.73 (m, 3H), 1.40 (t, *J* = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.7, 158.7, 158.2, 154.3, 152.5, 137.3, 136.5, 131.1, 130.2, 129.5, 129.1, 128.7, 128.2, 126.5, 125.2, 124.0, 115.9, 115.4, 114.9, 114.4, 113.7, 113.5, 71.3, 70.1, 63.7, 57.4, 55.9, 52.1, 42.9, 35.5, 29.9, 28.5, 15.0. HRMS calcd. for $C_{27}H_{27}NO_4F_3$, 486.18867 $[M + H]^+$; found, 486.18989 $[M + H]^+$. Anal ($C_{27}H_{26}F_3NO_4$): C, H, N.



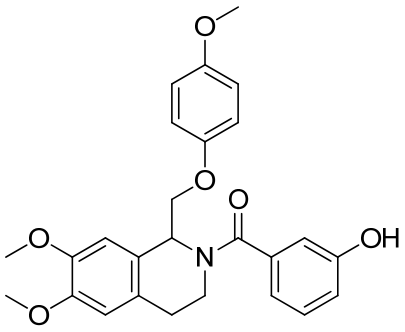
**(3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1390).** Compound **1390** was prepared according to Procedure H using tetrahydroisoquinoline **6** (0.4 g, 1 mmol) and 3-chlorobenzoyl chloride (0.2 mL, 1 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to give the title compound(mixture of rotamers, 0.24 g, 42%) as a white solid. TLC (EtOAc:hexanes, 1:1 v/v): $R_f$ = 0.56; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.62-7.28 (m, 4H), 6.89-6.80 (m, 4H), 1H [6.68, 6.62 (s, s)], 6.48-5.96 (m, 1H), 1H [5.10, 4.87 (dd, $J_1$ = 9.6 Hz, $J_2$ = 4 Hz, dd, $J_1$ = 9.6 Hz, $J_2$ = 4 Hz)], 4.37-3.95 (m, 2H), 3.88-3.76 (m, 9H), 3.70-2.70 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 154.4, 154.3, 152.9, 152.5, 148.8, 148.4, 148.x0, 147.8, 138.3, 134.9, 134.5, 130.2, 129.9, 129.8, 128.2, 127.3, 127.0, 126.3, 125.9, 125.2, 124.9, 124.0, 115.9, 115.5, 115.0, 114.9, 112.0, 111.5, 110.4, 109.9, 71.1, 70.2, 57.4, 56.2, 56.1, 55.9, 51.9, 42.9, 35.7, 29.2, 27.8. HRMS calcd. for $C_{26}H_{27}NO_5Cl$ , 468.15723 $[M + H]^+$; found, 468.15820 $[M + H]^+$; Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N. HPLC: Reverse Phase Chiral OD-RH column. Conditions: 75% MeCN/25% water plus 0.1% formic acid isocratic over 20 minutes. Peak 1: (RT = 8.113 minutes, 50%), Peak 2 (9.140 minutes, 50%).



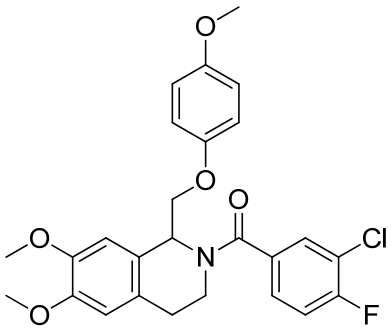
**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-iodophenyl)methanone (1180-11).** Compound **1180-11** was prepared according to Procedure I using **6** (0.2 g, 0.6 mmol, 1.0 equiv) and 3-iodobenzoic acid (0.2 g, 0.6 mmol, 1.0 equiv). The crude material was subjected to silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.2 g, 59%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1H [7.94, 7.70 (s, s)], 7.74 (d, *J* = 7.6 Hz, 1H), 1H [7.46, 7.33 (d, *J* = 8.0 Hz; d, *J* = 7.6 Hz)], 7.13 (q, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 9.6 Hz, 1H), 6.80 (m, 3H), 1H [ 6.66, 6.61 (s, s)], 1H [6.47, 5.92 (s, m)], 1H [5.07, 4.83 (dd, $J_1$ = 3.8 Hz, $J_2$ = 9.8 Hz; dd, $J_1$ = 6.8 Hz, $J_2$ = 13 Hz)], 4.33 (m, 1H), 4.17-4.01 (m, 1H), 3.97-3.60 (m, 1H), 3.86-3.74 (m, 9H), 3.27-3.04 (m, 1H), 2.90-2.64 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.0, 169.3, 154.4, 154.3, 153.0, 152.5, 148.9, 148.4, 148.0, 147.8, 138.8, 138.6, 138.5, 136.7, 135.6, 130.3, 127.3, 126.8, 126.2, 125.2, 124.0, 115.9, 115.5, 114.9, 112.0, 111.5, 109.9, 94.5, 94.4, 71.1, 70.2, 57.5, 56.3, 56.1, 55.9, 43.0, 35.7, 29.2. HRMS calcd. for $C_{26}H_{27}NO_5I$, 560.09285 $[M + H]^+$; found, 560.09224 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5I$): C, H, N.



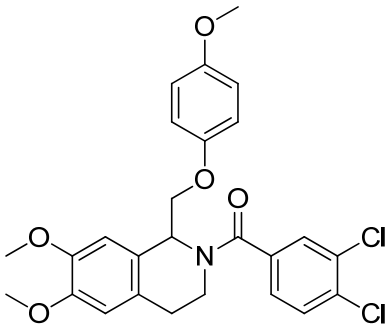
**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-nitrophenyl)methanone (1180-16).** Compound **1180-16** was prepared according to Procedure H using **6** (0.2 g, 0.6 mmol, 1.0 equiv) and 3-nitrobenzoyl chloride (0.1 g, 0.6 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as a white solid (0.1, 33%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1H [8.57, 8.30 (s, s)], 8.28 (d, *J* = 7.6 Hz, 1H), 1H [7.86, 7.74 (d, *J* = 8.0 Hz; d, *J* = 7.2 Hz), 7.64-7.57 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.86-6.81 (m, 3H), 1H [ 6.70, 6.65 (s, s)], 1H [6.46, 5.98 (s, m)], 1H [5.04, 4.90 (dd, $J_1$ = 3.4 Hz, $J_2$ = 9.8 Hz; dd, $J_1$ = 5.6 Hz, $J_2$ = 13.2 Hz)], 4.39 (d, *J* = 5.2 Hz, 1H), 4.23-3.97 (m, 1H), 3.88-3.74 (m, 9H), 3.74-3.72 (m, 1H), 3.30-3.12 (m, 1H), 2.91-2.71 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.3,168.5, 154.5, 152.9, 152.3, 149.0, 148.6, 148.2, 147.9, 138.1, 133.9, 133.0, 130.2, 129.8, 127.2, 126.0, 124.9, 124.5, 123.5, 122.1, 115.9, 115.4, 115.0, 112.1, 111.5, 110.3, 109.8, 71.0, 69.9, 57.7, 56.3, 56.2, 55.9, 52.2, 43.1, 35.7, 29.2, 27.7. HRMS calcd. for $C_{26}H_{27}N_2O_7$, 479.18128 $[M + H]^+$; found, 479.18062 $[M + H]^+$. Anal ($C_{26}H_{26}N_2O_7$): C, H, N.



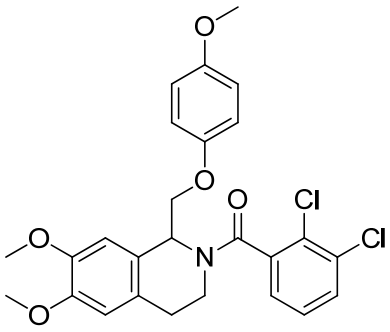
**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(3-hydroxyphenyl)methanone (1180-3).** Compound **1180-3** was prepared according to Procedure I using **6** (0.16 g, 0.5 mmol) and 3-hydroxybenzoic acid (0.07 g, 0.5 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.09 g, 41%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.14-8.02 (m, 1H), 7.72-7.40 (m, 3H), 7.34-7.04 (m, 2H), 6.84-6.74 (m, 2H), 6.65-5.98 (m, 2H), 1H [5.20, 4.83 (m, m)], 4.32 (m, 1H), 4.18-3.90 (m, 1H), 3.84-3.70 (m, 9H), 3.70-3.68 (m, 1H), 3.30-3.02 (m, 1H), 2.84-2.59 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.7, 157.1, 154.3, 153.0, 152.6, 148.4, 147.9, 137.0, 130.0, 126.4, 125.1, 117.9, 117.5, 117.1, 115.9, 115.6, 115.4, 114.9, 114.3, 112.0, 111.5, 110.4, 71.1, 67.7, 63.2, 56.2, 56.1, 55.9, 52.0, 42.9, 29.2, 27.9. HRMS calcd. for $C_{26}H_{28}NO_6$, 450.19111 $[M + H]^+$; found, 459.19206 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_6$) C, H, N.



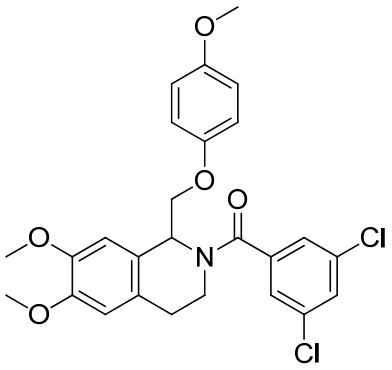
**(3-chloro-4-fluorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-18).** Compound **1180-18** was prepared according to Procedure I using **6** (0.1 g, 0.3 mmol) and 3-chloro-4-fluorobenzoic acid (0.06 g, 0.4 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.10 g, 68%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.08-7.74 (m, 1H), 7.46-7.13 (m, 2H), 6.88-6.80 (m, 4H), 6.72-6.63 (m, 1H) 1H [6.50, 5.95 (s, m)], 1H [5.10, 4.84 (m, dd, $J_1$ = 5.2 Hz, $J_2$ = 12 Hz)], 4.36 (m, 1H), 4.22-3.97 (m, 1H), 3.87-3.76 (m, 9H), 3.73-3.66 (m, 1H), 3.30-3.07 (m, 1H), 2.88-2.70 (m, 2H). $^{13}$C NMR ($CDCl_3$, 400 MHz) δ: 169.7, 154.5, 152.9, 152.5, 148.9, 148.5, 148.1, 147.8, 133.5, 130.8, 127.3, 126.1, 125.1, 123.8, 115.9, 115.5, 114.9, 112.0, 109.8, 70.3, 57.7, 56.2, 56.1,55.9, 43.0, 35.8, 29.9, 29.2, 27.7, 15.5. HRMS (m/z): $[M]^+$ calcd. for $C_{26}H_{26}NO_5ClF$, 486.14781; found, 486.14826. Anal. ($C_{26}H_{25}NO_5ClF$ ) C, H, N.



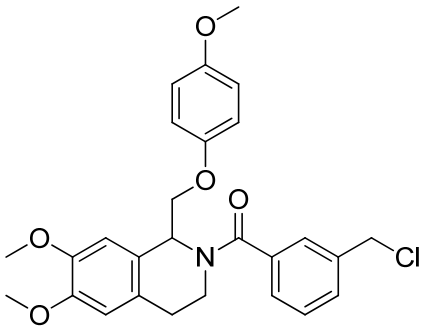
**(3,4-dichlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-10).** Compound **1180-10** was prepared according to Procedure H using **6** (0.2 g, 0.6 mmol) and 3,4-dichlorobenzoyl chloride (0.2 g, 0.7 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (mixture of two rotamers, 0.2 g, 67%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.74-7.44 (m, 2H), 7.37-7.20 (m, 1H), 6.86-6.77 (m, 4H), 1H [6.66, 6.60 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.07, 5.05 (dd, $J_1$ = 3.6 Hz, $J_2$ = 9.2 Hz; dd, $J_1$ = 6.0 Hz, $J_2$ = 13 Hz)], 4.34 (d, $J$ = 4.0 Hz, 1H), 1H [4.16, 3.96 (t, $J$ = 10.0 Hz; dd, $J_1$ = 4.0 Hz, $J_2$ = 10.0 Hz)], 3.86-3.74 (m, 10H), 1H [td, $J_1$ = 4.0 Hz, $J_2$ = 13 Hz; td, $J_1$ = 5.2 Hz, $J_2$ = 10.0 Hz), 2.92-2.66 (m, 2H). $^{13}$C NMR ($CDCl_3$, 400 MHz) δ: 169.6, 154.5, 154.3, 152.9, 152.4, 149.0, 148.5, 148.1, 136.3, 134.0, 132.9, 131.0, 130.7, 130.2, 127.2, 126.1, 125.0, 123.8, 115.9, 115.5, 114.9, 112.0, 111.5, 109.8, 96.8, 57.6, 56.3, 56.2, 56.0, 43.0, 35.8, 29.2, 27.7. HRMS calcd. for $C_{26}H_{26}NO_5Cl_2$ , 502.11826 $[M + H]^+$; found, 502.11841 $[M + H]^+$. Anal. ($C_{26}H_{25}NO_5Cl_2$): C, H, N.



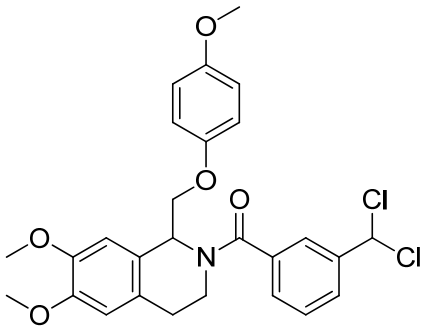
**(2,3-dichlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-12).** Compound **1180-12** was prepared according to Procedure I using **6** (0.2 g, 0.6 mmol, 1.0 equiv) and 2,3-dichlorobenzoic acid (0.1 g, 0.6 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (mixture of two rotamers, 0.1 g, 33%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.50-7.45 (m, 1H), 7.30-7.22 (m, 1H), 1H [7.19, 7.12 (dd, $J_1$ = 1.6 Hz, $J_2$ = 5.2 Hz; dd, $J_1$ = 1.6 Hz, $J_2$ = 5.2 Hz)], 6.87-6.83 (m, 1H), 6.83-6.70 (m, 3H), 6.67-6.60 (m, 1H), 6.50-5.92 (m, 1H), 1H [4.93, 4.76 (m, m)], 4.41-4.32 (m, 1H), 1H [4.08, 3.93 (t, $J_1$ =10.0 Hz; dd, $J_1$ = 4.2 Hz, $J_2$ = 10.0 Hz), 3.86-3.72 (m,9H), 3.60-3.44 (m, 1H), 3.27-2.96 (m, 1H), 2.84-2.64 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 174.1, 167.2, 166.8, 154.2, 152.8, 152.6, 148.4, 148.0, 147.8, 138.2, 133.8, 133.2, 130.9, 128.2, 127.2, 126.4, 126.2, 125.7, 125.1, 124.8, 124.0, 115.8, 115.4, 114.8, 111.9, 111.5, 109.9, 81.3, 70.9, 70.5, 56.3, 56.1, 55.9, 51.8, 42.4, 29.0, 28.0. HRMS calcd. for $C_{26}H_{26}NO_5Cl_2$ , 502.11826 $[M + H]^+$; found, 502.11832$[M + H]^+$. Anal. ($C_{26}H_{25}NO_5Cl_2$ ): C, H, N.



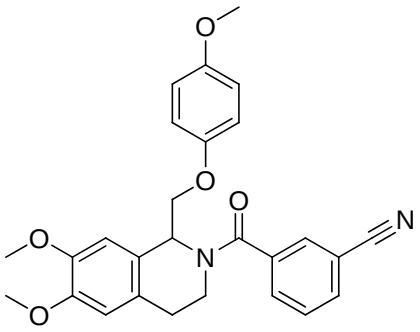
**(3,5-dichlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-34).** Compound **1180-34** was prepared according to Procedure H using **6** (0.11 g, 0.33 mmol) and 3,5-dichlorobenzoyl chloride (0.08 g, 0.37 mmol. 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.06 g, 36%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.51 (s, 1H), 7.42 (s, 1H), 7.25 (m, 1H), 6.9-6.79 (m, 4H), 1H [6.68, 6.64 (s, s)], 1H [6.51, 5.94 (s, m)], 1H [5.06, 4.85 (dd, $J_1$ = 2.8 Hz, $J_2$ = 9.6 Hz; dd, $J_1$ = 5.6 Hz, $J_2$ = 13.2 Hz)], 4.36 (d, $J$ = 4.4 Hz, 1H), 1H [4.21, 3.99 (t, $J$ = 10.0 Hz; dd, $J_1$ = 3.6 Hz, $J_2$ = 10.0 Hz), 3.89-3.73 (m, 9H), 3.72-3.68 (m, 1H), 3.27-3.08 (m, 1H), 2.94-2.70 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.2, 154.5, 154.4, 149.0, 148.5, 148.1, 147.9, 139.2, 135.7, 135.3, 129.9, 129.8, 127.2, 126.5, 126.1, 125.3, 124.9, 123.7, 115.9, 115.4, 115.0, 114.9, 112.0, 111.5, 110.3, 109.8, 71.0, 70.1, 57.6, 56.3, 56.2, 55.9, 52.1, 42.9, 35.8, 29.2, 27.7. HRMS calcd. for $C_{26}H_{26}NO_5Cl_2$ , 502.11826 $[M + H]^+$; found, 502.11748 $[M + H]^+$. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 99% purity (retention time = 2.058 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 98% purity (retention time = 2.057 minutes).



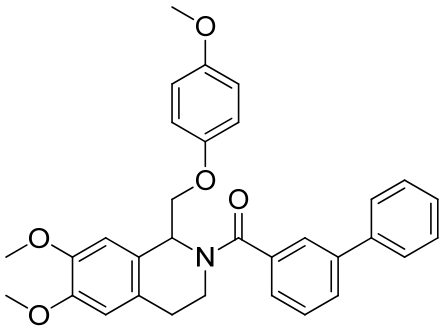
**(3-(chloromethyl)phenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-36).** Compound **1180-36** was prepared according to Procedure H using**6** (0.8 g, 2.4 mmol) and 3-(chloromethyl)benzoyl chloride (0.5 g, 2.9 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (mixture of rotamers, 0.30 g, 26%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.57-7.34 (m, 3H), 6.92-6.77 (m, 4H), 6.69-6.62 (m, 2H), 1H [6.50, 5.98 (s, m)], 1H [5.15, 4.90 (m, dd, $J_1$ = 5.6 Hz, $J_2$ = 13.2 Hz)], 4.60 (m, 2H), 4.43-4.31 (m, 1H), 4.19-4.11 (m, 1H), 3.88-3.67 (m, 10H), 3.32-3.08 (m, 1H), 2.96-2.66 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.7, 169.6, 154.4, 154.3, 153.0, 152.6, 148.8, 148.4, 148.0, 138.3, 138.0, 137.0, 133.5, 130.8, 130.3, 130.2, 130.0, 129.3, 129.1, 128.1, 127.7, 127.3, 127.1, 126.8, 126.3, 125.3, 124.2, 115.9, 115.6, 114.9, 112.0, 111.5, 110.4, 109.9, 71.1, 70.3, 57.5, 56.2, 56.1, 55.9, 51.9, 46.0, 45.7, 43.0, 35.7, 29.2, 27.9. HRMS calcd. for $C_{27}H_{29}NO_5Cl$, 482.17288 $[M + H]^+$; found, 482.17250 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_5Cl$): C, H, N. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 98% purity (retention time = 1.740 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 99% purity (retention time = 1.741 minutes).



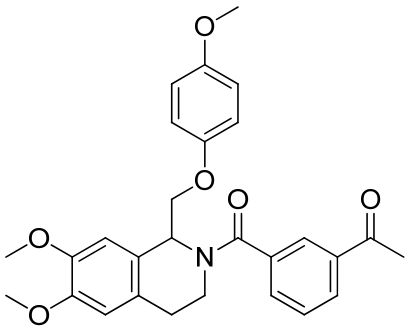
**(3-(dichloromethyl)phenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-52).** Compound **1180-52** was prepared according to Procedure H using **6** (0.2 g, 0.6 mmol) and 3-(dichloromethyl)benzoyl chloride (0.16 g, 0.72 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as a white solid (0.07 g, 21%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.76-7.44 (m, 4H), 6.91-6.64 (m, 6H), 1H [6.50, 5.99 (s, m)], 1H [5.13, 4.90 (m, m)], 4.39 (m, 1H), 4.20-3.94 (m, 1H), 3.88-3.69 (m, 10H), 3.29-3.13 (m, 1H), 2.98-2.70 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.8, 170.1, 154.3, 153.0, 152.5, 148.9, 147.8, 141.1, 137.1, 129.4, 129.3, 128.3, 127.5, 125.8, 125.2, 124.8, 124.0, 115.5, 114.9, 71.2, 64.3, 57.5, 56.3, 56.2, 56.1, 55.9, 52.0, 43.0, 27.2. HRMS calcd. for $C_{27}H_{28}NO_5Cl_2$, 516.13391 $[M + H]^+$; found, 516.13457 $[M + H]^+$. Anal. ($C_{27}H_{27}NO_5Cl_2$): C, H, N.



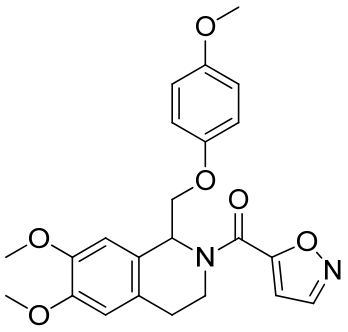
**3-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzonitrile (1180-37).** Compound **1180-37** was prepared according to Procedure H using **6** (0.21 g, 0.63 mmol) and 3-cyanobenzoyl chloride (0.13 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.28 g, 99%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.00-7.44 (m, 4H), 6.98-6.75 (m, 4H), 1H [6.70, 6.62 (s, s)], 1H [6.48, 6.00 (s, m)], 1H [5.02, 4.88 (m, m)], 4.38 (m, 1H), 4.06-3.71 (m, 10H), 3.28 (m, 1H), 3.14 (m, 1H), 2.96-2.69 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.4, 168.6, 154.4, 154.2, 152.7, 152.2, 148.9, 148.4, 147.9, 147.7, 137.6, 134.5, 134.0, 133.1, 133.0, 132.0, 131.5, 131.0, 130.3, 129.7, 129.3, 127.1, 125.9, 124.7, 123.4, 118.2, 118.0, 115.7, 115.3, 114.9, 114.7, 113.0, 112.6, 111.4, 110.2, 109.7, 70.8, 70.0, 57.5, 56.1, 55.9, 55.7, 51.9, 43.0, 35.6, 29.0, 27.6. HRMS calcd. for $C_{27}H_{27}N_2O_5$, 459.19145 $[M + H]^+$; found, 459.19087 $[M + H]^+$. Anal. ($C_{27}H_{27}N_2O_5$): C, H, N.



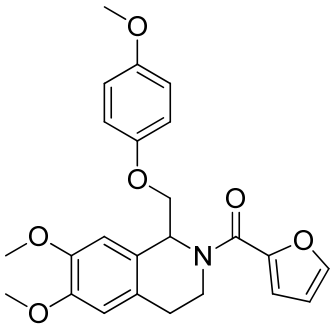
**[1,1'-biphenyl]-3-yl(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-57).** Compound **1180-57** was prepared according to Procedure I using **6** (0.5 g, 1.5 mmol) and 3-phenylbenzoic acid (0.3 g, 1.5 mmol, 1.0 equiv) in DCM (10 mL) and DMF (2.0 mL). The crude yellow residue was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.26 g, 34%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.83-7.30 (m, 8H), 6.92-6.74 (m, 5H), 1H [6.68, 6.62 (s, s)], 1H [6.49, 6.01 (s, m)], 1H [ 5.21, 4.91 (dd, $J_1$ = 3.8 Hz, $J_2$ = 9.0 Hz; dd, $J_1$ = 5.6 Hz, $J_2$ = 12.8 Hz), 4.43-4.35 (m, 1H), 1H [4.22, 4.00 (m, m)], 3.90-3.72 (m, 9H), 1H [3.67, 3.26 (m, m)], 1H [3.15, 2.89 (m, m)], 2.78-2.65 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.8, 171.1, 154.4, 154.3, 153.1, 152.6, 148.8, 148.4, 148.0, 147.7, 141.8, 141.5, 140.6, 140.4, 137.2, 129.3, 129.1, 128.5, 128.4, 128.0, 127.9, 127.4, 126.6, 126.5 (2), 125.6, 125.5, 124.5, 115.9, 115.6, 114.9, 112.1, 111.6, 110.5, 110.0, 71.2, 70.5, 57.5, 56.3, 56.1, 55.9, 51.8, 43.0, 35.8, 29.3, 27.8. HRMS calcd. for $C_{32}H_{32}NO_5$, 510.22750 $[M + H]^+$; found, 510.22802 $[M + H]^+$. Anal. ($C_{32}H_{31}NO_5$): C, H, N.



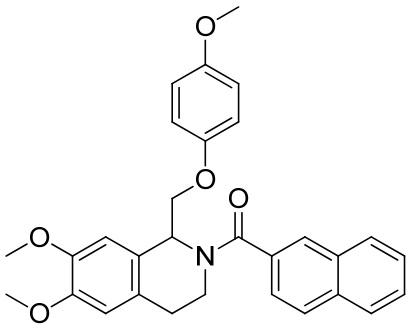
**1-(3-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)ethanone (1180-58).** Compound **1180-58** was prepared according to Procedure I using **6** (1.0 g, 3.0 mmol) and 3-acetylbenzoic acid (0.5 g, 3.04 mmol, 1.0 equiv) in DCM (10 mL) and DMF (2.0 mL). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.32 g, 22%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.15-7.97 (m, 2H), 7.72-7.46 (m, 2H), 6.87-6.78 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.43, 5.95 (s, m)], 1H [5.06, 4.87 (dd, $J_1$ = 3.6 Hz, $J_2$ = 9.2 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ = 13 Hz)], 4.39-4.31 (m, 1H), 1H [4.14, 3.96 (m, m)], 3.84-3.72 (m, 9H), 1H [3.66, 3.25 (m, m)], 1H [3.12, 2.86 (m, m)], 2.77-2.61 (2H), 3H [2.58, 2.56 (s, s)]. $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 197.8, 197.6, 170.9, 170.2, 154.5, 154.3, 153.0, 152.5, 148.9, 148.4, 148.0, 137.6, 137.4, 137.1, 132.3, 131.3, 129.6, 129.4, 129.2, 128.9, 128.0, 127.3, 126.8, 126.2, 125.2, 124.0, 115.9, 115.6, 114.9 (2), 112.1, 111.5, 110.4, 109.8, 71.1, 70.3, 57.5, 56.2, 56.1, 55.9, 51.9, 43.1, 35.7, 29.2, 27.8, 27.0. HRMS calcd. for $C_{28}H_{30}NO_6$, 476.20676 [M + H]$^+$; found, 476.20717 [M + H]$^+$. Anal. ($C_{28}H_{29}NO_6$): C, H, N.



**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(isoxazol-5-yl)methanone (1180-5).** Compound **1180-5** was synthesized according to Procedure H using **6** (0.1 g, 0.3 mmol) and isoxazole-5-carbonyl chloride (0.05 g, 0.4 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.1 g, 99%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1H [8.37, 8.34 (d, $J$ = 2Hz; dd, $J_1$ = 3.6 Hz, $J_2$ = 1.6 Hz)], 1H [6.99, 6.93 (d, $J$ = 2 Hz; d, $J$ = 2 Hz)], 6.96-6.67 (m, 6H), 1H [5.87, 5.65 (dd, $J_1$ = 5.2 Hz, $J_2$ = 5.6 Hz; dd, $J_1$ = 4.4 Hz, $J_2$ = 8.8 Hz)], 4.83-4.11 (m, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.74 (s, 3H), 3.36-2.79 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 164.1, 163.8, 158.6, 158.3, 158.1, 154.4, 154.3, 152.7, 152.4, 151.0, 150.5, 148.9, 148.6, 148.0, 126.9, 126.4, 124.6, 123.5, 115.9, 115.6, 114.9, 111.8, 111.5, 110.3, 110.0, 109.6, 108.1, 70.9, 70.6, 56.6, 56.3, 56.1, 55.9, 53.2, 42.6, 37.1, 29.3, 27.9. HRMS calcd. for $C_{23}H_{25}N_2O_6$, 425.17071 $[M + H]^+$; found, 425.17159 $[M + H]^+$. Anal. ($C_{23}H_{25}N_2O_6$): C, H, N.

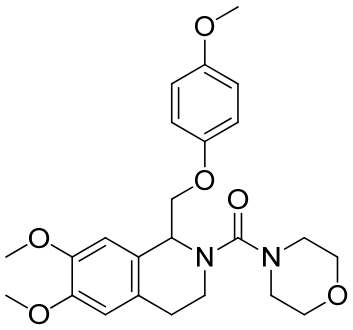


**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(furan-2-yl)methanone (1180-4).** Compound **1180-4** was synthesized according to Procedure H using **6** (0.1 g, 0.3 mmol) and 2-furoyl chloride (0.05 g, 0.4 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.1 g, 99%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.50-6.60 (m, 7H), 6.48 (m, 1H), 5.79 (t, *J* = 5.8 Hz, 1H), 4.73-4.20 (m, 3H), 3.85-3.83 (m, 6H), 3.73 (s, 3H), 3.25 (m, 1H), 3.09-2.99 (m, 1H), 2.88-2.71 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 164.1, 163.8, 158.6, 158.1, 154.4, 154.3, 152.7, 152.4, 151.0, 150.5, 148.2, 144.1, 126.9, 126.4, 123.5, 116.6, 115.9, 114.8, 111.4, 111.0, 110.2, 109.3, 108.4, 71.0, 70.4, 56.2, 56.1, 55.9, 42.2, 37.5, 29.1, 27.4. HRMS calcd. for $C_{24}H_{26}NO_6$, 424.17546 $[M + H]^+$; found, 424.17636 $[M + H]^+$. Anal. ($C_{24}H_{25}NO_6$): C, H, N.



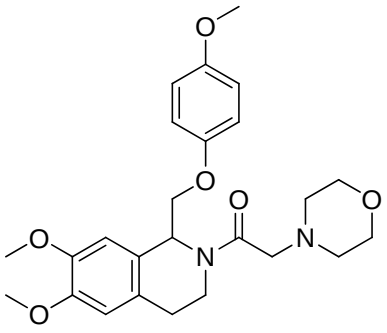
**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(naphthalen-2-yl)methanone (1180-35).** Compound **1180-35** was prepared according to Procedure H using **6**

(0.13 g, 0.4 mmol) and 2-napthoyl chloride (0.09 g, 0.5 mmol). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white solid (mixture of rotamers, 0.04 g, 21%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.07-7.83 (m, 4H), 7.66-7.49 (m, 3H), 6.95-6.84 (m, 2H), 6.80 (s, 2H), 1H [6.72, 6.65 (s, s)], 1H [6.45, 6.07 (s, m)], 1H [5.26, 4.97 (dd, $J_1$ = 4.0 Hz, $J_2$ = 8.8 Hz; dd, $J_1$ = 5.4 Hz, $J_2$ = 13 Hz)], 4.48-4.39 (m, 1H), 4.22-3.96 (m, 1H), 3.89-3.75 (m, 10H), 3.71-3.28 (m, 1H), 3.23-2.87 (m, 1H), 2.86-2.64 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.0, 171.2, 154.4, 153.1, 152.7, 148.8, 148.4, 147.9, 147.7, 133.9, 133.8, 133.0, 128.7, 128.0, 127.4, 127.3, 127.0, 126.5, 125.5, 125.4, 124.4, 124.2, 115.9, 115.4, 115.0, 110.5, 110.4, 110.0, 71.2, 56.2, 56.1, 51.8, 29.3. HRMS calcd. for $C_{30}H_{30}NO_5$ , 484.21185 $[M + H]^+$; found, 484.21169 $[M + H]^+$. Anal. ($C_{30}H_{29}NO_5$): C, H, N.



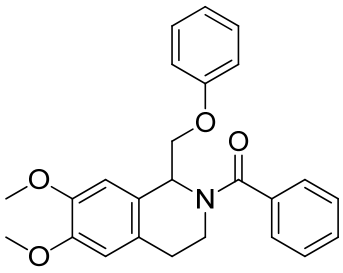
**(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(morpholino)methanone ( 1180-23).** Compound **1180-23** was synthesized according to Procedure H using **6** (0.12 g, 0.36 mmol) and morpholine-4-carbonyl chloride (0.07 g, 0.44 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.05 g, 31%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.82 (s, 4H), 6.72 (s, 1H), 6.62 (s, 1H), 5.23-5.20 (m, 1H), 4.24-4.19 (m, 1H), 4.13-4.09 (m, 1H), 3.86 (m, 7H), 3.76 (s, 3H), 3.69 (m, 4H), 3.50-3.24 (m, 5H), 3.30-2.95 (m, 1H), 2.68-2.62 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 154.2,

153.1, 148.1, 147.4, 128.2, 126.5, 115.8, 114.8, 112.1, 109.7, 71.5, 56.2, 56.0, 55.9, 54.9, 39.9, 29.3. HRMS calcd. for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$; found, 330.16968 $[M + H]^+$. Anal. ($C_{19}H_{24}NO_4$): C, H, N.



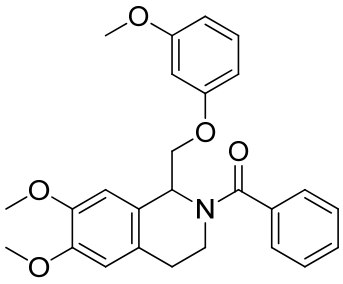
**1-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)-2-morpholinoethanone (1180-24).** Compound **1180-24** was prepared via a two step sequence. **6** (0.7 g, 2.1 mmol) was dissolved in dry DCM (20 mL) and cooled to 0°C in an ice bath. Triethylamine (0.22 g, 2.1 mmol, 1.0 equiv) was added to the cooled mixture followed by dropwise addition of chloroacetyl chloride (0.24 g, 2.1 mmol, 1.0 equiv). The reaction was warmed to room temperature and stirred for an additional 2 hours. The reaction was quenched with 1M HCl and extracted into DCM (2x). The combined organics were washed with brine and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the α-chloro amide (0.67 g, 78%, mixture of rotamers) as a white solid. $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.85-6.78 (m, 4H), 1H [6.74, 6.71 (s, s)], 1H [6.66, 6.65 (s, s)], 1H [5.72, 4.26 (t, *J* = 5.2 Hz; m)], 1H [ 5.25, 4.74 (dd, $J_1$ = 3.8 Hz, $J_2$ = 9.8 Hz; m)], 1H [4.58, 4.34 (d, *J* = 12.4 Hz; d, *J* = 12.4 Hz)], 4.22-4.07 (m, 3H), 3.89-3.74 (m, 10H), 3.13-2.68 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.7, 166.0, 154.6, 154.3, 152.3, 148.9, 148.4, 148.0, 127.5, 126.4, 125.3, 123.2, 115.9, 115.6, 114.9, 114.8, 111.9, 111.3, 110.4, 110.0, 70.9, 70.7, 56.3, 56.2, 56.1, 55.9, 42.3, 42.0, 41.8, 31.8, 27.8,

22.9. HRMS calcd. for $C_{21}H_{25}NO_5Cl$, 406.14158 $[M + H]^+$; found, 406.14197 $[M + H]^+$. The α-chloro amide (0.20 g, 0.49 mmol, 1.0 equiv) was dissolved in absolute EtOH (10 mL). Morpholine (0.22 g, 0.22 mL, 2.5 mmol, 5.0 equiv) was added to this solution and the reaction was stirred at room temperature for 18 hours. After TLC indicated complete conversion, the volatiles were removed *in vacuo* and the crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient, dry load) to afford the title compound as a white solid (0.12 g, 53%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.84-6.77 (m, 4H), 1H [6.74, 6.71 (s, s)], 1H [6.64, 6.63 (s, s)], 1H [5.75, 5.63 (m, m)], 1H [4.74, 4.25 (dd, $J_1$ = 4.4 Hz, $J_2$ = 13 Hz; dd, $J_1$ =5.4 Hz, $J_2$ = 9.8 Hz)], 4.18-4.06 (m, 2H), 3.91-3.82 (m, 6H), 3.75-3.35 (m, 9H), 3.32-3.23 (m, 1H), 3.09-2.78 (m, 2H), 2.70-2.46 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 168.6, 154.4, 154.2, 152.9, 152.6, 148.7, 148.3, 147.8, 127.5, 126.7, 125.7, 124.6, 115.7, 115.5, 114.8, 111.9, 111.4, 110.5, 110.1, 70.9, 67.1, 62.3, 61.6, 56.2, 53.8, 51.7, 29.3, 28.0. HRMS calcd. for $C_{25}H_{33}N_2O_6$, 457.23331 $[M + H]^+$; found, 457.23263 $[M + H]^+$. Anal. ($C_{25}H_{32}N_2O_6$): C, H, N.



