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Article

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Potent and Selective Tetrahydroisoquinoline Kappa Opioid Receptor Antagonists of Lead Compound (3*R*)-7-Hydroxy-*N*-[(1*S*)-2-methyl-1-(piperidin-1-ylmethyl)propyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (PDTic)

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ABSTRACT: Past studies have shown that it has been difficult to discover and develop potent and selective κ opioid receptor antagonists, particularly compounds having potential for clinical development. In this study, we present a structural activity relationship (SAR) study of a recently discovered new class of tetrahydroisoquinoline κ opioid receptor antagonists which led to (3*R*)-

7-hydroxy-*N*-{(1*S*)-2-methyl-1-[(-4-methylpiperidine-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (**12**) (4-Me-PDTic). Compound **12** had a K_e = 0.37 nM in a [^{35}S]GTPγS binding assay and was 645- and >8100-fold selective for the κ relative to the μ and δ opioid receptors, respectively. Calculated logBB and CNS (central nervous system) multiparameter optimization (MPO) and low molecular weight values all predict that **12** will penetrate the brain and pharmacokinetic studies in rats shows that **12** does indeed penetrate the brain.

INTRODUCTION

Over the years it has proven to be very difficult to develop potent and highly selective pure κ opioid receptor antagonists. The first such compound developed was nor-BNI (nor-binaltorphimine) (Figure 1).[1] In 2000, GNTI (5'-guanidinonaltrindole) (Figure 1), a slightly more potent κ opioid receptor antagonist, was developed.[2] The naltrexone-derived norBNI and GNTI depend on the *N*-cyclopropylmethyl group for their antagonistic properties. In 2001, we reported the discovery of JDTic (Figure 1), a potent and selective κ opioid receptor antagonist with a novel chemical structure.[3-5] JDTic displayed robust effectiveness in rodent models of depression,[5] anxiety,[6] stress induced cocaine relapse,[5] nicotine withdrawal,[7] and alcohol seeking, relapse, and withdrawal.[8,9] Besides JDTic, PF-4455242 and LY2456302 have been identified as new classes of κ opioid receptor antagonists. However, both LY2456302 and PF-4455242 have lower potency and selectivity at the κ relative to the μ and δ opioid receptors compared to JDTic, nor-BNI, and GNTI. Nevertheless, JDTic, LY2456302, and PF-4455242 all proceeded through preclinical development and were evaluated in phase 1 clinical studies.[10-13] The compound LY2456302, now known as CERC-501, is the only one still in clinical evaluation to the best of

our knowledge. More recently, CYM51317 (structure not available) was reported as a new κ opioid receptor antagonist for migraine prevention.[14]

We recently reported **1** (PDTic), a pure opioid receptor antagonist with a substantially simple tetrahydroisoquinoline moiety, as the lead compound for the design and development of novel class of potent and selective antagonists for the κ opioid receptor.[15] In this study we report the design, synthesis, and in vitro opioid receptor binding properties of compounds **3**–**39** and **41**, **43**, **45**, and **47**, which are structural analogues of **1** (structures for these compounds along with JDTic analogues **40**, **42**, **44**, and **46** are given in Tables 1–7), using [^{35}S]GTPγS binding assays. The physiochemical properties of the more potent compounds were calculated to determine if the compound(s) would be predicted to enter the brain and further pharmacokinetic studies in rats were conducted on the most potent and selective κ opioid receptor antagonist identified to determine if the compound did indeed penetrate the brain.

Results and Discussion

Chemistry. The syntheses of the various analogues substituted at four positions R^1, R^2, R^3, and R^4 in structure **2** (Figure 1) are outlined in Schemes 1–12. Synthesis of the azepanyl and morpholinyl compounds **3** and **6** respectively, is shown in Scheme 1. L-Valinol (**48**), prepared according to a literature method,[16] was coupled with Boc-7-hydroxy-D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Boc-7-hydroxy-D-Tic-OH) using coupling agent *N,N′*-dicyclohexylcarbodiimide (DCC) to afford **49**. The phenol in **49** was protected as the methyl ether using trimethylsilyldiazomethane and the alcohol was oxidized with Dess-Martin periodinane to afford the aldehyde **50**. Reductive amination with either azepane or morpholine using sodium triacetoxyborohydride followed by concomitant methyl ether and Boc deprotection

with boron tribromide in dichloromethane and subsequent treatment with ammonium hydroxide afforded compounds **3** and **6**.

As shown in Scheme 2, a variety of commercially available amines (pyrrolidine, azabicyclo[2.2.1]heptane, 4-methylpiperazine, diethylamine, dipropylamine, and diisobutylamine) were each subjected to coupling with *N*-Boc-L-valine (**51**), using *O*-(benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HBTU) and triethylamine in acetonitrile, stirred at room temperature overnight, to provide the *tert*-butyloxycarbonyl-protected intermediate, which, upon treatment with hydrogen chloride in a solvent mixture of dioxane and acetonitrile or trifluoroacetic acid in dichloromethane provided compounds **52a–f**. Amides **52a–f** were reduced with borane dimethylsulfide in tetrahydrofuran to furnish diamines **53a–f**. Subsequent coupling of the diamines **53a–f** with Boc-7-hydroxy-D-Tic-OH using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), catalytic amounts of 1-hydroxybenzotriazole (HOBt) and triethylamine in dichloromethane followed by Boc-deprotection (via treatment with methanolic hydrochloric acid or hydrogen chloride in dioxane and acetonitrile) furnished final compounds **4**, **5** and **7–10**.

The synthesis of a 2-oxopiperidine derived compound **11**, as outlined in Scheme 3, commenced from L-valinol (**48**). The amine in **48** was protected as a benzylcarbamate (**54**) and the alcohol converted to mesylate using methanesulfonyl chloride to yield **55**. Compound **55** was heated at reflux with 2-hydroxypyridine in the presence of tetrabutylammonium bromide (TBAB), potassium carbonate, toluene and a catalytic amount of water to provide **56**.[17] Catalytic hydrogenation of **56** using palladium on carbon catalyst yielded **57**, which was subsequently coupled with Boc-7-hydroxy-D-Tic-OH, followed by the *tert*-butyloxycarbonyl group deprotection using hydrogen chloride in dioxane to provide compound **11**.

A plethora of substituted commercially available piperidines (**58a–58c**, **58f–g**, **58i**, **58k–n**), as well as some lab-prepared known piperidines (**58d–e**, **58h**, **58j**), were employed for the synthesis of substituted piperidine analogues **12–26** (Scheme 4). (Difluoromethyl)piperidine (**58j**) was prepared in three steps from 4-hydroxymethylpiperidine via an aldehyde that was subsequently converted to 1-*N*-Boc-difluoromethylpiperidine using diethylaminosulfur trifluoride (DAST) as previously reported.[18] For the preparation of *trans*-3,4-dimethylpiperidine (**(±)-58e**), the glutaric acid **(±)-61** was prepared in three steps following a literature precedence,[19] then was subjected to ring closure by heating in a melt with urea at 180 °C for 3 h to provide 3,4-dimethylpiperidine-2,6-dione as a mixture of the trans and cis isomers in a 2:1 ratio (Scheme 5). Recrystallization of the mixture from ethyl acetate with hexanes provided the pure *trans* product **(±)-62** that was subsequently reduced using sodium borohydride and boron trifluoride etherate in tetrahydrofuran to furnish **(±)-58e** (Scheme 5). The *cis*-3,4-dimethylpiperidine (**(±)-58d**) and 4-ethylpiperidine (**58h**) were prepared from 3,4-lutidine (**63c**) and 4-ethylpyridine (**63d**), respectively, via a three-step protocol reported in the literature,[20] followed by subsequent catalytic hydrogenation to provide **(±)-58d** and **58h** (Scheme 6). Each of the piperidines (**58a–58n**) was coupled with Boc-L-valine (**51**) using HBTU in acetonitrile, followed by removal of the Boc-protection using either hydrogen chloride or trifluoroacetic acid to provide compounds **59a–59n** (Scheme 4). Reduction of these amides using borane dimethylsulfide gave the diamines **60a–60n**. Some of the 4-cyano intermediate (**60n**) was subjected to an acid catalyzed conversion of the nitrile using aqueous sulfuric acid, stirred at room temperature for 24 h, to furnish the 4-carboxamide (**60o**). The diamine intermediates **60a–60o** were next coupled with Boc-7-hydroxy-D-Tic-OH using EDC/HOBt followed the *tert*-butyloxycarbonyl group deprotection using methanolic hydrogen

chloride or hydrogen chloride in a dioxane acetonitrile mixture to yield the desired final compounds **12**–**26**, respectively (Scheme 4).

