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Design and Synthesis of Novel Sigma Receptor Ligands Through Scaffold Minimization and Their Application Towards Targeted Drug Delivery

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Design and Synthesis of Novel Sigma Receptor Ligands Through Scaffold Minimization and Their Application Towards Targeted Drug Delivery

by

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Dedication

To Rocky, one document I hope you won’t shred.

Acknowledgements

First and foremost, I would like to thank Professor Stephen F. Martin for his guidance and support throughout my time here. I also say thanks to all of my labmates for none of this would have been possible without you. I must also thank my mom and dad for always being proud, never disappointed. And most importantly Rob, thank you. Your patience was more than I deserved, your support was everything I needed.

Abstract

Design and Synthesis of Novel Sigma Receptor Ligands Through Scaffold Minimization and Their Application Towards Targeted Drug Delivery

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The University of Texas at Austin, 2017

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Sigma receptors are a class of proteins in which both subtypes (sigma 1 and sigma 2) have been implicated in the pathology of most central nervous system disorders and various lines of cancer. A series of norbenzomorphan compounds were recently discovered to bind sigma receptors with tunable subtype selectivity depending on the substitution pattern. To further probe the structure-activity relationship of this new class of sigma ligands, a collection of isoindoline, tetrahydroisoquinoline, and benzazepine derivatives were prepared. This new set of compounds showed affinity for sigma receptors, and have been useful tools in refining the pharmacophore model of the binding sites. Additionally, these novel sigma receptor ligands were applied towards a ligand-targeted cancer therapeutic. By chemically conjugating an anticancer agent to a ligand that will selectively target cancer cells, the therapeutic index of the drug will be improved**.** Herein, a sigma receptor ligand has been chemically conjugated to the chemotherapeutic, gemcitabine, and is undergoing cellular uptake and cytotoxicity tests.

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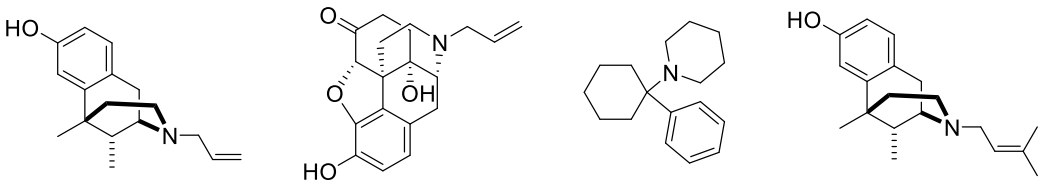
CHAPTER 1: DESIGN OF NOVEL SIGMA RECEPTOR LIGANDS THROUGH SCAFFOLD MINIMIZATION

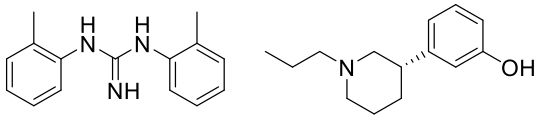
1.1 Introduction

The sigma receptors (SigRs), which once were considered enigmatic proteins, have become increasingly implicated in the pathology of many diseases, including most central nervous system (CNS) disorders as well as some lines of cancer. Martin *et al*. originally proposed sigma receptors as a subclass of the opioid receptor while studying the physiological responses of nondependent and morphine-dependent chronic spinal dog to benzomorphan derivatives. During their study, they found that the morphine-like derivative, (±)SKF-10047, displayed a unique pharmacology for an opiate. Namely, unlike most opioids, (±)SKF-10047 showed hallucinogenic effects and delirium rather than analgesic effects alone.[1] Upon resolution of (±)SKF-10047, it was shown that (+)-SKF-10047 (**1.1**) was more selective for the sigma receptors and the levorotary isomer was selective for the opioid receptors (Figure 1.1). Additionally, naloxone (**1.2**), a prototypical opioid antagonist, did not block the effects of (+)-SKF-10047 (**1.1**), thus separating the sigma receptor from the opioid receptors.[2–4] Further confusion over the identity of the sigma receptor occurred when it was found that (+)-SKF-10047 (**1.1**) binds with high affinity to the phenylcyclidine (PCP (**1.3**)) binding site of the NMDA receptor. However extensive binding assays using sigma selective ligands, like (+)-pentazocine (**1.4**), successfully differentiated the sigma receptor from the PCP site.[5] Further studies, by Hellewell and Bowen, of selective sigma ligands (like DTG (**1.5**) and (+)-3-PPP (**1.6**)) lead to the elucidation of two subtypes (Sig1R and Sig2R).[6] Using [^{3}H]-DTG to radiolabel

sigma sites, Hellewell and Bowen, exclusively labeled a protein of 25 kDa in guinea pig brain, but in PC12 cells exclusively labeled a protein of 18kDa and 21kDa. Additionally, the sigma site labeled in PC12 sites showed atypical affinity for dextrorotary benzomorphans, and was thus identified as the sigma 2 receptor.



1.1: (+)-SKF-10047 **1.2:** naloxone **1.3:** PCP **1.4:** (+)-pentazocine



1.5: DTG **1.6:** (+)-3-PPP

Figure 1.1: Sigma receptor selective ligands utilized in the identification and elucidation of the sigma 1 and sigma 2 receptors

Sig1R is a transmembrane protein that is 25.3 kDa in size and is found throughout the body with high concentrations in the liver, heart, pancreas, and the CNS with the highest densities in limbic structures and sensory regions of the brain.[7] It has been cloned from numerous mammalian sources, including human brain tissue, and has recently been characterized by X-ray crystallography.[8–10] The 223 amino acid sequence of the protein shows about 90% identity between species but shows no homology with any other known mammalian protein.[11] Sig1R is located primarily at the mitochondria associated endoplasmic reticulum (ER) membrane (MAM) where it acts as a molecular chaperone to regulate intracellular Ca^{2+} homeostasis. Upon activation or cellular stress, it acts as a molecular chaperone at the inositol 1,4,5-triphosphate receptors, where it sustains the

correct conformation to ensure proper Ca^{2+} transport between the ER and mitochondria. It is also known to translocate from the ER to the cell membrane to help regulate ion flow at K^+, Ca^{2+}, and Cl^- channels as well as neurotransmitter release.[12,13]

No endogenous ligand has been discovered for Sig1R; however, some neurosteroids, like progesterone, have been proposed as a possible candidate. Although it binds Sig1R with high nanomolar affinities, there is no evidence suggesting any physiological role played by these interactions.[14] It has also been suggested that dimethyltryptamine, may be an endogenous ligand, but studies showed that its binding affinity (K_D= 14.75 μM) is much lower than expected for an endogenous ligand.[15] Without a verified endogenous ligand, it is difficult to define an agonist or antagonist response of a ligand, and unfortunately, to date there is no operationally simple *in vitro* functional assay. However, it is generally agreed upon that agonists induce dystonia in rats, and any ligand that reverses those effects are considered antagoists.[16] Because Sig1R exhibits no known homology to other receptors, genetic manipulation also can be used in experimental systems giving a more accurate idea of functional activity. By convention, an antagonist of Sig1R are compounds that recapitulate the gene knockdown phenotype; conversely, agonists of Sig1R are compounds that recapitulate the phenotypes of receptor overexpression.[17]

Since the discovery of Sig1R, several therapeutic drugs for treatment of depression, schizophrenia, Parkinson's disease (PD), and Alzheimer's disease (AD) were identified as having affinity for Sig1R, suggesting Sig1R may be involved in pathology of CNS disorders (Figure 1.2).[18–20] It has been shown that many antipsychotics (haloperidol (**1.7**)),

selective-serotonin reuptake inhibitors (fluoxetine, (**1.8**)), and monoamine oxidase inhibitors (clorgyline, (**1.8**)) have high affinities for sigma receptors, particularly Sig1R, suggesting that Sig1R may play a role in schizophrenia and depression.[21] Although the exact role of Sig1R in schizophrenia and depression is unknown, it is generally accepted that antagonists are associated with antipsychotic effects and agonists are associated with antidepressant properties.[7] Sig1R also plays a role in neuropathic pain; studies in Sig1R knock out mice show decreased pain response in both a formalin test and a capsaicin hypersensitization assay.[22] It is believed that Sig1R activation plays a role in brain plasticity during reinforcement and addictive processes. In studies on both cocaine and alcohol addiction, administration of a Sig1R antagonist showed a reduction in the drug-induced conditioned place preference.[23,24] The possible therapeutic benefit of targeting Sig1R for treating neurodegenerative disorders, like AD, PD, Amyotrophic Lateral Sclerosis (ALS), and Huntington's Disease (HD), is also being investigated.[25–28] Sig1R has been shown modulate many of the mechanisms associated with neuronal degradation such as excitotoxicity, Ca^{2+} dysregulation, oxidative stress, ER and mitochondria dysfunction.[17,29] Interestingly, Sig1R selective agonists as well as non-selective Sig1R agonists like donepezil (**1.10**) (a clinically approved AChE inhibitor for treatment of AD) have shown to block Aβ peptide toxicity, a hallmark of the pathology of AD, and attenuate learning and memory deficits in mice models.[25,30]

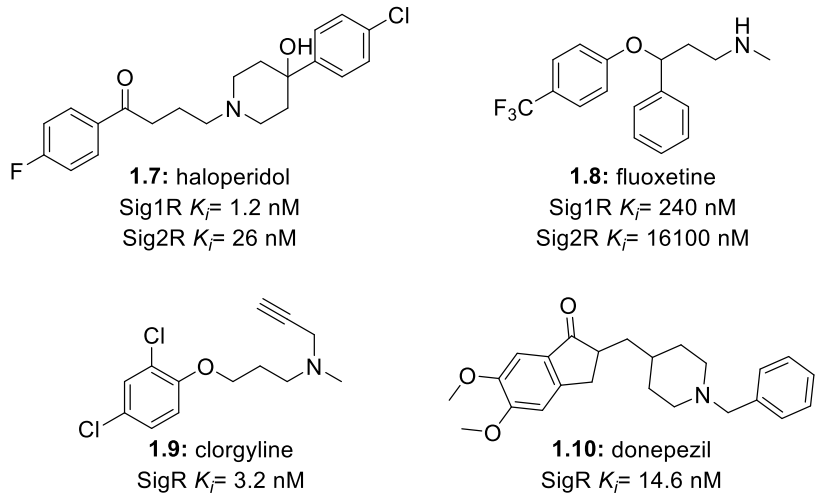


Figure 1.2: Representative neuroleptics shown to bind sigma receptors

Due to the vast therapeutic potential of the sigma receptors, much work has gone into developing sigma receptor subtype selective ligands.[31] Figure 1.3 illustrates a sample of some of the most potent and selective Sig1R ligands, which display significant structural diversity.[32–35] Features that other Sig1R ligands have that are not shown in the table include a series of piperazine sulfonamide moieties, substituted cyclopropanes and mannose-morphan derived structures.[31] Despite the wide array of Sig1R ligands, there is a proposed pharmacophore model for Sig1R. Glennon and coworkers used the SAR of N-substituted phenyl-2aminopropanes to develop the pharmacophore model.[36] They proposed that the binding site requires a proton donor that is in a region that tolerates only small groups. There is a primary hydrophobic site that is 6-10 Å away from the proton donor site, and the highest affinity was observed when this hydrophobic group was 8.3 Å away. Lastly, they proposed a secondary hydrophobic site 2.5-3.9 Å away from the proton donor site that

tolerates bulky substituents. Most potent and selective Sig1R ligands that have been identified seem to have the features proposed in this model.

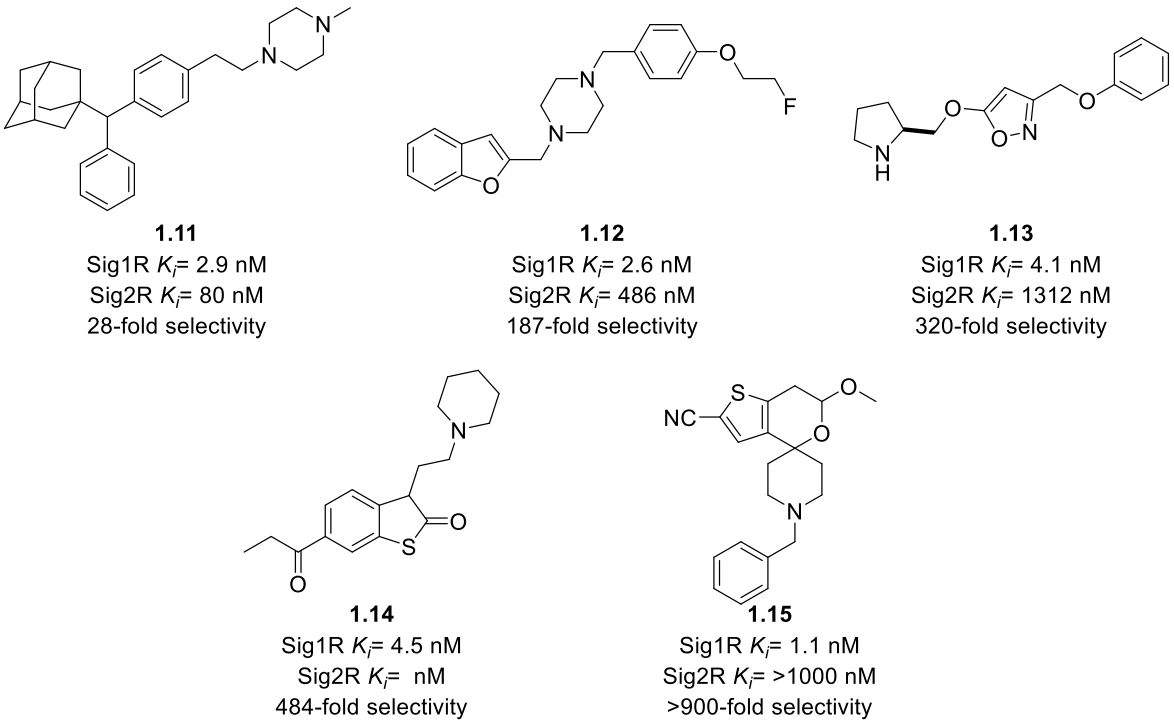


Figure 1.3: Sig1R selective ligands from several structural classes

Recently, Kruse and coworkers reported the crystal structure of the sigma 1 receptor.[10] The structure was obtained in complex with two chemically divergent ligands, antagonist, PD144418 (**1.16**) and agonist, 4-IBP (**1.17**) (Figure 1.4**)**. The Sig1R exists as a timer with a single transmembrane domain. The binding pocket features primarily hydrophobic residues with Glu172 responsible for the major ionic interaction. Both structures show very little deviation in the receptor conformation despite the structural differences in the bound ligands. The major interaction was a charge-charge interaction with Glu172 and the basic nitrogen atom of the ligand. A secondary interaction between

Tyr103 and Glu172 is also important for binding. The hydrogen bond between the two residues stabilizes Glu172; in a mutant without Tyr103, a significant loss in binding affinity is observed. Additionally, a second acidic residue, Asp126, which forms a hydrogen bond to Glu172 is also required for binding. Now that the crystal structure of Sig1R is available, structure-based design, rather than pharmacophore based design, can be used towards the development of Sig1R ligands.

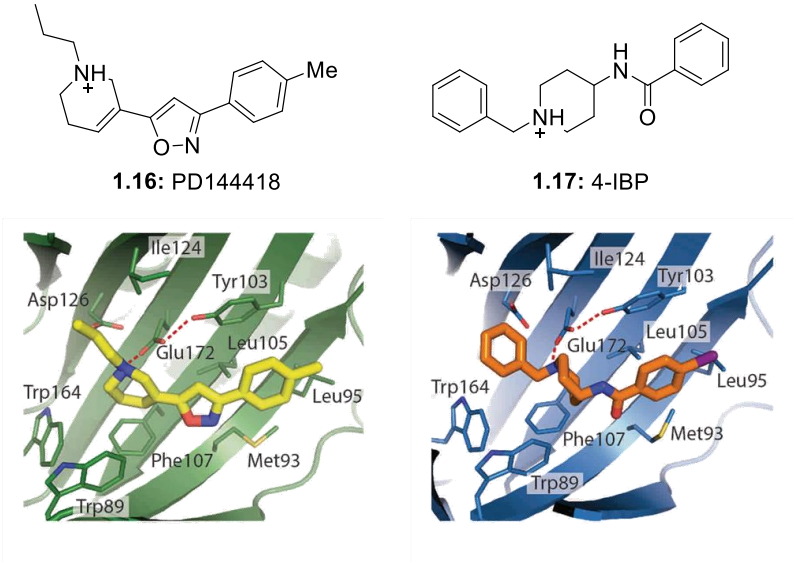
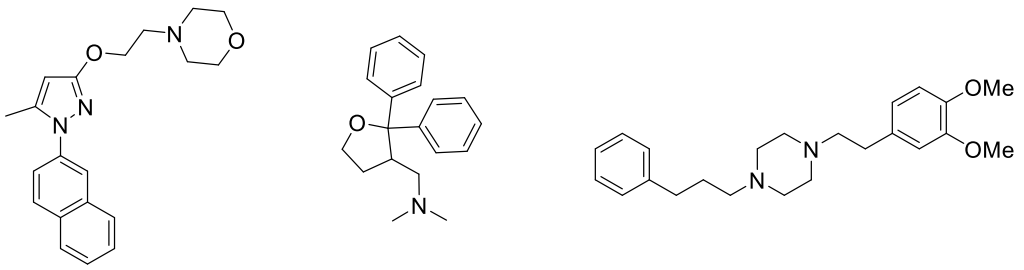


Figure 1.4: X-ray crystal structure of PD144418 and 4-IBP bound to Sig1R

The extensive structure-activity relationship (SAR) investigations of the Sig1R ligands have resulted in several compounds progressing to clinical trials (Figure 1.5). S1RA (**1.18**) is a selective Sig1R antagonists (K_i = 17.0 ± 7.0 nM) that is currently in phase II clinical trials for the treatment of neuropathic pain.[37] ANAVEX2-73 (**1.19**) binds both Sig1R and muscarinic acetylcholine receptors with low micromolar binding affinities. It is showing great therapeutic potential for the treatment of AD and is currently pending the

phase II clinical trials.[38] Lastly, cutamesine (**1.20**) is currently in phase II clinical trials for the treatment of ischemic stroke. Early *in vivo* assays showed that cutamesine (**1.20**) inhibited hypoxia/hypoglycemia induced neurotoxicity.[39] It is also suggested that cutamesine (**1.20**) may play a role in inhibition of motor neuron degeneration and symptom progression in ALS.[27]



1.18: S1RA **1.19:** ANAVEX2-73 **1.20:** cutamesine

Figure 1.5: Compounds targeting Sig1R currently undergoing clinical trials

Despite its discovery in the early 1990's, little is known about the identity of Sig2R because, for decades, it has evaded cloning, sequencing, and crystallization. From photoaffinity labeling experiments, it is known to have a molecular weight of ~21 kDa protein and is found in some periphery tissues such as the liver and kidneys as well as the brain, but to a lesser extent than Sig1R. Sig2R is found in a high abundance on lipid rafts, and while exact mechanisms are unknown it seems to play major roles in intracellular Ca^{2+} release, and cellular proliferation and survival.[9,40] It is overexpressed in many cancer cell lines, where activation of Sig2R promotes cell death pathways.[40] In an attempt to determine the molecular identify of Sig2R, Mach and coworkers conducted several photoaffinity, proteomic, and binding studies, and their findings suggested that Sig2R is part of the same

bio-molecular complex as progesterone receptor membrane component 1 (PGRMC1).[41] However, subsequent reports suggested that Sig2R and PGRMC1 (a well characterized heme binding protein) are two distinct molecular entities.[42–44] These reports have shown that overexpression of PGRMC1 does not increase Sig2R binding and that knockdown or knockout experiments do not decrease Sig2R binding of a variety of different Sig2R ligands and fluorescent Sig2R ligands.

Recently, Kruse *et al*., in collaboration with the Martin group, have identified the gene that codes for the Sig2R.[45] Using chemical biology techniques, the Sig2R was identified as transmembrane protein 97 (TMEM97). Of the proteins identified from affinity purification, only TMEM97 overexpressing cells resulted in a significant increase in [^{3}H]-DTG binding. Furthermore, the binding affinities measured for both Sig2R and TMEM97 selective ligands were identical when measured in MCF-7 cells (classical Sig2R cell line) or *sf9* insect membranes expressing TMEM97, and knockdown of TMEM97 decreased binding of Sig2R ligands. TMEM97 is an ER-resident transmembrane protein, and like Sig2R, the molecular function of TMEM97 is poorly understood. It is involved in cholesterol homeostasis and is overexpressed in several lines of cancer where RNA silencing of TMEM97 can inhibit gastric cancer cell growth, both of which correlate to roles in which Sig2R is implicated.[46–49] The identification of Sig2R as TMEM97 has opened the door to study this protein and begin to understand its mechanistic roles in the body through modern molecular biology techniques rather than pharmacological studies.

Though the molecular identity of Sig2R remained elusive for so long, significant progress has been made towards understanding the cellular roles Sig2R plays through the

use of Sig2R selective ligands. Unfortunately, without knowing the molecular identify or the endogenous ligands, a uniformly-accepted definition of functional activity has not yet been adopted. In addition, there currently exists no efficient functional assay. To date, the best functional assay for Sig2R activity was developed by Mach and coworkers, and uses cell viability assays and caspase-3 activity to determine agonists and antagonists.[50] Using the cell viability assay, agonists are defined if the cytotoxicity is >90% relative to siramesine (**1.24**) and antagonists are defined if the cytotoxicity is <10%. Anything ligand with cytotoxicity between 90-10% is defined as a partial agonist. Results from the caspase-3 assay were comparable to the cell viability assay, but were not used for defining agonism/antagonism.

Given the presence of Sig2R in the brain and its binding affinity for neuroleptics, it is unsurprising that Sig2R has become increasingly implicated in the pathology of CNS disorders.[51] The potent Sig2R selective ligand, siramesine (**1.24)**, exhibits an anxiolytic and anti-depressant effect. In rats, siramesine reversed shock-induced drinking suppression, a common parameter to measure depression and anxiety.[52,53] It should be noted that siramesine retains high affinity for Sig1R, so it is unclear whether the effects observed are solely due to activity at Sig2R. There is also evidence showing that activation of Sig2R may play a role is modulating the activity of dopaminergic neurons.[54] When treated with DTG, a dose dependent rise in dopamine was observed in the rat nucleus accumbens shell, an effect attenuated in a dose-dependent manner by Sig2R selective antagonists but not Sig1R antagonists. This suggests that Sig2R may play a role in addictive behavior through dopamine modulation, and Sig2R antagonists may offer promise in

developing addiction therapies.[55] Dysregulated Ca^{2+} levels in the cells plays a major role in neurodegenerative pathways like excitotoxicity (Ca^{2+} overload), ER stress, and mitochondria dysfunction. It has been suggested that Sig2R plays a role in modulating Ca^{2+} homeostasis, suggesting it may be a possible target for neuroprotective agent. DTG (**1.5**) has shown cytoprotective effects against excitotoxic mechanisms, although the exact mechanism is unknown. Additionally, Sig2R agonists have been reported promote caspase-dependent apoptosis at the mitochondria, which provides a logical link that antagonists may be neuroprotective.[29] Recent work by Cognition Therapeutics has shown that Sig2R/PGRMC1 plays a role in the pathology of AD. These studies showed that Aβ oligomers bind to Sig2R/PGRMC1, thereby inducing changes that lead to synapse loss and neuronal death; Sig2R antagonists reduced synapse loss and cognitive deficits caused by Aβ oligomers *in vitro*.[56] Their compound, CT1812, is currently undergoing Phase 1 clinical trials, marking the first compound targeting Sig2R for AD to make it to the clinic.

To expand our understanding of the biological roles Sig2R plays, the development of highly selective Sig2R ligands is essential. Like Sig1R, Sig2R also binds a range of ligands from many different structural classes, including tetrahydroisoquinolines, tropanes, cyclohexyl piperazines, indoles, benzylidenes, benzamides, and more.[40,51] In general, Sig2R ligands can be divided into two very different classes: flexible and constrained. Generally, flexible ligands have two regions of functionality connected by a flexible chain of varying length. By contrast, constrained ligands contain a ridged amine containing bicycle from which functionality is appended. Because there is less structural information about the Sig2R, development of Sig2R selective ligands has not been straightforward.

More often than not, Sig2R ligands have been identified from projects targeting other receptors such as acetylcholine receptors, serotonin receptors, dopamine receptors, etc. Despite the challenges for developing Sig2R selective ligands, many highly potent and selective Sig2R ligands have been developed (Figure 1.6).[57–60] In particular, Mach and coworkers have developed many highly potent benzamide and napthamide analogs that have impressive selectivity, which they are utilizing for cancer imaging, therapy, and targeted delivery of cancer therapies.[61–64]

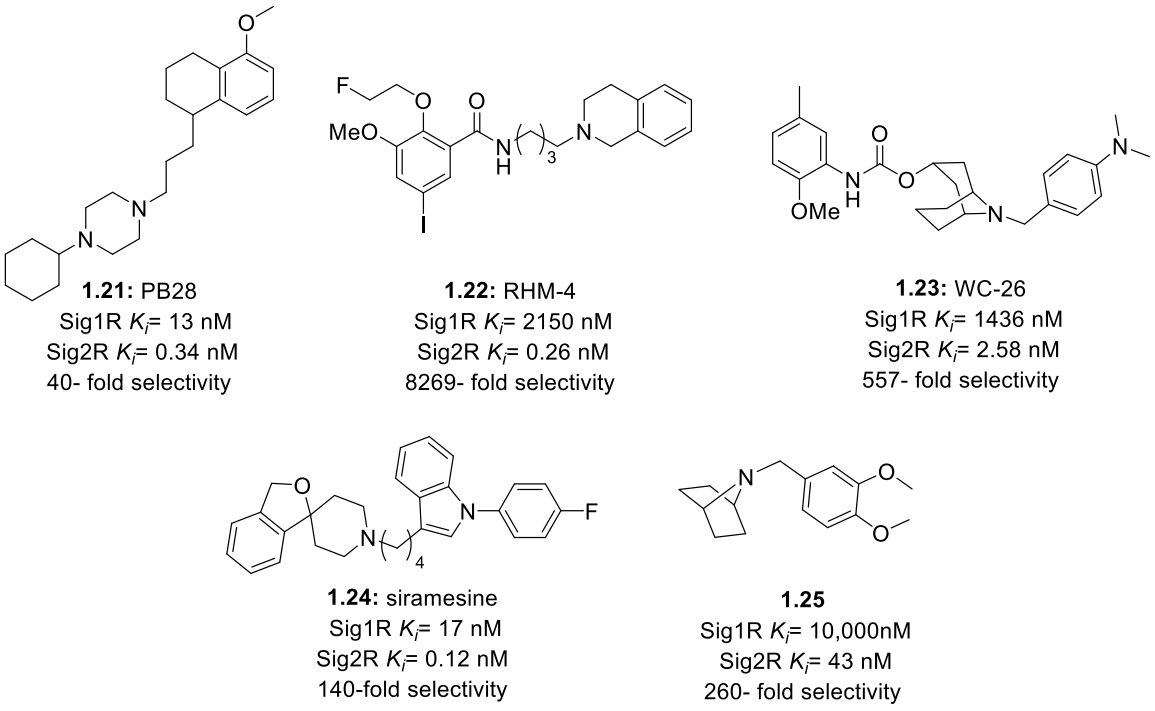


Figure 1.6: Sig2R selective ligands from several structural classes

Due to the diversity of Sig2R ligands and the lack of structural information, the binding requirements for designing selective Sig2R ligands remain unclear. There have been several proposed pharmacophore models for the Sig2R ligands; however, these were

based on a limited set of Sig2R ligands.[65–67] Recently, Rhoads and coworkers proposed a more comprehensive pharmacophore model based on 50 Sig2R ligands from seven different structural classes.[68] These seven structural classes were used to generate a series of pharmacophore models that were used to represent different receptor binding modes. Through clustering of these binding modes, they were able to produce a robust model of the Sig2R binding site. The analysis suggests that the Sig2R binding pocket is 21 Å long, 11 Å wide, and 10 Å deep. It includes two large hydrophobic regions, four negative charged /hydrogen bond acceptors (NG/HBA), and at least two hydrogen donor groups, which they say contribute little to Sig2R binding. The two hydrophobic groups are separated by ~9 Å, and the first hydrophobic region is necessary for Sig2R binding. One of the NG/HBA groups is adjacent to the second hydrophobic group, another is in the center of the binding pocket, and the remaining NG/HBA groups are positioned around the pocket. In general, it seems that ligands with high affinity for Sig2R contain a basic nitrogen atom and at least one hydrophobic group. Any additional nitrogen atoms or hydrophobic groups are not essential but do enhance binding. It should be noted that there was a lot of deviation within the different binding modes of which they based their comprehensive model, and therefore the conclusions may still not be an accurate view of the binding pocket.

In addition to cloning Sig2R, Kruse and coworkers ran a series of experiments to give insight into the binding pocket of Sig2R/TMEM97 (Figure 1.7).[45] To map the ligand binding site, a series of mutagenesis experiments were run on all Glu and Asp residues, hypothesizing that these acidic residues interact with the basic amine found in all Sig2R ligands. Like Sig1R, two acidic residues, Asp29 and Asp56, are required for ligand

binding. Based on their predicted structural model, these two residues are close in proximity and may interact directly via a hydrogen bond network with the basic amine like the Sig1R binding pocket. Despite the recent identification of Sig2R, it remains important to continue to develop Sig2R selective ligands in hopes of furthering the understanding of what drives selectivity for one subtype over another.

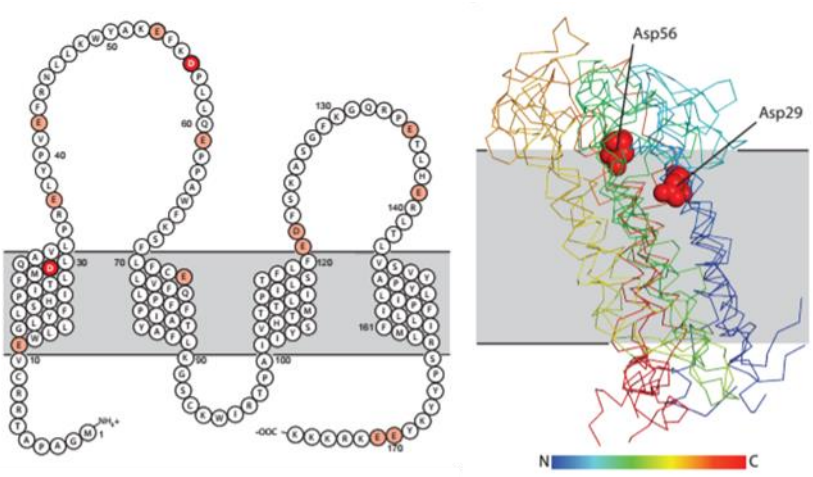


Figure 1.7: Structural analysis of TMEM97 and mapping of the ligand binding site

1.2 Martin Group Work

As part of an effort towards identifying novel bioactive compounds, the Martin group developed a platform for the rapid synthesis of drug-like scaffolds with functional handles for rapid diversification.[69] In this multicomponent assembly process, aryl aldehydes and primary amines were combined to form a diverse array of imines, which could undergo reactions with a variety of acylating reagents and nucleophiles to give highly functionalized intermediates in a single operation. Subsequent cyclization reactions to

increase skeletal complexity led to the generation of a variety of heterocyclic scaffolds (Figure 1.8).

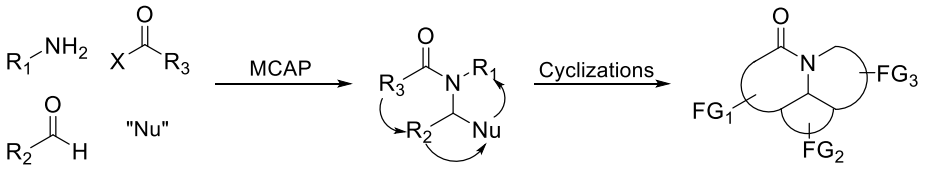
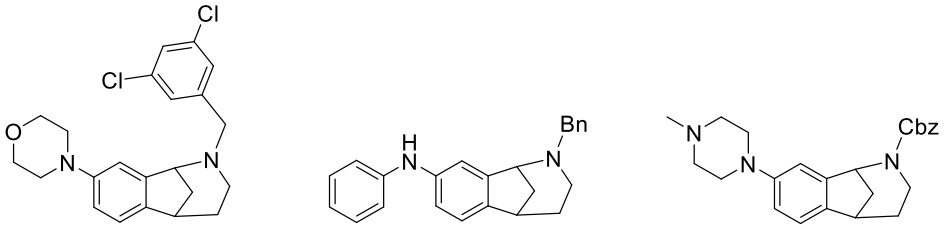


Figure 1.8: General overview of the Martin group multicomponent assembly process

From this effort, a diverse library of compounds was synthesized and screened against a comprehensive panel of CNS proteins, including 45 GPCRs, ion channels, and neurotransmitter transporters. This screen identified a subclass of substituted norbenzomorphans that displayed high affinity for the sigma receptors, as well as selectivity between sigma subtypes.[70] Interestingly, these compounds are structurally distinct from all other identified sigma ligands. Due to the possible involvement of Sig2R in neurodegenerative disorders, it was of interest to see if any of the initial compounds could be used as a pharmacological tool for studying Sig2R modulation in AD.[71]



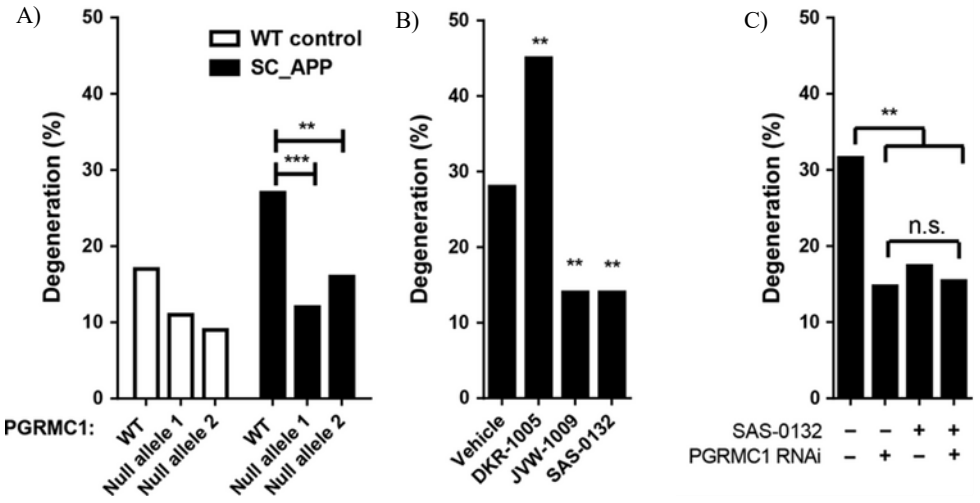
1.26: DKR-1005
Sig1R K_i= 2224 ± 416 nM
Sig2R K_i= 157 ± 49 nM

1.27: JVW-1009
Sig1R K_i= 96 ± 2 nM
Sig2R K_i= 70 ± 9 nM

1.28: SAS-0132
Sig1R K_i= 90 ± 20 nM
Sig2R K_i= 841 ± 395 nM

Figure 1.9: Several sigma receptor hits from initial norbenzomorphan library of compounds

Several Sig2R-selective norbenzomorphans (Figure 1.9) were advanced into an *in vivo* AD model using transgenic *C. elegans* with a single copy of human amyloid precursor protein (APP). These worms have neurons which are easily visualized and begin to display symptoms of neurodegeneration of cholinergic neurons in 5-7 days making this an ideal platform for assaying neurodegeneration. While these compounds were identified as Sig2R ligands, we found that in *C. elegans*, these compounds modulate a PGRMC1-related pathway through PGRMC1 ortholog, *vem*1 (Figure 1.10). Worms treated with compound JVW-1009 (**1.27**) and SAS-0132 (**1.28**) for five days showed decreased neurodegeneration on day five compared to the vehicle-treated group. Therefore, these two compounds were putatively assigned as Sig2R antagonists. Conversely, worms treated with DKR-1005 (**1.26**) showed increased neurodegeneration on day five compared to vehicle and were thus putatively assigned as Sig2R agonists.

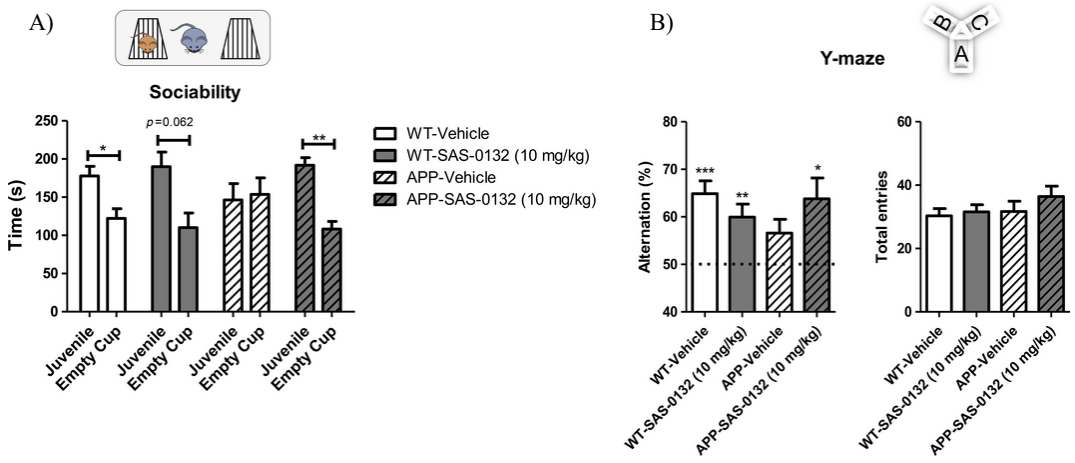


A) *Transgenic worm and PCRMC1/vem-1 knockout:* C. elegans vem-1 knockout exhibits reduced neurodegeneration relative to WT. B) *Transgenic worm treated with Sig2R ligands:* DKR-1005 show increased neurodegeneration whereas JVW-1009 and SAS-0132 show reduced neurodegeneration compared to control. C) *Transgenic worm and PGRMC1/vem-1 RNAi:* Neurodegeneration in APP strain treated with PGRMC1-directed RNAi and/or SAS0132 shows that SAS-0132 proceeds via a PGRMC1-mediated pathway.

Figure 1.10: Effects of norbenzomorphan compounds on neurodegeneration in *C. elegans*

It was also of interest to study how modulation of Sig2R would affect cognition in transgenic APP mice. SAS-0132 (**1.28**) emerged as an attractive target for these *in vivo* tests because not only was it identified as an antagonist but it exhibits 9-fold selectivity for Sig2R and has low off-target affinity for other CNS receptors. In several behavioral and learning tests, SAS-0132 (**1.28**) showed cognitive enhancement in sociability, spatial memory, and long-term memory (Figure 1.11). In a chronic dose-response study, SAS-0132 (**1.28**) improves AD-related deficits in the social discrimination test and improves spatial memory in the Y-maze test. In a chronic dose-response study, SAS-0132 (**1.28**) improves spatial and long-term memory in both APP and wildtype mice in the Morris water maze. All tests were performed a day after treatment, suggesting that the effects are due to chronic treatment with SAS-0132 (**1.28**) and not acute effects because SAS-0132 (**1.28**) is

cleared from the brain in 24 h. Additionally, SAS-0132 (**1.28**) has good bioavailability, was well tolerated and brain penetrant.



A) *Social discrimination test:* APP mice treated with SAS-0132 (10 mg/kg) showed normal sociability unlike vehicle treated APP mice which showed lack of sociability. B) *Y-maze test:* APP mice treated with vehicle showed impared spontaneous alternation performace and APP mice treated with SAS-0132 (10 mg/kg) showed spontaneous alternation behavior at a level comparable to WT mice

Figure 1.11: Effects of SAS-0132 on cognitive ability of APP mice in a chronic dose study

With lead compounds exhibiting therapeutic potential in *in vivo* models of AD, a SAR campaign was launched to optimize the binding affinity and selectivity of our compouds.[72] SAR analysis of our library of norbenzomorphans (Figure 1.12) shows that subtype selectivity can be tuned depending on the placement of the aryl subsituent.[72] This finding is unique to our norbenzomorphan compounds; no other known classes of sigma ligands show a reversal in subtype selectivity by making a small structural change to the ligand. When the C(8) position of the norbenzomorphan is substituted with a piperazine moiety, high levels of Sig2R selectivity are achieved. Subtype selectivity for Sig2R can also be tuned depending on the nature of the substitution of the piperazine. While the *N*-

alkyl groups on the piperazine have small changes in the Sig2R affinity, the nature of the alkyl group can cause pronounced changes in the Sig1R binding affinity. In addition, Sig2R selectivity significantly spikes when a polar group is on the piperazine nitrogen atom and R_1 is a benzyl carbamate. While some of the most selective Sig2R ligands were achieved when R_1= -Cbz and R_2= piperazine, Sig2R selectivity could be improved 2-3 fold when R_1 was a sulfonamide. Additionally, when C(8) was subsituted with a morpholine moiety, high affinity and selectivity for Sig2R was achieved as long as there was another ionizable nitrogen in the molecule (i.e. R^1= 3,5-dichlorobenzyl). Conversely, high affinity and selectivity for Sig1R was achieved when C(7) was substituted. While R_3 tolerated similar alkyl piperazine substituents as R_2, the best selectivity obtained for Sig1R was for compounds with aryl or morpholine moieties at R_3 and benzyl groups at R^1.

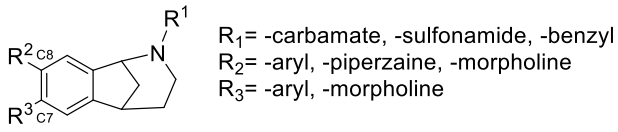


Figure 1.12: Chemical space explored off the norbenzomorphan scaffold

To further understand the SAR of this class of compounds, we were interested in probing the effects of scaffold minimization. Scaffold hopping strategies often simplify the synthetic strategy and lead to improved binding and pharmacokinetic properties.[73] By systematically reducing the structural complexity of the carbon framework of the norbenzomorphan, a new library of isoindoline (n = 1), tetrahydroisoquinoline (n = 2), and tetrahydro-2-benzazepine (n = 3) derivatives were envisioned. (Figure 1.13). By removing the bridging methylene group, a feature that conformationally locks the norbenzomorphan

scaffold, we introduce flexibility in the molecule and the ability to vary the ring size. Both increased flexibility and ring contraction change the spatial orientation of the substituents on the nitrogen atom. This may allow access to a more favorable binding mode within the binding pocket, as it is thought that the Sig2R may be able to adopt a variety of acceptable binding conformations due to the structural diversity of high affinity ligands. These new derivatives were modeled after the most potent and selective norbenzomorphan derivatives. Holding the substitution patterns constant while changing the carbon framework of the compounds will help determine the necessary features of the norbenzomorphan scaffold for sigma receptor binding.

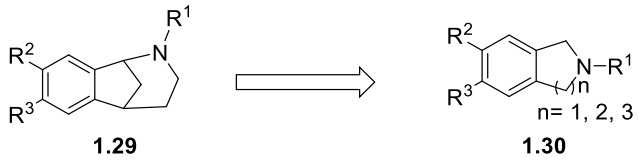
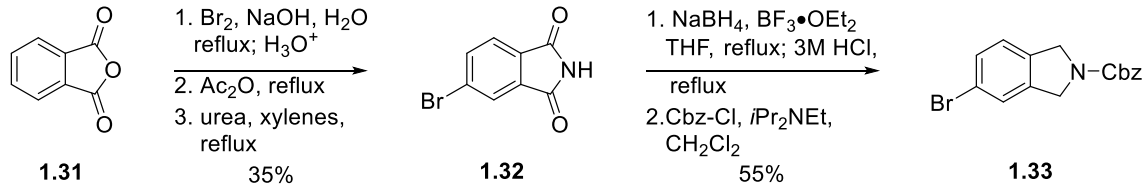


Figure 1.13: Removal of bridging methylene to access new classes of derivatives

1.3 Results and Discussion

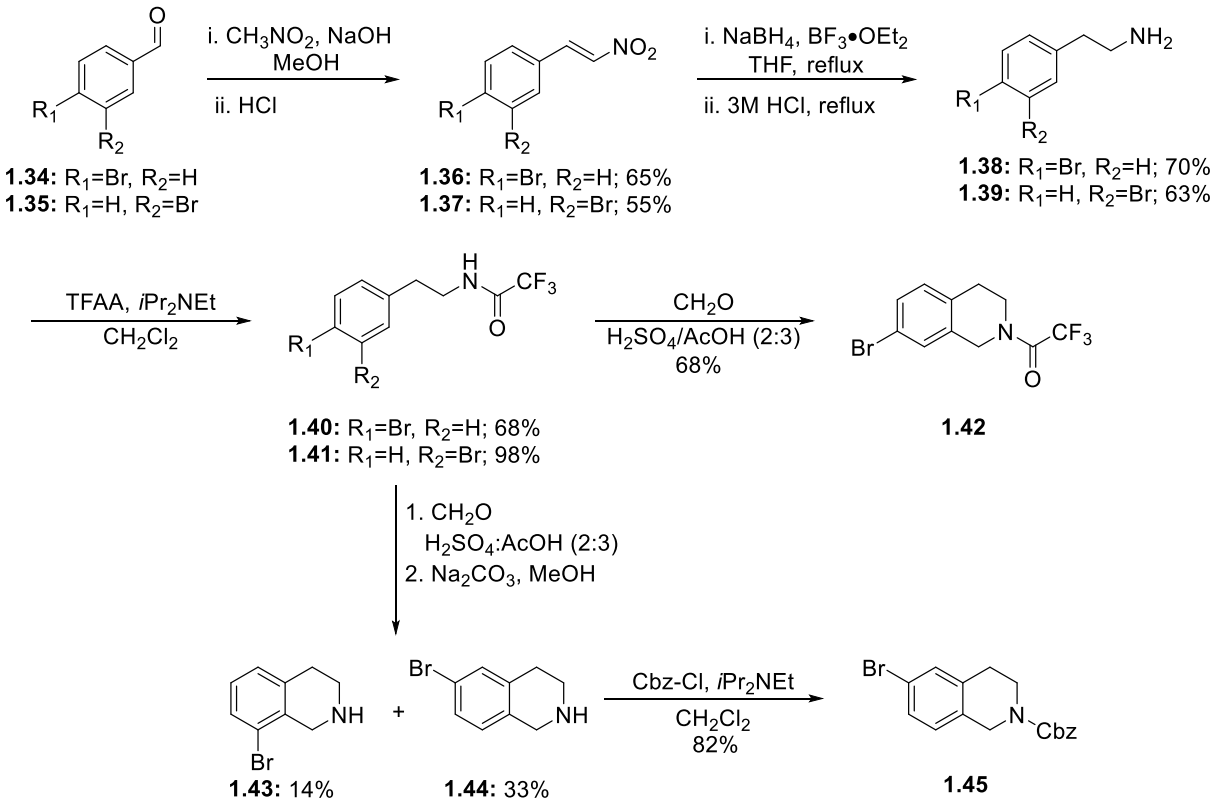
With the goal of creating a novel library of compounds of general type **1.30** with varying ring size, we first sought to synthesize the requite scaffolds with suitable functional handles for derivatization. The synthetic approach for the preparation of the isoindoline scaffold **1.33** is outlined in Scheme 1.1. Bromination of phthalic anhydride (**1.31)** proceeded in 36% yield, and subsequent imide formation afforded **1.32** in 98% yield over two-steps.[74,75] Borane reduction followed by -Cbz protection provided the isoindoline scaffold, **1.31,** in 55% yield over two steps.[76]



1.31 **1.32** **1.33**

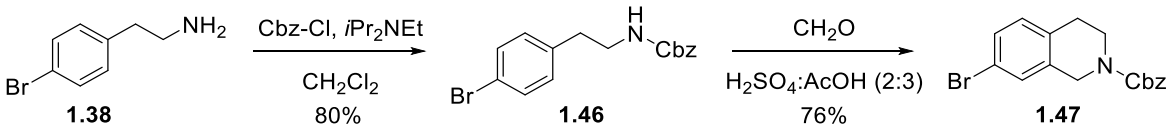
Scheme 1.1: Synthetic route to access isoindoline scaffold

We envisioned the tetrahydroisoquinoline scaffold could arise from a Pictet-Spengler reaction of bromo-phenethylamine and paraformaldehyde. The necessary phenethylamines were synthesized via Henry reactions[77] of **1.34** and **1.35**, respectively (Scheme 1.2). Borane reduction of the resulting nitrostyrenes **1.36** and **1.37** afforded amines **1.38** and **1.39** in 70% and 63% yields, respectively.[78] Because both **1.38** and **1.39** are electron poor arenes, attempts to cyclize via a Pictet-Spengler reaction using paraformaldehyde were unsuccessful. Acylation of the amine to generate the highly reactive *N*-acyliminium ion intermediate is a known strategy to overcome poor reactivity in Pictet-Spengler reactions.[79] Therefore, trifluoroacetamide **1.40** was synthesized and subjected to cyclization with paraformaldehyde to give **1.42** in 68% yield. Pictet-Spengler cyclization of **1.41** afforded an inseparable mixture (1:2) of regioisomers **1.43** and **1.44**. Fortunately, removal of the -TFA group with Na_2CO_3 in MeOH allowed for chromatographic separation of the two isomeric amines. Protection of **1.44** proceeded smoothly to give **1.45** in 82% yield (Scheme 1.2).



Scheme 1.2: Tetrahydroisoquinoline scaffold synthesis

As previously mentioned, benzyl carbamate derivatives displayed high Sig2R affinity and selectivity. therefore, it was of interest to prepare the benzyl carbamate **1.46** and subject it to Pictet-Spengler cyclization conditions. **1.46** was prepared via -Cbz protection of **1.38** (Scheme 1.3). Initial attempts under the same conditions used to synthesize **1.43**, resulted in hydrolysis of the benzyl carbamate. After some effort, it was found that cooling the acid mixture prior to addition of paraformaldehyde and **1.46**, and gave tetrahydroisoquinoline **1.47** in 76% yield. Unfortunately, Pictet-Spengler cyclization of benzyl (3-bromophenethyl) carbamate gave an inseparable mixture of regioisomers.



Scheme 1.3: Acyl Pictet-Spengler reaction with benzyl carbamate

With isoindoline **1.33** and tetrahydroisoquinolines **1.45** and **1.47** in hand, we set our sights on the synthesis of the benzazepine scaffolds. This series is the most important data point in our investigation on scaffold simplification, as it directly probes the effects of the bridging methylene group in the norbenzomorphan scaffold. The benzazepine scaffold is also currently being investigated for its sigma receptor binding properties by other groups. Wunsch and coworkers have synthesized a library of functionalized tetrahydro-2-benzazepines and -3-benzazepines (Figure 1.14).[80–82] Derivatives of compound **1.48** showed high affinity for Sig1R; in particular, when R_1= $CH_2CHC(CH_3)_2$ and R_2= Bn the K_i for Sig1R was 3.6 nM with 71-fold selectivity.[80] Conversely derivatives of **1.49** and 1.**50** only had micromolar affinity for both receptors.[81] Their work has shown that benzazepine scaffold has an intrinsic affinity for the sigma receptors to some degree. This knowledge, coupled with our finding on regiochemical selectivity may allow us to synthesize high affinity sigma ligands with tunable selectivity.

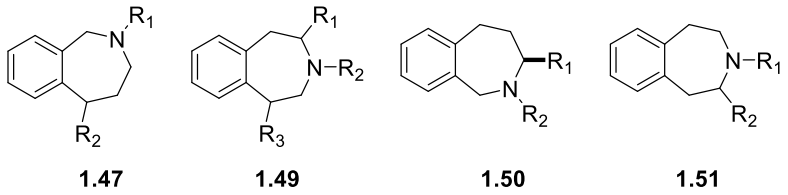
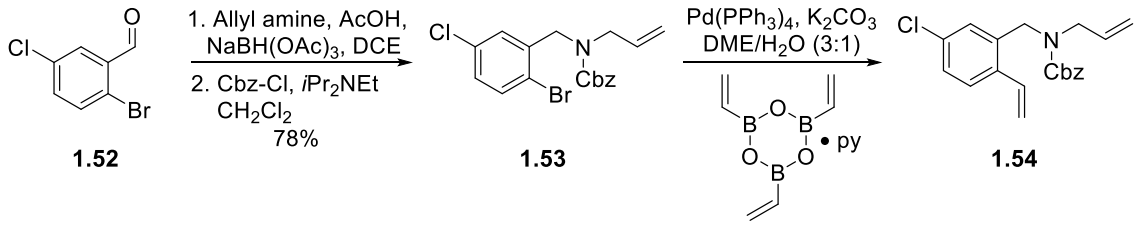


Figure 1.14: Representative benzazepine derivatives with high binding affinity for SigRs designed by Wunsch *et al.*

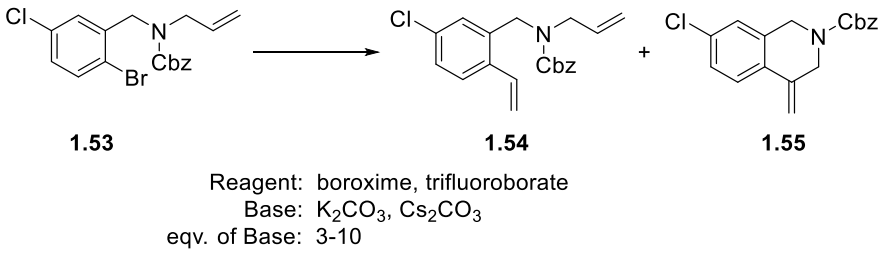
Initial attempts to access the benzazepine scaffold began with a reductive amination of **1.52** with allylamine and $NaBH(OAc)_3$, followed by treatment with Cbz-Cl and Hünig's base in CH_2Cl_2 to give **1.53** in 78% over two steps (Scheme 1.4). A Suzuki cross coupling reaction with the corresponding boroxime then gave **1.54** in 79% yield on small scale.



Scheme 1.4: Second generation synthesis towards benzazepine scaffold

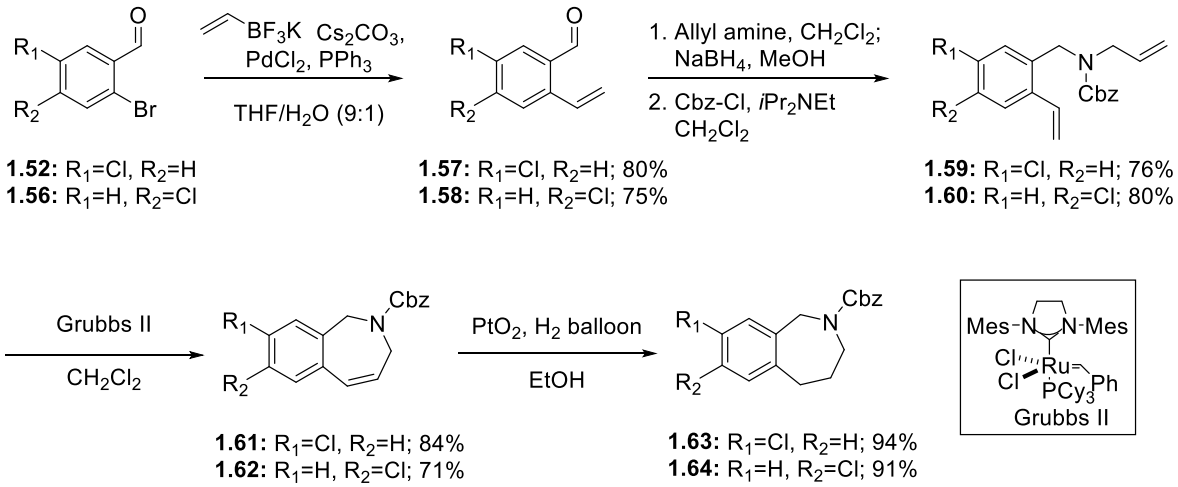
However, upon scale up, this result was not reproducible; instead significant amount of a byproduct was formed. This by-product was the result of a competing intramolecular Heck reaction to give **1.55**. In an attempt to suppress the competing Heck reaction a screen of conditions was performed that included: changing the boron reagent to a more nucleophilic boron reagent[83], changing the base, and changing the amount of base to increase the basicity of the solution which is known to accelerate Suzuki reaction (Equation 1.1). Although the product ratio was improved from 1.2:1 of **1.54** and **1.55** to 3:1 **1.54** and **1.55**,

it became clear that the Suzuki cross-coupling step needed to be performed before the reductive amination.



1.53 **1.54** **1.55** (1.1)

The Suzuki cross-coupling of **1.52** and **1.56** proceeded in 80% yield to give **1.57** and in 75% yield to give **1.58** (Scheme 1.5). Initially, the reductive amination between the vinyl benzaldehyde and allyl amine with $NaBH(OAc)_3$ as the reducing agent followed by -Cbz protection gave **1.59** in only 35% yield over two-steps. Unfortunately, $NaBH(OAc)_3$ was not a strong enough reducing agent for this substrate; after 24 h there was still incomplete reduction of the imine attributing to the low yield of **1.59**. It was well established in literature that with these vinyl benzaldehydes, preformation of the imine followed by reduction with $NaBH_4$ will give the desired amine in high yield.[84] Hence, treating the **1.57** and **1.58** with allyl amine in CH_2Cl_2 with $MgSO_4$ followed by reduction with $NaBH_4$ and -Cbz protection gave **1.59** and **1.60** 76% yield and 80% yield respectively, over two-steps. Ring closing metathesis of **1.59** and **1.60** with Grubbs 2nd generation catalyst gave **1.61** in 84% yield and **1.62** in 71% yield. Subsequent hydrogenation of **1.61** and **1.62** with Adam's catalyst gave the desired benzazepine scaffolds **1.63** and **1.64** in 94% and 91% yields, respectively.



