I. Development of Bisamides as Kappa Opioid Receptor Agonists. II. Potency Enhancement of Sulfonamide-based Kappa Opioid Receptor Antagonists. III. Asymmetric Acyl Transfer Reactions Catalyzed by a Cyclic Peptide.

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Abstract

Development of Bisamides as Kappa Opioid Receptor Agonists. The structure-activity relationship (SAR) expansion was carried out on bisamides KOR agonists. Previous four-step linear synthetic route was replaced by Ugi multicomponent reaction, affording final compound in one step. Parallel synthesis was adopted using Bohdan MiniBlock synthesis platform in combination with subsequent purification with MS-directed HPLC. A total of 80 analogues with diverse substitutions were prepared, including three pairs of enantiomers obtained by chiral HPLC separation of racemic precursors. All of the final compounds were tested in [^{35}S]GTPγS functional assay. Enantiopure analogues were also accessed by βarrestin2 imaging assay. Several analogues with improved potency and bias toward G-protein signaling were obtained. A useful SAR was established based on the biological results obtained, which would direct the study of this chemotype in future.

Potency Enhancement of Sulfonamide-based Kappa Opioid Receptor Antagonists. Structural modification on a sulfonamide-based KOR antagonists was accomplished. A total of 34 analogues were prepared through linker replacement, constraint manipulation, and substitution introduction. All of the final compounds were assayed using a DiscoveRx PathHunter β-arrestin assay platform. One compound with four-fold increase of potency (IC_{50} = 18.9 ± 4 nM) was obtained, compared with the lead compound (IC_{50} = 83.5 ± 20.3 nM). A putative binding mode of sulfonamide analogues with the KOR were generated based on the data obtained previously and this study. The enriched SAR and putative binding mode provide insights into the interactions between sulfonamide analogues and the KOR which will direct further study on this chemotype.

Asymmetric Acyl Transfer Reactions Catalyzed by a Cyclic Peptide. Kinetic resolution of secondary alcohols by a cyclic peptide was described. The cyclic peptide was designed as a modified version of Miller's peptide catalyst, which was synthesized in five steps. Single crystal X-ray experiments demonstrated that it adopted a conformation close to type II β-turn. Selectivity of this proposed catalyst was examined on five secondary alcohols, with best selectivity factor as about 24.

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Chapter 1

Development of Bisamides as Kappa Opioid Receptor Agonists.

Introduction

A Brief History of Opium and Opioid

Opioid receptors are important targets for the treatment of pain. Clinically used analgesics like morphine (Figure 1.1), which was isolated originally from opium, act primarily through the mu opioid receptor (MOR) and remain the gold standard for the treatment of severe pain. Humans have been utilizing opium for religious or therapeutic purposes for a long time.[1] It is believed that the Sumerians, inhabiting what is presently Iraq, cultivated poppies and isolated opium from their seed capsules at the end of the third millennium B.C. They called opium "gil," the word for joy, and the poppy "hul gil," plant for joy. It is suggested that opium originated from Sumeria then spread to the other parts of the old world. Opium was brought to India[2] and China[3] as early as the eighth century A.D., and then spread to all parts of Europe from Anatolia. Originally opium may have been ingested, taken by mouth or inhaled from heated vessel, at religious rituals.[1] It was also used along with hemlock to help people die quickly and painlessly, owning to its known euphoric effect after administration. In addition, it was even used as a remedy to prevent excessive crying of children, in a cautious manner.[4] Nevertheless, opioid drug abuse and tolerance were described in manuscripts in Turkey, Egypt, Germany, and England starting from 16th century. Nowhere was the problem of addiction greater than in China, where smoking opium became popular during the

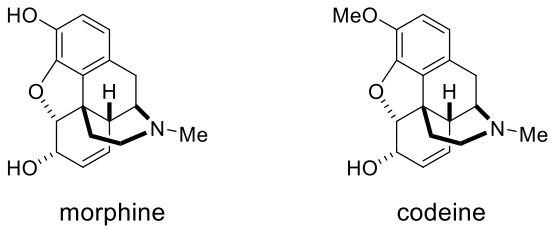
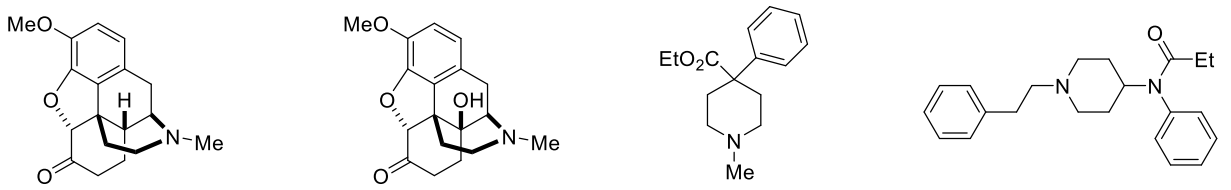


Figure 1.1. Morphine and codeine

mid of 17th century.[3] Unfortunately, the reason and mechanism causing tolerance and dependence were completely unknown at that time.



hydrocodone oxycodone pethidine fentanyl

Figure 1.2. Representatives of semi-synthetic and synthetic opioids

It was not until 1806 that the active ingredient was isolated from opium by Sertürner and named morphine, after the Greek god of dreams, Morpheus.[4] Shortly after its discovery, morphine was used for minor surgical procedures, postoperatives and chronic pain. In addition to morphine, a number of morphine related compounds were identified from opium, including codeine (Figure 1.1) which is a methylated version of morphine used for pain management. Thereafter, medicinal chemistry efforts in the search for non-addictive analgesics yielded thousands of morphine analogues and structurally distinct opioids, including oxycodone, hydrocodone, pethidine, and fentanyl (Figure 1.2). These opioids are all MOR agonists and remain the most prescribed analgesics for the management of pain presently, though high abuse potential remains a concern.

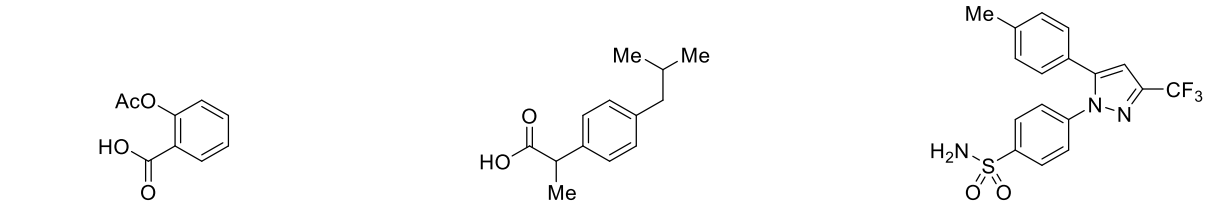
Opioid Receptor Subtypes

Opioid receptors belong to the G protein-coupled receptor superfamily. There are four subtypes of opioid receptors, including mu (μ, MOP), kappa (κ, KOP), delta (δ, DOR), and nociceptin (NOP) opioid receptors. In 1973, three independent teams demonstrated the existence of opioid receptors in the nervous system. Pert and Snyder showed that tritiated naloxone

specifically bound to opioid receptors in both mammalian brain and guinea pig intestine, which supported that the opioid receptor was expressed in the nervous system, although at that time it was unknown which subtype.[5] Soon after that, Simon and coworkers reported the stereospecific binding of tritiated etorphine to rat-brain homogenate.[6] Additionally, Terenius and coworkers reported the stereospecific interaction between tritiated dihydromorphine and synaptic plasma membrane fraction of rat cerebral cortex.[7] These three reports collectively lent strong support to the existence of a specific opioid receptor. A few years later, three distinct opioid receptor types were identified based on physiological observations.[8-9] Each receptor was named after the drug or assay system with which it was characterized: MOP for morphine, KOR for ketocyclazocine, and the DOR for the mouse vas deferens. However, the opioid receptors were solely classified according to the physiology response until the first DOR was cloned in 1992.[10] Though all subtypes of opioid receptors belong to GPCR family and share similar signaling pathways, their outcomes upon agonist binding are different. Activation of the MOR lead to a series of physiological responses including pain relief, euphoria, respiratory depression, immune suppression, and constipation.[11-13] Similarly, activation of the KOR by endogenous ligands dynorphin, typically dynorphin A, could also lead to pain relief and anti-pruritus effect, but dysphoria is another negative effect of its activation.[13-16] The activation of the DOR by its endogenous ligands called enkephalins leads to analgesia, immune stimulation, and respiratory depression,[13,17,18] while the most recently discovered nociceptin receptor regulates a wide range of physiological functions including sensations of pain, food intake, and memory processes.[19-22]

Pain Management and KOR as a Target for Pain Treatments

Pain is usually associated with a wide range of injuries and diseases, and can be considered a disease itself. Acute pain is usually a normal sensation triggered in the nervous system to alert people of possible injury. In other words, acute pain is a necessary and helpful pain and prevents people from further injury.[23] However, chronic pain persists and keeps firing signals in the nervous system for a longer than useful or helpful duration of time.[24] Pain is such a universal response that millions of American people suffer from acute or chronic pain annually.[25] Chronic unrelieved pain often results in longer hospital stays, rehospitalization, and increased outpatient visits. As a result, approximately $635 billion are cost due to pain related problems besides low work productivity. Currently, the analgesics used to alleviate pain can be categorized into two general classes: nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids.



aspirin
non-selective COX inhibitor

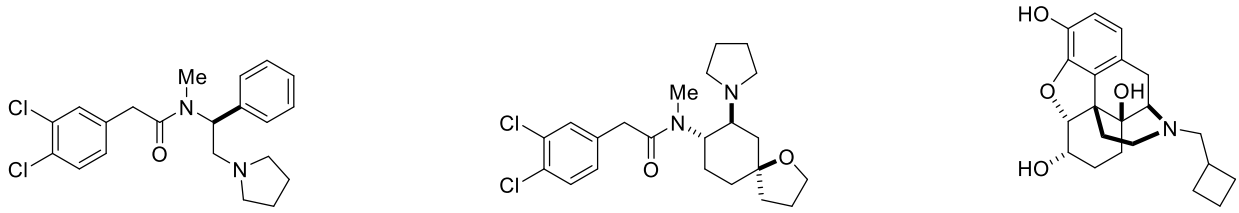
ibuprofen
non-selective COX inhibitor

celecoxib
COX-2-selective inhibitor

Figure 1.3. Representatives of NSAID

NSAIDs, represented by aspirin and ibuprofen (Figure 1.3), are amongst the most commonly used drugs for the treatment of pain associated with inflammation. The target of NSAIDs was identified as the cyclooxygenase (COX) enzyme that was essential in the synthesis of prostaglandin.[26] Thus far, two isoforms of COX are identified in human, which are COX-1 and COX-2.[27,28] Interestingly, COX-1 is expressed constitutively while COX-2 is found in low levels under normal conditions but overexpressed during inflammation.[29] Thus, non-selective inhibition of COX-1/2 for a prolonged period with traditional NSAIDs like aspirin or ibuprofen, is not

preferred and could result in ulcers due to the reduced production of protective prostaglandin found in the stomach lining.[30] COX-2-selective NSAIDs, represented by celecoxib (Figure 1.3), are favored in terms of minimal gastrointestinal side effects.



ICI199,441 spiradoline nalbuphine

Figure 1.4. ICI199,441, spiradoline, and nalbuphine

The opioid class of analgesics has been used for the treatment of pain since the discovery of morphine, and remains the "gold standard" for pain management. However, the use of most opioid analgesics is limited by side effects including addiction potentials, respiratory depression, and constipation.[31] Moreover, use of opioid analgesics leads to development of tolerance and dependence after patients are exposed to these drugs for a long period of time. In the past several decades, tremendous efforts have been spent toward the understanding and development of opioid analgesics with less side effects.[32-36] KOR agonists are of great interest in terms of development of pain-relief treatment without addiction potential, since they do not activate the dopamine reward pathway. KOR agonists alleviated pain with good potency in a wide variety of visceral pain models in which rank order of analgesic potencies were consistent with the results from cloned receptors.[37-39] Furthermore, the analgesic effects of KOR agonists could be blocked by peripherally restricted KOR antagonists, indicating that these KOR agonists exert analgesic effects through periphery neuronal system.[40-43] However, KOR agonists produced side effects like dysphoria,

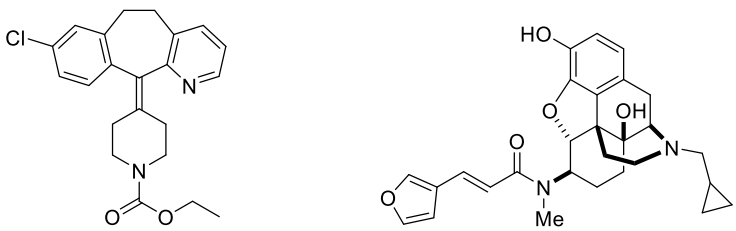
sedation, and diuresis, which led to the discontinuation of several clinical trials (ICI199441, spiradoline, Figure 1.4.).[44-46] Thereafter, research focus shifted to investigation of peripherally selective KOR agonists that would avoid side effects like sedation and dysphoria by not crossing the blood brain barrier.[44] Another attempt to develop analgesics with an ideal pharmacological profile was the development of mixed-efficacy KOR/MOR agonists, which could produce strong analgesic effects devoid of side effects like euphoria and dysphoria. For instance, nalbuphine (Figure 1.4), a mixed-efficacy KOR/MOR agonist, exhibited significant analgesic effects when compared with placebo in a female patient group.[47] However, the difference of analgesic effects between nalbuphine and placebo were not dose dependent in the male group. Furthermore, in this experiment, greater analgesic effects of nalbuphine were observed in female group compared with the male group at all dose levels. Nalbuphine is indicated for the moderate to severe pain, and is the treatment of choice especially in obstetrical analgesia during labor and delivery. Overall, the KOR remains an attractive target in terms of the development of effective analgesic with less side effects, especially less addiction potential.

KOR Potential for the Treatment of Pruritus/Uremic Pruritus

Pruritus is defined as an unpleasant sensation that provokes the desire to scratch, which is the predominant symptom of skin disease and can be caused by a variety of dermatological conditions or systemic disorders like uremia, chronic hepatic obstruction, and haematological disorders, etc.[48-49] However, the pathophysiology of pruritus is still poorly understood, there is no universally accepted therapy and the development of new effective treatment for pruritus is challenging. Uremic pruritus is a common complication of end-stage renal disease (ESRD), which

is observed in about one-third of dialysis patients. The pathogenesis of uremic pruritus is multifaceted and may include uremia-related abnormalities (particularly involving calcium, and phosphorus levels and parathyroid hormone metabolism), accumulation of uremic toxins, systemic inflammation, cutaneous xerosis, and common co-morbidities, such as diabetes mellitus and viral hepatitis. Though the understanding about pathophysiology of uremic pruritus is still not complete, topical and systemic agents, as well as broadband ultraviolet phototherapy, are proven to be beneficial.[50]

The use of antihistamines as systemic agents, especially H_1-receptor antagonists, are supported by an old trial for the treatment of uremic pruritus.[51] However, no significant difference was found between H_1-receptor inverse agonist loratadine and placebo.[52] In clinical setting, antihistamines are still used as first-line therapy for uremic pruritus though frustrating results are often observed and further clinical trials are needed to confirm the effectiveness of this class of drugs.[49]



loratadine nalfurafine

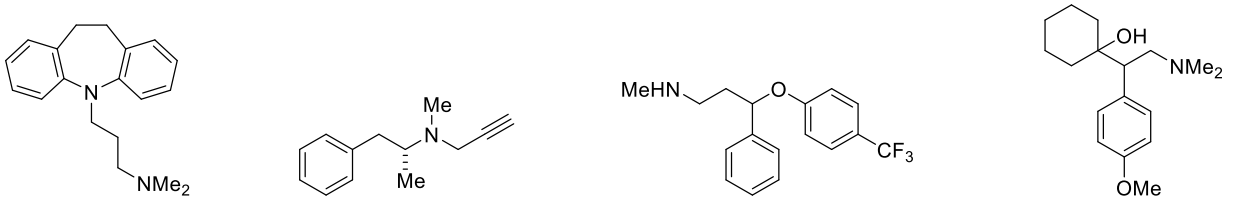
Figure 1.5. Loratadine and nalfurafine

A relatively new hypothesis that has received increased attention is that balance between MOR and KOR can regulate pruritus. This hypothesis was developed based on two main phenomena: (a) itch was induced by central MOR in mice experiments by injecting morphine;[54] (b) dynorphin suppressed itch by binding and activating KOR. In addition, naltrexone as a MOR

antagonist is proven to be effective for the treatment of cholestatic pruritus.[15] In an attempt to develop new analgesics, a synthetic opioid called nalfurafine (Figure 1.5) was discovered.[55-56] In Phase II clinical trials of treating patients of postoperative surgery, nalfurafine possessed sufficient analgesic effect but an insufficient safety margin.[55] However, nalfurafine was shown to suppress the histamine-induced scratching behavior in mice.[56-57] Moreover, this compound was proven to be effective in treating morphine induced scratching behavior in mice, which was resistant to the treatment of antihistamine drugs.[58] Taken together, it is suggested that nalfurafine is more effective than antihistamines at treating opioid-derived pruritus. Thus, nalfurafine was moved to clinical trials aiming at the development of antipruritus agent, followed by confirmation on various animal itching models. It was reported that nalfurafine is significantly effective than placebo in the treatment of uremic pruritus. In addition, only mild to moderate adverse drug reactions (e.g. insomnia) were observed in a Phase III clinical trial, which were transient and readily resolved. Thus, nalfurafine was considered as effective and safe in the treatment of uremic pruritus. A one-year open-label study about nalfurafine hydrochloride was carried out, during which neither tolerance or dependence was observed. In 2009, nalfurafine was approved for clinical use in Japan and have become the first KOR agonist on the market for the treatment of pruritus. In conclusion, the KOR is steadily rising as target for the treatment of uremic pruritus. Further research and investigations are needed for a complete understanding of role of the KOR and KOR agonist in pruritus.

KOR Potential for the Treatment of Depression

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. Depression can be classified into several subcategories including major depression, persistent depressive disorder, seasonal affective disorder, and perinatal depression, and psychotic depression. According to World Health Organization, more than 300 million people worldwide suffer from depression.[59] National Institute of Mental Health estimated that approximately 16 million adults in United States had at least one major depressive episode in 2012.[60] Currently, most prescribed antidepressants (Figure 1.6) are divided into subclasses including tricyclics antidepressants (TCAs, e.g. imipramine), monoamine inhibitors (MOAIs, e.g. selegiline), selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine), and serotonin–norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine). Despite the availability of antidepressants, it is still challenging to treat depression and avoid relapse. Unfortunately, stress is a prominent trigger in depression relapse and is one of the most common experiences in daily life. In fact, the rate of depression relapse is about 80%.[61]



imipramine TCA | selegiline MOAI | fluoxetine SSRI | venlafaxine SNRI

Figure 1.6. Representatives of major subclasses of antidepressants

The opioid system modulates dopaminergic signaling in the brain. Opposing effects on mesolimbic dopamine system were observed via activation of MOR and KOR, with MOR agonists increasing dopamine levels while KOR agonists decreasing levels of dopamine.[62] In addition,

activation of the MOR produced euphoria, whereas KOR activation led to dysphoria and psychotomimetic effects in human.[63] Furthermore, anhedonia-, dysphoria-, and anxiety-like effects were observed in rodents upon activation of the KOR.[64-65] The location of KOR and distribution of dynorphin in the brain are critical for the physiological response of KOR activation.[66-68]

KOR activation by acute stress can facilitate the motivation to escape from threats. However, sustained KOR activation resulting from chronic stress can have adverse effects such as increased risk of depression, increased propensity to participate in drug-seeking behaviors, and increased drug-craving.[65] These adverse effects are believed to occur via a mechanism involving increased levels of dynorphin.[69] Cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) function in the nucleus accumbens (NAc) could be increased by rewarding and stressful stimuli.[70] In addition, subsequently increased dynorphin level resulting from activation of CREB after stress stimuli could contribute to symptoms of emotional numbing.[71] Furthermore, elevated CREB function in NAc elicited the equivalent signs of major depression in rodents according to several studies.[72-73] Stress as a trigger for addictive as well as depressive disorders, was shown to activate CREB in the NAc.[73] In contrast, antidepressant-like effects indistinguishable from standard antidepressants was observed by disruption of CREB function in NAc.[70] In summation, activation of CREB in NAc mediates aversive or depressive-like symptoms.

The profound influence on behavior by the KOR agonists are thought to reflect motivational and emotional states in animal models of depression and anxiety, which lead to interest in use of selective KOR antagonists as potential therapies for treating mood disorders.[75-76] KOR antagonist nor-BNI (Figure 1.7) produced

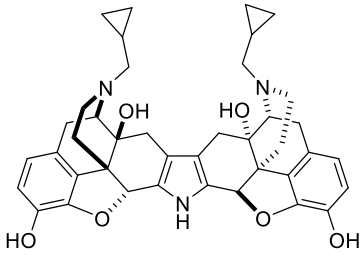


Figure 1.7. Structure of nor-BNI

antidepressant-like effects in the forced-swim tests (FST) in rats, which was followed up by other studies with similar findings.[69] In addition, KOR antagonists inhibited stress-induced, but not cocaine-primed, reinstatement of cocaine-associated conditioned place preference (CCP) in mice.[77-78] Furthermore, this stress-induced reinstatement of CPP in mice was abolished by genetic deletion of the KOR or prodynorphin.[80] Overall, KOR antagonists were demonstrated to be potential therapies of stress-induced depression and stress triggered relapse of drug addiction.

KOR Agonists

Numerous of KOR agonists have been reported to date, which can be roughly classified in several categories. The first category is morphine-derived KOR agonists, which feature a morphinan scaffold, like 6´-guanidinonaltrindole (6´-GNTI, Figure 1.8) or nalfurafine (discussed above). Compound 6´-GNTI, as a DOR-KOR heteromer-selective agonist,[79] produced a prolonged antinociceptive response in a rat behavioral model of thermal allodynia.[80] In addition, 6´-GNTI was a potent partial agonist at the KOR for G-protein activation (EC_{50} = 1.6 ± 1.3 nM, E_{max} = 64 ± 6%) while it did not recruit arrestin to the KOR.[81] Considering arrestin recruitment is an essential step in GPCR downregulation (responsible for tolerance) and induction of an array of kinase activation and signaling (believed to be responsible for side effects), 6´-GNTI is an attractive candidate to undergo further investigation as a KOR agonist.

The second scaffold category consists of arylacetamides, including U-50,488, U69,593 (Figure 1.8), and, as previously described, spiradoline. U69,593 was originally prepared as [^{3}H]U69,593 for the *in vitro* studies as a standard in 1985 as no tritiated ligand selective for KOR was available prior to its discovery.[82] This tritiated ligand was active on the mouse tail flick test

with an ED_{50} of 3.6 mg/kg, which was close to its analogue U50,488 and morphine (ED_{50} = 2.7 and 1.6 mg/kg, respectively). In cross-tolerance studies, the EC_{50} of U69,693 was lightly increased to 7.0 mg/kg by chronic administration of morphine. In comparison the EC_{50} of U69,693 was increased from 3.6 to 50 mg/kg, by chronic dosing of U50,488, indicating U69,693 exerted its analgesic effects through KOR rather than MOR.[82] The binding affinity of U69,693 to the KOR was much higher than that with MOR and DOR (approximately 100- and 2830-fold, respectively).[83] Thus, this compound has been predominantly used as a tool compound in research owning to its high selectivity for the KOR over the MOR and DOR. In addition, this compound produced analgesic effect in animal models using rhesus monkeys. However, U69,593 suppressed respiration of rhesus monkeys in a dose-related manner.[83] Despite the good selectivity for KOR and effectiveness in analgesic studies using animals, the development of U69,593 as analgesic therapy was hindered by its side effects.

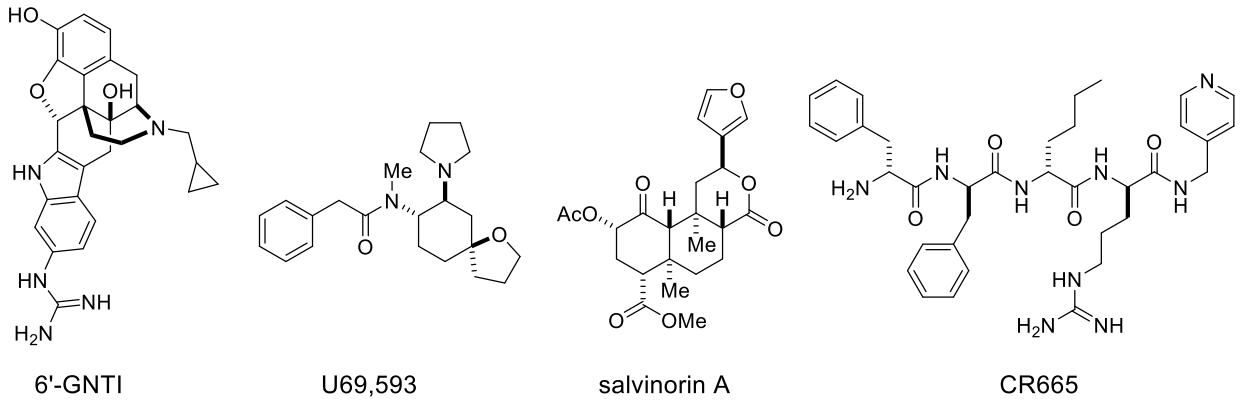


Figure 1.8. Representatives of KOR agonists

The third scaffold category is neoclerodane diterpenes isolated from the ethnomedical plant *Salvia divinorum*. As a representative in this category, salvinorin A was the first reported nonnitrogenous opioid receptor agonist, demonstrated to be a powerful hallucinogen in humans.[84] Salvinorin A is unique from several aspects: (a) it is the first plant-derived KOR agonist with high

selectivity over the MOR and DOR; (b) it has no structural resemblance to any previously known KOR agonist; (c) the hallucination effect is not mediated by 5-HT2A like typical hallucinogen. Salvinorin A was shown to be highly selective for the KOR (K_i = 4.3 nM) over the MOR and DOR (both K_i > 5,000 nM) in radioligand binding assays.[85] Sedative-like and locomotor-decreasing effects were observed in rodent and non-human primate models after admiministration of salvinorin A. In addition, the effects of salvinorin A in humans could be blocked by naltrexone, confirming the hallucination effect was mediated by the KOR.[86] Besides hallucination, salvinorin A suffers from a very short duration of action. Thus, efforts were carried out to improve pharmacological profile and phamarcokinetics of salvinorin A.[87-88]

The last scaffold category is peptide-derived analogues. Peptides are interesting in terms of their high hydrophilicity, which intrinsically prohibit them from crossing biological membranes passively.[89] Thus, it is believed that peptides possess the potential to be developed as peripherally selective KOR agonist to avoid side effects caused by activation of KOR in CNS. A tetrapeptide named CR665 (Figure 1.8), identified as a KOR agonist, consist of all D-amino acids.[89-90] Interestingly, this peptide is not structurally related to KOR endogenous ligands. CR665 was shown to be highly selective for the KOR (K_i = 0.24 nM) over the MOR and DOR (approximately 17,000- and 85,000-fold, respectively) in radioligand binding assays. In addition, high potency and efficacy (EC_{50} = 0.03 nM, E_{max} = 130%) was demonstrated in [^{35}S]GTPγS binding assays. More importantly, higher doses of this compound were required to induce centrally-mediated effects in the rotarod assay (548-fold higher dose), and antinociception determined in the mouse tail-flick assay (>1429-fold higher dose) after peripheral administration, indicating its peripheral selectivity. With the satisfying results of preclinical studies, CR665 was tested in Phase I clinical trials.[91] This peptide significantly increased the pain rating threshold to esophageal distension (a type of visceral

pain model), but reduced the pain tolerance threshold to skin pinching. The side effect was mainly limited to mild pruritus at the site of administration and to mild facial tingling which was believed to be associated with KOR activation. Further updates about this peptide in clinical trials are not currently available.

Discovery and Synthesis of Bisamide KOR Agonists

To search for novel KOR modulators with novel scaffold and therapeutic potential, a high throughput screening (HTS) campaign was initiated by collaborative efforts of Specialized Chemistry Center (the University of Kansas) and Sanford-Burnham Medical Research Center (California). In this HTS campaign, the bisamide class (chemotype I) KOR agonists was discovered, along with three other new classes of KOR agonists (Figure 1.9). [92]

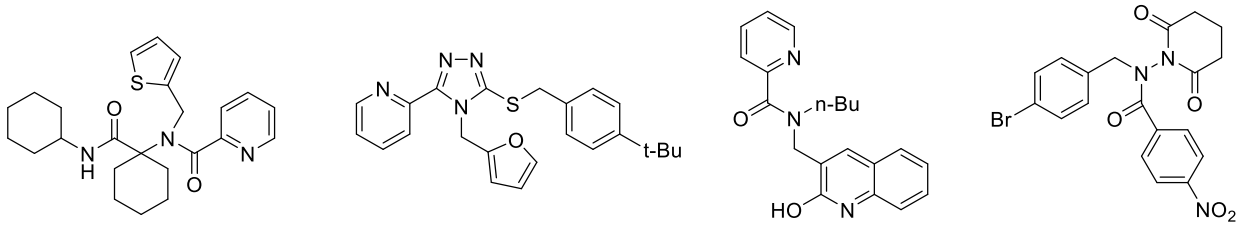
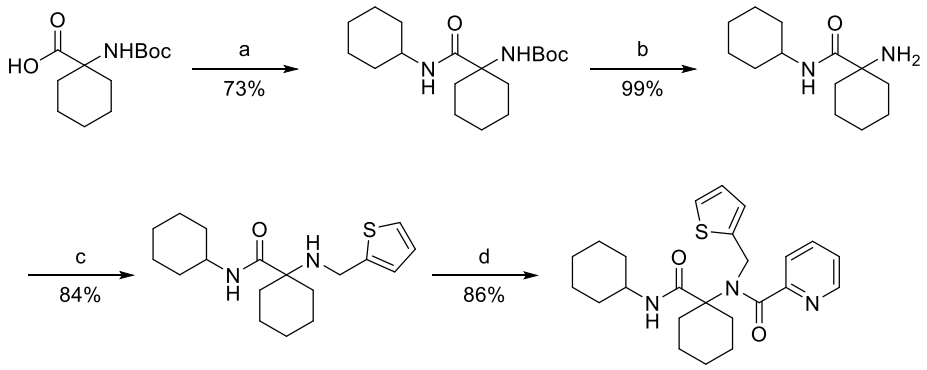


Figure 1.9. Representative compounds illustrating validated KOR agonists from HTS

ML139 is attractive in terms of: (a) good selectivity for the KOR over the MOR and DOR, and no measurable affinity for other 41 CNS-relevant targets; (b) a novel scaffold without any resemblance to previously known opioid modulators; (c) modular structure allowing for selective improvement of unfavorable properties while retaining the positive attributes. Thus, bisamide class

was prioritized for optimization toward probe molecule nomination. The probe discovery efforts were carried out with a four-step linear synthetic route (Scheme 1.1). For instance, the synthesis of hit molecule ML139 began with DCC-promoted amide coupling between N-boc amino acid and cyclohexylamine, which afforded an N-boc amino amide intermediate. Then, the boc group was removed with a 1:1 mix of TFA and DCM, yielding a free amine. Then, the free amine was alkylated by reductive amination with thiophene-2-carboxaldehyde, followed by acylation to afford the desired compound. By using this route, 10 analogues were prepared. However, none of them possess higher potency than ML139. In addition, the purity profiles are not obtained for majority of these analogues.[92] Thus, it is not convincing to draw a structure activity relationship (SAR) based on the preliminary studies on this class until enough analogues with decent purity would be available.

Scheme 1.1. Representative Synthesis of Bisamide Chemotype[a]



[a]Reagents and conditions: (a) cyclohexylamine, DIC, HOBt, CH_3CN, microwave irradiation 100 °C, 10 min (73% yield); (b) TFA/CH_2Cl_2 (1:1), rt, 14 h; (c) thiophene-2-carboxaldehyde, $NaBH(OAc)_3$, DCE; (d) picolynyl chloride, Et_3N, CH_2Cl_2

Results and Discussion

Design and synthesis of analogues

In the preliminary study on this bisamide class of KOR agonists, a four-step linear synthetic route was established which afforded 10 analogues. My goal on this project is to streamline the synthesis of the bisamide class of KOR agonists and provide analogues with new structural elements to expand the SAR.

Multicomponent reactions (MCRs) are one pot reactions in which more than two starting materials react to form a final product.[93-94] This convergent transformation is attractive in terms of atom economy that the majority if not all of the atoms of starting materials are incorporated in the product. In addition, MCRs are efficient, since it takes one step to install multicomponent into one molecule rather than several steps. The efficient and easy access to biologically relevant compounds by MCRs makes them useful in drug discovery. With this concept in mind, we noticed the scaffold of bisamide class of KOR agonists can be accessed by Ugi multicomponent reaction which use ketone, amine, carboxylic acid, and isocyanide as starting materials.[95] To fully take advantage of this one-step transformation and make the analogue synthesis more efficient, the reaction conditions were modified for parallel synthesis on the Bohdan MiniBlock synthesis platform, followed by MS-directed HPLC purification. Then quenching methods (TFA vs Amberlyst 15) and purification methods were briefly surveyed based on a model reaction. (Figure 1.10). Both methods were efficient enough to quench the uncomsumed isocyanide and remove its unpleasant smell. However, TFA was chosen as the reagent to quench the reaction, since it gave higher yield and was easier to handle than Amberlyst 15.

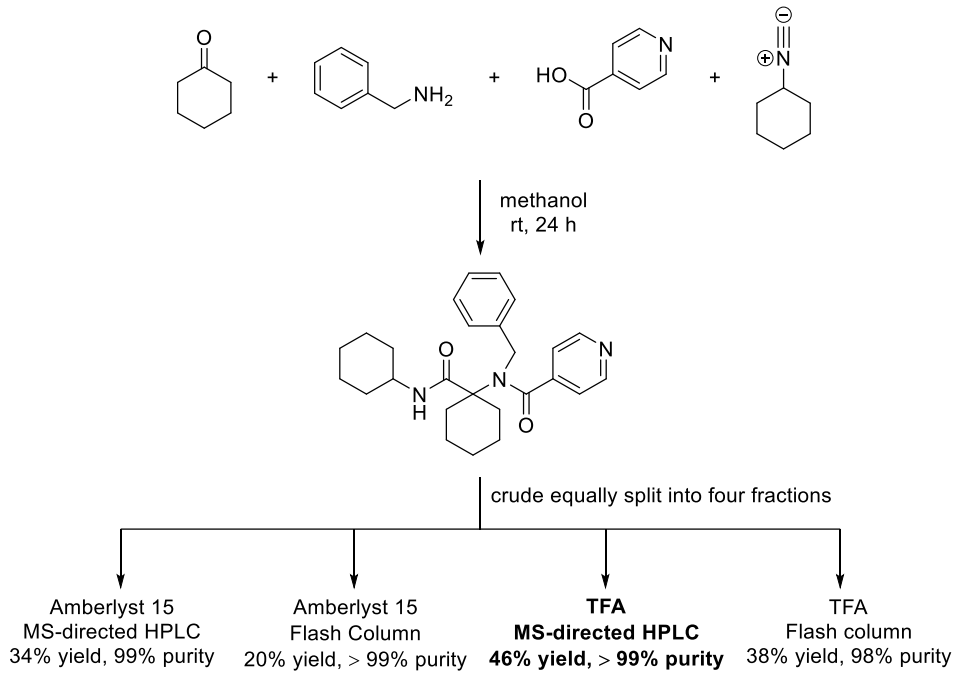


Figure 1.10 Quenching and purification survey

Once the reaction condition and workup method were finalized, the first set of analogues was proposed with diverse building blocks (Figure 1.11). Cyclohexanone and cyclopentanone were chosen as ketone components to briefly survey how a 5- vs 6-membered ring ketone impacts the biological activity. Four amines were selected as amine components, with furfurylamine and benzylamine as bioisosterie of 2-thiophenemethylamine to probe their influence on bioactivity and to potentially bypass metabolic liability issues associated thiophene moiety, with tetrahydrofurfurylamine, cyclohexanemethylamine as saturated version of furfurylamine and benzylamine for comparison and to evaluate if there would be pi interactions between ligand and receptor. Three carboxylic acid components were chosen including picolinic acid, nicotinic acid, and isonicotinic acid in order to survey the influence on the bioactivity by the position of nitrogen atom on pyridine ring. Lastly, cyclohexyl isocyanide and 2,6-dimethylphenyl isocyanide were nominated as isocyanide components to compare impacts by aromatic ring and aliphatic ring on

bioactivity. By every possible combination, 48 reactions were set up using two Bohdan MiniBlocks, each one accommodating 24 reaction tubes. The reactions were run at room temperature for 24 h in methanol with agitation from a shaker station. Then each reaction was quenched with TFA, followed by 30 min of shaking on the shaker station. Mixtures of each reaction was concentrated under N_2 and was then submitted for purification by MS-directed HPLC. A total of 47 analogues (Figure 1.12) were obtained with high purity (43 analogues with 95% and above purity, 4 analogues with 90%-94% purity), which were suitable for biological assays. The only failed reaction was due to the leaking of the reaction tube.

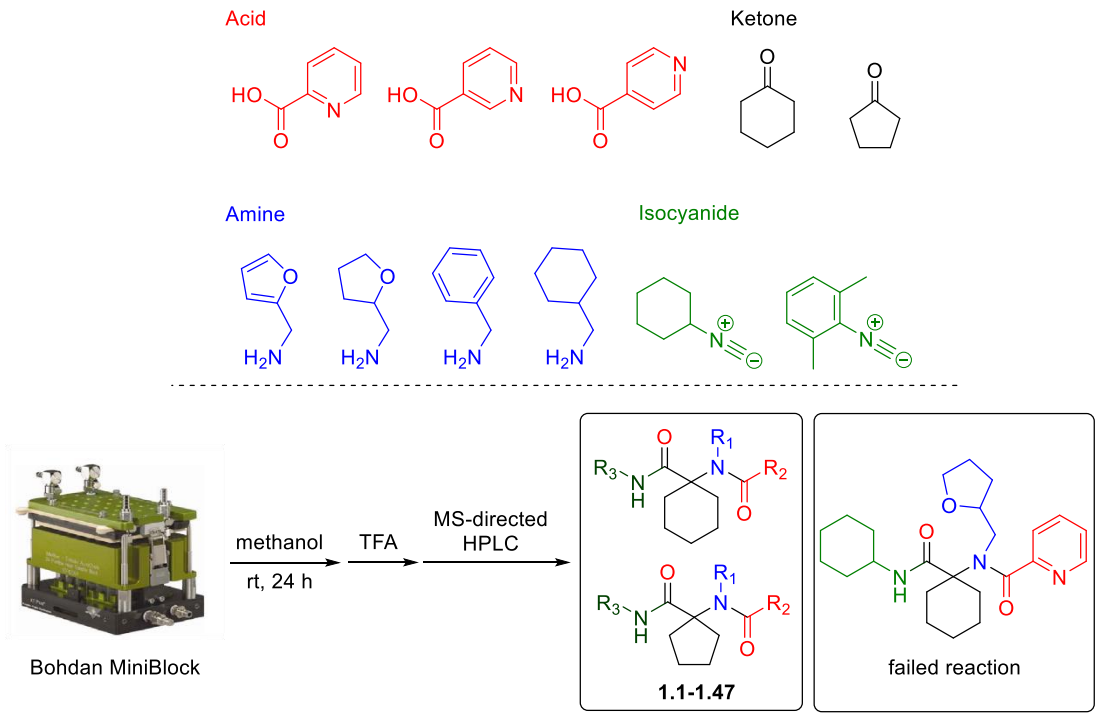


Figure 1.11. Building blocks and setup of first library

With the success of synthesis and purification of first set of analogues, a second set was proposed to explore the ketone/aldehyde scope, by fixing the carboxylic acid, amine and isocyanide while using a different ketone or aldehyde component (Figure 1.12) for each reaction. The setup of reaction and subsequent purification were the same with that of the first set. A total

of 13 compounds out of 22 reactions were obtained from the second set with satisfying purity (see experimental section). However, products were not isolated from reactions using sterically hindered ketones (Q, U, and V), 1,1,1-trifluoroacetone (T), and aliphatic aldehydes (R and S) due to the low percentage of product in the crude sample. Two products were obtained in reaction with ketone G. In contrast, only one product was isolated from each reaction (using ketones B, C, D, E, F) although two products were expected.

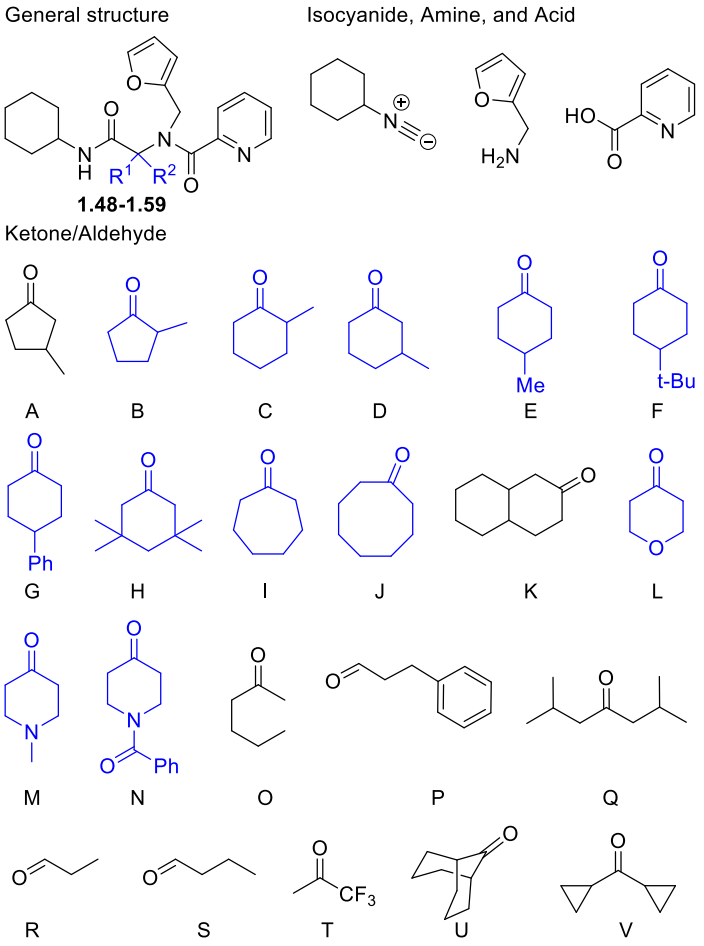


Figure 1.12. Building blocks employed in the second set

The reason causing this phenomena was not quite understood. It may be caused by diastereoselectivity or one of the products was lost during MS-directed HPLC purification. After obtaining some interesting bioassay results of this set of analogues, four reactions (using ketones C, E, F, and G) were revisited on relatively larger scale, which all afforded two diastereomeric products after challenging but successful chromatography separations. The relative stereochemistry of each of the four pairs of diastereomers were determined by single crystal X-ray diffraction experiments.

Nine one-off analogues were designed and synthesized separately in flasks rather than Bohdan MiniBlocks (Figure 1.14). The first two analogues (**1.60** and **1.61**) in this set were

designed to replace the thiophene or furan ring by a metabolically more stable 2-fluorophenyl ring while another two analogues (**1.62** and **1.63**) contained an *n*-butyl group on the spiro amide nitrogen to compare the effects of aliphatic chain with that of aromatic or aliphatic rings used previously. The next four analogous (**1.64** to **1.67**) were designed to see the effects of chain length between the phenyl ring and nitrogen atom. Another two analogues (**1.68** and **1.69**) were designed to further explore the ketone component. The last analogue (**1.70**) was obtained as a hydrolyzed byproduct formed during the purification of its precursor (**1.69**) by reverse-phase flash column chromatography.

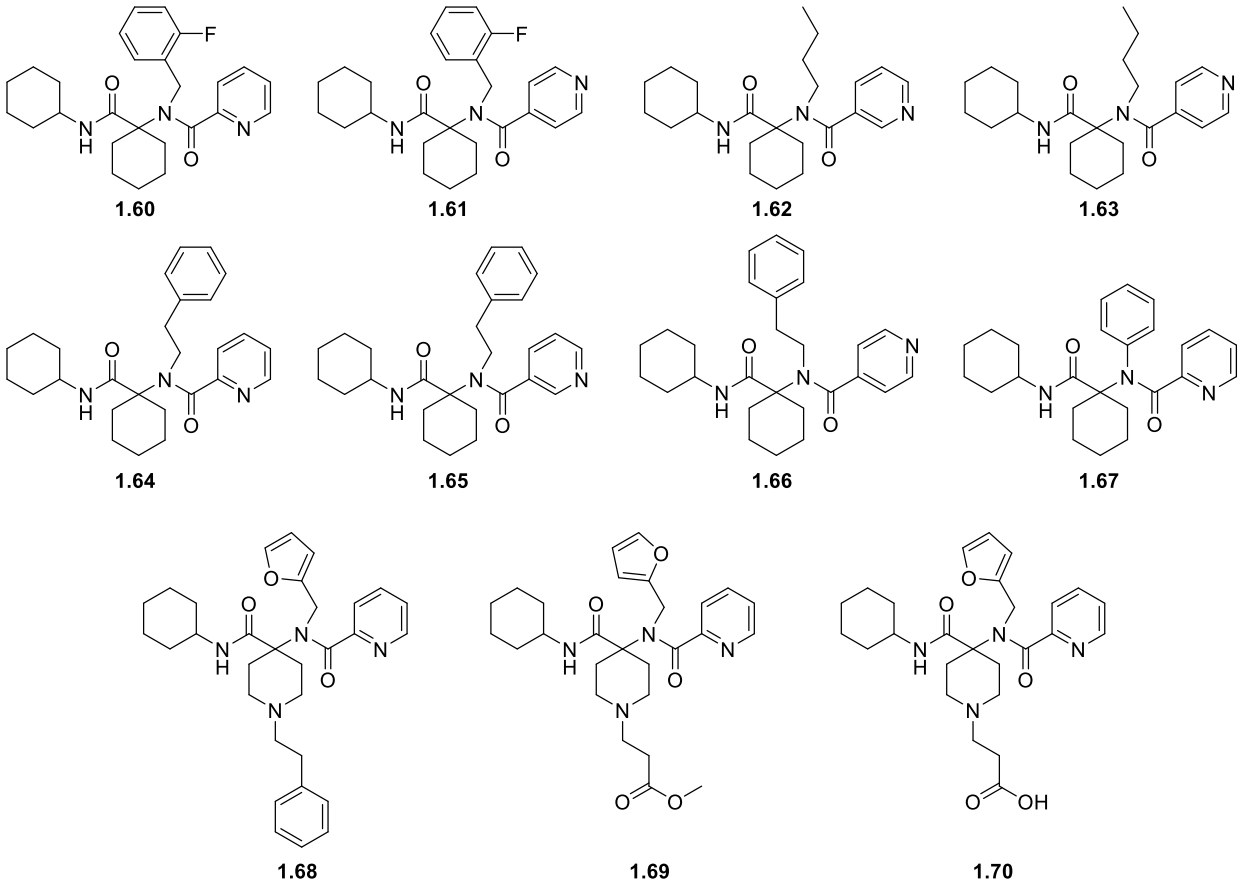
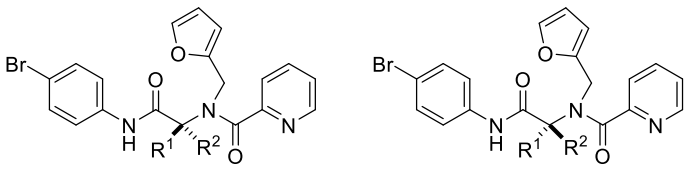


Figure 1.13. Structures of one-off set

When using a non-symmetric ketone as starting material, a stereogenic center is formed at the amino acid carbon. To explore how the absolute configuration of this stereogenic center would influence the bioactivity, three pairs of enantiomers were designed as a set (Figure 1.14). By gradually increasing the size of R^1 while fixing R^2 as methyl group, the difference of biological activities between the two enantiomers (eudismic ratio) would be explored. The three racemic compounds was synthesized using Ugi reaction, each of which was then separated with chiral HPLC to afford a pair of enantiomers. Then, one enantiomer from each pair was randomly selected for single crystal X-ray experiments. The absolute configuration was unambiguously determined by anomalous scattering of Cu X-rays by the bromine atoms. The activity and eudismic ratio will be discussed in the biological assay section.



(***S***)-**1.71**, R^1 = Me, R^2 = Et
(***S***)-**1.72**, R^1 = Me, R^2 = *iso*-Bu
(***S***)-**1.73**, R^1 = Me, R^2 = *n*-Bu

(***R***)-**1.71**, R^1 = Me, R^2 = Et
(***R***)-**1.72**, R^1 = Me, R^2 = *iso*-Bu
(***R***)-**1.73**, R^1 = Me, R^2 = *n*-Bu

Figure 1.14. Enantiopure bisamide analogues

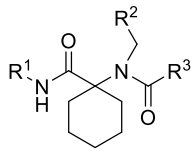
In Vitro Assay Studies

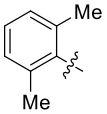
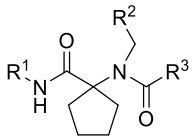
To assess the biological activity of bisamide compounds (**1.1** to **1.73**), two assay methods were employed, with [^{35}S]GTPγ binding assays as the primary screening method and βarrestin2 imaging assays as the secondary method for specific interesting compounds. In [^{35}S]GTPγ binding assays, cellular membranes expressed with KOR receptor were collected, then treated with drug molecules in the presence of radioactive non-hydrolyzable [^{35}S]GTPγ. Membranes were washed to remove the non-bound [^{35}S]GTPγ, then radioactivity of membranes were measured to determine the KOR activation as a function of [^{35}S]GTPγ binding. The βarrestin2 imaging assays were run

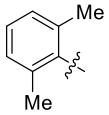
in 384 well plates. The U2OS-hKOR-βarrestin2-GFP cells were expressed the KOR and GFP-tagged βarrestin2 which upon recruitment to the receptor will form small fluorescent aggregates (spots). The spot count per cell was determined and used as a measure of the KOR activation.

In the first set of bisamide library, 47 compounds (**1.1** to **1.47**) were synthesized using two Bohdan MiniBlocks, in which compound **1.1** which was made previously during the previous SAR study and used as starting point in this set. All of the bioactivity data from this set are listed in the Table 1.1. When the 2-pyridyl group of **1.1** is replaced with a 3- or 4-pyridyl group, the resulting compound were completely inactive (**1.3** and **1.5**). Bioactivity was also lost when replacing 2-pyridyl group on **1.2** with 3- or 4-pyridyl group (**1.4** and **1.6**). This trend was observed again in another subset (**1.36**, **1.38**, and **1.40**), suggesting the nitrogen atom on 2-pyridyl group was interacting with receptor. When the furan group on **1.1** was replaced with an aromatic phenyl group, decreased potency was observed (**1.36**, EC_{50} = 140.4 ± 35.7 nM). However, aliphatic rings (cyclohexyl group) replacement of furan were not tolerated (**1.42**). Similar phenomena were observed in another subset (**1.2**, **1.7**, and **1.43**), indicating that the furan could be involved in pi interactions with the receptor which could not be established by aliphatic rings. Replacing the left cyclohexyl group on **1.1** by an aromatic 2,6-dimethylphenyl group led to decreased activity (about 3-fold). The ketone effects on bioactivity were mild, which somehow were dependent on other components (**1.1** vs **1.2**, **1.12** vs **1.13,** and **1.36** vs **1.37**).

Table 1.1. Bioactivities of the First Set of Bisamide Library

cmpd. #				KOR ([^{35}S]GTPγ)	
	R^1	R^2	R^3	[a]EC_{50} ± SEM (nM)	E_{max}± SEM

1.1		2-furyl	2-pyridyl	55 ± 10 (n = 3)	97 ± 1
1.3		2-furyl	3-pyridyl	11210	77
1.5		2-furyl	4-pyridyl	NC	
1.8		2-tetrahydrofuryl	3-pyridyl	NC	
1.10		2-tetrahydrofuryl	4-pyridyl	NC	
1.12		phenyl	2-pyridyl	480 ± 104 (n = 4)	96 ± 2
1.14		phenyl	3-pyridyl	NC	
1.16		phenyl	4-pyridyl	NC	
1.18		cyclohexyl	2-pyridyl	15120	84
1.20		cyclohexyl	3-pyridyl	NC	
1.22		cyclohexyl	4-pyridyl	NC	
1.24		2-furyl	2-pyridyl	153 ± 29 (n = 4)	97 ± 0
1.26		2-furyl	3-pyridyl	NC	
1.28		2-furyl	4-pyridyl	NC	
1.30		2-tetrahydrofuryl	2-pyridyl	NC	
1.32		2-tetrahydrofuryl	3-pyridyl	NC	
1.34		2-tetrahydrofuryl	4-pyridyl	NC	
1.36		phenyl	2-pyridyl	140 ± 36 (n = 3)	98 ± 1
1.38		phenyl	3-pyridyl	NC	
1.40		phenyl	4-pyridyl	NC	
1.42		cyclohexyl	2-pyridyl	>10000	
1.44		cyclohexyl	3-pyridyl	NC	
1.46		cyclohexyl	4-pyridyl	NC	
cmpd. #				KOR ([^{35}S]GTPγ)	
	R^1	R^2	R^3	[a]EC_{50} ± SEM (nM)	E_{max}± SEM
1.2		2-furyl	2-pyridyl	58 ± 15 (n = 3)	99 ± 1
1.4		2-furyl	3-pyridyl	[b]NC	
1.6		2-furyl	4-pyridyl	[b]NC	

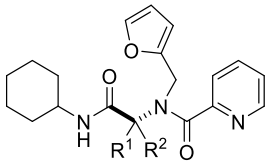
1.7		2-tetrahydrofuryl	2-pyridyl	12410	106
1.9		2-tetrahydrofuryl	3-pyridyl	[b]NC	
1.11		2-tetrahydrofuryl	4-pyridyl	[b]NC	
1.13		phenyl	2-pyridyl	281 ± 51 (n = 4)	95 ± 2
1.15		phenyl	3-pyridyl	[b]NC	
1.17		phenyl	4-pyridyl	[b]NC	
1.19		cyclohexyl	2-pyridyl	[b]NC	
1.21		cyclohexyl	3-pyridyl	[b]NC	
1.23		cyclohexyl	4-pyridyl	[b]NC	
1.25		2-furyl	2-pyridyl	150 ± 21 (n = 3)	95 ± 0
1.27		2-furyl	3-pyridyl	[b]NC	
1.29		2-furyl	4-pyridyl	[b]NC	
1.31		2-tetrahydrofuryl	2-pyridyl	[b]NC	
1.33		2-tetrahydrofuryl	3-pyridyl	[b]NC	
1.35		2-tetrahydrofuryl	4-pyridyl	[b]NC	
1.37		phenyl	2-pyridyl	67 ± 7 (n = 4)	98 ± 1
1.39		phenyl	3-pyridyl	[b]NC	
1.41		phenyl	4-pyridyl	[b]NC	
1.43		cyclohexyl	2-pyridyl	[b]NC	
1.45		cyclohexyl	3-pyridyl	[b]NC	
1.47		cyclohexyl	4-pyridyl	[b]NC	

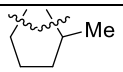
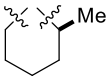
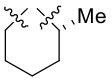
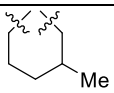
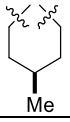
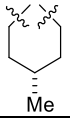
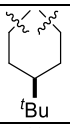
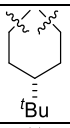
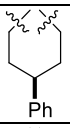
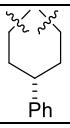
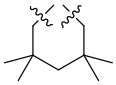
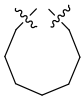
[a] [^{35}S]GTPγ functional assay (Membrane G protein Signaling) with n = 1 unless noted, compared to U69,693 (EC_{50} = 35 ± 4 nM); [b]NC: non-convergent curve caused by insignificant potency.

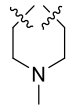
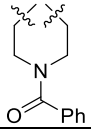
In the second set of bisamide library, 16 compounds (**1.48** to **1.59,** including four pairs of diastereomers) were synthesized, in order to expand the ketone scope of the reaction and explore their effects on bioactivity (Table 1.2). The first compound **1.48** was a methylated version of compound **1.2** (from first set). However, the relative stereochemistry was not assigned and a

decreased bioactivity (about 2-fold) was observed by this methylation. Effects of substituents on cyclohexanone moiety of **1.1** were explored by compounds **1.49** to **1.54**. Two diastereomeric compounds (***trans*-1.49** and ***cis*-1.49**) were methylated version of **1.1** at the C-2 position, demonstrating increased bioactivity with trans-methylation (***trans*-1.49**, relative to spiro amide nitrogen on C-1 positon) and decreased bioactivity with cis-methylation (***cis*-1.49**). Similarly, methylations at the C-4 position of ketone moiety of **1.1** resulted in 5-fold increase of potency for ***trans*-1.51** and 2-fold decrease of potency for ***cis*-1.51**. By increasing the size of substituents at C-4 position, *trans*-*tert*-butyl group and *trans*-phenyl groups led to decreased bioactivity compared with *cis*-methylation (***trans*-1.51** vs ***trans*-1.52**, ***trans*-1.51** vs ***trans*-1.53**). Not surprisingly, the *cis*-*tert*-butyl group and *cis*-phenyl group were not favored (***cis*-1.52** and ***cis*-1.53**) compared with the corresponding *trans*-diastereomers (***trans*-1.52** and ***trans*-1.53**). The methylation at C-3 position (**1.51**) resulted in much lower bioactivity (16-fold) compared with **1.1,** whose stereochemistry was not assigned. Tetramethylation at 3- and 5-position (**1.54**) was detrimental to the bioactivity. Expanding of the ring size of ketone moiety to 7-member (**1.55**) led to a slightly increased bioactivity (2-fold). But further expanding the ring size to 8-member (**1.56**) resulted in an equally potent compound compared with **1.1**. Heterocycle replacements afforded 3 compounds (**1.57** to **1.59**), with slightly increased bioactivity for **1.57** and decreased bioactivity for **1.58** and **1.59**.

Table 1.2. Bioactivities of the Second Set of Bisamide Library

Cmpd.#			KOR ([^{35}S]GTPγ)	
	R^1	R^2	$^{a}EC_{50}$ ± SEM (nM)	E_{max}± SEM

1.48	 single diastereomer relative stereochemistry not assigned	112	98
***trans*-1.49**		9 ± 4 (n = 2)	99 ± 1
***cis*-1.49**		224	132
1.50	 single diastereomer relative stereochemistry not assigned	806	95
***trans*-1.51**		10 ± 5 (n = 2)	95 ± 1
***cis*-1.51**		113	102
***trans*-1.52**		44	106
***cis*-1.52**		119	88
***trans*-1.53**		45	95
***cis*-1.53**		371 ± 126 (n = 2)	94 ± 0
1.54		5476	84.7
1.55		24.4 ± 7.7 (n = 3)	98 ± 1
1.56		49.0	99
1.57		32.4 ± 8.9 (n = 2)	100 ± 1

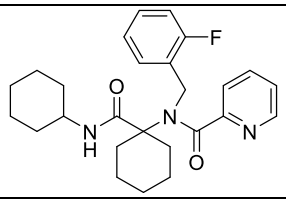
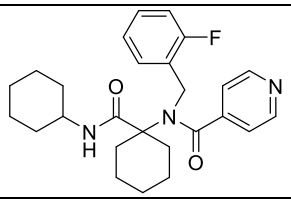
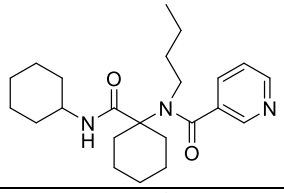
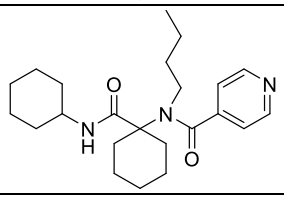
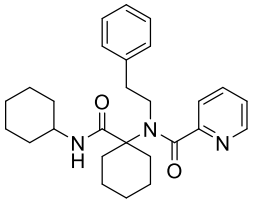
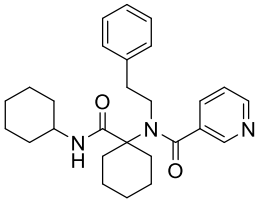
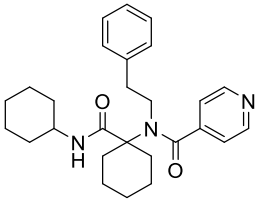
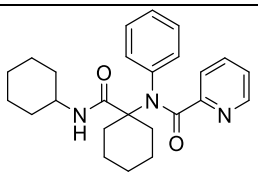
1.58		197.2 ± 56.1 (n = 2)	99 ± 0
1.59		87 ± 9 (n = 3)	96 ± 1

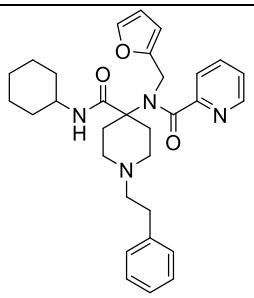
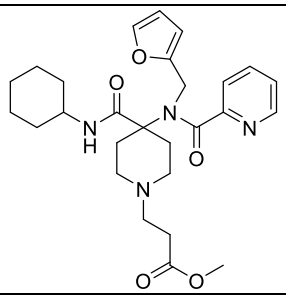
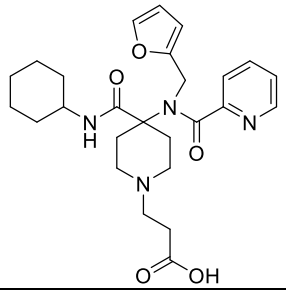
[a] [^{35}S]GTPγ functional assay (membrane G protein signaling) with n = 1 unless noted, compared to U69,693 (EC_{50} = 35 ± 4 nM).

A total of 11 compounds in the one-off set were prepared, with their bioactivity data listed in the Table 1.3. The replacement of the furan ring on **1.1** with a 2-fluorophenyl group was shown to benefit the bioactivity (**1.60**, 2-fold increase). Not surprisingly, replacing 2-pyridyl of **1.60** by 4-pyridyl was shown to be detrimental to bioactivity. Similarly, the next two analogues (**1.62** and **1.63**) were not active, containing 3- and 4-pyridyl groups, respectively. The compounds **1.64** was designed with increased length (two carbon away) between the aromatic ring and nitrogen atom, which turned out to be detrimental to bioactivity. Not surprisingly, replacing 2-pyridyl of **1.64** with 3- or 4-pyridyl (**1.65** and **1.66**) did not restore the bioactivity. In contrast, compound **1.67** was designed by attach the phenyl ring directly on the nitrogen atom, which resulted in complete loss of bioactivity. Another two analogues (**1.68** and **1.69**) were designed to further explore the ketone component, both of which possessed much lower activity compared with a similar compound **1.1**. Lastly, compound **1.70**, the byproduct obtained during the preparation of **1.69**, was shown to had similar activity as its precursor.

Table 1.3. Bioactivities of One-Off Bisamide Series

cmpd.#	Structure	KOR ([^{35}S]GTPγ)	
		[a]EC_{50} ± SEM (nM)	E_{max}± SEM

1.60		26	102
1.61		[b]NC	
1.62		[b]NC	
1.63		[b]NC	
1.64		[b]NC	
1.65		[b]NC	
1.66		[b]NC	
1.67		[b]NC	

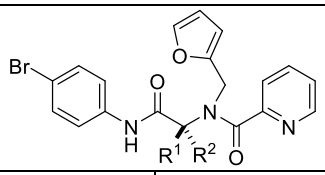
1.68		1089	81
1.69		919	81
1.70		1189	85

[a][^{35}S]GTPγ functional assay (membrane G protein signaling) with n = 1, compared to U69,693 (EC_{50} = 35 ± 4 nM); [b]NC: non-convergent curve caused by insignificant activity.

A total of three pairs of enantiomers were prepared in this set, which were all screened in both [^{35}S]GTPγ binding assay (membrane G protein signaling) and βarrestin2 imaging assay (Table 1.4). All of these compounds have two alkyl substitution at the stereogenic center, which are a methyl group and a larger one. Interestingly, there was a general trend that the compound with *R*-configuration was more potent than its corresponding enantiomer which possessed *S*-configuration (**(*R*)-1.71** vs **(*S*)-1.71**, **(*R*)-1.72** vs **(*S*)-1.72**, and **(*R*)-1.73** vs **(*S*)-1.73**). In addition, eudismic ratio (potency difference between two enantiomers) was dependent on the differences of the size of two alkyl substitutions on the stereogenic center. Furthermore, it appeared that compound with smaller substitutions (**(*R*)-1.71** vs **(*S*)-1.71**) were more potent in the biological

assay. Compared to the canonical KOR agonist U69,693, this set of bisamide compounds demonstrated biased activity toward G-protein signaling. It has been proposed that the physiological effects of KOR activation result from different signaling cascades, with analgesia being G protein-mediated and dysphoria being mediated through βarrestin2 recruitment.[96] Thus, these enantiopure bisamide analogues are promising in terms of the development of analgesics with little dysphoric effect.

Table 1.4. Bioactivities of Enantiopure bisamide Series

Comp.#			KOR				[c]Bias factor
			[^{35}S]GTPγ		Arrestin		
	R^1	R^2	[a]EC_{50} ± SEM (nM)	E_{max}± SEM	[b]EC_{50} ± SEM (nM)	E_{max}± SEM	
(*S*)-1.71	Et	Me	11 ± 1	95 ± 3	252 ± 78	73 ± 16	4
(*R*)-1.71	Me	Et	10 ± 1	98 ± 2	219 ± 49	64 ± 20	5
(*S*)-1.72	*iso*-Bu	Me	165 ± 32 (n = 4)	95 ± 1	16705 ± 10553 (n = 5)	33 ± 17	16
(*R*)-1.72	Me	*iso*-Bu	21 ± 4 (n = 4)	97 ± 1	1307 ± 324 (n = 5)	53 ± 6	13
(*S*)-1.73	*n*-Bu	Me	170 ± 26 (n = 4)	93 ± 1	10136 ± 3197 (n = 3)	20 ± 3	18
(*R*)-1.73	Me	*n*-Bu	57 ± 13	95 ± 3	2172 ± 561	65 ± 18	8

[a][^{35}S]GTPγ functional assay (membrane G protein signaling) with n = 3 unless otherwise noted, compared to U69,693 (EC_{50} = 35 ± 4 nM); [b]βArrestin2 imaging assay with n = 2 unless otherwise noted, compared to U69,693 (EC_{50} = 1.2 ± 0.2 nM); [c]Bias factor obtained by method in reference 96

Conclusions

In this study, the original four-step synthetic route for bisamide chemotype KOR agonists was replaced by a one-step Ugi multicomponent reaction, which streamlined the SAR study of this chemotype. In addition, parallel synthesis was employed using Bohdan MiniBlock synthesis platform in combination with subsequent MS-directed HPLC purification, which further facilitated the generation of bisamide KOR agonists. A total of 80 bisamide compounds were synthesized, which had diverse substitutions on the bisamide scaffold. All of the bisamide compounds were tested in [^{35}S]GTPγS functional assay, and a useful SAR was obtained (Figure 1.15).

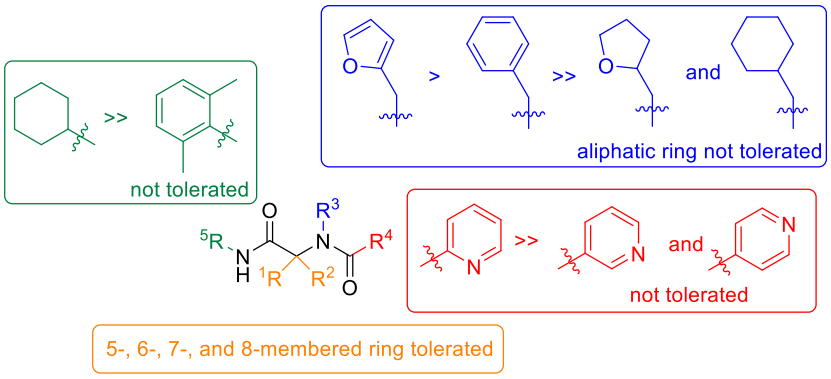


Figure 1.15. SAR summary of the bisamide chemotype KOR agonists

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Chapter 2

Potency Enhancement of Sulfonamide-based Kappa Opioid Receptor Antagonists

Introduction

KOR Antagonists

Selective KOR antagonists, initially developed as tools for studying properties of KOR agonists in the 1980s, are receiving increased attention as potential pharmacotherapies for treatment of mood disorders and drug addictions.[1-2] The first KOR antagonist named TENA (Figure 2.1), was reported by Portoghese and co-workers in 1982.[3] However, the selectivity of TENA for the KOR over the MOR and DOR was about 4- and 2.5-fold, respectively. Thus, it was not developed into a very useful compound for studying the KOR. In 1987, nor-BNI (Figure 2.1) was reported by Portoghese and co-workers as a potent and selective KOR antagonist in animal studies, which featured a slow onset and long duration (28 days).[4-9] Another KOR antagonist, GNTI (Figure 2.1), reported by Portoghese and co-workers, showed higher selectivity and better potency.[10-13] Like nor-BNI, however, GNTI also suffers a slow onset and long duration of action as demonstrated in studies with rhesus monkeys.[12] Moreover, GNTI was not active when administered systemically, which was attributed to its basic guanidine moiety.[14] In addition to the KOR antagonists mentioned above, there are numerous morphine-derived compounds developed in the 1980s and 1990s. Collectively, these ligands demonstrated the therapeutic potentials of antagonizing the KOR, and also suggested needs for seeking novel antagonists with better pharmacological profiles.[2]

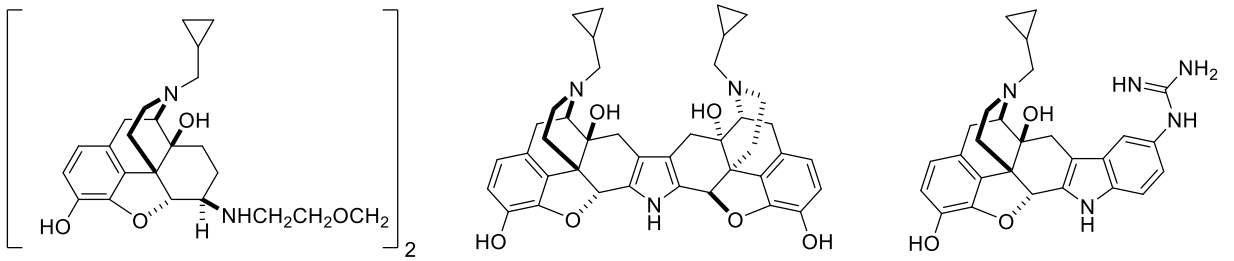


Figure 2.1. Representatives of morphine-derived KOR antagonists

In efforts to seek non-morphine-derived KOR antagonists, a series of *N*-substituted *trans*-3,4-dimethyl-4 (3-hydroxyphenyl)-piperidines were identified as KOR antagonists.[15] As a representative of this series, JDTic (Figure 2.2) was reported by Carroll and co-workers in 2001, and shown to be a selective and potent KOR antagonist.[16] JDTic entered into Phase I clinical trials for the treatment of cocaine abuse, but was discontinued due to ventricular tachycardia.[17] In 2012, an X-ray crystallographic study of the human KOR complexed with JDTic was reported by Raymond and collaborators. Thiswhich was made possible by the high affinity between this ligand and receptor.[18]

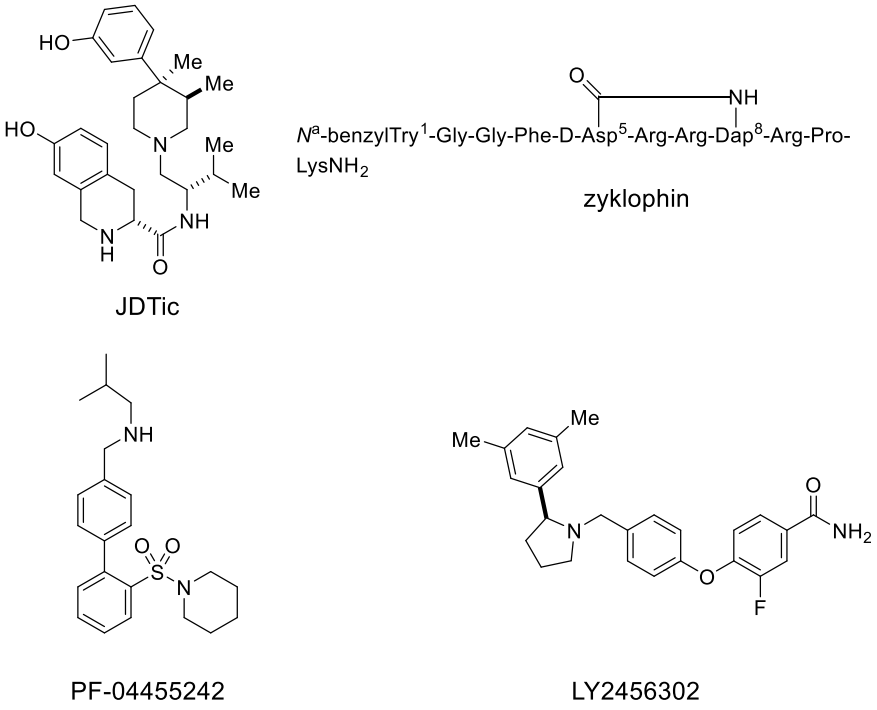


Figure 2.2. JDTic, zyklophin, PF-04455242, and LY2456302

In addition to small molecules, peptides have also been KOR antagonists. For example, zyklophin (Figure 2.2) is a dynorphin A-based peptide KOR antagonist, reported by Aldrich and co-workers in 2005.[19] Zyklophin is highly selective for the KOR over the MOR and DOR (K_i = 30.3, 5880, and > 10000 nM, respectively). More importantly, It was shown that zyklophin was able to antagonize the nociception induced by the selective KOR agonist U50,488 in C57BL/6J mice tested in the 55 °C warm water tail withdrawal assay in a dose-dependent manner.[20] Additionally, this peptide showed no effect on antinociception mediated by morphine or SNC-80 (a DOR agonist), implying its selectivity for the KOR over the MOR and DOR *in vivo*. Lastly, there have been other cyclic peptide small molecules identified as novel KOR antagonist by different groups.[21-22]

Several antagonists, including JDTic as mentioned previously, have entered clinical trials. PF-04455242 (Figure 2.2) was reported to have K_i values of 3 and 65 nM in radioligand binding assay using CHO cell membranes expressing human KOR and MOR, respectively.[23] This compound antagonized the effects of U50,488 and morphine with AD_{50} values of 0.67 and 12.03 mg/kg, respectively.[24] In addition, PF-04455242 proved to be effective in a series of animal models including the rat tail-flick test, social deficit stress assay, and cocaine CPP experiments.[23] Thus, clinical trials of PF-04455242 were initiated for the treatment of bipolar disorder, depression and substance abuse. However, the clinical trials were halted due to toxicity demonstrated in animals after three months of drug exposure in 2010.[25] Another KOR antagonist that entered clinical trials is LY2456302 (Figure 2.2) from Eli Lilly. This primary amide-bearing compound had a K_i value of 0.949 nM at the KOR and modest selectivity over the MOR and DOR (24- and 175-fold, respectively). In addition, decreased ethanol consumption was observed after administration of LY2456302 in an ethanol-drinking maintenance test using female P rat. LY2456302 also reduced

immobility of experiment mice at 10 mg/kg, po, in Porsolt forced swimming test.[26] This compound was further pursued in Phase II clinical trials (under the new developmental code name of CERC-501) for nicotine withdrawal. Hence are still ongoing as of this writing.[27]

Sulfonamide KOR Antagonists

The sulfonamide chemotype KOR antagonist was originally discovered via a high throughput screening (HTS) campaign, along with three other new classes of KOR antagonists (Figure 2.3).[28] In this HTS campaign, 290,000 compounds were evaluated on KOR activity and selectivity: the KOR DiscoveRx β-arrestin PathHunter assay and an imaging based β-arrestin translocation assay for confirmatory and selectivity assays. The sulfonamide compound ML140 was deemed due to its little structural similarity relative to known opioid ligands. Although modest at potency (IC_{50} = 0.91 μM) at the KOR, ML140 had good selectivity over MOR and DOR (IC_{50} > 24 and > 32 μM, respectively).

