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Article

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Potent and Selective Tetrahydroisoquinoline Kappa Opioid Receptor Antagonists of Lead Compound (3*R*)-*N*-[1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (CDTic)

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ABSTRACT: Animal pharmacological studies suggest that potent and selective κ opioid receptor antagonists have potential as pharmacotherapies targeting depression, anxiety, and substance abuse (opiates, alcohol, nicotine, cocaine). We recently reported lead compound **1** as a

new class of κ opioid receptor antagonists with only one basic amine group. Analogues were synthesized and evaluated for their in vitro opioid receptor antagonist properties using a [^{35}S]GTPγS binding assay. All analogues were pure opioid receptor antagonists with no agonist activity. Compounds **1**, **8**, **9**, **13**, and **14** (K_e values 0.058–0.64 nM) are highly potent and highly selective for the κ relative to the μ and δ opioid receptors. Favorable calculated physiochemical properties were confirmed in rat PK studies, demonstrating brain penetration for selected compounds **1**, **9**, and **13**. High κ opioid receptor potency and selectivity, and highly favorable calculated physiochemical and PK properties for brain penetration, suggest these compounds should be considered for further development.

INTRODUCTION

The opioid receptors belong to the superfamily of G-protein coupled receptors (GPCRs) and consist of the μ, δ, κ subtype[1-4] with the κ opioid receptor being the most abundant of the three subtypes in the human brain.[5] Since activation of the κ opioid receptor by the endogenous dynorphin results in mood modulation, learning and memory behavioral responses to drugs of abuse, κ opioid receptor antagonists are of high interest as potential pharmacotherapies as treatments for substance abuse as well as depression and anxiety disorders.[6] Studies from our laboratory led to the development of the potent and selective κ opioid receptor antagonist JDTic (Figure 1) that was evaluated in a Phase I clinical study.[7-15] In addition to JDTic, LY2456302[16] and PF4455242[17,18] were developed as κ opioid receptor antagonists which reached clinical evaluation (Figure 1). To our knowledge LY2456302, now referred to as CERC-501, is the only one of the three compounds still in clinical evaluation. CYM51317 (no structure provided) has been reported as a new κ opioid antagonist for migraine prevention.[19]

In a recent communication, we reported that the structurally simple tetrahydroisoquinoline **1** (CDTic) was a pure opioid receptor antagonist lead structure for the design and development of a new structural class of potent and selective κ opioid receptor antagonists.[20] In the current study, we report the design, synthesis, and in vitro opioid receptor binding properties using the [^{35}S]GTPγS binding assay of analogues of **1** represented by the general structure **2** where the R^1, R^2, R^3, R^4, and R^5 groups were varied to afford the target compounds **3**–**20** (see Tables 1–5 for structures). In addition, physiochemical properties were calculated to determine if the compounds would be predicted to enter the brain and pharmacokinetic studies were conducted on the most potent and selective κ opioid receptor antagonists which showed that the compounds did enter the brain.

RESULTS AND DISCUSSION

Chemistry. The synthetic methods (Schemes 1–5) used to prepare the analogues of **1** presented in this study were analogous to the synthetic methods reported for the synthesis of **1**.[20] As shown in Scheme 1, target compounds **3**, **10**, and **11** could be prepared from the same amine **21**[20] which had previously been used in the synthesis of **1**. Amide coupling of **21** using dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) with commercially available Boc-7-hydroxy-(*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid was followed by acid deprotection using hydrogen chloride in methanol to afford **3**, a diastereomer of **1**. Coupling of amine **21** and commercially available Boc-(*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid using conditions similar to those used for the synthesis and deprotection of **3** afforded **10**. To prepare the target compound **11**, amine **21** was coupled with Boc-7-fluoro-(*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, prepared as previously reported,[21] using DCC and HOBt followed by deprotection with hydrogen chloride in methanol.

Target compounds **9**, **12**, and **19** (also Scheme 1) were prepared using the previously prepared Boc-protected intermediate **22**.[20] Compound **9** was prepared using a sequence and conditions similar to those previously used to synthesize JDTic analogues.[21] First, the phenol in **22** was converted to an aryl triflate using *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhNTf_2$) followed by palladium-catalyzed cyanation to give the intermediate *N*-Boc-7-cyano-tetrahydroisoquinoline which on basic hydrolysis provided the *N*-Boc-7-carbamoyl-tetrahydroisoquinoline intermediate. Finally, acid deprotection using hydrogen chloride in methanol provided **9**. O-Methylation of the phenol in **22** using methyl iodide and potassium carbonate in acetone was followed by acid deprotection using hydrogen chloride in methanol to afford **12**. Reductive amination of formaldehyde with **1** (obtained by treating **22** with hydrogen chloride in methanol) using sodium triacetoxyborohydride afforded the *N*-methyl final product **19**.

In order to prepare the analogues **4** and **5**, which are diastereomers of **1**, the chiral amine **26** was prepared as shown in Scheme 2. Cyclohexylacetaldehyde (**23a**) was condensed with the chiral auxiliary (*S*)-*tert*-butylsulfinamide to afford the sulfinimine **24**. Isopropylmagnesium chloride was added to **24** to afford the chiral sulfinamide **25**. As with the preparation of amine **21**,[20] this reaction proceeded with high stereoselectivity. The minor diastereomer was separable by silica gel chromatography. The chirally pure sulfinamide **25** was then cleaved to the amine **26** with hydrogen chloride in a methanol dioxane mixture. Amide coupling of **26** with the (*R*)- and (*S*)- isomers of Boc-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid using DCC and HOBt and subsequent Boc deprotection with hydrogen chloride in methanol afforded the desired diastereomers **4** and **5**, respectively. Compounds **1**, **3**, **4**, **5** were found to be single peaks by HPLC analysis, whereas a co-injection of a either pair of diastereomers resolved as two peaks.

As shown in Scheme 3, the same chiral auxiliary strategy was implemented with a variety of starting aldehydes and (*R*)-*tert*-butylsulfinamide in order to afford the preferred chirality for amines **29a**–**29e**. Cyclohexylacetaldehyde (**23a**) was converted to sulfinimine **27a** then treated with phenylmagnesium bromide or cyclopropylmagnesium bromide to afford sulfinamides **28a** and **28b**, respectively. Cyclopentylacetaldehyde (**23b**) was converted to sulfinimine **27b** which was treated with isopropylmagnesium chloride or cyclopropylmagensium bromide to afford the sulfinamides **28c** and **28d**, respectively. Cycloheptylacetaldehyde (**23c**) was carried through sulfinimine **27c** then treated with isopropylmagnesium chloride to afford sulfinamide **28e** using conditions similar to that used to synthesize **28a**. The sulfinamides **28a**–**28e** were separated from the minor diastereomer by silica gel chromatography then treated with hydrogen chloride in methanol and dioxane to afford the chirally pure amines **29a**–**29e**, which were used to synthesize **7**, **8**, **13**, **14**, **16**, **17**, and **20** (see Schemes 4–6).

As shown in Scheme 4, commercially available amine **30** was coupled to 7-hydroxy-Boc-D-Tic-OH using DCC and HOBt and deprotected in methanol with hydrochloric acid to afford target compound **6**. Amines **29a** and **29b** (Scheme 3) were coupled with 7-hydroxy-Boc-D-Tic-OH using DCC and HOBt followed by treatment with hydrogen chloride in dioxane and methanol to afford target compounds **7** and **8**, respectively. As shown in Scheme 5, compound **14** was synthesized by coupling amine **29e** (Scheme 3) with 7-hydroxy-Boc-D-Tic-OH using DCC and HOBt in THF followed by treatment with 4 N HCl in dioxane and acetonitrile.

Scheme 6 illustrates the synthesis of the analogues **13**, **16**, **17**, and **20** starting with **29c** or **29d**, where R^1 = cyclopentyl in the general structure **2**. Amines **29c** and **29d** (Scheme 3) were coupled to 7-hydroxy-Boc-D-Tic-OH using DCC and HOBt to give **31** and Boc-**17**, respectively. Removal of the BOC groups with hydrogen chloride in dioxane and acetonitrile or methanol

afforded the target compounds **13** and **17**, respectively**.** A sample of **31** was converted to the aryl triflate **32** using *N*-phenyl-*bis*(trifluoromethanesulfonamide). As an alternative to the cyanation chemistry which was used to synthesize **9**, palladium-catalyzed aminocarbonylation under sealed vessel microwave heating directly afforded the benzamide **33**. Removal of the protecting BOC group using hydrogen chloride in dioxane and acetonitrile afforded target compound **16**. Amine **29c** (Scheme 3) was also coupled to 7-methoxy-3-methyl-Boc-D-Tic-OH.[22] Global deprotection with boron tribromide in dichloromethane yielded the target compound **20**.

Due to the immediate availability of starting materials, the cyclobutyl analogue **15** (Scheme 7) was prepared by inverting the Grignard and sulfinimine chemistry previously illustrated in Scheme 3. Isobutryaldehyde (**34**) was condensed with (*S*)-*tert*-butylsulfinamide using magnesium sulfate as a dehydrating agent and pyridinium p-toluenesulfonate as an acid catalyst to afford the sulfinimine **35**. Magnesium metal was used to prepare the cyclobutylmethylmagnesium reagent from the alkyl bromide. Addition of this Grignard reagent to the sulfinimine **35** afforded the desired sulfinamide **36**. Treatment of a methanol solution of **36** with 4 N HCl in dioxane afforded the amine **37** hydrochloride, which was coupled to 7-hydroxy-Boc-D-Tic-OH using propylphosphonic anhydride (T3P) and *N*-ethyldiisopropylamine in ethyl acetate and tetrahydrofuran. Subsequent deprotection using anhydrous hydrogen chloride in methanol afforded the desired target compound **15**.

Finally, target compound **18** was accessed according to Scheme 8. Birch reduction of the toluene derivative **38** was followed by catalytic hydrogenation using palladium on carbon catalyst to afford the saturated ethanol derivative **39**. Swern oxidation afforded the acetaldehyde, which was condensed to the sulfinamide **40** using the same conditions used to prepare **27a**–**27c** in Scheme 3. Addition of isopropylmagnesium chloride to **40** and subsequent treatment with

hydrogen chloride in dioxane and methanol afforded the amine **41** hydrochloride. This amine was coupled with 7-hydroxy-Boc-D-Tic-OH using DCC and HOBt in THF followed by deprotection using anhydrous hydrogen chloride in methanol to afford **18**.

Pharmacology Studies. All the synthesized compounds were tested for their abilities to inhibit agonist-stimulated [^{35}S]GTPγS binding in membranes prepared from CHO cells expressing the μ, δ, and κ opioid receptors.[20] In these assays, concentration response curves of control agonists (U69,593 (κ), DAMGO (μ), or DPDPE (δ)) were run in the presence and absence of a single concentration of test compound. K_e values were calculated with the equation $K_e = [L]/(ER - 1)$ where [L] is the concentration of test compound and ER is the ratio of EC_{50} values in the presence and absence of test compound. K_e values were considered valid when the ER was at least 4. Compounds were also evaluated for agonist activity at 10 μM final concentration in the [^{35}S]GTPγS binding assays.

In contrast to JDTic with four stereocenters, **1** has only two asymmetric centers and thus three diastereomeric isomers: **3**, **4**, and **5** (Table 1). In order to determine if one of these isomers is a more potent and selective κ opioid receptor antagonist, the three isomers were synthesized and tested. The three isomers (**3**, **4**, and **5**) had K_e values at the κ opioid receptor of 14.2, 12.6, and 4.40 nM, respectively, and thus were 101-, 90- and 31-fold less potent κ opioid antagonists than **1**. Compounds **3**, **4**, and **5** had μ/κ values of 80, 41, and >682, respectively, and thus were selective for the κ opioid receptor relative to the μ opioid receptor. All three isomers have K_e values of >3000 nM at the δ opioid receptor, making them highly selective for the κ relative to the δ opioid receptor. However, none of the three diastereomers have better κ opioid receptor potency and selectivity than **1**. Given the stereochemical similarity of **1** and JDTic, they may interact with the κ opioid receptor in the same fashion. This is supported by initial docking

studies of **1** to the x-ray structure, which predicted the two compounds to interact similarly with the κ opioid receptor.[20]

The data in Table 2 gives information on the importance of the isopropyl group to the κ opioid receptor potency of **1**. Replacement of the isopropyl group in **1** with a hydrogen to give **6** changes its K_e value at the κ opioid receptor from 0.14 nM for **1** to 23.5 nM for **6**, a 168-fold loss in κ antagonist potency (Table 2). Changing the isopropyl in **1** to a phenyl ring gives **7**, which has a K_e = 15.2 nM at the κ opioid receptor and thus is a 109-fold less potent κ opioid receptor antagonist than **1**. Compound **8**, with a cyclopropyl group replacing the similarly-sized isopropyl group in **1**, has a K_e = 0.64 nM at the κ opioid receptor and thus is only 4.6-times less potent than **1** as κ opioid receptor antagonist. With a μ/κ = 417 and δ/κ of >4690, **8** is also a very selective κ opioid receptor antagonist relative to the μ and δ opioid receptors. These results, while limited, strongly suggest that a substituent in the 2-position is required for potent antagonism and, like JDTic, a 2-position isopropyl group is preferred.