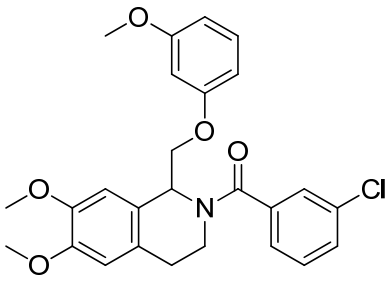

**(6,7-dimethoxy-1-(phenoxymethyl))-3,4-dihydroisoquinolin-2(1*H*)-yl(phenyl)methanone (1180-2).** Compound **1180-2** was prepared according to Procedure H using **31d** (0.6 g, 2 mmol) and benzoyl chloride (0.4 g, 0.3 mL, 3 mmol, 1.3 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, gradient 0-60% EtOAc/hexanes) to afford the title compound as a white solid (mixture of two rotamers, 0.8 g, 99% yield). $^1$H NMR ($CDCl_3$, 400

MHz) δ: 7.50 (m, 1H), 7.38 (m, 4H), 7.23 (m, 2H), 6.94-6.89 (m, 2H), 1H [6.81, 6.60 (s, s)], 1H [6.78, 6.66 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.16, 4.84 (dd, $J_1$ = 4.0 Hz, $J_2$ = 9.0 Hz; dd, $J_1$ = 6.0 Hz, $J_2$ = 9.4 Hz), 4.39 (m, 1H), 1H [4.18, 3.99 (m, m)], 3.84-3.75 (m, 6H), 1H [3.78, 3.63 (m, m)], 3.28-3.02 (m, 1H), 2.91-2.61 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.9, 171.2, 158.9, 158.5, 148.8, 148.4, 148.0, 147.7, 136.6, 129.8, 128.8, 128.6, 127.7, 127.5, 126.8, 126.5, 125.4, 124.3, 121.5, 121.3, 114.9, 114.6, 112.1, 111.6, 110.5, 110.0, 70.3, 69.6, 57.2, 56.2, 56.1, 51.7, 43.0, 35.7, 29.3, 27.9. HRMS calcd. for $C_{25}H_{25}NO_4$, 404.18564 $[M + H]^+$; found, 404.18538 $[M + H]^+$. Anal. ($C_{25}H_{24}NO_4$): C, H, N.

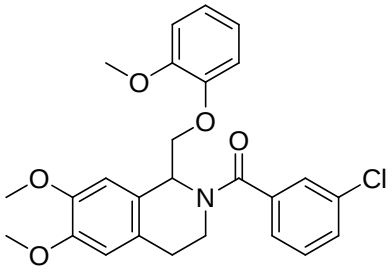


**(6,7-dimethoxy-1-((3-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-7).** Compound **1180-7** was prepared according to Procedure H using **31e** (0.2 g, 0.6 mmol, 1.0 equiv) and benzoyl chloride (0.1 g, 0.7 mmol, 1.2 equiv, 0.08 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.18 g, 60%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 8.06-7.12 (m, 6H), 6.80-5.98 (m, 4H), 1H [5.16, 4.89 (dd, $J_1$ = 4.0 Hz, $J_2$ = 8.8 Hz; dd, $J_1$ = 6.0 Hz, $J_2$ = 12 Hz)], 4.40-3.96 (m, 2H), 3.85-3.75 (m, 10H), 3.66-2.64 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.9, 171.3, 161.1, 160.1, 159.7, 148.8, 148.4, 147.9, 147.7, 136.5, 133.5, 130.3, 129.9, 128.8, 128.6, 127.7, 127.5, 126.9, 126.4, 125.3, 124.2, 112.0, 111.5, 110.4, 109.9, 107.0, 106.8, 101.3, 70.4, 69.7, 57.2, 56.2, 56.1, 55.6, 51.6, 43.0,

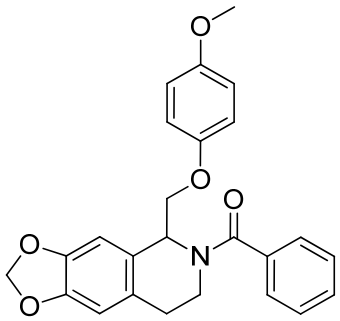
35.7, 29.3, 27.9. HRMS calcd. for $C_{26}H_{28}NO_5$, 434.19620 $[M + H]^+$; found, 434.19602 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_5$): C, H, N.



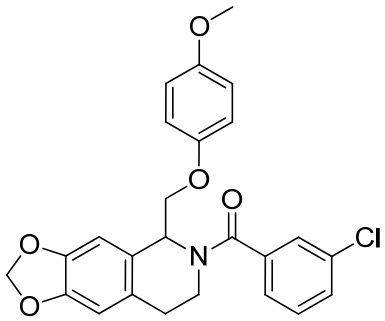
**(3-chlorophenyl)(6,7-dimethoxy-1-((3-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-6).** Compound **1180-6** was prepared according to Procedure H using **31f** (0.2 g, 0.6 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.1 g, 0.7 mmol, 1.2 equiv, 0.07 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.20 g, 67%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 8.03-7.46 (m, 1H), 7.39-7.29 (m, 3H), 7.16 (t, $J$ = 8.4 Hz, 1H), 1H [6.78,6.66 (s, s)], 1H [6.61, 6.47 (s,s)], 6.52-5.95 (m, 3H), 1H [5.10, 4.86 (dd, $J_1$ = 3.0 Hz $J_2$ = 9.0 Hz; dd, $J_1$ = 5.6 Hz, $J_2$ = 13 Hz)], 4.38 (m, 1H), 1H [4.20, 3.98 (m, m)], 3.85-3.75 (m, 9H), 3.75-3.45 (m, 1H), 3.28-3.04 (m, 1H), 2.92-2.66 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.6, 161.1, 160.0, 148.0, 147.8, 138.2, 134.6, 132.3, 130.3,130.0, 128.2, 128.0, 127.3, 127.1, 125.7, 125.0, 123.8, 111.5, 110.3, 109.9, 107.3, 107.0, 106.5, 101.3, 101.0, 70.3, 57.4, 56.2, 56.1, 55.6, 42.9, 35.7, 29.2, 27.8. HRMS calcd. for $C_{26}H_{27}NO_5Cl$, 468.15723 $[M + H]^+$; found, 468.15689 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N.



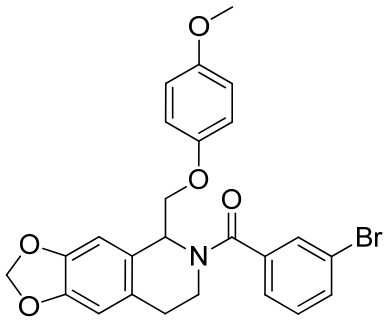
**(3-chlorophenyl)(6,7-dimethoxy-1-((2-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-8).** Compound **1180-8** was prepared according to Procedure H using **31f** (0.5 g, 2 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.3 g, 2 mmol, 1.2 equiv, 0.22 mL). The crude residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of rotamers, 0.5 g, 70%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.81-7.23 (m, 4H), 6.98-6.72 (m, 5H), 1H [6.64, 6.59 (s, s)], 1H [6.48, 5.98 (s, m)], 1H [5.12, 4.84 (dd, $J_1$ = 4.0 Hz, $J_2$ = 9.6 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ =13 Hz)], 4.42-4.38 (m, 1H), 4.05-4.01 (m, 1H), 3.89-3.66 (m, 10H), 3.30-3.04 (m, 1H), 2.93-2.60 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.5, 169.6, 149.9, 149.7, 147.9, 147.7, 138.3, 138.2, 134.8, 134.6, 132.0, 130.2, 129.9, 128.3, 127.3, 127.1, 126.2, 126.1, 125.8, 125.2, 124.9, 124.1, 122.1, 121.1, 120.8, 114.2, 113.4, 112.3, 112.0, 111.8, 111.5, 110.6, 110.0, 71.1, 70.1, 57.5, 56.1, 56.0, 55.8, 51.7, 42.8, 35.6, 29.2, 27.7. HRMS calcd. for $C_{26}H_{27}NO_5Cl$, 468.15723 $[M + H]^+$; found, 468.15685 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N. HPLC: 95% ISO MeCN, RT = 1.875 min; 85% ISO MeOH, RT = 1.874 min.



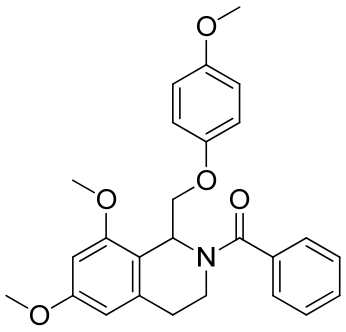
**(5-((4-methoxyphenoxy)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)(phenyl)methanone (1180-47).** Compound **1180-47** was prepared according to Procedure H using **31g** (0.14 g, 0.45 mmol) and benzoyl chloride (0.09 g, 0.68 mmol, 1.5 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4g column, 0-60% EtOAc/hexanes gradient) afforded the title compound as a white solid (mixture of rotamers, 0.14 g, 73%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.50-7.41 (m, 5H), 6.90-6.77 (m, 4H), 1H [6.66, 6.47 (s, s)], 6.61 (s, 1H), 5.91 (s, 2H), 1H [5.13, 5.85 (m, m)], 4.36 (m, 1H), 1H [4.12, 3.94 (m, m)], 3.81-3.71 (m, 4H), 1H [3.66, 3.26 (m, m)], 1H [3.09, 2.85 (m, m)], 2.78-2.64 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.1, 171.4, 154.5, 153.3, 152.9, 147.2, 146.9, 136.9, 130.1, 129.0, 128.8, 128.0, 127.9, 127.1, 126.8, 125.7, 116.1, 115.9, 115.1, 109.6, 108.9, 107.8, 107.3, 101.5, 71.6, 70.6, 57.8, 56.2, 52.4, 43.2, 35.8, 30.0, 28.6. HRMS calcd. for $C_{25}H_{24}NO_5$, 418.16490 $[M + H]^+$; found, 418.16432 $[M + H]^+$. Anal. ($C_{25}H_{23}NO_5$): C, H, N.



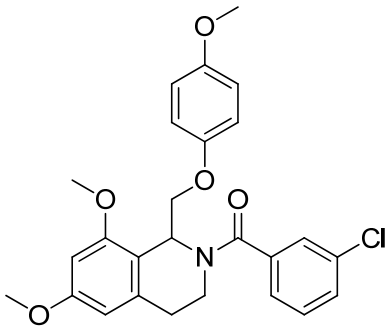
**(3-chlorophenyl)(5-((4-methoxyphenoxy)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methanone (1180-25).** Compound **1180-25** was prepared according to Procedure H using **31g** (0.1 g, 0.3 mmol) and 3-chlorobenzoyl chloride (0.07 g, 0.05 mL, 0.4 mmol, 1.2 equiv.). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.08 g, 56%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.05-7.5 (m, 1H), 7.41-7.28 (m, 3H), 6.89-6.48 (m, 6H), 5.95-5.90 (m, 2H), 1H [5.07, 4.84 (dd, $J_1$ = 3.4 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.6 Hz, $J_2$ = 13 Hz)], 4.36-4.34 (m, 1H), 4.17-3.92 (m, 1H), 3.77 (s, 3H), 3.75-3.66 (m, 1H), 3.30-3.03 (m, 1H), 2.90-2.66 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 157.6, 154.3, 152.9, 152.5, 147.6, 147.1, 146.5, 138.1, 134.9, 134.6, 130.2, 129.9, 128.6, 128.1, 127.6, 127.0, 126.2, 125.8, 124.9, 115.9, 115.5, 114.9, 108.8, 107.4, 101.3, 71.2, 57.7, 56.0, 55.9, 52.3, 43.0, 35.6, 29.7, 28.2. HRMS calcd. for $C_{25}H_{23}NO_5Cl$, 452.12593 $[M + H]^+$; found, 452.12608 $[M + H]^+$. Anal. ($C_{25}H_{22}NO_5Cl$): C, H, N.



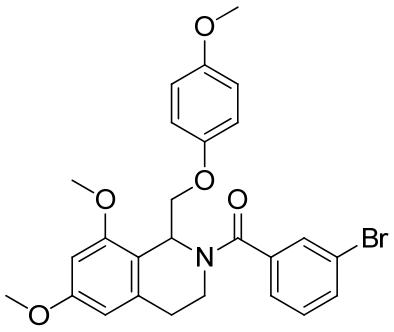
**(3-bromophenyl)(5-((4-methoxyphenoxy)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methanone (1180-48).** Compound **1180-48** was prepared according to Procedure H using **31g** (0.14 g, 0.5 mmol) and 3-bromobenzoyl chloride (0.15 g, 0.68 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.08 g, 56%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.73-7.52 (m, 2H), 7.42-7.28 (m, 2H), 6.89-6.81 (m, 4H), 1H [6.78, 6.61 (s, s)], 1H [6.67, 6.49 (s, s)], 5.96-5.91 (m, 2H), 1H [5.06, 4.83 (m, m)], 4.35 (d, *J* = 4.4 Hz, 1H), 4.16-3.93 (m, 1H), 3.77 (s, 3H), 3.75-3.63 (m, 1H), 3.28-3.04 (m, 1H), 2.90-2.66 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.6, 154.6, 153.2, 147.3, 147.0, 138.7, 133.1, 133.0, 131.2, 130.7, 130.4, 130.1, 128.8, 127.8, 126.4, 125.6, 125.3, 123.2, 122.9, 116.1, 115.7, 115.2, 115.1, 109.6, 109.0, 107.7, 107.3, 101.6, 71.4, 70.4, 58.0, 56.2, 52.6, 43.2, 35.8, 29.9, 28.4. HRMS calcd. for $C_{25}H_{23}NO_5Br$, 496.07541 $[M + H]^+$; found, 496.07478 $[M + H]^+$. Anal. ($C_{25}H_{22}NO_5Br$): C, H, N.



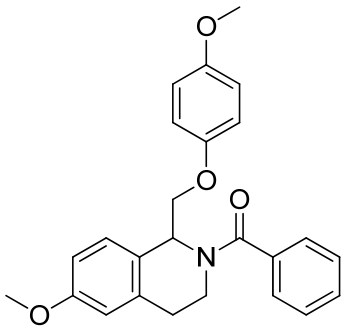
**(6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-19).** Compound **1180-19** was prepared according to Procedure H using **31h** (0.11 g, 0.3 mmol) and benzoyl chloride (0.06 g, 0.4 mmol, 1.2 equiv). The crude material was as a white solid (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.09 g, 62%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.48-7.29 (m, 5H), 6.88-6.78 (m, 4H), 6.36-6.24 (m, 2H), 1H [5.43, 4.88 (dd, $J_1$ = 3.4 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 6.0 Hz, $J_2$ = 13.2 Hz)], 1H [4.47, 4.32 (dd, $J_1$ = 3.2 Hz, $J_2$ = 10.4 Hz; dd, $J$ = 7.4 Hz, $J$ = 9.8 Hz)], 4.09-3.99 (m, 1H), 3.84-3.71 (m, 10H), 3.35-3.10 (m, 1H), 2.89-2.69 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.1, 160.2, 157.0, 154.1, 153.5, 153.0, 137.7, 137.0, 136.5, 130.3, 129.6, 128.8, 128.3, 127.8, 126.8, 115.8, 115.5, 114.8, 114.0, 105.0, 96.9, 67.4, 56.0, 55.6, 53.4, 48.2, 42.0, 35.1, 29.8. HRMS calcd. for $C_{26}H_{28}NO_5$, 434.19620 $[M + H]^+$; found, 434.19690 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_5$): C, H, N.



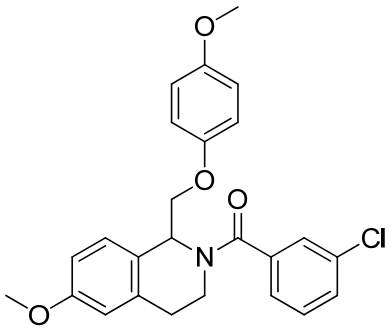
**(3-chlorophenyl)(6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-20).** Compound **1180-20** was prepared according to Procedure H using **31h** (0.11 g, 0.3 mmol) and 3-chlorobenzoyl chloride (0.07 g, 0.4 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.08 g, 51%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.22 (m, 4H), 6.88-6.79 (m, 4H), 6.37-6.22 (m, 2H), 1H [5.36, 4.85 (dd, $J_1$ = 3.2 Hz, $J_2$ = 9.2 Hz; dd, $J_1$ = 6.2 Hz, $J_2$ = 13.4 Hz)], 1H [4.46, 4.30 (dd, $J_1$ = 2.8 Hz, $J_2$ = 10.0 Hz; dd, $J_1$ = 7.2 Hz, $J_2$ = 10.0 Hz)], 4.10-3.95 (m, 1H), 3.84-3.74 (m, 9H), 3.75-3.70 (m, 1H), 3.36-3.08 (m, 1H), 2.72-2.87 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.5, 160.3, 159.9, 157.0, 154.1, 153.3, 152.8, 138.9, 138.1, 137.5, 136.5, 134.4, 130.2, 129.6, 128.3, 125.8, 115.8, 115.3, 114.9, 114.3, 113.6, 105.0, 104.5, 96.9, 67.3, 56.0, 55.6, 53.5, 42.0, 35.1, 30.0. HRMS calcd. for $C_{26}H_{27}NO_5Cl$ , 468.15723 $[M + H]^+$; found, 468.15753 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_5Cl$): C, H, N.



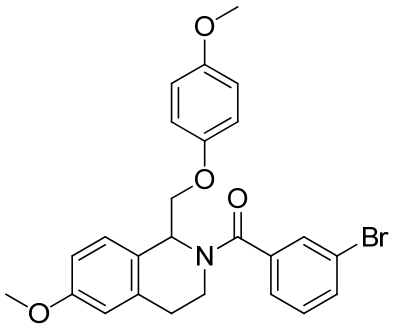
**(3-bromophenyl)(6,8-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-21).** Compound **1180-21** was prepared according to Procedure H using **31h** (0.11 g, 0.3 mmol) and 3-bromobenzoyl chloride (0.09 g, 0.4 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.10 g, 58%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.70-7.13 (m, 4H), 6.86-6.76 (m, 4H), 6.34-6.18 (m, 2H), 1H [ 5.34, 4.82 (dd, $J_1$ = 3.4 Hz, $J_2$ = 10.2 Hz; dd, $J_1$ = 6.4 Hz, $J_2$ = 13.2 Hz)], 1H [4.43, 4.27 (dd, $J_1$ = 3.4 Hz, $J_2$ = 10.2 Hz; dd, $J_1$ = 7.2 Hz, $J_2$ = 10.0 Hz), 4.10-3.92 (m, 2H), 3.81-3.69 (m, 9H), 3.33-3.06 (m, 1H), 2.84-2.69 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.4, 160.3, 159.9, 157.0, 154.1, 152.8, 138.3, 137.5, 136.5, 132.6, 131.1, 129.9, 126.3, 122.5, 115.8, 115.3, 114.9, 113.6, 105.0, 104.5, 96.9, 67.2, 56.0, 55.6, 53.5, 42.0, 35.1, 28.5. HRMS calcd. for $C_{26}H_{27}NO_5Br$ , 512.10671 $[M + H]^+$; found, 512.10713 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Br$): C, H, N.



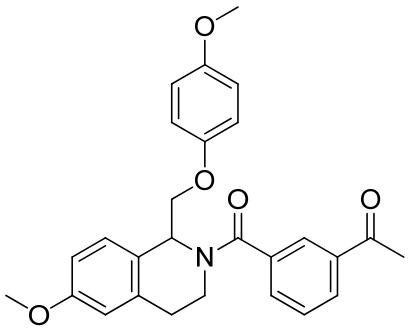
**(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-46).** Compound **1180-46** was prepared according to Procedure H using **31i** (0.6 g, 2.0 mmol) and benzoyl chloride (0.34 g, 2.4 mmol, 1.2 equiv). The crude material was subjected to flash column chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.6 g, 74%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.22 (m, 5H), 6.92-6.00 (m, 7H), 1H [5.20, 4.87 (dd, $J_1$ = 3.2 Hz, $J_2$ = 8.0 Hz; dd, $J_1$ = 5.2 Hz, $J_2$ = 12.0 Hz)], 4.35 (m, 1H), 4.13-3.90 (m, 1H), 3.80-3.63 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.30-3.14 (m, 1H), 2.94-2.70 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.3, 159.2, 158.7, 154.4, 154.2, 153.2, 152.7, 136.8, 135.8, 129.8, 128.8. 128.6, 127.7, 126.8, 125.7, 124.8, 116.0, 115.6, 114.9, 113.7, 113.1, 71.4, 56.0, 55.9, 55.6, 51.8, 42.8,35.4, 30.1, 28.7. HRMS calcd. for $C_{25}H_{26}NO_5$ , 404.18564 $[M + H]^+$; found, 404.18527 $[M + H]^+$. Anal. ($C_{25}H_{25}NO_5$): C, H, N.



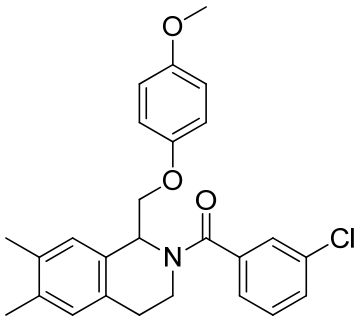
**(3-chlorophenyl)(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-26).** Compound **1180-26** was prepared according to Procedure H using **31i** (0.25 g, 0.8 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.1 g, 27%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.61-6.94 (m, 5H), 6.89-5.98 (m, 6H), 1H [5.15, 4.87 (dd, $J_1$ = 3.6 Hz, $J_2$ = 9.6 Hz; dd, $J_1$ = 5.4 Hz, $J_2$ = 12.6 Hz)], 4.36 (m, 1H), 1H [4.15, 3.94 (m, m)], 3.81 (s, 3H), 3.77 (s, 3H), 3.76-3.69 (m, 1H), 3.31-3.14 (m, 1H), 2.98-2.74 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.7, 159.2, 158.8, 154.4, 153.0, 152.6, 138.4, 138.2, 136.6, 135.6, 134.9, 134.5, 130.2, 129.9, 128.7, 128.3, 128.2, 127.1, 125.8, 125.4, 124.9, 124.4, 115.9, 115.5, 115.0, 114.9, 114.2, 113.8, 113.2, 113.0, 71.3, 70.2, 57.3, 55.9, 55.5, 52.0, 42.8, 35.4, 35.4, 30.0, 28.5. HRMS calcd. for $C_{25}H_{24}NO_4Cl$ , 438.14636 $[M + H]^+$; found, 438.14666 $[M + H]^+$. Anal. ($C_{25}H_{23}NO_4Cl$): C, H, N.



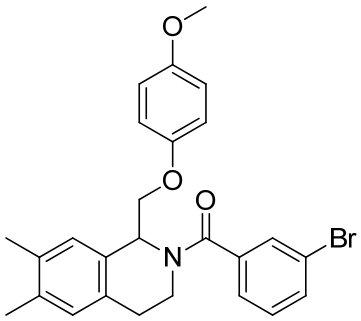

**(3-bromophenyl)(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-27).** Compound **1180-27** was prepared according to Procedure H using **31i** (0.25 g, 0.8 mmol) and 3-bromobenzoyl chloride (0.22 g, 1.0 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.22 g, 55%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.19-7.50 (m, 2H), 7.42-7.20 (m, 3H), 6.93-5.96 (6H), 1H [5.14, 5.12 (dd, *J* = 3.4 Hz, *J* = 9.4 Hz; dd, *J* = 5.2 Hz, 12.8 Hz)], 4.35-4.32 (m, 1H), 1H [4.12, 3.68 (m, m)], 3.98-3.84 (m, 1H), 3.30-3.08 (m, 1H), 2.94-2.72 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 158.8, 154.4, 153.1, 152.6, 138.5, 136.6, 136.3, 135.6, 133.2, 132.9, 131.0, 130.5, 130.1, 129.9, 128.8, 128.7, 128.3, 126.3, 125.3, 124.4, 122.7, 115.9, 115.5, 115.0, 114.9, 114.3, 113.8, 113.2, 113.0, 71.3, 70.2, 57.3, 55.9, 55.5, 52.0, 42.9, 35.5, 29.9, 28.5. HRMS calcd. for $C_{25}H_{25}NO_4Br$ , 482.09615 $[M + H]^+$; found, 482.09600 $[M + H]^+$. Anal. ($C_{25}H_{24}NO_4Br$): C, H, N.



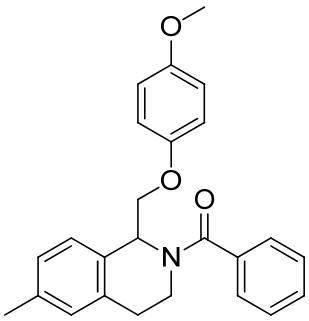
**1-(3-(6-methoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)ethanone (1180-67).** Compound **1180-67** was prepared according to Procedure I using tetrahydroisoquinoline **31i** (0.4 g, 1.3 mmol, 1.0 equiv) and 3-acetylbenzoic acid (0.22 g, 1.3 mmol, 1.0 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (mixture of two rotamers, 0.3 g, 50%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.13-7.97 (m, 2H), 7.71-7.45 (m, 2H), 6.91-5.97 (m, 7H), 1H [5.10, 4.87 (dd, $J_1$ = 3.4 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ = 12.6 Hz)], 4.36 (m, 1H), 4.13-3.91 (m, 1H), 3.77-3.69 (m, 8H), 3.31-2.73 (m, 2H), 2.62-2.51 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 197.7, 171.0, 170.2, 159.3, 158.8, 154.5, 152.6, 137.6, 137.3, 137.1, 136.6, 132.2, 131.3, 129.4, 129.2, 128.9, 128.3, 128.0, 126.9, 115.9, 115.6, 114.9, 114.9, 114.3, 113.8, 113.2, 113.0, 71.4, 70.3, 57.4, 55.9, 55.5, 52.0, 43.0, 35.4, 30.0, 28.5, 27.0. HRMS calcd. for $C_{27}H_{28}NO_5$ , 446.19620 $[M + H]^+$; found, 446.19649 $[M + H]^+$. Anal. ($C_{27}H_{27}NO_5$): C, H, N.



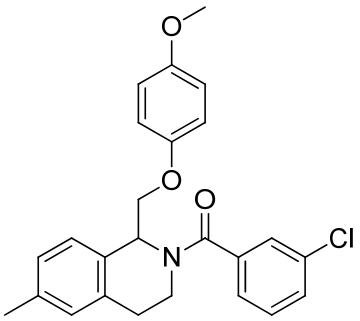

**(3-chlorophenyl)(1-((4-methoxyphenoxy)methyl)-6,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-44).** Compound **1180-44** was prepared according to Procedure H using **31j** (0.25 g, 0.8 mmol) and 3-chlorobenzoyl chloride (0.18 g, 1.0 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes) to afford the title compound as a white solid (mixture of two rotamers, 0.3 g, 82%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.61-7.25 (m, 4H), 7.07-5.97 (m, 6H), 1H [5.14, 4.87 (dd, $J_1$ = 3.2 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ = 13.0 Hz)], 4.38 (m, 1H), 1H [4.16, 3.96 (m, m)], 3.76 (s, 3H), 3.72-3.67 (m, 1H), 3.30-3.06 (m, 1H), 2.86-2.72 (m, 2H), 2.30-2.19 (m, 7H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.5, 169.7, 154.4, 153.1, 152.6, 138.3, 136.7, 136.0, 135.2, 135.0, 134.9, 134.5, 132.5, 131.6, 130.8, 130.3, 129.9, 129.8, 129.6, 128.2, 127.1, 125.9, 124.9, 115.9,115.5, 114.9, 71.3, 57.5, 55.9, 55.9, 52.1, 43.1, 35.8, 27.8, 19.7. HRMS calcd. for $C_{26}H_{27}NO_3Cl$ , 436.16740 $[M + H]^+$; found, 436.16736 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_3Cl$): C, H, N.



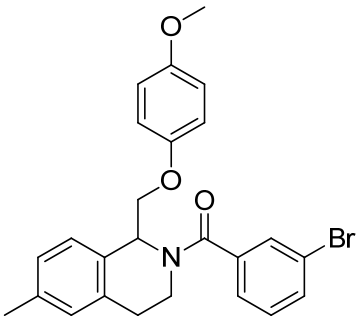

**(3-bromophenyl)(1-((4-methoxyphenoxy)methyl)-6,7-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-45).** Compound **1180-45** was prepared according to Procedure H using **31j** (0.25 g, 0.8 mmol) and 3-bromobenzoyl chloride (0.22 g, 1.0 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-60% EtOAc/hexanes) to afford the title compound as a white solid (mixture of two rotamers, 0.3 g, 74%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.77-7.22 (m, 4H), 7.07-5.98 (6H), 1H [dd, $J_1$ = 3.2 Hz, $J_2$ = 9.2 Hz; dd, $J_1$ = 5.6 Hz, $J_2$ = 12.8 Hz)], 4.38 (m, 1H), 1H [4.15, 3.96 (m, m)], 3.76 (s, 3H), 3.74-3.64 (m, 1H), 3.30-3.05 (m, 1H), 2.9-2.68 (m, 2H), 2.25-2.21 (m, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.5, 154.4, 154.2, 153.1, 152.6, 138.7, 138.5, 136.7, 135.9, 135.2, 135.0, 132.8, 132.5, 131.6, 130.8, 130.5, 130.1, 129.9, 129.6, 128.5, 126.3, 125.4, 122.9, 122.7, 115.9, 115.5, 114.9, 76.8, 71.3, 70.2, 57.6, 56.0, 55.9, 52.1, 43.1, 35.8, 27.8, 19.8, 19.7. HRMS calcd. for $C_{26}H_{27}NO_3Br$ , 480.11688 $[M + H]^+$; found, 480.11704 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_3Br$): C, H, N.



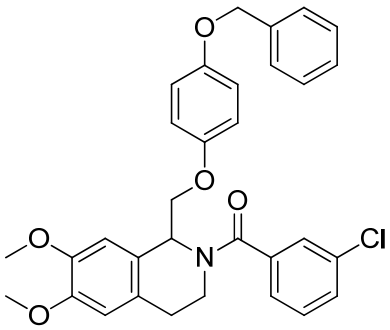
**(1-((4-methoxyphenoxy)methyl)-6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-69).** Compound **1180-69** was prepared according to Procedure H using **31k** (0.18 g, 0.64 mmol, 1.0 equiv) and benzoyl chloride (0.11 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white solid (mixture of two rotamers, 0.11 g, 45%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.50-6.02 (m, 12H), 1H [5.21, 4.88 (m, m)], 1H [4.38, 4.27 (m, m)], 3.92-3.46 (m, 6H), 3.27-2.70 (m, 2H), 2.39-2.25 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.5, 171.3, 154.2, 138.4, 138.1, 137.0, 136.8, 134.4, 130.4, 129.8, 129.5, 128.8, 128.7, 128.6, 127.7, 127.6, 127.2, 126.8, 126.6, 126.0, 115.9, 115.6, 114.9, 71.5, 70.4, 67.1, 57.5, 56.0, 52.7, 52.0, 45.6, 43.0, 35.5, 34.0, 29.8, 28.3, 21.6, 21.3. HRMS calcd. for $C_{25}H_{27}NO_3$, 390.20637 $[M + H]^+$; found, 390.20671 $[M + H]^+$. Anal ($C_{25}H_{26}NO_3$): C, H, N.



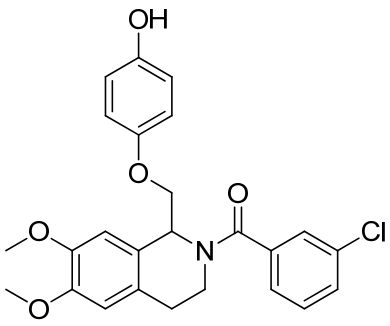

**(3-chlorophenyl)(1-((4-methoxyphenoxy)methyl)-6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-70).** Compound **1180-70** was prepared according to Procedure H using **31k** (0.18 g, 0.64 mmol, 1.0 equiv) and 3-chlorobenzoyl chloride (0.13 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white solid (mixture of two rotamers, 0.10 g, 37%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.57-5.99 (m, 11H), 1H [5.14, 4.85 (m; dd, $J_1$ = 5.6 Hz, $J_2$ = 13.2 Hz)], 1H [4.36, 4.25 (m, m)], 4.20-3.56 (m, 6H), 3.48-2.71 (m, 3H), 2.33-2.26 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.9, 154.4, 138.2, 137.8, 134.6, 130.2, 129.8, 129.6, 128.8, 128.2, 127.7, 127.4, 127.0, 126.9, 126.1, 124.8, 115.9, 115.6, 115.5, 115.0, 70.2, 66.9, 57.6, 56.0, 52.6, 52.2, 45.5, 43.0, 35.6, 35.2, 29.7, 21.6, 21.3. HRMS calcd. for $C_{25}H_{25}NO_3Cl$, 422.15175 $[M + H]^+$; found, 422.15201 $[M + H]^+$. Anal. ($C_{25}H_{24}NO_3Cl$): C, H, N.




**(3-bromophenyl)(1-((4-methoxyphenoxy)methyl)-6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-71).** Compound **1180-71** was prepared according to Procedure H using **31k** (0.18 g, 0.64 mmol, 1.0 equiv) and 3-bromobenzoyl chloride (0.17 g, 0.76 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes) to afford the title compound as an off-white solid (mixture of two rotamers, 0.11 g, 37%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.74-5.99 (11H), 1H [5.15, 4.85 (m; dd, $J_1$ = 5.6 Hz, $J_2$ = 13.2 Hz)], 1H [4.36, 4.26 (m, m)], 4.17-3.57 (m, 6H), 3.45-3.08 (m, 1H), 2.98-2.72 (m, 2H), 2.34-2.27 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.7, 154.3, 152.6, 138.5, 137.8, 134.2, 132.8, 132.5, 130.3, 130.1,129.8, 129.7, 128.8, 127.8, 127.5, 127.2, 126.1, 125.2, 122.6, 115.9, 115.5, 114.9, 71.3, 57.6, 55.9, 52.7, 45.5, 28.2, 21.6, 21.3. HRMS calcd. for $C_{25}H_{25}NO_3Br$, 466.10123 [M + H]$^+$; found, 466.10158 [M + H]$^+$. Anal. ($C_{25}H_{24}NO_3Br$): C, H, N.

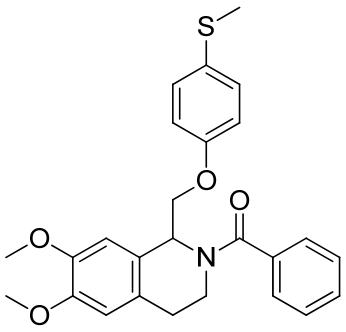


**(1-((4-(benzyloxy)phenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)(3-chlorophenyl)methanone (1180-22).** Compound **1180-22** was prepared according to Procedure H using **31l** (0.18 g, 0.44 mmol) and 3-chlorobenzoyl chloride (0.09 g, 0.5 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (mixture of two rotamers, 0.13 g, 52%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.61-7.24 (m, 9H), 6.90-6.78 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.94 (s, m)], 1H [5.08, 4.85 (dd, $J_1$ = 3.2 Hz, $J_2$ = 6.0 Hz; dd, $J_1$ = 5.4 Hz, $J_2$ = 13.0 Hz)], 5.00 (s, 2H), 4.34 (m, 1H), 1H [4.16, 3.95 (m, m)], 3.85-3.78 (m, 6H), 3.75-3.64 (m, 1H), 3.28-3.05 (m, 1H), 2.92-2.64 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.6, 153.5, 152.7, 148.9, 148.0, 147.8, 138.3, 137.4, 134.9, 134.6, 130.0, 128.8, 128.2, 127.7, 127.3, 127.1, 126.3, 126.0, 125.2, 124.0. 116.1, 115.5, 111.6, 109.9, 70.8, 57.5, 56.3, 56.2, 42.9, 29.2, 14.4. HRMS calcd. for $C_{32}H_{31}NO_5Cl$ , 544.18853 $[M + H]^+$; found, 544.18945 $[M + H]^+$. Anal. ($C_{32}H_{30}NO_5Cl$): C, H, N.

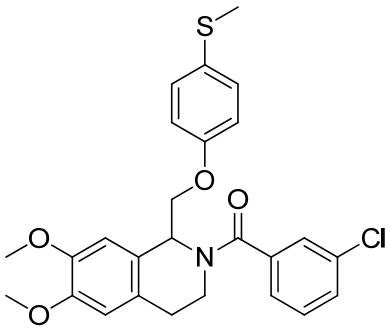



**(3-chlorophenyl)(1-((4-hydroxyphenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-65).** Compound **1180-22** (0.4 g, 0.74 mmo) was dissolved in dry chloroform (10 mL). Methanesulfonic acid (21.2 g, 14.3 ml, 221 mmol) was added to this solution and the reaction was stirred at room temperature for 1 hour. After 1 hour, the solution was poured onto ice. EtOAc was added and the organic layer was washed with saturated $NaHCO_3$ solution and brine. The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the 13 mg of the title compound as a white solid. An additional 90 mg of an inseperable mixture of starting material and product was obtained and resubjected to the above conditions for an additional hour. The pure products from both reactions were combined (mixture of two rotamers, 0.10 g, 30%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 9.86 (s, 1H, broad), 7.39-5.93 (m, 10H), 1H [5.06, 4.82 (m, m)], 4.29 (d, *J* = 5.2 Hz, 1H), 4.13-4.04 (m, 1H), 3.94-3.63 (m, 7H), 3.30-2.67 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 169.3, 154.3, 152.7, 152.1, 148.9, 148.2, 148.0, 147.4, 139.1, 134.8, 134.5, 130.2, 130.0, 129.6, 128.2, 127.2, 127.0, 126.3, 125.6, 125.2, 124.4, 124.0, 116.0, 115.5, 115.1, 114.9, 112.4, 111.2, 110.1, 109.9, 71.1, 70.7, 56.2, 56.1, 55.9, 51.2, 42.9, 36.4, 28.2, 27.8. HRMS calcd. for $C_{25}H_{25}NO_5Cl$ , 454.14158 $[M + H]^+$; found, 454.14204 $[M + H]^+$. HPLC: Reverse Phase $C_{18}$ column. Method 1: 75% MeOH/25% water/0.1% formic acid to 95% MeOH/Water/0.1 % formic acid gradient over 3 minutes at 1 mL/min; 96% purity (retention time = 0.990 minutes). Method 2: 95% MeCN/5% water/0.1%

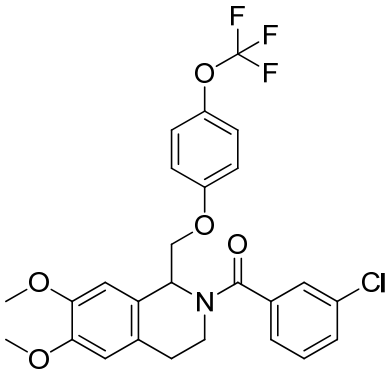
formic acid isocratic over 5 minutes at 1 mL/min; 99% purity (retention time = 1.342 minutes). Anal. ($C_{25}H_{24}NO_5Cl$): C, H, N.