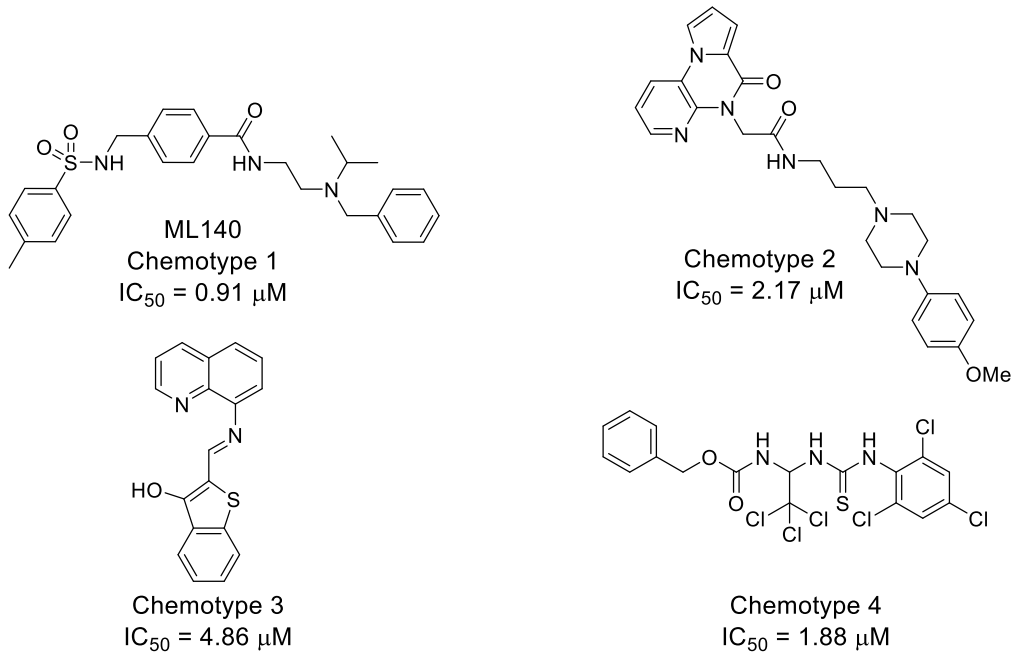
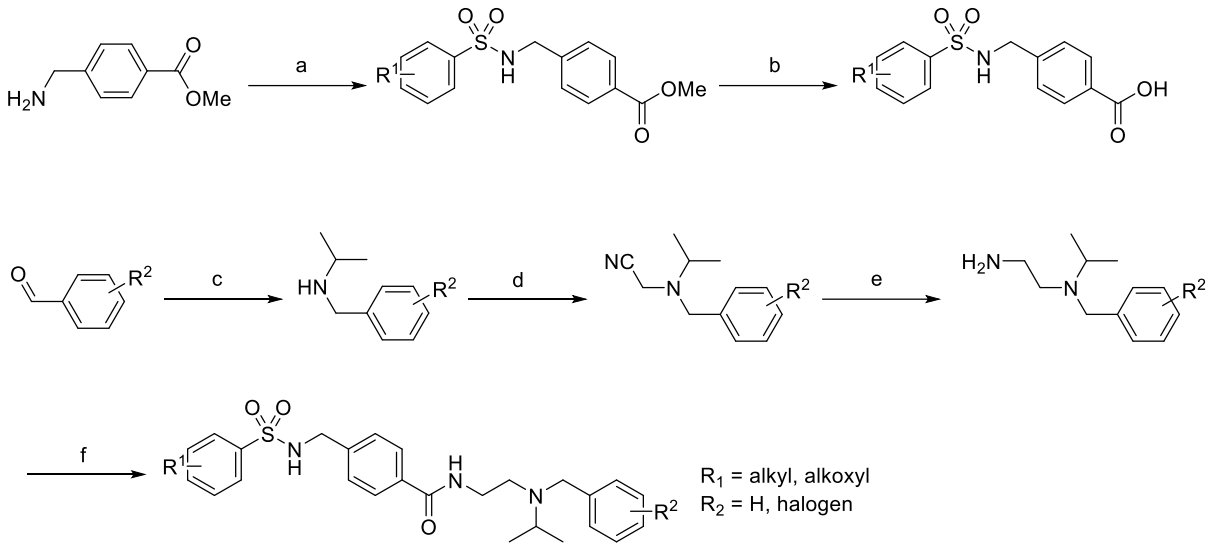


Figure 2.3. Representative compounds illustrating validated KOR antagonists from HTS

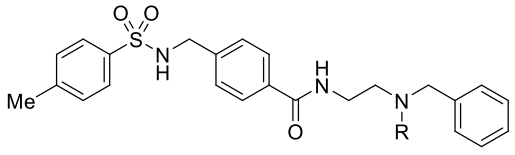
Initial SAR studies were carried out via a modular synthetic route, which involved the preparation of carboxylic acid intermediate and diamine intermediates (Scheme 2.1). The synthesis of the carboxylic acid intermediate began with the coupling between a sulfonyl chloride and an ester-bearing amine, which afforded a sulfonamide ester. Subsequent hydrolysis of the ester afforded the carboxylic acid intermediate. The diamine synthesis began with reductive amination followed by a nucleophilic substitution reaction with chloroacetonitrile. Reduction with $LiAlH_4$ provided the diamine intermediate. With both intermediates in hand, the carboxylic acid was converted to the corresponding acyl chloride (with $SOCl_2$), which was then coupled with diamine to afford the final sulfonamide compound.

Scheme 2.1. General Synthetic Route of Sulfonamide Analogues[a]



[a]Reagents and conditions: a) sulfonyl chloride (1.0 equiv), TEA (3.0 equiv), DCM, rt, 3 h; b) NaOH (1 N), H_2O, THF; c) *iso*-propylamine (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), DCE, rt, 24 h; d) $ClCH_2CN$ (1.0 equiv), KI (1.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, rt, 12 h; e) $LiAlH_4$ (1.1 to 4.4 equiv), ether, 4 h; f) $SOCl_2$, TEA (2.6 equiv), diamine (1.0 equiv), DCM, rt, 48 h

Initial SAR studies focused on the diamine portion of the molecule by varying the substitutions on, and introducing constraint to, the basic nitrogen. It appeared that bulkier aliphatic substitution was preferred on this basic nitrogen (*t*-Bu > *i*Pr > Et), while aromatic benzyl group was not tolerated (Figure 2.4). Several constraints (five and six member ring) on the basic nitrogen were introduced, all of which turned out to be detrimental to bioactivity (Figure 2.5). Additional efforts were directed toward the modification of the central phenyl fragment of sulfonamide antagonists. Employing the constraint strategy again, a tetrahydroisoquinoline core was introduced as a tethered phenyl ring, resulting in further potency enhancement (Figure 2.5). Through combining the *tert*-



R = Et, IC_{50} = 5,57 ± 1.15 μM
R = *i*Pr, IC_{50} = 0.86 ± 0.06 μM
R = *t*-Bu, IC_{50} = 0.06 ± 0.01 μM
R = Bn, IC_{50} = > 18.0 μM

Figure 2.4. Sulfonamide analogues with various *N*-alkylation

butyl and tetrahydroisoquinoline modification, a number of analogues with single digit nanomolar IC_{50} were obtained based on the [^{35}S]GTPγS functional assay which measures the level of G protein activation following agonist occupation of a GPCR by determining the binding of the non-hydrolyzable analog [^{35}S]GTPγS to G alpha subunits.).

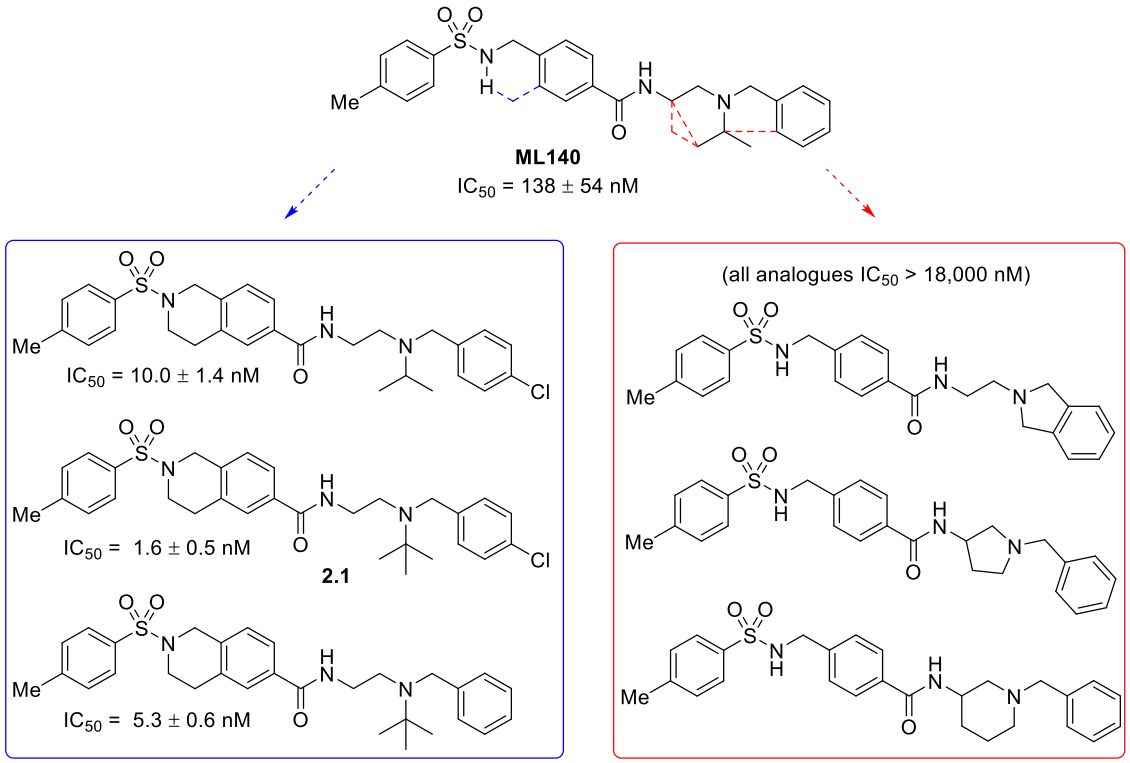
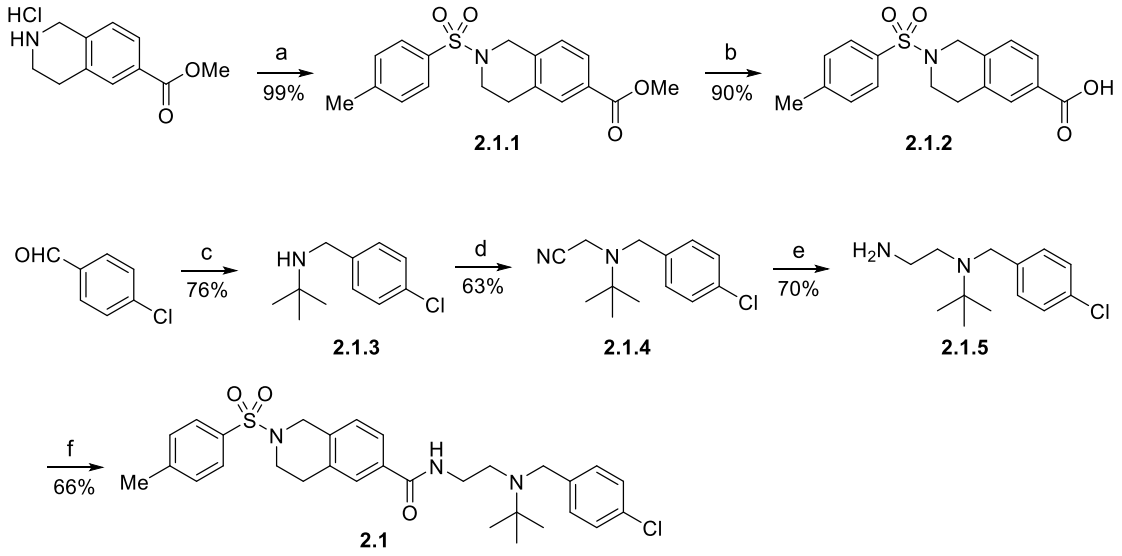


Figure 2.5. Two directions of constraint introduction

Through the SAR studies described above, compound **2.1** (IC_{50} = 1.6 ± 0.47 nM in GTPγ assay, IC_{50} = 83.5 ± 20.3 nM in DiscoveRx Pathhunter β-Arrestin assay) was chosen as lead compound for further optimization and SAR study. The synthesis of **2.1** employed same sequence as the general synthetic route, except switching $SOCl_2$ to HATU at the last step (Scheme 2.2).

Scheme 2.2. Synthesis of Lead Compound **2.1**[a]



[a]Reagents and conditions: a) p-toluenesulfonyl chloride (1.0 equiv), TEA (3.0 equiv), DCM, rt, 3 h; b) NaOH (1 N), H_2O, MeOH, THF, rt, 24 h; c) *tert*-butylamine (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), AcOH (1 drop), DCE, rt, 12 h; d) $ClCH_2CN$ (1.1 equiv), KI (1.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, rt, 12 h; e) $LiAlH_4$ (1.1 equiv), rt, overnight; f) HATU (1.0 equiv), DIPEA (3.0 equiv), compound **2.1.2**, anhydrous DMF, rt, 12 h

Results and Discussion

Design and Synthesis of Analogues

Our initial goal on optimization of analogue **2.1** is to reduce unnecessary portions of the molecule to simpler structures with retention of biological action, with the idea that pharmacophore which is responsible for drug-target interaction could be a small portion of the molecule.[29] Thus, it was interesting to test if the carboxylic acid or diamine portions of analogue **2.1** were part of the pharmacophore and thus essential for the biological effect. To address this question, analogues **2.2, 2.3** and **2.4** were designed, replacing acid or diamine moiety of **2.1** with a simple and smaller chemical group (Figure 2.6). The synthesis of these three analogues employed

common intermediates (either acid or diamine) to couple with a simple amide coupling partner (see Experimental Section).

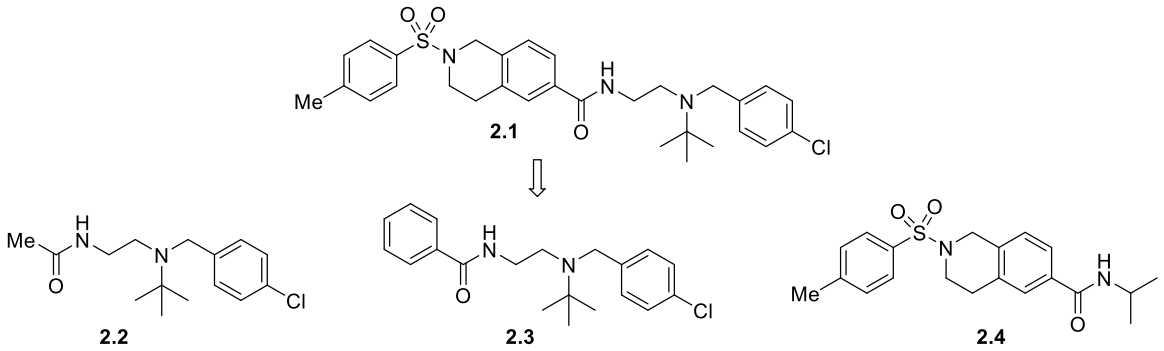


Figure 2.6. Structures of simplified sulfonamide analogues

Linker modification is common in medicinal chemistry, which help extend SAR and give useful information about ligand receptor interactions. At this stage, none of the analogues made by us contained linkers other than the sulfonamide bond. Thus, to determine whether this sulfonamide moiety is replaceable or not, we made analogues without sulfonamide linker.

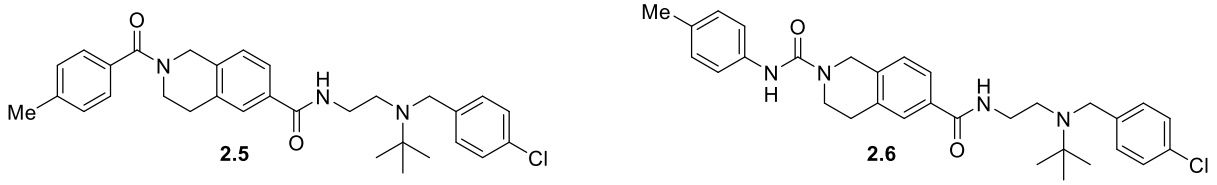
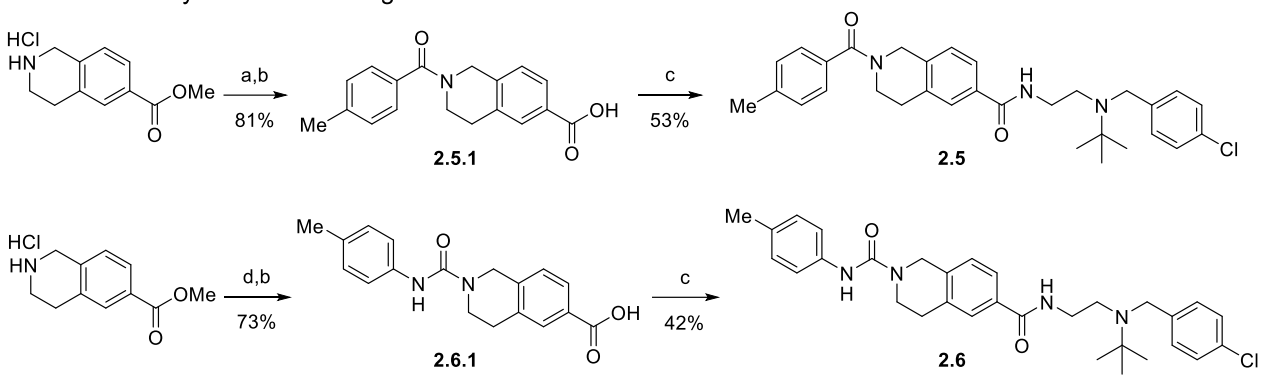


Figure 2.7. Structures of sulfonamide analogues with amide and urea linkers

Analogue **2.5** and its urea derivative **2.6** (Figure 2.7) were proposed to probe the necessity of sulfonamide linker. The synthesis of compound **2.5** followed a route similar to that used in the sulfonamide series except a minor difference in the preparation of carboxylic acid intermediate (Scheme 2.3). To form the amide bond containing acid intermediate **2.5.1**, *p*-toluoyl chloride was reacted with tetrahydroisoquinoline core fragment followed by ester hydrolysis. Then HATU promoted amide coupling between **2.5.1** and **2.1.5** afforded the final compound **2.5**. The

preparation of analogue **2.6** started with the reaction between *p*-tolyl isocynate and the tetrahydroisoquinoline core, which followed by hydrolysis to afford the intermediate **2.6.1**. With urea linker intermediate **2.6.1**, HATU promoted amide coupling with diamine **2.1.5** afforded the final compound **2.6** smoothly.

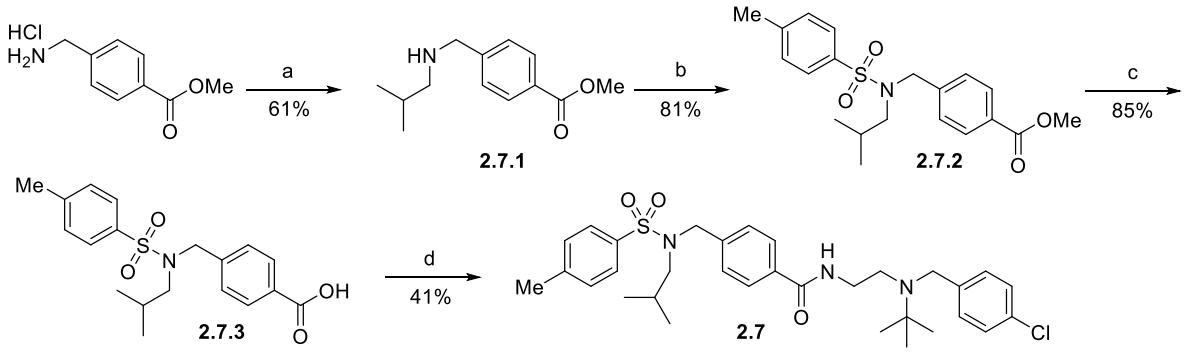
Scheme 2.3. Synthesis of Analogues with Amide and Urea Linker[a]



[a] Reagents and conditions: a) *p*-toluoyl chloride (1.0 equiv), TEA (3.0 equiv), DCM, rt, overnight; b) NaOH (1 N), H_2O, MeOH, THF, rt, 24 h; c) HATU (1.0 equiv), DIPEA (3.0 equiv), diamine **2.1.5**, DMF, rt, 12 h; d) *p*-tolyl isocyanate (1.0 eq), DCM, rt, overnight;

Introducing constraint has proven to be an effective strategy to improve potency in medicinal chemistry. Though the tetrahydroisoquinoline core was originally introduced as a constraint to the molecule that enhanced potency, the possible effect of a hydrophobic contribution to potency warranted further investigation. Thus compound **2.7** was designed as an analogue could involve similar hydrophobic interaction to the tetrahydroisoquinoline moiety. The synthesis of this analogue started with sulfonamide coupling between sulfonyl chloride and ester-bearing amine to afford intermediate **2.7.1**. Subsequent hydrolysis by aqueous NaOH gave acid intermediate **2.7.2**. HATU promoted amide coupling between this acid intermediate **2.7.2** and diamine **2.1.5** afforded compound **2.7** (Scheme 2.4).

Scheme 2.4. Synthesis of Compound **2.7**[a]



[a] Reagents and conditions: a) isobutyraldehyde (1.0 equiv), NaBH(OAc) (1.4 equiv), DCE, rt, 12 h; b) p-toluenesulfonyl chloride (1.0 equiv), TEA (3.0 equiv), DCM, rt, 3 h; c) NaOH (1 N), H_2O, MeOH, THF, rt, 24 h; d) HATU (1.0 equiv), DIPEA (3.0 equiv), **2.1.5** (1.0 equiv), DMF, rt, 12 h

As discussed previously, introduction of central tetrahydroisoquinoline resulted in potency enhancement. Following the same strategy, compound **2.8** was proposed in which another tetrahydroisoquinoline moiety was introduced as a new constraint on compound **2.1**, to explore this class (Figure 2.8). The synthesis of compound **2.8** started with Fischer esterification of (*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, which afforded compound **2.8.1**. (Scheme 2.5) Subsequent reductive amination installed the isopropyl group on nitrogen atom, yielding compound **2.8.2**. Then transamination in aqueous NH_3 at 60 °C and 90 °C for 1 h respectively, yielded the amide intermediate **2.8.3**. However, the stereogenic carbon on tetrahydroisoquinoline racemized under these conditions, which was shown by chiral HPLC (see experiment part). Then this racemate was reduced to a primary amine **2.8.4** with $LiAlH_4$. Subsequent HATU promoted amide coupling between obtained primary amine **2.8.4** and acid intermediate **2.1.2** afforded the final product **2.8** as a racemate, which was used in the bioassay without chiral resolution.

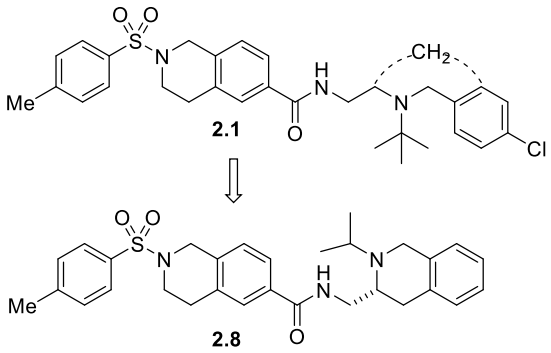
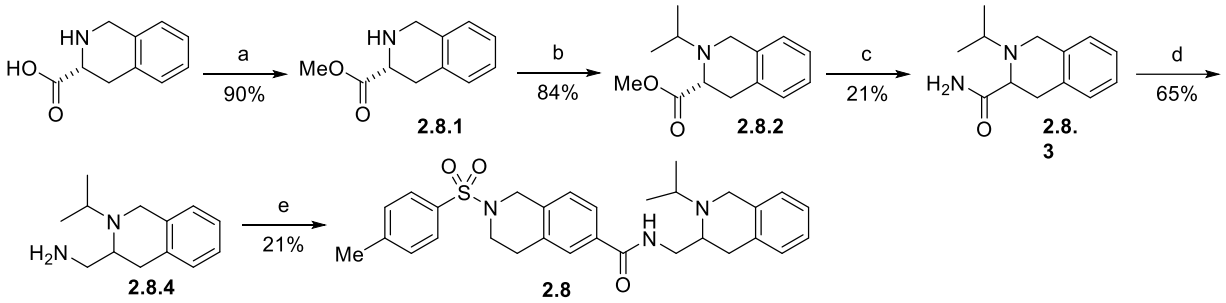


Figure 2.8. Design of constrained compound **2.8**

Scheme 2.5. Synthesis of Constrained Compound **2.8**[a]



[a] Reagents and conditions: a) H_2SO_4 (catalytic), MeOH, reflux, 3 h; b) acetone (1.4 equiv), NaBH(OAc) (1.4 equiv), AcOH (1.0 equiv), DCE, rt, 24 h; c) aqueous NH_3 (28-30%), Parr reactor, 60 °C for 24 h, then 90 °C for 24 h; d) $LiAlH_4$ (4.0 equiv), THF, relflux, 3 h; e) HATU (1.0 equiv), DIPEA (3.0 equiv), **2.1.2** (1.0 equiv), DMF, rt, 12 h

As mentioned previously, JDTic discovered by F. Ivy Carroll and his colleagues, is a selective and potent KOR antagonist.[16] Our sulfonamide opioids and JDTic share some common features. First, they both possess a diamine moiety in which the two nitrogen atom are separated by an ethylene fragment. Secondly, they both contain aromatic rings at either end of molecule. In previous work, we have not explored substitutions on the diamine linker (like isopropyl on JDTic) nor introduced a hydroxyl substituent on the two aromatic rings. Thus, two groups of analogues having these substitutions were proposed (Figure 2.9).

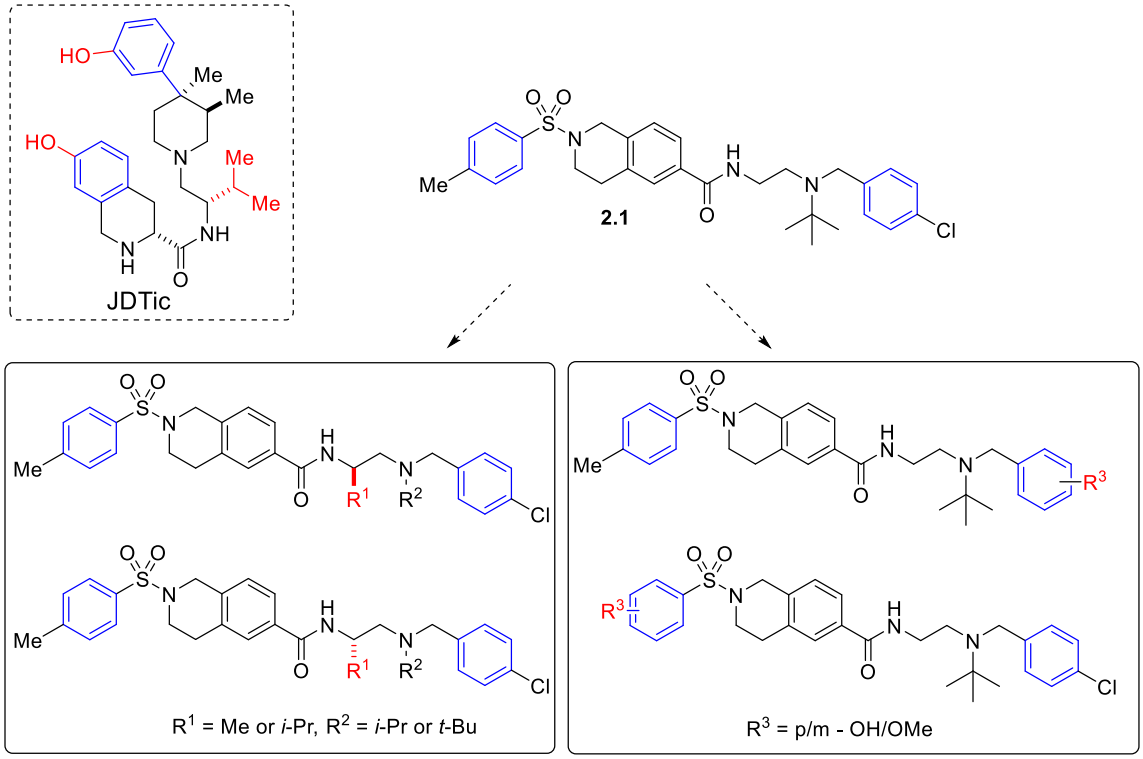
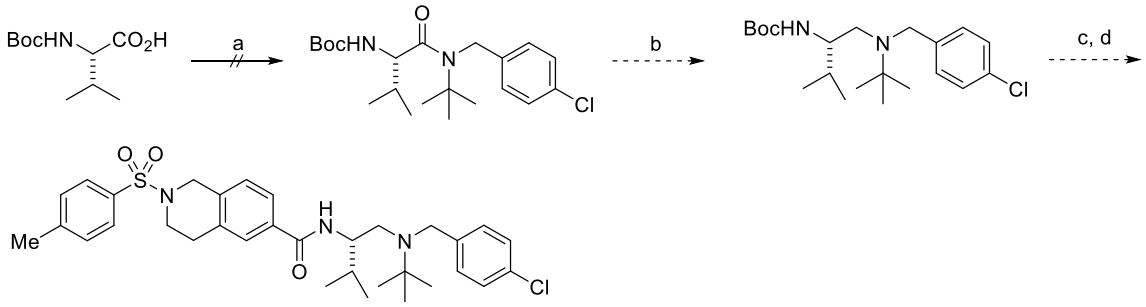


Figure 2.9. JDTic inspired sulfonamide analogues

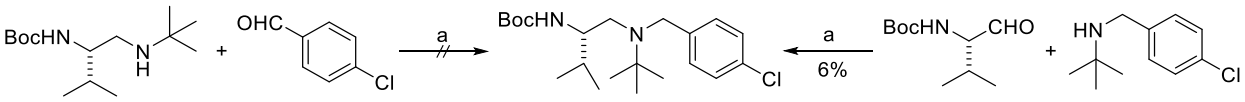
However, the first group of analogues could not be synthesized via the general route above. To prepare this group of analogues, a synthetic strategy similar to that utilized in the preparation of JDTic and its related analogues was first attempted.[30] This route started with amide coupling between Boc-protected amino acid and amine, which was followed by reduction of amide by BH_3 to afford Boc-protected diamine intermediate. Then Boc deprotection followed by amide synthesis would yield the final product (Scheme 2.6). The first step of this synthetic route failed when coupling between Boc-L-valine and intermediate **2.1.3** was attempted using a number of coupling reagents (HATU, CDI, PyBOP, etc.) at varied temperatures. The sluggishness of this transformation was possibly caused by the steric hindrance of the two reactants.

Scheme 2.6. Initial Synthetic Route of Sulfonamide with Alkyl Substituted Diamine Linker[a]



[a]Reagents and conditions: a) coupling reagent (1.0 equiv), compound **2.1.3**, DMF; b) BH_3, reflux, overnight; c) TFA, DCM, rt, 3 h; d) **2.1.2**, HATU (1.0 equiv), DIPEA (4.0 equiv), DMF, rt, 12 h

Scheme 2.7. Two Reductive Amination Approaches to Boc-diamine Linker with Alkyl Substitution[a]

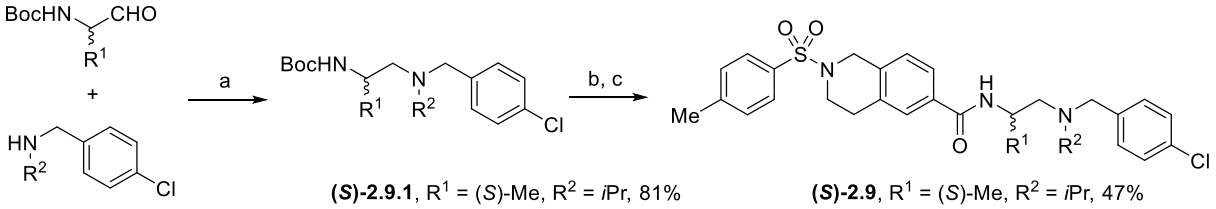


[a]Reagents and conditions: a) $NaBH(OAc)_3$ (1.4 equiv), AcOH (1.0 equiv), DCE, rt, 7 d

In light of this failure, two reductive amination approaches were examined (Scheme 2.7), given the idea that an electronic aldehyde would be much smaller and easier accessed by amine, compared with the activated ester as electrophile in amide coupling.[31] Satisfyingly, one approach (with aliphatic aldehyde) offered the desired product. The other approch (with aromatic aldehyde) failed, which could be potentially caused by the relatively low reactivity of 4-chlorobenzyldehyde. After the success of reductive amination with most steric hindered reactants in this series, all other Boc-diamine linkers were prepared via this method (Scheme 2.8). Once this intermediate was obtained, Boc-deprotection with TFA and subsequent HATU promoted amide coupling with acid

2.1.2, afforded the final sulfonamide product (Scheme 2.8).

Scheme 2.8. Synthesis of JDTic Inspired Sulfonamide-Group 1[a]



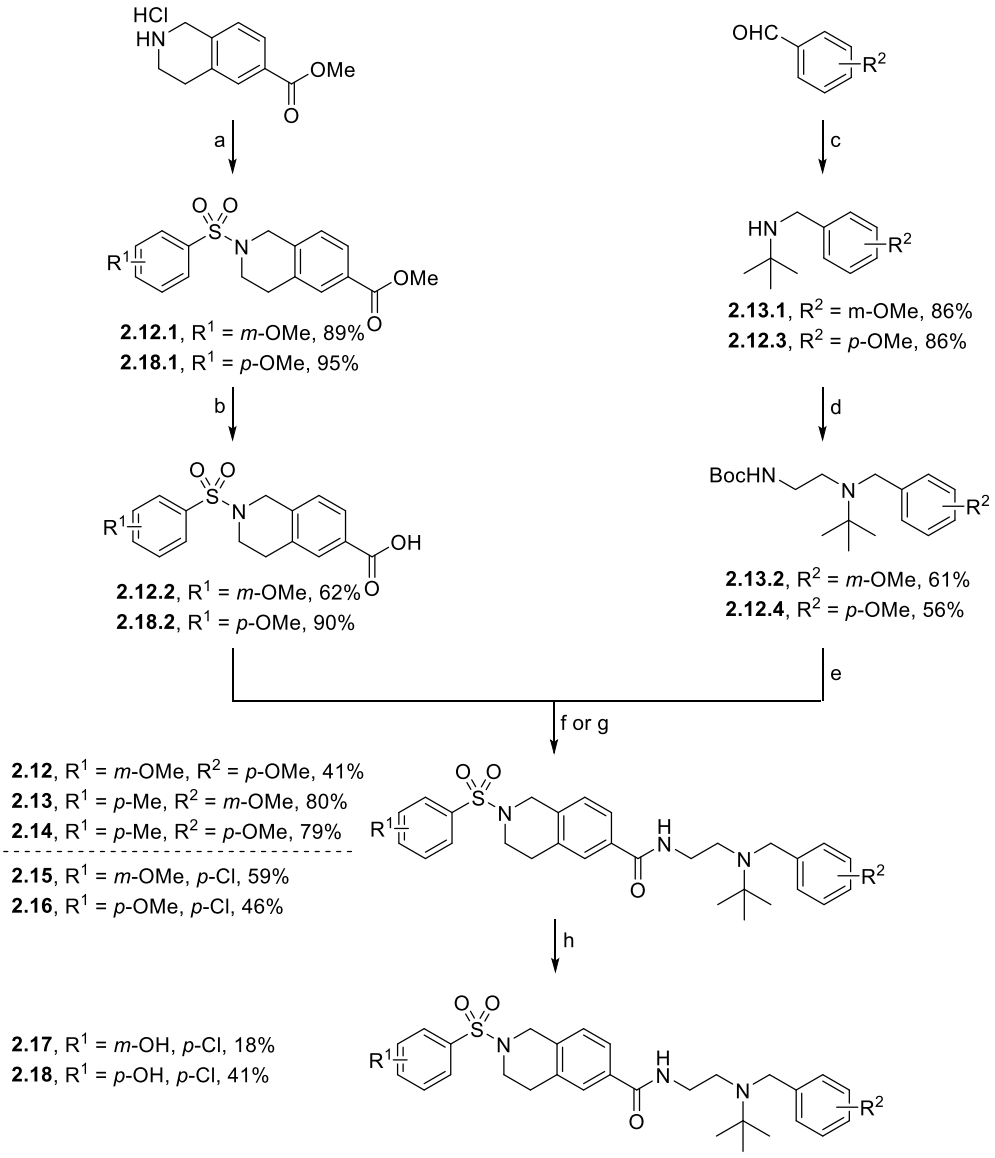
(***S***)-**2.9.1**, R^1 = (*S*)-Me, R^2 = *i*Pr, 81%
(***R***)-**2.9.1**, R^1 = (*R*)-Me, R^2 = *i*Pr, 81%
(***S***)-**2.10.1**, R^1 = (*S*)-Me, R^2 = *t*-Bu, 47%
(***R***)-**2.10.1**, R^1 = (*R*)-Me, R^2 = *t*-Bu, 46%
(***S***)-**2.11.1**, R^1 = (*S*)-*i*Pr, R^2 = *t*-Bu, 6%
(***R***)-**2.11.1**, R^1 = (*R*)-*i*Pr, R^2 = *t*-Bu, 37%

(***S***)-**2.9**, R^1 = (*S*)-Me, R^2 = *i*Pr, 47%
(***R***)-**2.9**, R^1 = (*R*)-Me, R^2 = *i*Pr, 52%
(***S***)-**2.10**, R^1 = (*S*)-Me, R^2 = *t*-Bu, 53%
(***R***)-**2.10**, R^1 = (*R*)-Me, R^2 = *t*-Bu, 68%
(***S***)-**2.11**, R^1 = (*S*)-*i*Pr, R^2 = *t*-Bu, 74%
(***R***)-**2.11**, R^1 = (*R*)-*i*Pr, R^2 = *t*-Bu, 87%

[a]Reagents and conditions: a) $NaBH(OAc)_3$ (1.4 equiv), AcOH (1.0 equiv), DCE, rt, 3 or 7 d; b) TFA, DCM, rt, 3 h; c) HATU (1.0 equiv), DIPEA (4.0 equiv), **2.1.2** (1.0 equiv), rt, 12 h

The synthesis of second group of analogues followed the same sequence discovered during the preparation of first group, except employing different building blocks as needed (Scheme 2.9). The hydroxyl-bearing analogue was prepared by BBr_3 demethylation of methoxy-bearing analogues.

Scheme 2.9. Synthesis of JDTic Inspired Sulfonamide-Group 2[a]



[a]Reagents and conditions: a) corresponding sulfonyl chloride (1.0 equiv), TEA (3.0 equiv), DCM, rt, 3 h; b) NaOH (1 N), H_2O, MeOH, THF, rt, 24 h; c) *tert*-butylamine (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), AcOH (1 drop), DCE, rt, 12 h; d) *N*-Boc-2-aminoacetaldehyde (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), AcOH (1 drop), DCE, rt, 24 h; e) TFA-DCM (1:1), rt, 3 h; f) HATU (1.0 equiv), DIPEA (4.0 equiv), corresponding acid component (1.0 equiv), anhydrous DMF, rt, 12 h; g) HATU (1.0 equiv), DIPEA (3.0 equiv), **2.1.5** (1.0 equiv), anhydrous DMF, rt, 12 h; h) BBr_3 (15 equiv), DCM, 0°C, 2 h

Eleven compounds (**2.19** to **2.29**) were proposed to explore the effects of substitutions on the right phenyl ring as well as replacement of this phenyl ring with pyridine (Figure 2.10). Methylthio, dimethylamino, methoxymethyl, hydroxymethyl, acetamido, and ethyl group (**2.19** to **2.22**, **2.25**, and **2.26**) were chosen to be incorporated into the para-position of phenyl ring, as direct

comparison with **2.1** and **2.14**. Dioxine and dioxole moiety were introduced as constrained oxygen-bearing substitutions on the phenyl ring (**2.23** and **2.24)**. Pyridine was a common moiety found in drug molecules, and often employed at early stage of drug discovery to adjust cLogP of small molecule. Thus three compounds (**2.27**, **2.28**, and **2.29**) with pyridine substitutions were proposed, which possess much lower cLogP (~ 4) compared compound **2.1** (5.8). It is worth noting that protonation of pyridine containing compounds under physiological condition would result in even lower cLogD and better solubility in aqueous meida.

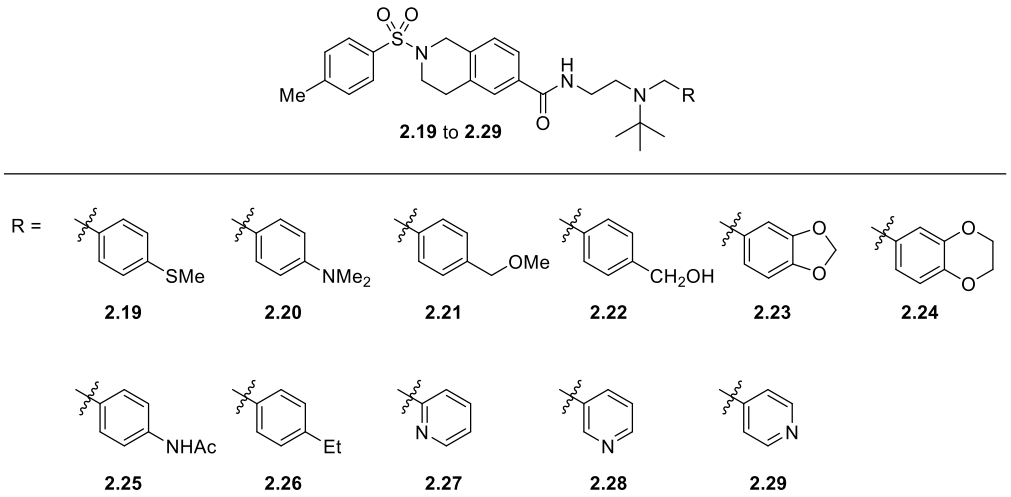
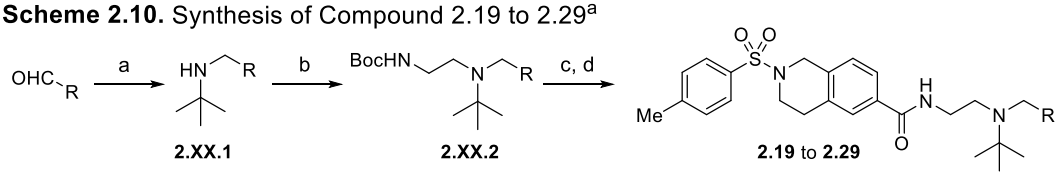


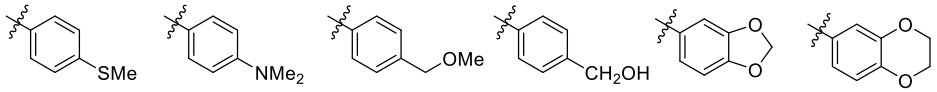
Figure 2.10. Structures of compound **2.19** to **2.29**

The successive reductive amination strategy was again employed to prepare this set (Scheme 2.10). Two successive reductive amination afforded the Boc-diamine intermediate. Then, deprotection of Boc-diamine, followed by amide bond formation promoted by HATU, afforded the final product. For the pyridine containing compounds, the two successive reductive aminations were carried out in one pot with only one workup and one purification to yield stable Boc-diamine intermediates (**2.27.2**, **2.28.2**, and **2.29.2**), in comparable overall yield with two-step procedure.

Scheme 2.10. Synthesis of Compound 2.19 to 2.29[a]



R =



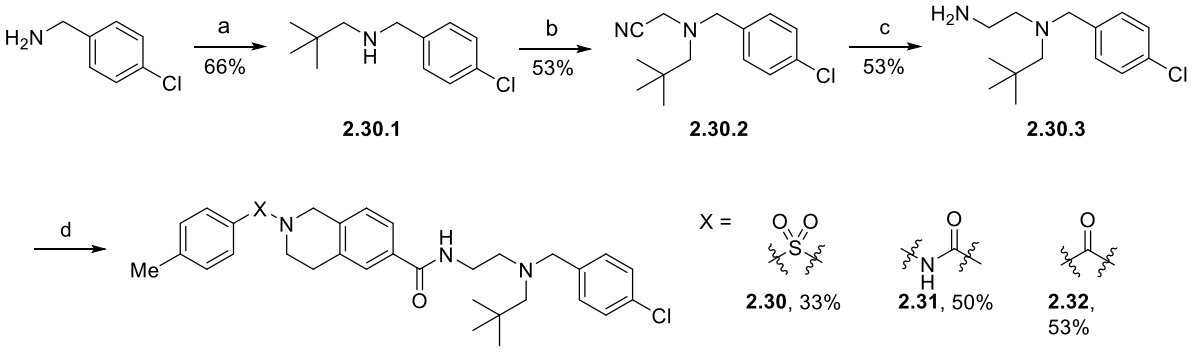
2.19.1, 60%	**2.20.1**, 78%	**2.21.1**, 72%	**2.22.1**, 72%	**2.23.1**, 82%	**2.24.1**, 88%
2.19.2, 68%	**2.20.2**, 57%	**2.21.2**, 50%	**2.22.2**, 50%	**2.23.2**, 68%	**2.24.2**, 60%
2.19, 63%	**2.20**, 53%	**2.21**, 53%	**2.22**, 64%	**2.23**, 51%	**2.24**, 47%

2.25.1, 86%	**2.26.1**, 39%			
2.25.2, 48%	**2.26.2**, 52%	**2.27.2**, 49%	**2.28.2**, 35%	**2.29.2**, 43%
2.25, 64%	**2.26**, 52%	**2.27**, 60%	**2.28**, 77%	**2.29**, 77%

[a]Reagents and conditions: a) *tert*-butylamine (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), AcOH (1 drop), DCE, rt, 12 h; b) *N*-Boc-2-aminoacetaldehyde (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), AcOH (1 drop), DCE, rt, 12 h; c) TFA, DCM, rt, 3 h; d) HATU (1.0 equiv), DIPEA (4.0 equiv), **2.1.2** (1.0 equiv), anhydrous DMF, rt, 12 h

Finally, a new diamine with bigger alkyl substitution on nitrogen was prepared to test the role of overall hydrophobicity at this position. This diamine was incorporated into final analogues containing three different bioisosteries (Scheme 2.11).

Scheme 2.11. Synthesis of Compound **2.30** to **2.32**[a]



[a]Reagents and conditions: a) trimethylacetaldehyde (1.0 equiv), $NaBH(OAc)_3$ (1.4 equiv), AcOH (1 drop), DCE, rt, 12 h; b) $ClCH_2CN$ (1.1 equiv), KI (1.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, rt, 12 h; c) LiAlH4 (1.1 equiv), THF, rt, overnight; d) HATU (1.0 equiv), DIPEA (4.0 equiv), correspongding acid (1.0 equiv), anhydrous DMF, rt, 12 h

In Vitro Assay Studies

The sulfonamide final compounds were assayed using a DiscoveRx PathHunter® β-arrestin GPCR assay platform.[32] This in vitro assay method uses U2OS cells expressing human KOR in an enzyme complementation system designed for detecting recruitment of β-arrestin to the KOR. In this system, KOR is fused in frame with the small 42 amino acid fragment of β-galactosidase (β-gal) called Pro-link™ and co-expressed with cells stably expressing a fusion protein of β-arrestin and the larger, N-terminal deletion mutant of β-gal (called enzyme acceptor or EA). Upon the activation of KOR, β-arrestin binds to the receptor which promotes the complementation of two enzyme fragments, resulting in active β-gal enzyme. This leads to an increase of enzyme activity which is measured by chemiluminescent reagent (Figure 2.11). Briefly, plates loaded with U2OS cells were incubated at 37 °C overnight, and then treated with increasing concentrations of antagonists in the presence of 1 μM U69,593 for 1 h and 30 min at 37 °C. Detection reagent was added for 1 h and luminescent counts were obtained using a Spectramax M5ᵉ.

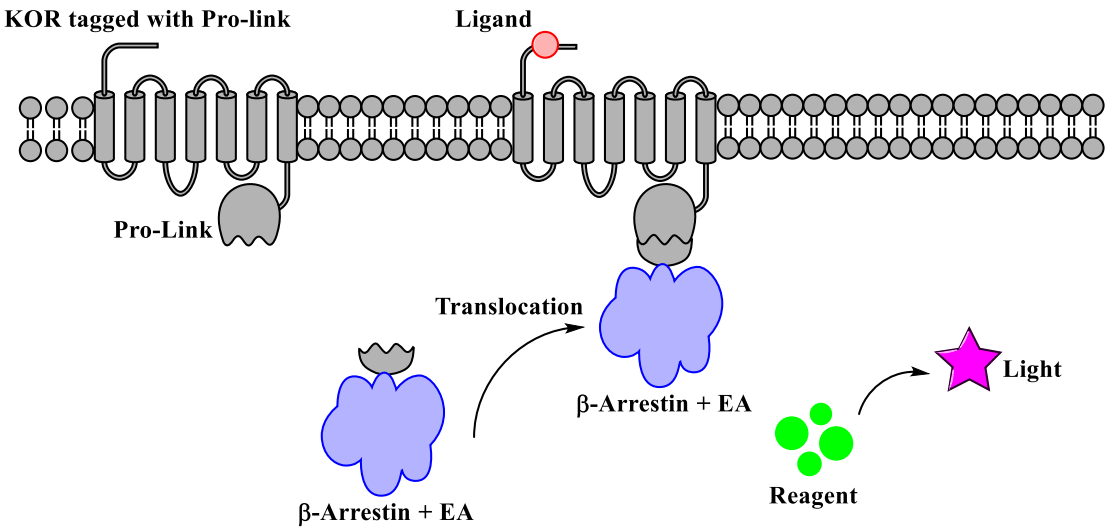
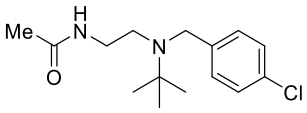


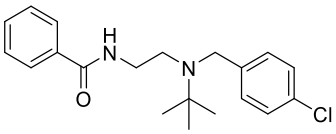
Figure 2.11. Pathhunter® β-arrestin assay principle

Compound **2.2** and **2.3**, designed by replacement of acid fragment of compound **2.1** with acetyl and benzoyl moieties, turned out to be inactive as KOR antagonists (Table 2.1). Similarly, the replacement of diamine fragment of **2.1** with an isopropyl group, as in **2.4**, resulted in complete loss of KOR antagonist activity (Table 2.1). Together, these attempts offer a message that both fragments of lead compound **2.1** are critical.

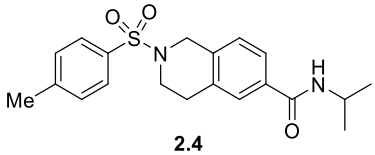
Table 2.1. KOR Antagonist Activity of Simplified Series



2.2



2.3



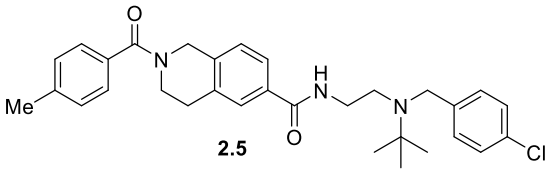
2.4

Entry	Compound	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**2.1**	83.5 ± 20.3	101.2 ± 4.9
2	**2.2**	NC[b]	12.4 ± 3.4
3	**2.3**	> 10,000	60.5 ± 1.5
4	**2.4**	NC[b]	-4.9 ± 2.2

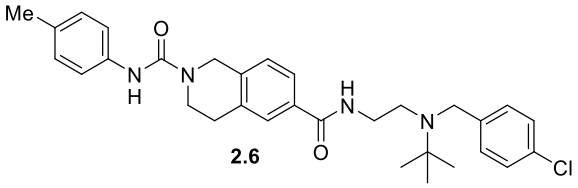
[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM); [b] NC: non-convergent curve caused by insignificant activity

Replacement of sulfonamide linker by amide or urea, turned out to be detrimental for KOR antagonist activity (**2.5** and **2.6**, Table 2.2).

Table 2.2. KOR Antagonist Activity of Amide and Urea Linker Bearing Analogues



2.5



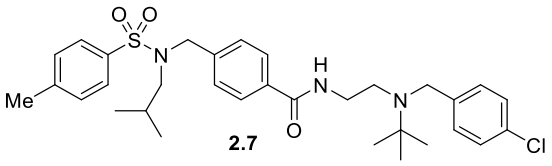
2.6

Entry	Compound	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**2.5**	> 10,000	41.1 ± 2.8
2	**2.6**	> 10,000	66.1 ± 3.4

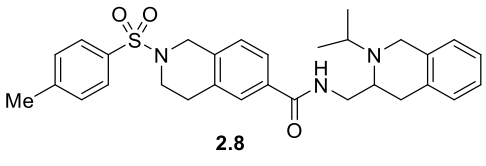
[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM)

Central fragment modification resulted in complete loss of KOR antagonist activity (**2.7**, Figure 2.3). Similarly, the introduction of another tetrahydroisoquinoline as a constraint on the right fragment led to dramatic decrease of KOR antagonist activity (**2.8**, IC_{50} = 1126.0 ± 193.8 nM).

Table 2.3. KOR Antagonist Activity of **2.7** and **2.8**



2.7



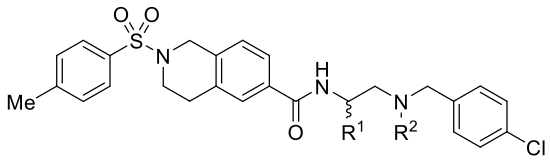
2.8

Entry	Compound	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**2.7**	NC[b]	12.6 ± 4.0
2	**2.8**	1126.0 ± 193.8	106.6 ± 1.1

[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM); [b] NC: non-convergent curve caused by insignificant activity

Alkyl substitution on diamine linker of **2.1** (Me or *i*Pr), of either *S* or *R* configuration, are not tolerated (**(*S*)**- and **(*R*)-2.10**, **(*S*)**- and **(*R*)-2.11**). Though **(*S*)-2.10** demonstrated marginal antagonist activity at the KOR (IC_{50} = 6945.0 ± 3244.0 nM), it was about 80-fold less potent than **2.1**. By switching the *tert*-butyl group of **(*S*)-2.10** to an *i*Pr group, bioactivity was slightly regained (**(*S*)-2.9**, IC_{50} = 3887.0 ± 945.8 nM). However, the enantiomer of **(*S*)-2.9** was completely inactive (**(*R*)-2.9**, Table 2.4). Thus, alkyl substitutions on the alpha-carbon of amide nitrogen are not tolerated.

Table 2.4. KOR Antagonist Activity of JDTic Inspired Series-Group 1

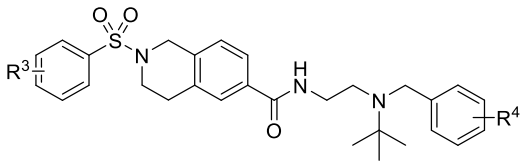


Entry	Compound	R^1	R^2	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**(*S*)-2.9**	(*S*)-Me	*i*Pr	3887.0 ± 945.8	73.2 ± 2.2
2	**(*R*)-2.9**	(*R*)-Me	*i*Pr	NC[b]	25.5 ± 12.3
3	**(*S*)-2.10**	(*S*)-Me	*t*-Bu	6945.0 ± 3244.0	70.4 ± 0.9
4	**(*R*)-2.10**	(*R*)-Me	*t*-Bu	> 10,000	39.9 ± 2.7
5	**(*S*)-2.11**	(*S*)-*i*Pr	*t*-Bu	> 10,000	16.0 ± 4.7
6	**(*R*)-2.11**	(*R*)-*i*Pr	*t*-Bu	NC[b]	-3.1 ± 8.6

[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM);
[b] NC: non-convergent curve caused by insignificant activity

Replacement of 4-methyl group on the left phenyl ring of **2.1** with *p*-hydroxyl group reduced potency (**2.18**, IC_{50} = 391.5 ± 89.9 nM) by about 5-fold, whereas moving the hydroxyl group to the *m*-position afforded compound **2.17** with comparable potency (IC_{50} = 361.6 ± 71.1 nM). Similarly, replacement of *p*-methyl group of **2.1** with methoxy group resulted in drastic decrease of potency (**2.16**, IC_{50} = 9417.0 ± 2720.0 nM). However, moving the methoxy group to *m*-position regained the bioactivity a bit (**2.15**, IC_{50} = 614.8 ± 280.3 nM). Interestingly, further replacement of *p*-chlorine on the right phenyl ring of **2.16** with methoxy group rescued the potency by about 14-fold (**2.12**, IC_{50} = 42.2 ± 2.9 nM), resulting in a compound with slightly better activity than **2.1**. By retaining the right *p*-methoxy group and switching the left *m*-methoxy group back to original *p*-methyl group, the obtained compound **2.14** had even better potency (IC_{50} = 18.9 ± 4.4 nM). In contrast, one single change of **2.14** by moving *p*-methoxy group to the *m*-position led to drastically decreased potency (**2.13**, IC_{50} = 216.8 ± 64.3 nM).

Table 2.5. KOR Antagonist Activity of JDTic Inspired Series-Group 2

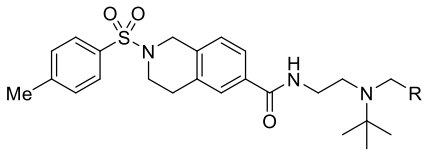


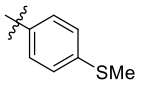
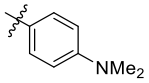
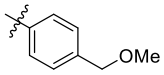
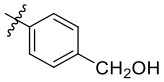
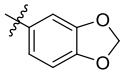
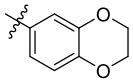
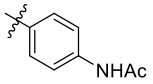
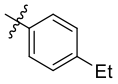
Entry	Compound	R^3	R^4	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**2.12**	*m*-OMe	*p*-OMe	42.2 ± 2.9	100.6 ± 0.3
2	**2.13**	*p*-Me	*m*-OMe	216.8 ± 64.3	102.5 ± 0.6
3	**2.14**	*p*-Me	*p*-OMe	18.9 ± 4.4	104.0 ± 2.4
4	**2.15**	*m*-OMe	*p*-Cl	614.8 ± 280.3	104.5 ± 5.8
5	**2.16**	*p*-OMe	*p*-Cl	9417.0 ± 2720.0	91.2 ± 3.3
6	**2.17**	*m*-OH	*p*-Cl	361.6 ± 71.1	102.8 ± 1.2
7	**2.18**	*p*-OH	*p*-Cl	391.5 ± 89.9	90.5 ± 4.7

[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM)

The bioisosterie replacement of the methoxy group on **2.14** with methylthio group and dimethylamino group, led to mild reduction of activity (**2.19** and **2.20**). Methoxylmethyl group (**2.21**) were tolerated, while hydroxymethyl group led to 7-fold reduction of activity (**2.22**). Dioxine and dioxole introduced as constrained oxygen-bearing group, could not increase potency but were well tolerated (**2.23** and **2.24**). Acetoamido and ethyl introduction led to reduction of potency (4-fold and 8-fold, respectively). Moving from various substituted phenyl ring to pyridine-containing analogues led to drop in potency. Compounds with 2-pyridyl and 3-pyridyl group (**2.27** and **2.28**) were 7-fold less potent than **2.14**. Unfortunately, when 4-pyridyl group was employed, the potency decreased dramatically (**2.29**, IC_{50} = 1521.0 ± 308.0 nM).

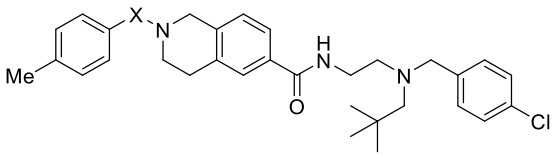
Table 2.6. KOR Antagonist Activity of Compound 2.19 to 2.29



Entry	Compound	R	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**2.19**		142.0 ± 4.2	107.5 ± 4.8
2	**2.20**		56.1 ± 10.9	108.8 ± 5.6
3	**2.21**		45.8 ± 5.4	108.1 ± 6.4
4	**2.22**		131.7 ± 27.6	105.2 ± 2.9
5	**2.23**		56.0 ± 10.1	105.7 ± 4.5
6	**2.24**		34.0 ± 1.8	108.6 ± 7.7
7	**2.25**		80.3 ± 15.2	106.0 ± 3.8
8	**2.26**		150.8 ± 16.0	100 ± 1.5
9	**2.27**		138.4 ± 26.7	102.5 ± 2.7
10	**2.28**		137.7 ± 19.9	100.2 ± 1.9
11	**2.29**		1521.0 ± 308.0	102.7 ± 1.6

[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM)

Table 2.7. KOR Antagonist Activity of Miscellaneous Series



X =  **2.30**  **2.31**  **2.32**

Entry	Compound	[a]IC_{50} (nM) ± SEM	I_{max} (%) ± SEM
1	**2.30**	NC[b]	5.4 ± 1.1
2	**2.31**	NC[b]	-2.3 ± 2.5
3	**2.32**	NC[b]	23.6 ± 2.6

[a] DiscoveRx Pathhunter β-arrestin assay with n = 3 unless noted, compared to NorBNI (IC_{50} = 2.0 ± 0.1 nM); [b] NC: non-convergent curve caused by insignificant activity

Replacement of *tert*-butyl group of **2.1** with neopentyl group, resulted in complete loss of bioactivity (**2.30**). It is interesting that a carbon extension had such a detrimental effect, suggesting there is not enough room in the receptor to accommodate this further elongation of alkyl substitution. Lastly, switching the sulfonamide linker of **2.30** to urea or amide (**2.31** and **2.32**) could not restore the activity.

Putative Binding Mode

Based on bioactivity data of analogues made previously and new data we obtained in this round of SAR exploration, modeling studies were carried out by Professor Phil Mosier from Virginia Commonwealth University.

Sulfonamide analogues were sketched using SYBYL-X 2.1.1 (Certara USA, Inc., Princeton, NJ) and energy minimization was carried out with the Tripos Force Field (TFF; Gasteiger–Hückel charges, distance-dependent dielectric constant ε = 4D/Å, nonbonded interaction cut-off = 8 Å, energy gradient termination = 0.05 kcal/(mol×Å) or 100,000 iterations). The KOR−JDTic co-crystal structure (PDB: 4DJH)[18] was prepared for docking through a series of process including extraction of the "B" chain (KOR protein only), removal of the JDTic ligand and addition of hydrogen atoms. Other crystal structures were prepared in an analogous fashion (*vide infra*). Additionally, to mitigate the bias imposed by the "imprint" caused by the original ligand and to explore alternative receptor conformational states, MODELLER 9.16[33] was used to create a population of 100 KOR homology models for each of three different KOR and MOR templates: 1) the antagonist-bound KOR–JDTic co-crystal structure (PDB: 4DJH; B chain), 2) the antagonist-bound MOR–β-FNA co-crystal structure (PDB: 4DKL; A chain)[34], and 3) the nanobody-stabilized

agonist-bound MOR–BU72 co-crystal structure (PDB: 5C1M; A chain).[35] To facilitate comparison of ligand binding modes, each homology model was spatially aligned to its crystal structure template.

Ligands were flexibly docked to the KOR crystal structure (PDB: 4DJH) and to each member of the three KOR homology model populations with GOLD Suite 5.2 (Cambridge Crystallographic Data Centre, Cambridge, UK)[36] in order to generate candidate binding modes. In each case, the Goldscore fitness function was employed, and cavity detection was enabled. In addition, the ligand binding site was defined to include all receptor amino acid residues within 15 Å of the gamma carbon atom of D138(3.32), encompassing all amino acids within the orthosteric binding site. Free ring corners and pyrimidal nitrogens were allowed to flip. To facilitate the interactions between the cationic ligands and D138(3.32), a constraint was introduced that disfavored solutions in which the ligand did not form a hydrogen bond with either oxygen of the D138 side chain carboxylate group (fitness function lowered by 10 Goldscore units).

An in-house clustering algorithm[37] was employed to facilitate the identification of common and disparate binding modes for the ligands. Briefly, each ligands was flexibly docked ten times into each of the spatially aligned homology models generated above. Then, the top scoring solution for each ligand at each receptor model was selected, which were subsequently clustered at a cutoff RMSD value of 2.0 Å to identify different binding modes for each ligand. The highest-scoring solution from each cluster (binding mode) was selected to represent that particular binding mode and referred to as the exemplar. All exemplars for all ligands were then combined and clustered based on the RMSD of their common scaffold structure to identify common binding modes among the series of compounds. The common binding modes were then manually evaluated for stereoelectronic complementarity and consistency with experimentally derived ligand SAR. A

commonly-shared binding mode among the ML140 analogues was identified in the KOR homology model population derived from the antagonist-bound MOR–β-FNA co-crystal structure (PDB: 4DKL); these solutions were selected for further refinement and analysis. In a few cases, manual modification of KOR side chains and ligand torsion angles were performed after completion of the automated docking routines to further optimize the proposed receptor–ligand interactions. The resulting receptor−ligand complexes were then energy-minimized in SYBYL-X 2.1.1 using the Tripos Force Field (TFF; Gasteiger–Hückel charges, distance-dependent dielectric constant ε = 4D/Å, nonbonded interaction cut-off = 8 Å, energy gradient termination = 0.05 kcal/(mol×Å) or 500 iterations).

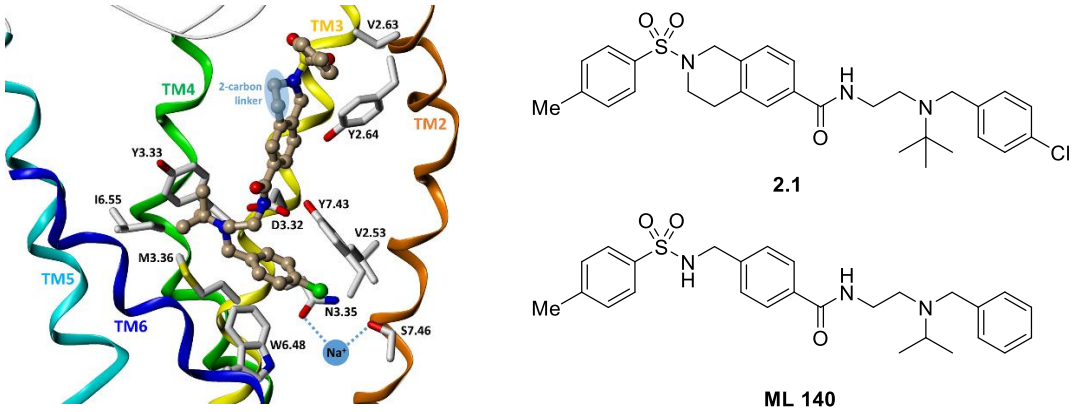


Figure 2.12. Putative binding mode of 2.1 with the KOR

Compound **2.1** was used to elucidate the putative binding mode between this chemotype and receptor (Figure 2.11). The western phenyl ring engages tight hydrophobic interactions with V2.63 and edge-face aromatic interactions with Y2.64. This tight binding site explains why bulk or multi-substitution on this phenyl ring decrease the potency. One oxygen in sulfonamide linker is involved in a hydrogen bond with the proton on an amide nitrogen of the backbone. The proton on central

amide moiety, together with protonated nitrogen on diamine fragment, is involved in two hydrogen bonds with side chain of D3.32, respectively. This explains why the methylation of amide nitrogen lead to complete loss of activity. In addition, the *tert*-butyl group has hydrophobic interactions with Y3.33 and I6.55. The phenyl ring on the diamine fragment is sandwiched between W6.48 and Y7.43 via pi-stacking interactions. Lastly, the 2-carbon linker on isoquinoline rigidifies the ML140 scaffold, which enhances the interactions mentioned previously.

Conclusions

Structural modification centered on compound **2.1** afforded a total of 34 new analogues, which further enriched the SAR of sulfonamide chemotype (Figure 2.13). Compared with compound **2.1**, several analogues with better potency were obtained. By collaborative efforts, a putative binding mode of this chemotype with the KOR were proposed (Figure 2.12), which would be used to guide the further optimization of lead compound.

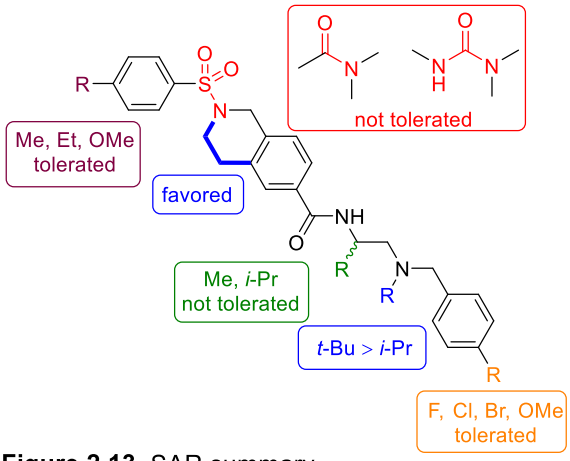


Figure 2.13. SAR summary

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Chapter 3

Asymmetric Acyl Transfer Reactions Catalyzed by a Cyclic Peptide

Introduction

Kinetic resolution (KR), according to IUPAC's 1996 recommendation, is "the achievement of partial or complete resolution by virtue of unequal rates of reaction of enantiomers in racemate with a chiral agent (reagent, catalyst, solvent, etc.)".[1] KR relies on the differences in reactivity between enantiomers in the presence of a chiral agent. In the simplest case, two competing diastereomeric transition states are generated by the interactions between the substrate enantiomers via interacting with a chiral agent respectively, and these two transition states possess different activation energies which govern the rate constants for the conversion of the enantiomers. Lastly, the product distribution is controlled by the ratio of rate constant k_{fast}/k_{slow} (equal to k_{rel} or enantioselectivity *s*), which describes how selective a KR is. With high k_{rel} and enough percentage of conversion, the majority of the fast-reacting enantiomer would be converted to product while slow-reacting enantiomer could be isolated in enantiopure form after the reaction (Figure 3.1).[2]

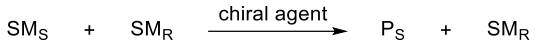
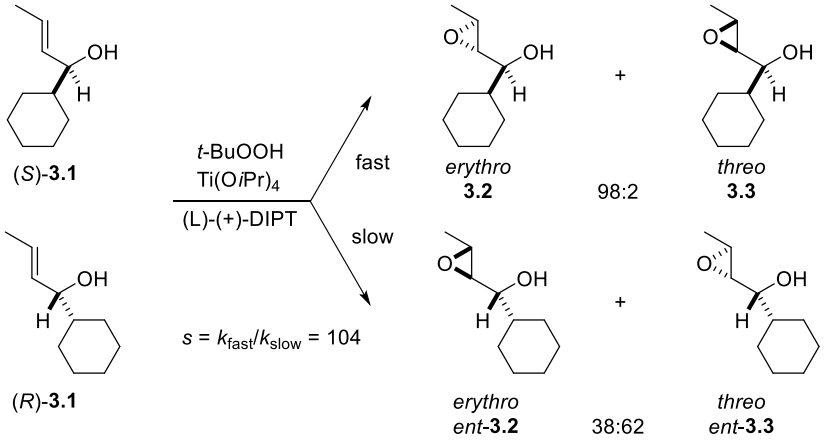


Figure 3.1. Kinetic resolution

The earliest phenomenon of KR, observed in 1858 by Pasteur, was that the dextrorotatory isomer of racemic ammonium tartrate was selectively destroyed during the fermentation with penicillium glaucum.[2] Though the structural basis was not yet known, Pasteur understood that the reactive and unreactive isomers were mirror image forms to one another. The first non-enzymatic KR was reported by Marckwald and Mckenzie. In this work, racemic mandelic acid was

enantioselectively esterified by (–)-menthol upon heating the reactants, with small amount of L-mandelic acid recovered after recrystallization.[4] In 1981, a milestone paper about KR of allylic alcohol substrates was reported by Sharpless and co-workers.[5] In one of the best examples in this report, allylic alcohol (*S*)-**3.1** was converted to epoxide products much faster than (*R*)-**3.1** (*s* = 104). The unreacted alcohol was recovered with high *ee* (>96%), while the epoxy alcohol product with good erythro/threo ratio (97:3). This significant work stimulated the development of chiral supports for HPLC and GC assays that could precisely measure enantiomeric ratios with 96–99.9% *ee*.

Scheme 3.1. Kinetic Resolution of (±)-3.1 Reported by Sharpless



Synthetic oligopeptides as mimics of enzyme have been increasingly investigated as catalyst for asymmetric transformation in the past several decades.[6-14] However, synthetic oligopeptides with high efficiency and low molecular weight are still in great demand. It is believed that the conformational rigidity is critical for a chiral inducing agent, which is also true for oligopeptide catalysts. Usually cyclic peptides possess reduced freedom of rotation, and are accordingly more rigid compared with liner peptides. For example, cyclic dipeptide **3.4** (Figure 3.2), reported by Inoue and co-workers, catalyzed asymmetric hydrocyanation of benzaldehyde with 90% *ee*.[15] In contrast, linear poly-L-alanine **3.5** (Figure 3.2) is a catalyst of the Julia-Colonna

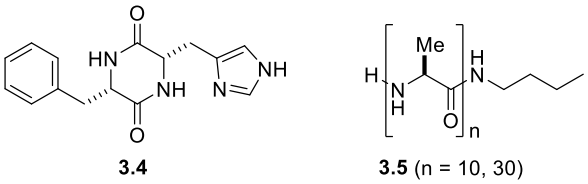


Figure 3.2. Representatives of oligopeptide catalysts

epoxidation but can only afford excellent asymmetric induction when it is longer than 10-mer and form the stable α-helix structure.[16]

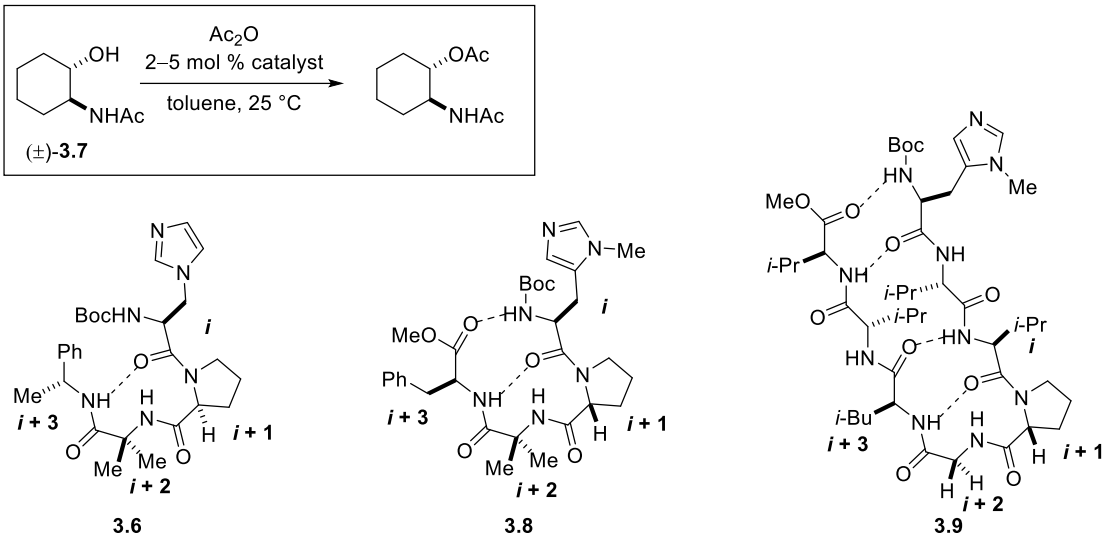


Figure 3.3. Illustration of KR by Miller's catalysts

Synthetic oligopeptides have been exploited as catalyst for KR. Starting from 1998, Miller's research group reported a series of oligopeptides as catalysts for asymmetric acyl-transfer reactions.[17-20] These oligopeptides contain a β-turn motif, including an intra-main-chain hydrogen bond between carbonyl of residue *i* and NH of residue *i* + 3 (Figure 3.3). Tripeptide **3.6**, reported in 1998, was the first in this series.[17] As the described in this report, **3.6** (Figure 3.3) was shown to catalyze the acetylation of (*S*,*S*)-**3.7** faster than (*R*,*R*)-**3.7** (*s* = 13). Optimization of reaction conditions revealed that selectivity was enhanced with solvents which do not interrupt hydrogen bonding. For example, optimum selectivities were obtained with toluene while decreased selectivities were observed by using DCM, $CHCl_3$, or $CHCl_3$–*t*-BuOH (1:1) as solvent. Optimization of **3.6** afforded several oligopeptide catalysts with enhanced selectivities, including a tetrapeptide (**3.8**) and an octapeptide (**3.9**), which promoted the same reaction with *s* values of

28 and 51, respectively.[18] Kinetic studies indicated the order of substrate (**3.7**) and catalyst (**3.9**) were each 1 under conditions of high dilution.

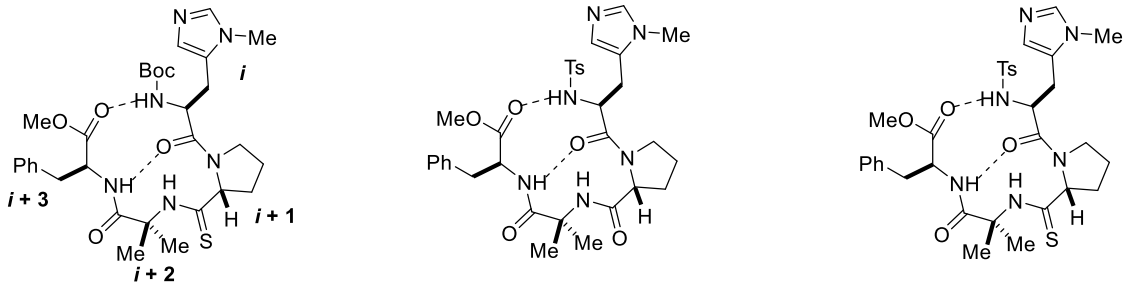


Figure 3.4. Representatives of Qu's tetrapeptide catalysts

In 2011, a series of tetrapeptides were reported by Qu's research group (Figure 3.4), which were designed by backbone modification of Miller's catalyst **3.8**.[21] Thioamide replacement of amide at the *i*+1 residue (**3.10**) afforded a peptide capable of acylating **(±)-3.7** with an *s* value of 20. This could be increased to a value of 63 by adding 0.2 equiv of *N*,*N*-diisopropylethylamine (DIPEA) to the reaction. It was believed the thioamide could reinforce the intermolecular hydrogen bond between the catalyst and the substrate while the DIPEA could absorb the proton generated in the reaction and maintain the imidazole in a neutral status which was critical for the catalysis. The replacement of the Boc group on the *i* residue with a tosyl group afforded catalyst **3.11** which acylated **(±)-3.7** with an *s* value of 40. This could be modestly elevated to a value of 44 by adding 0.2 equiv of DIPEA in the reaction. It was believed that the introduction of tosyl group made the proton of NH on *i* residue more acidic, which resulted in a strengthened intramolecular hydrogen bond and a more rigid conformation for the catalyst. By introducing the thioamide and tosyl group at the same time, a tetrapeptide **3.12** that afforded the best selectivities (*s* = 109 on substrate **(±)-3.7**) in this series was obtained.