The effect on κ opioid antagonist potency by replacing the 7-hydroxyl group in **1** with other substituents is given in Table 3. Replacing the 7-hydroxyl group in **1** with a carboxamido group gives **9**, which has K_e values of 178, 1220, and 0.24 nM at the μ, δ and κ opioid receptors, respectively, and thus is almost as potent and selective a κ opioid receptor antagonist as **1**. Replacing the 7-hydroxyl group in **1** with a hydrogen or fluorine gives **10** and **11**, with K_e values of 5.49 and 10.7 nM, respectively, making the two compounds 39- and 76-fold less potent than **1** as κ opioid receptor antagonists. The methoxy compound **12** with a K_e = 77.4 nM at the κ opioid receptor is a much less potent κ antagonist than any of the other three 7-substituted compounds **9**–**11**. Even though **10** and **11** are not highly potent κ opioid receptor antagonists they remain very selective at κ relative to the μ and δ opioid receptors. These results show the hydroxyl group

in **1** can be replaced with a carboxamido group with little loss in κ antagonist potency. However, replacement of the hydroxyl group with a hydrogen, fluoro, or methoxy group results in a significant loss in κ opioid receptor antagonism.

In order to determine if the cyclohexyl group in **1** offered the optimum κ opioid receptor potency and selectivity, the cyclopentyl **13**, cycloheptyl **14**, and cyclobutyl **15** analogues were synthesized and tested (Table 4). It was extremely pleasing to find that the cyclopentanyl analogue **13** had a K_e = 0.058 nM at the κ opioid receptor and was 5900- and 27,000-fold selective for the κ relative to the μ and δ receptors, respectively. With a K_e = 0.20 nM at the κ opioid receptor, the cycloheptyl analogue **14** was almost as potent as the lead compound **1** as a κ opioid receptor antagonist. Compound **14** also has μ/κ and δ/κ values of 292 and 3760, respectively, and thus is very selective for the κ relative to the μ and δ opioid receptors. In contrast to **1**, **13**, and **14**, which possess cyclohexyl, cyclopentyl, and cycloheptyl rings, respectively, the smaller cyclobutane ring analogue **15** had a K_e = 2.61 nM at the κ opioid receptor and was only 69-fold selective for the κ relative to the μ opioid receptor. However, with a δ/κ value >1150, **15** remained highly selective for the κ relative to the δ opioid receptor. Since the carboxamide **9** (see Table 3) and the cyclopropyl **8** analogues of **1** (see Table 2) both had subnanomolar κ potencies and high selectivity for the κ relative to the μ and δ receptors, the carboxamide **16** and cyclopropyl **17** analogues of **13** were synthesized and tested (Table 4). Although the carboxamide analogue **16** had a K_e = 2.04 nM at the κ opioid receptor and was 102- and 1245-fold selective for the κ relative to the μ and δ opioid receptors, respectively, it was not as potent and κ selective as the carboxamide analogue **9**. Similarly, the cyclopropyl analogue **17**, with a K_e = 3.74 nM at the κ opioid receptor, did not retain the potency nor selectivity of the analogous cyclopropyl analogue **8**. The most important finding from this study is that

replacement of the cyclohexyl group in **1** with a cyclopentyl group resulted in a significant increase in κ opioid receptor antagonist potency. It is also interesting that replacement of the isopropyl group in **13** with a cyclopropyl group to give **17** resulted in a large loss in κ antagonist potency.

It is well documented that methyl groups can have a significant effect on the potency of target compounds.[21,23] Furthermore, in a recent study[24] we found that the addition of a methyl group to the 4-position on the piperidine ring of compound **42** to give the 4-methyl analogue 4-MePDTic (**43**) resulted in a 18-fold increase in the κ opioid receptor potency relative to **42**; therefore, we investigated the effect of adding a 4-methyl group to **1** (Table 5). Compound **18**, which is the 4-methyl analogue of **1**, has a K_e = 1.27 nM at the κ opioid receptor and thus is 9 times less potent than **1**, which has a K_e = 0.14 nM at the κ opioid receptor. With μ/κ and δ/κ values of >174 and >2400, **18** remains very selective for κ relative to μ and δ opioid receptors.

Two methyl-substituted JDTic-analogues, **44** and **45**, were potent and selective κ opioid receptor antagonists with shorter durations of action in a mouse antinociception test.[22,25] For comparison, the *N*-methyl **19** analogue of **1** and the 3-methyl **20** analogue of **13** were synthesized and tested (Table 5). The *N*-methyl analogue **19** (Table 5) had K_e values of 245, >3000, and 4.23 nM at the μ, δ, and κ opioid receptors, respectively. Thus, **19** is 30-fold less potent than its parent **1** at the κ opioid receptor. In the JDTic series, the *N*-methyl analogue **44**, with a K_e = 0.16 nM represented only an 8-fold decrease in potency from its parent, JDTic. The 3-methyl analogue **20** had K_e values of 1650, >3000, and 6.20 nM at the μ, δ, and κ opioid receptors, respectively. Thus, **20** is 107-fold less potent at the κ opioid receptor than its parent compound **13**. In contrast, the methylated-JDTic analogue **45** had K_e values of 3.6, 854, and 0.03 nM at the μ, δ and κ opioid receptors, respectively, and was thus only 1.5-times less potent than JDTic at the κ opioid

receptor. These comparisons show that this new tetrahydroisoquinoline class of opioid antagonists has a different structure–activity relationship than JDTic, **44**, and **45**.

Table 6 shows a comparison of the calculated physiochemical properties of six of the more potent κ opioid receptor antagonists from this study, along with JDTic. Reports from other laboratories predict that compounds with topological polar surface area (TPSA) values less than 76 Å,[26] cLogP values in the range of 2–4,[27] logBB values greater than –1,[28] and CNS MPO values greater than 4 will penetrate the brain.[29] All the compounds represented in Table 6 except **9** have TPSA values of 61.36 Å, which is less than 76 Å. Like JDTic, compound **9** has a TPSA value of 84.22 Å which is similar to the 84.83 Å value for JDTic. The cLogP values for the six new tetrahydroisoquinolines ranged from 3.31 for **9** to 4.48 for **14** compared to 3.60 for JDTic. All six new tetrahydroisoquinoline analogues, as well as JDTic, have logBB values greater than –1 and thus would be predicted to penetrate the brain. Compounds **8**, **13**, and **9** have favorable CNS MPO values of 4.2, 4.2, and 4.4, respectively. Compounds **1**, **14**, and **18** had CNS MPO scores of 3.7, 3.4, and 3.5, respectively. In a recent review concerning the various methods used for predicting the ability of a compound to cross the blood/brain barrier, Pike pointed out that lower molecular weight compounds tended to penetrate the brain better than higher molecular weight compounds.[29,30] The six new tetrahydroisoquinoline compounds in Table 6 had molecular weights ranging from 330.4 Daltons for **13** up to 371.5 Daltons for **9**. The highly potent and selective κ opioid receptor antagonist **13**, with a molecular weight of 330.4 Daltons, has a molecular weight 135.2 Daltons less than JDTic at 465.8 Daltons.

Pharmacokinetic Studies. Rats were administered a single 5 mg/kg s.c. dose for **1**, **9**, or **13**, and each compound was quantitated in plasma and brain homogenate at times between 1 and 168 h. Concentration versus time data was analyzed by a noncompartmental analysis using Phoenix

WinNonlin 6.3 (Pharsight, Cary, NC). In plasma, t_{max} for **1** was 1 h in plasma and brain, with C_{max} values of 111 and 524 ng/mL, respectively, indicating rapid absorption (Table 7 and Figure 2). Compound **1** was readily determined throughout the 168 h collection period in both brain and plasma. The half-life was determined to be 34.2 h in plasma and 78.2 h in brain. The levels of **1** in brain remained elevated while the levels in plasma dropped substantially, resulting in a substantially higher value for area under the curve (AUC) in brain, and a ratio of AUC in brain:plasma of 8.15:1; the clearance was 11.7 times slower from the brain relative to plasma. Compound **9** was rapidly cleared from plasma and brain with C_{max} in both at 1 h, with values of 376 and 131 ng/mL, respectively (Figure 2, see Figure S1 in Supporting Information for an extra depiction of Figure 2.). Compound **9** was not detected in plasma or brain at timepoints after 24 h, with the half-lives of 1.9 h in plasma, and 2.3 h in brain (Table 7). In plasma, **13** reached C_{max} of 136 ng/mL at 1 h post dose; in brain, a C_{max} of 575 ng/mL was also achieved at 1 h post dose. The half-life was determined to be 32 h in plasma, and 45 h in brain. Compound **13** crossed the blood-brain barrier and persisted in plasma and brain for 168 h post dose. The ratio of brain:plasma AUC was 6.08:1 and the clearance was 6.1 times slower from the brain relative to the plasma, indicating that **13** crossed the blood-brain barrier and persisted in brain. JDTic in comparison had a half life of 28.4 and 51.8 h in plasma and brain, respectively, and a ratio of brain/plasma AUClast of 6.87.[31] Both **1** and **13** have similar pharmacokinetic behavior to JDTic, whereas **9** is very different, with a much shorter half life in both brain and plasma, and no differential persistence in the brain.

Conclusions

In conclusion, analogues **3**–**20** of the lead structure **1** were synthesized and evaluated for their ability to antagonize [^{35}S]GTPγS binding at the μ, δ, and κ opioid receptors. The data showed

that **13**, which has a cyclopentyl in place of the cyclohexyl in **1**, with a K_e = 0.058 nM at the κ opioid receptor and 5900- and 27,000-fold selectivity for the κ relative to the μ and δ receptors, respectively, was the most potent and selective κ opioid receptor analogue of **1**. In addition, the 7-carboxamido analogue **9** and the cycloheptyl analogue **14** had subnanomolar K_e values at the κ opioid receptor and were highly selective for the κ relative to the μ and δ opioid receptors. Calculated logBB and CNS MPO values along with low molecular weight values relative to JDTic suggested that **1**, **9**, and **13** would penetrate the brain. Data from PK studies in rats showed that **1** and **13** did indeed penetrate the brain. The cyclopentyl group (**13**) in place of the cyclohexyl group (**1**) did not make a significant change in C_{max}, t_{max}, or AUC in plasma, but in brain, the change substantially decreased half-life and AUC. Substitution of the hydroxy group in **1** with the carboxamido group in **9** substantially reduced the half-lives in brain and plasma, as well as the AUC values in brain and plasma.

Experimental Procedures

Melting points were determined using a MEL-TEMP II capillary melting point apparatus. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) spectra were obtained on a Bruker Avance DPX-300 MHz NMR spectrometer or a Varian Unity Inova 500 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were run on a Perkin-Elmer Sciex API 150 EX mass spectrometer equipped with ESI (turbospray) source. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. The purity of the compounds (>95%) was established by elemental analysis. Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Analytical thin-layer chromatography (TLC) was carried out using EMD silica gel 60 F_{254} TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash

column chromatography was done on a CombiFlash Rf system using ISCO prepacked silica gel columns or using EM Science silica gel 60Å (230–400 mesh). Solvent system: DMA80 = 80:18:2 CH_2Cl_2:CH_3OH:conc. NH_4OH. Unless otherwise stated, reagent-grade chemicals were obtained from commercial sources and were used without further purification. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen. Sealed tube reactions were run in a CEM Discover SP microwave synthesizer. Hydrochloride salts were prepared by dissolving the compound freebase in cold methanol, adding a slight excess of 2 N HCl in diethyl ether, then evaporating to dryness under vacuum.