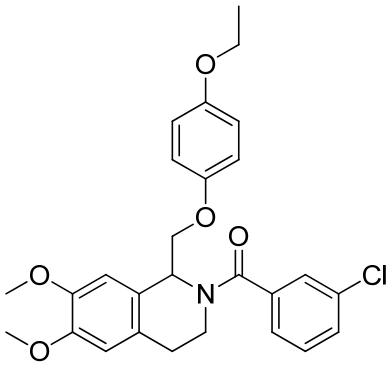
**(6,7-dimethoxy-1-((4-(methylthio)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-14).** Compound **1180-14** was prepared according to Procedure H using **31m** (0.4 g, 1.2 mmol) and benzoyl chloride (0.8 g, 1.3 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (mixture of rotamers, 0.12 g, 23%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 1H [7.93, 7.79 (m, m)], 7.67 (dd, $J_1$ = 1.4 Hz, $J_2$ = 8.2 Hz, 1H), 7.60-7.47 (m, 1H), 7.44-7.36 (m, 1H), 7.28 (m, 2H), 7.16-7.07 (m, 2H), 6.77 (d, $J$ = 8.8 Hz, 1H), 6.67-6.59 (m, 2H), 5.08-4.92 (m, 1H), 4.31-4.23 (m, 1H), 4.12-4.02 (m, 1H), 3.97-3.79 (m, 8H), 3.49-3.35 (m, 1H), 2.62-2.67 (m, 1H), 2.39 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.8, 161.4, 161.3, 157.1, 148.6, 148.4, 147.6, 134.4, 133.6, 132.1, 130.7, 130.6, 130.1, 129.5, 128.7, 127.7, 126.9, 126.8, 125.0, 115.4, 112.0, 110.4, 70.2, 66.1, 56.2, 56.1, 54.4, 54.2, 38.4, 27.9, 18.0, 15.5. HRMS calcd. for $C_{26}H_{28}NO_4S$ , 450.17336 $[M + H]^+$; found, 450.17413 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_4S$): C, H, N.



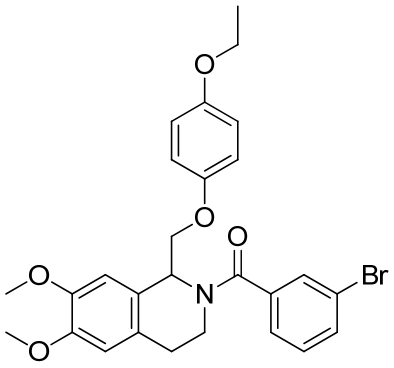
**(3-chlorophenyl)(6,7-dimethoxy-1-((4-(methylthio)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-13).** Compound **1180-13** was prepared according to Procedure H using **31m** (0.17 g, 0.5 mmol) and 3-chlorobenzoyl chloride (0.10 g, 0.6 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of two rotamers,0.16 g, 68%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.86-7.65 (m, 1H), 7.59-7.44 (m, 2H), 7.37-7.30 (m, 1H), 7.24-7.20 (m, 1H), 7.16-7.07 (m, 2H), 6.77-6.74 (m, 1H), 6.65-6.59 (m, 2H), 5.05 - 4.92 (m, 1H), 4.28-4.23 (m, 1H), 4.09-4.00 (m, 1H), 3.98-3.80 (m, 8H), 3.47-3.36 (m, 1H), 3.08-2.86 (m, 1H), 2.39 (s, 3H). $^{13}$C NMR ($CDCl_3$,100 MHz) δ: 170.3, 169.7, 157.3, 156.8, 148.9, 148.5, 148.0, 147.8, 138.2, 134.9, 134.6, 130.3, 130.1, 129.9, 129.7, 128.2, 127.4, 127.0, 126.3, 125.8, 124.9, 123.8, 115.6, 115.2, 112.1, 111.6, 110.4, 109.9, 70.5, 69.7, 57.3, 56.3, 56.1, 51.8, 42.9, 35.7, 29.2, 27.8, 18.0, 17.9. HRMS (m/z): $[M]^+$ calcd. for $C_{26}H_{27}NO_4SCl$, 484.13438 $[M + H]^+$; found, 484.13530 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_4SCl$): C, H, N. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 1.984 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 1.983 minutes).



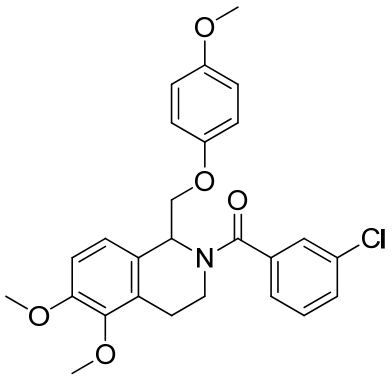
**(3-chlorophenyl)(6,7-dimethoxy-1-((4-(trifluoromethoxy)phenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-9).** Compound **1180-9** was prepared according to Procedure H using **31n** (0.33 g, 0.9 mmol) and 3-chlorobenzoyl chloride (0.2 g, 1.0 mmol, 1.3 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of two rotamers, 0.3 g, 67%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.34 (m, 3H), 7.27-7.25 (m, 1H), 7.16-7.13 (m, 2H), 6.95-6.79 (m, 2H), 6.69-6.64 (m, 1H), 1H [6.49, 5.98 (s, m)], 1H [5.14, 4.86 (dd, $J_1$ = 3.2 Hz, $J_2$ = 9.6 Hz; dd, $J_1$ = 5.4 Hz, $J_2$ = 12.6 Hz)], 4.41-4.38 (m, 1H), 4.02-3.98 (m, 1H), 3.91-3.65 (m, 7H), 3.29-3.00 (m, 1H), 2.95-2.74 (2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.7, 157.3, 156.8, 149.0, 148.6, 148.1, 147.9, 143.3, 138.1, 134.9, 134.6,130.3, 130.1, 129.9, 128.1, 127.4, 127.0, 126.3, 125.8, 124.9, 124.8, 123.5, 122.8, 122.7, 122.0, 115.7, 115.3, 112.1, 11.6, 110.3, 109.8, 70.7, 69.9, 57.3, 56.2, 56.1, 51.8, 43.0, 35.7, 29.2, 27.7. HRMS calcd. for $C_{26}H_{23}NO_5ClF_3$, 522.12896 $[M + H]^+$; found, 522.12847 $[M + H]^+$. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 2.023 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 2.024 minutes).



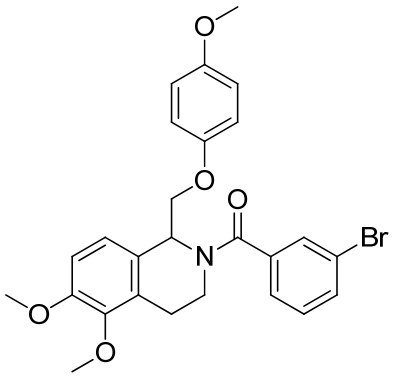
**(3-chlorophenyl)(1-((4-ethoxyphenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-53).** Compound **1180-53** was prepared according to Procedure H using **31o** (0.14 g, 0.4 mmol) and 3-chlorobenzoyl chloride (0.08 g, 0.5 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of two rotamers, 0.1 g, 47%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.60-7.24 (m, 4H), 6.86-6.76 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.07, 4.84 (, $J_1$ = 3.8 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.4 Hz, $J_2$ = 13 Hz)], 4.33 (m, 1H), 4.18-3.93 (m, 3H), 3.86-3.73 (m, 7H), 1H [3.65, 3.23 (m, m)], 1H [3.09, 2.85 (m, m)], 2.77-2.65 (m, 1H), 1.37 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 153.6, 152.9, 152.5, 148.9, 148.0, 147.8, 138.3, 124.9, 134.5, 130.2, 130.0, 129.8, 128.2, 127.3, 127.1, 126.2, 125.9, 125.2, 124.9, 124.0, 115.9, 115.7, 115.6, 115.4, 112.0, 111.5, 110.4, 109.9, 71.1, 70.2, 64.2, 57.5, 56.2, 56.1, 51.9, 42.9, 35.7, 29.2, 27.8, 15.1. HRMS calcd. for $C_{27}H_{29}NO_5Cl$, 482.17288 $[M + H]^+$; found, 482.17324 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_5Cl$): C, H, N.



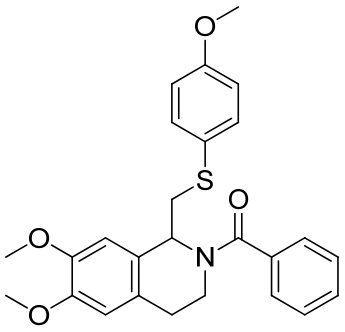
**(3-bromophenyl)(1-((4-ethoxyphenoxy)methyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-54).** Compound **1180-54** was prepared according to Procedure H using **31o** (0.14 g, 0.4 mmol) and 3-bromobenzoyl chloride (0.10 g, 0.5 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Silicycle 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (mixture of two rotamers, 0.1 g, 51%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.76-7.50 (m, 2H), 7.44-7.23 (m, 2H), 6.86-6.79 (m, 4H), 1H [6.66, 6.61 (s, s)], 1H [6.47, 5.93 (s, m)], 1H [5.07, 4.84 (dd, $J_1$ = 3.2 Hz, $J_2$ = 9.2 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ = 13 Hz)], 4.33 (m, 1H), 4.18-3.92 (m, 3H), 3.85-3.73 (m, 7H), 1H [3.65, 3.23 (m, m)], 1H [3.09, 2.85 (m, m)], 2.76-2.65 (m, 1H), 1.36 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 169.5, 153.8, 153.6, 152.9, 152.5, 148.9, 148.0, 147.8, 138.5, 132.9, 132.7, 131.0, 130.5, 130.2, 129.9, 127.3, 126.3, 125.4, 125.2, 124.0, 122.9, 122.7, 115.9, 115.7, 115.6, 115.4, 112.0,111.5, 110.4, 109.8, 71.1, 70.2, 64.2, 57.5, 56.3, 56.2,51.9, 42.9, 35.7, 29.2, 27.8, 15.2. HRMS calcd. for $C_{27}H_{29}NO_5Br$, 526.12236 $[M + H]^+$; found, 526.12256 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_5Br$): C, H, N.



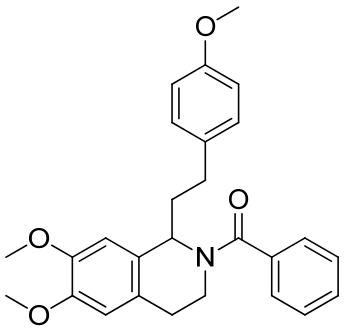
**(3-chlorophenyl)(5,6-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-49).** Compound **1180-49** was prepared according to Procedure H using **31p** (0.20 g, 0.61 mmol) and 3-chlorobenzoyl chloride (0.12 g, 0.67 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.14 g, 49%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.58-7.24 (m, 4H), 7.03-5.97 (m, 6H), 1H [5.12, 4.87 (dd, $J_1$ = 3.2 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ = 13 Hz)], 4.33 (d, $J$ = 4.8 Hz, 1H), 4.15-3.88 (m, 1H), 3.84-3.73 (m, 10H), 1H [3.60, 3.17 (m, m)], 3.08-2.68 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 154.4, 154.3, 153.0, 152.5, 152.1, 151.5, 147.0, 146.4, 138.2, 134.9, 134.5, 130.2, 129.8, 129.7, 128.8, 128.2, 127.1, 126.2, 125.9, 125.3, 124.9, 122.6, 115.9, 115.4, 114.9, 110.7, 71.2, 60.4, 57.2, 57.1, 56.1, 56.0, 55.9, 51.7, 42.4, 24.2, 22.9. HRMS calcd. for $C_{26}H_{27}NO_5Cl$, 468.15723 $[M + H]^+$; found, 468.15639 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N.



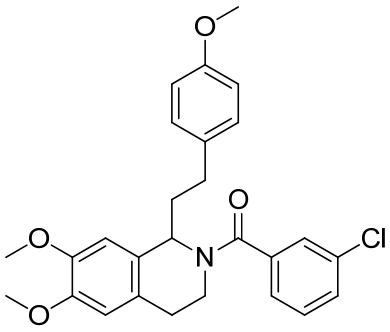
**(3-bromophenyl)(5,6-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-50).** Compound **1180-50** was prepared according to Procedure H using **31p** (0.20 g, 0.61 mmol) and 3-chlorobenzoyl chloride (0.15 g, 0.67 mmol, 1.1 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes) to afford the title compound as a white solid (0.16 g, 51%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.73-7.50 (m, 2H), 7.43-7.21 (m, 2H), 6.89-5.96 (m, 6H), 1H [5.12, 4.87 (dd, $J_1$ = 3.4 Hz, $J_2$ = 9.4 Hz; dd, $J_1$ = 5.8 Hz, $J_2$ = 13 Hz), 4.32 (d, $J$ = 4.4 Hz, 1H), 4.15-3.88 (m, 1H), 3.84-3.73 (m, 10H), 1H [3.60, 3.17 (m, m)], 3.08-2.66 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 169.5, 154.3, 153.0, 152.5, 152.0, 151.5, 146.4, 138.4, 132.9, 132.7, 131.0, 130.4, 129.9, 129.7, 128.8, 126.2, 125.3, 123.0, 122.7, 115.5, 114.8, 110.6, 71.2, 60.3, 57.2, 56.1, 56.0, 55.9, 51.7, 42.5, 35.1, 24.2, 22.9. HRMS calcd. for $C_{26}H_{27}NO_5Br$, 512.10671 $[M + H]^+$; found, 512.10571 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_5Br$): C, H, N.



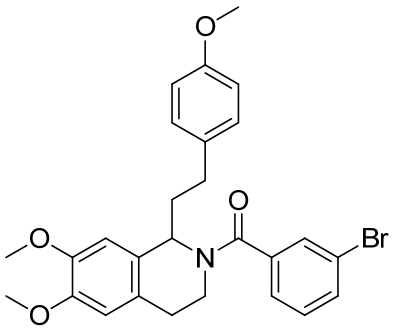
**(6,7-dimethoxy-1-(((4-methoxyphenyl)thio)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-51).** Compound **1180-51** was prepared according to Procedure H using **31q** (0.2 g, 0.58 mmol) and benzoyl chloride (0.10 g, 0.70 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Silicycle 4 g column, 0-60% EtOAc/hexanes gradient) to afford the tile compound as an off-white solid (0.10 g, 36%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.48 (d, *J* = 8.8 Hz, 2H) 7.43-7.37 (m, 5H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.62 (s, 1H), 6.57 (s, 1H), 5.86 (m, 1H), 1H [4.92, 4.75 (m, m)], 3.86-3.76 (m, 9H), 3.60-3.53 (m, 1H), 3.46-3.35 (m, 1H), 3.14-3.07 (m, 1H), 2.86-2.61 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ:171.2, 159.3, 148.3, 147.8, 136.7, 133.6, 129.8, 128.8, 127.8, 127.5, 126.9, 126.7, 125.7, 114.9, 114.8, 111.5, 110.6, 56.3, 56.2, 56.0, 55.6, 55.5, 51.3, 42.3, 29.1. HRMS calcd. for $C_{26}H_{28}NO_4S$, 450.17336 $[M + H]^+$; found, 450.17354 $[M + H]^+$. Anal. ($C_{26}H_{27}NO_4S$): C, H, N.



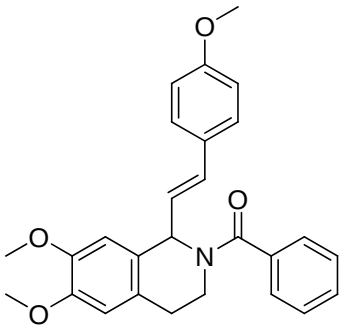
**(6,7-dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-42).** Compound **1180-42** was prepared according to Procedure H using **31r** (0.20 g, 0.6 mmol) and benzoyl chloride (0.10 g, 0.73 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.10 g, 38%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.32 (m, 5H), 2H [7.18, 6.94 (d, *J* = 5.5 Hz; d, *J* = 5.5 Hz)], 2H [6.84, 6.76 (d, *J* = 5.5 Hz; d, *J* = 5.5 Hz), 1H [6.65, 6.63 (s, s)], 1H [6.57, 6.32 (s, s)], 1H [5.83, 4.82 (dd, *J* = 2.8 Hz, *J* = 6.4 Hz; m), 3.86-3.71 (m, 10H), 3.53-3.28 (m, 1H), 3.12-2.73 (m, 3H), 2.62-2.55 (m, 1H), 2.39-1.93 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.1, 158.1, 148.0, 137.0, 134.1, 129.7, 129.5, 129.3, 128.8, 127.2, 126.7, 125.0, 114.1, 112.0, 111.6, 110.5, 109.6, 57.9, 56.3, 56.1, 55.5, 52.0, 41.2, 39.6, 38.9, 35.7, 32.1, 29.2, 27.9. HRMS calcd. for $C_{27}H_{30}NO_4$, 432.21694 $[M + H]^+$; found, 432.21737 $[M + H]^+$. Anal. ($C_{27}H_{29}NO_4$): C, H, N.



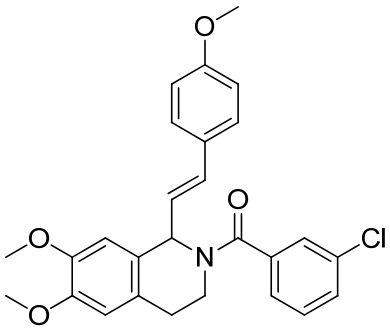
**(3-chlorophenyl)(6,7-dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-40).** Compound **1180-40**was prepared according to Procedure H using **31r (**0.20 g, 0.6 mmol) and 3-chlorobenzoyl chloride (0.13 g, 0.73 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.21 g, 74%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.40-7.23 (m, 4H), 2H [7.16, 6.95 (d, *J* = 8.4 Hz; d, *J* = 8.4 Hz)], 2H (d, *J* = 8.4 Hz; d, *J* = 8.4 Hz), 1H [6.63, 6.59 (s, s)], 1H [6.55, 6.32 (s, s)], 1H [5.77, 4.73 (dd, $J_1$ = 4.8 Hz, $J_2$ = 10 Hz; m)], 3.88-3.70 (m, 10H), 1H [3.49, 3.31 (m, m)], 3.15-2.21 (m, 4H), 2.25-1.95 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.5, 158.1, 148.1, 147.9, 138.5, 134.9, 133.8, 130.3, 129.9, 129.4, 129.2, 126.9, 124.7, 114.1, 111.5, 110.3, 56.2, 56.1, 55.5, 52.2, 41.2, 38.7, 32.1, 29.0. HRMS calcd. for $C_{27}H_{29}NO_4Cl$, 466.17796 $[M + H]^+$; found, 466.17859 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_4Cl$): C, H, N.



**(3-bromophenyl)(6,7-dimethoxy-1-(4-methoxyphenethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-41).** Compound **1180-41** was prepared according to Procedure H using **31r** (0.20, 0.6 mmol) and 3-bromobenzoyl chloride (0.16 g, 0.73 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.18 g, 58%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.59-7.48 (m, 2H), 7.31-7.22 (m, 2H), 2H [7.18, 6.97 (d, *J* = 8.4 Hz, 2H; d, *J* = 8.4 Hz)], 2H [6.85, 6.78 (d, *J* = 8.8 Hz; d, *J* = 8.8 Hz)], 1H [6.66, 6.62 (s, s)], 1H [6.58, 6.35 (s, s)], 1H [4.82, 4.71 (m, m)], 3.87-3.76 (m, 10H), 3.54 (m, 1H), 2.93-2.80 (m, 2H), 2.80-2.70 (m, 1H), 2.68-2.53 (m, 1H), 2.21-2.59 (m, 2H). $^{13}$C NMR ($CDCl_3$, 400 MHz) δ: 169.3, 158.1, 148.1, 148.0, 147.7, 138.8, 138.6, 133.8, 132.9, 132.7, 130.5, 130.1, 129.7, 129.5, 129.2, 128.9, 125.9, 125.7, 125.2, 124.8, 123.0, 114.1, 112.0, 111.5, 110.4, 109.5, 56.2, 56.1, 55.5, 52.2, 41.2, 38.7, 32.1. 29.1. HRMS calcd. for $C_{27}H_{29}NO_4Br$, 510.12745 $[M + H]^+$; found, 510.12812 $[M + H]^+$. Anal. ($C_{27}H_{28}NO_4Br$): C, H, N.

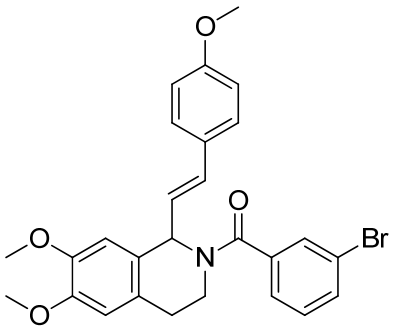


**(E)-(6,7-dimethoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)(phenyl)methanone (1180-33).** Compound **1180-33** was prepared according to Procedure H using **31s** (0.15 g, 0.46 mmol) and 3-chlorobenzoyl chloride (0.07 g, 0.55 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.10 g, 51%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.48-7.36 (m, 5H), 7.30-7.15 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.69-6.54 (m, 1H), 6.42-6.16 (m, 3H), 1H [5.29, 4.76 (m, m)], 3.86-3.76 (m, 10H), 3.48-3.20 (m, 1H), 3.15-2.86 (m, 1H), 2.80-2.56 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 171.3, 170.5, 159.6, 148.3, 147.8, 136.5, 132.8, 131.5, 130.4, 129.9, 129.5, 128.7, 128.0, 126.9, 126.0, 114.2, 111.4, 52.3, 56.2, 56.1, 55.6, 55.5, 41.5, 29.3, 19.2, 14.4. HRMS calcd. for $C_{27}H_{28}NO_4$, 430.20129 $[M + H]^+$; found, 430.20090 $[M + H]^+$. Anal. ($C_{27}H_{27}NO_4$): C, H, N.



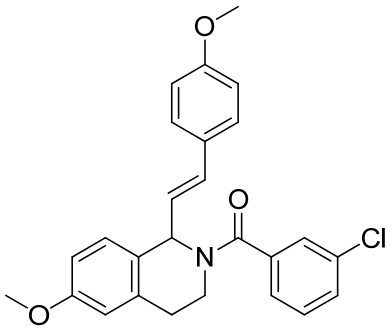
**(E)-(3-chlorophenyl)(6,7-dimethoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-31).** Compound **1180-31** was prepared according to Procedure H using **31s**

(0.15 g, 0.46 mmol) and 3-chlorobenzoyl chloride (0.10 g, 0.55 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.12 g, 56%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.48-7.22 (m, 6H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.67-6.54 (m, 1H), 6.43-6.33 (m, 1H), 6.30 (s, 1H), 6.19 (s, 1H), 1H [5.20, 4.73 (m, m)], 3.95-3.68 (m, 10H), 3.50-3.18 (m, 1H), 3.14-2.58 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 159.7, 148.4, 147.9, 138.2, 134.8, 133.1, 131.8, 130.2, 129.4, 128.9, 128.1, 127.2, 126.9, 126.5, 125.8, 125.0, 114.2, 111.5, 56.3, 56.2, 56.1, 55.6, 55.5, 54.1, 41.5, 37.1, 29.2. HRMS calcd. for $C_{27}H_{27}NO_4Cl$, 464.16231 $[M + H]^+$; found, 464.16185 $[M + H]^+$. Anal. ($C_{27}H_{26}NO_4Cl$): C, H, N.



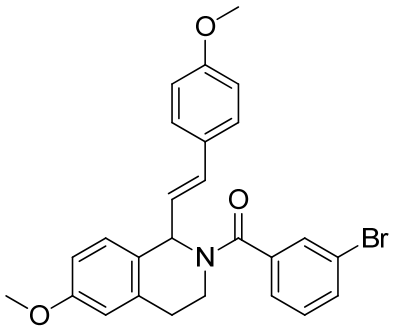

**(E)-(3-bromophenyl)(6,7-dimethoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-32).** Compound **1180-32** was prepared according to Procedure H using **31s** (0.15 g, 0.46 mmol) and 3-bromobenzoyl chloride (0.12 g, 0.55 mmol, 1.2 equiv). The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as an off-white solid (0.15 g, 64%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.62-7.21 (m, 6H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.66-6.54 (m, 1H), 6.43-6.19 (m, 3H), 1H [5.19, 4.72 (m, m)], 3.86-3.67 (m, 10H), 3.56-3.42 (m, 1H), 3.12-2.84 (m, 1H), 2.80-2.61 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 159.7, 148.4, 147.9, 138.4, 133.1.31.8, 130.4, 129.4, 128.1, 126.5, 125.8, 125.4, 122.9, 114.2, 112.8, 111.2,

56.3, 56.2, 56.1, 55.6, 55.5, 54.2, 41.6, 29.1, 24.2, 19.9, 13.9. HRMS calcd. for $C_{27}H_{27}NO_4Br$, 508.11096 $[M + H]^+$; found, 508.11132 $[M + H]^+$. Anal. ($C_{27}H_{26}NO_4Br$): C, H, N. HPLC: Reverse Phase $C_{18}$ column. Method 1: 95% MeCN/5% Water/0.1 % formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 1.991 minutes). Method 2: 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 1.989 minutes).



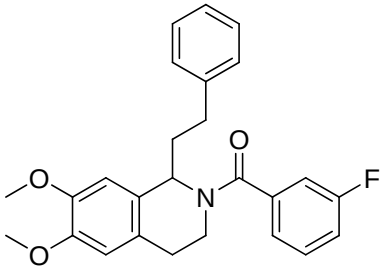

**(E)-(3-chlorophenyl)(6-methoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-38).** Compound **31u** was prepared according to Procedure D using **25c** (4.1 g, 13 mmol, 1.0 equiv). The crude solid was filtered and carried on without further purification. The crude dihydroisoquinoline (3.0 g, 10.2 mmol) was treated according to Procedure F. The crude residue was subjected to flash column chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford **31u** (0.6 g, 20%) in an impure form. The impurities were inseparable by chromatography. The product was visible by LCMS and was carried on without further purification. HRMS calcd. for $C_{19}H_{22}NO_2$ , 296.16451 $[M + H]^+$; found, 269.16476 $[M + H]^+$. Compound **1180-38** was prepared according to Procedure H using **31u** (0.3 g, 1.0 mmol) and 3-chlorobenzoyl chloride (0.21 g, 1.2 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 20-70% EtOAc/hexanes gradient) to afford

the title compound as an off-white solid (0.37 g, 84%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.44-7.24 (m, 6H), 7.14 (m, 1H), 6.96-6.81 (m, 3H), 6.69 (m, 1H), 6.32-6.16 (m, 2H), 1H [5.25, 4.71 (m, m)], 3.80-3.75 (m, 6H), 1H [3.71, 3.48 (m, m)], 1H [3.45, 3.10 (m, m)], 2.96-2.69 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 159.6, 158.7, 158.4, 158.1, 138.6, 138.2, 134.9, 133.9, 133.3, 132.7, 130.1, 129.8, 129.5, 128.8, 128.1, 127.2, 126.8, 125.0, 124.7, 114.2, 114.1, 113.1, 60.6, 55.5, 54.1, 52.2, 41.6, 41.2, 38.9, 32.1, 29.8, 28.7, 14.4. HRMS calcd. for $C_{26}H_{25}NO_3Cl$, 434.15175 $[M + H]^+$; found, 434.15147 $[M + H]^+$. Anal. ($C_{26}H_{24}NO_3Cl$): C, H, N.

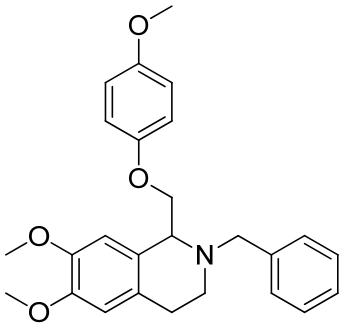



**(E)-(3-bromophenyl)(6-methoxy-1-(4-methoxystyryl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1180-39).** Compound **31u** was prepared according to Procedure D using **25c** (4.1 g, 13 mmol, 1.0 equiv). The crude solid was filtered and carried on without further purification. The crude dihydroisoquinoline (3.0 g, 10.2 mmol) was treated according to Procedure F. The crude residue was subjected to flash column chromatography (ISCO, Redisep 24 g column, 0-10% MeOH/DCM gradient) to afford **31u** (0.6 g, 20%) in an impure form. The impurities were inseparable by chromatography. The product was visible by LCMS and was carried on without further purification. HRMS calcd. for $C_{19}H_{22}NO_2$, 296.16451 $[M + H]^+$; found, 269.16476 $[M + H]^+$. Compound **1180-39** was prepared according to Procedure H with **31u** (0.3 g, 1.0 mmol) and 3-bromobenzoyl chloride (0.27 g, 1.2 mmol, 1.2 equiv). The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 20-70% EtOAc/hexanes gradient) to afford the

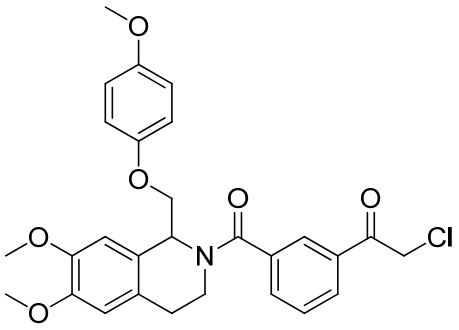
title compound as an off-white solid (0.30 g, 62%, mixture of rotamers) as an off-white solid. . $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.59-7.55 (m, 2H), 7.37-7.13 (m, 5H), 6.93-6.69 (m, 4H), 6.32-6.17 (m, 2H), 1H [5.24, 4.71 (m, m)], 3.78-3.68 (m, 7H), 3.48-2.69 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.4, 159.6, 158.6, 138.4, 133.5, 132.9, 130.4, 130.0, 129.4, 128.8, 128.1, 126.8, 125.4, 122.9, 115.8, 114.2, 113.6, 113.1, 104.0, 55.5, 54.1, 41.6, 29.9, 28.7, 15.2. HRMS calcd. for $C_{26}H_{25}NO_3Br$, 478.10123 $[M + H]^+$; found, 478.10162 $[M + H]^+$. Anal. ($C_{26}H_{24}NO_3Br$): C, H, N.



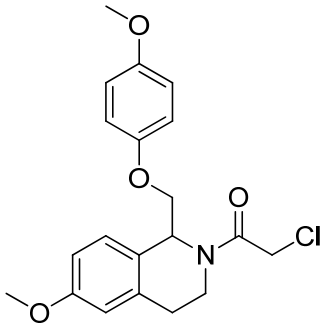

**(6,7-dimethoxy-1-phenethyl-3,4-dihydroisoquinolin-2(1H)-yl)(3-fluorophenyl)methanone. (1180-1).** Compound **1180-1** was prepared via Procedure H using **31t** (0.8 g, 3.0 mmol) and 3-fluorobenzoyl chloride (0.6 g, 3.0 mmol). The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-60% EtOAc/hexanes gradient) to afford the title compound as a white solid (0.8 g, 71%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.03 (m, 8H), 1H [6.64, 6.61 (s, s)], 1H [6.56, 6.34 (s, s)], 5.81 (m, 1H), 1H [4.82, 4.73 (m, m)], 3.85-3.78 (m, 6H), 3.73 (m, 1H), 3.50 (m, 1H), 1H [3.32, 3.09 (m, m)], 2.97 (m, 2H), 2.69-2.40 (m, 1H), 2.31-1.90 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 169.6, 164.1, 161.6, 148.1, 148.0, 141.9, 141.0, 138.9, 138.8, 130.8, 130.7, 129.4, 128.7, 128.5, 128.3, 126.4, 126.2, 125.9, 124.8, 122.8, 122.3, 116.9, 116.6, 114.1,113.9, 112.0, 111.5, 110.3, 109.5, 58.0, 56.2, 56.1, 52.2, 41.2, 39.2, 38.5, 35.9, 33.1, 29.1, 27.8. HRMS calcd. for $C_{26}H_{27}NO_3F$, 420.19695 $[M + H]^+$; found, 420.19789 $[M + H]^+$. Anal. ($C_{26}H_{26}NO_3F$): C, H, N.



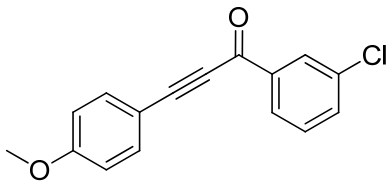
**2-benzyl-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (1180-17).** The tetrahydroisoquinoline **6** (0.1 g, 0.30 mmol) was dissolved in dry THF (20 mL). Potassium carbonate (0.17 g, 1.2 mmol, 4.0 equiv) was added and the mixture was allowed to stir for 2 hours. Benzyl bromide (0.04 mL, 0.36 mmol, 1.2 mmol) was added and the reaction was allowed to stir at room temperature for 24 hours. Saturated aqueous $NH_4Cl$ was added and the resulting mixture was extracted into EtOAc (2x). The organics were combined and washed with brine and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-50% EtOAc/hexanes gradient) to afford the title compound as a white amorphous solid (0.05 g, 39%). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.51-7.24 (m, 5H), 6.86-6.60 (m, 6H), 4.38-4.24 (m, 1H), 4.12-3.98 (m, 1H), 3.97-3.74 (m, 12H), 3.29-3.15 (m, 1H), 2.98-2.82 (m, 2H), 2.65-2.50 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 158.2, 152.3, 148.2, 147.6, 146.2, 134.1, 129.6, 129.2, 127.6, 126.8, 125.2, 114.7, 114.5, 110.6, 78.5, 63.1, 56.3, 56.0, 55.6, 51.2, 42.2, 29.3. HRMS calcd. for $C_{26}H_{30}NO_4$, 420.21694 $[M + H]^+$; found, 420.21721 $[M + H]^+$. Anal. ($C_{26}H_{29}NO_4$): C, H, N.



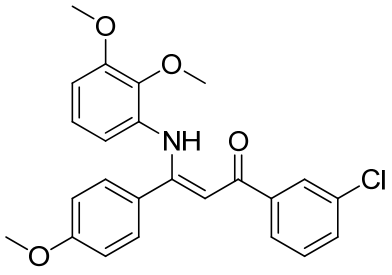
**2-chloro-1-(3-(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)ethanone (1180-66).** Compound **1180-58** (0.10 g, 0.21 mmol) and *p*-toluenesulfonic acid monohydrate (0.02 g, 0.10 mmol) were dissolved in MeOH (1 mL). A solution of 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (0.021 g, 0.105 mmol) was added dropwise over 15 minutes. After the addition was complete, the reaction was stirred at 30-35 $^{o}$C for 18 hours. The solvent was removed *in vacuo* and the resulting crude amorphous solid was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.05 g, 42%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.11-7.95 (m, 2H), 7.71-7.54 (m, 2H), 6.94-6.67 (m, 6H), 1H [5.92, 5.13 (t, $J$ = 6.0 Hz; dd, $J_1$ = 3.6 Hz, $J_2$ = 9.6 Hz)], 4.91 (m, 1H), 4.83 (s, 2H), 4.79-4.70 (m, 1H), 4.44-4.32 (m, 1H), 4.22-4.04 (m, 1H), 3.71-3.69 (m, 7H), 3.40-3.28 (1H), 3.20-2.54 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 191.8, 191.4, 170.7, 170.1, 154.7, 154.2, 152.8, 152.4, 148.9, 148.4, 148.0, 137.5, 137.4, 137.2, 132.4, 131.3, 129.9, 129.4, 129.1, 128.9, 128.0, 127.4, 126.8, 126.2, 125.3, 124.1, 115.9, 115.8, 114.7, 114.2, 112.3, 111.7, 110.5, 109.8, 71.1, 70.2, 57.5, 56.2, 56.1, 55.7, 51.8, 47.1, 46.3, 43.1, 35.8, 29.2. HRMS calcd. for $C_{28}H_{29}NO_6Cl$, 510.16779 $[M + H]^+$; found, 510.16691 $[M + H]^+$. HPLC: Method 1: Reverse Phase $C_{18}$ column, 85% MeOH/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 96% purity (retention time = 2.118 minutes). Method 2: Reverse Phase $C_8$ column, 85% MeCN/15% water/0.1% formic acid isocratic over 5 minutes at 1 mL/min; 100% purity (retention time = 0.717 minutes).