Results and Discussion

Employment of 6-aminocaproic acid (Aca) as a dipeptide linker was reported by Woody and Scheraga, who demonstrated that such macrocycles adopted a β-turn around the dipeptide unit (Figure 3.5).[22-23] They also pointed out that the conformation adopted by such macrocycles was quite dependent on the amino acid stereochemistry. In general, type I β-turn was preferred by macrocycles derived from L,L-dipeptides, whereas type II subtype was favored by L,D-dieptides. Our research lab also observed this phenomena by employing similar linkers (Figure 3.5)[24-25].

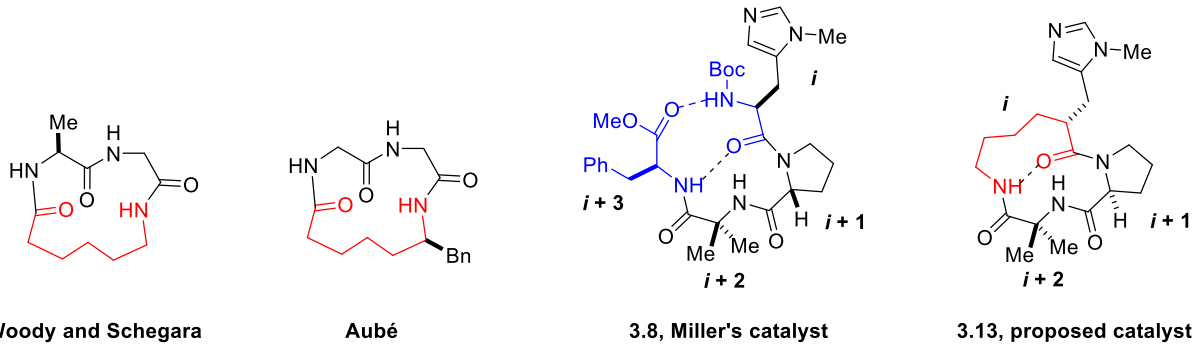
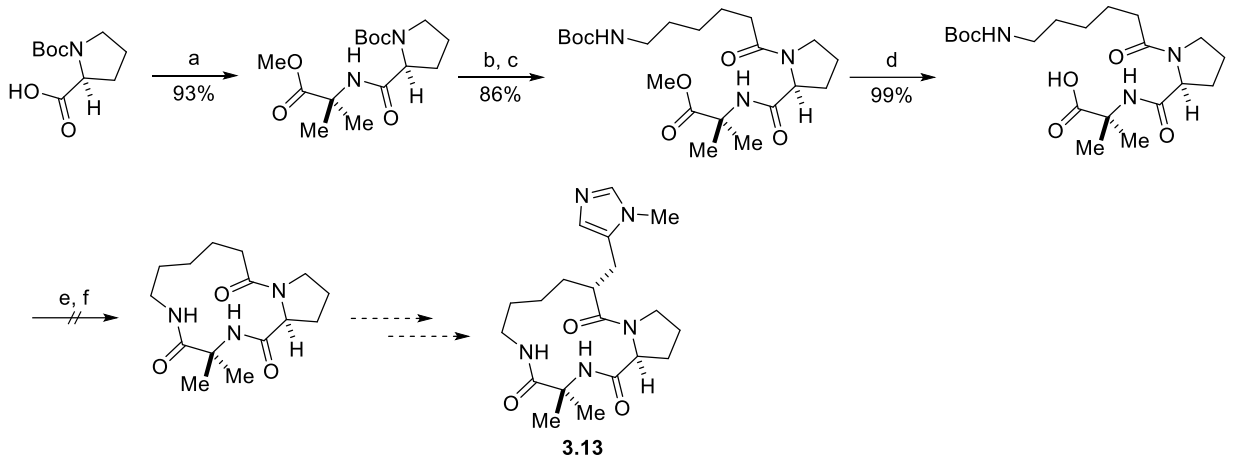


Figure 3.5. Design of cyclic peptide **3.13**

We proposed to replace the hydrogen bond between *i* and *i* +3 amino-acid residues of **3.8** with an Aca linker, which afforded a cyclic peptide **3.13** (Figure 3.5). This Aca linker could possibly bring some degree of restriction rather than distortion of β-turn conformation, which hopefully would be beneficial for the selectivity.

Scheme 3.2. Macrolactamization Synthetic Route of Cyclic Peptide **3.13**[a]



[a] Reagents and conditions: a) HATU (1.0 equiv), DIPEA (3.0 equiv), methyl 2-amino-2-methylpropanoate (1.0 equiv), DCM, rt, overnight; b) TFA, DCM, rt, 3 h; c) HATU (1.0 equiv), DIPEA (4.0 equiv), 6-(Boc-amino)carproic acid (1.0 equiv), rt, overnight; d) LiOH (0.5 N), H_2O, THF, rt, 12 h; e) TFA, DCM, rt, 3 h; f) coupling reagents

Proposed catalyst **3.13** consists of two amino acid residues plus the Aca linker. We first attempted the synthesis of **3.13** with a macrolactamization route (Scheme 3.2). However, this route failed at the macrolactamization step, despite examining several coupling reagents (HATU, PyBOP, and DMAP) for this transformation. This difficult transformation may be caused by ring strain of the product.

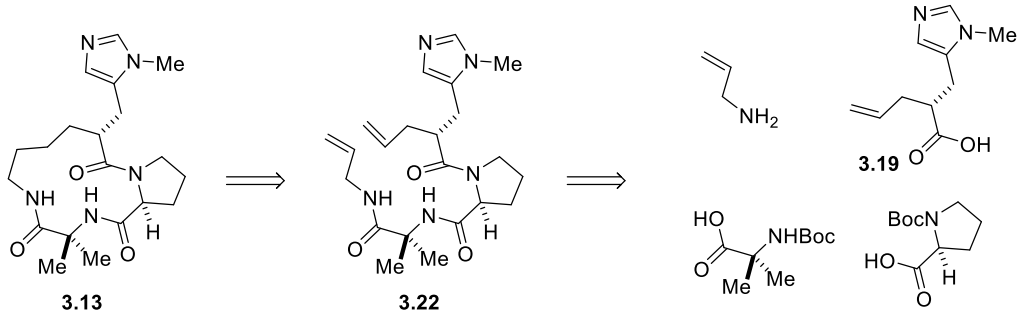
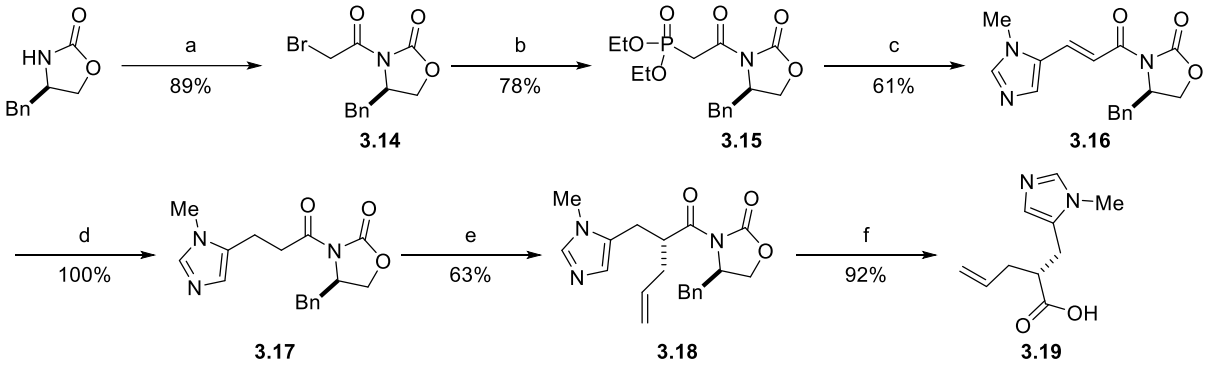


Figure 3.6. Retrosynthetic analysis of **3.13**

To overcome the ring strain, a ring closing metathesis (RCM) strategy was conceived (Figure 3.6). The building block **3.19** was prepared in 6 steps (Scheme 3.2). Reaction between (*R*)-4-benzyloxazolidinone and bromoacetyl bromide afforded **3.14**, which was converted to **3.15** by

an Arbuzov reaction. Subsequent Horner-Wadsworth-Emmons reaction converted **3.15** to the alkene intermediate **3.16,** which was readily hydrogenated to give intermediate **3.17**. Then Evans chiral auxiliary reaction installed the allyl group to yield **3.18**. Subsequent hydrolysis of **3.18** removed the oxazolidinone moiety and afford compound **3.19**.

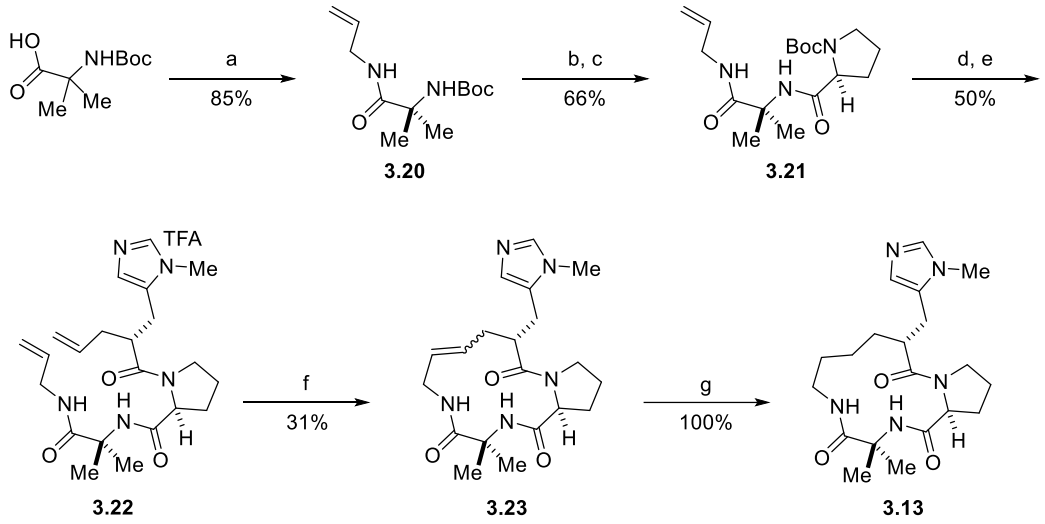
Scheme 3.3. Synthesis of Compound **3.19**[a]



[a] Reagents and conditions: a) *n*-BuLi (1.05 equiv), bromoacetyl bromide (1.05 equiv), THF, –78 °C to rt, 3 h; b) $(EtO)_3P$ (2.0 equiv, neat), reflux, 2 h; c) NaH (1.0 equiv), 1-methyl-1H-imidazole-5-carbaldehyde (0.95 equiv), THF, –78 °C to rt, 3 h; d) H_2 balloon, Pd/C, EtOAc, rt, 16 h; e) NaHMDS (1.1 equiv), allyl iodide (1.6 equiv),THF, –78 to –20 °C, 3 h; f) LiOH (2.0 equiv), H_2O_2 (4.9 equiv), H_2O, 0 °C, 2 h

With compound **3.19** in hand, the synthesis of cyclic peptide **3.1** was carried out in five steps (Scheme 3.4). HATU promoted amide coupling between 2-(Boc-amino)isobutyric acid and allylamine afforded **3.20**. Subsequent Boc deprotection of **3.20** followed by amide coupling with Boc-L-proline gave intermediate **3.21**. Then Boc-deprotection of **3.21** and amide coupling with **3.19** provide diene **3.22** as its TFA salt after reverse phase flash column chromatography purification (0-100% CH3CN/0.5% TFA in H_2O). RCM reaction of **3.22** catalyzed by Hoveyda-Grubbs 2 catalyst afforded **3.23** as an inseparable mixture of cis/trans isomers. Subsequent hydrogenation of **3.23** merged the mixture into one product **3.13**.

Scheme 3.4. Synthesis of Cyclic Peptide **3.13**[a]



[a] Reagents and conditions: a) HATU (1.0 equiv), DIPEA (3.0 equiv), allylamine (1.0 equiv), DCM, rt, 12 h; b) TFA, DCM, 3 h; c) HATU (1.0 equiv), DIPEA (4.0 equiv), Boc-L-proline (1.0 equiv), DCM, rt, 12 h; d) TFA, DCM, 3 h; e) HATU (1.0 equiv), DIPEA (5.0 equiv), **3.19** (1.0 equiv), 12 h; f) Hoveyda-Grubbs 2 (10 mol%), DCM, rt, 15 h; g) H_2 balloon, Pd/C, MeOH, rt, 12 h

The single crystal X-ray structure of **3.13** was obtained for the analysis of its conformation (Figure 3.7). Though **3.13** is not an acyclic peptide and consists of 3 amino-acid residues, the crystal structure clearly displayed its conformation is very close to type II β-turn ($\phi_{i+1} = -67.8°$, $\psi_{i+1} = +116.9°$, $\phi_{i+2} = +59.8°$, $\psi_{i+1} = +26.5°$). The distance between carbonyl and NH of *i* residue is 2.12 Å, which indicates a strong hydrogen bond.

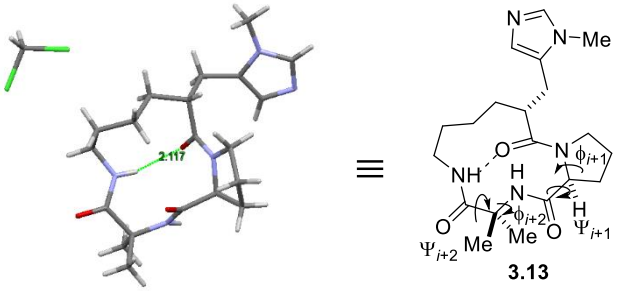
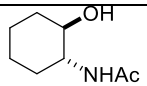
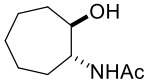
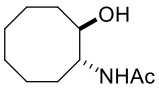


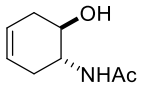
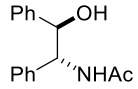
Figure 3.7. X-ray crystal structure and conformation analysis of **3.13**

The substrate scope of the asymmetric acyl-transfer reaction using the cyclic peptide **3.13** were examined (Table 3.1). The reactions were run under conditions of high dilution (0.128 mmol of substrate in 12.8 mL of toluene) with 2.5 mol % of catalyst, 0.2 equiv of DIPEA, and 8.3 equiv of Ac_2O at 25 °C. After quench with CH_3OH (10 mL), products and starting materials were isolated with reverse phase flash column chromatography. Then chiral HPLC was employed to obtain the *ee* (enantiomeric excess of staring material) and *ee´* (enantiomeric excess of product). Conversion percentage (C) and *s* were obtained via the equations described by Kagan ($\frac{ee}{ee\prime} = \frac{C}{1-C}$, $s = \frac{\ln[1 - C(1 + ee\prime)]}{\ln[1 - C(1 - ee\prime)]}$).[26]

Cyclic peptide **3.13** was shown to have slightly lower selectivity for six-membered-ring *trans* cyclic acetamide-functionalized alcohol (**3.7**) than Miller's catalyst **3.8** which gave an *s* value of 28. The selectivity of **3.13** on seven-membered-ring functionalized alcohol (**3.24**) was higher than **3.8** which gave an *s* value of 17. For substrate **3.25**, an eight-membered-ring functionalized alcohol, the selectivity was much lower compared with six- and seven-membered substrates. For substrate **3.26**, the enantioselectivity of cyclic peptide catalyst was lower than six- and seven-membered-ring substrates but higher than the eight-membered-ring one. For the last substrate **3.27**, an acyclic functionalized alcohol, the catalyst demonstrated a negligible selectivity (*s* = 1.3).

Table 3.1. Kinetic Resolutions with Cyclic Peptide **3.13**

cmpd. #	substrates	time	ee[a]	ee´[a]	C[b]	*s*[b]
3.7		2.5 h	70.3%	82.6%	46.0%	21.9
3.24		2.5 h	58.6%	86.1%	40.5%	24.3
3.25		3 h	57.9%	43.9%	56.9%	4.4

3.26		2 h	28.9%	73.3%	28.3%	8.6
3.27		5 h	3.8%	11.4%	25.1%	1.3

[a] Determined by chiral HPLC; [b] Obtained via calculation according to equations described by Kagan[27]

Conclusions

Cyclic peptide **3.13** was synthesized in five steps, followed by the analysis of conformation and assessment of selectivities on five substrates. Cyclic peptide adopt a conformation close to type II β-turn. The selectivities of this catalyst is comparable to Miller's catalyst **3.8** (slightly higher on substrate **3.24**, slightly lower on substrate **3.7**) while it is less selective compared with Qu's catalyst **3.12**. Much work is still needed in terms of the optimization of structure of the cyclic peptide and conditions. In summary, we demonstrated that the cyclic peptide could be used as catalyst for the KR of functionalized alcohols.

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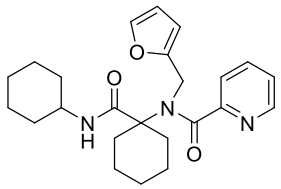
Experimental Section

General Information. All reactions were performed in glassware dried in an oven at 120 ºC overnight and cooled under a stream of argon. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with dry argon prior to use. Plastic syringes were flushed with dry argon before use. Methanol and THF were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. Anhydrous methylene chloride and anhydrous toluene were purchased from Sigma-Aldrich and used as received. All chemicals were used as received from commercial source without further purification. Reactions and chromatography was monitored by thin-layer chromatography (TLC) on 0.25 mm Analtech GHLF silica gel plates and visualized by UV light (254 nm) or Seebach's stain by heating. Purification was achieved by flash chromatography on a CombiFlash Rf (automated flash chromatography) system. MS-directed HPLC purification was carried out by mass-directed fractionation (MDF) with gradient elution (a narrow CH_3CN gradient was chosen based on the retention time of the target from LCMS analysis of the crude sample) on an Agilent 1200 instrument with photodiode array detector, an Agilent 6120 quadrupole mass spectrometer, and a HTPAL LEAP autosampler. HPLC/MS analysis was carried out with gradient elution (5% CH_3CN to 100% CH_3CN) on an Agilent 1200 RRLC with a photodiode array UV detector (214 nm) and an Agilent 6224 TOF mass spectrometer (also used to produce high resolution mass spectra). ^{1}H and ^{13}C NMR spectra were acquired on a 600 MHz Bruker AVIII spectrometer equipped with a cryogenically-cooled carbon observe probe, or a 500 MHz Bruker AVIII spectrometer equipped with a cryogenically-cooled carbon observe probe, or a 400 MHz Bruker AVIIIHD spectrometer, or a 400 MHz Varian 400MR spectrometer. HRMS data were collected with a LCT Premier time-

of-flight mass spectrometer and an electrospray ion source. IR spectra were acquired on a PerkinElmer Spectrum 100 FT-IR spectrometer or a Bruker Alpha FT-IR spectrometer.

Procedure for Chapter 1

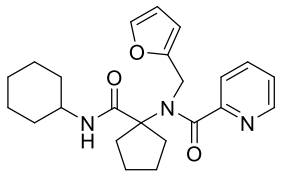
General Procedure for the Ugi Multicomponent Reactoin in Bisamide Library Synthesis. On a 24-position Bohdan MiniBlock, reaction tubes were installed. Each reaction tube was charged with a suspension of carboxylic acid (0.4 mmol), amine (0.4 mmol), and ketone/aldehyde (0.4 mmol) in methanol (0.5 mL), was added isocyanide (0.4 mmol) at room temperature. The Bohdan MiniBlock was agitated for 24 h on the shaker station. To each reaction tube, was added TFA (0.14 mL) prior to 30 min of shaking at room temperature. Each reaction mixture was transferred to a CCT tube then concentrated under N_2. The crude sample was purified via MS-directed HPLC to afford the title compound.



1.1

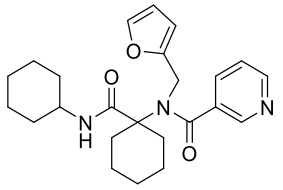
***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide**. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.086 mg, 0.210 mmol, 52% yield, 93.1% purity). Mp = 88–92 ºC; IR (neat) 2929, 1655 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.66–7.57 (m, 1H), 7.45–7.33 (m, 1H), 7.25 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.04 (d, *J* = 9.8 Hz, 1H), 6.20 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.95 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.78 (s, 2H),

3.71–3.58 (m, 1H), 2.23–2.11 (m, 3H), 1.78 (ddt, *J* = 19.3, 12.5, 7.0 Hz, 5H), 1.71–1.42 (m, 8H), 1.40–1.05 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 172.0, 155.3, 151.4, 148.2, 141.9, 137.3, 124.8, 124.3, 110.8, 108.3, 66.5, 47.9, 43.0, 33.0, 32.8, 25.9, 25.8, 24.8, 22.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_3O_3$ $[M + H]^+$ 410.2438, found 410.2472.



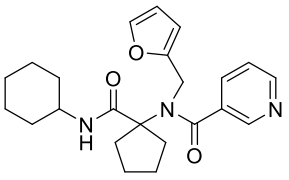
1.2

***N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-(furan-2-ylmethyl)picolinamide**. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as yellow solid (0.022 mg, 0.056 mmol, 14% yield, ≥ 99% purity). Mp = 126–130 ºC; IR (neat) 2931, 1655 (v br), 1514 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.33 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.24 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.89 (br, 1H), 6.21 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 4.82 (s, 2H), 3.65 (tdt, *J* = 10.2, 7.9, 3.9 Hz, 1H), 2.57 (dd, *J* = 12.4, 7.3 Hz, 2H), 2.05–1.95 (m, 2H), 1.90–1.85 (m, 1H), 1.84–1.62 (m, 8H), 1.60–1.51 (m, 1H), 1.39–1.27 (m, 2H), 1.26–1.01 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 171.0, 155.1, 151.4, 148.0, 141.9, 137.3, 124.8, 124.2, 110.8, 108.3, 73.9, 48.0, 44.0, 36.4, 33.0, 25.8, 24.8, 23.9; HRMS (ESI) calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2282, found 396.2288.



1.3

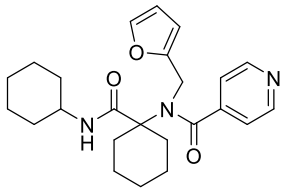
***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.109 g, 0.266 mmol, 67% yield, 98.6% purity). Mp = 136–139 ºC; IR (neat) 2929, 1652 (v br), 1520 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.2, 0.9 Hz, 1H), 8.66 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.85 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.38 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 7.30 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.08–7.02 (m, 1H), 6.26 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.06 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.54 (d, *J* = 0.9 Hz, 2H), 3.63–3.52 (m, 1H), 2.35–2.27 (m, 2H), 2.16–2.07 (m, 2H), 1.83–1.62 (m, 6H), 1.60–1.05 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 172.4, 150.7, 150.1, 147.9, 142.4, 135.8, 133.9, 123.8, 111.0, 108.9, 66.4, 48.0, 44.3, 32.9, 32.5, 25.8, 25.6, 24.7, 22.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_3O3$ $[M + H]^+$ 410.2438, found 410.2433.



1.4

***N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-(furan-2-ylmethyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.064 g, 0.162 mmol, 40% yield, 98.9% purity). Mp = 105–108 ºC; IR (neat) 2932, 1646 (v br), 1524 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 – 8.62 (m, 2H), 7.79 (dt,

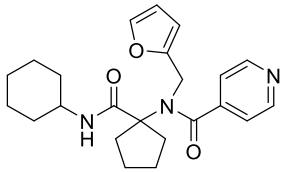
J = 1.91, 7.85 Hz, 1H), 7.39 – 7.32 (m, 2H), 6.70 (d, *J* = 7.97 Hz, 1H), 6.31 (dd, *J* = 1.86, 3.28 Hz, 1H), 6.09 (dd, *J* = 0.91, 3.31 Hz, 1H), 4.55 (s, 2H), 3.69–3.62 (m, 1H), 2.66–2.62 (m, 2H), 2.04–1.94 (m, 2H), 1.87–1.63 (m, 8H), 1.62–1.53 (m, 1H), 1.41–1.29 (m, 2H), 1.23–1.06 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.4, 150.5, 150.3, 147.2, 142.4, 135.4, 133.5, 123.7, 111.1, 108.6, 73.8, 48.1, 45.7, 36.3, 33.0, 25.8, 24.8, 23.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2282, found 396.2280.



1.5

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)isonicotinamide.**

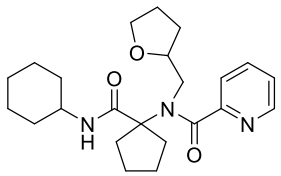
Prepared according to the general procedure for ugi multicomponent reaction, the title compound was obtained as a white solid (0.100 g, 0.244 mmol, 61% yield, 98.9% purity). Mp = 98–100 ºC; IR (neat) 2932, 1648 (v br), 1537 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71–8.65 (m, 2H), 7.37–7.34 (m, 2H), 7.33 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.82–6.77 (m, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.09 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.49 (s, 2H), 3.63 – 3.58 (m, 1H), 2.23–2.14 (m, 4H), 1.84–1.61 (m, 6H), 1.53 (qt, *J* = 14.0, 4.0 Hz, 5H), 1.40–1.28 (m, 2H), 1.25–1.08 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 172.2, 150.2, 150.1, 145.4, 142.3, 121.4, 111.0, 108.8, 66.3, 48.0, 43.9, 32.9, 32.4, 25.8, 25.6, 24.7, 22.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_3O3$ $[M + H]^+$ 410.2438, found 410.2439.



1.6

***N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-(furan-2-ylmethyl)isonicotinamide**.

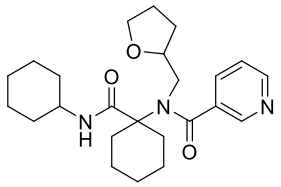
Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.111 g, 70% yield, 98.6% purity). Mp = 138–141 ºC; IR (neat) 2927, 1658, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 4.8 Hz, 2H), 7.44–7.34 (m, 3H), 6.57–6.43 (m, 1H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.12 (dd, *J* = 3.1, 0.9 Hz, 1H), 4.50 (s, 2H), 3.74–3.62 (m, 1H), 2.66–2.55 (m, 3H), 2.05–1.94 (m, 2H), 1.89–1.53 (m, 9H), 1.43–1.30 (m, 2H), 1.29–1.04 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.1, 150.4, 149.3, 145.8, 142.4, 121.5, 111.2, 108.7, 73.7, 48.2, 45.4, 36.2, 33.1, 25.8, 24.8, 23.6; HRMS (ESI) *m/z* calcd for $C_{23}H_{30}N_3O_3$ $[M + H]^+$ 396.2282, found 396.2281.



1.7

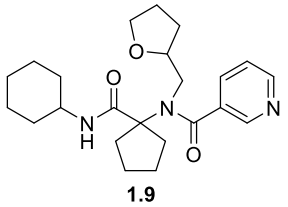
(±)-*N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-((tetrahydrofuran-2-yl)methyl)picolinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.009 g, 0.023 mmol, 6% yield, 96.0% purity). IR (neat) 2926, 1649 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H), 7.64–7.60 (m, 1H), 7.56 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.29

(ddd, *J* = 7.6, 4.9, 1.3 Hz, 0H), 3.98 (p, *J* = 6.7, 5.3 Hz, 1H), 3.85–3.72 (m, 2H), 3.65 (d, *J* = 16.1 Hz, 1H), 3.56 (dt, *J* = 8.4, 6.9 Hz, 1H), 3.40–3.27 (m, 1H), 2.64 (d, *J* = 25.9 Hz, 1H), 2.43 (d, *J* = 10.3 Hz, 1H), 2.12–2.01 (m, 1H), 2.01–1.06 (m, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 170.4, 156.2, 147.7, 137.0, 124.8, 124.1, 73.5, 67.7, 50.4, 48.2, 37.5, 36.1, 33.1, 33.0, 29.1, 25.9, 25.8, 24.9, 24.6, 24.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}N_3O_3$ $[M + H]^+$ 400.2595, found 400.2616.



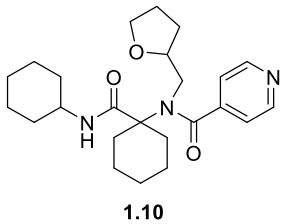
1.8

(±)-*N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-((tetrahydrofuran-2-yl)methyl)nicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.033 g, 0.080 mmol, 20% yield, ≥ 99% purity). IR (neat) 2927, 1641 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.62 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.75 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.34 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 3.99–3.90 (m, 1H), 3.81–3.70 (m, 1H), 3.59 (dt, *J* = 8.2, 6.6 Hz, 1H), 3.50–3.34 (m, 3H), 2.77–2.69 (m, 1H), 2.19–2.05 (m, 2H), 1.99–1.61 (m, 10H), 1.60–1.30 (m, 7H), 1.29–1.15 (m, 3H), 1.15–1.05 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 173.0, 150.6, 148.7, 135.9, 134.6, 123.5, 76.6, 67.7, 65.8, 52.2, 48.1, 32.8, 32.6, 32.5, 32.2, 29.2, 25.9, 25.6, 24.7, 22.3, 22.3; HRMS (ESI) *m/z* calcd for $C_{24}H_{36}N_3O_3$ $[M + H]^+$ 414.2751, found 414.2769.



1.9

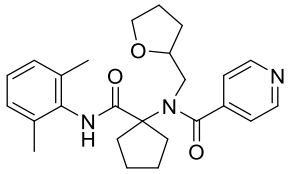
(±)-*N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-((tetrahydrofuran-2-yl)methyl)nicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.084 g, 0.210 mmol, 53% yield, ≥ 99% purity). Mp = 148–151 ºC; IR (neat) 2929, 1637 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.59 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.71 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.38 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 4.09–4.01 (m, 1H), 3.81–3.72 (m, 1H), 3.69–3.61 (m, 1H), 3.58–3.50 (m, 1H), 3.47–3.33 (m, 2H), 2.83–2.75 (m, 1H), 2.45–2.35 (m, 1H), 2.08–1.98 (m, 1H), 1.97–1.75 (m, 7H), 1.76–1.64 (m, 4H), 1.63–1.51 (m, 2H), 1.45–1.31 (m, 2H), 1.26–1.13 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 170.9, 149.3, 147.4, 135.9, 134.6, 123.6, 76.7, 73.3, 67.9, 52.2, 48.3, 37.7, 36.1, 33.0, 32.9, 29.1, 25.9, 25.9, 24.9, 24.8, 24.2, 23.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}N_3O_3$ $[M + H]^+$ 400.2595, found 400.2608.



1.10

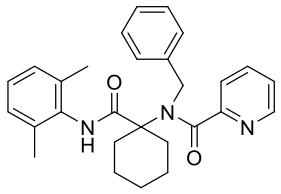
(±)-*N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-((tetrahydrofuran-2-yl)methyl)isonicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.051 g, 0.123 mmol, 31% yield, ≥

99% purity). IR (neat) 2927, 1638 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 3.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.36–7.31 (m, 2H), 3.99–3.93 (m, 1H), 3.81–3.73 (m, 1H), 3.63 (ddd, *J* = 8.2, 7.1, 6.2 Hz, 1H), 3.56–3.49 (m, 1H), 3.43 (dd, *J* = 15.3, 2.9 Hz, 1H), 3.30 (dd, *J* = 15.4, 9.9 Hz, 1H), 2.19 (ddd, *J* = 14.6, 10.6, 3.8 Hz, 2H), 2.10–1.96 (m, 2H), 1.93–1.68 (m, 8H), 1.67–1.53 (m, 3H), 1.52–1.32 (m, 5H), 1.23 (dddd, *J* = 19.3, 12.6, 10.2, 3.6 Hz, 3H), 1.15–1.07 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 172.5, 149.5, 147.1, 122.3, 76.6, 67.8, 66.0, 51.9, 48.2, 32.9, 32.7, 32.6, 32.3, 29.3, 25.9, 25.9, 25.6, 24.8, 22.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{36}N_3O_3$ $[M + H]^+$ 414.2751, found 414.2740.



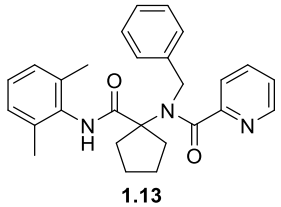
1.11

(±)-*N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclopentyl)-*N*-((tetrahydrofuran-2-yl)methyl)isonicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.037 g, 0.088 mmol, 22% yield, ≥ 99% purity). IR (neat) 2958, 1677, 1639 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.71–8.65 (m, 2H), 7.25–7.21 (m, 2H), 7.06 (s, 3H), 4.16 (br s, 1H), 3.68–3.53 (m, 2H), 3.48 (dd, *J* = 15.4, 2.9 Hz, 1H), 3.40 (dd, *J* = 15.4, 10.4 Hz, 1H), 2.96 (br s, 1H), 2.51 (br s, 1H), 2.29 (s, 6H), 2.19-2.06 (m, 2H), 2.00–1.84 (m, 4H), 1.84–1.69 (m, 3H), 1.65–1.49 (m, 1H), 1.22 (ddq, *J* = 12.4, 8.1, 6.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.0, 150.2, 145.6, 135.5, 134.9, 128.2, 126.6, 121.3, 73.7, 68.3, 51.8, 41.1, 37.6, 36.2, 29.2, 25.9, 24.4, 24.0, 18.7; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_3$ $[M + H]^+$ 422.2438, found 422.2450.



1.12

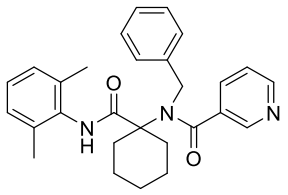
***N*-Benzyl-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclohexyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.102 g, 0.231 mmol, 58% yield, ≥ 99% purity). Mp = 144–146 ºC; IR (neat) 2929, 1676, 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (br, 1H), 8.53 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.31–7.13 (m, 6H), 7.11–7.01 (m, 3H), 4.87 (s, 2H), 2.50–2.41 (m, 2H), 2.28–2.16 (m, 8H), 1.89–1.77 (m, 2H), 1.76–1.66 (m, 2H), 1.63–1.52 (m, 1H), 1.48–1.37 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.8, 155.5, 148.2, 139.0, 137.2, 135.2, 134.5, 128.7, 128.3, 127.6, 127.4, 126.7, 124.7, 123.9, 67.7, 50.5, 33.5, 25.7, 22.8, 19.1; HRMS (ESI) *m/z* calcd for $C_{28}H_{32}N_3O_2$ $[M + H]^+$ 442.2489, found 442.2480.



1.13

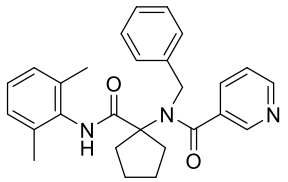
***N*-Benzyl-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclopentyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.042 g, 0.098 mmol, 25% yield, 98.2% purity). Mp = 148–150 ºC; IR

(neat) 2959, 1672, 1636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.71 (td, *J* = 7.8, 1.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.33–7.16 (m, 6H), 7.11–7.02 (m, 3H), 4.91 (s, 2H), 2.86–2.67 (br s, 2H), 2.20 (s, 6H), 2.13–1.99 (m, 2H), 1.86–1.64 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.5, 155.2, 148.1, 138.9, 137.3, 135.4, 134.4, 128.7, 128.3, 127.3, 127.2, 126.9, 124.7, 123.8, 74.9, 52.0, 36.8, 23.6, 18.7; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_3O_2$ $[M + H]^+$ 428.2333, found 428.2348.



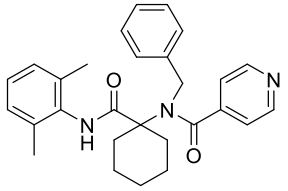
1.14

***N*-Benzyl-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclohexyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.066 g, 0.149 mmol, 37% yield, 97.6% purity). Mp = 200–203 ºC; IR (neat) 2936, 1668, 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 – 8.75 (m, 1H), 8.62 (s, 1H), 8.53 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.28 (ddd, *J* = 7.8, 5.0, 0.8 Hz, 1H), 7.23–7.16 (m, 3H), 7.15–7.03 (m, 5H), 4.74 (s, 2H), 2.54–2.45 (m, 2H), 2.43–2.34 (m, 2H), 2.21 (s, 6H), 1.87–1.79 (m, 2H), 1.73–1.64 (m, 2H), 1.63–1.57 (m, 1H), 1.57–1.52 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.4, 149.4, 146.3, 138.1, 136.3, 134.9, 134.6, 134.5, 129.0, 128.5, 127.8, 127.4, 126.8, 124.1, 67.7, 51.6, 33.2, 25.5, 22.9, 19.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{32}N_3O_2$ $[M + H]^+$ 442.2489, found 442.2497.



1.15

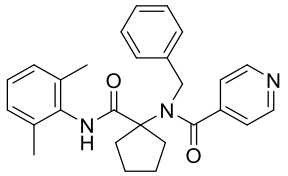
***N*-Benzyl-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclopentyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.066 g, 0.154 mmol, 39% yield, 98.9% purity). Mp = 190–193 ºC; IR (neat) 2961, 1664, 1636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.54 (dd, *J* = 5.0, 1.7 Hz, 1H), 8.07 (s, 1H), 7.71 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.32 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.29–7.18 (m, 4H), 7.14–7.03 (m, 3H), 4.75 (s, 2H), 2.86 (dd, *J* = 13.0, 5.7 Hz, 2H), 2.27 (s, 6H), 2.24–2.12 (m, 2H), 1.84 (dtd, *J* = 10.3, 5.9, 2.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 171.7, 149.4, 146.2, 138.6, 135.6, 135.3, 134.2, 133.8, 129.1, 128.4, 127.7, 127.2, 126.4, 123.8, 74.7, 53.2, 36.8, 23.8, 18.8; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_3O_2$ $[M + H]^+$ 428.2333, found 428.2347.



1.16

***N*-Benzyl-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclohexyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.123 g, 0.279 mmol, 70% yield, 94.0% purity). Mp = 191–193 ºC; IR (neat) 2932, 1681, 1639 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61–8.52 (m, 2H), 8.20 (s, 1H),

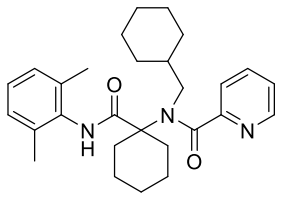
7.31–7.28 (m, 2H), 7.29–7.20 (m, 3H), 7.20–7.14 (m, 2H), 7.11–7.04 (m, 3H), 4.68 (s, 2H), 2.70–2.50 (m, 2H), 2.35–2.16 (m, 8H), 1.89–1.77 (m, 2H), 1.77–1.59 (m, 3H), 1.54–1.39 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 170.9, 148.7, 146.6, 138.0, 134.8, 134.2, 129.0, 128.4, 127.7, 126.9, 126.8, 121.2, 67.5, 50.9, 33.1, 25.3, 23.0, 19.1; HRMS (ESI) *m/z* calcd for $C_{28}H_{32}N_3O_2$ $[M + H]^+$ 442.2489, found 442.2495.



1.17

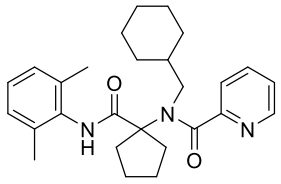
***N*-Benzyl-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclopentyl)isonicotinamide.**

Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.078 g, 0.182 mmol, 46% yield, 98.5% purity). IR (neat) 2963, 1690, 1617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 – 8.50 (m, 2H), 7.80 (s, 1H), 7.34 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.31–7.27 (m, 3H), 7.24–7.19 (m, 2H), 7.14–7.06 (m, 3H), 4.67 (s, 2H), 2.95–2.78 (m, 2H), 2.28 (s, 6H), 2.25–1.60 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 148.8, 146.1, 138.5, 135.4, 134.0, 129.2, 128.5, 127.8, 127.3, 126.2, 121.1, 74.6, 52.9, 36.7, 23.8, 18.8; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_3O_2$ $[M + H]^+$ 428.2333, found 428.2349.



1.18

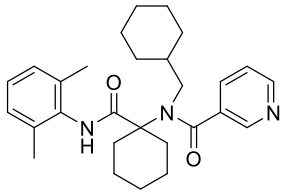
***N*-(Cyclohexylmethyl)-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclohexyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white foam (0.030 g, 0.067 mmol, 17% yield, 98.4% purity). Mp = 68–71 ºC; IR (neat) 2926, 1681, 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74–9.70 (br, 1H), 8.61 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.61 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.36 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 7.06 (s, 3H), 3.46 (d, *J* = 6.3 Hz, 2H), 2.53 (br, 2H), 2.30 (m, 7H), 1.89–1.76 (m, 2H), 1.73–1.58 (m, 7H), 1.57–1.47 (m, 4H), 1.19–1.06 (m, 2H), 1.00–0.87 (m, 1H), 0.57–0.45 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 172.8, 155.9, 148.6, 137.2, 135.0, 134.8, 128.3, 126.5, 124.8, 124.8, 66.6, 54.1, 37.5, 33.0, 31.1, 26.2, 25.8, 25.5, 22.6, 19.3; HRMS (ESI) *m/z* calcd for $C_{28}H_{38}N_3O_2$ $[M + H]^+$ 448.2959, found 448.2981.



1.19

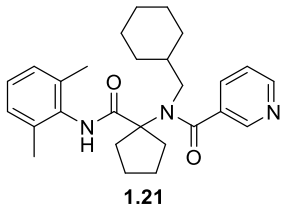
***N*-(Cyclohexylmethyl)-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclopentyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.027 g, 0.062 mmol, 16% yield, 98.9% purity). Mp = 101–103 ºC; IR (neat) 2924, 1678, 1633 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (br, 1H), 8.57 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.36 (ddd, *J* = 7.7, 4.9, 1.2 Hz, 1H), 7.06 (s, 3H), 5.29 (s, 1H), 3.53 (d, *J* = 6.3 Hz, 2H), 2.84 (br s, 2H), 2.27 (s, 6H), 2.19–2.09 (m, 2H), 1.92–1.78 (m, 4H), 1.72–1.59 (m, 3H), 1.58–1.47 (m, 3H), 1.11 (qt, *J* = 12.9, 3.4 Hz, 2H), 1.00–0.87 (m, 1H),

0.56–0.44 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 172.0, 155.6, 148.3, 137.4, 135.0, 134.8, 128.3, 126.6, 124.7, 124.6, 74.2, 54.8, 37.6, 36.4, 31.0, 26.2, 25.6, 23.1, 19.0; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_3O_2$ $[M + H]^+$ 434.2802, found 434.2802.



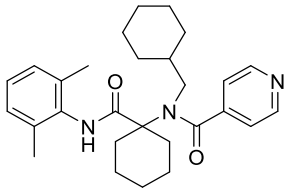
1.20

***N*-(Cyclohexylmethyl)-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclohexyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.017 g, 0.038 mmol, 9% yield, ≥ 99% purity). Mp = 119–121 ºC; IR (neat) 2925, 1678, 1617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.77–8.68 (m, 2H), 7.83 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.41 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.07 (s, 3H), 3.36 (d, *J* = 6.0 Hz, 2H), 2.71 (br s, 2H), 2.32 (s, 6H), 2.17–2.07 (m, 2H), 1.85–1.60 (m, 8H), 1.58–1.42 (m, 3H), 1.19–1.06 (m, 2H), 1.01–0.87 (m, 1H), 0.62–0.50 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 172.7, 151.4, 149.3, 136.4, 135.0, 134.3, 134.0, 128.4, 126.4, 123.8, 66.5, 55.7, 37.2, 32.7, 31.1, 26.1, 25.5, 25.3, 22.6, 19.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{38}N_3O_2$ $[M + H]^+$ 448.2959, found 448.2970.



1.21

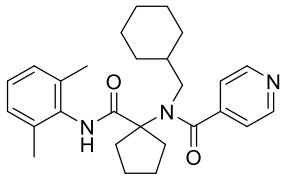
***N*-(Cyclohexylmethyl)-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclopentyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.035 g, 0.079 mmol, 20% yield, 98.9% purity). IR (neat) 2925, 1687, 1665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.82–8.60 (m, 2H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 7.7, 5.1 Hz, 1H), 7.07 (s, 3H), 3.35 (d, *J* = 6.6 Hz, 2H), 2.82 (br s, 2H), 2.30 (s, 6H), 2.17 (q, *J* = 8.3 Hz, 2H), 1.97–1.81 (m, 4H), 1.81–1.44 (m, 6H), 1.19–1.05 (m, 2H), 1.01–0.86 (m, 1H), 0.51 (q, *J* = 12.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.2, 149.4, 147.1, 137.2, 134.8, 134.6, 134.4, 128.5, 126.7, 124.3, 74.3, 56.5, 37.3, 36.4, 31.0, 26.1, 25.5, 22.7, 19.0; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_3O_2$ $[M + H]^+$ 434.2802, found 434.2819.



1.22

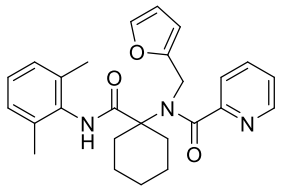
***N*-(Cyclohexylmethyl)-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclohexyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.034 g, 0.076 mmol, 19% yield, 95.6% purity). IR (neat) 2921, 1681, 1630 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.75 (br s, 2H), 7.38 (d, *J* = 5.4 Hz, 2H), 7.07 (s, 3H), 3.29 (d, *J* = 6.1 Hz, 2H), 2.63 (br s, 1H), 2.31 (s, 6H), 2.25–2.15 (m, 2H), 1.88–1.77 (m, 2H), 1.75–1.61 (m, 4H), 1.60–1.47 (m, 6H), 1.18–1.08 (m, 2H), 1.02–0.92 (m, 1H), 0.91–0.80 (m, 1H), 0.63–0.49 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 172.2, 150.1, 146.3, 134.9, 134.4, 128.5, 126.6, 122.6,

66.6, 55.3, 37.4, 32.8, 31.1, 26.1, 25.5, 25.4, 22.8, 19.4; 34 mg, HRMS (ESI) *m/z* calcd for $C_{28}H_{38}N_3O_2$ $[M + H]^+$ 448.2959, found 448.2975.



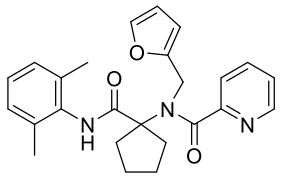
1.23

***N*-(Cyclohexylmethyl)-*N*-(1-((2,6-dimethylphenyl)carbamoyl)cyclopentyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.029 g, 0.065 mmol, 17% yield, 97.7% purity). Mp = 189–191 ºC; IR (neat) 2926, 1656, 1635, 1506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.73 (d, *J* = 5.9 Hz, 2H), 7.39 (d, *J* = 5.9 Hz, 2H), 7.08 (s, 3H), 3.26 (d, *J* = 6.6 Hz, 2H), 2.81 (br s, 1H), 2.30 (s, 6H), 2.22–2.07 (m, 3H), 1.97–1.79 (m, 4H), 1.78–1.45 (m, 6H), 1.19–1.05 (m, 2H), 1.02–0.90 (m, 1H), 0.53 (q, *J* = 11.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 171.1, 148.7, 147.2, 134.7, 134.6, 128.5, 126.9, 122.5, 74.2, 56.0, 37.4, 36.4, 31.0, 26.1, 25.5, 22.8, 19.0; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_3O_2$ $[M + H]^+$ 434.2802, found 434.2794.



1.24

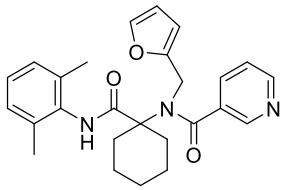
***N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.106 g, 0.246 mmol, 61% yield, ≥ 99% purity). Mp = 75–78 ºC; IR (neat) 2930, 1656 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59–8.52 (m, 2H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.33 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 7.19 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.07–6.99 (m, 3H), 6.15 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.89 (d, *J* = 3.2 Hz, 1H), 4.93 (s, 2H), 2.42–2.29 (m, 4H), 2.19 (s, 6H), 1.91– 1.80 (m, 2H), 1.74–1.62 (m, 2H), 1.59–1.50 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.9, 155.1, 151.4, 148.1, 142.0, 137.2, 135.4, 134.5, 128.1, 126.6, 124.8, 124.1, 110.9, 108.2, 67.1, 43.0, 32.9, 25.7, 22.6, 18.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_3O_3$ $[M + H]^+$ 432.2282, found 432.2280.



1.25

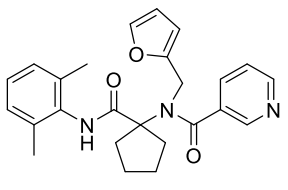
***N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclopentyl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.067 g, 0.160 mmol, 40% yield, 96.8% purity). Mp = 158–161 ºC; IR (neat) 2958, 1661 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 1H), 8.44 (br s, 1H), 7.77 (td, *J* = 7.7, 1.7 Hz, 1H), 7.57 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.34 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.22 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.10–6.98 (m, 3H), 6.20 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.01 (d, *J* = 2.9 Hz, 1H), 4.92 (s, 2H), 4.84 (br s, 1H), 2.76 (br s, 2H), 2.18 (s, 6H), 2.15–2.10 (m, 2H), 1.93–1.65 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8,

171.0, 154.8, 151.4, 148.0, 142.1, 137.4, 135.5, 134.4, 128.1, 126.8, 124.9, 124.1, 110.9, 108.3, 74.4, 44.1, 36.5, 23.9, 18.6; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_3O_3$ $[M + H]^+$ 418.2125, found 418.2141.



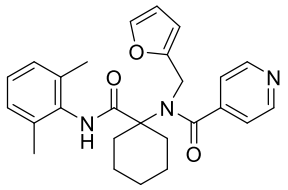
1.26

***N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (68 mg, 0.158 mmol, 39% yield, ≥ 99% purity). Mp = 180–183 ºC; IR (neat) 2930, 1659, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.64 (s, 1H), 8.57 (d, *J* = 5.2 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.45–7.39 (m, 1H), 7.27 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.09–7.00 (m, 3H), 6.23 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.07–6.02 (m, 1H), 4.68 (s, 2H), 2.46–2.29 (m, 4H), 2.19 (s, 6H), 1.90–1.81 (m, 2H), 1.70–1.48 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 171.2, 150.1, 149.1, 146.3, 142.4, 136.7, 135.1, 134.4, 134.2, 128.2, 126.6, 124.2, 111.1, 108.8, 67.1, 44.5, 32.7, 25.4, 22.6, 18.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_3O_3$ $[M + H]^+$ 432.2282, found 432.2280.



1.27

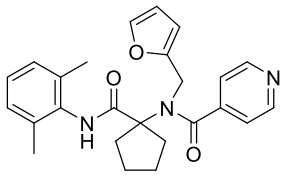
***N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclopentyl)-*N*-(furan-2-ylmethyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.042 g, 0.101 mmol, 25% yield, 97.0% purity). Mp = 206–208 ºC; IR (neat) 2954, 1656, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 8.60 (dd, *J* = 5.1, 1.6 Hz, 1H), 8.25 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.49–7.42 (m, 1H), 7.34 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.10–7.02 (m, 3H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.13 (dd, *J* = 3.3, 1.0 Hz, 1H), 4.66 (s, 2H), 2.92–2.76 (m, 2H), 2.21 (s, 6H), 2.17–2.10 (m, 2H), 1.92–1.73 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 170.7, 150.4, 148.4, 145.7, 142.7, 137.2, 135.5, 134.3, 134.1, 128.4, 127.1, 124.4, 111.3, 108.7, 74.4, 46.0, 36.5, 23.8, 18.7; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_3O_3$ $[M + H]^+$ 418.2125, found 418.2117.



1.28

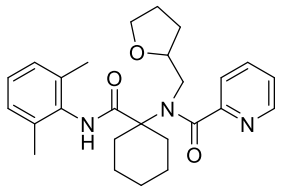
***N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.070 g, 0.162 mmol, 41 yield, ≥ 99% purity). Mp = 194–197 ºC; IR (neat) 2932, 1662, 1642, 1493 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70–8.65 (m, 2H), 8.31 (s, 1H), 7.42–7.37 (m, 2H), 7.30 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.11–7.01 (m, 3H), 6.28 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.07 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.62 (s, 2H), 2.45–2.36 (m, 2H),

2.34–2.25 (m, 2H), 2.19 (s, 6H), 1.92–1.81 (m, 2H), 1.69–1.48 (m, 4H); HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_3O_3$ $[M + H]^+$ 432.2282, found 432.2288.



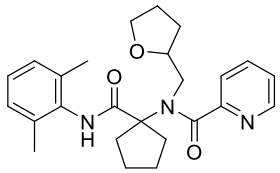
1.29

***N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclopentyl)-*N*-(furan-2-ylmethyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.046 g, 0.110 mmol, 28% yield, 97.9% purity). Mp = 178–180 ºC; IR (neat) 2962, 1663, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.69–8.64 (m, 2H), 8.02 (s, 1H), 7.39–7.32 (m, 3H), 7.13–7.02 (m, 3H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.14 (dd, *J* = 3.3, 1.0 Hz, 1H), 4.58 (s, 2H), 2.84–2.75 (m, 2H), 2.21 (s, 6H), 2.19–2.12 (m, 2H), 1.93–1.74 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 171.2, 150.6, 150.0, 145.0, 142.6, 135.4, 134.2, 128.4, 127.1, 121.1, 111.3, 108.5, 74.2, 45.5, 36.5, 23.9, 18.7; HRMS (ESI) *m/z* calcd for $C_{25}H_{28}N_3O_3$ $[M + H]^+$ 418.2125, found 418.2135.



1.30

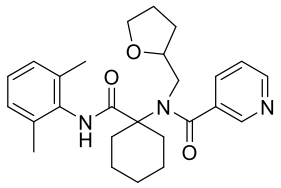
(±)-*N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclohexyl)-*N*-((tetrahydrofuran-2-yl)methyl)picolinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a light yellow film (0.026 g, 0.060 mmol, 15% yield, 94.4% purity). IR (neat) 2927, 1679, 1640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.56 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.63 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.31 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.05 (s, 3H), 4.17–3.69 (m, 3H), 3.55 (dt, *J* = 8.2, 6.6 Hz, 1H), 3.42 (br s, 1H), 2.58 (br s, 1H), 2.47–2.37 (m, 1H), 2.31 (s, 6H), 2.29–2.23 (m, 1H), 2.20–2.11 (m, 3H), 1.97–1.87 (m, 1H), 1.81–1.46 (m, 6H), 1.29–1.18 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1 (2 carbonyl), 156.1, 148.0, 137.1, 135.6, 135.2, 128.2, 126.4, 124.9, 124.3, 77.9, 67.9, 66.5, 50.4, 33.4, 32.4, 31.1, 29.3, 25.8, 25.7, 22.8, 22.6, 18.9; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_3$ $[M + H]^+$ 436.2595, found 436.2610.



1.31

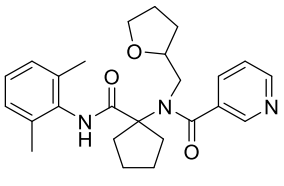
(±)-*N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclopentyl)-*N*-((tetrahydrofuran-2-yl)methyl)picolinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow film (0.016 g, 0.038 mmol, 9% yield, 95.7% purity). IR (neat) 2961, 1677, 1638 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (br, 1H), 8.55 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.80 (td, *J* = 7.7, 1.8 Hz, 1H), 7.62 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.31 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.05 (s, 3H), 4.23–2.48 (m, 6H), 2.37–2.19 (m, 7H), 2.15–1.67 (m, 8H), 1.59–1.19 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (2 Carbonyl), 155.9, 147.8, 137.2, 135.6,

135.2, 128.1, 126.5, 124.8, 124.2, 74.0, 68.1, 56.1, 50.3, 37.6, 36.2, 29.1, 25.8, 24.7, 24.3, 18.8; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_3$ $[M + H]^+$ 422.2438, found 422.2454.



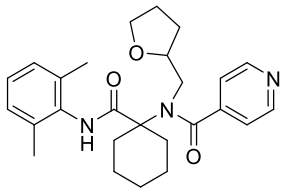
1.32

(±)-*N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclohexyl)-*N*-((tetrahydrofuran-2-yl)methyl)nicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.110 g, 0.253 mmol, 63% yield, 96.4% purity). Mp = 115–118 ºC; IR (neat) 2929, 1677, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (br, 1H), 8.69 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.64 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.77 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.37 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 7.05 (s, 3H), 4.14–4.04 (m, 1H), 3.63–3.41 (m, 4H), 2.87 (br s, 1H), 2.35–2.24 (m, 7H), 2.23–2.18 (m, 1H), 1.95–1.63 (m, 6H), 1.59–1.44 (m, 4H), 1.22–1.11 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (2 carbonyl), 150.6, 148.5, 135.7, 135.3, 135.0, 134.4, 128.2, 126.5, 123.5, 76.9, 68.0, 66.2, 52.3, 32.8, 32.5, 29.3, 25.8, 25.5, 22.7, 22.5, 18.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_3$ $[M + H]^+$ 436.2595, found 436.2601.



1.33

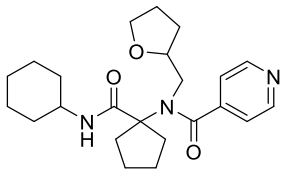
(±)-*N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclopentyl)-*N*-((tetrahydrofuran-2-yl)methyl)nicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.049 g, 0.116 mmol, 29% yield, 98.1% purity). IR (neat) 2948, 1678, 1630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.71 – 8.59 (m, 2H), 7.80 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.44 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.06 (s, 3H), 4.19 (br s, 1H), 3.71–3.41 (m, 4H), 3.01 (br s, 1H), 2.61–2.47 (m, 1H), 2.29 (s, 6H), 2.20–2.05 (m, 2H), 2.01–1.87 (m, 3H), 1.85–1.70 (m, 3H), 1.64–1.49 (m, 1H), 1.30–1.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9, 170.7, 148.9, 146.7, 136.4, 135.4, 134.9, 134.7, 128.3, 126.7, 124.0, 73.8, 68.3, 57.9, 52.3, 37.7, 36.3, 29.2, 25.9, 24.3, 23.9, 18.8; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_3$ $[M + H]^+$ 422.2438, found 422.2464.



1.34

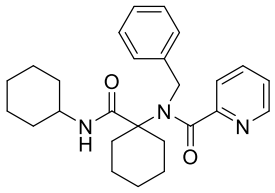
(±)-*N*-(1-((2,6-Dimethylphenyl)carbamoyl)cyclohexyl)-*N*-((tetrahydrofuran-2-yl)methyl)isonicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.090 g, 0.207 mmol, 52% yield, ≥ 99% purity). Mp = 56–59 ºC; IR (neat) 2928, 1680, 1639 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.77–8.72 (m, 2H), 7.55–7.50 (m, 2H), 7.07 (s, 3H), 4.14–4.08 (m, 1H), 3.67–3.58 (m, 2H), 3.54–3.46 (m, 1H), 3.39–3.30 (m, 1H), 2.81–2.77 (m, 1H), 2.40–2.23 (m, 8H), 2.17–2.10 (m, 1H), 1.95–1.72 (m, 4H), 1.72–1.44 (m, 5H), 1.21–1.10 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9,

171.3, 156.3, 147.0, 135.2, 134.8, 128.4, 126.8, 123.2, 68.1, 66.6, 52.1, 36.8, 32.8, 32.7, 29.4, 26.0, 25.5, 22.9, 22.7, 18.9; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_3$ $[M + H]^+$ 436.2595, found 436.2596.



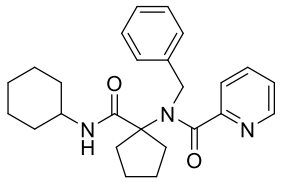
1.35

(±)-*N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-((tetrahydrofuran-2-yl)methyl)isonicotinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.086 g, 0.215 mmol 54% yield, 96.1% purity). Mp = 137–140 ºC; IR (neat) 2929, 1645 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68–8.59 (m, 2H), 7.53 (d, *J* = 6.9 Hz, 1H), 7.23–7.12 (m, 2H), 4.08–3.95 (m, 1H), 3.79–3.69 (m, 1H), 3.69–3.60 (m, 1H), 3.60–3.50 (m, 1H), 3.41–3.25 (m, 2H), 2.75 (br s, 1H), 2.15–2.11 (m, 1H), 2.04–1.49 (m, 14H), 1.41–1.27 (m, 2H), 1.24–1.02 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 170.8, 150.0, 145.7, 121.4, 76.6, 73.1, 67.9, 51.6, 48.2, 37.4, 35.9, 32.9, 32.9, 29.0, 25.8, 25.8, 24.8, 24.7, 24.3, 24.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{34}N_3O_3$ $[M + H]^+$ 400.2595, found 400.2611.



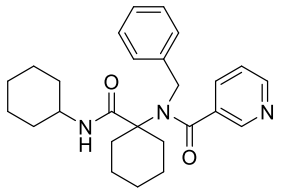
1.36

***N*-Benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclohexyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.121 g, 0.288 mmol, 72% yield, 96.3% purity). Mp = 104–107 ºC; IR (neat) 2927, 1652, 1628 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.50 (m, 1H), 7.65 (tt, *J* = 7.7, 1.4 Hz, 1H), 7.43 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.28 – 7.13 (m, 6H), 7.06 (s, 1H), 4.72 (s, 2H), 3.73–3.61 (m, 1H), 2.27–2.17 (m, 2H), 2.14–2.05 (m, 2H), 1.89–1.81 (m, 2H), 1.75–1.45 (m, 8H), 1.42–1.27 (m, 3H), 1.26–1.11 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 172.2, 155.5, 148.4, 138.7, 137.0, 128.4, 127.5, 127.2, 124.5, 123.7, 66.8, 50.3, 48.1, 33.1, 32.9, 25.8, 25.7, 24.8, 22.6; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_2$ $[M + H]^+$ 420.2646, found 420.2667.



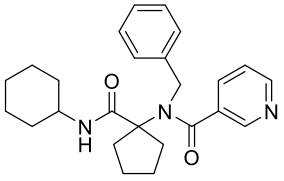
1.37

***N*-Benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclopentyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.077 g, 0.190 mmol, 47% yield, 90.8% purity). Mp = 126–129 ºC; IR (neat) 2929, 1650 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (dt, *J* = 4.8, 1.2 Hz, 1H), 7.69 (td, *J* = 7.6, 1.6 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.30 (dd, *J* = 8.0, 5.1 Hz, 1H), 7.25–7.14 (m, 5H), 4.79 (s, 2H), 3.76–3.67 (m, 1H), 2.57 (br s, 2H), 1.97 (br s, 2H), 1.90–1.83 (m, 2H), 1.75–1.51 (m, 7H), 1.43–1.30 (m, 2H), 1.28–1.12 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 171.2, 155.1, 147.6, 138.8, 137.6, 128.5, 127.3, 127.3, 124.8, 124.0, 74.5, 52.1, 48.3, 36.6, 33.0, 25.8, 24.9, 23.5; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_2$ $[M + H]^+$ 406.2489, found 406.2491.



1.38

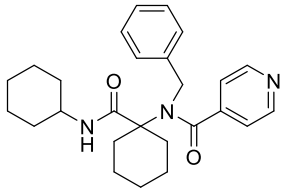
***N*-Benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclohexyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.103 g, 0.245 mmol, 61% yield, ≥ 99% purity). Mp = 50–53 ºC; IR (neat) 2929, 1653, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.60 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.71 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.32–7.16 (m, 4H), 7.15–7.10 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 4.60 (s, 2H), 3.72–3.61 (m, 1H), 2.30–2.17 (m, 4H), 1.91–1.82 (m, 2H), 1.75–1.43 (m, 9H), 1.43–1.31 (m, 2H), 1.29–1.15 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (2 carbonyl), 150.2, 147.3, 137.8, 135.7, 134.3, 128.8, 127.7, 127.3, 123.8, 66.8, 51.3, 48.3, 32.9, 32.8, 25.8, 25.6, 24.8, 22.8; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_2$ $[M + H]^+$ 420.2646, found 420.2634.



1.39

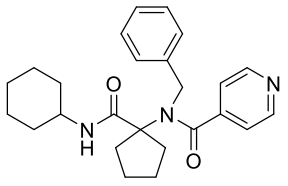
***N*-Benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclopentyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.095 g, 0.234 mmol, 59% yield, 98.3% purity). Mp = 75–79 ºC; IR (neat) 2931, 1639 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 1.5 Hz, 1H), 8.58 (dd, *J* = 5.0, 1.6 Hz,

1H), 7.70 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.32–7.26 (m, 3H), 7.25–7.21 (m, 1H), 7.18–7.12 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 4.64 (s, 2H), 3.82–3.68 (m, 1H), 2.70–2.63 (m, 2H), 2.06–1.96 (m, 2H), 1.95–1.84 (m, 2H), 1.78–1.65 (m, 6H), 1.64–1.54 (m, 1H), 1.45–1.33 (m, 2H), 1.28–1.13 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.4, 149.1, 146.1, 138.3, 136.0, 134.0, 129.0, 127.7, 126.6, 123.9, 74.3, 53.1, 48.5, 36.3, 33.0, 25.8, 24.9, 23.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_2$ $[M + H]^+$ 406.2489, found 406.2509.



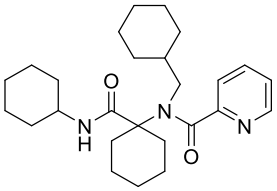
1.40

***N*-Benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclohexyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.079 g, 0.188 mmol, 47% yield, 97.1% purity). Mp = 89–92 ºC; IR (neat) 2929, 1650 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.5 Hz, 2H), 7.40 (d, *J* = 5.4 Hz, 2H), 7.33–7.16 (m, 5H), 6.55 (d, *J* = 8.0 Hz, 1H), 4.55 (s, 2H), 3.82–3.71 (m, 1H), 2.45–2.36 (m, 2H), 2.11–1.97 (m, 2H), 1.95–1.88 (m, 2H), 1.77–1.68 (m, 2H), 1.67–1.58 (m, 5H), 1.46–1.32 (m, 3H), 1.30–1.17 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.8, 148.8, 146.6, 137.7, 129.0, 127.9, 126.9, 122.2, 67.1, 50.7, 48.6, 33.0, 32.7, 25.8, 25.5, 24.9, 23.0; HRMS (ESI) *m/z* calcd for $C_{26}H_{34}N_3O_2$ $[M + H]^+$ 420.2646, found 420.2639.



1.41

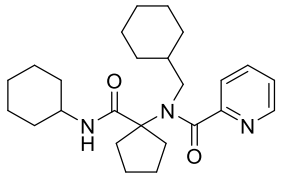
***N*-Benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclopentyl)isonicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.085 g, 0.210 mmol, 52% yield, 98.9% purity). Mp = 140–142 ºC; IR (neat) 2928, 1661, 1623 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57–8.52 (m, 2H), 7.36–7.22 (m, 5H), 7.21–7.15 (m, 2H), 6.41 (d, *J*=7.5 Hz, 1H), 4.59 (s, 2H), 3.83–3.72 (m, 1H), 2.67–2.58 (m, 2H), 2.07–1.88 (m, 4H), 1.78–1.57 (m, 7H), 1.46–1.33 (m, 2H), 1.28–1.15 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.3, 148.0, 146.9, 138.2, 129.1, 127.8, 126.4, 121.5, 74.1, 52.7, 48.6, 36.2, 33.0, 25.7, 24.9, 23.4; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_2$ $[M + H]^+$ 406.2489, found 406.2500.



1.42

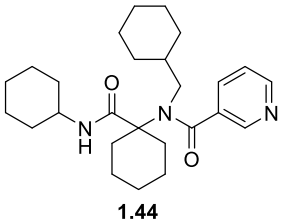
***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(cyclohexylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.092 g, 0.216 mmol, 54% yield, 96.7% purity). IR (neat) 2925, 1661, 1617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63–8.58 (m, 1H), 8.29 (d, *J* = 7.4 Hz, 1H), 7.83–7.75 (m, 1H), 7.61–7.55 (m, 1H), 7.33 (ddd, *J* = 7.5, 4.9, 1.4 Hz, 1H), 3.83–3.66 (m, 1H), 3.24 (d, *J* = 6.9 Hz, 2H), 2.08–1.81 (m, 5H), 1.75–1.04 (m, 23H), 0.99–0.85 (m, 1H), 0.44 (q, *J* = 11.3 Hz, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 173.8, 156.0, 148.9, 137.0, 124.7, 124.6, 65.7, 54.5, 48.1, 37.2, 32.8, 32.7, 31.0, 26.3, 25.8, 25.8, 25.6, 24.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}N_3O_2$ $[M + H]^+$ 426.3115, found 426.3116.



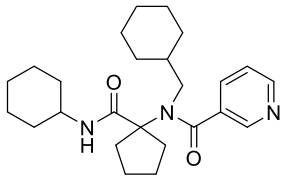
1.43

***N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-(cyclohexylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.066 g, 0.160 mmol, 40% yield, 95.8% purity). Mp = 74–76 ºC; IR (neat) 2932, 1665, 1615 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.3 Hz, 1H), 8.16 (br s, 1H), 7.83 (t, *J* = 7.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.43–7.32 (m, 1H), 3.83–3.68 (m, 1H), 3.36 (d, *J* = 6.7 Hz, 2H), 2.84–2.62 (m, 2H), 2.18–1.49 (m, 17H), 1.45–1.06 (m, 7H), 1.02–0.86 (m, 1H), 0.63–0.28 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 172.1, 155.5, 148.1, 137.6, 124.8, 124.7, 73.5, 55.4, 48.2, 37.1, 36.2, 32.9, 31.0, 26.3, 25.8, 25.7, 24.9, 22.7; HRMS (ESI) *m/z* calcd for $C_{25}H_{38}N_3O_2$ $[M + H]^+$ 412.2959, found 412.2964.



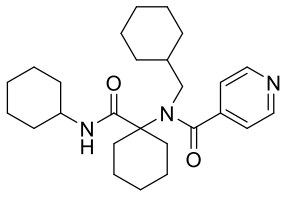
1.44

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(cyclohexylmethyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.070 g, 0.164 mmol, 41% yield, ≥ 99% purity). Mp = 129–131 ºC; IR (neat) 2926, 1676, 1623 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80–8.69 (m, 2H), 8.28 (d, *J* = 6.5 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.65–7.51 (m, 1H), 3.83–3.68 (m, 1H), 3.18 (d, *J* = 6.2 Hz, 2H), 2.51 (br s, 2H), 2.08–1.80 (m, 4H), 1.79–1.06 (m, 22H), 1.02–0.89 (m, 1H), 0.47 (q, *J* = 11.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 172.0, 148.4, 146.6, 138.8, 135.3, 124.7, 65.8, 55.9, 48.1, 37.2, 32.7, 32.2, 31.0, 26.1, 25.7, 25.5, 25.4, 24.6, 22.3; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}N_3O_2$ $[M + H]^+$ 426.3115, found 426.3112.



1.45

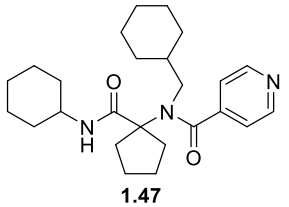
***N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-(cyclohexylmethyl)nicotinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.057 g, 0.138 mmol, 35% yield, 98.0% purity). IR (neat) 2925, 1662, 1618 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67–8.62 (m, 1H), 8.61–8.56 (m, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 7.75–7.68 (m, 1H), 7.38–7.31 (m, 1H), 3.78–3.67 (m, 1H), 3.20 (d, *J* = 6.9 Hz, 2H), 2.67–2.58 (m, 2H), 2.02–1.47 (m, 17H), 1.42–1.31 (m, 2H), 1.28–1.18 (m, 3H), 1.16–1.04 (m, 2H), 0.97–0.85 (m, 1H), 0.51–0.31 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 172.7, 151.0, 148.8, 135.8, 133.6, 123.5, 73.3, 56.8, 48.1, 36.8, 36.1, 32.8, 30.8, 26.2, 25.7, 25.5, 24.7, 22.2; HRMS (ESI) *m/z* calcd for $C_{25}H_{38}N_3O_2$ $[M + H]^+$ 412.2959, found 412.2964.



1.46

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(cyclohexylmethyl)isonicotinamide.**

Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.024 g, 0.056 mmol, 14% yield, ≥ 99% purity). IR (neat) 2925, 1684, 1618 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 5.5 Hz, 2H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 5.5 Hz, 2H), 3.81–3.70 (m, 1H), 3.12 (d, *J* = 6.4 Hz, 2H), 2.48 (s, 2H), 2.00 (br s, 2H), 1.92–1.83 (m, 2H), 1.80–1.53 (m, 13H), 1.50–1.07 (m, 11H), 1.03–0.91 (m, 1H), 0.55–0.43 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 172.8, 148.6, 148.0, 123.2, 65.9, 55.5, 48.3, 37.3, 32.9, 32.4, 31.1, 26.2, 25.8, 25.6, 25.6, 24.7, 22.6; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}N_3O_2$ $[M + H]^+$ 426.3115, found 426.3122.

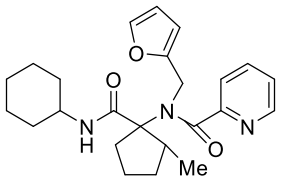


1.47

***N*-(1-(Cyclohexylcarbamoyl)cyclopentyl)-*N*-(cyclohexylmethyl)isonicotinamide.**

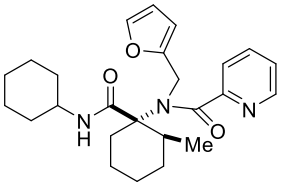
Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.066 g, 0.160 mmol, 40% yield, ≥ 99% purity). Mp = 138–140 ºC; IR (neat) 2921, 1673, 1616 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75–8.70 (m, 2H), 7.98 (d, *J* =

7.3 Hz, 1H), 7.41–7.35 (m, 2H), 3.81–3.70 (m, 1H), 3.15 (d, *J* = 7.0 Hz, 2H), 2.70–2.63 (m, 2H), 2.00–1.94 (m, 2H), 1.92–1.84 (m, 2H), 1.83–1.64 (m, 7H), 1.63–1.54 (m, 5H), 1.46–1.34 (m, 2H), 1.31–1.10 (m, 6H), 1.02–0.90 (m, 1H), 0.52–0.40 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 172.0, 148.7, 147.3, 122.7, 73.5, 56.5, 48.3, 37.0, 36.1, 32.9, 31.0, 26.2, 25.8, 25.6, 24.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{38}N_3O_2$ $[M + H]^+$ 412.2959, found 412.2946.

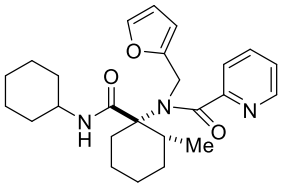


1.48
relative streochemistry not assigned

(±)-*N*-(1-(Cyclohexylcarbamoyl)-2-methylcyclopentyl)-*N*-(furan-2-ylmethyl)picolinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (0.008 g, 0.020 mmol, 5% yield, HPLC purity = 92.8%). IR (neat) 2933, 1664 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 7.58–7.50 (m, 1H), 7.38–7.19 (m, 3H), 6.25–6.16 (m, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 5.08 (d, *J* = 16.9 Hz, 1H), 4.56 (d, *J* = 16.9 Hz, 1H), 3.69–3.58 (m, 1H), 3.32–3.22 (m, 1H), 2.39 (br, 1H), 2.13–1.91 (m, 2H), 1.87–1.51 (m, 7H), 1.48–1.28 (m, 3H), 1.26–1.02 (m, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 171.5, 155.1, 151.3, 148.2, 141.8, 137.2, 124.8, 124.2, 110.7, 108.4, 76.3, 51.0, 47.9, 45.1, 38.8, 32.9, 32.1, 30.9, 25.9, 24.8, 24.7, 19.9, 17.7; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_3O_2$ $[M + H]^+$ 410.2438, found 410.2427.