The pyridines used to prepare compounds **66b–66d**, **(±)-58d** and **58h** are shown in Scheme 6. The tetrahydropyridines **66b–66d** were prepared following a protocol similar to what has been previously reported[20] from 4-picoline (**63a**), 3-picoline (**63b**) and 3,4-lutidine (**63c**), respectively, via the *N*-benzyl pyridinium salt, followed by reduction and subsequent cleavage of the benzyl group to give **66b–66d**. Intermediate **66a**, as shown in Scheme 6, was commercially available. Compounds **66a–66d** were subjected to chemistry analogous to that described for the piperidines: couplings with Boc-L-valine (**51**) and removal of the Boc-protection to yield **67a**–**67d**, reduction with borane dimethylsulfide to give **68a**–**68d**, subsequent coupling of those products with Boc-7-hydroxy-D-Tic-OH, and a final Boc-deprotection provided the final compounds **27–30** (Scheme 7).

As shown in Scheme 8, the diastereomers **31–33** of **12** were synthesized using the different enantiomers of the coupling intermediates. Coupling of **60a** with Boc-7-hydroxy-L-Tic-OH yielded the diastereomer **31**. On the other hand, the reactions starting with 4-methypiperidine (**58a**) and *N*-Boc-D-valine (**51**) provided the intermediate **69** which was subsequently coupled with either Boc-7-hydroxy-D-Tic-OH or Boc-7-hydroxy-L-Tic-OH to yield **32** and **33**, in that order.

Other analogues were synthesized where the isopropyl group, the phenol group or the tetrahydroisoquinoline ring in **12** were changed or substituted by other groups (Schemes 9–12). Commercially available *N*-(2-aminoethyl)piperidine (**70**) was coupled with 7-hydroxy-Boc-D-Tic-OH using dicyclohexylcarbodiimide (DCC) as the coupling agent in tetrahydrofuran, followed by removal of the Boc-protection group using methanolic hydrogen chloride to provide

analogue **34** (Scheme 9). As shown in Scheme 10, *N*-Boc-L-cyclopropylglycine was substituted for Boc-L-valine for coupling with **58a** to provide **71**. Reduction of **71** using borane dimethylsulfide in THF to give **72** followed by coupling with Boc-7-hydroxy-D-Tic-OH provided **73a**, which upon removal of the Boc-protection using hydrogen chloride in methanol, furnished the cyclopropyl analogue **35**. Coupling **60a** with Boc-D-tyrosine in place of Boc-7-hydroxy-D-Tic-OH using EDC/HOBt and triethylamine in dichloromethane, followed by a Boc-deprotection using hydrogen chloride in methanol, provided compound **36**. Coupling of 6-hydroxynapthalene-2-carboxylic acid with **60a** in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) in dimethylformamide as solvent, heated at 100 °C for 3 h, furnished analogue **37**. Boc-7-carbamoyl-D-Tic-OH, prepared in three steps as previously reported,[21] was coupled with diamine **60a** to yield **73b** which yielded **41** after the removal of the Boc-protecting group. Similarly, Boc-7-fluoro-D-Tic-OH, also previously reported,[21] was employed for the synthesis of **73d** which upon Boc-deprotection, furnished compound **45**. The phenolic hydroxy group in **73c** was converted to the methyl ether upon treatment with trimethylsilyl diazomethane followed by the removal of the Boc-protecting group to provide compound **43** (Scheme 10). For the synthesis of analogue **38**, (Scheme 11), 6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**74a**)[22] was demethylated using hydrogen bromide in acetic acid heated at reflux for 5 h to provide **74b**, which was subsequently coupled with **60a** using (benzotriazole-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and triethylamine in tetrahydrofuran stirred at room temperature overnight to provide **38** as a mixture of diastereomers. Finally, as shown in Scheme 12, the reduced and *N*-methyl analogues of **12**, compounds **39** and **47**, were both synthesized in one step from **12**. Treatment of **12** in tetrahydrofuran with borane dimethylsulfide heated at reflux overnight furnished the reduced

analogue **39**. On the other hand, treatment of **12** in dichloroethane with formalin followed by sodium triacetoxyborohydride stirred at room temperature for 24 h yielded the *N*-methyl analogue **47**.

Pharmacology Studies. As we recently reported, the structurally simple tetrahydroisoquinoline analogue **1** had a K_e = 6.80 nM at κ, with K_e values of 144 and >3000 nM at the μ and δ opioid receptors, respectively.[15] Thus the compound was 21- and >441-fold selective for the κ opioid receptor relative to the μ and δ opioid receptors, respectively.[15] Given these encouraging results, we set out to examine the structure activity relationships of a variety of **1** analogues. All synthesized compounds were evaluated for antagonist activity at the μ, δ, and κ opioid receptors using our established assays[15] that measure the ability of antagonists to inhibit agonist-stimulated [^{35}S]GTPγS binding in membranes prepared from CHO cells expressing human opioid receptors. Concentration response curves of U69,593 (κ), DAMGO (μ), or DPDPE (δ) were run in the absence and presence 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 in the assays and none of our synthesized analogues displayed any activity at 10 μM final concentration.

In order to determine the effect of changes in the piperidine ring size and type of ring on the κ potency and selectivity of this new class of κ opioid receptor antagonists, we synthesized and tested the larger ring size eight membered azepane, the smaller ring size, five membered pyrrolidine analogues **3** and **4**, respectively, as well as the bicyclic analogue **5** (Table 1). Similar to **1**, compounds **3**, **4**, and **5** were pure opioid antagonists. With a K_e = 48.5 nM at the κ opioid

receptor, the pyrrolidine analogue **4** was seven times less potent at the κ opioid receptor than **1**. With a K_e = 17 nM at the κ opioid receptor, the azepane analogue **3** was only 2.5 times less potent at the κ opioid receptor than **1**, and with a K_e = 2.53 nM, the bicyclic analogue **5** was 2.7 times more potent than **1**. Compounds **4** and **3** had μ/κ values of 14 and 41, respectively, and like **1**, were not very selective for the κ opioid receptor relative to the μ opioid receptor. In contrast, **5** had a μ/κ value of 296 and was highly selective for the κ relative to the μ receptor. With a δ/κ value of >1186, **5** was also highly selective for the κ receptor relative to the δ receptor. With δ/κ values of >62 and >177, **4** and **3**, respectively, were a little less selective for the κ opioid receptor relative to the δ opioid receptor than **1**. Changing the methylene group at the 4-position of the piperidine ring of **1** with an oxygen or *N*-methyl group to give the morpholino and *N*-methylpiperazine ring analogues, **6** and **7**, respectively, resulted in large losses in potency for all three receptors. Overall results from these changes to the piperidine ring of **1** suggest that the piperidine analogue **1** is a better lead compound than the pyrrolidine and azepane analogues **4** and **3**, respectively, as well as the morpholino and *N*-methylpiperazino analogues **6** and **7**, respectively.