(3*S*)-*N*-[(1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (3) Hydrochloride. A solution of dicyclohexylcarbodiimide (DCC) (120 mg, 0.58 mmol) in THF (2 mL) was added to a solution of HOBt (72 mg, 0.54 mmol) and 7-hydroxy-Boc-L-Tic-OH (150 mg, 0.51 mmol) in THF (3 mL). After 1 h, the amine **21** (120 mg, 0.6 mmol) and NEt_3 (0.2 mL, 1.4 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl (aq) (5 mL). After 1 h, the solution was concentrated, and the resulting residue partitioned between EtOAc and 7 M NH_4OH (aq). The organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was subjected to chromatography on silica gel eluting with a gradient EtOAc in hexanes to afford the **3** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 9.98 Hz, 1H), 6.97 (d, J = 8.29 Hz, 1H), 6.66 (dd, J = 2.54, 8.19 Hz, 1H), 6.54 (d, J = 2.45 Hz, 1H), 3.85–3.97 (m, 3H), 3.58 (dd, J = 5.27, 9.98 Hz, 1H), 3.12 (dd, J = 5.18, 16.11 Hz, 1H), 2.76

(dd, J = 9.98, 16.01 Hz, 1H), 1.54–1.92 (m, 9H), 1.04–1.38 (m, 6H), 0.72–1.02 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 154.8, 135.7, 129.9, 125.1, 114.2, 112.2, 56.5, 51.2, 46.9, 39.8, 34.6, 34.2, 32.6, 32.3, 30.5, 26.5, 26.4, 26.1, 19.1, 17.5. The freebase was converted into the hydrochloride salt to afford 123.3 mg (63% over two steps) of a white powder: MS (ESI) m/z 345.2 $(M + H)^+$; mp 149–153 °C (fusion); $[\alpha]_D$ = –43° (c 0.10, CH_3OH). Anal. ($C_{21}H_{33}ClN_2O_2 \cdot 0.5\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*S*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (4) Hydrochloride. A solution of DCC (110 mg, 0.53 mmol) in THF (2 mL) was added to a solution of HOBt (70. mg, 0.52 mmol) and 7-hydroxy-Boc-D-Tic-OH (150 mg, 0.50 mmol) in THF (3 mL). After 1 h, the amine **26** (90. mg, 0.44 mmol) and NEt_3 (0.3 mL, 2.2 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids which precipitated during the course of the reaction were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with 0–100% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl (aq) (5 mL). After 1 h, the solution was concentrated, and the residue partitioned between EtOAc and sat. $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% EtOAc in hexanes to afford the **4** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (d, J = 8.29 Hz, 1H), 6.66 (dd, J = 2.45, 8.29 Hz, 1H), 6.52 (d, J = 2.26 Hz, 1H), 3.95 (d, J = 8.48 Hz, 2H), 3.88 (td, J = 4.59, 9.47 Hz, 1H), 3.63 (dd, J = 5.09, 10.17 Hz, 1H), 3.06 (dd, J = 5.09, 16.01 Hz, 1H), 2.71–2.84 (m, 1H), 1.82 (d, J = 13.19 Hz, 1H), 1.54–1.76 (m, 5H), 1.07–1.38 (m, 7H), 0.87–1.04 (m, 1H), 0.83 (d, J = 6.97 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 155.1, 135.3, 129.8, 124.6,

114.3, 112.2, 56.4, 51.2, 46.7, 39.7, 34.6, 34.1, 32.6, 32.3, 30.5, 26.5, 26.3, 26.1, 19.0, 17.4. The freebase was converted into the hydrochloride salt to afford 14.5 mg (9% over two steps) of a white powder: MS (ESI) *m*/*z* 345.2 $(M + H)^+$; mp 150–154 °C (fusion); $[\alpha]_D$ = +38° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}ClN_2O_2 \cdot 1.15\ H_2O$) C, H, N.

(3*S*)-*N*-[(1*S*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (5) Hydrochloride. A solution of DCC (120 mg, 0.58 mmol) in THF (2 mL) was added to a solution of HOBt (72 mg, 0.54 mmol) and 7-hydroxy-Boc-L-Tic-OH (150 mg, 0.51 mmol) in THF (3 mL). After 1 h, the amine **26** hydrochloride (116 mg, 0.57 mmol) and NEt_3 (0.2 mL, 1.4 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl (aq) (5 mL). After 1 h, the solution was concentrated and taken up in 50% DMA80. The solids were separated by filtration and the organic layer was concentrated. The resulting residue was subjected to chromatography on silica gel eluting with a 25% DMA80 in CH_2Cl_2 to afford the **5** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83–7.02 (m, 2H), 6.61 (dd, *J* = 2.45, 8.10 Hz, 1H), 6.49 (d, *J* = 2.26 Hz, 1H), 3.76–3.97 (m, 3H), 3.52 (dd, *J* = 5.09, 10.17 Hz, 1H), 3.07 (dd, *J* = 5.18, 16.11 Hz, 1H), 2.67 (dd, *J* = 10.17, 16.01 Hz, 1H), 1.40–1.82 (m, 6H), 0.93–1.33 (m, 7H), 0.61–0.92 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 154.7, 136.3, 130.0, 125.4, 114.3, 112.3, 56.7, 51.2, 47.2, 39.7, 34.6, 34.2, 32.6, 32.4, 30.6, 26.5, 26.3, 26.1, 19.1, 17.7. The freebase was converted into the hydrochloride salt to afford 68.3 mg (36% over two steps) of a white powder: MS (ESI) *m*/*z*

345.3 $(M + H)^+$; mp 265–269 °C (fusion); $[\alpha]_D = -101°$ (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}ClN_2O_2$) C, H, N.

(3*R*)-*N*-(2-Cyclohexylethyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6) Hydrochloride. A solution of DCC (120 mg, 0.58 mmol) in THF (2 mL) was added to a solution of HOBt (72 mg, 0.54 mmol) and 7-hydroxy-Boc-D-Tic-OH (150 mg, 0.51 mmol) in THF (3 mL). After 1 h, 2-cyclohexylethylamine (**30**) hydrochloride (96 mg, 0.6 mmol) and NEt_3 (0.25 mL, 1.7 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 4 N HCl in dioxane (5 mL). After 12 h, the solution was concentrated, and the residue partitioned between EtOAc and sat. $NaHCO_3$ (aq). The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–100% EtOAc in hexanes to afford the **6** freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 8.38 (br. s., 1H), 7.08 (d, *J* = 8.48 Hz, 1H), 6.75 (dd, *J* = 2.45, 8.48 Hz, 1H), 6.63 (s, 1H), 4.33 (s, 2H), 4.11 (dd, *J* = 4.80, 11.77 Hz, 1H), 3.53–3.78 (m, 1H), 3.22 (d, *J* = 4.71 Hz, 1H), 2.92–3.13 (m, 1H), 1.60–1.82 (m, 6H), 1.07–1.53 (m, 7H), 0.80–1.06 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.5, 169.4, 158.1, 131.1, 129.7, 122.1, 116.9, 113.7, 56.9, 45.6, 38.5, 38.4, 37.8, 36.5, 34.3, 34.2, 30.4, 27.6, 27.3. The freebase was converted into the hydrochloride salt to afford 50 mg (28%) of an off-white powder: MS (ESI) *m*/*z* 303.1 $(M + H)^+$; mp 78–82 °C (fusion); $[\alpha]_D = +99°$ (*c* 0.32, CH_3OH). Anal. ($C_{18}H_{27}ClN_2O_2 \cdot 0.75\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-2-Cyclohexyl-1-phenylethyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (7) Hydrochloride. A solution of DCC (120 mg, 0.58 mmol) in THF (2 mL) was

added to a solution of HOBt (72 mg, 0.54 mmol) and 7-hydroxy-Boc-D-Tic-OH (150 mg, 0.51 mmol) in THF (3 mL). After 1 h, the amine **29a** (144 mg, 0.60 mmol) and NEt_3 (0.2 mL, 1.4 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were removed by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 4 N HCl in dioxane (5 mL). After 12 h, the solution was concentrated, and the residue partitioned between EtOAc and sat. $NaHCO_3$ (aq). The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–100% EtOAc in hexanes to afford the **7** freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 7.14–7.38 (m, 5H), 6.88 (d, *J* = 8.10 Hz, 1H), 6.57 (dd, *J* = 2.54, 8.19 Hz, 1H), 6.48 (d, *J* = 2.26 Hz, 1H), 5.00 (dd, *J* = 6.03, 9.42 Hz, 1H), 3.91 (s, 2H), 3.53 (dd, *J* = 4.71, 10.17 Hz, 1H), 2.74–2.90 (m, 1H), 2.58–2.74 (m, 1H), 1.47–1.87 (m, 8H), 1.07–1.36 (m, 5H), 0.80–1.06 (m, 3H); ^{13}C NMR (75 MHz, CD_3OD) d 174.7, 156.8, 144.8, 137.1, 130.8, 129.6, 128.1, 127.5, 125.5, 114.9, 113.1, 58.0, 52.0, 47.8, 45.5, 35.6, 34.7, 33.9, 32.1, 27.6, 27.3, 27.2. The freebase was converted into the hydrochloride salt to afford 25.3 mg (12%) of an off-white powder: MS (ESI) *m*/*z* 379.5 $(M + H)^+$; mp 139–143 °C (fusion); $[\alpha]_D$ = +67° (*c* 0.10, CH_3OH). Anal. ($C_{24}H_{31}ClN_2O_2 \cdot 0.75\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-2-Cyclohexyl-1-cyclopropylethyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8) Hydrochloride. A solution of DCC (120 mg, 0.58 mmol) in THF (2 mL) was added to a solution of HOBt (72 mg, 0.54 mmol) and 7-hydroxy-Boc-D-Tic-OH (150 mg, 0.51 mmol) in THF (3 mL). After 1 h, the amine **29b** (120 mg, 0.59 mmol) and NEt_3 (0.2 mL, 1.4 mmol) were added to the suspension. The reaction mixture was stirred at room temperature

for 12 h. The solids were removed by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl (aq) (5 mL). After 12 h, the solution was concentrated, and the residue partitioned between EtOAc and sat. $NaHCO_3$ (aq). The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–100% EtOAc in hexanes to afford 51.8 mg (30%) of the **8** freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 6.91 (d, J = 8.29 Hz, 1H), 6.60 (dd, J = 2.45, 8.29 Hz, 1H), 6.49 (d, J = 2.26 Hz, 1H), 3.83–4.00 (m, 2H), 3.37–3.55 (m, 2H), 2.67–2.99 (m, 2H), 1.79 (d, J = 12.43 Hz, 1H), 1.55–1.73 (m, 4H), 1.40–1.50 (m, 2H), 1.05–1.39 (m, 6H), 0.72–1.04 (m, 4H), 0.25–0.57 (m, 3H), 0.11–0.25 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.8, 156.8, 137.1, 130.9, 125.6, 115.0, 113.2, 58.0, 51.8, 47.8, 44.2, 35.4, 35.2, 33.9, 32.4, 27.7, 27.4, 27.3, 17.9, 4.2, 2.9. The freebase was converted into the hydrochloride salt to afford an off-white powder: MS (ESI) m/z 343.4 $(M + H)^+$; mp >250 °C; $[\alpha]_D$ = +88° (c 0.10, CH_3OH). Anal. ($C_{21}H_{31}ClN_2O_2$) C, H, N.

(3*R*)-*N*^{3}-[(1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxamide (9) Hydrochloride. A sample of the white foam **22** (3.16 g, 7.1 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with $PhNTf_2$ (3.6 g, 10 mmol) and NEt_3 (22 mmol, 3 mL). After 12 h, the reaction mixture was washed with sat. NH_4Cl (aq) then $NaHCO_3$ and dried over Na_2SO_4. The organic layer was concentrated to a residue which was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes to afford 3.57 g (87%) of the desired aryl triflate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.29 Hz, 1H), 7.15 (d, J = 8.10 Hz, 1H), 7.10 (br. s., 1H), 5.30–6.03 (m, 1H), 4.74–5.13 (m, 1H), 4.63 (br. s., 2H), 3.77 (br. s., 1H), 3.34–3.52 (m, 1H), 2.88–3.15 (m, 1H), 1.31–1.73 (m, 16H), 0.89–1.23 (m, 5H),