1.52: R_1=Cl, R_2=H
1.56: R_1=H, R_2=Cl

1.57: R_1=Cl, R_2=H; 80%
1.58: R_1=H, R_2=Cl; 75%

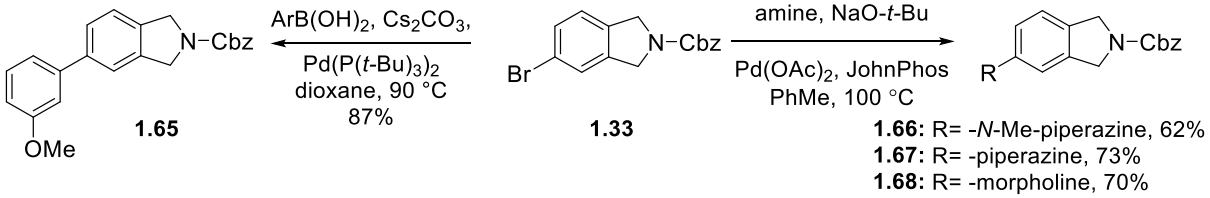
1.59: R_1=Cl, R_2=H; 76%
1.60: R_1=H, R_2=Cl; 80%

1.61: R_1=Cl, R_2=H; 84%
1.62: R_1=H, R_2=Cl; 71%

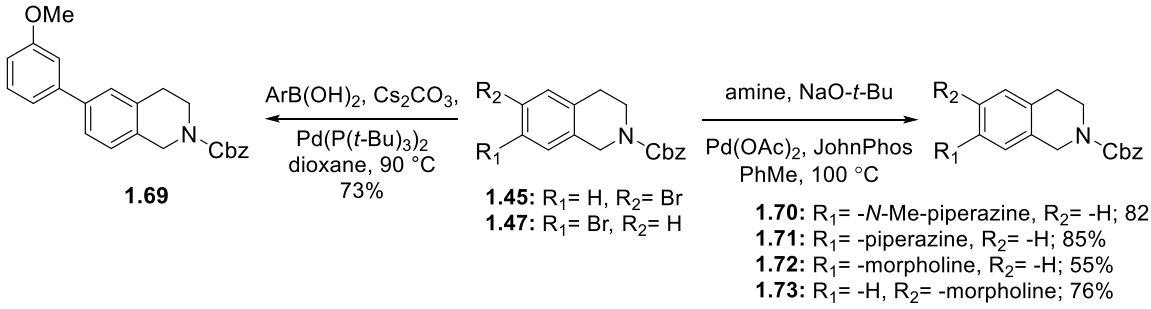
1.63: R_1=Cl, R_2=H; 94%
1.64: R_1=H, R_2=Cl; 91%

Scheme 1.5: Preparation of benzazepine scaffolds

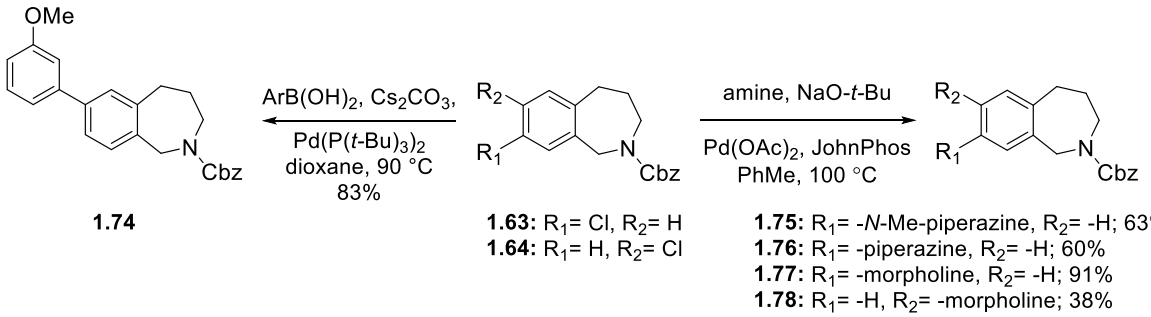
With all three scaffolds in hand, a diverse library of compounds was synthesized. The desired biaryl compounds were synthesized via Suzuki cross-coupling reactions of **1.33**, **1.45**, and **1.64** to give **1.65**, **1.69**, and **1.74**. Buchwald-Hartwig aminations were performed on **1.31**, **1.45**, **1.47**, **1.63**, and **1.64** using a premixed solution of JohnPhos and $Pd(OAc)_2$, with a slight excess of amine to give the desired aniline derivatives **1.66-1.68**, **1.70-1.73**, and **1.75-1.78** (Scheme 1.6-1.8). For piperazine derivatives at least five equivalents of the amine were used to prevent coupling at both nitrogen atoms of piperazine.



Scheme 1.6: Suzuki and Buchwald-Hartwig cross-coupling reactions on isoindoline scaffold



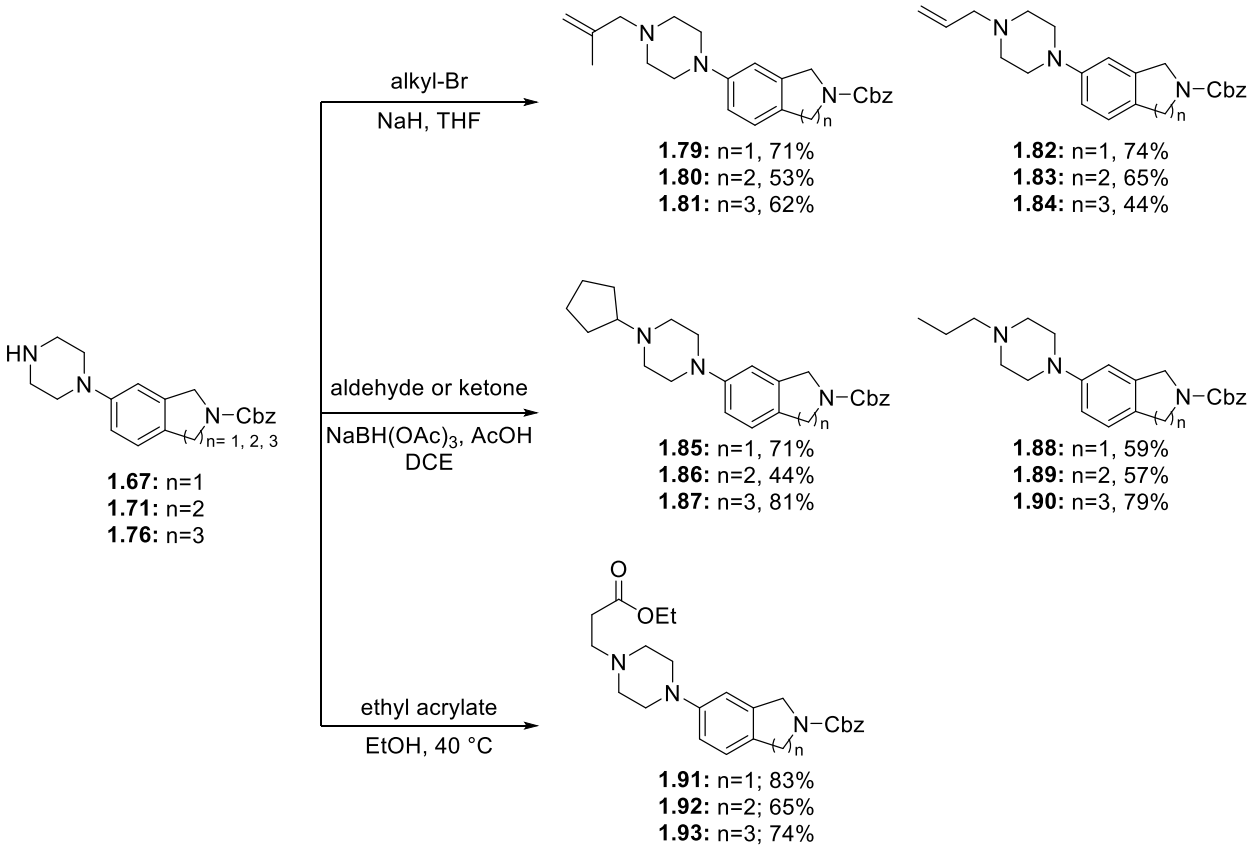
Scheme 1.7: Suzuki and Buchwald-Hartwig cross-coupling reactions on tetrahydroisoquinoline scaffold



Scheme 1.8: Suzuki and Buchwald-Hartwig cross-coupling reactions on benzazepine scaffold

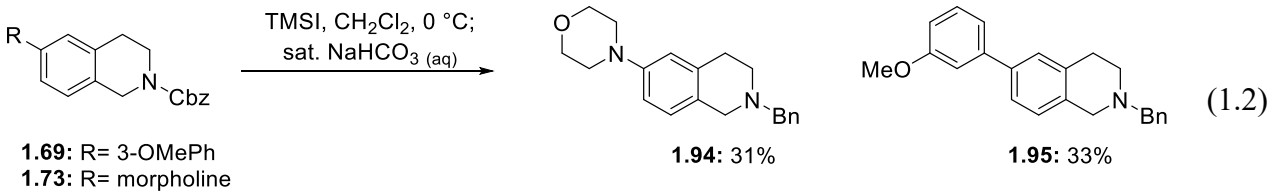
With the necessary intermediates **1.65-1.78** in hand, an initial library based on 1 norbenzomorphan compounds was prepared. These model compounds were carefully

selected to represent different classes of compounds explored around the norbenzomorphan SAR study. A variety of functionalized piperazine, benzyl carbamate norbenzomorphan model derivatives that showed varying degrees of Sig2R affinity and selectivity were selected and analogous substitution patterns were prepared in all three scaffold sizes (Scheme 1.9). Allylamines **1.79-1.84** were prepared through standard alkylation conditions from intermediates **1.67**, **1.71**, and **1.76**. Reductive amination of **1.67**, **1.71**, and **1.76**. with a variety of aldehydes or ketones in the presence of $NaBH(OAc)_3$ gave **1.85-1.90**. Finally, **1.67**, **1.71**, and **1.76**. was treated with ethyl acrylate to give **1.91-1.93**.



Scheme 1.9: Piperazine derivatization reactions

To probe whether the effects of scaffold swapping was more general, compounds, based on both Sig2R and Sig1R selective norbenzomorphan compounds, containing benzylamines or sulfonamides substitution patterns were prepared on the three scaffolds. Treatment of tetrahydroisoquinolines **1.69** or **1.73** with TMSI, followed by a basic workup gave benzylamines **1.94** and **1.95** in ~30% yield (Equation 1.2). Benzylamine derivatives **1.96-1.102** were prepared via reductive amination in a two-step procedure (Equation 1.3 and 1.4).

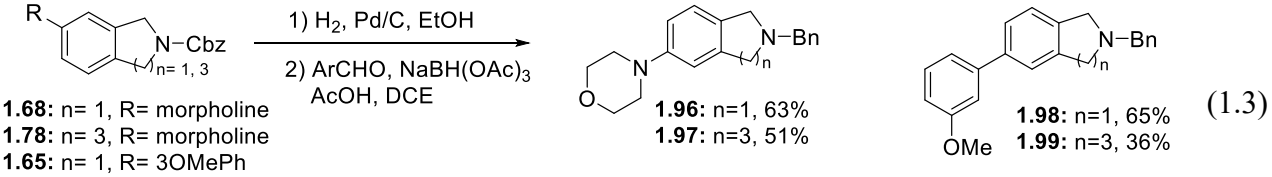


1.69: R= 3-OMePh
1.73: R= morpholine

1.94: 31%

1.95: 33%

(1.2)

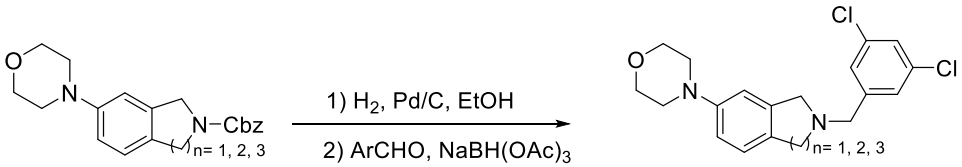


1.68: n= 1, R= morpholine
1.78: n= 3, R= morpholine
1.65: n= 1, R= 3OMePh
1.74: n= 3, R= 3OMePh

1.96: n=1, 63%
1.97: n=3, 51%

1.98: n=1, 65%
1.99: n=3, 36%

(1.3)



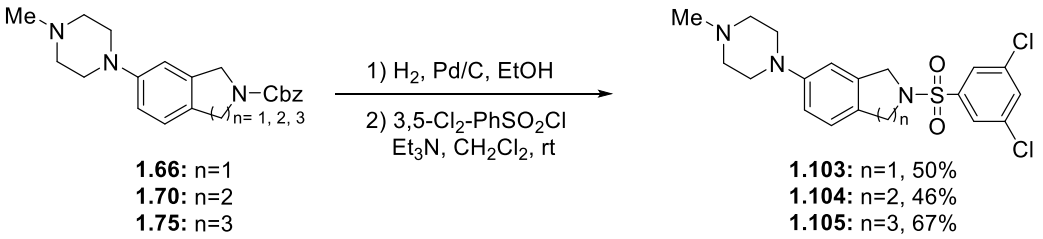
1.68: n=1
1.72: n=2
1.77: n=3

1.100: n=1, 25%
1.101: n=2, 35%
1.102: n=3, 42%

(1.4)

Sulfonamide derivatives **1.103-1.108** were prepared in a two-step procedure beginning with -Cbz deprotection followed by sulfonylation with the appropriate sulfonyl chloride (Equation 1.5). For allyl derivatives, the -Cbz group was removed via treatment

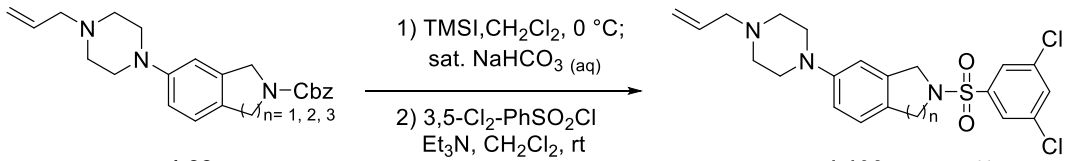
with TMSI followed by an acidic work-up to prevent reduction of the allyl group under hydrogenation conditions (Equation 1.6).



1.66: n=1
1.70: n=2
1.75: n=3

1.103: n=1, 50%
1.104: n=2, 46%
1.105: n=3, 67%

(1.5)



1.82: n=1
1.83: n=2
1.84: n=3

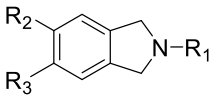
1.106: n=1, 53%
1.107: n=2, 45%
1.108: n=3, 50%

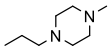
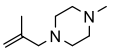
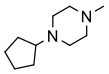
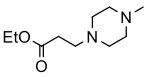
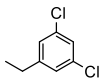
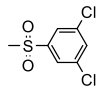
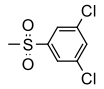
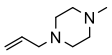
(1.6)

This new library of compounds containing all three scaffold classes have been screened by the Psychoactive Drug Screening Program (PDSP) at The University of North Carolina at Chapel Hill against a panel of CNS receptors. The sigma receptor binding data for the isoindoline compounds are presented in Table 1.1. Compounds **1.96** and **1.98**, which were based on Sig1R norbenzomorphans, maintained high affinity (K_i= 5.9 nM and 4.1 nM respectively) and moderate selectivity for Sig1R. The isoindoline scaffold overlays the substituents similarly to the norbenzomorphan, so the retention of Sig1R affinity is unsurprising. The remaining derivatives in the isoindoline series were designed based on Sig2R norbenzomorphan ligands and suffered from a significant decrease in affinity and selectivity for Sig2R. The isoindoline scaffold is symmetrical about the nitrogen atom, eliminating the possibility of regioisomers. The loss of subtype selectivity in this series

suggests that the regiochemistry of the substituent on the arene is important for Sig2R selectivity.

Table 1.1: Binding affinity data for isoindoline series



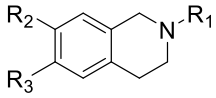
No.	R_1	R_2	R_3	K_i (nM)[a] Sig1R	K_i (nM)[a] Sig2R	Sig1R / Sig2R
1.96	-Bn	-H		5.9 (16.5)	166 (562)	0.04 (0.03)
1.98	-Bn	-H		4.1 (11.1)	65 (121)	0.06 (0.09)
1.66	-Cbz		-H	250 (841)	553 (86)	0.5 (6.9)
1.88	-Cbz		-H	19 (230)	77 (5.1)	0.3 (33)
1.79	-Cbz		-H	92 (413)	153 (17.5)	0.6 (24)
1.85	-Cbz		-H	44 (130)	8.2 (3.6)	5.4 (36)
1.91	-Cbz		-H	352 (6659)	134 (24)	2.6 (280)
1.100			-H	114 (2224)	89 (157)	1.3 (14)
1.103			-H	205 (582)	95 (67)	2.2 (8.7)
1.106[b]			-H	23	25	0.9

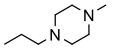
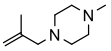
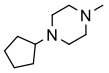
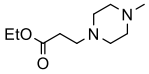
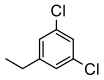
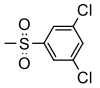
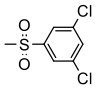
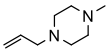
K_i values reported from a single experiment. [a] Norbenzomorphan data in parentheses under data. [b]no analagous norbenzomorphan compound

The tetrahydroisoquinoline series reintroduces the potential for regioisomers, and the binding data for these compounds are presented in Table 1.2. Unsurprisingly, the regiochemistry of the tetrahydroisoquinoline predictably lead to preferential Sig1R or Sig2R binding, consistent with the selectivity observed with the analogous

norbenzomorphan compounds. While the tetrahydroisoquinoline series restored some of Sig2R selectivity that was lost with the isoindoline scaffold, a significant decrease in selectivity between the two subtypes was observed for all derivatives in this series when compared to the analogous norbenzomorphan. Notably, compound **1.86** shows single digit nanomolar affinity for Sig2R (K_i= 2.7 nM) with 19-fold selectivity. Despite the decrease in selectivity, compounds **1.94** and **1.95** have comparable affinity for Sig1R as the norbenzomorphan (K_i= 1.7 nM and 4.9 nM respectively). When switching to the tetrahydroisoquinoline scaffold from the norbenzomorphan scaffold, the nitrogen atom shifts in space as a consequence of ring contraction and diminished conformation constraint. This change in spatial arrangement of the substituents going from the norbenzomorphan to the tetrahydroisoquinoline could potentially explain the observed decrease in selectivity. These data suggest that the orientation of the substituents in these classes of compounds is important for high Sig2R subtype selectivity.

Table 1.2: Binding affinity data for tetrahydroisoquinoline series



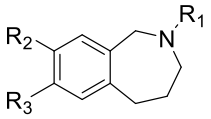
No.	R_1	R_2	R_3	K_i (nM)[a] Sig1R	K_i (nM)[a] Sig2R	Sig1R / Sig2R
1.94	-Bn	-H		1.7 (16.5)	33 (562)	0.05 (0.03)
1.95	-Bn	-H		4.9 (11.1)	57 (121)	0.09 (0.09)
1.70	-Cbz		-H	314 (841)	129 (86)	2.4 (9.4)
1.89	-Cbz		-H	85 (230)	50 (5.1)	1.7 (33)
1.80	-Cbz		-H	245 (413)	25 (17.5)	9.8 (24)
1.86	-Cbz		-H	52 (130)	2.7 (3.6)	19.3 (36)
1.92	-Cbz		-H	407 (6659)	198 (24)	2.1 (280)
1.101			-H	703 (2224)	86 (157)	8.2 (14)
1.104			-H	123 (582)	27 (67)	4.6 (8.7)
1.107[b]			-H	54	17	3.2

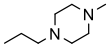
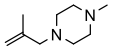
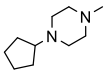
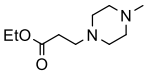
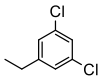
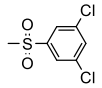
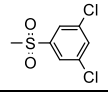
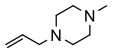
K_i values reported from a single experiment. [a] Norbenzomorphan data in parentheses under data. [b]no analagous norbenzomorphan compound

The binding affinity data for the series of benzazepine compounds is presented in Table 1.3 and gives insight into the importance of the bridging methylene group, the feature which locks the norbenzomorphan in its rigid conformation. Unsurprisingly, compounds **1.97** and **1.99**, which were modeled after Sig1R compounds, show preferential binding to Sig1R over Sig2R, like the corresponding isoindoline and tetrahydroisoquinoline derivatives. Although the remaining compounds (modeled after Sig2R selective

norbenzomorphan ligands) have comparable Sig2R binding affinity as the corresponding tetrahydroisoquinolines, these compounds also have a more favorable interaction with Sig1R. This led to a series of compounds having little subtype selectivity, like the isoindoline series. These data suggest that the conformational rigidity imparted by the bridging methylene of the norbenzomorphan scaffold preorganizes the substituents in an appropriate conformation that is necessary for high affinity and selective Sig2R binding.

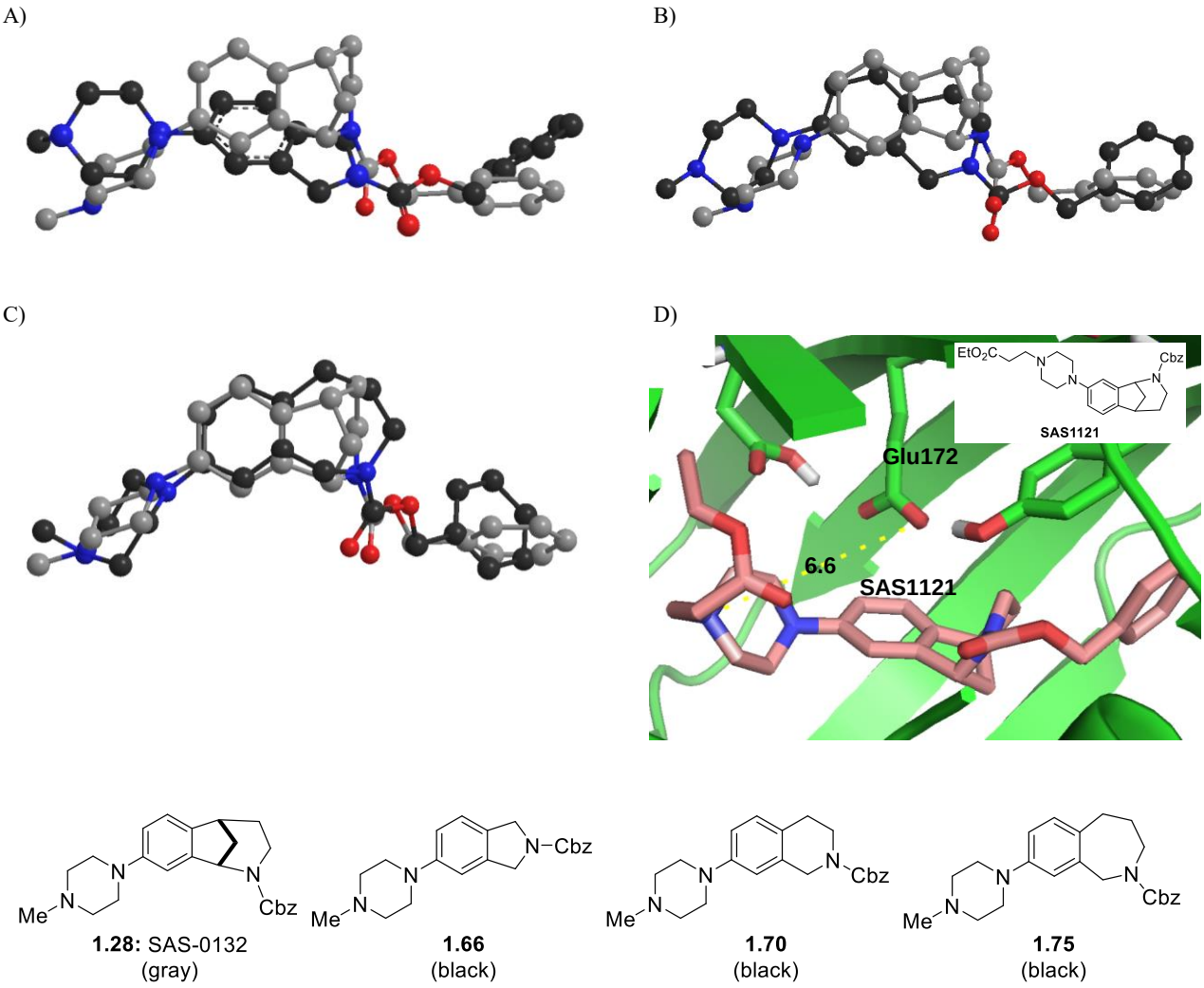
Table 1.3: Binding affinity data for benzazepine series



No.	R_1	R_2	R_3	K_i (nM)[a] Sig1R	K_i (nM)[a] Sig2R	Sig1R / Sig2R
1.97	-Bn	-H		6.1 (16.5)	81 (562)	0.08 (0.03)
1.99	-Bn	-H		21 (11.1)	440 (121)	0.05 (0.09)
1.75	-Cbz		-H	355 (841)	151 (86)	2.4 (9.4)
1.90	-Cbz		-H	15 (230)	14 (5.1)	1.1 (33)
1.91	-Cbz		-H	48 (413)	19 (17.5)	2.5 (24)
1.87	-Cbz		-H	49 (130)	13 (3.6)	3.8 (36)
1.93	-Cbz		-H	368 (6659)	83 (24)	4.4 (280)
1.102			-H	1892 (2224)	443 (157)	4.3 (14)
1.105b			-H	100 (582)	52 (67)	1.9 (8.7)
1.108[b]			-H	56	159	0.4

K_i values reported from a single experiment. [a] Norbenzomorphan data in parentheses under data. [b]no analagous norbenzomorphan compound

Collectively, these series of compounds were more potent for Sig1R and had moderate to little selectivity for Sig2R compared to the comparable norbenzomorphan compounds. These findings suggest that to achieve high levels of subtype selectivity for Sig2R in these classes of compounds, the relative orientation between the substituents on the scaffold is important (Figure 1.15). The bridging methylene group of the norbenzomorphan creates a sharp U-shape in the molecule when C8 is functionalized which may not place the basic nitrogen of the molecule favorably in the linear Sig1R binding pocket (Figure 1.15D). Based on the crystal structure of the Sig1R binding pocket, the ionic interaction of a basic amine with Glu172 is responsible for high affinity Sig1R binding. This suboptimal ionic interaction, as seen with a Sig2R selective norbenzomorphan, may explain the high degrees of selectivity obtained for our norbenzomorphan compounds. In contrast, the isoindoline and the C(7) functionalized tetrahydroisoquinoline scaffolds have a more linear orientation between the substituents and overlay poorly with C(8) functionalized norbenzomorphan. This may allow these compounds to fit more favorably in the Sig1R binding pocket. Although C(8) functionalized benzazepines overlay nicely with C(8) functionalized norbenzomorphans, the benzazepine scaffold has more conformation flexibility, and easily adopt different conformations for binding that the norbenzomorphan. This may explain the increase in affinity for Sig1R of the benzazepine compounds.

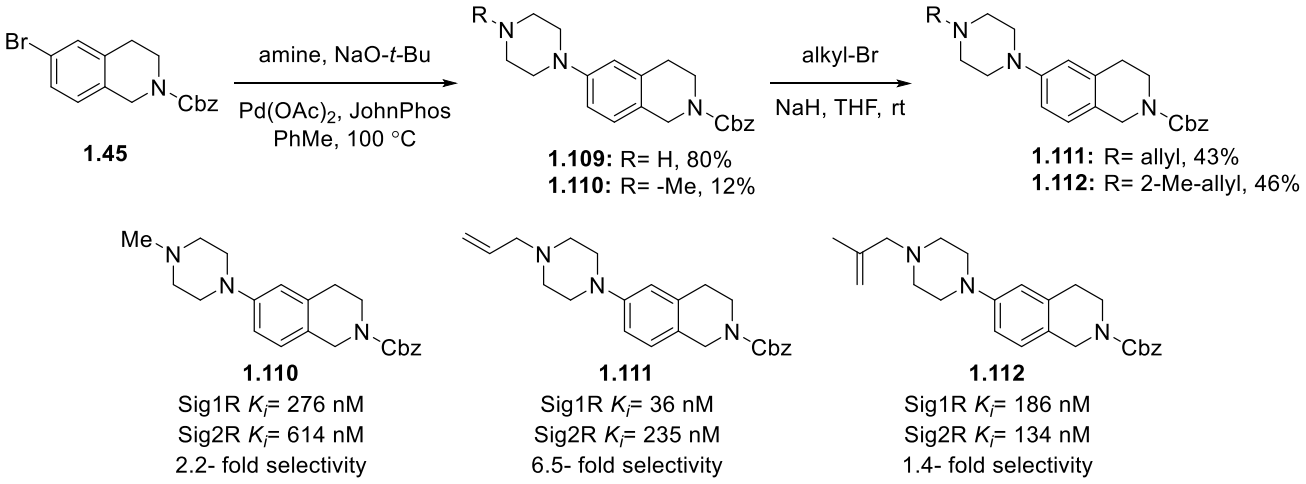


Structures were minimized in Avogadro using Force Field MMFF94s with a conjugate gradients algorithm. These outputs were saved and compounds were overlaid in Chem3D using fast overlay program: A) Overlay of compound **1.28** and **1.66**. B) Overlay of compound **1.28** and **1.70**. C) Overlay of compound **1.28** and **1.75**. D) Docking of norbenzomorphan Sig2R selective ligand SAS1121 in Sig1 binding pocket done by the Kruse group.

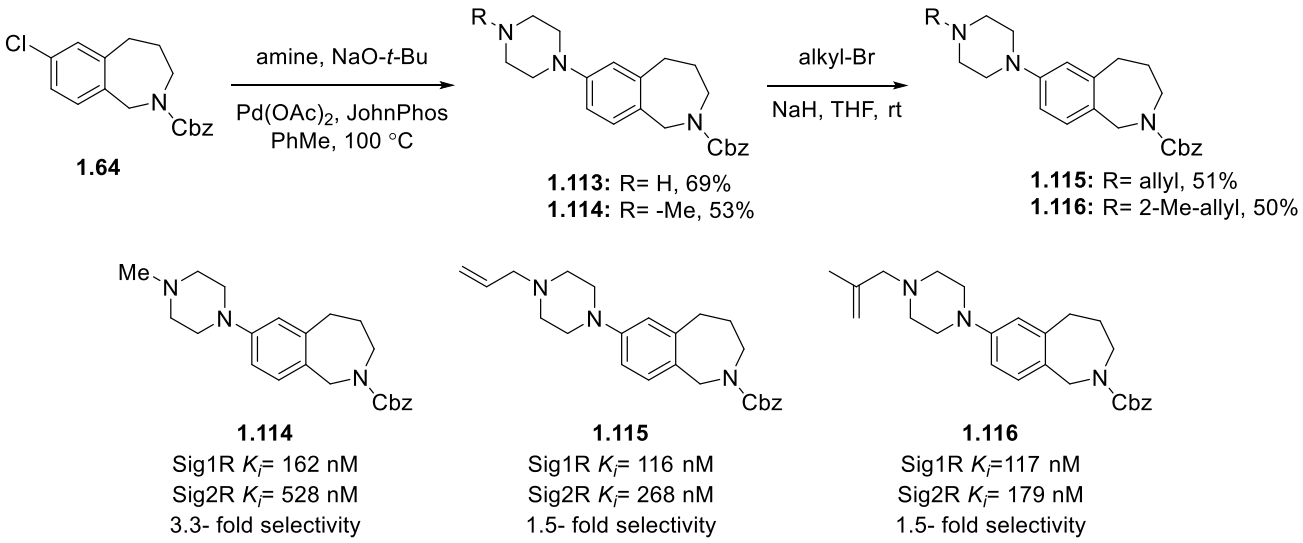
Figure 1.15: Overlay of norbenzomorphan sigma 2 selective ligand **1.28** with compounds **1.66**, **1.70**, and **1.75**

Despite the observed decreased selectivity, most compounds were still potent binders for sigma receptors. Interestingly, compounds **1.66** and **1.79** were modeled after Sig2R selective ligands, yet they showed higher affinity for Sig1R (K_i = 250 nM and 92

nM respectively). Analogous derivatives were made on scaffolds **1.45** and **1.64** to see if introducing the regiochemistry would increase Sig1R binding and selectivity (Scheme 1.10 and 1.11). These new novel compounds **1.110-1.112** and **1.114-1.116** did show some selectivity for Sig1R with compound **1.111** being the most potent and selective for Sig1R (K_i= 36 nM, 6.5-fold selectivity). Overall little improvement was observed with most of these new compounds having comparable or lower affinity for Sig1R compared to the parent compounds **1.66** and **1.79**.

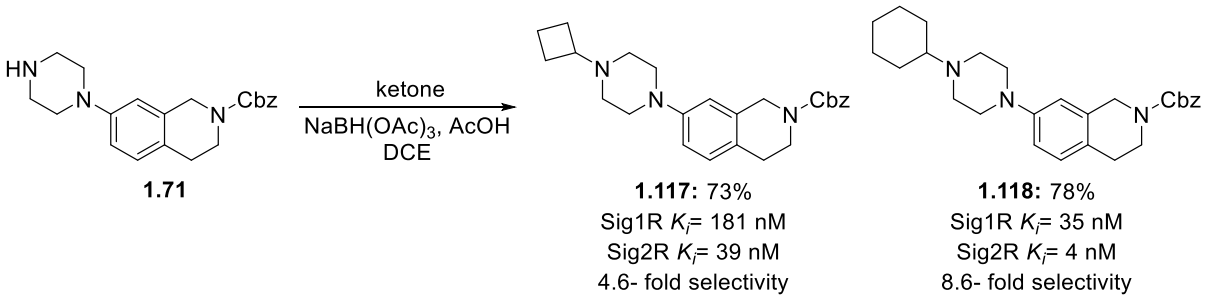


Scheme 1.10: Synthesis of piperazines derivatives on 6-bromo-tetrahydroisoquinoline scaffold in an attempt to optimize binding



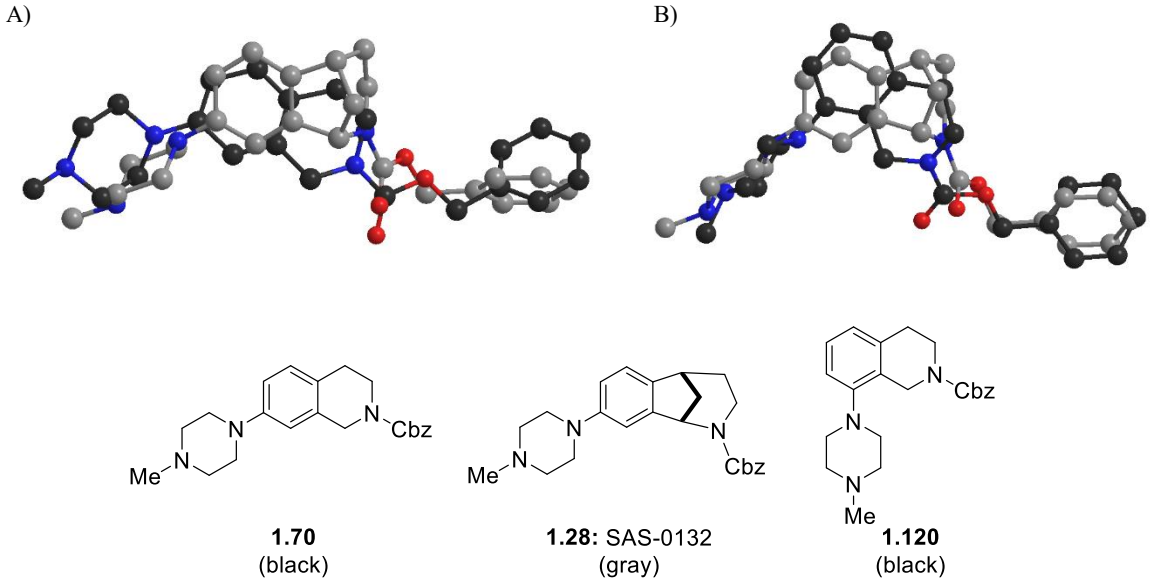
Scheme 1.11: Synthesis of piperazines derivatives on 7-chloro-benzazepine scaffold in an attempt to optimize binding

In the tetrahydroisoquinoline series, compound **1.86** was the most potent Sig2R binder with a (K_i= 2.7 nM, 18.9- fold selectivity). From this result, the cyclobutyl- and cyclohexyl-piperazine derivatives were made to see how ring size might affect binding in this position, in hopes of optimizing binding (Equation 1.7). Again, little change was observed, with compound **1.117** having lower affinity and compound **1.118** having comparable binding affinity for Sig2R than **1.86**. Additionally, both compounds were less selective than **1.86**.



(1.7)

To further probe how the relative orientation of the substituents on the ring plays a role in the design of Sig2R selective compounds, the chemical space around the tetrahydroisoquinoline ring was explored. The collection of tetrahydroisoquinolines with C7 functionalized suffered from a loss of selectivity compared to the norbenzomorphan compounds; however, these two scaffolds place the substituents off of the scaffold in very different areas of space (Figure 1.16). Instead of functionalizing the tetrahydroisoquinoline off C7, we could instead functionalize C8. These compounds bring the substituents closer in space by contracting the distance between the nitrogen atom of the scaffold and the substituent on the arene, creating a shape more similar to the norbenzomorphan compounds.

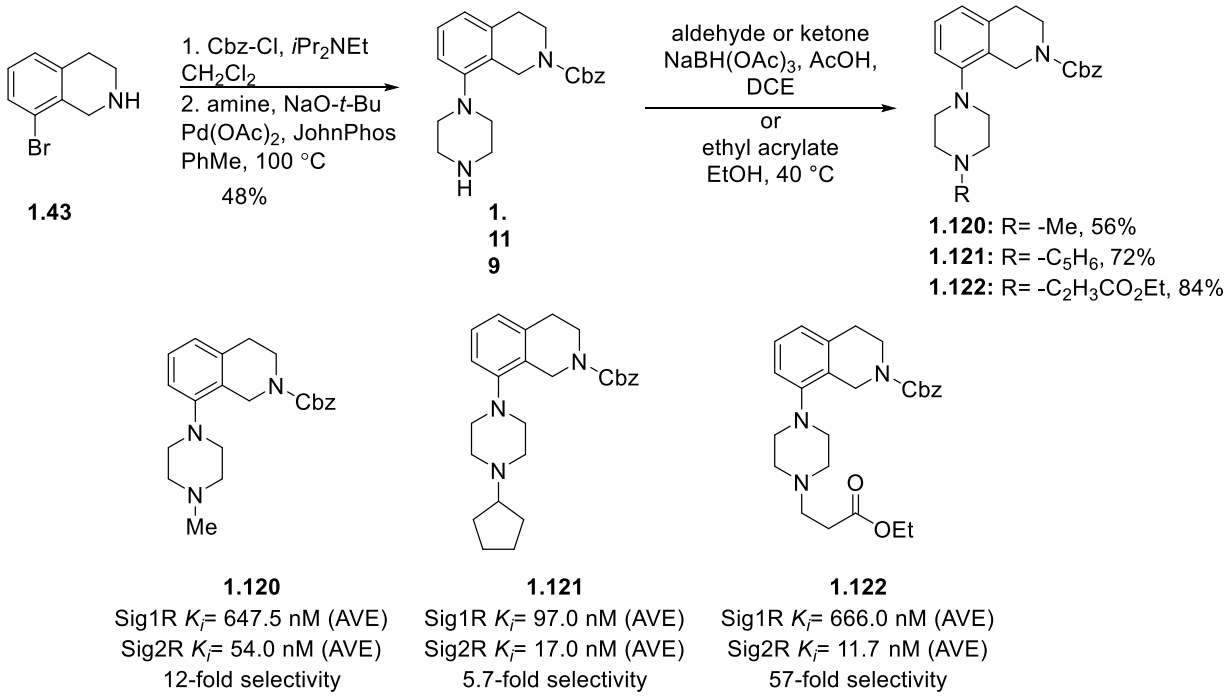


Structures were minimized as defined in Figure 1.15: A) Overlay of compound **1.28** and **1.70**. B) Overlay of compound **1.28** and **1.120**.

Figure 1.16: Overlay comparison of norbenzomorphan and tetrahydroisoquinoline derivatives with both C7 and C8 functionalized

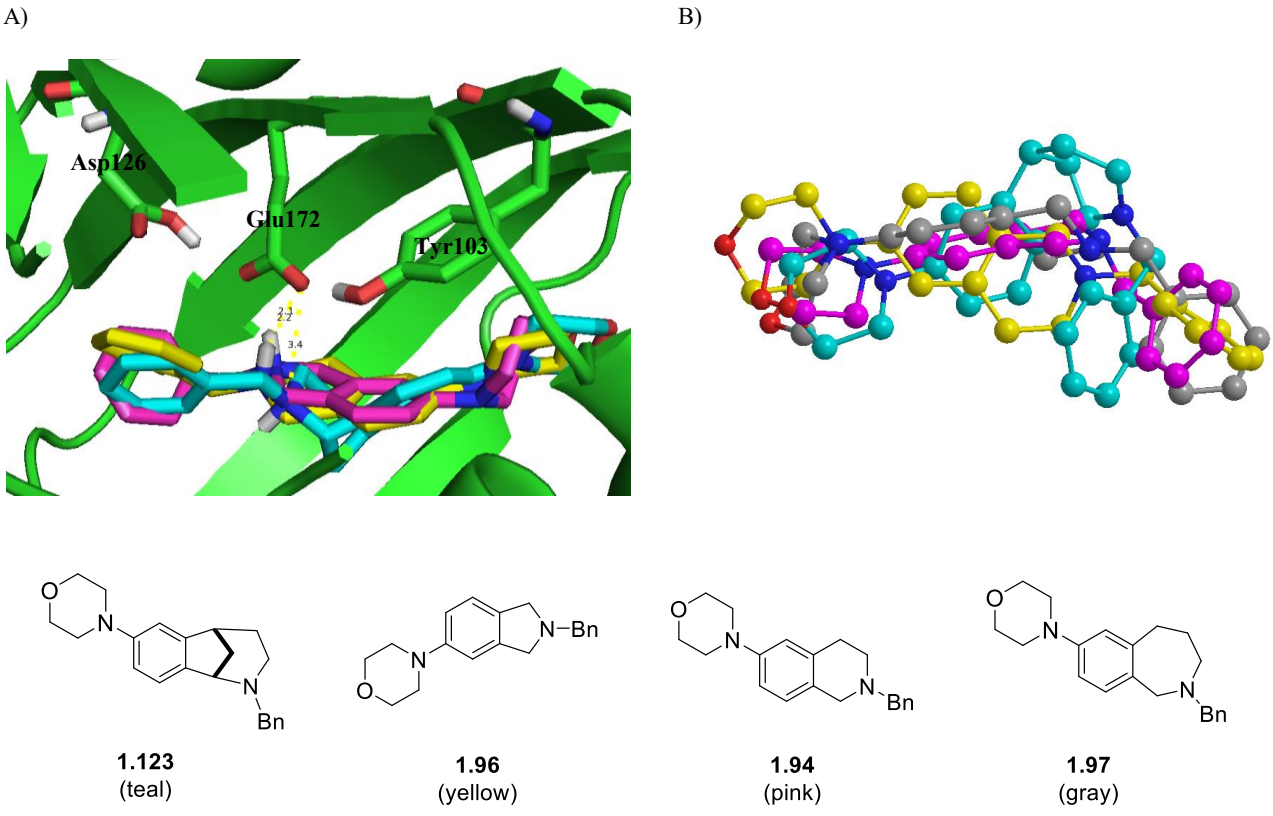
Starting from compound **1.43**, several new derivatives were made via Buchwald-Hartwig cross-coupling, followed by reductive amination or conjugate addition of ethyl acrylate (Scheme 1.12). These three compounds were modeled after the best norbenzomorphan and the best tetrahydroisoquinoline compounds. While little improvement was achieved for **1.121** compared to **1.86**, the affinity and selectivity for Sig2R for **1.120** and **1.122** improved. Going from **1.70** to **1.120** resulted in a five-fold increase in binding affinity for Sig2R. Even more encouraging, when C7 of the tetrahydroisoquinoline contained -$CH_2CH_2CO_2Et$ substituted piperazine, the binding affinity (K_i) for Sig2R was 198 nM, but at C8 the Sig2R binding affinity increased to 11.7 nM in **1.122**, resulting in a 17-fold improvement in binding affinity. In addition to

improved Sig2R binding, all three compounds suffered a decrease in binding affinity for Sig1R compared to the corresponding C7 substituted tetrahydroisoquinoline compounds. This resulted in a six-fold increase in selectivity for Sig2R for **1.120** compared to **1.70**, and a 57-fold increase in selectivity for Sig2R for **1.122** compared to **1.86**. This result seems to support that high affinity and selective Sig2R ligands of this class need to have a close spatial orientation between the two substituents off the scaffold. Furthermore, the loss in affinity in these compounds for Sig1R supports that high Sig1R affinity and selectivity is driven by linearity in the molecule. It is important to note that compounds **1.120-1.122** are not a comprehensive data set, but these results offer a point for further exploration into the SAR of these classes of compounds.



Scheme 1.12: Synthesis of C(8) functionalized tetrahydroisoquinoline derivatives

In summary, we have prepared a library of isoindoline (n = 1), tetrahydroisoquinoline (n = 2), and tetrahydro-2-benzazepine (n = 3) compounds to explore the SAR of a novel class sigma ligands. Through scaffold minimization, we were able to begin to build a pharmacophore model for these new classes of ligands for both Sig2R and Sig1R. For achieving Sig1R selectivity, we have shown that there is little dependence on the scaffold (Figure 1.17). As long as the scaffold can arrange the substituents in a linear manner, analogous substitution patterns showed very similar binding profiles.



A) Docking of compounds **1.94**, **1.96**, and **1.123** in the Sig1R binding pocket done by the Kruse group. B) Overlay of compounds **1.94**, **1.96**, **1.97** and **1.123**: structures were minimized as defined in Figure 1.15.

Figure 1.17: Sig1R selective compounds docked in Sig1R binding pocket and structural overlay of Sig1R selective compounds from all four scaffold classes

Conversely, we discovered that the orientation between the substituents off the scaffold plays an important role in achieving high Sig2R. When the scaffold is symmetrical (isoindolines), there is no selectivity for Sig2R, and if the scaffold is too conformationally flexible (benzazepines), there is also a loss in selectivity for Sig2R. However, when on a more conformationally ridged scaffold (tetrahydroisoquinoline), the carbon of which the piperazine substituent is off of seems to play an important role for driving Sig2R selectivity. Together these results suggest that Sig2R selective compounds of these classes must place substituents on the scaffold close in space. Despite achieving only moderate levels of subtype selectivity, this new library of compounds were still potent binders of both sigma receptors. Recently, experiments have suggested that compounds that can bind both sigma receptors may be useful in both the diagnosis and treatment of cancer.[85,86] Thus, these scaffolds may serve as a future platform for the development of more potent "pan modulators" of the sigma receptors. Additionally, these compounds showed little off-target activity, and given the synthetic simplicity, it is also possible that these ligands could be used as tool compounds to further advance the understanding of sigma receptors.

CHAPTER 2: SYNTHESIS OF SIGMA RECEPTOR LIGAND-GEMCITABINE CONJUGATES FOR TARGETED DRUG DELIEVERY

2.1 Introduction

Cancer is a group of diseases characterized by uncontrollable growth of abnormal cells, and failure to regulate and prevent the replication and spread of cancerous cells leads to patient death. Cancer represents one of the most common causes of death in the United States; it is estimated that in 2017, 1,700,000 new cancer cases will be diagnosed, and 600,900 patients will suffer cancer related deaths.[87] Significant advances have been made in cancer therapy, and survival rates have increased from 49%-68% over the past 50 years, yet current chemotherapies suffer a number of shortcomings.[87] The major disadvantage of current chemotherapeutic agents is that they are nonspecific. With regular dosing of chemotherapeutics, the drug enters cancer and healthy cells, usually with the same kinetics, resulting in dose limiting toxic effects. This causes a number of side effects that can lead to suboptimal dosing regiments or termination of the chemotherapeutic plan. Tumor cells can also develop resistance mechanisms over time, causing the chemotherapy to lose its efficacy. To overcome these shortcomings, therapeutic strategies must be developed that increase the therapeutic window of these agents while also decreasing toxicity.[88]

One strategy that is currently being investigated is targeted drug delivery, in which a targeting moiety is chemically conjugated to a potent (and typically nonspecific) cytotoxic agent via a spacer that contains a cleavable bond.[89,90] This rapidly growing class of anticancer therapeutics uses a targeting moiety, such as antibodies, aptamers, peptides,

small molecule ligands, etc., to selectively deliver the toxic payload to malignant cells. Achieving selective delivery of therapeutic agents to cancer cells will improve the therapeutic window by increasing the drug concentration at malignant cells while reducing drug concentrations at non-tumor sites, thereby minimizing off-target effects.[91] However, it is important to remember that the efficacy of these conjugates is predominately controlled by the potency of the targeting ligand and the chosen receptor. The targeted receptor must be overexpressed in tumor cells and allow for the internalization of therapeutic quantities of the conjugate. Ideally, the receptor will also be located on the cell membrane and recycle fast after internalization. The chosen targeting ligand must have high affinity and selectivity for the chosen receptor to prevent off target interactions that may cause off target selectivity. Through careful selection of target receptor and ligand, this strategy is a powerful way to overcome the shortcomings of modern chemotherapies.

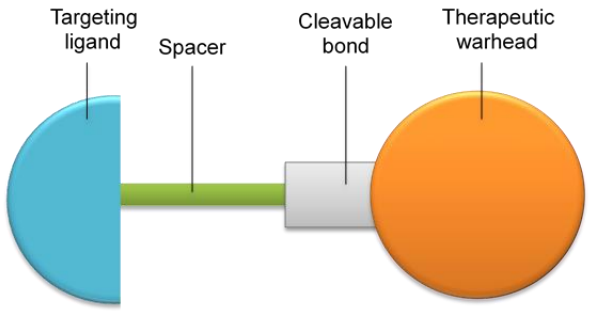


Figure 2.1: Design of a typical ligand-drug conjugate

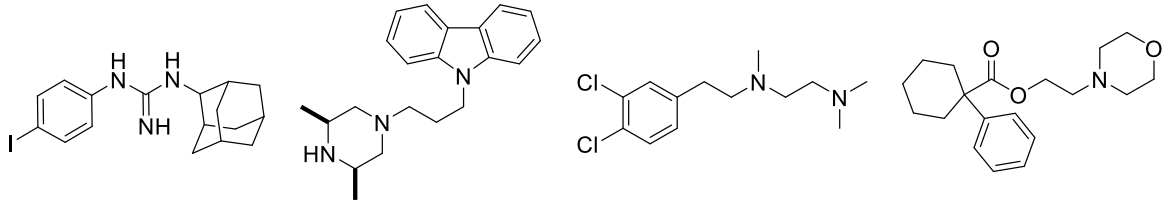
2.1.1 Sigma Receptors and Their Role in Oncology

Sigma receptors, while extensively studied for their functions in the central nervous system, have also been implicated in cancer pathology and are current targets for the development of novel cancer therapies and diagnostic tools. As mentioned in the previous

chapter, SigRs are widely distributed throughout the body, suggesting it may play important roles in peripheral cells, not just neurons. Overexpression of SigRs in cancer cells was first observed in a panel of brain tumors via competition binding assays using tritiated DTG. Of the 16 tumors examined, non-specific SigR binding was detected in 15, with very high levels found in neuroblastoma and a brain metastasis from a lung adenocarcinoma.[92] Subsequent research based on the binding of labeled non-subtype specific ligands have shown increased levels of SigRs in nonsmall cell lung carcinoma, breast, lung, melanoma, leukemia, glioblastoma, neuroblastoma, and prostate tumors.[93] Specifically, Sig1R overexpression has been shown in lung, breast, and prostate cancer cell lines.[19] Using Sig2R selective ligands, overexpression of Sig2R has been observed in breast, colon, lung, melanoma, brain, sarcoma, pancreatic, ovarian, and prostate cancer.[94] Additionally, Sig2R is upregulated 10-fold in proliferating cancer cells compared to quiescent cells, and therefore it is considered an excellent biomarker for proliferation.[61]

The discovery of the presence of both SigR subtypes in a multitude of cancer cell lines has prompted research toward an investigation of their involvement in cancer. Studies involving classical Sig1R antagonists like IPAG (**2.1**), rimcazole (**2.2**), BD1047 (**2.3**) (Figure 2.2), and reduced haloperidol (RHAL) showed dose-dependent decline in tumor cell viability (Figure 2.2).[95,96] These ligands mediated caspase activated apoptosis via a rapid increase in cytoplasmic Ca^{2+}. Additionally, Sig1R agonists, (+)-SKF-10047 and (+)-pentazocine, abolished the effects of the antagonists, suggesting Sig1R agonists show cytoprotective activity and antagonists show cytotoxic activity. This was further supported by a study in an animal model of lung cancer that demonstrated that Sig1R agonist, PRE-

084 (**2.4**), promoted tumor growth. The exact biological mechanisms that connect Sig1R to apoptotic pathways are currently under investigation; however, it is believed that antagonists induce ER stress, activating the unfolded protein response and resulting in autophagy and apoptosis.



2.1: IPAG
SigR K_i= 2.8

2.2: rimcazole
SigR K_i= ~560

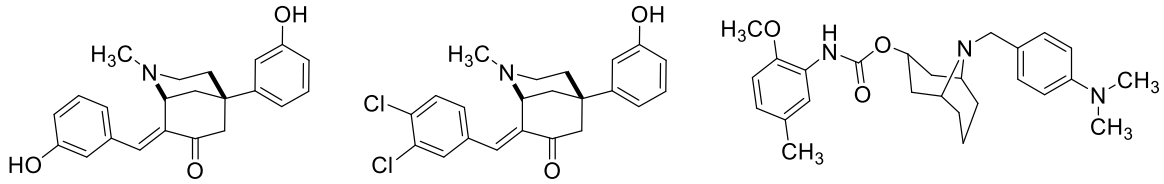
2.3: BD1047
Sig1R K_i= 7.4

2.4: PRE-084
Sig1R K_i= 44

Figure 2.2: Sig1R ligands and their effects in cancerous cells

Selective Sig2R ligands have also been found to regulate tumor growth, but the exact mechanisms are unknown. Evidence suggests that activation of Sig2R with selective agonists can promote both caspase dependent and caspase independent cell death pathways in cancerous cells.[40,61] Mach and coworkers reported several highly selective, potent Sig2R ligands that induced cytotoxicity in several lines of cancer, including mouse EMT-6 breast cancer cells and human MDA-MB-435 melanoma tumor cells. When dosed with the Sig2R agonist WC-26 (**2.7**) (Figure 2.3), caspase-3 activation and apoptosis was observed. However, the induced cytotoxicity of WC-26 (**2.7**) was partially blocked when co-administered with caspase inhibitor, Z-VAD-FMK, supporting that cell death is caused in part by caspase-mediated apoptosis.[97] Bowen *et al.* reported that Sig2R selective ligands CB-64D (**2.5**) and CB-184 (**2.6**) induced dose dependent apoptotic cell death in MCF-7 breast tumor cells.[98] In SK-N-SH neuroblastoma cells, CB-64D (**2.5**) produced an

immediate and transient rise in Ca^{2+} ion concentration that was attenuated by the partial Sig2R agonist CM572.[99,100] This result suggests that Sig2R ligands induce cytotoxicity through dysregulating Ca^{2+} homeostasis. Together, these studies suggest that the cytotoxicity of Sig2R ligands is dependent on ligand and cell type. Interestingly, Sig2R agonists show no cytotoxicity in healthy cells. Sig2R ligands WC-26 (**2.7**) and SV119 both induce cell death in cancerous cells, but show nominal toxicity to normal tissue as measured by caspase-3 activity.[101,102]



2.5: CB-46
Sig1R K_i= 3,063 nM
Sig2R K_i= 16.5 nM

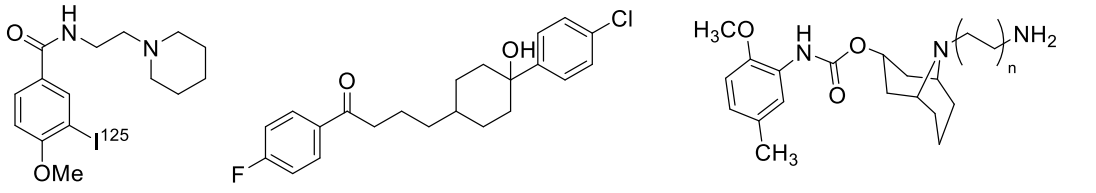
2.6: CB-184
Sig1R K_i= 7,436 nM
Sig2R K_i= 13.4 nM

2.7: WC-26
Sig1R K_i= 1,437 nM
Sig2R K_i= 2.6 nM

Figure 2.3: Sig2R ligands and their effects in cancerous cells

With these findings on the role SigRs play in cancer pathology, much research is being directed into the design of selective sigma ligands to improve treatment.[40,61] It is also known that SigRs are able to rapidly internalize their ligands, in part by endocytosis, which has motivated the development of SigR ligands for diagnostic imaging.[103] The overexpression of SigRs has not only made them an attractive target for cancer diagnosis and treatment, but also for anticancer drug delivery using SigR ligands to deliver toxic payloads (Figure 2.4). For many years, work by Huang *et al.* was directed towards developing liposome or nanoparticle conjugates tethered to a benzamide analog, based on the Sig1R selective derivative [I^{125}]PIMBA (**2.8**) (Figure 2.4), for targeted delivery to

cancer cells.[104] Prior to injection, the carriers were loaded with a variety of anticancer agents including, doxorubicin, antisense oligonucleotides, and siRNA.[105–111] One example targeting prostate cancer cells showed that the resulting anisamide-conjugated liposomal doxorubicin had significantly higher cytotoxicity compared to nontargeted liposomal doxorubicin *in vitro*. Additionally, the conjugate showed improved accumulation within the prostate tumor *in vivo.*[105] In an attempt to target lung cancer, Huang *et al.* demonstrated that anisamide conjugated nanoparticles resulted in significant increases of siRNA uptake compared to nontargeted control *in vitro*. In H460 lung cancer cells, the targeted nanoparticles showed a 4-fold increased delivery to tumor cells in mice. Additionally, in mice bearing both A549 and H460, repeated injections of the targeted nanoparticle significantly inhibited tumor growth up to 4-fold in 31 days.[107]



2.8: [^{125}I]PIMBA
Sig1R K_i= 11.8 nM
Sig2R K_i= 206 nM

2.9: Haloperidol
Sig1R K_i= 1.2 nM
Sig2R K_i= 26 nM

2.10: SV119 (n=3)
Sig1R K_i= 1,418nM
Sig2R K_i= 5.2 nM

2.11: SW43 (n=5)
Sig1R K_i= 134.3 nM
Sig2R K_i= 7.1 nM

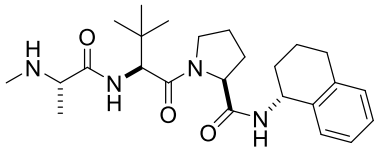
Figure 2.4: Sigma ligands used in conjugates for targeted drug delivery

Another early example utilized the nonselective sigma ligand, haloperidol. Inspired by the work by Huang's group, Banerjee *et al.* designed a liposome conjugated to haloperidol (**2.9**) via a PEG linker armed with a payload of plasmid DNA containing either a reporter or therapeutic gene.[112] In human MCF-7 breast cancer cells, the targeted liposome showed >10-fold greater uptake of a reported gene than nontargeted liposomes.

The expression of the reporter gene was blocked when the targeted liposome was administered in the presence of either DTG or free haloperidol (**2.9**), suggesting that SigRs are responsible for the increased uptake of the targeted liposomes. Lastly, cancer cells lines that do not overexpress SigRs (Hela, KB, and HepG2), the targeted liposome showed 5-10-fold less transfection compared to MCF-7 cells.