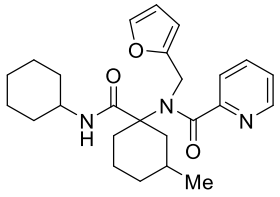
trans-1.49



cis-1.49

***N*-((1*S*,2*S*)-rel-1-(Cyclohexylcarbamoyl)-2-methylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (trans-1.49) and *N*-((1*S*,2*R*)-rel-1-(Cyclohexylcarbamoyl)-2-methylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (cis-1.49).** To a suspension of picolinic acid (0.246 g, 2.00 mmol, 1.0 equiv), furfuryl amine (0.194 g, 2.0 mmol, 1.0 equiv), and 2-methylcyclohexanone (0.224 g, 2.00 mmol, 1.0 equiv) in methanol (5 mL), was added cyclohexyl isocyanide (0.218 g, 2.00 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.7 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification afforded two racemic diastereomers **trans-1.49** (0.097 g, 0.229 mmol, 11% yield, 94.9% purity) as a white solid and **cis-1.49** (0.083 g, 0.196 mmol, 10% yield, 96.2% purity) as a white solid. The relative stereochemistry was assigned by single crystal X-ray diffraction crystallography of **trans-1.49**. Characterization of **trans-1.49**: Mp = 101–103 ºC; IR (neat) 2929, 2856, 1664 (v br) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (dt, *J* = 4.9, 1.2 Hz, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.33 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 7.20 (d, *J* = 1.7 Hz, 1H), 6.15 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.88 (d, *J* = 3.2 Hz, 1H), 4.91 (d, *J* = 16.9 Hz, 1H), 4.52 (d, *J* = 16.9 Hz, 1H), 3.68–3.56 (m, 1H), 3.03 (br s, 1H), 2.38 (t, *J* = 12.4 Hz, 1H), 1.96–1.01 (m, 20H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.5, 171.7, 155.6, 151.2, 148.3, 141.9, 137.1, 124.8, 124.5, 110.6, 108.4, 69.7, 47.8, 43.2, 33.0, 32.8, 32.5, 29.1, 25.8, 24.8, 24.7, 22.2, 16.7; HRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_3NaO_3$ $[M + Na]^+$ 446.2414, found 446.2411. Characterization

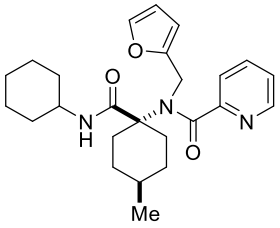
of **cis-1.49**: Mp = 98–100 ºC; IR (neat) 3417, 2927, 2855, 1677 (v br) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44–7.37 (m, 1H), 7.29 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 6.70 (br s, 1H), 6.21 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.83 (d, *J* = 3.3 Hz, 1H), 5.17 (d, *J* = 17.3 Hz, 1H), 4.55 (d, *J* = 17.2 Hz, 1H), 3.81–3.70 (m, 1H), 3.30 (br s, 1H), 2.51–2.37 (m, 1H), 2.11–0.99 (m, 20H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 170.2, 155.8, 152.2, 148.1, 141.7, 137.0, 124.3, 123.7, 111.0, 107.6, 69.6, 47.9, 42.5, 33.3, 31.2, 29.93, 29.87, 25.9, 24.9, 23.2, 20.2, 15.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_3NaO_3$ $[M + Na]^+$ 446.2414, found 446.2412.



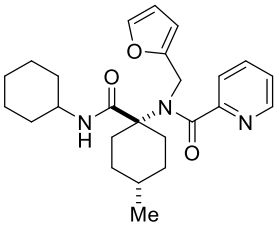
1.50

relative stereochemistry not assigned

(±)-*N*-(1-(Cyclohexylcarbamoyl)-3-methylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless oil (0.023 g, 0.054 mmol, 14% yield, 96.3% purity). IR (neat) 2927, 1666 (v br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.75 (td, *J* = 7.6, 1.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.46–7.30 (m, 2H), 7.25–7.19 (m, 1H), 6.20–6.12 (m, 1H), 5.86 (d, *J* = 3.4 Hz, 1H), 4.73 (br s, 2H), 3.63–3.48 (m, 1H), 3.03–2.36 (m, 2H), 1.93–1.44 (m, 10H), 1.41–0.79 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 173.1, 155.3, 151.0, 148.3, 141.9, 137.2, 125.0, 124.5, 110.7, 108.7, 67.5, 47.9, 43.6, 40.5, 34.5, 32.9, 31.9, 28.1, 25.9, 24.7, 22.6, 21.9; HRMS (ESI) *m/z* calcd for $C_{25}H_{34}N_3O_3$ $[M + H]^+$ 424.2595, found 424.2584.



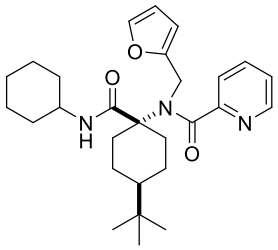
trans-1.51



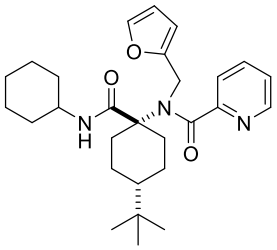
cis-1.51

***N*-((1*r*,4*r*)-1-(Cyclohexylcarbamoyl)-4-methylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide and (trans-1.51) *N*-((1*s*,4*s*)-1-(Cyclohexylcarbamoyl)-4-methylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (cis-1.51).** To a suspension of picolinic acid (0.246 g, 2.00 mmol, 1.0 equiv), furfuryl amine (0.194 g, 2.0 mmol, 1.0 equiv), and 4-methylcyclohexanone (0.224 g, 2.00 mmol, 1.0 equiv) in methanol (5 mL), was added cyclohexyl isocyanide (0.218 g, 2.00 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.7 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification afforded two racemic diastereomers **trans-1.51** (0.228 g, 0.538 mmol, 27% yield, 98.4% purity) as a white solid and **cis-1.51** (0.287 g, 0.678 mmol, 34% yield, ≥ 99% purity) as a white solid. The relative stereochemistry was assigned by single crystal X-ray diffraction crystallography of **trans-1.51.** Characterization of **trans-1.51**: Mp = 87–89 ºC; IR (neat) 3410, 2927, 2856, 1656 (v br) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 7.7, 1.6 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 0.9 Hz, 1H), 7.27 (d, *J* = 0.9 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 6.24 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.02 (d, *J* = 3.1 Hz, 1H), 4.79 (s, 2H), 3.79–3.68 (m, 1H), 2.54 (d, *J* = 12.4 Hz, 2H), 1.91–1.81 (m, 2H), 1.72–1.48 (m, 9H), 1.44–1.28 (m, 3H), 1.22–1.04 (m, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 170.9,

155.6, 151.9, 148.2, 141.8, 137.2, 124.5, 124.0, 110.8, 107.8, 66.0, 48.0, 42.3, 33.2, 32.8, 31.9, 31.3, 25.9, 24.9, 21.8; HRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_3NaO_3$ $[M + Na]^+$ 446.2414, found 446.2413. Characterization of **cis-1.51**: Mp = 74–76 ºC; IR (neat) 2926, 2854, 1657 (v br) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.62 – 8.56 (m, 1H), 7.74 (td, *J* = 7.8, 1.6 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.33 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 2H), 7.23–7.19 (m, 1H), 6.15 (t, *J* = 2.9, 1.8 Hz, 1H), 5.86 (d, *J* = 2.9 Hz, 1H), 4.77 (s, 2H), 3.63–3.52 (m, 1H), 2.69 (d, *J* = 13.3 Hz, 2H), 1.93 (td, *J* = 14.2, 3.3 Hz, 2H), 1.82–1.73 (m, 2H), 1.71–1.63 (m, 4H), 1.61–1.50 (m, 2H), 1.38–1.29 (m, 2H), 1.29–1.15 (m, 3H), 1.14–1.05 (m, 2H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 173.0, 155.3, 151.2, 148.4, 141.9, 137.0, 124.9, 124.4, 110.7, 108.7, 66.5, 48.0, 43.5, 32.9, 32.1, 32.0, 30.5, 25.9, 24.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_3NaO_3$ $[M + Na]^+$ 446.2414, found 446.2413.



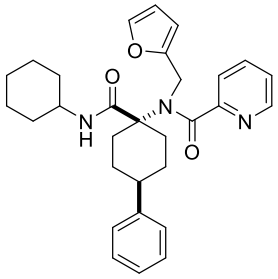
trans-1.52



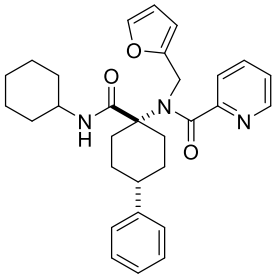
cis-1.52

***N*-((1*r*,4*r*)-4-(*tert*-Butyl)-1-(cyclohexylcarbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (trans-1.52) and *N*-((1*s*,4*s*)-4-(*tert*-Butyl)-1-(cyclohexylcarbamoyl)cyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (cis-1.52).** To a suspension of picolinic acid (0.123 g, 1.00 mmol, 1.0 equiv), furfurylamine (0.097 g, 1.0 mmol, 1.0 equiv), and 4-*tert*-butylcyclohexanone (0.154 g, 1.00 mmol, 1.0 equiv) in methanol (2.5 mL), was added cyclohexyl isocyanide (0.109 g, 1.00 mmol, 1.0 equiv) at room temperature. The

mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.35 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification afforded two racemic diastereomers **trans-1.52** (0.070 g, 0.150 mmol, 15% yield, 94.7% purity) as a white solid and **cis-1.52** (0.082 g, 0.176 mmol, 18% yield, 97.8% purity) as a white solid. The relative stereochemistry was assigned by single crystal X-ray diffraction crystallography of **cis-1.52.** Characterization of **trans-1.52**: Mp = 103–105 ºC; IR (neat) 2931, 2855, 1660 (v br) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.73 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.32–7.27 (m, 2H), 6.39 (d, *J* = 7.8 Hz, 1H), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.07 (d, *J* = 2.9 Hz, 1H), 4.77 (s, 2H), 3.75 (dtd, *J* = 10.3, 7.0, 6.6, 4.1 Hz, 1H), 2.72–2.61 (m, 2H), 1.88 (dd, *J* = 13.0, 4.1 Hz, 2H), 1.70–1.52 (m, 9H), 1.40–1.29 (m, 2H), 1.21–1.05 (m, 3H), 1.03–0.94 (m, 1H), 0.84 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.0, 170.8, 155.6, 152.1, 148.2, 141.7, 137.1, 124.4, 123.7, 110.8, 107.8, 66.0, 48.0, 47.7, 42.4, 33.6, 33.2, 32.5, 27.7, 25.9, 24.9, 24.2; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}N_3NaO_3$ $[M + Na]^+$ 488.2884, found 488.2882. Characterization of **cis-1.52**: Mp = 96–98 ºC; IR (neat) 2935, 2857, 1662 (v br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.47 (d, *J* = 6.1 Hz, 1H), 7.32 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.19 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.12 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.84 (d, *J* = 3.2 Hz, 1H), 4.71 (s, 2H), 3.65–3.45 (m, 1H), 2.77 (br s, 2H), 1.95–1.46 (m, 9H), 1.41–0.98 (m, 8H), 0.87 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 173.1, 154.8, 150.8, 148.3, 141.9, 137.1, 125.1, 124.3, 110.6, 108.7, 66.3, 48.0, 47.2, 43.6, 32.8, 32.5, 32.5, 27.5, 25.8, 24.7, 22.5; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}N_3NaO_3$ $[M + Na]^+$ 488.2884, found 488.2882.



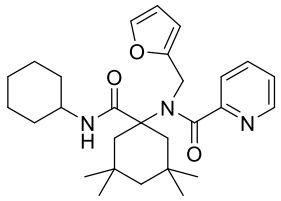
trans-1.53



cis-1.53

***N*-((1r,4r)-1-(Cyclohexylcarbamoyl)-4-phenylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (trans-1.53) and *N*-((1s,4s)-1-(Cyclohexylcarbamoyl)-4-phenylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide (cis-1.53).** To a suspension of picolinic acid (0.123 g, 1.00 mmol, 1.0 equiv), furfurylamine (0.097 g, 1.0 mmol, 1.0 equiv), and 4-phenylcyclohexanone (0.174 g, 1.00 mmol, 1.0 equiv) in methanol (2.5 mL), was added cyclohexyl isocyanide (0.109 g, 1.00 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.35 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification afforded two racemic diastereomers **trans-1.53** (0.102 g, 0.210 mmol, 21% yield, ≥ 99% purity) and **cis-1.53** (0.128 g, 0.264 mmol, 26% yield, ≥ 99% purity). The relative stereochemistry was assigned by single crystal X-ray diffraction crystallography of **trans-1.53.** Characterization of **trans-1.53**: Mp = 107–109 ºC; IR (neat) 2929, 2856, 1658 (v br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.35–7.29 (m, 2H), 7.29–7.21 (m, 4H), 7.19–7.13 (m, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.06 (dd, *J* = 3.3, 0.6 Hz, 1H), 4.85 (s, 2H), 3.78 (tdt, *J* = 10.5, 8.0, 3.9 Hz, 1H), 2.68 (d, *J* = 13.1 Hz, 2H), 2.50 (tt, *J* = 12.4, 3.5 Hz, 1H), 2.22–2.07 (m, 2H), 1.95–1.53 (m, 9H), 1.43–1.28 (m, 2H), 1.23–1.03 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 170.7, 155.3, 151.8, 148.1, 146.7, 141.9, 137.3, 128.3, 127.1,

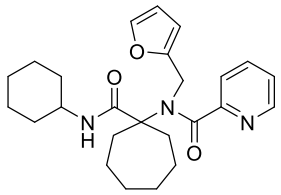
126.1, 124.5, 123.9, 110.9, 107.8, 65.5, 48.0, 43.9, 42.2, 33.3, 33.2, 30.7, 25.8, 24.9; HRMS (ESI) *m/z* calcd for $C_{30}H_{35}N_3NaO_3$ $[M + Na]^+$ 508.2571, found 508.2569. Characterization of **cis-1.53**: Mp = 64–66 ºC; IR (neat) 2930, 2855, 1665 (v br)cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.68 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.67 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.57 (br s, 1H), 7.40 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.22–7.18 (m, 1H), 6.16 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.88 (d, *J* = 2.9 Hz, 1H), 4.77 (s, 2H), 3.66–3.53 (m, 1H), 2.88 (br s, 2H), 2.76–2.67 (m, 1H), 2.14–1.98 (m, 2H), 1.92–1.73 (m, 6H), 1.72–1.64 (m, 2H), 1.60–1.52 (m, 1H), 1.40–1.30 (m, 2H), 1.27–1.19 (m, 1H), 1.18–1.09 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 173.6, 154.9, 150.8, 148.4, 146.9, 142.1, 137.4, 128.5, 127.2, 126.3, 125.3, 124.7, 110.8, 108.9, 66.1, 48.1, 43.8, 43.7, 32.8, 32.5, 29.3, 25.9, 24.7; HRMS (ESI) *m/z* calcd for $C_{30}H_{35}N_3NaO_3$ $[M + Na]^+$ 508.2571, found 508.2571.



1.54

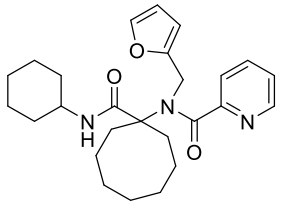
***N*-(1-(Cyclohexylcarbamoyl)-3,3,5,5-tetramethylcyclohexyl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a white solid (0.007 g, 0.015 mmol, 4% yield, ≥ 99% purity). Mp = 131–133 ºC; IR (neat) 2930, 1651 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.45–7.38 (m, 1H), 7.31 (ddd, *J* = 7.7, 4.8, 1.3 Hz, 1H), 7.17 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.13 (dd, *J* = 3.3,

1.8 Hz, 1H), 5.86–5.82 (m, 1H), 4.82 (s, 2H), 3.60–3.49 (m, 1H), 2.39 (d, *J* = 14.7 Hz, 2H), 2.02 (d, *J* = 14.8 Hz, 2H), 1.86–1.72 (m, 3H), 1.70–1.59 (m, 2H), 1.59–1.49 (m, 1H), 1.39–1.08 (m, 12H), 0.99 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 173.4, 155.2, 151.2, 148.1, 141.8, 137.1, 124.9, 124.8, 110.6, 108.5, 67.7, 51.3, 48.1, 43.9, 42.4, 34.4, 32.7, 31.3, 30.5, 25.9, 24.7; HRMS (ESI) *m/z* calcd for $C_{28}H_{40}N_3O_3$ $[M + H]^+$ 466.3064, found 466.3061.



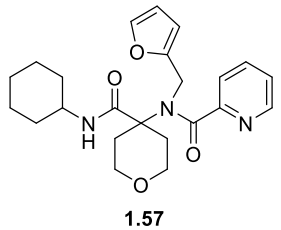
1.55

***N*-(1-(Cyclohexylcarbamoyl)cycloheptyl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.010 g, 0.024 mmol, 6% yield, ≥ 99% purity). Mp = 86–89 ºC; IR (neat) 2927, 1664, 1617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60–8.51 (m, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.53–7.45 (m, 1H), 7.37–7.27 (m, 2H), 6.36–6.18 (m, 2H), 5.85 (d, *J* = 3.3 Hz, 1H), 4.89 (s, 2H), 3.78–3.66 (m, 1H), 2.55–2.46 (m, 2H), 2.08–1.99 (m, 2H), 1.95–1.44 (m, 13H), 1.39–1.26 (m, 2H), 1.19–0.97 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 170.2, 155.3, 151.9, 147.8, 142.0, 137.4, 124.6, 124.1, 110.9, 107.7, 69.9, 48.2, 42.4, 35.6, 33.2, 30.3, 25.8, 25.0, 24.1; HRMS (ESI) m/z calcd for $C_{25}H_{34}N_3O_3$ $[M+H]^+$ 424.2595, found 424.2595.



1.56

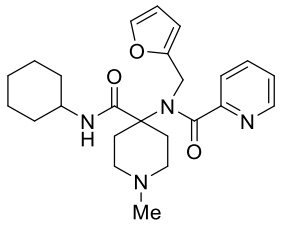
***N*-(1-(Cyclohexylcarbamoyl)cyclooctyl)-*N*-(furan-2-ylmethyl)picolinamide**. Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a colorless film (8 mg, 0.018 mmol, 5% yield, ≥ 99% purity). IR (neat) 2927, 1665, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57–8.51 (m, 1H), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H), 7.41 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.34–7.26 (m, 2H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.21 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.89 (d, *J* = 3.2 Hz, 1H), 4.94 (s, 2H), 3.82–3.69 (m, 1H), 2.47–2.38 (m, 2H), 2.22–2.13 (m, 2H), 1.99–0.97 (m, 20H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 169.9, 155.6, 152.3, 148.0, 141.7, 137.1, 124.4, 123.8, 111.0, 107.5, 70.0, 48.1, 42.8, 33.3, 29.8, 28.5, 25.9, 25.4, 24.9, 22.4; HRMS (ESI) m/z calcd for $C_{25}H_{34}N_3O_3$ $[M+H]^+$ 438.2751, found 438.2750.



1.57

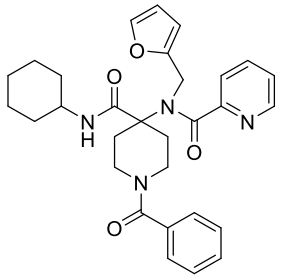
***N*-(4-(Cyclohexylcarbamoyl)tetrahydro-2H-pyran-4-yl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.100 g, 0.243 mmol, 61% yield, ≥ 99% purity). Mp = 109–112 ºC; IR (neat) 2926, 1660, 1622 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (dt, *J* = 4.9, 1.4 Hz, 1H), 7.85–7.77 (m, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.41–7.32 (m, 1H),

7.27 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.00 (s, 1H), 6.23 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.98 (d, *J* = 3.2 Hz, 1H), 4.80 (s, 2H), 3.97–3.79 (m, 4H), 3.75–3.63 (m, 1H), 2.51–2.42 (m, 2H), 2.19–2.10 (m, 2H), 1.91–1.51 (m, 5H), 1.41 1.28 (m, 2H), 1.23–1.04 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 171.3, 154.7, 150.9, 147.8, 142.1, 137.9, 125.1, 124.4, 110.9, 108.4, 64.6, 64.0, 48.1, 42.8, 33.5, 33.0, 25.8, 24.9; HRMS (ESI) m/z calcd for $C_{23}H_{30}N_3O_4$ $[M+H]^+$ 412.2231, found 412.2231.



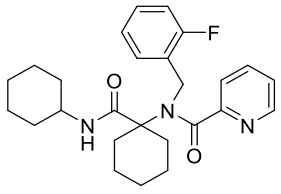
1.58

***N*-(4-(Cyclohexylcarbamoyl)-1-methylpiperidin-4-yl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow solid (0.088 g, 0.207 mmol, 52% yield, ≥ 99% purity). Mp = 91–94 ºC; IR (neat) 2927, 1660, 1628 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.8 Hz, 1H), 7.53 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.37–7.23 (m, 2H), 6.85–6.80 (m, 1H), 6.21 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 4.78 (s, 2H), 3.72–3.61 (m, 1H), 2.69–2.52 (m, 3H), 2.48–2.15 (m, 8H), 1.86–1.77 (m, 2H), 1.70–1.60 (m, 2H), 1.59–1.50 (m, 1H), 1.38–1.26 (m, 2H), 1.22–1.01 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.5, 155.0, 151.3, 148.2, 141.9, 137.2, 124.8, 124.0, 110.9, 108.1, 64.0, 52.1, 48.0, 45.9, 42.8, 33.0, 32.5, 25.8, 24.8; HRMS (ESI) m/z calcd for $C_{24}H_{33}N_4O_3$ $[M+H]^+$ 425.2547, found 425.2556.



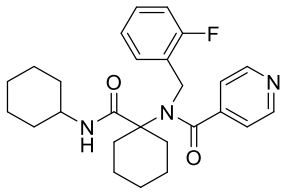
1.59

***N*-(1-Benzoyl-4-(cyclohexylcarbamoyl)piperidin-4-yl)-*N*-(furan-2-ylmethyl)picolinamide.** Prepared according to the general procedure for Ugi multicomponent reaction, the title compound was obtained as a yellow film (0.135 g, 0.262 mmol, 66% yield, ≥ 99% purity). IR (neat) 2929, 1665, 1625 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.41–7.32 (m, 6H), 7.28 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.24 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.98 (dd, *J* = 3.3, 0.9 Hz, 1H), 4.86–4.74 (m, 2H), 4.32–4.23 (m, 1H), 3.85–3.76 (m, 1H), 3.72–3.61 (m, 1H), 3.59–3.48 (m, 2H), 2.57–2.49 (m, 1H), 2.36–2.24 (m, 2H), 2.21–2.17 (m, 1H), 1.89–1.72 (m, 3H), 1.68–1.43 (m, 2H), 1.39–1.21 (m, 2H), 1.20–1.00 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 171.4, 170.4, 154.6, 150.7, 148.2, 142.3, 137.5, 136.0, 129.7, 128.5, 126.9, 125.1, 124.3, 110.9, 108.4, 64.3, 48.1, 45.0, 42.7, 41.0, 38.7, 33.0, 32.9, 32.7, 25.7, 24.8; HRMS (ESI) m/z calcd for $C_{30}H_{35}N_4O_4$ $[M+H]^+$ 515.2653, found 515.2654.



1.60

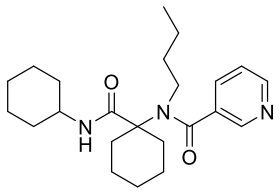
***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(2-fluorobenzyl)picolinamide.** To a suspension of picolinic acid (0.100 g, 0.081 mmol, 1.0 equiv), 2-fluorobenzylamine (0.102 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as yellow solid (0.027 g, 0.062 mmol, 8% yield, ≥ 99% purity). Mp = 95–98 ºC; IR (neat) 2930, 1656 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.66–7.57 (m, 1H), 7.45–7.33 (m, 1H), 7.25 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.04 (d, *J* = 9.8 Hz, 1H), 6.20 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.95 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.78 (s, 2H), 3.71–3.58 (m, 1H), 2.23–2.11 (m, 3H), 1.78 (ddt, *J* = 19.3, 12.5, 7.0 Hz, 5H), 1.71–1.42 (m, 8H), 1.40–1.05 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 172.5, 161.6, 159.6, 155.3, 148.3, 137.3, 130.5, 130.4, 129.3, 129.3, 125.3, 125.2, 124.8, 124.2, 124.2, 115.4, 115.2, 66.6, 48.2, 44.7, 44.7, 32.8, 31.1, 25.9, 25.8, 24.8, 22.5; HRMS (ESI) *m/z* calcd for $C_{26}H_{33}FN_3O_2$ $[M + H]^+$ 438.2551, found 438.2539.



1.61

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-(2-fluorobenzyl)isonicotinamide.** To a suspension of isonicotinic acid (0.100 g, 0.081 mmol, 1.0 equiv), 2-fluorobenzylamine (0.102 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL),

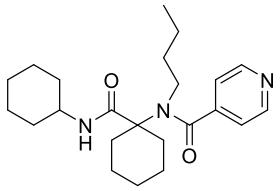
was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as a yellow solid (0.130 mg, 0.297 mmol, 37% yield, ≥ 99% purity). Mp = 108–111 ºC; IR (neat) 2935, 1660 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.0 Hz, 2H), 7.53 (td, *J* = 7.7, 1.7 Hz, 1H), 7.37 (d, *J* = 6.1 Hz, 2H), 7.26–7.21 (m, 1H), 7.13 (td, *J* = 7.5, 0.9 Hz, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.94–6.88 (m, 1H), 4.55 (s, 2H), 3.58–3.44 (m, 1H), 2.27–2.16 (m, 4H), 1.88–1.77 (m, 2H), 1.75–1.63 (m, 4H), 1.61–1.47 (m, 5H), 1.41–1.16 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 172.2, 161.7, 159.8, 149.9, 145.6, 130.3, 130.2, 129.9, 129.9, 124.5, 124.4, 124.2, 124.0, 121.7, 115.5, 115.4, 66.4, 48.4, 45.9, 45.9, 32.7, 32.4, 25.8, 25.6, 24.7, 22.7; HRMS (ESI) *m/z* calcd for $C_{26}H_{33}FN_3O_2$ $[M + H]^+$ 438.2551, found 438.2556.



1.62

***N*-Butyl-*N*-(1-(cyclohexylcarbamoyl)cyclohexyl)nicotinamide.** To a suspension of nicotinic acid (0.100 g, 0.081 mmol, 1.0 equiv), *n*-butylamine (0.059 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography

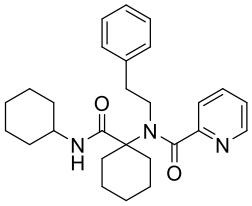
purification (0-100% CH_3CN/H_2O) afforded the title compound as a white solid (0.088 g, 0.228 mmol, 28% yield, 98.7% purity). Mp = 77–80 ºC; IR (neat) 2921, 1647 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81–8.63 (m, 2H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.84 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.42 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.86–3.70 (m, 1H), 3.35 (t, *J* = 7.6 Hz, 2H), 2.51 (d, *J* = 12.2 Hz, 2H), 2.05–1.93 (m, 2H), 1.93–1.80 (m, 2H), 1.77–1.54 (m, 6H), 1.50–1.19 (m, 10H), 1.04 (h, *J* = 7.4 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 173.0, 150.7, 148.2, 136.1, 134.2, 123.9, 65.6, 48.7, 48.0, 32.8, 32.5, 32.0, 25.8, 25.7, 24.7, 22.4, 20.2, 13.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{36}N_3O_2$ $[M + H]^+$ 368.2802, found 386.2791.



1.63

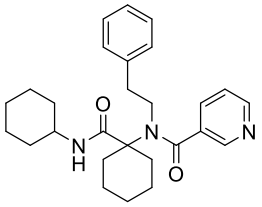
***N*-Butyl-*N*-(1-(cyclohexylcarbamoyl)cyclohexyl)isonicotinamide.** To a suspension of isonicotinic acid (0.100 g, 0.081 mmol, 1.0 equiv), *n*-butylamine (0.059 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as white solid (0.142 g, 0.368 mmol, 45% yield, ≥ 99% purity). Mp = 133–136 ºC; IR (neat) 2931, 1657 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.78–8.72 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.42–7.33 (m, 2H), 3.87–3.74 (m, 1H), 3.33–3.26 (m, 2H), 2.49–2.35 (m, 2H), 2.12–2.03 (m, 2H), 1.96–1.84 (m, 2H), 1.79–1.56

(m, 6H), 1.55–1.15 (m, 10H), 1.05 (h, *J* = 7.4 Hz, 2H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 172.8, 150.1, 146.3, 121.6, 65.7, 48.1, 48.1, 32.8, 32.6, 32.2, 25.8, 25.6, 24.7, 22.6, 20.1, 13.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{36}N_3O_2$ $[M + H]^+$ 368.2802, found 386.2812.



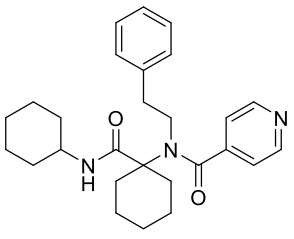
1.64

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-phenethylpicolinamide.** To a suspension of picolinic acid (0.100 g, 0.081 mmol, 1.0 equiv), 2-phenethylamine (0.098 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as white solid (0.155 g, 44% yield, 97.6% purity). Mp = 77–79 ºC; IR (neat) 2931, 1661 (v br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65–8.57 (m, 1H), 7.77 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 (d, *J* = 6.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.36 (ddd, *J* = 7.6, 4.9, 1.0 Hz, 1H), 7.19–7.10 (m, 3H), 6.82 (dd, *J* = 7.2, 1.8 Hz, 2H), 3.89–3.75 (m, 1H), 3.69–3.52 (m, 2H), 2.90–2.76 (m, 2H), 2.46–2.14 (m, 4H), 1.97–1.84 (m, 2H), 1.78–1.17 (m, 14H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 172.5, 155.7, 148.4, 138.5, 137.4, 128.7, 128.6, 126.5, 124.6, 123.3, 66.1, 48.8, 48.2, 36.9, 33.2, 32.9, 25.8, 25.8, 24.8, 22.7; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_3O_2$ $[M + H]^+$ 434.2802, found 434.2801.



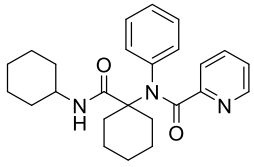
1.65

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-phenethylnicotinamide.** To a suspension of nicotinic acid (0.100 g, 0.081 mmol, 1.0 equiv), 2-phenethylamine (0.098 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as yellow oil (0.156 g, 44% yield, 90.9% purity). IR (neat) 2931, 1656 (v br) cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.73 (dd, *J* = 5.3, 1.4 Hz, 1H), 8.49 (d, *J* = 1.5 Hz, 1H), 7.81 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.62 (dd, *J* = 7.9, 5.3 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.24–7.14 (m, 3H), 6.91–6.83 (m, 2H), 3.88–3.74 (m, 1H), 3.62 (t, *J* = 7.3 Hz, 2H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.41–2.18 (m, 4H), 2.00–1.86 (m, 2H), 1.80–1.20 (m, 14H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 173.1, 170.4, 146.3, 144.1, 140.1, 138.4, 136.3, 129.4, 129.3, 127.4, 126.0, 66.5, 50.2, 49.0, 36.7, 33.3, 33.2, 26.2, 26.0, 25.2, 23.3; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_3O_2$ $[M + H]^+$ 434.2802, found 434.2815.



1.66

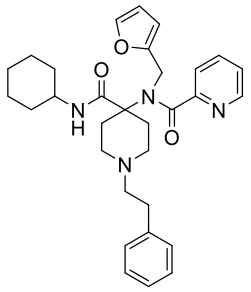
***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-phenethylisonicotinamide** To a suspension of isonicotinic acid (0.100 g, 0.081 mmol, 1.0 equiv), 2-phenethylamine (0.098 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as white solid (0.098 g, 0.226 mmol, 28% yield). 99% purity; Mp = 99–102 ºC; IR (neat) 2934, 1657 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73–8.67 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.26–7.11 (m, 5H), 6.79 (dt, *J* = 6.7, 2.2 Hz, 2H), 3.89–3.77 (m, 1H), 3.55–3.46 (m, 2H), 2.78–2.70 (m, 2H), 2.50–2.42 (m, 2H), 2.24–2.08 (m, 2H), 1.96–1.87 (m, 2H), 1.76–1.66 (m, 4H), 1.64–1.55 (m, 2H), 1.54–1.35 (m, 5H), 1.33–1.20 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 172.8, 150.4, 145.6, 137.7, 128.8, 128.6, 126.9, 121.2, 65.8, 49.7, 48.2, 36.6, 32.9, 32.8, 25.8, 25.6, 24.7, 22.7; HRMS (ESI) *m/z* calcd for $C_{27}H_{36}N_3O_2$ $[M + H]^+$ 434.2802, found 434.2831.



1.67

***N*-(1-(Cyclohexylcarbamoyl)cyclohexyl)-*N*-phenylpicolinamide.** To a suspension of picolinic acid (0.100 g, 0.081 mmol, 1.0 equiv), aniline (0.076 g, 0.081 mmol, 1.0 equiv), and cyclohexanone (0.080 g, 0.081 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.088 g, 0.081 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room

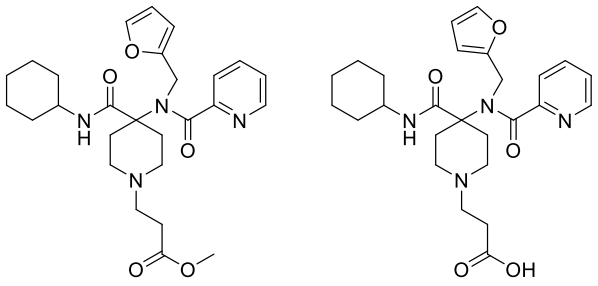
temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the title compound as white solid (0.216 g, 0.533 mmol, 66% yield, ≥ 99% yield). Mp = 67–69 ºC; IR (neat) 2929, 1658 (v br) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.31–8.25 (m, 1H), 7.45 (td, *J* = 7.6, 1.7 Hz, 2H), 7.38–7.21 (m, 2H), 7.22–7.06 (m, 4H), 6.99 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 3.96–3.84 (m, 1H), 2.49–2.35 (m, 2H), 2.07–1.95 (m, 2H), 1.78–1.49 (m, 10H), 1.47–1.13 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 170.0, 155.6, 148.2, 139.4, 136.3, 131.9, 128.3, 127.9, 123.2, 122.6, 66.9, 48.6, 34.0, 33.1, 25.8, 25.5, 25.0, 22.9; HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_2$ $[M + H]^+$ 406.2489, found 406.2493.



1.68

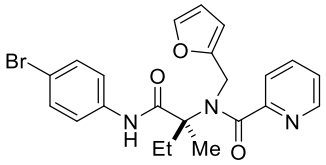
***N*-(4-(cyclohexylcarbamoyl)-1-phenethylpiperidin-4-yl)-*N*-(furan-2-ylmethyl)picolinamide.** To a suspension of picolinic acid (0.123 g, 1.00 mmol, 1.0 equiv), furfurylamine (0.097 g, 1.00 mmol, 1.0 equiv), and 1-phenethyl-4-piperidone (0.203 g, 1.00 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.109 g, 1.00 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O)

afforded the title compound as brown solid (0.281 g, 0.546 mmol, 55% yield, ≥ 99% purity). Mp = 76–78 ºC; IR (neat) 2928, 1651 (v br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.39–7.15 (m, 7H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.24 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.99 (d, *J* = 3.1 Hz, 1H), 4.82 (s, 2H), 3.80–3.62 (m, 1H), 2.90–2.60 (m, 8H), 2.56–2.40 (m, 2H), 2.37–2.20 (m, 2H), 1.94–1.78 (m, 2H), 1.76–1.50 (m, 3H), 1.42–1.05 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.7, 155.1, 151.3, 148.2, 141.8, 140.6, 137.1, 128.8, 128.4, 126.0, 124.7, 124.0, 110.8, 108.1, 64.7, 60.3, 50.0, 47.9, 42.9, 33.8, 33.0, 32.6, 25.8, 24.7; HRMS (ESI) *m/z* calcd for $C_{31}H_{39}N_4O_3$ $[M + H]^+$ 515.3017, found 515.3025.

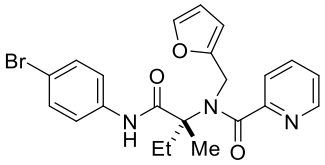


Methyl 3-(4-(cyclohexylcarbamoyl)-4-(*N*-(furan-2-ylmethyl)picolinamido)piperidin-1-yl)propanoate (1.69) and 3-(4-(Cyclohexylcarbamoyl)-4-(*N*-(furan-2-ylmethyl)picolinamido)piperidin-1-yl)propanoic acid (1.70). To a suspension of picolinic acid (0.123 g, 1.00 mmol, 1.0 equiv), furfurylamine (0.097 g, 1.00 mmol, 1.0 equiv), and methyl 3-(4-oxopiperidin-1-yl)propanoate (0.185 g, 1.00 mmol, 1.0 equiv) in methanol (2 mL), was added cyclohexyl isocyanide (0.109 g, 1.00 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.3 mL), stirred for 30 min at room temperature, and then concentrated *in vacuo*. Reverse-phase flash

column chromatography purification (0-100% CH_3CN/H_2O) afforded the desired product (1.73) which was partially hydrolyzed in the aqueous solution. The partially hydrolyzed mixture was further purified with normal phase flash column chromatography (0-20% CH_3OH/DCM) to afford **1.69** (0.185 g, 0.371 mmol, 37% yield, ≥ 99% purity) as a colorless oil and **1.70** (0.035 g, 0.073mmol, 7% yield, ≥ 99% purity) as a white solid. Characterization of **1.69**: IR (neat) 2930, 1656 (v br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.53 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.31 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.24 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.20 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 4.76 (s, 2H), 3.73–3.57 (m, 4H), 2.76–2.54 (m, 6H), 2.53–2.35 (m, 4H), 2.31–2.16 (m, 2H), 1.88–1.74 (m, 2H), 1.71–1.49 (m, 3H), 1.39–1.01 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 172.0, 171.8, 155.1, 151.3, 148.3, 141.9, 137.2, 124.8, 124.1, 110.8, 108.2, 64.6, 53.4, 51.7, 49.8, 48.0, 42.9, 33.0, 32.6, 32.4, 25.8, 24.8; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}N_4O_5$ $[M + H]^+$ 497.2758, found 497.2760. Characterization of **1.70**: Mp = 101–103 ºC; IR (neat) 2972 (v br), 1716, 1652 (v br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 3H), 7.56 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.35 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 7.29 (d, *J* = 1.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.24 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.04 (d, *J* = 3.2 Hz, 1H), 4.83 (s, 2H), 3.72–3.58 (m, 1H), 3.30–3.22 (m, 2H), 3.20–3.09 (m, 2H), 2.99 (t, *J* = 6.1 Hz, 2H), 2.58–2.33 (m, 6H), 1.85–1.74 (m, 2H), 1.71–1.50 (m, 2H), 1.39–1.23 (m, 2H), 1.21–0.98 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 171.8, 171.0, 154.4, 150.8, 148.2, 142.1, 137.4, 124.9, 124.0, 111.0, 108.4, 62.7, 53.8, 49.1, 48.1, 42.4, 32.9, 31.2, 30.7, 25.6, 24.7; HRMS (ESI) *m/z* calcd for $C_{26}H_{35}N_4O_5$ $[M + H]^+$ 483.2602, found 483.2594.



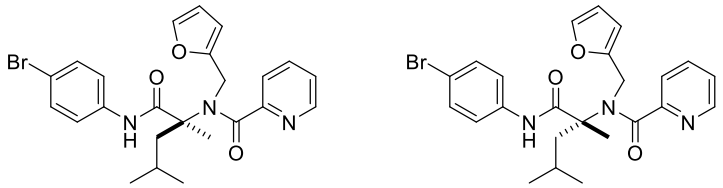
(*S*)-1.71



(*R*)-1.71

(*S*)-*N*-(1-((4-Bromophenyl)amino)-2-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)picolinamide ((*S*)-1.71) and (*R*)-*N*-(1-((4-Bromophenyl)amino)-2-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)picolinamide ((*R*)-1.71). To a suspension of picolinic acid (0.295 g, 2.40 mmol, 1.0 equiv), furfurylamine (0.233 g, 2.40 mmol, 1.0 equiv), and 2-butanone (0.173 g, 2.40 mmol, 1.0 equiv) in methanol (6 mL), was added 4-bromophenyl isocyanide (0.437 g, 2.40 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.84 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the racemic mixture (0.400 g, 0.877 mmol, 37% yield). Reaction was repeated to obtain enough racemic material for chiral separation. The racemic mixture (0.600 g dissolved in 4 mL of DCM, 0.15 mL for every injection) was separated by Chiral HPLC (CHIRALPAK IA SFC Semi-Prep column, 25% EtOH/hexanes) to afford **(*S*)-1.71** (0.250 g, t_R = 16.2 min) as a white solid and **(*R*)-1.71** (0.240 g, t_R = 28.0 min) as a white solid. The absolute configuration of **(*S*)-1.71** was unambiguously determined by anomalous scattering of the Cu X-rays of the Br atoms while that of **(*R*)-1.71** was then assigned accordingly. Characterization of **(*S*)-1.71**: $[\alpha]_D^{20}$ = −66.4 (*c* 1.0, DCM); Mp = 108–110 ºC; Characterization of **(*R*)-1.71**: $[\alpha]_D^{20}$ = +66.1 (*c* 1.0, DCM); Mp = 107–109 ºC; IR (neat) 2982, 1691, 1641cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.57 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.35 (s, 1H), 7.79 (td, *J* = 7.8, 1.7 Hz, 1H), 7.54–7.49 (m, 1H), 7.44–7.35 (m, 6H), 6.28 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.96 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.16 (d, *J* = 17.3 Hz, 1H), 4.69 (d, *J* = 17.3 Hz, 1H), 2.32 (dq, *J* = 13.4, 7.5 Hz, 1H), 1.96 (dq, *J* = 13.4, 7.5 Hz,

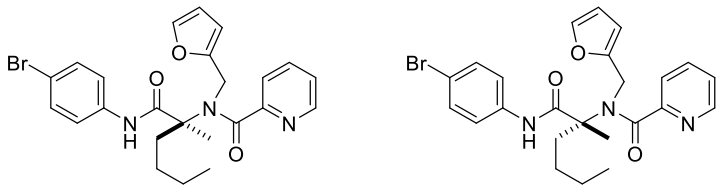
1H), 1.51 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 172.5, 170.8, 155.0, 152.1, 148.4, 142.7, 138.6, 138.1, 132.2, 125.4, 124.4, 121.8, 116.3, 111.5, 108.2, 67.3, 42.9, 29.4, 20.7, 8.7; HRMS (ESI) m/z calcd for $C_{22}H_{22}BrN_3NaO_3$ $[M+Na]^+$ 478.0737, found 478.0737.



(*S*)-1.72 (*R*)-1.72

(*S*)-*N*-(1-((4-Bromophenyl)amino)-2,4-dimethyl-1-oxopentan-2-yl)-*N*-(furan-2-ylmethyl)picolinamide ((*S*)-1.72) and (*R*)-*N*-(1-((4-Bromophenyl)amino)-2,4-dimethyl-1-oxopentan-2-yl)-*N*-(furan-2-ylmethyl)picolinamide ((*R*)-1.72). To a suspension of picolinic acid (0.590 g, 4.80 mmol, 1.0 equiv), furfurylamine (0.466 g, 4.80 mmol, 1.0 equiv), and 4-methylpentan-2-one (0.481 g, 4.80 mmol, 1.0 equiv) in methanol (12 mL), was added 4-bromophenyl isocyanide (0.874 g, 4.80 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (1.70 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification (0-100% CH_3CN/H_2O) afforded the racemic mixture (0.512 g, 1.057 mmol, 22% yield). The racemic mixture (0.512 g dissolved in 4 mL of DCM, 0.25 mL for every injection) was separated by Chiral HPLC (CHIRALPAK IA SFC Semi-Prep column, 25% EtOH/hexanes) to afford **(*S*)-1.72** (0.167 g, t_R = 11.7 min) as a white solid and **(*R*)-1.72** (0.199 g, t_R = 24.9 min) as a white solid. The absolute configuration of **(*S*)-1.72** was unambiguously determined by anomalous scattering of the Cu X-rays of the Br atoms while that of **(*R*)-1.72** was

then assigned accordingly. Characterization of **(*S*)-1.72**: $[\alpha]_D^{20}$ = –78.7 (*c* 1.0, DCM); Mp = 120–122 ºC. Characterization of **(*R*)-1.72**: $[\alpha]_D^{20}$ = +76.6 (*c* 1.0, DCM); Mp = 118–121 ºC; IR (neat) 2958, 1690, 1643 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 8.62–8.53 (m, 1H), 8.35 (s, 1H), 7.78 (tdd, *J* = 7.8, 1.8, 0.7 Hz, 1H), 7.45–7.33 (m, 6H), 6.28 (ddd, *J* = 3.1, 1.9, 0.7 Hz, 1H), 6.00–5.90 (m, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 4.69 (d, *J* = 17.2 Hz, 1H), 2.20 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.90 (dd, *J* = 13.9, 4.8 Hz, 1H), 1.87–1.79 (m, 1H), 1.55 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 172.6, 170.7, 155.1, 152.1, 148.5, 142.7, 138.6, 138.0, 132.2, 125.3, 124.5, 121.8, 116.3, 111.5, 108.3, 67.0, 44.8, 42.8, 25.4, 25.1, 24.4, 21.8; HRMS (ESI) m/z calcd for $C_{24}H_{26}BrN_3NaO_3$ $[M+Na]^+$ 506.1050, found 506.1045.

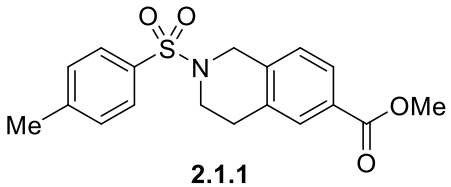


(*S*)-1.73 (*R*)-1.73

(*S*)-*N*-(1-((4-Bromophenyl)amino)-2-methyl-1-oxohexan-2-yl)-*N*-(furan-2-ylmethyl)picolinamide ((*S*)-1.73) and (*R*)-*N*-(1-((4-Bromophenyl)amino)-2-methyl-1-oxohexan-2-yl)-*N*-(furan-2-ylmethyl)picolinamide ((*R*)-1.73). To a suspension of picolinic acid (0.295 g, 2.40 mmol, 1.0 equiv), furfurylamine (0.233 g, 2.40 mmol, 1.0 equiv), and 2-hexanone (0.240 g, 2.40 mmol, 1.0 equiv) in methanol (6 mL), was added 4-bromophenyl isocyanide (0.437 g, 2.40 mmol, 1.0 equiv) at room temperature. The mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with TFA (0.84 mL) followed by 30 min of stirring at room temperature, then concentrated *in vacuo*. Reverse-phase flash column chromatography purification

(0-100% CH_3CN/H_2O) afforded the racemic mixture (0.396 g, 0.818 mmol, 34% yield). The racemic mixture (0.396 g dissolved in 3 mL of DCM, 0.25 mL for every injection) was separated by Chiral HPLC (CHIRALPAK IA SFC Semi-Prep column, 40% Isopropanol/hexanes) to afford **(*S*)-1.73** (0.197 g, t_R = 12.3 min) as a white solid and **(*R*)-1.73** (0.174 g, t_R = 20.0 min) as a white solid. The absolute configuration of **(*S*)-1.73** was unambiguously determined by anomalous scattering of the Cu X-rays of the Br atoms while that of **(*R*)-1.73** was then assigned accordingly. Characterization of **(*S*)-1.73**: $[\alpha]_D^{20} = -56.7$ (*c* 0.9, DCM); Mp = 98–100 ºC; IR (neat) 2958, 1691, 1644 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 8.61–8.53 (m, 1H), 8.33 (s, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.47–7.33 (m, 6H), 6.28 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.97 (d, *J* = 3.3 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 4.69 (d, *J* = 17.2 Hz, 1H), 2.29–2.19 (m, 1H), 1.94–1.86 (m, 1H), 1.52 (s, 3H), 1.42–1.25 (m, 4H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 172.0, 170.4, 154.5, 151.6, 148.0, 142.1, 138.0, 137.4, 131.7, 124.7, 123.8, 121.2, 115.8, 110.9, 107.6, 66.3, 42.3, 35.9, 26.0, 23.1, 20.7, 13.8; HRMS (ESI) m/z calcd for $C_{24}H_{26}BrN_3NaO_3$ $[M+Na]^+$ 506.1050, found 506.1051. Characterization of **(*R*)-1.73**: $[\alpha]_D^{20}$ = +56.3 (*c* 1.0, DCM); Mp = 100–102 ºC.

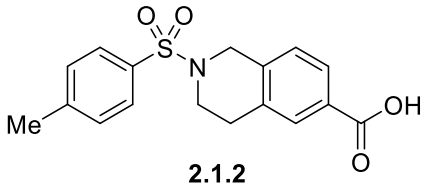
Procedure for Chapter 2



2.1.1

Methyl 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylate. To a suspension of methyl 1,2,3,4-tetrahydroisoquinoline-6-carboxylate hydrochloride (1.000 g, 4.39 mmol, 1.0 equiv) in

anhydrous DCM (12 mL) were added triethylamine (1.33 g, 13.17 mmol, 3.0 equiv) and 4-methylbenzenesulfonyl chloride (0.837 g, 4.39 mmol, 1.0 equiv) at room temperature, then stirred overnight. The reaction mixture was acidified with aqueous HCl (2 N) to pH 3, then extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white solid (1.50 g, 4.34 mmol, 99% yield). Mp = 143–145 °C; IR (neat) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 2H), 7.75–7.69 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 4.28 (s, 2H), 3.89 (s, 3H), 3.37 (t, *J* = 5.9 Hz, 2H), 2.97 (t, *J* = 5.9 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 144.0, 136.9, 133.5, 133.3, 130.3, 129.9, 128.8, 127.9, 127.5, 126.6, 52.3, 47.8, 43.7, 28.9, 21.7; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_4S$ $[M+H]^+$ 346.1108, found 346.1106.

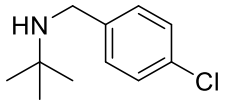


2.1.2

2-Tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid. To a solution of methyl 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (0.660 g, 2.13 mmol, 1.0 equiv) in methanol (10 mL) and THF (10 mL) was added aqueous NaOH (1 N, 20 mL) at room temperature. The mixture was stirred overnight, and concentrated *in vacuo*. The concentrated mixture was acidified with aqueous HCl (2 N) to pH 2, then filtered to afford the title compound as a white solid (0.100 g, 0.29 mmol, 90% yield). Mp = 235–237 °C; IR (neat) 1678 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.89 (br s, 1H); 7.74–7.70 (m, 4H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 4.25 (s, 2H), 3.30 (t, *J* = 6.0 Hz, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz,

DMSO-d_6,) δ 167.0, 143.7, 136.7, 133.4, 133.0, 129.9, 129.7, 129.1, 127.4, 126.9, 126.7, 47.3, 43.3, 27.9, 21.0; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_4S$ $[M-H]^-$330.0806, found 330.0807.

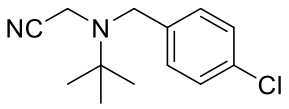
General procedure for reductive amination. To a solution of ketone/aldehyde, amine in DCE were added $NaBH(OAc)_3$ and AcOH at room temperature. The resulting mixture were stirred for 12 or 24 h as needed for the completion of reaction. The reaction was quenched at room temperature with aqueous NaOH (1 N) to pH 10, then extracted with EtOAc three times. The combined organic phase was washed with brine, dried over Na_2SO_4, concentrated *in vacuo*. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the product.



2.1.3

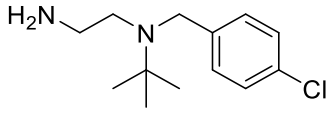
***N*-(4-Chlorobenzyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using 4-chlorobenzaldehyde (5.000 g, 35.57 mmol, 1.0 equiv), tert-butylamine (2.602 g, 35.57 mmol, 1.0 equiv), $NaBH(OAc)_3$ (10.56 g, 49.80 mmol, 1.4 equiv), AcOH (1 drop) and DCE (50 mL), which was stirred at room temperature for 12 h. Reverse-phase flash column chromatography (0− 100% CH_3CN/H_2O) afforded the title compound as a light yellow oil (5.340 g, 27.01 mmol, 76% yield). IR (neat) 1590 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.40–7.19 (m, 4H), 3.70 (s, 2H), 1.15 (s, 9H), 0.95 (br s, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ

141.5, 132.6, 130.1, 128.8, 51.1, 46.9, 29.5; HRMS (ESI) m/z calcd for $C_{11}H_{17}ClN$ $[M+H]^+$ 198.1044, found 198.1047.



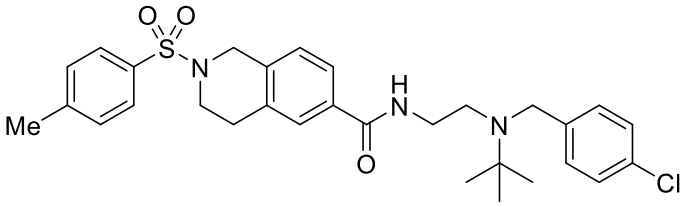
2.1.4

2-(*tert*-Butyl(4-chlorobenzyl)amino)acetonitrile. To a solution of *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (1.970 g, 9.96 mmol, 1.0 equiv) in acetonitrile (25 mL) were added K_2CO_3 (2.760 g, 19.97 mmol, 2.0 equiv), KI (1.660 g, 10.00 mmol, 1.0 equiv) and $ClCH_2CN$ (0.831 g, 11.01 mmol, 1.1 equiv) at room temperature. The reaction was stirred at this temperature for 16 h, then diluted with saturated aqueous Na_2CO_3 (50 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel chromatography (0-20% EtOAc/hexanes) afforded the title compound as a yellowish oil (1.490 g, 6.29 mmol, 63% yield). IR 2975, 1597, 1490, (neat) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 4H), 3.80 (s, 2H), 3.43 (s, 2H), 1.28 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.4, 133.3, 129.9, 128.8, 117.9, 55.4, 50.9, 35.8, 27.4; HRMS (ESI) m/z calcd for $C_{13}H_{18}ClN_2$ $[M+H]^+$ 237.1153, found 237.1141.



2.1.5

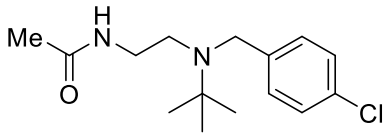
***N*^{1}-(*tert*-Butyl)-*N*^{1}-(4-chlorobenzyl)ethane-1,2-diamine.** To a solution of 2-(*tert*-butyl(4-chlorobenzyl)amino)acetonitrile (1.360 g, 5.74 mmol, 1.0 equiv) in anhydrous THF (115 mL) was added $LiAlH_4$, (1 N in THF, 23 mL, 23.0 mmol, 4.0 equiv) dropwise at room temperature. The resulting mixture was stirred at this temperature for 4 h, then quenched with Glaubler's salt ($Na_2SO_4 \cdot 10H_2O$, 90 g) at 0 °C. The reaction was warmed to room temperature and stirred for 15 min, then filtrated and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as colorless oil (0.967 g, 4.02 mmol, 70% yield). IR 2969, 2869, 1488 (neat) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (m, 4H), 3.63 (s, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.44 (t, *J* = 6.4 Hz, 2H), 1.33 (br s, 2H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 131.9, 129.0, 128.3, 55.2, 54.7, 54.6, 42.2, 27.5; HRMS (ESI) m/z calcd for $C_{13}H_{22}ClN_2$ $[M+H]^+$ 241.1466, found 241.1462.



2.1

***N*-(2-(tert-Butyl(4-chlorobenzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (1.000 g, 3.02 mmol, 1.0 equiv) in anhydrous DMF (15 mL) were added DIPEA (1.170 g, 9.05 mmol, 3.0 equiv) and HATU (1.148 g, 3.02 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of *N*^{1}-(*tert*-butyl)-*N*^{1}-(4-chlorobenzyl)ethane-1,2-diamine (0.727 g, 3.02 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated

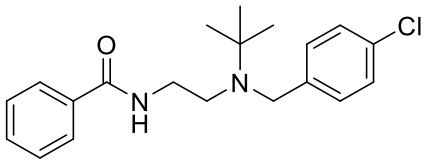
under N_2. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (1.108 g, 2.00 mmol, 66% yield, ≥ 99% purity). Mp = 95–97 ºC; IR (neat) 2969, 1644, 1541, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.53 (m, 2H), 7.45–7.39 (m, 4H), 7.31 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 4.20 (s, 2H), 3.69 (s, 2H), 3.28 (t, *J* = 6.0 Hz, 2H), 3.04 (m, 2H), 2.87 (t, *J* = 6.0 Hz, 2H), 2.64 (m, 2H), 2.39 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 143.6, 142.1, 134.6, 132.9, 132.84, 132.77, 130.5, 129.9, 129.3, 127.8, 127.45, 127.42, 126.3, 124.7, 54.8, 53.4, 49.9, 47.2, 43.4, 40.4, 28.0, 27.1, 21.0; HRMS (ESI) m/z calcd for $C_{30}H_{37}ClN_3O_3S$ $[M+H]^+$ 554.2244, found 554.2261.



2.2

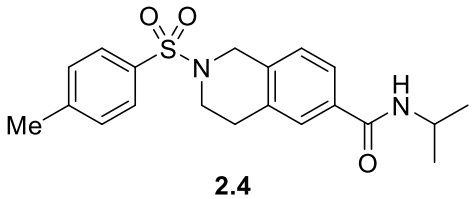
***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)acetamide.** To a solution of N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)ethane-1,2-diamine (0.050 g, 0.208 mmol, 1.0 equiv) in anhydrous DCM (1 mL) was added trimethylamine (0.064 g, 0.632 mmol, 3.0 equiv) and solution of acetyl chloride (0.016 g, 0.208 mmol, 1.0 equiv) in anhydrous DCM (1 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h, then concentrated *in vacuo*, diluted with water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless film (0.025 g, 0.088 mmol, 42% yield, 94.3% purity). IR (neat) 3286, 2971, 1648, 1553; 1488 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.36–

7.25 (m, 4H), 5.42 (br s, 1H), 3.64 (s, 2H), 2.97–2.90 (m, 2H), 2.67 (t, J = 6.3 Hz, 2H), 1.73 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 169.2, 141.9, 132.0, 129.4, 128.3, 55.3, 54.4, 50.1, 39.8, 27.0, 22.8; HRMS (ESI) m/z calcd for $C_{15}H_{24}ClN_2O$ $[M+H]^+$ 283.1572, found 283.1564.



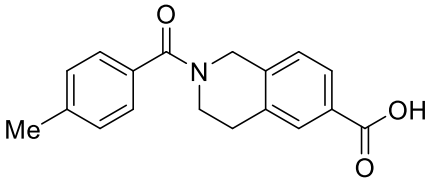
2.3

***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)benzamide.** To a solution of N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)ethane-1,2-diamine (0.050 g, 0.208 mmol, 1.0 equiv) in anhydrous DCM (1 mL) was added trimethylamine (0.064 g, 0.632 mmol, 3.0 equiv) and solution of benzoyl bromide (0.038 g, 0.205 mmol, 1.0 equiv) in anhydrous DCM (1 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h, then concentrated *in vacuo*, diluted with water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.041 g, 0.119 mmol, 57% yield, ≥ 99% purity). IR (neat) 3327, 2969, 1638, 1541, 1488 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.60–7.55 (m, 2H), 7.52–7.47 (m, 1H), 7.45–7.40 (m, 2H), 7.36–7.29 (m, 2H), 7.24–7.17 (m, 2H), 6.24 (br s, 1H), 3.69 (s, 2H), 3.22–3.14 (m, 2H), 2.82 (t, J = 6.2 Hz, 2H), 1.16 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 167.2, 142.4, 135.5, 132.5, 131.6, 129.8, 129.0, 128.9, 127.2, 56.0, 55.0, 50.7, 40.5, 27.6; IR (neat) 3326, 2971, 1639, 1541 cm^{-1} HRMS (ESI) m/z calcd for $C_{20}H_{26}ClN_2O$ $[M+H]^+$ 345.1726, found 345.1728.



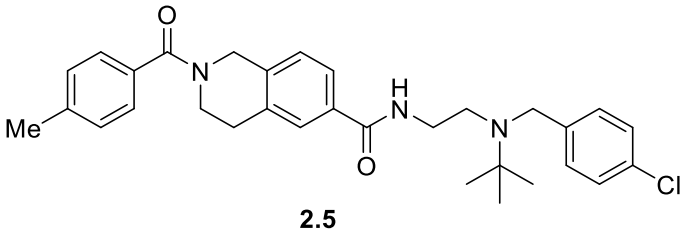
2.4

***N*-iso-Propyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.025 g, 0.075 mmol, 1.0 equiv) in anhydrous DMF (0.5 mL) were added DIPEA (0.029 g, 0.226 mmol, 3.0 equiv) and HATU (0.029 g, 0.075 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of isopropylamine (0.005 g, 0.085 mmol, 1.1 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.007 g, 0.019 mmol, 25% yield, ≥99% purity). IR (neat) 3318, 2972, 1633, 1543 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 5.95 (d, *J* = 7.1 Hz, 1H), 4.23–4.13 (m, 3H), 3.30 (t, *J* = 5.9 Hz, 2H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.41 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 166.2, 144.6, 135.4, 134.0, 133.9, 132.9, 130.2, 128.1, 127.9, 126.9, 124.8, 48.0, 44.1, 42.3, 29.2, 22.9, 21.8; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O_3S$ $[M+H]^+$ 373.1580, found 373.1580.



2.5.1

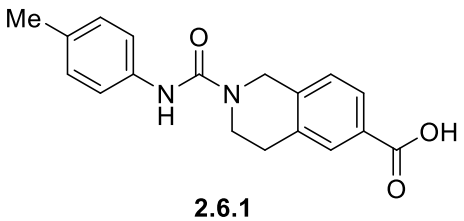
2-(4-Methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid. To a solution of methyl 2-(4-methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (0.660 g, 2.13 mmol, 1.0 equiv) in a mixture of THF and methanol (1:1, 20 mL) was added aqueous NaOH (1 N, 20 mL) at room temperature. The resulting mixture was stirred at this temperature for 24 h, then acidified with aqueous HCl (1 N) to pH 2. Filtration followed by purification with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a white solid (0.520 g, 1.76 mmol, 84% yield). Mp = 70–72 °C IR 1675; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.84–7.65 (m, 2H), 7.47–7.12 (m, 5H), 4.76 (br s, 2H), 3.63 (m, 2H), 2.91 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.6, 167.0, 139.3, 138.2, 134.7, 133.0, 129.6, 128.9, 128.8, 126.90, 126.87, 126.6, 49.2, 44.4, 28.6, 20.8; HRMS (ESI) m/z calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281, found 296.1280.



2.5

***N*-(2-(tert-Butyl(4-chlorobenzyl)amino)ethyl)-2-(4-methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-(4-methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.030 g, 0.10 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.039 g, 0.302 mmol, 3.0 equiv) and HATU (0.038 g, 0.10 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)ethane-1,2-diamine (0.034 g, 0.10 mmol, 1.0 equiv). The reaction was

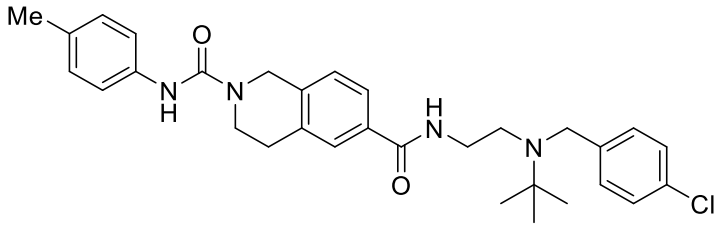
stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a light yellow film (0.022 g, 0.041 mmol, 53% yield, 98.7% purity). IR (neat) 2931, 1667 (v br) cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.21 (t, J = 5.4 Hz, 1H), 7.66–7.53 (m, 2H), 7.47–7.19 (m, 9H), 4.72 (br s, 2H), 3.95 – 3.47 (m, 5H), 3.33 (q, J = 6.1 Hz, 2H), 2.87 (s, 2H), 2.61–2.52 (m, 2H), 2.39–2.28 (m, 5H), 0.83 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.5, 165.6, 139.2, 139.0, 136.1, 134.2, 133.0, 132.7, 131.1, 130.1, 128.8, 127.9, 127.4, 126.8, 126.2, 124.7, 66.4, 59.5, 54.8, 44.4, 40.1, 37.2, 32.7, 28.7, 27.9, 20.8; HRMS (ESI) m/z calcd for $C_{31}H_{37}ClN_3O_2$ $[M+H]^+$ 518.2569, found 518.2556.



2.6.1

2-(*p*-Tolylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid. To a solution of methyl ester (0.324 g, 1.00 mmol, 1.0 equiv) in THF (3.3 mL) were added methanol (3.3 mL) and aqueous NaOH solution (1 N, 3.3 mL) at room temperature. The mixture was stirred at this temperature for 12 h, then concentrated *in vacuo*, diluted with water (20 mL), and extracted with EtOAc (20 mL). The aqueous layer was acidified with aqueous HCl solution (1 N) to pH 2, then filtered to afford the title compound as a white solid (0.237 g, 0.76 mmol, 76% yield). Mp = 206–208 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.80–7.72 (m, 2H), 7.39–7.34 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.3 Hz, 2H), 4.69 (s, 2H), 3.71 (t, J = 5.9 Hz, 2H), 2.90 (t, J = 5.8 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.2, 155.1, 139.1, 137.8, 135.1,

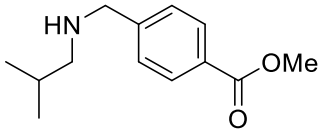
130.6, 129.7, 128.7, 126.9, 126.5, 120.0, 45.7, 41.2, 28.3, 20.4; IR (neat) 3417, 2922, 1668, 1650, 1517 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1390, found 311.1391.



2.6

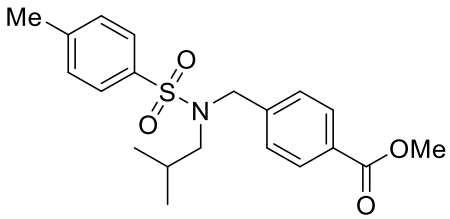
***N*^{6}-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)-*N*^{2}-(*p*-tolyl)-3,4-dihydroisoquinoline-2,6(1*H*)-dicarboxamide.** To a solution of 2-(*p*-tolylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.025 g, 0.080 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.031 g, 0.240 mmol, 3.0 equiv) and HATU (0.031 g, 0.082 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of *N*^{1}-(*tert*-butyl)-*N*^{1}-(4-chlorobenzyl)ethane-1,2-diamine (0.019 g, 0.079 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.018 g, 0.034 mmol, 42% yield, ≥99% purity). IR (neat) 3310, 2969, 1635, 1597, 1517 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.43 (s, 1H), 7.35 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.33–7.29 (m, 2H), 7.29–7.25 (m, 2H), 7.23–7.16 (m, 3H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.49 (s, 1H), 6.21 (t, *J* = 4.7 Hz, 1H), 4.68 (s, 2H), 3.74–3.66 (m, 4H), 3.18 (q, *J* = 5.9 Hz, 2H), 2.96 (t, *J* = 5.9 Hz, 2H), 2.81 (t, *J* = 6.2 Hz, 2H), 2.30 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.0, 155.3, 141.5, 136.8, 136.4, 135.4, 133.4, 133.0, 132.4, 129.6, 129.3, 128.7, 127.3, 126.6, 124.6,

120.5, 55.7, 54.7, 50.3, 45.8, 41.7, 40.2, 29.2, 27.5, 20.9; HRMS (ESI) m/z calcd for $C_{31}H_{38}ClN_4O_2$ $[M+H]^+$ 533.2678, found 533.2681.



2.7.1

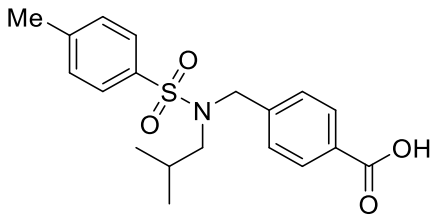
Methyl 4-((iso-butylamino)methyl)benzoate. Prepared according to the general procedure using isobutyraldehyde (0.358 g, 4.96 mmol, 1.0 equiv), methyl 4-(aminomethyl)benzoate hydrochloride (1.0 g, 4.96 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.472 g, 6.94 mmol, 1.4 equiv), and DCE (10 ml), stirred at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a light yellow oil (0.670 g, 3.03 mmol, 61% yield). IR (neat) 2954, 1722 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.02–7.96 (m, 2H), 7.42–7.37 (m, 2H), 3.91 (s, 3H), 3.84 (s, 2H), 2.43 (d, *J* = 6.8 Hz, 2H), 1.82–1.71 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 146.4, 129.8, 128.9, 128.0, 57.7, 53.9, 52.2, 28.6, 20.8; HRMS (ESI) m/z calcd for $C_{13}H_{20}ClNO_2$ $[M+H]^+$ 222.1489, found 222.1484.



2.7.2

Methyl 4-(((*N*-iso-butyl-4-methylphenyl)sulfonamido)methyl)benzoate. To a solution of methyl 4-((iso-butylamino)methyl)benzoate (0.040 g, 0.181 mmol, 1.0 equiv) and trimethylamine

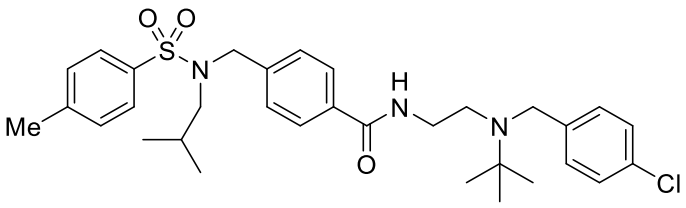
(0.055 g, 0.544 mmol, 3.0 equiv) in anhydrous DCM (1 mL) was added *p*-toluenesulfonyl chloride (0.035 g, 0.184 mmol, 1.0 equiv) at room temperature. The resulting mixture was stirred at this temperature for 3 h, then diluted with water, extracted with DCM (2 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography afforded the title compound as a colorless oil (0.055 g, 0.146 mmol, 81% yield). IR (neat) 2958, 1720 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99–7.94 (m, 2H), 7.74–7.69 (m, 2H), 7.37–7.29 (m, 4H), 4.33 (s, 2H), 3.91 (s, 3H), 2.89 (d, *J* = 7.6 Hz, 2H), 2.44 (s, 3H), 1.65–1.56 (m, 1H), 0.73 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.0, 143.5, 142.3, 136.9, 129.9, 129.9, 129.7, 128.4, 127.4, 57.1, 53.0, 52.3, 27.1, 21.7, 20.1; HRMS (ESI) m/z calcd for $C_{20}H_{26}NO_4S$ $[M+H]^+$ 376.1577, found 376.1574.



2.7.3

4-(((*N*-iso-Butyl-4-methylphenyl)sulfonamido)methyl)benzoic acid. To a solution of methyl 4-(((*N*-iso-butyl-4-methylphenyl)sulfonamido)methyl)benzoate (0.043 g, 0.115 mmol, 1.0 equiv) in a THF (1 mL) was added methanol (1 mL) and aqueous NaOH solution (1 N, 1 mL) at room temperature. The resulting mixture was stirred at this temperature for 12 h, then concentrated *in vacuo*, diluted with water, acidified with aqueous HCl solution (1 N) to pH 2. Filtration afforded the title compound as a white solid (0.035 g, 0.097 mmol, 85% yield). Mp = 105–108 °C; IR (neat) 2964, 1708 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 7.93–7.87 (m, 2H), 7.77–7.72

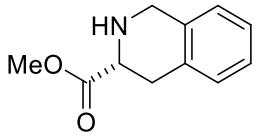
(m, 2H), 7.47–7.40 (m, 4H), 4.32 (s, 2H), 2.85 (d, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 1.58–1.41 (m, 1H), 0.66 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.1, 143.3, 142.7, 135.9, 129.9, 129.9, 129.3, 128.1, 127.1, 57.2, 52.5, 26.5, 21.0, 19.7; HRMS (ESI) m/z calcd for $C_{19}H_{24}NO_4S$ $[M+H]^+$ 362.1421, found 362.1422.



2.7

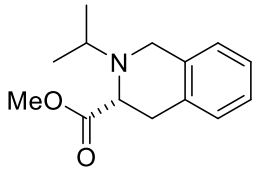
***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)-4-(((*N*-iso-butyl-4-methylphenyl)sulfonamido)methyl)benzamide.** To a solution of 4-(((*N*-iso-butyl-4-methylphenyl)sulfonamido)methyl)benzoic acid (0.024 g, 0.067 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.026 g, 0.201 mmol, 3.0 equiv) and HATU (0.025 g, 0.067 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)ethane-1,2-diamine (0.031 g, 0.15 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.016 g, 0.027 mmol, 41% yield, ≥ 99% purity). IR (neat) 3338, 2965, 1642 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.39–7.29 (m, 6H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.25 (t, *J* = 5.4 Hz, 1H), 4.31 (s, 2H), 3.69 (s, 2H), 3.17 (q, *J* = 5.9 Hz, 2H), 2.89 (d, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 6.2 Hz, 2H), 2.44 (s, 3H), 1.64–1.56 (m, 1H), 1.16 (s, 9H), 0.74 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 166.8, 144.1, 142.3, 141.0, 137.3, 134.7, 132.5, 130.3, 129.8, 128.9, 128.8, 127.7, 127.3, 57.5,

56.0, 55.0, 53.3, 50.7, 40.5, 27.6, 27.4, 21.8, 20.3; HRMS (ESI) m/z calcd for $C_{32}H_{43}ClN_3O_3S$ $[M+H]^+$ 584.2708, found 584.2720.



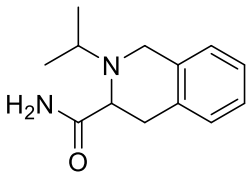
2.8.1

Methyl (*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate. To a solution of (*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.0 g, 5.64 mmol, 1.0 equiv) in anhydrous methanol (25 mL) was added sulfuric acid (95-98%, 0.5 mL) at room temperature. The reaction was refluxed for 24 h, followed by removal of solvent *in vacuo*. The residue was diluted with water (100 mL), then extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (0-10% CH_3OH/CH_2Cl_2) afforded the title compound as yellowish oil (0.97 g, 5.07 mmol, 90% yield). $[\alpha]_D^{20}$ = +58.3 (*c* 0.5, MeOH); IR (neat) 3331, 2951, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.08 (m, 3H), 7.07–7.00 (m, 1H), 4.19–4.04 (m, 2H), 3.81–3.73 (m, 4H), 3.09 (dd, *J* = 16.2, 4.7 Hz, 1H), 2.97 (dd, *J* = 16.2, 10.1 Hz, 1H), 2.31–2.22 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 134.9, 133.2, 129.3, 126.4, 126.3, 126.2, 56.0, 52.3, 47.4, 31.7; HRMS (ESI) m/z calcd for $C_{11}H_{14}NO_2$ $[M+H]^+$ 192.1019, found 192.1017.



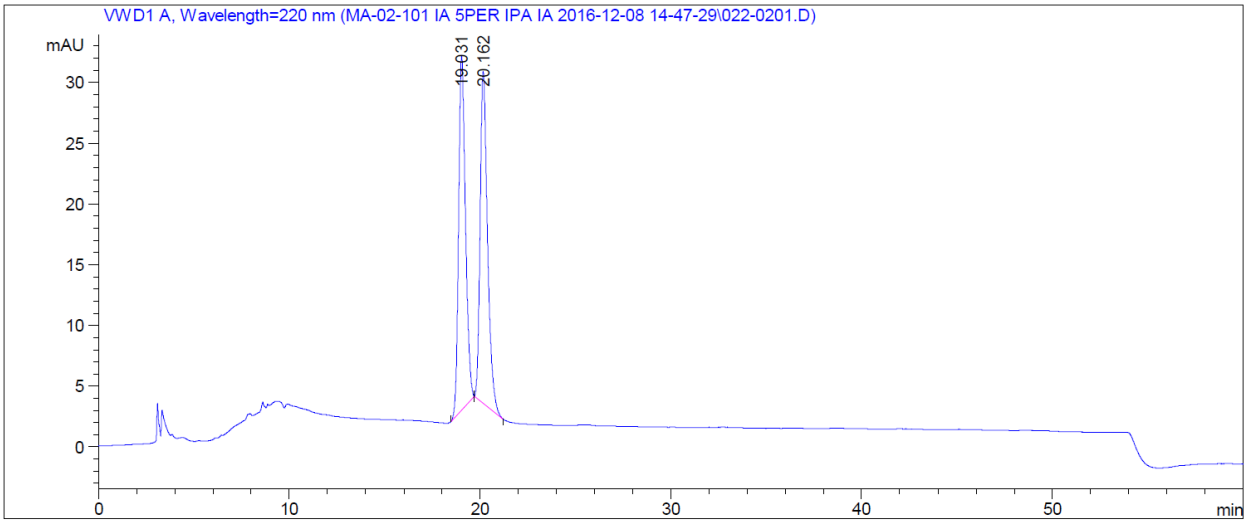
2.8.2

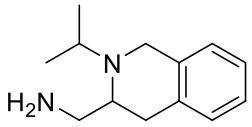
Methyl (*R*)-2-isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate. To a solution of acetone (2.61 g, 44.87 mmol, 1.4 equiv) in DCE (30 mL) were added methyl (*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (6.13 g, 32.05 mmol, 1.0 equiv), $NaBH(OAc)_3$ (9.51 g, 44.87 mmol, 1.4 equiv) and acetic acid (1.92 g, 32.05 mmol, 1.0 equiv) at room temperature. The reaction was stirred at this temperature for 24 h, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with EtOAc (3 × 200 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as an orange oil (6.26 g, 26.8 mmol, 84% yield). $[\alpha]_D^{20} = -3.3$ (*c* 1.0, MeOH); IR (neat) 2966, 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.04 (m, 4H), 4.09 (d, *J* = 15.2 Hz, 1H), 3.97–3.90 (m, 2H), 3.65 (s, 3H), 3.20–3.03 (m, 3H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 135.1, 132.4, 128.3, 126.4, 126.1, 126.0, 56.9, 52.5, 51.6, 47.4, 32.7, 21.1, 19.1; HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1489, found 234.1487.