In order to determine if the intact piperidine ring in **1** is needed for high potency at the κ opioid receptor, the simple *N,N*-diethyl (**8**), *N,N*-dipropyl (**9**), and *N,N*-diisobutyl (**10**) analogues were synthesized and evaluated for their potency and selectivity as κ opioid receptor antagonists (Table 1). Even though all three compounds were pure opioid antagonists, they were no better than **1**. The *N,N*-dipropyl analogue **9**, with a K_e = 14.5 nM at κ and μ/κ and δ/κ values of 20.7 and >207, respectively, has the best κ potency and selectivity of the three analogues. However, the results did not suggest that **9** would be a better lead compound than **1**.

In order to gain information concerning the need for the basic nature of the amino group in the piperidine ring of **1**, the 2-oxopiperidine analogue **11** was synthesized and evaluated (Table 1). The observation that **11** had a K_e of 61.5 nM at the κ opioid receptor suggests that the amino nature of **1** is required. However, low κ potency could be due to steric or other factors.

Since the importance that methyl groups can have in drug discovery is well-documented[23,24] we investigated the opioid receptor efficacy of the monomethyl and dimethyl analogues **12**–**17**. Compounds **13**–**17** were tested as isomeric mixtures, where the incorporated piperidine was either a racemate or, in the case of **17**, purchased and used as a *cis*/*trans* mixture. These methylated-**1** analogues had K_e values at the κ opioid receptors ranging from 0.37 to 3.46 nM (Table 2). Compound **12**, with a K_e = 0.37 nM at the κ receptor and μ/κ and δ/κ values of 646 and >8100, respectively, was the most potent and selective κ opioid receptor antagonist. However, **15**, which has a K_e = 1.26 nM at κ with μ/κ and δ/κ values of 86 and 2381, respectively, has good κ opioid receptor potency and selectivity. Compounds **16** and **17** with K_e values at the κ opioid receptor of 2.3 and 3.46 nM, respectively, were also a little more potent than **1**. It is possible that one of the isomers of compounds **13**–**17** may be more potent than that observed for the mixture of isomers.

The high κ antagonist potency and selectivity of **12** led us to investigate the opioid receptor properties of compounds where the 4-methyl group was replaced by other substituents such as the 4,4-dimethyl **18**, 4-ethyl **19**, 4-trifluoromethyl **20**, 4-(difluoromethyl) **21**, 4-methoxy **22**, 4-(dimethylamino) **23**, 4,4-difluoro **24**, 4-cyano **25**, and the 4-carboxamide **26**. These analogues of **12** were synthesized and tested in the [^{35}S]GTPγS binding assay (Table 3) and found to have κ opioid receptor K_e values ranging between 2.48 and 12.7 nM and thus were 7 to 34 times less potent κ opioid receptor antagonists than the 4-methyl analogue **12**. With μ/κ values ranging

from 14 to 51, none of the compounds were very selective for the κ relative to the μ opioid receptor. Since the δ/κ values for the compounds in Table 3 ranged from >236 to 1004, all of the compounds are highly selective for the κ relative to the δ opioid receptor.

To determine the effect on opioid antagonist potency by adding a 3,4-double bond to **1**, **12**, and **15** or **16**, we synthesized and evaluated corresponding analogues **27**–**30** (Table 4). The addition of the 3,4-double bond to **1** to give **27** results in a 6.4-fold increase in κ antagonist potency: K_e = 6.8 nM for **1** (Table 1) compared to a K_e = 1.07 nM for **27** (Table 4). The change also resulted in a small increase in κ relative to μ selectivity. In contrast, the addition of a 3,4-double bond to **12** (Table 2) to give **28** caused a 2.4-fold loss in κ antagonist potency (K_e = 0.37 nM for **12** compared to K_e = 0.88 nM for **28**) (Table 4). The change also caused a 20-fold increase in μ antagonist potency (K_e = 239 nM for **12** compared to K_e = 11.8 nM for **28**), thus reducing its selectivity for the κ receptor relative to the μ opioid receptor. Compound **29**, which is the 3,4-double bond analogue of **13** (Table 2) resulted in very little change in the κ opioid receptor potency, K_e = 15.6 nM for **13** and 9.43 nM for **29**. Both compounds have very low selectivity at the κ relative to the μ opioid receptor; however, both compounds were highly selective for the κ relative to the δ opioid receptor. The most striking change resulted from adding a 3,4-double bond to **15** or **16**, which both afford analogue **30**. The K_e for the κ opioid receptor only changed from 1.26 nM for **15** to K_e = 1.81 nM for **30**. However, the K_e value at the μ opioid receptor changed from 108 nM for **15** to K_e = 1.09 nM for **30**. Thus **15** (Table 2) and **30** (Table 4) have about equal κ opioid receptor potency at both the μ and κ opioid receptors. This results in **30** not being selective for the κ relative to the μ receptor. With a δ/κ value of 1066, **30** is highly selective for both the μ and the κ relative to the δ opioid receptor.

Compound **12** has two asymmetric centers and thus three possible diastereomers (**31**–**33**). In order to confirm **12** had the best overall properties, the three isomers **31**–**33**, were synthesized and tested. The three compounds had K_e values for the κ opioid receptor ranging between 9.29 and 42.8 nM and thus were much less potent κ opioid receptor antagonists than **12**. Compound **31**, with a K_e = 9.29 nM and μ/κ and δ/κ values of 103 and >323, respectively, was the most κ potent and selective of the three diastereomers (Table 5), but **12** retained the preferred chirality.

In order to determine the importance of the isopropyl group on the efficacy of **1** and **12**, the analogues **34** and **35** were synthesized and evaluated. Replacement of the isopropyl groups in **1** with a hydrogen to give **34** changes its κ opioid receptor K_e value from 6.80 nM to a K_e = 113 nM, a 16.6-fold loss in κ opioid receptor antagonist potency (Table 6). Replacement of the isopropyl group in **12** with a similar sized cyclopropyl group results in a change at the κ opioid receptor from a K_e = 0.37 nM for **12** (Table 2) to a K_e = 5.58 nM for **35**, a 15-fold loss in antagonist potency (Table 6). This unexpected finding suggests that the isopropyl group may be essential for the high κ potency and selectivity of **12**. Replacing the 7-hydoxyl-D-Tic group in **12** with the D-tyrosine in **36** results in an over 1000-fold loss in κ antagonist potency showing the importance of the intact 7-hydroxy-D-Tic group to the κ opioid potency and selectivity of **12**.

The need for the 7-hydroxytetrahydroisoquinoline group in **12** was further substantiated by the finding that analogues **37** and **38**, which have a hydroxynaphthalene and 7-hydroxy-1,2,3,4-tetrahydronaphthalene group, respectively, replacing the 7-hydroxytetrahydroisoquinoline group in **12**, had K_e values of 20.5 and 11.1 nM, respectively, at the κ opioid receptor (Table 6). Analogue **39**, which has the amide group reduced to a methyleneamino group, has a K_e = 17.2 nM, thus showing that the amide carbonyl group is also needed for the high κ potency of **12**.