Although these initial targeting attempts showed promising results, the ligands used for these complexes were non-selective and have off target affinity for neurotransmitter binding sites. More recent attempts by Mach's group have instead employed the highly Sig2R selective ligands SV119 (**2.10**) and SW43 (**2.11**) that were developed in their lab. SV119 (**2.10**) has been conjugated to liposomes and gold nanocages and showed increased uptake of the conjugate in melanoma, prostate, lung, and breast cancer cells compared to controls.[113] Mach has also focused his efforts towards designing Sig2R conjugates with peptides and second mitochondria-derived activator of caspases (Smac) mimetics. Initial work towards this end began with conjugating SV119 (**2.10**) with Bim, a peptide of Bcl-2 antagonist.[114] The conjugate not only retained affinity for Sig2R but also elicited dose-dependent cytotoxicity and apoptosis in pancreatic tumor cell lines. This work led to the development of an optimized conjugate, SW IV-134, which utilized a cytotoxic Sig2R ligand SW43 (**2.11**) and second mitochondria-derived activator of caspases (Smac) protein mimetic SW IV-52s (**2.12**) (Figure 2.5).[64,115,116] This conjugate showed high affinity for Sig2R (K_i= 22.6 nM) and 250-fold selectivity between subtypes. Against a panel of human and mouse pancreatic cancer cells lines, SW IV-134 decreased IC_{50} 8-fold compared to both SW43 (**2.11**) and SW IV-52s (**2.12**) individually and in combination.[115] In addition,

the conjugate induced target cell apoptosis. In a panel of ovarian cancer cell lines, SW IV-134 induced apoptotic cell death at substantially lower concentrations than the Sig2R ligand alone. The *in vivo* efficacy of SW IV-134 was measured in female mice inoculated interperitoneally with SKOV3-Luc cells via bioluminescence imaging. These experiments showed that SW IV-134 is a potent single agent therapeutic that increased survival of the mice when compared to SW43 (**2.11**) alone.[116] Lastly, SW IV-134 was also effective in reducing cell viability in triple negative breast cancer cell lines that overexpress Sig2R, and its effects were attenuated when Sig2R was saturated with the Sig2R ligand RHM1.[64]



2.12: SW IV-52s
inhibitor of apopotosis inhibitors

Figure 2.5: Smac mimetic used as cytotoxic payload with SW43 ligand

Together, these studies validate the utility of SigRs binding ligands for the development of targeted drug delivery to cancer cells with the potential for dual action cytotoxicity. However, to date, no SigR ligand has been conjugated to a chemotherapeutic currently used in patients today directly via a cleavable bond. Doxorubicin has been used in the above studies; however, the toxic payload was encapsulated in a liposome. While large drug carriers have their advantages, such as the enhanced permeability and retention effect which allows these liposomes/nanoparticles to accumulate in tumor tissue, the large molecule carries also fail to penetrate solid tumors.[117,118] Low-molecular-weight drug conjugates offer the distinct advantage of passively diffusing to cancer masses more

thoroughly. Additionally, these small molecule conjugates will be excreted more readily minimizing the risk of off target delivery and toxicity.[119]

2.1.2 GEMCITABINE: SHORTCOMINGS AND FUTURE PROSPECTS

Gemcitabine (**2.13**) is a nucleoside analog with broad spectrum antitumor activity, and it can be used as a single agent or in combination therapy to treat lung, pancreatic, breast, colon, bladder and ovarian cancer.[120] It is a prodrug that upon entering the cell is phosphorylated by deoxycytidine kinase to the monophosphate form (dFdCMP (**2.14**)). It then undergoes two additional phosphorylations to give gemcitabine triphosphate (dFdCTP (**2.15**)), which competes with deoxycytidine triphosphate for incorporation into DNA as fraudulent base. Once incorporated at the end of the DNA strand, one deoxynucleotide is added, and thereafter DNA polymerases are unable to proceed (Figure 2.6). This action, called "masked chain termination", locks the drug into the DNA because proof reading exonucleases are unable to remove gemcitabine.[121]

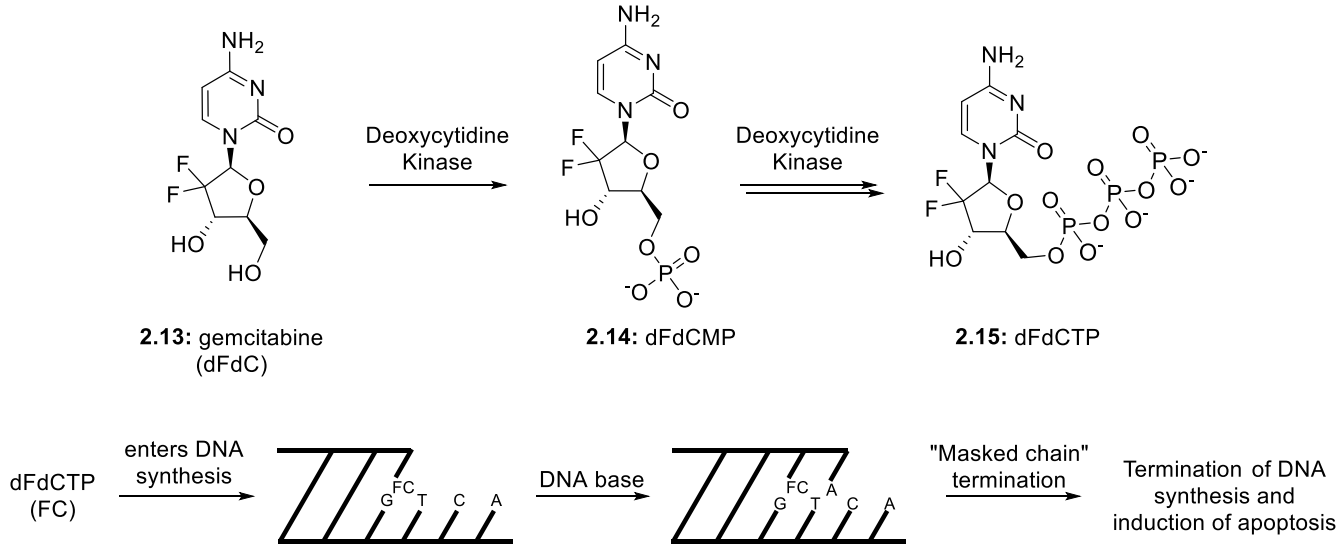


Figure 2.6: Gemcitabine mechanism of action

Although gemcitabine is a well-tolerated and potent chemotherapeutic agent, the reason for its low systemic toxicity is the fact that it is readily deaminated by cytidine deaminase (CDA) to its less effective difluoro-uridine derivative.[122] This results in rapid renal excretion giving gemcitabine a half-life of approximately 70 min. To combat the rapid elimination, higher doses are administered. Unfortunately, major toxicity can be observed at these higher doses, such as hematotoxicity, hepatotoxicity, and renal and gastrointestinal toxicity.[123] Clinical trials have suggested that prolonged infusion times with lower doses with longer infusion times can be effective while also lowering toxicity;[124] unfortunately, another downfall of gemcitabine is that tumors acquire resistance over time. A major cause of resistance is due to changes in expression of transports on the cell membrane.[125] Gemcitabine is transported into the cell by a transporter hENT1 and resistance has been correlated to decreased expression of hENT1. Additionally, resistance has been correlated to higher levels of CDA, which lowers levels of active gemcitabine. These resistance pathways make it necessary for higher doses of gemcitabine that in turn leads to toxicity. Lastly, gemcitabine suffers from poor bioavailability due to the hydrophilic nature of the drug, and it can only be administered intravenously.

To date, the major strategy to overcome the shortcomings of gemcitabine is modifying the deoxycytidine nitrogen atom by installing a hydrolyzable amide bond.[122,123] These prodrugs facilitate slow release of gemcitabine so long infusion times are unnecessary, and lower dose requirements by protecting the deoxycytidine nitrogen atom thereby decreasing deamination by CDA. These prodrugs can also increase the bioavailability by increasing the lipophilicity of gemcitabine depending on the choice of

side chain. Additionally, these conjugates have the potential to bypass transporter resistance mechanisms by changing the mechanisms by which the prodrug can enter the cell. To date, gemcitabine has been modified with poly(ethylene glycol) (**2.16)**,[126] squalene (**2.18)**,[127–129] and aliphatic acyl derivatives.[130,131] Currently, N4-valproyl gemcitabine (LY2334737 (**2.19**)) is an orally available prodrug in phase I clinical trial and shows increased systemic stability by avoiding first pass metabolism.[132] Some of these gemcitabine prodrugs have also been designed to include a targeting group. One conjugate (**2.17)** links gemcitabine to folic acid via a PEG linker. In KB-3-1 cells, which over express folate receptors, the targeted PEG conjugate was more cytotoxic than the nontargeted PEG conjugate.[133] In another study, a peripheral benzodiazepine receptor ligand was used to target brain cancer. The conjugate PK11195-GEM (**2.20**) showed a two-fold increase in drug concentration at the tumor site than gemcitabine alone. Although it was not proven definitively, it can be inferred that it was the PK11195 receptor ligand that facilitated greater tumor selective due to receptor-mediated drug delivery.[134]

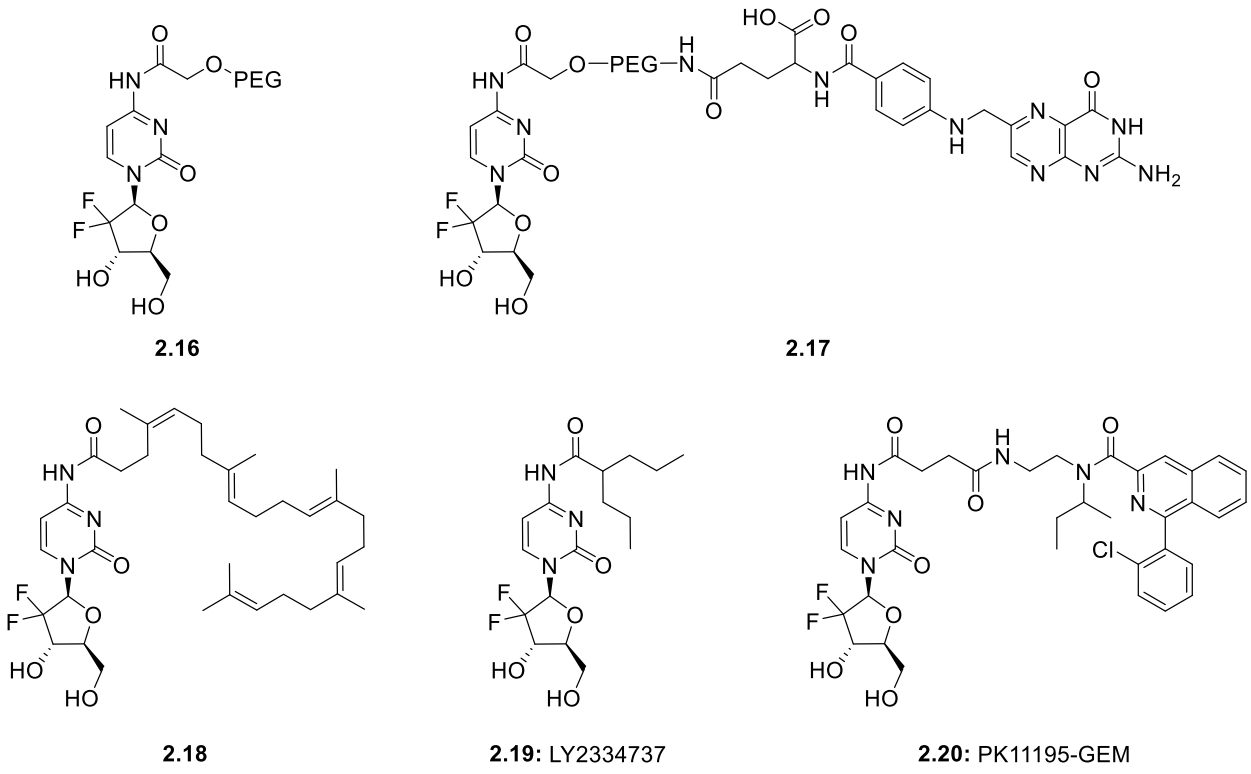
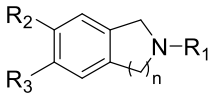
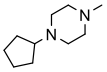
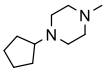
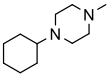


Figure 2.7: Gemcitabine prodrugs designed for improved stability or targeted delivery

To overcome some of the shortcomings associated with gemcitabine, the Martin group, in collaboration with the Cui group, became interested in developing a drug conjugate where gemcitabine is chemically tethered to a SigR ligand. As reported in the previous chapter, the Martin group recently developed a unique set of high affinity (<100 nM) norbenzomorphan SigR ligands with tunable selectivity (>80-fold) for Sig1R or Sig2R. To expand upon the SAR of this new class of sigma ligands, a collection of isoindoline (n = 1), tetrahydroisoquinoline (n = 2), and tetrahydro-2-benzazepine (n = 3) derivatives have been synthesized. From this new library, several potent and moderately selective compounds were identified (Table 2.1).

Table 2.1: Binding affinity data for isoindoline and tetrahydroisoquinoline derivatives with single digit nM potency for Sig1R or Sig2R



No.	n	R_1	R_2	R_3	K_i (nM) Sig1R	K_i (nM) Sig2R	Sig1R / Sig2R
2.21	1	-Bn	-H		4.1	65	0.06
2.22	1	-Cbz		-H	44	8.2	5.4
2.23	2	-Bn	-H		1.7	33	0.05
2.24	2	-Bn	-H		4.9	57	0.09
2.25	2	-Cbz		-H	52	2.7	19.3
2.26	2	-Cbz		-H	35	4.0	8.8

Due to the synthetic simplicity of these new compounds, moderate degree of selectivity for the respective sigma receptor subtype and clean off target profile, we were interested in attaching both a Sig1R and a Sig2R selective ligand to the exocyclic N4 amine of gemcitabine. We hypothesized that our sigma selective ligands will selectively deliver gemcitabine to cancer cells, thus increasing the concentration of gemcitabine in cancerous cells vs. healthy cells. In addition to targeted delivery, we hypothesized that our conjugate could improve systemic stability and prevent gemcitabine resistance, both of which will improve the efficacy of gemcitabine. Our conjugate is designed to mask exocyclic nitrogen, which will decrease metabolism by CDA. Additionally, sigma ligands are also known to be internalized, in part by endocytosis, which can prevent uptake resistance by providing a new uptake mechanism independent to gemcitabine transporters. Lastly, while the functional activity of our sigma ligands is currently unknown, we recognize the potential

for dual action therapy in our design. Taken together, a Sig2R-gemcitabine conjugate offers immense therapeutic potential through targeted, dual-action therapy, which would be a powerful way to address some of the most resistant cancers of today.

2.2 Results and Discussion

With the goal of synthesizing a small molecule conjugate with gemcitabine, our library of Sig2R ligands was analyzed for a compound that was potent and selective for Sig2R. From the library of tetrahydroisoquinoline compounds, **2.25** is the most potent and selective Sig2R ligand, so it was selected as our targeting ligand. Unfortunately, **2.25** does not have a functional handle to rapidly install a linker for conjugation to gemcitabine. However, it was recognized that aldehyde **2.27** could be extended to a dihalogenated tetrahydroisoquinoline scaffold **2.25** (Figure 2.8). With two halogen atoms on the scaffold, it was envisioned that a Heck cross-coupling reaction could be performed with methyl acrylate to give a functional handle for conjugation via a diamide linker. Subsequent Buchwald-Hartwig amination would then give the piperazine functionality required for binding Sig2R. This dihalogenated scaffold also enables the installation of a linker off a position on the molecule that is distal from positions sensitive to SAR changes.

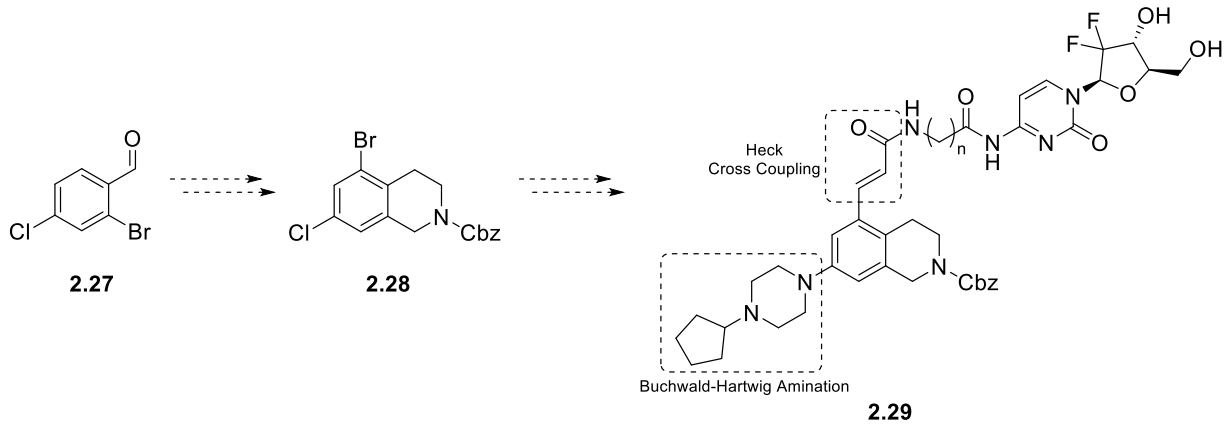
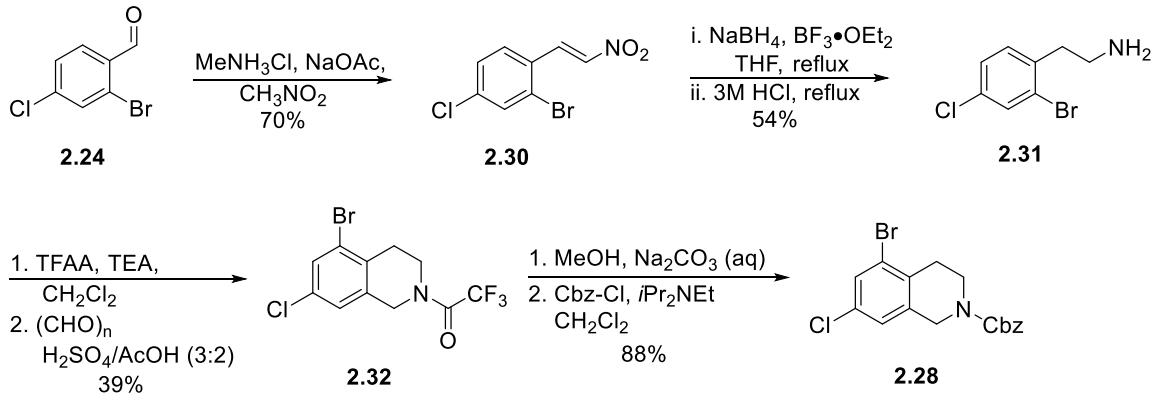


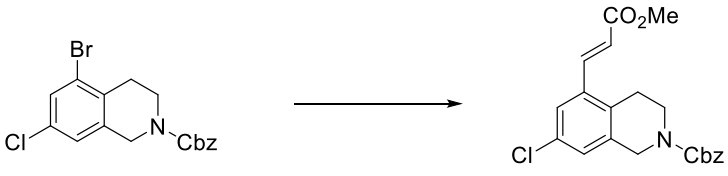
Figure 2.8: Design of Sig2R ligand-gemcitabine conjugate

A Henry reaction of **2.27** with $MeNH_3Cl$ and NaOAc in nitromethane gave nitrostyrene **2.30** in 70% yield, and subsequent borane reduction gave phenethylamine **2.31** in 54% yield (Scheme 2.1). Activation of the amine with trifluoroacetic anhydride, followed by a Pictet-Spengler reaction gave tetrahydroisoquinoline **2.32** in 39% yield over two steps. Finally, saponification of the trifluroacetamide and installation of the benzyl carbamate gave **2.28** in 88% yield over two steps.



Scheme 2.1: Synthesis of dihalogenated tetrahydroisoquinoline scaffold

With **2.28** in hand, we needed to install the handle for conjugation due to the placement and reactivity of the two halogen atoms. A Heck cross coupling reaction with **2.28** and methyl acrylate would append an ester functionality that could be used as a means of conjugation via a diamide linker. Initial attempts at this Heck reaction using PPh_3 as the ligand resulted in no conversion of starting material (Equation 2.1). In hopes of promoting oxidative addition, we switched to a more electron rich ligand P(o-tol)$_3$. This resulted 20% conversion to the desired product **2.33**; however, there were still significant amounts of starting material after heating at 125 °C for 24 h. Using microwave conditions based on a similar system[135] did not promote any conversion after 30 min. However, when the solvent was changed from MeCN to DMF and tributylammonium chloride, a common additive for rate enhancement, was added, the reaction was complete after 1 h, giving **2.33** in 60% yield.

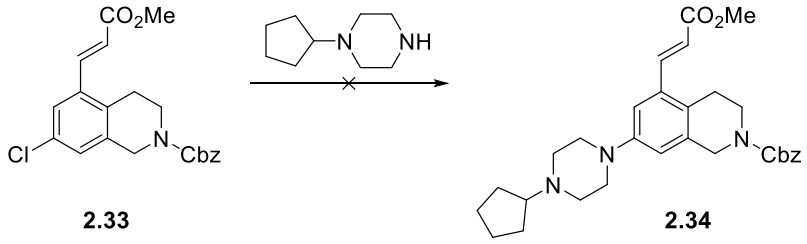


2.28 **2.33** (2.1)

Conditions

Cs_2CO_3, nBu_4Br, PPh_3, $Pd(OAc)_2$, MeCN, 75 °C, 5 h:	no rxn
TEA, $Pd(tBu_3P)_2$, DMF, 100 °C, 16h:	43%
TEA, o-Tol_3P, $Pd(OAc)_2$, DMF, 125 °C, 24 h:	20% conversion
TEA, o-Tol_3P, $Pd(OAc)_2$, MeCN, 160 °C, microwave, 35 min:	no rxn
TEA, o-Tol_3P, $Pd(OAc)_2$, Bu_4NCl, DMF, 125 °C, microwave, 60 min:	60%

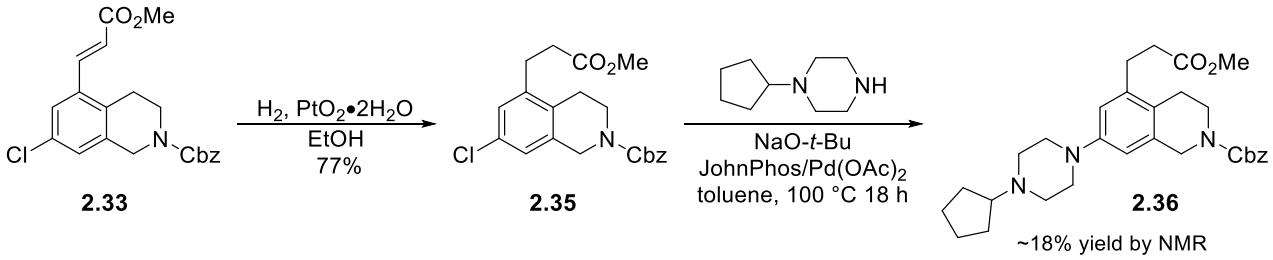
With optimized conditions for the Heck cross coupling reaction, only a Buchwald-Hartwig cross coupling reaction remained to obtain **2.34**. Initial attempts using conditions optimized in the Martin lab with JohnPhos and $Pd(OAc)_2$ led to no conversion of starting material.



2.33 **2.34** (2.2)

Ligands: JohnPhos, DavePhos, RuPhos, XPhos, SPhos, Dppf, BINAP
Pd Source: $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(t\text{-}Bu_3P)_2$
Additives: $CuBr_2$, AgOTf
Solvent: PhMe, DMSO
Temperature: 100 °C-170 °C
Time: 5-24 h

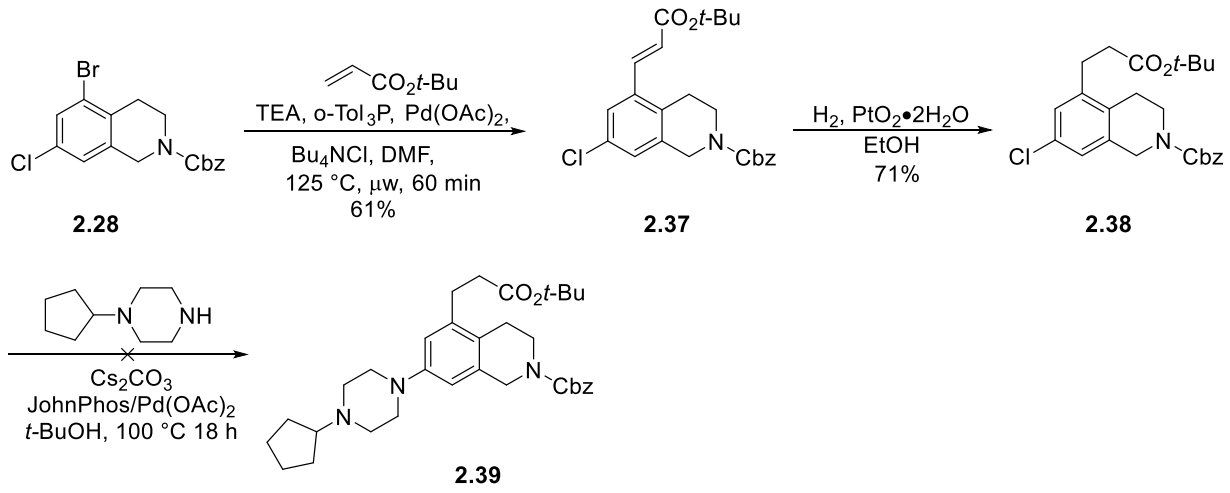
This experiment suggested that oxidative addition did not occur under these reaction conditions. A screen of other electron rich phosphine ligands unfortunately led to no improvement (Equation 2.2).[136] Copper and silver salts, which have been shown to increase the rate of reactions by forming a more active palladium species,[137] did not facilitate the amination reaction either. Switching from toluene to DMSO also led to no reaction. Given the lack of success in this cross-coupling, it was hypothesized that the enoate moiety on the scaffold was the problem. Fortunately, after reduction of **2.35** with Adam's catalyst, preliminary results showed **2.35** underwent Buchwald-Hartwig amination in 18% yield by ^{1}H NMR to give **2.36** (Scheme 2.2).



Scheme 2.2: Revised synthetic strategy towards Sig2R ligand conjugate

With this promising result, we set off to optimize the reaction conditions. First, we chose a weaker base, Cs_2CO_3 to prevent enolization of **2.35**. Although the reaction proceeded in toluene, it is known that *tert*-BuOH is a better solvent when using inorganic bases such as Cs_2CO_3. Initial attempts using *tert*-BuOH did lead to full consumption of starting material; however, undesired hydrolysis of the methyl ester was a major problem making isolation very difficult.

In hopes of preventing ester hydrolysis, the synthetic strategy was revised to use a more sterically hindered ester instead of a methyl ester. Heck cross-coupling of **2.28** with *tert*-butyl acrylate gave **2.37** in 61% yield (Scheme 2.3). Subsequent reduction of **2.37** with Adam's catalyst gave **2.38** in 71% yield. Unfortunately, the Buchwald-Hartwig cross-coupling reaction was still inconsistent. While hydrolysis was suppressed, keeping the reaction dry was very challenging. Due to the scale, the presence of any amount of water caused the Cs_2CO_3 to clump, decreasing the surface area of the base needed to facilitate the reaction. Despite the best efforts to dry the solvent, base, and remaining reagents, the presence of water was unavoidable and the reaction would not consistently proceed to give **2.39**. At this point, we had run out of material and this conjugate was put on hold.



Scheme 2.3: Revised synthetic strategy to prevent hydrolysis during Buchwald-Hartwig cross-coupling

For the Sig1R/gemcitabine conjugate, Sig1R selective ligand **2.21** was selected because the respective norbenzomorphan ligand had shown promising preliminary results. This study showed that conjugation of a liposome at the position of the -OMe group of the norbenzomorphan ligand resulted in increased cellular uptake compared to the free liposome.[138] Compound **2.21** was selected rather than the norbenzomorphan for this project because it has a comparable binding profile to the norbenzomorphan and is easier to synthesize. It was envisioned that converting the -OMe group to a phenol would enable conjugation of gemcitabine via an ether/amide linker (**2.42**) (Figure 2.9). To do so in the most synthetically efficient fashion, a gemcitabine derivative like **2.41** will be prepared and coupled to ligand **2.40** via a substitution reaction.

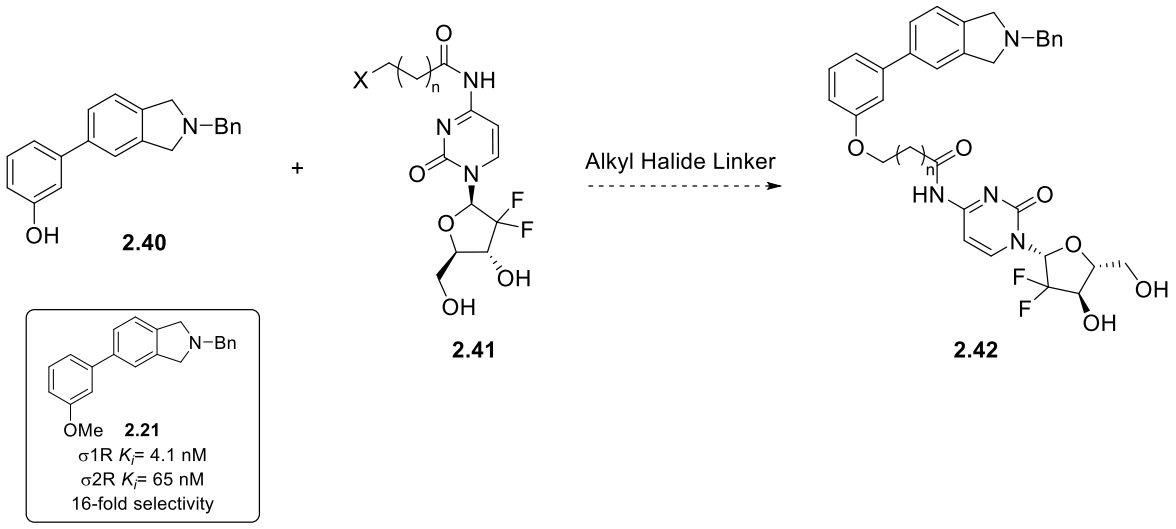
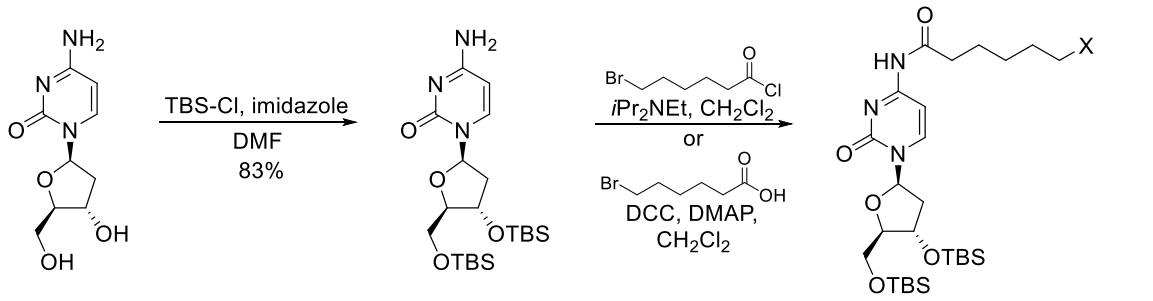


Figure 2.9: Proposed Sig1R ligand-gemcitabine conjugate

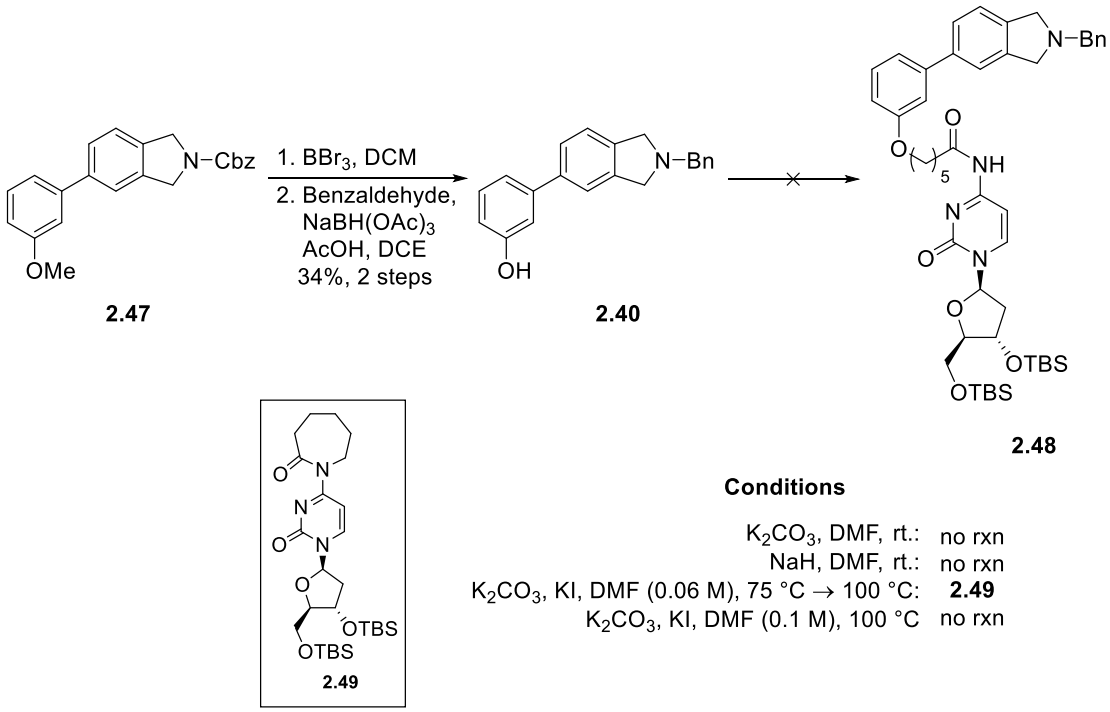
Deoxycytidine (**2.43)** was chosen as an initial model system to reduce cost. TBS protection of **2.43** under standard conditions gave **2.44** in 83% yield (Scheme 2.4). Initially 6-bromohexanoyl chloride was chosen for the linker. While attempts to acylate deoxycytidine with 6-bromohexanoyl chloride produced the desired product **2.45** in 43% yield as a mixture of chloride and bromide, optimization of the reaction was a problem. With only one equivalent of acyl chloride, the reaction did not go to completion and increasing the number of equivalents of acylating agent led to a diacylated product. Attempts to overcome this problem were investigated using 6-bromohexanoic acid, DCC, and DMAP. These conditions gave **2.46** in an improved 60% yield; however, complete consumption of deoxycytidine was still problematic.



2.43 **2.44** **2.45:** X= Cl, Br (1:1); 43% (57%brsm)
or
2.46: X= Br; 60%

Scheme 2.4: Acylation of deoxycytidine to use in conjugation model system

To synthesize **2.40**, intermediate **2.47** was deprotected with boron tribromide, followed by reductive amination to give **2.40** in 34% yield over two steps (Scheme 2.5). We then attempted to alkylate **2.40** with **2.46**. Initial attempts using K_2CO_3 as the base led to no conversion to **2.48**. Switching to a NaH as the base in an attempt to quantitatively deprotonate the phenol and increase its nucleophilicity, also led to no alkylation. We hypothesized that increasing the electrophilicity of the alkylating agent might facilitate the reaction. However, an *in situ* Finkelstein reaction with KI and K_2CO_3 did not lead to the desired product. Instead, **2.46** underwent intramolecular cyclization to give **2.49**. Increasing the concentration of the reactants did not facilitate the intermolecular substitution reaction.



Scheme 2.5: Efforts towards alkylating phenol

Due to the difficulty alkylating compound **2.40**, a new conjugation strategy was desired. Rather than use an ether/amide linker, it was envisioned that the Sig1R ligand/gemcitabine conjugate could also arise via a diamide linker using ligand **2.50** (Figure 2.10).

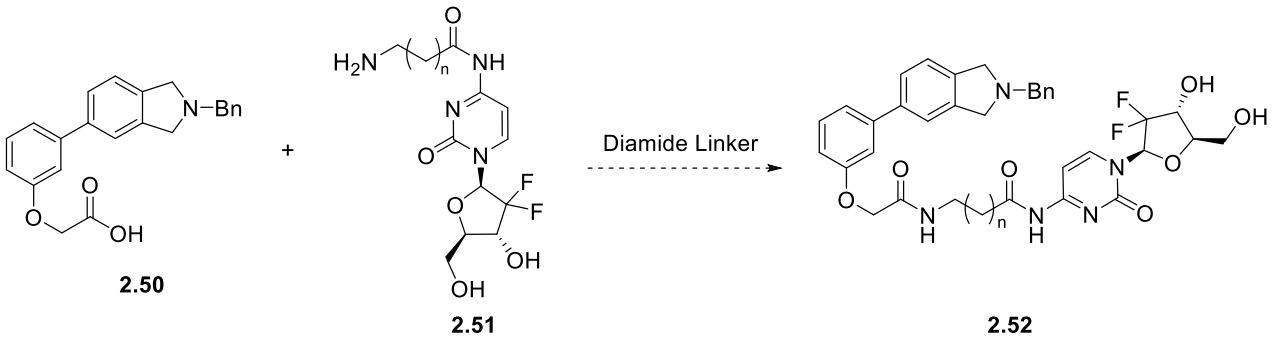
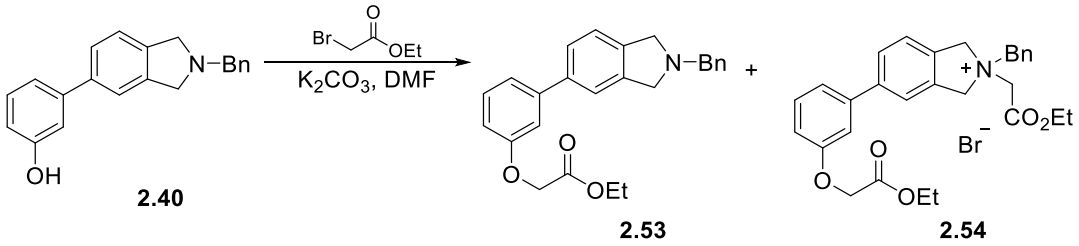


Figure 2.10: Revised Sig1R ligand-gemcitabine conjugate

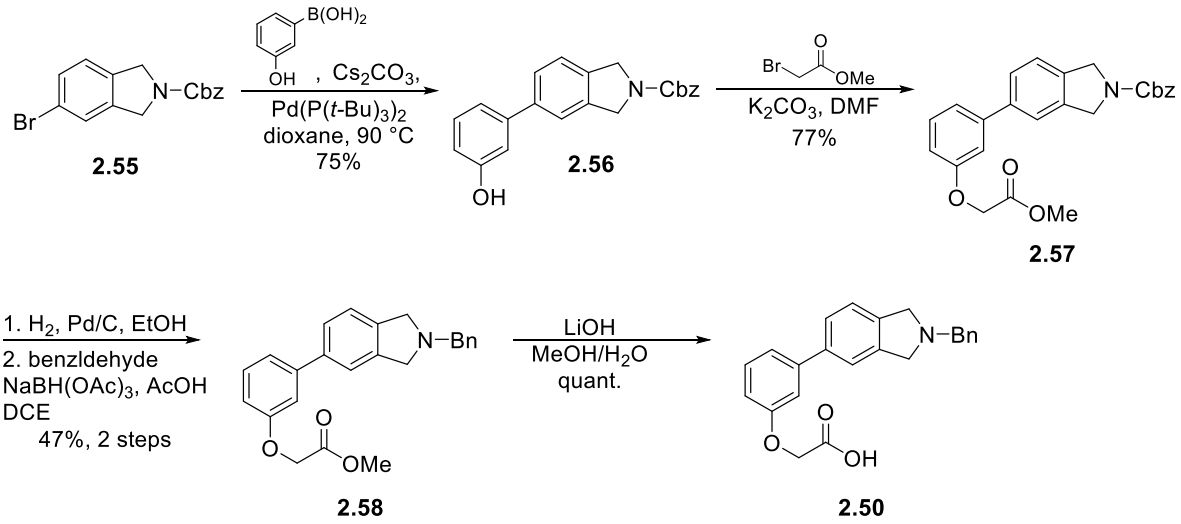
We recognized that alkylation of **2.40** with a bromoacetic acid derivative would give an appropriate functional handle for a diamide linkage. Unfortunately, alkylation of **2.40** with K_2CO_3 and ethyl bromoacetate led to low conversion to the desired product **2.53** (Equation 2.3). When two equivalents of alkylating agent were used, the dialkylated product **2.54** was formed due to the high electrophilicity of the alkylating agent. When reduced to one equivalent of the alkylating agent, a mixture of desired product and quaternary ammonium salt and starting material was obtained.



(2.3)

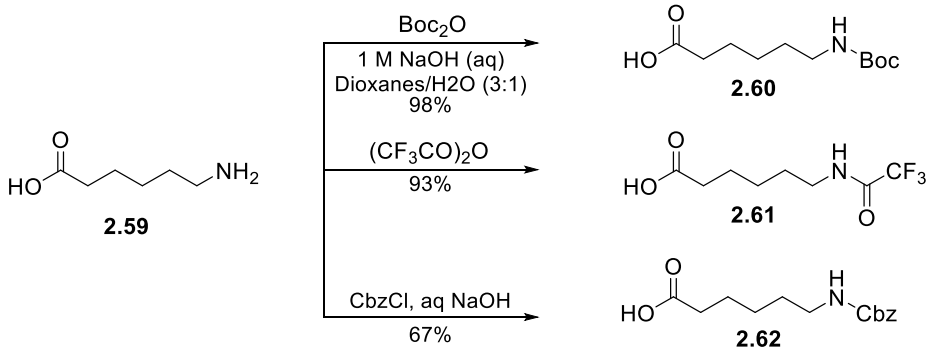
Given the nucleophilic nature of the nitrogen atom, we designed a new synthetic strategy to circumvent this problem. Starting from **2.55**, a Suzuki cross-coupling with 3-hydroxyphenyl boronic acid, gave compound **2.56** in 75% yield (Scheme 2.6). Alkylation of **2.57** with methyl bromoacetate gave **2.58** in 77% yield. Hydrogenolysis and subsequent

reductive amination with benzaldehyde gave compound **2.58** in 47% yield over two steps. Finally, saponification of **2.58** with LiOH gave the desired acid **2.50**.



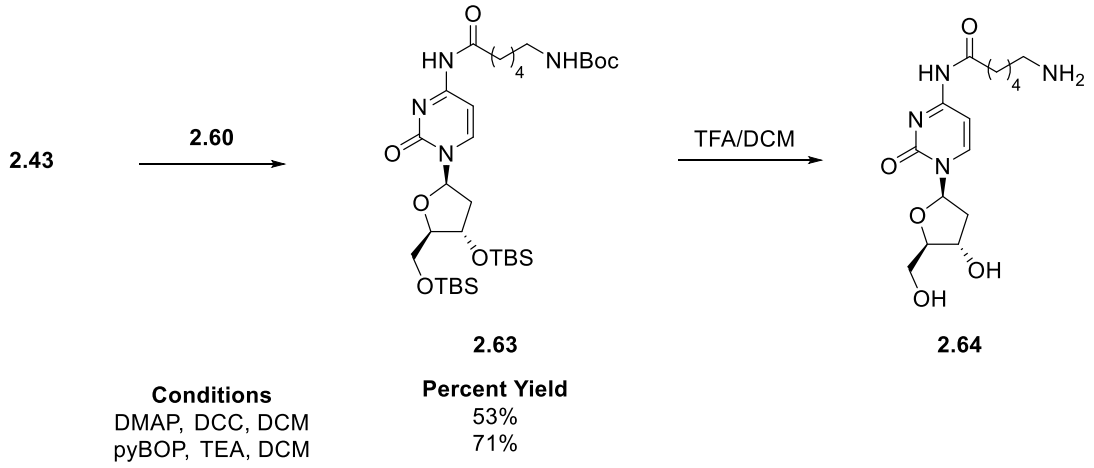
Scheme 2.6: Revised synthesis of compound **2.47**

We then turned our attention to the deoxycytidine model system to obtain the requisite substrate for conjugation. Starting from 6-aminohexanoic acid (**2.59**), the -Boc (**2.60)**, -TFA (**2.62)**, and -Cbz (**2.63**) protected acids were synthesized (Scheme 2.7).

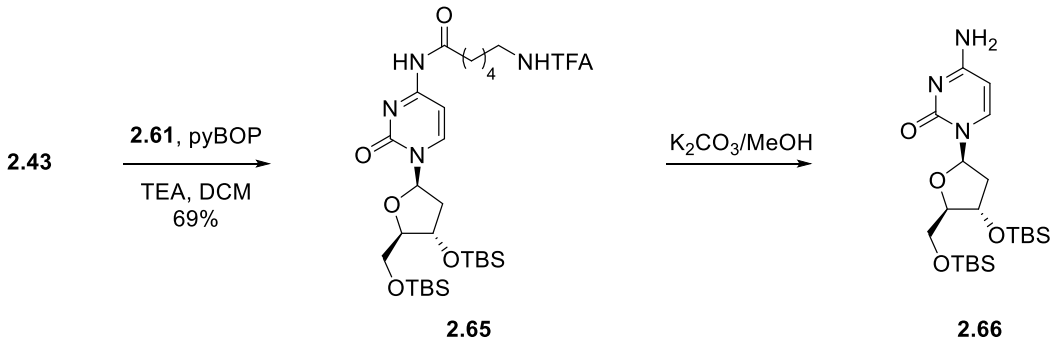


Scheme 2.7: Preparation of amino acid derivatives

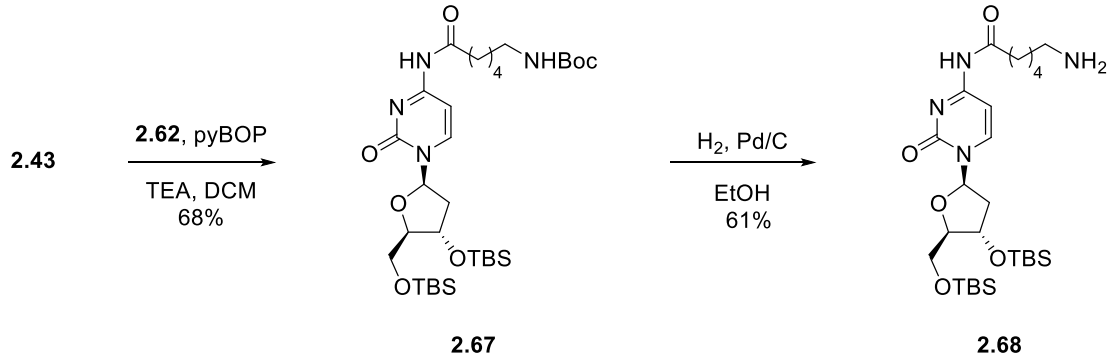
Compound **2.43** and acid **2.60** were coupled with DCC and DMAP to give **2.63** in 47% yield by ^{1}H NMR (Scheme 2.8). Using pyBOP with TEA gave **2.63** in 71% yield by ^{1}H NMR. With compound **2.63** in hand, the -Boc group was removed under standard deprotection conditions, unfortunately the -TBS groups were also removed to give **2.64**. Silyl groups tend to be labile under highly acidic conditions, so the -TFA protected amino acid, **2.61** was chosen next, because -TFA groups are base labile. Treatment of **2.43** and acid **2.61** with pyBOP and TEA gave **2.65** in 69% yield (Scheme 2.9). Subjection of **2.65** to K_2CO_3 in methanol, unfortunately gave exclusively **2.66**. Lastly, the -Cbz protected amino acid, **2.62** was selected, because benzyl carbamates can be removed under neutral conditions. Amide coupling gave **2.67** in 68% yield and subsequent hydrogenation with Pd/C in ethanol gave **2.68** in 61% yield (Scheme 2.10).



Scheme 2.8: Deoxycytidine model system using -Boc as a protecting group



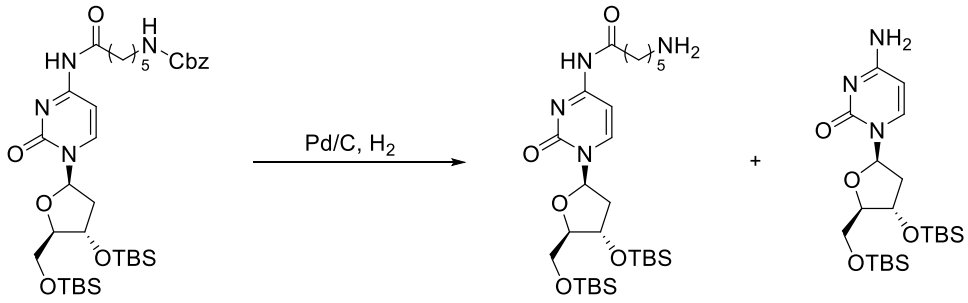
Scheme 2.9: Deoxycytidine model system using -TFA as a protecting group



Scheme 2.10: Deoxycytidine model system using -Cbz as a protecting group

However, upon scale-up, under the same reaction conditions, a mixture (1:1) of **2.68** and **2.43** was obtained (Equation 2.4) suggesting the amide bond is highly labile. Because ethanol is a nucleophilic solvent, it is possible that ethanol cleaved the amide of **2.67** and released **2.43**. It is also possible that once the amine is deprotected, it can cyclize to an ε-lactam and release **2.43**. Accordingly, isopropanol was chosen as solvent because of its steric bulk. When 50 mg of **2.67** was subjected to catalytic hydrogenation, the deprotection was complete in 3 h, giving **2.68** in 60% yield. With this promising result, the reaction was scaled up to 100 mg, but unfortunately after two hours a mixture (1:1) of **2.68**

to **2.43** was again obtained. Additionally, coupling **2.50** with **2.68** was unsuccessful and a new strategy was needed.



2.67 **2.68** **2.43** (2.4)

Solvent	Ratio
EtOH, 1 h	1:1
i-PrOH, 3 h, 50 mg	1:0
i-PrOH, 2 h, 100 mg	1:1

At this point, we turned out attention to aminotetralin Sig2R ligands that were being developed in our lab. Based on **2.69**, these ligands showed that the aminotetralin scaffold tolerates a long aliphatic chain off the exocyclic nitrogen of the scaffold, with **2.70** exhibiting high affinity for Sig2R (Figure 2.11). Until this point, it was unclear which position any of our SigR ligands would tolerate a linker. Given the synthetic difficulties in preparing **2.39 and 2.50**, we decided to utilize the aminotetralin scaffold in our efforts. It was envisioned that an aminotetralin ligand could be conjugated to gemcitabine via an amide linkage. To prepare **2.73**, tetralone **2.71** will undergo reductive amination with an amino acid derivative like **2.72**. This intermediate will have a terminal acid functionality which can be used to chemically link gemcitabine to the Sig2R ligand (**2.73**).

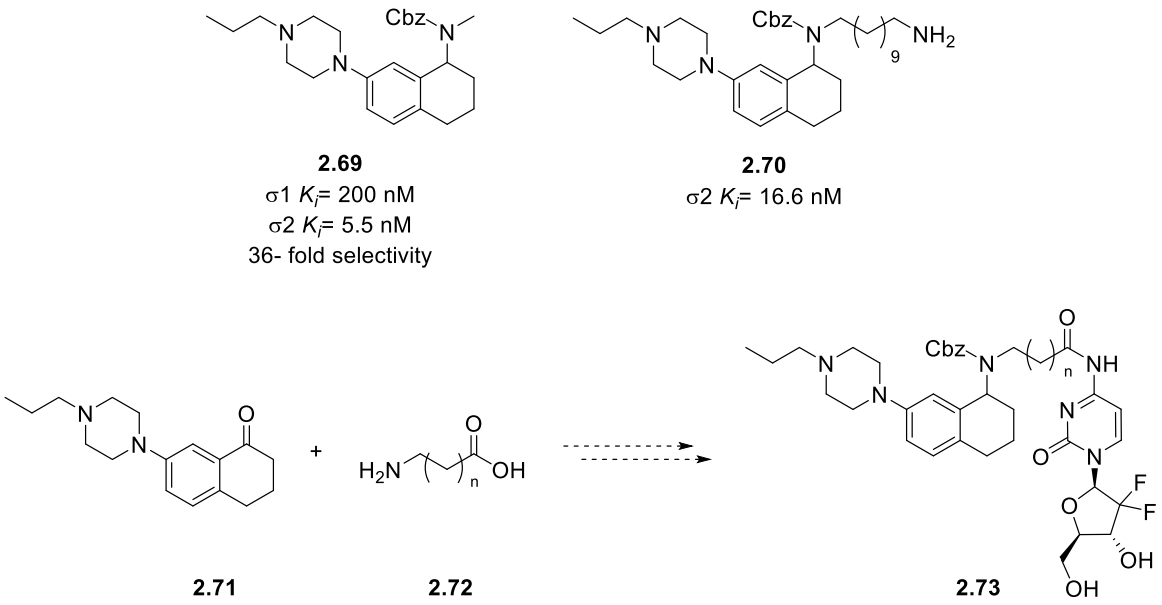
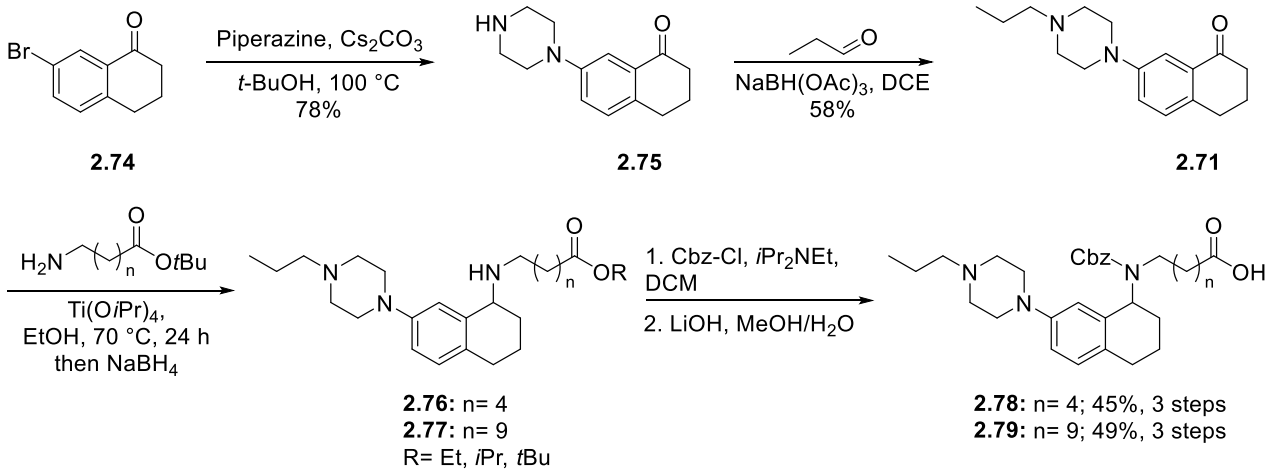


Figure 2.11: Proposed conjugate between aminotetralin Sig2R ligand and gemcitabine

The synthetic route to **2.73** was based on the reported synthesis of **2.70**. Starting from **2.74**, Buchwald-Hartwig cross-coupling with piperazine gave **2.75** in 78% yield, and reductive amination then gave **2.71** in 58% yield (Scheme 2.11). To install the linker, we envisioned that **2.71** would undergo reductive amination with an aliphatic amine with a terminal functional handle. A *tert*-butyl ester was chosen with an aliphatic chain of both 5 and 10 methylene units to probe the effects of chain length between the ligand and gemcitabine. Compound **2.71** was thus subjected to reductive amination with *tert*-butyl 6-aminohexanoate and *tert*-butyl 11-undecanoate in the presence of Ti(O*i*Pr)$_4$ to give **2.76** and **2.77**. It was necessary to heat the reaction to 70-80 °C and 20 equivalents of Ti(O*i*Pr)$_4$ was required; any less would not promote complete conversion to the imine. Unfortunately, Ti(O*i*Pr)$_4$ is also known to facilitate transesterification,[139] even with bulky esters, and a

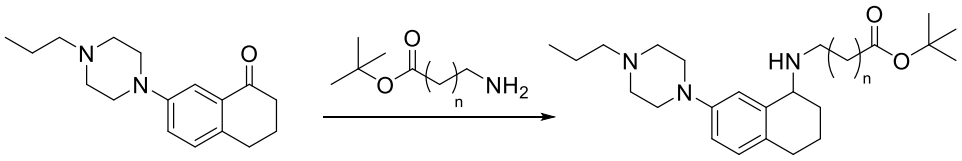
mixture of *tert*-butyl, *iso*-propyl, and ethyl esters was obtained. Subsequent -Cbz protection gave an inseparable mixture of the three esters. Fortunately, all three esters were hydrolyzed with LiOH in methanol to give **2.78** in 45% yield and **2.79** in 49% yield, over three steps.



Scheme 2.11: Synthesis of aminotetralin derivative with conjugate linker

While sufficient quantities were able to be prepared via the above synthesis, the transesterification is a major problem. Ideally, conditions needed to be developed to prevent transesterification so only one product is obtained. One change that could be made would be to choose an aprotic solvent. Using two equivalents of Ti(O*i*Pr)$_4$, toluene at 80 °C led to full conversion to the imine; however, upon reduction there was still a mixture of the *iso*-propyl and *t*ert-butyl esters. Another strategy to overcome the transesterification is to have only one alcohol present by matching the titanium alkoxide with the ester and solvent. Fortunately, Ti(O*t*Bu)$_4$ is a commercially available reagent and was chosen to prevent the use of the ethyl or *iso*-propyl amino esters which may be less stable. In addition,

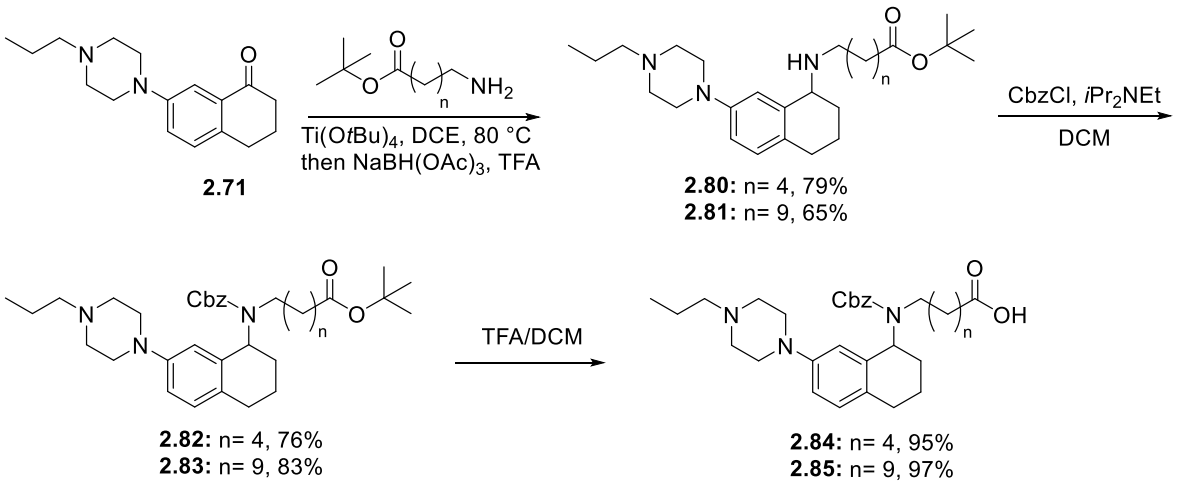
toluene was chosen as the solvent because fewer equivalents of titanium were needed to facilitate imine formation. Treatment of **2.71** with the required amine and Ti(O*t*Bu)$_4$ in toluene followed by reduction with NaBH$_4$ in *tert*-BuOH gave solely **2.80** and **2.81** in 46% yield and 50% yield respectively. In order to get >90% conversion it was necessary to use three equivalents of the amine and four equivalents of Ti(O*t*Bu)$_4$ and heat for 24 h. *Tert*-BuOH did facilitate reduction of the imine, but when diglyme was used instead, compound **2.80** was obtained in 64% yield.