**2-chloro-1-(6-methoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (1180-68).** Compound **31i** (0.2 g, 0.67 mmol) was dissolved in dry DCM (5 mL). The resulting solution was cooled in an ice bath to 0$^{o}$C and triethylamine (0.07 g, 0.09 mL, 0.67 mmol) was added followed by dropwise addition of 2-chloroacetyl chloride (0.08 g, 0.05 mL, 0.67 mmol). The reaction was allowed to warm to room temperature and stirred for two hours. Water was added to quench and the mixture was extracted with DCM (2x). The organics were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the title compound as an off-white amorphous solid (0.23 g, 92%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 6.84-6.64 (m, 8H), 1H [5.72, 5.25 (t, $J$ = 10.4 Hz; dd, $J_1$ = 3.8 Hz, $J_2$ = 9.8 Hz)], 4.78-4.56 (m, 1H), 4.35-4.25 (m, 1H), 4.22-4.07 (m, 3H), 3.89-3.74 (m, 6H), 3.12-2.68 (m, 2H). HRMS calcd. for $C_{20}H_{23}NO_4Cl$, 376.13101 $[M + H]^+$; found, 376.13133 $[M + H]^+$. Anal. ($C_{20}H_{22}NO_4Cl$): C, H, N.

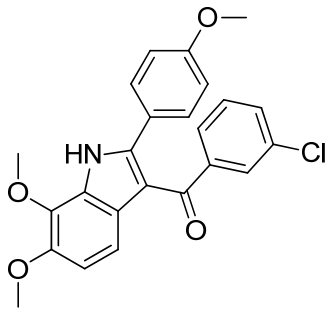


**1-(3-chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (43).** A stirred mixture of bis(triphenylphosphine)palladium(II) chloride (0.11 g, 0.15 mmol, 0.2% catalyst loading) and copper(I) iodide (0.06 g, 0.30 mmol, 0.4% catalyst loading) in THF (40 ml) was stirred and degassed with nitrogen. Triethylamine (1.1 ml, 7.6 mmol) was added followed by addition of 3-chlorobenzoyl chloride (1.0 ml, 7.6 mmol) followed by addition of 1-ethynyl-4-methoxybenzene (**42**, 1.0 ml, 7.6 mmol). The reaction mixture was stirred for 1 hour at room temperature until TLC indicated complete conversion. Solvents were evaporated in vacuo and subjected to column chromatography (ISCO, Redisep 24 g column, 0-30% EtOAc/hexanes gradient) afforded the title compound (1.9 g, 93 % yield) as a yellow-orange solid. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 8.14-8.03 (m, 2H), 7.65-7.55 (m, 3H), 7.48-7.42 (m, 1H), 6.95-6.91 (m, 2H), 3.85 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 176.8, 162.2, 138.8, 135.5, 134.0, 130.1, 129.6, 129.5, 127.8, 114.7, 111.7, 95.5, 86.9, 55.8. HRMS calcd. for $C_{16}H_{12}O_2Cl$, 271.05203 $[M + H]^+$; found, 271.05201 $[M + H]^+$.



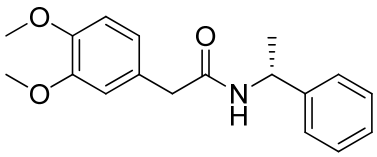

**(Z)-1-(3-chlorophenyl)-3-((2,3-dimethoxyphenyl)amino)-3-(4-methoxyphenyl)prop-2-en-1-one (44).** A flame-dried microwave flask was charged with **43** (0.3 g, 0.9 mmol) and 2,3-dimethoxyaniline (0.12 mL, 0.9 mmol) in dry MeOH (1 mL). The flask was sealed and placed in a microwave reactor at 80 $^{o}$C for 6 hours. The solvent was evaporated and the resulting residue was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes

gradient) afforded 0.43 g of a yellow solid. By LCMS and NMR, a 1:3 mixture of starting material to product was present as an inseperable mixture. $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 12.79 (s, 1H, broad), 7.95-7.83 (m, 2H), 7.45-7.42 (m, 1H), 7.39-7.35 (m, 2H), 6.89-6.83 (m, 2H), 6.69 (t, *J* = 8.2 Hz, 1H), 6.59-6.57 (m, 1H), 6.41-6.33 (m, 1H), 6.10-6.07 (m, 1H), 6.01 (s, 1H), 4.03 (s, 3H), 3.87-3.83 (m, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 187.8, 161.5, 161.1, 153.3, 142.2, 134.7, 131.2, 129.9, 127.7, 125.6, 123.2, 116.1, 114.2, 114.1, 108.0, 97.3, 61.2, 61.1, 56.2, 56.0, 55.6, 55.5. HRMS calcd. for $C_{24}H_{23}NO_4Cl$, 424.13101 $[M + H]^+$; found, 424.13076 $[M + H]^+$.



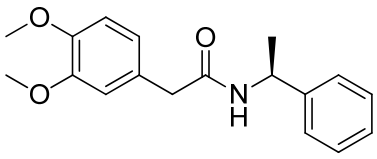

**(3-chlorophenyl)(6,7-dimethoxy-2-(4-methoxyphenyl)-1H-indol-3-yl)methanone (1180-43).** A screwcap flask was charged with **44** (0.43 g, 1.0 mmol), copper (I) iodide (9.7 mg, 0.05 mmol, 0.05 equiv), 1,10-phenanthroline (0.03 g, 0.18 mmol, 0.18 mmol, 0.18 equiv), lithium carbonate (0.15 g, 2.0 mmol, 2.0 equiv) and DMF (10 mL) under an atmosphere of air. The flask was sealed and heated to 100 $^{o}$C for 24 hours. The reaction mixture was diluted with diethyl ether and washed with 1M HCl and brine. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient). The resulting foam was triturated with hexanes and ether to give the title compound as an orange solid (0.1 g, 23%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 9.04 (s, 1H, broad), 7.68 (d, *J* = 8.6 Hz, 1H), 7.54-7.50 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.23-7.19 (m, 3H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 2H),

4.04 (s, 3H), 3.95 (s, 3H), 3.73 (s, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 191.7, 160.3, 148.2, 145.0, 141.6, 134.0, 133.9, 131.2, 130.9, 130.8, 130.3, 129.2, 127.8, 124.8, 124.1, 116.9, 114.1, 114.0, 113.2, 110.4, 61.4, 57.3, 55.6, 55.5. HRMS calcd. for $C_{24}H_{21}NO_4Cl$, 422.11536 $[M + H]^+$; found, 422.11507 $[M + H]^+$. Anal. ($C_{24}H_{20}NO_4Cl$): C, H, N.

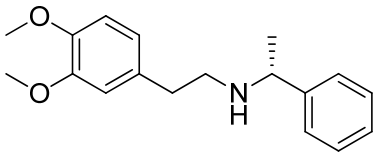


**(R)-2-(3,4-dimethoxyphenyl)-N-(1-phenylethyl)acetamide (51-*R*).**

(*R*)-1-phenylethanamine (**50-*R*,** 1.1 g, 1.2 mL, 9.3 mmol) was dissolved in dry DCM (20 mL). A 5% aqueous solution of NaOH (30 mL) was added and the biphasic mixture was allowed to stir for 15 minutes. 3,4-dimethoxyacetyl chloride (**49**, 2.0, 1.6 mL, 37.5 mmol, 4.2 equiv) was added dropwise. The reaction was allowed to stir for 1 hour until TLC indicated complete conversion. The water was quenched by addition of water and extracted with DCM (2x). The combined organics were washed with brine, dried over MgSO4, filtered and concentrated in vacuo to give a light brown solid. The crude material was purified by silica gel chromatography (ISCO, Redisep 40 g column, 30-70% EtOAc/hexanes gradient) to afford the title compound as a white solid (2.5 g, 90%). $[\alpha]^{20} = -12.1$. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.24-7.21 (m, 5H), 6.79-6.72 (m, 3H), 6.04 (s, 1H, broad), 5.10 (quin, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.41 (s, 2H), 1.35 (d, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 170.6, 149.3, 148.4, 143.5, 128.8, 127.7, 127.4, 126.2, 121.7, 112.4, 111.6, 56.1, 56.0, 48.8, 43.5, 22.0. HRMS calc'd for $C_{18}H_{22}NO_3$, 300.15942 $[M+H]^+$, found 300.15942 $[M+H]^+$.

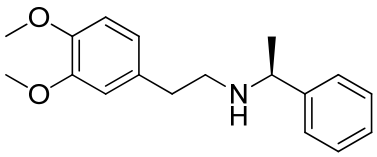


**(*S*)-2-(3,4-dimethoxyphenyl)-N-(1-phenylethyl)acetamide (51-*S*).** Compound **51-*S*** was synthesized as above for the *R*-enantiomer using (*S*)-1-phenylethanamine (**50-*S***, 1.1 g, 1.2 mL, 9.3 mmol) and 3,4-dimethoxyacetyl chloride (**49**, 2.0, 1.6 mL, 37.5 mmol, 4.2 equiv). The title compound was obtained as a white solid (2.0 g, 72%). $[\alpha]^{20}$ = +12.2. $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.25-7.14 (m, 5H), 6.78-6.71 (m, 3H), 6.04 (s, 1H, broad), 5.06 (quin, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.43 (s, 2H), 1.34 (d, *J* = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 170.4, 149.3, 148.6, 143.5, 129.0, 127.4, 127.4, 126.2, 121.7, 112.4, 111.3, 56.1, 56.2, 48.6, 43.5, 21.8. HRMS m/z calc'd for $C_{18}H_{22}NO_3$, 300.15942 $[M+H]^+$, found 300.15951 $[M+H]^+$.

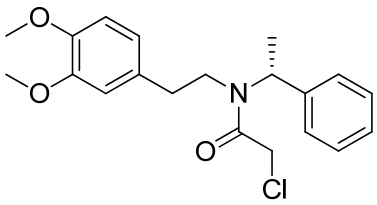


**(*R*)-N-(3,4-dimethoxyphenethyl)-1-phenylethanamine (52-*R*).** Compound **51-*R*** (3.6 g, 12 mmol) was dissolved in dry THF (50 mL). Boron trifluoride etherate (0.7 g, 0.6 mL, 4.8 mmol, 0.4 equiv) was added to the reaction and it was heated to reflux. Borane methyl sulfide complex (1.0 M in THF, 30.1 mL, 2.5 equiv) was added to the refluxing solution and the reaction was stirred at reflux for 2 hours. After cooling to room temperature, the reaction was cooled in an ice bath to 0 $^{o}$C and 4.5 M HCl (40 mL) was added carefully. The resulting solution was allowed to stir at 0 $^{o}$C for an additional 1 hour. The solution was allowed to warm to room temperature and stirred at room temperature for 1 hour. The volatiles were removed *in vacuo* and the resulting mixture was cooled to 0 $^{o}$C and basified to pH 13 with solid KOH. Water and DCM were added to

solubilize any salts that formed. The mixture was then extracted with DCM (4x) and combined organics were dried over $MgSO_4$. The title compound was afforded as a clear oil (3.1 g, 90%). $^1H$ NMR ($CDCl_3$, 400 MHz) δ: 7.27-7.17 (m, 5H), 6.72 (d, *J*=8.4 Hz, 1H), 6.65 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.72 (q, *J*=6.4 Hz, 1H), 2.63-2.73 (m, 4H), 1.29 (d, 3H, *J*= 6.4 Hz). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ: 149.1, 147.6, 145.6, 132.7, 128.6, 127.1, 126.7, 120.8, 112.0, 111.4, 58.4, 56.1, 56.0, 49.1, 36.0, 24.4. HRMS calc'd for $C_{18}H_{24}NO_2$, 286.18016 $[M + H]^+$, found 286.18019, $[M + H]^+$.

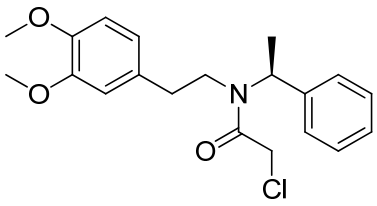


**(*S*)-N-(3,4-dimethoxyphenethyl)-1-phenylethanamine (52-*S*).** Compound **52-*S*** was synthesized as above with **51-*S*** (2.1 g, 7.0 mmol) to afford the title compound as a clear oil (1.9 g, 95%). $^1H$ NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.19 (m, 5H), 6.76 (d, *J*=8.4 Hz, 1H), 6.71-6.65 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (q, *J*=6.4 Hz, 1H), 2.74-2.65 (m, 4H), 1.30 (d, *J*= 6.4 Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ: 149.0, 147.6, 145.8, 132.8, 128.6, 127.1, 126.7, 120.8, 112.0, 111.4, 58.4, 56.1, 56.0, 49.1, 36.1, 24.5. HRMS calc'd for $C_{18}H_{24}NO_2$, 286.18016 $[M + H]^+$, found 286.18015, $[M + H]^+$.



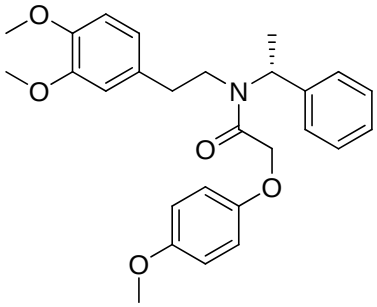
**(*R*)-2-chloro-N-(3,4-dimethoxyphenethyl)-*N*-(1-phenylethyl)acetamide (53-*R*).** Compound **52-*R*** (3.1 g, 10.9 mmol) was dissolved in dry DCM (40 ml). Triethylamine (3.3 g, 4.5 mL, 33 mmol, 3.0 equiv) was added and the reaction was cooled to 0 °C in an ice bath. 2-chloroacetyl chloride (1.5

g, 1.0 mL, 13 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to warm to room temperature. After 1 hour, TLC indicated the reaction was complete. Water and 1M HCl were added to quench followed by extraction into DCM (2x). The combined organics were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, Redisep 24 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as an off-white solid (3.1 g, 78%, mixture of rotamers). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.29 (m, 5H), 6.73-6.68 (m, 1H), 6.51-6.45 (m, 2H), 1H [5.94, 5.15 (m, m)], 2H [4.21, 4.97 (m, m)], 3.79 (s, 6H), 3.30-3.17 (m, 2H), 2.77-2.48 (m, 1H), 2.37-2.24 (m, 1H), 1.64-1.60 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ:167.0, 166.6, 149.3, 149.0, 148.1, 147.6, 140.2, 139.7, 132.1, 130.6, 129.0, 128.9, 128.3, 128.1, 127.3, 120.8, 120.7, 112.2, 111.8, 111.6, 56.2, 56.1, 56.0, 52.7, 50.0, 46.3, 46.2, 42.0, 41.8, 37.0, 34.3, 18.4, 16.8. HRMS calc'd for $C_{20}H_{25}NO_3Cl$, 362.15175 $[M + H]^+$, found 362.15131, $[M + H]^+$.

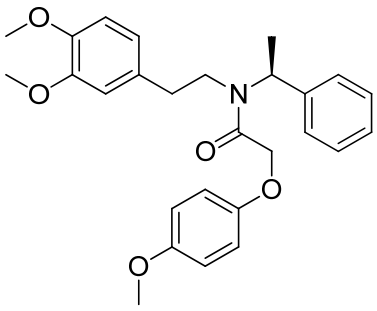



**(*S*)-2-chloro-N-(3,4-dimethoxyphenethyl)-N-(1-phenylethyl)acetamide (53-*S*).** Compound **53-*S*** was synthesized as above using **52-*S*** (1.9 g, 6.6 mmol). The title compound was obtained as an off-white solid (1.8 g, 76%, mixture of rotamers). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.34 (m, 5H), 6.76-6.71 (m, 1H), 6.54-6.36 (m, 2H), 1H [5.99, 5.18 (m, m)], 2H [4.26, 4.00 (m, m)], 3.82 (s, 6H), 3.32-3.19 (m, 2H), 2.80-2.51 (m, 1H), 2.40-2.25 (m, 1H), 1.64-1.60 (m, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 166.6, 149.0, 147.7, 140.2, 139.7, 132.1, 129.0, 128.8, 128.3, 127.3, 120.8, 120.6,

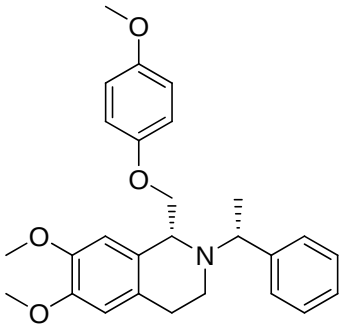
112.2, 111.8, 111.6, 111.3, 56.2, 56.1, 56.0, 52.6, 46.3, 46.2, 42.0, 41.8, 36.9, 34.3, 18.4, 16.8, 14.4. HRMS calc'd for $C_{20}H_{25}NO_3Cl$, 362.15175 $[M + H]^+$, found 362.15172, $[M + H]^+$.



**(*R*)-*N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenoxy)-*N*-(1-phenylethyl)acetamide (54-*R*).** 4-methoxyphenol (0.25 g, 2.0 mmol, 1.2 equiv) was dissolved in dry MeCN (10 mL). To this solution was added cesium carbonate (2.2 g, 6.6 mmol, 4.0 equiv) and the reaction mixture was allowed to stir at room temperature for 1 hour. **53-*R*** (0.6 g, 1.7 mmol, 1.0 equiv) was dissolved in MeCN (10 mL) and then added to the reaction. The resulting mixture was allowed to stir at room temperature for 16 hours. After LCMS indicated complete consumption of starting material, the reaction was quenched by addition of saturated aqueous $NH_4Cl$ solution and extracted into EtOAc (3x). The combined organics were washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as a pale yellow oil (0.6 g, 76%, mixture of rotamers). $^1$H NMR ($CDCl_3$, 400 MHz) δ: 7.37-7.21 (m, 5H), 6.93-6.81 (m, 4H), 6.70-6.65 (m, 1H), 6.49-6.33 (m, 2H), 1H [5.95, 5.30 (m, m)], 4.77-4.57 (m, 2H), 3.78-3.72 (m, 9H), 3.28-3.17 (m, 2H), 2.74-2.49 (m, 1H), 2.37-2.19 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 168.5, 154.6, 153.3, 152.3, 150.9, 149.0, 148.0, 147.6, 140.4, 139.9, 132.2, 131.0, 128.9, 128.3, 128.1, 127.5, 120.8, 116.3, 115.9, 115.8, 115.0, 114.9, 112.2, 111.9, 111.6, 111.3, 69.0, 56.1, 56.0, 55.2, 52.7, 46.0, 36.8, 34.5, 18.2, 16.9, 14.4.

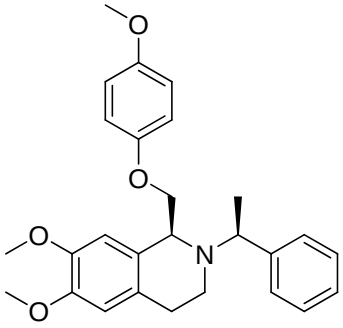


**(*S*)-*N*-(3,4-dimethoxyphenethyl)-2-(4-methoxyphenoxy)-*N*-(1-phenylethyl)acetamide (54-*S*).** Compound **54-*S*** was synthesized as above with **53-*S*** (1.8 g, 5.1 mmol, 1.0 equiv), 4-methoxyphenol (0.76 g, 6.1 mmol, 1.2 equiv), and cesium carbonate (6.6 g, 20.3 mmol, 4.0 equiv). The title compound was obtained as a pale yellow oil (1.7 g, 74%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.26 (m, 5H), 6.91-6.78 (m, 4H), 6.70-6.64 (m, 1H), 6.49-6.32 (m, 2H), 1H [5.95, 5.28 (m, m)], 4.77-4.57 (m, 2H), 3.75-3.69 (m, 9H), 3.29-3.13 (m, 2H), 2.75-2.53 (m, 1H), 2.35-2.22 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 168.2, 154.6, 152.4, 149.2, 149.0, 148.0, 140.5, 140.1, 132.3, 131.0, 128.9, 128.8, 128.3, 127.5, 120.8, 120.7, 115.9, 115.7, 114.9, 112.2, 111.9, 111.6, 111.3, 69.0, 68.6, 56.1, 56.0, 55.8, 55.1, 45.9, 36.8, 34.5, 18.2, 16.9.

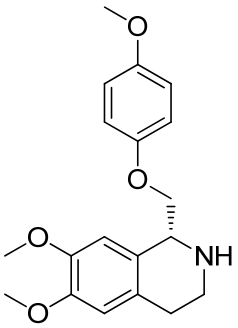


**(*R*)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-2-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (55-*R*,*R*).** The amide **54-*R*** (0.57g, 1.3 mmol, 1.0 equiv) was dissolved in

dry toluene (20 mL). Phosphorous oxychloride (0.58 g, 0.36 mL, 3.58 mmol, 3.0 equiv) was added to this solution and the reaction was heated to reflux. After 4 hours, LCMS ($C_8$ column, 75-95% MeOH/water with 0.1% formic acid) indicated complete conversion of the starting material. The reaction was removed from heat and allowed to cool to room temperature. The volatiles were removed *in vacuo.* The resulting residue was dissolved in dry MeOH (15 mL) and cooled in a dry ice/acetone bath to -78 $^{o}$C. Sodium borohydride (0.14 g, 3.8 mmol, 3.0 equiv) was added in portions of 50 mg at a time every 30 minutes. After the addition was complete, the reaction was allowed to stir at -78 $^{o}$C for an additional 1 hour. Once the starting material was consumed as monitored by LCMS, the reaction was quenched by addition of 10% aqueous HCl solution at -78 $^{o}$C. The MeOH was removed via rotary evaporation and the resulting mixture was cooled in an ice bath to 0 $^{o}$C. The reaction mixture was basified to pH 13 with solid KOH. Water was added and the aqueous mixture was extracted with DCM (3x). The combined organics were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, Redisep 12 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as a white amorphous solid (0.15 g, 27%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.40 (d, *J*= 7.6 Hz, 2H), 7.30 (m, 2H), 7.23-7.21 (m, 1H), 6.76-6.69 (m, 4H), 6.61-6.60 (m, 2H), 4.25-4.20 (m, 1H), 4.04 (t, *J* = 6.4 Hz, 1H), 3.92-3.86 (m, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 3.29-3.13 (m, 2H), 2.94-2.83 (m, 1H), 2.41-2.48 (m, 1H), 1.44 (d, *J*= 6.4 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 153.8, 153.2, 147.9, 147.3, 146.4, 128.5, 127.8, 127.7, 127.2, 115.4, 114.7, 111.8, 111.5, 72.2, 59.5, 57.8, 56.0 (2), 55.8, 40.9, 24.3, 21.2. HRMS calc'd for $C_{27}H_{32}NO_4$, 434.23259 $[M + H]^+$, found 434.23219, $[M + H]^+$.

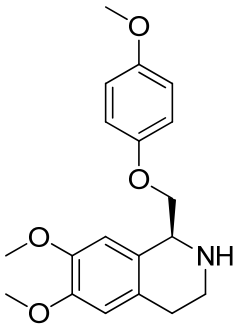


**(*S*)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-2-((*S*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (55-*S*,*S*).** The compound **55-*S*,*S*** was synthesized according to the above procedure starting with **54-*S*** (1.3 g, 2.9 mmol). The resulting crude residue from the cyclization was subjected to sodium borohydride (0.34 g, 9.0 mmol, 3.0 equiv). Upon purification, the title compound was obtained as a white amorphous solid (0.6 g, 46%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.44 (d, *J*=7.2 Hz, 2H), 7.34 (t, *J*= 8.0 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J*= 9.2 Hz, 2H), 6.74 (d, *J*=9.2 Hz, 2H), 6.65 (s, 1H), 6.64 (s, 1H), 4.27 (q, *J*= 6.8 Hz, 1H), 4.08 (t, *J* = 6.8 Hz, 1H), 3.93 (m, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.25 (m, 2H), 2.92 (m, 1H), 2.49 (m, 1H), 1.46 (d, *J*= 8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl3) δ: 153.9, 153.3, 148.0, 147.3, 146.4, 128.6, 127.9, 127.8, 127.2, 127.2, 115.5, 114.8, 111.9, 111.5, 72.3, 59.6, 57.9, 56.1, 56.1, 55.9, 40.9, 24.3, 21.7. HRMS calc'd for $C_{27}H_{32}NO_4$, 434.23259 $[M + H]^+$, found 434.23285, $[M + H]^+$.



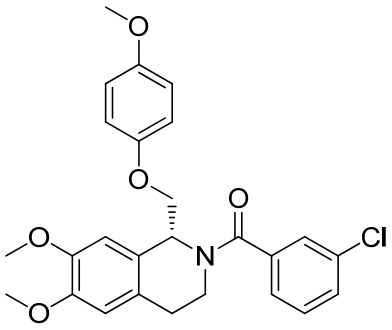
**(*R*)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (6-*R*).** Compound **55-*R*,*R*** (0.15 g, 0.35 mmol) was dissolved in 200 proof EtOH (10 mL). Palladium on

carbon (10%, 0.07 g, 0.07 mmol, 0.2 equiv) was added. The reaction vessel was purged (2x) with argon and vacuum. The flask was fitted with a septum and hydrogen balloon and was allowed to stir at room temperature for 24 hours. The reaction mixture was then filtered over a pad of celite and washed with MeOH and EtOAc. The solution was concentrated *in vacuo* and the resulting off-white amorphous solid was taken onto the next step without further purification (0.05 g, 44%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 6.91-6.69 (m, 4H), 6.64 (s, 1H), 6.61 (s, 1H), 6.24 (s, 1H, broad), 4.49 (m, 1H), 4.29-4.17 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79-3.71 (m, 3H), 3.38-3.10 (m, 2H), 2.94-2.81 (m, 2H). $^{13}$C NMR (100 MHz, CDCl3) δ: 154.5, 152.6, 148.5, 147.8, 126.9, 123.9, 116.0, 114.8, 111.9, 109.3, 70.5, 56.3, 56.1, 55.8, 39.8, 27.7. HRMS calc'd for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$, found 330.17039, $[M + H]^+$.

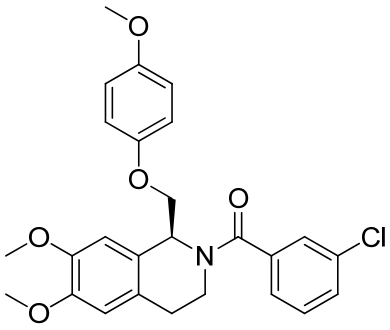



**(S)-6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-1,2,3,4-tetrahydroisoquinoline (6-*S*).**

Compound **6-*S*** was synthesized as above with **55-*S*,*S*** (0.6 g, 1.4 mmol). The crude material was carried on without purification (0.4 g, 88%). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 6.98 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 6.59 (s, 1H), 4.45 (m, 1H), 4.25-4.13 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.76-3.72 (m, 3H), 3.40-3.12 (m, 2H), 2.91-2.79 (m, 2H). $^{13}$C NMR (100 MHz, CDCl3) δ: 154.8, 152.0, 149.2, 148.4, 125.1, 120.2, 116.6, 114.8, 111.8, 108.9, 69.2, 56.3, 56.1, 55.9, 39.8, 27.3. HRMS calc'd for $C_{19}H_{24}NO_4$, 330.16999 $[M + H]^+$, found 330.17021, $[M + H]^+$.



**(*R*)-(3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1390-*R*).** Compound **6-*R*** (0.10 g, 0.30 mmol) was dissolved in dry DCM (3 mL). Triethylamine (0.06 g, 0.08 mL, 0.6 mmol, 2.0 equiv) was added followed by dropwise addition of 3-chlorobenzoyl chloride (0.06 g, 0.04 mL, 0.33 mmol, 1.1 equiv). The reaction was allowed to stir at room temperature for 1 hour. Water was added to quench and the reaction was extracted with DCM (3x). The combined organics were washed with brine and dried over MgSO4, filtered and concentrated in vacuo. The crude material was purified by silica gel chromatography (ISCO, Redisep 4 g column, 0-70% EtOAc/hexanes gradient) to afford the final product as a white amorphous solid (0.04 g, 28%). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.62-7.28 (m, 4H), 6.89-6.80 (m, 4H), 1H [6.68, 6.62 (s, s)], 6.48-5.96 (m, 1H), 1H [5.10, 4.87 (dd, $J_1$ = 9.6 Hz, $J_2$ = 4 Hz, dd, $J_1$ = 9.6 Hz, $J_2$ = 4 Hz)], 4.37-3.95 (m, 2H), 3.88-3.76 (m, 9H), 3.70-2.70 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.3, 169.6, 154.4, 154.3, 152.9, 152.5, 148.8, 148.4, 148.x0, 147.8, 138.3, 134.9, 134.5, 130.2, 129.9, 129.8, 128.2, 127.3, 127.0, 126.3, 125.9, 125.2, 124.9, 124.0, 115.9, 115.5, 115.0, 114.9, 112.0, 111.5, 110.4, 109.9, 71.1, 70.2, 57.4, 56.2, 56.1, 55.9, 51.9, 42.9, 35.7, 29.2, 27.8. HRMS calcd. for $C_{26}H_{27}NO_5Cl$ , 468.15723 $[M + H]^+$; found, 468.15728 $[M + H]^+$; Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N. HPLC: Reverse Phase Chiral OD-RH column. Conditions: 75% MeCN/25% water plus 0.1% formic acid isocratic over 20 minutes, read at $\lambda_{max}$ = 285 nM, RT = 9.192 minutes, 95%. (*S*-enantiomer, RT = 8.141 minutes, 5%).



**(S)-(3-chlorophenyl)(6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone (1390-*S*).** Compound **1390-*S*** was synthesized as described above with the crude material from **6-*S*** (0.4 g, 1.2 mmol). After purification, the title compound was obtained as a white amorphous solid (0.4 g, 70%, mixture of rotamers). $^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 7.63-7.29 (m, 4H), 6.90-6.81 (m, 4H), 1H [6.69, 6.64 (s, s)], 6.50-5.96 (m, 1H), 1H [5.10, 4.88 (dd, $J_1$ = 9.6 Hz, $J_2$ = 4 Hz, dd, $J_1$ = 9.6 Hz, $J_2$ = 4 Hz)], 4.38-3.96 (m, 2H), 3.88-3.77 (m, 9H), 3.71-2.68 (m, 4H). $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 169.8, 154.1, 154.3, 152.9, 152.5, 148.9, 148.4, 148.1, 147.8, 138.3, 135.1, 134.6, 130.2, 129.9, 129.9, 128.2, 127.2, 127.0, 126.4, 125.9, 125.2, 124.9, 123.8, 115.7, 115.5, 115.0, 114.9, 112.1, 111.7, 110.4, 110.0, 71.4, 70.1, 57.4, 56.2, 56.0, 55.8, 51.9, 42.7, 35.6, 29.2, 27.6. HRMS calcd. for $C_{26}H_{27}NO_5Cl$ , 468.15723 $[M + H]^+$; found, 468.15857 $[M + H]^+$; Anal. ($C_{26}H_{26}NO_5Cl$): C, H, N. HPLC: Reverse Phase Chiral OD-RH column. Conditions: 75% MeCN/25% water plus 0.1% formic acid isocratic over 20 minutes, read at 254 nM, RT = 8.140 minutes, 100%.

*2.6.2 Combustion Analysis (Atlantic Microlabs, Norcross, GA)*

| Compound ID | Molecular Formula | Theoretical | Experimental |
|---|---|---|---|
| **1390** | $C_{26}H_{26}NO_5Cl$ | C: 66.73, H: 5.60, N: 2.99 | C: 66.49, H: 5.44, N: 3.06 |
| **1390-*S*** | $C_{26}H_{26}NO_5Cl$ | C: 66.73, H: 5.60, N: 2.99 | C: 66.41, H: 5.61, N: 2.85 |
| **1180-1** | $C_{26}H_{26}NO_3F$ | C: 74.44, H: 6.25, N: 3.34 | C: 73.99, H: 6.15, N: 3.34 |
| **1180-2**‡ | $C_{25}H_{25}NO_4$ | C: 74.42, H: 6.25, N: 3.47 | C: 73.97, H: 6.17, N: 3.50 |

| | | | |
|---|---|---|---|
| **1180-3** | $C_{26}H_{27}NO_6$ | C: 69.47, H: 6.05, N: 3.12 | C: 69.40, H: 5.86, N: 2.83 |
| **1180-4** | $C_{24}H_{25}NO_6$ | C: 68.07, H: 5.95, N: 3.31 | C: 67.98, H: 5.96, N: 3.36 |
| **1180-5** | $C_{23}H_{24}N_2O_6$ | C: 65.08, H: 5.70, N: 6.60 | C: 64.82, H: 5.70, N: 6.42 |
| **1180-6** | $C_{26}H_{26}NO_5Cl$ | C: 66.73, H: 5.60, N: 2.99 | C: 66.55, H: 5.24, N: 3.32 |
| **1180-7**‡ | $C_{26}H_{27}NO_5$ | C: 72.04, H: 6.28, N: 3.23 | C: 71.23, H: 6.15, N: 3.29 |
| **1180-10** | $C_{26}H_{25}NO_5Cl_2$ | C: 62.16, H: 5.02, N: 2.79 | C: 62.11, H: 5.06, N: 2.76 |
| **1180-11** | $C_{26}H_{26}NO_5I$ | C: 55.82, H: 4.68, N: 2.50 | C: 55.64, H: 4.58, N: 2.43 |
| **1180-12** | $C_{26}H_{25}NO_5Cl_2$ | C: 62.16, H: 5.02, N: 2.79 | C: 62.27, H: 5.03, N: 2.85 |
| **1180-14** | $C_{26}H_{27}NO_4S$ | C: 69.46, H: 6.05, N: 3.12 | C: 69.88, H: 6.20, N: 3.14 |
| **1180-16** | $C_{26}H_{26}N_2O_7$ | C: 65.26, H: 5.48, N: 5.85 | C: 65.01, H: 5.32, N: 5.62 |
| **1180-17**‡ | $C_{26}H_{29}NO_4$ | C: 74.44, H: 6.97, N: 3.34 | C: 74.01, H: 7.02, N: 3.21 |
| **1180-18** | $C_{26}H_{25}NO_5ClF$ | C: 64.26, H: 5.19, N: 2.88 | C: 64.39, H: 5.45, N: 2.54 |
| **1180-19**‡ | $C_{26}H_{27}NO_5$ | C: 72.04, H: 6.28, N: 3.23 | C: 71.55, H: 6.21, N: 3.14 |
| **1180-20** | $C_{26}H_{26}NO_5Cl$ | C: 66.73, H: 5.60, N: 2.99 | C: 66.74, H: 5.66, N: 2.88 |
| **1180-21** | $C_{26}H_{26}NO_5Br$ | C: 60.95, H: 5.11, N: 2.73 | C: 60.71, H: 5.10, N: 2.66 |
| **1180-22** | $C_{32}H_{30}NO_5Cl$ | C: 70.65, H: 5.56, N: 2.57 | C: 70.46, H: 5.46, N: 2.72 |
| **1180-23** | $C_{24}H_{30}N_2O_6$ | C: 65.14, H: 6.83, N: 6.33 | C: 64.95, H: 6.97, N: 6.21 |
| **1180-24** | $C_{25}H_{32}N_2O_6$ | C: 65.77, H: 7.07, N: 6.14 | C: 65.75, H: 7.09, N: 6.05 |
| **1180-25** | $C_{25}H_{22}NO_5Cl$ | C: 66.45, H: 4.91, N: 3.10 | C: 65.97, H: 4.87, N: 3.22 |
| **1180-26** | $C_{25}H_{24}NO_4Cl$ | C: 68.57, H: 5.52, N: 3.20 | C: 68.32, H: 5.52, N: 3.26 |
| **1180-27** | $C_{25}H_{24}NO_4Br$ | C: 62.25, H: 5.01, N: 2.90 | C: 62.11, H: 5.79, N: 2.79 |
| **1180-31** | $C_{27}H_{26}NO_4Br$ | C: 69.90, H: 5.65, N: 3.02 | C: 70.23, H: 5.63, N: 2.98 |
| **1180-32** | $C_{27}H_{26}NO_4Br$ | C: 63.79, H: 5.15, N: 2.76 | C: 64.02, H: 5.20, N: 2.78 |
| **1180-33** | $C_{27}H_{27}NO_4$ | C: 75.50, H: 6.34, N: 3.26 | C: 75.74, H: 6.38, N: 3.13 |
| **1180-34** | $C_{26}H_{25}NO_5Cl_2$ | C: 62.16, H: 5.02, N: 2.79 | C: 62.51, H: 4.97, N: 2.61 |
| **1180-35** | $C_{30}H_{29}NO_5$ | C: 74.52, H: 6.04, N: 2.90 | C: 74.52, H: 6.06, N: 2.79 |
| **1180-36** | $C_{27}H_{28}NO_5Cl$ | C: 67.28, H: 5.86, N: 2.91 | C: 67.43, H: 5.46, N: 2.74 |
| **1180-37** | $C_{27}H_{26}N_2O_5$ | C: 70.73, H: 5.72, N: 6.11 | C: 70.84, H: 5.68, N: 6.04 |
| **1180-38** | $C_{26}H_{24}NO_3Cl$ | C: 71.97, H: 5.57, N: 3.23 | C: 72.31, H: 6.05, N: 3.13 |
| **1180-39** | $C_{26}H_{24}NO_3Br$ | C: 65.28, H: 5.06, N: 2.93 | C: 64.99, H: 5.04, N: 2.99 |
| **1180-40** | $C_{27}H_{28}NO_4Cl$ | C: 69.59, H: 6.06, N: 3.01 | C: 69.37, H: 5.98, N: 2.90 |
| **1180-41** | $C_{27}H_{28}NO_4Br$ | C: 63.53, H: 5.53, N: 2.74 | C: 63.87, H: 5.42, N: 2.65 |
| **1180-42** | $C_{27}H_{29}NO_4$ | C: 75.15, H: 6.77, N: 3.25 | C: 75.03, H: 6.72, N: 3.24 |
| **1180-43** | $C_{24}H_{20}NO_4Cl$ | C: 68.33, H: 4.78, N: 3.32 | C: 68.05, H: 5.10, N: 3.26 |
| **1180-44** | $C_{26}H_{26}NO_3Cl$ | C: 71.63, H: 6.01, N: 3.21 | C: 71.79, H: 6.00, N: 3.34 |
| **1180-45** | $C_{26}H_{26}NO_3Br$ | C: 65.00, H: 5.46, N: 2.92 | C: 64.85, H: 5.42, N: 2.75 |
| **1180-46** | $C_{25}H_{25}NO_4$ | C: 74.42, H: 6.25, N: 3.47 | C: 74.21, H: 6.30, N: 3.50 |
| **1180-47** | $C_{25}H_{23}NO_5$ | C: 71.93, H: 5.55, N: 3.36 | C: 71.85, H: 5.63, N: 3.29 |
| **1180-48** | $C_{25}H_{22}NO_5Br$ | C: 60.50, H: 4.47, N: 2.82 | C: 60.91, H: 4.67, N: 2.76 |
| **1180-49** | $C_{26}H_{26}NO_5Cl$ | C: 66.73, H: 5.60, N: 2.99 | C: 66.35, H: 5.57, N: 2.98 |
| **1180-50** | $C_{26}H_{26}NO_5Br$ | C: 60.95, H: 5.11, N: 2.73 | C: 60.86, H: 5.01, N: 2.71 |
| **1180-51** | $C_{26}H_{27}NO_4S$ | C: 69.46, H: 6.05, N: 3.12 | C: 69.20, H: 6.02, N: 3.20 |
| **1180-52** | $C_{27}H_{27}NO_5Cl_2$ | C: 62.80, H: 5.27, N: 2.71 | C: 62.50, H: 5.27, N: 2.57 |
| **1180-53** | $C_{27}H_{28}NO_5Cl$ | C: 67.28, H: 5.86, N: 2.91 | C: 66.98, H: 5.79, N: 2.76 |
| **1180-54** | $C_{27}H_{28}NO_5Br$ | C: 61.60, H: 5.36, N: 2.66 | C: 61.51, H: 5.39, N: 2.51 |
| **1180-55** | $C_{27}H_{28}NO_4Cl$ | C: 69.59, H: 6.06, N: 3.01 | C: 69.44, H: 5.97, N: 3.02 |
| **1180-57** | $C_{32}H_{31}NO_5$ | C: 75.42, H: 6.13, N: 2.75 | C: 75.11, H: 6.19, N: 2.69 |
| **1180-58** | $C_{28}H_{29}NO_6$ | C: 70.72, H: 6.15, N: 2.95 | C: 70.50, H: 6.15, N: 2.94 |

| | | | |
|---|---|---|---|
| **1180-65** | $C_{25}H_{24}NO_5Cl$ | C: 66.15, H: 5.33, N: 3.09 | C: 66.50, H: 5.45, N: 3.10 |
| **1180-66** | $C_{28}H_{28}NO_6Cl$ | C: 65.94, H: 5.53, N: 2.75 | C: 66.13, H: 5.62, N: 2.81 |
| **1180-67** | $C_{27}H_{27}NO_5$ | C: 72.79, H: 6.11, N: 3.14 | C: 73.01, H: 6.09, N: 3.12 |
| **1180-68** | $C_{20}H_{22}ClNO_4$ | C: 63.91, H: 5.90, N: 3.73 | C: 64.21, H: 6.01, N: 3.74 |
| **1180-69** | $C_{25}H_{25}NO_3$ | C: 77.49, H: 6.50, N: 3.61 | C: 77.72, H: 6.62, N: 3.67 |
| **1180-70** | $C_{25}H_{24}NO_3Cl$ | C: 71.17, H: 5.73, N: 3.32 | C: 71.42, H: 5.48, N: 3.30 |
| **1180-71**‡ | $C_{25}H_{24}NO_3Br$ | C: 64.38, H: 5.19, N: 3.00 | C: 65.02, H: 5.21, N: 3.02 |
| **1180-93** | $C_{26}H_{26}NO_4Cl$ | C: 69.10, H: 5.80, N: 3.10 | C: 69.24, H: 5.83, N: 3.14 |
| **1180-94** | $C_{26}H_{26}NO_4Br$ | C: 62.91, H: 5.28, N: 2.82 | C: 63.05, H: 5.22, N: 2.74 |
| **1180-95** | $C_{26}H_{27}NO_4$ | C: 74.80, H: 6.52, N: 3.35 | C: 75.15, H: 6.53, N: 3.34 |
| **1180-96** | $C_{27}H_{26}NO_4F_3$ | C: 66.80, H: 5.40, N: 2.89 | C: 66.84, H: 5.41, N: 2.97 |
| **1180-97** | $C_{31}H_{28}NO_4Cl$ | C: 72.44, H: 5.49, N: 2.72 | C: 72.09, H: 5.12, N: 2.61 |
| **1180-98** | $C_{31}H_{28}NO_4Br$ | C: 66.67, H: 5.05, N: 2.51 | C: 66.75, H: 5.25, N: 2.42 |
| **1180-99**‡ | $C_{31}H_{29}NO_4$ | C: 77.64, H: 6.10, N: 2.92 | C: 78.12, H: 6.13, N: 3.09 |

‡Value did not fall within ± 0.4

**2.7 BIOLOGY EXPERIMENTAL DETAIL**

Biological experiments described below were performed by the laboratory of Dr. Stephen Traynelis in the Department of Pharmacology at Emory University's School of Medicine, unless otherwise indicated.