In Table 7, the effect of replacing the phenolic hydroxyl group in **12** with other substituents was determined and the results are compared to similar analogues of JDTic.[21] Replacing the 7-hydroxyl substituent in **12** with a carboxamido (**41**, K_e = 1.37 nM), methoxy (**43**, K_e = 25.6 nM), and fluoro (**45**, K_e = 182 nM) substituent resulted in a 3.7-, 69-, and 492-fold loss in κ opioid receptor antagonist potency, respectively. In addition, the compounds were much less selective for the κ relative to the μ opioid receptor. A comparison of the results for **12** to the results for similar substituted JDTic analogues are given in Table 7. While not as potent as JDTic, compound **12**, which like JDTic has a hydroxyl group in position 7, is a potent and selective κ opioid receptor antagonist. The JDTic analogue **40**, which has a carboxamido substituent in position 7, is as potent as JDTic.[21] However, compound **41**, which has a carboxamido in place of the hydroxyl in **12**, is 3.7 times less potent than **12**. Additionally, compound **42**, which is the 7-methoxy analogue of JDTic, is only 3-fold less potent than JDTic and, like JDTic, is highly selective for the κ opioid receptor relative to the μ and δ opioid receptors.[25] In contrast, compound **43** (the methoxy analogue of **12**) with a K_e = 25.6 nM at the κ opioid receptor, is 69 times less potent than **12** and is not very selective for κ relative to μ. The 7-fluoro analogue **44**, with a K_e = 2.20 nM, is 110-fold less potent than JDTic.[21] In comparison, the 7-fluoro analogue of **12**, compound **45** with a K_e = 182 nM at the κ opioid receptor, is 492-fold less potent than **12**. Thus, changes in the 7-hydroxyl group of **12** are more sensitive to similar changes in JDTic and thus do not follow the same SAR found in JDTic.[21]

The difference between the SAR of the new tetrahydroisoquinoline analogues in this study and the SAR of JDTic analogues is also shown by comparing the results obtained for **46** and **47**, which are the N-methyl analogues of JDTic and **12**, respectively. The JDTic analogue **46**, with a K_e = 0.16 nM at the κ opioid receptor, is a potent κ opioid receptor antagonist.[26] In contrast, **47**

has a K_e = 36.7 nM at the κ opioid receptor and is thus a much weaker κ opioid receptor antagonist.

Table 8 shows a comparison of the calculated physiochemical properties of **12** and **15** to those of JDTic. Both **12** and **15** have TPSA (topological polar surface area) values of 64.60 $Å^2$ compared to 84.83 for JDTic. The cLogP values for **12** and **15** are 2.32 and 2.49, respectively, compared to 3.60 for JDTic. The logBB values for **12** and **15** are –0.46 and –0.44, respectively, compared to –0.57 for JDTic. The CNS MPO values for **12** and **15** are 4.5 and 4.1, respectively, compared to a 3.1 value for JDTic. Compounds that have TPSA values less than 76 $Å^2$,[3,27] cLogP values in the range of 2–4,[28] calculated logBB values less than –1,[28,29] and CNS MPO values greater than 4,[30] are predicted to penetrate the brain; therefore, both compounds **12** and **15** are predicted to penetrate the brain. In addition, CNS penetration has been correlated with lower molecular weights.[31] The fact that molecular weights of 359.5 and 373.5 Daltons for **12** and **15** are 106 and 92 Daltons, respectively, less than JDTic, which is known to penetrate the brain, further suggests that both **12** and **15** will penetrate the brain.

Pharmacokinetic Studies. The pharmacokinetics of **12** was assessed in plasma and brain following a single dose to determine uptake into brain (Figure 2). In plasma, **12** reached a Cmax of 333 ng/mL at 1 h after dosing, while in brain, a Cmax of 239 ng/mL was achieved at 4 h post dose (Table 9). The half-life was determined to be 30.7 h in plasma and 57.2 h in brain. The ratio of brain:plasma concentration rose between 1 and 72 h and then declined. Compound **12** crossed the blood-brain barrier and persisted in plasma and brain for 168 h post dose. The AUC_{last} was approximately 10-fold higher in brain compared with plasma and the clearance from the brain was 11.2 times slower than from the plasma. The behavior of **12** was similar to that of JDTic, which at a dose of 5 mg/kg in male rats had a half life of 28.4 h in plasma and 51.8 h in brain,

and the AUC_{last} was approximately 7-fold higher in brain.[26] Of four JDTic analogues investigated previously, only RTI-194 ((3*R*)-7-hydroxy-*N*-[(1*S*)-1-[[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylbutyl]-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide) had a similar longer half life in brain, and AUC_{last} was approximately10 fold higher in brain.[26]

Conclusions

A SAR study directed towards the recently discovered new structural class of κ opioid receptor antagonists based on lead structure **1** involving changes to the piperidine ring, absolute stereochemistry, the 7-hydroxy group on the tetrahydroisoquinoline and the isopropyl group, led to the identification of the potent and selective κ opioid receptor antagonist **12**. LogBB, CNS MPO and molecular size predicted that **12** would penetrate the brain. Follow up pharmacokinetic studies in rats showed that **12** did indeed readily penetrate the brain. These studies strongly suggest that compound **12** should be considered for further development.

Experimental Section

Melting points were determined using a MEL-TEMP II capillary melting point apparatus. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were obtained on a Bruker Avance DPX-300 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 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: CMA80 (or DMA80) = 80:18:2 $CHCl_3$ (or 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. See Supporting Information for the synthesis of all intermediate compounds.

General Synthetic Procedures

General Method 1. Coupling of amines with Boc-7-hydroxy-D-Tic-OH. To a solution of the amine (1.0 equiv) in CH_2Cl_2 (30–50 mL) was added Boc-7-hydroxy-D-Tic-OH (1.1 equiv), EDC (1.2 equiv), HOBt (0.11 equiv) and NEt_3 (5.0–8.0 equiv). The mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (30 mL) was added to the mixture and the organic product extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered through Celite and concentrated in vacuo. Purification of the residue on silica gel eluted with CMA80 (or DMA80) in CH_2Cl_2 to provide the desired Boc-protected product that was then subjected to General Method 2 for the cleavage of the Boc group. Alternatively, acid in THF (0.1 M) was treated with DCC (1.2 eq.) and HOBt (1.1 eq). After 1 h at room temperature, the amine (1.2 eq) was added. If the amine was a hydrochloride salt, NEt_3 (3 eq) was also added. After 12 h, the reaction mixture was filtered, concentrated, and the residue subjected to silica gel chromatography to afford the desired amide.

General Method 2. Removal of Boc-protection. 2a. The Boc-protected compound in CH_3CN was treated with HCl (4M in 1,4-dioxane, 4 equiv.) and stirred at room temperature overnight. The solvent was then removed in vacuo and the residue was neutralized with 1 N NaOH until the

pH of 8–9 was obtained. Purification of the residue on silica gel and eluted with CMA80 (or DMA80) in CH_2Cl_2 provided the product. **2b.** Alternatively, the Boc-protected compound was dissolved in CH_3OH (5 mL) then treated with 6 N aq HCl (5 mL) and stirred at room temperature overnight. The solvent was evaporated, and the residue purified as above.

Preparation of the Hydrochloride salts. 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*R*)-*N*-[(1*S*)-1-(Azepan-1-ylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (3) Dihydrochloride. Compound **50** (0.15 g, 0.4 mmol) and homopiperidine (110 mg, 1 mmol) in 1,2-dichloroethane (3 mL) was treated with sodium triacetoxyborohydride (200 mg, 0.9 mmol). After 12 h, the solution was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and subjected to chromatography on silica gel eluting with a gradient up to 10% CH_3OH in EtOAc to afford 99 mg (52%) of the Boc protected intermediate. The intermediate was dissolved in CH_2Cl_2 (10 mL) and treated with BBr_3 (5 mL, 1.0 M in CH_2Cl_2, 5 mmol) at –78 °C, then allowed to warm to room temperature overnight. The solution was cooled to –78 °C, quenched with methanol, concentrated and then dissolved in dilute aqueous NH_4OH (1:1). The aqueous solution was brought to a reflux, then cooled and the solvent removed in vacuo. The residue obtained was purified bychromatography on silica gel eluted with a gradient of 0–50% CMA80 in CH_2Cl_2 to afford **3** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 9.42 Hz, 1H), 6.85 (d, J = 8.29 Hz, 1H), 6.49 (d, J = 8.29 Hz, 1H), 6.43 (s, 1H), 4.14 (td, J = 7.30, 14.41 Hz, 1H), 3.57–3.76 (m, 2H), 3.30 (dd, J = 5.09, 11.49 Hz, 1H), 2.75–3.03 (m, 5H), 2.69 (d, J = 6.78 Hz, 2H), 2.35 (dd, J = 11.96, 15.92 Hz, 1H), 1.77–1.94 (m, 1H), 1.46–1.78 (m, 8H), 0.94 (dd, J = 1.79, 6.69 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5,