2.71 **2.80:** n= 4 **2.81:** n= 9 (2.5)

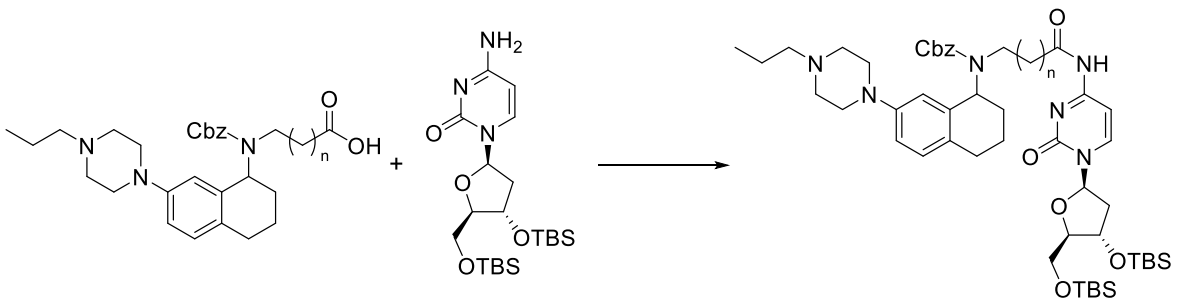
Conditions	**Results**
Ti(O*i*Pr)$_4$, PhMe, 80 °C, then MeOH, NaBH$_4$	full conversion to imine,mixture of *i*Pr and *t*Bu ester
Ti(O*t*Bu)$_4$, PhMe, 80 °C, then *t*BuOH, NaBH$_4$, 50 °C	46-50%
Ti(O*t*Bu)$_4$, PhMe, 80 °C, then diglyme, NaBH$_4$, 50 °C	64%

Despite eliminating the transesterification side reaction, the solvent swap that was necessary for the use of NaBH$_4$ was not ideal, so the use of NaBH(OAc)$_3$ was investigated. Treatment of **2.71** and amine in DCE with Ti(O*t*Bu)$_4$ at 80 °C for 18 h led to full conversion of the imine (Scheme 2.12). The imine could be reduced with NaBH(OAc)$_3$ and AcOH, but a significant rate enhancement was observed when TFA was used as the acid, giving **2.80** in 79% yield and **2.81** in 65% yield. For the full consumption of the ketone, four and six equivalents of amine were required when n=4 and n=9 respectively. Both **2.80** and **2.81** were then acylated with Cbz-Cl to give **2.82** and **2.83** in 76% and 83% yields, respectively. Lastly treatment of **2.82** and **2.83** with TFA gave **2.84** and **2.85** in nearly quantitative yield.



Scheme 2.12: Optimized synthetic route for preparation of aminotetralin derivative with functional handle for conjugation

With significant quantities of **2.84** and **2.85**, a series of conditions were screened for the coupling of compound **2.43** and ligands **2.84** and **2.85** (Equation 2.6). The results were monitored by ^{1}H NMR by comparing the integration of the C6-H peak, which shifts upon acylation of the exocyclic nitrogen atom. After a screen of several peptide coupling reagents, we found that EDCI·HCl and HOBt led to full conversion to **2.86**.



(2.6)

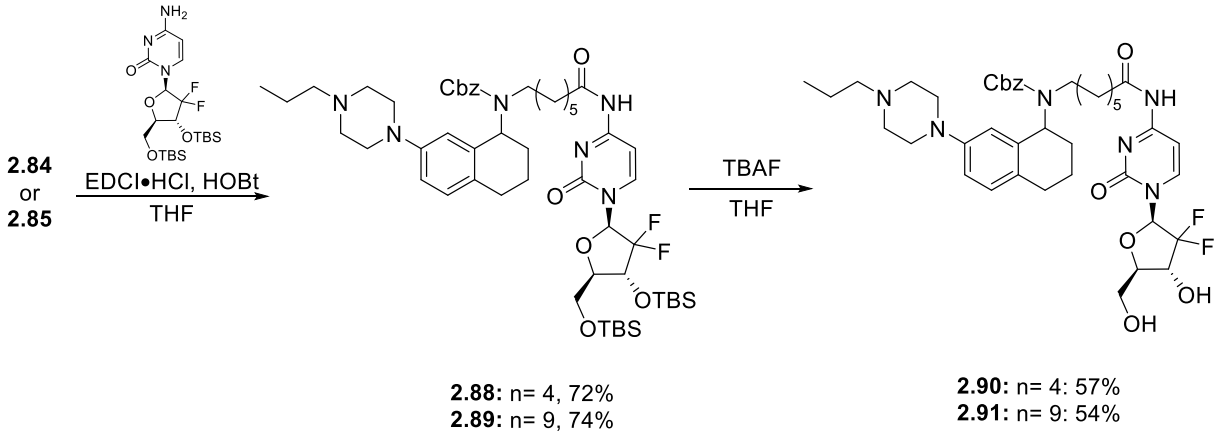
2.84: n= 4
2.85: n= 9

2.43

2.86: n= 4
2.87: n= 9

Conditions	% Yield by ^{1}H NMR	
	n= 4	n= 9
pyBOP, TEA, DCM or DMF	no rxn	62%
DIC, DMAP, TEA, DCM	81%	84%
EDCI•HCl, DMAP, TEA, DCM	38%	45%
EDCI•HCl, HOBt, THF	100%	N/A

With optimized conditions for the peptide coupling reaction, the stage was set to prepare the gemcitabine analog. Ligand **2.84** and TBS-gemcitabine were coupled using EDCI·HCl and HOBt to give **2.88** in 72% isolated yield. Similarly, **2.87** was prepared in 74% isolated yield. Subsequent TBS deprotection using TBAF gave the target conjugates **2.90** and **2.91** (Scheme 2.13). It is important to note that these conjugates are not stable as the amine salts. Both conjugates were purified by HPLC using a buffered MeCN/H_2O (0.1% TFA) solvent system. Upon lyophilization of the desired fractions, the product was isolated as the TFA salt, which decomposed over time. Therefore, it was necessary to basify the fractions and isolate the free base of the conjugates.



Scheme 2.13: Preparation of Sig2R ligand-gemcitabine conjugate

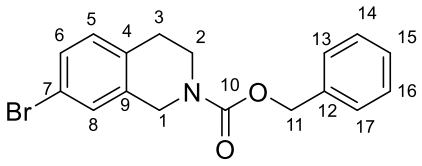
In conclusion, we have successfully conjugated a Sig2R selective ligands to the anticancer agent, gemcitabine, which represent the first examples of gemcitabine conjugated to a Sig2R ligand. The two conjugates were prepared with varying linker lengths between the ligand and gemcitabine to ensure that the Sig2R ligand will be recognized by the receptor. Currently these conjugates are undergoing biological assays in human (Panc01) and mouse (Panc02) pancreatic cancer cell lines known to overexpress Sig2R. The cellular uptake of both the conjugate and free gemcitabine will be evaluated in both Panc01/Panc02 and a control cell line, BXPC3 (human pancreatic adenocarcinoma cells that do not overexpress Sig2R), to probe whether the conjugate shows improved uptake and if this increase is mediated by Sig2R. Additionally, the cytotoxicity of the conjugate, the Sig2R ligand, gemcitabine, and the ligand/gemcitabine in combination will be evaluated in both cell lines. Based on the results of these two studies, we hope to show that our conjugate is the most cytotoxic, mediated by not only increased uptake through Sig2R uptake mechanisms, but also through dual action cytotoxicity through use of a Sig2R agonist. If our conjugates meet these criteria, they will represent a potential gemcitabine

prodrug with a unique mechanism of action. Such a discovery would open the door to new therapeutic strategies for treating some of the most resistant lines of cancer.

CHAPTER 3: EXPERIMENTAL METHODS

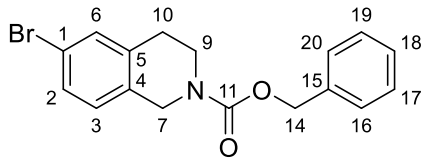
General. All solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. All reagents were reagent grade and used without purification unless otherwise noted. Methylene chloride (CH_2Cl_2), triethylamine (Et_3N) and diisopropylethylamine (*i*-Pr_2NEt) were distilled from calcium hydride immediately prior to use. Where required, solvents were degassed by sparging with argon prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator. Thin-layer chromatography (TLC) was performed on EMD 60 F254 glass-backed pre-coated silica gel plates and were visualized using one or more of the following methods: UV light (254 nm) and staining with basic potassium permanganate ($KMnO_4$) or acidic *p*-anisaldehyde (PAA). Infrared (IR) spectra were obtained with a Thermo Scientific Nicolet IR-100 FT-IR series spectrometer as thin films on sodium chloride plates and reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent and are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.

Preparation of tetrahydroisoquinoline scaffolds



1.47

Benzyl 7-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.47). KTL-01-221. A solution of H_2SO_4 (3 ml) and AcOH (6 mL) was cooled in an ice bath for 10 min. Paraformaldehyde (1.00 g, 33.3 mmol) and benzyl (4-bromophenethyl)carbamate (0.92 g, 2.75 mmol) were added to the cooled solution and the reaction was stirred for 10 min at 0 °C, where upon the reaction was poured onto ice (ca. 50 g). When the ice melted, the aqueous solution was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (5:95) to give 720 mg (76%) of **1.47** as a clear oil. ^{1}H NMR was consistent with literature.

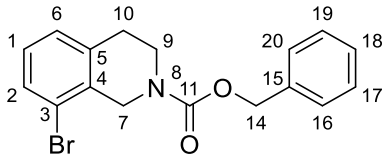


1.45

Benzyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.45). KTL-01-202. A solution of 6-bromo-dihydroisoquinoline (300 mg, 1.42 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C and iPr_2NEt (243 mg, 1.88 mmol) and CbzCl (322 mg, 1.88 mmol) were

added. The reaction was stirred at room temperature for16 h. The reaction was diluted with CH_2Cl_2 (10 mL) and poured into water (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography eluting with EtOAc:hexanes (5:95) to give 400 mg (81%) of **1.45** as a clear oil: ^{1}H NMR (400 MHz) δ 7.41 – 7.27 (comp, 7 H), 6.97 (d, *J* = 10.3 Hz, 1 H), 5.18 (s, 2 H), 4.59 (s, 2 H), 3.70 (br s, 2 H), 2.82 (br s, 2 H); HRMS (ESI) m/z $C_{17}H_{16}BrNO_2$ $(M+Na)^+$ calcd for 368.0257 and 370.0238; found 368.0257 and 370.0238.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.41 – 7.27 (comp, 7 H, C2-H, C6-H, and C16-H thru C20-H), 6.97 (d, *J* = 10.3 Hz, 1 H, C3-H), 5.18 (s, 2 H, C14-H), 4.59 (s, 2 H, C7-H), 3.70 (br s, 2 H, C9-H), 2.82 (br s, 2 H, C10-H).



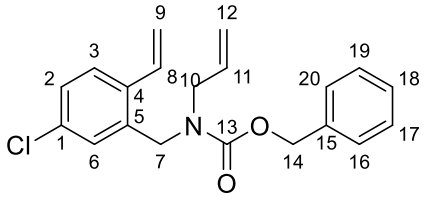
1.43a

Benzyl 6-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.43a). KTL-02-108. A solution of 8-bromo-dihydroisoquinoline (300 mg, 1.42 mmol) in CH_2Cl_2 (14 mL) was cooled to 0 °C and iPr_2NEt (370 mg, 2.8 mmol) and CbzCl (480 mg, 2.8 mmol) were added. The reaction was stirred at room temperature for16 h. The reaction was diluted with CH_2Cl_2 (10 mL) and poured into water (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified via flash column

chromatography eluting with EtOAc:hexanes (5:95) to give 401 mg (83%) of **1.43a** as a clear oil: ^{1}H NMR (400 MHz) δ 7.44 – 7.29 (comp, 6 H), 7.11 – 7.01 (comp, 2 H), 5.21 (s, 2 H), 4.62 (s, 2 H), 3.71 (t, *J* = 5.8 Hz, 2 H), 2.85 (br s, 2 H).

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.44 – 7.29 (comp, 6 H, C2-H, C16-H thru C20-H), 7.11 – 7.01 (comp, 2 H, C1-H and C6-H), 5.21 (s, 2 H, C14-H), 4.62 (s, 2 H, C7-H), 3.71 (t, *J* = 5.8 Hz, 2 H, C9-H), 2.85 (br s, 2 H, C10-H).

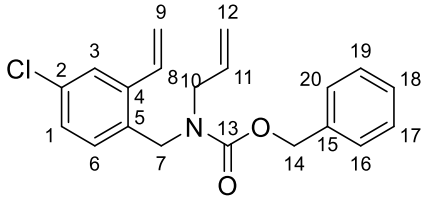
Representative procedure for reductive amination/-Cbz protection of benzaldehydes



1.59

Benzyl allyl(5-chloro-2-vinylbenzyl)carbamate (1.59). KTL-02-076. A solution of **1.52** (815 mg, 4.9 mmol) and allyl amine (750 ul, 9.8 mmol) in CH_2Cl_2 (30 mL) with $MgSO_4$ (2.6 g) was stirred overnight. The reaction was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in MeOH (24 mL), and $NaBH_4$ (400 mg) was added. The reaction was stirred for 20 min and then concentrated to half volume. Aqueous NaOH (1 M, 60 mL) was added and the aqueous layer was extracted with Et_2O (3 x 60 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 1.1 g (70%) of the secondary amine intermediate as a clear oil of sufficient purity for use in subsequent reactions As solution of the secondary amine (700 mg, 3.36 mmol) in CH_2Cl_2 (34 mL) was cooled to 0 °C and *i*Pr_2NEt (0.87 g, 6.73 mmol) and CbzCl (1.15 g, 6.73 mmol) were added. The bath was removed, and the reaction

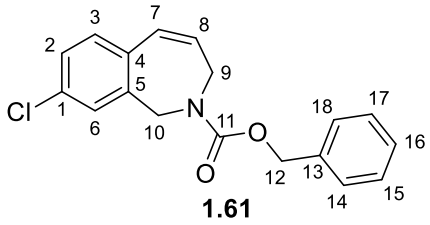
was stirred at room temperature for 16 h. The reaction was diluted with CH_2Cl_2 (30 mL) and poured into water (60 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (5:95) to give 950 mg (83%) of **1.59** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.35 (comp, 6 H), 7.23 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.14 (d, *J* = 12.9 Hz, 1 H), 6.86 (m, 1 H), 5.74 (s, 1 H), 5.59 (d, *J* = 17.1 Hz, 1 H), 5.34 – 5.01 (comp, 5 H), 4.54 (comp, 2 H), 3.83 (comp, 2 H); HRMS (ESI) *m/z* $C_{20}H_{20}ClNO_2$ $(M+Na)^+$ calcd for 364.1075 and 366.1053; found 364.1079 and 366.1051.



1.60

Benzyl allyl(4-chloro-2-vinylbenzyl)carbamate (1.60). KTL-02-084. Prepared according to the representative procedure outlined for reductive amination/-Cbz protection of benzaldehydes. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (5:95) to give 1.61 g (80% over two steps) of **1.60** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.52 – 7.28 (comp, 7 H), 7.22 – 7.15 (m, 1 H), 7.08 (d, *J* = 25.3 Hz, 1 H), 6.84 (dt, *J* = 45.8, 16.0 Hz, 1 H), 5.76 (d, *J* = 26.2 Hz, 1 H), 5.62 (d, *J* = 17.7 Hz, 1 H), 5.37 – 5.24 (m, 1 H), 5.22 – 4.98 (comp, 5 H), 4.55 (s, 1.13 H), 4.51 (s, 0.84 H), 3.83 (s, 0.83 H), 3.74 (s, 1.26 H).

Representative procedure for RCM

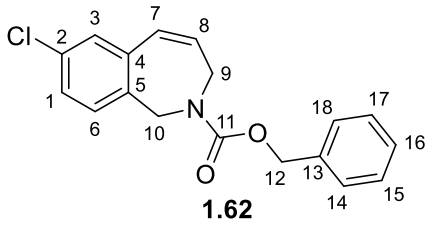


1.61

Benzyl 8-chloro-1,3-dihydro-2H-benzo[c]azepine-2-carboxylate (1.61). KTL-02-077. Grubbs second generation catalyst (118 mg, 0.14 mmol) was added to a solution of intermediate **1.59** (950 mg, 2.78 mmol) in CH_2Cl_2 (56 mL) and the reaction was stirred at room temperature overnight. The reaction was concentrated under reduced pressure and DMSO (1 mL) was added to the crude material and the solution was stirred overnight. The crude material was purified via flash column chromatography eluting EtOAc:hexanes (1:9) to give 650 mg (75%) of **1.61** as a white solid: ^{1}H NMR (400 MHz, rotamers) δ 7.34-7.30 (comp, 4 H), 7.26-7.19 (comp, 2 H), 7.11-7.09 (comp, 2 H), 6.45-6.39 (comp, 1 H), 5.85-5.75 (comp, 1 H), 5.09 (s, 0.70 H), 5.07 (s, 1.30 H), 4.48 – 4.30 (comp, 4 H); ^{13}C NMR (101 MHz, rotamers) δ 155.7, 155.4, 139.5, 139.3, 136.7, 136.6, 134.2, 133.9, 133.0, 132.5, 132.4, 132.2, 130.9, 130.2, 129.0, 128.8, 128.4, 128.33, 128.29, 128.26, 128.18, 127.82, 127.7, 67.7, 67.6, 51.4, 50.9, 50.8, 50.5.

NMR Assignment. : ^{1}H NMR (400 MHz, rotamers) δ 7.34-7.30 (comp, 4 H, C14-H, C15-H, C17-H, and C18-H), 7.26-7.19 (comp, 2 H, C3-H and C16-H), 7.11-7.09 (comp, 2 H, C2-H and C6-H), 6.45-6.39 (comp, 1 H, C7-H), 5.85-5.75 (comp, 1 H, C8-H), 5.09 (s, 0.70 H, C12-H), 5.07 (s, 1.30 H, C12-H), 4.48 – 4.30 (comp, 4 H, C9-H and C10-H); ^{13}C NMR (101 MHz, rotamers) δ 155.7 (C11), 155.4 (C11), 139.5 (C5), 139.3 (C5), 136.7

(C13), 136.6 (C13), 134.2 (C4), 133.9 (C4), 133.0 (C7), 132.5 (C1), 132.4 (C7), 132.2 (C1), 130.9 (C8), 130.2 (C8), 128.9 (C6), 128.8 (C15 and C17), 128.37 (C6), 128.33 (C3), 128.29 (C3), 128.26 (C16), 128.18 (C14 and C18), 127.8 (C2), 127.7 (C2), 67.7 (C12), 67.6 (C12), 51.4 (C9), 50.9 (C9), 50.8 (C10), 50.5 (C10).



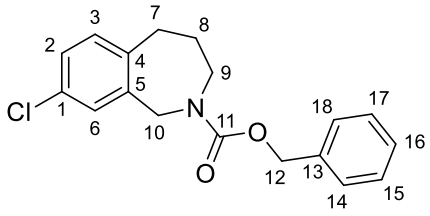
1.62

Benzyl 7-chloro-1,3-dihydro-2H-benzo[c]azepine-2-carboxylate (1.62). KTL-02-085. Prepared according to the representative procedure outlined for RCM. The crude material was purified via flash column chromatography eluting EtOAc:hexanes (5:95) to give 661 mg (72%) of **1.62** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.33 – 7.28 (comp, 4 H), 7.21 – 7.13 (comp, 3 H), 7.05 (dd, *J* = 8.0, 2.1 Hz, 0.80 H), 6.99 (d, *J* = 8.0 Hz, 0.80 H), 6.43 – 6.38 (m, 1 H), 5.92 – 5.80 (m, 1 H), 5.06 (s, 0.80 H), 5.04 (s, 1.20 H), 4.45 (t, *J* = 2.9 Hz, 1.20 H), 4.41 – 4.40 (comp, 1.60 H), 4.37 (s, 1.20 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.2, 137.1, 136.9, 136.5, 136.0, 135.9, 133.2, 131.7, 131.1, 130.5, 130.4, 130.1, 129.7, 128.5, 128.4, 128.03, 127.97, 127.8, 127.0, 126.5, 67.3, 50.9, 50.51, 50.48, 50.2.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.33 – 7.28 (comp, 4 H, C14-H, C15-H, C17-H, and C18-H), 7.21 – 7.13 (comp, 2.8 H, C1-H, C3-H, C6-H, and C16-H), 7.05 (dd, *J* = 8.0, 2.1 Hz, 0.80 H, C1-H), 6.99 (d, *J* = 8.0 Hz, 0.80 H, C6-H), 6.43 – 6.38 (m, 1 H, C7-H), 5.92 – 5.80 (m, 1 H, C8-H), 5.06 (s, 0.80 H, C12-H), 5.04 (s, 1.20 H, C12-H), 4.45 (t, *J* = 2.9 Hz, 1.20 H, C9-H), 4.41 – 4.40 (comp, 1.60 H, C9-H and C10-H), 4.37 (s,

1.20 H, C10-H); ^{13}C NMR (101 MHz, rotamers) δ 155.5 (C11), 155.2 (C11), 137.1 (C4), 136.9 (C4), 136.5 (C13), 136.0 (C5), 135.9 (C5), 133.2 (C7), 131.7 (C7), 131.1 (C3), 130.5 (C8), 130.4 (C8), 130.1 (C2), 129.7 (C2), 128.5 (C15 and C17), 128.4 (C15 and C17), 128.03 (C14 and C18), 127.97 (C14 and C18), 127.8 (C16), 127.0 (C1), 126.5 (C1), 67.3 (C12), 50.9 (C10), 50.51 (C10), 50.48 (C9), 50.2 (C9).

Representative procedure for hydrogenation with Adam's catalyst

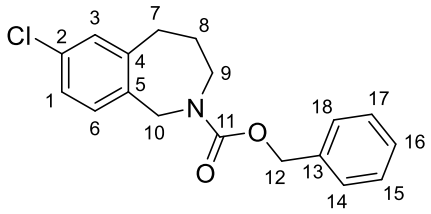


1.63

Benzyl 8-chloro-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.63). KTL-02-078. A solution of carbamate **1.61** (650 mg, 2.07 mmol) in EtOH (24 mL) and Pt_2O (30 mg, 0.13 mmol) was stirred under an atmosphere of H_2 until consumption of starting material was observed. The reaction was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure to provide 550 mg (84%) of **1.63** as a brown solid that was of sufficient purity for use in subsequent reactions: ^{1}H NMR (400 MHz, rotamers) δ 7.40-7.27 (comp, 5.5 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.08 (s, 1.5 H), 5.07 (s, 0.70 H), 5.04 (s, 1.30 H), 4.43 (s, 0.70 H), 4.37 (s, 1.30 H), 3.77-3.70 (comp, 2 H), 2.94-2.91 (comp, 2 H), 1.83-1.72 (comp, 2 H); ^{13}C NMR (126 MHz, rotamers) δ 155.5, 155.3, 140.4, 140.2, 140.1, 140.0, 136.8, 136.5, 131.8, 131.5, 131.0, 130.9, 129.6, 129.4, 128.65, 128.56, 128.2, 128.2, 128.1, 128.0, 127.53, 127.46, 67.6, 67.2, 52.2, 51.7, 51.1, 50.6, 34.8, 28.6, 28.0;

HRMS (ESI) *m/z* $C_{18}H_{18}ClNO_2$ $(M+Na)^+$ calcd for 338.0918 and 340.0895; found 338.0920 and 340.0895.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.40-7.27 (comp, 5.5 H, C6-H and C14-H thru C18-H), 7.13 (d, *J* = 8.0 Hz, 1 H, C2-H), 7.08 (s, 1.5 H, C3-H and C6-H), 5.07 (s, 0.70 H, C12-H), 5.04 (s, 1.30 H, C12-H), 4.43 (s, 0.70 H, C10-H), 4.37 (s, 1.30 H, C10-H), 3.77-3.70 (comp, 2 H, C9-H), 2.94-2.91 (comp, 2 H, C7-H), 1.83-1.72 (comp, 2 H, C8-H); ^{13}C NMR (126 MHz, rotamers) δ 155.5 (C11), 155.3 (C11), 140.4 (C4 or C5), 140.2 (C4 or C5), 140.1 (C4 or C5), 140.0 (C4 or C5), 136.8 (C13), 136.5 (C13), 131.8 (C1), 131.5 (C1), 131.0 (C3), 130.9 (C3), 129.6 (C6), 129.4 (C6), 128.65 (C15 and C17), 128.56 (C15 and C17), 128.2 (C14 and C18), 128.2 (C14 and C18), 128.1 (C16), 128.0 (C16), 127.53 (C2), 127.46 (C2), 67.6 (C12), 67.2 (C12), 52.2 (C10), 51.7 (C10), 51.1 (C9), 50.6 (C9), 34.8 (C7), 28.6 (C8), 28.0 (C8).



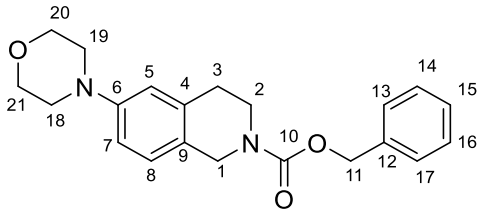
1.64

Benzyl 7-chloro-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.64). KTL-02-086. Prepared according to the representative procedure outlined for hydrogenation with Adam's catalyst. The reaction was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure to provide 620 mg (94%) of **1.64** as a brown oil that was of sufficient purity for use in subsequent reactions: ^{1}H NMR (400 MHz, rotamers) δ 7.37 – 7.26 (m, 5 H), 7.16 – 7.11 (comp, 1.40 H), 7.03 (dd, *J* = 8.0, 2.2 Hz, 0.60 H), 6.98

(d, *J* = 8.0 Hz, 0.60 H), 5.05 (s, 0.70 H), 5.04 (s, 1.30 H), 4.43 (s, 0.70 H), 4.40 (s, 1.30 H), 3.75 (br s, 2 H), 2.95 – 2.87 (comp, 2 H), 1.85 – 1.70 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.4, 155.2, 143.8, 143.5, 136.9, 136.7, 136.6, 133.0, 130.9, 130.6, 129.6, 129.5, 128.5, 128.4, 128.0, 127.9, 127.8, 126.1, 125.8, 67.2, 67.1, 51.9, 51.3, 50.8, 50.5, 35.1, 28.4, 27.8; LRMS (ESI+APCI) *m/z* $C_{18}H_{18}ClNO_2$ $(M+H)^+$ calcd for 316.11; found 316.2.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.37 – 7.26 (m, 5 H, C14-H thru C18-H), 7.16 – 7.11 (comp, 1.40 H, C1-H, C3-H, and C6-H), 7.03 (dd, *J* = 8.0, 2.2 Hz, 0.60 H, C1-H), 6.98 (d, *J* = 8.0 Hz, 0.60 H, C6-H), 5.05 (s, 0.70 H, C12-H), 5.04 (s, 1.30 H, C12-H), 4.43 (s, 0.70 H, C10-H), 4.40 (s, 1.30 H, C10-H), 3.75 (br s, 2 H, C9-H), 2.95 – 2.87 (comp, 2 H, C7-H), 1.85 – 1.70 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.4 (C11), 155.2 (C11), 143.8 (C4), 143.5 (C4), 136.9 (C5), 136.7 (C13), 136.6 (C5), 133.0 (C3), 130.9 (C2), 130.6 (C2), 129.6 (C6), 129.5 (C6), 128.5 (C15 and C17), 128.4 (C15 and C17), 128.0 (C14 and C18), 127.9 (C14 and C18), 127.8 (C16), 126.1 (C1), 125.8 (C1), 67.2 (C12), 67.1 (C12), 51.9 (C10), 51.3 (C10), 50.8 (C9), 50.5 (C9), 35.1 (C7), 28.4 (C8), 27.8 (C8).

Representative procedure for Buchwald-Hartwig cross-coupling

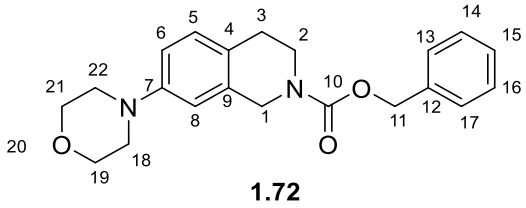


1.73

Benzyl 7-morpholino-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.73). KTL-01-215. A solution of carbamate **1.47** (100 mg 0.29 mmol), NaO-*t*-Bu (38 mg 0.40 mmol), morpholine (35 mg 0.40 mmol) in degassed toluene was stirred for 5 min. A freshly prepared solution of $Pd(OAc)_2$ and JohnPhos (1:1, 0.19 mL, 0.1 M) that had been stirred for 30 min, was added via syringe. The solution was heated at 100 °C for 5 h, where upon the reaction was cooled to room temperature, poured into 2 mL of water, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (25:75) to give 78 mg (76%) of **1.73** as a clear oil: ^{1}H NMR (400 MHz) δ 7.42-7.29 (comp, 5 H), 7.03 (dd, *J* = 18.8, 7.6 Hz, 1 H), 6.78 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.67 (s, 1 H), 5.18 (s, 2 H), 4.58 (s, 2 H), 3.84 (t, *J* = 4.8 Hz, 4 H), 3.71 (br s, 2 H), 3.13 (t, *J* = 4.8 Hz, 4 H), 2.82 (br s, 2 H); ^{13}C NMR (100 MHz, rotamers) δ 155.5, 155.4, 149.9, 136.8, 135.4, 135.2, 128.5, 128.0, 127.9, 127.1, 126.9, 125.1, 124.6, 115.6, 115.4, 114.4, 67.1, 66.9, 49.5, 45.2, 41.6, 41.4, 29.4, 29.2; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 375.1679; found 375.1684.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.42-7.29 (comp, 5 H, C12-H thru C17-H), 7.03 (dd, *J* = 18.8 Hz, 7.6 Hz, 1 H, C8-H), 6.78 (dd, *J* = 8.4 Hz, 2.4 Hz, 1 H, C7-H),

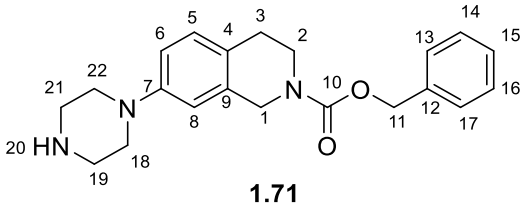
6.67 (s, 1 H, C5-H), 5.18 (s, 2 H, C11-H), 4.58 (s, 2 H, C1-H), 3.84 (t, *J* = 4.8 Hz, 4 H, C18-H and C19-H), 3.71 (br s, 2 H, C2-H), 3.13 (t, *J* = 4.8 Hz, 4 H, C20-H and C21-H), 2.82 (br s, 2 H, C3-H); ^{13}C NMR (100 MHz, rotomers) δ 155.5 (C10), 155.4 (C10), 149.9 (C6), 136.8 (C12), 135.4 (C4), 135.2 (C4), 128.5 (C13 and C17), 128.0 (C14 and C16), 127.9 (C15), 127.1 (C8), 126.9 (C8), 125.1 (C9), 124.6 (C9), 115.6 (C5), 115.4 (C5), 114.4 (C7), 67.1 (C11), 66.9 (C20 and C21), 49.5 (C18 and C19), 45.2 (C1), 41.6 (C2), 41.4 (C2), 29.4 (C3), 29.2 (C3).



1.72

Benzyl 7-morpholino-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.72). KTL-03-138. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (20:80) to give 30 mg (55%) of **1.72** as an off white solid: ^{1}H NMR (499 MHz) δ 7.44 – 7.29 (comp, 5 H), 7.05 (d, *J* = 8.4 Hz, 1 H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.64 (d, *J* = 25.5 Hz, 1 H), 5.18 (s, 2 H), 4.62 (s, 2 H), 3.86 (t, *J* = 4.7 Hz, 4 H), 3.76 – 3.63 (comp, 2 H), 3.11 (t, *J* = 4.7 Hz, 4 H), 2.83 – 2.72 (comp, 2 H); ^{13}C NMR (126 MHz, rotamers) δ 155.5, 149.9, 136.8, 134.2, 133.7, 129.5, 129.3, 128.5, 128.0, 127.9, 126.2, 126.1, 114.8, 114.7, 113.3, 113.1, 67.23, 67.15, 66.9, 49.6, 46.1, 46.0, 42.0, 41.7, 28.1, 27.9; LRMS (ESI+APCI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 353.19; found 353.2.

NMR Assignment. ^{1}H NMR (499 MHz) δ 7.44 – 7.29 (comp, 5 H, C13-H thru C17-H), 7.05 (d, *J* = 8.4 Hz, 1 H, C5-H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1 H, C6-H), 6.64 (d, *J* = 25.5 Hz, 1 H, C8-H), 5.18 (s, 2 H, C11-H), 4.62 (s, 2 H, C1-H), 3.86 (t, *J* = 4.7 Hz, 4 H, C19-H and C21-H), 3.76 – 3.63 (comp, 2 H, C2-H), 3.11 (t, *J* = 4.7 Hz, 4 H, C18-H and C22-H), 2.83 – 2.72 (comp, 2 H, C3-H); ^{13}C NMR (126 MHz, rotamers) δ 155.5 (C10), 149.9 (C7), 136.8 (C12), 134.2 (C9), 133.7 (C9), 129.5 (C5), 129.3 (C5), 128.5 (C14 and C16), 128.0 (C13 and C17), 127.9 (C15), 126.2 (C4), 126.1 (C4), 114.8 (C6), 114.7 (C6), 113.3 (C8), 113.1 (C8), 67.23 (C11), 67.15 (C11), 66.9 (C19 and C21), 49.6 (C18 and C22), 46.1 (C1), 46.0 (C1), 42.0 (C2), 41.7 (C2), 28.1 (C3), 27.9 (C3).

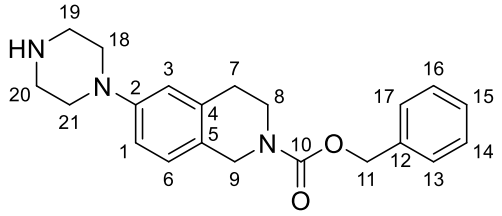


1.71

Benzyl 7-(piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.71). KTL-01-226. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with MeOH:TEA:CH_2Cl_2 (1:1:98) to give 170 mg (85%) of **1.71** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 5 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.78 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.65 (d, *J* = 20.8 Hz, 1 H), 5.18 (s, 2 H), 4.61 (s, 2 H), 3.70 (br s, 2 H), 3.12 – 3.05 (comp, 4 H), 3.05 – 2.97 (comp, 4 H), 2.76 (br s, 2 H), 1.84 (s, 1 H); ^{13}C NMR (126 MHz, rotamers) δ 155.5, 150.1, 136.8, 134.1, 133.7, 129.5, 129.2, 128.5, 128.0, 127.9, 126.3,

126.1, 115.4, 115.3, 115.1, 114.0, 113.7, 67.2, 50.0, 46.0, 45.6, 42.0, 41.7, 28.1, 27.9; LRMS (ESI+APCI) *m/z* $C_{21}H_{25}N_3O_2$ $(M+H)^+$ calcd for 352.20; found 352.3.

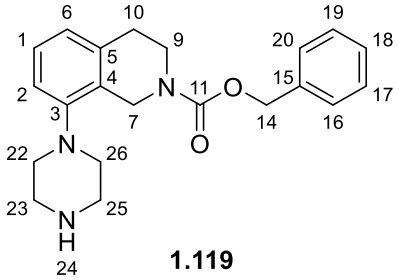
NMR Assignment. ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 5 H, C13-H thru C17-H), 7.03 (d, *J* = 8.0 Hz, 1 H, C5-H), 6.78 (dd, *J* = 8.4, 2.4 Hz, 1 H, C6-H), 6.65 (d, *J* = 20.8 Hz, 1 H, C8-H), 5.18 (s, 2H, C11-H), 4.61 (s, 2H, C1-H), 3.70 (br s, 2H, C2-H), 3.12 – 3.05 (comp, 4 H, C19-H and C21-H), 3.05 – 2.97 (comp, 4 H, C18-H and C22-H), 2.76 (br s, 2 H, C2-H), 1.84 (s, 1 H, 20-H). ^{13}C NMR (126 MHz, rotamers) δ 155.5 (C10), 150.1 (C7), 136.8 (C12), 134.1 (C9), 133.7 (C9), 129.5 (C5), 129.2 (C5), 128.5 (C14 and C16), 128.0 (C13 and C17), 127.9 (C15), 126.3 (C4), 126.1 (C4), 115.4 (C6), 115.1 (C6), 114.0 (C8), 113.7 (C8), 67.2 (C11), 50.0 (C18 and C22), 46.0 (C1), 45.6 (C19 and C21)), 42.0 (C2), 41.7 (C2), 28.1 (C3), 27.9 (C3).



1.109

Benzyl 6-(piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.109). KTL-02-069. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with MeOH:TEA:CH_2Cl_2 (1:1:98) to give 163 mg (80%) of **1.109** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.42 – 7.29 (comp, 5 H), 7.06 – 6.94 (m, 1 H), 6.79 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.68 (s, 1 H), 5.17 (s, 2 H), 4.57 (s, 2 H), 3.70 (br s, 2 H), 3.18 – 3.10 (comp, 4 H), 3.09 – 3.01 (comp, 4 H), 2.81 (br s, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 150.1, 149.6,

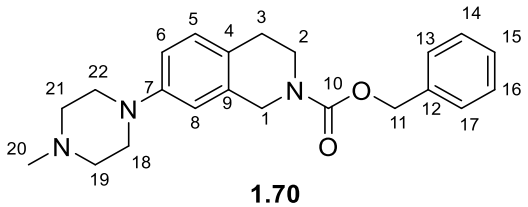
136.8, 135.4, 135.3, 128.5, 128.0, 127.0, 116.5, 115.8, 115.3, 114.8, 67.1, 51.5, 49.3, 48.9, 48.6, 45.2, 44.8, 41.5, 29.4, 29.2.



1.119

Benzyl 8-(piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.119). KTL-02-111. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with MeOH:TEA:CH_2Cl_2 (1:1:98) to give 35 mg (69%) of **1.119** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.43 – 7.28 (comp, 5 H), 7.18 (t, *J* = 7.7 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.91 (s, 1 H), 5.18 (s, 2 H), 4.67 (s, 2 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 3.12 – 2.96 (comp, 4 H), 2.86 (s, 6 H), 2.42 (s, 1 H); LRMS (ESI+APCI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 353.19; found 353.3.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.43 – 7.28 (comp, 5 H, C16-H thru C20-H), 7.18 (t, *J* = 7.7 Hz, 1 H, C1-H), 6.98 (d, *J* = 8.0 Hz, 1 H, C6-H), 6.91 (s, 1 H, C2-H), 5.18 (s, 2 H, C14-H), 4.67 (s, 2 H, C7-H), 3.68 (t, *J* = 6.1 Hz, 2 H, C9-H), 3.12 – 2.96 (comp, 4 H, C22-H and C26-H), 2.86 (s, 6 H, C10-H, C23-H, and C25-H), 2.42 (s, 1 H, N24-H).

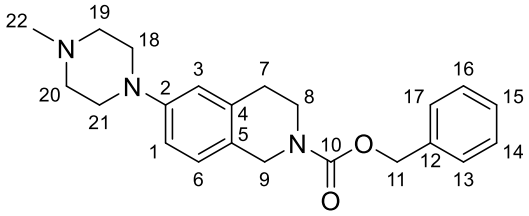


1.70

Benzyl 7-(4-methylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.70). KTL-01-229. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (50:1:49) to give 129 mg (82%) of **1.70** as a yellow oil: ^{1}H NMR (499 MHz) δ 7.41 – 7.29 (m, 5 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.78 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.65 (d, *J* = 26.7 Hz, 1 H), 5.17 (s, 2 H), 4.61 (s, 2 H), 3.75 – 3.65 (comp, 2 H), 3.17 (t, *J* = 4.9 Hz, 4 H), 2.80 – 2.70 (comp, 2 H), 2.58 (t, *J* = 5.0 Hz, 4 H), 2.36 (s, 3 H); ^{13}C NMR (126 MHz, rotamers) δ 155.5, 149.9, 136.8, 134.1, 133.6, 129.5, 129.2, 128.6, 128.5, 128.0, 127.9, 125.9, 125.7, 115.1, 115.0, 113.7, 113.4, 67.2, 67.1, 55.1, 49.3, 46.1, 42.0, 41.8, 28.1, 27.9; LRMS (ESI+APCI) *m/z* $C_{22}H_{27}N_3O_2$ $(M+H)^+$ calcd for 366.22; found 366.3.

NMR Assignment. ^{1}H NMR (499 MHz) δ 7.41 – 7.29 (m, 5 H, C13-H thru C17-H), 7.03 (d, *J* = 8.3 Hz, 1 H, C5-H), 6.78 (dd, *J* = 8.5, 2.6 Hz, 1 H, C6-H), 6.65 (d, *J* = 26.7 Hz, 1 H, C8-H), 5.17 (s, 2 H, C11-H), 4.61 (s, 2 H, C1-H), 3.75 – 3.65 (comp, 2 H, C2-H), 3.17 (t, *J* = 4.9 Hz, 4 H, C18-H and C22-H), 2.80 – 2.70 (comp, 2 H, C3-H), 2.58 (t, *J* = 5.0 Hz, 4 H, C19-H and C21-H), 2.36 (s, 3 H, C20-H); ^{13}C NMR (126 MHz, rotamers) δ 155.5 (C10), 149.9 (C7), 136.8 (C12), 134.1 (C9), 133.6 (C9), 129.5 (C5), 129.2 (C5), 128.6 (C14 and C16), 128.5 (C14 and C16), 128.0 (C13 and C17), 127.9 (C15), 125.9 (C4),

125.7 (C4), 115.1 (C6), 115.0 (C6), 113.7 (C8), 113.4 (C8), 67.2 (C11), 67.1 (C11), 55.1 (C18 and C22), 49.3 (C19 and C22), 46.1 (C9 and C20), 42.0 (C2), 41.8 (C2), 28.1 (C3), 27.9 (C3).

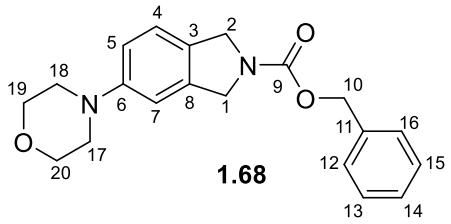


1.110

Benzyl 6-(4-methylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.110). KTL-02-061. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (50:1:49) to give 12 mg (11%) of **1.110** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 5 H), 7.00 (dd, *J* = 19.8, 8.0 Hz, 1 H), 6.79 (dd, *J* = 8.5, 2.1 Hz, 1 H), 6.68 (s, 1 H), 5.17 (s, 2 H), 4.57 (s, 2 H), 3.69 (s, 2 H), 3.25 – 3.15 (comp, 4 H), 2.80 (s, 2 H), 2.65 – 2.58 (comp, 4 H), 2.38 (s, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 149.8, 136.8, 135.3, 135.2, 128.5, 128.0, 127.9, 127.0, 124.9, 124.5, 116.0, 115.8, 114.8, 67.1, 55.0, 49.1, 46.0, 45.2, 41.6, 41.5, 29.5, 29.2; HRMS (ESI) *m/z* $C_{22}H_{27}N_3O_2$ $(M+H)^+$ calcd for 366.2176; found 366.2176.

NMR Assignment. : ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 5 H, C13-H thru C17-H), 7.00 (dd, *J* = 19.8, 8.0 Hz, 1 H, C6-H), 6.79 (dd, *J* = 8.5, 2.1 Hz, 1 H, C1-H), 6.68 (s, 1 H, C3-H), 5.17 (s, 2 H, C11-H), 4.57 (s, 2 H, C9-H), 3.69 (s, 2 H, C8-H), 3.25 – 3.15 (comp, 4 H, C18-H and C21-H), 2.80 (s, 2 H, C7-H), 2.65 – 2.58 (comp, 4 H, C19-H and C20-H), 2.38 (s, 3 H, C22-H); ^{13}C NMR (101 MHz, rotamers) δ 155.5 (C10), 149.8 (C2),

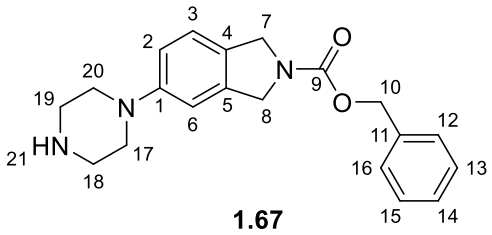
136.8 (C12), 135.3 (C5), 135.2 (C5), 128.5 (C14 and C16), 128.0 (C13 and C17), 127.9 (C15), 127.0 (C3), 126.9 (C3), 124.9 (C4), 124.5 (C4), 11.6 (C1), 115.8 (C1), 114.8 (C3), 67.1 (C11), 55.0 (C18 and C22), 49.1 (C19 and C20), 46.0 (C22), 45.2 (C9), 41.4 (C8), 41.4 (C8), 29.5 (C7), 29.2 (C7).



Benzyl 5-(3-methoxyphenyl)isoindoline-2-carboxylate (1.68). KTL-01-174. Prepared according to the representative procedure outlined Buchwald-Hartwig cross-coupling. The crude material was purified by flash column chromatography using EtOAc:Hexanes (25:75) to give 73 mg (70%) of **1.68** as a white solid: ^{1}H NMR (400 MHz) δ 7.41-7.29 (comp, 5 H), 7.14 (dd, *J* = 22.6, 8.4 Hz, 1 H), 6.85 (q, *J* = 7.9 Hz, 1 H), 6.83 – 6.74 (m, 1 H), 5.22 (s, 2 H), 4.70 (comp, 4 H), 3.86 (comp, 4 H), 3.13 (comp, 4 H); ^{13}C NMR (101 MHz, rotomers) δ 156.1, 154.8, 154.8, 151.3, 138.0, 137.7, 136.8, 128.5, 128.3, 128.1, 128.0, 127.8, 123.2, 123.1, 115.7, 115.6, 109.8, 109.7, 66.9, 66.8, 52.7, 52.3, 52.1, 51.6, 49.8, 49.7; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 361.1423; found 361.1526.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.41-7.29 (comp, 5 H, C12-H thru C-16-H), 7.14 (dd, *J* = 22.6, 8.4 Hz, 1 H, C4-H), 6.85 (q, *J* = 7.9 Hz, 1 H, C5-H), 6.83 – 6.74 (m, 1 H, C7-H), 5.22 (s, 2 H, C10-H), 4.70 (comp, 4 H, C1-H and C2-H), 3.86 (comp, 4 H, C19-H and C20-H), 3.13 (comp, 4 H, C17-H and C18-H); ^{13}C NMR (101 MHz, rotomers) δ 154.8 (C9), 154.8 (C9), 151.3 (C6), 138.0 (C8), 137.7 (C8), 136.8 (C11), 128.5 (C13

and C15), 128.3 (C4), 128.1 (C4), 128.0 (C14), 127.8 (C12 and C16), 123.2 (C3), 123.1 (C3), 115.7 (C5), 115.6 (C5), 109.8 (C7), 109.7 (C7), 66.9 (C10), 66.8 (C19 and C20), 52.7 (C1 or C2), 52.3 (C1 or C2), 52.1 (C1 or C2), 51.6 (C1 or C2), 49.8 (C17 and C18), 49.7 (C17 and C18).

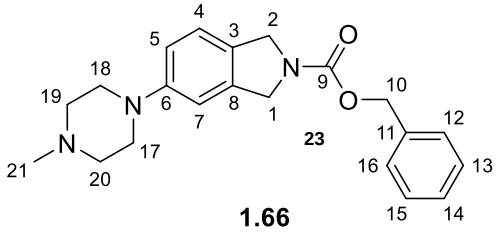


1.67

Benzyl 5-(piperazin-1-yl)isoindoline-2-carboxylate (1.67). KTL-01-268. Prepared according to the representative procedure outlined Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting MeOH:TEA:CH_2Cl_2 (1:1:98) to give 150 mg (73%) of **1.67** as a yellow solid: ^{1}H NMR (400 MHz, rotamers) δ 7.41-7.30 (comp, 5 H), 7.13 (dd, *J* = 23.3, 8.4 Hz, 1 H), 6.86 (ddd, *J* = 8.0, 5.6, 2.1 Hz, 1 H), 6.79 (d, *J* = 24.0 Hz, 1 H), 5.20 (s, 2 H), 4.69 (t, *J* = 10.3 Hz, 4 H), 3.15-3.11 (dd, *J* = 9.9, 5.2 Hz, 4 H), 3.09 – 3.01 (comp, 3 H), 2.31 (s, 1 H); ^{13}C NMR (126 MHz) δ 154.9, 154.9, 151.9, 138.0, 137.7, 136.9, 136.9, 128.5, 128.1, 128.0, 127.9, 127.8, 123.2, 123.0, 116.2, 116.1, 110.3, 110.1, 66.9, 52.8, 52.3, 52.1, 51.7, 50.94, 50.91, 46.2; LRMS (ESI+APCI) *m/z* $C_{20}H_{23}N_3O_2$ $(M+H)^+$ calcd for 338.19; found 338.2.

NMR Assignment. ^{1}H NMR (400 MHz,) δ 7.41-7.30 (comp, 5 H, C12-H thru C16-H), 7.13 (dd, *J* = 23.3, 8.4 Hz, 1 H, C3-H), 6.86 (ddd, *J* = 8.0, 5.6, 2.1 Hz, 1 H, C2-H), 6.79 (d, *J* = 24.0 Hz, 1 H, C6-H), 5.20 (s, 2 H, C10-H), 4.69 (t, *J* = 10.3 Hz, 4 H, C7-H and C8-H), 3.15-3.11 (comp, 4 H C17-H and C20-H), 3.09 – 3.01 (comp, 4 H, C18-H and C19-H),

2.31 (s, 1 H, N21-H). ^{13}C NMR (126 MHz) δ 154.9 (C9), 154.9 (C9), 151.9 (C1), 138.0 (C5), 137.7 (C5), 136.9 (C11), 136.9 (C11), 128.5 (C13 and C15), 128.1 (C3), 128.0 (C14), 127.9 (C12 and C16), 127.8 (C3), 123.2 (C4), 123.0 (C4), 116.2 (C2), 116.1 (C2), 110.3 (C6), 110.1 (C6), 66.9 (C10), 52.8 (C7 or C8), 52.3 (C7 or C8), 52.1 (C7 or C8), 51.7 (C7 or C8), 50.94 (C17 and C20), 50.91 (C17 and C20), 46.2 (C18 and C19).

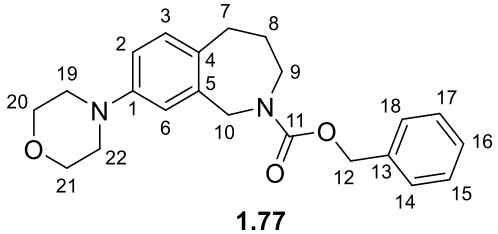


1.66

Benzyl 5-(4-methylpiperazin-1-yl)isoindoline-2-carboxylate (1.66). KTL-01-140. Prepared according to the representative procedure outlined Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography using EtOAc:TEA:hexanes (75:1:24) to give 65 mg (62%) of **1.66** as a pale yellow solid: ^{1}H NMR (400 MHz) δ 7.43-7.29 (comp, 5 H), 7.16 (dd, *J* = 23.4, 8.3 Hz, 1 H), 6.87 (dd, *J* = 11.3, 4.9 Hz, 1 H), 6.80 (d, *J* = 24.1 Hz, 1 H), 5.21 (s, 2 H), 4.69 (t, *J* = 10.5 Hz, 4 H), 3.19 (comp, 4 H), 2.58 (comp, 4 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, rotomers) δ 154.9, 154.8, 151.3, 137.9, 137.6, 136.8, 128.4, 127.9, 127.8, 127.7, 123.1, 123.0, 116.1, 115.9, 110.2, 110.0, 66.9, 55.0, 52.7, 52.3, 52.0, 51.6, 49.5, 49.5, 46.1; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 352.2020; found 352.2038; IR (neat) 2938, 2858, 2798, 1706, 1453, 1416, 1361, 1247, 1104 cm^{-1}

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.43-7.29 (comp, 5 H, C12-H thru C16-H), 7.13 (dd, *J* = 23.4, 8.3 Hz, 1 H, C4-H), 6.87 (dd, *J* = 11.3, 4.9 Hz, 1 H, C5-H), 6.80 (d,

J = 24.1 Hz, 1 H, C7-H), 5.21 (s, 2 H, C10-H), 4.69 (t, *J* = 10.5 Hz, 4 H, C1-H and C2-H), 3.19 (comp, 4 H, C19-H and C20-H), 2.58 (comp, 4 H, C17-H and C18-H), 2.35 (s, 3 H, C21-H); ^{13}C NMR (100 MHz, rotomers) δ 154.9 (C9), 154.8 (C9), 151.3 (C6), 137.9 (C8), 137.6 (C8), 136.8 (C11), 128.4 (C13 and C15), 127.9 (C14), 127.8 (C12 and C16), 127.7 (C4), 123.1 (C3), 123.0 (C3), 116.1 (C5), 115.9 (C5), 110.2 (C7), 110.0 (C7), 66.9 (C10), 55.0 (C17 and C18), 52.7 (C1 or C2), 52.3 (C1 or C2), 52.0 (C1 or C2), 51.6 (C1 or C2), 49.5 (C19 and C 20), 49.5 (C19 and C 20), 46.1 (C21).

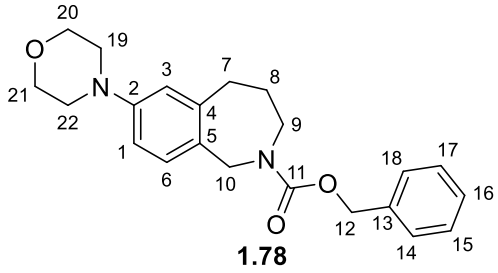


1.77

Benzyl 8-morpholino-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.77). KTL-02-057. Prepared according to the representative procedure outlined Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (25:75) to give 53 mg (91%) of **1.77** as a white solid: ^{1}H NMR (400 MHz, rotamers) δ 7.40-7.28 (comp, 5 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 6.93 (d, *J* = 2.4 Hz, 0.35 H), 6.68 (td, *J* = 8.5, 2.6 Hz, 1 H), 6.61 (d, *J* = 2.5 Hz, 0.65 H), 5.06 (s, 0.70 H), 5.04 (s, 1.30 H), 4.45 (s, 0.70 H), 4.40 (s, 1.30 H), 3.87 – 3.81 (comp, 1.50 H), 3.81 – 3.70 (comp, 4.50 H), 3.19 – 3.10 (comp, 1.50 H), 2.94 – 2.85 (comp, 4.50 H), 1.81-1.71 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.4, 155.2, 149.6, 149.4, 139.0, 138.9, 136.9, 136.7, 133.3, 132.9, 130.2, 130.2, 128.4, 128.0, 127.9, 127.8, 117.5, 117.2, 114.2,

113.9, 67.3, 66.9, 66.9, 53.0, 52.5, 51.0, 50.5, 49.4, 49.3, 34.4, 34.3, 28.9, 28.4; HRMS (ESI) *m/z* $C_{22}H_{26}N_3O_2$ $(M+Na)^+$ calcd for 389.1836; found 389.1845.

NMR Assignemnt. ^{1}H NMR (400 MHz, rotamers) δ 7.40-7.28 (comp, 5 H, C14-H thru C18-H), 7.04 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.93 (d, *J* = 2.4 Hz, 0.35 H, C6-H), 6.68 (td, *J* = 8.5, 2.6 Hz, 1 H, C2-H), 6.61 (d, *J* = 2.5 Hz, 0.65 H, C6-H), 5.06 (s, 0.70 H, C12-H), 5.04 (s, 1.30 H, C12-H), 4.45 (s, 0.70 H, C10-H), 4.40 (s, 1.30 H, C10-H), 3.87 – 3.81 (comp, 1.5 H, C19-H and C22-H), 3.81 – 3.70 (comp, 4.5 H, C9-H, C19-H and C22-H), 3.19 – 3.10 (comp, 1.5 H, C20-H and C21-H), 2.94 – 2.85 (comp, 4.5 H, C7-H, C20-H and C21-H), 1.81-1.71 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.42 (C11), 155.22 (C11), 149.58 (C1), 149.44 (C1), 139.01 (C5), 138.87 (C5), 136.87 (C13), 136.73 (C13), 133.31 (C4), 132.88 (C4), 130.23 (C3), 130.15 (C3), 128.40 (C15 and C17), 128.00 (C14 and C18), 127.86 (C14 and C18), 127.80 (C16), 117.46 (C2), 117.15 (C2), 114.21 (C6), 113.94 (C6), 67.26 (C12), 66.94 (C20 and C21), 66.89 (C20 and C21), 53.04 (C10), 52.49 (C10), 51.03 (C9), 50.48 (C9), 49.39(C19 and C22), 49.30 (C19 and C22), 34.38 (C7), 34.34 (C7), 28.91 (C8), 28.42 (C8).