0.83 (dd, J = 6.78, 12.62 Hz, 6H), 0.42–0.74 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –126.3. A solution of the aryl triflate (1.0 g, 1.7 mmol) with $Zn(CN)_2$ (347 mg, 3.0 mmol) in DMF (2.1 mL) was de-gassed before $Pd(PPh_3)_4$ (70 mg, 3.5 mol%) was added. The reaction mixture was heated in a sealed microwave tube for 4 h at 100 °C. The reaction mixture was diluted with ether, washed with water, then sat. $NaHCO_3$ (aq), then LiCl (aq), then brine. The resulting organic layer was dried (Na_2SO_4) then concentrated. The resulting residue was subjected to chromatography on silica gel elution with a gradient of 0–50% EtOAc in hexanes to afford 0.60 g (75%) of the desired benzonitrile: MS (ESI) m/z 454.3 $(M + H)^+$. The benzonitrile (0.60 g, 1.3 mmol) was dissolved in dioxane (8 mL) and treated with $LiOH{\cdot}H_2O$ (133 mg, 3.2 mmol) in water (4 mL). Finally, 30% H_2O_2 (1 mL) was added and the reaction mixture was stirred for 48 h. The reaction mixture was diluted with ether, washed with sat. NH_4Cl (aq), dried (Na_2SO_4) and then concentrated. The resulting residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes to afford the Boc protected compound. This intermediate was dissolved in CH_3OH (5 mL) and added to a cold solution of methanoic HCl prepared earlier from CH_3OH (5 mL) and acetyl chloride (1 mL). After 12 h under a stream of nitrogen, the solids were re-dissolved in a minimum of methanol and diluted with EtOAc. A small addition of hexanes initiated crystallization. The solids were collected and dried to afford 510 mg (89% over two steps) of the desired hydrochloride salt as a white crystalline solid. A sample of the **9** hydrochloride salt was converted to the **9** freebase for NMR characterization: ^{1}H NMR (300 MHz, CD_3OD) δ 7.65 (d, J = 8.10 Hz, 1H), 7.59 (s, 1H), 7.19 (d, J = 7.91 Hz, 1H), 3.95–4.15 (m, 2H), 3.86 (d, J = 5.65 Hz, 1H), 3.54–3.70 (m, 1H), 3.33–3.39 (m, 1H), 2.82–3.16 (m, 2H), 1.98–2.08 (m, 2H), 1.85 (d, J = 12.06 Hz, 1H), 1.53–1.77 (m, 5H), 1.05–1.40 (m, 7H), 0.69–1.04 (m, 8H); ^{13}C NMR (75 MHz, CD_3OD) δ 173.6, 170.9, 138.4, 135.7, 131.7, 129.0,

125.6, 125.3, 56.1, 51.5, 46.4, 39.5, 34.5, 34.3, 32.8, 32.5, 32.0, 26.6, 26.4, 26.1, 18.7, 17.3. The compound was further characterized as the hydrochloride salt: MS (ESI) *m*/*z* 372.3 $(M + H)^+$; mp 132–136 °C (fusion); $[\alpha]_D$ = +96° (*c* 0.10, CH_3OH). Anal. ($C_{22}H_{35}ClN_3O_2 \cdot 1.75\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10) Hydrochloride. Dicyclohexylcarbodiimide (47.5 mg, 0.23 mmol) was added to a solution of HOBt (29 mg, 0.22 mmol) and Boc-D-Tic-OH (55.4 mg, 0.20 mmol) in THF (2 mL). After 1 h, the amine **21** hydrochloride (49.4 mg, 0.24 mmol) and NEt_3 (0.08 mL, 0.6 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl (aq) (5 mL). After 1 h, the solution was concentrated, and the residue partitioned between CH_2Cl_2 and sat. Na_2CO_3 (aq). The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient EtOAc in hexanes to afford the **10** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12–7.23 (m, 3H), 7.03–7.12 (m, 1H), 6.97 (d, *J* = 9.80 Hz, 1H), 4.04 (s, 2H), 3.85–3.99 (m, 1H), 3.74–3.82 (m, 1H), 3.56–3.70 (m, 2H), 3.25 (dd, *J* = 5.09, 16.39 Hz, 1H), 2.85 (dd, *J* = 10.17, 16.39 Hz, 1H), 1.51–1.89 (m, 6H), 1.05–1.40 (m, 6H), 0.71–1.01 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 135.8, 134.4, 129.1, 126.7, 126.2, 125.6, 56.5, 50.9, 47.4, 39.8, 34.6, 34.2, 32.6, 32.4, 31.4, 26.5, 26.4, 26.1, 19.1, 17.7. The freebase was converted into the hydrochloride salt to afford 48.5 mg (66% over two steps) of a white powder: MS (ESI) *m*/*z* 329.3 $(M + H)^+$; mp 210–214 °C (fusion); $[\alpha]_D$ = +104° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}ClN_2O$) C, H, N.

(3R)-*N*-[(1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-fluoro-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (11) Hydrochloride. Dicyclohexylcarbodiimide (63 mg, 0.31 mmol) was added to a solution of HOBt (44 mg, 0.33 mmol) and 7-fluoro-Boc-D-Tic-OH (81 mg, 0.27 mmol) in THF (2.5 mL). After 1 h, the amine **21** (62 mg, 0.30 mmol) and NEt_3 (0.2 mL, 1.4 mmol) in THF (0.5 mL) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl (aq) (5 mL). After 12 h, the solution was concentrated, and the residue partitioned between EtOAc and sat. Na_2CO_3 (aq). The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% EtOAc in hexanes to afford the **11** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 5.65, 8.29 Hz, 1H), 6.83–7.00 (m, 2H), 6.78 (dd, *J* = 2.45, 9.04 Hz, 1H), 4.01 (d, *J* = 5.09 Hz, 2H), 3.93 (dt, *J* = 4.90, 9.80 Hz, 1H), 3.59 (dd, *J* = 5.27, 9.80 Hz, 1H), 3.20 (dd, *J* = 5.18, 16.29 Hz, 1H), 2.81 (dd, *J* = 9.80, 16.20 Hz, 1H), 1.95 (br. s., 1H), 1.51–1.87 (m, 6H), 1.02–1.40 (m, 6H), 0.70–1.01 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 161.2 (d, *J* = 243 Hz), 137.4 (d, *J* = 7.3 Hz), 130.5 (d, *J* = 7.3 Hz), 129.9 (d, *J* = 3.6 Hz), 113.7 (d, *J* = 21 Hz), 112.1 (d, *J* = 21 Hz), 56.4, 50.9, 47.3, 39.8, 34.6, 34.2, 32.6, 32.4, 30.6, 26.5, 26.3, 26.1, 19.1, 17.7. The freebase was converted into the hydrochloride salt to afford 58.1 mg (56% over two steps) of a white powder: MS (ESI) *m*/*z* 347.5 $(M + H)^+$; mp 232–236 °C (fusion); $[\alpha]_D$ = +107° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{32}ClFN_2O \cdot 0.25\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (12) Hydrochloride. A solution of **22** (127 mg, 0.29

mmol) in acetone (5 mL) was treated with K_2CO_3 (140 mg, 1 mmol) and iodomethane (460 mg, 3.2 mmol). After stirring 12 h at ambient temperature, the suspension was filtered. The filtrate was concentrated, and the resulting residue dissolved in CH_3OH (5 mL) and treated with 6 M HCl (aq) (5 mL). After 2 h, the solution was concentrated, and the resulting residue was dissolved in EtOAc and washed with sat. Na_2CO_3 (aq). The organic layer was concentrated and the residue subjected to chromatography on silica gel eluting with a gradient of EtOAc in hexanes to afford the **12** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.48 Hz, 1H), 6.95 (d, *J* = 9.98 Hz, 1H), 6.76 (dd, *J* = 2.64, 8.29 Hz, 1H), 6.62 (d, *J* = 2.64 Hz, 1H), 3.86–4.05 (m, 3H), 3.79 (s, 3H), 3.53–3.66 (m, 1H), 3.19 (dd, *J* = 5.18, 16.11 Hz, 1H), 2.78 (dd, *J* = 10.17, 16.20 Hz, 1H), 1.51–1.88 (m, 6H), 1.05–1.40 (m, 7H), 0.71–1.00 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 158.0, 136.6, 130.0, 126.4, 112.6, 110.7, 56.8, 55.3, 50.9, 47.6, 39.8, 34.6, 34.2, 32.6, 32.4, 30.6, 26.5, 26.3, 26.1, 19.1, 17.7. The freebase was converted into the hydrochloride salt to afford 29.4 mg (25% over two steps) of a white powder: MS (ESI) *m*/*z* 359.5 $(M + H)^+$; mp 238–242 °C (fusion); $[\alpha]_D$ = +84° (*c* 0.10, CH_3OH). Anal. ($C_{22}H_{35}ClN_2O_2 \cdot 0.25\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-1-(Cyclopentylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (13) Hydrochloride. A solution of DCC (76 mg, 0.37 mmol) in THF (1 mL) was added to a solution of HOBt (46 mg, 0.33 mmol) and 7-hydroxy-Boc-D-Tic-OH (94 mg, 0.32 mmol) in THF (2 mL). After 1 h, the amine **29c** hydrochloride (55.8 mg, 0.29 mmol) and NEt_3 (0.125 mL, 0.90 mmol) were added to the suspension. The reaction mixture was stirred at room temperature overnight. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes. The fractions containing product **31** were

concentrated and the residue dissolved in CH_3CN (5 mL) and treated with 4 N HCl in dioxane (5 mL). After 1 h, the solution was concentrated, and the residue was subjected to chromatography on silica gel eluting with a gradient of 0–100% EtOAc in hexanes to afford the freebase **13**: ^{1}H NMR (300 MHz, CD_3OD) δ 8.12 (d, *J* = 9.23 Hz, 1H), 7.09 (d, *J* = 8.48 Hz, 1H), 6.75 (dd, *J* = 2.35, 8.38 Hz, 1H), 6.64 (d, *J* = 2.26 Hz, 1H), 4.34 (d, *J* = 4.14 Hz, 2H), 4.15 (dd, *J* = 4.71, 11.87 Hz, 1H), 3.76–3.92 (m, 1H), 3.23–3.37 (m, 2H), 3.10 (d, *J* = 11.87 Hz, 1H), 1.38–1.94 (m, 11H), 1.01–1.20 (m, 2H), 0.92 (d, *J* = 6.59 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.5, 169.4, 158.1, 131.1, 129.8, 122.1, 116.9, 113.7, 56.9, 55.6, 55.5, 45.5, 39.1, 39.1, 38.4, 34.2, 34.0, 33.4, 30.9, 26.1, 26.0, 19.8, 18.2. The freebase was converted into the hydrochloride salt to afford 56.6 mg (51% over two steps) of a white powder: MS (ESI) *m*/*z* 331.6 $(M + H)^+$; mp 142–146 °C (fusion); $[\alpha]_D$ = +99° (*c* 0.20, CH_3OH). Anal. ($C_{20}H_{31}ClN_2O_2 \cdot 0.75\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-1-(Cycloheptylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (14) Hydrochloride. A solution of DCC (62 mg, 0.30 mmol) in THF (1 mL) was added to a solution of HOBt (38 mg, 0.28 mmol) and 7-hydroxy-Boc-D-Tic-OH (76 mg, 0.26 mmol) in THF (2 mL). After 1 h, the amine **29e** (135 mg, 0.61 mmol) and NEt_3 (0.1 mL, 0.72 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 3 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–100% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_3CN (10 mL) and treated with 4 N HCl in dioxane (4 mL). After 1 h, the solution was concentrated, and the residue partitioned between EtOAc and sat. $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient EtOAc in hexanes to afford the **14** freebase: ^{1}H NMR (300

MHz, $CDCl_3$) δ 6.78–7.04 (m, 2H), 6.61 (dd, *J* = 2.17, 8.19 Hz, 1H), 6.49 (d, *J* = 1.70 Hz, 1H), 3.71–3.96 (m, 3H), 3.50 (dd, *J* = 5.09, 10.17 Hz, 1H), 3.06 (dd, *J* = 5.09, 16.01 Hz, 1H), 2.67 (dd, *J* = 10.17, 16.01 Hz, 1H), 1.57–1.74 (m, 2H), 0.94–1.57 (m, 13H), 0.74–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 154.9, 136.4, 130.0, 125.3, 114.3, 112.3, 56.8, 51.7, 47.3, 40.3, 35.9, 35.8, 33.4, 32.4, 30.7, 28.6, 28.4, 26.4, 26.1, 19.2, 17.7. The freebase was converted into the hydrochloride salt to afford 23.1 mg (23% over two steps) of a white powder: MS (ESI) *m*/*z* 359.4 $(M + H)^+$; mp 138–142 °C (fusion); $[\alpha]_D$ = +84° (*c* 0.10, CH_3OH). Anal. ($C_{22}H_{35}ClN_2O_2 \cdot H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-1-(Cyclobutylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (15) Hydrochloride. A solution of the amine **37** hydrochloride (250 mg, 1.4 mmol) and 7-hydroxy-Boc-D-Tic-OH (154 mg, 0.5 mmol) in THF (5 mL) was treated with T3P (50 wt.% in EtOAc, 0.9 mL) and diisopropylethylamine (0.5 mL) in an ice bath. The reaction mixture warmed to room temperature overnight then was partitioned between sat. $NaHCO_3$ (aq) and EtOAc. The aqueous layer was extracted with EtOAc and the combine organic layers were washed with water, then dried (Na_2SO_4) and concentrated. The resulting residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% EtOAc in hexanes to afford 120.2 mg (58%) of the desired Boc-protected product. Acetyl chloride (0.5 mL) was added to CH_3OH (2.5 mL) at –50 °C and the resulting solution was allowed to warm to 0 °C. A solution of the Boc-protected compound (120.2 mg, 0.29 mmol) in CH_3OH (2.5 mL) was then added to the HCl solution at –50 °C. External cooling was removed then the reaction mixture was concentrated, the residue was dissolved in fresh CH_3OH and then concentrated, then concentrated again from EtOAc to afford 100 mg (quantitative yield) of **15** hydrochloride as a white solid. A sample of the hydrochloride salt was converted to the freebase

for NMR characterization: ^{1}H NMR (300 MHz, CD_3OD) δ 6.94 (d, J = 8.29 Hz, 1H), 6.55–6.68 (m, 1H), 6.50 (s, 1H), 3.95 (s, 1H), 3.65 (td, J = 4.69, 9.65 Hz, 1H), 3.56 (dd, J = 4.80, 10.27 Hz, 1H), 2.70–2.99 (m, 2H), 2.14–2.38 (m, 1H), 1.94–2.11 (m, 2H), 1.39–1.93 (m, 8H), 0.89 (dd, J = 3.49, 6.69 Hz, 6H); ^{13}C NMR (126 MHz, CD_3OD) δ 175.0, 157.1, 136.9, 130.9, 125.5, 115.2, 113.3, 58.1, 54.0, 47.8, 40.2, 34.8, 33.8, 32.7, 29.7, 29.6, 19.9, 19.5, 18.4. The compound was further characterized as the hydrochloride salt: MS (ESI) m/z 317.3 $(M + H)^+$; mp begins at 115 °C (fusion); $[\alpha]_D$ = +102° (c 0.10, CH_3OH). Anal. ($C_{19}H_{29}ClN_2O_2 \cdot 0.5\ H_2O$) C, H, N.