*2.7.1 in vitro analysis of 1180 series*

Two-electrode voltage-clamp recordings were performed on *Xenopus* oocytes expressing recombinant rat GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, GluN1/GluN2D, GluA1, or GluK2 receptors. cDNAs for rat GluN1-1a (GenBank accession numbers U11418 and U08261; hereafter GluN1), GluN2A (D13211), GluN2B (U11419), GluN2C (M91563), GluN2D (L31611), GluA1 (X17184), GluK2 (Z11548) were provided by Drs. S. Heinemann (Salk Institute), S. Nakanishi (Kyoto University), and P. Seeburg (University of Heidelberg). Oocyte isolation, RNA synthesis, and RNA injection were completed as described in detail elsewhere (Erreger et al., 2007); all protocols involving *Xenopus laevis* were approved by the Emory University Institutional Animal Care and Use Committee. During two-electrode voltage-clamp recordings,

oocytes were placed into a perfusion chamber and continually washed with recording solution containing (in mM) 90 NaCl, 1.0 KCl, 0.5 $BaCl_2$, 0.005 EDTA, and 10 HEPES at pH 7.4 ($23^oC$). Glass electrodes with a tip resistance of 0.5-2.5 MΩ were pulled from thin-walled glass capillary tubes and filled with 0.3-3.0 M KCl. An OC-725C amplifier (Warner Instrument Co) was used to hold the membrane potential of the oocytes at -40 mV during current recording. All compounds were made as 20 mM stock solutions in DMSO, and dissolved to reach the desired final concentration in recording solution containing 100 μM glutamate and 30 μM glycine for use on oocytes expressing NMDA receptors. Final DMSO content was 0.05-0.5% (vol/vol). Oocytes expressing GluK2 receptors were pre-treated with 10 μM concanavalin A for 10 minutes. Recombinant GluA1 and GluK2 receptors were activated by 100 μM glutamate. In order to prevent a gradual increase in current response over the course of the experiment, which appears to be a common feature of GluN1/GluN2A receptor responses when expressed in oocytes, some oocytes expressing GluN1/GluN2A were either pretreated with 50 μM BAPTA-AM (1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid tetraacetoxymethyl ester) for 10 minutes or injected with 50 nl of 2 mM K-BAPTA (potassium 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid). For every test compound, we recorded 5-7 concentrations in at least 4 oocytes obtained from two different frogs. We subsequently determined the $EC_{50}$ (half-maximally effective concentration of potentiator) by fitting the equation

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

to the mean composite concentration-response data normalized to the current in the absence of potentiator (100%). N is the Hill slope, and *maximum* is the maximal response predicted for saturating concentration of potentiator. A few compounds produced modest inhibition (>30% inhibition at 100 μM); these inhibitory actions were not studied further.

$Ca^{2+}$ imaging experiments were performed as described previously[94] with the following modifications. One day prior to the experiment, the cells were seeded in 20 µl media at 600,000 cells/ml in black clear bottom 384 well plates (Corning CellBind). On the day of the experiment, the media was gently aspirated and replaced with Flou-4 NW (Invitrogen) dissolved in HEPES-buffered saline (HBSS, Gibco #14175-053) comprised of (in mM) 5.33 KCl, 0.441 $KH_2PO_4$, 4.17 $NaHCO_3$, 137.9 NaCl, 0.338 $Na_2HPO_4$, 5.56 D-glucose, 2 $CaCl_2$, and 20 HEPES (pH 7.4), with 2.5 mM (1 %) Probenecid, and 30 µM 7-chlorokynurenic acid for 60 minutes at 37° C in the dark. Cells were then gently washed again with 30 µl/well using the same buffer without the Flou-4 dye, and placed in 20 µl/well buffer. Using a FDSS7000 instrument (Hamamatsu) real time recordings of changes in Fluo-4 emission was performed (excitation 480 nm and emission 540 nm) at room temperature (20-22° C). After 10 seconds of baseline recordings, 10 µl/well of 3x concentrated test compound, controls, or assay buffer in HBSS (pH 7.4) and 1 mM glycine (final concentration) were added. After 2 minutes, an additional 10 µl/well were added containing a 4x concentrated solutions of NMDA (GluN2C: 1000 µM and GluN2D: 300 µM). Changes in fluorescence were recorded for subsequent 2 minutes. For determination of the concentration-response relationships, test compounds were 3-fold serial diluted over 10 concentration steps. Responses (fluorescence units, FU) were normalized to the first recording and expressed as percent of maximally effective concentration of NMDA (see above). The $EC_{50}$ value was determined by non-linear least squares fitting of equation 1 to the data.

The maximum solubility (20 µM) was determined for compound **1390** using a BMG Labtech Nephelostar nephelometer (Offenburg, Germany), according to manufacturer's instructions. Only responses for concentrations below the experimentally determined limit of solubility were measured; whenever necessary we repeated experiments with 1-10 mM 2-hydroxypropyl-β-cyclodextrin added to the recording solution to ensure that the compounds

remained in solution up to 100 μM. 2-hydroxypropyl-β-cyclodextrin had no detectable effect on NMDA response amplitude. We also evaluated the time course of potentiator activity using a bioassay of compounds **1390**. We made up a solution of 10 μM 1390, and then repeatedly tested the potentiating actions of this solution (filtered through a 0.2 μm filter) on *Xenopus* oocytes expressing GluN1/GluN2D. Similarly, we tested the concentration-response effects of **1390** on maximal responses induced by NMDA on GluN1/GluN2C in BHK cells by measuring changes in fluorescence of Fluo-4 at different time points after making the compound solutions. Activity (potency and efficacy) was retained without loss until 360 minutes, whereas no activity was seen after 24 hours. Results from these two experiments suggested that compound **1390** remain fully active in solution up to 2-3 hours, with activity decreasing thereafter until by 24 hours there is no detectable activity.

*2.7.2 Separation of Enantiomers of 1390*

The separation of the enantiomers of **1390** was performed by Lundbeck. The enantiomers were obtained by supercritical fluid chromatography (SFC) on a Berger Multigram II operating at 50 ml/min at 35 °C and 100 bar backpressure. The column was a Phenomenex Lux 5u Cellulose-1 (250 x 21.2 mm). The eluent was $CO_2$ (60 %) and methanol + 0.1 % diethylamine (40%). 15 mg was dissolved in methanol and 200 stacked injections of 0.4 ml were performed. Enantiomeric excess (EE) was determined on an Aurora Fusion A5 SFC system operating at 3 ml/min at 40 °C and 100 bar backpressure. The column was a Phenomenex Lux 3u Cellulose-1 (150 x 4.6 mm). The eluent was $CO_2$ (70 %) and ethanol + 0.1 % diethylamine (30%). EE of peak 1 (rt 1.584 min) determined at 220 nM 98.3 %. Peak 2 (rt 2.708 min) 98.2 %.

*2.7.3 In vitro analysis of selectivity for 1390*

Receptor binding profile, $K_i$ determinations, and HERG activity for 1390 were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscol at NIMH, Bethesda MD. For receptor binding and HERG activity, 1390 was tested at a final concentration of 10 μM using assays described at http://pdsp.med.unc.edu/pdspw/binding.php. 1390 was also tested at $GABA_A$, glycine, 5-HT3, P2X, and nicotinic ion channels under two electrode voltage clamp.

*2.7.4 in vivo analysis of 1390 for pharmacokinetic properties*

Measurement of 1390 concentrations in plasma and brain following IP or IV administration of 1390 was performed by Ricerca Biosciences, LLC (Concord, OH). For these experiments, two groups of nine C57Bl/6 mice (Charles River) approximately 6-8 weeks of age were used. One group of mice received an IV injection of 5 mg/kg 1390 (5 mL/kg of a 1 mg/mL solution) *via* the tail vein. The other group received an IP injection of 20 mg/kg 1390 (20 mL/kg of a 1 mg/mL solution). Samples were collected from blood and brain at 0.5, 1, and 3 hours after administration (3 mice per time point) following isofluorane anesthesia. Plasma was obtained from whole blood via centrifugation (approx. 1500 x g) for 10 min at 5 $^{o}$C. 1390 concentrations were measured using LC-MS/MS.

*2.7.5 Evaluation of 1390 in a fear extinction animal model – Kevin Ogden, Kerry Ressler, Scott Heldt*

This work was performed by Kevin Ogden, Dr. Kerry Ressler, and Scott Heldt at Emory University. All experiments were reviewed and were approved by the Emory University Institutional Animal Care and Use Committees, and were in compliance with National Institutes of Health guidelines for the care and use of laboratory animals. Experiments were performed on adult, male C57Bl/6 mice that were group-housed with *ad libitum* access to food and water and maintained on a 12/12 h light/dark cycle. All experiments were performed in the light cycle. Separate groups of animals were used for the conditioned fear experiment and the extinction experiment. A third group of animals was used for experiments testing spatial memory, locomotor activity, and motor function.

*Fear Conditioning*

SR-LAB startle response systems (San Diego Instruments) were used for fear conditioning and fear extinction training as previously described.[95,96] The conditioned stimulus (CS) used in these experiments was a 30 second, 70 dB SPL, 6 kHz tone. The unconditioned stimulus (US) used was a 0.25 s, 0.6 mA foot shock.

On the day of fear conditioning, each mouse was placed in a chamber and 5 minutes later presented with a 30 second tone co-terminating with a 0.25 second footshock. This was repeated 5 times with an inter-trial interval of 3-5 minutes. After the 5 tone-foot shock pairings, mice were infused with 0.3 µL of 10 µg/µL 1390 or vehicle per side and returned to their home cages. Twenty-four hours later, mice were placed in the chambers and 5 minutes later presented with 5 tone-alone trials. Each trial consisted of a 30 second tone in the absence of footshock and the inter-trial interval was 4.5 minutes. Freezing during each trial was measured.

*Fear Extinction Training*

Mice were first subjected to fear conditioning without drug. Twenty-four hours after fear conditioning, mice were assessed for freezing. They were distributed into two groups based on matching freezing levels. Twenty-four hours later, mice were again placed into the startle response chambers. Five minutes later, the mice were presented with nine 15-minute blocks each consisting of 10 tone-alone trials. Each trial comprised a 30 second tone in the absence of foot shock with an inter-trial interval of 1 minute. Each 15-minute block was separated by 3 minutes. Immediately after the last block, mice were infused with 0.3 µL of 10 µg/µL 1390 or vehicle per side and returned to their home cages. Twenty-four hours later, mice were placed in the chambers and three minutes later were presented with 15 tone-alone trials. Each trial consisted of a 30 second tone in the absence of footshock with an inter-trial interval of 1.5 minutes. Freezing was measured during each trial.

*Freezing*

Fear expression was assessed by calculating freezing scores as previously described.[95,96] Voltage outputs from the accelerometer were digitized at 1 kHz and averaged over each second of a 5 second activity window. Based on the average voltages, an immobility score of 1 or 0 was given for each second and the five immobility scores were averaged and multiplied by 100 to calculate a mean percent immobility score for each trial.

*Morris water maze*

A round tub (52 inch diameter) was placed in an environment rich with extra maze cues and filled with water at 25 °C. An invisible escape platform 1 cm below the water surface was

located in the same spatial location independent of the start position on a particular trial so that mice were able to utilize extra maze cues to determine the platform's location. Each mouse was given 4 trials per day for 5 days with a 15-min inter-trial interval. Each day, mice were injected with 10 mg/kg 1390 or vehicle IP 30 minutes prior to the first trial. Mice were placed in the water maze with their paws touching the wall from 4 different starting positions (N, S, E, W). The maximum trial length was 60 seconds and if mice did not reach the platform in the allotted time, they were manually guided to it. Upon reaching the escape platform, mice were left on it for an additional 5 seconds to allow for survey of the spatial cues in the environment to guide future navigation to the platform. On the day following the 5 days of task acquisition, a probe trial was presented in the absence of drug during which the platform was removed and the amount of time and distance swam in each quadrant of the maze was measured over 60 seconds. All trials were videotaped and performance analyzed by MazeScan (Clever Sys, Inc.)

*Locomotor Activity*

Mice were injected with 10 mg/kg 1390 or vehicle IP 30 minutes before being placed in Plexiglass activity cages with cobb bedding equipped with infrared photobeams (San Diego Instruments) for 2 hours. Ambulations were defined as consecutive beam breaks and were counted by an interfacing computer.

*Rotarod*

Mice were given two practice trials on a rotating cylinder at the slow rotational speed of 4 rpm. Mice were then injected with 10 mg/kg 1390 IP and 30 minutes later placed on the cylinder rotating at 4 rpm and rotational speed was gradually increased over a 5-minute test session up to a maximum rotational speed of 40 rpm. Latency to fall off of the accelerating rotarod was measured.

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**Appendix**

Select spectra for compounds in Chapter 1:

$^1$H NMR for 96-65

$^1$H NMR for 96-66

Select spectra for compounds in Chapter 2:

Chiral HPLC (OD-RH) spectrum for 1390, racemic

Chiral HPLC (OD-RH) spectrum for purified enantiomers of 1390

$^1$H NMR for two tetrahydroisoquinoline intermediates

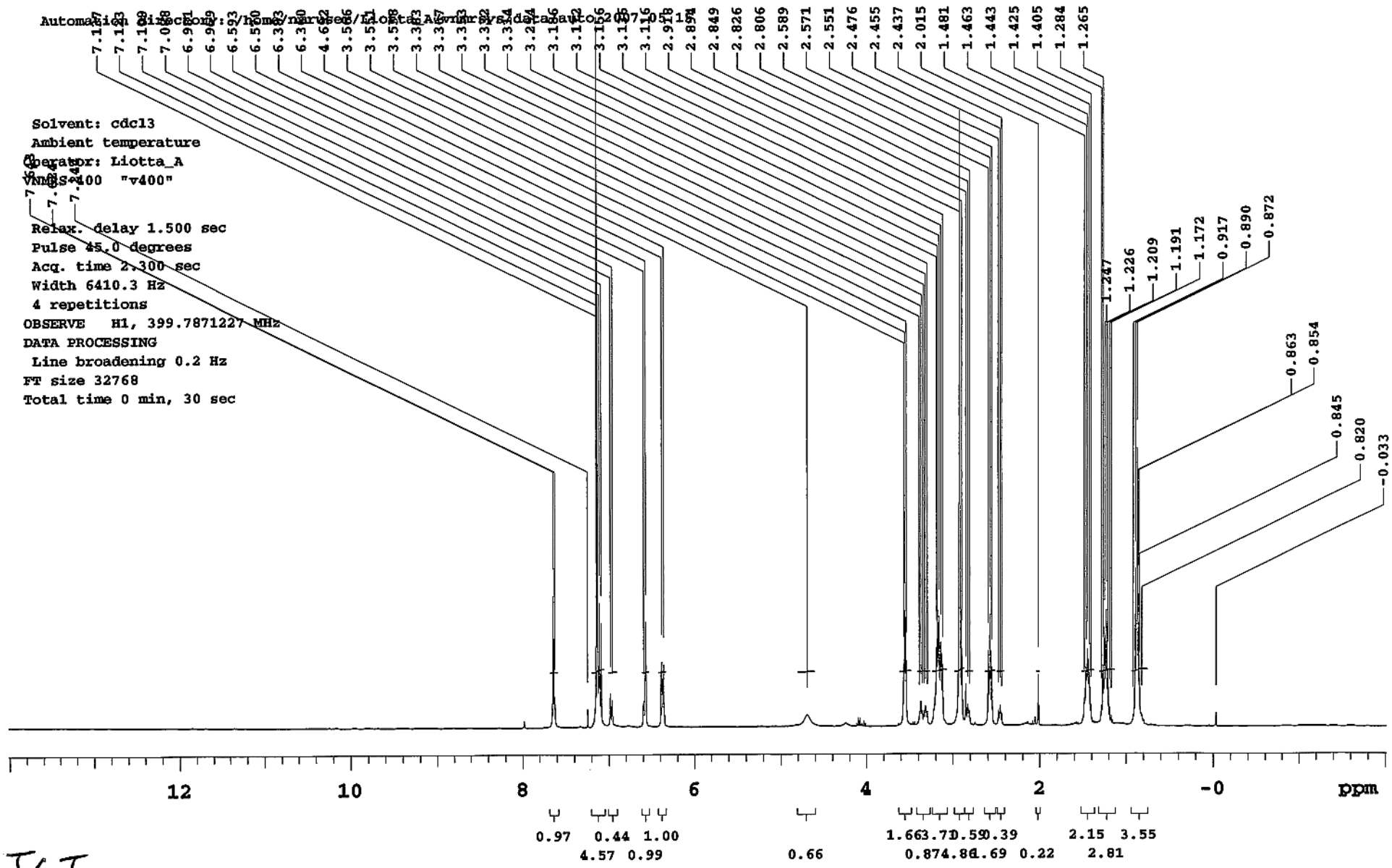
$^1$H NMR for 1390

$^1$H NMR for 1180-26

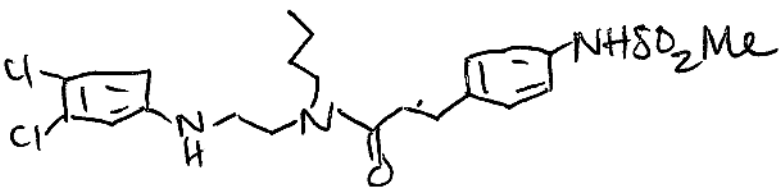
$^1$H NMR for 1180-55

$^1$H NMR for 1180-98

RMS-II-233




TGT



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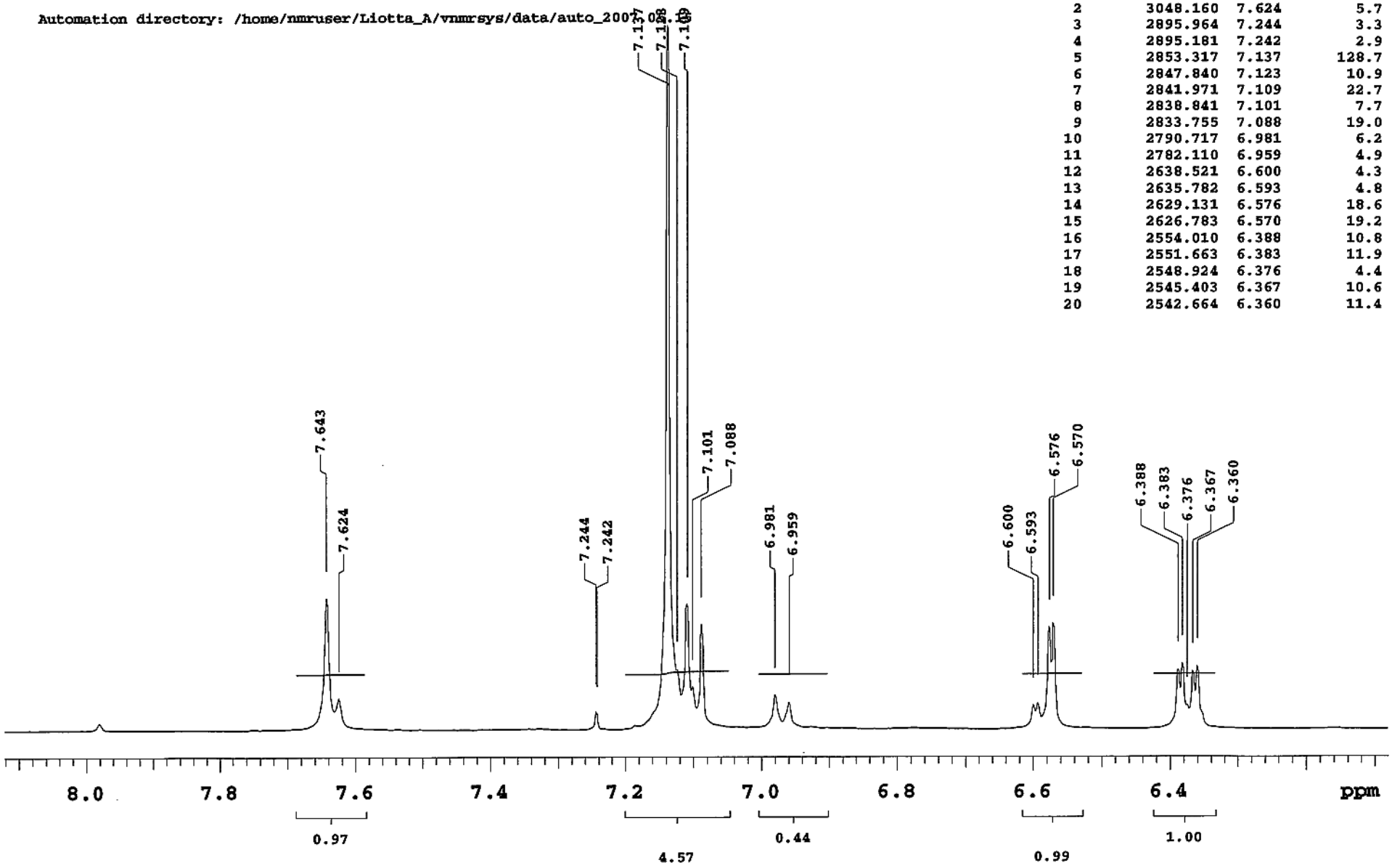
| 2 | 3048.160 | 7.624 | 5.7 |
| 3 | 2895.964 | 7.244 | 3.3 |
| 4 | 2895.181 | 7.242 | 2.9 |
| 5 | 2853.317 | 7.137 | 128.7 |
| 6 | 2847.840 | 7.123 | 10.9 |
| 7 | 2841.971 | 7.109 | 22.7 |
| 8 | 2838.841 | 7.101 | 7.7 |
| 9 | 2833.755 | 7.088 | 19.0 |
| 10 | 2790.717 | 6.981 | 6.2 |
| 11 | 2782.110 | 6.959 | 4.9 |
| 12 | 2638.521 | 6.600 | 4.3 |
| 13 | 2635.782 | 6.593 | 4.8 |
| 14 | 2629.131 | 6.576 | 18.6 |
| 15 | 2626.783 | 6.570 | 19.2 |
| 16 | 2554.010 | 6.388 | 10.8 |
| 17 | 2551.663 | 6.383 | 11.9 |
| 18 | 2548.924 | 6.376 | 4.4 |
| 19 | 2545.403 | 6.367 | 10.6 |
| 20 | 2542.664 | 6.360 | 11.4 |



RMS-II-233

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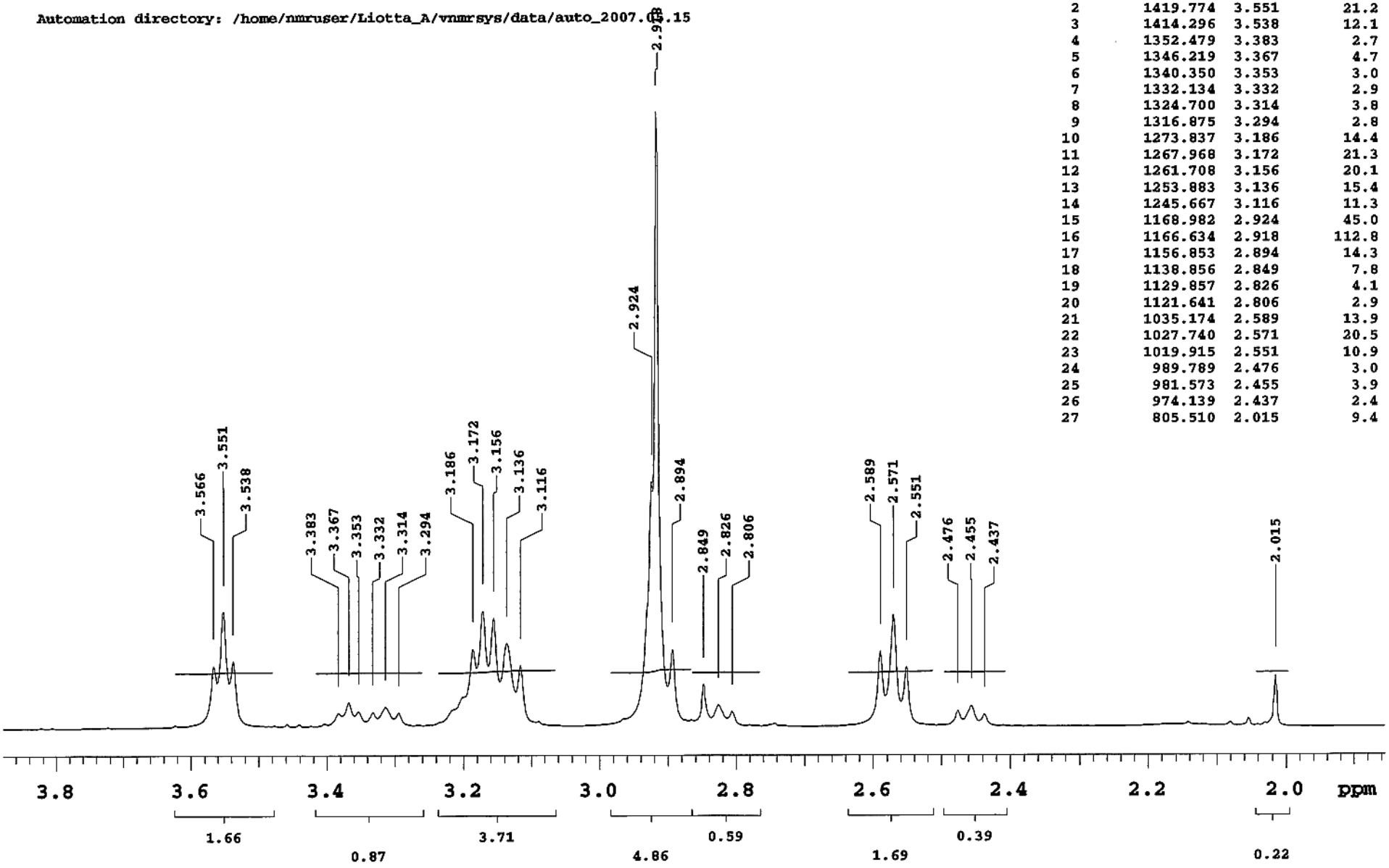
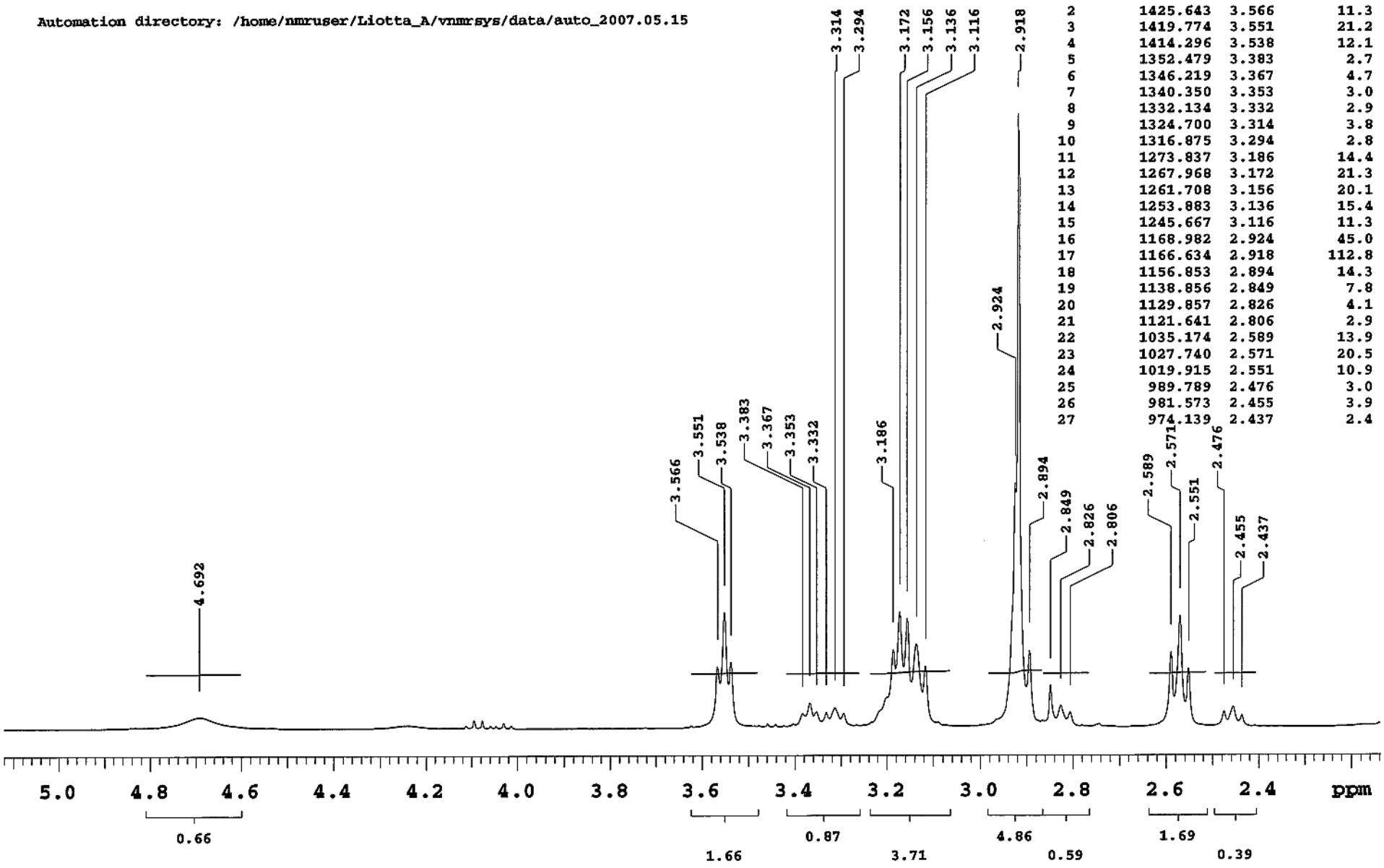
| 3 | 1414.296 | 3.538 | 12.1 |
| 4 | 1352.479 | 3.383 | 2.7 |
| 5 | 1346.219 | 3.367 | 4.7 |
| 6 | 1340.350 | 3.353 | 3.0 |
| 7 | 1332.134 | 3.332 | 2.9 |
| 8 | 1324.700 | 3.314 | 3.8 |
| 9 | 1316.875 | 3.294 | 2.8 |
| 10 | 1273.837 | 3.186 | 14.4 |
| 11 | 1267.968 | 3.172 | 21.3 |
| 12 | 1261.708 | 3.156 | 20.1 |
| 13 | 1253.883 | 3.136 | 15.4 |
| 14 | 1245.667 | 3.116 | 11.3 |
| 15 | 1168.982 | 2.924 | 45.0 |
| 16 | 1166.634 | 2.918 | 112.8 |
| 17 | 1156.853 | 2.894 | 14.3 |
| 18 | 1138.856 | 2.849 | 7.8 |
| 19 | 1129.857 | 2.826 | 4.1 |
| 20 | 1121.641 | 2.806 | 2.9 |
| 21 | 1035.174 | 2.589 | 13.9 |
| 22 | 1027.740 | 2.571 | 20.5 |
| 23 | 1019.915 | 2.551 | 10.9 |
| 24 | 989.789 | 2.476 | 3.0 |
| 25 | 981.573 | 2.455 | 3.9 |
| 26 | 974.139 | 2.437 | 2.4 |
| 27 | 805.510 | 2.015 | 9.4 |