154.9, 137.2, 130.4, 125.1, 113.8, 112.2, 57.4, 56.8, 55.0, 50.6, 48.1, 31.4, 29.7, 27.4, 25.5, 19.1, 18.0; MS (ESI) *m*/*z* 360.4 $(M + H)^+$. The freebase **3** was converted to 25.5 mg (14% from **50**) of the dihydrochloride salt as a pale-yellow powder: mp 160–164 °C (fusion), $[\alpha]_D^{25}$ +65.5° (*c* 0.165, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2$•1.5 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-2-methyl-1-(pyrrolidin-1-ylmethyl)propyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (4) Dihydrochloride. Compound **53a** (1.03 g, 6.02 mmol) was coupled with Boc-7-hydroxy-D-Tic-OH (1.77 g, 6.02 mmol) following the protocol described in General Method 1 to provide the Boc protected product **Boc-4** (1.43 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (br. s., 1H), 6.91 (d, *J* = 8.10 Hz, 1H), 6.48–6.70 (m, 2H), 5.94–6.31 (m, 1H), 4.58–4.87 (m, 1H), 4.31–4.57 (m, 2H), 3.56–3.81 (m, 1H), 3.07–3.31 (m, 2H), 2.91 (d, *J* = 10.17 Hz, 1H), 2.08–2.35 (m, 4H), 1.71–1.91 (m, 1H), 1.57 (br. s., 4H), 1.38–1.50 (m, 9H), 1.07–1.34 (m, 1H), 0.77 (dd, *J* = 6.69, 13.28 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.5, 134.0, 129.0, 123.8, 114.7, 113.1, 81.3, 60.4, 57.9, 56.5, 54.0, 53.1, 44.9, 44.5, 30.9, 30.2, 28.3, 23.4, 18.8, 17.5; MS (ESI) *m*/*z* 432.3 $(M + H)^+$. **Boc-4** (1.43 g, 3.32 mmol) was subjected to Boc-cleavage according to General Method 2b to provide amine **4** (839 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 10.17 Hz, 1H), 6.78 (d, *J* = 8.10 Hz, 1H), 6.22–6.39 (m, 2H), 5.75–6.17 (m, 1H), 4.16 (t, *J* = 10.55 Hz, 1H), 3.59–3.73 (m, 1H), 3.47–3.58 (m, 1H), 3.20 (dd, *J* = 5.27, 11.68 Hz, 1H), 2.95 (t, *J* = 12.15 Hz, 1H), 2.84 (dd, *J* = 5.09, 16.58 Hz, 1H), 2.72 (br. s., 2H), 2.61 (br. s., 2H), 2.27 (dd, *J* = 2.64, 12.43 Hz, 1H), 2.01–2.15 (m, 1H), 1.70–1.92 (m, 5H), 0.75–1.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 155.1, 137.6, 130.8, 125.0, 113.2, 112.0, 57.2, 56.5, 54.0, 51.8, 48.5, 32.0, 28.9, 23.1, 19.0, 18.0; MS (ESI) *m*/*z* 332.5 $(M + H)^+$. A white solid was obtained of the dihydrochloride salt of **4**. mp 148 °C (dec.); $[\alpha]_D^{25}$ = +67.3° (*c* 1.1, CH_3OH). Anal. ($C_{19}H_{31}Cl_2N_3O_2$•H_2O) C, H, N. To make a fumarate salt, **4** (376.6

mg, 1.14 mmol) was dissolved in chloroform (2 mL) in a vial and treated with fumaric acid in MeOH (2.0 equiv. 3.5 mL, 0.65 M in MeOH) and allowed to stand in a refrigerator overnight. The excess solvent was then removed under reduced pressure and the residue salt was redissolved in minimal amount of MeOH. The fumarate salt was recrystallized from MeOH using diethyl ether to provide 329 mg of **4**•$2C_4H_4O_4$ as a beige solid; mp 152 °C (dec.); $[\alpha]_D^{25}$ = +65.0° (*c* 1.1, CH_3OH). Anal. ($C_{27}H_{37}N_3O_{10}$•1.25 H_2O) C, H, N.

(3*R*)-*N*-[(1*S*)-1-(7-Azabicyclo[2.2.1]hept-7-ylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (5) Dihydrochloride. A solution of dicyclohexylcarbodiimide (DCC) (120 mg, 0.58 mmol) in THF (2 mL) was treated with a THF (3 mL) solution of HOBt (72 mg, 0.54 mmol) and 7-hydroxy-Boc-D-Tic-OH (150 mg, 0.51 mmol)and stirred at room temperature for 1 h. Amine **53b** (140 mg, 0.77 mmol) and NEt_3 (0.2 mL, 1.4 mmol) were added to the suspension and stirred for an additional 12 h at room temperature. . The solids were removed by filtration and the filtrate concentrated under reduced pressure. The residue obtained was purified by chromatography on silica gel eluted with a gradient of 0–50% DMA80 in CH_2Cl_2. The fractions containing the product were concentrated and the residue dissolved in CH_3OH (5 mL) and treated with 6 N HCl aq (5 mL). After 12 h, the solvent was removed in vacuo, and the residue partitioned between CH_2Cl_2 and 7 M aq NH_4OH. The organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was subjected to chromatography on silica gel eluting with a gradient of 0–75% DMA80 in CH_2Cl_2 to afford 36.4 mg (10%) of the freebase **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 9.61 Hz, 1H), 6.78 (d, *J* = 8.10 Hz, 1H), 6.44 (dd, *J* = 2.35, 8.19 Hz, 1H), 6.32 (d, *J* = 2.26 Hz, 1H), 3.86–4.00 (m, 1H), 3.36–3.68 (m, 4H), 3.08 (dd, *J* = 5.09, 11.68 Hz, 1H), 2.81 (dd, *J* = 4.90, 16.39 Hz, 1H), 2.51–2.71 (m, 1H), 2.40 (dd, *J* = 2.54, 12.90 Hz, 1H), 2.13–2.30 (m, 1H), 1.63–1.91 (m, 5H), 1.23–

1.44 (m, 4H), 0.72–0.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 155.2, 137.4, 130.6, 125.0, 113.8, 112.1, 59.8, 56.7, 52.2, 48.4, 48.0, 31.7, 29.7, 28.2, 18.8, 18.3. The freebase was converted into a pale yellow powder as the dihydrochloride salt: MS (ESI) *m*/*z* 358.4 $(M + H)^+$; m.p. 194–198 °C (fusion); $[\alpha]_D^{25}$ = +72° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}Cl_2N_3O_2$•1.5 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-2-methyl-1-(morpholin-4-ylmethyl)propyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (6) Dihydrochloride. A solution of **50** (0.15 g, 0.4 mmol) in dichloroethane (3 mL) was treated with morpholine (0.09 mL, 1 mmol) then sodium triacetoxyborohydride (200 mg, 0.9 mmol). After 12 h, the solution was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and subjected to chromatography on silica gel eluting with EtOAc to afford 100 mg (54%) of the Boc-protected intermediate. The Boc intermediate was dissolved in CH_2Cl_2 (10 mL), cooled to –78 °C, treated with BBr_3 (5 mL, 1.0 M in CH_2Cl_2, 5 mmol) and allowed to warm to room temperature overnight. The solution was cooled to –78 °C, quenched with methanol, concentrated and then dissolved in 50% dilute aqueous NH_4OH. The aqueous solution was brought to a reflux, then cooled and concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% CMA80 in CH_2Cl_2 to afford **6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 9.80 Hz, 1H), 6.91 (d, *J* = 8.29 Hz, 1H), 6.60 (dd, *J* = 2.45, 8.29 Hz, 1H), 6.45 (d, *J* = 2.07 Hz, 1H), 4.11–4.18 (m, 1H), 3.63–3.78 (m, 6H), 3.37 (dd, *J* = 5.18, 10.83 Hz, 1H), 2.98 (dd, *J* = 5.09, 16.39 Hz, 1H), 2.47–2.68 (m, 4H), 2.29–2.43 (m, 3H), 1.85 (dd, *J* = 6.78, 11.87 Hz, 1H), 0.89–0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 154.7, 137.1, 130.4, 125.3, 114.0, 112.2, 66.6, 60.5, 56.7, 53.8, 49.7, 47.8, 31.1, 29.8, 19.2, 17.8; MS (ESI) *m*/*z* 348.3 $(M + H)^+$. The freebase was converted to 42.2 mg (44%) of