(3*R*)-*N*^{3}-[(1*R*)-1-(Cyclopentylmethyl)-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxamide (16) Hydrochloride. The Boc-protected compound (**33**) (55.4 mg, 0.12 mmol) was dissolved in CH_3CN (5 mL) and treated with HCl (4 N in dioxane, 4 mL). After 1 h, the reaction mixture was concentrated and the residue subjected to chromatography on silica gel eluting with a gradient of 0–50% DMA80 in CH_2Cl_2 to afford 37.7 mg (88%) of the desired **16** freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 7.53–7.73 (m, 2H), 7.22 (d, J = 7.91 Hz, 1H), 3.94–4.18 (m, 2H), 3.76 (dd, J = 4.43, 9.70 Hz, 1H), 3.66 (dd, J = 5.09, 9.61 Hz, 1H), 2.82–3.14 (m, 2H), 1.85–1.96 (m, 3H), 1.29–1.84 (m, 10H), 0.97–1.17 (m, 2H), 0.91 (dd, J = 3.01, 6.78 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.6, 172.1, 139.4, 136.6, 133.0, 130.1, 126.8, 126.4, 57.2, 54.8, 47.4, 39.2, 38.3, 34.3, 34.0, 33.4, 33.1, 26.1, 26.0, 19.8, 18.3. The freebase was converted into the hydrochloride salt to afford a pale yellow powder: MS (ESI) m/z 358.2 $(M + H)^+$; mp 153–157 °C (fusion); $[\alpha]_D$ = +98° (c 0.10, CH_3OH). Anal. ($C_{21}H_{32}ClN_3O_2 \cdot H_2O$) C, H, N.

(3*R*)-*N*-[(1*R*)-2-Cyclopentyl-1-cyclopropylethyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (17) Hydrochloride. To a rapidly stirring solution of DCC (0.66 g, 3.2 mmol) and HOBt (0.36 g, 2.6 mmol) in THF (7.5 mL) was added 7-hydroxy-Boc-D-Tic-OH (752 g, 2.5 mmol). After 1 h, the amine **29d** hydrochloride (519 mg, 2.7 mmol)

was converted to the freebase, dissolved in THF (2.5 mL), and added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–5% isopropanol in CH_2Cl_2 to afford 1.03 g (96%) of the Boc-protected intermediate as a white foam. A cold volume of methanol (5 mL) was treated with acetyl chloride (1 mL) at –78 °C then allowed to warm to room temperature. The solution was chilled before the addition of a sample of the Boc-protected compound (253 mg, 0.59 mmol), prepared above, in methanol (5 mL). After 12 h under a stream of nitrogen, the solids were re-dissolved in a minimum of methanol and diluted with EtOAc. A small addition of hexanes initiated crystallization. The solids were collected and dried to afford 197 mg (92%) of the desired **17** hydrochloride salt as a white crystalline solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (d, *J* = 9.04 Hz, 1H), 7.10 (d, *J* = 8.29 Hz, 1H), 6.76 (dd, *J* = 1.98, 8.38 Hz, 1H), 6.65 (s, 1H), 4.24–4.44 (m, 2H), 4.03–4.19 (m, 1H), 3.19–3.55 (m, 2H), 2.99–3.14 (m, 1H), 1.02–2.06 (m, 13H), 0.82–1.01 (m, 1H), 0.56 (dt, *J* = 4.99, 8.62 Hz, 1H), 0.45 (dt, *J* = 3.86, 8.52 Hz, 1H), 0.14–0.37 (m, 2H); mp 145–150 °C; $[\alpha]_D$ = +78° (*c* 0.10, CH_3OH). Anal. ($C_{20}H_{29}ClN_2O\cdot 0.5\ H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*R*)-2-methyl-1-[(4-methylcyclohexyl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (18) Hydrochloride. To a rapidly stirring solution of DCC (0.66 g, 3.2 mmol) and HOBt (0.33 g, 2.5 mmol) in THF (7.5 mL) was added 7-hydroxy-Boc-D-Tic-OH (600 mg, 2.0 mmol). After 1 h, the freebase amine **41** (419 mg, 2.3 mmol) in THF (2.5 mL) was added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel to afford the Boc-protected

intermediate, which was treated with a solution of methanoic HCl (10 mL) prepared from acetyl chloride (1 mL). The solvent was concentrated to afford 236 mg (60%) of the **18** hydrochloride salt. A sample of the hydrochloride salt was converted into the freebase for NMR characterization: ^{1}H NMR (300 MHz, CD_3OD) δ 8.12 (d, J = 9.04 Hz, 1H), 7.09 (d, J = 8.29 Hz, 1H), 6.75 (d, J = 7.54 Hz, 1H), 6.65 (s, 1H), 4.24–4.45 (m, 2H), 4.17 (dd, J = 4.62, 11.77 Hz, 1H), 3.81–4.00 (m, 1H), 3.48 (q, J = 7.10 Hz, 1H), 2.98–3.17 (m, 1H), 1.91 (d, J = 7.54 Hz, 1H), 1.61–1.82 (m, 4H), 1.08–1.59 (m, 7H), 0.75–1.07 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 168.0, 156.6, 129.7, 128.3, 120.6, 115.4, 112.2, 55.4, 55.4, 52.1, 52.0, 44.0, 39.0, 38.9, 35.0, 34.8, 33.9, 33.9, 32.6, 32.5, 32.1, 29.4, 21.6, 18.3, 16.7. The compound was further characterized as the hydrochloride salt: mp 173–177 °C (fusion); MS (ESI) *m*/*z* 459.4 $[M+H]^+$; $[\alpha]_D$ = +94.2° (*c* 1.00, CH_3OH). Anal. ($C_{22}H_{35}ClN_2O_2 \cdot 0.5\ H_2O$) C, H, N.

(3R)-*N*-[(1*R*)-1-(Cyclohexylmethyl)-2-methylpropyl]-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (19) Hydrochloride. A sample of **1** hydrochloride (60 mg, 0.16 mmol) in 1,2-dichloroethane (1.6 mL) was treated with 37% formaldehyde (0.1 mL, 1.3 mmol) and $NaBH(OAc)_3$ (170 mg, 0.8 mmol). The sealed vial was left to stir for 72 h. The reaction mixture was then diluted with CH_2Cl_2 and dried with Na_2SO_4. The solids were separated by filtration and washed with EtOAc. The filtrates and washing were combined and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% EtOAc in hexanes to afford 54.4 mg (95%) of the **19** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br. s., 1H), 7.20–7.33 (m, 1H), 6.94 (d, *J* = 8.10 Hz, 1H), 6.72 (dd, *J* = 2.26, 8.10 Hz, 1H), 6.60 (d, *J* = 2.07 Hz, 1H), 3.82–3.95 (m, 1H), 3.60–3.82 (m, 2H), 3.39 (t, *J* = 6.78 Hz, 1H), 2.90–3.11 (m, 2H), 2.50 (s, 3H), 1.53–1.83 (m, 4H), 1.46 (d, *J* = 12.24 Hz, 1H), 1.03–1.34 (m, 6H), 0.61–0.99 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.3, 135.0, 128.9, 124.1,

114.6, 113.0, 64.2, 55.3, 51.2, 42.2, 39.4, 34.2, 34.2, 32.5, 32.3, 28.9, 26.5, 26.2, 26.0, 19.1, 17.7. The freebase was converted into the hydrochloride salt as a white powder: MS (ESI) *m*/*z* 359.5 $(M + H)^+$; mp 248–250 °C (fusion); $[\alpha]_D$ = +105° (*c* 0.10, CH_3OH). Anal. ($C_{22}H_{35}ClN_2O_2$) C, H, N.

(3*R*)-*N*-[(1*R*)-1-(Cyclopentylmethyl)-2-methylpropyl]-7-hydroxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (20) Hydrochloride. A solution of DCC (132 mg, 0.64 mmol) in THF (2.5 mL) was added to a solution of HOBt (83 mg, 0.62 mmol) and 7-methoxy-3-methyl-Boc-D-Tic-OH[22] (172 mg, 0.54 mmol) in THF (3 mL). After 1 h, the amine **29c** (127 mg, 0.66 mmol) and NEt_3 (0.30 mL, 2.0 mmol) were added to the suspension. The reaction mixture was stirred at room temperature for 12 h. The solids were separated by filtration, and the filtrate concentrated to a residue. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–40% EtOAc in hexanes. The product containing fractions were concentrated and the residue dissolved in CH_2Cl_2 (5 mL), cooled to –78 °C and treated with BBr_3 (4 mL, 1.0 M in CH_2Cl_2) and left to warm to room temperature. After 12 h, the solution was cooled then quenched with CH_3OH and concentrated. The residue was partitioned between CH_2Cl_2 and sat. $NaHCO_3$ (aq). The organic layer was dried (Na_2SO_4) and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–100% EtOAc in hexanes to afford the **20** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.98 Hz, 1H), 6.95 (d, *J* = 8.10 Hz, 1H), 6.69 (dd, *J* = 2.35, 8.19 Hz, 1H), 6.61 (d, *J* = 2.07 Hz, 1H), 3.97 (s, 1H), 3.78–3.88 (m, 1H), 3.63–3.78 (m, 1H), 3.08 (d, *J* = 15.64 Hz, 1H), 2.74 (d, *J* = 15.45 Hz, 1H), 1.57–1.79 (m, 3H), 1.27–1.56 (m, 10H), 0.89–1.10 (m, 2H), 0.84 (dd, *J* = 5.37, 6.69 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) d 176.1, 155.2, 136.4, 129.7, 125.3, 114.1, 112.2, 58.5, 53.1, 45.2, 38.5, 37.0, 36.4, 33.3, 32.4, 26.6, 25.1, 25.0, 19.2, 17.5. The freebase was converted into the hydrochloride

salt to afford 43.1 mg (20% over two steps) of a white powder: MS (ESI) *m/z* 345.4 $(M + H)^+$; mp 157–161 °C (fusion); $[\alpha]_D$ = +33° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}ClN_2O_2 \cdot 0.75\ H_2O$) C, H, N.