2.8.3

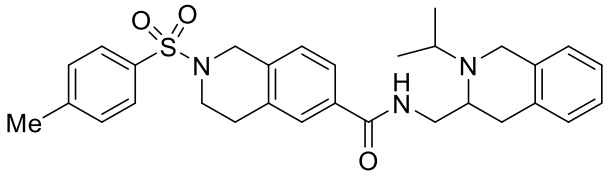
(±)-2-Isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide. The suspension of methyl (*R*)-2-isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (5.69 g, 24.388 mmol, 1.0 equiv) in aqueous NH_3 solution (28-30% NH_3 basis, 150 mL) was loaded in Parr reactor. The reaction was stirred for 24 h at 60 °C, followed by another 24 h at 90 °C. The solvent was removed in vacuo. Reverse-phase column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a yellow solid (1.120 g, 5.131 mmol, 21% yield). IR (neat) 3414, 2966, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.09 (m, 5H), 5.58 (br s, 1H), 3.80–3.72 (m, 2H), 3.52 (dd, *J* = 7.0, 4.4 Hz, 1H), 3.09 (dd, *J* = 15.1, 4.4 Hz, 1H), 3.05–2.92 (m, 2H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 137.3, 135.2, 127.5, 127.2, 126.5, 125.7, 59.2, 53.6, 47.0, 31.7, 19.8, 18.7; HRMS (ESI) m/z calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$ 219.1492, found 219.1490. The compound demonstrated no optical rotation, and was then evidenced as a racemate by chiral HPLC (ChiralPak IA column 4.6 × 250 mm, 5% isopropanol/hexanes, UV length 220 nm).





2.8.4

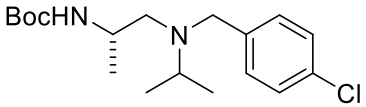
(±)-(2-Isopropyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine. To a solution of **(±)-**2-isopropyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (0.36 g, 1.65 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added $LiAlH_4$ (1 N in THF, 6.6 mL, 6.6 mmol, 4.0 equiv) dropwise at 0 °C. The reaction was refluxed for 3 h, then quenched with Glauber's salt at -20 °C and warmed to room temperature to stir for 15 min. The mixture was filtered through Celite amd concentrated *in vacuo*. Reverse-phase column chromatography (0-100% CH_3CN/0.5% aqueous NH_3) afforded the title compound as a colorless oil (0.22 g, 1.077 mmol, 65% yield). IR (neat) 2965, 1576, 1456 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.18–7.04 (m, 4H), 3.79 (AB q, $\Delta\delta_{AB}$ = 0.07, J=15.5 Hz, 2H), 3.15–2.90 (m, 3H), 2.80–2.69 (m, 2H), 2.52 (dd, *J* = 12.7, 7.7 Hz, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 136.5, 135.4, 129.5, 127.5, 127.2, 127.0, 57.3, 52.1, 47.4, 43.1, 31.3, 21.4, 18.7; HRMS (ESI) m/z calcd for $C_{13}H_{21}N_2$ $[M+H]^+$ 205.1699, found 205.1697.



2.8

(±)-*N*-((2-Isopropyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.05 g, 0.15 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA

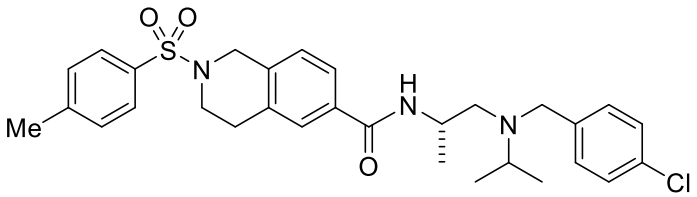
(0.058 g, 0.449 mmol, 3.0 equiv) and HATU (0.057 g, 0.150 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of (2-isopropyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine (0.031 g, 0.152 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.016 g, 0.031 mmol, 21% yield, HPLC purity = 100%). IR (neat) 3330, 2967, 1643, 1537, 1494 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.75–7.70 (m, 2H), 7.43–7.32 (m, 4H), 7.18–7.05 (m, 5H), 6.65 (br s, 1H), 4.25 (s, 2H), 3.89–3.76 (m, 2H), 3.51–3.31 (m, 5H), 3.08 (hept, *J* = 6.5 Hz, 1H), 3.00 (dd, *J* = 16.2, 5.8 Hz, 1H), 2.95 (t, *J* = 5.9 Hz, 2H), 2.69 (dd, *J* = 16.2, 3.6 Hz, 1H), 2.44 (s, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 167.1, 144.6, 136.7, 135.6, 135.2, 134.1, 133.9, 133.6, 130.3, 128.8, 128.2, 128.0, 127.0, 126.5, 126.4, 126.3, 125.1, 53.7, 51.7, 42.6, 31.5, 29.4, 21.9, 21.8, 18.6; HRMS (ESI) m/z calcd for $C_{30}H_{36}N_3O_3S$ $[M+H]^+$ 518.2472, found 518.2461.



(*S*)-2.9.1

***tert*-Butyl (*S*)-(1-((4-chlorobenzyl)(isopropyl)amino)propan-2-yl)carbamate.** To a solution of *tert*-butyl (*S*)-(1-oxopropan-2-yl)carbamate (0.346 g, 2.0 mmol, 1.0 equiv) in DCE (3 mL) were added *N*-(4-chlorobenzyl)propan-2-amine (0.367 g, 2.0 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.593 g, 2.8 mmol, 1.4 equiv) and acetic acid (1 drop). The mixture was stirred at room temperature for 3 d, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with ether (3 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-

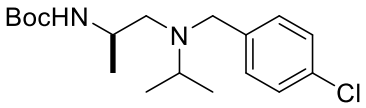
phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.550 g, 1.613 mmol, 81% yield). $[\alpha]_D^{20}$ = –26.4 (*c* 1.0, $CHCl_3$); IR (neat) 2966, 1698, 1489 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.28 (q, *J* = 8.5 Hz, 4H), 4.51 (br s, 1H), 3.65–3.45 (m, 3H), 2.87 (hept, *J* = 6.6 Hz, 1H), 2.32 (d, *J* = 7.0 Hz, 2H), 1.42 (s, 9H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 156.1, 140.4, 132.6, 130.5, 128.7, 79.0, 55.5, 54.2, 50.2, 45.5, 28.8, 19.7, 18.7, 17.4; HRMS (ESI) m/z calcd for $C_{18}H_{30}ClN_2O_2$ $[M+H]^+$ 341.1990, found 341.1990.



(*S*)-2.9

(*S*)-*N*-(1-((4-Chlorobenzyl)(isopropyl)amino)propan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of (*S*)-N^1-(4-chlorobenzyl)-N^1-isopropylpropane-1,2-diamine (0.024 g, 0.1 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-(*p*-tolylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.1 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.039 g, 0.3 mmol, 3.0 equiv) and HATU (0.038 g, 0.1 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.1 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then

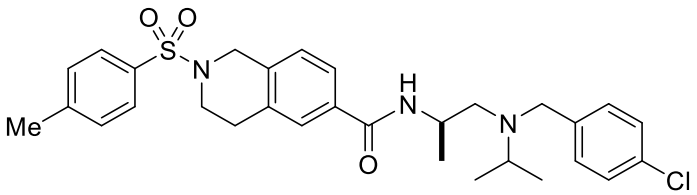
concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (0.026 g, 0.047 mmol, 47% yield, HPLC purity =99.7%). $[\alpha]_D^{20}$ = –7.8 (*c* 0.2, $CHCl_3$); Mp = 102–104 °C; IR (neat) 2965, 1638, 1536, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.67 (m, 2H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.35–7.30 (m, 4H), 7.22–7.12 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.17 (d, *J* = 5.9 Hz, 1H), 4.27 (s, 2H), 4.08–3.93 (m, 1H), 3.58 (d, *J* = 14.1 Hz, 1H), 3.42 (d, *J* = 14.1 Hz, 1H), 3.36 (t, *J* = 5.9 Hz, 2H), 2.99–2.86 (m, 3H), 2.51 (dd, *J* = 13.2, 5.6 Hz, 1H), 2.45–2.36 (m, 4H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 144.0, 139.4, 135.1, 133.6, 133.6, 133.4, 132.5, 130.0, 129.9, 128.5, 127.8, 127.7, 126.6, 124.6, 54.7, 53.4, 49.7, 47.6, 44.3, 43.7, 29.0, 21.6, 19.4, 19.1, 16.6; HRMS (ESI) m/z calcd for $C_{30}H_{37}ClN_3O_3S$ $[M+H]^+$ 554.2239, found 554.2255.



(*R*)-2.9.1

***tert*-Butyl (*R*)-(1-((4-chlorobenzyl)(isopropyl)amino)propan-2-yl)carbamate.** To a solution of *tert*-butyl (*R*)-(1-oxopropan-2-yl)carbamate (0.346 g, 2.0 mmol, 1.0 equiv) in DCE (3 mL) were added *N*-(4-chlorobenzyl)propan-2-amine (0.0.367 g, 2.0 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.593 g, 2.8 mmol, 1.4 equiv) and acetic acid (1 drop). The mixture was stirred at room temperature for 3 d, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with ether (3 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.555 g, 1.628 mmol, 81% yield). $[\alpha]_D^{20}$ = +20.4 (*c* .0, $CHCl_3$); IR (neat) 2967,

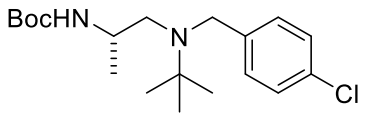
1701, 1470 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.34–7.22 (m, 4H), 4.49 (br s, 1H), 3.53 (q, *J* = 14.3 Hz, 3H), 2.87 (hept, *J* = 6.6 Hz, 1H), 2.32 (d, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 156.2, 140.4, 132.6, 130.5, 128.7, 79.1, 55.6, 54.3, 50.3, 45.6, 28.8, 19.7, 18.7, 17.4; HRMS (ESI) m/z calcd for $C_{18}H_{30}ClN_2O_2$ $[M+H]^+$ 341.1990, found 341.1990.



(*R*)-2.9

(*R*)-*N*-(1-((4-chlorobenzyl)(isopropyl)amino)propan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of (*R*)-N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)-3-methylbutane-1,2-diamine (0.028 g, 0.1 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.1 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.039 g, 0.3 mmol, 3.0 equiv) and HATU (0.038 g, 0.1 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.1 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (0.029 g, 0.052 mmol, 52% yield, 98.5% purity). $[\alpha]_D^{20}$ = +6.0 (*c* 0.1, $CHCl_3$); Mp = 73–76 °C; IR

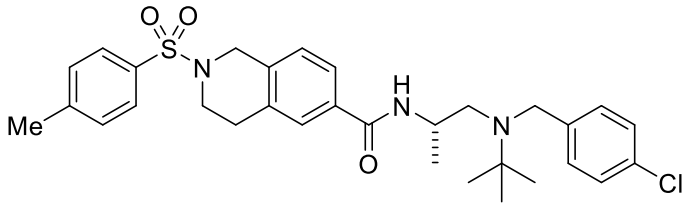
(neat) 2965, 1639, 1537, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.69 (m, 2H), 7.43 (d, *J* = 1.7 Hz, 1H), 7.40–7.30 (m, 3H), 7.22–7.12 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.15 (d, *J* = 5.7 Hz, 1H), 4.28 (s, 2H), 4.07–3.94 (m, 1H), 3.59 (d, *J* = 14.1 Hz, 1H), 3.46–3.30 (m, 3H), 3.03–2.84 (m, 3H), 2.57–2.36 (m, 5H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.02 (dd, *J* = 15.8, 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 144.0, 139.4, 135.2, 133.7, 133.6, 133.4, 132.6, 130.0, 129.9, 128.6, 127.8, 127.7, 126.6, 124.6, 54.8, 53.4, 49.8, 47.7, 44.3, 43.7, 29.0, 21.6, 19.5, 19.1, 16.5; HRMS (ESI) m/z calcd for $C_{30}H_{37}ClN_3O_3S$ $[M+H]^+$ 554.2239, found 554.2254.



(*S*)-2.10.1

***tert*-Butyl (*S*)-(1-(*tert*-butyl(4-chlorobenzyl)amino)propan-2-yl)carbamate.** To a solution of *tert*-butyl (*S*)-(1-oxopropan-2-yl)carbamate (0.520 g, 3.0 mmol, 1.0 equiv) in DCE (4 mL) were added *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (0.593 g, 3.0 mmol, 1.0 equiv) and $NaBH(OAc)_3$ (0.890 g, 4.2 mmol, 1.4 equiv) and acetic acid (1 drop). The mixture was stirred at room temperature for 3 d, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with ether (3 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.497 g, 1.400 mmol, 47% yield). $[\alpha]_D^{20}$ = +14.1 (*c* 0.4, $CHCl_3$); IR (neat) 2972, 1699, 1488 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.35–7.28 (m, 2H), 7.27–7.21 (m, 2H), 4.42 (br s, 1H), 3.74 (d, *J* = 16.2 Hz, 1H), 3.64 (d, *J* = 16.2 Hz, 1H), 3.24 (br s, 1H), 2.53 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.45 (dd, *J* = 13.3, 6.4 Hz, 1H), 1.39 (s, 9H), 1.08 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H); ^{13}C

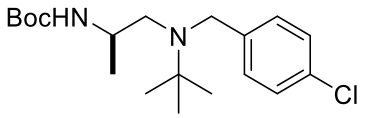
NMR (151 MHz, CD_2Cl_2) δ 155.9, 142.8, 132.0, 129.6, 128.6, 79.0, 57.7, 55.8, 55.2, 47.0, 28.7, 27.5, 19.6; HRMS (ESI) m/z calcd for $C_{19}H_{32}ClN_2O_2$ $[M+H]^+$ 355.2147, found 355.2145.



(*S*)-2.10

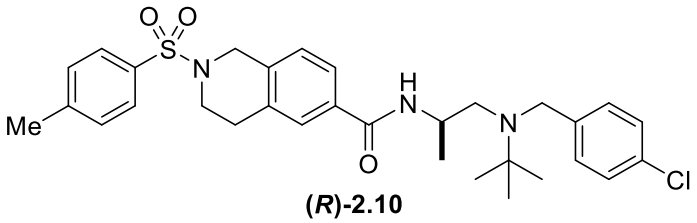
(*S*)-*N*-(1-(*tert*-Butyl(4-chlorobenzyl)amino)propan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of *tert*-butyl (*S*)-(1-(*tert*-butyl(4-chlorobenzyl)amino)propan-2-yl)carbamate (0.035 g, 0.1 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.1 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.039 g, 0.3 mmol, 3.0 equiv) and HATU (0.038 g, 0.1 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of TFA salt of crude diamine (0.1 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (0.030 g, 0.053 mmol, 53% yield, 98.9% purity). $[\alpha]_D^{20}$ = +58.5 (*c* 0.2, $CHCl_3$) IR (neat) 2971, 1638, 1536, 1488 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.76–7.68 (m, 2H), 7.40–7.34 (m, 3H), 7.34–7.29 (m, 1H), 7.27–7.19 (m, 2H), 7.12–7.03 (m, 3H), 6.02 (d, *J* = 6.1 Hz, 1H), 4.33–4.19 (m,

2H), 3.80–3.58 (m, 3H), 3.39–3.28 (m, 2H), 2.95 (t, *J* = 5.9 Hz, 2H), 2.70–2.59 (m, 2H), 2.42 (s, 3H), 1.17–1.06 (m, 12H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 166.9, 144.6, 142.4, 135.6, 134.3, 134.1, 133.9, 132.2, 130.3, 129.7, 128.7, 128.2, 128.0, 127.0, 124.9, 57.3, 56.0, 55.5, 48.2, 46.6, 44.3, 29.4, 27.6, 21.8, 19.3; HRMS (ESI) m/z calcd for $C_{31}H_{39}ClN_3O_3S$ $[M+H]^+$ 568.2395, found 568.2390.



(*R*)-2.10.1

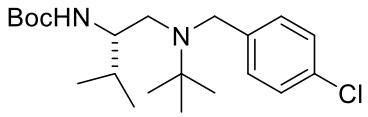
***tert*-Butyl (*R*)-(1-(*tert*-butyl(4-chlorobenzyl)amino)propan-2-yl)carbamate.** To a solution of *tert*-butyl (*R*)-(1-oxopropan-2-yl)carbamate (0.520 g, 3.0 mmol, 1.0 equiv) in DCE (5 mL) were added *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (0.593 g, 3.0 mmol, 1.0 equiv) and $NaBH(OAc)_3$ (0.890 g, 4.2 mmol, 1.4 equiv) and acetic acid (1 drop). The mixture was stirred at room temperature for 3 d, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with ether (3 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.490 g, 1.381 mmol, 46% yield). $[\alpha]_D^{20} = -13.0$ (*c* 0.3, $CHCl_3$); IR (neat) 2972, 1699, 1489 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.31 (m, 2H), 7.27–7.22 (m, 2H), 4.43 (br s, 1H), 3.74 (d, *J* = 16.2 Hz, 1H), 3.63 (d, *J* = 16.2 Hz, 1H), 3.24 (br s, 1H), 2.53 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.45 (dd, *J* = 13.3, 6.4 Hz, 1H), 1.38 (s, 9H), 1.08 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 156.0, 142.8, 132.0, 129.6, 128.6, 79.0, 57.7, 55.8, 55.2, 47.0, 28.7, 27.5, 19.6; HRMS (ESI) m/z calcd for $C_{19}H_{32}ClN_2O_2$ $[M+H]^+$ 355.2147, found 355.2144.



(*R*)-2.10

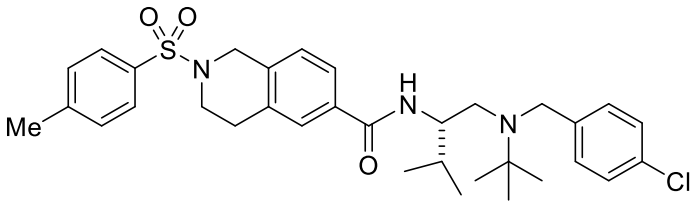
(*R*)-*N*-(1-(*tert*-Butyl(4-chlorobenzyl)amino)propan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of *tert*-butyl (*R*)-(1-(*tert*-butyl(4-chlorobenzyl)amino)propan-2-yl)carbamate (0.071 g, 0.20 mmol, 1.0 equiv) in DCM (2 mL) was added TFA (2 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.066 g, 0.20 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.078 g, 0.60 mmol, 3.0 equiv) and HATU (0.076 g, 0.20 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.20 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.077 g, 0.135 mmol, 68% yield, 92.9% purity). $[\alpha]_D^{20} = -61.0$ (*c* 0.2, $CHCl_3$); IR (neat) 2970, 1638, 1537, 1489 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.76–7.68 (m, 2H), 7.40–7.34 (m, 3H), 7.31 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.2 –7.19 (m, 2H), 7.12–7.04 (m, 3H), 5.99 (d, *J* = 6.0 Hz, 1H), 4.34–4.18 (m, 2H), 3.80–3.58 (m, 3H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 2.70–2.59 (m, 2H), 2.42 (s, 3H), 1.16 – 1.09 (m, 12H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 166.9, 144.6, 142.4, 135.6, 134.3, 134.2, 133.8, 132.2, 130.3, 129.7, 128.7, 128.3, 128.0, 127.0, 124.9, 57.3,

56.0, 55.5, 48.2, 46.6, 44.3, 29.4, 27.6, 21.8, 19.3; HRMS (ESI) m/z calcd for $C_{31}H_{39}ClN_3O_3S$ $[M+H]^+$ 568.2395, found 568.2400.



(*S*)-2.11.1

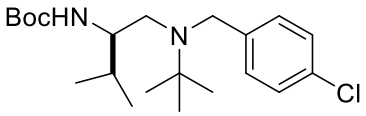
***tert*-Butyl ((2*S*)-1-(*tert*-butyl((4-chlorocyclohexa-1,5-dien-1-yl)methyl)amino)-3-methylbutan-2-yl)carbamate.** To a solution of *tert*-butyl (*S*)-(3-methyl-1-oxobutan-2-yl)carbamate (0.830 g, 4.12 mmol, 1.0 equiv) in DCE (5 mL) were added *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (0.815 g, 4.12 mmol, 1.0 equiv) and $NaBH(OAc)_3$ (1.223 g, 5.77 mmol, 1.4 equiv) and acetic acid (2 drops). The mixture was stirred at room temperature for 7 d, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with ether (3 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.100 g, 0.261 mmol, 6% yield). $[\alpha]_D^{20}$ = +10.9 (*c* 1.1, $CHCl_3$); IR (neat) 2965, 1702, 1489 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 7.36–7.29 (m, 2H), 7.27–7.20 (m, 2H), 4.23 (br s, 1H), 3.69 (AB q, $\Delta\delta_{AB}$ = 0.77, *J* = 16.2 Hz, 2H), 3.24 (br s, 1H), 2.62 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.38 (dd, *J* = 13.6, 8.0 Hz, 1H), 1.95–1.86 (m, 1H), 1.07 (s, 9H), 0.80–0.70 (m, 6H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 156.4, 143.0, 132.0, 129.7, 128.6, 78.8, 56.0, 55.7, 55.2, 53.4, 29.9, 28.8, 27.6, 19.7, 17.0; HRMS (ESI) m/z calcd for $C_{21}H_{36}ClN_2O_2$ $[M+H]^+$ 383.2460, found 383.2482.



(*S*)-2.11

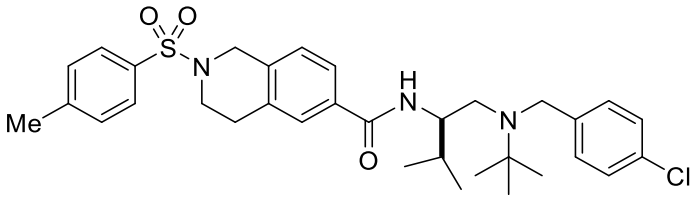
(*S*)-*N*-(1-(*tert*-Butyl(4-chlorobenzyl)amino)-3-methylbutan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of *tert*-butyl ((2*S*)-1-(*tert*-butyl((4-chlorocyclohexa-1,5-dien-1-yl)methyl)amino)-3-methylbutan-2-yl)carbamate (0.038 g, 0.1 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.1 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.039 g, 0.3 mmol, 3.0 equiv) and HATU (0.038 g, 0.1 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.1 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.044 g, 0.074 mmol, 74% yield, 99.0% purity). $[\alpha]_D^{20}$ = +26.7 (*c* 0.3, $CHCl_3$); IR (neat) 2964, 1643, 1535 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76–7.70 (m, 2H), 7.39–7.28 (m, 4H), 7.20–7.14 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.05 – 7.00 (m, 3H), 5.69 (d, *J* = 7.8 Hz, 1H), 4.29 (AB q, $\Delta\delta_{AB}$ = 0.34, *J* = 15.6 Hz, 2H), 3.85–3.76 (m, 1H), 3.73 (d, *J* = 12.5 Hz, 1H), 3.56 (d, *J* = 12.5 Hz, 1H), 3.44–3.31 (m, 2H), 2.96 (t, *J* = 4.7 Hz, 2H), 2.81 (dd, *J* = 11.1, 4.8 Hz, 1H), 2.48 (dd, *J* = 11.1, 6.8 Hz, 1H), 2.42 (s, 3H), 2.11–2.00 (m, 1H), 1.10 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 144.0, 141.4, 135.0, 133.8,

133.6, 133.2, 131.9, 129.9, 129.3, 128.3, 127.8, 127.7, 126.6, 124.5, 55.7, 55.0, 54.5, 51.9, 47.6, 43.7, 29.4, 29.0, 27.4, 21.7, 19.1, 17.3; HRMS (ESI) m/z calcd for $C_{33}H_{41}ClN_3O_3S$ $[M-H]^-$ 594.2563, found 594.2562.



(*R*)-2.11.1

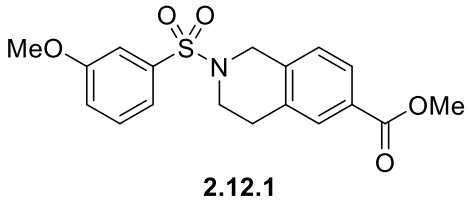
***tert*-Butyl (*R*)-(1-(*tert*-butyl(4-chlorobenzyl)amino)-3-methylbutan-2-yl)carbamate.** To a solution of *tert*-butyl (*R*)-(3-methyl-1-oxobutan-2-yl)carbamate (0.830 g, 4.12 mmol, 1.0 equiv) in DCE (5 mL) were added *N*-(4-chlorobenzyl)-2-methylpropan-2-amine (0.815 g, 4.12 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.223 g, 5.77 mmol, 1.4 equiv) and acetic acid (2 drops). The mixture was stirred at room temperature for 7 d, then basified with aqueous NaOH (1 N) to pH 10. The mixture was extracted with ether (3 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.590 g, 1.541 mmol, 37% yield). $[\alpha]_D^{20} = -10.1$ (*c* 1.2, $CHCl_3$); IR (neat) 2966, 1701, 1489 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.35–7.29 (m, 2H), 7.27–7.22 (m, 2H), 4.23 (br s, 1H), 3.69 (AB q, $\Delta\delta_{AB} = 0.78$, $J = 16.2$ Hz, 2H), 3.24 (br s, 1H), 2.63 (dd, $J = 13.6$, 6.2 Hz, 1H), 2.38 (dd, $J = 13.6$, 8.0 Hz, 1H), 1.98–1.82 (m, 1H), 1.41 (s, 9H), 1.07 (s, 9H), 0.81–0.72 (m, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 156.4, 143.0, 132.0, 129.7, 128.6, 78.9, 56.0, 55.7, 55.1, 53.3, 29.8, 28.8, 27.6, 19.6, 16.9; HRMS (ESI) m/z calcd for $C_{21}H_{36}ClN_2O_2$ $[M+H]^+$ 383.2460, found 383.2457.



(*R*)-2.11

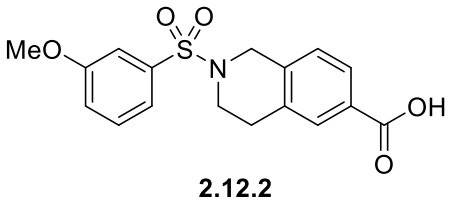
(*R*)-*N*-(1-(*tert*-Butyl(4-chlorobenzyl)amino)-3-methylbutan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide. To a solution of *tert*-butyl (*R*)-(1-(*tert*-butyl(4-chlorobenzyl)amino)-3-methylbutan-2-yl)carbamate (0.038 g, 0.1 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.1 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.039 g, 0.3 mmol, 3.0 equiv) and HATU (0.038 g, 0.1 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.1 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.052 g, 0.087 mmol, 87% yield, ≥ 99% purity). $[\alpha]_D^{20} = -26.0$ (*c* 0.2, $CHCl_3$); IR (neat) 2963, 1640, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.69 (m, 2H), 7.39–7.27 (m, 4H), 7.21–7.13 (m, 2H), 7.10–6.99 (m, 3H), 5.69 (d, *J* = 7.8 Hz, 1H), 4.31, 4.26 (AB q, $\Delta\delta_{AB}$ = 0.33, *J* = 15.6 Hz, 2H), 3.86–3.77 (m, 2H), 3.73 (d, *J* = 15.6 Hz, 1H), 3.56 (d, *J* = 15.6 Hz, 1H), 3.45 – 3.30 (m, 2H), 2.96 (t, *J* = 6.0 Hz, 2H), 2.81 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.49 (dd, *J* = 13.8, 8.4 Hz, 4H), 2.42 (s, 3H), 2.12–1.99 (m, 1H), 1.10 (s, 9H), 0.82 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 143.9,

141.5, 135.1, 133.9, 133.7, 133.5, 132.0, 129.9, 129.3, 128.3, 127.8, 127.7, 126.6, 124.5, 55.8, 55.0, 54.6, 52.0, 47.6, 43.7, 29.5, 29.0, 27.4, 21.6, 19.2, 17.4; HRMS (ESI) m/z calcd for $C_{33}H_{43}ClN_3O_3S$ $[M+H]^+$ 596.2708, found 596.2716.



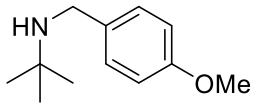
2.12.1

Methyl 2-((3-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate. To a suspension of methyl 1,2,3,4-tetrahydroisoquinoline-6-carboxylate hydrochloride (0.273 g, 1.20 mmol, 1.0 equiv) in anhydrous DCM (12 mL) were added triethylamine (0.364 g, 3.60 mmol, 3.0 equiv) and 3-methoxybenzenesulfonyl chloride (0.248 g, 1.20 mmol, 1.0 equiv) at room temperature, then stirred for overnight. The reaction mixture was acidified with aqueous HCl (2 N) to pH 3, then extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white solid (0.386 g, 1.07 mmol, 89% yield). Mp = 117–119 ºC; IR (neat) 1717, 1596, 1479 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H), 7.47–7.38 (m, 2H), 7.34–7.30 (m, 1H), 7.13–7.07 (m, 2H), 5.29 (d, *J* = 0.9 Hz, 2H), 4.32 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.40 (t, *J* = 5.9 Hz, 2H), 2.96 (t, *J* = 5.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 160.1, 137.5, 136.8, 133.5, 130.4, 130.3, 128.8, 127.5, 126.6, 119.9, 119.1, 112.7, 55.8, 52.3, 47.7, 43.7, 28.9; HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_5S$ $[M+H]^+$ 362.1057, found 362.1057.



2.12.2

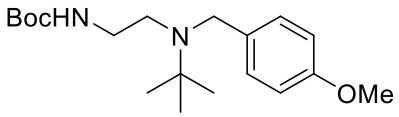
6-((3-Methoxyphenyl)sulfonyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid. To a solution of methyl 2-((4-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (0.181 g, 0.50 mmol, 1.0 equiv) in methanol (2 mL) was added aqueous NaOH solution (1 N, 2 mL) and THF (2 mL). The mixture was stirred overnight and organic solvent was removed *in vacuo*. The concentrated mixture was acidified with aqueous HCl (2 N) to pH 2, then filtered to afford the title compound as a white solid (0.107 g, 0.31 mmol, 62% yield). Mp = 161–164 ºC; IR (neat) 1683, 1596 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 7.74–7.63 (m, 2H), 7.59–7.49 (m, 1H), 7.43–7.36 (m, 1H), 7.33–7.22 (m, 3H), 4.30 (s, 2H), 3.82 (s, 3H), 3.35 (t, J = 5.9 Hz, 2H), 2.89 (t, J = 5.9 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.0, 159.5, 137.3, 136.7, 133.4, 130.6, 129.7, 129.1, 126.8, 126.7, 119.4, 119.1, 112.1, 55.6, 47.3, 43.3, 27.8; HRMS (ESI) m/z calcd for $C_{17}H_{18}NO_5S$ $[M+H]^+$ 348.0900, found 348.0900.



2.12.3

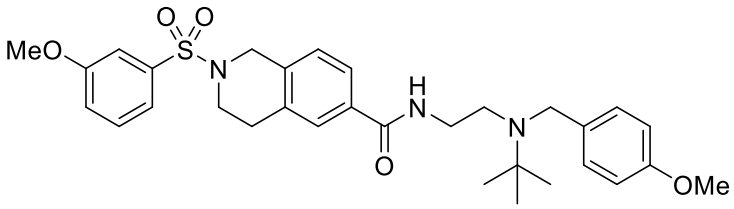
***N*-(4-Methoxybenzyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using 4-methoxybenzaldehyde (1.86 g, 13.7 mmol, 1.0 equiv), *tert*-butylamine (1.00 g, 13.7 mmol, 1.0 equiv), $NaBH(OAc)_3$ (4.06 g, 19.2 mmol, 1.4 equiv), AcOH (1 drop) and DCE (20 mL), at room temperature for 12 h. Reverse-phase flash column

chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (2.270 g, 11.74 mmol, 86% yield). IR (neat) 2961, 1613, 1511 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.29–7.21 (m, 2H), 6.91–6.79 (m, 2H), 3.77 (s, 3H), 3.65 (s, 2H), 1.15 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.0, 134.6, 129.8, 114.1, 55.7, 51.0, 46.9, 29.4; HRMS (ESI) m/z calcd for $C_{12}H_{20}NO$ $[M+H]^+$ 194.1539, found 194.1540.



2.12.4

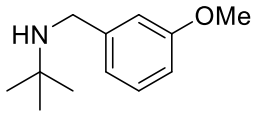
***tert*-Butyl (2-(*tert*-butyl(4-methoxybenzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.0 mmol, 1.0 equiv), *N*-(4-methoxybenzyl)-2-methylpropan-2-amine (0.193 g, 1.0 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.187 g, 0.56 mmol, 56% yield). IR (neat) 3415, 2971, 1707, 1612, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25–7.20 (m, 2H), 6.86–6.79 (m, 2H), 4.55 (br s, 1H), 3.78 (s, 3H), 3.59 (s, 2H), 2.88–2.75 (m, 2H), 2.64 (t, *J* = 6.1 Hz, 2H), 1.38 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 156.1, 134.9, 129.1, 113.8, 78.7, 55.3, 55.3, 54.5, 50.4, 40.9, 28.5, 27.5; HRMS (ESI) m/z calcd for $C_{19}H_{33}N_2O_3$ $[M+H]^+$ 337.2486, found 337.2480.



2.12

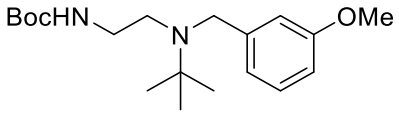
***N*-(2-(*tert*-Butyl(4-methoxybenzyl)amino)ethyl)-2-((3-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-methoxybenzyl)amino)ethyl)carbamate (0.039 g, 0.115 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-((3-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.040 g, 0.115 mmol, 1.0 equiv) in anhydrous DMF (1 mL) were added DIPEA (0.059 g, 0.460 mmol, 4.0 equiv) and HATU (0.044 g, 0.115 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.115 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.027 g, 0.048 mmol, 41% yield, ≥ 99% purity). IR (neat) 3334, 2955, 1647, 1598, 1510 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.39 (m, 2H), 7.37–7.32 (m, 2H), 7.25–7.19 (m, 3H), 7.12 (ddd, *J* = 7.9, 2.6, 1.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.796.71 (m, 2H), 6.18 (t, *J* = 4.7 Hz, 1H), 4.30 (s, 2H), 3.86 (s, 3H), 3.70 (s, 3H), 3.61 (s, 2H), 3.40 (t, *J* = 5.9 Hz, 2H), 3.21–3.14 (m, 2H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.84–2.78 (m, 2H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 160.1, 158.5, 137.5, 134.8, 134.6, 133.5, 133.5, 130.4, 129.2,

127.8, 126.5, 124.6, 119.9, 119.2, 114.0, 112.7, 77.4, 55.8, 55.6, 55.3, 54.7, 49.9, 47.7, 43.8, 40.2, 28.9, 27.5; HRMS (ESI) m/z calcd for $C_{31}H_{40}N_3O_5S$ $[M+H]^+$ 566.2683, found 566.2688.



2.13.1

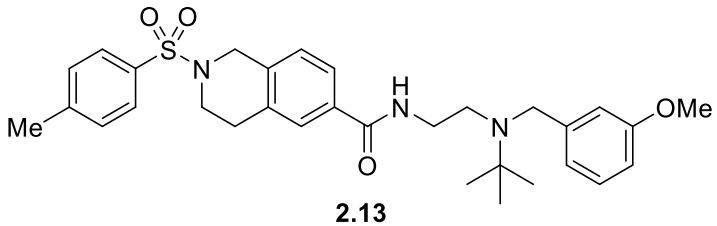
***N*-(3-Methoxybenzyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using 3-methoxybenzaldehyde (1.86 g, 13.7 mmol, 1.0 equiv), *tert*-butylamine (1.00 g, 13.7 mmol, 1.0 equiv), $NaBH(OAc)_3$ (4.06 g, 19.2 mmol, 1.4 equiv), AcOH (1 drop) and DCE (20 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (2.260 g, 11.69 mmol, 86% yield). IR (neat) 2961, 1601, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 1H), 6.96–6.88 (m, 2H), 6.81–6.73 (m, 1H), 3.81 (s, 3H), 3.71 (s, 2H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 143.3, 129.5, 120.6, 113.9, 112.3, 55.3, 50.8, 47.4, 29.3; HRMS (ESI) m/z calcd for $C_{12}H_{20}NO$ $[M+H]^+$ 194.1539, found 194.1540.



2.13.2

***tert*-Butyl (2-(*tert*-butyl(3-methoxybenzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), *N*-(3-methoxybenzyl)-2-methylpropan-2-amine (0.193 g, 1.00 mmol, 1.0 equiv),

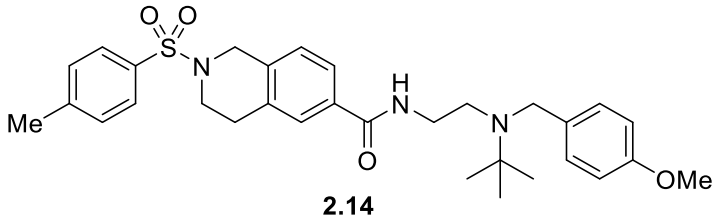
$NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.205 g, 0.61 mmol, 61% yield). IR (neat) 3416, 2971, 1706, 1600, 1488 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.8 Hz, 1H), 6.97–6.87 (m, 2H), 6.77–6.69 (m, 1H), 4.64 (br s, 1H), 3.80 (s, 3H), 3.65 (s, 2H), 2.92–2.79 (m, 2H), 2.67 (t, *J* = 6.1 Hz, 2H), 1.39 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 156.1, 144.9, 129.3, 120.1, 113.3, 112.0, 78.8, 55.3, 55.2, 55.1, 28.5, 27.4; HRMS (ESI) m/z calcd for $C_{19}H_{33}N_2O_3$ $[M+H]^+$ 337.2486, found 337.2484.



2.13

***N*-(2-(*tert*-Butyl(3-methoxybenzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(3-methoxybenzyl)amino)ethyl)carbamate (0.101 g, 0.302 mmol, 1.0 equiv) in DCM (3 mL) was added TFA (3 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.100 g, 0.302 mmol, 1.0 equiv) in anhydrous DMF (6 mL) were added DIPEA (0.155 g, 1.207 mmol, 4.0 equiv) and HATU (0.114 g, 0.302 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.302 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2

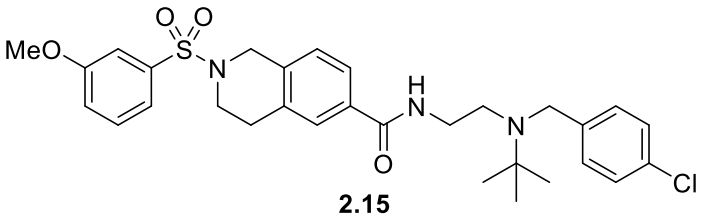
stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.133 g, 0.242 mmol, 80% yield, ≥ 99% yield). IR (neat) 3327, 2966, 1646, 1599 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77–7.69 (m, 2H), 7.39–7.31 (m, 3H), 7.28 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.18–7.12 (m, 1H), 7.07–7.02 (m, 1H), 6.96–6.89 (m, 2H), 6.71–6.65 (m, 1H), 6.26 (t, *J* = 4.9 Hz, 1H), 4.27 (s, 2H), 3.70 (s, 3H), 3.67 (s, 2H), 3.36 (t, *J* = 5.9 Hz, 2H), 3.26–3.17 (m, 2H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.85–2.79 (m, 2H), 2.42 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 159.9, 144.9, 144.0, 134.9, 133.5, 133.5, 133.2, 129.9, 129.6, 127.9, 127.8, 126.5, 124.6, 120.1, 113.7, 111.8, 55.6, 55.3, 55.2, 50.4, 47.7, 43.7, 39.8, 29.0, 27.5, 21.7; HRMS (ESI) m/z calcd for $C_{31}H_{40}N_3O_4S$ $[M+H]^+$ 550.2734, found 550.2735.



2.14

***N*-(2-(*tert*-Butyl(4-methoxybenzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-methoxybenzyl)amino)ethyl)carbamate (0.101 g, 0.302 mmol, 1.0 equiv) in DCM (3 mL) was added TFA (3 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.100 g, 0.302 mmol, 1.0 equiv) in anhydrous DMF (6 mL) were added DIPEA (0.155 g, 1.207 mmol, 4.0 equiv) and HATU (0.114

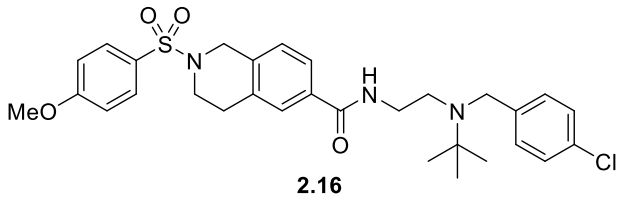
g, 0.302 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.302 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.131 g, 0.238 mmol, 79% yield, 97.2% purity). IR (neat) 3319, 2965, 1646, 1579, 1510 cm^{-1}; ^1H NMR (500 MHz, CD_3Cl) δ 7.79–7.67 (m, 2H), 7.36–7.31 (m, 3H), 7.25–7.19 (m, 3H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.77–6.72 (m, 2H), 6.17 (t, *J* = 5.5 Hz, 1H), 4.26 (s, 2H), 3.70 (s, 3H), 3.61 (s, 2H), 3.36 (t, *J* = 5.9 Hz, 2H), 3.20–3.12 (m, 2H), 2.95 (t, *J* = 5.8 Hz, 2H), 2.83–2.77 (m, 2H), 2.42 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 158.5, 144.0, 134.9, 134.6, 133.5, 133.2, 132.2, 129.9, 129.2, 127.9, 127.8, 126.5, 124.5, 114.0, 55.6, 55.3, 54.7, 49.9, 47.7, 43.7, 40.2, 29.0, 27.5, 21.7; HRMS (ESI) m/z calcd for $C_{31}H_{40}N_3O_4S$ $[M+H]^+$ 550.2734, found 550.2719.



2.15

***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)-2-((3-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-((3-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.080 g, 0.230 mmol, 1.0 equiv) in anhydrous DMF (4.6 mL) were added DIPEA (0.089 g, 0.689 mmol, 3.0 equiv) and HATU (0.087 g, 0.229 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)ethane-1,2-diamine (0.055 g, 0.230 mmol, 1.0 equiv). The

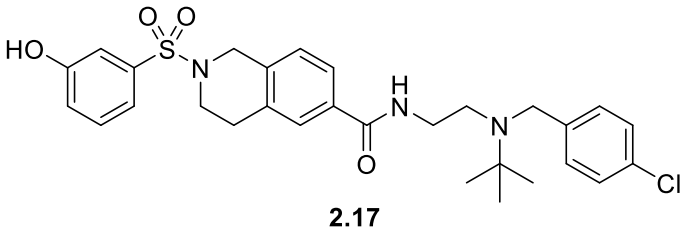
reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless oil (0.078 g, 0.137 mmol, 59% yield, 91.5% purity). IR (neat) 3317, 2970, 1645, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 2H), 7.28–7.21 (m, 2H), 7.20–7.12 (m, 3H), 7.10–6.92 (m, 4H), 6.21–6.05 (m, 1H), 4.20 (s, 2H), 3.74 (s, 3H), 3.55 (s, 2H), 3.29 (t, *J* = 5.9 Hz, 2H), 3.09 (q, *J* = 5.8 Hz, 2H), 2.84 (t, *J* = 5.8 Hz, 2H), 2.69 (t, *J* = 6.1 Hz, 2H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 160.1, 141.5, 137.6, 134.9, 133.5, 133.4, 132.2, 130.3, 129.2, 128.5, 127.7, 126.5, 124.4, 119.8, 119.0, 112.7, 55.7, 55.6, 54.6, 50.2, 47.6, 43.7, 40.2, 28.9, 27.4; HRMS (ESI) m/z calcd for $C_{30}H_{37}ClN_3O_4S$ $[M+H]^+$ 570.2188, found 570.2159.



2.16

***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)-2-((4-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-((4-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.080 g, 0.230 mmol, 1.0 equiv) in anhydrous DMF (4.6 mL) were added DIPEA (0.089 g, 0.689 mmol, 3.0 equiv) and HATU (0.087 g, 0.229 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of N^1-(*tert*-butyl)-N^1-(4-chlorobenzyl)ethane-1,2-diamine (0.055 g, 0.230 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to

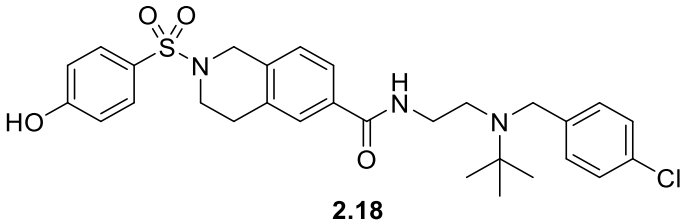
afford the title compound as a colorless oil (0.061 g, 0.107 mmol, 46% yield, 92.9% purity). IR (neat) 3326, 2970, 1644, 1596 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.80–7.73 (m, 2H), 7.35 (s, 1H), 7.32–7.27 (m, 3H), 7.20–7.16 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.06–6.99 (m, 2H), 6.13 (t, *J* = 5.4 Hz, 1H), 4.26 (s, 2H), 3.86 (s, 3H), 3.68 (s, 2H), 3.35 (t, *J* = 5.9 Hz, 2H), 3.16 (q, *J* = 5.9 Hz, 2H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.80 (t, *J* = 6.2 Hz, 2H), 1.15 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 166.3, 163.2, 141.8, 135.1, 133.6, 133.4, 131.9, 129.8, 129.2, 128.3, 127.8, 127.4, 126.5, 124.2, 114.3, 55.7, 55.4, 54.5, 50.2, 47.6, 43.7, 40.0, 28.8, 27.1; HRMS (ESI) m/z calcd for $C_{30}H_{37}ClN_3O_4S$ $[M+H]^+$ 570.2188, found 570.2170.



2.17

***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)-2-((3-hydroxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of compound *N*-(2-(*tert*-butyl(4-chlorobenzyl)amino)ethyl)-2-((3-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide (0.025 g, 0.044 mmol, 1.0 equiv) in DCM (6 mL) was added dropwise BBr_3 (1 N in DCM, 0.68 ml, 0.680 mmol, 17.0 equiv) at -40 °C. The reaction was warmed to 0 °C and stirred for 2 h, then quenched with methanol at -20 °C. The organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless film (4 mg, 0.008 mmol, 18% yield, HPLC purity = 93.3%). IR (neat) 2970, 1636, 1575, 1542, 1489 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2)

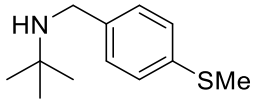
δ 7.42–7.21 (m, 7H), 7.19–7.13 (m, 2H), 7.09–6.97 (m, 2H), 6.34 (br s, 1H), 4.18 (s, 2H), 3.67 (s, 2H), 3.26–3.13 (m, 4H), 2.89–2.75 (m, 4H), 1.16 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 167.7, 157.7, 142.2, 137.5, 135.9, 134.3, 133.5, 132.6, 130.9, 129.9, 128.9, 128.1, 127.2, 124.8, 121.0, 119.8, 114.9, 56.1, 55.1, 50.5, 48.1, 44.2, 40.8, 29.4, 27.6; HRMS (ESI) m/z calcd for $C_{29}H_{35}ClN_3O_4S$ $[M+H]^+$ 556.2031, found 556.2024.



2.18

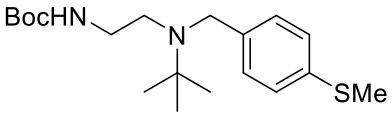
***N*-(2-(*tert*-Butyl(4-chlorobenzyl)amino)ethyl)-2-((4-hydroxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of compound *N*-(2-(*tert*-butyl(4-chlorobenzyl)amino)ethyl)-2-((4-methoxyphenyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide (0.025 g, 0.044 mmol, 1.0 equiv) in anhydrous DCM (6 mL) was added dropwise BBr_3 (1 N in DCM, 0.68 mL, 0.680 mmol, 15.0 equiv) at -40 °C. The reaction was warmed to 0 °C and stirred for 2 h, then quenched with methanol at -20 °C. The organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (10 mg, 0.018mmol, 41% yield, 97.7% purity). IR (neat) 2947, 1637, 1580 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.54 (br s, 2H), 8.20 (t, J = 5.7 Hz, 1H), 7.68–7.61 (m, 2H), 7.56–7.48 (m, 2H), 7.43–7.38 (m, 2H), 7.36–7.28 (m, 2H), 7.19 (d, J = 6.4 Hz, 1H), 6.98 – 6.89 (m, 2H), 4.14 (s, 2H), 3.68 (s, 2H), 3.23 (t, J = 6.0 Hz, 2H), 3.07–3.00 (m, 2H), 2.86 (m, 2H), 2.66–2.60 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.6, 161.7, 142.2, 134.8, 133.0, 132.8, 130.6, 129.9,

129.4, 127.9, 127.5, 126.4, 124.8, 115.8, 54.8, 53.4, 49.9, 47.3, 43.5, 40.4, 28.1, 27.1; HRMS (ESI) m/z calcd for $C_{29}H_{35}ClN_3O_4S$ $[M+H]^+$ 556.2031, found 556.2009.



2.19.1

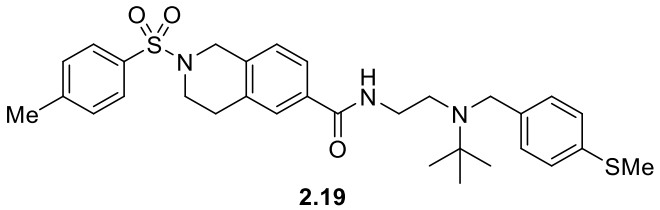
2-Methyl-*N*-(4-(methylthio)benzyl)propan-2-amine. Prepared according to the general procedure for reductive amination using 4-(methylthio)benzaldehyde (0.761 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.630 g, 3.01 mmol, 60% yield). IR (neat) 2961, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 4H), 3.68 (s, 2H), 2.46 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 136.5, 128.9, 127.2, 50.8, 46.9, 29.3, 16.4; HRMS (ESI) m/z calcd for $C_{13}H_{22}N$ $[M+H]^+$ 210.1311; found 210.1306.



2.19.2

***tert*-Butyl (2-(*tert*-butyl(4-(methylthio)benzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), 2-methyl-*N*-(4-(methylthio)benzyl)propan-2-amine (0.209 g, 1.00

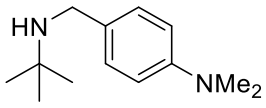
mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.238 g, 0.68 mmol, 68% yield). IR (neat) 2971, 1709, 1492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 4H), 7.22–7.17 (m, 2H), 4.56 (s, 1H), 3.62 (s, 2H), 2.89–2.80 (m, 2H), 2.65 (t, *J* = 6.3 Hz, 2H), 2.46 (s, 3H), 2.17 (s, 2H), 1.39 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 140.3, 136.2, 128.5, 127.1, 78.9, 55.4, 54.7, 50.7, 40.9, 28.6, 27.5, 16.4; HRMS (ESI) m/z calcd for $C_{19}H_{33}N_2O_2S$ $[M+H]^+$ 353.2257; found 353.2290.



2.19

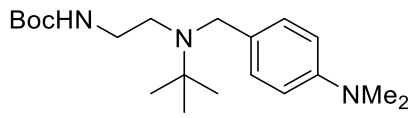
***N*-(2-(*tert*-Butyl(4-(methylthio)benzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-(methylthio)benzyl)amino)ethyl)carbamate (0.025 g, 0.071 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.023 g, 0.069 mmol, 1.0 equiv) in anhydrous DMF (1.4 mL) were added DIPEA (0.036 g, 0.28 mmol, 4.0 equiv) and HATU (0.027 g, 0.071 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.071 mmol, 1.0 equiv). The reaction was stirred for 12 h

at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as white solid (0.025 g, 0.044 mmol, 63% yield, ≥ 99% purity). Mp = 59–62 ºC; IR (neat) 2992, 1626, 1542, 1497 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.92 (t, *J* = 5.7 Hz, 1H), 7.78–7.71 (m, 2H), 7.53–7.44 (m, 2H), 7.43–7.33 (m, 4H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.08–7.01 (m, 2H), 4.62–4.50 (m, 1H), 4.26 (s, 2H), 3.83 (dd, *J* = 12.9, 8.8 Hz, 1H), 3.74–3.65 (m, 1H), 3.58–3.48 (m, 1H), 3.45–3.31 (m, 3H), 3.16–3.06 (m, 1H), 3.00 (t, *J* = 6.1 Hz, 2H), 2.45 (s, 3H), 2.28 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 172.0, 144.7, 142.5, 137.2, 134.3, 133.3, 131.9, 130.3, 128.6, 128.2, 127.2, 126.6, 125.8, 125.1, 66.1, 56.4, 48.2, 44.1, 40.3, 29.3, 25.5, 21.8, 15.0; HRMS (ESI) m/z calcd for $C_{31}H_{40}N_3O_3S_2$ $[M+H]^+$ 566.2506, found 566.2519.



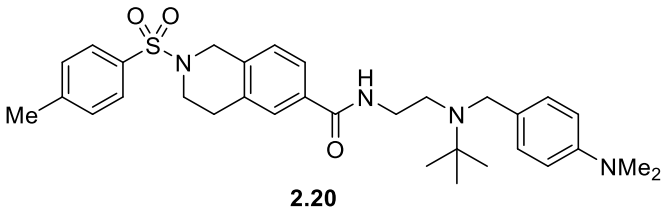
2.20.1

4-((*tert*-Butylamino)methyl)-*N*,*N*-dimethylaniline. Prepared according to the general procedure for reductive amination using 4-(dimethylamino)benzaldehyde (0.746 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.803 g, 3.89 mmol, 78% yield). IR (neat) 2957, 1613, 1518, 1479 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.22–7.14 (m, 2H), 6.79–6.70 (m, 2H), 3.58 (s, 2H), 2.88 (s, 6H), 1.18 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 151.5, 130.5, 129.4, 114.3, 51.9, 47.3, 41.2, 28.7; HRMS (ESI) m/z calcd for $C_{13}H_{21}N_2O$ $[M+H]^+$ 207.1856; found 207.1858.



2.20.2

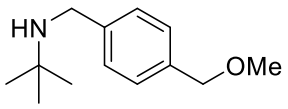
***tert*-Butyl (2-(*tert*-butyl(4-(dimethylamino)benzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), 4-((*tert*-butylamino)methyl)-*N*,*N*-dimethylaniline (0.206 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.200 g, 0.57 mmol, 57% yield). IR (neat) 2964, 1710, 1614, 1518 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.23–7.14 (m, 2H), 6.78–6.69 (m, 2H), 3.60 (s, 2H), 2.88 (s, 6H), 2.79–2.71 (m, 2H), 2.67–2.59 (m, 2H), 1.38 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 158.2, 151.2, 132.1, 130.1, 114.4, 79.7, 56.1, 55.3, 51.0, 42.2, 41.4, 28.8, 27.7; HRMS (ESI) m/z calcd for $C_{20}H_{36}N_3O_2$ $[M+H]^+$ 350.2802; found 350.2806.



2.20

***N*-(2-(*tert*-Butyl(4-(dimethylamino)benzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-(dimethylamino)benzyl)amino)ethyl)carbamate (0.035 g, 0.100 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this

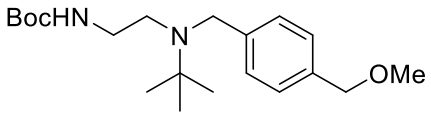
temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.030 g, 0.053 mmol, 53% yield, HPLC purity = 96.6%). IR (neat) 3357, 2967, 1645, 1521 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.67–7.58 (m, 2H), 7.31–7.24 (m, 3H), 7.20–7.13 (m, 1H), 7.12–7.03 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.54–6.45 (m, 2H), 4.16 (s, 2H), 3.49 (s, 2H), 3.25 (t, *J* = 5.9 Hz, 2H), 3.07–2.98 (m, 2H), 2.90–2.79 (m, 2H), 2.77–2.65 (m, 8H), 2.33 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 166.7, 150.3, 144.6, 135.4, 134.2, 134.0, 133.8, 130.8, 130.3, 129.3, 128.2, 128.1, 126.9, 125.0, 113.1, 55.8, 55.0, 50.2, 48.2, 44.3, 41.0, 40.5, 29.5, 27.7, 21.8; HRMS (ESI) m/z calcd for $C_{32}H_{43}N_4O_3S$ $[M+H]^+$ 563.3050, found 563.3027.



2.21.1

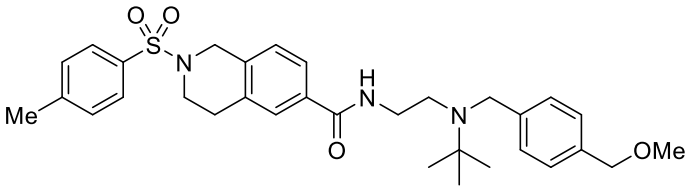
***N*-(4-(Methoxymethyl)benzyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using 4-(methoxymethyl)benzaldehyde (0.150 g, 1.0 mmol, 1.0 equiv), *tert*-butylamine (0.073 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 12 h. Reverse-phase

flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.150 g, 0.72 mmol, 72% yield). IR (neat) 2963, 1474, 1385 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.45–7.32 (m, 4H), 4.46 (s, 2H), 3.88 (s, 2H), 3.37 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 139.1, 137.7, 130.2, 129.3, 75.2, 58.3, 54.5, 47.1, 27.6; HRMS (ESI) m/z calcd for $C_{13}H_{22}NO$ $[M+H]^+$ 208.1696; found 208.1694.



2.21.2

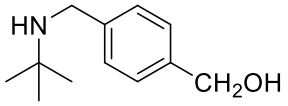
***tert*-Butyl (2-(*tert*-butyl(4-(methoxymethyl)benzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.054 g, 0.34 mmol, 1.0 equiv), *N*-(4-(methoxymethyl)benzyl)-2-methylpropan-2-amine (0.070 g, 0.34 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.100 g, 0.47 mmol, 1.4 equiv), AcOH (1 drop) and DCE (0.68 mL), at room temperature for 24 h. Reverse-phase column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.060 g, 0.17 mmol, 50% yield). IR 2972, 1710, 1500 (neat) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.42 (s, 2H), 3.71 (s, 2H), 3.35 (s, 3H), 2.85–2.72 (m, 2H), 2.70–2.60 (m, 2H), 1.39 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 158.2, 143.6, 137.2, 129.2, 129.0, 80.0, 75.4, 58.1, 56.2, 55.5, 51.2, 28.7, 27.6; HRMS (ESI) m/z calcd for $C_{20}H_{35}N_2O_3$ $[M+H]^+$ 351.2642; found 351.2653.



2.21

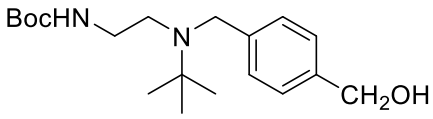
***N*-(2-(*tert*-Butyl(4-(methoxymethyl)benzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-(methoxymethyl)benzyl)amino)ethyl)carbamat*e* (0.035 g, 0.100 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as white solid (0.030 g, 0.053 mmol, 53% yield, ≥ 99% purity). Mp = 83–85 ºC; IR (neat) 3341, 2970, 1645, 1538 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.76–7.68 (m, 2H), 7.44 (dd, *J* = 8.0, 1.8 Hz, 3H), 7.42–7.33 (m, 5H), 7.22–7.16 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 4.33 (s, 2H), 4.23 (s, 2H), 3.73 (s, 2H), 3.37–3.28 (m, 2H), 3.18 – 3.09 (m, 2H), 2.89 (t, *J* = 5.9 Hz, 1H), 2.83–2.74 (m, 2H), 2.41 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.4, 145.4, 143.7, 137.5, 136.7, 134.8, 134.7, 134.2, 130.9, 129.2, 128.9, 128.9, 128.7, 127.6, 126.0, 75.5, 58.2, 56.3, 55.8, 51.0,

48.7, 45.0, 42.1, 29.7, 27.7, 21.5; HRMS (ESI) m/z calcd for $C_{32}H_{42}N_3O_4S$ $[M+H]^+$ 564.2891, found 564.2869.



2.22.1

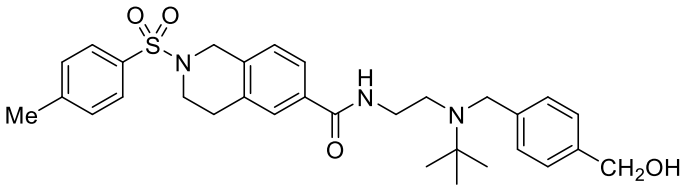
(4-((*tert*-Butylamino)methyl)phenyl)methanol. Prepared according to the general procedure for reductive amination using 4-(hydroxymethyl)benzaldehyde (0.681 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL) at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.700 g, 3.62 mmol, 72% yield). IR (neat) 3260, 2965, 1487, 1390 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.37–7.28 (m, 5H), 4.58 (s, 2H), 3.70 (s, 2H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 141.6, 140.3, 129.7, 128.1, 65.0, 52.1, 47.6, 28.7; HRMS (ESI) m/z calcd for $C_{12}H_{20}NO$ $[M+H]^+$ 194.1539; found 194.1538.



2.22.2

***tert*-Butyl (2-(*tert*-butyl(4-(hydroxymethyl)benzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), *N*-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-2-

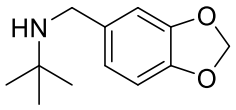
methylpropan-2-amine (0.193 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.169 g, 0.50 mmol, 50% yield). IR (neat) 2972, 1687, 1509 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.35 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.57 (s, 2H), 3.71 (s, 2H), 2.86–2.72 (m, 2H), 2.72–2.60 (m, 2H), 1.39 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 158.2, 143.3, 140.8, 129.1, 128.0, 79.8, 65.1, 56.1, 55.7, 51.5, 42.2, 28.8, 27.7; HRMS (ESI) m/z calcd for $C_{19}H_{33}N_2O_3$ $[M+H]^+$ 337.2486; found 337.2484.



2.22

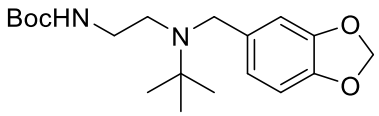
***N*-(2-(*tert*-Butyl(4-(hydroxymethyl)benzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-(hydroxymethyl)benzyl)amino)ethyl)carbamate (0.034 g, 0.100 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h

at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.035 g, 0.064 mmol, 64% yield, ≥ 99% purity). IR (neat) 3371, 2968, 1640, 1538, 1495 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.77–7.70 (m, 2H), 7.46 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.44–7.35 (m, 5H), 7.26–7.20 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 1H), 4.51 (s, 2H), 4.26 (s, 2H), 3.75 (s, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 3.16 – 3.09 (m, 2H), 2.92 (t, *J* = 5.9 Hz, 2H), 2.82–2.76 (m, 2H), 2.42 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (126 MHz, CD_3OD) δ 169.5, 145.5, 140.9, 136.8, 134.8, 134.2, 130.9, 129.3, 128.9, 128.7, 128.0, 127.7, 126.0, 65.1, 56.3, 55.7, 50.9, 48.8, 45.0, 42.1, 29.7, 27.7, 21.5; HRMS (ESI) m/z calcd for $C_{31}H_{40}N_3O_4S$ $[M+H]^+$ 550.2734, found 550.2748.



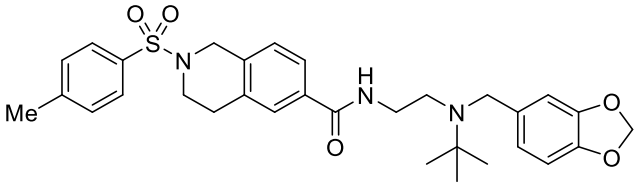
2.23.1

***N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using benzo[d][1,3]dioxole-5-carbaldehyde (0.750 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.850 g, 4.10 mmol, 82% yield). IR (neat) 2962, 1488, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87–6.83 (m, 1H), 6.80–6.71 (m, 2H), 5.91 (s, 2H), 3.63 (s, 2H), 1.16 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 146.4, 135.7, 121.2, 109.0, 108.2, 100.9, 50.7, 47.2, 29.3; HRMS (ESI) m/z calcd for $C_{13}H_{22}N$ $[M+H]^+$ 208.1332; found 208.1329.



2.23.2

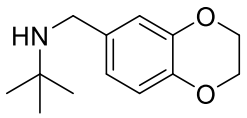
***tert*-Butyl (2-((benzo[d][1,3]dioxol-5-ylmethyl)(*tert*-butyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), 2-methyl-*N*-(4-(methylthio)benzyl)propan-2-amine (0.207 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.240 g, 0.68 mmol, 68% yield), at room temperature for 24 h. IR (neat) 2972, 1701, 1487, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88–6.83 (m, 1H), 6.79–6.67 (m, 2H), 5.92 (s, 2H), 4.56 (br s, 1H), 3.57 (s, 2H), 2.90–2.80 (m, 2H), 2.65 (t, *J* = 6.1 Hz, 2H), 1.39 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 147.8, 146.3, 137.1, 120.7, 108.5, 108.1, 100.9, 78.8, 55.3, 55.1, 50.6, 41.0, 28.5, 27.5; HRMS (ESI) m/z calcd for $C_{19}H_{31}N_2O_4$ $[M+H]^+$ 351.2278; found 351.2284.



2.23

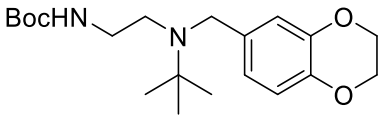
***N*-(2-((Benzo[d][1,3]dioxol-5-ylmethyl)(*tert*-butyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-((benzo[d][1,3]dioxol-5-

ylmethyl)(*tert*-butyl)amino)ethyl)carbamate (0.025 g, 0.071 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.023 g, 0.069 mmol, 1.0 equiv) in anhydrous DMF (1.4 mL) were added DIPEA (0.036 g, 0.279 mmol, 4.0 equiv) and HATU (0.027 g, 0.071 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.071 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.020 g, 0.035 mmol, 51% yield, 98.8% purity). IR (neat) 2988, 1627, 1540, 1495 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) 7.89 (t, *J* = 5.7 Hz, 1H), 7.77–7.71 (m, 2H), 7.56–7.50 (m, 2H), 7.44–7.37 (m, 2H), 7.19–7.13 (m, 1H), 6.96 (dd, *J* = 7.9, 1.9 Hz, 1H), 6.89 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.66 (d, *J* = 1.4 Hz, 1H), 4.56–4.49 (m, 1H), 4.27 (s, 2H), 3.78 (dd, *J* = 13.0, 8.9 Hz, 1H), 3.74–3.65 (m, 1H), 3.56 (dddd, *J* = 15.7, 7.9, 5.7, 2.0 Hz, 1H), 3.46–3.30 (m, 3H), 3.17 (dtd, *J* = 14.9, 6.5, 2.0 Hz, 1H), 3.00 (t, *J* = 6.0 Hz, 2H), 2.62 (s, 20H), 2.46 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 172.1, 149.7, 148.9, 144.7, 137.3, 134.4, 133.3, 130.4, 130.3, 128.9, 128.2, 127.2, 126.0, 125.7, 122.4, 111.2, 109.4, 102.4, 66.0, 56.8, 53.7, 48.2, 44.2, 40.4, 29.3, 25.5, 21.8; HRMS (ESI) m/z calcd for $C_{31}H_{38}N_3O_5S$ $[M+H]^+$ 564.2527, found 564.2535.



2.24.1

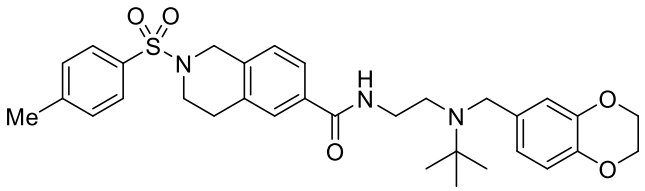
***N*-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using 2,3-dihydrobenzo[b][1,4]dioxine-6-carbaldehyde (0.821 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.970 g, 4.38 mmol, 88% yield). IR (neat) 2963, 1591, 1506, 1431 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.87 (dd, *J* = 1.8, 0.7 Hz, 2H), 6.84–6.76 (m, 4H), 4.23 (s, 4H), 3.62 (s, 2H), 1.21 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 144.9, 144.2, 134.0, 122.6, 118.5, 118.1, 65.6, 65.6, 52.3, 47.3, 28.5; HRMS (ESI) m/z calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1489; found 222.1485.



2.24.2

***tert*-Butyl (2-(*tert*-butyl((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)amino)ethyl) carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), *N*-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-2-methylpropan-2-amine (0.221 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL) at room temperature for 24 h. Reverse-phase

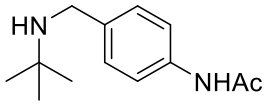
flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as colorless oil (0.217 g, 0.60 mmol, 60% yield). IR (neat) 2972, 1701, 1590 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 6.86–6.69 (m, 3H), 4.24–4.15 (m, 4H), 3.58 (s, 2H), 2.84–2.73 (m, 2H), 2.68–2.59 (m, 2H), 1.39 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 158.2, 144.7, 143.6, 137.2, 121.8, 117.8, 117.8, 79.8, 65.6, 65.5, 56.1, 55.3, 51.4, 42.2, 28.8, 27.7; HRMS (ESI) m/z calcd for $C_{20}H_{33}N_2O_4$ $[M+H]^+$ 365.2435; found 365.2428.



2.24

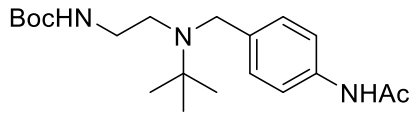
***N*-(2-(*tert*-Butyl((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide**. To a solution of *tert*-butyl (2-(*tert*-butyl((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)amino)ethyl)carbamate (0.036 g, 0.100 mmol, 1.0 equiv). in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound

as colorless film (0.027 g, 0.047 mmol, 47% yield, ≥ 99% purity). IR (neat) 2970, 1646, 1504 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.76–7.68 (m, 2H), 7.44 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.42–7.36 (m, 4H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 1.9 Hz, 2H), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 4.24 (s, 2H), 4.13–4.05 (m, 4H), 3.59 (s, 2H), 3.35–3.32 (m, 2H), 3.19–3.10 (m, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.81–2.73 (m, 2H), 2.41 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.4, 145.5, 144.7, 143.6, 137.1, 136.8, 134.9, 134.8, 134.2, 130.9, 128.9, 128.7, 127.7, 126.1, 121.9, 117.9, 117.9, 65.5, 65.5, 56.3, 55.4, 50.8, 48.8, 45.0, 42.1, 29.7, 27.7, 21.5; HRMS (ESI) m/z calcd for $C_{32}H_{40}N_3O_5S$ $[M+H]^+$ 578.2683, found 578.2678.



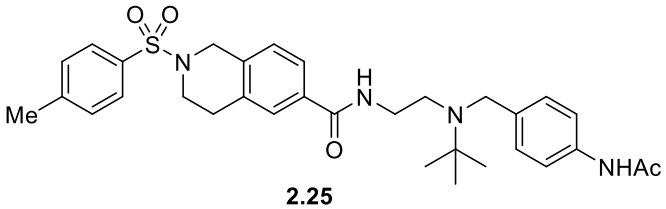
2.25.1

***N*-(4-((*tert*-Butylamino)methyl)phenyl)acetamide.** Prepared according to the general procedure for reductive amination using N-(4-formylphenyl)acetamide (0.816 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.943 g, 4.28 mmol, 86% yield). IR (neat) 3273, 1603, 1551, 1515 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53–7.44 (m, 2H), 7.27–7.19 (m, 2H), 3.57 (s, 2H), 2.02 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.9, 137.4, 136.7, 128.1, 118.6, 49.9, 45.8, 28.9, 23.9; HRMS (ESI) m/z calcd for $C_{13}H_{21}N_2O$ $[M+H]^+$ 221.1648; found 221.1647.



2.25.2

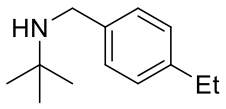
***tert*-Butyl (2-((4-acetamidobenzyl)(*tert*-butyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), *N*-(4-((*tert*-butylamino)methyl)phenyl)acetamide (0.220 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.176 g, 0.48 mmol, 48% yield). IR (neat) 2972, 1668, 1603, 1510 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.51–7.43 (m, 2H), 7.34–7.26 (m, 2H), 3.66 (s, 2H), 2.83–2.74 (m, 2H), 2.68–2.60 (m, 2H), 2.10 (s, 3H), 1.38 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 171.4, 158.2, 139.9, 138.3, 129.4, 121.0, 79.8, 56.1, 55.4, 51.4, 42.2, 28.8, 27.7, 23.8; HRMS (ESI) m/z calcd for $C_{20}H_{34}N_3O_3$ $[M+H]^+$ 364.2595; found 364.2594.



2.25

***N*-(2-((4-Acetamidobenzyl)(*tert*-butyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-((4-acetamidobenzyl)(*tert*-butyl)amino)ethyl)carbamate (0.036 g, 0.100 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly

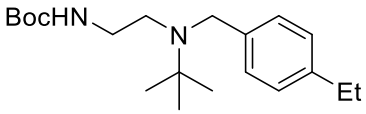
in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.037 g, 0.064 mmol, 64% yield, ≥ 99% purity). IR (neat) 3307, 2970, 1641 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.23 (s, 1H), 7.75–7.67 (m, 2H), 7.42–7.33 (m, 6H), 7.32–7.24 (m, 2H), 7.14–7.06 (m, 1H), 6.67 (t, *J* = 5.6 Hz, 1H), 4.22 (s, 2H), 3.64 (s, 2H), 3.30 (t, *J* = 5.9 Hz, 2H), 3.06 (dt, *J* = 7.0, 6.0 Hz, 2H), 2.89 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.39 (s, 3H), 1.99 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, CD_3CN) δ 169.3, 167.1, 145.2, 139.2, 138.5, 136.0, 134.5, 134.4, 134.4, 130.8, 129.3, 128.7, 128.4, 127.5, 125.5, 120.1, 56.0, 55.2, 50.8, 48.5, 44.7, 41.3, 29.4, 27.6, 24.3, 21.5; HRMS (ESI) m/z calcd for $C_{32}H_{41}N_4O_4S$ $[M+H]^+$ 577.2843, found 577.2828.



2.26.1

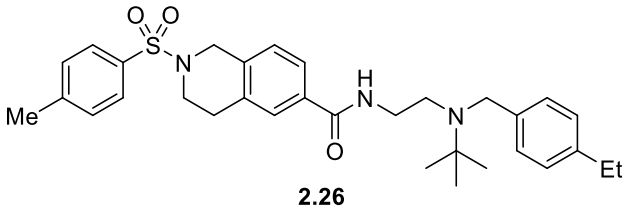
***N*-(4-Ethylbenzyl)-2-methylpropan-2-amine.** Prepared according to the general procedure for reductive amination using 4-ethylbenzaldehyde (0.671 g, 5.00 mmol, 1.0 equiv), *tert*-butylamine (0.366 g, 5.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (1.483 g, 7.00 mmol, 1.4 equiv), AcOH (1 drop) and DCE (10 mL), at room temperature for 12 h. Reverse-phase flash column

chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.370 g, 1.93 mmol, 39% yield). IR (neat) 2962, 1513 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 3.66 (s, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (151 MHz, CD_3CN) δ 143.4, 140.6, 129.1, 128.6, 51.1, 47.3, 29.3, 29.1, 16.2; HRMS (ESI) m/z calcd for $C_{13}H_{22}N$ $[M+H]^+$ 192.1747; found 192.1746.



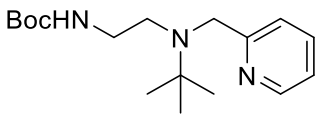
2.26.2

***tert*-Butyl (2-(*tert*-butyl(4-ethylbenzyl)amino)ethyl)carbamate.** Prepared according to the general procedure for reductive amination using *N*-Boc-2-aminoacetaldehyde (0.159 g, 1.00 mmol, 1.0 equiv), *N*-(4-ethylbenzyl)-2-methylpropan-2-amine (0.191 g, 1.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.297 g, 1.40 mmol, 1.4 equiv), AcOH (1 drop) and DCE (2 mL), at room temperature for 24 h. Reverse-phase column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a colorless oil (0.173 g, 0.52 mmol, 52% yield). IR (neat) 2966, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 3.64 (s, 2H), 2.88–2.78 (m, 2H), 2.69–2.56 (m, 4H), 1.39 (s, 9H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.13 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 142.5, 140.2, 127.9, 127.9, 78.8, 55.3, 54.9, 50.6, 40.9, 28.6, 28.6, 27.5, 15.7; HRMS (ESI) m/z calcd for $C_{20}H_{35}N_2O_2$ $[M+H]^+$ 335.2693; found 355.2702.