the dihydrochloride salt as a white powder: mp 186–190 °C (fusion), $[\alpha]_D^{25}$ +62° (*c* 0.16, CH_3OH). Anal. ($C_{19}H_{31}Cl_2N_3O_3$•1.5 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methylpiperizin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (7) Trihydrochloride. Diamine **53c** (937 mg, 5.06 mmol) and Boc-7-hydroxy-D-Tic-OH (1.6 g, 5.31 mmol) in a solvent mixture of THF (4 mL) and CH_3CN were coupled using HBTU (2.32 g, 6.07 mmol) (instead of EDC/HOBt) and triethylamine (2.8 mL, 20.5 mmol) to provide Boc-protected product **Boc-7** (1.82 g mg, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.65 (s, 1H), 5.97–6.41 (m, 1H), 4.71–4.80 (br. s., 1H), 4.40–4.58 (m, 2H), 3.83 (br. s., 1H), 3.18–3.24 (dd, *J* = 2.5, 15.3 Hz, 1H), 2.95–3.02 (m, 1H), 2.74–2.82 (m, 2H), 2.20–2.25 (m, 2H), 1.85–1.92 (m, 2H), 1.51 (s, 9H), 1.40–1.60 (m, 3H), 1.12–1.33 (m, 6H), 0.85–0.95 (m, 3H), 0.45–0.59 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.2, 134.0, 129.1, 123.9, 114.7, 113.2, 81.1, 65.8, 59.5, 57.9, 54.3, 53.8, 51.2, 45.1, 34.1, 31.4, 30.8, 30.5, 29.6, 28.4 (3Cs), 21.8, 18.5, 16.6; MS (ESI) *m*/*z* 460.4 $(M + H)^+$. **Boc-7** (689 mg, 1.5 mmol) was treated according to the General Method 2b for removal of the Boc-protection to provide 348 mg (64%) of the freebase amine **7**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.97 (d, *J* = 8.3 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 4.07–4.16 (m, 2H), 3.95–4.01 (m, 1H), 3.78–3.82 (dd, *J* = 5.0, 4.4 Hz, 1H), 2.87–3.09 (m, 2H), 2.60–2.80 (m, 6H), 2.48 (s, 3H), 2.45–2.57 (m, 3H), 1.78–1.87 (m, 1H), 0.93–0.96 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.0, 157.1, 135.4, 131.1, 124.7, 115.6, 113.5, 60.7, 58.4, 57.7, 55.4, 52.8, 52.6, 47.1, 45.1, 32.2, 31.8, 20.2, 18.5, 18.3; MS (ESI) *m*/*z* 360.3 $(M + H)^+$. A white solid was obtained as the trihydrochloride salt of **7**: mp >240 °C; $[\alpha]_D^{25}$ = +71.2° (*c* 1.1, CH_3OH) Anal. ($C_{20}H_{35}Cl_3N_4O_2$•1.75 H_2O) C, H, N.

(3*R*)-*N*-{(1*S*)-1-[(4,4-Diethylamino)methyl]-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (8) Dihydrochloride. Diamine **53d** (336 mg, 1.45 mmol) in CH_2Cl_2 (30 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (426 mg, 1.45 mmol) following the protocol described in General Method 1 to provide 200 mg (32%) of the product **Boc-8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br. s., 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.66 (dd, *J* = 2.6, 8.3 Hz, 1H), 6.61 (s, 1H), 6.25–6.40 (m, 1H), 4.70–4.85 (m, 1H), 4.43–4.55 (m, 2H), 3.77 (br s, 1H), 3.17–3.24 (dd, *J* = 3.8, 15.6 Hz, 1H), 2.95–3.02 (dd, *J* = 6.2, 16.2 Hz, 1H), 2.51–2.78 (m, 2H), 2.25–2.50 (m, 3H), 1.83–2.12 (m, 2H), 2.05 (s, 1H), 1.49 (s, 9H), 1.18–1.35 (m, 4H), 0.78–1.07 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.6, 134.1, 129.1, 124.2, 114.6, 113.2, 81.5, 56.7, 52.9, 51.7, 46.5, 44.9, 30.9, 29.4, 28.4 (3Cs), 21.0, 18.8, 17.4, 14.1; MS (ESI) *m*/*z* 434.5 $(M + H)^+$. A solution of **Boc-8** (517 mg, 1.19 mmol) in CH_3CN (20 mL) was subjected to Boc cleavage following the General Method 2a to provide the freebase **8**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.98 (d, *J* = 8.6 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 4.06–4.21 (m, 2H), 4.11 (s, 1H), 3.83–3.89 (dd, *J* = 5.1, 11.3 Hz, 1H), 3.10–3.33 (m, 5H), 3.36 (s, 1H), 2.84–3.07 (m, 2H), 1.84–1.95 (m, 1H), 1.28–1.34 (m, 5H), 0.91–1.05 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.5, 157.2, 134.7, 131.2, 124.7, 115.7, 113.5, 58.1, 55.4, 51.2, 47.3, 32.6, 31.3, 20.0, 18.5, 9.2; MS (ESI) *m*/*z* 334.5 $(M + H)^+$. The freebase was converted into a white solid as the dihydrochloride salt (332 mg, 84%): mp 152–155 °C; $[\alpha]_D^{25}$ = +70.5° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•1.25 H_2O) C, H, N.

(3*R*)-*N*-{(1*S*)-1-[(Dipropylamino)methyl]-2-methylpropyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (9) Dihydrochloride. To a solution of **53e** (544 mg, 2.1 mmol) in CH_2Cl_2 (45 mL) was added Boc-7-hydroxy-D-Tic-OH (677 mg, 2.31 mmol), EDC (483 mg, 2.52 mmol), HOBt (35.3 mg, 0.23 mmol) and NEt_3 (0.7 mL, 5.04 mmol) and reacted as

described in General Method 1 to provide **Boc-9** (864.8 mg, 89% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.7 Hz, 1H), 6.67 (d, *J* = 9.5 Hz, 1H), 6.59 (s, 1H), 5.90–6.00 (m, 1H), 4.38–4.67 (m, 3H), 3.69 (br. s., 1H), 3.47 (s, 1H), 3.16 (d, *J* = 11.4 Hz, 1H), 2.94–3.02 (dd, *J* = 6.7, 4.7 Hz, 1H), 1.94–2.40 (m, 7H), 1.50 (s, 9H), 1.26–1.34 (m, 4H), 0.76–0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 155.6, 134.2, 129.0, 124.1, 123.9, 114.7, 113.1, 81.5, 56.7, 55.9, 54.2, 51.9, 50.3, 44.9, 31.1, 30.0, 28.9, 28.4, 28.3, 19.6, 18.8, 16.9, 11.8; MS (ESI) *m*/*z* 462.8 $(M + H)^+$. **Boc-9** was subjected to Boc cleavage following General Method 2a to provide 533 mg (79% yield) of the freebase **9**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.91 (d, *J* = 8.1 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.9 Hz, 1H), 6.50 (d, *J* = 2.9 Hz, 1H),3.90–4.30 (m, 1H), 3.92 (d, *J* = 2.2 Hz, 1H), 3.53–3.58 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.37 (s, 1H), 2.92–2.99 (dd, *J* = 5.2, 3.4 Hz, 1H), 2.74–2.82 (m, 1H), 2.33–2.64 (m, 6H), 1.91–1.97 (m, 1H), 1.43–1.56 (m, 4H), 0.88–1.04 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4, 156.9, 137.3, 130.9, 125.6, 115.1, 113.3, 58.3, 57.4, 57.2, 56.0, 53.0, 48.1, 32.3, 31.6, 21.0, 20.8, 20.3, 19.3, 17.7, 12.3; MS (ESI) *m*/*z* 362.4 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **9**: mp 160 °C (sublime); $[\alpha]_D^{25}$ = +55.1° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{37}Cl_2N_3O_2$•2 H_2O) C, H, N.