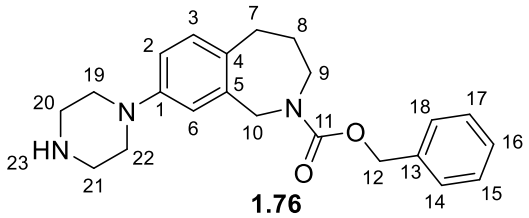


1.78

Benzyl 7-morpholino-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.78). KTL-02-087. Prepared according to the representative procedure outlined for Buchwald-

Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting EtOAc:hexanes (25:75) to give 45 mg (38%) of **1.78** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.33 (comp, 5 H), 7.24 (s, 0.45 H), 7.01 (d, *J* = 8.2 Hz, 0.55 H), 6.73 (s,1 H), 6.68 (dd, *J* = 8.2, 2.4 Hz, 0.45 H), 6.61 (dd, *J* = 8.2, 2.5 Hz, 0.55 H), 5.06 (s, 2 H), 4.42 (s, 0.87 H), 4.39 (s, 1.13 H), 3.87-3.84 (comp, 4 H), 3.78-3.66 (comp, 2 H), 3.20 – 3.10 (comp, 4 H), 2.93-2.89 (comp, 2 H), 1.85-1.71 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.2, 150.7, 142.8, 142.4, 136.9, 130.4, 130.1, 130.0, 129.8, 128.4, 128.3, 127.84, 127.82, 127.80, 117.1, 112.8, 112.5, 67.0, 66.9, 66.89, 51.9, 51.3, 50.7, 50.2, 49.4, 35.8, 28.8, 28.2; LRMS (ESI+APCI) *m/z* $C_{22}H_{26}N_2O_3$ $(M+H)^+$ calcd for 367.20; found 367.2.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.33 (comp, 5 H, C14-H thru C18-H), 7.24 (s, 0.45 H, C6-H), 7.01 (d, *J* = 8.2 Hz, 0.55 H, C6-H), 6.73 (s,1 H, C3-H), 6.68 (dd, *J* = 8.2, 2.4 Hz, 0.45 H, C1-H), 6.61 (dd, *J* = 8.2, 2.5 Hz, 0.55 H, C1-H), 5.06 (s, 2 H, C12-H), 4.42 (s, 0.87 H, C10-H), 4.39 (s, 1.13 H, C10-H), 3.87-3.84 (comp, 4 H, C20-H and C21-H), 3.78-3.66 (comp, 2 H, C9-H), 3.20 – 3.10 (comp, 4 H, C19-H and C22-H), 2.93-2.89 (comp, 2 H, C7-H), 1.85-1.71 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.5 (C11), 155.2 (C11), 150.7 (C2), 142.8 (C4), 142.4 (C4), 136.9 (C13), 130.4 (C6), 130.1 (C6), 130.0 (C5), 129.8 (C5), 128.4 (C15 and C17), 128.3 (C15 and C17), 127.84 (C16), 127.82 (C14 and C18), 128.80 (C14 and C18), 117.1 (C3), 112.8 (C1), 112.5 (C1), 67.0 (C12), 66.9 (C20 and C21), 66.89 (C12), 51.9 (C10), 51.3 (C10), 50.7 (C9), 50.2 (C9), 49.4 (C19 and C22), 35.8 (C7), 28.8 (C8), 28.2 (C8).

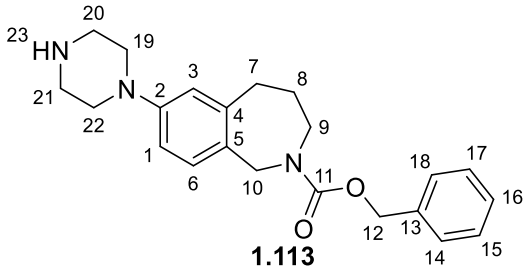


1.76

Benzyl 8-(piperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.76). KTL-02-035. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with MeOH:TEA:CH_2Cl_2 (1:1:98) to give 104 mg (60%) of **1.76** as a yellow oil: ^{1}H NMR (400 MHz, rotamers) δ 7.40-7.27 (s, 5 H), 7.01 (d, *J* = 8.2 Hz, 1 H), 6.93 (d, *J* = 2.5 Hz, 0.35 H), 6.70 – 6.65 (m, 1 H), 6.63 (d, *J* = 2.6 Hz, 0.65 H), 5.05 (s, 0.70 H), 5.02 (s, 1.30 H), 4.43 (s, 0.70 H), 4.38 (s, 1.30 H), 3.80-6.69 (comp, 2 H), 3.15 – 3.07 (comp, 1.5 H), 3.03 – 2.97 (comp, 1.5 H), 2.97 – 2.90 (m, 5 H), 2.86-2.83 (comp, 2 H), 1.79-1.67 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.4, 155.2, 149.9, 149.8, 138.9, 138.7, 136.8, 136.7, 133.1, 132.7, 130.2, 130.1, 128.4, 127.8, 118.0, 117.7, 117.6, 114.6, 114.6, 114.4, 67.2, 66.9, 52.5, 51.0, 50.1, 50.0, 45.9, 45.8, 34.4, 34.3, 28.9, 28.4; LRMS (ESI+APCI) *m/z* $C_{22}H_{27}N_3O_2$ $(M+H)^+$ calcd for 366.21; found 366.3.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.40-7.27 (s, 5 H, C14-H thru C18-H), 7.01 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.93 (d, *J* = 2.5 Hz, 0.35 H, C6-H), 6.70 – 6.65 (m, 1 H, C2-H), 6.63 (d, *J* = 2.6 Hz, 0.65 H, C6-H), 5.05 (s, 0.70 H, C12-H), 5.02 (s, 1.30 H, C12-H), 4.43 (s, 0.70 H, C10-H), 4.38 (s, 1.30 H, C10-H), 3.80-6.69 (comp, 2 H, C9-H), 3.15 – 3.07 (comp, 1.5 H, C19-H and C22-H), 3.03 – 2.97 (comp, 1.5 H, C20-H and C21-H), 2.97 – 2.90 (m, 5 H, C19-H thru C22-H), 2.86-2.83 (comp, 2 H, C7-H), 1.79-1.67

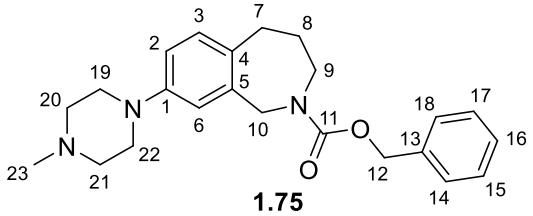
(comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.4 (C11), 155.2 (C11), 149.9 (C1), 149.8 (C1), 138.9 (C5), 138.7 (C5), 136.8 (C13), 136.7 (C13), 133.1 (C4), 132.7 (C4), 130.2 (C3), 130.1 (C3), 128.4 (C15 and C17), 127.8 (C14, C16, and C18), 118.0 (C2), 117.7 (C2), 117.6, 114.6 (C6), 114.6 (C6), 114.4 (C6), 67.2 (C12), 66.9 (C12), 53.0 (C10), 52.5 (C10), 50.1 (C19 and C22), 50.0(C19 and C22), 45.9 (C9, C20, and C21), 45.8(C9, C20, and C21), 34.4 (C9), 34.3 (C9), 28.9 (C8), 28.4 (C8).



1.113

Benzyl 7-(piperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.113). KTL-02-096. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with MeOH:TEA:CH_2Cl_2 (1:1:98) to give 80 mg (69%) of **1.113** as a yellow oil: ^{1}H NMR (400 MHz, rotamers) δ 7.39-7.27 (comp, 5 H), 7.23 (d, *J* = 8.2 Hz, 0.40 H), 7.00 (d, *J* = 8.2 Hz, 0.60 H), 6.74 (s, 1 H), 6.69 (dd, *J* = 8.1, 2.4 Hz, 0.40 H), 6.62 (dd, *J* = 8.2, 2.4 Hz, 0.60 H), 5.05 (s, 2 H), 4.41 (s, 0.70 H), 4.38 (s, 1.30 H), 3.73 (s, 2 H), 3.15-3.08 (comp, 4 H), 3.05-2.97 (comp, 4 H), 2.94-2.89 (comp, 2 H), 1.81-1.74 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.2, 151.2, 142.7, 142.3, 136.93, 136.91, 130.3, 130.0, 129.6, 129.4, 128.4, 128.4, 127.8, 117.53, 117.51, 113.1, 112.8, 67.0, 66.9, 51.9, 51.3, 50.7, 50.42, 50.40, 50.2, 46.2, 35.8, 35.6, 28.8, 28.3.

NMR Assignment. : ^{1}H NMR (400 MHz, rotamers) δ 7.39-7.27 (comp, 5 H, C14-H thru C18-H), 7.23 (d, *J* = 8.2 Hz, 0.40 H, C6-H), 7.00 (d, *J* = 8.2 Hz, 0.60 H, C6-H), 6.74 (s, 1 H, C3-H), 6.69 (dd, *J* = 8.1, 2.4 Hz, 0.40 H, C1-H), 6.62 (dd, *J* = 8.2, 2.4 Hz, 0.60 H, C1-H), 5.05 (s, 2 H, C12-H), 4.41 (s, 0.70 H, C10-H), 4.38 (s, 1.30 H, C10-H), 3.73 (s, 2 H, C9-H), 3.15-3.08 (comp, 4 H, C19-H and C22-H), 3.05-2.97 (comp, 4 H, C20-H and C21-H), 2.94-2.89 (comp, 2 H, C7-H), 1.81-1.74 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.47 (C11), 155.20 (C11), 151.21 (C2), 142.67 (C4), 142.29 (C4), 136.93 (C13), 136.91 (C13), 130.31 (C6), 130.04 (C6), 129.58 (C5), 129.38 (C5), 128.40 (C15 and C17), 128.35 (C15 and C17), 127.80 (C14, C16, and C18), 117.53 (C3), 117.51 (C3), 113.11 (C1), 112.79 (C1), 67.01 (C12), 66.86 (C12), 51.92 (C10), 51.33 (C10), 50.69 (C9), 50.42 (C19 and C22), 50.40 (C19 and C22), 50.18 (C9), 46.16 (C20 and C21), 35.81 (C7), 35.75 (C7), 28.79 (C8), 28.25 (C8).

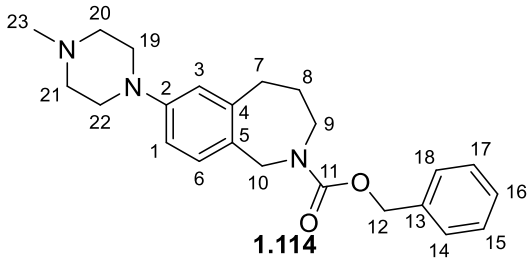


1.75

Benzyl 8-(4-methylpiperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.75). KTL-02-027. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (25:1:74) to give 38 mg (63%) of **1.75** as a yellow oil: ^{1}H NMR (400 MHz, rotamers) δ 7.29 (comp, 5 H), 7.02 (d, *J* =8.2 Hz, 1 H), 6.95 (d, *J* =2.5 Hz, 0.33 H), 6.69 (d, *J* =15.2 Hz, 1 H), 6.65 (d, *J* =2.6 Hz, 0.67

H), 5.06 (s, 0.7 H), 5.03 (s, 1.3 H), 4.44 (s, 0.67 H), 4.39 (s, 1.33 H), 3.80 – 3.70 (m, 2 H), 3.23 – 3.17 (m, 1.5 H), 3.03 – 2.98 (m, 2.5 H), 2.87 (comp, 2 H), 2.58 – 2.53 (m, 1.5 H), 2.53 – 2.47 (m, 2.5 H), 2.34 (s, 3 H), 1.76 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.4, 155.2, 149.6, 149.4, 138.9, 138.7, 136.9, 136.7, 132.8, 132.4, 130.2, 130.0, 128.4, 127.9, 127.83, 127.80, 127.79, 117.8, 117.4, 114.3, 114.1, 67.2, 66.9, 55.2, 55.1, 53.0, 52.5, 51.0, 50.4, 49.05, 48.98, 46.2, 34.4, 34.3, 28.9, 28.4; HRMS (ESI) *m/z* $C_{23}H_{29}N_3O_2$ $(M+H)^+$ calcd for 380.2333; found 320.2337.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.29 (comp, 5 H, C14-H thru C18-H), 7.02 (d, *J* =8.2 Hz, 1 H, C3-H), 6.95 (d, *J* =2.5 Hz, 0.33 H, C6-H), 6.69 (d, *J* =15.2 Hz, 1 H, C2-H), 6.65 (d, *J* =2.6 Hz, 0.67 H, C6-H), 5.06 (s, 0.7 H, C12-H), 5.03 (s, 1.3 H, C12-H), 4.44 (s, 0.67 H, C10-H), 4.39 (s, 1.33 H, C10-H), 3.80 – 3.70 (m, 2 H, C9-H), 3.23 – 3.17 (m, 1.5 H, C19-H and C22-H), 3.03 – 2.98 (m, 2.5 H, C19-H and C22-H), 2.87 (comp, 2 H, C7-H), 2.58 – 2.53 (m, 1.5 H, C20-H and C21-H), 2.53 – 2.47 (m, 2.5 H, C20-H and C21-H), 2.34 (s, 3 H, C23-H), 1.76 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.4 (C11), 155.2 (C11), 149.6 (C1), 149.4 (C1), 138.9 (5), 138.7 (C5), 136.9 (C13), 136.7 (C13), 132.8 (C4), 132.4 (C4), 130.2 (C3), 130.0 (C3), 128.4 (C15 and C17) , 127.9 (C14 and C18), 127.83 (C16), 127.80 (C14 and C18), 127.79 (C16), 117.8 (C2), 117.4 (C2), 114.3 (C6), 114.1 (C6), 67.2 (C12), 66.9 (C12), 55.2 (C19 and C22), 55.1 (C19 and C22), 53.0 (C10), 52.5 (C10), 51.0 (C9), 50.4 (C10), 49.05 (C20 and C21), 48.98 (C20 and C21), 46.2 (C23), 34.4 (C7), 34.3 (C7), 28.9 (C8), 28.4 (C8).



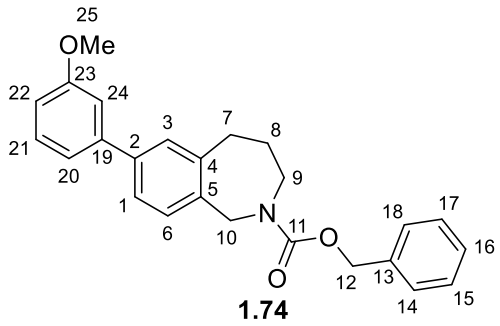
1.114

Benzyl 7-(4-methylpiperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.114). KTL-02-089. Prepared according to the representative procedure outlined for Buchwald-Hartwig cross-coupling. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (75:1:24) to give 32 mg (53%) of **1.114** as a yellow oil: ^{1}H NMR (400 MHz, rotamers) δ 7.39-7.27 (comp, 5 H), 7.23 (d, *J* = 8.2 Hz, 0.45 H), 6.99 (d, *J* = 8.2 Hz, 0.55 H), 6.74 (s, 1 H), 6.69 (dd, *J* = 8.1, 2.4 Hz, 0.45 H), 6.62 (dd, *J* = 8.2, 2.5 Hz, 0.55 H), 5.05 (s, 2 H), 4.41 (s, 0.80 H), 4.38 (s, 1.20 H), 3.79 – 3.66 (comp, 2 H), 3.25 – 3.13 (comp, 4 H), 2.95 – 2.85 (comp, 2 H), 2.61 – 2.50 (comp, 4 H), 2.36 (s, 1.85 H), 2.35 (s, 1.15 H), 1.85-1.73 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.2, 150.6, 142.7, 142.3, 136.92, 136.90, 130.3, 130.0, 129.6, 129.4, 128.4, 128.3, 127.82, 127.80, 127.8, 117.5, 113.1, 112.8, 67.0, 66.9, 55.1, 51.9, 51.3, 50.7, 50.2, 49.0, 46.1, 35.8, 35.7, 28.8, 28.2; LRMS (ESI+APCI) *m/z* $C_{23}H_{29}N_3O_2$ $(M+H)^+$ calcd for 380.24; found 380.3.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.39-7.27 (comp, 5 H, C14-H thru C18-H), 7.23 (d, *J* = 8.2 Hz, 0.45 H, C6-H), 6.99 (d, *J* = 8.2 Hz, 0.55 H, C6-H), 6.74 (s, 1 H, C3-H), 6.69 (dd, *J* = 8.1, 2.4 Hz, 0.45 H, C1-H), 6.62 (dd, *J* = 8.2, 2.5 Hz, 0.55 H, C1-H), 5.05 (s, 2 H, C12-H), 4.41 (s, 0.80 H, C10-H), 4.38 (s, 1.20 H, C10-H), 3.79 – 3.66 (comp, 2 H, C9-H), 3.25 – 3.13 (comp, 4 H, C19-H and C22-H), 2.95 – 2.85

(comp, 2 H, C7-H), 2.61 – 2.50 (comp, 4 H, C20-H and C21-H), 2.36 (s, 1.85 H, C23-H), 2.35 (s, 1.15 H, C23-H), 1.85-1.73 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 155.47 (C11), 155.21 (C11), 150.62 (C2), 142.69 (C4), 142.31 (C4), 136.92 (C13), 136.90 (C13), 130.33 (C6), 130.05 (C6), 129.57 (C5), 129.38 (C5), 128.39 (C15 and C17), 128.34 (C15 and C17), 127.82 (C16), 127.80 (C14 and C16), 127.77 (C14 and C16), 117.45 (C3), 113.09 (C1), 112.75 (C1), 67.01 (C12), 66.87 (C12), 55.13 (C19 and C22), 51.91 (C10), 51.32 (C10), 50.68 (C9), 50.18 (C9), 49.04 (C20 and C21), 46.12 (C23), 35.81 (C7), 35.74 (C7), 28.77 (C8), 28.23 (C8).

Representative procedure for Suzuki cross-coupling

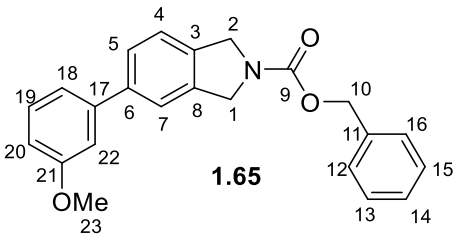


1.74

Benzyl 7-(3-methoxyphenyl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.74). KTL-02-090. A solution of **1.64** (50 mg, 0.16 mmol), 3-methoxyphenylboronic acid (49 mg, 0.32 mmol), Cs_2CO_3 (104 mg, 0.32 mmol), and palladium (bis)(t-butyl)$_3$ phosphine (4 mg, 0.008mmol) in degassed 1,4-dioxane (0.5 mL) was stirred for 24 h at 90 °C. The reaction was cooled to room temperature and poured into water (1 mL). The material was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified

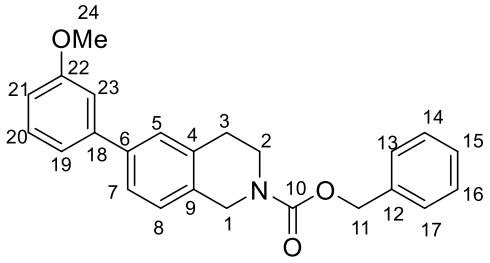
via flash column chromatography eluting with EtOAc:hexanes (1:9) to give 51 mg (83%) of **1.74** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.44-7.30 (comp, 9 H), 7.17 (dd, *J* = 8.1, 1.9 Hz, 1 H), 7.12 (t, *J* = 2.4 Hz, 1 H), 6.95 – 6.87 (m, 1 H), 5.09 (s, 2 H), 4.54 (s, 0.81 H), 4.50 (s, 1.20 H), 3.88 (s, 1.70 H), 3.87 (s, 1.30 H), 3.80 (s, 2 H), 3.04-3.02 (comp, 2 H), 1.92-1.79 (s, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 159.9, 155.5, 155.3, 142.5, 142.4, 142.3, 141.9, 140.4, 140.38, 137.53, 137.35, 136.83, 136.77, 130.00, 129.74, 129.72, 128.51, 128.44, 128.40, 127.91, 127.4, 125.0, 124.7, 119.6, 112.82, 112.77, 112.7, 77.4, 77.1, 76.7, 67.2, 67.0, 55.3, 52.3, 51.7, 50.9, 50.5, 35.5, 28.6, 28.1.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.44-7.30 (comp, 9 H, C1-H, C3-H, C6-H, C14-H thru C18-H, and C21-H), 7.17 (dd, *J* = 8.1, 1.9 Hz, 1 H, C20-H), 7.12 (t, *J* = 2.4 Hz, 1 H, C22-H), 6.95 – 6.87 (m, 1 H, C24-H), 5.09 (s, 2 H, C12-H), 4.54 (s, 0.81 H, C10-H), 4.50 (s, 1.20 H, C10-H), 3.88 (s, 1.70 H, C25-H), 3.87 (s, 1.30 H, C25-H), 3.80 (s, 2 H, C9-H), 3.04-3.02 (comp, 2 H, C7-H), 1.92-1.79 (s, 2 H, C8-H); ^{13}C NMR (101 MHz, rotamers) δ 159.91 (C23), 155.50 (C11), 155.34 (C11), 142.47 (C19), 142.38 (C19), 142.29 (C4), 141.94 (C4), 140.42 (C5), 140.38 (C5), 137.53 (C2), 137.35 (C2), 136.83 (C13), 136.77 (C13), 130.00 (C21), 129.74, 129.72, 128.51, 128.44, 128.40 (C15 and C17), 127.91 (C14 and C18), 127.85 (C1), 125.03 (C1), 124.66 (C6), 119.61 (C20), 112.82 (C24), 112.77 (C24), 112.66 (C22), 77.37, 77.06, 76.74, 67.19 (C12), 67.02 (C12), 55.31 (C25), 52.27 (C10), 51.69 (C10), 50.91 (C9), 50.48 (C9), 35.46 (C7), 28.64 (C8), 28.07 (C8).



Benzyl 5-(3-methoxyphenyl)isoindoline-2-carboxylate (1.65). KTL-02-130. Prepared according to the representative procedure outlined for Suzuki cross-coupling. The crude material was purified by flash column chromatography eluting with EtOAc:hexanes (5:95) to give 150 mg (87%) of **1.65** as an orange oil: ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 9 H), 7.16 (s, 1 H), 7.10 (s, 1 H), 6.91 (s, 1 H), 5.25 (s, 2 H), 4.81 (s, 4 H), 3.87 (s, 3 H); ^{13}C NMR (101 MHz, cdcl$_3$, rotomers) δ 159.9, 154.8, 142.3, 142.2, 140.8, 140.7, 137.5, 137.25, 136.7, 136.1, 135.8, 129.8, 128.5, 128.0, 127.9, 126.7, 126.6, 123.0, 122.8, 121.5, 121.3, 119.6, 119.61, 112.9, 112.8, 112.7, 112.7, 67.0, 55.3, 55.2, 52.5, 52.35, 52.1, 51.9; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 382.1414; found 382.1416.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.40-7.29 (comp, 9 H,C4-H, C5-H, C7-H, C12-h thru C16-H and C19-H), 7.16 (m, 1 H, C18-H), 7.10 (m, 1 H, C22-H), 6.91 (ddd, 1 H, C20-H), 5.25 (s, 2 H, C10-H), 4.81 (comp, 4 H, C1-H and C2-H), 3.87 (s, 3 H, C23-H); ^{13}C NMR (101 MHz, rotomers) δ 159.9 (C21), 154.88 (C9), 142.3 (C17), 142.2 (C17), 140.8 (C8), 140.7 (C8), 137.5 (C4), 137.2 (C4), 136.7 (C11), 136.1 (C6), 135.8 (C6), 129.8 (C19), 128.5 (C13 and C15), 128.0 (C14), 127.9 (C12 and C16), 126.7 (C5), 126.6 (C5), 123.0 (C7), 122.8 (C7), 121.5 (C4), 121.3 (C4), 119.6 (C18), 119.6 (C18), 112.9 (C22), 112.8 (C22), 112.7 (C20), 112.7 (C20), 67.0 (C10), 55.3 (C23), 55.2 (C23), 52.5 (C1), 52.3 (C1), 52.1 (C2), 51.9 (C2).

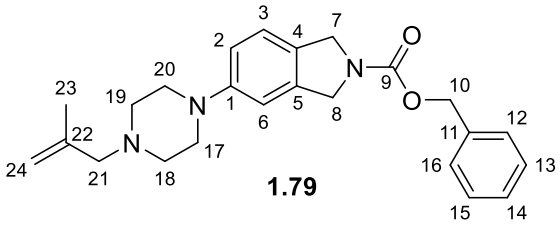


1.69

Benzyl 6-(3-methoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.69). KTL-02-139. Prepared according to the representative procedure outlined for Suzuki cross-coupling. The crude material was purified by flash column chromatography eluting with EtOAc:hexanes (5:95) to give 40 mg (73%) of **1.69** as a clear oil: ^{1}H NMR (400 MHz) δ 7.44-7.35 (comp, 8 H), 7.18 (ddd, 1 H), 7.11 (s, 1 H), 6.90 (s, 1 H), 5.21 (s, 2 H), 4.71 (s, 2 H), 3.87 (s, 3 H), 3.78 (br s, 2 H), 2.93 (br s, 2 H); ^{13}C NMR (101 MHz, rotomers) δ 159.9, 155.5, 142.3, 139.5, 136.7, 135.0, 134.8, 132.7, 132.3, 129.8, 128.5, 128.1, 127.5, 127.3, 126.8, 126.6, 125.2, 119.54, 112.8, 112.7, 67.3, 55.3, 45.6, 41.7, 41.4, 29.2, 28.9; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 396.1570; found 396.1574.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.44-7.35 (comp, 8 H, C5-H, C7-H, C8-H, and C13-H thru C17-H), 7.18 (comp, 2 H, C19-H and C20-H), 7.11 (t, *J* = 2.4 Hz, 1 H, C23-H), 6.90 (ddd, 1 H, C21-H), 5.21 (s, 2 H, C11-H), 4.71 (s, 2 H, C1-H), 3.87 (s, 3 H, C24-H), 3.78 (br s, 2 H, C2-H), 2.93 (br s, 2 H, C3-H); ^{13}C NMR (101 MHz, rotomers) δ 159.9 (C22), 155.5 (C10), 142.3 (C18), 139.5 (C6), 136.7 (C12), 135.0 (C4), 134.8 (C4), 132.7 (C9), 132.3 (C9), 129.8 (C20), 128.5 (C14 and C16), 128.1 (C13 and C17), 127.5 (C5), 127.3 (C5), 126.8 (C7), 126.6 (C7), 125.2 (C15), 119.5 (C19), 112.8 (C23), 112.7 (C21), 67.3 (C11), 55.3 (C24), 45.6 (C1), 41.7 (C2), 41.4 (C2), 29.2 (C3), 28.9 (C3).

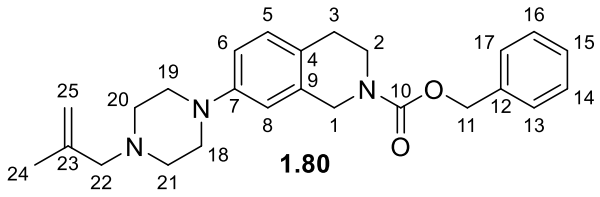
Representative procedure for alkylation of piperazines with alkyl bromides



Benzyl 5-(4-(2-methylallyl)piperazin-1-yl)isoindoline-2-carboxylate (1.79). KTL-01-228. NaH (14 mg, 0.30 mmol) and 3-bromo-2-methylpropene (47 mg, 0.35 mmol) were added to a solution of intermediate **1.67** (20 mg, 0.06 mmol) in THF (2.5 mL). The suspension was stirred at room temperature overnight. The reaction was quenched with aqueous NH_4Cl^+ (1 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (15:1:84) to give 16.5 mg (71%) of **1.79** as a white solid: ^{1}H NMR (400 MHz) δ 7.43 – 7.29 (comp, 5 H), 7.12 (dd, *J* =23.4, 8.4 Hz, 1 H), 6.86 (t, *J* =5.3 Hz, 1 H), 6.79 (d, *J* =26.4 Hz, 1 H), 5.21 (s, 2 H), 4.91 (s, 1 H), 4.88 (s, 1 H), 4.69 (t, *J* =10.5 Hz, 4 H), 3.17 (dd, *J* =10.2, 5.4 Hz, 4 H), 2.92 (s, 2 H), 2.57 – 2.51 (m, 4 H), 1.77 (s, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 154.92, 154.88, 151.5, 142.5, 137.9, 137.6, 136.9, 128.0, 127.85, 127.79, 127.6, 123.2, 123.0, 116.0, 115.9, 113.1, 110.1, 109.9, 66.9, 65.3, 53.1, 52.8, 52.3, 52.1, 51.6, 49.6, 49.6, 20.9; HRMS (ESI) *m/z* $C_{24}H_{29}N_2O_2$ $(M+H)^+$ calcd for 392.2333; found 392.2334.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.43 – 7.29 (comp, 5 H, C12-H thru C16-H), 7.12 (dd, *J* =23.4, 8.4 Hz, 1 H, C3-H), 6.86 (t, *J* =5.3 Hz, 1 H, C2-H), 6.79 (d, *J*

=26.4 Hz, 1 H, C6-H), 5.21 (s, 2 H, C10-H), 4.91 (s, 1 H, C24-H), 4.88 (s, 1 H, C24-H), 4.69 (comp, 4 H, C7-H and C8-H), 3.17 (dd, *J* =10.2, 5.4 Hz, 4 H, C17-H and C20-H), 2.92 (s, 2 H, C21-H), 2.57 – 2.51 (m, 4 H, C18-H and C19-H), 1.77 (s, 3 H, C23-H); ^{13}C NMR (101 MHz, rotamers) δ 154.92 (C9), 154.88 (C9), 151.5 (C1), 142.5 (C22), 137.9 (C5), 137.6 (C5), 136.9 (C11), 128.6 (C13 and C15) 128.0 (C14), 127.85 (C4), 127.79 (C12 and C16), 127.6 (C4) , 123.2 (C3), 123.0 (C3), 116.0 (C2), 115.9 (C2), 113.1 (C24), 110.1 (C6), 109.9 (C6), 66.9 (C10), 65.3 (C21), 53.1 (C17 and C20), 52.8 (C7 or C8), 52.3 (C7 or C8), 52.1 (C7 or C8), 51.6 (C7 or C8), 49.6 (C18 and C19), 49.6 (C18 and C19), 20.9 (C23).

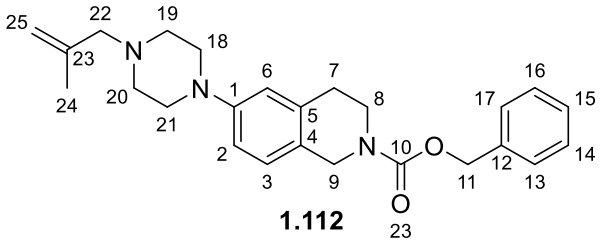


1.80

Benzyl 7-(4-(2-methylallyl)piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.80). KTL-01-222. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via column chromatography eluting with EtOAc:TEA:hexanes (5:1:94) to give 30 mg (53%) of **1.80** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.43-7.30 (comp, 5 H), 7.03 (d, *J* = 8.6 Hz, 1 H), 6.79 (dd, *J* = 8.4, 2.3 Hz, 1 H), 6.65 (d, *J* = 20.9 Hz, 1 H), 5.18 (s, 2 H), 4.91 (s, 1 H), 4.89 (s, 1 H), 4.61 (s, 2 H), 3.72 (br s, 2 H), 3.15 (t, *J* = 4.8 Hz, 4 H), 2.93 (s, 2 H), 2.77 (br s, 2 H), 2.54 (t, *J* = 4.8 Hz, 4 H), 1.78 (s, 3 H); ^{13}C NMR (101 MHz, rotomers) δ 155.5, 150.1, 142.5, 136.8, 133.9, 133.5, 129.4, 129.1, 128.5, 128.0, 127.9, 125.6, 125.4, 114.9, 113.5, 113.3, 113.1, 67.1, 65.3, 53.1, 49.4, 46.1, 46.1, 42.0, 41.7, 28.1, 27.9, 20.9;

HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 406.2489; found 406.2493; IR (neat) 2935, 2816, 1702, 1508, 1431, 1232, 1104 cm^{-1}.

NMR Assignment. : ^{1}H NMR (400 MHz) δ 7.43-7.30 (comp, 5 H, C13-H-C17-H), 7.03 (d, *J* = 8.6 Hz, 1 H, C5-H), 6.79 (dd, *J* = 8.4, 2.3 Hz, 1 H, C6-H), 6.65 (d, *J* = 20.9 Hz, 1 H, C8-H), 5.18 (s, 2 H, C11), 4.91 (s, 1 H, C25-H), 4.89 (s, 1 H, C25-H), 4.61 (s, 2 H, C1-H), 3.72 (br s, 2 H, C2-H), 3.15 (t, *J* = 4.8 Hz, 4 H, C18-H and C19-H), 2.93 (s, 2 H, C22-H), 2.77 (br s, 2 H, C3-H), 2.54 (t, *J* = 4.8 Hz, 4 H, C20-H and C21-H), 1.78 (s, 3 H, C24-H); ^{13}C NMR (101 MHz, rotomers) δ 155.5 (C10), 150.1 (C7), 142.5 (C23), 136.8 (C12), 133.9 (C9), 133.5 (C9), 129.4 (C5), 129.1 (C5), 128.5 (C13 and C17), 128.0 (C14 and C16), 127.9 (C15), 125.6 (C4), 125.4 (C4), 114.8 (C6), 113.5 (C8), 113.3 (C8), 113.1 (C25), 67.1 (C11), 65.3 (C22), 53.1 (C20 and C21), 49.4 (C18 and C19), 46.1 (C1), 46.1 (C1), 42.0 (C2), 41.7 (C2), 28.1 (C3), 27.9 (C3), 20.9 (C24).

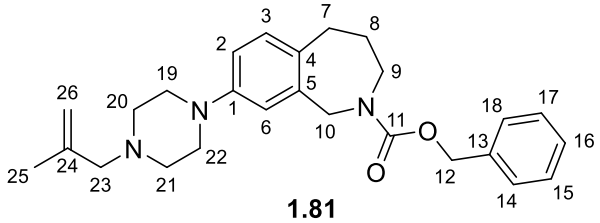


1.112

Benzyl 6-(4-(2-methylallyl)piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.112). KTL-02-071. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 16 mg (46%) of **1.112** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.29 (comp, 5 H), 6.99 (dd, *J* = 21.2, 9.3 Hz, 1 H), 6.79 (dd, *J* = 8.3, 2.3 Hz, 1 H), 6.68 (s, 1 H), 5.17 (s, 2 H), 4.89 (d, *J*

=10.9 Hz, 2 H), 4.57 (s, 2 H), 3.69 (s, 2 H), 3.20 – 3.12 (comp, 4 H), 2.93 (s, 2 H), 2.80 (s, 2 H), 2.57 – 2.49 (m, 4 H), 1.77 (s, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.4, 150.1, 142.4, 136.8, 135.3, 135.1, 128.5, 128.0, 127.0, 126.80 124.6, 124.1, 115.9, 115.7, 114.7, 113.3, 113.2, 67.1, 65.3, 53.0, 49.3, 45.2, 41.7, 41.4, 29.4, 29.2, 21.0; HRMS (ESI) *m/z* $C_{25}H_{31}N_3O_2$ $(M+H)^+$ calcd for 406.2489; found 406.2493.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.29 (comp, 5 H, C13-H thru C17-H), 6.99 (dd, *J* = 21.2, 9.3 Hz, 1 H, C3-H), 6.79 (dd, *J* = 8.3, 2.3 Hz, 1 H, C2-H), 6.68 (s, 1 H, C6)), 5.17 (s, 2 H, C11-H), 4.89 (d, *J* =10.9 Hz, 2 H, C25-H), 4.57 (s, 2 H, C9-H), 3.69 (s, 2 H, C8-H), 3.20 – 3.12 (comp, 4 H, C18-H and C21-H), 2.93 (s, 2 H, C22-H), 2.80 (s, 2 H, C8-H), 2.57 – 2.49 (m, 4 H, C19-H and C20-H), 1.77 (s, 3 H, C24-H); ^{13}C NMR (101 MHz, rotamers) δ 155.5 (C10), 155.4 (C10), 150.1 (C1), 142.4 (C23), 136.8 (C12), 135.3 (C4), 135.1 (C4), 128.5 (C14 and C16), 128.0 (C13, C15, and C17), 127.0 (C3), 126.8 (C3), 124.6 (C5), 124.1 (C5), 115.9 (C2), 115.7 (C2), 114.7 (C25), 113.3 (C6), 113.2 (C6), 67.1 (C11), 65.3 (C22), 53.0 (C18 and C21), 49.3 (C19 and C20), 45.2 (C9), 41.7 (C8), 41.4 (C8), 29.4 (C7), 29.2 (C7), 21.0 (C24).



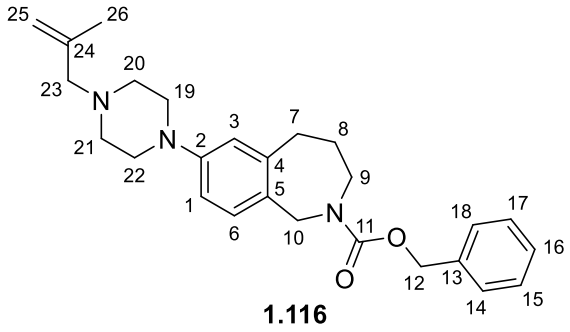
1.81

Benzyl 8-(4-(2-methylallyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.81). KTL-02-099. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified

via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 21 mg (62%) of **1.81** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.27 (s, 5 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.94 (d, *J* = 2.5 Hz, 0.35 H), 6.70 (dt, *J* = 8.2, 2.9 Hz, 1 H), 6.64 (d, *J* = 2.6 Hz, 0.65 H), 5.06 (s, 0.70 H), 5.03 (s, 1.30 H), 4.94 – 4.85 (comp, 2 H), 4.44 (s, 0.70 H), 4.39 (s, 1.30 H), 3.81 – 3.67 (comp , 2 H), 3.22 – 3.14 (comp, 1.50 H), 3.02 – 2.95 (comp, 2.50 H), 2.91 (s, 2 H), 2.89-2.85 (comp, 2 H), 2.55 – 2.49 (comp, 1.50 H), 2.49 – 2.43 (comp, 2.50 H), 1.82 – 1.70 (comp, 5 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.2, 149.8, 149.7, 142.6, 138.8, 138.6, 136.9, 136.8, 132.7, 132.2, 130.1, 130.0, 128.4, 128.0, 127.81, 127.78, 117.7, 117.3, 114.5, 114.2, 113.0, 67.2, 66.9, 65.3, 53.1, 53.1, 52.5, 51.0, 50.3, 49.2, 34.4, 34.2, 28.9, 28.4, 20.9; HRMS (ESI) *m/z* $C_{26}H_{33}N_3O_2$ $(M+Na)^+$ calcd for 442.2465; found 442.2469.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.27 (s, 5 H, C14-H thru C18-H), 7.02 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.94 (d, *J* = 2.5 Hz, 0.35 H, C6-H), 6.70 (dt, *J* = 8.2, 2.9 Hz, 1 H, C2-H), 6.64 (d, *J* = 2.6 Hz, 0.65 H, C6-H), 5.06 (s, 0.70 H, C12-H), 5.03 (s, 1.30 H, C12-H), 4.94 – 4.85 (comp, 2 H, C26-H), 4.44 (s, 0.70 H, C10-H), 4.39 (s, 1.30 H, C10-H), 3.81 – 3.67 (comp , 2 H, C9-H), 3.22 – 3.14 (comp, 1.50 H, C19-H and C22-H), 3.02 – 2.95 (comp, 2.50 H, C19-H and C22-H), 2.91 (s, 2 H, C23-H), 2.89-2.85 (comp, 2 H, C7-H), 2.55 – 2.49 (comp, 1.50 H, C20-H and C21-H), 2.49 – 2.43 (comp, 2.50 H, C20-H and C21-H), 1.82 – 1.70 (comp, 5 H, C8-H and C25-H); ^{13}C NMR (101 MHz, rotamers) δ 155.45 (C11), 155.21 (C11), 149.78 (C1), 149.66 (C1), 142.60 (C24), 138.84 (C5), 138.63 (C5), 136.92 (C13), 136.75 (C13), 132.70 (C4), 132.23 (C4), 130.14 (C3), 130.02 (C3), 128.40 (C17 and C15), 127.95 (C14 and C18), 127.81 (C14 and C18), 127.78 (C16),

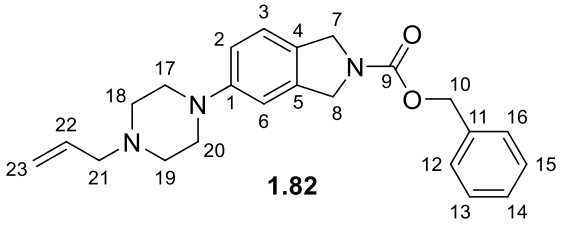
117.72 (C2), 117.34 (C2), 114.54 (C6), 114.19 (C6), 112.96 (C26), 67.23 (C12), 66.91 (C12), 65.31 (C23), 53.13 (C10), 53.10 (C19 and C22), 52.54 (C10), 50.97 (C9), 50.32 (C9), 49.17 (C20 and C21), 34.37 (C7), 34.25 (C7), 28.91 (C8), 28.43 (C8), 20.89 (C25).



1.116

Benzyl 7-(4-(2-methylallyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.116). KTL-02-101. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 19 mg (50%) of **1.116** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.37-7.29 (comp, 5 H), 7.22 (d, *J* = 8.1 Hz, 0.40 H), 6.99 (d, *J* = 8.2 Hz, 0.60 H), 6.74 (s, 1 H), 6.69 (dd, *J* = 8.2, 2.4 Hz, 0.40 H), 6.62 (dd, *J* = 8.2, 2.5 Hz, 0.60 H), 5.05 (s, 2 H), 4.91 (s, 1 H), 4.88 (s, 1 H), 4.41 (s, 0.80 H), 4.38 (s, 1.2 H), 3.72 (s, 2 H), 3.24 – 3.13 (comp, 4 H), 2.92-2.89 (comp, 4 H), 2.56 – 2.46 (comp, 4 H), 1.83-1.72 (comp, 5 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 155.2, 150.8, 142.61, 142.58, 142.2, 136.9, 130.3, 130.0, 129.3, 129.1, 128.4, 128.3, 127.80, 127.75, 117.4, 113.03, 112.99, 112.6, 67.0, 66.8, 65.3, 53.1, 51.9, 51.3, 50.6, 50.1, 49.1, 35.8, 35.7, 28.8, 28.2, 20.9; LRMS (ESI+APCI) *m/z* $C_{26}H_{33}N_3O_2$ $(M+H)^+$ calcd for 420.26; found 420.3.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.37-7.29 (comp, 5 H, C14-H thru C18-H), 7.22 (d, *J* = 8.1 Hz, 0.40 H, C6-H), 6.99 (d, *J* = 8.2 Hz, 0.60 H, C6-H), 6.74 (s, 1 H, C3-H), 6.69 (dd, *J* = 8.2, 2.4 Hz, 0.40 H, C1-H), 6.62 (dd, *J* = 8.2, 2.5 Hz, 0.60 H, C1-H), 5.05 (s, 2 H, C12-H), 4.91 (s, 1 H, C25-H), 4.88 (s, 1 H, C25-H), 4.41 (s, 0.80 H, C10-H), 4.38 (s, 1.2 H, C10-H), 3.72 (s, 2 H, C9-H), 3.24 – 3.13 (comp, 4 H, C19-H and C22-H), 2.92-2.89 (comp, 4 H, C7-H and C32-H), 2.56 – 2.46 (comp, 4 H, C20-H and C21-H), 1.83-1.72 (comp, 5 H, C8-H and C26-H); ^{13}C NMR (101 MHz, rotamers) δ 155.49 (C11), 155.21 (C11), 150.82 (C2), 142.61 (C4), 142.58 (C24), 142.22 (C4), 136.94 (C13), 130.30 (C6), 130.01 (C6), 129.34 (C5), 129.12 (C5), 128.38 (C15 and C17), 128.33 (C15 and C17), 127.80 (C14 and C18), 127.75 (C16), 117.36 (C3), 113.03 (C25), 112.99(C1), 112.65 (C1), 67.00 (C12), 66.85 (C12), 65.33 (C23), 53.13 (C19 and C22), 51.92 (C10), 51.34 (C10), 50.65 (C9), 50.11 (C9), 49.14 (C20 and C21), 35.80 (C7), 35.72 (C7), 28.79 (C8), 28.25 (C8), 20.90 (C26).

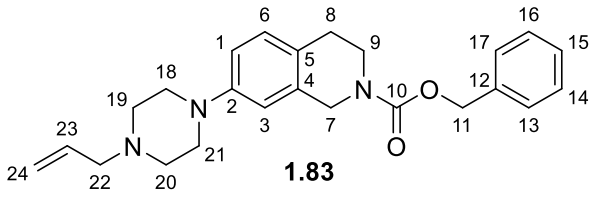


1.82

Benzyl 5-(4-allylpiperazin-1-yl)isoindoline-2-carboxylate (1.82). KTL-01-270. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (15:1:84) to give 60 mg (74%) of **1.82** as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* =48.7 Hz, 5 H), 7.12 (dd, *J* =23.4, 8.4 Hz, 1 H), 6.86

(d, *J* =17.0 Hz, 1 H), 6.79 (d, *J* =25.9 Hz, 1 H), 5.86 (s, 1 H), 5.29 (s, 2 H), 5.27 – 5.17 (comp, 4 H), 4.69 (t, *J* =10.4 Hz, 4 H), 3.20 (dd, *J* =10.1, 5.6 Hz, 4 H), 3.08 (d, *J* =6.6 Hz, 2 H), 2.65 – 2.60 (comp, 4 H); LRMS (ESI+APCI) *m/z* $C_{23}H_{27}N_3O_2$ $(M+H)^+$ calcd for 378.22; found 378.2.

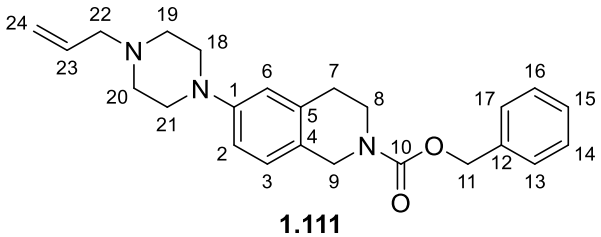
NMR Assignment. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* =48.7 Hz, 5 H, C12-H thru C16-H), 7.12 (m, 1 H, C3-H), 6.86 (d, *J* =17.0 Hz, 1 H, C2-H), 6.79 (d, *J* =25.9 Hz, 1 H, C6-H), 5.86 (m, 1 H, C22-H), 5.29 (s, 2 H, C10-H), 5.27 – 5.17 (comp, 2 H, C23-H), 4.69 (t, *J* =10.4 Hz, 4 H, C7-H and C8-H), 3.20 (dd, *J* =10.1, 5.6 Hz, 4 H, C17-H and C20-H), 3.08 (d, *J* =6.6 Hz, 2 H, C21-H), 2.65 – 2.60 (comp, 4 H, C18-H and C19-H).



1.83

Benzyl 6-(4-allylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.83). KTL-01-236. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (15:1:84) to give 56 mg (65%) of **1.83** as a clear oil: ^{1}H NMR (400 MHz) δ 7.42 (comp, 5 H), 7.03 (d, *J* =7.6 Hz, 1 H), 6.79 (d, *J* =8.4 Hz, 1 H), 6.65 (d, *J* =21.7 Hz, 1 H), 5.90 (m, 1 H), 5.23 (comp, 2 H), 5.18 (s, 2 H), 4.61 (s, 2 H), 3.71 (s, 2 H), 3.22 – 3.12 (comp, 4 H), 3.06 (d, *J* =6.6 Hz, 2 H), 2.77 (s, 2 H), 2.66 – 2.56 (comp, 4 H); ^{13}C NMR (101 MHz) δ 155.5, 149.9, 136.8, 134.8, 134.0, 133.6, 129.4, 129.0, 128.5, 128.0, 127.9, 125.8, 125.6, 118.3, 115.0, 115.0, 113.6, 113.3, 61.8, 53.0, 49.4, 46.1, 46.0, 42.0, 41.7, 28.1, 27.9;

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.42 (comp, 5 H, C13-H thru C17-H), 7.03 (d, *J* =7.6 Hz, 1 H, C6-H), 6.79 (d, *J* =8.4 Hz, 1 H, C1-H), 6.65 (d, *J* =21.7 Hz, 1 H, C3-H), 5.90 (m, 1 H, C23-H), 5.23 (comp, 2 H, C24-H), 5.18 (s, 2 H, C11-H), 4.61 (s, 2 H, C7-H), 3.71 (s, 2 H, C9-H), 3.22 – 3.12 (comp, 4 H, C18-H and C21-H), 3.06 (d, *J* =6.6 Hz, 2 H, C22-H), 2.77 (s, 2 H, C8-H), 2.66 – 2.56 (comp, 4 H, C19-H and C20-H); ^{13}C NMR (101 MHz) δ 155.5 (C10), 149.9 (C2), 136.8 (C12), 134.8 (C23), 134.0 (C4), 133.6 (C4), 129.4 (C6), 129.0 (C6), 128.5 (C13 and C17), 128.0 (C14 and C16), 127.9 (C15), 125.8 (C5), 125.6 (C5), 118.3 (24), 115.0 (C1), 113.6 (C3), 113.3 (C3), 61.8 (C11), 53.0 (C22), 49.4 (C18 and C21), 46.1 (C19 and C20), 46.0 (C7), 42.0 (C9), 41.7 (C9), 28.1 (C8), 27.9 (C8).

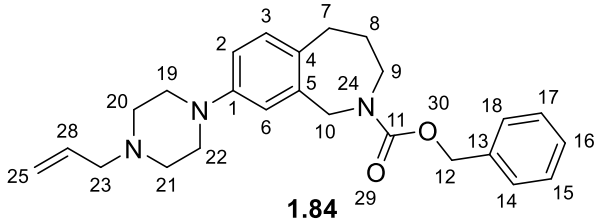


1.111

Benzyl 6-(4-allylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.111). KTL-02-072. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (15:1:84) to give 14 mg (43%) of **1.111** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.41-7.29 (comp, 5 H), 7.00 (dd, *J* = 19.6, 8.7 Hz, 1 H), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.68 (s, 1 H), 5.91 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1 H), 5.27 – 5.19 (comp, 2 H), 5.17 (comp, 3 H), 4.57 (s, 2 H), 3.70 (s, 2 H), 3.22 – 3.14 (comp, 4H), 3.07 (d, *J* =6.5 Hz, 2H), 2.80 (s, 2H), 2.66 – 2.57 (comp, 4 H); ^{13}C NMR (101 MHz,

rotamers) δ 155.6, 155.4, 149.9, 136.8, 135.3, 135.1, 134.5, 128.5, 128.0, 127.9, 127.0, 126.8, 124.8, 124.3, 118.5, 115.9, 115.7, 114.8, 114.7, 67.1, 61.7, 52.8, 49.2, 45.2, 41.7, 41.4, 29.4, 29.2; HRMS (ESI) *m/z* $C_{24}H_{29}N_3O_2$ $(M+H)^+$ calcd for 392.2333; found 392.2334.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.41-7.29 (comp, 5 H, C13-H thru C17-H), 7.00 (dd, *J* = 19.6, 8.7 Hz, 1 H, C3-H), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1 H, C2-H), 6.68 (s, 1 H, C6-H), 5.91 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1 H, C23-H), 5.27 – 5.19 (comp, 2 H, C24-H), 5.17 (comp, 3 H, C11-H and C24-H), 4.57 (s, 2 H, C9-H), 3.70 (s, 2 H, C8-H), 3.22 – 3.14 (comp, 4H, C18-H and C21-H), 3.07 (d, *J* =6.5 Hz, 2H, C22-H), 2.80 (s, 2H, C7-H), 2.66 – 2.57 (comp, 4 H, C19-H and C20-H); ^{13}C NMR (101 MHz, rotamers) δ 155.5 (C10), 155.4 (C10), 149.9 (C1), 136.8 (C12), 135.3 (C4), 135.1 (C4), 134.5 (C23), 128.5 (C14 and C16), 128.0 (C13 and C16), 127.9 (C15), 127.0 (C3), 126.8 (C3), 124.8 (C5), 124.3 (C5), 118.5 (C24), 115.9 (C2), 115.7 (C2), 114.8 (C6), 114.7 (C6), 67.1 (C11), 61.7 (C22), 53.0 (C18 and C21), 49.2 (C19 and C20), 45.2 (C9), 41.7 (C8), 41.4 (C8), 29.4 (C7), 29.2 (C7).

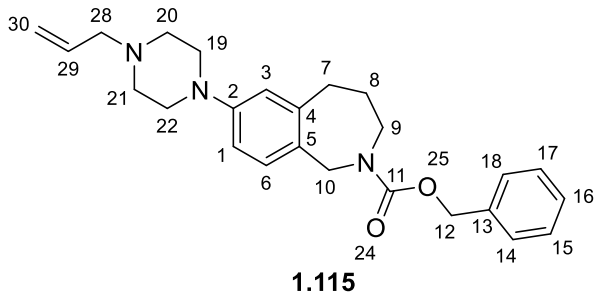


1.84

Benzyl 8-(4-allylpiperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.84). KTL-02-038. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified

via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 21 mg (44%) of **1.84** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.37 – 7.27 (comp, 5 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.95 (d, *J* = 2.6 Hz, 0.35 H), 6.71 – 6.67 (comp, 1 H), 6.65 (d, *J* = 2.7 Hz, 0.60 H), 5.90 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1 H), 5.27 – 5.15 (comp, 2 H), 5.06 (s, 0.75 H), 5.03 (s, 1.25 H), 4.44 (s, 0.75 H), 4.39 (s, 1.25 H), 3.80 – 3.68 (comp, 2 H), 3.27 – 3.17 (comp, 1.50 H), 3.05 (dt, *J* = 6.6, 1.3 Hz, 2 H), 3.03 – 2.97 (comp, 2.50 H), 2.90 – 2.83 (comp, 2 H), 2.62 – 2.57 (comp, 1.50 H), 2.56 – 2.50 (comp, 2.5 H), 1.83 – 1.68 (m, 2 H); LRMS (ESI+APCI) *m/z* $C_{25}H_{31}N_3O_2$ $(M+H)^+$ calcd for 406.55; found 406.3.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.37 – 7.27 (comp, 5 H, C14-H thru C18-H), 7.02 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.95 (d, *J* = 2.6 Hz, 0.35 H, C6-H), 6.71 – 6.67 (comp, 1 H, C2-H and C6-H), 6.65 (d, *J* = 2.7 Hz, 0.60 H, C6-H), 5.90 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1 H, C28-H), 5.27 – 5.15 (comp, 2 H, C25-H), 5.06 (s, 0.75 H, C12-H), 5.03 (s, 1.25 H, C12-H), 4.44 (s, 0.75 H, C10-H), 4.39 (s, 1.25 H, C10-H), 3.80 – 3.68 (comp, 2 H, C9-H), 3.27 – 3.17 (comp, 1.50 H, C19-H and C22-H), 3.05 (dt, *J* = 6.6, 1.3 Hz, 2 H, C23-H), 3.03 – 2.97 (comp, 2.50 H, C19-H and C22-H), 2.90 – 2.83 (comp, 2 H, C7-H), 2.62 – 2.57 (comp, 1.50 H, C20-H and C21-H), 2.56 – 2.50 (comp, 2.5 H, C20-H and C21-H), 1.83 – 1.68 (m, 2 H, C8-H).



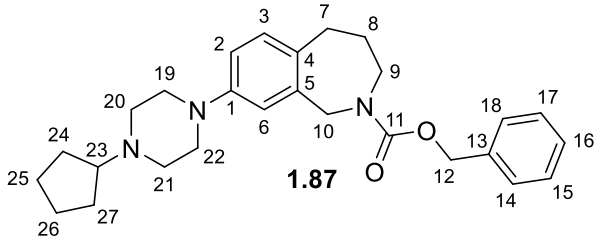
1.115

Benzyl 7-(4-allylpiperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.115). KTL-02-102. Prepared according to the representative procedure outlined for alkylation of piperazines with alkyl bromides. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 20 mg (51%) of **1.115** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.38 – 7.28 (comp, 5 H), 7.24 (d, *J* = 8.2 Hz, 0.35 H), 6.99 (d, *J* = 8.2 Hz, 0.65 H), 6.74 (d, *J* = 2.4 Hz, 1 H), 6.69 (dd, *J* = 8.2, 2.6 Hz, 0.65 H), 6.62 (dd, *J* = 8.2, 2.6 Hz, 0.65 H), 5.96 – 5.84 (m, 1 H), 5.27 – 5.16 (comp, 2 H), 5.05 (s, 2 H), 4.41 (s, 0.80 H), 4.38 (s, 1.20 H), 3.77–3.68 (comp, 2 H), 3.22–2.17 (comp, 4 H), 3.08-3.02 (comp, 2 H), 2.93 – 2.87 (comp, 2 H), 2.63 – 2.57 (comp, 4 H), 1.85 – 1.71 (comp, 2 H); ^{13}C NMR (126 MHz, rotamers) δ 155.6, 155.4, 150.8, 142.8, 142.4, 137.09, 137.06, 134.9, 130.5, 130.2, 129.7, 129.5, 128.5, 128.5, 127.95, 127.92, 118.4, 117.6, 113.2, 112.9, 67.2, 67.0, 61.9, 53.2, 52.1, 51.5, 50.8, 50.3, 49.2, 36.0, 35.9, 28.9, 28.4; LRMS (ESI+APCI) m/z $C_{25}H_{31}N_3O_2$ (M+H)+¬ calcd for 406.55; found 406.3.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.38 – 7.28 (comp, 5 H, C14-H thru C18-H), 7.24 (d, *J* = 8.2 Hz, 0.35 H, C6-H), 6.99 (d, *J* = 8.2 Hz, 0.65 H, C6-H), 6.74 (d, *J* = 2.4 Hz, 1 H, C3-H), 6.69 (dd, *J* = 8.2, 2.6 Hz, 0.65 H, C1-H), 6.62 (dd, *J* = 8.2,

2.6 Hz, 0.65 H, C1-H), 5.96 – 5.84 (m, 1 H, C29-H), 5.27 – 5.16 (comp, 2 H, C30-H), 5.05 (s, 2 H, C12-H), 4.41 (s, 0.80 H, C10-H), 4.38 (s, 1.20 H, C10-H), 3.77–3.68 (comp, 2 H, C9-H), 3.22–2.17 (comp, 4 H, C19-H and C22-H), 3.08-3.02 (comp, 2 H, C28-H), 2.93 – 2.87 (comp, 2 H, C7-H), 2.63 – 2.57 (comp, 4 H, C20-H and C21-H), 1.85 – 1.71 (comp, 2 H, C8-H); ^{13}C NMR (126 MHz, rotamers) δ 155.6 (C11), 155.4 (C11), 150.8 (C20), 142.8 (C4), 142.4 (C4), 137.09 (C13), 137.06 (C13), 134.9 (C29), 130.5 (C6), 130.2 (C6), 129.7 (C5), 129.5 (C5), 128.5 (C15 and C17), 128.5 (C15 and C17), 127.95 (C14 and C18), 127.92 (C16), 118.4 (C3), 117.6 (C30), 113.2 (C1), 112.9 (C1), 67.2 (C12), 67.0 (C12), 61.9 (C28), 53.2 (C19 and C22), 52.1 (C10), 51.5 (C10), 50.8 (C9), 50.3 (C9), 49.2 (C20 and C21), 36.0 (C7), 35.9 (C7), 28.9 (C8), 28.4 (C8).