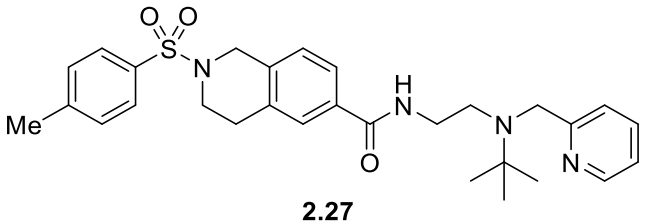
2.26

***N*-(2-(*tert*-Butyl(4-ethylbenzyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(4-ethylbenzyl)amino)ethyl)carbamate (0.023 g, 0.069 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.023 g, 0.069 mmol, 1.0 equiv) in anhydrous DMF (1.4 mL) were added DIPEA (0.036 g, 0.279 mmol, 4.0 equiv) and HATU (0.027 g, 0.071 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.069 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (0.020 g, 0.037 mmol, 52% yield, HPLC purity = 96.7%). Mp = 133–135 ºC; IR (neat) 3339, 2966, 1644 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.76–7.68 (m, 2H), 7.46–7.35 (m, 4H), 7.33–7.23 (m, 2H), 7.18–7.01 (m, 3H), 6.68–6.60 (m, 1H), 4.24 (s, 2H), 3.69 (s, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 3.13 – 3.04 (m, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.53 (q, *J* = 7.8 Hz, 2H), 2.40 (s, 3H), 2.15 (s, 2H), 1.45 (s, 1H), 1.27 (s, 1H); ^{13}C NMR (101 MHz, CD_3CN) δ 167.1, 145.2, 143.3, 141.5, 136.1, 134.6, 134.5, 134.4, 130.8, 128.9, 128.7, 128.6, 128.4, 127.5, 125.5, 55.9, 55.3, 50.8, 48.5, 44.7, 41.1, 29.4, 29.0, 27.7, 21.5, 16.1; HRMS (ESI) m/z calcd for $C_{32}H_{42}N_3O_3S$ $[M+H]^+$ 548.2941, found 548.2917.



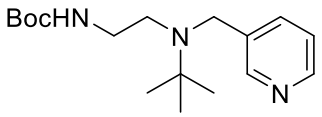
2.27.2

***tert*-Butyl (2-(*tert*-butyl(pyridin-2-ylmethyl)amino)ethyl)carbamate.** To a solution of *tert*-butylamine (0.219 g, 3.00 mmol, 1.0 equiv) and picolinaldehyde (0.321 g, 3.00 mmol, 1.0 equiv) in DCE (6 mL) was added $NaBH(OAc)_3$ (0.890 g, 4.20 mmol, 1.4 equiv) at room temperature. The reaction mixture was stirred at this temperature overnight, prior to the addition of *N*-Boc-2-aminoacetaldehyde (0.478 g, 3.00 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.890 g, 4.20 mmol, 1.4 equiv) and DCE (4 mL). The reaction was stirred for 24 h at room temperature, then quenched with aqueous NaOH solution (1 N, 12 mL), extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title product as a colorless oil (0.450 g, 1.46 mmol, 49% yield). IR (neat) 3348, 2972, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53–8.43 (m, 1H), 7.61 (td, *J* = 7.7, 1.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.13–7.04 (m, 1H), 5.26 (br s, 1H), 3.81 (s, 2H), 2.94 (t, *J* = 6.2 Hz, 2H), 2.73 (t, *J* = 6.2 Hz, 2H), 1.40 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 156.2, 149.0, 136.4, 122.2, 121.6, 78.8, 57.1, 55.5, 51.0, 40.8, 28.6, 27.3; HRMS (ESI) m/z calcd for $C_{17}H_{30}N_3O_2$ $[M+H]^+$ 308.2333, found 308.2327.



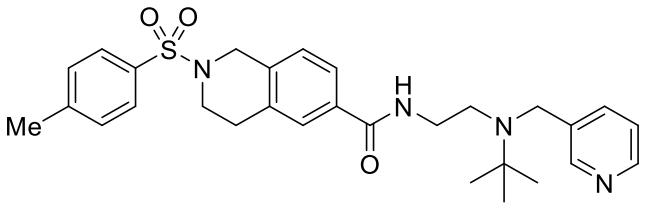
2.27

***N*-(2-(*tert*-Butyl(pyridin-2-ylmethyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(pyridin-2-ylmethyl)amino)ethyl)carbamate (0.031 g, 0.100 mmol. 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.031 g, 0.060 mmol, 60% yield, 98.0% purity). IR (neat) 3292, 2970, 1646, 1538 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 8.51–8.29 (m, 2H), 7.76–7.68 (m, 2H), 7.67–7.54 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.11–7.05 (m, 1H), 4.27 (s, 2H), 3.85 (s, 2H), 3.43 – 3.30 (m, 4H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.85 (t, *J* = 5.7 Hz, 2H), 2.42 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 166.7, 163.9, 149.4, 144.6, 136.9, 135.2, 134.6, 133.9, 133.7, 130.3, 128.4, 128.2, 126.9, 125.3, 122.6, 122.1, 56.0, 55.9, 50.2, 48.2, 44.3, 39.6, 29.5, 27.5, 21.8; HRMS (ESI) m/z calcd for $C_{29}H_{37}N_4O_3S$ $[M+H]^+$ 521.2581, found 521.2570.



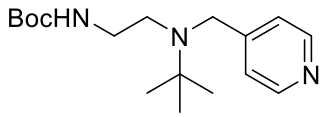
2.28.2

***tert*-Butyl (2-(*tert*-butyl(pyridin-3-ylmethyl)amino)ethyl)carbamate.** To a solution of *tert*-butylamine (0.110 g, 1.50 mmol, 1.0 equiv) and nicotinaldehyde (0.161 g, 1.50 mmol, 1.0 equiv) in DCE (3 mL) was added $NaBH(OAc)_3$ (0.445 g, 2.10 mmol, 1.4 equiv) at room temperature. The reaction mixture was stirred at this temperature overnight, prior to the addition of *N*-Boc-2-aminoacetaldehyde (0.239 g, 1.50 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.445 g, 2.10 mmol, 1.4 equiv) and DCE (2 mL). The reaction was stirred for 24 h at room temperature, then quenched with aqueous NaOH solution (1 N, 6 mL), extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title product as a colorless oil (0.163 g, 0.53 mmol, 35% yield). IR (neat) 3346, 2972, 1702 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.56 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.40 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.79 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.33–7.21 (m, 1H), 5.69 (br s, 1H), 3.78 (s, 2H), 2.93–2.84 (m, 2H), 2.73–2.66 (m, 2H), 1.36 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 156.5, 150.3, 148.6, 139.4, 136.1, 123.9, 78.3, 55.9, 52.9, 51.5, 42.0, 28.6, 27.6; HRMS (ESI) m/z calcd for $C_{17}H_{30}N_3O_2$ $[M+H]^+$ 308.2333, found 308.2329.



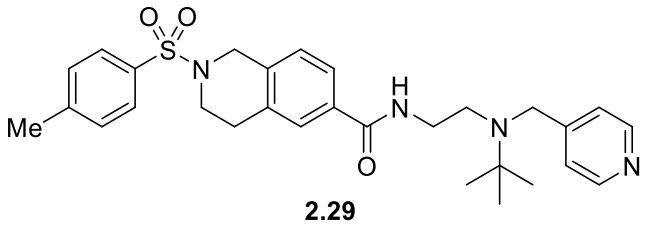
2.28

***N*-(2-(*tert*-Butyl(pyridin-3-ylmethyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(pyridin-3-ylmethyl)amino)ethyl)carbamate (0.031 g, 0.100 mmol. 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (0.040 g, 0.077 mmol, 77% yield, 95.0% purity). Mp = 120–123 ºC; IR (neat) 3321, 2969, 1647, 1538 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 8.57 (s, 1H), 8.39–8.31 (m, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.40–7.29 (m, 4H), 7.13 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.20 (t, *J* = 5.5 Hz, 1H), 4.25 (s, 2H), 3.73 (s, 2H), 3.34 (t, *J* = 5.9 Hz, 2H), 3.18–3.11 (m, 2H), 2.96 (t, *J* = 5.8 Hz, 2H), 2.80 (t, *J* = 6.3 Hz, 2H), 2.42 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 166.8, 150.1, 148.6, 144.6, 138.7, 135.9, 135.6, 134.2, 133.8, 133.6, 130.3, 128.2, 128.0, 127.0, 124.9, 123.7, 56.1, 53.1, 50.7, 48.1, 44.2, 40.5, 29.4, 27.6, 21.8; HRMS (ESI) m/z calcd for $C_{29}H_{37}N_4O_3S$ $[M+H]^+$ 521.2581, found 521.2571.



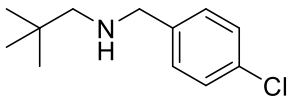
2.29.2

***tert*-Butyl (2-(*tert*-butyl(pyridin-4-ylmethyl)amino)ethyl)carbamate.** To a solution of *tert*-butylamine (0.110 g, 1.5 mmol, 1.0 equiv) and isonicotinaldehyde (0.161 g, 1.50 mmol, 1.0 equiv) in DCE (3 mL) was added $NaBH(OAc)_3$ (0.445 g, 2.10 mmol, 1.4 equiv) at room temperature. The reaction mixture was stirred at this temperature overnight, prior to the addition of *N*-Boc-2-aminoacetaldehyde (0.239 g, 1.50 mmol, 1.0 equiv), $NaBH(OAc)_3$ (0.445 g, 2.10 mmol, 1.4 equiv) and DCE (2 mL). The reaction was stirred for 24 h at room temperature, then quenched with aqueous NaOH solution (1 N, 6 mL), extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title product as a light yellow oil (0.196 g, 0.44 mmol, 43% yield). IR (neat) 3349, 2972, 1703 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.51–8.40 (m, 2H), 7.46–7.34 (m, 2H), 5.80 (br s, 1H), 3.78 (s, 2H), 2.98–2.89 (m, 2H), 2.76–2.66 (m, 2H), 1.37 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (101 MHz, acetone-d_6) δ 156.5, 153.8, 150.3, 123.5, 78.4, 55.8, 54.6, 51.9, 41.9, 28.6, 27.5; HRMS (ESI) m/z calcd for $C_{17}H_{30}N_3O_2$ $[M+H]^+$ 308.2333, found 308.2330.



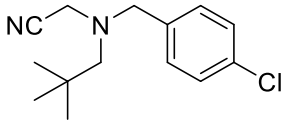
2.29

***N*-(2-(*tert*-Butyl(pyridin-4-ylmethyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of *tert*-butyl (2-(*tert*-butyl(pyridin-4-ylmethyl)amino)ethyl)carbamate (0.031 g, 0.100 mmol. 1.0 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. The resulting mixture was stirred for 3 h at this temperature, then concentrated *in vacuo*. The obtained crude TFA salt of diamine was used directly in the following HATU promoted amide coupling without further purification. To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.033 g, 0.100 mmol, 1.0 equiv) in anhydrous DMF (2 mL) were added DIPEA (0.052 g, 0.402 mmol, 4.0 equiv) and HATU (0.038 g, 0.100 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of crude TFA salt of diamine (0.100 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as white solid (0.040 g, 0.077 mmol, 77% yield, 99.0% purity). Mp = 89–70 ºC; IR (neat) 3313, 2969, 1646, 1541 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 8.41 (d, *J* = 5.9 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.34 (m, 4H), 7.31 (d, *J* = 5.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.26 (s, 1H), 4.25 (s, 2H), 3.74 (s, 2H), 3.34 (t, *J* = 5.9 Hz, 2H), 3.24–3.15 (m, 2H), 2.95 (t, *J* = 5.8 Hz, 2H), 2.81 (t, *J* = 6.1 Hz, 2H), 2.42 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 166.9, 153.2, 150.2, 144.6, 135.7, 134.2, 133.8, 133.6, 130.3, 128.2, 128.0, 127.1, 124.8, 123.2, 56.0, 54.7, 51.1, 48.1, 44.2, 40.4, 29.4, 27.5, 21.8; HRMS (ESI) m/z calcd for $C_{29}H_{37}N_4O_3S$ $[M+H]^+$ 521.2581, found 521.2569.



2.30.1

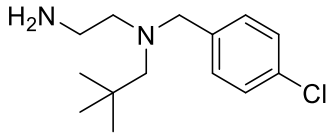
***N*-(4-Chlorobenzyl)-2,2-dimethylpropan-1-amine.** Prepared according to the general procedure for reductive amination using pivalaldehyde (1.034 g, 12.0 mmol, 1.0 equiv), methyl 4-chlorobenzylamine (1.70 g, 12.0 mmol, 1.0 equiv), $NaBH(OAc)_3$ (3.56 g, 16.8 mmol, 1.4 equiv), AcOH (1 drop) and DCE (20 mL), at room temperature for 12 h. Reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) afforded the title compound as a light yellow oil (1.68 g, 7.93 mmol, 66% yield). IR (neat) 2952, 1490 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2) δ 9.27 (br s, 1H), 7.56–7.48 (m, 2H), 7.41–7.34 (m, 2H), 4.06 (s, 2H), 2.66 (s, 2H), 1.01 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 136.1, 132.7, 129.8, 129.6, 58.6, 52.0, 31.1, 27.7; HRMS (ESI) m/z calcd for $C_{12}H_{19}ClN$ $[M+H]^+$ 212.1201, found 212.1205.



2.30.2

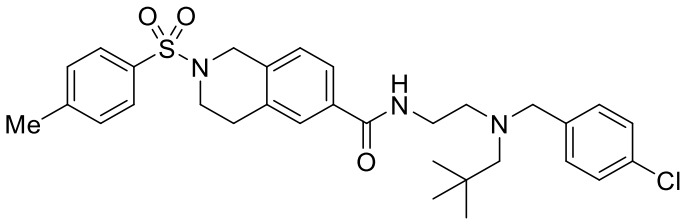
2-((4-Chlorobenzyl)(neopentyl)amino)acetonitrile. To a solution of *N*-(4-chlorobenzyl)-2,2-dimethylpropan-1-amine (1.58 g, 7.46 mmol, 1.0 equiv) in acetonitrile (20 mL) were added K_2CO_3 (2.06 g, 14.9 mmol, 2.0 equiv), KI (1.24 g, 7.46 mmol, 1.0 equiv) and chloroacetonitrile (0.62 g, 8.21 mmol, 1.1 equiv) at room temperature. The resulting mixture was stirred at this temperature overnight, then diluted with saturated aqueous Na_2CO_3. The aqueous phase was extracted with ether (3 × 50 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel chromatography (0-20% EtOAc/hexanes) afforded the title compound as a colorless oil (0.996 g, 3.97 mmol, 53% yield). IR (neat) 2953, 1484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–

7.29 (m, 4H), 3.74 (s, 2H), 3.37 (s, 2H), 2.43 (s, 2H), 0.95 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 133.7, 130.3, 129.0, 115.8, 67.0, 60.1, 44.0, 33.5, 27.9. HRMS (ESI) m/z calcd for $C_{14}H_{20}ClN_2$ $[M+H]^+$ 251.1310, found 251.1310.



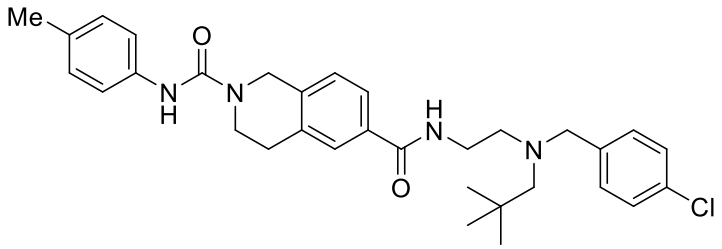
2.30.3

***N*^{1}-(4-Chlorobenzyl)-*N*^{1}-neopentylethane-1,2-diamine.** To a solution of 2-((4-chlorobenzyl)(neopentyl)amino)acetonitrile (0.687 g, 2.74 mmol, 1.0 equiv) in anhydrous THF (6 mL) was added $LiAlH_4$, (1 N in THF, 3.0 mL, 3.0 mmol, 1.1 equiv) dropwise at room temperature. The resulting mixture was stirred overnight, then gradually quenched with EtOAc and water. The solution was acidified with aqueous HCl (2 N) to pH 5, then washed with EtOAc. The aqueous phase was basified with aqueous NaOH (2 N) to pH 11, then extracted with EtOAc (3 × 50 mL), washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (0-10% CH_3OH/DCM, CH_3OH containing 10% diethylamine) afforded the title compound as colorless oil (0.370 g, 1.45 mmol, 53% yield). IR (neat) 2961, 1489 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.38–7.22 (m, 4H), 3.59 (s, 2H), 2.65 (t, *J* = 6.3 Hz, 2H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.28 (s, 2H), 0.89 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 139.9, 132.7, 130.7, 128.7, 67.9, 61.7, 60.3, 40.7, 33.4, 28.7; HRMS (ESI) m/z calcd for $C_{14}H_{24}ClN_2$ $[M+H]^+$ 255.1623, found 255.1622.



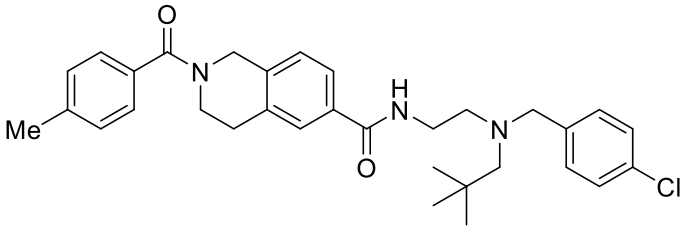
2.30

***N*-(2-((4-Chlorobenzyl)(neopentyl)amino)ethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-tosyl-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.025 g, 0.075 mmol, 1.0 equiv) in anhydrous DMF (0.5 mL) were added DIPEA (0.029 g, 0.224 mmol, 3.0 equiv) and HATU (0.031 g, 0.082 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of N^1-(4-chlorobenzyl)-N^1-neopentylethane-1,2-diamine (0.019 g, 0.075 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a yellow film (0.014 g, 0.025 mmol, 33% yield, ≥ 99% purity). IR (neat) 2950, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.45 (s, 1H), 7.41–7.34 (m, 3H), 7.29 (t, *J* = 4.2 Hz, 3H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.38 (t, *J* = 4.4 Hz, 1H), 4.32 (s, 2H), 3.63 (s, 2H), 3.47–3.34 (m, 4H), 3.00 (t, *J* = 5.8 Hz, 2H), 2.63–2.57 (m, 2H), 2.45 (s, 3H), 2.37 (s, 2H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 144.0, 138.6, 135.3, 133.8, 133.3, 133.3, 132.9, 130.3, 129.9, 128.7, 127.9, 127.8, 126.7, 124.5, 67.4, 61.0, 54.8, 47.7, 43.7, 38.0, 33.1, 29.0, 28.6, 21.7; HRMS (ESI) m/z calcd for $C_{31}H_{39}ClN_3O_3S$ $[M+H]^+$ 568.2395, found 568.2399.



2.31

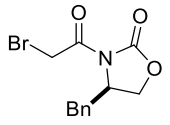
***N*^{6}-(2-((4-Chlorobenzyl)(neopentyl)amino)ethyl)-*N*^{2}-(*p*-tolyl)-3,4-dihydroisoquinoline-2,6(1*H*)-dicarboxamide.** To a solution of 2-(*p*-tolylcarbamoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.025 g, 0.081 mmol, 1.0 equiv) in anhydrous DMF (0.5 mL) were added DIPEA (0.031 g, 0.240 mmol, 3.0 equiv) and HATU (0.031 g, 0.082 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of *N*^{1}-(4-chlorobenzyl)-*N*^{1}-neopentylethane-1,2-diamine (0.021 g, 0.082 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a colorless film (0.022 g, 0.040 mmol, 50% yield, HPLC purity = 100%). IR (neat) 3320, 3222, 2948, 1633 cm^{-1}; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.51 (s, 1H), 7.44 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.29–7.26 (m, 2H), 7.26–7.21 (m, 3H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.44 (s, 1H), 6.37 (t, *J* = 5.2 Hz, 1H), 4.70 (s, 2H), 3.72 (t, *J* = 5.9 Hz, 2H), 3.63 (s, 2H), 3.39 (q, *J* = 5.6 Hz, 2H), 2.98 (t, *J* = 5.8 Hz, 2H), 2.61 (t, *J* = 6.0 Hz, 2H), 2.37 (s, 2H), 2.30 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 167.0, 155.4, 139.4, 137.5, 137.2, 136.1, 133.8, 133.2, 133.1, 130.9, 129.8, 128.9, 127.6, 127.0, 125.0, 120.8, 67.7, 61.3, 55.4, 46.3, 42.2, 38.4, 33.3, 29.6, 28.8, 21.0; HRMS (ESI) m/z calcd for $C_{32}H_{40}ClN_4O_2$ $[M+H]^+$ 547.2834, found 547.2838.



2.32

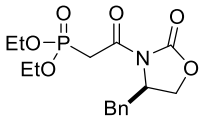
***N*-(2-((4-Chlorobenzyl)(neopentyl)amino)ethyl)-2-(4-methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxamide.** To a solution of 2-(4-methylbenzoyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid (0.024 g, 0.080 mmol, 1.0 equiv) in anhydrous DMF (0.5 mL) were added DIPEA (0.031 g, 0.240 mmol, 3.0 equiv) and HATU (0.030 g, 0.079 mmol, 1.0 equiv) at room temperature. The mixture was stirred for 5 min, followed by addition of N^1-(4-chlorobenzyl)-N^1-neopentylethane-1,2-diamine (0.020 g, 0.078 mmol, 1.0 equiv). The reaction was stirred for 12 h at room temperature, then concentrated under N_2 stream. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title compound as a white solid (0.022 g, 0.041 mmol, 53% yield, HPLC purity = 98.6%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.21 (t, J = 5.4 Hz, 1H), 7.66–7.53 (m, 2H), 7.47–7.19 (m, 9H), 4.72 (br s, 2H), 3.95–3.47 (m, 5H), 3.33 (q, J = 6.1 Hz, 2H), 2.87 (s, 2H), 2.61–2.52 (m, 2H), 2.39–2.28 (m, 5H), 0.83 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.5, 165.6, 139.2, 139.0, 136.1, 134.2, 133.0, 132.7, 131.1, 130.1, 128.8, 127.9, 127.4, 126.8, 126.2, 124.7, 66.4, 59.5, 54.8, 44.4, 40.1, 37.2, 32.7, 28.7, 27.9, 20.8. HRMS (ESI) m/z calcd for $C_{32}H_{39}ClN_3O_2$ $[M+H]^+$ 532.2725, found 532.7726

Procedure for Chapter 3



3.14

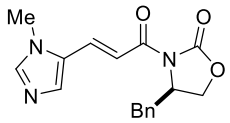
(*R*)-4-Benzyl-3-(2-bromoacetyl)oxazolidin-2-one. To a solution of (*R*)-4-benzyloxazolidin-2-one (10.63 g, 60.0 mmol, 1.0 equiv) in THF (300 mL) was added *n*-BuLi (2.5 N in hexanes, 25.20 mL, 63.0 mmol, 1.05 equiv) dropwise at –78 °C. The mixture was stirred for 1 h at this temperature, followed by addition of neat bromoacetyl bromide (12.72 g, 63.0 mmol, 1.05 equiv) at –78 °C. The reaction was slowly warmed to room temperature and stirred for 3 h, followed by quenching with aqueous NH_4Cl solution at –20 °C. The aqueous layer was extracted with EtOAc (3 × 200 mL), then the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Normal phase flash column chromatography (0-40% EtOAc/hexanes) afforded the title compound as yellow oil (15.98 g, 53.6 mmol, 89% yield). $[\alpha]_D^{20}$ = −71.2 (*c* 1.0, $CHCl_3$); IR (neat) 3029, 1774, 1698 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.39–7.23 (m, 5H), 4.80 (m, 1H), 4.61 (AB q, $\Delta\delta_{AB}$ = 0.10, *J* = 12.8 Hz, 2H), 4.44 (m, 1H), 4.31 (dd, *J* = 8.9, 3.2 Hz, 1H), 3.20 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.99 (dd, *J* = 13.6, 8.2 Hz, 1H); ^{13}C NMR (101 MHz, acetone-d_6) δ 166.5, 154.1, 136.5, 130.5, 129.6, 127.9, 67.5, 56.0, 37.7, 29.6; HRMS (ESI) m/z calcd for $C_{12}H_{13}BrNO_3$ $[M+H]^+$ 298.0073, found 298.0073.



3.15

(*R*)-Diethyl 2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethylphosphonate. A mixture of (*R*)-4-benzyl-3-(2-bromoacetyl)oxazolidin-2-one (15.780 g, 52.90 mmol, 1.0 equiv) and triethyl phosphite (17.58 g, 105.8 mmol, 2.0 equiv) was heated under reflux for 2 h. The mixture was

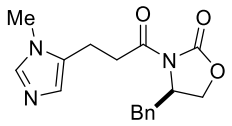
cooled to room temperature and loaded directly on silica gel column for purification (0-100% EtOAc/hexanes) to afford the title compound as a light yellow oil (14.57 g, 41.0 mmol, 78% yield). $[\alpha]_D^{20} = -44.0$ (*c* 0.5, $CHCl_3$); IR (neat) 2985, 1776, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.15 (m, 5H), 4.75–4.64 (m, 1H), 4.26–4.10 (m, 6H), 3.90–3.67 (m, 2H), 3.32 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.8 Hz, 1H), 1.34 (td, *J* = 7.1, 0.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 164.9, 153.3, 135.1, 129.4, 128.9, 127.3, 66.0, 62.7, 62.7, 55.4, 37.6, 35.0, 33.7, 16.3, 16.3; HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_6P$ $[M+H]^+$ 356.1258, found 356.1251.



3.16

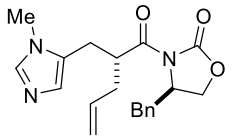
(*R*,*E*)-4-Benzyl-3-(3-(1-methyl-1*H*-imidazol-5-yl)acryloyl)oxazolidin-2-one. To a solution of diethyl (*R*)-(2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)phosphonate (14.32 g, 40.3 mmol, 1.05 equiv) in anhydrous THF (200 mL), was added NaH (60% dispersion in mineral oil, 1.61 g, 40.3 mmol, 1.05 equiv) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and 45 min at room temperature. This solution was cooled to –78 °C prior to addition of 1-methyl-1H-imidazole-5-carbaldehyde (4.230 g, 38.38 mmol, 1.0 equiv) in anhydrous THF (200 mL). The reaction was slowly warmed to room temperature and stirred for 3 h, followed by quenching with water at 0 °C. The mixture was extracted with EtOAc (3 × 200 mL), then combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified via flash column chromatography (0-80% EtOAc/hexanes) to afford title compound as a white solid (7.34 g, 23.6 mmol, 61% yield). Mp = 120–122 °C; $[\alpha]_D^{20} = +66.0$ (*c* 1.0, $CHCl_3$); IR (neat)

3029, 1768, 1672, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (AB q, $\Delta\delta_{AB}$ = 0.03, *J* = 15.9 Hz, 2H), 7.57 (s, 1H), 7.55 (s, 1H), 7.39–7.20 (m, 5H), 4.85–4.74 (m, 1H), 4.29–4.17 (m, 2H), 3.79 (s, 3H), 3.36 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.84 (dd, *J* = 13.4, 9.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 153.7, 141.9, 135.4, 135.0, 131.4, 129.6, 129.2, 129.1, 127.5, 114.3, 66.3, 55.6, 38.1, 33.0; HRMS (ESI) m/z calcd for $C_{17}H_{18}N_3O_3$ $[M+H]^+$ 312.1343, found 312.1338.



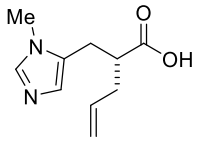
3.17

(*R*)-4-Benzyl-3-(3-(1-methyl-1*H*-imidazol-5-yl)propanoyl)oxazolidin-2-one. A round-bottom flask was flushed with N_2, then charged with a solution of (*R*,*E*)-4-benzyl-3-(3-(1-methyl-1*H*-imidazol-5-yl)acryloyl)oxazolidin-2-one (5.00 g, 16.1 mmol, 1.0 equiv) in EtOAc (160 mL) and Pd/C (0.500 g, 10 wt%). The resulting suspension was and stirred under an H_2 atmosphere (balloon) at room temperature for 16 h. The mixture was filtered through Celite, and concentrated to afford the title product as a yellow oil (5.03 g, 16.1 mmol, 100% yield). $[\alpha]_D^{20} = -65.2$ (*c* 0.5, $CHCl_3$); IR (neat) 2982, 1776, 1733, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 4H), 7.20–7.14 (m, 2H), 6.83 (s, 1H), 4.71–4.61 (m, 1H), 4.27–4.13 (m, 2H), 3.61 (s, 3H), 3.37–3.20 (m, 3H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 153.6, 137.9, 135.2, 130.5, 129.5, 129.1, 127.5, 126.7, 66.5, 55.3, 38.0, 34.6, 31.4, 18.7; HRMS (ESI) m/z calcd for $C_{17}H_{20}N_3O_3$ $[M+H]^+$ 314.1499, found 314.1496.



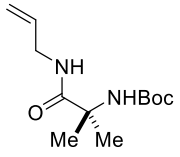
3.18

(*R*)-4-Benzyl-3-((*R*)-2-((1-methyl-1*H*-imidazol-5-yl)methyl)pent-4-enoyl)oxazolidin-2-one. To a solution of (*R*)-4-benzyl-3-(3-(1-methyl-1H-imidazol-5-yl)propanoyl)oxazolidin-2-one (5.02 g, 16.0 mmol, 1.0 equiv) in anhydrous THF (140 mL) was added NaHMDS (1 N in THF, 17.62 mL, 17.62 mmol, 1.1 equiv) dropwise over 10 min at −78 °C. The resulting mixture was warmed to room temperature and stirred for 1 h. The mixture was cooled to −78 °C, followed by slow addition of allyl iodide (4.31 g, 25.6 mmol, 1.6 equiv) at this temperature. The reaction was stirred at −78 °C for 1 h, followed by another 2 h of stirring at −20 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at −20 °C and slowly warmed to room temperature while stirring. The reaction mixture was extracted with EtOAc (3 × 100 mL), then the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified with reverse-phase flash column chromatography (0–100% CH_3CN/H_2O) to afford title product as yellow oil (3.55 g, 10.1 mmol, 63% yield). $[\alpha]_D^{20}$ = −95.2 (*c* 1.1, $CHCl_3$); IR (neat) 1770, 1692, 1502 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.37–7.23 (m, 4H), 7.23–7.18 (m, 2H), 6.69 (s, 1H), 5.87 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.21–5.08 (m, 2H), 4.67–4.53 (m, 1H), 4.30–4.19 (m, 1H), 4.11–4.03 (m, 2H), 3.56 (s, 3H), 3.20 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.97 (dd, *J* = 15.0, 9.9 Hz, 1H), 2.79–2.68 (m, 2H), 2.63–2.51 (m, 1H), 2.43–2.32 (m, 1H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 175.2, 153.7, 138.3, 136.0, 135.3, 130.0, 129.8, 129.3, 127.7, 127.6, 118.1, 66.7, 55.8, 42.3, 38.5, 37.1, 31.7, 26.2; HRMS (ESI) m/z calcd for $C_{20}H_{24}N_3O_3$ $[M+H]^+$ 354.1812, found 354.1806.



3.19

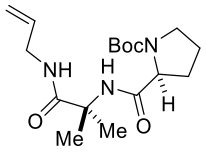
(*R*)-2-((1-Methyl-1*H*-imidazol-5-yl)methyl)pent-4-enoic acid. To a solution of (*R*)-4-benzyl-3-((*R*)-2-((1-methyl-1H-imidazol-5-yl)methyl)pent-4-enoyl)oxazolidin-2-one (3.00 g, 8.49 mmol, 1.0 equiv) in THF (42.5 mL), was added a solution of LiOH (0.713 g, 17.0 mmol) and H_2O_2 (30% weight in water, 4.25 mL, 41.6 mmol, 4.9 equiv) in H_2O (42.5 mL) at 0 °C. The reaction was stirred for 2 h, followed by quenching with saturated aqueous solution of Na_2SO_3 at 0 °C, and concentrated *in vacuo*. The residue was purified with reverse-phase flash column chromatography (0−100% CH_3CN/H_2O) to afford the title compound as colorless oil. (1.481 g, 8.49 mmol, 90% yield). $[\alpha]_D^{20}$ = +6.2 (*c* 0.5, EtOH); IR (neat) 3364, 1590 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.45 (s, 1H), 6.76 (s, 1H), 5.91–5.80 (m, 1H), 5.05 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.98 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 3.61 (s, 3H), 2.86 (dd, *J* = 15.3, 8.9 Hz, 1H), 2.63 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.57–2.49 (m, 1H), 2.44–2.35 (m, 1H), 2.27–2.17 (m, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 182.7, 138.4, 138.1, 132.8, 126.7, 116.4, 49.4, 38.5, 31.6, 27.4; HRMS (ESI) m/z calcd for $C_{10}H_{15}N_2O_2$ $[M+H]^+$ 195.1128, found 195.1129.



3.20

***tert*-Butyl (1-(allylamino)-2-methyl-1-oxopropan-2-yl)carbamate.** To a solution of α-(Boc-amino)isobutyric acid (6.10 g, 30.0 mmol, 1.0 equiv) in DCM (150 mL), were added DIPEA

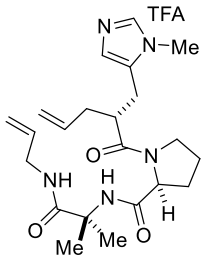
(11.63 g, 90.0 mmol, 3.0 equiv) and HATU (11.41 g, 30.0 mmol, 1.0 equiv) at room temperature. The resulting mixture was stirred for 5 min, followed by addition of allylamine (1.71 g, 30.0 mmol, 1.0 equiv) dropwise at room temperature. The reaction was stirred for 12 h, then diluted with water. The aqueous layer was extracted with DCM (2 × 100 mL), then the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified with reverse-phase flash column chromatography to afford the title compound as a white solid (4.79 g, 19.8 mmol, 66% yield). Mp = 123−124 °C; IR (neat) 3321, 1684, 1656 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 6.57 (s, 1H), 5.83 (ddt, *J* = 17.2, 10.3, 5.5 Hz, 1H), 5.20 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.11 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.89 (s, 1H), 3.88 (tt, *J* = 5.7, 1.6 Hz, 2H), 1.49 (s, 6H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CHCl_3$) δ 174.6, 154.9, 134.4, 116.2, 80.4, 57.0, 42.1, 28.4, 25.9; HRMS (ESI) m/z calcd for $C_{12}H_{22}N_2NaO_3$ $[M+Na]^+$ 265.1523, found 265.1522.



3.21

***tert*-Butyl (*S*)-2-((1-(allylamino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate.** To a solution of *tert*-butyl (1-(allylamino)-2-methyl-1-oxopropan-2-yl)carbamate (3.16 g, 13.0 mmol, 1.0 equiv) in DCM (26 mL) was added TFA (26 mL) at room temperature. The resulting mixture was stirred for 3 h at room temperature, then concentrated *in vauco* to afford a crude TFA salt of *N*-allyl-2-amino-2-methylpropanamide, which was used directly in the subsequent HATU promoted amide coupling without further purification. To a solution of *N*-Boc-L-proline (2.81 g, 13.0 mmol, 1.0 equiv) in DCM (35 mL), were added DIPEA (6.74 g, 52.2 mmol,

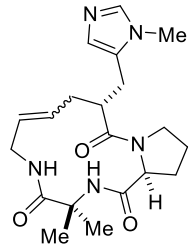
4.0 equiv) and HATU (4.96 g, 13.0 mmol, 1.0 equiv) at room temperature. The resulting mixture was stirred at room temperature for 5 min, followed by addition of the previously obtained TFA salt of *N*-allyl-2-amino-2-methylpropanamide (13.04 mmol, 1.0 equiv). The reaction was stirred for 12 h, then concentrated. The crude sample was purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the title as a white solid (2.64 g, 7.78 mmol, 60% yield). mp = 161−164 °C; $[\alpha]_D^{20}$ = −27.0 (*c* 0.5, DMSO); IR (neat) 3321, 2978, 1674, 1656, 1537 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6, 40 ºC) δ 8.22–7.67 (m, 1H), 7.51 (s, 1H), 5.85–5.65 (m, 1H), 5.19–5.08 (m, 1H), 5.08–4.94 (m, 1H), 4.14–4.00 (m, 1H), 3.81–3.51 (m, 2H), 3.41–3.26 (m, 2H), 2.16–1.63 (m, 4H), 1.57–1.14 (m, 15H); major rotamer ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 171.8, 154.1, 135.2, 114.5, 79.1, 59.7, 56.2, 46.8, 41.0, 29.5, 28.1, 26.6, 24.2, 24.2; minor rotamer ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.7, 171.7, 153.3, 135.4, 114.5, 78.4, 59.6, 55.8, 46.5, 41.1, 30.7, 28.0, 25.5, 24.3, 23.0; HRMS (ESI) m/z calcd for $C_{17}H_{29}N_3NaO_4$ $[M+Na]^+$ 362.2050, found 362.2050.



3.22

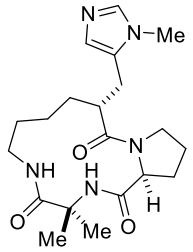
(*S*)-*N*-(1-(Allylamino)-2-methyl-1-oxopropan-2-yl)-1-((*R*)-2-((1-methyl-1*H*-imidazol-5-yl)methyl)pent-4-enoyl)pyrrolidine-2-carboxamide 2,2,2-trifluoroacetate. To a solution of *tert*-butyl (*S*)-2-((1-(allylamino)-2-methyl-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (2.60 g, 7.66 mmol, 1.0 equiv) in DCM (16 mL) was added TFA (16 mL) at room

temperature. The resulting mixture was stirred for 3 h. The reaction was concentrated *in vacuo* to afford a TFA salt of (*S*)-*N*-(1-(allylamino)-2-methyl-1-oxopropan-2-yl)pyrrolidine-2-carboxamide, which was used directly in the subsequent HATU promoted amide coupling without further purification. To the solution of (*R*)-2-((1-methyl-1*H*-imidazol-5-yl)methyl)pent-4-enoic acid (1.49 g, 7.66 mmol, 1.0 equiv) and DIPEA (4.95 g, 38.3 mmol, 5.0 equiv) in anhydrous DMF (50 mL) was added HATU (2.91 g, 7.66 mmol, 1.0 equiv) at room temperature. The resulting mixture was stirred for 5 min, followed by addition of the TFA salt of (*S*)-*N*-(1-(allylamino)-2-methyl-1-oxopropan-2-yl)pyrrolidine-2-carboxamide (7.66 mmol, 1.0 equiv) in anhydrous DMF (20 mL). After stirred for 12 h at room temperature, the reaction was concentrated under an N_2 stream. The residue was purified with reverse-phase flash column chromatography (0–100% CH_3CN/0.5% TFA in H_2O) to afford the title product as a yellow foam (1.969 g, 3.84 mmol, 50% yield). mp = 42−44 °C. $[\alpha]_D^{20} = -56.1$ (*c* 1.0, $CHCl_3$); IR (neat) 3326, 2980, 1625 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.53 (br s, 1H), 6.70 (br s, 1H), 5.94–5.76 (m, 2H), 5.26–5.01 (m, 4H), 4.21 (dd, *J* = 7.7, 6.3 Hz, 1H), 3.85 (ddt, *J* = 16.0, 5.2, 1.8 Hz, 1H), 3.71 (ddt, *J* = 15.9, 5.3, 1.8 Hz, 1H), 3.65–3.52 (m, 4H), 3.22 (ddd, *J* = 9.8, 7.3, 5.2 Hz, 1H), 3.02–2.71 (m, 3H), 2.53–2.40 (m, 1H), 2.32–2.17 (m, 1H), 2.14–1.94 (m, 2H), 1.93–1.81 (m, 1H), 1.78–1.64 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 176.8, 175.4, 174.3, 138.8, 136.6, 135.6, 131.6, 126.8, 117.8, 115.8, 61.9, 58.2, 48.9, 44.8, 43.1, 38.0, 31.7, 30.2, 27.4, 26.5, 26.0, 24.3; HRMS (ESI) m/z calcd for for $C_{22}H_{34}N_5O_3$ $[M+H]^+$ 416.2656, found 416.2650.



3.23
mixture of *cis*/*trans* isomers

(10*R*,15a*S*,*E*)-3,3-dimethyl-10-((1-methyl-1*H*-imidazol-5-yl)methyl)-2,3,5,6,9,10,13,14,15,15a-decahydro-1*H*-pyrrolo[1,2-a][1,4,7]triazacyclotridecine-1,4,11-trione (*trans*-3.23) and (10*R*,15a*S*,*Z*)-3,3-dimethyl-10-((1-methyl-1*H*-imidazol-5-yl)methyl)-2,3,5,6,9,10,13,14,15,15a-decahydro-1*H*-pyrrolo[1,2-a][1,4,7]triazacyclotridecine-1,4,11-trione (*cis*-3.23). To a solution of **3.22** (1.960 g, 3.82 mmol, 1.0 equiv) in anhydrous DCM (350 mL) was added Hoveyda-Grubbs 2 catalyst (0.359 g, 0.574 mmol, 0.15 equiv) at room temperature, then stirred for 15 h at this temperature. The reaction was quenched by addition of DMSO (7.470 g, 96.0 mmol, 25.0 equiv), and stirred for 2 h. The mixture was concentrated *in vacuo* to remove DCM, with residue purified with reverse-phase flash column chromatography (0-100% CH_3CN/H_2O) to afford the majority of products as inseparable mixture of cis/trans isomers (0.460 g, 1.19 mmol, 31% yield). Only small fraction of trans-**3.23** was isolated (0.002 g), which was characterized with ^{1}H NMR and HRMS. ^{1}H NMR (600 MHz, CD_3OD) δ 7.50 (s, 1H), 6.67 (s, 1H), 5.68 (ddd, *J* = 15.1, 10.0, 5.0 Hz, 1H), 5.30 (ddd, *J* = 15.1, 9.6, 5.2 Hz, 1H), 4.39 (dd, *J* = 8.5, 3.7 Hz, 1H), 4.13 (dd, *J* = 12.7, 5.2 Hz, 1H), 3.72 (dd, *J* = 6.2, 3.7 Hz, 1H), 3.65 (s, 3H), 3.55 (dt, *J* = 10.0, 6.8 Hz, 1H), 3.19 (dd, *J* = 12.6, 9.7 Hz, 1H), 3.11 (dd, *J* = 15.2, 10.0 Hz, 1H), 2.72–2.64 (m, 1H), 2.40 (ddd, *J* = 13.2, 10.0, 5.3 Hz, 1H), 2.35–2.23 (m, 2H), 2.03 (dq, *J* = 14.5, 9.3, 8.3 Hz, 1H), 1.95–1.86 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H); HRMS (ESI) m/z calcd for for $C_{20}H_{30}N_5O_3$ $[M+H]^+$ 388.2343, found 388.2344.

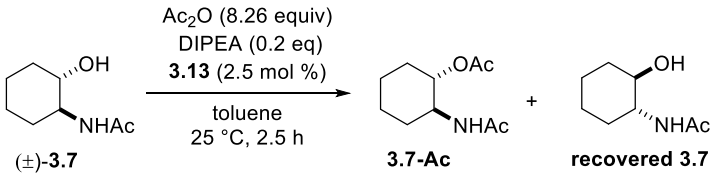


3.13

(10*R*,15*aS*)-3,3-dimethyl-10-((1-methyl-1H-imidazol-5-yl)methyl)dodecahydro-1*H*-pyrrolo[1,2-*a*][1,4,7]triazacyclotridecine-1,4,11-trione. A solution of **3.23** (0.460 g, 1.187 mmol, 1.0 equiv) in CH_3OH (40 mL) was stirred under an H_2 atmosphere (balloon) for 18 h. The reaction nixture was filtered through Celite, then concentrated in vacuo to afford the title compound as a white solid (0.460 g, 1.18 mmol, 100% yield). Mp = 163−165 °C. $[\alpha]_D^{20}$ = −24.0 (*c* 0.5, EtOH); IR (neat) 3326, 2944, 1667, 1613 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.52 (s, 1H), 6.71 (s, 1H), 4.50 (dd, *J* = 7.8, 5.8 Hz, 1H), 3.64 (s, 3H), 3.59 (ddd, *J* = 13.8, 5.0, 2.3 Hz, 1H), 3.50 (dt, *J* = 9.8, 7.6 Hz, 1H), 3.03–2.68 (m, 5H), 2.17–1.99 (m, 2H), 1.92 (dtd, *J* = 12.8, 7.0, 5.4 Hz, 1H), 1.81–1.32 (m, 11H), 1.30–1.01 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.0, 176.8, 174.7, 139.0, 131.5, 127.1, 61.3, 58.8, 48.7, 37.2, 31.6, 30.6, 29.0, 28.3, 27.3, 27.3, 26.3, 23.3, 21.6; HRMS (ESI) m/z calcd for for $C_{20}H_{32}N_5O_3$ $[M+H]^+$ 390.2500, found 390.2500. The structure was confirmed with single crystal X-ray experiment (see appendices)

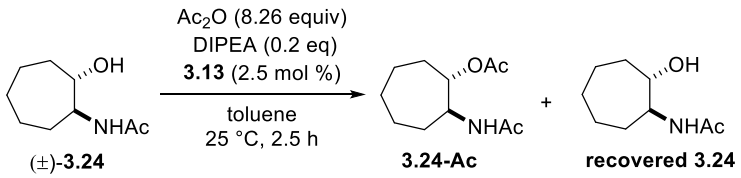
General Procedure for the Kinetic Resolution of Racemic Alcohols. A stock solution of catalyst was prepared by dissolving **3.13** (0.025 g, 0.064 mmol) in anhydrous DCM (20 mL). A stock solution of DIPEA was prepared by dissolving the base (0.033 g, 0.26 mmol) in anhydrous toluene (1 mL). A solution of substrate was prepared by dissolving alcohol (0.128 mmol, 1.0 equiv) in anhydrous toluene (12.8 mL). To an oven-dried flask was added 1.0 mL of catalyst solution

(0.0032 mmol, 2.5 mol %), followed by removal of DCM *in vacuo*. To the flask containing catalyst was added the previously prepared substrate solution. The resulting mixture was stirred at 25 °C for 30 min, then DIPEA (0.10 mL of stock solution, 0.026 mmol, 0.2 equiv) and Ac_2O (0.108 g, 1.058 mmol, 8.26 equiv) were introduced. During the reaction, aliquot of 0.05 mL were removed per 15 min, quenched with 0.05 mL of CH_3OH, and directed monitored by chiral HPLC in order to estimate an appropriate time to quench the reaction. The reaction was quenched with 10 mL of CH_3OH, concentrated *in vacuo*, and purified with reverse-phase flash column chromatography (0–100% CH_3CN/H_2O) to afford the product and recovered starting material. The enantiomeric excess of both product and recovered starting material was obtained by chiral HPLC analysis. Conversion and selectivity factor *s* were calculated by the method of Kagan.[22]



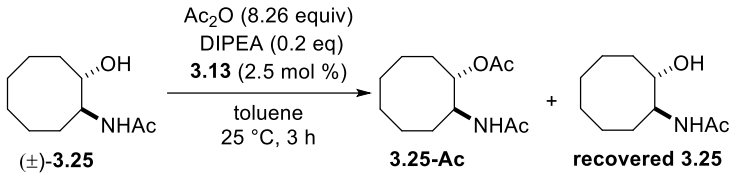
***trans*-2-Acetamidocyclohexyl acetate (3.7-Ac).** The reaction was quenched at 2.5 h and afforded **3.7-Ac** (0.010 g, 0.050 mmol, 39%) and **recovered 3.7** (0.010 g, 0.064 mmol, 50%) after purification. IR (neat) 3282, 1729, 1731, 1642, 1556 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.73 (d, *J* = 8.2 Hz, 1H), 4.62 (ddd, *J* = 11.2, 10.1, 4.6 Hz, 1H), 3.83 (dddd, *J* = 11.2, 10.1, 8.2, 4.3 Hz, 1H), 2.01 (s, 4H), 1.89 (s, 4H), 1.78–1.71 (m, 1H), 1.70–1.61 (m, 1H), 1.5–1.40 (m, 1H), 1.37–1.20 (m, 2H), 1.19–1.08 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.0, 169.8, 74.8, 53.0, 32.2, 31.2, 24.2, 23.5, 21.3; HRMS (ESI) m/z calcd for $C_{10}H_{18}NO_3$ $[M+H]^+$ 200.1281, found 200.1278. Chiral HPLC analysis of **3.7-Ac**: **3.7-Ac** was hydrolyzed with NaOH (1 N in 1:1 EtOH-H_2O) to

free alcohol (**3.7**) for *ee* analysis. Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1 mL/min, isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 20.3 min (1*R*, 2*R*, minor), 25.9 (1*S*, 2*S*, major). Chiral HPLC analysis of **recovered 3.7**: Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1 mL/min, isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 19.7 min (1*R*,2*R*, major), 26.5 (1*S*,2*S*, minor). The absolute configuration was determined by comparing with the t_R of **(1*R*,2*R*)-3.7** (18.9 min) and t_R of racemic **3.7** (20.2 min, 26.8 min) under the same conditions.

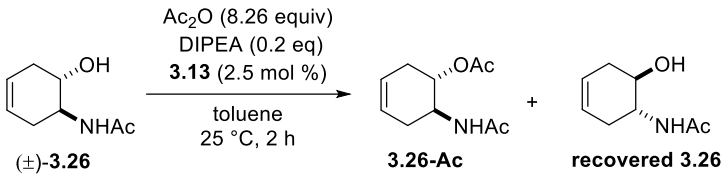


***trans*-2-Acetamidocycloheptyl acetate (3.24-Ac).** The reaction was quenched at 2.5 h and afforded **3.24-Ac** (0.010 g, 0.047 mmol, 37%) and **recovered 3.24** (0.011 g, 0.064 mmol, 50%) after purification.IR (neat) 3272, 2931, 1731, 1646 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 7.4 Hz, 1H), 4.84–4.74 (m, 1H), 4.00 (qd, *J* = 9.0, 3.4 Hz, 1H), 2.02 (s, 3H), 1.91 (s, 3H), 1.86–1.43 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 169.6, 77.6, 55.4, 31.6, 31.5, 27.8, 24.1, 23.5, 22.6, 21.4; HRMS (ESI) m/z calcd for $C_{11}H_{20}NO_3$ $[M+H]^+$ 214.1438, found 214.1436. Chiral HPLC analysis of **3.24-Ac**: **3.24-Ac** was inseparable with all methods surveyed, which was then hydrolyzed with NaOH (1 N in 1:1 EtOH/H_2O) to free alcohol (**3.24**) for *ee* analysis. Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1 mL/min, isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 21.6 min (1*R*, 2*R*, minor), 27.1 (1*S*, 2*S*, major). Chiral HPLC analysis of **recovered 3.24**: Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1 mL/min,

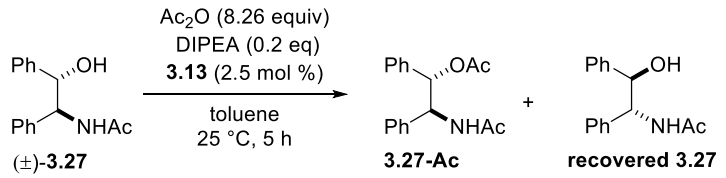
isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 21.9 min (1*R*,2*R*, major), 29.3 (1*S*,2*S*, minor). The absolute configuration was determined by comparing with the t_R of **(1*S*,2*S*)-3.24** (28.4 min) and t_R of racemic **3.24** (21.7 min, 28.7 min) at the same conditions.



***trans*-2-Acetamidocyclooctyl acetate (3.25-Ac).** The reaction was quenched at 3.0 h and afforded **3.25-Ac** (0.014 g, 0.062 mmol, 48%) and **recovered 3.25** (0.010 g, 0.054 mmol, 42%) after purification. IR (neat) 3287, 2926, 1647, 1556 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.90 (ddd, *J* = 10.0, 6.9, 2.1 Hz, 1H), 4.13 (ddd, *J* = 10.0, 7.2, 2.8 Hz, 1H), 1.98 (s, 3H), 1.90 (s, 3H), 1.88–1.43 (m, 12H). ^{13}C NMR (101 MHz, CD_3OD) δ 172.6, 172.5, 78.1, 53.5, 31.7, 30.0, 26.7, 26.7, 26.1, 25.3, 22.6, 21.1; HRMS (ESI) m/z calcd for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1594, found 228.1591. Chiral HPLC analysis of **3.25-Ac**: Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1 mL/min, isocratic (2% isopropanol/hexanes), detector wavelength (220 nm); t_R = 16.8 min (1*R*,2*R*, minor), 20.1 (1*S*,2*S*, major). Chiral HPLC analysis of **recovered 3.25**: Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1 mL/min, isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 18.5 min (1*R*, 2*R*, major), 24.3 (1*S*, 2*S*, minor). The absolute configuration was determined by comparing the specific optical rotation of **recovered 3.25** $[\alpha]_D^{20}$ = −9.1 (c 0.2, EtOH) with reported (1*S*,2*S*)-2-amino-cyclooctanol $[\alpha]_D^{20}$ = +19 (c 0.765, EtOH).[23]



***trans*-6-Acetamidocyclohex-3enyl acetate (3.26-Ac).** The reaction was quenched at 2.0 h and afforded **3.26-Ac** (0.006 g, 0.030 mmol, 24%) and **recovered 3.26** (0.013 g, 0.084 mmol, 65%) after purification. IR (neat) 3283, 1729, 1650, 1548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (d, J = 7.1 Hz, 1H), 5.63–5.53 (m, 2H), 4.97 (ddd, J = 9.9, 8.6, 5.9 Hz, 1H), 4.26–4.14 (m, 1H), 2.65–2.52 (m, 1H), 2.49–2.37 (m, 1H), 2.35 – 2.24 (m, 1H), 2.06 (d, J = 0.4 Hz, 3H), 2.02–1.91 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.0, 124.8, 124.1, 71.0, 49.0, 31.8, 30.7, 23.5, 21.3; HRMS (ESI) m/z calcd for $C_{10}H_{15}NNaO_3$ $[M+Na]^+$ 220.0944, found 220.0941. Chiral HPLC analysis of **3.26-Ac**: Chiralpak IC analytical column (4.6 × 250 mm), flow rate 0.6 mL/min, isocratic (10% isopropanol/hexanes), detector wavelength (220 nm); t_R = 26.4 min (major), 36.2 (minor). Chiral HPLC analysis of **recovered 3.26**: Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1.0 mL/min, isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 19.4 min (major), 27.0 (minor). The absolute configuration was not determined.



(1*S*,2*S*)-rel-2-acetamido-1,2-diphenylethyl acetate (3.27-Ac). The reaction was quenched at 5.0 h and afforded **3.27-Ac** (0.008 g, 0.027 mmol, 21%) and **recovered 3.27** (0.021 g, 0.082 mmol, 64%) after purification. IR (neat) 3273, 1736, 1649, 1541 cm^{-1}; ^1H NMR (400 MHz,

CD_3OD) δ 7.30–7.13 (m, 10H), 5.98 (d, *J* = 7.2 Hz, 1H), 5.38 (d, *J* = 7.2 Hz, 1H), 2.05 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 172.8, 171.6, 139.9, 139.0, 129.3, 129.2, 129.1, 128.6, 128.6, 128.1, 79.2, 58.9, 22.4, 20.8; HRMS (ESI) m/z calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 298.1438, found 298.1439. Chiral HPLC analysis of **3.27-Ac**: Chiralpak IA analytical column (4.6 × 250 mm), flow rate 1.0 mL/min, isocratic (5% isopropanol/hexanes), detector wavelength (220 nm); t_R = 22.8 min (minor), 27.3 (major). Chiral HPLC analysis of **recovered 3.27**: Chiralpak IC analytical column (4.6 × 250 mm), flow rate 0.6 mL/min, isocratic (10% isopropanol/hexanes), detector wavelength (220 nm); t_R = 26.1 min (minor), 34.6 (major). The absolute configuration was not determined.

Appendices

X-ray crystallographic data of trans-1.49

Table A1.1. Crystal data and structure refinement for trans-1.49

Identification code	v74b	
Empirical formula	C25 H35 N3 O4	
Formula weight	441.56	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.9057(9) Å	α= 90°.
	b = 18.4019(15) Å	β= 112.106(2)°.
	c = 12.5970(10) Å	γ = 90°.
Volume	2342.2(3) $Å^3$	
Z	4	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.684 mm^{-1}	
F(000)	952	
Crystal size	0.250 x 0.090 x 0.040 mm^3	
Theta range for data collection	4.486 to 68.108°.	
Index ranges	-10<=h<=13, -19<=k<=22, -14<=l<=10	
Reflections collected	15007	
Independent reflections	4154 [R(int) = 0.0229]	
Completeness to theta = 66.000°	99.4 %	

Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.876
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4154 / 0 / 429
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1168
R indices (all data)	R1 = 0.0497, wR2 = 0.1214
Extinction coefficient	n/a
Largest diff. peak and hole	0.540 and -0.276 e.$Å^{-3}$

Table A1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for trans-1.49. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3368(2)	1714(1)	3478(2)	28(1)
C(2)	3842(2)	1210(1)	4548(2)	33(1)
C(3)	3030(2)	498(1)	4307(2)	41(1)
C(4)	3159(2)	74(1)	3316(2)	43(1)
C(5)	2657(2)	529(1)	2228(2)	38(1)
C(6)	3341(2)	1265(1)	2406(2)	34(1)
C(7)	3825(2)	1554(1)	5639(2)	37(1)
N(8)	4293(1)	2342(1)	3631(1)	23(1)
C(9)	3906(2)	2873(1)	2818(1)	24(1)
O(10)	2844(1)	2867(1)	1999(1)	30(1)
C(11)	4788(2)	3527(1)	2940(1)	24(1)
N(12)	4978(1)	3970(1)	3833(1)	27(1)
C(13)	5632(2)	4591(1)	3868(2)	30(1)
C(14)	6131(2)	4787(1)	3052(2)	35(1)
C(15)	5952(2)	4316(1)	2149(2)	37(1)
C(16)	5258(2)	3679(1)	2084(2)	30(1)
C(17)	5700(2)	2292(1)	4401(1)	24(1)
C(18)	6533(2)	1823(1)	3984(1)	26(1)
O(19)	6550(1)	1976(1)	2922(1)	31(1)

C(20)	7496(2)	1529(1)	2790(2)	38(1)
C(21)	8048(2)	1111(1)	3721(2)	37(1)
C(22)	7418(2)	1296(1)	4495(2)	31(1)
C(23)	1984(2)	2028(1)	3308(1)	27(1)
O(24)	972(1)	1711(1)	2682(1)	34(1)
N(25)	1946(2)	2616(1)	3909(1)	28(1)
C(26)	720(2)	2964(1)	3836(2)	30(1)
C(27)	293(2)	2685(1)	4787(2)	35(1)
C(28)	-944(2)	3074(1)	4780(2)	44(1)
C(29)	-736(2)	3890(1)	4861(2)	44(1)
C(30)	-365(2)	4164(1)	3883(2)	42(1)
C(31)	886(2)	3788(1)	3885(2)	35(1)
O(1W)	4013(1)	3532(1)	5595(1)	32(1)

Table A1.3. Bond lengths [Å] and angles [°] for trans-1.49

C(1)-N(8)	1.498(2)
C(1)-C(23)	1.554(2)
C(1)-C(2)	1.555(2)
C(1)-C(6)	1.573(3)
C(2)-C(7)	1.518(3)
C(2)-C(3)	1.547(3)
C(2)-H(2)	1.06(2)
C(3)-C(4)	1.523(3)
C(3)-H(3A)	1.02(3)
C(3)-H(3B)	1.00(2)
C(4)-C(5)	1.521(3)
C(4)-H(4A)	1.05(3)
C(4)-H(4B)	1.11(3)
C(5)-C(6)	1.522(3)
C(5)-H(5A)	1.09(2)
C(5)-H(5B)	1.06(2)
C(6)-H(6A)	1.06(2)
C(6)-H(6B)	0.99(2)
C(7)-H(7A)	1.09(3)
C(7)-H(7B)	1.00(2)
C(7)-H(7C)	1.05(3)
N(8)-C(9)	1.363(2)

N(8)-C(17)	1.478(2)
C(9)-O(10)	1.227(2)
C(9)-C(11)	1.512(2)
C(11)-N(12)	1.340(2)
C(11)-C(16)	1.386(2)
N(12)-C(13)	1.339(2)
C(13)-C(14)	1.380(3)
C(13)-H(13)	0.97(2)
C(14)-C(15)	1.383(3)
C(14)-H(14)	0.95(2)
C(15)-C(16)	1.382(3)
C(15)-H(15)	0.99(3)
C(16)-H(16)	0.95(2)
C(17)-C(18)	1.486(2)
C(17)-H(17A)	0.98(2)
C(17)-H(17B)	0.95(2)
C(18)-C(22)	1.348(2)
C(18)-O(19)	1.374(2)
O(19)-C(20)	1.377(2)
C(20)-C(21)	1.340(3)
C(20)-H(20)	0.98(3)
C(21)-C(22)	1.430(3)
C(21)-H(21)	1.00(3)
C(22)-H(22)	0.93(2)

C(23)-O(24)	1.236(2)
C(23)-N(25)	1.330(2)
N(25)-C(26)	1.453(2)
N(25)-H(25N)	0.82(2)
C(26)-C(31)	1.525(3)
C(26)-C(27)	1.529(2)
C(26)-H(26)	0.93(2)
C(27)-C(28)	1.525(3)
C(27)-H(27A)	1.04(2)
C(27)-H(27B)	1.07(2)
C(28)-C(29)	1.516(3)
C(28)-H(28A)	1.07(3)
C(28)-H(28B)	1.06(3)
C(29)-C(30)	1.520(3)
C(29)-H(29A)	1.00(3)
C(29)-H(29B)	1.04(2)
C(30)-C(31)	1.529(3)
C(30)-H(30A)	1.00(3)
C(30)-H(30B)	0.94(3)
C(31)-H(31A)	0.99(2)
C(31)-H(31B)	0.94(2)
O(1W)-H(1W1)	0.86(3)
O(1W)-H(1W2)	0.88(3)

N(8)-C(1)-C(23)	107.55(13)
N(8)-C(1)-C(2)	111.11(13)
C(23)-C(1)-C(2)	109.28(14)
N(8)-C(1)-C(6)	108.05(14)
C(23)-C(1)-C(6)	111.94(14)
C(2)-C(1)-C(6)	108.93(15)
C(7)-C(2)-C(3)	109.22(16)
C(7)-C(2)-C(1)	115.04(16)
C(3)-C(2)-C(1)	110.84(15)
C(7)-C(2)-H(2)	108.8(11)
C(3)-C(2)-H(2)	105.4(12)
C(1)-C(2)-H(2)	107.1(11)
C(4)-C(3)-C(2)	111.87(17)
C(4)-C(3)-H(3A)	111.6(14)
C(2)-C(3)-H(3A)	110.3(14)
C(4)-C(3)-H(3B)	113.6(13)
C(2)-C(3)-H(3B)	111.0(13)
H(3A)-C(3)-H(3B)	97.6(18)
C(5)-C(4)-C(3)	110.10(18)
C(5)-C(4)-H(4A)	110.4(13)
C(3)-C(4)-H(4A)	108.4(13)
C(5)-C(4)-H(4B)	108.1(13)
C(3)-C(4)-H(4B)	109.9(13)
H(4A)-C(4)-H(4B)	110.0(19)

C(4)-C(5)-C(6)	111.53(16)
C(4)-C(5)-H(5A)	109.7(12)
C(6)-C(5)-H(5A)	106.0(12)
C(4)-C(5)-H(5B)	111.8(11)
C(6)-C(5)-H(5B)	106.1(11)
H(5A)-C(5)-H(5B)	111.5(16)
C(5)-C(6)-C(1)	116.35(15)
C(5)-C(6)-H(6A)	108.6(12)
C(1)-C(6)-H(6A)	104.9(12)
C(5)-C(6)-H(6B)	107.5(12)
C(1)-C(6)-H(6B)	113.0(12)
H(6A)-C(6)-H(6B)	105.9(16)
C(2)-C(7)-H(7A)	108.2(14)
C(2)-C(7)-H(7B)	113.4(12)
H(7A)-C(7)-H(7B)	111.3(19)
C(2)-C(7)-H(7C)	105.2(14)
H(7A)-C(7)-H(7C)	103.6(19)
H(7B)-C(7)-H(7C)	114.4(19)
C(9)-N(8)-C(17)	119.27(13)
C(9)-N(8)-C(1)	116.98(13)
C(17)-N(8)-C(1)	121.29(13)
O(10)-C(9)-N(8)	123.58(15)
O(10)-C(9)-C(11)	117.09(14)
N(8)-C(9)-C(11)	119.26(14)

N(12)-C(11)-C(16)	123.00(16)
N(12)-C(11)-C(9)	117.46(14)
C(16)-C(11)-C(9)	119.27(15)
C(13)-N(12)-C(11)	117.29(15)
N(12)-C(13)-C(14)	123.62(17)
N(12)-C(13)-H(13)	115.5(12)
C(14)-C(13)-H(13)	120.8(12)
C(13)-C(14)-C(15)	118.38(17)
C(13)-C(14)-H(14)	117.2(13)
C(15)-C(14)-H(14)	124.4(13)
C(16)-C(15)-C(14)	118.99(17)
C(16)-C(15)-H(15)	120.6(15)
C(14)-C(15)-H(15)	120.4(15)
C(15)-C(16)-C(11)	118.69(17)
C(15)-C(16)-H(16)	123.4(13)
C(11)-C(16)-H(16)	117.9(13)
N(8)-C(17)-C(18)	115.22(13)
N(8)-C(17)-H(17A)	107.0(11)
C(18)-C(17)-H(17A)	108.6(11)
N(8)-C(17)-H(17B)	111.8(11)
C(18)-C(17)-H(17B)	107.8(12)
H(17A)-C(17)-H(17B)	106.0(16)
C(22)-C(18)-O(19)	110.05(15)
C(22)-C(18)-C(17)	132.26(16)

O(19)-C(18)-C(17)	117.32(14)
C(18)-O(19)-C(20)	106.24(14)
C(21)-C(20)-O(19)	110.36(17)
C(21)-C(20)-H(20)	132.4(15)
O(19)-C(20)-H(20)	117.2(15)
C(20)-C(21)-C(22)	106.64(17)
C(20)-C(21)-H(21)	127.9(14)
C(22)-C(21)-H(21)	125.4(14)
C(18)-C(22)-C(21)	106.70(16)
C(18)-C(22)-H(22)	124.4(13)
C(21)-C(22)-H(22)	128.9(13)
O(24)-C(23)-N(25)	122.37(17)
O(24)-C(23)-C(1)	120.00(16)
N(25)-C(23)-C(1)	117.50(14)
C(23)-N(25)-C(26)	123.17(15)
C(23)-N(25)-H(25N)	121.2(16)
C(26)-N(25)-H(25N)	115.6(16)
N(25)-C(26)-C(31)	110.07(15)
N(25)-C(26)-C(27)	110.26(15)
C(31)-C(26)-C(27)	111.60(16)
N(25)-C(26)-H(26)	106.0(12)
C(31)-C(26)-H(26)	110.8(13)
C(27)-C(26)-H(26)	107.9(12)
C(28)-C(27)-C(26)	111.59(17)

C(28)-C(27)-H(27A)	111.0(12)
C(26)-C(27)-H(27A)	107.4(12)
C(28)-C(27)-H(27B)	111.6(13)
C(26)-C(27)-H(27B)	106.5(12)
H(27A)-C(27)-H(27B)	108.4(17)
C(29)-C(28)-C(27)	110.77(17)
C(29)-C(28)-H(28A)	110.9(15)
C(27)-C(28)-H(28A)	110.1(15)
C(29)-C(28)-H(28B)	105.0(15)
C(27)-C(28)-H(28B)	109.4(14)
H(28A)-C(28)-H(28B)	111(2)
C(28)-C(29)-C(30)	110.68(18)
C(28)-C(29)-H(29A)	110.1(15)
C(30)-C(29)-H(29A)	108.8(15)
C(28)-C(29)-H(29B)	108.0(12)
C(30)-C(29)-H(29B)	111.0(12)
H(29A)-C(29)-H(29B)	108.2(18)
C(29)-C(30)-C(31)	110.91(17)
C(29)-C(30)-H(30A)	109.7(14)
C(31)-C(30)-H(30A)	108.0(14)
C(29)-C(30)-H(30B)	112.4(15)
C(31)-C(30)-H(30B)	111.9(15)
H(30A)-C(30)-H(30B)	103(2)
C(26)-C(31)-C(30)	110.99(16)

C(26)-C(31)-H(31A)	109.6(12)
C(30)-C(31)-H(31A)	108.2(12)
C(26)-C(31)-H(31B)	110.3(12)
C(30)-C(31)-H(31B)	110.9(12)
H(31A)-C(31)-H(31B)	106.6(16)
H(1W1)-O(1W)-H(1W2)	104(2)

Symmetry transformations used to generate equivalent atoms:

Table A1.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for trans-1.49. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	26(1)	26(1)	29(1)	1(1)	6(1)	-5(1)
C(2)	35(1)	31(1)	29(1)	3(1)	9(1)	-3(1)
C(3)	49(1)	34(1)	35(1)	2(1)	10(1)	-7(1)
C(4)	55(1)	31(1)	38(1)	-2(1)	13(1)	-8(1)
C(5)	43(1)	34(1)	35(1)	-6(1)	12(1)	-6(1)
C(6)	37(1)	32(1)	34(1)	-1(1)	15(1)	-3(1)
C(7)	41(1)	34(1)	36(1)	0(1)	12(1)	-3(1)
N(8)	22(1)	24(1)	22(1)	1(1)	5(1)	-2(1)
C(9)	26(1)	26(1)	20(1)	0(1)	9(1)	0(1)
O(10)	27(1)	35(1)	22(1)	3(1)	4(1)	-3(1)
C(11)	23(1)	25(1)	23(1)	3(1)	6(1)	2(1)
N(12)	27(1)	26(1)	27(1)	0(1)	10(1)	0(1)
C(13)	33(1)	24(1)	33(1)	-2(1)	12(1)	-1(1)
C(14)	40(1)	26(1)	40(1)	3(1)	17(1)	-4(1)
C(15)	44(1)	35(1)	37(1)	6(1)	22(1)	-3(1)
C(16)	35(1)	29(1)	28(1)	0(1)	14(1)	0(1)
C(17)	22(1)	26(1)	21(1)	0(1)	3(1)	-2(1)
C(18)	27(1)	25(1)	23(1)	-2(1)	5(1)	-2(1)
O(19)	35(1)	33(1)	25(1)	0(1)	10(1)	7(1)

C(20)	39(1)	42(1)	32(1)	-6(1)	13(1)	8(1)
C(21)	37(1)	35(1)	34(1)	-7(1)	7(1)	10(1)
C(22)	34(1)	28(1)	26(1)	-1(1)	5(1)	2(1)
C(23)	27(1)	31(1)	21(1)	4(1)	6(1)	-6(1)
O(24)	26(1)	42(1)	30(1)	-6(1)	5(1)	-10(1)
N(25)	22(1)	36(1)	22(1)	-1(1)	4(1)	-6(1)
C(26)	24(1)	39(1)	24(1)	-3(1)	7(1)	-5(1)
C(27)	38(1)	40(1)	31(1)	-3(1)	17(1)	-7(1)
C(28)	42(1)	55(1)	42(1)	-7(1)	24(1)	-8(1)
C(29)	39(1)	52(1)	40(1)	-5(1)	16(1)	5(1)
C(30)	39(1)	42(1)	41(1)	2(1)	9(1)	4(1)
C(31)	31(1)	40(1)	33(1)	5(1)	10(1)	-2(1)
O(1W)	27(1)	39(1)	24(1)	-2(1)	6(1)	-5(1)

Table A1.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for trans-1.49

	x	y	z	U(eq)
H(2)	4820(20)	1050(12)	4687(17)	35(5)
H(3A)	2060(30)	605(13)	4170(20)	48(6)
H(3B)	3240(20)	205(13)	5020(20)	41(6)
H(4A)	2600(20)	-408(14)	3200(20)	51(6)
H(4B)	4220(30)	-59(14)	3510(20)	57(7)
H(5A)	1600(20)	643(13)	1991(19)	44(6)
H(5B)	2850(20)	276(11)	1550(17)	33(5)
H(6A)	4350(20)	1183(12)	2537(18)	36(5)
H(6B)	2950(20)	1539(11)	1676(18)	33(5)
H(7A)	4350(30)	1194(14)	6350(20)	57(7)
H(7B)	4200(20)	2054(13)	5777(18)	38(6)
H(7C)	2840(30)	1520(14)	5570(20)	56(7)
H(13)	5780(20)	4892(11)	4535(17)	31(5)
H(14)	6580(20)	5238(13)	3153(18)	40(6)
H(15)	6320(20)	4433(14)	1570(20)	51(7)
H(16)	5070(20)	3338(12)	1472(19)	37(6)
H(17A)	6058(19)	2788(11)	4502(16)	25(5)
H(17B)	5800(19)	2128(11)	5148(17)	25(5)

H(20)	7640(20)	1566(14)	2070(20)	53(7)
H(21)	8790(20)	755(14)	3880(20)	50(6)
H(22)	7570(20)	1108(12)	5220(20)	37(5)
H(25N)	2620(20)	2796(12)	4370(20)	37(6)
H(26)	80(20)	2820(11)	3136(18)	29(5)
H(27A)	1080(20)	2763(12)	5559(19)	38(6)
H(27B)	130(20)	2112(14)	4650(20)	46(6)
H(28A)	-1210(30)	2879(15)	5460(20)	63(8)
H(28B)	-1730(30)	2988(15)	3980(20)	58(7)
H(29A)	-1560(30)	4139(14)	4830(20)	54(7)
H(29B)	10(20)	4006(12)	5652(19)	37(5)
H(30A)	-1100(20)	4058(14)	3140(20)	50(6)
H(30B)	-290(20)	4672(15)	3880(20)	45(6)
H(31A)	1630(20)	3926(11)	4600(18)	32(5)
H(31B)	1105(19)	3951(11)	3275(17)	25(5)
H(1W1)	4400(30)	3678(15)	5150(20)	57(8)
H(1W2)	4670(30)	3455(14)	6260(20)	55(7)

Table A1.6. Torsion angles [°] for trans-1.49

N(8)-C(1)-C(2)-C(7)	65.3(2)
C(23)-C(1)-C(2)-C(7)	-53.2(2)
C(6)-C(1)-C(2)-C(7)	-175.77(16)
N(8)-C(1)-C(2)-C(3)	-170.17(15)
C(23)-C(1)-C(2)-C(3)	71.31(19)
C(6)-C(1)-C(2)-C(3)	-51.3(2)
C(7)-C(2)-C(3)-C(4)	-172.38(17)
C(1)-C(2)-C(3)-C(4)	59.9(2)
C(2)-C(3)-C(4)-C(5)	-60.2(2)
C(3)-C(4)-C(5)-C(6)	54.1(2)
C(4)-C(5)-C(6)-C(1)	-50.4(2)
N(8)-C(1)-C(6)-C(5)	169.31(15)
C(23)-C(1)-C(6)-C(5)	-72.4(2)
C(2)-C(1)-C(6)-C(5)	48.5(2)
C(23)-C(1)-N(8)-C(9)	-52.47(18)
C(2)-C(1)-N(8)-C(9)	-172.02(14)
C(6)-C(1)-N(8)-C(9)	68.54(18)
C(23)-C(1)-N(8)-C(17)	145.49(14)
C(2)-C(1)-N(8)-C(17)	25.9(2)
C(6)-C(1)-N(8)-C(17)	-93.50(17)
C(17)-N(8)-C(9)-O(10)	164.17(15)
C(1)-N(8)-C(9)-O(10)	1.7(2)

C(17)-N(8)-C(9)-C(11)	-18.7(2)
C(1)-N(8)-C(9)-C(11)	178.84(14)
O(10)-C(9)-C(11)-N(12)	112.27(17)
N(8)-C(9)-C(11)-N(12)	-65.0(2)
O(10)-C(9)-C(11)-C(16)	-61.9(2)
N(8)-C(9)-C(11)-C(16)	120.79(17)
C(16)-C(11)-N(12)-C(13)	1.4(2)
C(9)-C(11)-N(12)-C(13)	-172.51(14)
C(11)-N(12)-C(13)-C(14)	-1.2(3)
N(12)-C(13)-C(14)-C(15)	-0.2(3)
C(13)-C(14)-C(15)-C(16)	1.4(3)
C(14)-C(15)-C(16)-C(11)	-1.2(3)
N(12)-C(11)-C(16)-C(15)	-0.3(3)
C(9)-C(11)-C(16)-C(15)	173.57(16)
C(9)-N(8)-C(17)-C(18)	-90.05(18)
C(1)-N(8)-C(17)-C(18)	71.59(19)
N(8)-C(17)-C(18)-C(22)	-132.38(19)
N(8)-C(17)-C(18)-O(19)	55.4(2)
C(22)-C(18)-O(19)-C(20)	-0.69(19)
C(17)-C(18)-O(19)-C(20)	173.15(15)
C(18)-O(19)-C(20)-C(21)	0.2(2)
O(19)-C(20)-C(21)-C(22)	0.3(2)
O(19)-C(18)-C(22)-C(21)	0.9(2)
C(17)-C(18)-C(22)-C(21)	-171.76(18)

C(20)-C(21)-C(22)-C(18)	-0.7(2)
N(8)-C(1)-C(23)-O(24)	147.01(15)
C(2)-C(1)-C(23)-O(24)	-92.28(18)
C(6)-C(1)-C(23)-O(24)	28.5(2)
N(8)-C(1)-C(23)-N(25)	-36.91(19)
C(2)-C(1)-C(23)-N(25)	83.80(18)
C(6)-C(1)-C(23)-N(25)	-155.45(15)
O(24)-C(23)-N(25)-C(26)	-3.8(3)
C(1)-C(23)-N(25)-C(26)	-179.77(14)
C(23)-N(25)-C(26)-C(31)	-141.51(16)
C(23)-N(25)-C(26)-C(27)	94.94(19)
N(25)-C(26)-C(27)-C(28)	176.44(16)
C(31)-C(26)-C(27)-C(28)	53.8(2)
C(26)-C(27)-C(28)-C(29)	-55.5(2)
C(27)-C(28)-C(29)-C(30)	57.6(2)
C(28)-C(29)-C(30)-C(31)	-58.0(2)
N(25)-C(26)-C(31)-C(30)	-176.55(15)
C(27)-C(26)-C(31)-C(30)	-53.8(2)
C(29)-C(30)-C(31)-C(26)	56.0(2)

Symmetry transformations used to generate equivalent atoms:

Table A1.7. Hydrogen bonds for trans-1.49 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(6)-H(6B)...O(10)	0.99(2)	2.49(2)	3.007(2)	112.2(14)
C(17)-H(17A)...N(12)	0.98(2)	2.47(2)	3.199(2)	131.3(14)
C(17)-H(17B)...O(10)#1	0.95(2)	2.55(2)	3.241(2)	129.5(15)
N(25)-H(25N)...O(1W)	0.82(2)	2.18(2)	2.972(2)	163(2)
C(31)-H(31A)...O(1W)	0.99(2)	2.53(2)	3.311(2)	135.7(15)
O(1W)-H(1W1)...N(12)	0.86(3)	2.06(3)	2.905(2)	168(3)
O(1W)-H(1W2)...O(24)#1	0.88(3)	1.85(3)	2.7289(18)	176(2)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+1/2,z+1/2

X-ray crystallographic data of trans-1.51

Table A2.1. Crystal data and structure refinement for trans-1.51.