RMS-II-233

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

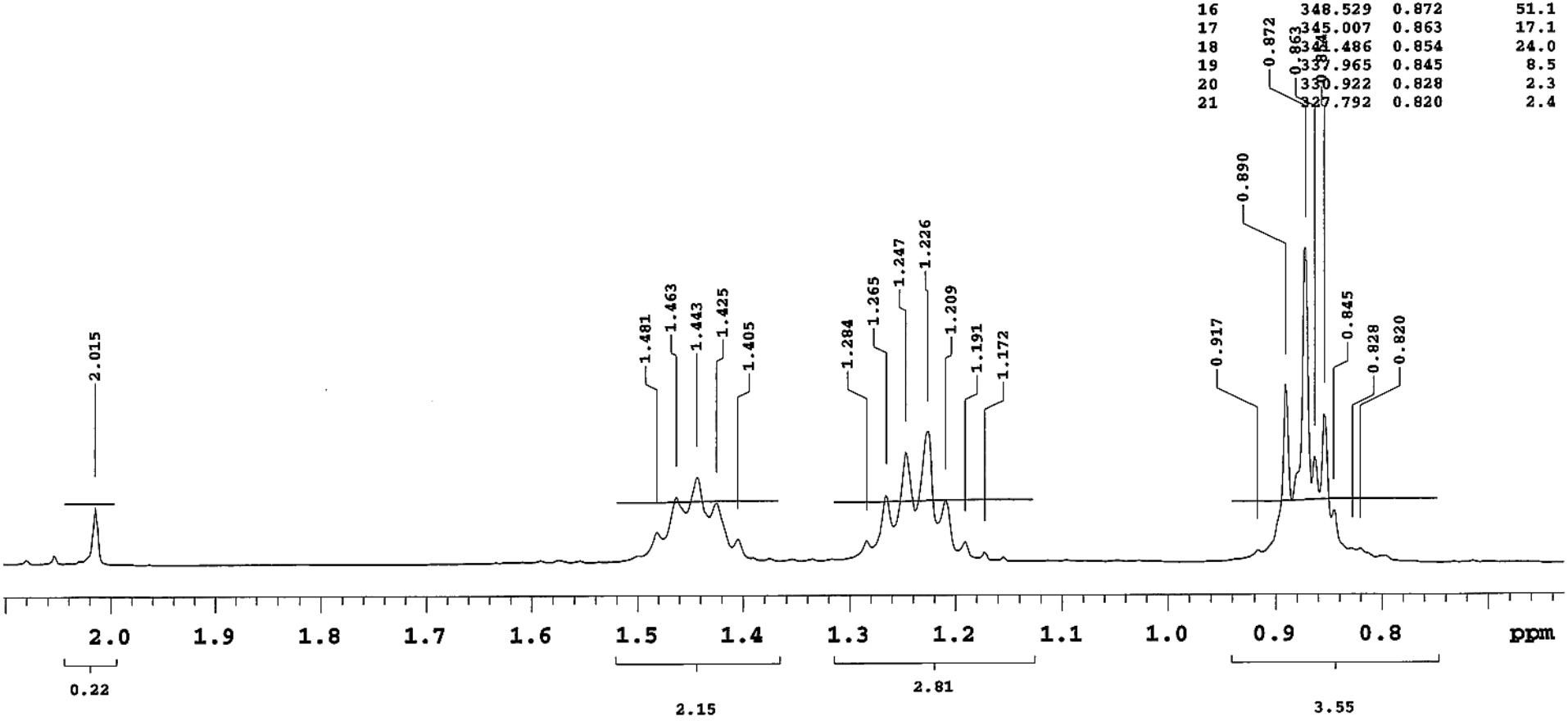



| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 1875.972 | 4.692 | 2.2 |
| 2 | 1425.643 | 3.566 | 11.3 |
| 3 | 1419.774 | 3.551 | 21.2 |
| 4 | 1414.296 | 3.538 | 12.1 |
| 5 | 1352.479 | 3.383 | 2.7 |
| 6 | 1346.219 | 3.367 | 4.7 |
| 7 | 1340.350 | 3.353 | 3.0 |
| 8 | 1332.134 | 3.332 | 2.9 |
| 9 | 1324.700 | 3.314 | 3.8 |
| 10 | 1316.875 | 3.294 | 2.8 |
| 11 | 1273.837 | 3.186 | 14.4 |
| 12 | 1267.968 | 3.172 | 21.3 |
| 13 | 1261.708 | 3.156 | 20.1 |
| 14 | 1253.883 | 3.136 | 15.4 |
| 15 | 1245.667 | 3.116 | 11.3 |
| 16 | 1168.982 | 2.924 | 45.0 |
| 17 | 1166.634 | 2.918 | 112.8 |
| 18 | 1156.853 | 2.894 | 14.3 |
| 19 | 1138.856 | 2.849 | 7.8 |
| 20 | 1129.857 | 2.826 | 4.1 |
| 21 | 1121.641 | 2.806 | 2.9 |
| 22 | 1035.174 | 2.589 | 13.9 |
| 23 | 1027.740 | 2.571 | 20.5 |
| 24 | 1019.915 | 2.551 | 10.9 |
| 25 | 989.789 | 2.476 | 3.0 |
| 26 | 981.573 | 2.455 | 3.9 |
| 27 | 974.139 | 2.437 | 2.4 |

RMS-II-233

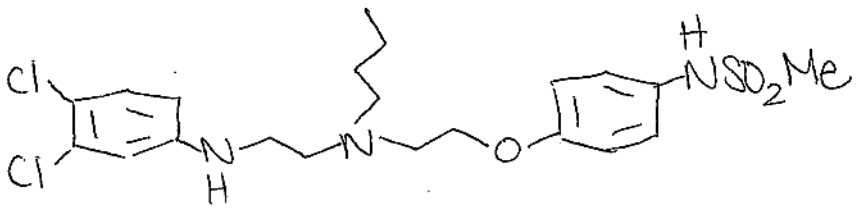
Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 805.510 | 2.015 | 9.4 |
| 2 | 592.278 | 1.481 | 5.2 |
| 3 | 584.844 | 1.463 | 10.8 |
| 4 | 577.019 | 1.443 | 14.1 |
| 5 | 569.585 | 1.425 | 9.9 |
| 6 | 561.760 | 1.405 | 4.0 |
| 7 | 513.245 | 1.284 | 3.7 |
| 8 | 505.811 | 1.265 | 11.1 |
| 9 | 498.378 | 1.247 | 18.0 |
| 10 | 490.161 | 1.226 | 21.3 |
| 11 | 483.510 | 1.209 | 10.3 |
| 12 | 476.076 | 1.191 | 3.5 |
| 13 | 468.643 | 1.172 | 1.9 |
| 14 | 366.526 | 0.917 | 2.1 |
| 15 | 355.962 | 0.890 | 28.8 |
| 16 | 348.529 | 0.872 | 51.1 |
| 17 | 345.007 | 0.863 | 17.1 |
| 18 | 341.486 | 0.854 | 24.0 |
| 19 | 337.965 | 0.845 | 8.5 |
| 20 | 330.922 | 0.828 | 2.3 |
| 21 | 327.792 | 0.820 | 2.4 |



NMDA 56

Pulse Sequence: s2pul




7.192
7.186
7.175
7.169
7.163
6.901
6.883
6.878
6.785
6.778
6.580
6.573
6.558
6.551

4.870
4.286
4.274
4.262
3.586
3.493
3.479
3.397
3.384
3.319
3.289
3.284
3.280
3.276
3.274
3.272
3.240
3.230
3.226
3.222
2.866
2.862

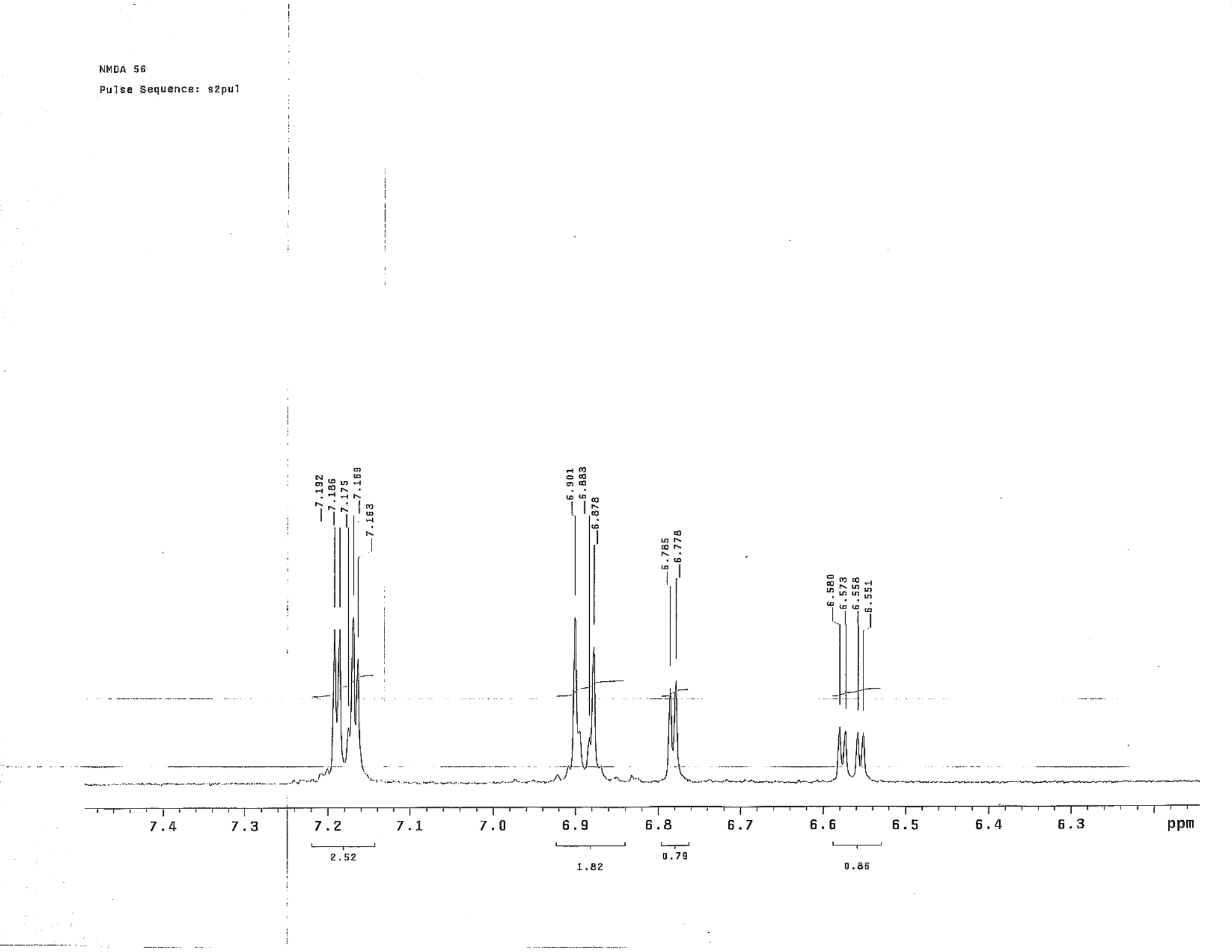
2.576
1.985
1.960
1.709
1.411
1.392
1.373
1.211
0.986
0.968
0.949
0.024

11 10 9 8 7 6 5 4 3 2 1 -0 ppm

2.52 0.79 1.66 1.93 0.97 2.04 0.48
1.82 0.86 1.61 3.64 3.00 1.03 2.22 2.68

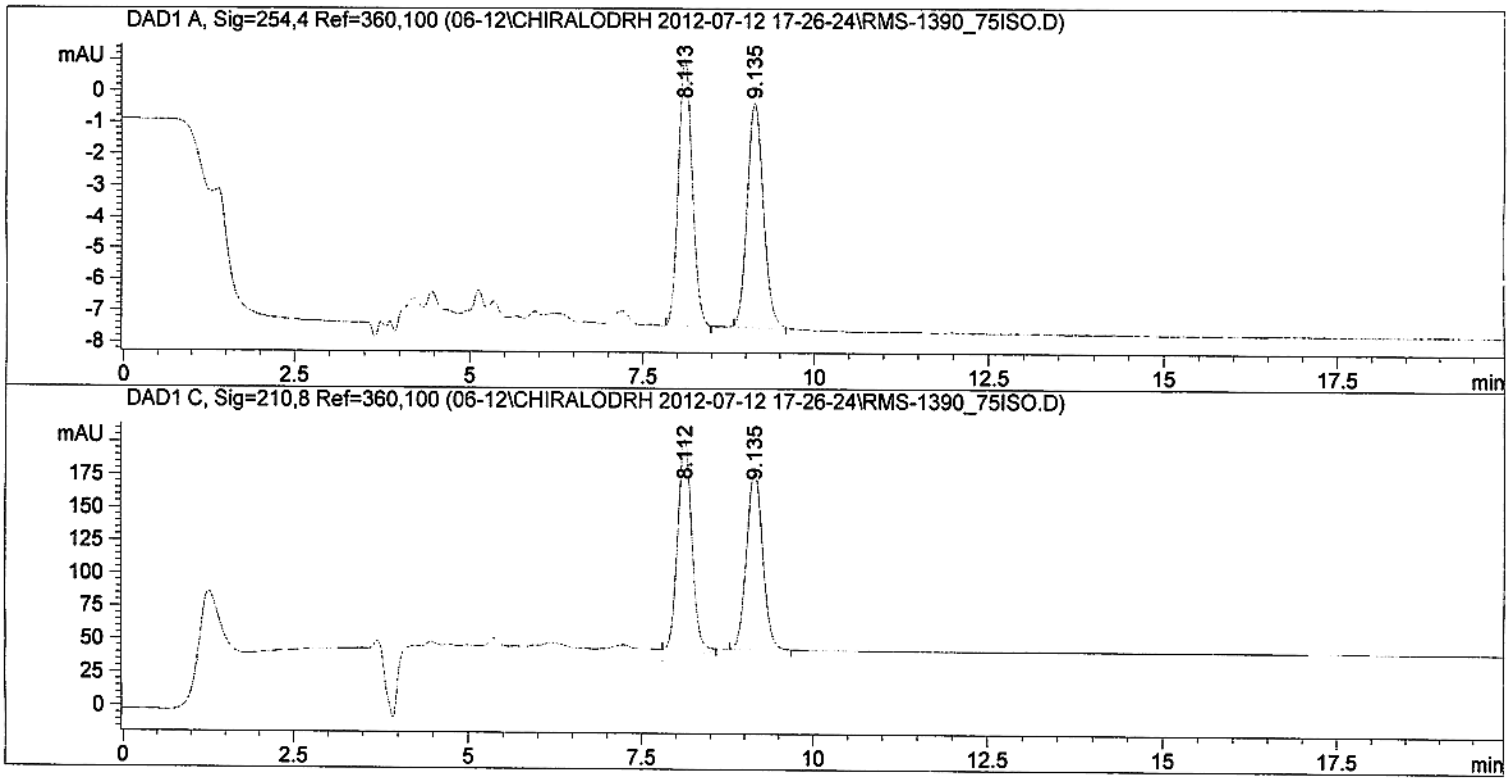
NMDA 56

Pulse Sequence: s2pul



Data File C:\LIOTTA LAB\DATA\06-12\CHIRALODRH 2012-07-12 17-26-24\RMS-1390_75ISO.D
Sample Name: RMS-1390_75ISO

```
==========================================================================
Acq. Operator   : Agilent                          Seq. Line :   3
Acq. Instrument : 1100 HPLC                        Location : Vial 61
Injection Date  : 7/12/2012 7:20:30 PM                 Inj :   1
                                                   Inj Volume : Inj prog
Acq. Method     : C:\LIOTTA LAB\DATA\06-12\CHIRALODRH 2012-07-12 17-26-24\75ACNISO_20MIN_
                  254_210.M
Last changed    : 7/12/2012 7:30:12 PM by Agilent
                  (modified after loading)
Analysis Method : C:\LIOTTA LAB\METHODS\CHIRAL_ODRH\75-95ACN_20MIN_254_210.M
Last changed    : 7/12/2012 6:52:48 PM by Agilent
Method Info     : 0.1 mL/min standby method. 85%
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.113 BB    0.2208  119.86259    8.48578  50.5727
   2   9.135 BB    0.2580  117.14796    7.11686  49.4273

Totals :                   237.01054   15.60264
```

Data File C:\LIOTTA LAB\DATA\06-12\CHIRALODRH 2012-07-12 17-26-24\RMS-1390_75ISO.D
Sample Name: RMS-1390_75ISO

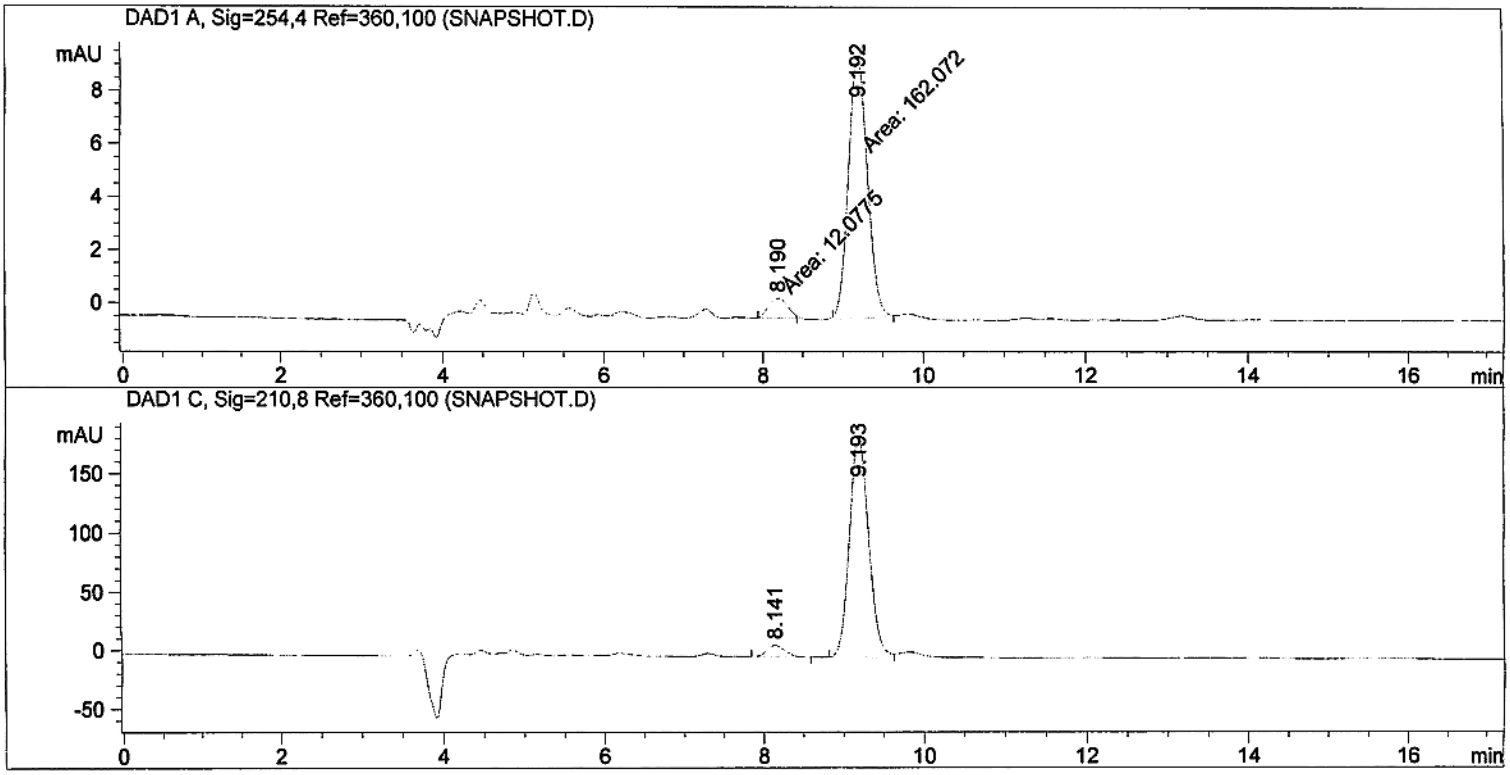
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.112 | BB | 0.2331 | 2511.91235 | 165.44202 | 53.1194 |
| 2 | 9.135 | BB | 0.2532 | 2216.89453 | 135.24524 | 46.8806 |
| Totals : | | | | 4728.80688 | 300.68726 | |

*** End of Report ***

Data File C:\LIOTTA LAB\DATA\SNAPSHOT.D
Sample Name: RMS-II-254_2

Acq. Operator : Agilent
Seq. Line : 2
Location : Vial 66
Injection Date : 20-Jul-12, 18:49:30
Inj : 1
Acq. Method : 75ACNISO_20MIN_254_210.M
Analysis Method : C:\LIOTTA LAB\METHODS\CHIRAL_ODRH\STANDBY_CHIRAL2.M
Last changed : 7/12/2012 5:01:05 PM by Agilent
Method Info : 0.1 mL/min standby method. 85%




## Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.190 | MM T | 0.2754 | 12.07747 | 7.30985e-1 | 6.9351 |
| 2 | 9.192 | MM T | 0.2742 | 162.07219 | 9.85255 | 93.0649 |
| Totals : | | | | 174.14965 | 10.58353 | |

Data File C:\LIOTTA LAB\DATA\SNAPSHOT.D
Sample Name: RMS-II-254_2

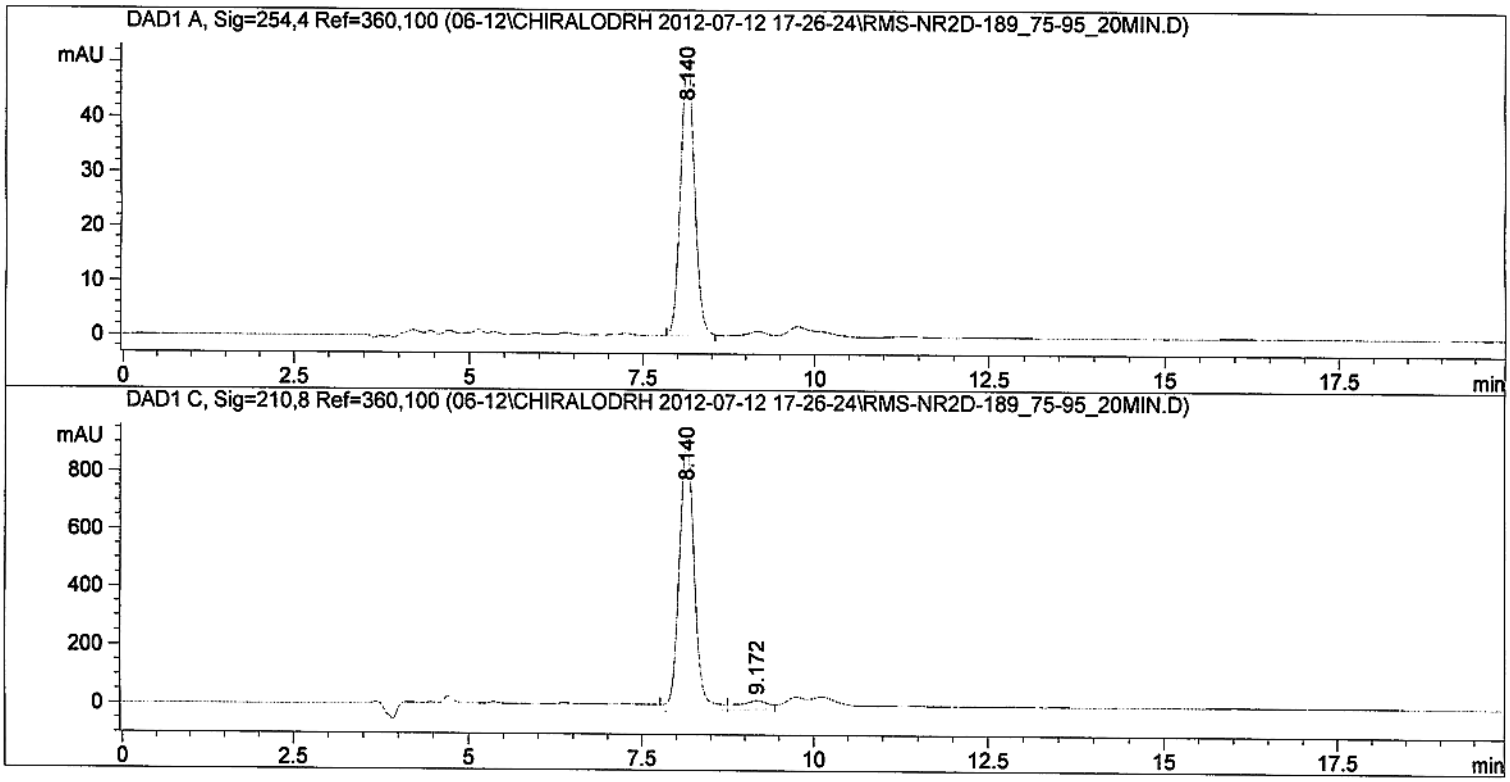
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.141 | BB | 0.2473 | 150.71622 | 9.70076 | 4.6095 |
| 2 | 9.193 | BV | 0.2580 | 3118.94312 | 187.57431 | 95.3905 |
| Totals : | | | | 3269.65933 | 197.27507 | |

*** End of Report ***

Data File C:\LIOTTA ...ATA\06-12\CHIRALODRH 2012-07-12 17-26-24\RMS-NR2D-189_75-95_20MIN.D
Sample Name: RMS-NR2D-189_75ISO_20min

```
Acq. Operator    : Agilent                          Seq. Line :   4
Acq. Instrument  : 1100 HPLC                         Location : Vial 41
Injection Date   : 7/12/2012 7:45:13 PM                  Inj :   1
                                                   Inj Volume : Inj prog
Acq. Method      : C:\LIOTTA LAB\DATA\06-12\CHIRALODRH 2012-07-12 17-26-24\75ACNISO_20MIN_
                   254_210.M
Last changed     : 7/12/2012 7:30:12 PM by Agilent
                   (modified after loading)
Analysis Method  : C:\LIOTTA LAB\METHODS\CHIRAL_ODRH\75-95ACN_20MIN_254_210.M
Last changed     : 7/12/2012 6:52:48 PM by Agilent
Method Info      : 0.1 mL/min standby method. 85%
```