Representative procedure for reductive alkylation of piperazines

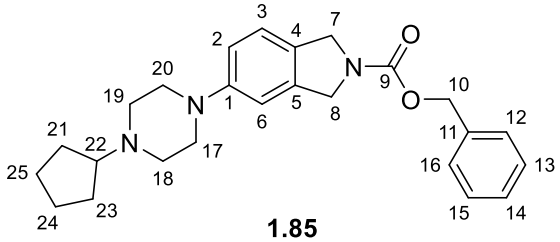


Benzyl 8-(4-cyclopentylpiperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.87). KTL-02-037. A solution of intermediate **1.76** (25 mg, 0.07 mmol), $NaBH(OAc)_3$ (44 mg, 0.21 mmol), cyclopentanone (19 mg, 0.22 mmol) and 10 μL AcOH was stirred for 4 h at room temperature. The reaction was quenched with an aqueous solution of sat. $NaHCO_3$ (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The crude material was purified via flash column

chromatography eluting EtOAc:TEA:hexanes (25:1:74) to give 22 mg (81%) of **1.87** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.27 (s, 5 H), 7.02 (d, *J* =8.1 Hz, 1 H), 6.94 (d, *J* =2.4 Hz, 0.37 H), 6.71 – 6.67 (m, 1 H), 6.65 (d, *J* =2.5 Hz, 0.63 H), 5.05 (s, 0.7 H), 5.03 (s, 1.3 H), 4.44 (s, 0.7 H), 4.39 (s, 1.3 H), 3.80 (comp, 2 H), 3.23 – 3.17 (m, 1.5 H), 3.05 – 2.98 (m, 2.5 H), 2.87 (comp, 2H), 2.67 – 2.62 (m, 1.5 H), 2.61 – 2.56 (m, 2.5 H), 2.56-2.48 (m, 1 H), 1.95 – 1.86 (comp, 2 H), 1.81-1.66 (comp, 4 H), 1.60 – 1.53 (comp, 2 H), 1.50-1.39 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 155.4, 155.2, 149.6, 149.5, 138.9, 138.6, 136.9, 136.8, 132.8, 132.4, 130.2, 130.0, 128.4, 127.9, 127.79, 127.76, 117.7, 117.4, 114.3, 114.0, 67.7, 67.51, 67.48, 67.2, 66.9, 53.0, 52.5, 52.4, 52.3, 50.9, 50.3, 49.1, 49.0, 34.4, 34.3, 30.4, 29.7, 28.9, 28.4, 24.2; HRMS (ESI) *m/z* $C_{27}H_{35}N_3O_2$ $(M+H)^+$ calcd for 434.2802; found 434.2805.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.27 (s, 5 H, C14-H thru C18-H), 7.02 (d, *J* =8.1 Hz, 1 H, C3-H), 6.94 (d, *J* =2.4 Hz, 0.37 H, C6-H), 6.71 – 6.67 (m, 1 H, C2-H), 6.65 (d, *J* =2.5 Hz, 0.63 H, C6-H), 5.05 (s, 0.7 H, C12-H), 5.03 (s, 1.3 H, C12-H), 4.44 (s, 0.7 H, C10-H), 4.39 (s, 1.3 H, C10-H), 3.80 (comp, 2 H, C9-H), 3.23 – 3.17 (m, 1.5 H, C19-H and C22-H), 3.05 – 2.98 (m, 2.5 H, C19-H and C22-H), 2.87 (comp, 2H, C7-H), 2.67 – 2.62 (m, 1.5 H, C20-H and C21-H), 2.61 – 2.56 (m, 2.5 H, C20-H and C21-H), 2.56-2.48 (m, 1 H, C23-H), 1.95 – 1.86 (comp, 2 H, C24-H or C27-H), 1.81-1.66 (comp, 4 H, C8-H and C24-H or C27-H), 1.60 – 1.53 (comp, 2 H, C25-H or C26-H), 1.50-1.39 (comp, 2 H, C25-H or C26-H); ^{13}C NMR (101 MHz, rotamers) δ 155.43 (C11), 155.20 (C11), 149.62 (C1), 149.48 (C1), 138.85 (C5), 138.65 (C5), 136.92 (C13), 136.81 (C13), 132.78 (C3), 132.36 (C3), 130.16 (C4), 130.04 (C4), 128.38 (C15 and C17), 127.89 (C14

and C18), 127.79 (C16), 127.76 (C14 and C18), 117.86 (C2), 117.39 (C2), 114.30 (C3), 114.03 (C3), 67.51 (C23), 67.48 (C23), 67.17 (C12), 66.91 (C12), 53.04 (C10), 52.52 (C10), 52.37 (C19 and C22), 52.32 (C19 and C22), 50.94 (C9), 50.30 (C9), 49.07 (C20 and C21), 49.03 (C20 and C21), 34.35 (C7), 34.25 (C7), 30.43 (C24 and C27), 29.68 (C24 and C27), 28.90 (C8), 28.41 (C8), 24.15 (C25 and C26).

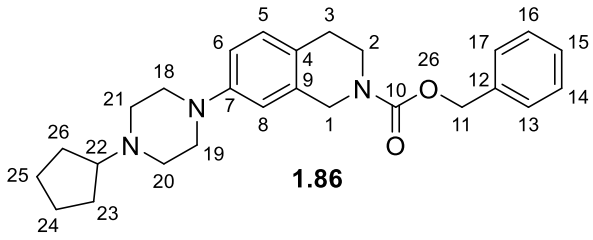


1.85

Benzyl 5-(4-cyclopentylpiperazin-1-yl)isoindoline-2-carboxylate (1.85). KTL-01-227. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (25:1:74) to give 23 mg (71%) of **1.85** as a white solid: ^{1}H NMR (400 MHz) δ 7.44 – 7.29 (comp, 5 H), 7.12 (dd, *J* = 23.4, 8.4 Hz, 1 H), 6.89 – 6.84 (m, 1 H), 6.79 (d, *J* =25.9 Hz, 1H), 5.21 (s, 2 H), 4.69 (t, *J* =10.8 Hz, 4 H), 3.19 (comp, 4 H), 2.70 – 2.63 (comp, 4 H), 2.53 (d, *J* =35.1 Hz, 1 H), 1.96 (comp, 2 H), 1.66 (comp, 2 H), 1.64 (comp, 2 H), 1.50 (comp, 2 H); ^{13}C NMR (101 MHz, rotamers) δ 154.9, 154.9, 151.4, 138.0, 137.6, 136.9, 128.5, 128.0, 127.9, 127.8, 127.7, 123.2, 123.0, 116.0, 115.8, 110.1, 109.9, 67.4, 66.9, 52.7, 52.3, 52.1, 51.6, 49.6, 49.5, 30.5, 24.2; HRMS (ESI) *m/z* $C_{25}H_{31}N_3O_2$ $(M+H)^+$ calcd for 406.2489; found 406.2496.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.44 – 7.29 (comp, 5 H, C12-H thru C16-H), 7.12 (dd, *J* =23.4, 8.4 Hz, 1 H, C3-H), 6.89 – 6.84 (m, 1 H, C2-H), 6.79 (d, *J*

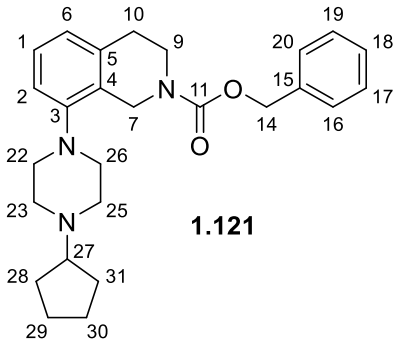
=25.9 Hz, 1 H, C1-H), 5.21 (s, 2 H, C10-H), 4.69 (t, *J* =10.8 Hz, 4 H, C7-H and C8-H), 3.19 (comp, 4 H, C17-H and C20-H), 2.70 – 2.63 (comp, 4 H, C18-H and C19-H), 2.53 (d, *J* =35.1 Hz, 1 H, C22-H), 1.96 (comp, 2 H, C21-H or C23-H), 1.66 (comp, 2 H, C21-H or C23-H), 1.64 (comp, 2 H, C24-H or C25-H), 1.50 (comp, 2 H, C24-H or C25-H); ^{13}C NMR (101 MHz, rotamers) δ 154.91 (C9), 154.87 (C9), 151.4 (C1), 138.0 (C5), 137.6 (C5), 136.9 (C11), 128.5 (C13 and C15), 128.0 (C14), 127.9 (C4), 127.8 (C12 and C16), 127.7 (C4), 123.2 (C3), 123.0 (C3), 116.0 (C2), 115.8 (C2), 110.1 (C6), 109.9 (C6), 67.4 (C22), 66.9 (C10), 52.7 (C8), 52.3 (C17 and C20), 52.1 (C7), 51.6 (C7), 49.6 (C18 and C19), 49.5 (C18 and C19), 30.5 (C21 and C23), 24.2 (C24 and C25).



Benzyl 7-(4-cyclopentylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.86). KTL-01-214. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 21 mg (44%) of **1.86** as a clear oil: ^{1}H NMR (400 MHz) δ 7.40-7.28 (comp, 5 H), 7.01 (d, *J* = 8.4, 1 H), 6.78 (dd, *J* = 8.4, 2 Hz, 1 H), 6.64 (d, *J* = 21.5 Hz, 1 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 3.70 (br s, 2 H), 3.17 (t, *J* = 4.8, 4 H), 2.77 (br s, 2 H), 2.65 (t, *J* = 4.8, 4 H), 2.58-2.47 (m, 1 H), 1.96-1.82 (comp, 2 H), 1.77-1.70 (comp, 2 H), 1.63-1.50 (comp, 2 H), 1.4-1.37 (comp, 2 H); ^{13}C NMR (101 MHz, rotomers) δ 155.5, 149.9, 136.8, 134.0, 133.5, 129.4, 129.1, 128.5,

127.9, 127.9, 125.8, 125.7, 114.9, 113.6, 113.3, 67.5, 67.1, 52.3, 49.4, 46.1, 46.0, 41.9, 41.7, 30.5, 28.1, 27.8, 24.2; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 442.2465; found 442.2468; IR (neat) 2926, 2857, 2763, 1702, 1508, 1450, 1429, 1242, 1101 cm^{-1}.

NMR Assignment. ^1H NMR (400 MHz) δ 7.40-7.28 (comp, 5 H C13-H-C17-H), 7.01 (d, *J* = 8.4, 1 H, C5-H), 6.78 (dd, *J* = 8.4, 2 Hz, 1 H, C6-H), 6.64 (d, *J* = 21.5 Hz, 1 H, C8-H), 5.17 (s, 2 H, C11-H), 4.60 (s, 2 H, C1-H), 3.70 (br s, 2 H, C3-H), 3.17 (t, *J* = 4.8, 4 H, C20-H and C21-H), 2.77 (br s, 2 H, C2-H), 2.65 (t, *J* = 4.8, 4 H, C18-H and C19-H), 2.58-2.47 (m, 1 H, C22-H), 1.96-1.82 (comp, 2 H, C26-H or C23-H), 1.77-1.70 (comp, 2 H, C26-H or C23-H), 1.63-1.50 (comp, 2 H, C24-H or C25-H), 1.4-1.37 (comp, 2 H, C24-H or C25-H); ^{13}C NMR (101 MHz, rotomers) δ 155.5 (C10), 149.9 (C7), 136.8 (C12), 134.0 (C9), 133.5 (C9), 129.4 (C5), 129.1 (C5), 128.5 (C13 and C17), 127.9 (C14 and 16), 127.9 (C15), 125.6 (C4), 125.7 (C4), 114.9 (C6), 113.6 (C8), 113.3 (C8), 67.5 (C22), 67.1 (C11), 52.3 (C20 and C21), 49.4 (C18 and C19), 46.1 (C1), 46.0 (C1), 41.9 (C2), 41.7 (C2), 30.5 (C23 and C26), 28.1 (C3), 27.8 (C3), 24.2 (C24 and C25).

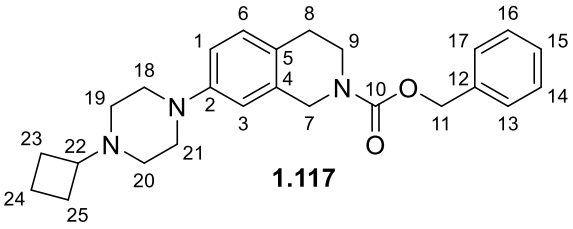


1.121

Benzyl 8-(4-cyclopentylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.121). KTL-02-113. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column

chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 29 mg (72%) of **1.212** as a clear oil: ^{1}H NMR (400 MHz) δ 7.43 – 7.28 (comp, 5 H), 7.17 (t, *J* = 7.7 Hz, 1 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 6.90 (s, 1 H), 5.18 (s, 2 H), 4.67 (s, 2 H), 3.68 (t, *J* = 6.2 Hz, 2 H), 3.01 – 2.79 (comp, 7 H), 2.61 (comp, 4 H), 1.94 – 1.84 (comp, 2 H), 1.72 (br s, 2 H), 1.58 (br s, 2 H), 1.43 (ddd, *J* = 11.9, 5.9, 2.8 Hz, 2 H); ^{13}C NMR (126 MHz, rotamers) δ 155.6, 150.4, 150.0, 137.1, 136.3, 136.0, 129.3, 129.0, 128.6, 128.1, 128.0, 127.6, 127.3, 124.1, 124.0, 117.8, 67.7, 67.1, 53.0, 52.9, 52.4, 42.5, 42.3, 41.8, 30.6, 29.5, 29.1, 24.3; LRMS (ESI+APCI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 420.27; found 420.3.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.43 – 7.28 (comp, 5 H, C16-H thru C20-H), 7.17 (t, *J* = 7.7 Hz, 1 H, C1-H), 6.99 (d, *J* = 8.0 Hz, 1 H, C6-H), 6.90 (s, 1 H, C2-H), 5.18 (s, 2 H, C14-H), 4.67 (s, 2 H, C7-H), 3.68 (t, *J* = 6.2 Hz, 2 H, C9-H), 3.01 – 2.79 (comp, 7 H, C10-H, C22-H, C26-H and C27-H), 2.61 (comp, 4 H, C13-H and C25-H), 1.94 – 1.84 (comp, 2 H, C28-H), 1.72 (br s, 2 H, C29-H), 1.58 (br s, 2 H, C30-H), 1.43 (ddd, *J* = 11.9, 5.9, 2.8 Hz, 2 H, C31-H); ^{13}C NMR (126 MHz, rotamers) δ 155.6 (C11), 150.4 (C3), 150.0 (C3), 137.1 (C15), 136.3 (C5, 136.0 (C5), 129.3 (C4), 129.0 (C4), 128.6 (C17 and C19), 128.1 (C16 and C20), 128.0 (C16 and C20), 127.6 (C15), 127.3 (C1), 124.1 (C2), 124.0 (C2), 117.8 (C6), 67.7 (C27), 67.1 (C14), 53.0 (C23 and C25), 52.9 (C23 and C25), 52.4 (C22 and C26), 42.5 (C7), 42.3 (C7), 41.8 (C9), 30.6 (C28 and C31), 29.5 (C10), 29.1 (C10), 24.3 (C29 and C30).

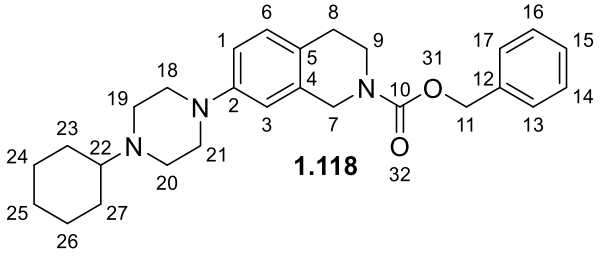


1.117

Benzyl 7-(4-cyclobutylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.117). KTL-02-068. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (15:1:84) to give 31 mg (73%) of **1.117** as a clear oil: ^{1}H NMR (400 MHz) δ 7.40 – 7.27 (comp, 5 H), 7.01 (d, *J* = 7.5 Hz, 1 H), 6.76 (dd, *J* = 8.3, 1.9 Hz, 1 H), 6.63 (d, *J* = 21.8 Hz, 1 H), 5.15 (s, 2 H), 4.59 (s, 2 H), 3.69 (s, 2 H), 3.19 – 3.09 (comp, 4 H), 2.83-2.69 (comp, 3 H), 2.52 – 2.43 (comp, 4 H), 2.08-2.01 (comp, 2 H), 1.97 – 1.84 (comp, 2 H), 1.77 – 1.63 (comp, 2 H); ^{13}C NMR (101 MHz) δ 155.5, 150.0, 136.8, 136.7, 134.0, 133.5, 129.4, 129.1, 128.5, 128.0, 127.8, 125.8, 125.6, 115.1, 115.0, 113.6, 113.3, 67.2, 60.3, 60.2, 49.4, 49.1, 46.1, 46.0, 41.9, 41.7, 28.1, 27.9, 27.0, 14.3; HRMS (ESI) *m/z* $C_{25}H_{31}N_3O_2$ $(M+H)^+$ calcd for 406.2489; found 406.2492.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.40 – 7.27 (comp, 5 H, C13-H thru C17-H), 7.01 (d, *J* = 7.5 Hz, 1 H, C6-H), 6.76 (dd, *J* = 8.3, 1.9 Hz, 1 H, C1-H), 6.63 (d, *J* = 21.8 Hz, 1 H, C3-H), 5.15 (s, 2 H, C11-H), 4.59 (s, 2 H, C7-H), 3.69 (s, 2 H, C9-H), 3.19 – 3.09 (comp, 4 H, C18-H and C21-H), 2.83-2.69 (comp, 3 H, C8-H and C22-H), 2.52 – 2.43 (comp, 4 H, C19-H and C20-H), 2.08-2.01 (comp, 2 H, C23-H or C25-H), 1.97 – 1.84 (comp, 2 H, C23-H or C25-H), 1.77 – 1.63 (comp, 2 H, C24-H); ^{13}C NMR (101 MHz) δ 155.5 (C10), 150.0 (C2), 136.8 (C12), 136.7 (C12), 134.0 (C4), 133.5 (C4), 129.4 (C6),

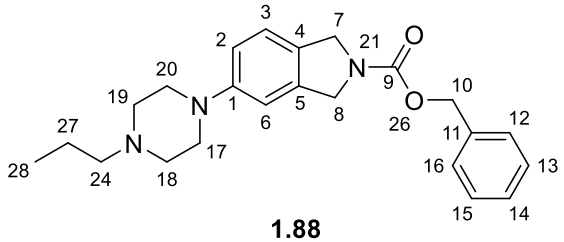
129.1 (C6), 128.5 (C14 and C16), 128.0 (13 and C17), 127.8 (C15), 125.8 (C5), 125.6 (C5), 115.1 (C1), 115.0 (C1), 113.6 (C3), 113.3 (C3), 67.2 (C11), 60.3 (C22), 60.2 (C22), 49.4 (C18 and C21), 49.1 (C19 and C20), 46.1 (C7), 46.0 (C7), 41.9 (C9), 41.7 (C9), 28.1 (C8), 27.9 (C8), 27.0 (C24), 14.3 (C23 and C25).



Benzyl 7-(4-cyclohexylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.118). KTL-02-067. Prepared according to the representative procedure for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (15:1:74) to give 29 mg (78%) of **1.118** as a clear oil: ^{1}H NMR (400 MHz) δ 7.41 – 7.29 (m, 5 H), 7.02 (d, *J* = 7.3 Hz, 1 H), 6.78 (dd, *J* = 8.4, 2.3 Hz, 1 H), 6.64 (d, *J* = 21.2 Hz, 1 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 3.70 (d, *J* = 4.8 Hz, 2 H), 3.16 (s, 4 H), 2.73 (s, 6 H), 2.30 (s, 1 H), 1.93 (s, 2 H), 1.81 (s, 2 H), 1.65 (d, *J* = 11.6 Hz, 1 H); ^{13}C NMR (126 MHz, rotamers) δ 155.5, 150.0, 136.8, 134.0, 133.6, 129.4, 129.1, 128.5, 128.0, 127.9, 125.8, 125.6, 115.1, 115.0, 113.7, 113.4, 67.2, 67.1, 63.6, 49.8, 49.0, 46.1, 46.0, 42.0, 41.8, 28.9, 28.1, 27.9, 26.3, 25.9; HRMS (ESI) *m/z* $C_{27}H_{35}N_3O_2$ $(M+H)^+$ calcd for 434.2802; found 434.2805.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.41 – 7.29 (m, 5 H, C13-H thru C17-H), 7.02 (d, *J* = 7.3 Hz, 1 H, C6-H), 6.78 (dd, *J* = 8.4, 2.3 Hz, 1 H, C1-H), 6.64 (d, *J* = 21.2 Hz, 1 H, C3-H), 5.17 (s, 2 H, C11-H), 4.60 (s, 2 H, C7-H), 3.70 (d, *J* = 4.8 Hz, 2 H, C9-

H)), 3.16 (s, 4 H, C18-H and C21-H), 2.73 (s, 6 H, C8-H, C19-H, and C20-H), 2.30 (s, 1 H, C22-H), 1.93 (s, 2 H, C23-H or C27-H), 1.81 (s, 2 H, C23-H or C27-H), 1.65 (d, *J* = 11.6 Hz, 1 H), 1.24 (comp, 6 H); ^{13}C NMR (126 MHz, rotamers) δ 155.5 (C10), 150.0 (C2), 136.8 (C12), 134.0 (C4), 133.6 (C4), 129.4 (C6), 129.1 (C6), 128.5 (C14 and C16), 128.0 (C13 and C17), 127.9 (C15), 125.8 (C5), 125.6 (C5), 115.1 (C1), 115.0 (C1), 113.7 (C3), 113.4 (C3), 67.2 (C11), 67.1 (C11), 63.6 (C22), 49.8 (C18 and C21), 49.0 (C19 and C20), 46.1 (C7), 46.0 (C7), 42.0 (C9), 41.8 (C9), 28.9 (C23 and C27), 28.1 (C8), 27.9 (C8), 26.3 (C25), 25.9 (C24 and C26).

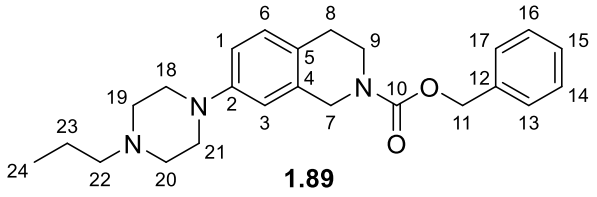


1.88

Benzyl 5-(4-propylpiperazin-1-yl)isoindoline-2-carboxylate (1.88). KTL-02-104. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (10:1:89) to give 10 mg (59%) of **1.88** as a clear oil: ^{1}H NMR (400 MHz) δ 7.45 – 7.28 (comp, 5 H), 7.12 (dd, *J* = 23.5, 8.4 Hz, 1 H), 6.87 (ddd, *J* = 8.5, 6.4, 2.3 Hz, 1 H), 6.80 (dd, *J* = 24.2, 2.3 Hz, 1 H), 5.21 (s, 2 H), 4.74 – 4.62 (comp, 4 H), 3.19 (td, *J* = 5.8, 3.3 Hz, 4 H), 2.61 (dd, *J* = 6.2, 3.9 Hz, 4 H), 2.39 – 2.31 (comp, 2 H), 1.56 (tt, *J* = 14.2, 6.8 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 154.9, 154.9, 151.4, 138.0, 137.6, 136.88, 136.87, 128.5, 128.0, 127.9, 127.8, 127.7, 123.2, 123.0,

116.1, 115.9, 110.1, 110.0, 66.9, 60.7, 53.2, 52.7, 52.3, 52.1, 51.6, 49.6, 49.6, 20.0, 12.0; LRMS (ESI+APCI) m/z $C_{23}H_{29}N_3O_2$ (M+H)+¬ calcd for 380.24; found 380.3.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.45 – 7.28 (comp, 5 H, C12-H thru C16-H), 7.12 (dd, *J* = 23.5, 8.4 Hz, 1 H, C3-H), 6.87 (ddd, *J* = 8.5, 6.4, 2.3 Hz, 1 H, C2-H), 6.80 (dd, *J* = 24.2, 2.3 Hz, 1 H, C6-H), 5.21 (s, 2 H, C10-H), 4.74 – 4.62 (comp, 4 H, C7-H and C8-H), 3.19 (td, *J* = 5.8, 3.3 Hz, 4 H, C17-H and C20-H), 2.61 (dd, *J* = 6.2, 3.9 Hz, 4 H, C18-H and C19-H), 2.39 – 2.31 (comp, 2 H, C24-H), 1.56 (tt, *J* = 14.2, 6.8 Hz, 2 H, C27-H), 0.93 (t, *J* = 7.4 Hz, 3 H, C28-H); ^{13}C NMR (101 MHz, rotamers) δ 154.9 (C9), 154.9 (C9), 151.4 (C1), 138.0 (C5), 137.6 (C5), 136.88 (C11), 136.87 (C11), 128.5 (C13 and C15), 128.0 (C14), 127.9 (C3), 127.8 (C12 and C16), 127.7 (C3), 123.2 (C4), 123.0 (C4), 116.1 (C2), 115.9 (C2), 110.1 (C6), 110.0 (C6), 66.9 (C10), 60.7 (C24), 53.2 (C17 and C20), 52.7 (C7 or C8), 52.3 (C7 or C8), 52.1 (C7 or C8), 51.6 (C7 or C8), 49.6 (C18 and C19), 49.6 (C18 and C19), 20.0 (C27), 12.0 (C28).

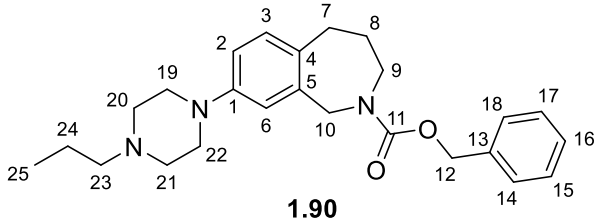


1.89

Benzyl 7-(4-propylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.89). KTL-02-036. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (10:1:89) to give 13 mg (57%) of **1.89** as a clear oil: ^{1}H NMR (400 MHz) δ 7.40-7.30 (comp, 5 H), 7.03 (d, *J* =7.8 Hz, 1 H), 6.78 (dd, *J* =8.4, 2.3 Hz, 1 H), 6.64 (d, *J* =21.3 Hz, 1 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 3.71 (s, 2 H),

3.20 – 3.13 (comp, 4 H), 2.76 (s, 2 H), 2.64 – 2.55 (comp, 4 H), 2.41 – 2.31 (comp, 2 H), 1.55 (comp, 2 H), 0.93 (t, *J* =7.4 Hz, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 155.5, 150.0, 136.8, 134.0, 133.6, 129.4, 129.1, 128.5, 128.0, 127.9, 125.8, 125.6, 115.0, 113.6, 113.3, 67.2, 60.6, 53.2, 49.3, 46.1, 46.0, 42.0, 41.7, 28.1, 27.8, 20.0, 11.9; HRMS (ESI) *m/z* $C_{24}H_{31}N_3O_2$ $(M+H)^+$ calcd for 416.2308; found 416.2310.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.40-7.30 (comp, 5 H, C13-H thru C17-H), 7.03 (d, *J* =7.8 Hz, 1 H, C6-H), 6.78 (dd, *J* =8.4, 2.3 Hz, 1 H, C1-H), 6.64 (d, *J* =21.3 Hz, 1 H, C3-H), 5.17 (s, 2 H, C11-H), 4.60 (s, 2 H, C7-H), 3.71 (s, 2 H, C9-H), 3.20 – 3.13 (comp, 4 H, C18-H and C21-H), 2.76 (s, 2 H, C8-H), 2.64 – 2.55 (comp, 4 H, C19-H and C20-H), 2.41 – 2.31 (comp, 2 H, C22-H), 1.55 (comp, 2 H, C23-H), 0.93 (t, *J* =7.4 Hz, 3 H, C24-H); ^{13}C NMR (101 MHz, rotamers) δ 155.5 (C10), 150.0 (C2), 136.8 (C12), 134.0 (C4), 133.6 (C4), 129.4 (C6), 129.1 (C6), 128.5 (C14 and C16), 128.0 (C13 and C17), 127.9 (C15), 125.8 (C5), 125.6 (C5), 115.0 (C1), 113.6 (C3), 113.3 (C3), 67.2 (C11), 60.6 (C22), 53.2 (C18 and C21), 49.3 (C19 and C20), 46.1 (C7), 46.0 (C7), 42.0 (C9), 41.7 (C9), 28.1 (C8), 27.8 (C8), 20.0 (C23), 11.9 (C24).



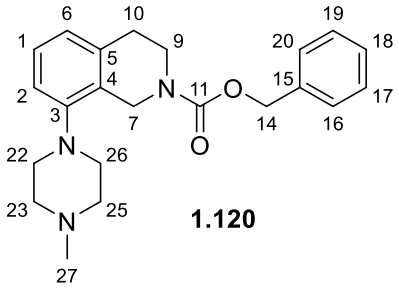
1.90

Benzyl 8-(4-propylpiperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.90). KTL-02-058. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash

column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 16 mg (79%) of **1.90** as a clear oil: ^{1}H NMR (400 MHz, rotamers) δ 7.32 (comp, 5 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.94 (d, *J* = 2.5 Hz, 0.35 H), 6.69 (dd, *J* = 8.1, 2.8 Hz, 1 H), 6.65 (d, *J* = 2.6 Hz, 0.65 H), 5.06 (s, 0.70 H), 5.03 (s, 1.30 H), 4.44 (s, 0.70 H), 4.39 (s, 1.30 H), 3.81-3.67 (comp, 2 H), 3.22 – 3.15 (comp, 1.50 H), 3.02-2.99 (comp, 2.50 H), 2.89-2.85 (comp, 2H), 2.62 – 2.55 (comp, 1.50 H), 2.55 – 2.49 (comp, 2.50 H), 2.38 – 2.31 (comp, 2H), 1.82-1.67 (comp, 2 H), 1.62 – 1.49 (m, 2 H), 0.93 (comp, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 155.4, 155.2, 149.7, 149.6, 138.9, 138.7, 136.9, 136.8, 132.8, 132.3, 130.2, 130.0, 128.4, 127.9, 127.8, 117.8, 117.4, 114.4, 114.1, 67.2, 66.9, 60.7, 53.3, 53.2, 53.1, 52.5, 51.0, 50.3, 49.12, 49.08, 34.4, 34.3, 28.9, 28.4, 20.0, 12.0; HRMS (ESI) *m/z* $C_{25}H_{33}N_3O_2$ $(M+H)^+$ calcd for 408.2646; found 408.2655.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.32 (comp, 5 H, C14-H thru C18-H), 7.02 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.94 (d, *J* = 2.5 Hz, 0.35 H, C6-H), 6.69 (dd, *J* = 8.1, 2.8 Hz, 1 H, C2-H), 6.65 (d, *J* = 2.6 Hz, 0.65 H, C6-H), 5.06 (s, 0.70 H, C12-H), 5.03 (s, 1.30 H, C12-H), 4.44 (s, 0.70 H, C10-H), 4.39 (s, 1.30 H, C10-H), 3.81-3.67 (comp, 2 H, C9-H), 3.22 – 3.15 (comp, 1.50 H, C19-H and C22-H), 3.02-2.99 (comp, 2.50 H, C19-H and C22-H), 2.89-2.85 (comp, 2H, C23-H), 2.62 – 2.55 (comp, 1.50 H, C20-H and C21-H), 2.55 – 2.49 (comp, 2.50 H, C20-H and C21-H), 2.38 – 2.31 (comp, 2H, C7-H), 1.82-1.67 (comp, 2 H, C8-H), 1.62 – 1.49 (m, 2 H, C24-H), 0.93 (comp, 3 H, C25-H); ^{13}C NMR (101 MHz, rotamers) δ 155.44 (C11), 155.21 (C11), 149.69 (C1), 149.56 (C1), 138.86 (C5), 138.65 (C5), 136.92 (C13), 136.77 (C13), 132.77 (C3), 132.33 (C3), 130.16 (C4), 130.03 (C4), 128.39 (C15 and C17), 127.92 (C14, C16, and C18), 127.79 (C14, C16, and

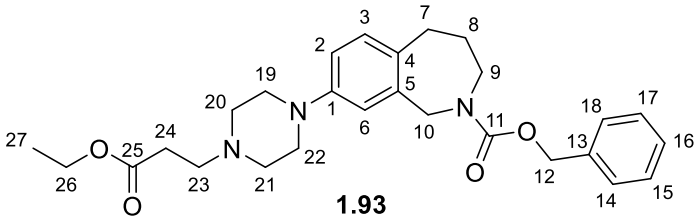
C18), 117.82 (C2), 117.39 (C2), 114.39 (C6), 114.09 (C6), 67.20 (C12), 66.91 (C12), 60.69 (C23), 53.27 (C19 and C22), 53.24 (C19 and C22), 53.05 (C10), 52.52 (C10), 50.95 (C9), 50.32 (C9), 49.12 (C20 and C21), 49.08 (C20 and C20), 34.36 (C7), 34.25 (C7), 28.91 (C8), 28.42 (C8), 20.03 (C24), 11.96 (C25).



1.120

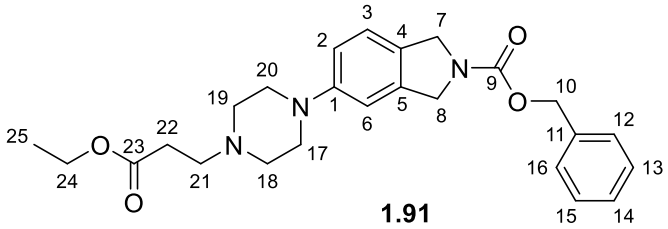
Benzyl 8-(4-methylpiperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.120). KTL-03-157. Prepared according to the representative procedure outlined for reductive alkylation of piperazines. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (49:1:50) to give 7 mg (56%) of **1.120** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.45 – 7.28 (comp, 5 H), 7.17 (t, *J* = 7.7 Hz, 1 H), 6.99 (d, *J* = 7.9 Hz, 1 H), 6.90 (s, 1 H), 5.18 (s, 2 H), 4.66 (s, 2 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 2.97 – 2.80 (comp, 6 H), 2.57 (d, *J* = 31.9 Hz, 3 H), 2.36 (s, 3 H); LRMS (ESI+APCI) m/z $C_{22}H_{27}N_3O_2$ $(M+H)^+$ calcd for 366.22; found 366.3.

Representative procedure for conjugate addition



Benzyl 8-(4-(3-ethoxy-3-oxopropyl)piperazin-1-yl)-1,3,4,5-tetrahydro-2H-benzo[c]azepine-2-carboxylate (1.93). KTL-02-023. Ethyl acrylate (23 mg, 0.22 mmol) was added to a solution of intermediate **1.76** (40 mg, 0.11 mmol) in EtOH (1 mL). The solution was heated to 40 °C for 16 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The crude material was purified via silica plug eluting with EtOAc:TEA:hexanes (49:1:50) to give 38 mg (74%) of **1.93** as a yellow oil: ^{1}H NMR (400 MHz, rotamers) δ 7.37-7.28 (comp, 5 H), 7.02 (d, *J* = 8.2 Hz, 1 H), 6.93 (d, *J* = 2.4 Hz, 0.35 H), 6.71 – 6.65 (m, 1 H), 6.63 (d, *J* = 2.5 Hz, 0.65 H), 5.05 (s, 0.70 H), 5.03 (s, 1.30 H), 4.43 (s, 0.70 H), 4.38 (s, 1.30 H), 4.19-4.12 (comp, 2 H), 3.81 – 3.68 (comp, 2 H), 3.22 – 3.14 (comp, 1.50 H), 3.01 – 2.94 (comp, 2.50 H), 2.89-2.85 (comp, 2 H), 2.75 (t, *J* = 7.4 Hz, 2 H), 2.64 – 2.58 (comp, 1.50 H), 2.54 (comp, 4.50 H), 1.75 (comp, 2 H), 1.27 (comp, 3 H); ^{13}C NMR (101 MHz) δ 172.44, 172.42, 155.4, 155.1, 149.5, 149.4, 138.9, 138.7, 136.9, 136.7, 132.9, 132.5, 130.2, 130.0, 128.4, 127.9, 127.8, 127.8, 117.8, 117.4, 114.5, 114.2, 67.2, 66.9, 60.45, 60.42, 53.6, 53.0, 52.9, 52.5, 51.0, 50.4, 49.1, 49.1, 34.4, 34.3, 32.4, 28.9, 28.4, 14.2; HRMS (ESI) *m/z* $C_{27}H_{35}N_3O_4$ $(M+H)^+$ calcd for 466.2700; found 466.2712.

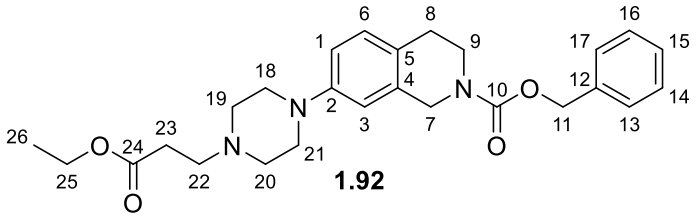
NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.37-7.28 (comp, 5 H, C14-H thru C18-H), 7.02 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.93 (d, *J* = 2.4 Hz, 0.35 H, C6-H), 6.71 – 6.65 (m, 1 H, C2-H), 6.63 (d, *J* = 2.5 Hz, 0.65 H, C6-H), 5.05 (s, 0.70 H, C12-H), 5.03 (s, 1.30 H, C12-H), 4.43 (s, 0.70 H, C10-H), 4.38 (s, 1.30 H, C10-H), 4.19-4.12 (comp, 2 H, C26-H), 3.81 – 3.68 (comp, 2 H, C9-H), 3.22 – 3.14 (comp, 1.50 H, C19-H and C22-H), 3.01 – 2.94 (comp, 2.50 H, C19-H and C22-H), 2.89-2.85 (comp, 2 H, C7-H), 2.75 (t, *J* = 7.4 Hz, 2 H, C23-H), 2.64 – 2.58 (comp, 1.50 H, C20-H and C21-H), 2.54 (comp, 4.50 H, C20-H, C21-H and C24-H), 1.75 (comp, 2 H, C8-H), 1.27 (comp, 3 H, C27-H); ^{13}C NMR (101 MHz, rotamers) δ 172.44 (C25), 172.42 (C25), 155.4 (C11), 155.1 (C11), 149.5 (C1), 149.4 (C1), 138.9 (C5), 138.7 (C5), 136.9 (C13), 136.7 (C13), 132.9 (C4), 132.5 (C4), 130.2 (C3), 130.0 (C3), 128.4 (C15 and C17), 127.9 (C14 or C18), 127.8 (C14 or C18), 127.8 (C16), 117.8 (C2), 117.4 (C2), 114.5 (C6), 114.2 (C6), 67.2 (C12), 66.9 (C12), 60.45 (C26), 60.42 (C26), 53.6 (C23), 53.0 (C10), 52.9 (C19 and C22), 52.5 (C10), 51.0 (C9), 50.4 (C9), 49.1 (C20 and C21), 49.0 (C20 and C21), 34.4 (C7), 34.3 (C7), 32.4 (C24), 28.9 (C8), 28.4 (C8), 14.2 (C27).



Benzyl 5-(4-(3-ethoxy-3-oxopropyl)piperazin-1-yl)isoindoline-2-carboxylate (1.91). KTL-03-135. Prepared according to the representative procedure outlined for conjugate addition. The crude material was purified via flash column chromatography eluting

EtOAc:TEA:hexanes (25:1:74) to give 27 mg (83%) of **1.91** as a white solid: ^{1}H NMR (400 MHz) δ 7.36 (comp, 5 H), 7.12 (dd, *J* =23.3, 8.4 Hz, 1 H), 6.89 – 6.82 (m, 1 H), 6.82 – 6.74 (m, 1 H), 5.20 (s, 2 H), 4.68 (t, *J* =10.3 Hz, 4 H), 4.15 (q, *J* =7.1 Hz, 2 H), 3.17 (dd, *J* =10.0, 5.6 Hz, 4 H), 2.76 (t, *J* =7.3 Hz, 2 H), 2.67 – 2.60 (m, 4 H), 2.54 (t, *J* =7.3 Hz, 2 H), 1.26 (t, *J* =7.1 Hz, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 172.4, 154.90, 154.86, 151.3, 138., 137.6, 136.9, 136.8, 128.5, 128.04, 127.96, 127.9, 127.8, 123.2, 123.0, 116.1, 116.0, 110.2, 110.0, 66.9, 60.5, 53.5, 52.9, 52.7, 52.3, 52.1, 51.6, 49.6, 49.5, 32.3, 14.2; HRMS (ESI) *m/z* $C_{25}H_{31}N_3O_4$ $(M+H)^+$ calcd for 438.2387; found 438.2392.

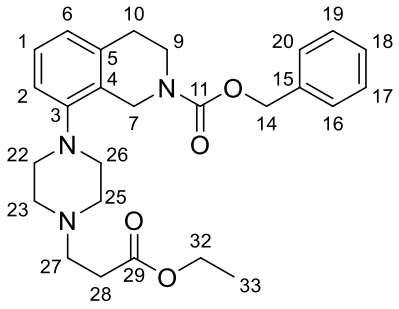
NMR Assignment. ^{1}H NMR (400 MHz) δ 7.36 (d, *J* =48.0 Hz, 5 H, C12-H thru C16-H), 7.12 (dd, *J* =23.3, 8.4 Hz, 1 H, C3-H), 6.89 – 6.82 (m, 1 H, C2-H), 6.82 – 6.74 (m, 1 H, C1-H), 5.20 (s, 2 H, C10-H), 4.68 (t, *J* =10.3 Hz, 4 H, C7-H and C8-H), 4.15 (q, *J* =7.1 Hz, 2 H, C24-H), 3.17 (dd, *J* =10.0, 5.6 Hz, 4 H, C17-H and C20-H), 2.76 (t, *J* =7.3 Hz, 2 H, C22-H), 2.67 – 2.60 (m, 4 H, C18-H and C19-H), 2.54 (t, *J* =7.3 Hz, 2 H, C21-H), 1.26 (t, *J* =7.1 Hz, 3 H, C25-H); ^{13}C NMR (101 MHz, rotamers) δ 172.4 (C23), 154.90 (C9), 154.86 (C9), 151.3 (C1), 138.0 (C5), 137.6 (C5), 136.9 (C11), 136.8 (C11), 128.5 (C13 and C15), 128.04 (C4), 127.96 (C14), 127.9 (C12 and C16), 127.8 (C4), 123.2 (C3), 123.0 (C3), 116.1 (C2), 116.0 (C2), 110.2 (C6), 110.0 (C6), 66.9 (C10), 60.5 (C24), 53.5 (C21), 52.9 (C17 and C20), 52.7 (C7 or C8), 52.3 (C7 or C8), 52.1 (C7 or C8), 51.6 (C7 or C8), 49.6 (C18 and C19), 49.5 (C18 and C19), 32.3 (C22), 14.2 (C25).



Benzyl 7-(4-(3-ethoxy-3-oxopropyl)piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.92). KTL-03-139. Prepared according to the representative procedure outlined for conjugate addition. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (20:1:79) to give 20 mg (65%) of **1.92** as a clear oil: ^{1}H NMR (400 MHz) δ 7.42-7.29 (comp, 5 H), 7.02 (d, *J* =7.8 Hz, 1 H), 6.77 (m, *J* =8.4 Hz, 1 H), 6.64 (d, *J* =21.1 Hz, 1 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 4.15 (q, *J* =7.1 Hz, 2 H), 3.69 (s, 2 H), 3.18 – 3.09 (comp, 4 H), 2.75 (t, *J* =7.3 Hz, 4 H), 2.64 – 2.58 (comp, 4 H), 2.53 (t, *J* =7.4 Hz, 2 H), 1.26 (t, *J* =8.0, 3 H); ^{13}C NMR (126 MHz, rotamers) δ 172.5, 155.5, 149.9, 136.8, 134.0, 133.6, 129.4, 129.2, 128.5, 128.0, 127.9, 125.9, 125.7, 115.1, 113.6, 113.4, 67.2, 60.5, 53.6, 52.9, 49.4, 46.1, 46.0, 42.0, 41.7, 32.4, 28.1, 27.9, 14.3; HRMS (ESI) *m/z* $C_{26}H_{33}N_3O_4$ $(M+H)^+$ calcd for 452.2544; found 452.2549.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.42-7.29 (comp, 5 H, C13-H thru C17-H), 7.02 (d, *J* =7.8 Hz, 1 H, C6-H), 6.77 (dd, *J* =10.8, 2.4 Hz, 1 H, C1-H), 6.64 (d, *J* =21.1 Hz, 1 H, C3-H), 5.17 (s, 2 H, C11-H), 4.60 (s, 2 H, C7-H), 4.15 (q, *J* =7.1 Hz, 2 H, C25-H), 3.69 (s, 2 H, C9-H), 3.18 – 3.09 (comp, 4 H, C18-H and C21-H), 2.75 (t, *J* =7.3 Hz, 4 H, C22-H), 2.64 – 2.58 (comp, 4 H, C19-H and C20-H), 2.53 (t, *J* =7.4 Hz, 2 H, C23-H), 1.26 (t, *J* =8.0, 3 H, C26-H); ^{13}C NMR (126 MHz, rotamers) δ 172.5 (C24), 155.5 (C10), 149.9 (C2), 136.8 (C12), 134.0 (C4), 133.6 (C4), 129.4 (C6), 129.2 (C6), 128.5 (C14 and

C16), 128.0 (C13 and C17), 127.9 (C15), 125.9 (C5), 125.7 (C5), 115.1 (C1), 113.6 (C3), 113.4 (C3), 67.2 (C11), 60.5 (C25), 53.6 (C22), 52.9 (C18 and C21), 49.4 (C19 and C20), 46.1 (C7), 46.0 (C7), 42.0 (C9), 41.7 (C9), 32.4 (C23), 28.1 (C8), 27.9 (C8), 14.3 (C26).



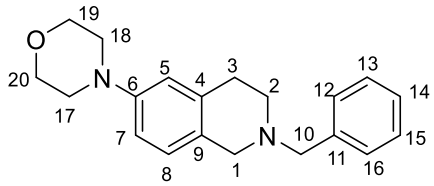
1.122

Benzyl 8-(4-(3-ethoxy-3-oxopropyl)piperazin-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1.122). KTL-02-119. Prepared according to the representative procedure outlined for alkylation of piperazines with acrylates. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (20:1:79) to give 30 mg (84%) of **1.122** as a clear oil: ^{1}H NMR (499 MHz, rotamers) δ 7.43 – 7.29 (m, 5 H), 7.17 (t, *J* = 7.7 Hz, 1 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 6.90 (s, 1 H), 5.18 (s, 2 H), 4.66 (s, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.68 (t, *J* = 6.1 Hz, 2 H), 2.93 – 2.80 (comp, 6 H), 2.76 (s, 2 H), 2.70 – 2.55 (comp, 4 H), 2.53 (t, *J* = 7.4 Hz, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, rotamers) δ 172.5, 155.5, 150.2, 149.8, 136.9, 136.2, 136.0, 129.2, 129.0, 128.5, 127.9, 127.6, 127.2, 124.1, 124.0, 117.7, 67.0, 60.5, 53.6, 53.4, 52.2, 42.4, 42.2, 41.7, 32.4, 29.4, 29.0, 14.3; LRMS (ESI+APCI) *m/z* $C_{26}H_{33}N_3O_4$ $(M+H)^+$ calcd for 452.25; found 452.3.

NMR Assignment. ^{1}H NMR (499 MHz, rotamers) δ 7.43 – 7.29 (m, 5 H, C16-H thru C20-H), 7.17 (t, *J* = 7.7 Hz, 1 H, C1-H), 6.97 (d, *J* = 7.9 Hz, 1 H, C6-H), 6.90 (s, 1 H, C2-H), 5.18 (s, 2 H, C14-H), 4.66 (s, 2 H, C7-H), 4.17 (q, *J* = 7.1 Hz, 2 H, C32-H), 3.68

(t, *J* = 6.1 Hz, 2 H, C9-H), 2.93 – 2.80 (comp, 6 H, C10-H, C22-H, and C26-H), 2.76 (s, 2 H, C27-H), 2.70 – 2.55 (comp, 4 H, C23-H and C25-H), 2.53 (t, *J* = 7.4 Hz, 2 H, C28-H), 1.28 (t, *J* = 7.1 Hz, 3 H, C33-H); ^{13}C NMR (126 MHz, rotamers) δ 172.5 (C29), 155.5 (C11), 150.2 (C3), 149.8 (C3), 136.9 (C15), 136.2 (C5), 136.0 (C5), 129.2 (C4), 129.0 (4), 128.5 (C17 and C19), 127.9 (C16 and C20), 127.6 (C18), 127.2 (C2), 124.1 (C2), 124.0 (C2), 117.7 (C6), 67.0 (C14), 60.5 (C32), 53.6 (C27), 53.4 (C23 and C25), 52.2 (C22 and C26), 42.4 (C7), 42.2 (C7), 41.7 (C9), 32.4 (C28), 29.4 (C10), 29.0 (C10), 14.3 (C33).

Representative procedure for TMSI promoted benzylation

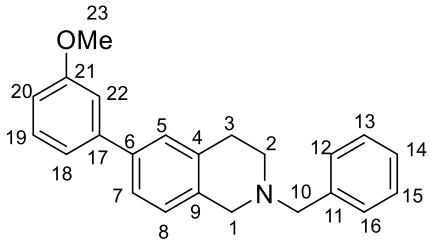


1.94

4-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine (1.94). KTL-01-175. (*Reaction carried out in the dark.)* A solution of carbamate **1.73** (70 mg, 0.2 mmol) in CH_2Cl_2 (3.3 mL) was cooled to 0 °C and TMSI (160 mg 0.8 mmol) was added. The solution was allowed warm to room temperature and stirred until consumption of starting material was observed. MeOH (2.4 mL) and sat. $NaHCO_3$ (2.4 mL) were added, and the mixture was stirred overnight. The methanol was removed under reduced pressure, and the aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with TEA:EtOAc:hexanes (1:5:94) to give 19mg (31%) of **1.94** as a white solid that turned green upon standing: ^{1}H NMR (400 MHz) δ 7.39 (d, *J*

= 6.8 Hz, 2 H), 7.33 (t, *J* = 7.1 Hz, 2 H), 7.28 (d, *J* = 7.0 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.72 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.65 (d, *J* = 2.4 Hz, 1 H), 3.85 (t, *J* = 4 Hz 4 H), 3.68 (s, 2 H), 3.57 (s, 2 H), 3.10 (t, *J* = 4 Hz, 4 H), 2.86 (t, *J* = 5.9 Hz, 2 H), 2.72 (t, *J* = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz) δ 149.8, 138.5, 135.1, 129.1, 128.3, 127.3, 127.0, 126.9, 115.7, 114.1, 66.9, 62.8, 55.6, 50.7, 49.8, 29.5; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 361.1523; found 361.1526; IR (neat) 2955, 2918, 2853, 2817, 1613, 1509, 1451, 1365, 1262, 1239, 1121 cm^{-1}.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.39 (d, *J* = 6.8 Hz, 2 H, C12-H and C16-H), 7.33 (t, *J* = 7.1 Hz, 2 H, C13-H and C15-H), 7.28 (d, *J* = 7.0 Hz, 1 H, C14-H), 6.91 (d, *J* = 8.4 Hz, 1 H, C8-H), 6.72 (dd, *J* = 8.4, 2.6 Hz, 1 H, C7-H), 6.65 (d, *J* = 2.4 Hz, 1 H, C5-H), 3.85 (t, *J* = 4 Hz, 4 H C20-H and C19-H), 3.68 (s, 2 H, C10-H), 3.57 (s, 2 H, C1-H), 3.10 (t, *J* = 4 Hz, 4 H, C17-H and C18-H), 2.86 (t, *J* = 5.9 Hz, 2 H, C3-H), 2.72 (t, *J* = 5.9 Hz, 2 H, C3-H); ^{13}C NMR (101 MHz) δ 149.8 (C6), 138.5 (C11), 135.1 (C4), 129.1 (C12 and C16), 128.3 (C13 and C15), 127.3 (C14), 127.0 (C8), 126.9 (C9), 115.7 (C5), 114.1 (C7), 66.9 (C19 and C20), 62.8 (C10), 55.6 (C1), 50.7 (C3), 49.8 (C17 and C18), 29.5 (C2).



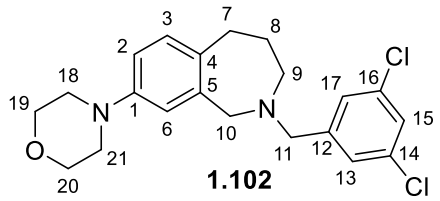
1.95

2-Benzyl-6-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1.95). KTL-01-176. Prepared according to the representative procedure outlined for TMSI promoted benzylation. The crude material was purified via flash column chromatography eluting with TEA:hexanes (1:99) to give 13 mg (33%) of **1.95** as a clear oil: ^{1}H NMR (400 MHz) δ 7.44 – 7.27 (comp, 8 H), 7.16 (dd, *J* = 7.6, 0.9 Hz, 1 H), 7.12 – 7.09 (m, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 6.88 (dd, *J* = 8.2, 2.6 Hz, 1 H), 3.87 (s, 3 H), 3.72 (s, 2 H), 3.68 (s, 2 H), 2.98 (t, *J* = 5.8 Hz, 2 H), 2.79 (t, *J* = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz) δ 159.9, 142.7, 139.0, 138.4, 134.8, 134.3, 129.7, 129.1, 128.3, 127.4, 127.1, 127.0, 124.5, 119.5, 112.7, 112.4, 62.8, 55.9, 55.3, 50.7, 29.3; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 338.1515; found 338.1534; IR (neat) 3027, 2921, 2832, 2801, 2733, 1603, 1571, 1482, 1453, 1224 cm^{-1}.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.44 – 7.27 (comp, 8 H, C5-H, C12-H thru C16-H, C18-H, C19-H), 7.16 (dd, *J* = 7.6, 0.9 Hz, 1 H, C20-H), 7.12 – 7.09 (t, *J* = 1.6 Hz, 1 H, C22-H), 7.07 (d, *J* = 8.4 Hz, 1 H, C8-H), 6.88 (dt, *J* = 8.2, 2.6 Hz, 1 H, C20-H), 3.87 (s, 3 H, C23-H), 3.72 (s, 2 H, C10-H), 3.68 (s, 2 H, C1-H), 2.98 (t, *J* = 5.8 Hz, 2 H, C2-H), 2.79 (t, *J* = 5.9 Hz, 2 H, C3-H); ^{13}C NMR (101 MHz) δ 159.9 (C21), 142.7 (C17), 139.0 (C11), 138.4 (C6), 134.8 (C9), 134.3 (C4), 129.7 (C19), 129.1 (C13 and C15), 128.3

(C12 and C16), 127.4 (C14), 127.1 (C5), 127.0 (C8), 124.5 (C7), 119.5 (C19), 112.7 (C22), 112.4 (C20), 62.8 (C11), 55.9 (C23), 55.3 (C1), 50.7 (C2), 29.3 (C3).

Representative procedure for deprotection/*N*-benzylation

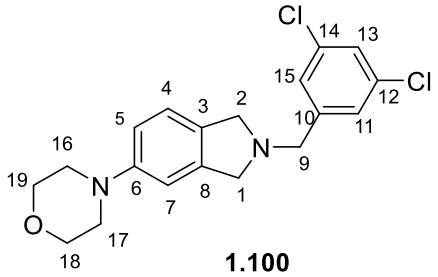


1.102

4-(2-(3,5-Dichlorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl)morpholine (1.102). KTL-02-054. A solution of carbamate **1.77** (40 mg, 0.11 mmol) in EtOH (3.3 mL) and 10% Pd/C (12 mg) was stirred under an atmosphere of H_2 until consumption of starting material was observed. The reaction was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide 20 mg (78%) of the secondary amine intermediate as a yellow solid that was of sufficient purity for use in subsequent reactions. A solution of the secondary amine (12 mg, 0.05 mmol), $NaBH(OAc)_3$ (22 mg, 0.10 mmol), 3,5-dichlorobenzaldehyde (18 mg, 0.10 mmol) and 10 μL AcOH in DCE (0.5 mL) was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of sat. $NaHCO_3$ (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (5:1:94) to give 11 mg (54%) of **1.102** as a clear oil: ^{1}H NMR (500 MHz) δ 7.25 (t, *J* = 1.9 Hz, 1 H), 7.22-7.20 (comp, 2 H), 7.06 (d, *J* = 8.2 Hz, 1 H), 6.71 (dd, *J* = 8.2, 2.7 Hz, 1 H), 6.45 (d, *J* = 2.6 Hz, 1 H), 3.87 – 3.83 (comp, 4 H), 3.79 (s, 2 H), 3.47 (s, 2 H), 3.19 – 3.15 (comp, 2 H), 3.12 – 3.08 (comp, 4 H),

2.88 – 2.83 (comp, 2 H), 1.75 – 1.69 (comp, 2 H); ^{13}C NMR (125 MHz) δ 149.4, 134.9, 134.7, 134.5, 129.3, 127.3, 127.2, 127.0, 117.8, 114.0, 67.0, 59.4, 58.8, 56.0, 49.6, 35.1, 25.3; HRMS (ESI) *m/z* $C_{21}H_{24}Cl_2N_2O$ $(M+H)^+$ calcd for 391.1338 and 393.1313; found 391.1341 and 393.1317.

NMR Assignment. ^{1}H NMR (500 MHz) δ 7.25 (t, *J* = 1.9 Hz, 1 H, C15-H), 7.22-7.20 (comp, 2 H, C13-H and C17-H), 7.06 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.71 (dd, *J* = 8.2, 2.7 Hz, 1 H, C2-H), 6.45 (d, *J* = 2.6 Hz, 1 H, C6-H), 3.87 – 3.83 (comp, 4 H, C19-H and C20-H), 3.79 (s, 2 H, C10-H), 3.47 (s, 2 H, C11-H), 3.19 – 3.15 (comp, 2 H, C9-H), 3.12 – 3.08 (comp, 4 H, C18-H and C21-H), 2.88 – 2.83 (comp, 2 H, C7-H), 1.75 – 1.69 (comp, 2 H, C8-H); ^{13}C NMR (125 MHz) δ 149.4 (C1), 134.9, 134.7, 134.5, 129.3, 127.3 (C14 and C16), 127.2, 127.0, 117.8 (C2), 114.0 (C6), 67.0 (C18 and C21), 59.4 (C10), 58.8 (C11), 56.0 (C9), 49.6 (C18 and C21), 35.1 (C7), 25.3 (C8).