Identification code	v76b	
Empirical formula	C25 H35 N3 O4	
Formula weight	441.56	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.0174(8) Å	α= 90°.
	b = 18.465(3) Å	β= 90°.
	c = 21.840(3) Å	γ = 90°.
Volume	2426.7(6) $Å^3$	
Z	4	
Density (calculated)	1.209 Mg/m^3	
Absorption coefficient	0.660 mm^{-1}	
F(000)	952	
Crystal size	0.590 x 0.050 x 0.025 mm^3	
Theta range for data collection	3.134 to 67.990°.	
Index ranges	-6<=h<=7, -21<=k<=18, -25<=l<=25	
Reflections collected	13187	
Independent reflections	4283 [R(int) = 0.0275]	
Completeness to theta = 66.000°	99.8 %	
Absorption correction	Multi-scan	

Max. and min. transmission	1.000 and 0.800
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4283 / 0 / 429
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0700
R indices (all data)	R1 = 0.0286, wR2 = 0.0711
Absolute structure parameter	0.51(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.110 and -0.176 e.$Å^{-3}$

Table A2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for trans-1.51. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5400(3)	5631(1)	6124(1)	20(1)
C(2)	6828(3)	6279(1)	5915(1)	23(1)
C(3)	6710(3)	6438(1)	5226(1)	27(1)
C(4)	4327(3)	6480(1)	4988(1)	29(1)
C(5)	3090(3)	5788(1)	5159(1)	26(1)
C(6)	3037(3)	5695(1)	5852(1)	22(1)
C(7)	4267(4)	6630(1)	4302(1)	40(1)
N(8)	5264(2)	5618(1)	6810(1)	20(1)
C(9)	7041(3)	5383(1)	7131(1)	22(1)
O(10)	8780(2)	5187(1)	6884(1)	26(1)
C(11)	6897(3)	5339(1)	7821(1)	23(1)
N(12)	5263(3)	4927(1)	8056(1)	27(1)
C(13)	5187(3)	4862(1)	8668(1)	31(1)
C(14)	6668(4)	5200(1)	9059(1)	32(1)
C(15)	8343(3)	5616(1)	8807(1)	34(1)
C(16)	8473(3)	5685(1)	8177(1)	30(1)
C(17)	3452(3)	6012(1)	7124(1)	22(1)
C(18)	3678(3)	6813(1)	7083(1)	25(1)
O(19)	5692(2)	7095(1)	7257(1)	32(1)
C(20)	5490(5)	7837(1)	7184(1)	43(1)

C(21)	3468(5)	8009(1)	6982(1)	47(1)
C(22)	2271(4)	7346(1)	6914(1)	36(1)
C(23)	6409(3)	4902(1)	5897(1)	21(1)
O(24)	7914(2)	4892(1)	5515(1)	25(1)
N(25)	5404(3)	4303(1)	6104(1)	24(1)
C(26)	6118(3)	3578(1)	5918(1)	24(1)
C(27)	4102(3)	3082(1)	5882(1)	31(1)
C(28)	4788(3)	2308(1)	5706(1)	34(1)
C(29)	6476(3)	2008(1)	6160(1)	33(1)
C(30)	8523(3)	2498(1)	6191(1)	34(1)
C(31)	7874(3)	3280(1)	6352(1)	30(1)
O(1W)	2238(2)	4211(1)	7186(1)	29(1)

Table A2.3. Bond lengths [Å] and angles [°] for trans-1.51

C(1)-N(8)	1.501(2)
C(1)-C(2)	1.543(2)
C(1)-C(6)	1.545(2)
C(1)-C(23)	1.558(2)
C(2)-C(3)	1.534(2)
C(2)-H(2A)	0.98(3)
C(2)-H(2B)	1.00(2)
C(3)-C(4)	1.527(3)
C(3)-H(3A)	0.98(2)
C(3)-H(3B)	0.96(2)
C(4)-C(7)	1.523(3)
C(4)-C(5)	1.525(3)
C(4)-H(4)	1.02(2)
C(5)-C(6)	1.525(2)
C(5)-H(5A)	0.99(2)
C(5)-H(5B)	1.00(2)
C(6)-H(6A)	0.99(2)
C(6)-H(6B)	0.97(2)
C(7)-H(7A)	0.99(3)
C(7)-H(7B)	0.98(3)
C(7)-H(7C)	1.03(3)
N(8)-C(9)	1.350(2)

N(8)-C(17)	1.479(2)
C(9)-O(10)	1.232(2)
C(9)-C(11)	1.513(2)
C(11)-N(12)	1.345(2)
C(11)-C(16)	1.383(3)
N(12)-C(13)	1.344(3)
C(13)-C(14)	1.384(3)
C(13)-H(13)	0.95(2)
C(14)-C(15)	1.380(3)
C(14)-H(14)	0.96(3)
C(15)-C(16)	1.384(3)
C(15)-H(15)	0.98(3)
C(16)-H(16)	0.97(3)
C(17)-C(18)	1.487(2)
C(17)-H(17A)	0.97(2)
C(17)-H(17B)	0.99(2)
C(18)-C(22)	1.349(3)
C(18)-O(19)	1.373(2)
O(19)-C(20)	1.385(3)
C(20)-C(21)	1.333(4)
C(20)-H(20)	0.93(3)
C(21)-C(22)	1.429(3)
C(21)-H(21)	0.96(3)
C(22)-H(22)	0.95(3)

C(23)-O(24)	1.231(2)
C(23)-N(25)	1.339(2)
N(25)-C(26)	1.464(2)
N(25)-H(25N)	0.87(3)
C(26)-C(27)	1.522(2)
C(26)-C(31)	1.522(3)
C(26)-H(26)	0.99(2)
C(27)-C(28)	1.535(3)
C(27)-H(27A)	1.04(3)
C(27)-H(27B)	0.98(3)
C(28)-C(29)	1.524(3)
C(28)-H(28A)	1.02(3)
C(28)-H(28B)	1.03(3)
C(29)-C(30)	1.529(3)
C(29)-H(29A)	1.01(3)
C(29)-H(29B)	0.99(3)
C(30)-C(31)	1.536(3)
C(30)-H(30A)	1.00(3)
C(30)-H(30B)	0.99(2)
C(31)-H(31A)	0.98(3)
C(31)-H(31B)	1.01(2)
O(1W)-H(1W1)	0.89(3)
O(1W)-H(1W2)	0.94(3)

N(8)-C(1)-C(2)	109.77(13)
N(8)-C(1)-C(6)	109.53(13)
C(2)-C(1)-C(6)	109.83(14)
N(8)-C(1)-C(23)	108.95(13)
C(2)-C(1)-C(23)	111.07(14)
C(6)-C(1)-C(23)	107.66(14)
C(3)-C(2)-C(1)	114.34(14)
C(3)-C(2)-H(2A)	112.0(14)
C(1)-C(2)-H(2A)	107.7(13)
C(3)-C(2)-H(2B)	108.0(13)
C(1)-C(2)-H(2B)	106.4(13)
H(2A)-C(2)-H(2B)	108.1(19)
C(4)-C(3)-C(2)	112.77(15)
C(4)-C(3)-H(3A)	109.7(13)
C(2)-C(3)-H(3A)	110.5(13)
C(4)-C(3)-H(3B)	110.6(13)
C(2)-C(3)-H(3B)	108.6(13)
H(3A)-C(3)-H(3B)	104.4(18)
C(7)-C(4)-C(5)	112.38(17)
C(7)-C(4)-C(3)	111.47(17)
C(5)-C(4)-C(3)	109.41(15)
C(7)-C(4)-H(4)	106.9(12)
C(5)-C(4)-H(4)	106.9(13)
C(3)-C(4)-H(4)	109.6(13)

C(4)-C(5)-C(6)	110.31(15)
C(4)-C(5)-H(5A)	109.7(12)
C(6)-C(5)-H(5A)	109.3(13)
C(4)-C(5)-H(5B)	108.9(13)
C(6)-C(5)-H(5B)	108.5(12)
H(5A)-C(5)-H(5B)	110.1(18)
C(5)-C(6)-C(1)	111.76(14)
C(5)-C(6)-H(6A)	107.7(12)
C(1)-C(6)-H(6A)	108.2(12)
C(5)-C(6)-H(6B)	111.2(13)
C(1)-C(6)-H(6B)	111.5(13)
H(6A)-C(6)-H(6B)	106.2(17)
C(4)-C(7)-H(7A)	109.5(15)
C(4)-C(7)-H(7B)	107.5(16)
H(7A)-C(7)-H(7B)	108(2)
C(4)-C(7)-H(7C)	110.5(16)
H(7A)-C(7)-H(7C)	108(2)
H(7B)-C(7)-H(7C)	114(2)
C(9)-N(8)-C(17)	120.07(14)
C(9)-N(8)-C(1)	118.73(14)
C(17)-N(8)-C(1)	119.64(13)
O(10)-C(9)-N(8)	122.66(16)
O(10)-C(9)-C(11)	118.02(15)
N(8)-C(9)-C(11)	119.31(15)

N(12)-C(11)-C(16)	123.29(17)
N(12)-C(11)-C(9)	116.85(15)
C(16)-C(11)-C(9)	119.78(16)
C(13)-N(12)-C(11)	117.04(17)
N(12)-C(13)-C(14)	123.47(19)
N(12)-C(13)-H(13)	117.5(14)
C(14)-C(13)-H(13)	119.1(14)
C(15)-C(14)-C(13)	118.43(18)
C(15)-C(14)-H(14)	121.5(15)
C(13)-C(14)-H(14)	120.0(15)
C(14)-C(15)-C(16)	119.21(19)
C(14)-C(15)-H(15)	119.9(15)
C(16)-C(15)-H(15)	120.8(15)
C(11)-C(16)-C(15)	118.55(19)
C(11)-C(16)-H(16)	120.3(15)
C(15)-C(16)-H(16)	121.2(15)
N(8)-C(17)-C(18)	113.22(15)
N(8)-C(17)-H(17A)	108.1(12)
C(18)-C(17)-H(17A)	108.8(11)
N(8)-C(17)-H(17B)	110.6(12)
C(18)-C(17)-H(17B)	109.5(12)
H(17A)-C(17)-H(17B)	106.4(17)
C(22)-C(18)-O(19)	110.65(17)
C(22)-C(18)-C(17)	133.14(19)

O(19)-C(18)-C(17)	116.21(16)
C(18)-O(19)-C(20)	105.47(17)
C(21)-C(20)-O(19)	110.7(2)
C(21)-C(20)-H(20)	137.9(17)
O(19)-C(20)-H(20)	111.4(17)
C(20)-C(21)-C(22)	106.92(19)
C(20)-C(21)-H(21)	124.0(19)
C(22)-C(21)-H(21)	128.9(19)
C(18)-C(22)-C(21)	106.3(2)
C(18)-C(22)-H(22)	126.0(17)
C(21)-C(22)-H(22)	127.8(17)
O(24)-C(23)-N(25)	123.35(16)
O(24)-C(23)-C(1)	120.95(15)
N(25)-C(23)-C(1)	115.45(15)
C(23)-N(25)-C(26)	121.92(15)
C(23)-N(25)-H(25N)	119.0(15)
C(26)-N(25)-H(25N)	118.3(15)
N(25)-C(26)-C(27)	109.32(15)
N(25)-C(26)-C(31)	111.19(15)
C(27)-C(26)-C(31)	111.61(16)
N(25)-C(26)-H(26)	107.1(13)
C(27)-C(26)-H(26)	108.9(14)
C(31)-C(26)-H(26)	108.6(14)
C(26)-C(27)-C(28)	110.99(16)

C(26)-C(27)-H(27A)	109.9(14)
C(28)-C(27)-H(27A)	111.7(13)
C(26)-C(27)-H(27B)	108.5(15)
C(28)-C(27)-H(27B)	109.1(15)
H(27A)-C(27)-H(27B)	107(2)
C(29)-C(28)-C(27)	110.80(17)
C(29)-C(28)-H(28A)	110.3(15)
C(27)-C(28)-H(28A)	109.3(14)
C(29)-C(28)-H(28B)	111.2(14)
C(27)-C(28)-H(28B)	107.0(14)
H(28A)-C(28)-H(28B)	108(2)
C(28)-C(29)-C(30)	110.51(17)
C(28)-C(29)-H(29A)	110.6(15)
C(30)-C(29)-H(29A)	108.0(16)
C(28)-C(29)-H(29B)	110.5(17)
C(30)-C(29)-H(29B)	109.7(17)
H(29A)-C(29)-H(29B)	107(2)
C(29)-C(30)-C(31)	111.16(16)
C(29)-C(30)-H(30A)	110.5(16)
C(31)-C(30)-H(30A)	109.2(15)
C(29)-C(30)-H(30B)	109.4(14)
C(31)-C(30)-H(30B)	109.8(13)
H(30A)-C(30)-H(30B)	107(2)
C(26)-C(31)-C(30)	111.92(16)

C(26)-C(31)-H(31A)	108.9(14)
C(30)-C(31)-H(31A)	108.8(14)
C(26)-C(31)-H(31B)	109.3(14)
C(30)-C(31)-H(31B)	108.2(13)
H(31A)-C(31)-H(31B)	109.7(19)
H(1W1)-O(1W)-H(1W2)	106(2)

Symmetry transformations used to generate equivalent atoms:

Table A2.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for trans-1.51. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	21(1)	19(1)	1(1)	0(1)	-1(1)
C(2)	21(1)	22(1)	25(1)	2(1)	1(1)	-2(1)
C(3)	32(1)	23(1)	25(1)	3(1)	4(1)	-3(1)
C(4)	35(1)	28(1)	23(1)	2(1)	0(1)	6(1)
C(5)	24(1)	32(1)	23(1)	1(1)	-4(1)	3(1)
C(6)	19(1)	25(1)	23(1)	0(1)	0(1)	0(1)
C(7)	50(1)	42(1)	28(1)	8(1)	-3(1)	2(1)
N(8)	20(1)	21(1)	19(1)	-1(1)	0(1)	0(1)
C(9)	22(1)	20(1)	23(1)	1(1)	0(1)	-2(1)
O(10)	20(1)	31(1)	26(1)	0(1)	0(1)	2(1)
C(11)	24(1)	22(1)	24(1)	0(1)	0(1)	4(1)
N(12)	32(1)	25(1)	23(1)	4(1)	-1(1)	-2(1)
C(13)	38(1)	29(1)	26(1)	6(1)	3(1)	-1(1)
C(14)	44(1)	32(1)	21(1)	2(1)	-3(1)	9(1)
C(15)	33(1)	42(1)	27(1)	-7(1)	-7(1)	3(1)
C(16)	26(1)	36(1)	28(1)	-2(1)	-1(1)	0(1)
C(17)	24(1)	23(1)	21(1)	1(1)	3(1)	2(1)
C(18)	29(1)	25(1)	22(1)	-4(1)	4(1)	-1(1)
O(19)	37(1)	28(1)	31(1)	-7(1)	3(1)	-7(1)
C(20)	67(2)	27(1)	36(1)	-9(1)	11(1)	-14(1)

C(21)	73(2)	26(1)	42(1)	-2(1)	4(1)	6(1)
C(22)	46(1)	28(1)	34(1)	0(1)	0(1)	8(1)
C(23)	19(1)	23(1)	21(1)	1(1)	-3(1)	0(1)
O(24)	25(1)	27(1)	22(1)	0(1)	4(1)	1(1)
N(25)	23(1)	22(1)	27(1)	-2(1)	4(1)	1(1)
C(26)	26(1)	21(1)	26(1)	-3(1)	3(1)	1(1)
C(27)	26(1)	25(1)	42(1)	-4(1)	-5(1)	0(1)
C(28)	32(1)	25(1)	45(1)	-6(1)	-2(1)	-2(1)
C(29)	35(1)	23(1)	42(1)	2(1)	4(1)	1(1)
C(30)	30(1)	26(1)	45(1)	-1(1)	-1(1)	4(1)
C(31)	26(1)	25(1)	37(1)	-2(1)	-3(1)	0(1)
O(1W)	27(1)	26(1)	33(1)	1(1)	-4(1)	2(1)

Table A2.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for trans-1.51

	x	y	z	U(eq)
H(2A)	8360(40)	6192(12)	6052(10)	32(6)
H(2B)	6240(40)	6715(12)	6138(10)	30(6)
H(3A)	7530(40)	6073(12)	4996(10)	28(5)
H(3B)	7490(40)	6883(13)	5146(10)	29(5)
H(4)	3520(40)	6897(12)	5197(10)	28(5)
H(5A)	1540(40)	5811(11)	5001(10)	27(5)
H(5B)	3890(40)	5365(12)	4976(10)	30(6)
H(6A)	2330(30)	6129(12)	6027(9)	20(5)
H(6B)	2110(40)	5288(12)	5970(10)	27(5)
H(7A)	4980(50)	6227(15)	4081(12)	47(7)
H(7B)	5140(50)	7071(15)	4228(12)	51(8)
H(7C)	2650(50)	6663(15)	4150(12)	54(8)
H(13)	4050(40)	4568(12)	8836(10)	28(5)
H(14)	6520(40)	5142(12)	9494(12)	38(6)
H(15)	9370(40)	5878(13)	9074(12)	43(7)
H(16)	9620(40)	5978(13)	7987(11)	38(6)
H(17A)	3460(30)	5872(10)	7551(9)	16(4)
H(17B)	1990(40)	5864(11)	6959(9)	23(5)

H(20)	6780(50)	8078(15)	7306(13)	50(7)
H(21)	2950(50)	8498(16)	6925(13)	57(8)
H(22)	780(50)	7283(15)	6783(13)	53(8)
H(25N)	4450(40)	4341(12)	6401(11)	33(6)
H(26)	6780(40)	3623(12)	5507(11)	33(6)
H(27A)	2940(40)	3294(13)	5576(11)	38(6)
H(27B)	3380(40)	3072(13)	6283(12)	39(6)
H(28A)	5440(40)	2310(13)	5275(12)	44(7)
H(28B)	3360(40)	1999(13)	5701(11)	40(6)
H(29A)	6980(50)	1508(14)	6032(12)	47(7)
H(29B)	5810(50)	1964(14)	6572(13)	53(8)
H(30A)	9600(50)	2314(14)	6501(12)	48(7)
H(30B)	9300(40)	2488(12)	5792(11)	34(6)
H(31A)	9200(40)	3586(13)	6328(11)	37(6)
H(31B)	7280(40)	3284(12)	6783(11)	36(6)
H(1W1)	3080(50)	4434(14)	7462(12)	46(7)
H(1W2)	1010(60)	4514(16)	7115(14)	63(9)

Table A2.6. Torsion angles [°] for trans-1.51

N(8)-C(1)-C(2)-C(3)	-168.49(14)
C(6)-C(1)-C(2)-C(3)	-48.0(2)
C(23)-C(1)-C(2)-C(3)	70.97(19)
C(1)-C(2)-C(3)-C(4)	49.8(2)
C(2)-C(3)-C(4)-C(7)	-179.39(16)
C(2)-C(3)-C(4)-C(5)	-54.5(2)
C(7)-C(4)-C(5)-C(6)	-175.41(16)
C(3)-C(4)-C(5)-C(6)	60.2(2)
C(4)-C(5)-C(6)-C(1)	-61.2(2)
N(8)-C(1)-C(6)-C(5)	174.23(13)
C(2)-C(1)-C(6)-C(5)	53.60(19)
C(23)-C(1)-C(6)-C(5)	-67.45(18)
C(2)-C(1)-N(8)-C(9)	-75.91(18)
C(6)-C(1)-N(8)-C(9)	163.42(14)
C(23)-C(1)-N(8)-C(9)	45.90(19)
C(2)-C(1)-N(8)-C(17)	89.86(17)
C(6)-C(1)-N(8)-C(17)	-30.8(2)
C(23)-C(1)-N(8)-C(17)	-148.32(14)
C(17)-N(8)-C(9)-O(10)	-164.82(16)
C(1)-N(8)-C(9)-O(10)	0.9(2)
C(17)-N(8)-C(9)-C(11)	16.7(2)
C(1)-N(8)-C(9)-C(11)	-177.64(14)

O(10)-C(9)-C(11)-N(12)	-121.34(18)
N(8)-C(9)-C(11)-N(12)	57.3(2)
O(10)-C(9)-C(11)-C(16)	55.5(2)
N(8)-C(9)-C(11)-C(16)	-125.90(18)
C(16)-C(11)-N(12)-C(13)	0.5(3)
C(9)-C(11)-N(12)-C(13)	177.25(16)
C(11)-N(12)-C(13)-C(14)	0.8(3)
N(12)-C(13)-C(14)-C(15)	-1.4(3)
C(13)-C(14)-C(15)-C(16)	0.6(3)
N(12)-C(11)-C(16)-C(15)	-1.2(3)
C(9)-C(11)-C(16)-C(15)	-177.88(17)
C(14)-C(15)-C(16)-C(11)	0.6(3)
C(9)-N(8)-C(17)-C(18)	95.80(18)
C(1)-N(8)-C(17)-C(18)	-69.8(2)
N(8)-C(17)-C(18)-C(22)	129.3(2)
N(8)-C(17)-C(18)-O(19)	-51.9(2)
C(22)-C(18)-O(19)-C(20)	-0.4(2)
C(17)-C(18)-O(19)-C(20)	-179.51(16)
C(18)-O(19)-C(20)-C(21)	0.5(2)
O(19)-C(20)-C(21)-C(22)	-0.3(3)
O(19)-C(18)-C(22)-C(21)	0.3(2)
C(17)-C(18)-C(22)-C(21)	179.1(2)
C(20)-C(21)-C(22)-C(18)	0.0(3)
N(8)-C(1)-C(23)-O(24)	-132.58(16)

C(2)-C(1)-C(23)-O(24)	-11.6(2)
C(6)-C(1)-C(23)-O(24)	108.72(17)
N(8)-C(1)-C(23)-N(25)	52.91(19)
C(2)-C(1)-C(23)-N(25)	173.94(15)
C(6)-C(1)-C(23)-N(25)	-65.79(19)
O(24)-C(23)-N(25)-C(26)	3.8(3)
C(1)-C(23)-N(25)-C(26)	178.21(15)
C(23)-N(25)-C(26)-C(27)	-146.03(18)
C(23)-N(25)-C(26)-C(31)	90.3(2)
N(25)-C(26)-C(27)-C(28)	-178.32(17)
C(31)-C(26)-C(27)-C(28)	-54.9(2)
C(26)-C(27)-C(28)-C(29)	57.1(2)
C(27)-C(28)-C(29)-C(30)	-57.6(2)
C(28)-C(29)-C(30)-C(31)	56.0(2)
N(25)-C(26)-C(31)-C(30)	175.92(16)
C(27)-C(26)-C(31)-C(30)	53.6(2)
C(29)-C(30)-C(31)-C(26)	-54.1(2)

Symmetry transformations used to generate equivalent atoms:

Table A2.7. Hydrogen bonds for trans-1.51 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2A)...O(10)	0.98(3)	2.61(2)	3.151(2)	115.0(16)
C(2)-H(2B)...O(19)	1.00(2)	2.56(2)	3.366(2)	136.8(17)
C(14)-H(14)...O(24)#1	0.96(3)	2.26(3)	3.195(2)	165(2)
C(17)-H(17A)...N(12)	0.97(2)	2.33(2)	3.057(2)	131.2(15)
C(17)-H(17B)...O(10)#2	0.99(2)	2.31(2)	3.240(2)	157.0(17)
C(20)-H(20)...O(1W)#3	0.93(3)	2.44(3)	3.192(3)	138(2)
N(25)-H(25N)...O(1W)	0.87(3)	2.18(3)	3.040(2)	169(2)
O(1W)-H(1W1)...N(12)	0.89(3)	2.06(3)	2.944(2)	175(3)
O(1W)-H(1W2)...O(10)#2	0.94(3)	1.90(3)	2.8313(18)	172(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,-y+1,z+1/2 #2 x-1,y,z #3 -x+1,y+1/2,-z+3/2

X-ray crystallographic data of cis-1.52

Table A3.1. Crystal data and structure refinement for cis-1.52

Identification code	x1611001
Empirical formula	$C_{28}H_{39}N_3O_3$
Formula weight	465.62
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	8.0902(10)
b/Å	12.2718(16)
c/Å	13.6660(18)
α/°	105.567(10)
β/°	102.637(10)
γ/°	90.859(10)
Volume/Å^3	1271.4(3)
Z	2
ρ_{calc}g/cm^3	1.216
μ/mm^{-1}	0.625
F(000)	504.0
Crystal size/mm^3	0.138 × 0.086 × 0.053
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.902 to 133.352
Index ranges	$-9 \leq h \leq 9$, $-14 \leq k \leq 14$, $-15 \leq l \leq 16$
Reflections collected	10318
Independent reflections	4318 [R_{int} = 0.0645, R_{sigma} = 0.0612]

Data/restraints/parameters	4318/0/310
Goodness-of-fit on F^2	1.018
Final R indexes [I>=2σ (I)]	R_1 = 0.0532, wR_2 = 0.1282
Final R indexes [all data]	R_1 = 0.0765, wR_2 = 0.1425
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.30

Table A3.2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for cis-1.52. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor

Atom	*x*	*y*	*z*	U(eq)
N1	3431(2)	6658.8(16)	4576.2(15)	22.2(4)
C2	3203(3)	6052(2)	3578.2(19)	25.4(5)
C3	3809(3)	6416(2)	2840.6(19)	29.4(6)
C4	4688(3)	7481(2)	3140.2(19)	28.5(5)
C5	4906(3)	8138(2)	4156.0(19)	25.3(5)
C6	4283(3)	7686.2(19)	4846.3(18)	20.6(5)
C7	4425(3)	8434.3(18)	5948.2(18)	20.5(5)
O8	3906(2)	9384.3(13)	6059.0(13)	25.6(4)
N9	5122(2)	8025.4(15)	6768.3(14)	19.2(4)
C10	6001(3)	6966.2(19)	6588.6(18)	20.9(5)
C11	7268(3)	6912.7(18)	5934.4(17)	19.9(5)
O12	8297.4(19)	7890.5(13)	6129.2(12)	23.3(4)
C13	9432(3)	7622(2)	5503.1(18)	25.4(5)
C14	9163(3)	6529(2)	4949.6(18)	26.1(5)
C15	7750(3)	6065(2)	5220.8(18)	24.6(5)
C16	5056(3)	8741.7(18)	7841.7(17)	20.6(5)
C17	6061(3)	9912.4(19)	8093.9(17)	21.8(5)
N18	7447(2)	9904.5(16)	7703.4(16)	24.1(4)
C19	8532(3)	10923.9(19)	7854.5(18)	22.4(5)
C20	9354(3)	10784(2)	6931.0(19)	29.5(5)
C21	10528(3)	11826(2)	7053(2)	31.2(6)
C22	11850(3)	12129(2)	8095(2)	27.0(5)

C23	10990(3)	12275(2)	9002.3(19)	27.2(5)
C24	9883(3)	11204(2)	8881.7(18)	24.7(5)
O25	5657(2)	10762.3(13)	8677.5(13)	27.2(4)
C26	5854(3)	8210.0(19)	8723.3(17)	22.2(5)
C27	4861(3)	7131(2)	8738.0(18)	23.9(5)
C28	2971(3)	7289.1(19)	8715.4(17)	21.0(5)
C29	1973(3)	6171(2)	8680.6(18)	24.2(5)
C30	2610(3)	5873(2)	9713(2)	36.9(6)
C31	71(3)	6361(2)	8560(2)	28.5(5)
C32	2134(3)	5174(2)	7764(2)	36.3(6)
C33	2218(3)	7794.6(19)	7823.2(17)	21.2(5)
C34	3197(3)	8901.5(19)	7906.6(18)	21.8(5)

Table 3.3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for x1611001. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	21.3(9)	22.2(10)	23.5(10)	7.9(8)	4.5(8)	2.6(8)
C2	24.0(11)	24.3(12)	25.4(12)	5.8(10)	1.8(9)	4.7(9)
C3	31.2(12)	33.1(13)	22.7(12)	5.7(10)	5.9(10)	11.1(11)
C4	26.5(12)	39.5(14)	29.4(12)	20.1(11)	13.2(10)	13.4(11)
C5	20.0(11)	26.5(12)	34.6(13)	16.7(11)	6.9(10)	4.5(9)
C6	15.8(10)	21.8(11)	26.1(11)	10.8(10)	3.5(8)	2.2(8)
C7	17.5(10)	18.3(11)	27.2(12)	8.5(9)	5.7(9)	-1.5(9)
O8	28.9(8)	18.3(8)	31.6(9)	9.8(7)	7.7(7)	4.2(7)
N9	18.5(9)	16.3(9)	23(1)	6.1(8)	4.4(7)	2.0(7)
C10	21.5(11)	18.9(11)	23.4(11)	8.3(9)	4.2(9)	4.4(9)
C11	18.4(10)	20.0(11)	21.1(11)	7.9(9)	1.2(8)	1.3(9)
O12	21.9(8)	21.6(8)	25.8(8)	3.5(7)	7.9(6)	-0.2(6)
C13	23.0(11)	33.5(13)	21.6(11)	8.3(10)	8.2(9)	0.1(10)
C14	27.4(12)	30.1(13)	21.2(11)	4.8(10)	8.8(9)	5.2(10)
C15	29.2(12)	21.9(11)	21.7(11)	4.2(9)	6.3(9)	2.5(10)
C16	21.4(11)	17.4(11)	21.8(11)	3.1(9)	5.9(9)	1.2(9)
C17	20.9(11)	20.5(11)	21.2(11)	3.7(9)	1.6(9)	1.3(9)
N18	21.3(9)	16.5(9)	31.8(11)	0.0(8)	9.3(8)	-1.4(8)
C19	20.7(10)	18.2(11)	27.6(12)	6.4(9)	4.1(9)	1.8(9)
C20	30.1(12)	28.7(13)	28.3(12)	7.3(11)	4.2(10)	0.7(10)
C21	35.3(13)	32.7(13)	31.0(13)	14.1(11)	12.2(11)	1.3(11)
C22	23.7(11)	21.6(11)	38.3(14)	11.2(11)	9.1(10)	-0.6(9)
C23	22.5(11)	28.9(13)	27.0(12)	6.8(10)	0.9(9)	-2.7(10)

C24	22.9(11)	26.7(12)	24.9(12)	8.8(10)	4.1(9)	-0.5(10)
O25	27.8(8)	18.9(8)	32.7(9)	1.7(7)	9.4(7)	2.3(7)
C26	18.8(10)	24.2(11)	22.1(11)	5.0(9)	3.0(9)	2.5(9)
C27	22.8(11)	27.8(12)	22.3(11)	8.9(10)	5.4(9)	3.7(9)
C28	20.4(11)	21.5(11)	19.4(11)	3.1(9)	4.3(9)	0.8(9)
C29	23.8(11)	23.5(12)	26.1(12)	7.2(10)	7.4(9)	0.7(9)
C30	28.2(12)	45.4(16)	42.4(15)	24.2(13)	4.9(11)	-1.4(12)
C31	23.8(12)	31.0(13)	30.5(13)	9.4(11)	5(1)	-1.8(10)
C32	37.3(14)	21.1(12)	47.8(16)	2.2(12)	14.0(12)	-3.1(11)
C33	16.5(10)	21.7(11)	23.8(11)	4.0(9)	4.2(8)	1.8(9)
C34	20.5(11)	19.5(11)	25.3(11)	5.5(9)	6.0(9)	5.1(9)

Table A3.4. Bond Lengths for cis-1.52

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C2	1.338(3)	C16	C34	1.539(3)
N1	C6	1.347(3)	C17	N18	1.342(3)
C2	C3	1.381(4)	C17	O25	1.228(3)
C3	C4	1.393(4)	N18	C19	1.458(3)
C4	C5	1.377(4)	C19	C20	1.523(3)
C5	C6	1.390(3)	C19	C24	1.531(3)
C6	C7	1.517(3)	C20	C21	1.531(3)
C7	O8	1.227(3)	C21	C22	1.532(3)
C7	N9	1.364(3)	C22	C23	1.522(3)
N9	C10	1.479(3)	C23	C24	1.531(3)
N9	C16	1.507(3)	C26	C27	1.545(3)
C10	C11	1.492(3)	C27	C28	1.539(3)
C11	O12	1.381(3)	C28	C29	1.565(3)
C11	C15	1.349(3)	C28	C33	1.528(3)
O12	C13	1.373(3)	C29	C30	1.534(4)
C13	C14	1.339(3)	C29	C31	1.540(3)
C14	C15	1.431(3)	C29	C32	1.529(3)
C16	C17	1.556(3)	C33	C34	1.526(3)
C16	C26	1.545(3)			

Table A3.5. Bond Angles for cis-1.52

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	N1	C6	116.4(2)	C34	C16	C26	106.41(18)
N1	C2	C3	123.8(2)	N18	C17	C16	115.72(18)
C2	C3	C4	118.7(2)	O25	C17	C16	120.9(2)
C5	C4	C3	118.9(2)	O25	C17	N18	123.2(2)
C4	C5	C6	118.1(2)	C17	N18	C19	123.22(19)
N1	C6	C5	124.1(2)	N18	C19	C20	109.57(19)
N1	C6	C7	117.5(2)	N18	C19	C24	112.24(19)
C5	C6	C7	118.2(2)	C20	C19	C24	110.75(19)
O8	C7	C6	118.2(2)	C19	C20	C21	111.9(2)
O8	C7	N9	123.0(2)	C20	C21	C22	111.5(2)
N9	C7	C6	118.82(19)	C23	C22	C21	110.7(2)
C7	N9	C10	119.99(18)	C22	C23	C24	111.0(2)
C7	N9	C16	116.92(17)	C19	C24	C23	110.24(19)
C10	N9	C16	122.95(18)	C16	C26	C27	115.18(18)
N9	C10	C11	114.99(19)	C28	C27	C26	113.06(18)
O12	C11	C10	116.37(18)	C27	C28	C29	112.21(18)
C15	C11	C10	133.5(2)	C33	C28	C27	108.91(18)
C15	C11	O12	109.9(2)	C33	C28	C29	113.89(18)
C13	O12	C11	106.25(17)	C30	C29	C28	109.31(19)
C14	C13	O12	110.5(2)	C30	C29	C31	108.0(2)
C13	C14	C15	106.8(2)	C31	C29	C28	109.37(19)
C11	C15	C14	106.6(2)	C32	C29	C28	112.7(2)
N9	C16	C17	110.27(18)	C32	C29	C30	110.0(2)
N9	C16	C26	113.55(17)	C32	C29	C31	107.3(2)

N9	C16	C34	109.87(17)	C34	C33	C28	112.12(18)
C26	C16	C17	106.21(17)	C33	C34	C16	112.59(18)
C34	C16	C17	110.40(17)				

Table A3.6. Torsion Angles for cis-1.52

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C2	C3	C4	-1.0(3)	C15	C11	O12	C13	0.5(2)
N1	C6	C7	O8	-123.7(2)	C16	N9	C10	C11	-126.8(2)
N1	C6	C7	N9	56.5(3)	C16	C17	N18	C19	179.50(19)
C2	N1	C6	C5	0.6(3)	C16	C26	C27	C28	-51.8(3)
C2	N1	C6	C7	174.76(19)	C17	C16	C26	C27	170.00(17)
C2	C3	C4	C5	-0.7(3)	C17	C16	C34	C33	-171.65(18)
C3	C4	C5	C6	2.1(3)	C17	N18	C19	C20	-150.9(2)
C4	C5	C6	N1	-2.2(3)	C17	N18	C19	C24	85.6(3)
C4	C5	C6	C7	-176.33(19)	N18	C19	C20	C21	-179.32(19)
C5	C6	C7	O8	50.9(3)	N18	C19	C24	C23	179.83(18)
C5	C6	C7	N9	-129.0(2)	C19	C20	C21	C22	53.7(3)
C6	N1	C2	C3	1.0(3)	C20	C19	C24	C23	57.0(2)
C6	C7	N9	C10	11.0(3)	C20	C21	C22	C23	-54.3(3)
C6	C7	N9	C16	-173.25(18)	C21	C22	C23	C24	57.0(3)
C7	N9	C10	C11	48.7(3)	C22	C23	C24	C19	-58.5(2)
C7	N9	C16	C17	-61.7(2)	C24	C19	C20	C21	-55.0(3)
C7	N9	C16	C26	179.29(18)	O25	C17	N18	C19	-5.7(4)
C7	N9	C16	C34	60.3(2)	C26	C16	C17	N18	88.8(2)
O8	C7	N9	C10	-168.9(2)	C26	C16	C17	O25	-86.2(2)
O8	C7	N9	C16	6.9(3)	C26	C16	C34	C33	-56.8(2)
N9	C10	C11	O12	41.7(3)	C26	C27	C28	C29	177.46(18)
N9	C10	C11	C15	-144.7(2)	C26	C27	C28	C33	50.4(2)
N9	C16	C17	N18	-34.7(3)	C27	C28	C29	C30	67.0(2)
N9	C16	C17	O25	150.4(2)	C27	C28	C29	C31	-174.95(19)

N9	C16	C26	C27	-68.6(2)	C27	C28	C29	C32	-55.7(3)
N9	C16	C34	C33	66.5(2)	C27	C28	C33	C34	-55.7(2)
C10	N9	C16	C17	114.0(2)	C28	C33	C34	C16	61.9(2)
C10	N9	C16	C26	-5.1(3)	C29	C28	C33	C34	178.22(17)
C10	N9	C16	C34	-124.1(2)	C33	C28	C29	C30	-168.73(19)
C10	C11	O12	C13	175.48(18)	C33	C28	C29	C31	-50.6(2)
C10	C11	C15	C14	-173.7(2)	C33	C28	C29	C32	68.6(2)
C11	O12	C13	C14	-0.9(3)	C34	C16	C17	N18	-156.3(2)
O12	C11	C15	C14	0.1(3)	C34	C16	C17	O25	28.8(3)
O12	C13	C14	C15	1.0(3)	C34	C16	C26	C27	52.3(2)
C13	C14	C15	C11	-0.6(3)					

Table A3.7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for cis-1.52

Atom	*x*	*y*	*z*	U(eq)
H2	2590	5330	3365	30
H3	3630	5949	2143	35
H4	5131	7750	2652	34
H5	5466	8878	4379	30
H10A	5136	6318	6248	25
H10B	6587	6873	7274	25
H13	10288	8139	5468	31
H14	9789	6137	4469	31
H15	7250	5308	4951	29
H18	7714	9252	7338	29
H19	7798	11574	7875	27
H20A	8454	10658	6282	35
H20B	10017	10107	6866	35
H21A	9840	12480	7012	37
H21B	11117	11672	6472	37
H22A	12637	11519	8099	32
H22B	12522	12841	8176	32
H23A	10276	12927	9033	33
H23B	11866	12442	9665	33
H24A	10604	10560	8891	30
H24B	9325	11321	9474	30
H26A	5955	8786	9402	27
H26B	7017	8021	8657	27

H27A	4952	6503	8127	29
H27B	5391	6912	9375	29
H28	2917	7863	9381	25
H30A	3792	5681	9776	55
H30B	1903	5223	9724	55
H30C	2539	6526	10297	55
H31A	-66	7070	9065	43
H31B	-518	5727	8687	43
H31C	-415	6406	7850	43
H32A	1840	5399	7115	54
H32B	1361	4530	7717	54
H32C	3306	4954	7873	54
H33A	2234	7240	7150	25
H33B	1019	7938	7830	25
H34A	3173	9457	8578	26
H34B	2624	9217	7337	26

X-ray crystallographic data of trans-1.53

Table A4.1. Crystal data and structure refinement for trans-1.53

Identification code	x1605004
Empirical formula	$C_{30}H_{37}N_3O_4$
Formula weight	503.62
Temperature/K	100
Crystal system	tetragonal
Space group	$P4_2/n$
a/Å	25.908(2)
b/Å	25.908(2)
c/Å	8.0598(8)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	5409.8(11)
Z	8
ρ_{calc}g/cm^3	1.237
μ/mm^{-1}	0.659
F(000)	2160.0
Crystal size/mm^3	0.26 × 0.206 × 0.144
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	4.824 to 140.416
Index ranges	$-31 \leq h \leq 31$, $-31 \leq k \leq 31$, $-9 \leq l \leq 9$
Reflections collected	48994

Independent reflections	5144 [R_{int} = 0.0352, R_{sigma} = 0.0162]
Data/restraints/parameters	5144/0/337
Goodness-of-fit on F^2	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0386, wR_2 = 0.0945
Final R indexes [all data]	R_1 = 0.0420, wR_2 = 0.0970
Largest diff. peak/hole / e $Å^{-3}$	0.34/-0.34

Table A4.2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for trans-1.53. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor

Atom	*x*	*y*	*z*	U(eq)
N1	7067.6(4)	4058.9(4)	-640.1(14)	23.9(2)
C2	7176.7(6)	3792.6(6)	-2024.1(18)	29.3(3)
C3	7564.9(6)	3428.5(6)	-2096(2)	34.2(3)
C4	7848.8(6)	3324.9(6)	-681(2)	35.4(3)
C5	7735.4(5)	3591.9(5)	762.5(19)	28.2(3)
C6	7347.4(5)	3958.7(5)	719.0(16)	20.7(3)
C7	7204.5(4)	4248.0(5)	2284.1(16)	18.9(3)
O8	7088.4(3)	3998.5(3)	3521.9(11)	23.1(2)
N9	7184.8(4)	4774.6(4)	2233.1(13)	17.3(2)
C10	7478.9(5)	5055.4(5)	955.5(15)	19.1(3)
C11	8020.8(5)	5171.8(5)	1462.6(16)	20.3(3)
O12	8303.9(3)	,,4757.4(3)	2000.3(12)	23.5(2)
C13	8792.9(5)	4938.5(6)	2283.8(17)	27.3(3)
C14	8821.9(5)	5444.5(6)	1941.5(18)	29.1(3)
C15	8317.7(5)	5597.5(5)	1408.6(17)	24.6(3)
C16	7010.3(5)	5048.7(5)	3768.7(15)	17.0(2)
C17	7419.1(5)	4995.5(5)	5145.5(15)	18.1(3)
C18	7318.5(5)	5330.9(5)	6674.8(15)	18.0(2)
C19	7212.3(5)	5897.6(5)	6234.3(15)	17.9(3)
C20	7113.7(5)	6210.5(5)	7783.4(16)	18.8(3)
C21	7494.3(5)	6537.6(5)	8402.4(17)	22.7(3)
C22	7414.7(6)	6818.7(5)	9845.6(18)	27.9(3)

C23	6949.3(6)	6782.5(5)	10688.1(17)	29.0(3)
C24	6565.8(5)	6458.5(5)	10087.0(17)	26.2(3)
C25	6650.1(5)	6171.1(5)	8658.6(17)	22.3(3)
C26	6775.5(5)	5926.6(5)	4957.1(16)	19.4(3)
C27	6923.3(5)	5626.6(5)	3394.4(15)	18.3(3)
C28	6480.8(5)	4813.2(4)	4277.9(16)	18.0(3)
O29	6386.0(3)	4697.2(4)	5720.4(11)	23.8(2)
N30	6133.1(4)	4778.0(4)	3045.3(13)	19.2(2)
C31	5662.8(5)	4467.4(5)	3219.9(16)	19.9(3)
C32	5216.6(5)	4705.6(5)	2262(2)	33.7(4)
C33	4732.1(5)	4367.7(6)	2401(2)	39.1(4)
C34	4834.3(6)	3815.3(6)	1844(2)	32.2(3)
C35	5287.9(5)	3583.0(5)	2766.4(19)	26.2(3)
C36	5768.3(5)	3920.6(5)	2620.9(18)	25.5(3)
O37	3784.2(5)	5251.0(5)	753.2(13)	40.5(3)

Table A4.3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for trans-1.53. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N1	25.4(6)	22.0(5)	24.2(6)	-3.1(4)	-1.5(5)	-1.5(4)
C2	33.7(7)	29.0(7)	25.3(7)	-5.1(6)	-0.5(6)	-6.5(6)
C3	34.3(8)	34.3(8)	34.0(8)	-13.7(6)	9.5(6)	-5.0(6)
C4	26.4(7)	32.6(8)	47.3(9)	-9.4(7)	6.5(7)	5.3(6)
C5	21.9(6)	28.5(7)	34.2(8)	-2.2(6)	0.0(6)	3.3(5)
C6	18.6(6)	18.7(6)	24.9(7)	-0.4(5)	1.6(5)	-3.4(5)
C7	14.6(5)	20.2(6)	21.9(6)	0.9(5)	-1.8(5)	-1.1(5)
O8	26.4(5)	19.3(4)	23.8(5)	2.7(4)	1.6(4)	-1.7(4)
N9	17.4(5)	17.7(5)	16.9(5)	0.5(4)	1.1(4)	-1.6(4)
C10	20.8(6)	19.1(6)	17.4(6)	1.4(5)	2.3(5)	-2.2(5)
C11	22.0(6)	21.0(6)	18.0(6)	-0.4(5)	3.2(5)	0.3(5)
O12	20.9(4)	23.8(5)	25.8(5)	2.0(4)	0.9(4)	-0.6(4)
C13	18.5(6)	36.7(8)	26.7(7)	-3.9(6)	0.4(5)	-0.7(5)
C14	22.6(7)	33.1(7)	31.6(8)	-8.2(6)	3.4(6)	-7.3(6)
C15	24.5(6)	22.4(6)	26.8(7)	-3.1(5)	5.5(5)	-3.8(5)
C16	16.4(6)	17.7(6)	16.9(6)	0.7(5)	0.5(5)	-0.7(4)
C17	16.2(6)	18.0(6)	19.9(6)	0.9(5)	-1.1(5)	0.9(4)
C18	16.4(6)	18.7(6)	18.9(6)	1.0(5)	-1.8(5)	0.7(4)
C19	15.7(6)	17.8(6)	20.1(6)	0.7(5)	1.3(5)	-1.6(4)
C20	20.4(6)	15.8(6)	20.4(6)	2.4(5)	-1.6(5)	2.5(5)
C21	20.2(6)	21.7(6)	26.3(7)	0.3(5)	-2.1(5)	0.3(5)
C22	32.1(7)	23.2(6)	28.5(7)	-3.9(6)	-7.8(6)	1.0(5)
C23	42.8(8)	24.0(7)	20.0(7)	-1.9(5)	-1.1(6)	8.4(6)

C24	30.3(7)	24.8(7)	23.6(7)	4.8(5)	6.9(6)	7.4(5)
C25	22.0(6)	19.3(6)	25.5(7)	1.9(5)	2.2(5)	0.0(5)
C26	18.2(6)	17.1(6)	22.7(6)	1.5(5)	-1.2(5)	1.6(5)
C27	17.3(6)	17.8(6)	19.8(6)	2.3(5)	-1.8(5)	-0.8(4)
C28	18.1(6)	14.9(5)	20.9(6)	-0.5(5)	0.9(5)	0.2(4)
O29	23.6(5)	29.6(5)	18.3(5)	1.9(4)	1.5(4)	-6.5(4)
N30	17.7(5)	20.2(5)	19.8(5)	2.3(4)	0.5(4)	-3.4(4)
C31	17.0(6)	22.4(6)	20.3(6)	0.0(5)	0.8(5)	-3.9(5)
C32	19.7(7)	22.4(7)	59.1(10)	9.2(7)	-6.2(7)	-1.6(5)
C33	17.5(7)	30.2(8)	69.6(12)	11.3(8)	-8.6(7)	-1.8(6)
C34	27.8(7)	33.2(8)	35.5(8)	3.3(6)	-8.8(6)	-11.5(6)
C35	25.0(7)	21.3(6)	32.3(7)	-0.6(6)	0.7(6)	-4.7(5)
C36	20.4(6)	21.5(6)	34.7(8)	-0.3(6)	1.1(6)	-1.5(5)
O37	44.2(6)	50.4(7)	27.0(6)	10.7(5)	9.6(5)	22.6(5)

Table A4.4. Bond Lengths for trans-1.53

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N1	C2	1.3418(18)	C17	C18	1.5305(17)
N1	C6	1.3389(17)	C18	C19	1.5353(16)
C2	C3	1.380(2)	C19	C20	1.5105(17)
C3	C4	1.383(2)	C19	C26	1.5316(17)
C4	C5	1.385(2)	C20	C21	1.3925(18)
C5	C6	1.3838(19)	C20	C25	1.3965(18)
C6	C7	1.5133(18)	C21	C22	1.3878(19)
C7	O8	1.2262(16)	C22	C23	1.387(2)
C7	N9	1.3657(16)	C23	C24	1.388(2)
N9	C10	1.4732(15)	C24	C25	1.3884(19)
N9	C16	1.4969(15)	C26	C27	1.5287(17)
C10	C11	1.4930(17)	C28	O29	1.2256(16)
C11	O12	1.3706(15)	C28	N30	1.3441(17)
C11	C15	1.3453(18)	N30	C31	1.4670(15)
O12	C13	1.3700(16)	C31	C32	1.5208(18)
C13	C14	1.342(2)	C31	C36	1.5212(18)
C14	C15	1.431(2)	C32	C33	1.5345(19)
C16	C17	1.5402(16)	C33	C34	1.523(2)
C16	C27	1.5439(16)	C34	C35	1.515(2)
C16	C28	1.5565(16)	C35	C36	1.5257(18)

Table A4.5. Bond Angles for trans-1.53

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
C6	N1	C2	117.80(12)	C18	C17	C16	114.35(10)
N1	C2	C3	122.67(14)	C17	C18	C19	112.78(10)
C2	C3	C4	119.05(14)	C20	C19	C18	110.63(10)
C3	C4	C5	118.88(14)	C20	C19	C26	113.84(10)
C6	C5	C4	118.40(14)	C26	C19	C18	109.55(10)
N1	C6	C5	123.18(12)	C21	C20	C19	120.19(11)
N1	C6	C7	116.97(11)	C21	C20	C25	118.20(12)
C5	C6	C7	119.78(12)	C25	C20	C19	121.58(11)
O8	C7	C6	118.49(11)	C22	C21	C20	120.96(12)
O8	C7	N9	122.81(11)	C23	C22	C21	120.27(13)
N9	C7	C6	118.61(11)	C22	C23	C24	119.49(13)
C7	N9	C10	119.68(10)	C23	C24	C25	120.08(13)
C7	N9	C16	117.40(10)	C24	C25	C20	120.99(12)
C10	N9	C16	119.99(9)	C27	C26	C19	110.11(10)
N9	C10	C11	113.25(10)	C26	C27	C16	111.63(10)
O12	C11	C10	115.58(10)	O29	C28	C16	121.51(11)
C15	C11	C10	133.98(12)	O29	C28	N30	123.39(11)
C15	C11	O12	110.26(11)	N30	C28	C16	114.98(10)
C13	O12	C11	106.22(10)	C28	N30	C31	121.53(10)
C14	C13	O12	110.62(12)	N30	C31	C32	111.10(10)
C13	C14	C15	106.33(12)	N30	C31	C36	109.33(10)
C11	C15	C14	106.57(12)	C32	C31	C36	110.69(11)
N9	C16	C17	110.21(9)	C31	C32	C33	110.68(12)

N9	C16	C27	110.04(10)	C34	C33	C32	111.85(13)
N9	C16	C28	107.36(9)	C35	C34	C33	111.31(12)
C17	C16	C27	109.14(10)	C34	C35	C36	111.54(11)
C17	C16	C28	112.40(10)	C31	C36	C35	111.27(11)
C27	C16	C28	107.64(9)				

Table A4.6. Hydrogen Bonds for trans-1.53

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O37	H37A	O29[1]	0.87	2.10	2.8794(14)	148.3
O37	H37B	N1[2]	0.87	1.98	2.8417(16)	172.0

[1]1-X,1-Y,1-Z; [2]1-X,1-Y,-Z

Table A4.7. Torsion Angles for trans-1.53

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
N1	C2	C3	C4	1.2(2)	C16	C28	N30	C31	166.58(10)
N1	C6	C7	O8	122.32(13)	C17	C16	C27	C26	-55.55(13)
N1	C6	C7	N9	-54.37(15)	C17	C16	C28	O29	13.37(16)
C2	N1	C6	C5	-0.81(19)	C17	C16	C28	N30	-170.42(10)
C2	N1	C6	C7	-177.67(11)	C17	C18	C19	C20	179.77(10)
C2	C3	C4	C5	-0.3(2)	C17	C18	C19	C26	53.47(13)
C3	C4	C5	C6	-1.1(2)	C18	C19	C20	C21	103.95(13)
C4	C5	C6	N1	1.7(2)	C18	C19	C20	C25	-74.18(14)
C4	C5	C6	C7	178.48(12)	C18	C19	C26	C27	-59.02(13)
C5	C6	C7	O8	-54.65(17)	C19	C20	C21	C22	-178.48(12)
C5	C6	C7	N9	128.65(13)	C19	C20	C25	C24	179.58(11)
C6	N1	C2	C3	-0.7(2)	C19	C26	C27	C16	61.73(13)
C6	C7	N9	C10	-23.12(16)	C20	C19	C26	C27	176.53(10)
C6	C7	N9	C16	176.24(10)	C20	C21	C22	C23	-0.8(2)
C7	N9	C10	C11	-87.33(13)	C21	C20	C25	C24	1.42(19)
C7	N9	C16	C17	69.20(13)	C21	C22	C23	C24	0.7(2)
C7	N9	C16	C27	-170.38(10)	C22	C23	C24	C25	0.4(2)
C7	N9	C16	C28	-53.51(13)	C23	C24	C25	C20	-1.5(2)
O8	C7	N9	C10	160.33(11)	C25	C20	C21	C22	-0.29(19)
O8	C7	N9	C16	-0.30(17)	C26	C19	C20	C21	-132.18(12)
N9	C10	C11	O12	52.76(14)	C26	C19	C20	C25	49.69(16)
N9	C10	C11	C15	-132.79(15)	C27	C16	C17	C18	49.99(13)
N9	C16	C17	C18	170.94(10)	C27	C16	C28	O29	-106.85(13)

N9	C16	C27	C26	-176.60(9)	C27	C16	C28	N30	69.36(13)
N9	C16	C28	O29	134.72(12)	C28	C16	C17	C18	-69.35(13)
N9	C16	C28	N30	-49.07(13)	C28	C16	C27	C26	66.71(12)
C10	N9	C16	C17	-91.37(12)	C28	N30	C31	C32	147.24(12)
C10	N9	C16	C27	29.04(14)	C28	N30	C31	C36	-90.29(14)
C10	N9	C16	C28	145.91(10)	O29	C28	N30	C31	-17.29(18)
C10	C11	O12	C13	175.71(11)	N30	C31	C32	C33	177.97(13)
C10	C11	C15	C14	-174.52(14)	N30	C31	C36	C35	-179.57(11)
C11	O12	C13	C14	-0.10(15)	C31	C32	C33	C34	-55.24(19)
O12	C11	C15	C14	0.14(15)	C32	C31	C36	C35	-56.87(15)
O12	C13	C14	C15	0.18(16)	C32	C33	C34	C35	54.09(18)
C13	C14	C15	C11	-0.20(16)	C33	C34	C35	C36	-54.14(17)
C15	C11	O12	C13	-0.03(14)	C34	C35	C36	C31	55.83(16)
C16	N9	C10	C11	72.80(13)	C36	C31	C32	C33	56.29(17)
C16	C17	C18	C19	-50.43(14)					

Table A4.8. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for trans-1.53

Atom	*x*	*y*	*z*	U(eq)
H2	6979	3857	-2994	35
H3	7636	3252	-3103	41
H4	8117	3075	-699	42
H5	7920	3525	1758	34
H10A	7299	5384	704	23
H10B	7485	4847	-74	23
H13	9073	4734	2669	33
H14	9118	5659	2034	35
H15	8213	5934	1081	29
H17A	7435	4630	5497	22
H17B	7761	5088	4680	22
H18A	7622	5313	7418	22
H18B	7018	5190	7287	22
H19	7531	6038	5698	21
H21	7813	6569	7828	27
H22	7680	7037	10258	34
H23	6893	6978	11669	35
H24	6245	6433	10654	31
H25	6389	5944	8271	27
H26A	6456	5780	5438	23
H26B	6708	6292	4668	23
H27A	7243	5775	2919	22

H27B	6645	5663	2559	22
H30	6189	4945	2112	23
H31	5567	4453	4421	24
H32A	5314	4743	1080	40
H32B	5142	5054	2707	40
H33A	4612	4366	3567	47
H33B	4454	4518	1710	47
H34A	4523	3603	2045	39
H34B	4906	3812	638	39
H35A	5363	3236	2310	31
H35B	5197	3542	3952	31
H36A	6050	3768	3289	31
H36B	5882	3931	1449	31
H37A	3838	5189	1799	61
H37B	3541	5480	652	61

X-ray crystallographic data of (S)-1.71

Table A5.1. Crystal data and structure refinement for (S)-1.71

Identification code	q07e	
Empirical formula	C22.50 H25 Br Cl N3 O4	
Formula weight	516.81	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 5.9999(3) Å	□= 91.5940(10)°.
	b = 12.1506(6) Å	□= 90.561(2)°.
	c = 16.4980(9) Å	□ = 102.873(2)°.
Volume	1171.90(10) $Å^3$	
Z	2	
Density (calculated)	1.465 Mg/m^3	
Absorption coefficient	3.723 mm^{-1}	
F(000)	530	
Crystal size	0.350 x 0.135 x 0.025 mm^3	
Theta range for data collection	2.680 to 69.680°.	
Index ranges	-7<=h<=6, -14<=k<=12, -20<=l<=20	
Reflections collected	12689	
Independent reflections	5679 [R(int) = 0.0342]	
Completeness to theta = 66.000°	95.0 %	
Absorption correction	Multi-scan	

Max. and min. transmission	1.000 and 0.645
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5679 / 3 / 732
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0297, wR2 = 0.0732
R indices (all data)	R1 = 0.0297, wR2 = 0.0732
Absolute structure parameter	0.055(8)
Extinction coefficient	n/a
Largest diff. peak and hole	0.564 and -0.672 e.$Å^{-3}$

Table A5.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (S)-1.71. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
C(1A)	255(6)	3333(3)	809(2)	16(1)
C(2A)	-1971(6)	3669(3)	539(2)	18(1)
C(3A)	-1576(7)	4798(3)	124(2)	27(1)
C(4A)	1603(6)	3057(3)	80(2)	20(1)
N(5A)	-333(5)	2340(2)	1350(2)	15(1)
C(6A)	1359(6)	2108(3)	1824(2)	16(1)
O(7A)	3325(4)	2680(2)	1820(2)	20(1)
C(8A)	806(6)	1161(3)	2419(2)	18(1)
N(9A)	-777(6)	1230(3)	2976(2)	23(1)
C(10A)	-1133(7)	440(4)	3543(2)	29(1)
C(11A)	30(8)	-424(4)	3570(3)	31(1)
C(12A)	1614(8)	-493(4)	2984(3)	35(1)
C(13A)	2031(7)	318(3)	2396(3)	28(1)
C(14A)	-2462(6)	1483(3)	1200(2)	18(1)
C(15A)	-2451(6)	824(3)	428(2)	22(1)
O(16A)	-594(5)	373(2)	299(2)	26(1)
C(17A)	-1024(8)	-241(4)	-419(3)	32(1)
C(18A)	-3048(9)	-185(4)	-733(3)	38(1)
C(19A)	-4003(8)	518(4)	-183(3)	32(1)
C(20A)	1708(6)	4364(3)	1305(2)	17(1)

O(21A)	3365(4)	4969(2)	1006(1)	20(1)
N(22A)	790(5)	4561(2)	2026(2)	16(1)
C(23A)	1743(6)	5429(3)	2600(2)	17(1)
C(24A)	4047(6)	5947(3)	2639(2)	20(1)
C(25A)	4862(7)	6744(3)	3256(2)	23(1)
C(26A)	3365(7)	6997(3)	3826(2)	21(1)
C(27A)	1067(7)	6499(3)	3797(2)	21(1)
C(28A)	255(7)	5721(3)	3171(2)	19(1)
Br(29)	4543(1)	8040(1)	4690(1)	29(1)
C(1B)	5344(6)	5965(3)	7789(2)	16(1)
C(2B)	7804(6)	6099(3)	8128(2)	19(1)
C(3B)	8474(7)	7021(3)	8788(2)	25(1)
C(4B)	3585(6)	5415(3)	8406(2)	20(1)
N(5B)	5107(5)	5276(2)	7012(2)	16(1)
C(6B)	3353(6)	5335(3)	6497(2)	17(1)
O(7B)	1932(4)	5887(2)	6668(1)	21(1)
C(8B)	3220(6)	4751(3)	5672(2)	18(1)
N(9B)	5152(5)	4912(3)	5239(2)	18(1)
C(10B)	5000(6)	4451(3)	4490(2)	20(1)
C(11B)	2993(7)	3806(3)	4149(2)	22(1)
C(12B)	1016(7)	3658(3)	4599(2)	24(1)
C(13B)	1127(7)	4146(3)	5375(2)	22(1)
C(14B)	6141(7)	4280(3)	6967(2)	20(1)
C(15B)	4782(8)	3302(3)	7409(2)	25(1)

O(16B)	2526(5)	2981(2)	7184(2)	31(1)
C(17B)	1567(10)	2082(4)	7649(3)	40(1)
C(18B)	3133(11)	1845(4)	8140(3)	47(1)
C(19B)	5250(9)	2625(4)	7993(2)	37(1)
C(20B)	5012(6)	7168(3)	7620(2)	18(1)
O(21B)	3889(4)	7632(2)	8078(1)	21(1)
N(22B)	6232(5)	7684(3)	6996(2)	19(1)
C(23B)	6097(6)	8744(3)	6691(2)	18(1)
C(24B)	4225(7)	9227(3)	6815(2)	21(1)
C(25B)	4090(7)	10209(3)	6418(2)	23(1)
C(26B)	5827(6)	10713(3)	5918(2)	22(1)
C(27B)	7779(7)	10271(3)	5822(2)	21(1)
C(28B)	7904(6)	9288(3)	6210(2)	20(1)
Br(2B)	5457(1)	11960(1)	5310(1)	26(1)
Cl(1S)	6529(2)	8434(1)	1588(1)	63(1)
Cl(2S)	1872(2)	7951(1)	930(1)	55(1)
C(1S)	4625(11)	7688(4)	816(4)	53(1)
O(1W)	-2933(5)	3136(2)	2895(2)	22(1)
O(2W)	8810(5)	6781(2)	5786(2)	22(1)

Table A5.3. Bond lengths [Å] and angles [°] for (S)-1.71

C(1A)-N(5A)	1.500(4)
C(1A)-C(4A)	1.526(4)
C(1A)-C(2A)	1.546(5)
C(1A)-C(20A)	1.562(5)
C(2A)-C(3A)	1.523(5)
C(2A)-H(2A)	1.02(4)
C(2A)-H(2B)	0.92(5)
C(3A)-H(3A)	0.9800
C(3A)-H(3B)	0.9800
C(3A)-H(3C)	0.9800
C(4A)-H(4A)	0.9800
C(4A)-H(4B)	0.9800
C(4A)-H(4C)	0.9800
N(5A)-C(6A)	1.359(4)
N(5A)-C(14A)	1.471(4)
C(6A)-O(7A)	1.229(4)
C(6A)-C(8A)	1.516(5)
C(8A)-N(9A)	1.341(5)
C(8A)-C(13A)	1.388(5)
N(9A)-C(10A)	1.344(5)
C(10A)-C(11A)	1.385(6)
C(10A)-H(10A)	1.03(7)

C(11A)-C(12A)	1.377(7)
C(11A)-H(11A)	1.01(8)
C(12A)-C(13A)	1.387(6)
C(12A)-H(12A)	0.95(6)
C(13A)-H(13A)	0.87(6)
C(14A)-C(15A)	1.486(5)
C(14A)-H(14A)	0.95(5)
C(14A)-H(14B)	0.87(5)
C(15A)-C(19A)	1.352(6)
C(15A)-O(16A)	1.363(5)
O(16A)-C(17A)	1.373(5)
C(17A)-C(18A)	1.331(7)
C(17A)-H(17A)	0.84(6)
C(18A)-C(19A)	1.438(6)
C(18A)-H(18A)	0.93(7)
C(19A)-H(19A)	0.97(7)
C(20A)-O(21A)	1.215(4)
C(20A)-N(22A)	1.352(4)
N(22A)-C(23A)	1.416(5)
N(22A)-H(22N)	0.80(5)
C(23A)-C(24A)	1.385(6)
C(23A)-C(28A)	1.396(5)
C(24A)-C(25A)	1.392(5)
C(24A)-H(24A)	1.01(5)

C(25A)-C(26A)	1.382(6)
C(25A)-H(25A)	1.02(5)
C(26A)-C(27A)	1.377(6)
C(26A)-Br(29)	1.902(3)
C(27A)-C(28A)	1.388(5)
C(27A)-H(27A)	0.91(6)
C(28A)-H(28A)	0.84(7)
C(1B)-N(5B)	1.500(4)
C(1B)-C(4B)	1.530(5)
C(1B)-C(2B)	1.546(5)
C(1B)-C(20B)	1.551(5)
C(2B)-C(3B)	1.525(5)
C(2B)-H(2C)	0.97(5)
C(2B)-H(2D)	1.06(5)
C(3B)-H(3D)	0.9800
C(3B)-H(3E)	0.9800
C(3B)-H(3F)	0.9800
C(4B)-H(4D)	0.9800
C(4B)-H(4E)	0.9800
C(4B)-H(4F)	0.9800
N(5B)-C(6B)	1.362(4)
N(5B)-C(14B)	1.479(4)
C(6B)-O(7B)	1.227(4)
C(6B)-C(8B)	1.509(4)

C(8B)-N(9B)	1.347(5)
C(8B)-C(13B)	1.384(6)
N(9B)-C(10B)	1.337(5)
C(10B)-C(11B)	1.386(6)
C(10B)-H(10B)	1.07(6)
C(11B)-C(12B)	1.385(6)
C(11B)-H(11B)	0.99(5)
C(12B)-C(13B)	1.391(5)
C(12B)-H(12B)	0.97(6)
C(13B)-H(13B)	0.86(6)
C(14B)-C(15B)	1.495(6)
C(14B)-H(14C)	0.95(6)
C(14B)-H(14D)	0.95(4)
C(15B)-C(19B)	1.352(6)
C(15B)-O(16B)	1.367(6)
O(16B)-C(17B)	1.375(5)
C(17B)-C(18B)	1.319(9)
C(17B)-H(17B)	0.99(10)
C(18B)-C(19B)	1.433(8)
C(18B)-H(18B)	0.9500
C(19B)-H(19B)	0.99(6)
C(20B)-O(21B)	1.224(4)
C(20B)-N(22B)	1.355(5)
N(22B)-C(23B)	1.413(5)

N(22B)-H(22B)	0.77(6)
C(23B)-C(24B)	1.393(5)
C(23B)-C(28B)	1.404(5)
C(24B)-C(25B)	1.395(6)
C(24B)-H(24B)	0.98(5)
C(25B)-C(26B)	1.379(6)
C(25B)-H(25B)	0.99(6)
C(26B)-C(27B)	1.401(5)
C(26B)-Br(2B)	1.893(4)
C(27B)-C(28B)	1.387(6)
C(27B)-H(27B)	0.89(5)
C(28B)-H(28B)	1.04(4)
Cl(1S)-C(1S)	1.787(7)
Cl(2S)-C(1S)	1.762(6)
C(1S)-H(1SA)	1.03(8)
C(1S)-H(1SB)	1.12(7)
O(1W)-H(1W1)	0.81(6)
O(1W)-H(1W2)	0.92(7)
O(2W)-H(2W1)	0.81(5)
O(2W)-H(2W2)	0.90(7)
N(5A)-C(1A)-C(4A)	110.6(3)
N(5A)-C(1A)-C(2A)	109.2(3)
C(4A)-C(1A)-C(2A)	111.3(3)
N(5A)-C(1A)-C(20A)	109.0(2)

C(4A)-C(1A)-C(20A)	109.7(3)
C(2A)-C(1A)-C(20A)	106.9(3)
C(3A)-C(2A)-C(1A)	113.9(3)
C(3A)-C(2A)-H(2A)	109(2)
C(1A)-C(2A)-H(2A)	110(2)
C(3A)-C(2A)-H(2B)	108(3)
C(1A)-C(2A)-H(2B)	112(3)
H(2A)-C(2A)-H(2B)	104(4)
C(2A)-C(3A)-H(3A)	109.5
C(2A)-C(3A)-H(3B)	109.5
H(3A)-C(3A)-H(3B)	109.5
C(2A)-C(3A)-H(3C)	109.5
H(3A)-C(3A)-H(3C)	109.5
H(3B)-C(3A)-H(3C)	109.5
C(1A)-C(4A)-H(4A)	109.5
C(1A)-C(4A)-H(4B)	109.5
H(4A)-C(4A)-H(4B)	109.5
C(1A)-C(4A)-H(4C)	109.5
H(4A)-C(4A)-H(4C)	109.5
H(4B)-C(4A)-H(4C)	109.5
C(6A)-N(5A)-C(14A)	120.3(3)
C(6A)-N(5A)-C(1A)	118.0(3)
C(14A)-N(5A)-C(1A)	119.6(3)
O(7A)-C(6A)-N(5A)	122.2(3)

O(7A)-C(6A)-C(8A)	118.0(3)
N(5A)-C(6A)-C(8A)	119.7(3)
N(9A)-C(8A)-C(13A)	123.6(3)
N(9A)-C(8A)-C(6A)	117.0(3)
C(13A)-C(8A)-C(6A)	119.3(3)
C(8A)-N(9A)-C(10A)	116.9(3)
N(9A)-C(10A)-C(11A)	123.3(4)
N(9A)-C(10A)-H(10A)	117(4)
C(11A)-C(10A)-H(10A)	120(4)
C(12A)-C(11A)-C(10A)	118.9(4)
C(12A)-C(11A)-H(11A)	119(5)
C(10A)-C(11A)-H(11A)	122(5)
C(11A)-C(12A)-C(13A)	119.0(4)
C(11A)-C(12A)-H(12A)	117(4)
C(13A)-C(12A)-H(12A)	124(4)
C(12A)-C(13A)-C(8A)	118.3(4)
C(12A)-C(13A)-H(13A)	121(4)
C(8A)-C(13A)-H(13A)	121(4)
N(5A)-C(14A)-C(15A)	113.0(3)
N(5A)-C(14A)-H(14A)	111(3)
C(15A)-C(14A)-H(14A)	110(3)
N(5A)-C(14A)-H(14B)	106(3)
C(15A)-C(14A)-H(14B)	107(3)
H(14A)-C(14A)-H(14B)	109(4)

C(19A)-C(15A)-O(16A)	110.6(3)
C(19A)-C(15A)-C(14A)	132.7(4)
O(16A)-C(15A)-C(14A)	116.6(3)
C(15A)-O(16A)-C(17A)	106.1(3)
C(18A)-C(17A)-O(16A)	111.0(4)
C(18A)-C(17A)-H(17A)	135(3)
O(16A)-C(17A)-H(17A)	114(3)
C(17A)-C(18A)-C(19A)	106.5(4)
C(17A)-C(18A)-H(18A)	121(4)
C(19A)-C(18A)-H(18A)	133(4)
C(15A)-C(19A)-C(18A)	105.9(4)
C(15A)-C(19A)-H(19A)	122(3)
C(18A)-C(19A)-H(19A)	132(3)
O(21A)-C(20A)-N(22A)	125.6(3)
O(21A)-C(20A)-C(1A)	120.4(3)
N(22A)-C(20A)-C(1A)	113.6(3)
C(20A)-N(22A)-C(23A)	125.8(3)
C(20A)-N(22A)-H(22N)	118(3)
C(23A)-N(22A)-H(22N)	116(3)
C(24A)-C(23A)-C(28A)	119.9(3)
C(24A)-C(23A)-N(22A)	123.4(3)
C(28A)-C(23A)-N(22A)	116.7(3)
C(23A)-C(24A)-C(25A)	119.5(3)
C(23A)-C(24A)-H(24A)	119(3)

C(25A)-C(24A)-H(24A)	121(3)
C(26A)-C(25A)-C(24A)	119.5(4)
C(26A)-C(25A)-H(25A)	123(3)
C(24A)-C(25A)-H(25A)	117(3)
C(27A)-C(26A)-C(25A)	122.0(3)
C(27A)-C(26A)-Br(29)	119.3(3)
C(25A)-C(26A)-Br(29)	118.7(3)
C(26A)-C(27A)-C(28A)	118.3(3)
C(26A)-C(27A)-H(27A)	122(4)
C(28A)-C(27A)-H(27A)	120(4)
C(27A)-C(28A)-C(23A)	120.8(4)
C(27A)-C(28A)-H(28A)	121(4)
C(23A)-C(28A)-H(28A)	119(4)
N(5B)-C(1B)-C(4B)	111.1(3)
N(5B)-C(1B)-C(2B)	108.7(2)
C(4B)-C(1B)-C(2B)	110.9(3)
N(5B)-C(1B)-C(20B)	109.7(3)
C(4B)-C(1B)-C(20B)	109.3(3)
C(2B)-C(1B)-C(20B)	107.0(3)
C(3B)-C(2B)-C(1B)	114.1(3)
C(3B)-C(2B)-H(2C)	112(3)
C(1B)-C(2B)-H(2C)	108(3)
C(3B)-C(2B)-H(2D)	112(3)
C(1B)-C(2B)-H(2D)	106(3)

H(2C)-C(2B)-H(2D)	105(4)
C(2B)-C(3B)-H(3D)	109.5
C(2B)-C(3B)-H(3E)	109.5
H(3D)-C(3B)-H(3E)	109.5
C(2B)-C(3B)-H(3F)	109.5
H(3D)-C(3B)-H(3F)	109.5
H(3E)-C(3B)-H(3F)	109.5
C(1B)-C(4B)-H(4D)	109.5
C(1B)-C(4B)-H(4E)	109.5
H(4D)-C(4B)-H(4E)	109.5
C(1B)-C(4B)-H(4F)	109.5
H(4D)-C(4B)-H(4F)	109.5
H(4E)-C(4B)-H(4F)	109.5
C(6B)-N(5B)-C(14B)	119.6(3)
C(6B)-N(5B)-C(1B)	117.8(3)
C(14B)-N(5B)-C(1B)	118.6(3)
O(7B)-C(6B)-N(5B)	122.1(3)
O(7B)-C(6B)-C(8B)	118.9(3)
N(5B)-C(6B)-C(8B)	119.0(3)
N(9B)-C(8B)-C(13B)	123.2(3)
N(9B)-C(8B)-C(6B)	117.4(3)
C(13B)-C(8B)-C(6B)	119.3(3)
C(10B)-N(9B)-C(8B)	117.3(3)
N(9B)-C(10B)-C(11B)	123.7(3)

N(9B)-C(10B)-H(10B)	114(3)
C(11B)-C(10B)-H(10B)	123(3)
C(12B)-C(11B)-C(10B)	118.3(3)
C(12B)-C(11B)-H(11B)	123(3)
C(10B)-C(11B)-H(11B)	118(3)
C(11B)-C(12B)-C(13B)	119.0(4)
C(11B)-C(12B)-H(12B)	122(3)
C(13B)-C(12B)-H(12B)	119(3)
C(8B)-C(13B)-C(12B)	118.5(3)
C(8B)-C(13B)-H(13B)	122(3)
C(12B)-C(13B)-H(13B)	119(3)
N(5B)-C(14B)-C(15B)	112.3(3)
N(5B)-C(14B)-H(14C)	109(3)
C(15B)-C(14B)-H(14C)	112(3)
N(5B)-C(14B)-H(14D)	107(3)
C(15B)-C(14B)-H(14D)	112(3)
H(14C)-C(14B)-H(14D)	105(4)
C(19B)-C(15B)-O(16B)	109.7(4)
C(19B)-C(15B)-C(14B)	135.1(4)
O(16B)-C(15B)-C(14B)	115.2(3)
C(15B)-O(16B)-C(17B)	106.9(4)
C(18B)-C(17B)-O(16B)	109.9(5)
C(18B)-C(17B)-H(17B)	133(5)
O(16B)-C(17B)-H(17B)	117(5)