[^{35}S]GTPγS Binding Assay. The [^{35}S]GTPγS assays were conducted using the methods previously reported.[20] Human κ (20 μg), μ (10 μg), or δ (7 μg) opioid receptor-expressing CHO cell membrane protein was incubated together with an eight-point concentration response curve of a control agonist, a single concentration of each antagonist, 10 μM final GDP, and approximately 132,000 cpm of [^{35}S]-GTPγS (0.1 nM) in 500 μL total volume of assay buffer (50 mM HEPES pH 7.4, 100 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA·$2H_2O$, 1 mM dithiothreitol, 0.1% BSA). The control agonist U69,593 was used for the κ assays (31.6 μM, 10 μM, 3.16 μM, 316 nM, 100 nM, 31.6 nM, 3.16 nM, 0.316 nM final). The control agonist DAMGO was used for the μ assays (31.6 μM, 10 μM, 3.16 μM, 316 nM, 100 nM, 31.6 nM, 3.16 nM, 0.316 nM final). The control agonist DPDPE was used for the δ assays (10 μM, 3.16 μM, 1 μM, 100 nM, 10 nM, 1 nM, 0.1 nM, 0.01 nM final). The assay mixture was incubated with shaking for 60 min at 22 °C. The assay was terminated by filtration onto pre-soaked PerkinElmer GF/B glass fiber filters under vacuum on a 96-well Brandel harvester (Gaithersburg, MD, USA) followed by three 1 mL washes with ice-cold wash buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 10 mM $MgCl_2$). Filter plates were dried for 1 h at 55 °C. Microscint 20 (50 μL) was added to each well and filter-bound radioactivity was counted on a Packard TopCount NXT microplate scintillation and luminescence counter. Total binding (TB) was determined in the absence of compounds and nonspecific binding (NSB) was determined in the presence of 10 μM unlabeled GTPγS. Percent specific bound (SB) was calculated using the equation % SB = (SB/MB) × 100 where maximal binding (MB) of the system is calculated by subtracting NSB from TB. Percent SB was plotted

against the log of compound concentration. Data were fit to a three-parameter logistic curve to generate EC_{50} values (GraphPad Prism, GraphPad Software, Inc., San Diego, CA). K_e values were calculated using the equation $K_e = [L]/((EC_{50}^{+}/EC_{50}^{-}) - 1)$ where [L] is the concentration of test compound, EC_{50}^{+} is the EC_{50} of the control agonist with test compound, and EC_{50}^{-} is the EC_{50} of control agonist alone. K_e values were considered valid when the EC_{50}^{+}/EC_{50}^{-} ratio was at least 4.

Pharmacokinetics. Pharmacokinetic studies were conducted at Mispro Biotech Services (RTP, NC) and were approved by RTI's Institutional Animal Care and Use Committee. Animals were housed in facilities that are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Animal procedures were in accordance with the "Guide for the Care and Use of Laboratory Animals."[32] Male Sprague Dawley CD rats were obtained from Charles River Laboratories (Raleigh, NC). The animals were acclimated for one week prior to use on study and had ad libitum access to food and Durham City (NC) tap water. Environmental conditions included: room temperature 72 ± 3 °F (22 ± 2 °C), relative humidity 35 to 65% and a 12 h light/dark cycle. Animals were 10 weeks old at dosing.

A single subcutaneous dose of each compound at 5 mg/kg was administered at a dose volume of 1 mL/kg dose volume. For each compound, three rats per timepoint were euthanized at 1, 4, 24, 72, and 168 h post dose by asphyxiation with CO_2. Blood was collected via cardiac puncture using K_3EDTA as anticoagulant. Plasma was prepared from blood by centrifugation at 2000 G for 10 min at 4 °C. Brains were collected, and flash frozen in liquid nitrogen and stored at –20 °C until analysis.

Sample preparation. Brains were weighed and homogenized at 1:5 (wt:vol) with 50:50 ethanol:water using a Geno/Grinder 2010 (SPEXSamplePrep, Metuchen, NJ) at 1750 rpm for 30

s (×2). Aliquots (50 μL) of plasma or brain homogenate was mixed with 300 μL of methanol containing buspirone as internal standard (50 ng/mL) in duplicate in a 96-well plate. The plate was shaken at 800 rpm for 5 min and then centrifuged at 4000 rpm for 10 min at 4 °C. Supernatant (50 μL) was mixed with 50 μL of mobile phase B in a new plate and analyzed by LC/MS-MS.

Standard Curve preparation. Stock solutions of were prepared and diluted serially to generate standard curve and quality control spiking solutions. The concentrations in plasma for **1** were 0.2, 0.5, 1, 5, 10, 50, 100, 500, 1000, and 2000 ng/mL for standard curves and 2, 20, and 200 ng/mL for quality control samples. In brain homogenate, standard curve sample concentrations were 0.1, 0.2, 0.5, 1, 5, 10, 50, 100, 500, 1000, and 2000 ng/mL, and 2, 20, and 200 ng/mL for quality control samples. The LOQ in plasma and brain homogenate for **1** was 0.2 and 0.1 ng/mL, respectively.

The concentrations in plasma for **9 (**except for the 24 h timepoint) were 0.5, 1, 5, 10 50, 100, 500, 1000, and 2000 ng/mL for standard curves and 2, 20, and 200 ng/mL for quality control samples. In brain homogenate **(**except for the 24 h timepoint), standard curve concentrations were 0.5, 1, 5, 10, 50, 100, 500, 1000, and 2000 ng/mL, and 2, 20, and 200 ng/mL for quality control samples. The concentrations in plasma and brain homogenate used for analysis of **9** at 24 h were 0.1, 0.2, 0.5, 1, 5, 10 50, 100, and 500 ng/mL for standard curves and 2, 20, and 200 ng/mL for quality control samples. LOQ in plasma and brain homogenate for **9** was 0.5 ng/mL for all of the samples, including 1 and 4 hours, and 0.1 ng/mL for samples at 24 hours that were reanalyzed with greater sensitivity.

The concentrations in plasma for **13** were 0.5, 1, 5, 10 50, 100, 500, 1000, and 2000 ng/mL for standard curves and 2, 20, and 200 ng/mL for quality control samples. In brain homogenate,

standard curve sample concentrations were 0.1, 0.2, 0.5, 1, 5, 10, 50, 100, 500, 1000, and 2000 ng/mL, and 2, 20, and 200 ng/mL for quality control samples. The LOQ values in plasma and brain for **13** were 0.5 and 0.1 ng/mL, respectively.

LC/MS-MS conditions. All chromatography, except for compound **9** at 24 h plasma and brain,was conducted using an Agilent 1100binary pump and autosampler (Santa Clara, CA) with injection of 10 μL of the processed samples/calibration standards onto a Phenomenex Luna C8 (150 mm × 4.6 mm, 5 μM) column (Torrance, CA). Mobile phase A consisted of 0.5% formic acid in water with 5 mM ammonium acetate, and mobile phase B consisted of 0.5% formic acid in 85:15 acetonitrile:water with 5 mM ammonium acetate. Chromatography was conducted using a linear gradient starting at initial conditions of 5% B, and holding for 1 min before increasing linearly to 95% B over 4 min, before returning to initial conditions over 0.1 min. Total run time was 8 min and flow rate was 0.750 ml/min. Quantitation was achieved by multiple reaction monitoring in positive ion mode using an Applied Biosystems Sciex API4000 (Foster City, CA) mass spectrometer with an electrospray ionization source. Compound **1** was quantitated by monitoring the transition of *m*/*z* 345.240 → 148.2, **9** was monitored by the transition of *m*/*z* 372.225 → 175.1, **13** was monitored by the transition of *m*/*z* 331.229 → 148.2, and the internal standard, buspirone, was monitored by *m*/*z* 386.243 → 122.1. Mass spectrometer parameters were as follows: CUR=16, GS1=50, GS2=40, TEM=650, CAD=12, and IS=2000. Calibration curves were processed using Analyst 1.6.2 software by plotting the analyte to internal standard peak area ratio against the calibration standard concentrations. Analysis of **9** in 24 h plasma and brain was conducted using a Waters (Milford, CT) Acquity UPLC system coupled to an Applied Biosystems SCIEX API5000 (Foster City, CA). Chromatography conditions were the same as above for the other timepoints. The mass spectrometer parameters changed from analysis of

other timepoints were as follows: Monitored transition *m/z* 372.339 → 175.0, CUR=18, GS1=55, and GS2=60.

ASSOCIATED CONTENT

Experimental Details for the Synthesis of Intermediate Compounds, Figure S1 Concentration Time and Brain Ratio (B:P) Rates from PK Studies of **1, 9,** and **13** for first 24 h, Elemental Analysis Data, and Molecular Formula Strings Table are available free of charge in the Supporting Information (ACS Publication Website at doi:).

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Author Contributions

CMK and PWO helped design and synthesize the compounds described. AMD and HAN planned and performed the in vitro pharmacology studies, TRF and RWS planned and performed the pharmacokinetic studies, SPR, JBT, and SWM reviewed the final version of the manuscript, FIC overall study design, data evaluation and compilation of the final manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

[^{35}S]GTPγS, sulfur-35 guanosine-5'-*O*-(3-thio)triphosphate; DAMGO, [D-Ala^2,MePhe^4,Gly-ol^5]enkephalin; DPDPE, [D-Pen^2,D-Pen^5]enkephalin; U69,593, (5α,7α,8β)-(–)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]benzeneacetamide; HOBt, hydroxybenzotriazole; D-Tic-OH, (3*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; $PhNTf_2$, *N*-phenyl-bis(trifluoromethanesulfonimide).

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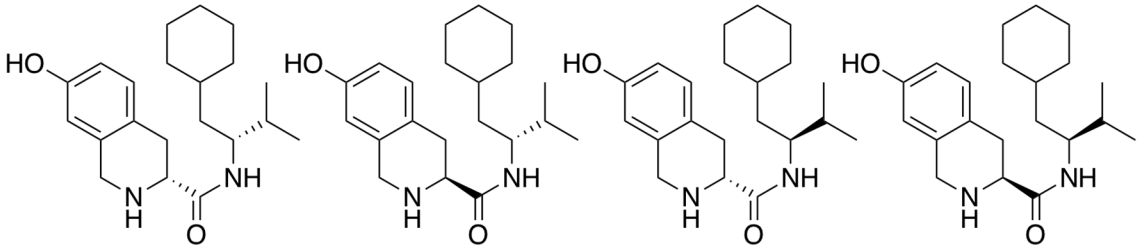
Table 1. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of stereochemistry

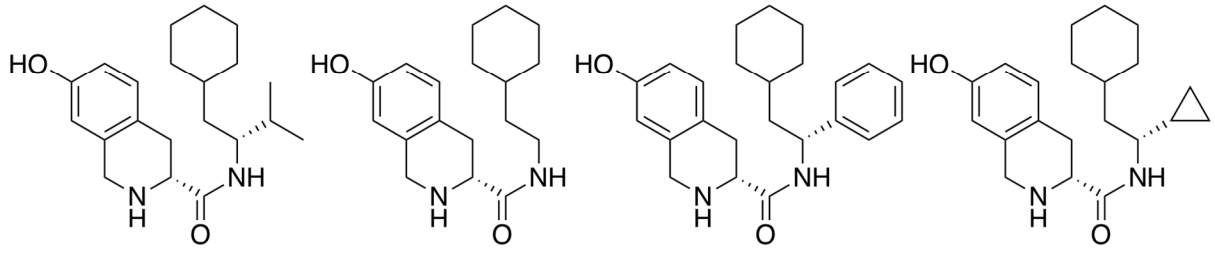


1 **3** **4** **5**

	K_e (nM)[a]				
Compound	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
JDTic[b]	25 ± 4	74 ± 2	0.02 ± 0.01	1250	3700
1[b]	242 ± 36	640 ± 170	0.14 ± 0.03	1730	4570
3	1140 ± 330	>3000	14.2 ± 4.5	80	>211
4	521 ± 160	>3000	12.6 ± 4.3	41	>238
5	>3000	>3000	4.40 ± 1.2	>682	>682

[a] Data are mean ± SEM of at least three independent experiments conducted in duplicate. None of the compounds had agonist activity at 10 μM. [b] Taken from Ref. 20.

Table 2. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of the isopropyl group

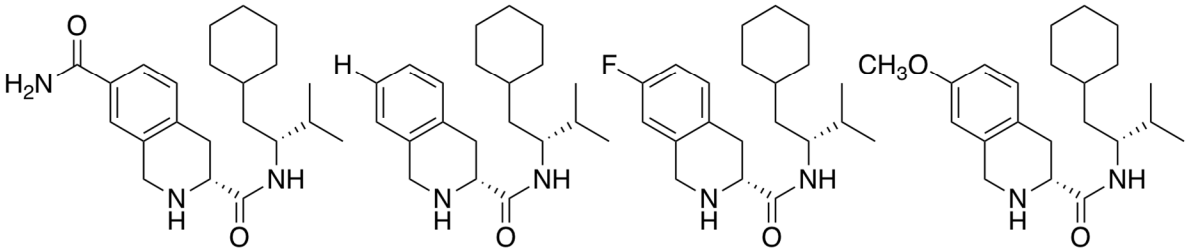


1 **6** **7** **8**

	K_e (nM)[a]				
Compound	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
1	242 ± 36	640 ± 170	0.14 ± 0.03	1730	4570
6	750 ± 150	>3000	23.5 ± 3.8	32	>128
7	880 ± 120	>3000	15.2 ± 1.7	58	>197
8	267 ± 33	>3000	0.64 ± 0.2	417	>4690

[a] Data are mean ± SEM of at least three independent experiments conducted in duplicate. None of the compounds had agonist activity at 10 μM.