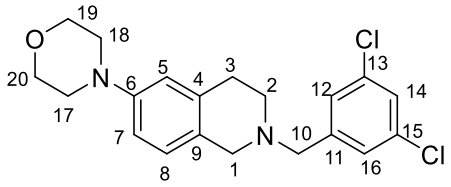


1.100

4-(2-(3,5-Dichlorobenzyl)isoindolin-5-yl)morpholine (1.100). KTL-01-121. Prepared according to the representative procedure outlined for deprotection/N-benzylation. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 25 mg (35% over two-steps) of **1.100** as a clear oil: ^{1}H NMR (400 MHz) δ 7.32 (d, *J* = 1.9 Hz, 2 H), 7.27 (t, *J* = 2 Hz, 1 H), 7.09 (d, *J* = 8.9

Hz, 1 H), 6.78 (comp, 2 H), 3.89 (s, 2 H), 3.86 (comp, 8 H), 3.11 (t, *J* = 4.8 Hz, 4 H); ^{13}C NMR (101 MHz) δ 151.0, 142.9, 140.9, 134.9, 131.6, 127.2, 126.9, 122.8, 115.1, 110.3, 66.9, 59.2, 59.2, 58.5, 50.1; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 363.1025 and 365.0999; found 363.1036 and 365.1006; IR (neat) 2923, 2853, 2817, 1567, 1497, 1445, 1430, 1241, 1122 cm^{-1}.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.32 (d, *J* = 1.9 Hz, 2 H, C11-H and C15-H), 7.27 (t, *J* = 2 Hz, 1 H, C13-H), 7.09 (d, *J* = 8.9 Hz, 1 H, C4-H), 6.78 (comp, 2 H, C5-H and C7-H), 3.89 (s, 2 H, C1-H), 3.86 (comp, 8 H, C2-H, C9-H, C18-H, and C19-H), 3.11 (t, *J* = 4.8 Hz, 4 H, C16-H and C17-H); ^{13}C NMR (101 MHz) δ 151.1 (C6), 142.9 (C8), 140.99 (C10), 134.9 (C11 and C15), 131.62 (C3), 127.2 (C13), 126.9 (C12 and C14), 122.8 (C4), 115.1 (C7), 110.3 (C5), 66.9 (C18 and C17), 59.2 (C9), 59.2 (C1), 58.5 (C2), 50.1 (C17 and C18).

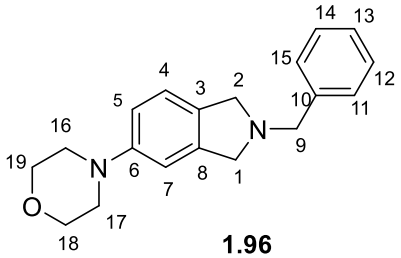


1.101

4-(2-(3,5-Dichlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)morpholine (1.101). KTL-01-184. Prepared according to the representative procedure outlined for deprotection/N-benzylation. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (5:1:94) to give 47 mg (35% over two-steps) of **1.101** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.31 (d, *J* = 1.9 Hz, 2 H), 7.27 (t, *J* = 1.9 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.77 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.55 (d, *J* = 2.4

Hz, 1 H), 3.85 (t, *J* = 4.8, 4 H), 3.62 (s, 2 H), 3.57 (s, 2 H), 3.09 (t, *J* = 4.8, 4 H), 2.84 (t, *J* = 5.8 Hz, 2 H), 2.74 (t, *J* = 5.8 Hz, 2 H); ^{13}C NMR (101 MHz) δ 149.5, 142.4, 135.1, 134.8, 129.4, 127.3, 127.2, 125.9, 114.8, 113.7, 66.9, 61.6, 56.2, 51.1, 49.8, 28.2; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 377.1182 and 379.1156; found 377.1183 and 379.1159; IR (neat) 2957, 2913, 2853, 2817, 1613, 1567, 1508, 1429, 1261, 1242, 1121 cm^{-1}.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.31 (d, *J* = 1.9 Hz, 2 H, C12-H and C16-H), 7.27 (t, *J* = 1.9 Hz, 1 H, C14-H), 7.04 (d, *J* = 8.4 Hz, 1 H, C5-H), 6.77 (dd, *J* = 8.4, 2.4 Hz, 1 H, C6-H), 6.55 (d, *J* = 2.4 Hz, 1 H, C8-H), 3.85 (t, *J* = 4.8, 4 H, C19-H and C20-H), 3.62 (s, 2H , C10-H), 3.57 (s, 2 H, C1-H), 3.09 (t, *J* = 4.8, 4 H, C17-H and C18-H), 2.84 (t, *J* = 5.8 Hz, 2 H, C2-H), 2.74 (t, *J* = 5.8 Hz, 2 H, C3-H); ^{13}C NMR (101 MHz) δ 149.5 (C7), 142.4 (C11), 135.1 (C9), 134.8 (C13 and C15), 129.4 (C5), 127.3 (C14), 127.2 (C12 and C16), 125.9 (C4), 114.8 (C6), 113.7 (C8), 66.9 (C19 and C20), 61.6 (C10), 56.2 (C1), 51.1 (C2), 49.8 (C17 and C18), 28.2 (C3).

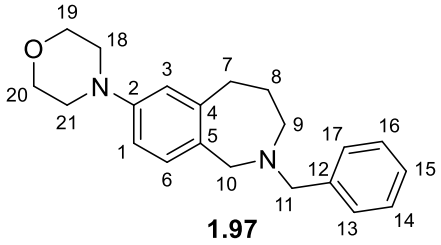


1.96

4-(2-Benzylisoindolin-5-yl)morpholine (1.96). KTL-01-153. Prepared according to the representative procedure outlined for deprotection/N-benzylation. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 15 mg (63%, over two-steps) of **1.96** as a white solid that turned blue upon standing: ^{1}H NMR (400 MHz, c_6d_6) δ 7.41 (d, *J* = 7.6 Hz, 2 H), 7.20 (t, *J* = 7.6 Hz, 2 H), 6.90 (d, *J*

= 8.2 Hz, 1 H), 6.54 (d, *J* = 8.2 Hz, 1 H), 6.48 (s, 1H), 3.77 (d, *J* = 9.1 Hz, 4 H), 3.70 (s, 2 H), 3.56 – 3.50 (t, *J* = 4.8 Hz, 4 H), 2.74 – 2.66 (t, *J* = 4.8 Hz, 4 H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 150.9, 141.4, 139.2, 132.2, 128.8, 128.4, 127.1, 122.8, 114.9, 110.4, 66.9, 60.4, 59.2, 58.5, 50.2; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+H)^+$ calcd for 295.1805; found 295.1822; IR (neat) 2955, 2922, 2855, 2780, 1453, 1262, 1244, 1123 cm $^{-1}$.

NMR Assignment. ^{1}H NMR (400 MHz, c_6d_6) δ 7.41 (d, *J* = 7.6 Hz, 2 H, C11-H and C15-H), 7.20 (t, *J* = 7.6 Hz, 2 H, C12-H and C14-H), 7.15 (C13-H under benzene peak), 6.90 (d, *J* = 8.2 Hz, 1 H, C6-H), 6.54 (d, *J* = 8.2 Hz, 1 H, C5-H), 6.48 (s, 1 H, C7-H), 3.78 (s, 2 H, C1-H), 3.76 (s, 2 H, C2-H), 3.70 (s, 2 H, C9-H), 3.54 (t, *J* = 4.8 Hz, 4 H, C18-H and C19-H), 2.74 – 2.66 (t, *J* = 4.8 Hz, 4 H, C16-H and C17-H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 150.9 (C6), 141.4 (C8), 139.2 (C10), 132.2 (C3), 128.8 (C11 and C15), 128.4 (C12 and C14), 127.1 (C4), 122. 8 (C10), 114.9 (C5), 110.4 (C4), 66.9 (C18 and C19), 60.4 (C9), 59.2 (C1), 58.5 (C2), 50.2 (C16 and C17).

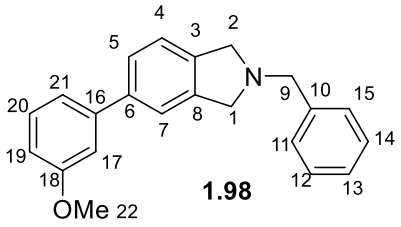


1.97

4-(2-Benzyl-2,3,4,5-tetrahydro-1H-benzo[c]azepin-7-yl)morpholine (1.97). KTL-02-094. Prepared according to the representative procedure outlined for deprotection/N-benzylation The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (10:1:89) to give 18 mg (51% over two-steps) of **1.97** as a clear oil: ^{1}H NMR (400 MHz) δ 7.33-7.21 (comp, 5 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.74 (d, *J* = 2.6

Hz, 1 H), 6.62 (dd, *J* = 8.1, 2.6 Hz, 1 H), 3.89 – 3.84 (comp, 4 H), 3.81 (s, 2 H), 3.51 (s, 2 H), 3.18 – 3.13 (comp, 4 H), 3.12 – 3.07 (comp, 2 H), 2.90 – 2.84 (comp, 2 H), 1.80 – 1.72 (comp, 2 H); ^{13}C NMR (101 MHz) δ 150.3, 143.9, 139.4, 130.9, 130.9, 129.0, 128.1, 126.8, 116.5, 112.4, 67.0, 58.7, 58.5, 57.5, 49.5, 36.8, 25.3; HRMS (ESI) *m/z* $C_{21}H_{26}N_2O$ $(M+H)^+$ calcd for 323.2118; found 323.2120.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.33-7.21 (comp, 5 H, C13-H thru C17-H), 6.86 (d, *J* = 8.2 Hz, 1 H, C6-H), 6.74 (d, *J* = 2.6 Hz, 1 H, C3-H), 6.62 (dd, *J* = 8.1, 2.6 Hz, 1 H, C1-H), 3.89 – 3.84 (comp, 4 H, C19 and C20), 3.81 (s, 2 H, C10-H), 3.51 (s, 2 H, C11-H), 3.18 – 3.13 (comp, 4 H, C18-H and C21-H), 3.12 – 3.07 (comp, 2 H, C9-H), 2.90 – 2.84 (comp, 2 H, C7-H), 1.80 – 1.72 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz) δ 150.3 (C2), 143.9 (C4), 139.4 (C12), 130.9 (C6), 130.8 (C5), 129.0 (C14 and C16), 128.1 (C13 and C17), 126.8 (C15), 116.5 (C3), 112.4 (C1), 67.0 (C19 and C20), 58.7 (C10), 58.5 (C11), 57.5 (C9), 49.5 (C18 and C21), 36.8 (C7), 25.3 (C8).

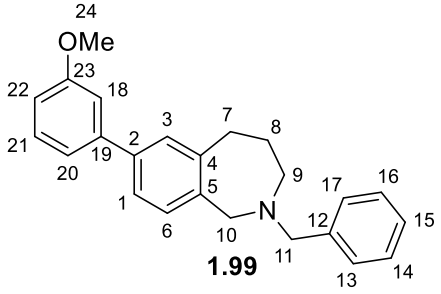


1.98

2-Benzyl-5-(3-methoxyphenyl)isoindoline (1.98). KTL-01-166. Prepared according to the representative procedure outlined for compound 32. The crude material was purified via flash column chromatography eluting with TEA:hexanes (1:99) to give 26 mg (65% over two-steps) of **1.98** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.47 – 7.30 (comp, 8 H), 7.26 (dd, *J* = 4.2, 3.3 Hz, 1 H), 7.16 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1 H), 7.11 (t, *J* = 2 Hz, 1 H),

6.90 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1 H), 4.00 (s, 2 H), 3.99 (s, 2 H), 3.96 (s, 2 H), 3.87 (s, 3 H); ^{13}C NMR (101 MHz) δ 159.9, 142.9, 141.0, 139.9, 139.7, 139.1, 129.7, 128.8, 128.42, 127.1, 125.9, 122.6, 121.2, 119.7, 112.9, 112.5, 60.3, 58.9, 58.7, 55.2; HRMS (ESI) *m/z* $C_{21}H_{24}N_2O_3$ $(M+Na)^+$ calcd for 361.1423; found 361.1526; IR (neat) 3060, 3028, 2935, 2833, 2786, 1601, 1574, 1493, 1479, 1348, 1269, 1180 cm^{-1}.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.47 – 7.30 (comp, 8 H, C4-H, C5-H, C7-H, and C11-H thru C15-H), 7.26 (dd, *J* = 4.2, 3.3 Hz, 1 H, C21-H), 7.16 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1 H, C20-H), 7.11 (t, *J* = 2 Hz, 1 H, C17-H), 6.90 (ddd, *J* = 8.2, 2.6, 0.8 Hz, 1 H, C19-H), 4.00 (s, 2 H, C1-H), 3.99 (s, 2 H, C2-H), 3.96 (s, 2 H, C9-H), 3.87 (s, 3 H, C23-H); ^{13}C NMR (101 MHz) δ 159.9 (C18), 142.9 (C16), 141.0 (C1 or C4), 139.9 (C1 or C4), 139.7 (C10), 139.1 (C3), 129.71 (C20), 128.8 (C12 and C14), 128.4 (C11 and C15), 127.1 (C13), 125.9 (C5), 122.6 (C7), 121.2 (C4), 119.7 (C21), 112.9 (C17), 112.5 (C19), 60.3 (C9), 58.9 (C1), 58.7 (C2), 55.3 (C22).



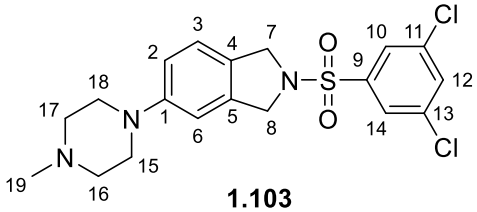
1.99

2-Benzyl-7-(3-methoxyphenyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (1.99). KTL-02-095. Prepared according to the representative procedure outlined for deprotection/N-benzylation. The crude material was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (2:1:97) to give 16 mg (36% over two-steps) of **1.99** as a clear

oil: ^{1}H NMR (400 MHz) δ 7.32 (comp, 8 H), 7.20 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1 H), 7.14 (t, *J* = 2.4, 1 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 6.89 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1 H), 3.92 (s, 2 H), 3.88 (s, 3 H), 3.58 (s, 2 H), 3.18 – 3.12 (comp, 2 H), 3.03 – 2.96 (comp, 2 H), 1.85 – 1.77 (comp, 2 H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 159.9, 143. 5, 142.6, 139.9, 139.2, 138.6, 130.4, 129.7, 129.0, 128.2, 127.7, 126.9, 124.5, 119.6, 112.7, 112.6, 58.9, 58.9, 57.9, 55.3, 36.3, 25.4. HRMS (ESI) *m/z* $C_{24}H_{25}Cl_2NO$ $(M+H)^+$ calcd for 344.2009; found 344.2017.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.39-7.24 (comp, 8 H, C1-H, C3-H, C13-H thru C17-H, and C21-H), 7.20 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1 H, C20-H), 7.14 (t, *J* = 2.4, 1 H, C18-H), 7.01 (d, *J* = 7.7 Hz, 1 H, C6-H), 6.89 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1 H, C22-H), 3.92 (s, 2 H, C10-H), 3.88 (s, 3 H, C24-H), 3.58 (s, 2 H, C11-H), 3.18 – 3.12 (comp, 2 H, C9-H), 3.03 – 2.96 (comp, 2 H, C7-H), 1.85 – 1.77 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz) δ 159.9 (C23), 143.5 (C4), 142.6 (C19), 139.9 (C5), 139.2 (C12), 138.6 (C2), 130.4 (C21), 129.7 (C3), 129.0 (C14 and C16), 128.2 (C13 and C17), 127.7 (C6), 126.9 (C15), 124.5 (C1), 119.6 (C20), 112.7 (C18), 112.6 (C22), 58.9 (C10), 58.9 (C11), 57.9 (C9), 55.3 (C24), 36.3 (C7), 25.4 (C8).

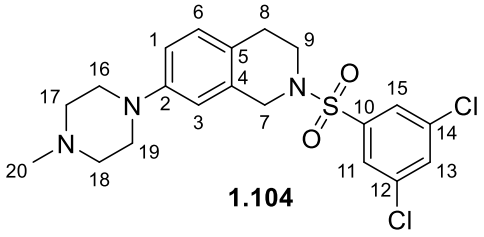
Representative procedure for deprotection/*N*-sulfonylation of methyl piperazine derivatives



1.103

2-((3,5-Dichlorophenyl)sulfonyl)-5-(4-methylpiperazin-1-yl)isoindoline (1.103). KTL-01-253. A solution of carbamate **1.66** (20 mg, 0.06 mmol) in EtOH (1.0 mL) and 10% Pd/C (8 mg) was stirred under an atmosphere of H_2 for 24 h. The reaction was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to provide 11 mg (89%) of secondary amine intermediate as a pink oil that was of sufficient purity for use in subsequent reactions. 3,5-dichlorobenzenesulfonylchloride (13 mg, 0.05 mmol) and Et_3N (13 mg, 0.09 mmol) were added to a solution of secondary amine (11 mg, 0.05 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature overnight and then concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (60:1:39) to give 17 mg (56%) of **1.103** as an off white solid: ^{1}H NMR (400 MHz) δ 7.74 (d, *J* =1.9 Hz, 2 H), 7.54 (t, *J* =1.9 Hz, 1 H), 7.07 (d, *J* =8.5 Hz, 1 H), 6.84 (dd, *J* =8.5, 2.3 Hz, 1 H), 6.72 (d, *J* =2.0 Hz, 1 H), 4.60 (s, 2 H), 4.57 (s, 2 H), 3.20 – 3.14 (comp, 4 H), 2.59 – 2.52 (comp, 4 H), 2.35 (s, 3 H); ^{13}C NMR (101 MHz) δ 151.6, 139.8, 136.6, 136.2, 132.7, 126.2, 125.7, 123.2, 116.4, 109.7, 54.9, 54.0, 53.4, 49.2, 46.0; HRMS (ESI) *m/z* $C_{19}H_{21}Cl_2N_3O_2S$ $(M+H)^+$ calcd for 426.0804 and 428.0777; found 426.0807 and 420.0778.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.74 (d, *J* =1.9 Hz, 2 H, C10-H and C14-H), 7.54 (t, *J* =1.9 Hz, 1 H, C12-H), 7.07 (d, *J* =8.5 Hz, 1 H, C3-H), 6.84 (dd, *J* =8.5, 2.3 Hz, 1 H, C2-H), 6.72 (d, *J* =2.0 Hz, 1 H, C6-H), 4.60 (s, 2 H, C7-H or C8-H), 4.57 (s, 2 H, C7-H or C8-H), 3.20 – 3.14 (comp, 4 H, C15-H and C18-H), 2.59 – 2.52 (comp, 4 H, C16-H and C17-H), 2.35 (s, 3 H, C19-H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 151.6 (C1), 139.8 (C9), 136.6 (C5), 136.2 (11 and C13), 132.7 (C12), 126.2 (C4), 125.7 (C10 and C14), 123.2 (C3), 116.4 (C2), 109.7 (C6), 54.9 (C15 and C18)), 54.0 (C7 or C8), 53.4 (C7 or C8), 49.2 (C16 and C17), 46.0 (C19).

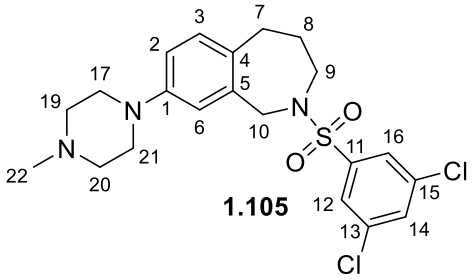


1.104

2-((3,5-Dichlorophenyl)sulfonyl)-7-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydroisoquinoline (1.104). KTL-01-257. Prepared according to the representative procedure outlined for *N*-sulfonylation. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (49:1:50) to give 26 mg (46% over two-steps) of **1.104** as an off white solid: ^{1}H NMR (400 MHz) δ 7.68 (d, *J* =1.9 Hz, 2 H), 7.54 (t, *J* =1.9 Hz, 1 H), 6.97 (d, *J* =8.5 Hz, 1 H), 6.77 (dd, *J* =8.5, 2.6 Hz, 1 H), 6.58 (d, *J* =2.4 Hz, 1 H), 4.27 (s, 2 H), 3.41 (t, *J* =6.0 Hz, 2 H), 3.19 – 3.11 (comp, 4 H), 2.83 (t, *J* =5.9 Hz, 2 H), 2.60 – 2.53 (comp, 4 H), 2.35 (s, 3 H); ^{13}C NMR (101 MHz) δ 149.9, 139.9, 136.1, 132.7, 131.5, 129.5, 125.8, 123.9, 115.6, 113.2, 54.9, 49.1, 47.7, 46.0, 44.1, 27.7;

HRMS (ESI) *m/z* $C_2H_{23}Cl_2N_3O_2S$ $(M+H)^+$ calcd for 440.0961 and 442.0934; found 440.0956 and 442.0931.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.68 (d, *J* =1.9 Hz, 2 H, C11-H and C15-H), 7.54 (t, *J* =1.9 Hz, 1 H, C13-H), 6.97 (d, *J* =8.5 Hz, 1 H, C6-H), 6.77 (dd, *J* =8.5, 2.6 Hz, 1 H, C8-H), 6.58 (d, *J* =2.4 Hz, 1 H, C7-H), 4.27 (s, 2 H, C7-H), 3.41 (t, *J* =6.0 Hz, 2 H, C9-H), 3.19 – 3.11 (comp, 4 H, C16-H and C19-H), 2.83 (t, *J* =5.9 Hz, 2 H, C8-H), 2.60 – 2.53 (comp, 4 H, C16-H and C19-H), 2.35 (s, 3 H, C20-H); ^{13}C NMR (101 MHz) δ 149.9 (C2), 139.9 (C10), 136.1 (C12 and C14), 132.7 (C4), 131.5 (C6), 129.5 (C13), 125.8 (C11 and C15), 123.9 (C5), 115.6 (C1), 113.2 (C3), 54.9 (C16 and C19), 49.1 (C17 and C18), 47.7 (C7), 46.0 (C20), 44.1 (C9), 27.7 (C8).



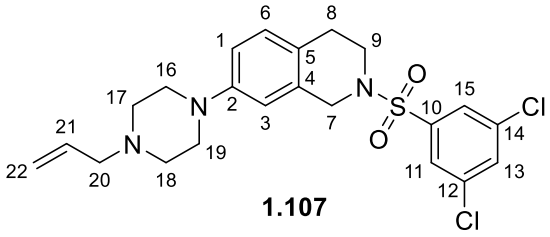
1.105

2-((3,5-Dichlorophenyl)sulfonyl)-8-(4-methylpiperazin-1-yl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (1.105). KTL-02-049. Prepared according to the representative procedure outlined for *N*-sulfonylation. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (40:1:59) to give 17 mg (67% over two-steps) of **1.105** as a yellow solid: ^{1}H NMR (400 MHz) δ 7.39 (comp, *J* =6.2 Hz, 3H), 6.92 (d, *J* =8.3 Hz, 1H), 6.88 (d, *J* =2.6 Hz, 1H), 6.71 (dd, *J* =8.2, 2.7 Hz, 1H), 4.47 (s, 2H), 3.68 – 3.62 (comp, 2H), 3.23 – 3.18 (comp, 4H), 2.75 (comp, 2H), 2.60 – 2.55 (comp, 4H),

2.36 (s, 3H), 1.56 – 1.50 (comp, 2H); ^{13}C NMR (101 MHz) δ 149.8, 143.4, 137.1, 135.5, 132.1, 132.1, 130.3, 125.6, 117.5, 115.2, 55.0, 53.9, 52.0, 48.9, 46.0, 33.7, 27.4; HRMS (ESI) *m/z* $C_{21}H_{25}Cl_2N_3O_2S$ $(M+H)^+$ calcd for 454.1117 and 456.1091; found 454.1118 and 454.1093.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.39 (comp, *J* =6.2 Hz, 3H, C12-H, C14-H and C16-H), 6.92 (d, *J* =8.3 Hz, 1H, C3-H), 6.88 (d, *J* =2.6 Hz, 1H, C6-H), 6.71 (dd, *J* =8.2, 2.7 Hz, 1H, C2-H), 4.47 (s, 2H, C10-H), 3.68 – 3.62 (comp, 2H, C9-H), 3.23 – 3.18 (comp, 4H, C17-H and C18-H), 2.75 (comp, 2H, C7-H), 2.60 – 2.55 (comp, 4H, C19-H and C20-H), 2.36 (s, 3H, C21-H), 1.56 – 1.50 (comp, 2H, C8-H); ^{13}C NMR (101 MHz) δ 149.8 (C1), 143.4 (C11), 137.1 (C5), 135.5 (C13 and C15), 132.1 (C4), 132.0 (C14), 130.3 (C3), 125.6 (C12 and C16), 117.5 (C2), 115.2 (C3), 55.0 (C17 and C18), 53.9 (C10), 52.0 (C9), 48.9 (C19 and C20), 46.0 (C21), 33.7 (C7), 27.4 (C8).

Representative procedure for deprotection/*N*-sulfonylation of allyl piperazine derivatives



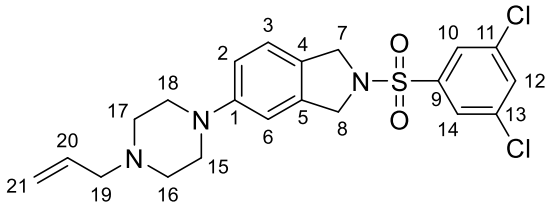
1.107

7-(4-Allylpiperazin-1-yl)-2-((3,5-dichlorophenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (1.107). KTL-01-264. A solution of carbamate **1.83** (61 mg, 0.18 mmol) in CH_2Cl_2 (3.0 mL) was brought to 0 °C and TMSI (141 mg 0.71 mmol) was added (*reaction carried out in the dark*). The solution was warmed to room temperature and

stirred for 2 h. The reaction was poured into cold aqueous HCl (6 mL, 2 M) that was vigorously stirring. The aqueous layer was washed with Et_2O (4 x 10 mL), basified, and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated under reduced pressure to give 35 mg (74%) of secondary amine intermediate as a yellow oil of sufficient purity for use in subsequent reactions. 3,5-dichlorobenzenesulfonylchloride (13 mg, 0.05 mmol) and Et_3N (13 mg, 0.09 mmol) were added to a solution of secondary amine (11 mg, 0.05 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature overnight and then concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (25:1:74) to give 40 mg (61%) of **1.107** as a clear oil: ^{1}H NMR (400 MHz) δ 7.68 (d, *J* =1.9 Hz, 2 H), 7.54 (t, *J* =1.9 Hz, 1 H), 6.97 (d, *J* =8.5 Hz, 1 H), 6.77 (dd, *J* =8.5, 2.6 Hz, 1 H), 6.57 (d, *J* =2.5 Hz, 1 H), 5.89 (ddt, *J* =16.8, 10.1, 6.6 Hz, 1 H), 5.24 (comp, 2 H), 4.27 (s, 2 H), 3.40 (t, *J* =6.0 Hz, 2 H), 3.18 – 3.11 (comp, 4 H), 3.05 (dt, *J* =6.6, 1.2 Hz, 2 H), 2.83 (t, *J* =5.9 Hz, 2 H), 2.62 – 2.56 (comp, 4 H); ^{13}C NMR (101 MHz) δ 150.0, 139.9, 136.1, 134.7, 132.7, 131.5, 129.5, 125.8, 123.7, 118.3, 115.6, 113.1, 61.7, 52.9, 49.2, 47.7, 44.1, 27.7; HRMS (ESI) *m/z* $C_{22}H_{25}Cl_2N_3O_2S$ $(M+H)^+$ calcd for 466.1117 and 468.1091; found 466.1121 and 468.1095.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.68 (d, *J* =1.9 Hz, 2 H, C11-H and C15-H), 7.54 (t, *J* =1.9 Hz, 1 H, C13-H), 6.97 (d, *J* =8.5 Hz, 1 H, C6-H), 6.77 (dd, *J* =8.5, 2.6 Hz, 1 H, C1-H), 6.57 (d, *J* =2.5 Hz, 1 H, C3-H), 5.89 (ddt, *J* =16.8, 10.1, 6.6 Hz, 1 H, C21-H), 5.24 (comp, 2 H, C22-H), 4.27 (s, 2 H, C7-H), 3.40 (t, *J* =6.0 Hz, 2 H, C9-H), 3.18 – 3.11 (comp, 4 H, C16-H and C19-H), 3.05 (dt, *J* =6.6, 1.2 Hz, 2 H, C20-H), 2.83 (t,

J =5.9 Hz, 2 H, C8-H), 2.62 – 2.56 (comp, 4 H, C17-H and C18-H); ^{13}C NMR (101 MHz) δ 150.0 (C2), 139.9 (C10), 136.1 (C23 and C25), 134.7 (C4), 132.7 (C21), 131.5 (C6), 129.5 (C13), 125.8 (C11 and C15), 123.7 (C5), 118.3 (C22), 115.6 (C1), 113.1 (C3), 61.7 (C20), 52.9 (C16 and C19), 49.2 (C17 and C18), 47.7 (C7), 44.1 (C9), 27.7 (C8).

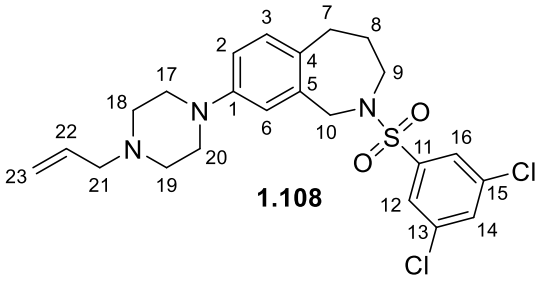


1.106

5-(4-Allylpiperazin-1-yl)-2-((3,5-dichlorophenyl)sulfonyl)isoindoline (1.106). KTL-01-276. Prepared according to the representative procedure outlined for deprotection/*N*-sulfonylation of allyl piperazine derivatives.. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (49:1:50) to give 29 mg (53% over two-steps) of **1.106** as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* =1.9 Hz, 2 H), 7.53 (t, *J* =1.9 Hz, 1 H), 7.06 (d, *J* =8.5 Hz, 1 H), 6.84 (dd, *J* =8.5, 2.2 Hz, 1 H), 6.72 (d, *J* =1.7 Hz, 1 H), 5.88 (d, *J* =40.5 Hz, 1 H), 5.20 (t, *J* =13.7 Hz, 2 H), 4.60 (s, 2 H), 4.57 (s, 2 H), 3.19 – 3.13 (comp, 4 H), 3.04 (d, *J* =6.6 Hz, 2 H), 2.62 – 2.56 (comp, 4 H); ^{13}C NMR (101 MHz) δ 151.7, 139.8, 136.6, 136.2, 134.7, 132.7, 126.2, 125.7, 123.1, 118.3, 116.3, 109.7, 61.7, 54.0, 53.5, 52.9, 49.3; HRMS (ESI) *m/z* $C_{21}H_{23}Cl_2N_3O_2S$ $(M+H)^+$ calcd for 45.0961 and 454.0935; found 452.0959 and 454.0933.

NMR Assignment. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* =1.9 Hz, 2 H, C10-H and C14-H), 7.53 (t, *J* =1.9 Hz, 1 H, C12-H), 7.06 (d, *J* =8.5 Hz, 1 H, C3-H), 6.84 (dd, *J* =8.5, 2.2 Hz, 1 H, C2-H), 6.72 (d, *J* =1.7 Hz, 1 H, C6-H), 5.88 (m, 1 H, C20-H), 5.20

(comp, 2 H, C21-H), 4.60 (s, 2 H, C7-H or C8-H), 4.57 (s, 2 H, C7-H or C8-H), 3.19 – 3.13 (m, 4 H, C15-H and C18-H), 3.04 (d, *J* =6.6 Hz, 2 H, C19-H), 2.62 – 2.56 (m, 4 H, C16-H and C17-H); ^{13}C NMR (101 MHz) δ 151.7 (C1), 139.8 (C9), 136.6 (C5), 136.2 (C11 and C13), 134.7 (C20), 132.7 (C12), 126.2 (C4), 125.7 (C10 and C14), 123.1 (C3), 118.3 (C21), 116.3 (C2), 109.7 (C6), 61.7 (C16), 54.0 (C7 or C8), 53.5 (C7 or C8), 52.9 (C15 and C18), 49.3 (C16 and C17).



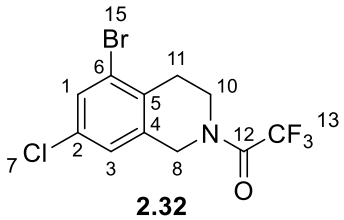
1.108

8-(4-Allylpiperazin-1-yl)-2-((3,5-dichlorophenyl)sulfonyl)-2,3,4,5-tetrahydro-1H-benzo[c]azepine (1.108). KTL-02-055. Prepared according to the representative procedure outlined for deprotection/*N*-sulfonylation of allyl piperazine derivatives. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (5:1:94) to give 17 mg (50% over two-steps) of **1.108** as a clear oil: ^{1}H NMR (400 MHz) δ 7.39 (s, 3 H), 6.92 (d, *J* =8.3 Hz, 1 H), 6.88 (d, *J* =2.6 Hz, 1 H), 6.70 (dd, *J* =8.2, 2.6 Hz, 1 H), 5.96-5.84 (m, 1 H), 5.22 (comp, 2 H), 4.47 (s, 2 H), 3.70 – 3.60 (comp, 2 H), 3.25 – 3.18 (comp, 4 H), 3.07 (dt, *J* =8.0, 2 Hz, 2 H), 2.75 (d, *J* =11.2 Hz, 2 H), 2.65 – 2.55 (comp, 4 H), 1.54 (comp, 2 H); ^{13}C NMR (101 MHz) δ 150.0, 143.4, 137.0, 135.5, 134.8, 132.0, 131.9, 130.2, 125.6, 118.2, 117.4, 115.1, 61.8, 53.9, 53.0, 52.0, 49.1, 33.7, 27.4; HRMS

(ESI) *m/z* $C_{23}H_{27}Cl_2N_3O_2S$ $(M+H)^+$ calcd for 480.1274 and 482.1248; found 480.1277 and 482.1251.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.39 (s, 3 H, C12-H, C14-H, and C16-H), 6.92 (d, *J* =8.3 Hz, 1 H, C3-H), 6.88 (d, *J* =2.6 Hz, 1 H, C6-H), 6.70 (dd, *J* =8.2, 2.6 Hz, 1 H, C2-H), 5.96-5.84 (m, 1 H, C22-H), 5.22 (comp, 2 H, C23-H), 4.47 (s, 2 H, C10-H), 3.70 – 3.60 (comp, 2 H, C9-H), 3.25 – 3.18 (comp, 4 H, C17-H and C20-H), 3.07 (dt, *J* =8.0, 2 Hz, 2 H, C21-H), 2.75 (comp, 2 H, C7-H), 2.65 – 2.55 (comp, 4 H, C18-H and C19-H), 1.54 (comp, 2 H, C8-H); ^{13}C NMR (101 MHz) δ 150.0 (C1), 143.4 (C11), 137.0 (C5), 135.5 (C13 and C15), 134.8 (C23), 132.0 (C4), 131.9 (C14), 130.2 (C3), 125.6 (C12 and C16), 118.2 (C23), 117.4 (C2), 115.1 (C6), 61.8 (C21), 53.9 (C10), 53.0 (C17 and C20), 52.0 (C9), 49.1 (C18 and C19), 33.7 (C7), 27.4 (C8).

Preparation of Dihalogenated Tetrahydroisoquinoline Scaffold

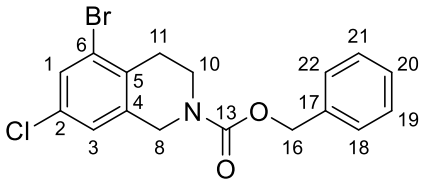


2.32

1-(5-Bromo-7-chloro-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethan-1-one (2.32). KTL-02-181. A solution of **2.31** (700 mg, 2.6 mmol) in CH_2Cl_2 was cooled 0 °C, and triethylamine (787 mg, 7.8 mmol) and trifluoroacetic anhydride (601 mg, 2.9 mmol) were added. This reaction was stirred at room temperature for 90 min and then washed with 1 M HCl (2 x 10 mL) and brine (1 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 750 mg (88 %) of the desired amide as a yellow solid of sufficient

purity. The amide (750 mg, 2.27 mmol) and paraformaldehyde (681 mg, 22.7 mmol) were added to a solution of sulfuric acid (4.2 mL) and acetic acid (2.8 mL). The resulting solution was stirred at room temperature for 24 h and then poured into ice (ca. 50 g). The resulting aqueous suspension was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (10:90) to give 450 mg (60%) of **2.32** as a white solid: ^{1}H NMR (400 MHz, rotamers) δ 7.49 (d, *J* = 2.0 Hz, 0.33 H), 7.47 (d, *J* = 2.1 Hz, 0.66 H), 7.12 – 7.10 (m, 0.66 H), 7.09 (d, *J* = 2.0 Hz, 0.33 H), 4.75 (s, 1.33 H), 4.69 (s, 0.66 H), 3.90 (t, *J* = 6.2 Hz, 0.66 H), 3.85 (t, *J* = 5.7 Hz, 1.33 H), 2.99 – 2.82 (comp, 2 H); ^{13}C NMR (101 MHz) δ 156.1, 155.8, 135.5, 135.2, 135.0, 133.3, 133.2, 132.5, 131.8, 131.4, 131.0, 125.9, 125.8, 125.5, 118.0, 115.1, 110.0, 47.0, 45.3, 43.3, 43.3, 41.6, 29.9, 28.4; HRMS (ESI) *m/z* $C_{11}H_8BrClF_3NO$ $(M+Na)^+$ calcd for 363.9322 and 365.9300; found 363.9326 and 365.9313.

NMR Assignment. ^{1}H NMR (400 MHz, rotamers) δ 7.49 (d, *J* = 2.0 Hz, 0.33 H, C1-H), 7.47 (d, *J* = 2.1 Hz, 0.66 H, C1-H), 7.12 – 7.10 (m, 0.66 H, C3-H), 7.09 (d, *J* = 2.0 Hz, 0.33 H, C3-H), 4.75 (s, 1.33 H, C8-H), 4.69 (s, 0.66 H, C8-H), 3.90 (t, *J* = 6.2 Hz, 0.66 H, C10-H), 3.85 (t, *J* = 5.7 Hz, 1.33 H, C10-H), 2.99 – 2.82 (comp, 2 H, C11-H).

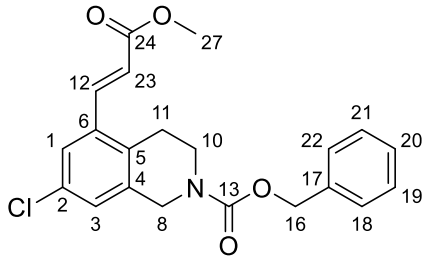


2.28

Benzyl 5-bromo-7-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.28). KTL-02-240. A saturated solution of Na_2CO_3 (5 mL) was added to a solution of **2.32** (450 mg, 1.31 mmol) in MeOH (5 mL) and the resulting mixture was heated under reflux for 16 h. The reaction was cooled to room temperature and the organics were removed under reduced pressure. The remaining aqueous fraction was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic fractions were dried (K_2CO_3) and concentrated under reduced pressure to give 311 mg (96%) of secondary amine intermediate as a white solid of sufficient purity for use in subsequent reactions. A solution of amine intermediate (570 mg, 2.31 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C, and *i*Pr_2NEt (651 mg, 4.6 mmol) and Cbz-Cl (864 mg, 4.6 mmol) were added. The reaction was stirred at room temperature for 16 h. The reaction concentrated under reduced pressure, and the crude mixture was purified via flash column chromatography eluting with EtOAc:hexanes (10:90) to give 800 mg (91%) of **2.28** as a white solid: ^{1}H NMR (300 MHz) δ 7.48 (d, *J* = 2.1 Hz, 1 H), 7.43 – 7.32 (comp, 5 H), 7.09 (s, 1 H), 5.20 (s, 2 H), 4.63 (s, 2 H), 3.76 (t, *J* = 6.0 Hz, 2 H), 2.84 (t, *J* = 5.6 Hz, 2 H); ^{13}C NMR (101 MHz) δ 155.1, 137.0, 136.6, 136.4, 132.8, 132.6, 132.4, 130.2, 128.6, 128.2, 128.1, 127.8, 127.7, 125.4, 67.5, 45.6, 41.3, 41.1, 29.1, 28.9; HRMS (ESI) *m/z* $C_{17}H_{15}BrClNO_2$ $(M+Na)^+$ calcd for 401.9867 and 403.9846; found 401.9864 and 403.9845.

NMR Assignment. ^{1}H NMR (300 MHz) δ 7.48 (d, *J* = 2.1 Hz, 1 H, C1-H), 7.43 – 7.32 (comp, 5 H, C18-H thru C22-H), 7.09 (s, 1 H, C3-H), 5.20 (s, 2 H, C16-H), 4.63 (s, 2 H, C8-H), 3.76 (t, *J* = 6.0 Hz, 2 H, C10-H), 2.84 (t, *J* = 5.6 Hz, 2 H, C11-H); ^{13}C NMR (101 MHz) δ 155.1 (C13), 137.0 (C4), 136.6 (C4), 136.4 (C17), 132.8 (C2), 132.6 (C2), 132.4 (C5), 130.2 (C6), 128.6 (C19 and C1), 128.2 (C20), 128.1 (C18 and C20), 127.8 (C1), 127.7 (C1), 125.4 (C3), 67.5 (C16), 45.6 (C8), 41.3 (C10), 41.1 (C10), 29.1 (C11), 28.9 (C11).

Representative procedure for Heck cross-coupling with acrylates

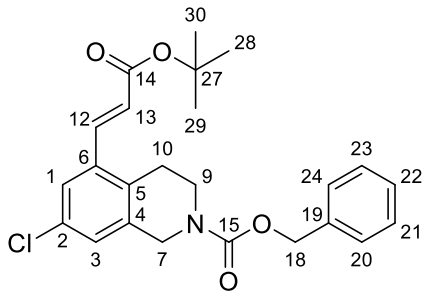


2.33

Benzyl (E)-7-chloro-5-(3-methoxy-3-oxoprop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.33). KTL-02-228. A solution of carbamate **2.28** (50 mg, 0.13 mmol) in DMF (0.93 mL) was added to a CEM microwave vial containing tetrabutylammonium chloride (36 mg, 0.13 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol) and $P(o\text{-}tol)_3$ (8 mg, 0.026 mmol). *i*Pr_2NEt (34 mg, 0.26 mmol) and methyl acrylate (13 mg, 0.16 mmol) were added and the vial was capped and flushed with argon. The mixture was stirred for 2 min at room temperature and then heated in the microwave (300 W) at 125 °C for 1 h. The mixture was poured into water and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified

by flash column chromatography eluting with EtOAc:hexanes (10:90) to give 30 mg (60%) of **2.33** as a yellow oil: ^{1}H NMR (300 MHz) δ 7.85 (d, *J* = 15.8 Hz, 1 H), 7.44 – 7.31 (comp, 6 H), 7.13 (s, 1 H), 6.36 (d, *J* = 15.8 Hz, 1 H), 5.19 (s, 2 H), 4.64 (s, 2 H), 3.83 (s, 3 H), 3.75 (t, *J* = 6.0 Hz, 2 H), 2.90 (t, *J* = 5.5 Hz, 2 H); ^{13}C NMR (101 MHz) δ 166.8, 155.1, 140.1, 136.5, 132.3, 128.5, 128.1, 128.0, 124.8, 121.2, 67.4, 51.9, 45.6, 41.1, 41.0, 25.8, 25.7; HRMS (ESI) *m/z* $C_{21}H_{20}ClNO_4$ $(M+Na)^+$ calcd for 408.0973 and 410.0952; found 408.0978 and 410.0959.

NMR Assignment. ^{1}H NMR (300 MHz) δ 7.85 (d, *J* = 15.8 Hz, 1 H, C12-H), 7.44 – 7.31 (comp, 6 H, C1-H and C18-H thru C22-H), 7.13 (s, 1 H, C3-H), 6.36 (d, *J* = 15.8 Hz, 1 H, C23-H), 5.19 (s, 2 H, C16-H), 4.64 (s, 2 H, C8-H), 3.83 (s, 3 H, C27-H), 3.75 (t, *J* = 6.0 Hz, 2 H, C10-H), 2.90 (t, *J* = 5.5 Hz, 2 H, C11-H); ^{13}C NMR (101 MHz) δ 166.8 (C24), 155.1 (C13), 140.1, 136.5 (C17), 132.3, 128.5 (C19 and C21), 128.1 (C20), 128.0 (C18 and C22), 124.8, 121.2 (C23), 67.4 (C16), 51.9 (C27), 45.6 (C8), 41.1 (C10), 41.0 (C10), 25.8 (C11), 25.7 (C11).



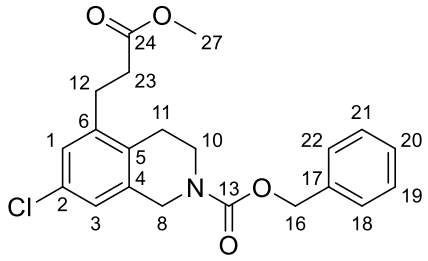
2.37

Benzyl (E)-7-chloro-5-(3-methoxy-3-oxoprop-1-en-1-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.37). KTL-02-295. Prepared according to the representative

procedure outlined for Heck cross-coupling with acrylates. The crude material was purified by flash column chromatography eluting with EtOAc:hexanes (10:90) to give 137 mg (61%) of **2.37** as a yellow oil: ^{1}H NMR (400 MHz) δ 7.73 (d, *J* = 15.8 Hz, 1 H), 7.42 – 7.30 (comp, 6 H), 7.09 (d, *J* = 11.9 Hz, 1 H), 6.27 (d, *J* = 15.7 Hz, 1 H), 5.17 (d, *J* = 1.1 Hz, 2 H), 4.61 (s, 2 H), 3.72 (t, *J* = 6.0 Hz, 2 H), 2.87 (br s, 2 H), 1.52 (s, 9 H).

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.73 (d, *J* = 15.8 Hz, 1 H, C12-H), 7.42 – 7.30 (comp, 6 H, C1-H and C20-H thru C24-H), 7.09 (d, *J* = 11.9 Hz, 1 H, C3-H), 6.27 (d, *J* = 15.7 Hz, 1 H, C13-H), 5.17 (d, *J* = 1.1 Hz, 2 H, C18-H), 4.61 (s, 2 H, C7-H), 3.72 (t, *J* = 6.0 Hz, 2 H, C9-H), 2.87 (br s, 2 H, C10-H), 1.52 (s, 9 H, C28-H thru C30-H).

Representative procedure for enoate reduction

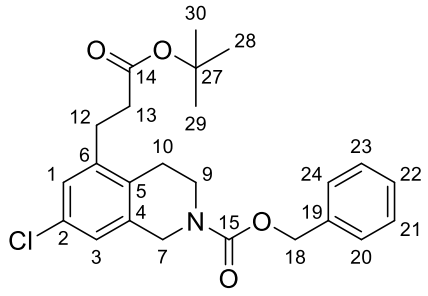


2.35

Benzyl 7-chloro-5-(3-methoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.35). KTL-02-250. A solution of **2.33** (110 mg, 0.28 mmol) in EtOH (2.8 mL) and $Pt_2O{\cdot}2H_2O$ (13 mg, 0.057 mmol) was stirred under an atmosphere of H_2 until consumption of starting material was observed. The reaction was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The crude material was run through a silica plug eluting EtOAc:hexanes (1:1) to provide 85 mg (78%) of **2.35** as a yellow oil: ^{1}H NMR (400 MHz,) δ 7.41 – 7.30 (m, 5 H), 7.03 (d, *J* = 2.1 Hz, 1 H), 6.97 (s,

1 H), 5.17 (s, 2 H), 4.60 (s, 2 H), 3.72 (t, *J* = 5.6 Hz, 2 H), 3.68 (s, 3 H), 2.88 (t, *J* = 7.9 Hz, 2 H), 2.76 (s, 2 H), 2.56 (t, *J* = 7.9 Hz, 2 H); ^{13}C NMR (101 MHz) δ 172.8, 155.2, 140.6, 140.4, 136.6, 135.7, 135.2, 131.9, 131.1, 128.5, 128.1, 128.02, 128.0, 126.8, 124.5, 67.3, 51.8, 45.8, 41.4, 41.2, 34.0, 27.3, 25.4, 25.2; HRMS (ESI) *m/z* $C_{21}H_{22}ClNO_4$ $(M+Na)^+$ calcd for 410.1130 and 412.1109; found 410.1137 and 412.1112.

NMR Assignment. ^{1}H NMR (400 MHz,) δ 7.41 – 7.30 (m, 5 H, C18-H thru C22-H), 7.03 (d, *J* = 2.1 Hz, 1 H, C1-H), 6.97 (s, 1 H, C3-H), 5.17 (s, 2 H, C16-H), 4.60 (s, 2 H, C8-H), 3.72 (t, *J* = 5.6 Hz, 2 H, C10-H), 3.68 (s, 3 H, C27-H), 2.88 (t, *J* = 7.9 Hz, 2 H, C12-H), 2.76 (s, 2 H, C11-H), 2.56 (t, *J* = 7.9 Hz, 2 H, C23-H); ^{13}C NMR (101 MHz) δ 172.8 (C24), 155.2 (C13), 140.6 (C4), 140.4 (C4), 136.6 (C17), 135.7 (C5), 135.2 (C5), 131.9 (C6), 131.1 (C2), 128.5 (C19 and C21), 128.1 (C20), 128.02 (C18 and C20), 128.0 (C18 and C20), 126.8 (C1), 124.5 (C3), 67.3 (C16), 51.8 (C27), 45.8 (C11), 41.4 (C10), 41.2 (C10), 34.0 (C23), 27.3 (C12), 25.4 (C11), 25.2 (C11).



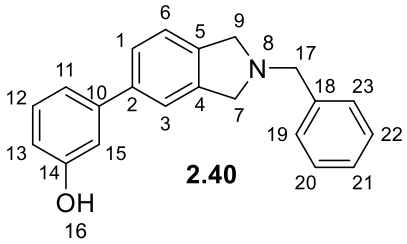
2.38

Benzyl 7-chloro-5-(3-methoxy-3-oxopropyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (2.38). KTL-02-296. Prepared according to the representative procedure outlined for enoate reduction. The crude material was run through a silica plug eluting

EtOAc:hexanes (1:1) to provide 70 mg (51%) of **2.38** as a yellow oil: ^{1}H NMR (300 MHz) δ 7.43 – 7.34 (m, 5 H), 7.07 (br s, *J* = 2.0 Hz, 1 H), 6.99 (br s, 1 H), 5.20 (s, *J* = 1.4 Hz, 2 H), 4.63 (s, 2 H), 3.74 (t, *J* = 6.0 Hz, 2 H), 2.92 – 2.72 (t, *J* = 6.0 Hz, 2 H), 2.79 (br s, 2 H), 2.49 (t, *J* = 6.0 Hz, 2 H), 1.46 (s, 9 H).

NMR Assignment. ^{1}H NMR (300 MHz) δ 7.43 – 7.34 (m, 5 H, C20-H thru C24-H), 7.07 (br s, *J* = 2.0 Hz, 1 H, C1-H), 6.99 (br s, 1 H, C3-H), 5.20 (s, *J* = 1.4 Hz, 2 H, C18-H), 4.63 (s, 2 H, C7-H), 3.74 (t, *J* = 6.0 Hz, 2 H, C9-H), 2.87 (t, *J* = 6.0 Hz, 2 H, C13-H), 2.79 (br s, 2 H, C10-H), 2.49 (t, *J* = 6.0 Hz, 2 H, C12-H), 1.46 (s, 9 H, C28-H thru C30-H).

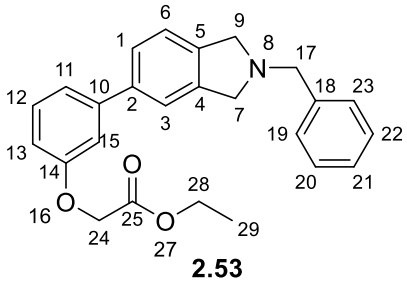
Preparation of Sig1R ligand for conjugation



3-(2-Benzylisoindolin-5-yl)phenol (2.40). KTL-02-136. A solution of carbamate **2.47** (260 mg, 0.72 mmol) in CH_2Cl_2 (9 mL) was cooled to 0 °C, BBr_3 (902 mg, 3.6 mmol) was added and the reaction was stirred at room temperature for 2 h. The reaction was cooled to 0 °C and H_2O (10 mL) was added. The resulting solid was collected via vacuum filtration to give 125 mg (82%) of the desired secondary amine intermediate as an off white solid. A solution of amine intermediate (76 mg, 0.33 mmol), $NaBH(OAc)_3$ (140 mg, 0.66 mmol), benzaldehyde (69 mg, 0.66 mmol) and 33 μL AcOH in DCE (3.3 mL) was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of sat. $NaHCO_3$

(3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (49:1:50) to give 41 mg (42%) of **2.40** as an orange oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 – 7.23 (comp, 8 H), 7.17 (t, J = 7.8 Hz, 1 H), 6.96 – 6.92 (comp, 2 H), 6.72 – 6.67 (m, 1 H), 3.91 (s, 2 H), 3.85-3.48 (comp, 4 H).

NMR Assignment. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 – 7.23 (comp, 8 H, C1-H, C3-H, C6-H, and C19-H thru C23-H), 7.17 (t, J = 7.8 Hz, 1 H, C12-H), 6.96 – 6.92 (comp, 2 H, C11-H and C15-H), 6.72 – 6.67 (m, 1 H, C13-H), 3.91 (s, 2 H, C17-H), 3.85-3.48 (comp, 4 H, C7-H and C9-H).

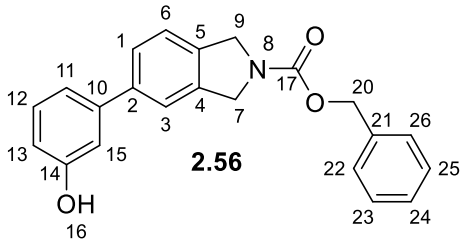


2.53

Ethyl 2-(3-(2-benzylisoindolin-5-yl)phenoxy)acetate (2.53). KTL-02-121. A mixture of **2.40** (11 mg, 0.037 mmol), ethyl bromoacetate (6 mg, 0.037 mmol), and K_2CO_3 (10 mg, 0.074 mmol) in DMF (0.5 mL) was stirred at room temperature for 3 h. The mixture was filtered and concentrated, and the crude material was purified via flash column chromatography eluting EtOAc:TEA:hexanes (49:2:29) to give **2.53** as a clear oil: ^{1}H NMR (400 MHz) δ 7.50 – 7.29 (comp, 8 H), 7.23 (d, J = 8.0 Hz, 1 H), 7.21 – 7.16 (m, 1 H), 7.11

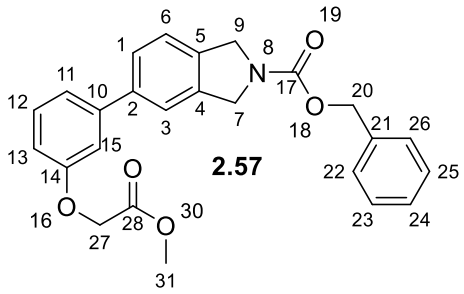
(dd, *J* = 2.7, 1.6 Hz, 1 H), 6.85 (d, *J* = 2.5 Hz, 1 H), 4.66 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 4.02 – 3.95 (m, 4 H), 3.94 (s, 2 H), 1.30 (t, *J* = 7.1, 3 H).

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.50 – 7.29 (comp, 8 H, C1-H, C3-H, C6-H, and C19-H thru C23-H), 7.23 (d, *J* = 8.0 Hz, 1 H, C12-H), 7.21 – 7.16 (m, 1 H, C15-H), 7.11 (dd, *J* = 2.7, 1.6 Hz, 1 H, C11-H), 6.85 (d, *J* = 2.5 Hz, 1 H, C13-H), 4.66 (s, 2 H, C24-H), 4.28 (q, *J* = 7.1 Hz, 2 H, C28-H), 4.02 – 3.95 (m, 4 H, C7-H and C9-H), 3.94 (s, 2 H, C17-H), 1.30 (t, *J* = 7.1, 3 H, C29-H).



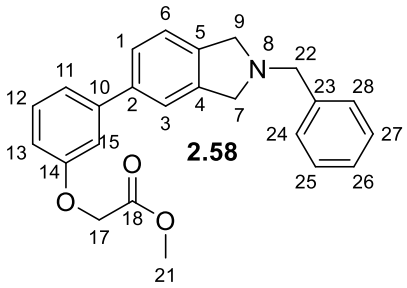
Benzyl 5-(3-hydroxyphenyl)isoindoline-2-carboxylate (2.56). KTL-02-165. A solution of **2.56** (250 mg, 0.75 mmol), 3-hydroxyphenylboronic acid (207 mg, 1.50 mmol), Cs_2CO_3 (490 mg, 1.59 mmol), and palladium (bis)(*t*-butyl)$_3$ phosphine (19 mg, 0.0375 mmol) in degassed 1,4-dioxane (2.3 mL) was stirred for 24 h at 90 °C. The reaction was cooled to room temperature and poured into water (5 mL). The material was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified via flash column chromatography eluting with EtOAc:hexanes (1:1) to give 197 mg (75%) of **2.56** as a white solid: ^{1}H NMR (400 MHz) δ 7.51 – 7.27 (comp, 9 H), 7.13 (t, *J* = 6.2 Hz, 1 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.23 (s, 2 H), 4.84 – 4.77 (comp, 4 H).

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.51 – 7.27 (comp, 9 H, C1-H, C3-H, C6-H, C12-H, and C22-H thru C26-H), 7.13 (t, *J* = 6.2 Hz, 1 H, C15-H), 7.05 (d, *J* = 7.5 Hz, 1 H, C11-H), 6.83 (d, *J* = 8.0 Hz, 1 H, C13-H), 5.23 (s, 2 H, C20-H), 4.84 – 4.77 (comp, 4 H, C7-H and C9-H).



Benzyl 5-(3-(2-methoxy-2-oxoethoxy)phenyl)isoindoline-2-carboxylate (2.57). KTL-02-192. Prepared according to the general procedure outlined for compound **2.53**. The crude mixture was purified via flash column chromatography eluting EtOA:hexanes (20:80) to give 131 mg (77%) of **2.57** as a light yellow oil: ^{1}H NMR (400 MHz) δ 7.51 – 7.26 (comp, 9 H), 7.23 – 7.17 (m, 1 H), 7.12 (ddd, *J* = 4.1, 2.6, 1.7 Hz, 1 H), 6.90 – 6.86 (m, 1 H), 5.23 (s, 2 H), 4.84 – 4.77 (comp, 4 H), 4.70 (d, *J* = 1.3 Hz, 2 H), 3.82 (s, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 169.3, 158.2, 154.9, 142.53, 142.50, 140.5, 140.4, 137.7, 137.3, 136.8, 136.3, 136.0, 129.9, 128.5, 128.0, 127.9, 126.7, 126.7, 123.1, 122.9, 121.5, 121.3, 120.75, 120.74, 114.0, 113.9, 113.21, 113.15, 67.1, 65.4, 52.5, 52.4, 52.3, 52.1, 51.9.