## Area Percent Report

```
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.140 | BB | 0.2217 | 715.96735 | 50.40002 | 100.0000 |
| Totals : | | | | 715.96735 | 50.40002 | |

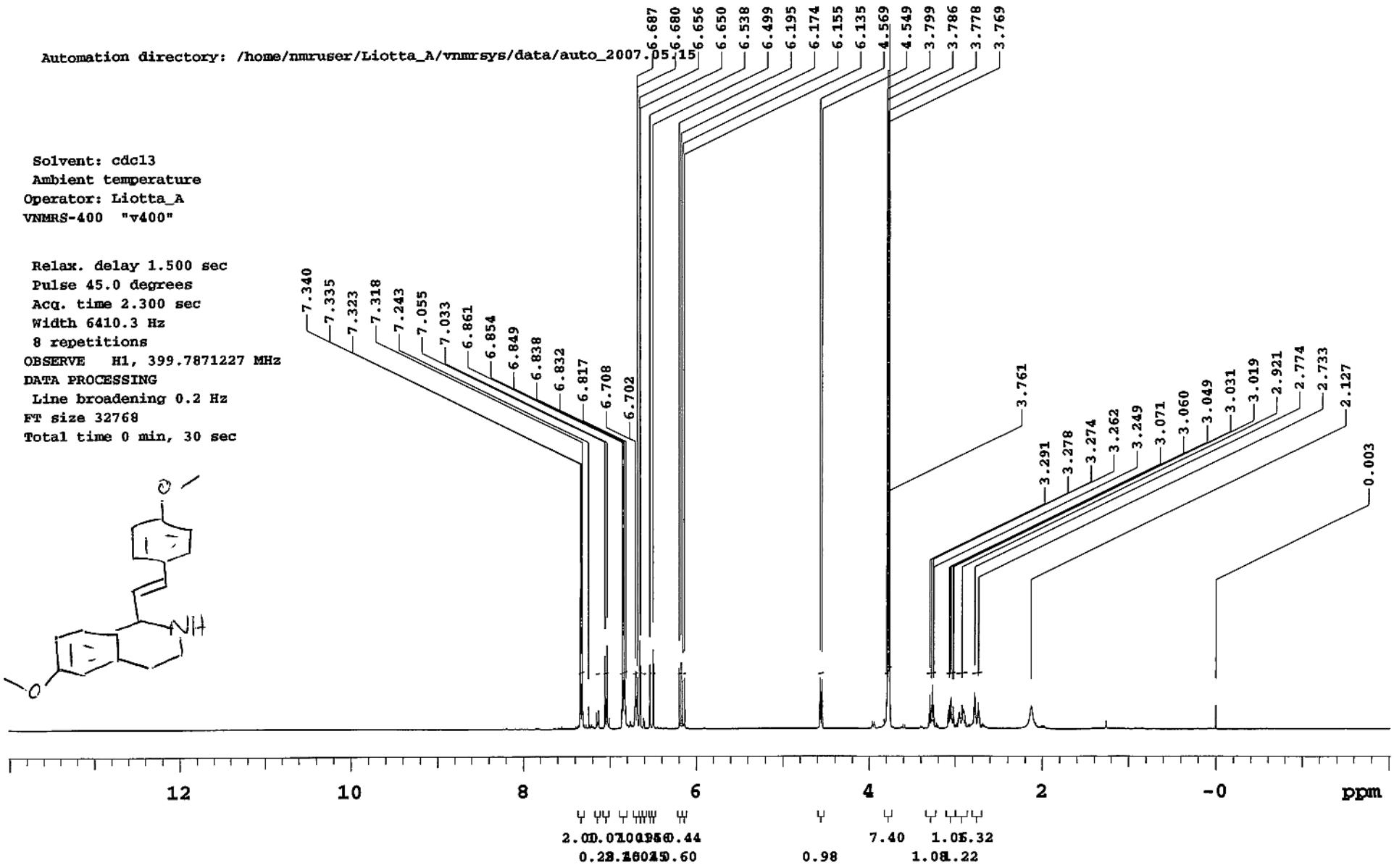
Data File C:\LIOTTA ...ATA\06-12\CHIRALODRH 2012-07-12 17-26-24\RMS-NR2D-189_75-95_20MIN.D
Sample Name: RMS-NR2D-189_75ISO_20min

Signal 2: DAD1 C, Sig=210,8 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 8.140 | VB | 0.2375 | 1.45063e4 | 932.64197 | 94.1973 |
| 2 | 9.172 | BV | 0.4132 | 893.61188 | 29.85426 | 5.8027 |
| Totals : | | | | 1.53999e4 | 962.49623 | |

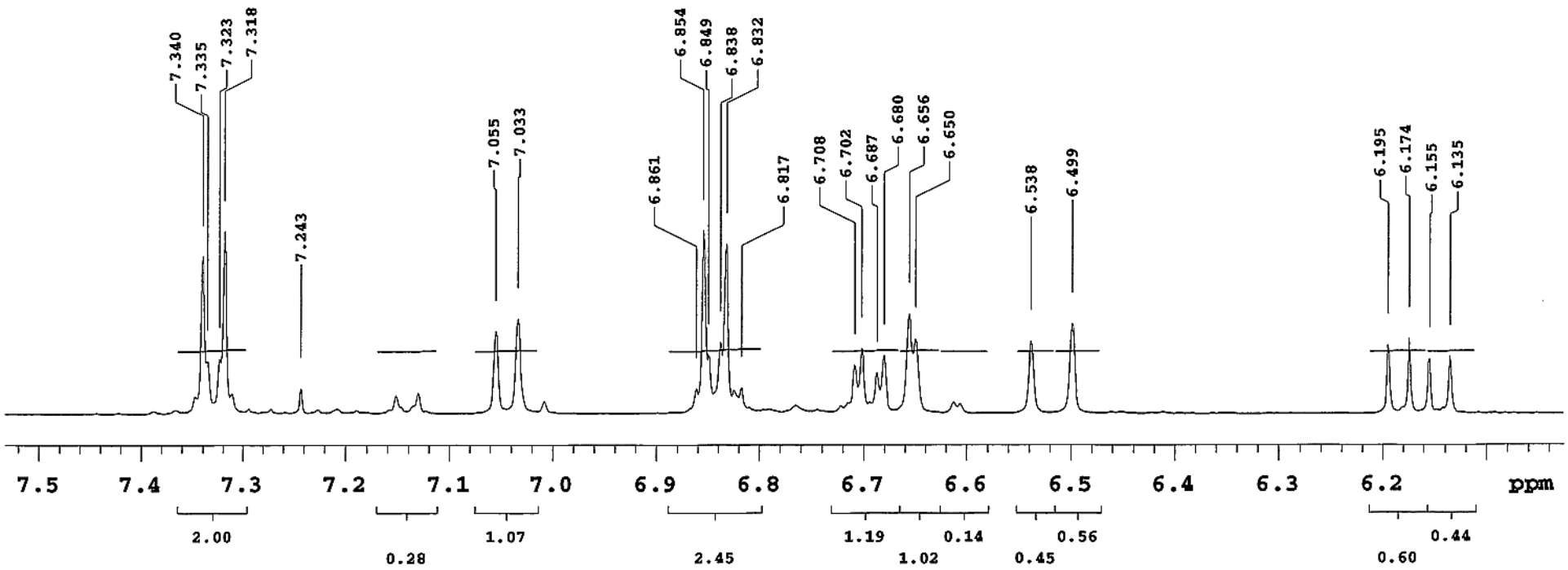
*** End of Report ***

NR2D-412


Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
Solvent: cdcl3
Ambient temperature
Operator: Liotta_A
VNMRS-400 "v400"
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871227 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec
6.687
6.680
6.656
6.650
6.538
6.499
6.195
6.174
6.155
6.135
4.569
4.549
3.799
3.786
3.778
3.769
7.340
7.335
7.323
7.318
7.243
7.055
7.033
6.861
6.854
6.849
6.838
6.832
6.817
6.708
6.702
3.761
3.291
3.278
3.274
3.262
3.249
3.071
3.060
3.049
3.031
3.019
2.921
2.774
2.733
2.127
0.003
NH
12
10
8
6
4
2
-0
ppm
2.00
0.28
7.40
0.98
1.05
1.08
5.32
1.22

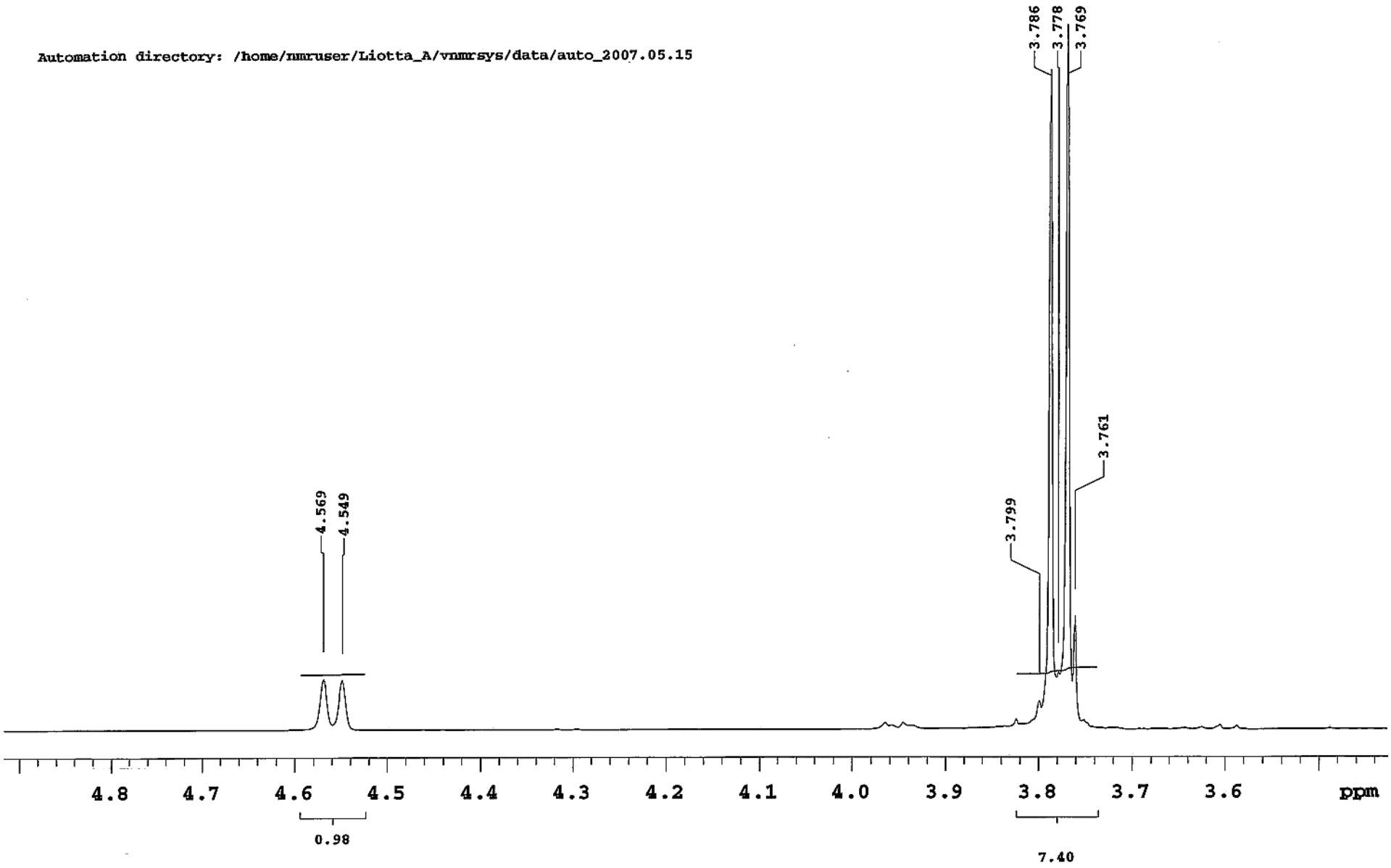
NR2D-412

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15



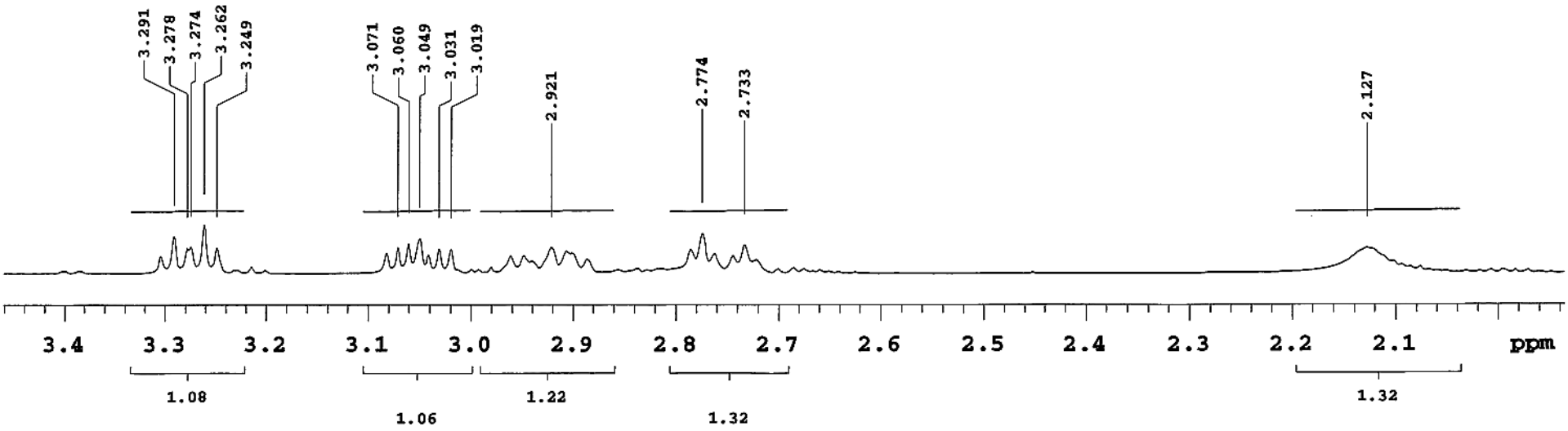
NR2D-412

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15



NR2D-412

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15



NR2D105

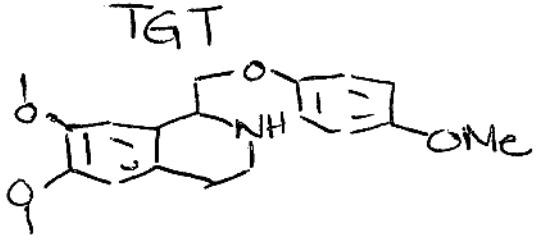
Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : /home/nmruser/Liotta_A/Santangelo/NR2D105proton.fid
Sample id : tmpstudy

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 23.0 C / 296.1 K
Operator: Liotta_A
File: NR2D105proton
VNMRS-400 "v400"

Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871133 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec

TGT



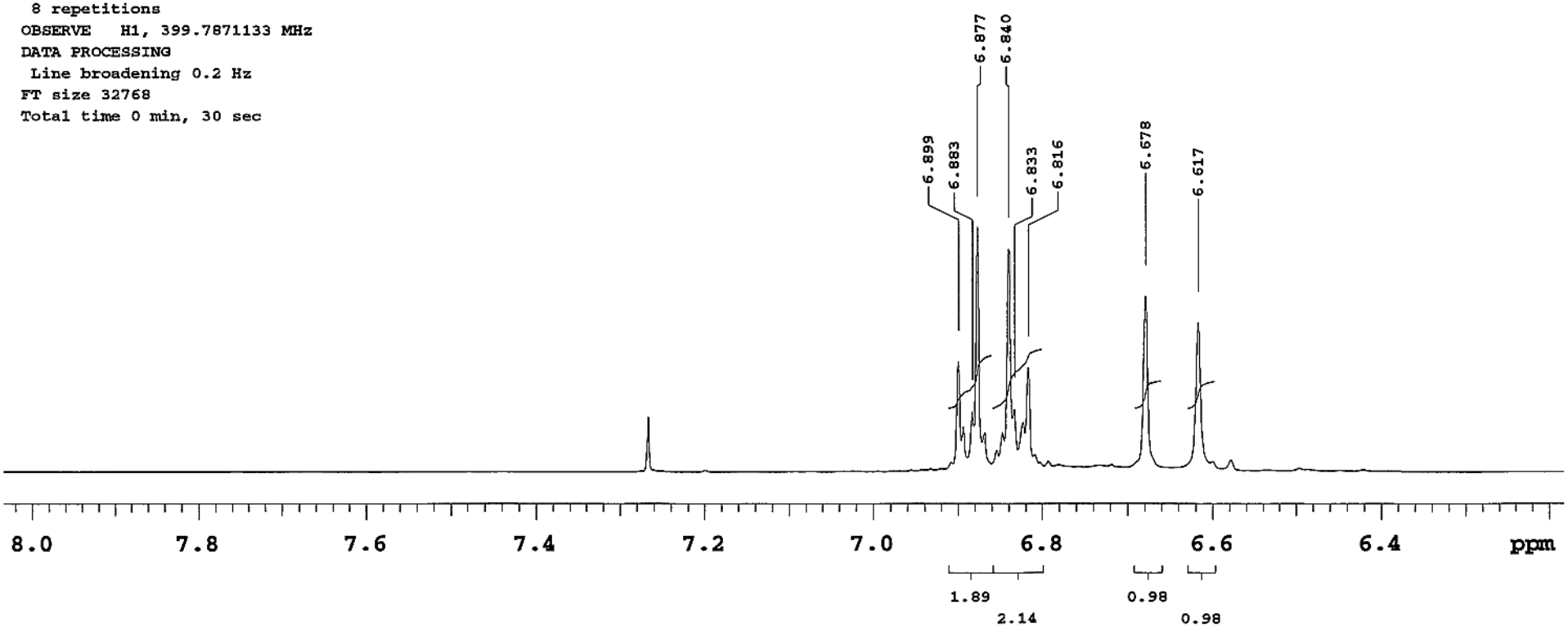
NR2D105

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : /home/nmruser/Liotta_A/Santangelo/NR2D105proton.fid
Sample id : tmpstudy

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 23.0 C / 296.1 K
Operator: Liotta_A
File: NR2D105proton
VNMRS-400 "v400"

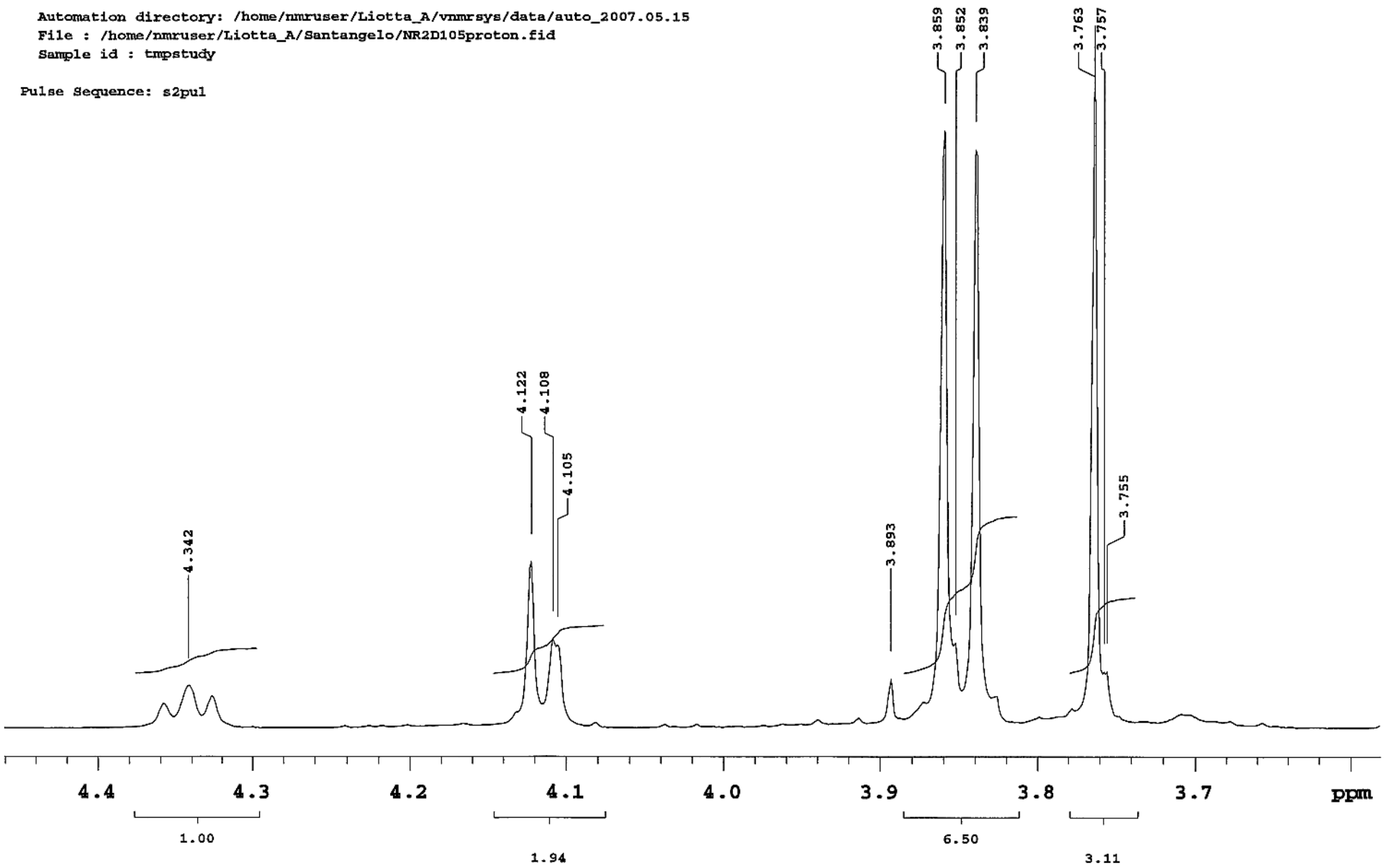
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871133 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec



NR2D105

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : /home/nmruser/Liotta_A/Santangelo/NR2D105proton.fid
Sample id : tmpstudy

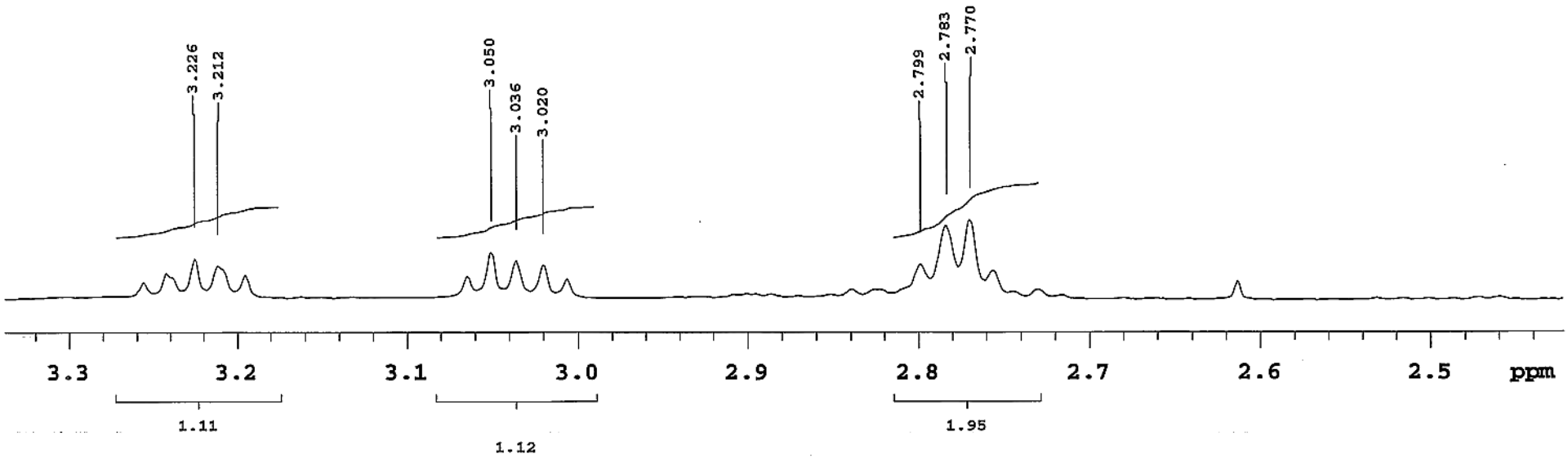
Pulse Sequence: s2pul



NR2D105

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : /home/nmruser/Liotta_A/Santangelo/NR2D105proton.fid
Sample id : tmpstudy

Pulse Sequence: s2pul



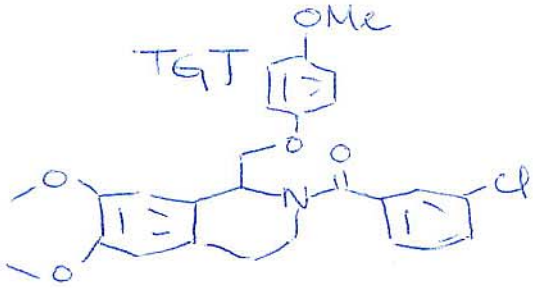
NR2D 109

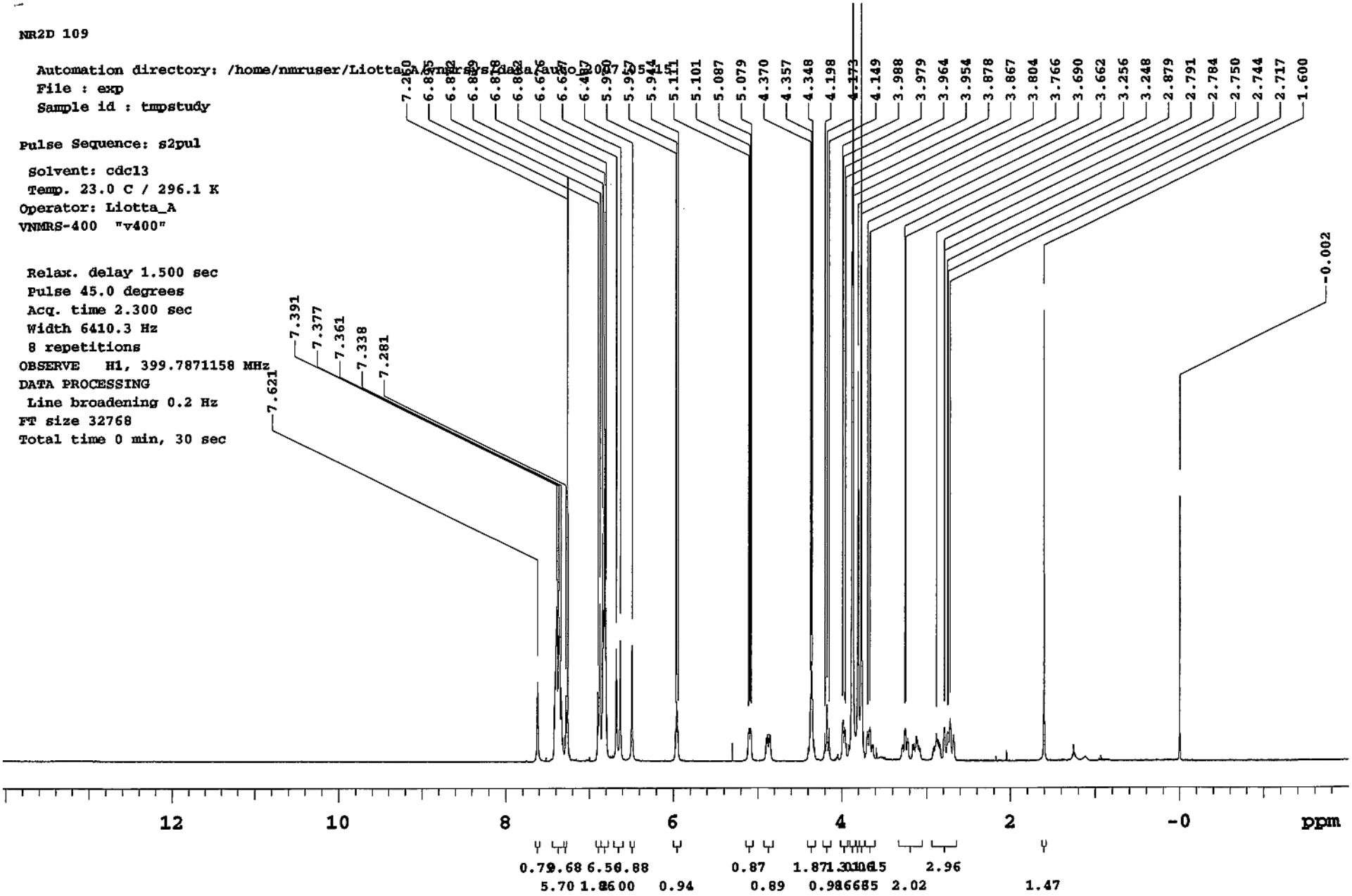
Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : exp
Sample id : tmpstudy

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 23.0 C / 296.1 K
Operator: Liotta_A
VNMRS-400 "v400"

Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871158 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec

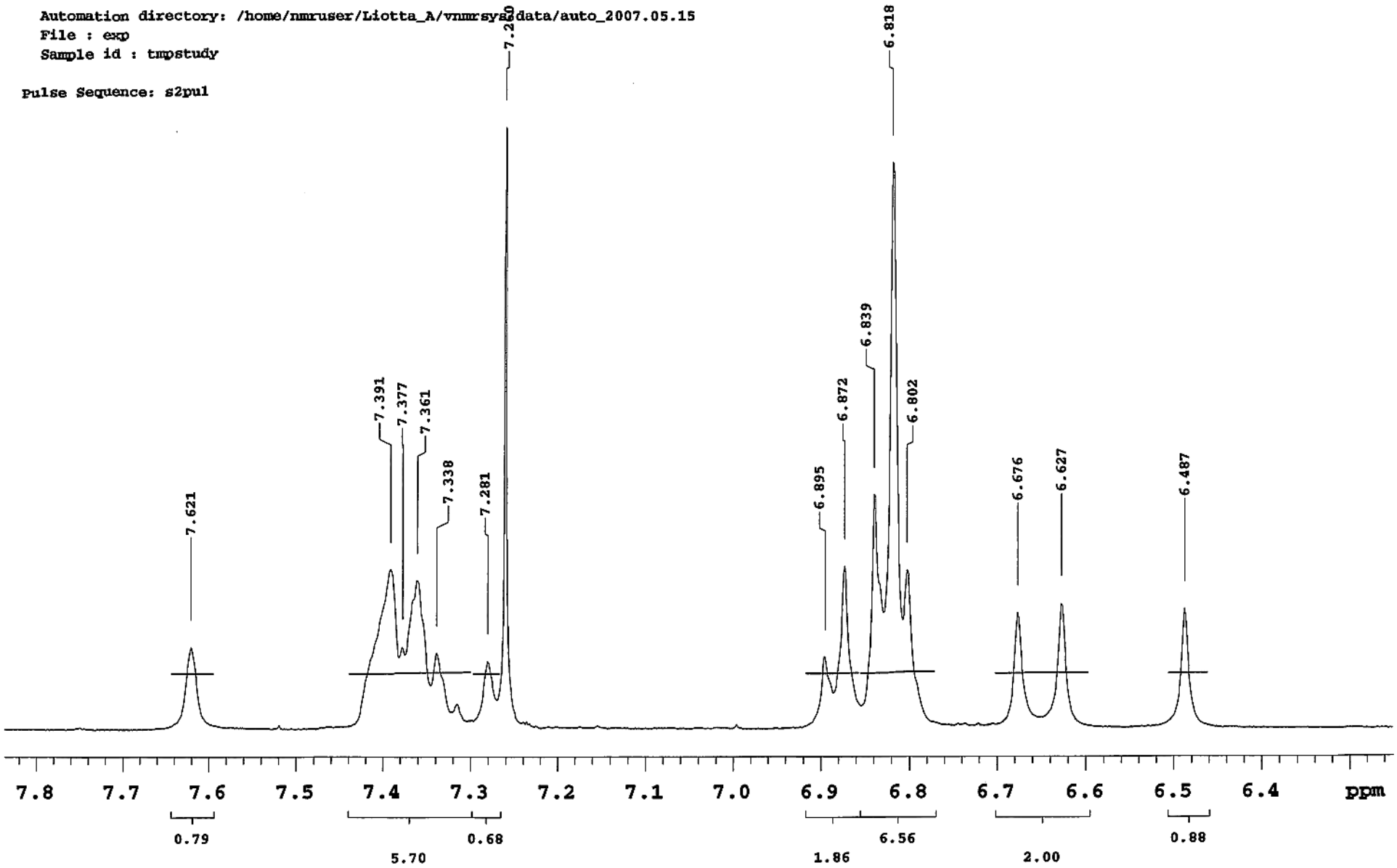



NR2D 109
Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007_2_54
File : exp
Sample id : tmpstudy
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 23.0 C / 296.1 K
Operator: Liotta_A
VNMRS-400 "v400"
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871158 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec
7.391
7.377
7.361
7.338
7.281
7.621
-0.002
12
10
8
6
4
2
-0
ppm

NR2D 109

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : exp
Sample id : tmpstudy

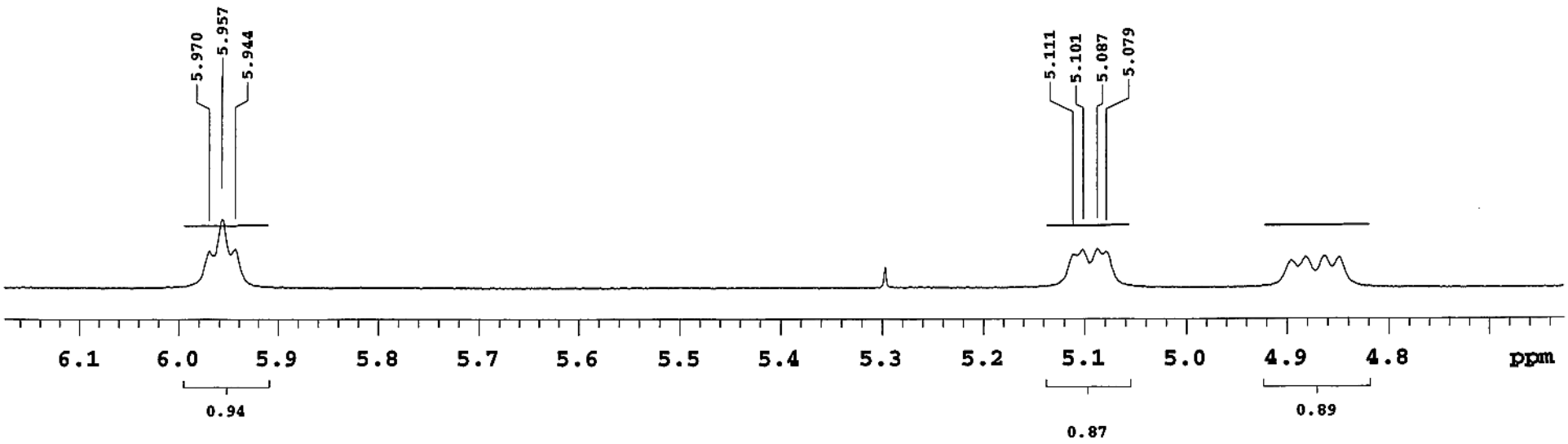
Pulse Sequence: s2pul



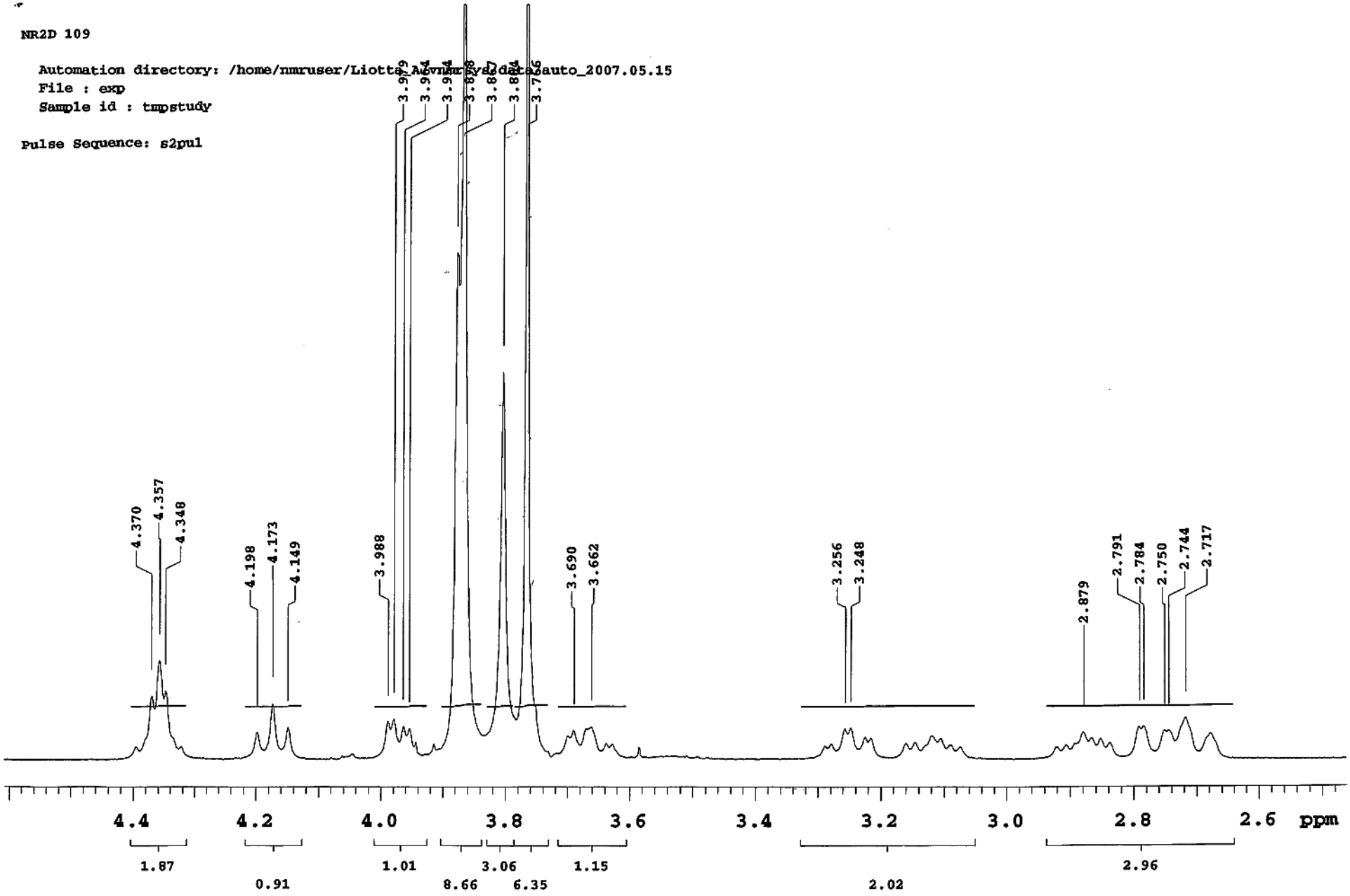
NR2D 109

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
File : exp
Sample id : tmpstudy

Pulse Sequence: s2pul

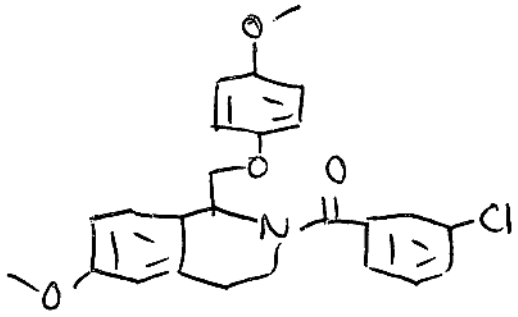



1 H [5.19 4.87 (dd, x Hz, x ; 2d ), 1H]


NR2D 109
Automation directory: /home/nmruser/Liotta_Advmatsysdata/auto_2007.05.15
File : exp
Sample id : tmpstudy
Pulse Sequence: s2pul
4.370
4.357
4.348
4.198
4.173
4.149
3.988
3.690
3.662
3.256
3.248
2.879
2.791
2.784
2.750
2.744
2.717
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
ppm
1.87
0.91
1.01
8.66
3.06
6.35
1.15
2.02
2.96

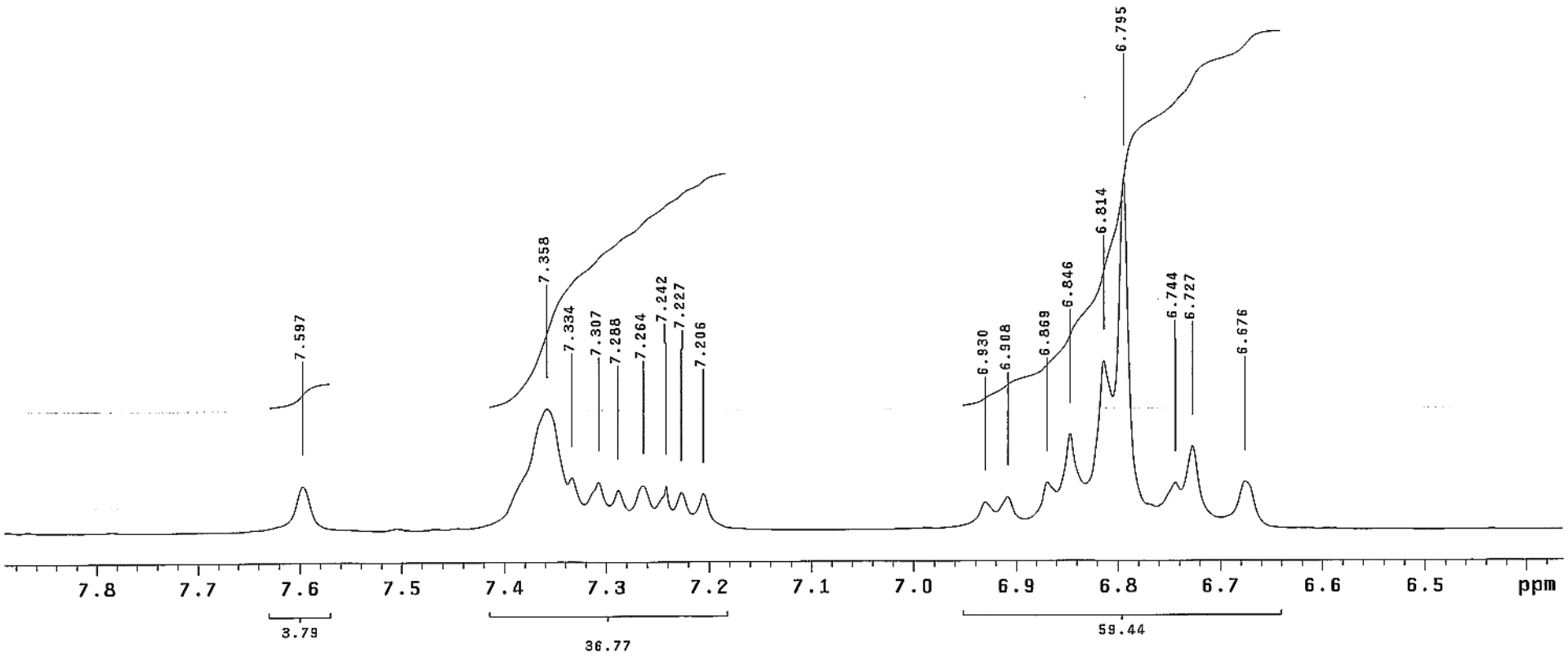
NR2D421

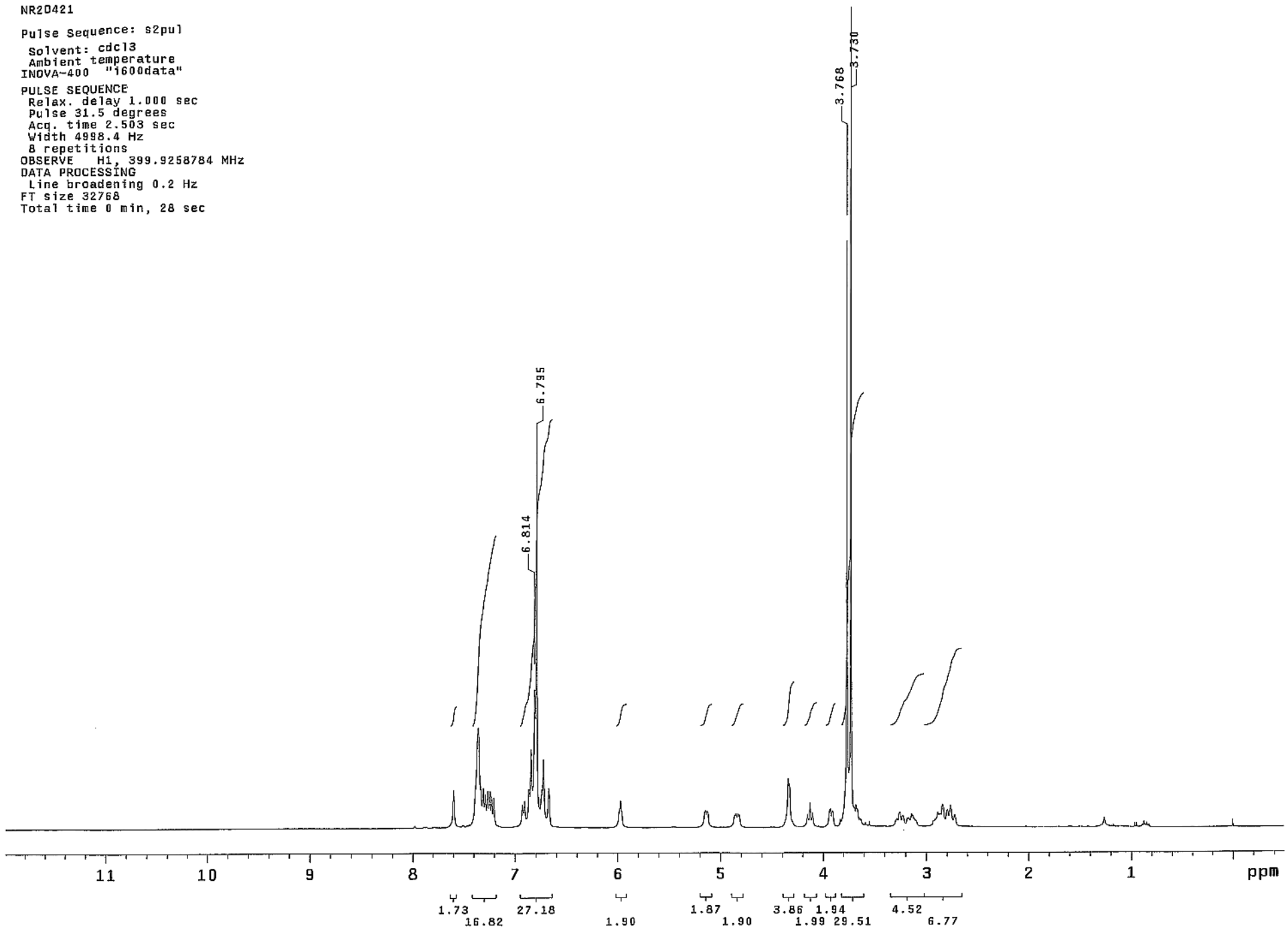
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
INOVA-400 "i600data"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 2.503 sec
Width 4998.4 Hz
8 repetitions
OBSERVE H1, 399.9258784 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 28 sec



NR2D421

Pulse Sequence: s2pul



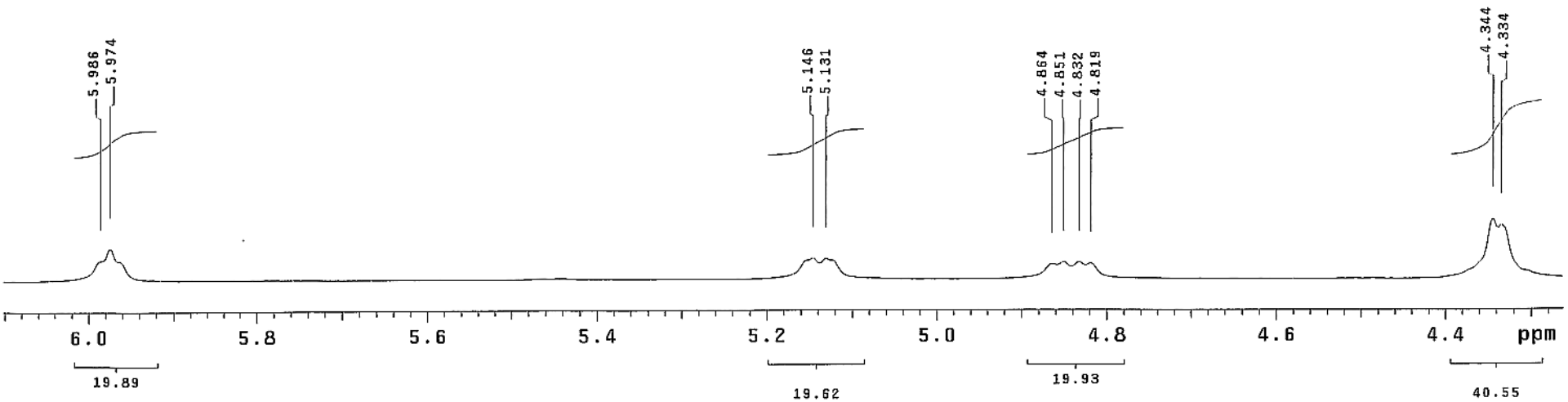

NR2D421
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
INOVA-400 "i600data"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 2.503 sec
Width 4998.4 Hz
8 repetitions
OBSERVE H1, 399.9258784 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 28 sec
3.768
3.730
6.795
6.814
11
10
9
8
7
6
5
4
3
2
1
ppm
1.73
16.82
27.18
1.90
1.87
1.90
3.86
1.94
1.99
29.51
4.52
6.77

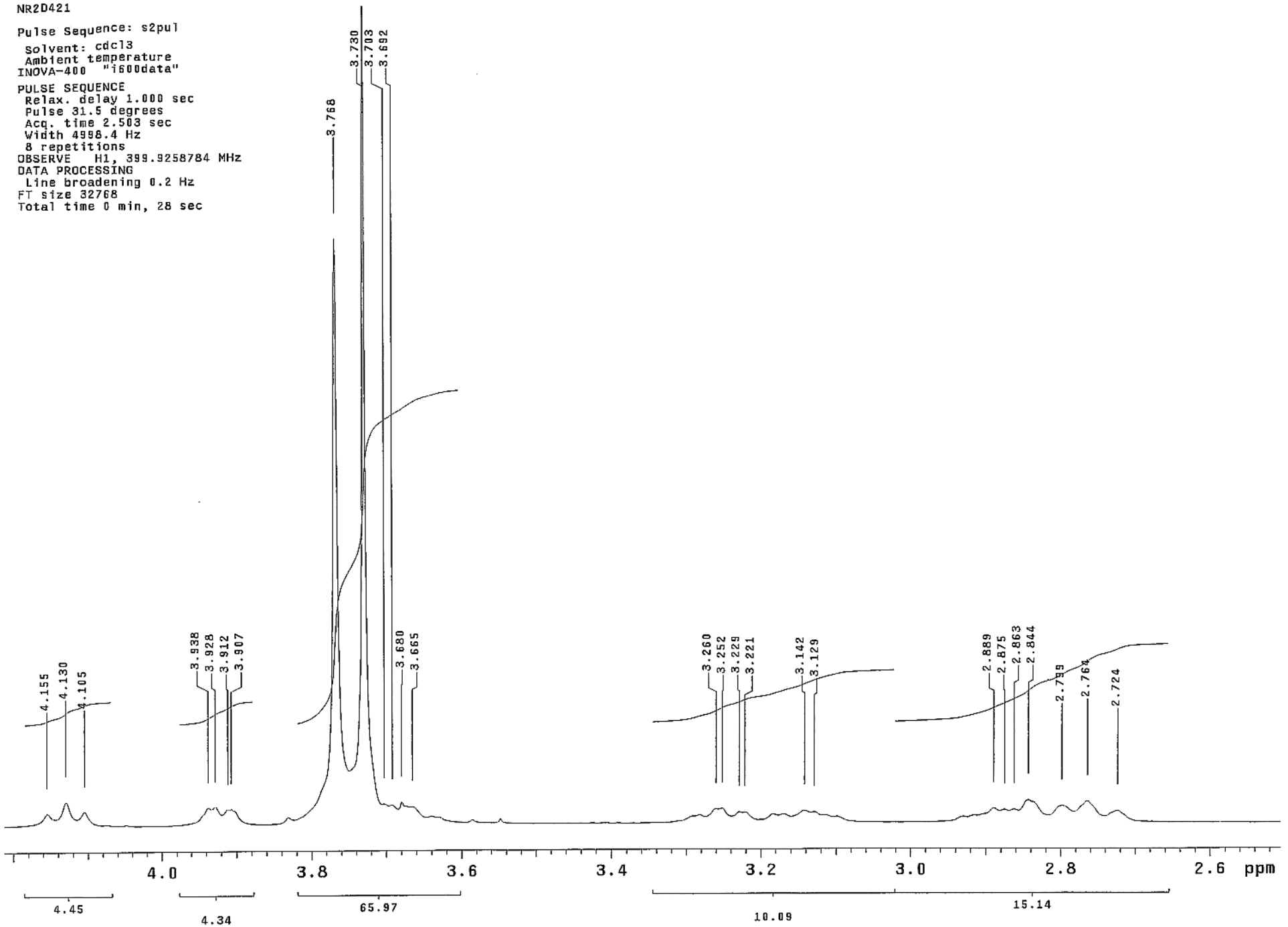
NR2D421

Pulse Sequence: s2pul