Table 3. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, effect of replacing the 7-hydroxyl of **1** with other substituents

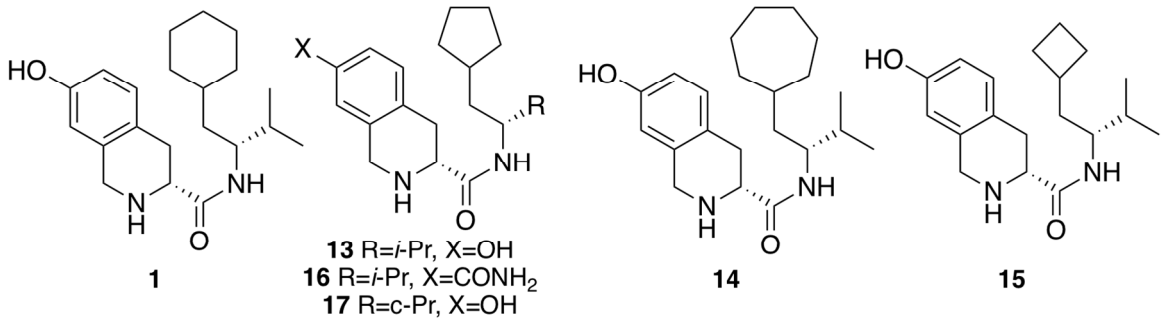


9 **10** **11** **12**

Compound	7-subst.	K_e (nM)[a]			μ/κ	δ/κ
		μ, DAMGO	δ, DPDPE	κ, U69,593		
1	-OH	242 ± 36	640 ± 170	0.14 ± 0.03	1730	4570
9	-$CONH_2$	178 ± 47	1220 ± 160	0.24 ± 0.05	742	5083
10	-H	1100 ± 260	>3000	5.49 ± 0.79	200	>547
11	-F	>3000	>3000	10.7 ± 3.1	>280	>280
12	-OCH_3	995 ± 230	>3000	77.4 ± 23	13	>39

[a] Data are mean ± SEM of at least three independent experiments conducted in duplicate. None of the compounds had agonist activity at 10 μM.

Table 4. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of the ring size and additional cyclopentyl analogues

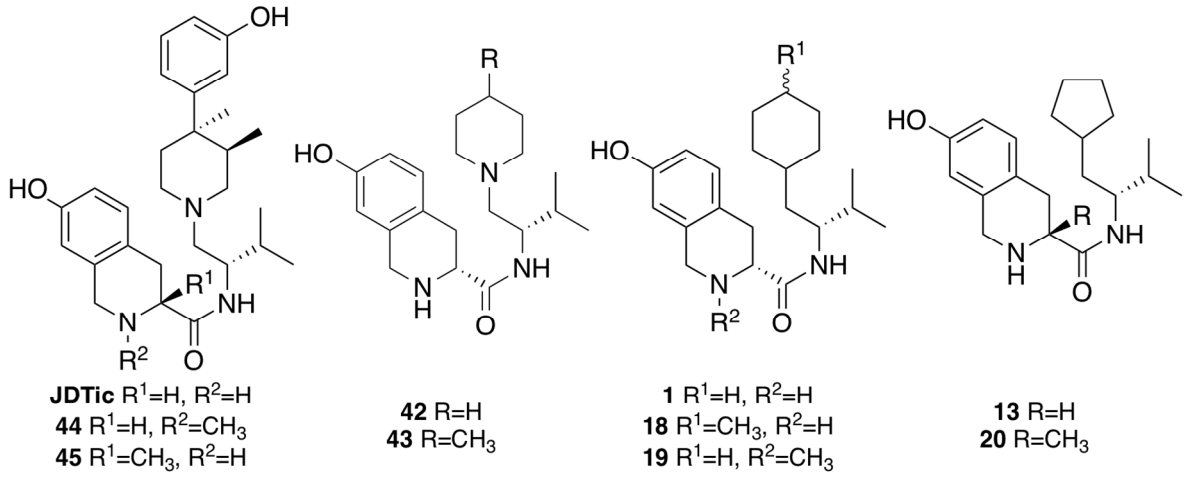


1 **13** R=*i*-Pr, X=OH; **16** R=*i*-Pr, X=$CONH_2$; **17** R=*c*-Pr, X=OH **14** **15**

	K_e (nM)[a]				
Compound	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
1	242 ± 36	640 ± 170	0.14 ± 0.03	1730	4570
13	344 ± 100	1570 ± 380	0.058 ± 0.006	5900	27,000
14	58.3 ± 4.2	751 ± 80	0.20 ± 0.05	292	3760
15	180 ± 17	>3000	2.61 ± 0.73	69	>1150
16	209 ± 27	2540 ± 160	2.04 ± 0.60	102	1245
17	325 ± 33	>3000	3.74 ± 0.80	87	>802

[a] Data are mean ± SEM of at least three independent experiments conducted in duplicate. None of the compounds had agonist activity at 10 μM.

Table 5. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of methyl substituent



	K_e (nM)[a]				
Compound	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
JDTic	25 ± 4	74 ± 2	0.02 ± 0.01	1250	3700
44[b]	210 ± 60	491 ± 120	0.16 ± 0.06	1313	3070
45[b]	3.6 ± 1	854 ± 210	0.03 ± 0.008	120	28,500
1	242 ± 36	640 ± 170	0.14 ± 0.03	1730	4570
13	344 ± 100	1570 ±380	0.058 ± 0.006	5900	27,000
18[c]	221 ± 41	>3000	1.27 ± 0.23	174	>2400
19	245 ± 62	>3000	4.23 ± 1.1	58	>709
20	1650 ± 3	>3000	6.20 ± 1.4	266	>484
42[d]	144 ± 37	>3000	6.80 ± 2.1	21	>441
4-MePDTic (**43**)[d]	239 ± 22	>3000	0.37 ± 0.09	646	>8100

[a] Data are mean ± SEM of at least three independent experiments conducted in duplicate. None of the compounds had agonist activity at 10 μM. [b] Taken from Ref. 22. [c] 88:12 mixture of isomers by HPLC. [d] Taken from Ref. 24.

Table 6. Summary of calculated physiochemical properties for JDTic, **1**, **8**, **9**, **13**, **14**, and **18**

Compound	TPSA	cLogP	logBB[a]	CNS MPO	MW
JDTic	84.83	3.60	–0.57	3.1	465.6
1	61.36	4.04	–0.16	3.7	344.5
8	61.36	3.57	–0.23	4.2	343.5
9	84.22	3.31	–0.60	4.4	371.5
13	61.36	3.59	–0.22	4.2	330.4
14	61.36	4.48	–0.09	3.4	358.5
18	61.36	4.33	–0.11	3.5	358.5

[a] Equation 6 from ref 28. [Log BB = –0.0148 × TPSA + 0.152 × log *P* + 0.139] was used for calculations of logBB values.

Table 7. Pharmacokinetic parameters for **1**, **9**, and **13** in Sprague Dawley rats after a 5 mg/kg i.p. dose.

Compound	Tissue	$t_{1/2}$ (h)	C_{max} (ng/mL) (t_{max})	**Clearance** (mL/h/kg)	AUC_{last} (h*ng/mL)	AUC_{total} (h*ng/mL)	Brain:Plasma AUC_{last}
1	plasma	34.2	111 (1 h)	5916	814	845	8.15
	brain	78.2	524 (4 h)	505	6638	9884	
9	plasma	1.90	376 (1 h)	4274	1170	1170	0.64
	brain	2.34	131 (1 h)	6697	746	747	
13	plasma	32.1	136 (1 h)	7781	632	643	6.08
	brain	45.3	575 (1h)	1280	3713	3908	

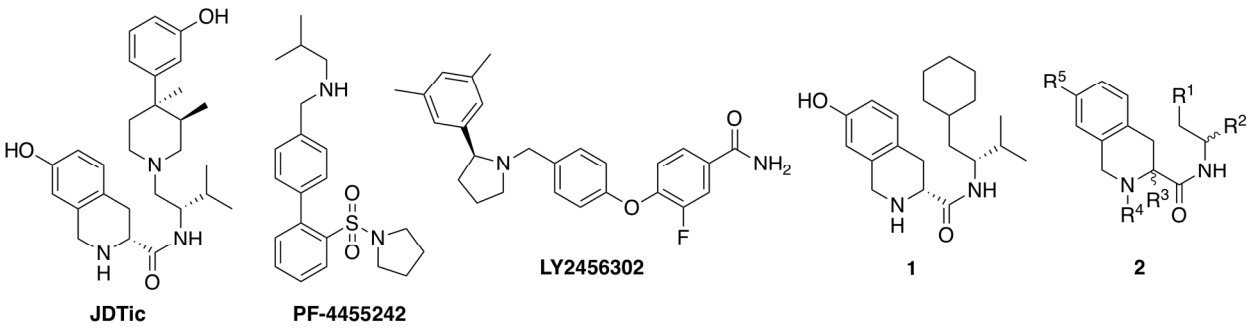


Figure **1.** Structures of JDTic, PF-4455242, LY2456302, lead compound **1** and general structure **2**.

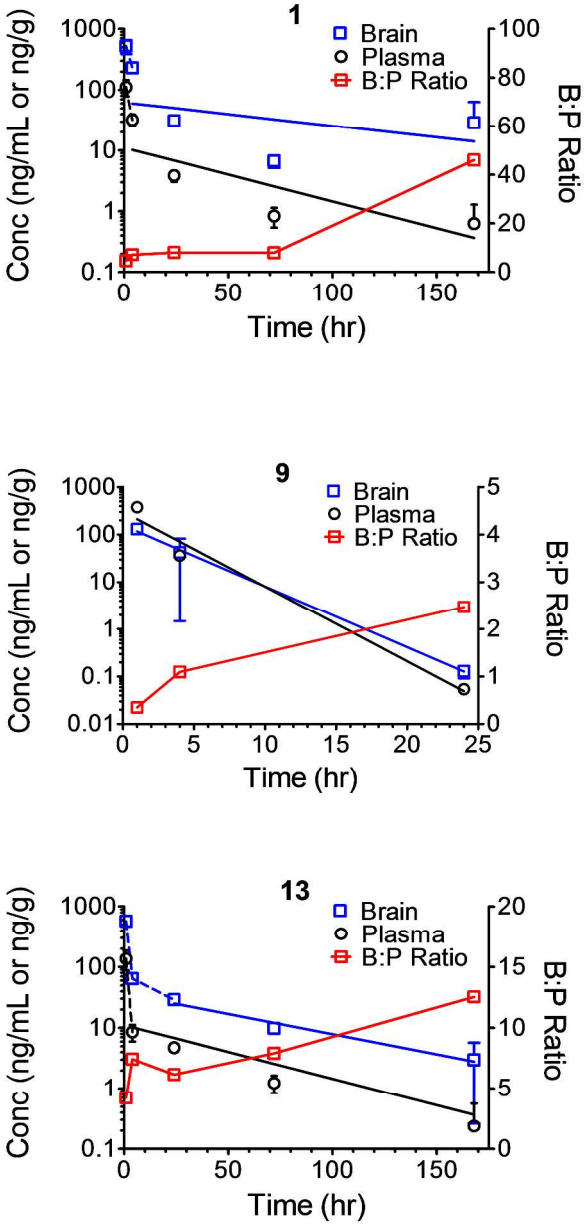
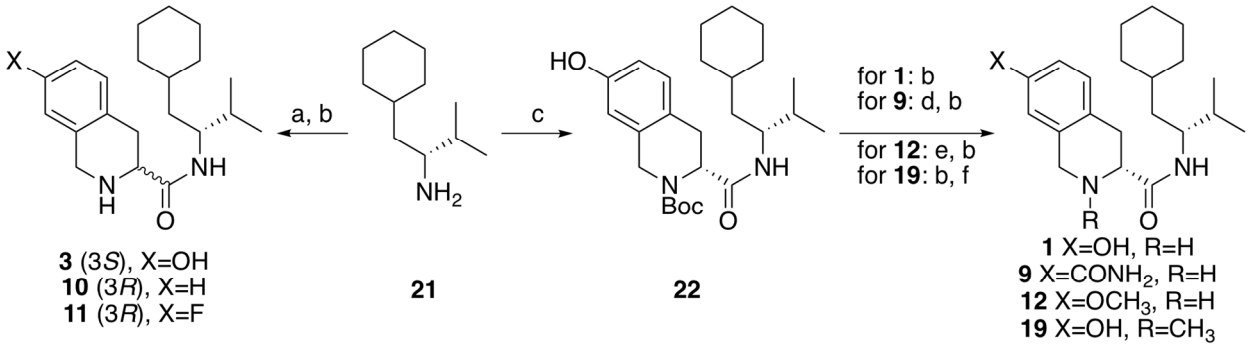


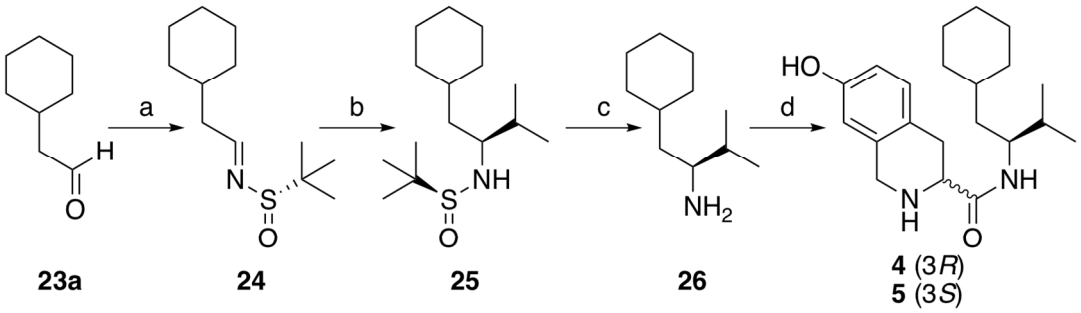
Figure 2. Concentration-time and brain to plasma ratio (B:P) plots for **1**, **9**, and **13** (in Sprague Dawley rats after a 5 mg/kg s.c. dose. N=3 for all data). The solid lines showing brain and plasma concentrations (left axis) are the best-fit lines to an apparent terminal elimination phase.