(3*R*)-*N*-{(1*S*)-1-{[Bis(2-methylpropyl)amino]methyl}-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (10) Dihydrochloride. The diamine **53f** (865 mg, 2.82 mmol) in CH_2Cl_2 (30 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (803 mg, 2.74 mmol) following the protocol described in General Method 1 to provide 537 mg (40%) of **Boc-10**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br. s., 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.66 (dd, *J* = 2.6, 8.3 Hz, 1H), 6.61 (s, 1H), 6.25–6.40 (m, 1H), 4.70–4.85 (m, 1H), 4.43–4.55 (m, 2H), 3.77 (br. s., 1H), 3.17–3.24 (dd, *J* = 3.8, 15.6 Hz, 1H), 2.95–3.02 (dd, *J* = 6.2, 16.2 Hz, 1H), 2.51–2.78 (m, 2H), 2.25–2.50 (m, 3H), 2.05 (s, 1H), 1.90–2.18 (m, 6H), 1.50 (s, 9H), 1.46–1.70 (m, 3H), 0.70–0.96

(m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.6, 134.3, 129.0, 124.3, 114.8, 113.1, 81.5, 64.1, 56.9, 56.6, 52.0, 44.9, 31.4, 29.4, 28.4 (3Cs), 28.0, 26.4, 26.3, 20.9, 20.8, 19.6, 15.7; MS (ESI) *m*/*z* 490.7 $(M + H)^+$. **Boc-10** (655 mg, 1.34 mmol) in CH_3CN (20 mL) was subjected to Boc cleavage following the General Method 2a afford the freebase **10**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.93 (d, *J* = 8.6 Hz, 1H), 6.61 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.51 (d, *J* = 2.1 Hz, 1H), 3.96–4.01 (m, 2H), 3.95 (s, 1H), 3.53–3.59 (dd, *J* = 4.7, 11.5 Hz, 1H), 2.94–3.01 (dd, *J* = 4.3, 15.8 Hz, 1H), 2.72–2.81 (dd, *J* = 10.5, 15.8 Hz, 1H), 2.48–2.55 (dd, *J* = 7.6, 13.4 Hz, 1H), 2.23–2.30 (dd, *J* = 7.2, 13.3 Hz, 1H), 2.05–2.20 (m, 5H), 1.67–1.80 (m, 2H), 0.89–1.05 (m, 18H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.1, 156.9, 137.1, 130.8, 125.5, 115.1, 113.2, 58.9, 58.2, 53.3, 47.9, 32.4, 30.7, 27.7, 21.5, 20.5, 16.8; MS (ESI) *m*/*z* 374.5 $(M + H)^+$. The freebase was converted into a white solid as the dihydrochloride salt (332 mg, 72% yield): mp 178–180 °C; $[\alpha]_D^{25}$ = +75.5° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•1.5 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(2-oxopiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (11) Hydrochloride. Compound **57** (400 mg, 2.2 mmol) was coupled with Boc-7-hydroxy-D-Tic-OH (638 mg, 2.2 mmol) following the protocol described in General Method 1 to provide **Boc-11** (389 mg, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86–7.15 (m, 1H), 6.50–6.77 (m, 2H), 6.34 (br. s., 1H), 4.73 (br. s., 1H), 4.55 (d, *J* = 16.58 Hz, 2H), 4.25–4.48 (m, 1H), 3.73–4.02 (m, 1H), 3.25 (br. s., 1H), 2.87–3.21 (m, 4H), 2.67 (br. s., 1H), 2.11–2.33 (m, 2H), 1.62–1.84 (m, 2H), 1.40–1.62 (m, 12H), 0.86 (br. s., 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.4, 155.9, 134.3, 128.8, 123.8, 114.4, 113.0, 80.9, 56.6, 54.9, 51.8, 47.6, 45.0, 44.3, 42.1, 31.8, 30.6, 30.3, 28.3, 22.7, 20.8, 19.0, 17.7; MS (ESI) *m*/*z* 460.3 $(M + H)^+$. **Boc-11** (370 mg, 0.81 mmol) was subjected to Boc-cleavage according to General Method 2a to provide the amine **11** (245 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.38 (m, 1H),

6.85 (d, *J* = 8.29 Hz, 1H), 6.54–6.71 (m, 1H), 6.40–6.53 (m, 1H), 4.21–4.40 (m, 1H), 3.99–4.19 (m, 1H), 3.48–3.79 (m, 3H), 3.34 (dd, *J* = 4.52, 11.30 Hz, 1H), 2.88–3.19 (m, 2H), 2.65 (dd, *J* = 2.83, 13.37 Hz, 1H), 2.20–2.53 (m, 3H), 1.38–1.89 (m, 5H), 1.13–1.34 (m, 1H), 0.70–1.01 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 171.4, 155.3, 136.8, 130.0, 124.7, 113.9, 112.1, 56.9, 51.4, 48.7, 47.8, 44.8, 41.8, 32.2, 30.8, 22.9, 20.9, 19.4, 18.3; MS (ESI) *m*/*z* 360.4 $(M + H)^+$. A white solid was obtained as the hydrochloride salt of **11**: mp 154–157 °C (dec.); $[\alpha]_D^{25}$ = +68.8° (*c* 1.1, CH_3OH). Anal. ($C_{20}H_{30}ClN_3O_3$•0.5 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (12) Dihydrochloride. Compound **60a** (908 mg, 3.53 mmol) in CH_2Cl_2 (50 mL), Boc-7-hydroxy-D-Tic-OH (1.14 g, 3.88 mmol), EDC (812 mg, 4.23 mmol), HOBt (59 mg, 0.39 mmol) and NEt_3 (1.2 mL, 8.48 mmol) were reacted as described in General Method 1 to provide 1.1 g (68%) of the **Boc-12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, *J* = 9.2 Hz, 1H), 6.65 (d, *J* = 9.7 Hz, 1H), 5.90–6.00 (m, 1H), 6.60 (s, 1H), 4.41–4.58 (m, 2H), 3.80 (br s, 1H), 3.45 (s, 1H), 3.17–3.29 (m, 1H), 2.95–3.02 (d, *J* = 11.4 Hz, 1H), 2.40–2.63 (m, 2H), 2.03–2.25 (m, 2H) 1.70–1.87 (m, 3H), 1.50 (s, 9H), 1.40–1.60 (m, 3H), 1.02–1.30 (m, 3H), 0.78–0.88 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.6, 134.1, 129.1, 123.9, 114.7, 113.1, 81.4, 59.3, 56.9, 56.5, 54.3, 53.5, 51.3, 45.1, 44.8, 34.2, 34.0, 30.5, 30.2, 28.4 (3Cs), 21.8, 18.9, 17.4; MS (ESI) *m*/*z* 460.2 $(M + H)^+$. **Boc-12** (1.1 g, 2.3 mmol) in CH_3CN (20 mL) was subjected to Boc-cleavage using General Method 2a to provide compound **12** (594 mg, 72%) as the freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 6.96 (d, *J* = 8.7 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.9 Hz, 4.16–4.21 (m, 1H), 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 4.09 (d, *J* = 3.3 Hz, 1H), 3.96–4.06 (m, 1H), 3.83–3.89 (dd, *J* = 5.6, 5.2 Hz, 1H), 3.58–3.64 (m, 1H), 3.37 (s, 1H) 3.31–3.39 (m, 2H), 3.10–3.17 (m, 2H), 3.00–3.07 (m, 1H), 2.86–2.96 (m, 2H), 2.71–2.79 (m, 1H), 1.96 (s, 1H), 1.78–1.91