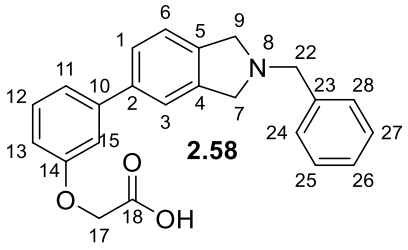
NMR Assignment. ^{1}H NMR (400 MHz) δ 7.51 – 7.26 (comp, 9 H, C1-H, C3-H, C6-H, C12-H, and C22-H thru C26-H), 7.23 – 7.17 (m, 1 H, C15-H), 7.12 (ddd, *J* = 4.1, 2.6, 1.7 Hz, 1 H, C11-H), 6.90 – 6.86 (m, 1 H, C13-H), 5.23 (s, 2 H, C20-H), 4.84 – 4.77 (comp, 4 H, C7-H and C9-H), 4.70 (d, *J* = 1.3 Hz, 2 H, C27-H), 3.82 (s, 3 H, C31-H).



Methyl 2-(3-(2-benzylisoindolin-5-yl)phenoxy)acetate (2.58). KTL-02-200. A solution of carbamate **2.56** (130 mg, 0.31 mmol) in EtOH (10 mL) and 10% Pd/C (33 mg) was stirred under an atmosphere of H_2 until consumption of starting material was observed. The reaction was filtered and the filtrate was concentrated under reduced pressure to provide 70 mg (79%) of the desired secondary amine intermediate sufficient purity for use in subsequent reactions. A solution of amine intermediate (70 mg, 0.25 mmol), $NaBH(OAc)_3$ (106 mg, 0.5 mmol), benzaldehyde (52 mg, 0.5 mmol) and 10 μL AcOH in DCE (2.5 mL) was stirred overnight at room temperature. The reaction was quenched with an aqueous solution of sat. $NaHCO_3$ (3 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (K_2CO_3) and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography eluting EtOA:TEA:hexanes (20:1:79) to give 55 mg (60%) of **2.58** as a brown oil: ^{1}H NMR (400 MHz) δ 7.47 – 7.28 (comp, 10 H), 7.25 – 7.22 (m, 1 H), 7.19 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1 H), 7.10 (dd, *J* = 2.6, 1.7 Hz, 1 H), 6.88 – 6.84 (m, 1 H), 4.68 (s, 2 H), 4.01 (d, *J* = 6.9 Hz, 4 H), 3.97 (s, 2 H), 3.82 (d, *J* = 0.7 Hz, 3 H); ^{13}C NMR (101 MHz) δ 169.4, 158.1, 143.2, 141.0, 139.7, 139.6, 139.0, 129.8, 128.8, 128.4, 127.2, 125.9,

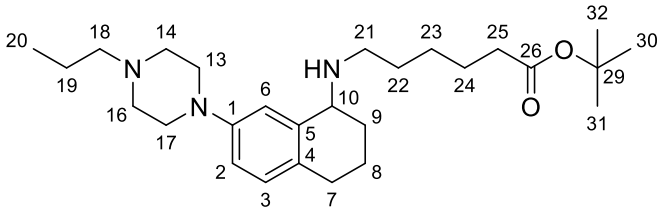
122.6, 121.2, 120.8, 113.9, 112.9, 65.4, 60.3, 58.9, 58.7, 52.3; HRMS (ESI) *m/z* $C_{24}H_{23}NO_3$ $(M+H)^+$ calcd for 374.1751; found 374.1760.

NMR Assignment. ^{1}H NMR (400 MHz) δ 7.47 – 7.28 (m, 9 H, C1-H, C3-H, C6-H, C24-H thru C28-H), 7.25 – 7.22 (m, 1 H, C12-H), 7.19 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1 H, C15-H), 7.10 (dd, *J* = 2.6, 1.7 Hz, 1 H, C11-H), 6.88 – 6.84 (m, 1 H, C13-H), 4.68 (s, 2 H, C17-H), 4.01 (d, *J* = 6.9 Hz, 4 H, C7-H and C9-H), 3.97 (s, 2 H, C22-H), 3.82 (d, *J* = 0.7 Hz, 3 H, C21-H); ^{13}C NMR (101 MHz) δ 169.4 (C18), 158.1 (C14), 143.2 (C10), 141.0 (C4), 139.7 (C2), 139.6 (C23), 139.0 (C5), 129.8 (C12), 128.8 (C25 and C27), 128.4 (C24 and C28), 127.2 (C26), 125.9 (C1), 122.6 (C3), 121.2 (C6), 120.8 (C11), 113.9 (C15), 112.9 (C13), 65.4 (C17), 60.3 (C22), 58.9 (C9), 58.7 (C7), 52.3 (C21).



2-(3-(2-Benzylisoindolin-5-yl)phenoxy)acetic acid (2.58). KTL-02-266. A solution of **2.58** (24 mg, 0.06 mmol) and LiOH (18 mg, 0.75 mmol) in MeOH/H_2O (3:1, 0.8 mL) was stirred at room temperature for 45 min. The MeOH was removed *in vacuo* and NH_4Cl (0.5 mL) was added. The resulting solid was filtered and dried to give 30 mg of **2.58** as a brown solid: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.60 (ddd, *J* = 5.6, 4.2, 2.0 Hz, 3 H), 7.57 (s, 2 H), 7.47 (dd, *J* = 5.1, 2.1 Hz, 3 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 7.16 (dt, *J* = 7.9, 1.1 Hz, 1 H), 7.13 (t, *J* = 2.1 Hz, 1 H), 6.91 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1 H), 4.60 – 4.56 (m, 4 H), 4.53 (s, 2 H), 4.44 (s, 2 H).

Representative procedure for reductive amination of tetralones

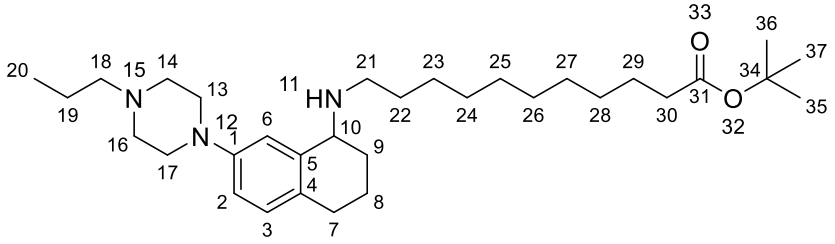


2.80

***tert*-Butyl 6-((7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)hexanoate (2.80). KTL-03-118.** Ti(O*t*Bu)$_4$ (159 mg, 0.37 mmol) was added to a solution of **2.71** (25 mg, 0.09 mmol) and *tert*-butyl 6-aminohexanoate (69 mg, 0.37 mmol) in DCE (1 mL) and the reaction was heated to 80 °C for 18 h. The reaction was cooled to room temperature and NaBH(OAc)$_3$ (78 mg, 1.4 mmol) and TFA (45 mg, 0.39 mmol) were added and the reaction was stirred for 2 h. Sat. NaHCO$_{3(aq)}$ (1 mL) was added and the reaction was stirred for 20 mins. The reaction was diluted with CH_2Cl_2 and filtered through a pad of celite. The filtrate was washed with sat. NaHCO$_3$ (1 x 2 mL) and the organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by flash column chromatography eluting EtOAc:TEA:hexanes (20:1:79) to give 31 mg (80%) of **2.80** as a yellow oil: ^{1}H NMR (400 MHz) δ 6.96 (d, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 2.6 Hz, 1 H), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1 H), 3.69 (t, *J* = 5.0 Hz, 1 H), 3.19 – 3.12 (comp, 4 H), 2.75 – 2.62 (comp, 4 H), 2.60 (comp, 4 H), 2.38 – 2.32 (comp, 2 H), 2.20 (t, *J* = 7.5 Hz, 2 H), 1.91 (m, 1 H), 1.86 – 1.77 (comp, 2 H), 1.71 – 1.63 (m, 1 H), 1.63 – 1.47 (comp, 7 H), 1.43 (s, 9 H), 1.36 (comp, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz) δ 173.2, 149.6, 139.9, 129.6, 128.8, 116.3, 115.4, 79.9, 60.7, 55.8, 53.3, 49.7, 47.0, 35.5,

30.3, 28.5, 28.1, 27.0, 25.0, 20.0, 19.3, 12.0; HRMS (ESI) *m/z* $C_{27}H_{45}N_3O_2$ $(M+H)^+$ calcd for 444.3585; found 444.3595.

NMR Assignment. ^{1}H NMR (400 MHz) δ 6.96 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.92 (d, *J* = 2.6 Hz, 1 H, C6-H), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1 H, C2-H), 3.69 (t, *J* = 5.0 Hz, 1 H, C10-H), 3.19 – 3.12 (comp, 4 H, C13-H and C17-H), 2.75 – 2.62 (comp, 4 H, C7-H and C21-H), 2.60 (comp, 4 H, C14-H and C16-H), 2.38 – 2.32 (comp, 2 H, C18-H), 2.20 (t, *J* = 7.5 Hz, 2 H, C25-H), 1.91 (m, 1 H, C8-H), 1.86 – 1.77 (comp, 2 H, C9-H), 1.71 – 1.63 (m, 1 H, C8-H), 1.63 – 1.47 (comp, 7 H, C19-H, C22-H and C24-H), 1.43 (s, 9 H, C30-H thru C32-H), 1.36 (comp, 2 H, C23-H), 0.92 (t, *J* = 7.4 Hz, 3 H, C20-H); ^{13}C NMR (101 MHz) δ 173.2 (C26), 149.6 (C1), 139.9 (C4), 129.6 (C3), 128.8 (C5), 116.3 (C6), 115.4 (C2), 79.9 (C29), 60.7 (C18), 55.8 (C10), 53.3 (C14 and C16), 49.7 (C13 and C17), 47.0 (C21) , 35.5 (C25), 30.3 (C22), 28.5 (C7 and C9), 28.1 (C30 thru C32), 27.0 (C23), 25.0 (C24), 20.0 (C19), 19.3 (C8), 12.0 (C20).



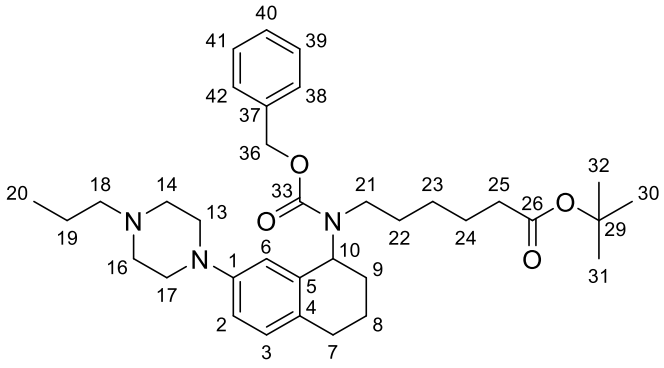
2.81

***tert*-Butyl 11-((7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)undecanoate (2.81). KTL-03-130.** Prepared according to the representative procedure outlined for reductive amination of tetralones. The crude material was purified by flash column chromatography eluting EtOAc:hexanes:TEA (15:1:84) to give 27 mg

(62%) of **2.81** as a yellow oil: ^{1}H NMR (400 MHz) δ 6.96 (d, *J* = 8.4 Hz, 1 H), 6.93 (d, *J* = 2.6 Hz, 1 H), 6.76 (dd, *J* = 8.4, 2.6 Hz, 1 H), 3.70 (t, *J* = 5.0 Hz, 1 H), 3.19 – 3.12 (comp, 4 H), 2.81 – 2.56 (comp, 9 H), 2.38 – 2.31 (comp, 2 H), 2.19 (t, *J* = 7.5 Hz, 2 H), 1.97 – 1.86 (m, 1 H), 1.84-1.80 (comp, 2 H), 1.72 – 1.63 (m, 1 H), 1.62 – 1.45 (comp, 9 H), 1.43 (s, 11 H), 1.27 (comp, 17 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz) δ 173.3, 149.6, 139.9, 129.6, 128.9, 116.2, 115.4, 79.8, 60.7, 55.8, 53.3, 49.7, 47.2, 35.6, 30.5, 29.6, 29.4, 29.3, 29.1, 28.5, 28.1, 27.5, 25.1, 20.0, 19.3, 12.0; HRMS (ESI) *m/z* $C_{32}H_{55}N_3O_2$ $(M+H)^+$ calcd for 514.4367; found 514.4377.

NMR Assignment. ^{1}H NMR (400 MHz) δ 6.96 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.93 (d, *J* = 2.6 Hz, 1 H, C6-H), 6.76 (dd, *J* = 8.4, 2.6 Hz, 1 H, C2-H), 3.70 (t, *J* = 5.0 Hz, 1 H, C10-H), 3.19 – 3.12 (comp, 4 H, C13-H and C17-H), 2.81 – 2.56 (comp, 9 H, C7-H, C14-H, C16-H and C21-H), 2.38 – 2.31 (comp, 2 H, C18-H), 2.19 (t, *J* = 7.5 Hz, 2 H, C30-H), 1.97 – 1.86 (m, 1 H, C8-H), 1.84-1.80 (comp, 2 H, C9-H), 1.72 – 1.63 (m, 1 H, C8-H), 1.62 – 1.45 (comp, 9 H, C22-H, C19-H, C29-H), 1.43 (s, 11 H, C35-H thru C37-H), 1.27 (comp, 17 H, C23-H thru C28-H), 0.92 (t, *J* = 7.4 Hz, 3 H, C20-H); ^{13}C NMR (101 MHz) δ 173.3 (C31), 149.6 (C1), 139.9 (C4), 129.6 (C3), 128.9 (C5), 116.2 (C6), 115.4 (C2), 79.8 (C24), 60.7 (C18), 55.8 (C10), 53.3 (C14 and C16), 49.7 (C13 and C17), 47.2 (C21), 35.6 (C30), 30.5 (C22), 29.6 (C25 and C6), 29.4 (C24), 29.3 (C27), 29.1 (C28), 28.5 (C7 and C9), 28.1 (C35 thru C37), 27.5 (C23), 25.1 (C29), 20.0 (C19), 19.3 (C8), 12.0 (C20).

Representative procedure for -Cbz protection

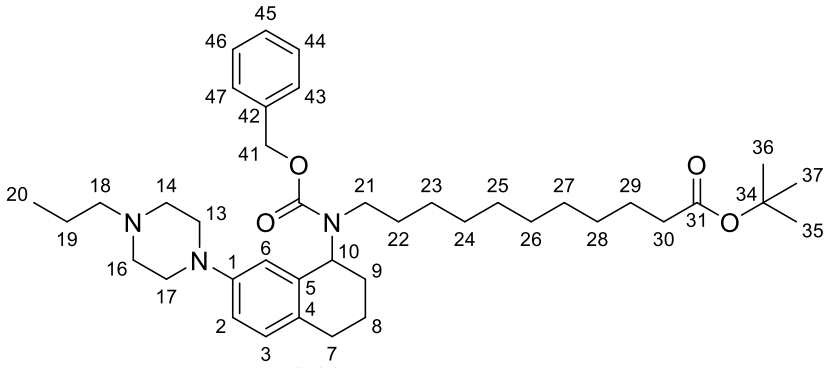


2.82

***tert*-Butyl 6-(((benzyloxy)carbonyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)hexanoate (2.82). KTL-03-098.** A solution of amine **2.80** (37 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and *i*Pr_2NEt (22 mg, 0.17 mmol) and Cbz-Cl (30 mg, 0.17 mmol) were added. The reaction was stirred at room temperature for 1 h. The reaction was quenched with sat $NaHCO_3$ (1 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography eluting with EtOAc:TEA:hexanes (10:1:89) to give 37 mg (77%) of **2.82** as a light yellow oil: ^{1}H NMR (400 MHz) δ 7.43 – 7.24 (comp, 5 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.76 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.58 (s, 1 H), 5.41 – 5.01 (comp, 3 H), 3.26 – 2.99 (comp, 5 H), 2.72 – 2.59 (comp, 3 H), 2.55 (q, *J* = 4.5, 3.9 Hz, 4 H), 2.38 – 2.30 (comp, 2 H), 2.13 (dt, *J* = 25.2, 7.5 Hz, 2 H), 2.06 – 1.91 (comp, 2 H), 1.85 – 1.62 (comp, 3 H), 1.52 (comp, 5 H), 1.42 (s, 9 H), 1.26 – 1.10 (comp, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 173.0, 172.9, 157.1, 156.5, 149.8, 149.7, 137.1, 136.9, 136.4, 129.8, 129.7, 129.3, 128.5, 128.4, 127.8, 127.8, 115.6, 115.3, 114.3, 113.8,

80.0, 79.9, 67.0, 66.9, 60.7, 56.3, 53.2, 49.5, 49.4, 44.6, 35.5, 35.3, 30.1, 29.7, 29.5, 29.1, 28.7, 28.6, 28.1, 26.7, 24.8, 24.6, 22.6, 22.3, 20.0, 12.0; HRMS (ESI) *m/z* $C_{35}H_{51}N_3O_4$ $(M+H)^+$ calcd for 578.3952; found 578.3954.

NMR Assignment. : ^{1}H NMR (400 MHz) δ 7.43 – 7.24 (comp, 5 H, C38-H thru C42-H), 6.97 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.76 (dd, *J* = 8.4, 2.6 Hz, 1 H, C2-H), 6.58 (s, 1 H, C6-H), 5.41 – 5.01 (comp, 3 H, C10-H and C36-H), 3.26 – 2.99 (comp, 5 H, C13-H, C17-H, and C21-H), 2.72 – 2.59 (comp, 3 H, C7-H and C21-H), 2.55 (q, *J* = 4.5, 3.9 Hz, 4 H, C14-H and C16-H), 2.38 – 2.30 (comp, 2 H, C18-H), 2.13 (dt, *J* = 25.2, 7.5 Hz, 2 H, C25-H), 2.06 – 1.91 (comp, 2 H, C9-H), 1.85 – 1.62 (comp, 3 H, C8-H, and C24-H), 1.52 (comp, 5 H, C8-H and C22-H), 1.42 (s, 9 H, C30-H thru C32-H,), 1.26 – 1.10 (comp, 2 H, C23-H), 0.93 (t, *J* = 7.4 Hz, 3 H, C20-H); ^{13}C NMR (101 MHz, rotamers) δ 173.0 (C30 thru C32), 172.9(C30 thru C32), 157.1 (C33), 156.5 (C33), 149.8 (C1), 149.7 (C1), 137.1 (C4), 136.9 (C4), 136.4 (C37), 129.8 (C3), 129.7 (C3), 129.3 (C5), 128.5 (C39 and C41), 128.4 (C39 and C41), 127.8 (C38, C40, and C42), 127.8 (C38, C40, and C42), 115.6 (C2), 115.3 (C2), 114.3 (C6), 113.8 (C6), 80.0 (C29), 79.9 (C29), 67.0 (C36), 66.9 (C36), 60.7 (C18), 56.3 (C10), 53.2 (C14 and C16), 49.5 (C13 and C17), 49.4 (C13 and C17), 44.6 (C21), 35.5 (C25), 35.3 (C25), 30.1 (C22), 29.5 (C9), 29.1 (C9), 28.7 (C7), 28.6 (C7), 28.1 (C30 thru C32), 26.7 (C23), 24.8 (C24), 24.6 (C24), 22.6 (C8), 22.3 (C8), 20.0 (C19), 12.0 (C20).



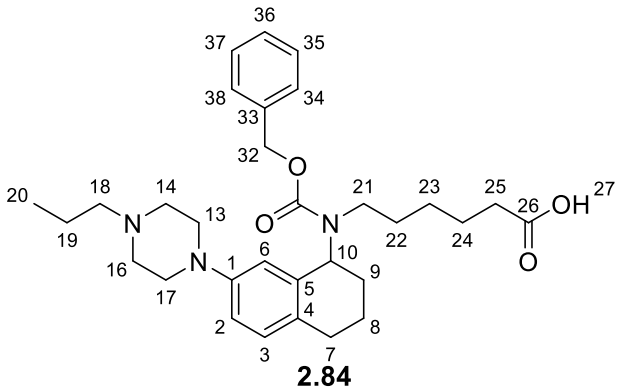
2.83

***tert*-Butyl 11-(((benzyloxy)carbonyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)undecanoate (2.83). KTL-03-104.** Prepared according to the representative procedure outlined for -Cbz protection. The crude mixture was purified via flash column chromatography eluting EtOAc:TEA:hexanes (10:1:89) to give 46 mg (76%) of **2.83** as a light yellow oil: ^{1}H NMR (400 MHz) δ 7.43 – 7.19 (comp, 5 H), 6.97 (d, *J* = 8.7 Hz, 1 H), 6.76 (dd, *J* = 8.3, 2.5 Hz, 1 H), 6.59 (d, *J* = 2.4 Hz, 1 H), 5.42 – 5.01 (comp, 3 H), 3.29 – 3.00 (comp, 6 H), 2.85 – 2.50 (comp, 8 H), 2.38 – 2.32 (comp, 2 H), 2.19 (t, *J* = 7.5 Hz, 2 H), 2.11 – 1.99 (m, 1 H), 1.99 – 1.90 (m, 1 H), 1.76 (comp, 3 H), 1.55 (p, *J* = 7.4 Hz, 6 H), 1.44 (s, 11 H), 1.32 – 1.04 (comp, 15 H), 0.93 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, rotamers) δ 173.3, 157.2, 156.4, 149.8, 149.7, 137.2, 136.9, 136.5, 129.8, 129.7, 128.4, 128.3, 127.8, 127.8, 115.6, 115.2, 114.3, 113.8, 79.8, 66.9, 66.8, 60.7, 56.3, 53.2, 49.5, 49.4, 44.8, 35.6, 30.4, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 28.6, 28.1, 27.2, 25.1, 22.6, 22.3, 20.0, 12.0; HRMS (ESI) *m/z* $C_{40}H_{61}N_3O_4$ $(M+H)^+$ calcd for 648.4735; found 648.4739.

NMR Assignment. : ^{1}H NMR (400 MHz) δ 7.43 – 7.19 (comp, 5 H, C43-H thru C47-H), 6.97 (d, *J* = 8.7 Hz, 1 H, C3-H), 6.76 (dd, *J* = 8.3, 2.5 Hz, 1 H, C2-H), 6.59 (d, *J*

= 2.4 Hz, 1 H, C6-H), 5.42 – 5.01 (comp, 3 H, C10-H and C41-H), 3.29 – 3.00 (comp, 5 H, C13-H, C17-H, and C21-H), 2.85 – 2.50 (comp, 7 H, C7-H, C14-H, C16-H, and C21-H), 2.38 – 2.32 (comp, 2 H, C18-H), 2.19 (t, *J* = 7.5 Hz, 2 H, C30-H), 2.11 – 1.99 (m, 1 H, C9-H), 1.99 – 1.90 (m, 1 H, C8-H), 1.76 (comp, 3 H, C8-H and C9-H), 1.55 (p, *J* = 7.4 Hz, 6 H, C19-H, C22-H and C29-H), 1.44 (s, 11 H, C35-H thru C37-H), 1.32 – 1.04 (comp, 15 H, C23-H thru C28-H), 0.93 (t, *J* = 7.4 Hz, 3 H, C20-H); ^{13}C NMR (101 MHz, rotamers) δ 173.3 (C31), 157.2 (C11), 156.4 (C11), 149.8 (C1), 149.7 (C1), 137.2 (C4), 136.9 (C4), 136.5 (C42), 129.8 (C3), 129.7 (C5), 128.4 (C44 and C46), 128.3 (C44 and C46), 127.8 (C43, C45, and C47), 127.8 (C43, C45, and C47), 115.6 (C2), 115.2 (C2), 114.3 (C6), 113.8 (C6), 79.8 (C34), 66.9 (C41), 66.8 (C41), 60.7 (C18), 56.3 (C10), 53.2 (C14 and C16), 49.5 (C13 and C17), 49.4 (C13 and C17), 44.8 (C21), 35.6 (C30), 30.4 (C22), 29.5 (C9), 29.5 (C25), 29.4 (C26), 29.3 (C9), 29.2 (C24), 29.1 (C28), 28.7 (C7), 28.6 (C7), 28.1 (C35 thru C37), 27.2 (C23), 25.1 (C29), 22.6 (C8), 22.3 (C8), 20.0 (C19), 12.0 (C20).

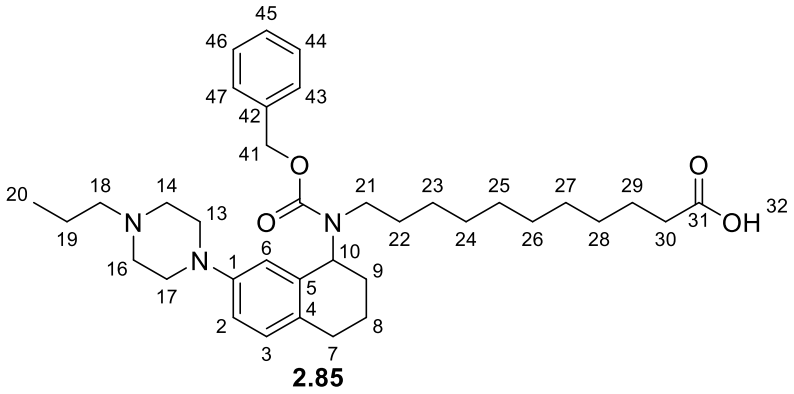
Representative procedure for deprotection of *tert*-butyl ester



2.84

6-(((Benzyloxy)carbonyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)hexanoic acid (2.84). KTL-03-143. TFA (0.8 mL) was added dropwise to a

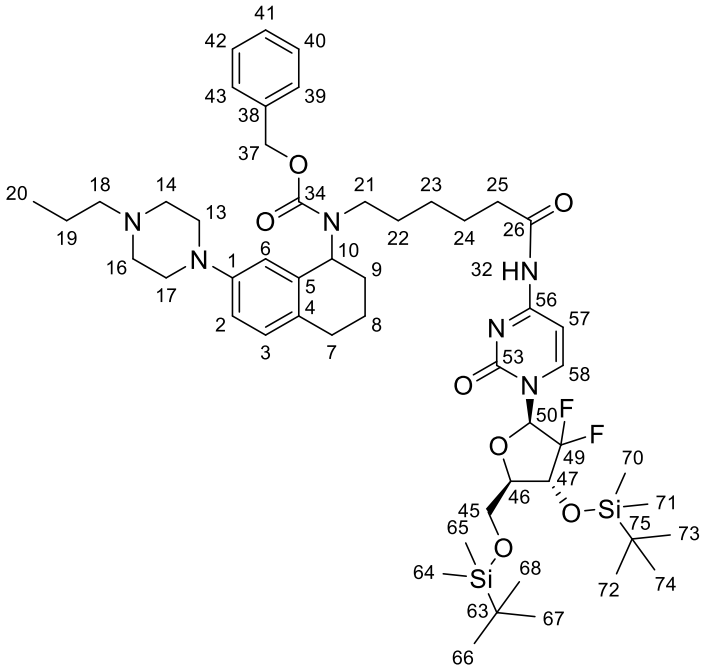
solution of carbamate **2.82** (129 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred at room temperature overnight. The reaction was concentrated and dried under vacuum overnight. The crude residue was taken up in CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_{3(aq)}$ (2 x 2 mL) and 1M $HCl_{(aq)}$ (2 x 2 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 118 mg (95%) of **2.84** as the HCl salt as a brown foam that turned to an oil: ^{1}H NMR (499 MHz, rotamers) δ 7.41 – 7.27 (comp, 4 H), 7.21 – 7.07 (m, 1 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 6.74 (d, *J* = 8.3 Hz, 1 H), 6.63 (s, 1 H), 5.33 – 4.83 (comp, 3 H), 3.64 – 3.5 (comp, 2 H), 3.53 – 3.28 (comp, 4 H), 3.25 – 3.03 (m, 1 H), 2.98 (t, *J* = 8.5 Hz, 4 H), 2.82 (d, *J* = 8.6 Hz, 1 H), 2.76 – 2.57 (m, 2 H), 2.27 (m, 1 H), 2.20 (m, 1 H), 2.02 (m, 1 H), 1.93 (dq, *J* = 12.3, 7.6, 7.0 Hz, 3 H), 1.84 – 1.62 (m, 2 H), 1.62 – 1.41 (m, 4 H), 1.32 – 1.24 (m, 1 H), 1.21 – 1.10 (m, 1 H), 1.00 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (126 MHz, rotamers) δ 177.0, 157.0, 156.5, 147.6, 147.1, 137.6, 137.1, 136.9, 136.7, 132.2, 131.8, 130.2, 128.5, 128.4, 128.0, 127.9, 116.4, 116.2, 115.6, 67.2, 67.0, 58.9, 57.1, 56.5, 51.6, 47.4, 46.9, 46.8, 44.9, 33.8, 29.7, 29.0, 28.7, 28.6, 26.6, 24.4, 24.3, 22.3, 22.2, 17.1, 11.2; HRMS (ESI) *m/z* $C_{31}H_{43}N_3O_4$ $(M+H)^+$ calcd for 522.3326; found 522.3331.



2.85

11-(((Benzyloxy)carbonyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)undecanoic acid (2.85). KTL-03-149. Prepared according to the representative procedure outlined for deprotection of *tert*-butyl ester. Compound **2.85** was isolated as the HCl salt (148 mg, 97%) as a brown foam that turned to an oil: ^{1}H NMR (499 MHz, rotamers) δ 7.45 – 7.08 (m, 5 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 6.71 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.55 (d, *J* = 4.6 Hz, 1 H), 5.37 – 4.99 (comp, 3 H), 3.72 – 3.52 (comp, 2 H), 3.51 – 3.32 (comp, 4 H), 3.30 – 3.16 (m, 1 H), 3.16 – 3.06 (m, 1 H), 3.06 – 2.75 (comp, 4 H), 2.75 – 2.59 (comp, 2 H), 2.29 (t, *J* = 7.4 Hz, 2 H), 2.09 – 2.00 (m, 1 H), 2.00 – 1.87 (comp, 3 H), 1.87 – 1.65 (comp, 2 H), 1.58 (p, *J* = 7.3 Hz, 2 H), 1.54 – 1.38 (m, 1 H), 1.38 – 1.05 (comp, 13 H), 1.00 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, rotamers) δ 177.9, 177.9, 157.2, 156.4, 147.8, 147.5, 137.1, 137.0, 136.8, 131.7, 131.4, 130.1, 128.5, 128.4, 127.9, 127.9, 127.8, 115.9, 115.6, 115.5, 67.1, 66.9, 58.8, 58.8, 56.2, 51.6, 51.5, 46.8, 44.9, 34.1, 30.3, 29.7, 29.3, 29.3, 29.2, 29.2, 29.1, 29.0, 29.0, 28.9, 28.8, 28.7, 28.6, 27.1, 24.8, 22.4, 22.3, 17.1, 11.2; HRMS (ESI) *m/z* $C_{36}H_{53}N_3O_4$ $(M+Na)^+$ calcd for 614.3941; found 614.3928.

Representative procedure for gemcitabine conjugation



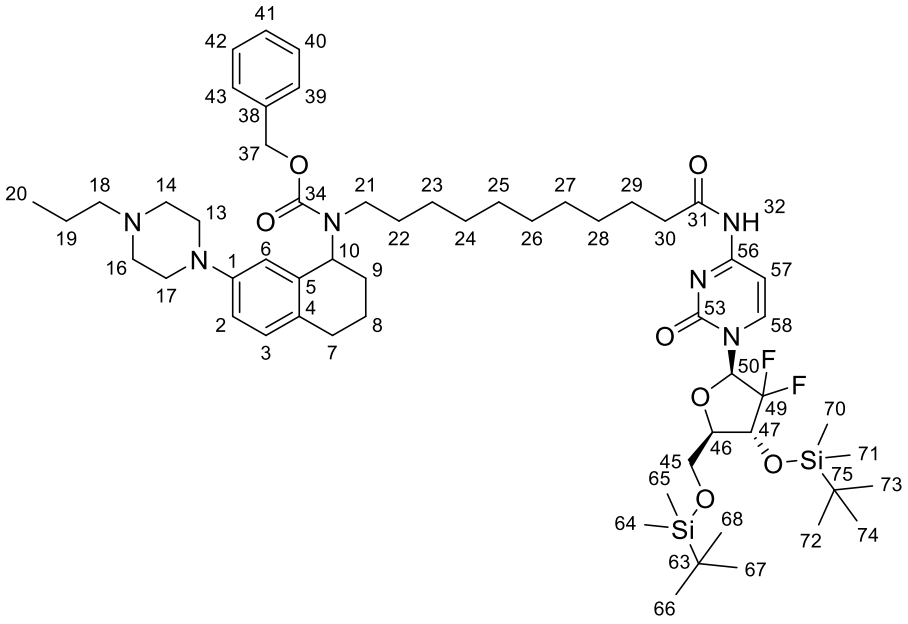
2.88

Benzyl (11-((1-((2R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-11-oxoundecyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (2.88). KTL-03-158. A solution of **2.84** (49 mg, 0.09 mmol), TBS-gemcitabine (25 mg, 0.05 mmol), EDCI·HCl (43 mg, 0.22 mmol), and HOBt (24 mg, 0.17 mmol) in THF (0.6 mL) was stirred at room temperature for 16 h under an atmosphere of N_2. The reaction was concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting EtOAc:TEA:hexanes (30:1:69) to give 38 mg (77%) of **2.88** as a yellow oil: ^{1}H NMR (499 MHz, rotamers) δ 8.05 (d, *J* = 7.6 Hz, 1 H), 7.44 – 7.22 (comp, 6 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 6.78 (d, *J* =

5.0 Hz, 1 H), 6.63 – 6.55 (m, 1 H), 6.33 (dd, *J* = 10.4, 3.5 Hz, 1 H), 5.43 – 5.01 (comp, 3 H), 4.33 (td, *J* = 11.5, 8.1 Hz, 1 H), 4.02 (dd, *J* = 12.0, 2.2 Hz, 1 H), 3.95 (d, *J* = 8.2 Hz, 1 H), 3.80 (dd, *J* = 11.9, 1.9 Hz, 1 H), 3.20 – 3.01 (comp, 5 H), 2.92 – 2.60 (comp, 3 H), 2.57 (q, *J* = 5.5 Hz, 4 H), 2.41 (t, *J* = 7.6 Hz, 1 H), 2.37 – 2.28 (comp, 3 H), 2.07 – 1.98 (m, 1 H), 1.97 – 1.88 (m, 1 H), 1.87 – 1.66 (comp, 3 H), 1.66 – 1.59 (comp, 2 H), 1.54 (dq, *J* = 14.3, 7.2 Hz, 5 H), 1.32 – 1.22 (m, 2 H), 1.22 – 1.11 (m, 1 H), 1.00 – 0.84 (m, 22 H), 0.27 – -0.00 (m, 12 H); ^{13}C NMR (126 MHz, rotamers) δ 173.6, 162.9, 157.2, 156.5, 154.9, 149.8, 149.7, 143.9, 137.1, 136.9, 136.7, 136.3, 129.9, 129.8, 129.4, 128.5, 128.4, 127.9, 127.8, 124.0, 121.9, 119.9, 115.8, 115.5, 114.4, 113.9, 96.9, 85.0, 84.8, 84.6, 84.4, 81.4, 81.3, 69.6, 69.5, 69.4, 69.3, 67.0, 66.9, 60.7, 60.0, 56.8, 56.3, 53.2, 49.5, 49.4, 45.9, 44.4, 37.3, 37.2, 29.5, 29.1, 28.9, 28.7, 28.6, 26.4, 26.3, 25.9, 25.5, 24.15, 24.07, 22.5, 22.3, 20.0, 18.3, 18.0, 12.0, -4.8, -5.3, -5.44, -5.45; HRMS (ESI) *m/z* $C_{52}H_{80}F_2N_6O_7Si_2$ $(M+Na)^+$ calcd for 1017.5499; found 1017.5487.

NMR Assignment. ^{1}H NMR (499 MHz, rotamers) δ 8.05 (d, *J* = 7.6 Hz, 1 H, C58-H), 7.44 – 7.22 (comp, 6 H, C39-H thru C43-H and C57-H), 6.97 (d, *J* = 8.3 Hz, 1 H, C3-H), 6.78 (d, *J* = 5.0 Hz, 1 H, C2-H), 6.63 – 6.55 (m, 1 H, C6-H), 6.33 (dd, *J* = 10.4, 3.5 Hz, 1 H, C50-H), 5.43 – 5.01 (comp, 3 H, C10-H and C37-H), 4.33 (td, *J* = 11.5, 8.1 Hz, 1 H, C46-H), 4.02 (dd, *J* = 12.0, 2.2 Hz, 1 H, C45-H), 3.95 (d, *J* = 8.2 Hz, 1 H, C47-H), 3.80 (dd, *J* = 11.9, 1.9 Hz, 1 H, C45-H), 3.20 – 3.01 (comp, 5 H, C13-H, C17-H, and C21-H), 2.92 – 2.60 (comp, 3 H, C7-H and C21-H), 2.57 (q, *J* = 5.5 Hz, 4 H, C14-H and C16-H), 2.41 (t, *J* = 7.6 Hz, 1 H, C25-H), 2.37 – 2.28 (comp, 3 H, C18-H and C25-H), 2.07 – 1.98 (m, 1 H, C9-H), 1.97 – 1.88 (m, 1 H, C8-H), 1.87 – 1.66 (comp, 3 H, C8-H and C9-H),

1.66 – 1.59 (comp, 2 H, C22-H), 1.54 (dq, *J* = 14.3, 7.2 Hz, 5 H, C19-H and C24-H), 1.32 – 1.22 (m, 2 H, C23-H), 1.22 – 1.11 (m, 1 H, C23-H), 1.00 – 0.84 (m, 22 H, C20-H, C66-H thru C68-H, and C72-H thru C74-H), 0.27 – -0.00 (m, 12 H, C64-H, C65-H, C70-H, and C71-H); ^{13}C NMR (126 MHz, rotamers) δ 173.6 (C26), 162.9 (C56), 157.2 (C34), 156.5 (C34), 154.9 (C53), 149.8 (C1), 149.7 (C1), 143.9 (C58), 137.1 (C4), 136.9 (C4), 136.7 (C38), 136.3 (C38), 129.9 (C3), 129.8 (C5), 129.4 (C3), 128.5 (C40 and C42), 128.4 (C40 and C42), 127.9 (C39, C41, and C43), 127.8 (C39, C41, and C43), 124.0 (C49), 121.9 (C49), 119.9 (C49), 115.8 (C2), 115.5 (C2), 114.4 (C6), 113.9 (C6), 96.9 (C57), 85.0 (C50), 84.8 (C50), 84.6 (C50), 84.4 (C50), 81.4 (C47), 81.3 (C47), 69.6 (C46), 69.5 (C46), 69.4 (C46), 69.3 (C46), 67.0 (C37), 66.9 (C37), 60.7 (C18), 60.0 (C45), 56.8 (C10), 56.3 (C10), 53.2 (C14 and C16), 49.5 (C13 and C17), 49.4 (C13 and C17), 45.9 (C21), 44.4 (C21), 37.3 (C25), 37.2 (C25), 29.5 (C22), 29.1 (C22), 28.9 (C9), 28.7 (C9), 28.7 (C7), 28.6 (C7), 26.4 (C23), 26.3 (C23), 25.9 (C66 thru C68 and C72 thru C74), 25.5 (C66 thru C68 and C72 thru C74), 24.15 (C24), 24.07 (C24), 22.5 (C8), 22.3 (C8), 20.0 (C19), 18.3 (C63 or C75), 18.0 (C63 or C75), 12.0 (C20), -4.8 (C64, C65, C70, and C71), -5.3 (C64, C65, C70, and C71), -5.44 (C64, C65, C70, and C71), -5.45 (C64, C65, C70, and C71).



2.89

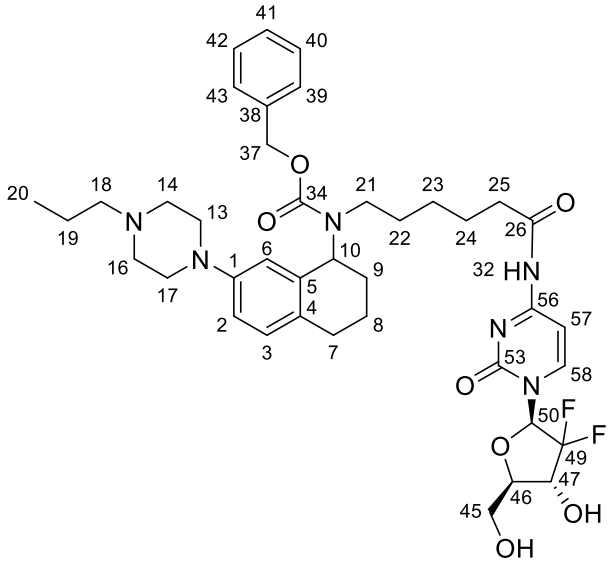
Benzyl (11-((1-((2R,4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-11-oxoundecyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (2.89). KTL-03-151. Prepared according to the representative procedure outlined for gemcitabine conjugation. The crude residue was purified by flash column chromatography eluting EtOAc:TEA:hexanes (30:1:69) to give 48 mg (74%) of **2.89** as a yellow oil: ^{1}H NMR (499 MHz, rotamers) δ 8.96 (s, 1 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 7.47 – 7.22 (comp, 6 H), 6.97 (dd, *J* = 8.6, 2.1 Hz, 1 H), 6.76 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.59 (d, *J* = 2.6 Hz, 1 H), 6.33 (dd, *J* = 10.4, 3.5 Hz, 1 H), 5.41 – 5.01 (comp, 3 H), 4.33 (td, *J* = 11.6, 8.1 Hz, 1 H), 4.02 (d, *J* = 11.9 Hz, 1 H), 3.95 (d, *J* = 8.1 Hz, 1 H), 3.81 (dd, *J* = 11.9, 2.0 Hz, 1 H), 3.26 – 3.09 (m, 1 H), 3.09 – 2.98 (comp, 4 H), 2.84 – 2.58 (comp, 3 H), 2.55 (q, *J* = 4.6 Hz, 4 H), 2.44 (td, *J* = 7.4, 4.7 Hz, 2 H), 2.37 –

2.31 (comp, 2 H), 2.04 (s, 1 H), 1.95 (s, 1 H), 1.83 (s, 2 H), 1.74 (s, 2 H), 1.65 (p, *J* = 7.5 Hz, 3 H), 1.54 (p, *J* = 7.6 Hz, 2 H), 1.50 – 1.41 (m, 1 H), 1.36 – 1.04 (m, 15 H), 0.97 – 0.85 (m, 22 H), 0.15 – 0.08 (m, 12 H); ^{13}C NMR (126 MHz, rotamers) δ 176.2, 173.5, 162.6, 157.2, 156.5, 154.8, 149.8, 149.6, 144.1, 137.2, 137.0, 136.5, 129.9, 129.7, 129.4, 128.4, 128.37, 127.8, 124.0, 121.9, 119.8, 115.6, 115.2, 114.4, 113.9, 96.7, 85.0, 84.8, 84.6, 84.4, 81.4, 69.7, 69.4, 69.3, 66.9, 66.8, 60.6, 60.0, 56.9, 56.3, 53.1, 49.3, 45.6, 44.8, 37.7, 30.4, 29.7, 29.5, 29.3, 29.0, 28.7, 27.2, 25.9, 25.5, 24.8, 22.6, 22.4, 19.9, 18.3, 18.0, 12.0, -4.8, -5.3, -5.4; HRMS (ESI) *m/z* $C_{57}H_{90}F_2N_6O_7Si_2$ $(M+Na)^+$ calcd for 1087.6290; found 1087.6270.

NMR Assignment. ^{1}H NMR (499 MHz, rotamers) δ 8.96 (s, 1 H, C58-H), 8.07 (d, *J* = 7.6 Hz, 1 H, C57-H), 7.47 – 7.22 (comp, 6 H, C39-H thru C43-H), 6.97 (dd, *J* = 8.6, 2.1 Hz, 1 H, C3-H), 6.76 (dd, *J* = 8.5, 2.5 Hz, 1 H, C2-H), 6.59 (d, *J* = 2.6 Hz, 1 H, C6-H), 6.33 (dd, *J* = 10.4, 3.5 Hz, 1 H, C50-H), 5.41 – 5.01 (comp, 3 H, C10-H and C37-H), 4.33 (td, *J* = 11.6, 8.1 Hz, 1 H, C46-H), 4.02 (d, *J* = 11.9 Hz, 1 H, C45-H), 3.95 (d, *J* = 8.1 Hz, 1 H, C47-H), 3.81 (dd, *J* = 11.9, 2.0 Hz, 1 H, C45-H), 3.26 – 3.09 (m, 1 H, C21-H), 3.09 – 2.98 (comp, 4 H, C13-H and C17-H), 2.84 – 2.58 (comp, 3 H, C7-H and C21-H), 2.55 (q, *J* = 4.6 Hz, 4 H, C14-H and C16-H), 2.44 (td, *J* = 7.4, 4.7 Hz, 2 H, C30-H), 2.37 – 2.31 (comp, 2 H, C18-H), 2.04 (s, 1 H, C9-H), 1.95 (s, 1 H, C8-H), 1.83 (s, 2 H, C21-H), 1.74 (s, 2 H, C8-H and C9-H), 1.65 (p, *J* = 7.5 Hz, 3 H, C29-H), 1.54 (p, *J* = 7.6 Hz, 2 H, C19-H), 1.50 – 1.41 (m, 1 H, C21-H), 1.36 – 1.04 (m, 15 H, C23-H thru C28-H), 0.97 – 0.85 (m, 22 H, C20-H, C66-H thru C68-H, and C72-H thru C74-H), 0.15 – 0.08 (m, 12 H, C64-H, C65-H, C70-H, and C71-H); ^{13}C NMR (126 MHz, rotamers) δ 176.2 (C31), 173.5(C31),

162.6 (C56), 157.2 (C34), 156.5 (C34), 154.8 (C53), 149.8 (C1), 149.6 (C1), 144.1 (C58), 137.2 (C34), 137.0 (C34), 136.5 (C4), 129.9 (C5), 129.7 (C3), 129.4 (C4), 128.4, 128.37, 127.8, 124.0 (C49), 121.9 (C49), 119.8 (C49), 115.6 (C2), 115.2 (C2), 114.4 (C6), 113.9 (C6), 96.7 (C57), 85.0 (C50), 84.8 (C50), 84.6 (C50), 84.4 (C50), 81.4 (C47), 69.7 (C46), 69.4 (C46), 69.3 (C46), 66.9 (C37), 66.8 (C37), 60.6 (C18), 60.0 (C45), 56.9 (C10), 56.3 (C10), 53.1 (C14 and C16), 49.3 (C13 and C17), 45.6 (C21), 44.8 (C21), 37.7 (C30), 30.4 (C22), 29.7 (C9), 29.5 (C9), 29.3 (C24 thru C28), 29.0 (C24 thru C28), 28.7 (C7), 27.2 (C7), 25.9 (C66 thru C68 and C72 thru C74), 25.5 (C66 thru C68 and C72 thru C74), 24.8 (C29), 22.6 (C8), 22.4 (C8), 19.9 (C19), 18.3 (C63 or C75), 18.0 (C63 or C75), 12.0 (C20), -4.8 (C64, C65, C70, and C71), -5.3 (C64, C65, C70, and C71), -5.4 (C64, C65, C70, and C71).

Representative procedure for TBAF deprotection



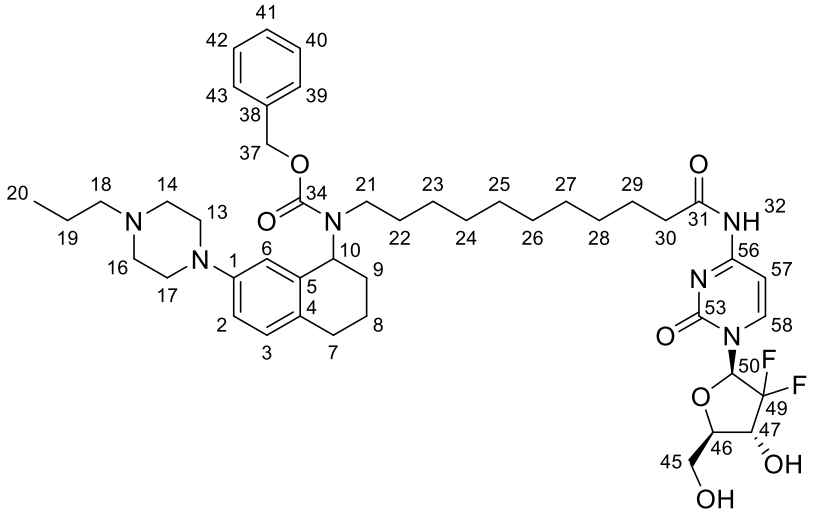
2.90

Benzyl (6-((1-((2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-6-oxohexyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (2.90). KTL-03-152. TBAF (90 mL, 1M solution in THF) was added to a solution of **2.88** (34 mg, 0.03 mmol) in THF (1.5 mL). The reaction was stirred at room temperature for 1 h and concentrated under reduced pressure. The crude residue was purified by HPLC using a solvent gradient of MeCN (0.1%TFA)/H_2O (0.1% TFA) 10:90 to MeCN (0.1%TFA)/H_2O (0.1% TFA) 95:5 over 30 min. The product containing fractions were combined and basified with sat. $NaHCO_{3(aq)}$ and the MeCN was removed under reduced pressure. The resulting aqueous fraction was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to

give 15 mg (65%) of **2.90** as a white solid: ^{1}H NMR (499 MHz, rotamers) δ 8.09 (d, *J* = 7.5 Hz, 1 H), 7.45 – 7.15 (comp, 6 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.79 – 6.74 (m, 1 H), 6.59 – 6.51 (m, 1 H), 6.22 (s, 1 H), 5.37 – 5.00 (comp, 3 H), 4.46 (s, 1 H), 4.05 – 3.96 (comp, 2 H), 3.87 (d, *J* = 12.7 Hz, 1 H), 3.15 (s, 1 H), 3.10 – 2.96 (comp, 5 H), 2.82 – 2.50 (comp, 8 H), 2.44 – 2.25 (comp, 5 H), 2.01 (s, 1 H), 1.93 (s, 1 H), 1.83 – 1.64 (comp, 3 H), 1.64 – 1.46 (comp, 7 H), 1.24 (s, 5 H), 1.14 (s, 2 H), 0.92 (t, *J* = 7.4 Hz, 4 H); ^{13}C NMR (126 MHz, rotamers) δ 173.9, 173.8, 163.1, 157.3, 156.7, 155.6, 155.4, 149.7, 149.4, 145.0, 137.0, 136.6, 136.3, 130.1, 129.9, 128.5, 128.4, 127.9, 127.7, 124.7, 122.6, 120.5, 116.1, 115.9, 114.4, 113.9, 113.8, 97.4, 85.4, 81.6, 68.6, 68.5, 68.3, 67.1, 60.6, 59.4, 56.9, 56.4, 53.1, 49.3, 45.8, 44.5, 37.2, 29.7, 29.4, 29.0, 28.7, 28.6, 26.4, 26.3, 24.1, 22.4, 22.3, 19.7, 11.9; HRMS (ESI) *m/z* $C_{40}H_{52}F_2N_6O_7$ $(M+H)^+$ calcd for 767.3938; found 767.3950.

NMR Assignment. ^{1}H NMR (499 MHz, rotamers) δ 8.09 (d, *J* = 7.5 Hz, 1 H, C58-H), 7.45 – 7.15 (comp, 6 H, C39-H thru C43-H and C57-H), 6.96 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.79 – 6.74 (m, 1 H, C2-H), 6.59 – 6.51 (m, 1 H, C6-H), 6.22 (s, 1 H, C50-H), 5.37 – 5.00 (comp, 3 H, C10-H and C37-H), 4.46 (s, 1 H, C46-H), 4.05 – 3.96 (comp, 2 H, C45-H and C47-H), 3.87 (d, *J* = 12.7 Hz, 1 H, C45-H), 3.15 (s, 1 H, C21-H), 3.10 – 2.96 (comp, 5 H, C13-H and C17-H), 2.82 – 2.50 (comp, 8 H, C7-H, C14-H, C16-H, and C21-H), 2.44 – 2.25 (comp, 5 H, C18-H and C25-H), 2.01 (s, 1 H, C9-H), 1.93 (s, 1 H, C8-H), 1.83 – 1.64 (comp, 3 H, C8-H and C9-H), 1.64 – 1.46 (comp, 7 H, C19-H, C22-H, and C24-H), 1.24 (s, 5 H, C23-H), 1.14 (s, 2 H, C23-H), 0.92 (t, *J* = 7.4 Hz, 4 H, C20-H); ^{13}C NMR (126 MHz, rotamers) δ 173.9 (C26), 173.8 (C26), 163.1 (C56), 157.3 (C34), 156.7 (C34), 155.6 (C53), 155.4 (C53), 149.7 (C1), 149.4 (C1), 145.0 (C58), 137.0 (C4), 136.6 (C5 and

C37), 136.3 (C37), 130.1 (C5), 129.9 (C3), 128.5 (C40 and C42), 128.4 (C40 and C42), 127.9 (C39, C41, and C43), 127.7, 124.7 (C49), 122.6 (C49), 120.5 (C49), 116.1 (C2), 115.9 (C2), 114.4 (C6), 113.9 (C6), 113.8 (C6), 97.4 (C57), 85.4 (C50), 81.6 (C47), 68.6 (C46), 68.5 (C46), 68.3 (C46), 67.1 (C37), 60.6 (C18), 59.4 (C45), 56.9 (C10), 56.4 (C10), 53.1 (C14 and C16), 49.3 (C13 and C17), 45.8 (C21), 44.5 (C21), 37.2 (C25), 29.7 (C22), 29.4 (C9), 29.0 (C9), 28.7 (C7), 28.6 (C7), 26.4 (C23), 26.3 (C23), 24.1 (C24), 22.4 (C8), 22.3 (C8), 19.7 (C19), 11.9 (C20).



2.91

Benzyl (11-((1-((2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)amino)-11-oxoundecyl)(7-(4-propylpiperazin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (2.91). KTL-03-153. Prepared according to the representative procedure outlined for TBAF deprotection. The combined organic layers were dried (Na_2SO_4) and

concentrated under reduced pressure to give 20 mg (54%) of **2.91** as a clear oil: ^{1}H NMR (499 MHz, rotamers) δ 8.21 – 8.11 (m, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.41 – 7.12 (m, 5 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 6.80 – 6.72 (m, 1 H), 6.62 – 6.53 (m, 1 H), 6.30 – 6.18 (m, 1 H), 5.40 – 4.98 (m, 3 H), 4.46 (q, *J* = 11.5, 10.7 Hz, 1 H), 4.06 – 3.95 (m, 2 H), 3.87 (d, *J* = 12.1 Hz, 1 H), 3.28 – 2.94 (m, 5 H), 2.85 – 2.62 (m, 3 H), 2.62 – 2.52 (m, 5 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 2.40 – 2.32 (m, 2 H), 2.03 (s, 1 H), 1.95 (s, 1 H), 1.88 – 1.41 (m, 9 H), 1.31 – 1.05 (m, 15 H), 0.92 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (126 MHz, rotamers) δ 174.1, 173.8, 163.1, 163.0, 157.3, 156.8, 155.5, 149.8, 149.5, 145.1, 137.1, 136.74, 136.67, 136.5, 130.1, 129.8, 128.5, 128.4, 127.9, 127.83, 127.76, 124.5, 122.5, 120.4, 116.0, 115.9, 115.7, 114.5, 114.4, 114.0, 113.9, 97.5, 97.4, 85.4, 81.5, 68.9, 68.7, 68.6, 67.0, 60.6, 59.5, 57.1, 56.4, 53.1, 49.4, 44.9, 37.6, 30.3, 29.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.85, 28.8, 28.7, 28.6, 27.1, 24.7, 22.5, 22.4, 19.7, 12.0; HRMS (ESI) *m/z* $C_{45}H_{62}F_2N_6O_7$ $(M+H)^+$ calcd for 837.4725; found 837.4721.

NMR Assignment. ^{1}H NMR (499 MHz, rotamers) δ 8.21 – 8.11 (m, 1 H, C58-H), 7.45 (d, *J* = 7.6 Hz, 1 H, C57-H), 7.41 – 7.12 (m, 5 H, C39-H thru C43-H), 6.96 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.80 – 6.72 (m, 1 H, C2-H), 6.62 – 6.53 (m, 1 H, C6-H), 6.30 – 6.18 (m, 1 H, C50-H), 5.40 – 4.98 (m, 3 H, C10-H and C37-H), 4.46 (q, *J* = 11.5, 10.7 Hz, 1 H, C46-H), 4.06 – 3.95 (m, 2 H, C45-H and C47-H), 3.87 (d, *J* = 12.1 Hz, 1 H, C45-H), 3.28 – 2.94 (m, 5 H, C13-H, C17-H, and C21-H), 2.85 – 2.62 (m, 3 H, C7-H and C21-H), 2.62 – 2.52 (m, 5 H, C14-H and C16-H), 2.44 (t, *J* = 7.2 Hz, 2 H, C30-H), 2.40 – 2.32 (m, 2 H, C18-H), 2.03 (s, 1 H, C9-H), 1.95 (s, 1 H, C8-H), 1.88 – 1.41 (m, 9 H, C8-H, C9-H, C19-H, C22-H, and C29-H), 1.31 – 1.05 (m, 15 H, C23-H thru C28-H), 0.92 (t, *J* = 7.4 Hz, 3 H,

C20-H); ^{13}C NMR (126 MHz, rotamers) δ 174.1 (C31), 173.8 (C31), 163.1 (C56), 163.0 (C56), 157.3 (C34), 156.8 (C34), 155.5 (C53), 149.8 (C1), 149.5 (C1), 145.1 (C58), 137.1 (C5), 136.74, (C4) 136.67 (C38), 136.5 (C38), 130.1 (C5), 129.8 (C3), 128.5 (C40 and C42), 128.4 (C40 and C42), 127.9 (C39, C41, and C43), 127.83 (C39, C41, and C43), 127.76 (C39, C41, and C43), 124.5 (C49), 122.5 (C49), 120.4 (C49), 116.0 (C2), 115.9 (C2), 115.7 (C2), 114.5 (C6), 114.4 (C6), 114.0 (C6), 113.9 (C6), 97.5 (C57), 97.4 (C57), 85.4 (C50), 81.5 (C47), 68.9 (C46), 68.7 (C46), 68.6 (C46), 67.0 (C37), 60.6 (C18), 59.5 (C45), 57.1 (C10), 56.4 (C10), 53.1 (C14 and C16), 49.4 (C13 and C17), 44.9 (C21), 37.6 (C30), 30.3 (C22), 29.7 (C22), 29.4 (C24 thru C28), 29.3 (C24 thru C28), 29.2 (C24 thru C28), 29.1 (C24 thru C28), 29.0 (C24 thru C28), 28.9 (C9), 28.85 (C9), 28.8 (C9), 28.7 (C7), 28.6 (C7), 27.1, (C23) 24.7 (C29), 22.5 (C8), 22.4 (C8), 19.7 (C19), 12.0 (C20).

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