Scheme 1. Synthesis of target compounds **1**, **3**, **9**–**12**, and **19** from common intermediate **21**



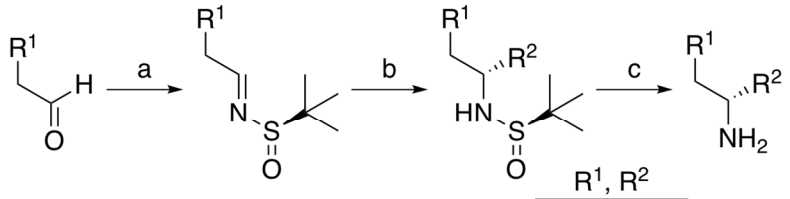
Reagents and conditions: a) 7-OH-Boc-L-Tic-OH (for **3**) or Boc-D-Tic-OH (for **10**) or 7-fluoro-Boc-D-Tic-OH (for **11**), DCC, HOBt, THF; b) HCl, CH_3OH; c) 7-OH-Boc-D-Tic-OH, DCC, HOBt, THF; d) 1. $PhNTf_2$, NEt_3, CH_2Cl_2; 2. $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF; 3. LiOH (aq), H_2O_2, dioxane; e) K_2CO_3, CH_3I, acetone; f) 37% formaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane.

Scheme 2. Synthesis of the diastereomeric target compounds **4** and **5**



Reagents and conditions: a) (*S*)-*tert*-Butylsulfinamide, Pyr·TsOH, $MgSO_4$, CH_2Cl_2; b) *i*-PrMgCl, CH_2Cl_2; c) 4 N HCl in dioxane, CH_3OH; d) 1. DCC, HOBt, 7-OH-Boc-D-Tic-OH for **4** or 7-OH-Boc-L-Tic-OH for **5**, NEt_3, THF; 2. 6 N HCl (aq), CH_3OH.

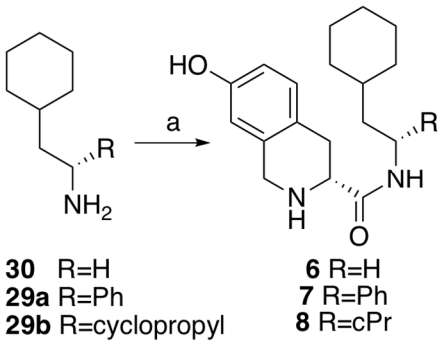
Scheme 3. Preparation of the chiral amines **29a**–**29e** via stereoselective Grignard additions to the chiral sulfinimines **27a**–**27c**



23a	R^1=cyclohexyl	**27a**	**28a**	c-C_6H_{11}, Ph	**29a**
23b	R^1=cyclopentyl	**27b**	**28b**	c-C_6H_{11}, c-Pr	**29b**
23c	R^1=cycloheptyl	**27c**	**28c**	c-C_5H_9, *i*-Pr	**29c**
			28d	c-C_5H_9, c-Pr	**29d**
			28e	c-C_7H_{13}, *i*-Pr	**29e**

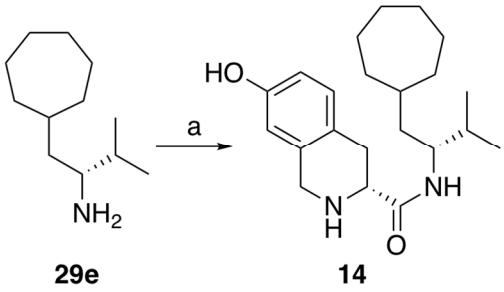
Reagents and conditions: a) (*R*)-*tert*-Butylsulfinamide, Pyr·TsOH, $MgSO_4$, CH_2Cl_2; b) PhMgBr (for **28a)** or c-PrMgCl (for **28b** and **28d**) or *i*-PrMgCl (for **28c** and **28e**), CH_2Cl_2; c) 4 N HCl in dioxane, CH_3OH.

Scheme 4. Synthesis of target compounds **6**–**8**



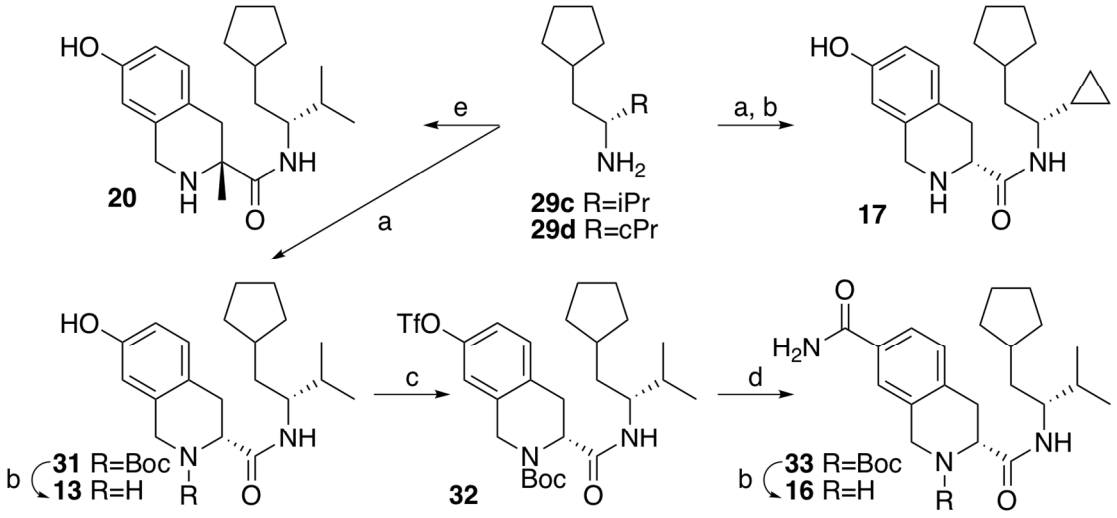
Reagents and conditions: a) 1. DCC, HOBt, 7-OH-Boc-D-Tic-OH, NEt_3, THF; 2. 4 N HCl in dioxane (for **6** and **7**) or 6 N HCl (aq) (for **8**), CH_3OH.

Scheme 5. Synthesis of the cycloheptyl target compound **14**



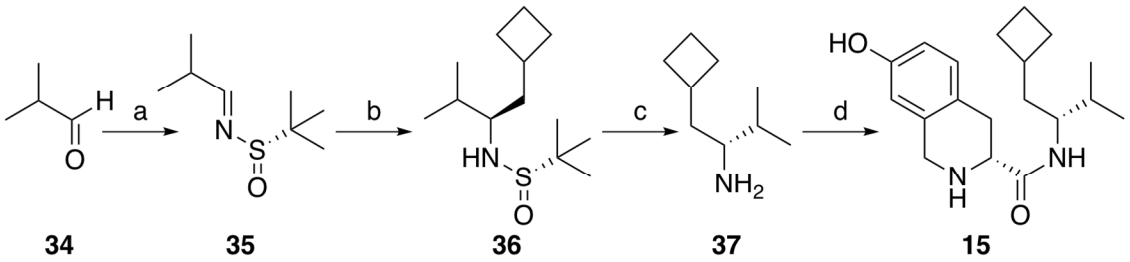
Reagents and conditions: a) 1. 7-OH-Boc-D-Tic-OH, DCC, HOBt, NEt_3, THF; 2. 4 N HCl in dioxane, CH_3CN.

Scheme 6. Synthesis of the cyclopentyl target compounds **13**, **16**, **17** and **20**



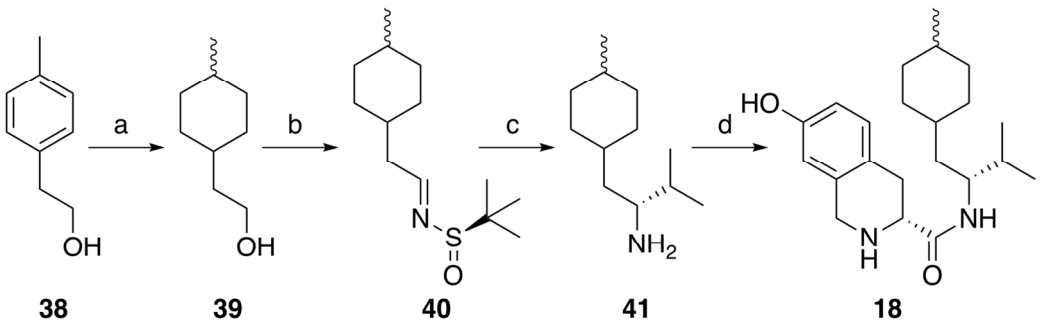
Reagents and conditions: a) 7-OH-Boc-D-Tic-OH, DCC, HOBt, THF; b) HCl, dioxane/CH_3CN (for **13** and **16**) or CH_3OH (for **17**); c) $PhNTf_2$, NEt_3, CH_2Cl_2; d) Hermann's palladacycle, XPhos, $NH_2OH{\cdot}HCl$, $Mo(CO)_6$, Cs_2CO_3, DMAP, dioxane; e) 1. 7-OMe-3-Me-Boc-D-Tic-OH, DCC, HOBt, NEt_3, THF; 2. BBr_3, CH_2Cl_2.

Scheme 7. Synthesis of the cyclobutyl target compound **15**



Reagents and conditions: a) (*S*)-*tert*-Butylsulfinamide, Pyr·TsOH, $MgSO_4$, CH_2Cl_2; b) cyclobutylmethylmagnesium bromide, CH_2Cl_2; c) 4 N HCl in dioxane, CH_3OH; d) 1. 7-OH-Boc-D-Tic-OH, propylphosphonic anhydride (T3P) in EtOAc, $NEt(i\text{-}Pr)_2$, THF; 2. HCl, CH_3OH.

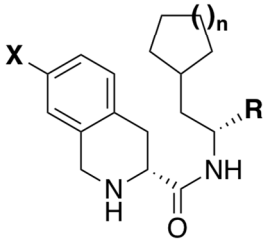
Scheme 8. Synthesis of target compound **18**



Reagents and conditions: a) 1. Na, NH_3, THF, *t*-BuOH; 2. H_2, $Pd(OH)_2/C$, EtOH; b) 1. $(COCl)_2$, DMSO, NEt_3; 2. (*R*)-*tert*-butylsulfinamide, Pyr·TsOH, $MgSO_4$; c) 1. *i*-PrMgCl, CH_2Cl_2; 2. HCl, dioxane, CH_3OH; d) 1. 7-OH-Boc-D-Tic-OH, DCC, HOBt, THF; 2. HCl, CH_3OH.

Table of Contents graphic

Potent and Selective Kappa Opioid Receptor Antagonists



	K_e (κ)	μ/κ	δ/κ
1 (n=2, R=*i*Pr, X=OH)	0.14 nM	1730	4570
8 (n=2, R=cPr, X=OH)	0.64 nM	417	4690
9 (n=2, R=*i*Pr, X=$CONH_2$)	0.24 nM	742	5083
13 (n=1, R=*i*Pr, X=OH)	0.058 nM	5900	27000
14 (n=3, R=*i*Pr, X=OH)	0.20 nM	292	3760