C(17B)-C(18B)-C(19B)	107.8(4)
C(17B)-C(18B)-H(18B)	126.1
C(19B)-C(18B)-H(18B)	126.1
C(15B)-C(19B)-C(18B)	105.7(5)
C(15B)-C(19B)-H(19B)	123(3)
C(18B)-C(19B)-H(19B)	131(3)
O(21B)-C(20B)-N(22B)	123.9(3)
O(21B)-C(20B)-C(1B)	120.5(3)
N(22B)-C(20B)-C(1B)	115.2(3)
C(20B)-N(22B)-C(23B)	125.6(3)
C(20B)-N(22B)-H(22B)	119(3)
C(23B)-N(22B)-H(22B)	115(3)
C(24B)-C(23B)-C(28B)	119.7(3)
C(24B)-C(23B)-N(22B)	123.0(3)
C(28B)-C(23B)-N(22B)	117.2(3)
C(23B)-C(24B)-C(25B)	119.7(3)
C(23B)-C(24B)-H(24B)	119(3)
C(25B)-C(24B)-H(24B)	121(3)
C(26B)-C(25B)-C(24B)	120.1(3)
C(26B)-C(25B)-H(25B)	122(3)
C(24B)-C(25B)-H(25B)	117(3)
C(25B)-C(26B)-C(27B)	120.8(3)
C(25B)-C(26B)-Br(2B)	118.9(3)
C(27B)-C(26B)-Br(2B)	120.2(3)

C(28B)-C(27B)-C(26B)	119.1(3)
C(28B)-C(27B)-H(27B)	120(3)
C(26B)-C(27B)-H(27B)	120(3)
C(27B)-C(28B)-C(23B)	120.4(3)
C(27B)-C(28B)-H(28B)	124(2)
C(23B)-C(28B)-H(28B)	115(2)
Cl(2S)-C(1S)-Cl(1S)	110.5(3)
Cl(2S)-C(1S)-H(1SA)	107(4)
Cl(1S)-C(1S)-H(1SA)	108(4)
Cl(2S)-C(1S)-H(1SB)	107(4)
Cl(1S)-C(1S)-H(1SB)	111(4)
H(1SA)-C(1S)-H(1SB)	112(5)
H(1W1)-O(1W)-H(1W2)	102(5)
H(2W1)-O(2W)-H(2W2)	98(5)

Symmetry transformations used to generate equivalent atoms:

Table A5.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (S)-1.71. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1A)	12(2)	17(2)	19(1)	2(1)	-2(1)	3(1)
C(2A)	12(2)	20(2)	23(2)	2(1)	-4(1)	5(1)
C(3A)	23(2)	29(2)	30(2)	11(2)	-2(1)	9(2)
C(4A)	17(2)	22(2)	20(1)	-1(1)	3(1)	4(1)
N(5A)	10(2)	16(1)	18(1)	2(1)	-2(1)	4(1)
C(6A)	14(2)	16(2)	20(2)	0(1)	-1(1)	8(1)
O(7A)	12(1)	20(1)	28(1)	3(1)	-2(1)	4(1)
C(8A)	15(2)	17(2)	23(2)	3(1)	-2(1)	3(1)
N(9A)	21(2)	24(2)	24(1)	2(1)	-1(1)	8(1)
C(10A)	30(2)	32(2)	25(2)	7(2)	1(2)	6(2)
C(11A)	30(2)	29(2)	35(2)	14(2)	-1(2)	6(2)
C(12A)	30(3)	26(2)	53(3)	15(2)	5(2)	13(2)
C(13A)	19(2)	24(2)	43(2)	9(2)	4(2)	9(2)
C(14A)	10(2)	18(2)	25(2)	2(1)	-2(1)	2(1)
C(15A)	16(2)	17(2)	31(2)	2(1)	-4(1)	3(1)
O(16A)	20(2)	22(1)	34(1)	-5(1)	-3(1)	6(1)
C(17A)	33(3)	24(2)	37(2)	-11(2)	-1(2)	6(2)
C(18A)	47(3)	33(2)	33(2)	-13(2)	-10(2)	7(2)
C(19A)	31(3)	28(2)	35(2)	-6(2)	-12(2)	6(2)

C(20A)	12(2)	16(2)	23(2)	3(1)	-2(1)	5(1)
O(21A)	15(1)	19(1)	24(1)	0(1)	1(1)	1(1)
N(22A)	11(2)	16(1)	21(1)	1(1)	0(1)	1(1)
C(23A)	19(2)	14(2)	19(2)	2(1)	-3(1)	7(1)
C(24A)	16(2)	21(2)	24(2)	1(1)	-2(1)	6(1)
C(25A)	16(2)	23(2)	31(2)	1(1)	-4(1)	3(1)
C(26A)	25(2)	16(2)	21(2)	-2(1)	-7(1)	5(1)
C(27A)	21(2)	20(2)	22(2)	1(1)	2(1)	8(1)
C(28A)	14(2)	19(2)	25(2)	3(1)	0(1)	2(1)
Br(29)	31(1)	27(1)	26(1)	-8(1)	-7(1)	1(1)
C(1B)	14(2)	19(2)	16(1)	-1(1)	-1(1)	6(1)
C(2B)	17(2)	23(2)	18(2)	-1(1)	-3(1)	9(1)
C(3B)	22(2)	28(2)	26(2)	-6(2)	-6(1)	10(2)
C(4B)	17(2)	22(2)	23(2)	3(1)	1(1)	8(1)
N(5B)	15(2)	18(1)	18(1)	0(1)	-2(1)	8(1)
C(6B)	12(2)	18(2)	21(2)	2(1)	-1(1)	6(1)
O(7B)	17(1)	26(1)	22(1)	0(1)	-3(1)	10(1)
C(8B)	18(2)	17(2)	20(2)	3(1)	2(1)	10(1)
N(9B)	13(2)	21(2)	19(1)	2(1)	-2(1)	6(1)
C(10B)	19(2)	23(2)	21(2)	6(1)	2(1)	10(1)
C(11B)	29(2)	21(2)	18(2)	1(1)	1(1)	13(2)
C(12B)	20(2)	26(2)	25(2)	-3(2)	-5(1)	7(1)
C(13B)	15(2)	28(2)	23(2)	0(1)	0(1)	7(1)
C(14B)	19(2)	22(2)	20(2)	-1(1)	-3(1)	12(1)

C(15B)	40(3)	21(2)	20(2)	-1(1)	0(1)	16(2)
O(16B)	31(2)	25(1)	35(1)	4(1)	8(1)	3(1)
C(17B)	52(3)	24(2)	43(2)	6(2)	20(2)	4(2)
C(18B)	78(4)	29(2)	35(2)	6(2)	19(2)	16(2)
C(19B)	58(3)	35(2)	25(2)	5(2)	1(2)	25(2)
C(20B)	13(2)	20(2)	22(2)	-1(1)	-5(1)	7(1)
O(21B)	21(1)	23(1)	22(1)	1(1)	3(1)	11(1)
N(22B)	17(2)	18(2)	24(1)	2(1)	0(1)	10(1)
C(23B)	19(2)	14(2)	19(1)	-1(1)	-4(1)	5(1)
C(24B)	23(2)	19(2)	24(2)	4(1)	-1(1)	10(1)
C(25B)	23(2)	17(2)	31(2)	2(1)	-2(1)	10(1)
C(26B)	21(2)	19(2)	24(2)	-3(1)	-7(1)	4(1)
C(27B)	19(2)	19(2)	25(2)	0(1)	-2(1)	4(1)
C(28B)	15(2)	20(2)	24(2)	1(1)	-3(1)	6(1)
Br(2B)	30(1)	18(1)	34(1)	6(1)	0(1)	10(1)
Cl(1S)	35(1)	39(1)	112(1)	34(1)	-7(1)	-2(1)
Cl(2S)	43(1)	48(1)	74(1)	-9(1)	-13(1)	15(1)
C(1S)	53(4)	27(2)	80(4)	8(2)	21(3)	11(2)
O(1W)	15(1)	23(1)	28(1)	0(1)	-2(1)	6(1)
O(2W)	15(1)	22(1)	31(1)	1(1)	-1(1)	8(1)

Table A5.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for (S)-1.71

	x	y	z	U(eq)
H(2A)	-2990(70)	3700(40)	1030(20)	13(9)
H(2B)	-2840(90)	3130(40)	190(30)	21(10)
H(3A)	-561	4788	-337	33(12)
H(3B)	-870	5405	511	29(12)
H(3C)	-3043	4928	-70	32(12)
H(4A)	2895	2755	268	33(13)
H(4B)	2174	3745	-220	33(13)
H(4C)	604	2493	-275	19(10)
H(10A)	-2360(120)	480(50)	3960(40)	49(16)
H(11A)	-160(140)	-970(70)	4030(50)	60(20)
H(12A)	2300(100)	-1130(50)	2990(30)	40(14)
H(13A)	3010(100)	290(50)	2020(30)	33(13)
H(14A)	-3750(90)	1820(40)	1210(30)	23(11)
H(14B)	-2570(80)	1010(40)	1590(30)	18(10)
H(17A)	70(100)	-520(40)	-570(30)	24(12)
H(18A)	-3590(120)	-580(60)	-1210(40)	51(17)
H(19A)	-5480(120)	710(50)	-170(30)	41(14)
H(22N)	-340(90)	4120(40)	2160(30)	17(10)

H(24A)	5090(90)	5750(40)	2210(30)	22(11)
H(25A)	6570(90)	7090(40)	3270(30)	18(10)
H(27A)	110(100)	6630(50)	4190(30)	36(13)
H(28A)	-1150(120)	5410(50)	3130(30)	35(14)
H(2C)	8840(90)	6220(40)	7680(30)	23(11)
H(2D)	7890(90)	5290(40)	8340(30)	26(12)
H(3D)	7413	6860	9239	15(9)
H(3E)	8408	7753	8566	44(15)
H(3F)	10032	7044	8983	14(10)
H(4D)	2041	5335	8178	40(14)
H(4E)	3751	5891	8902	20(11)
H(4F)	3836	4669	8533	19(10)
H(10B)	6600(90)	4570(40)	4190(30)	30(12)
H(11B)	3030(90)	3500(50)	3590(30)	29(13)
H(12B)	-420(110)	3200(50)	4400(30)	34(13)
H(13B)	-100(90)	4060(40)	5660(30)	24(11)
H(14C)	7680(100)	4500(40)	7170(30)	26(12)
H(14D)	6270(80)	4100(40)	6410(30)	14(9)
H(17B)	-50(170)	1700(80)	7520(50)	80(20)
H(18B)	2898	1263	8523	56
H(19B)	6770(110)	2750(50)	8270(30)	35(13)
H(22B)	7050(90)	7380(40)	6770(30)	16(10)
H(24B)	2940(90)	8830(40)	7130(30)	22(11)
H(25B)	2660(110)	10480(50)	6470(30)	38(14)

H(27B)	8930(90)	10620(40)	5520(30)	22(11)
H(28B)	9180(70)	8850(30)	6120(20)	12(9)
H(1SA)	4480(130)	6830(60)	890(40)	56(18)
H(1SB)	5220(130)	7960(60)	200(40)	59(18)
H(1W1)	-2440(90)	2570(50)	2860(30)	19(10)
H(1W2)	-4270(120)	2940(50)	2590(40)	36(14)
H(2W1)	7900(90)	6240(40)	5600(30)	11(10)
H(2W2)	9860(120)	6420(50)	5960(40)	42(15)

Table A5.6. Torsion angles [°] for (S)-1.71

N(5A)-C(1A)-C(2A)-C(3A)	168.8(3)
C(4A)-C(1A)-C(2A)-C(3A)	-68.8(4)
C(20A)-C(1A)-C(2A)-C(3A)	51.0(4)
C(4A)-C(1A)-N(5A)-C(6A)	74.8(3)
C(2A)-C(1A)-N(5A)-C(6A)	-162.4(3)
C(20A)-C(1A)-N(5A)-C(6A)	-45.9(4)
C(4A)-C(1A)-N(5A)-C(14A)	-88.6(3)
C(2A)-C(1A)-N(5A)-C(14A)	34.2(4)
C(20A)-C(1A)-N(5A)-C(14A)	150.6(3)
C(14A)-N(5A)-C(6A)-O(7A)	163.3(3)
C(1A)-N(5A)-C(6A)-O(7A)	0.0(4)
C(14A)-N(5A)-C(6A)-C(8A)	-20.7(4)
C(1A)-N(5A)-C(6A)-C(8A)	176.0(3)
O(7A)-C(6A)-C(8A)-N(9A)	118.5(4)
N(5A)-C(6A)-C(8A)-N(9A)	-57.6(4)
O(7A)-C(6A)-C(8A)-C(13A)	-57.7(5)
N(5A)-C(6A)-C(8A)-C(13A)	126.2(4)
C(13A)-C(8A)-N(9A)-C(10A)	1.2(6)
C(6A)-C(8A)-N(9A)-C(10A)	-174.8(3)
C(8A)-N(9A)-C(10A)-C(11A)	-0.5(6)
N(9A)-C(10A)-C(11A)-C(12A)	-0.8(7)
C(10A)-C(11A)-C(12A)-C(13A)	1.5(7)

C(11A)-C(12A)-C(13A)-C(8A)	-0.8(7)
N(9A)-C(8A)-C(13A)-C(12A)	-0.6(6)
C(6A)-C(8A)-C(13A)-C(12A)	175.3(4)
C(6A)-N(5A)-C(14A)-C(15A)	-95.9(4)
C(1A)-N(5A)-C(14A)-C(15A)	67.2(4)
N(5A)-C(14A)-C(15A)-C(19A)	-133.7(4)
N(5A)-C(14A)-C(15A)-O(16A)	50.1(4)
C(19A)-C(15A)-O(16A)-C(17A)	-0.3(4)
C(14A)-C(15A)-O(16A)-C(17A)	176.7(3)
C(15A)-O(16A)-C(17A)-C(18A)	0.0(5)
O(16A)-C(17A)-C(18A)-C(19A)	0.3(5)
O(16A)-C(15A)-C(19A)-C(18A)	0.5(5)
C(14A)-C(15A)-C(19A)-C(18A)	-175.9(4)
C(17A)-C(18A)-C(19A)-C(15A)	-0.5(5)
N(5A)-C(1A)-C(20A)-O(21A)	137.5(3)
C(4A)-C(1A)-C(20A)-O(21A)	16.3(4)
C(2A)-C(1A)-C(20A)-O(21A)	-104.6(3)
N(5A)-C(1A)-C(20A)-N(22A)	-49.4(4)
C(4A)-C(1A)-C(20A)-N(22A)	-170.6(3)
C(2A)-C(1A)-C(20A)-N(22A)	68.5(3)
O(21A)-C(20A)-N(22A)-C(23A)	-7.9(6)
C(1A)-C(20A)-N(22A)-C(23A)	179.4(3)
C(20A)-N(22A)-C(23A)-C(24A)	-22.7(5)
C(20A)-N(22A)-C(23A)-C(28A)	160.4(3)

C(28A)-C(23A)-C(24A)-C(25A)	0.9(5)
N(22A)-C(23A)-C(24A)-C(25A)	-176.0(3)
C(23A)-C(24A)-C(25A)-C(26A)	0.8(6)
C(24A)-C(25A)-C(26A)-C(27A)	-1.2(6)
C(24A)-C(25A)-C(26A)-Br(29)	177.2(3)
C(25A)-C(26A)-C(27A)-C(28A)	-0.1(5)
Br(29)-C(26A)-C(27A)-C(28A)	-178.5(3)
C(26A)-C(27A)-C(28A)-C(23A)	1.8(5)
C(24A)-C(23A)-C(28A)-C(27A)	-2.2(5)
N(22A)-C(23A)-C(28A)-C(27A)	174.9(3)
N(5B)-C(1B)-C(2B)-C(3B)	164.9(3)
C(4B)-C(1B)-C(2B)-C(3B)	-72.7(4)
C(20B)-C(1B)-C(2B)-C(3B)	46.4(4)
C(4B)-C(1B)-N(5B)-C(6B)	76.8(4)
C(2B)-C(1B)-N(5B)-C(6B)	-160.9(3)
C(20B)-C(1B)-N(5B)-C(6B)	-44.1(4)
C(4B)-C(1B)-N(5B)-C(14B)	-80.7(4)
C(2B)-C(1B)-N(5B)-C(14B)	41.6(4)
C(20B)-C(1B)-N(5B)-C(14B)	158.4(3)
C(14B)-N(5B)-C(6B)-O(7B)	153.9(3)
C(1B)-N(5B)-C(6B)-O(7B)	-3.4(5)
C(14B)-N(5B)-C(6B)-C(8B)	-29.2(5)
C(1B)-N(5B)-C(6B)-C(8B)	173.5(3)
O(7B)-C(6B)-C(8B)-N(9B)	129.9(4)

N(5B)-C(6B)-C(8B)-N(9B)	-47.0(4)
O(7B)-C(6B)-C(8B)-C(13B)	-45.9(5)
N(5B)-C(6B)-C(8B)-C(13B)	137.1(3)
C(13B)-C(8B)-N(9B)-C(10B)	-0.4(5)
C(6B)-C(8B)-N(9B)-C(10B)	-176.1(3)
C(8B)-N(9B)-C(10B)-C(11B)	-1.4(5)
N(9B)-C(10B)-C(11B)-C(12B)	2.1(6)
C(10B)-C(11B)-C(12B)-C(13B)	-1.0(5)
N(9B)-C(8B)-C(13B)-C(12B)	1.4(5)
C(6B)-C(8B)-C(13B)-C(12B)	177.0(3)
C(11B)-C(12B)-C(13B)-C(8B)	-0.7(6)
C(6B)-N(5B)-C(14B)-C(15B)	-81.6(4)
C(1B)-N(5B)-C(14B)-C(15B)	75.5(4)
N(5B)-C(14B)-C(15B)-C(19B)	-126.5(5)
N(5B)-C(14B)-C(15B)-O(16B)	54.3(4)
C(19B)-C(15B)-O(16B)-C(17B)	0.5(4)
C(14B)-C(15B)-O(16B)-C(17B)	179.9(3)
C(15B)-O(16B)-C(17B)-C(18B)	-0.2(4)
O(16B)-C(17B)-C(18B)-C(19B)	-0.2(5)
O(16B)-C(15B)-C(19B)-C(18B)	-0.7(4)
C(14B)-C(15B)-C(19B)-C(18B)	-179.9(4)
C(17B)-C(18B)-C(19B)-C(15B)	0.5(5)
N(5B)-C(1B)-C(20B)-O(21B)	138.1(3)
C(4B)-C(1B)-C(20B)-O(21B)	16.0(4)

C(2B)-C(1B)-C(20B)-O(21B)	-104.1(4)
N(5B)-C(1B)-C(20B)-N(22B)	-48.5(4)
C(4B)-C(1B)-C(20B)-N(22B)	-170.6(3)
C(2B)-C(1B)-C(20B)-N(22B)	69.3(4)
O(21B)-C(20B)-N(22B)-C(23B)	-11.5(6)
C(1B)-C(20B)-N(22B)-C(23B)	175.4(3)
C(20B)-N(22B)-C(23B)-C(24B)	-20.9(5)
C(20B)-N(22B)-C(23B)-C(28B)	162.3(3)
C(28B)-C(23B)-C(24B)-C(25B)	4.2(5)
N(22B)-C(23B)-C(24B)-C(25B)	-172.5(3)
C(23B)-C(24B)-C(25B)-C(26B)	-1.4(6)
C(24B)-C(25B)-C(26B)-C(27B)	-2.2(5)
C(24B)-C(25B)-C(26B)-Br(2B)	174.1(3)
C(25B)-C(26B)-C(27B)-C(28B)	2.8(5)
Br(2B)-C(26B)-C(27B)-C(28B)	-173.4(3)
C(26B)-C(27B)-C(28B)-C(23B)	0.0(5)
C(24B)-C(23B)-C(28B)-C(27B)	-3.5(5)
N(22B)-C(23B)-C(28B)-C(27B)	173.4(3)

Symmetry transformations used to generate equivalent atoms:

Table A5.7. Hydrogen bonds for (S)-1.71 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2A)-H(2A)...O(7A)#1	1.02(4)	2.66(4)	3.553(4)	147(3)
C(4A)-H(4A)...O(7A)	0.98	2.58	3.122(4)	115.1
C(14A)-H(14A)...O(7A)#1	0.95(5)	2.45(5)	3.340(4)	157(4)
C(14A)-H(14B)...N(9A)	0.87(5)	2.50(5)	3.134(5)	131(4)
C(18A)-H(18A)...O(21B)#2	0.93(7)	2.59(7)	3.425(5)	148(5)
N(22A)-H(22N)...O(1W)	0.80(5)	2.15(5)	2.919(4)	162(4)
C(24A)-H(24A)...O(21A)	1.01(5)	2.31(5)	2.901(4)	116(3)
C(2B)-H(2C)...O(7B)#3	0.97(5)	2.60(5)	3.517(4)	159(4)
C(4B)-H(4D)...O(7B)	0.98	2.60	3.134(4)	114.3
C(14B)-H(14D)...N(9B)	0.95(4)	2.35(4)	3.059(4)	131(3)
C(14B)-H(14D)...Br(2B)#4	0.95(4)	3.07(4)	3.823(3)	137(3)
N(22B)-H(22B)...O(2W)	0.77(6)	2.14(5)	2.877(4)	159(4)
C(24B)-H(24B)...O(21B)	0.98(5)	2.32(5)	2.863(4)	114(4)
C(28B)-H(28B)...O(2W)	1.04(4)	2.52(4)	3.270(4)	129(3)
C(1S)-H(1SA)...O(21A)	1.03(8)	2.23(8)	3.245(6)	168(6)
O(1W)-H(1W1)...N(9A)	0.81(6)	2.10(6)	2.900(4)	168(4)
O(1W)-H(1W2)...O(7A)#1	0.92(7)	1.88(7)	2.793(4)	169(6)
O(2W)-H(2W1)...N(9B)	0.81(5)	2.10(5)	2.901(4)	171(5)
O(2W)-H(2W2)...O(7B)#3	0.90(7)	1.92(7)	2.784(4)	162(5)

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z #2 x-1,y-1,z-1 #3 x+1,y,z #4 x,y-1,z

X-ray crystallographic data of (S)-1.72

Table A6.1. Crystal data and structure refinement for (S)-1.72

Identification code	v13b	
Empirical formula	C24 H28 Br N3 O4	
Formula weight	502.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.961(3) Å	α= 90°.
	b = 6.1312(17) Å	β= 104.859(7)°.
	c = 18.282(5) Å	γ = 90°.
Volume	1187.5(6) $Å^3$	
Z	2	
Density (calculated)	1.405 Mg/m^3	
Absorption coefficient	2.646 mm^{-1}	
F(000)	520	
Crystal size	0.240 x 0.060 x 0.030 mm^3	
Theta range for data collection	4.280 to 67.972°.	
Index ranges	-12<=h<=13, -7<=k<=4, -21<=l<=21	
Reflections collected	7711	
Independent reflections	3031 [R(int) = 0.0182]	
Completeness to theta = 66.000°	98.3 %	
Absorption correction	Multi-scan	

Max. and min. transmission	1.000 and 0.798
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3031 / 1 / 378
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0198, wR2 = 0.0511
R indices (all data)	R1 = 0.0203, wR2 = 0.0515
Absolute structure parameter	0.077(8)
Extinction coefficient	0.0013(3)
Largest diff. peak and hole	0.318 and -0.395 e.$Å^{-3}$

Table A6.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (S)-1.72. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
C(1)	3505(2)	2119(4)	1685(1)	24(1)
C(2)	2924(2)	118(4)	1203(1)	26(1)
C(3)	1845(3)	650(5)	494(2)	30(1)
C(4)	552(2)	67(5)	616(2)	33(1)
C(5)	2049(3)	-581(6)	-190(2)	42(1)
C(6)	4229(2)	3546(4)	1252(1)	27(1)
N(7)	4360(2)	1351(3)	2412(1)	23(1)
C(8)	4682(2)	2816(5)	2988(1)	25(1)
O(9)	4291(2)	4715(3)	2934(1)	30(1)
C(10)	5500(2)	2068(4)	3745(1)	27(1)
N(11)	5136(2)	288(4)	4058(1)	28(1)
C(12)	5826(2)	-294(5)	4756(2)	32(1)
C(13)	6873(3)	862(6)	5146(2)	37(1)
C(14)	7229(2)	2695(8)	4814(2)	40(1)
C(15)	6531(3)	3316(5)	4103(2)	36(1)
C(16)	5121(2)	-640(4)	2418(1)	25(1)
C(17)	6139(2)	-328(4)	2022(1)	27(1)
O(18)	6924(2)	1408(3)	2267(1)	32(1)
C(19)	7760(3)	1445(5)	1820(2)	39(1)

C(20)	7529(3)	-201(6)	1324(2)	39(1)
C(21)	6473(3)	-1366(5)	1451(2)	32(1)
C(22)	2403(2)	3451(4)	1840(1)	24(1)
O(23)	2032(2)	5106(3)	1476(1)	34(1)
N(24)	1832(2)	2565(4)	2354(1)	24(1)
C(25)	990(2)	3689(4)	2692(1)	23(1)
C(26)	411(2)	5648(4)	2412(2)	27(1)
C(27)	-290(2)	6790(5)	2822(2)	30(1)
C(28)	-437(2)	5937(5)	3492(2)	30(1)
C(29)	40(2)	3916(5)	3747(1)	30(1)
C(30)	758(2)	2790(6)	3345(1)	28(1)
Br(31)	-1265(1)	7696(1)	4083(1)	38(1)
O(1W)	2732(2)	-1380(4)	3247(1)	31(1)

Table A6.3. Bond lengths [Å] and angles [°] for (S)-1.72

C(1)-N(7)	1.493(3)
C(1)-C(6)	1.531(3)
C(1)-C(22)	1.543(3)
C(1)-C(2)	1.549(3)
C(2)-C(3)	1.548(3)
C(2)-H(2A)	1.01(3)
C(2)-H(2B)	0.98(4)
C(3)-C(5)	1.527(4)
C(3)-C(4)	1.533(4)
C(3)-H(3)	0.96(4)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(5)-H(5C)	0.9800
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
N(7)-C(8)	1.360(3)
N(7)-C(16)	1.477(3)
C(8)-O(9)	1.236(4)

C(8)-C(10)	1.515(3)
C(10)-N(11)	1.340(3)
C(10)-C(15)	1.382(4)
N(11)-C(12)	1.354(3)
C(12)-C(13)	1.382(4)
C(12)-H(12)	0.95(3)
C(13)-C(14)	1.381(6)
C(13)-H(13)	0.99(3)
C(14)-C(15)	1.382(4)
C(14)-H(14)	0.91(4)
C(15)-H(15)	0.84(4)
C(16)-C(17)	1.490(3)
C(16)-H(16A)	0.93(3)
C(16)-H(16B)	0.97(3)
C(17)-C(21)	1.351(4)
C(17)-O(18)	1.370(3)
O(18)-C(19)	1.375(3)
C(19)-C(20)	1.337(5)
C(19)-H(19)	0.95(5)
C(20)-C(21)	1.428(4)
C(20)-H(20)	0.93(4)
C(21)-H(21)	1.02(3)
C(22)-O(23)	1.225(3)
C(22)-N(24)	1.368(3)

N(24)-C(25)	1.414(3)
N(24)-H(24N)	0.86(4)
C(25)-C(26)	1.394(4)
C(25)-C(30)	1.396(3)
C(26)-C(27)	1.392(4)
C(26)-H(26)	0.99(3)
C(27)-C(28)	1.379(4)
C(27)-H(27)	0.90(4)
C(28)-C(29)	1.379(4)
C(28)-Br(31)	1.913(3)
C(29)-C(30)	1.391(4)
C(29)-H(29)	0.98(3)
C(30)-H(30)	0.94(3)
O(1W)-H(1W1)	0.85(4)
O(1W)-H(1W2)	0.80(6)

N(7)-C(1)-C(6)	110.49(19)
N(7)-C(1)-C(22)	110.19(19)
C(6)-C(1)-C(22)	109.09(19)
N(7)-C(1)-C(2)	109.21(18)
C(6)-C(1)-C(2)	110.51(19)
C(22)-C(1)-C(2)	107.30(19)
C(3)-C(2)-C(1)	115.0(2)
C(3)-C(2)-H(2A)	108.6(15)

C(1)-C(2)-H(2A)	109.6(16)
C(3)-C(2)-H(2B)	111.1(19)
C(1)-C(2)-H(2B)	109(2)
H(2A)-C(2)-H(2B)	103(3)
C(5)-C(3)-C(4)	109.8(2)
C(5)-C(3)-C(2)	109.9(2)
C(4)-C(3)-C(2)	111.5(2)
C(5)-C(3)-H(3)	106.9(18)
C(4)-C(3)-H(3)	107.8(17)
C(2)-C(3)-H(3)	110.9(18)
C(3)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(3)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(3)-C(5)-H(5A)	109.5
C(3)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(3)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
C(1)-C(6)-H(6A)	109.5
C(1)-C(6)-H(6B)	109.5

H(6A)-C(6)-H(6B)	109.5
C(1)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(8)-N(7)-C(16)	120.4(2)
C(8)-N(7)-C(1)	117.4(2)
C(16)-N(7)-C(1)	119.42(19)
O(9)-C(8)-N(7)	123.0(2)
O(9)-C(8)-C(10)	118.1(2)
N(7)-C(8)-C(10)	118.9(3)
N(11)-C(10)-C(15)	123.1(2)
N(11)-C(10)-C(8)	117.7(2)
C(15)-C(10)-C(8)	119.0(2)
C(10)-N(11)-C(12)	117.5(2)
N(11)-C(12)-C(13)	122.7(3)
N(11)-C(12)-H(12)	115.0(18)
C(13)-C(12)-H(12)	122.3(18)
C(14)-C(13)-C(12)	118.8(3)
C(14)-C(13)-H(13)	123(2)
C(12)-C(13)-H(13)	118(2)
C(13)-C(14)-C(15)	119.2(3)
C(13)-C(14)-H(14)	125(2)
C(15)-C(14)-H(14)	116(2)
C(14)-C(15)-C(10)	118.7(3)

C(14)-C(15)-H(15)	118(2)
C(10)-C(15)-H(15)	123(2)
N(7)-C(16)-C(17)	112.5(2)
N(7)-C(16)-H(16A)	110.3(15)
C(17)-C(16)-H(16A)	111.1(14)
N(7)-C(16)-H(16B)	105.2(18)
C(17)-C(16)-H(16B)	112.3(16)
H(16A)-C(16)-H(16B)	105(2)
C(21)-C(17)-O(18)	110.3(2)
C(21)-C(17)-C(16)	134.4(2)
O(18)-C(17)-C(16)	115.3(2)
C(17)-O(18)-C(19)	106.1(2)
C(20)-C(19)-O(18)	110.5(2)
C(20)-C(19)-H(19)	136.0(19)
O(18)-C(19)-H(19)	113(2)
C(19)-C(20)-C(21)	106.8(3)
C(19)-C(20)-H(20)	124(2)
C(21)-C(20)-H(20)	129(2)
C(17)-C(21)-C(20)	106.3(3)
C(17)-C(21)-H(21)	127.0(15)
C(20)-C(21)-H(21)	126.6(15)
O(23)-C(22)-N(24)	123.8(2)
O(23)-C(22)-C(1)	120.3(2)
N(24)-C(22)-C(1)	115.7(2)

C(22)-N(24)-C(25)	124.8(2)
C(22)-N(24)-H(24N)	118(2)
C(25)-N(24)-H(24N)	116(2)
C(26)-C(25)-C(30)	119.3(2)
C(26)-C(25)-N(24)	123.1(2)
C(30)-C(25)-N(24)	117.6(3)
C(27)-C(26)-C(25)	119.9(2)
C(27)-C(26)-H(26)	118.9(18)
C(25)-C(26)-H(26)	121.1(18)
C(28)-C(27)-C(26)	119.6(3)
C(28)-C(27)-H(27)	118(2)
C(26)-C(27)-H(27)	123(2)
C(27)-C(28)-C(29)	121.4(2)
C(27)-C(28)-Br(31)	117.9(2)
C(29)-C(28)-Br(31)	120.6(2)
C(28)-C(29)-C(30)	118.9(3)
C(28)-C(29)-H(29)	123.5(18)
C(30)-C(29)-H(29)	117.6(18)
C(29)-C(30)-C(25)	120.6(3)
C(29)-C(30)-H(30)	120.4(17)
C(25)-C(30)-H(30)	119.1(18)
H(1W1)-O(1W)-H(1W2)	108(4)

Symmetry transformations used to generate equivalent atoms:

Table A6.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (S)-1.72. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	32(1)	14(1)	26(1)	-1(1)	11(1)	-2(1)
C(2)	34(1)	15(1)	30(1)	-3(1)	12(1)	-2(1)
C(3)	39(1)	22(1)	29(1)	3(1)	9(1)	-4(1)
C(4)	33(1)	32(1)	32(1)	-2(1)	7(1)	0(1)
C(5)	46(2)	51(2)	32(1)	-5(1)	14(1)	-6(2)
C(6)	37(1)	18(1)	29(1)	0(1)	16(1)	-5(1)
N(7)	30(1)	16(1)	26(1)	-1(1)	13(1)	-2(1)
C(8)	31(1)	18(1)	31(1)	-5(1)	16(1)	-6(1)
O(9)	42(1)	15(1)	35(1)	-4(1)	15(1)	-3(1)
C(10)	30(1)	25(1)	29(1)	-4(1)	14(1)	-2(1)
N(11)	32(1)	27(1)	27(1)	-1(1)	11(1)	-2(1)
C(12)	36(1)	34(2)	30(1)	1(1)	12(1)	4(1)
C(13)	35(1)	46(2)	30(1)	-7(1)	8(1)	7(1)
C(14)	33(1)	49(2)	38(1)	-12(2)	8(1)	-7(2)
C(15)	40(1)	34(2)	38(1)	-6(1)	15(1)	-10(1)
C(16)	33(1)	17(1)	28(1)	0(1)	13(1)	0(1)
C(17)	28(1)	22(1)	31(1)	3(1)	10(1)	0(1)
O(18)	31(1)	30(1)	35(1)	1(1)	7(1)	-8(1)

C(19)	29(1)	41(2)	48(2)	12(1)	12(1)	-8(1)
C(20)	34(1)	42(2)	47(2)	8(1)	24(1)	2(1)
C(21)	36(1)	26(1)	37(1)	-2(1)	18(1)	-1(1)
C(22)	34(1)	13(1)	29(1)	0(1)	14(1)	-3(1)
O(23)	47(1)	20(1)	41(1)	8(1)	24(1)	6(1)
N(24)	32(1)	16(1)	25(1)	2(1)	11(1)	2(1)
C(25)	24(1)	20(1)	25(1)	-3(1)	8(1)	-4(1)
C(26)	29(1)	25(1)	29(1)	0(1)	9(1)	0(1)
C(27)	28(1)	25(1)	38(1)	0(1)	10(1)	3(1)
C(28)	27(1)	31(1)	33(1)	-10(1)	12(1)	-4(1)
C(29)	32(1)	34(2)	28(1)	0(1)	12(1)	-4(1)
C(30)	32(1)	24(1)	29(1)	2(1)	10(1)	-1(1)
Br(31)	38(1)	34(1)	47(1)	-14(1)	23(1)	-5(1)
O(1W)	33(1)	22(1)	37(1)	2(1)	9(1)	-4(1)

Table A6.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (S)-1.72

	x	y	z	U(eq)
H(2A)	2600(20)	-950(50)	1527(15)	22(7)
H(2B)	3600(30)	-690(70)	1066(19)	49(9)
H(3)	1840(30)	2170(60)	375(17)	38(8)
H(4A)	393	960	1027	43(9)
H(4B)	540	-1479	750	39(8)
H(4C)	-106	348	150	35(8)
H(5A)	2080	-2152	-87	35(7)
H(5B)	2847	-117	-290	48(9)
H(5C)	1352	-267	-633	50(10)
H(6A)	4888	2675	1116	42(7)
H(6B)	4618	4771	1572	44(9)
H(6C)	3645	4105	791	39(8)
H(12)	5540(30)	-1570(60)	4958(16)	34(8)
H(13)	7310(30)	370(60)	5665(18)	39(9)
H(14)	7890(30)	3580(70)	5030(18)	45(9)
H(15)	6790(30)	4390(70)	3895(17)	35(8)
H(16A)	4610(20)	-1800(50)	2215(13)	14(6)
H(16B)	5450(30)	-1000(50)	2947(17)	28(7)

H(19)	8330(30)	2650(80)	1922(17)	47(8)
H(20)	7940(30)	-390(70)	942(19)	48(9)
H(21)	6090(20)	-2760(50)	1184(15)	26(7)
H(24N)	2130(30)	1350(70)	2564(19)	42(9)
H(26)	530(30)	6300(50)	1940(17)	31(8)
H(27)	-640(30)	8090(60)	2674(16)	32(8)
H(29)	-90(20)	3230(50)	4204(15)	31(7)
H(30)	1090(30)	1400(50)	3506(16)	28(7)
H(1W1)	3470(40)	-1060(70)	3510(20)	51(10)
H(1W2)	2770(40)	-2560(100)	3060(20)	60(13)

Table A6.6. Torsion angles [°] for (S)-1.72

N(7)-C(1)-C(2)-C(3)	170.02(19)
C(6)-C(1)-C(2)-C(3)	-68.2(3)
C(22)-C(1)-C(2)-C(3)	50.6(3)
C(1)-C(2)-C(3)-C(5)	133.8(2)
C(1)-C(2)-C(3)-C(4)	-104.2(3)
C(6)-C(1)-N(7)-C(8)	75.7(2)
C(22)-C(1)-N(7)-C(8)	-44.9(3)
C(2)-C(1)-N(7)-C(8)	-162.49(19)
C(6)-C(1)-N(7)-C(16)	-85.6(2)
C(22)-C(1)-N(7)-C(16)	153.82(19)
C(2)-C(1)-N(7)-C(16)	36.2(3)
C(16)-N(7)-C(8)-O(9)	161.8(2)
C(1)-N(7)-C(8)-O(9)	0.7(3)
C(16)-N(7)-C(8)-C(10)	-21.6(3)
C(1)-N(7)-C(8)-C(10)	177.26(19)
O(9)-C(8)-C(10)-N(11)	124.9(3)
N(7)-C(8)-C(10)-N(11)	-51.8(3)
O(9)-C(8)-C(10)-C(15)	-50.9(3)
N(7)-C(8)-C(10)-C(15)	132.4(2)
C(15)-C(10)-N(11)-C(12)	-0.4(4)
C(8)-C(10)-N(11)-C(12)	-175.9(2)
C(10)-N(11)-C(12)-C(13)	-0.2(4)

N(11)-C(12)-C(13)-C(14)	0.4(4)
C(12)-C(13)-C(14)-C(15)	-0.1(5)
C(13)-C(14)-C(15)-C(10)	-0.4(4)
N(11)-C(10)-C(15)-C(14)	0.7(4)
C(8)-C(10)-C(15)-C(14)	176.2(3)
C(8)-N(7)-C(16)-C(17)	-91.4(3)
C(1)-N(7)-C(16)-C(17)	69.4(3)
N(7)-C(16)-C(17)-C(21)	-125.3(3)
N(7)-C(16)-C(17)-O(18)	53.5(3)
C(21)-C(17)-O(18)-C(19)	0.8(3)
C(16)-C(17)-O(18)-C(19)	-178.3(2)
C(17)-O(18)-C(19)-C(20)	-0.8(3)
O(18)-C(19)-C(20)-C(21)	0.5(3)
O(18)-C(17)-C(21)-C(20)	-0.5(3)
C(16)-C(17)-C(21)-C(20)	178.4(3)
C(19)-C(20)-C(21)-C(17)	0.0(3)
N(7)-C(1)-C(22)-O(23)	139.5(2)
C(6)-C(1)-C(22)-O(23)	18.1(3)
C(2)-C(1)-C(22)-O(23)	-101.7(3)
N(7)-C(1)-C(22)-N(24)	-45.4(3)
C(6)-C(1)-C(22)-N(24)	-166.9(2)
C(2)-C(1)-C(22)-N(24)	73.4(3)
O(23)-C(22)-N(24)-C(25)	-18.6(4)
C(1)-C(22)-N(24)-C(25)	166.6(2)

C(22)-N(24)-C(25)-C(26)	15.9(4)
C(22)-N(24)-C(25)-C(30)	-162.9(2)
C(30)-C(25)-C(26)-C(27)	6.2(4)
N(24)-C(25)-C(26)-C(27)	-172.6(2)
C(25)-C(26)-C(27)-C(28)	-2.0(4)
C(26)-C(27)-C(28)-C(29)	-3.5(4)
C(26)-C(27)-C(28)-Br(31)	173.9(2)
C(27)-C(28)-C(29)-C(30)	4.5(4)
Br(31)-C(28)-C(29)-C(30)	-172.88(19)
C(28)-C(29)-C(30)-C(25)	-0.1(4)
C(26)-C(25)-C(30)-C(29)	-5.2(4)
N(24)-C(25)-C(30)-C(29)	173.6(2)

Symmetry transformations used to generate equivalent atoms:

Table A6.7. Hydrogen bonds for (S)-1.72 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2A)...O(23)#1	1.01(3)	2.49(3)	3.301(3)	137(2)
C(6)-H(6B)...O(9)	0.98	2.61	3.141(3)	114.5
C(15)-H(15)...Br(31)#2	0.84(4)	2.90(4)	3.619(3)	144(3)
C(16)-H(16A)...O(9)#1	0.93(3)	2.58(3)	3.205(3)	125.5(18)
C(16)-H(16B)...N(11)	0.97(3)	2.29(3)	3.048(3)	135(2)
N(24)-H(24N)...O(1W)	0.86(4)	2.09(4)	2.943(3)	169(3)
C(26)-H(26)...O(23)	0.99(3)	2.16(3)	2.785(3)	119(2)
C(29)-H(29)...Br(31)#3	0.98(3)	3.12(3)	3.919(3)	140(2)
C(30)-H(30)...O(1W)	0.94(3)	2.61(3)	3.384(4)	139(2)
O(1W)-H(1W1)...N(11)	0.85(4)	2.02(4)	2.860(3)	169(4)
O(1W)-H(1W2)...O(9)#1	0.80(6)	2.42(5)	3.079(3)	140(4)

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z #2 x+1,y,z #3 -x,y-1/2,-z+1

X-ray crystallographic data of (S)-1.73

Table A7.1. Crystal data and structure refinement for (S)-1.73

Identification code	q15e	
Empirical formula	C24 H28 Br N3 O4	
Formula weight	502.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.8713(2) Å	α= 90°.
	b = 10.2542(2) Å	β= 99.8400(10)°.
	c = 11.1197(2) Å	γ = 90°.
Volume	1221.35(4) $Å^3$	
Z	2	
Density (calculated)	1.366 Mg/m^3	
Absorption coefficient	2.573 mm^{-1}	
F(000)	520	
Crystal size	0.210 x 0.045 x 0.030 mm^3	
Theta range for data collection	4.035 to 69.911°.	
Index ranges	-13<=h<=13, -10<=k<=11, -13<=l<=12	
Reflections collected	13304	
Independent reflections	3648 [R(int) = 0.0219]	
Completeness to theta = 66.000°	98.8 %	
Absorption correction	Multi-scan	

Max. and min. transmission	1.000 and 0.809
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3648 / 1 / 401
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0245, wR2 = 0.0608
R indices (all data)	R1 = 0.0250, wR2 = 0.0611
Absolute structure parameter	0.037(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.515 and -0.265 e.$Å^{-3}$

Table A7.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (S)-1.73. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
C(1)	-66(2)	2570(3)	1653(2)	17(1)
C(2)	-561(2)	3963(2)	1793(2)	19(1)
C(3)	-1982(2)	4073(3)	1610(2)	21(1)
C(4)	-2392(3)	5408(3)	1995(2)	24(1)
C(5)	-3804(3)	5523(3)	1881(3)	27(1)
C(6)	-291(2)	1687(3)	2709(2)	19(1)
N(7)	1293(2)	2616(2)	1592(2)	16(1)
C(8)	1799(2)	1493(2)	1239(2)	17(1)
O(9)	1158(2)	540(2)	876(2)	20(1)
C(10)	3192(2)	1398(3)	1284(2)	19(1)
N(11)	3756(2)	2320(2)	720(2)	22(1)
C(12)	4988(2)	2181(3)	743(3)	28(1)
C(13)	5678(2)	1159(3)	1317(3)	31(1)
C(14)	5080(3)	212(3)	1872(3)	32(1)
C(15)	3806(3)	322(3)	1856(3)	25(1)
C(16)	2081(2)	3609(3)	2322(2)	19(1)
C(17)	2279(2)	3333(3)	3654(3)	22(1)
O(18)	2801(2)	2144(2)	3991(2)	28(1)
C(19)	2879(3)	2054(4)	5230(3)	36(1)

C(20)	2431(3)	3136(4)	5669(3)	37(1)
C(21)	2042(3)	3986(3)	4650(3)	30(1)
C(22)	-798(2)	2038(2)	437(2)	16(1)
O(23)	-1686(2)	1297(2)	442(2)	21(1)
N(24)	-517(2)	2564(2)	-601(2)	17(1)
C(25)	-1249(2)	2466(3)	-1771(2)	17(1)
C(26)	-2500(2)	2073(2)	-1989(2)	20(1)
C(27)	-3176(2)	2081(3)	-3160(2)	23(1)
C(28)	-2616(2)	2487(4)	-4118(2)	27(1)
C(29)	-1377(3)	2868(3)	-3934(3)	30(1)
C(30)	-697(2)	2858(3)	-2766(2)	25(1)
Br(31)	-3566(1)	2479(1)	-5726(1)	43(1)
O(1W)	1907(2)	-6288(2)	-1063(2)	26(1)

Table A7.3. Bond lengths [Å] and angles [°] for (S)-1.73

C(1)-N(7)	1.492(2)
C(1)-C(6)	1.536(3)
C(1)-C(2)	1.544(4)
C(1)-C(22)	1.546(3)
C(2)-C(3)	1.527(3)
C(2)-H(2A)	1.03(4)
C(2)-H(2B)	0.99(4)
C(3)-C(4)	1.524(4)
C(3)-H(3A)	0.96(4)
C(3)-H(3B)	0.91(4)
C(4)-C(5)	1.523(4)
C(4)-H(4A)	0.98(4)
C(4)-H(4B)	0.90(5)
C(5)-H(5A)	0.95(3)
C(5)-H(5B)	0.97(4)
C(5)-H(5C)	0.92(6)
C(6)-H(6A)	0.97(4)
C(6)-H(6B)	0.97(4)
C(6)-H(6C)	0.87(4)
N(7)-C(8)	1.363(3)
N(7)-C(16)	1.481(3)
C(8)-O(9)	1.228(3)

C(8)-C(10)	1.509(3)
C(10)-N(11)	1.339(4)
C(10)-C(15)	1.387(4)
N(11)-C(12)	1.343(3)
C(12)-C(13)	1.380(5)
C(12)-H(12)	0.96(4)
C(13)-C(14)	1.373(5)
C(13)-H(13)	0.92(4)
C(14)-C(15)	1.386(4)
C(14)-H(14)	0.87(5)
C(15)-H(15)	0.89(4)
C(16)-C(17)	1.487(4)
C(16)-H(16A)	0.96(3)
C(16)-H(16B)	0.96(4)
C(17)-C(21)	1.356(4)
C(17)-O(18)	1.370(4)
O(18)-C(19)	1.369(4)
C(19)-C(20)	1.336(5)
C(19)-H(19)	0.86(5)
C(20)-C(21)	1.434(5)
C(20)-H(20)	0.86(4)
C(21)-H(21)	0.99(5)
C(22)-O(23)	1.229(3)
C(22)-N(24)	1.356(3)

N(24)-C(25)	1.408(3)
N(24)-H(24N)	0.83(4)
C(25)-C(26)	1.399(3)
C(25)-C(30)	1.404(3)
C(26)-C(27)	1.382(4)
C(26)-H(26)	0.87(4)
C(27)-C(28)	1.379(4)
C(27)-H(27)	1.00(3)
C(28)-C(29)	1.385(4)
C(28)-Br(31)	1.906(2)
C(29)-C(30)	1.380(4)
C(29)-H(29)	1.00(4)
C(30)-H(30)	0.99(4)
O(1W)-H(1W1)	0.68(5)
O(1W)-H(1W2)	0.94(5)

N(7)-C(1)-C(6)	110.02(18)
N(7)-C(1)-C(2)	109.9(2)
C(6)-C(1)-C(2)	111.40(18)
N(7)-C(1)-C(22)	109.69(16)
C(6)-C(1)-C(22)	109.6(2)
C(2)-C(1)-C(22)	106.19(18)
C(3)-C(2)-C(1)	114.6(2)
C(3)-C(2)-H(2A)	107(2)

C(1)-C(2)-H(2A)	110(2)
C(3)-C(2)-H(2B)	110(2)
C(1)-C(2)-H(2B)	110(2)
H(2A)-C(2)-H(2B)	105(3)
C(4)-C(3)-C(2)	111.5(2)
C(4)-C(3)-H(3A)	111(2)
C(2)-C(3)-H(3A)	109(2)
C(4)-C(3)-H(3B)	108(2)
C(2)-C(3)-H(3B)	110(2)
H(3A)-C(3)-H(3B)	107(3)
C(5)-C(4)-C(3)	112.6(2)
C(5)-C(4)-H(4A)	109(2)
C(3)-C(4)-H(4A)	110(2)
C(5)-C(4)-H(4B)	113(3)
C(3)-C(4)-H(4B)	108(3)
H(4A)-C(4)-H(4B)	103(3)
C(4)-C(5)-H(5A)	111.0(17)
C(4)-C(5)-H(5B)	112(2)
H(5A)-C(5)-H(5B)	105(3)
C(4)-C(5)-H(5C)	112(3)
H(5A)-C(5)-H(5C)	109(3)
H(5B)-C(5)-H(5C)	108(4)
C(1)-C(6)-H(6A)	110.1(18)
C(1)-C(6)-H(6B)	110(2)

H(6A)-C(6)-H(6B)	109(3)
C(1)-C(6)-H(6C)	112(2)
H(6A)-C(6)-H(6C)	103(3)
H(6B)-C(6)-H(6C)	113(3)
C(8)-N(7)-C(16)	121.00(19)
C(8)-N(7)-C(1)	116.0(2)
C(16)-N(7)-C(1)	118.79(19)
O(9)-C(8)-N(7)	122.2(2)
O(9)-C(8)-C(10)	118.0(2)
N(7)-C(8)-C(10)	119.8(2)
N(11)-C(10)-C(15)	123.6(2)
N(11)-C(10)-C(8)	118.4(2)
C(15)-C(10)-C(8)	117.9(2)
C(10)-N(11)-C(12)	116.8(2)
N(11)-C(12)-C(13)	123.4(3)
N(11)-C(12)-H(12)	111.7(19)
C(13)-C(12)-H(12)	124.8(19)
C(14)-C(13)-C(12)	118.9(2)
C(14)-C(13)-H(13)	122(3)
C(12)-C(13)-H(13)	119(3)
C(13)-C(14)-C(15)	119.1(3)
C(13)-C(14)-H(14)	122(3)
C(15)-C(14)-H(14)	119(3)
C(14)-C(15)-C(10)	118.2(3)

C(14)-C(15)-H(15)	125(2)
C(10)-C(15)-H(15)	117(2)
N(7)-C(16)-C(17)	112.8(2)
N(7)-C(16)-H(16A)	108(2)
C(17)-C(16)-H(16A)	111(2)
N(7)-C(16)-H(16B)	110(2)
C(17)-C(16)-H(16B)	108(2)
H(16A)-C(16)-H(16B)	106(3)
C(21)-C(17)-O(18)	110.1(3)
C(21)-C(17)-C(16)	134.8(3)
O(18)-C(17)-C(16)	115.1(2)
C(19)-O(18)-C(17)	106.7(2)
C(20)-C(19)-O(18)	110.3(3)
C(20)-C(19)-H(19)	136(3)
O(18)-C(19)-H(19)	114(3)
C(19)-C(20)-C(21)	107.1(3)
C(19)-C(20)-H(20)	122(3)
C(21)-C(20)-H(20)	131(3)
C(17)-C(21)-C(20)	105.8(3)
C(17)-C(21)-H(21)	124(2)
C(20)-C(21)-H(21)	130(2)
O(23)-C(22)-N(24)	122.8(2)
O(23)-C(22)-C(1)	120.1(2)
N(24)-C(22)-C(1)	116.5(2)

C(22)-N(24)-C(25)	125.8(2)
C(22)-N(24)-H(24N)	116(2)
C(25)-N(24)-H(24N)	118(2)
C(26)-C(25)-C(30)	118.7(2)
C(26)-C(25)-N(24)	124.0(2)
C(30)-C(25)-N(24)	117.2(2)
C(27)-C(26)-C(25)	120.4(2)
C(27)-C(26)-H(26)	120(2)
C(25)-C(26)-H(26)	119(2)
C(28)-C(27)-C(26)	119.7(2)
C(28)-C(27)-H(27)	120.9(18)
C(26)-C(27)-H(27)	119.2(18)
C(27)-C(28)-C(29)	121.2(2)
C(27)-C(28)-Br(31)	118.94(19)
C(29)-C(28)-Br(31)	119.83(19)
C(30)-C(29)-C(28)	119.2(2)
C(30)-C(29)-H(29)	120(2)
C(28)-C(29)-H(29)	121(2)
C(29)-C(30)-C(25)	120.8(2)
C(29)-C(30)-H(30)	119(2)
C(25)-C(30)-H(30)	119(2)
H(1W1)-O(1W)-H(1W2)	102(4)

Symmetry transformations used to generate equivalent atoms:

Table A7.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (S)-1.73. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	17(1)	13(1)	20(1)	1(1)	3(1)	-1(1)
C(2)	22(1)	14(1)	21(1)	0(1)	4(1)	0(1)
C(3)	24(1)	17(1)	22(1)	2(1)	6(1)	2(1)
C(4)	27(1)	22(1)	24(1)	-4(1)	6(1)	4(1)
C(5)	30(2)	25(2)	26(1)	0(1)	6(1)	8(1)
C(6)	21(1)	19(1)	17(1)	2(1)	2(1)	0(1)
N(7)	17(1)	13(1)	18(1)	0(1)	2(1)	-1(1)
C(8)	21(1)	16(1)	15(1)	1(1)	1(1)	1(1)
O(9)	20(1)	14(1)	26(1)	-2(1)	3(1)	-2(1)
C(10)	18(1)	18(1)	21(1)	-6(1)	1(1)	-2(1)
N(11)	19(1)	21(1)	27(1)	-4(1)	6(1)	-2(1)
C(12)	21(1)	30(2)	34(1)	-10(1)	8(1)	-5(1)
C(13)	18(1)	37(2)	37(2)	-16(1)	2(1)	0(1)
C(14)	24(1)	30(2)	38(2)	-7(1)	-5(1)	9(1)
C(15)	23(1)	21(1)	31(1)	-1(1)	1(1)	1(1)
C(16)	20(1)	15(1)	23(1)	-2(1)	3(1)	-2(1)
C(17)	20(1)	22(1)	25(1)	-1(1)	3(1)	-4(1)
O(18)	29(1)	32(1)	23(1)	5(1)	2(1)	4(1)
C(19)	32(2)	53(2)	22(1)	9(1)	0(1)	-2(1)

C(20)	32(2)	57(2)	19(1)	-2(1)	1(1)	-15(1)
C(21)	32(1)	34(2)	26(1)	-9(1)	7(1)	-10(1)
C(22)	15(1)	13(1)	21(1)	1(1)	3(1)	2(1)
O(23)	20(1)	19(1)	23(1)	2(1)	2(1)	-3(1)
N(24)	17(1)	14(1)	20(1)	0(1)	2(1)	-1(1)
C(25)	22(1)	11(1)	18(1)	-3(1)	3(1)	2(1)
C(26)	20(1)	19(1)	23(1)	2(1)	6(1)	3(1)
C(27)	21(1)	21(1)	26(1)	-2(1)	1(1)	0(1)
C(28)	30(1)	31(1)	18(1)	-2(1)	-3(1)	1(1)
C(29)	33(1)	39(2)	20(1)	1(1)	7(1)	-6(1)
C(30)	25(1)	26(2)	23(1)	2(1)	4(1)	-6(1)
Br(31)	37(1)	69(1)	19(1)	4(1)	-4(1)	-7(1)
O(1W)	28(1)	17(1)	31(1)	0(1)	-1(1)	-1(1)

Table A7.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (S)-1.73

	x	y	z	U(eq)
H(2A)	-220(30)	4310(40)	2650(30)	27(9)
H(2B)	-230(30)	4560(40)	1230(30)	28(8)
H(3A)	-2320(30)	3900(30)	770(30)	22(8)
H(3B)	-2300(30)	3460(40)	2060(30)	22(8)
H(4A)	-2000(30)	5590(40)	2840(40)	29(9)
H(4B)	-2060(40)	6010(40)	1570(40)	39(10)
H(5A)	-4210(30)	5310(30)	1080(30)	11(6)
H(5B)	-4130(40)	4910(40)	2410(40)	34(9)
H(5C)	-4040(40)	6350(50)	2070(40)	52(12)
H(6A)	10(30)	820(40)	2600(30)	15(7)
H(6B)	-1180(40)	1650(40)	2740(40)	35(9)
H(6C)	150(30)	1930(30)	3400(30)	20(8)
H(12)	5330(30)	2900(40)	350(30)	24(8)
H(13)	6510(40)	1090(40)	1240(40)	39(10)
H(14)	5480(40)	-430(50)	2280(40)	49(12)
H(15)	3350(30)	-240(40)	2200(30)	22(7)
H(16A)	2870(30)	3650(30)	2030(30)	22(8)
H(16B)	1710(30)	4460(40)	2190(30)	26(8)

H(19)	3210(40)	1340(50)	5530(40)	50(12)
H(20)	2440(40)	3250(40)	6440(40)	36(10)
H(21)	1640(40)	4850(50)	4620(40)	43(10)
H(24N)	140(30)	3000(30)	-520(30)	19(8)
H(26)	-2860(30)	1870(40)	-1370(40)	30(9)
H(27)	-4080(30)	1840(30)	-3290(30)	19(7)
H(29)	-980(40)	3170(40)	-4640(40)	40(10)
H(30)	150(30)	3230(40)	-2620(30)	28(8)
H(1W1)	2360(40)	-6540(40)	-620(40)	31(11)
H(1W2)	1800(40)	-5450(50)	-770(40)	44(10)

Table A7.6. Torsion angles [°] for (S)-1.73

N(7)-C(1)-C(2)-C(3)	168.29(18)
C(6)-C(1)-C(2)-C(3)	-69.5(3)
C(22)-C(1)-C(2)-C(3)	49.7(2)
C(1)-C(2)-C(3)-C(4)	169.2(2)
C(2)-C(3)-C(4)-C(5)	-177.2(2)
C(6)-C(1)-N(7)-C(8)	69.0(2)
C(2)-C(1)-N(7)-C(8)	-168.04(19)
C(22)-C(1)-N(7)-C(8)	-51.7(3)
C(6)-C(1)-N(7)-C(16)	-88.2(3)
C(2)-C(1)-N(7)-C(16)	34.8(3)
C(22)-C(1)-N(7)-C(16)	151.2(2)
C(16)-N(7)-C(8)-O(9)	163.6(2)
C(1)-N(7)-C(8)-O(9)	7.0(3)
C(16)-N(7)-C(8)-C(10)	-16.6(3)
C(1)-N(7)-C(8)-C(10)	-173.22(19)
O(9)-C(8)-C(10)-N(11)	126.7(2)
N(7)-C(8)-C(10)-N(11)	-53.1(3)
O(9)-C(8)-C(10)-C(15)	-50.0(3)
N(7)-C(8)-C(10)-C(15)	130.1(2)
C(15)-C(10)-N(11)-C(12)	-1.2(4)
C(8)-C(10)-N(11)-C(12)	-177.8(2)
C(10)-N(11)-C(12)-C(13)	-0.5(4)

N(11)-C(12)-C(13)-C(14)	1.6(4)
C(12)-C(13)-C(14)-C(15)	-1.0(4)
C(13)-C(14)-C(15)-C(10)	-0.6(4)
N(11)-C(10)-C(15)-C(14)	1.8(4)
C(8)-C(10)-C(15)-C(14)	178.3(2)
C(8)-N(7)-C(16)-C(17)	-84.9(3)
C(1)-N(7)-C(16)-C(17)	71.1(3)
N(7)-C(16)-C(17)-C(21)	-121.5(3)
N(7)-C(16)-C(17)-O(18)	57.2(3)
C(21)-C(17)-O(18)-C(19)	0.6(3)
C(16)-C(17)-O(18)-C(19)	-178.5(2)
C(17)-O(18)-C(19)-C(20)	-0.2(3)
O(18)-C(19)-C(20)-C(21)	-0.2(3)
O(18)-C(17)-C(21)-C(20)	-0.7(3)
C(16)-C(17)-C(21)-C(20)	178.1(3)
C(19)-C(20)-C(21)-C(17)	0.6(3)
N(7)-C(1)-C(22)-O(23)	141.3(2)
C(6)-C(1)-C(22)-O(23)	20.4(3)
C(2)-C(1)-C(22)-O(23)	-100.0(2)
N(7)-C(1)-C(22)-N(24)	-47.3(3)
C(6)-C(1)-C(22)-N(24)	-168.2(2)
C(2)-C(1)-C(22)-N(24)	71.4(2)
O(23)-C(22)-N(24)-C(25)	7.3(4)
C(1)-C(22)-N(24)-C(25)	-163.9(2)

C(22)-N(24)-C(25)-C(26)	15.6(4)
C(22)-N(24)-C(25)-C(30)	-168.1(2)
C(30)-C(25)-C(26)-C(27)	-0.4(4)
N(24)-C(25)-C(26)-C(27)	175.9(2)
C(25)-C(26)-C(27)-C(28)	-0.5(4)
C(26)-C(27)-C(28)-C(29)	1.1(5)
C(26)-C(27)-C(28)-Br(31)	179.6(2)
C(27)-C(28)-C(29)-C(30)	-0.9(5)
Br(31)-C(28)-C(29)-C(30)	-179.4(2)
C(28)-C(29)-C(30)-C(25)	0.0(4)
C(26)-C(25)-C(30)-C(29)	0.6(4)
N(24)-C(25)-C(30)-C(29)	-175.9(3)

Symmetry transformations used to generate equivalent atoms:

Table A7.7. Hydrogen bonds for (S)-1.73 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(2B)...O(9)#1	0.99(4)	2.59(4)	3.345(3)	133(3)
C(6)-H(6A)...O(9)	0.97(4)	2.47(3)	3.020(3)	116(2)
C(13)-H(13)...O(23)#2	0.92(4)	2.30(4)	3.183(3)	160(3)
C(16)-H(16A)...N(11)	0.96(3)	2.32(4)	3.057(3)	132(3)
N(24)-H(24N)...O(1W)#3	0.83(4)	2.23(3)	3.010(3)	155(3)
C(26)-H(26)...O(23)	0.87(4)	2.28(4)	2.812(3)	120(3)
C(30)-H(30)...O(1W)#3	0.99(4)	2.40(4)	3.246(3)	144(3)
O(1W)-H(1W1)...N(11)#4	0.68(5)	2.27(5)	2.941(3)	171(5)
O(1W)-H(1W2)...O(23)#5	0.94(5)	1.83(5)	2.760(3)	169(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z #2 x+1,y,z #3 x,y+1,z #4 x,y-1,z

#5 -x,y-1/2,-z

X-ray crystallographic data of 3.13

Table A8.1. Crystal data and structure refinement for 3.13

Identification code	x1605008
Empirical formula	$C_{21}H_{33}N_5O_3Cl_2$
Formula weight	474.42
Temperature/K	100
Crystal system	orthorhombic
Space group	$C222_1$
a/Å	14.8861(3)
b/Å	14.8873(3)
c/Å	21.3167(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4724.08(17)
Z	8
ρ_{calc}g/cm^3	1.334
μ/mm^{-1}	2.738
F(000)	2016.0
Crystal size/mm^3	0.27 × 0.148 × 0.108
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.296 to 144.632
Index ranges	$-18 \leq h \leq 16$, $-18 \leq k \leq 18$, $-26 \leq l \leq 25$
Reflections collected	22334
Independent reflections	4587 [R_{int} = 0.0370, R_{sigma} = 0.0348]
Data/restraints/parameters	4587/0/283

Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0267, wR_2 = 0.0653
Final R indexes [all data]	R_1 = 0.0278, wR_2 = 0.0660
Largest diff. peak/hole / e $Å^{-3}$	0.25/-0.20
Flack parameter	0.020(4)

Table A8.2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 3.13. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	3705.3(13)	6790.6(14)	3030.9(9)	21.7(4)
N2	2867.6(12)	7113.3(12)	2879.2(8)	22.5(4)
C3	2357.4(14)	6900.6(14)	3357.0(9)	21.2(4)
N4	2816.6(12)	6463.7(11)	3811.9(8)	18.5(3)
C5	2449.5(15)	6117.5(14)	4401.7(10)	25.2(4)
C6	3693.2(13)	6385.8(12)	3609.5(9)	17.9(4)
C7	4424.1(14)	5984.2(13)	3999.2(10)	19.6(4)
C8	5003.0(13)	6696.9(12)	4335.7(9)	17.0(4)
C9	5552.6(12)	7200.2(12)	3844.5(8)	15.1(4)
O10	6083.8(9)	6781.4(9)	3506.3(6)	17.7(3)
N11	5488.9(10)	8097.7(11)	3802.5(7)	16.6(3)
C12	4889.7(15)	8696.9(13)	4166.3(10)	22.8(4)
C13	5295.6(15)	9626.7(14)	4055.9(10)	25.0(4)
C14	5731.9(14)	9556.0(13)	3405.9(10)	22.5(4)
C15	6098.7(13)	8588.3(12)	3378.4(8)	16.9(4)
C16	7056.8(13)	8514.8(12)	3643.3(9)	16.6(4)
O17	7229(1)	8828.5(9)	4164.8(7)	22.4(3)
N18	7656.2(10)	8083.6(11)	3283.6(7)	16.8(3)
C19	8567.9(13)	7871.3(13)	3504.0(9)	19.4(4)
C20	9103.7(15)	8726.1(15)	3638.8(11)	29.0(5)
C21	9034.4(13)	7323.0(16)	2992.6(10)	25.3(4)
C22	8555.3(14)	7265.9(13)	4095.8(9)	19.6(4)

O23	9215.3(11)	7235.6(12)	4440.4(7)	31.4(4)
N24	7835.4(11)	6741.0(11)	4168.6(7)	17.9(3)
C25	7759.8(14)	6096.9(13)	4680.8(9)	20.1(4)
C26	7253.0(14)	6467.7(13)	5252.3(9)	19.4(4)
C27	6338.9(13)	6884.9(12)	5092.3(8)	18.1(4)
C28	5671.6(14)	6231.2(13)	4782.4(9)	19.2(4)
Cl1	6243.8(4)	5614.6(4)	6839.7(3)	35.18(14)
Cl2	8169.8(4)	5257.0(4)	6866.9(3)	34.21(14)
C29	7103.0(15)	4936.8(15)	7157.9(11)	26.8(4)

Table A8.3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 3.13. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	19.2(9)	29.8(9)	16.1(9)	2.5(8)	1.0(7)	-4.1(7)
N2	23.6(8)	27.9(9)	16.0(7)	1.1(6)	-1.1(7)	-0.5(6)
C3	21.5(10)	23.0(9)	19.2(9)	-2.3(7)	-0.5(7)	0.1(7)
N4	22.5(8)	18.2(7)	14.8(7)	-1.3(6)	3.1(7)	-3.1(6)
C5	31.6(11)	23.4(9)	20.5(10)	3.1(8)	10.9(8)	0.4(8)
C6	19.0(9)	18.4(8)	16.3(9)	-1.8(7)	-0.4(7)	-6.0(7)
C7	21.0(9)	17.8(9)	20.1(9)	1.8(7)	-2.1(7)	-4.9(7)
C8	18.5(9)	16.7(9)	15.9(8)	0.8(7)	0.6(7)	-3.3(7)
C9	15.1(8)	18.3(9)	12.0(8)	0.2(7)	-3.4(7)	-3.2(7)
O10	21.1(7)	16.8(6)	15.1(6)	-1.9(5)	2.1(5)	-1.5(5)
N11	19.0(7)	17.1(7)	13.9(7)	0.7(6)	2.5(6)	-0.3(6)
C12	26.3(10)	19.1(9)	23(1)	1.6(7)	8.3(8)	4.5(7)
C13	32.1(11)	18.1(9)	24.8(10)	0.2(8)	7.6(8)	4.2(8)
C14	27.5(11)	17.9(9)	22.1(9)	5.5(7)	1.8(8)	2.0(7)
C15	20.8(9)	16.9(8)	13.1(8)	2.6(6)	0.8(7)	-1.8(7)
C16	22.7(10)	12.7(8)	14.4(9)	3.1(6)	0.2(7)	-3.6(7)
O17	30.2(8)	21.4(7)	15.7(7)	-3.0(5)	-4.0(6)	0.8(5)
N18	17.0(7)	19.9(7)	13.3(7)	0.5(6)	-1.1(6)	-3.8(6)
C19	16.1(9)	23.6(9)	18.5(9)	3.0(7)	-1.8(7)	-4.3(7)
C20	23.2(10)	31.6(11)	32.1(12)	5.9(9)	-6.9(9)	-12.6(8)
C21	17.9(9)	37.9(11)	20(1)	4.5(8)	1.8(8)	2.0(8)
C22	20.7(9)	22.4(9)	15.6(9)	-1.3(7)	-1.8(7)	-2.1(7)

O23	27.7(8)	41.5(9)	25.2(8)	9.3(6)	-12.4(7)	-11.1(7)
N24	18.9(8)	18.9(8)	15.9(7)	1.3(6)	-2.4(6)	-0.2(6)
C25	23.2(10)	17.2(9)	19.9(10)	3.2(7)	-0.9(8)	1.2(7)
C26	23.7(10)	19.2(9)	15.4(8)	1.8(7)	-3.2(8)	-1.3(7)
C27	22.3(9)	18.2(8)	13.7(8)	0.3(7)	-0.2(7)	-0.2(8)
C28	23.8(10)	17.1(8)	16.8(9)	3.0(7)	-0.6(8)	-3.0(7)
Cl1	28.9(3)	36.3(3)	40.4(3)	-6.2(2)	-6.8(2)	5.1(2)
Cl2	24.7(2)	43.7(3)	34.2(3)	-3.2(2)	1.2(2)	-4.9(2)
C29	25.4(11)	28.7(11)	26.4(10)	0.8(8)	-0.2(9)	-2.0(8)

Table A8.4. Bond Lengths for 3.13

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	N2	1.375(3)	C14	C15	1.542(3)
C1	C6	1.373(3)	C15	C16	1.538(3)
N2	C3	1.309(3)	C16	O17	1.233(2)
C3	N4	1.353(3)	C16	N18	1.340(3)
N4	C5	1.465(3)	N18	C19	1.471(2)
N4	C6	1.379(3)	C19	C20	1.529(3)
C6	C7	1.494(3)	C19	C21	1.529(3)
C7	C8	1.544(3)	C19	C22	1.550(3)
C8	C9	1.525(3)	C22	O23	1.227(3)
C8	C28	1.542(3)	C22	N24	1.335(3)
C9	O10	1.238(2)	N24	C25	1.458(2)
C9	N11	1.343(3)	C25	C26	1.535(3)
N11	C12	1.481(2)	C26	C27	1.534(3)
N11	C15	1.475(2)	C27	C28	1.540(3)
C12	C13	1.529(3)	Cl1	C29	1.765(2)
C13	C14	1.534(3)	Cl2	C29	1.770(2)

Table A8.5. Bond Angles for 3.13

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	C1	N2	110.66(18)	N11	C15	C14	102.80(15)
C3	N2	C1	104.99(17)	N11	C15	C16	108.09(14)
N2	C3	N4	112.38(18)	C16	C15	C14	112.40(16)
C3	N4	C5	126.57(18)	O17	C16	C15	119.80(18)
C3	N4	C6	107.11(16)	O17	C16	N18	123.99(18)
C6	N4	C5	126.30(18)	N18	C16	C15	116.19(16)
C1	C6	N4	104.86(18)	C16	N18	C19	122.31(16)
C1	C6	C7	131.75(19)	N18	C19	C20	111.26(17)
N4	C6	C7	123.28(17)	N18	C19	C21	107.82(16)
C6	C7	C8	112.95(16)	N18	C19	C22	111.95(15)
C9	C8	C7	108.55(15)	C20	C19	C22	109.71(16)
C9	C8	C28	107.37(15)	C21	C19	C20	109.97(17)
C28	C8	C7	109.77(15)	C21	C19	C22	105.98(16)
O10	C9	C8	119.65(16)	O23	C22	C19	119.91(18)
O10	C9	N11	120.48(17)	O23	C22	N24	123.46(19)
N11	C9	C8	119.79(16)	N24	C22	C19	116.38(17)
C9	N11	C12	127.38(16)	C22	N24	C25	122.27(17)
C9	N11	C15	119.37(16)	N24	C25	C26	113.32(16)
C15	N11	C12	113.17(15)	C27	C26	C25	113.88(16)
N11	C12	C13	103.10(16)	C26	C27	C28	114.31(15)
C12	C13	C14	104.14(17)	C27	C28	C8	113.40(15)
C13	C14	C15	104.39(15)	Cl1	C29	Cl2	111.19(12)

Table A8.6. Hydrogen Bonds for 3.13

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N18	H18	N2[1]	0.88	2.13	2.973(2)	161.3
N24	H24	O10	0.88	2.12	2.966(2)	161.6

[1]1-X,+Y,1/2-Z

Table 7 Torsion Angles for 3.13

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	N2	C3	N4	0.4(2)	C12	N11	C15	C14	-9.8(2)
C1	C6	C7	C8	77.3(3)	C12	N11	C15	C16	109.18(18)
N2	C1	C6	N4	0.3(2)	C12	C13	C14	C15	-35.9(2)
N2	C1	C6	C7	-175.89(19)	C13	C14	C15	N11	27.8(2)
N2	C3	N4	C5	-178.82(18)	C13	C14	C15	C16	-88.16(19)
N2	C3	N4	C6	-0.2(2)	C14	C15	C16	O17	51.1(2)
C3	N4	C6	C1	0.0(2)	C14	C15	C16	N18	-130.33(17)
C3	N4	C6	C7	176.54(17)	C15	N11	C12	C13	-12.1(2)
N4	C6	C7	C8	-98.3(2)	C15	C16	N18	C19	-172.92(15)
C5	N4	C6	C1	178.55(18)	C16	N18	C19	C20	-63.4(2)
C5	N4	C6	C7	-4.9(3)	C16	N18	C19	C21	175.94(17)
C6	C1	N2	C3	-0.4(2)	C16	N18	C19	C22	59.7(2)
C6	C7	C8	C9	-69.1(2)	O17	C16	N18	C19	5.6(3)
C6	C7	C8	C28	173.85(16)	N18	C19	C22	O23	-159.16(19)
C7	C8	C9	O10	-59.6(2)	N18	C19	C22	N24	26.5(2)
C7	C8	C9	N11	123.63(18)	C19	C22	N24	C25	176.00(17)
C7	C8	C28	C27	174.54(16)	C20	C19	C22	O23	-35.1(3)
C8	C9	N11	C12	-3.6(3)	C20	C19	C22	N24	150.49(18)
C8	C9	N11	C15	172.90(16)	C21	C19	C22	O23	83.5(2)
C9	C8	C28	C27	56.7(2)	C21	C19	C22	N24	-90.8(2)
C9	N11	C12	C13	164.57(19)	C22	N24	C25	C26	94.8(2)
C9	N11	C15	C14	173.18(16)	O23	C22	N24	C25	1.8(3)
C9	N11	C15	C16	-67.8(2)	N24	C25	C26	C27	51.3(2)
O10	C9	N11	C12	179.61(18)	C25	C26	C27	C28	59.9(2)

O10	C9	N11	C15	-3.9(3)	C26	C27	C28	C8	-150.55(16)
N11	C12	C13	C14	29.1(2)	C28	C8	C9	O10	59.0(2)
N11	C15	C16	O17	-61.7(2)	C28	C8	C9	N11	-117.77(18)
N11	C15	C16	N18	116.93(17)					

Table A8.8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 3.13

Atom	*x*	*y*	*z*	U(eq)
H1	4221	6841	2771	26
H3	1735	7038	3382	25
H5A	1817	6293	4439	38
H5B	2790	6367	4755	38
H5C	2496	5461	4406	38
H7A	4816	5615	3727	24
H7B	4153	5582	4317	24
H8	4612	7124	4574	20
H12A	4896	8539	4618	27
H12B	4265	8666	4009	27
H13A	5749	9770	4380	30
H13B	4824	10096	4060	30
H14A	6224	9999	3360	27
H14B	5284	9659	3070	27
H15	6067	8343	2942	20
H18	7499	7922	2902	20
H20A	9150	9085	3255	43
H20B	9707	8565	3784	43
H20C	8798	9076	3964	43
H21A	8688	6776	2910	38
H21B	9640	7160	3132	38
H21C	9074	7681	2608	38

H24	7391	6785	3898	21
H25A	8370	5913	4813	24
H25B	7445	5555	4526	24
H26A	7160	5974	5557	23
H26B	7631	6929	5458	23
H27A	6436	7400	4807	22
H27B	6066	7121	5483	22
H28A	5330	5916	5115	23
H28B	6013	5774	4544	23
H29A	6988	4300	7050	32
H29B	7099	4992	7621	32