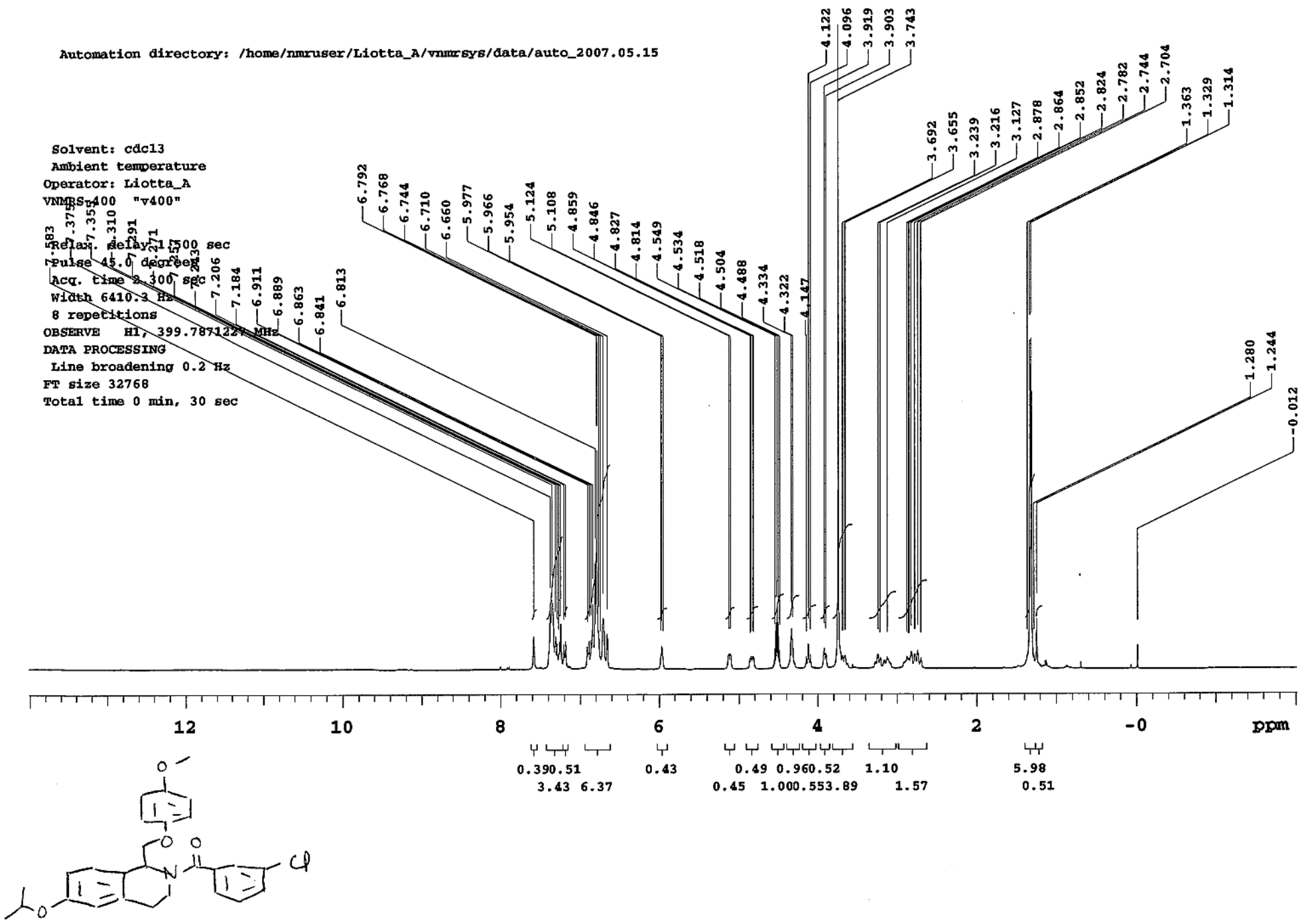
Solvent: cdcl3
Ambient temperature
INOVA-400 "i600data"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 2.503 sec
Width 4998.4 Hz
8 repetitions
OBSERVE H1, 399.9258784 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 28 sec



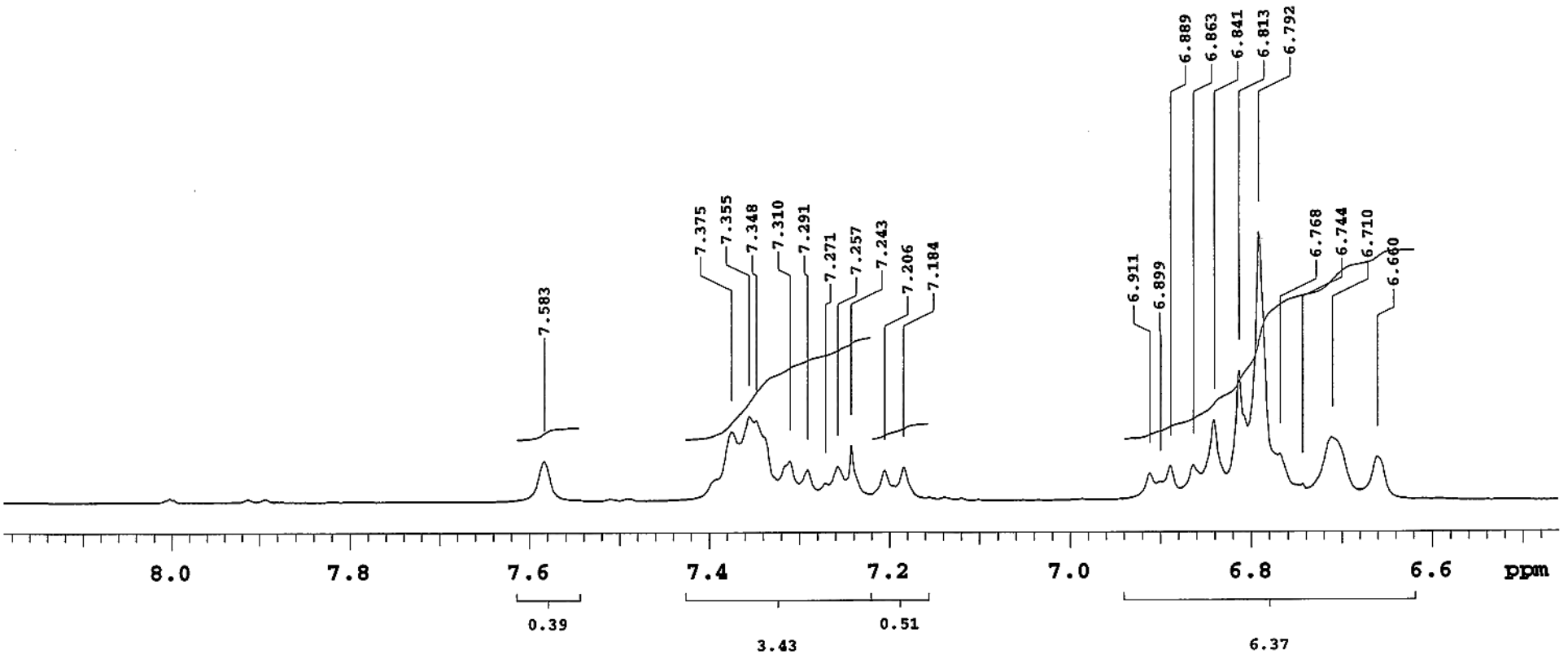

NR2D421
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
INOVA-400 "i600data"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 31.5 degrees
Acq. time 2.503 sec
Width 4998.4 Hz
8 repetitions
OBSERVE H1, 399.9258784 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 28 sec
4.155
4.130
4.105
3.938
3.928
3.912
3.907
3.768
3.730
3.703
3.692
3.680
3.665
3.260
3.252
3.229
3.221
3.142
3.129
2.889
2.875
2.863
2.844
2.799
2.764
2.724
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
ppm
4.45
4.34
65.97
10.09
15.14

NR2D-497


Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
Solvent: cdcl3
Ambient temperature
Operator: Liotta_A
VNMRS-400 "v400"
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871227 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec
7.583
7.375
7.355
7.310
7.291
7.271
7.257
7.233
7.206
7.184
6.911
6.889
6.863
6.841
6.813
6.792
6.768
6.744
6.710
6.660
5.977
5.966
5.954
5.124
5.108
4.859
4.846
4.827
4.814
4.549
4.534
4.518
4.504
4.488
4.334
4.322
4.147
4.122
4.096
3.919
3.903
3.743
3.692
3.655
3.239
3.216
3.127
2.878
2.864
2.852
2.824
2.782
2.744
2.704
1.363
1.329
1.314
1.280
1.244
-0.012
12
10
8
6
4
2
-0
ppm
0.39 0.51
3.43 6.37
0.43
0.49 0.96 0.52
0.45 1.00 0.55 3.89
1.10
1.57
5.98
0.51

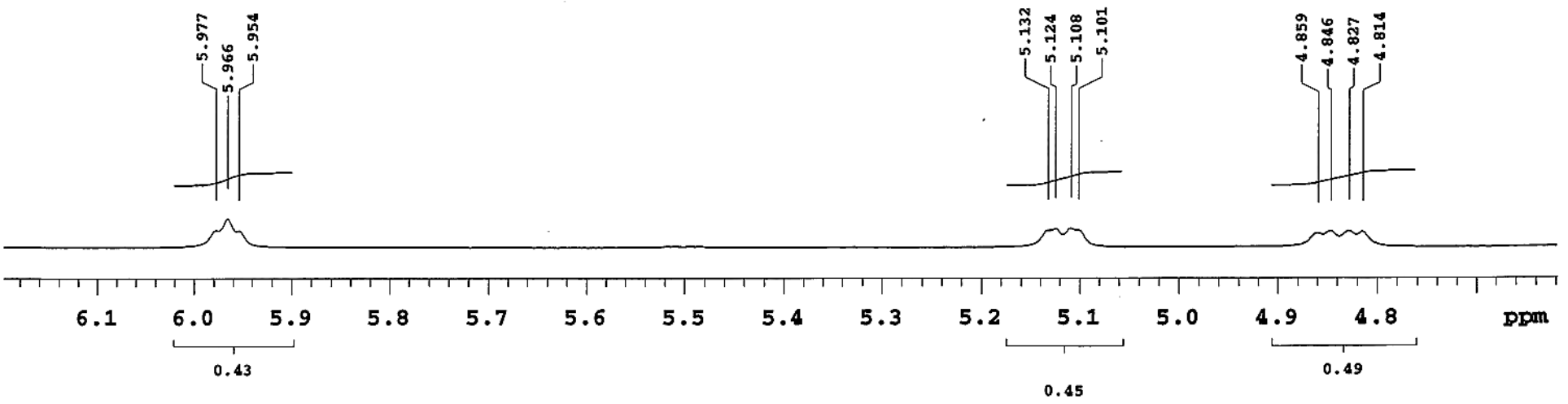
NR2D-497

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

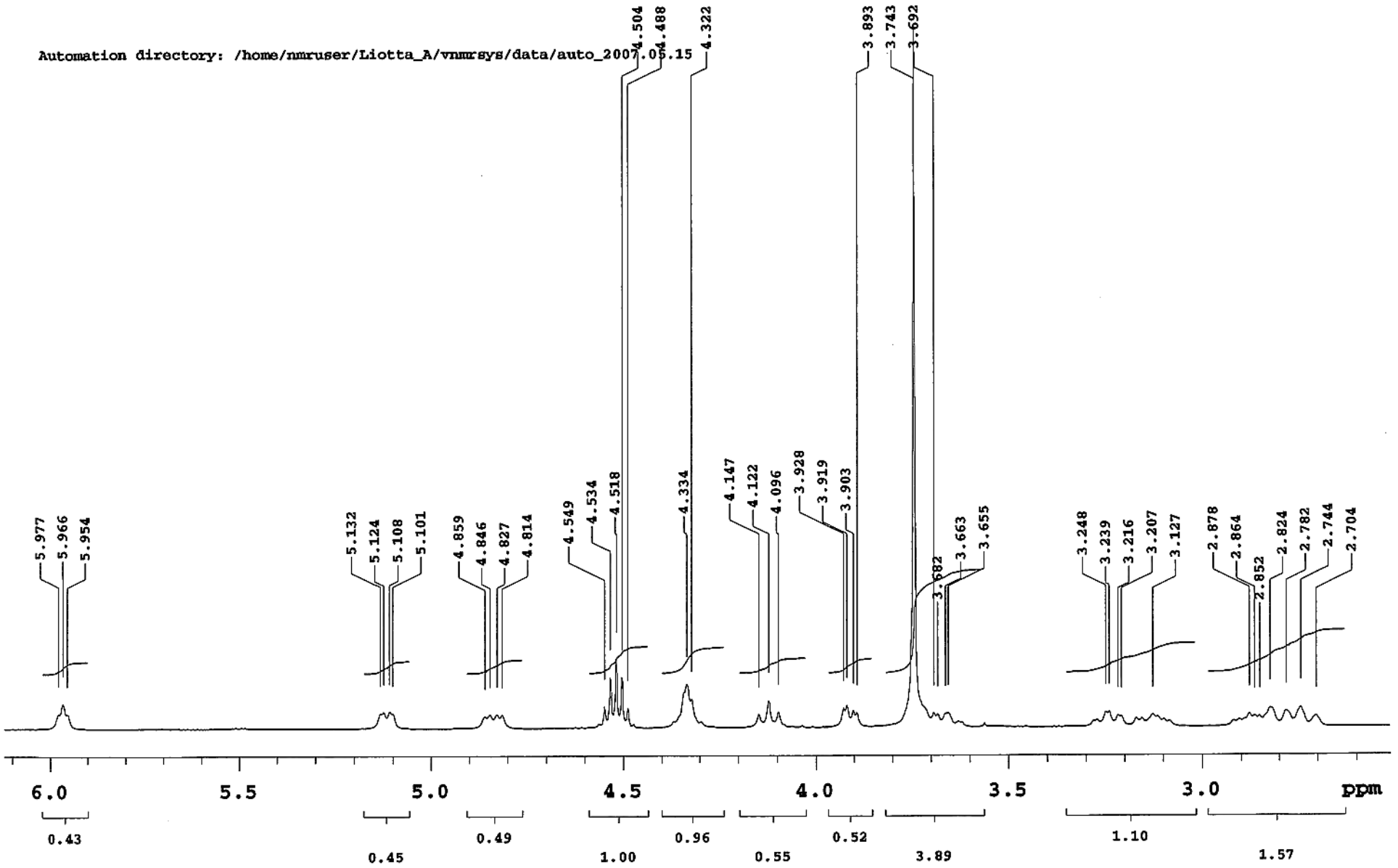


NR2D-497

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

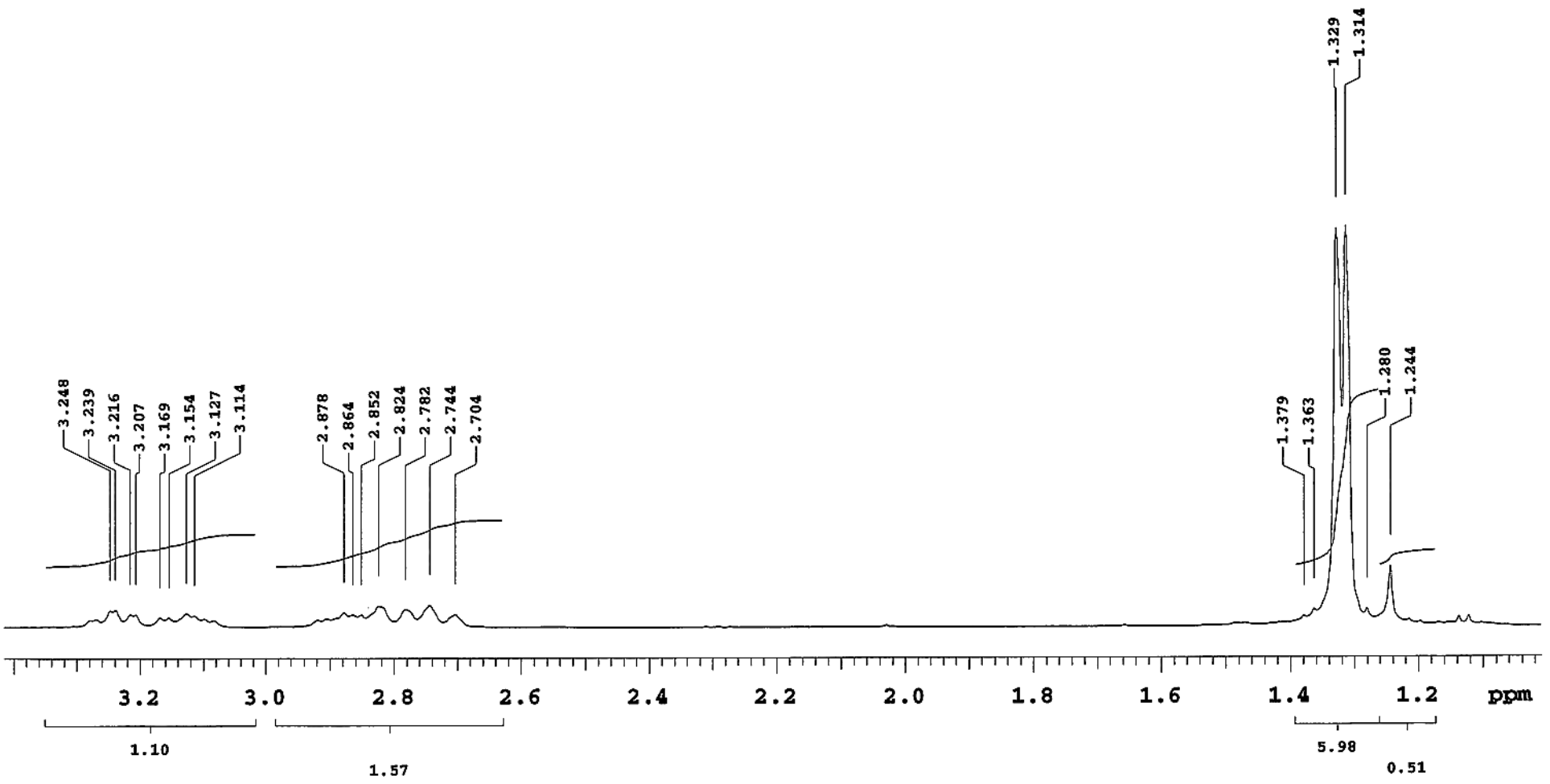


NR2D-497


Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15
4.504
4.488
4.322
3.893
3.743
3.692
5.977
5.966
5.954
5.132
5.124
5.108
5.101
4.859
4.846
4.827
4.814
4.549
4.534
4.518
4.334
4.147
4.122
4.096
3.928
3.919
3.903
3.682
3.663
3.655
3.248
3.239
3.216
3.207
3.127
2.878
2.864
2.852
2.824
2.782
2.744
2.704
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
0.43
0.45
0.49
1.00
0.96
0.55
0.52
3.89
1.10
1.57

NR2D-497

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

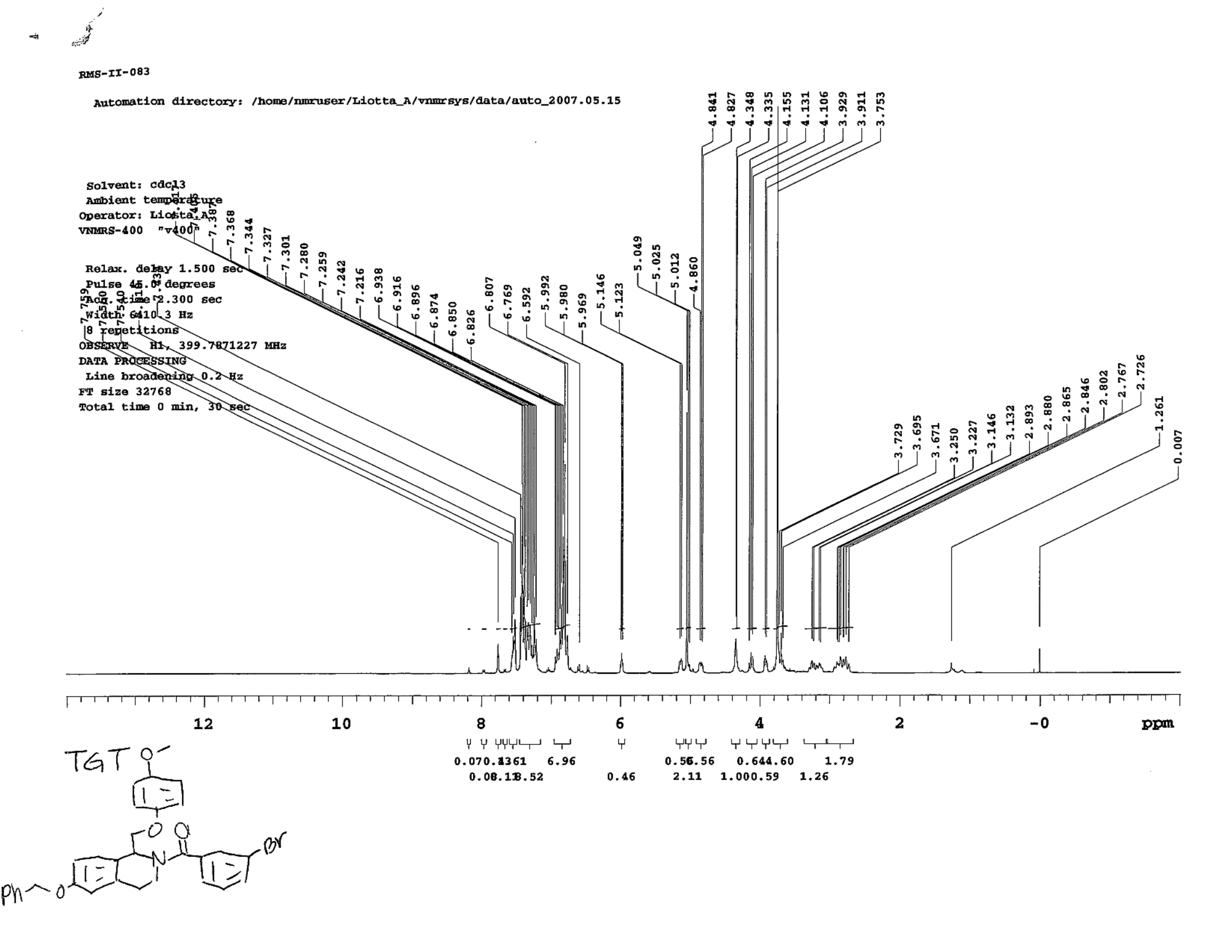


RMS-II-083

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

Solvent: cdcl3
Ambient temperature
Operator: Liotta_A
VNMRS-400 "v400"

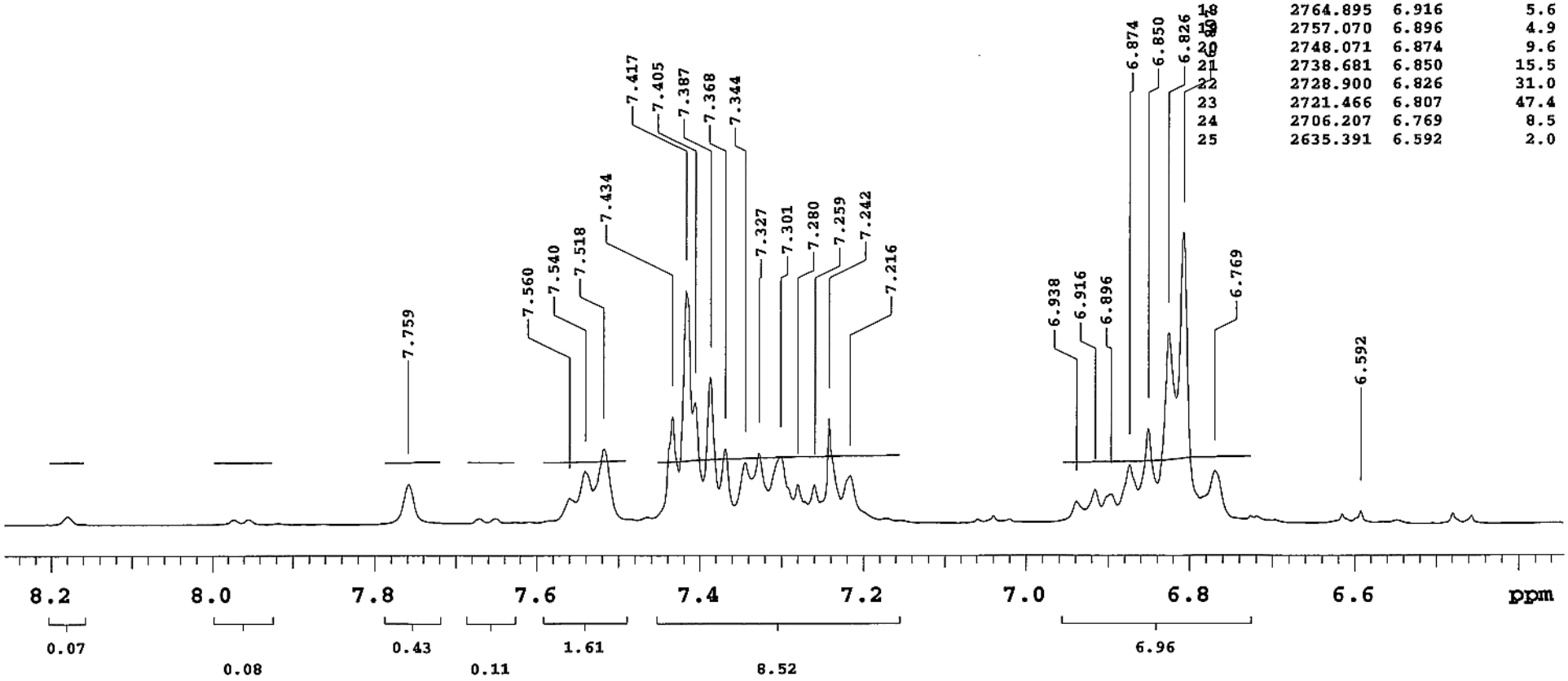
Relax. delay 1.500 sec
Pulse 45.0 degrees
Acq. time 2.300 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.7871227 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 30 sec



RMS-II-083

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

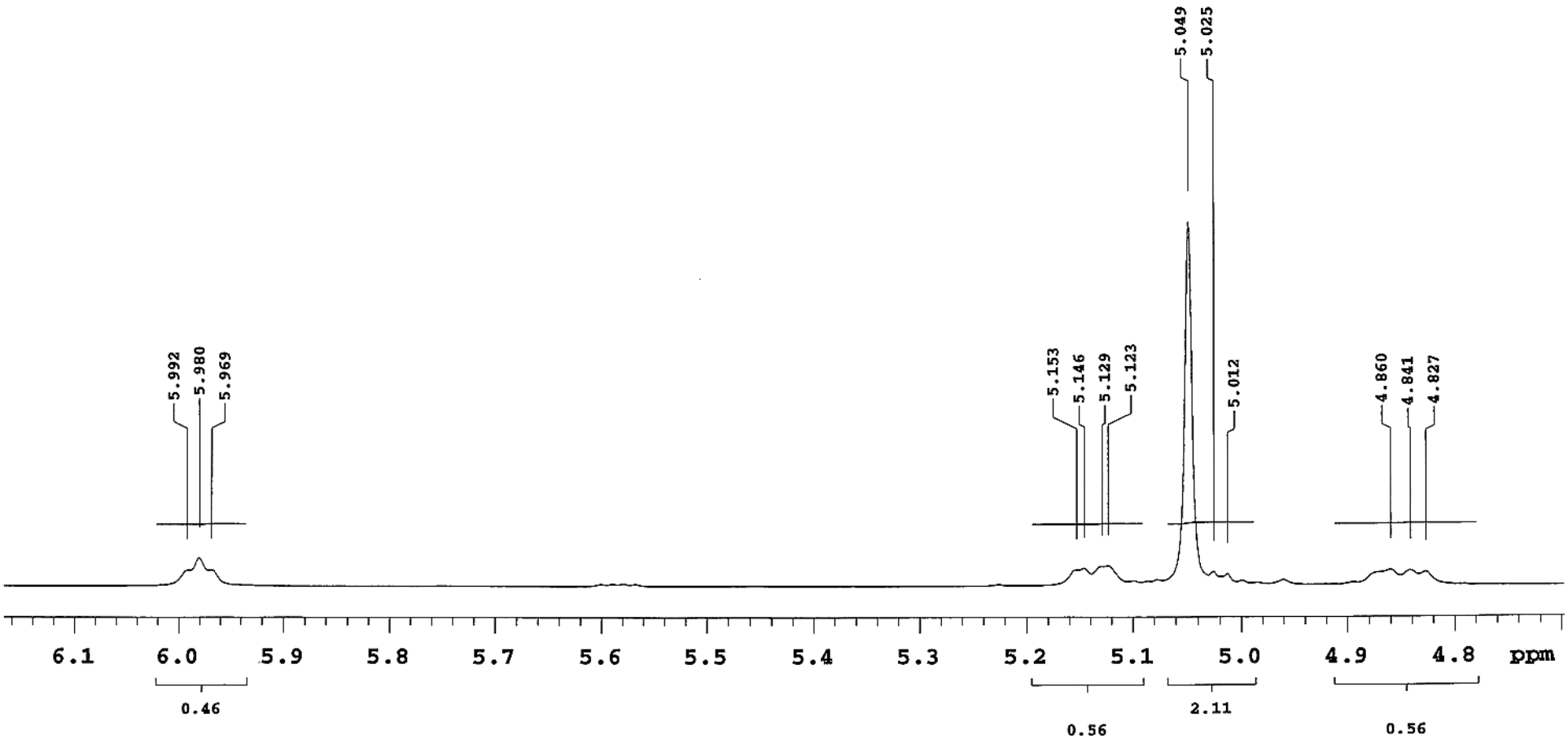
| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 3101.762 | 7.759 | 6.6 |
| 2 | 3022.338 | 7.560 | 4.1 |
| 3 | 3014.513 | 7.540 | 8.5 |
| 4 | 3005.514 | 7.518 | 12.2 |
| 5 | 2971.867 | 7.434 | 17.5 |
| 6 | 2965.215 | 7.417 | 37.9 |
| 7 | 2960.520 | 7.405 | 19.6 |
| 8 | 2953.086 | 7.387 | 23.8 |
| 9 | 2945.653 | 7.368 | 12.2 |
| 10 | 2935.871 | 7.344 | 10.1 |
| 11 | 2929.220 | 7.327 | 11.5 |
| 12 | 2918.656 | 7.301 | 10.8 |
| 13 | 2910.440 | 7.280 | 6.4 |
| 14 | 2902.224 | 7.259 | 6.3 |
| 15 | 2895.181 | 7.242 | 17.1 |
| 16 | 2885.009 | 7.216 | 7.8 |
| 17 | 2773.894 | 6.938 | 3.7 |
| 18 | 2764.895 | 6.916 | 5.6 |
| 19 | 2757.070 | 6.896 | 4.9 |
| 20 | 2748.071 | 6.874 | 9.6 |
| 21 | 2738.681 | 6.850 | 15.5 |
| 22 | 2728.900 | 6.826 | 31.0 |
| 23 | 2721.466 | 6.807 | 47.4 |
| 24 | 2706.207 | 6.769 | 8.5 |
| 25 | 2635.391 | 6.592 | 2.0 |



RMS-II-083

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/auto_2007.05.15

| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 2395.554 | 5.992 | 2.6 |
| 2 | 2390.859 | 5.980 | 4.6 |
| 3 | 2386.164 | 5.969 | 2.7 |
| 4 | 2060.252 | 5.153 | 2.6 |
| 5 | 2057.122 | 5.146 | 2.9 |
| 6 | 2050.470 | 5.129 | 3.2 |
| 7 | 2048.123 | 5.123 | 3.3 |
| 8 | 2018.388 | 5.049 | 59.3 |
| 9 | 2008.998 | 5.025 | 2.3 |
| 10 | 2003.912 | 5.012 | 1.9 |
| 11 | 1942.876 | 4.860 | 2.5 |
| 12 | 1935.443 | 4.841 | 2.5 |
| 13 | 1929.574 | 4.827 | 2.2 |



RMS-II-083

Automation directory: /home/nmruser/Liotta_A/vnmrsys/data/Auto_2007.05.15

| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 1738.252 | 4.348 | 7.8 |
| 2 | 1733.166 | 4.335 | 5.1 |
| 3 | 1661.176 | 4.155 | 2.3 |
| 4 | 1651.394 | 4.131 | 4.6 |
| 5 | 1641.613 | 4.106 | 3.8 |
| 6 | 1573.927 | 3.937 | 3.3 |
| 7 | 1570.797 | 3.929 | 3.9 |
| 8 | 1563.754 | 3.911 | 3.2 |
| 9 | 1560.233 | 3.903 | 2.8 |
| 10 | 1500.372 | 3.753 | 128.7 |
| 11 | 1490.981 | 3.729 | 6.0 |
| 12 | 1480.026 | 3.702 | 4.1 |
| 13 | 1477.288 | 3.695 | 9.1 |
| 14 | 1470.636 | 3.679 | 2.8 |
| 15 | 1467.506 | 3.671 | 3.0 |
| 16 | 1302.790 | 3.259 | 2.6 |
| 17 | 1299.268 | 3.250 | 2.8 |
| 18 | 1290.270 | 3.227 | 2.3 |
| 19 | 1286.748 | 3.219 | 2.2 |
| 20 | 1257.796 | 3.146 | 2.3 |
| 21 | 1252.318 | 3.132 | 2.0 |
| 22 | 1156.462 | 2.893 | 2.6 |
| 23 | 1151.376 | 2.880 | 2.1 |
| 24 | 1145.507 | 2.865 | 2.1 |
| 25 | 1137.682 | 2.846 | 3.6 |
| 26 | 1120.076 | 2.802 | 3.1 |
| 27 | 1106.382 | 2.767 | 3.7 |
| 28 | 1089.949 | 2.726 | 2.1 |