(m, 3H), 1.39–1.63 (m, 3H), 0.97–1.00 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.5, 157.2, 135.0, 131.2, 124.5, 115.7, 113.5, 60.7, 58.1, 55.5, 53.5, 51.1, 50.0, 47.5, 32.6, 32.5, 31.5, 30.1, 21.6, 20.0, 18.5; MS (ESI) *m*/*z* 360.3 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **12**: mp 180 °C (dec.); $[\alpha]_D^{25}$ = +65° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2$•1.25 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[((3*RS*)-3-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (13) Dihydrochloride. Diamine **60b** (839 mg, 4.55 mmol) and Boc-7-hydroxy-D-Tic-OH (1.6 g, 5.46 mmol) were coupled according to the General Method 1 to provide desired product **Boc-13** (1.6 g, 59%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82–7.18 (m, 2H), 6.51–6.82 (m, 3H), 5.85–6.40 (m, 1H), 4.68 (br. s., 1H), 4.50–4.64 (m, 1H), 4.29–4.49 (m, 1H), 3.65–3.92 (m, 1H), 3.08–3.34 (m, 2H), 2.81–3.08 (m, 1H), 2.58 (br. s., 2H), 1.95–2.30 (m, 2H), 1.85 (d, *J* = 15.45 Hz, 1H), 1.69 (d, *J* = 9.98 Hz, 1H), 1.50 (s., 9H), 1.34–1.61 (m, 4H), 0.67–0.97 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.5, 134.1, 129.1, 124.0, 114.7, 113.0, 81.1, 62.6, 60.4, 59.3, 54.6, 53.2, 51.4, 44.9, 32.8, 30.7, 30.1, 28.4, 28.3 (3 C's), 25.3, 19.6, 18.8, 17.5; MS (ESI) *m*/*z* 460.5 $(M + H)^+$. **Boc-13** (1.24 g, 2.69 mmol) was treated as described in General Method 2a to remove the Boc-protection and 626 mg (65% yield) of the freebase compound **13** was obtained as a mixture of diastereomers: ^{1}H NMR (300 MHz, CD_3OD) δ 6.86–6.95 (m, 1H), 6.61 (dd, *J* = 2.45, 8.10 Hz, 1H), 6.49 (d, *J* = 2.26 Hz, 1H), 3.97–4.09 (m, 1H), 3.83–3.97 (m, 2H), 3.44–3.67 (m, 3H), 2.87–3.09 (m, 2H), 2.64–2.87 (m, 2H), 2.32–2.61 (m, 2H), 1.75–2.00 (m, 2H), 1.45–1.75 (m, 4H), 0.77–1.06 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.3, 156.8, 137.4, 130.9, 125.6, 115.0, 113.3, 66.9, 63.8, 62.7, 61.7, 58.2, 55.8, 54.5, 52.3, 34.0, 32.3, 26.4, 20.0, 18.5, 18.0; MS (ESI)

m/*z* 360.4 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **13**: mp 178 °C (dec.); $[\alpha]_D^{22}$ = +75.5° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2 \bullet H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[((2*RS*)-2-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (14) Dihydrochloride. The diamine **60c** (1.37 g, 5.34 mmol) and Boc-7-hydroxy-D-Tic-OH (1.57 g, 5.34 mmol) were coupled according to the General Method 1 to provide desired product **Boc-14** (1.1 g, 44%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 9.3 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 5.70–6.40 (br. m., 3H), 4.70–4.84 (m, 1H), 4.43–4.58 (m, 2H), 3.98 (br. s., 1H), 3.63–3.85 (m, 3H), 3.25–3.60 (m, 3H), 3.13–3.23 (m, 1H), 2.82–3.05 (m, 2H), 2.10–2.60 (m, 2H), 1.78–1.98 (m, 1H), 1.65–1.69 (m, 1H), 1.50 (s, 9H), 1.30–1.45 (m, 1H), 1.02–1.29 (m, 2H), 0.74–0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 155.6, 135.1, 134.0, 130.0, 129.1, 124.0, 114.5, 113.1, 81.6, 62.4, 56.0, 52.2, 47.1, 34.2, 33.8, 30.7, 29.9, 28.4 (3Cs), 25.7, 23.2, 18.7, 16.4; MS (ESI) *m*/*z* 460.5 $(M + H)^+$. **Boc-14** (1.1 g, 2.4 mmol) was treated according to the General Method 2a for removal of the Boc-protection to provide 853 mg, (99% yield) of the freebase compound **14** as a mixture of diastereomers: ^{1}H NMR (300 MHz, CD_3OD) δ 6.95 (d, *J* = 8.3 Hz, 1H), 6.63 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 4.01–4.10 (m, 1H), 3.93–3.95 (dd, *J* = 5.6, 5.2 Hz, 1H), 3.53–3.64 (m, 2H), 3.35 (s, 1H), 3.31–3.39 (m, 2H), 3.10–3.17 (m, 2H), 3.00–3.07 (m, 1H), 2.80–2.99 (m, 4H), 2.38–2.56 (m, 1H), 1.80–1.87 (m, 1H), 1.55–1.72 (m, 2H), 1.39–1.47 (m, 1H), 0.85–0.96 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4156.7, 137.2, 131.0, 125.6, 115.1, 113.3, 67.0, 63.5, 61.9, 61.2, 58.3, 52.2, 50.0, 43.1, 32.6, 32.2, 31.8, 20.0, 18.5, 18.1; MS (ESI) *m*/*z* 360.3 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **14**: mp 164–166 °C; $[\alpha]_D^{23}$ = +76.2° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2 \bullet 1.25\ H_2O$) C, H, N.

(3*R*)-*N*-[(1*S*)-1-{[(3*RS*,4*RS*)-3,4-Dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (15) Dihydrochloride. Compound **60d** (864 mg, 4.40 mmol) in CH_2Cl_2 (30 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (1.36 g, 4.62 mmol) following the protocol described in General Method 1 to provide **Boc-15** (1.38 g, 66%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.29 Hz, 1H), 6.67 (d, *J* = 8.29 Hz, 1H), 6.59 (br. s., 1H), 5.76–6.35 (m, 1H), 4.64–4.93 (m, 1H), 4.48–4.63 (m, 1H), 4.33–4.48 (m, 1H), 3.80 (br. s., 1H), 3.08–3.32 (m, 2H), 2.81–3.08 (m, 1H), 2.44–2.70 (m, 1H), 1.80–2.39 (m, 6H), 1.69 (d, *J* = 11.30 Hz, 1H), 1.45–1.58 (m, 11H), 1.29–1.42 (m, 1H), 0.71–1.04 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.6, 134.0, 129.1, 124.1, 114.7, 113.0, 81.4, 62.4, 59.0, 58.2, 56.5, 54.9, 53.6, 51.6, 44.7, 37.3, 34.3, 33.7, 32.0, 30.6, 29.8, 28.4 (3 C's), 19.2, 17.1; MS (ESI) *m*/*z* 474.7 $(M + H)^+$. **Boc-15** (1.38 g, 2.92 mmol) in CH_3CN (20 mL) was subjected to Boc cleavage following the General Method 2a to provide **15** (1.05 g, 96%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, CD_3OD) δ 6.93 (d, *J* = 8.29 Hz, 1H), 6.61 (dd, *J* = 2.54, 8.19 Hz, 1H), 6.44–6.54 (m, 1H), 3.85–4.06 (m, 2H), 3.44–3.64 (m, 1H), 2.67–3.01 (m, 3H), 2.09–2.63 (m, 4H), 1.74–1.98 (m, 2H), 1.39–1.72 (m, 3H), 1.05–1.37 (m, 2H), 0.81–1.02 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.3, 156.8, 137.4, 130.9, 125.6, 115.0, 113.2, 63.7, 61.5, 58.2, 56.1, 54.8, 54.1, 53.2, 52.5, 38.7, 35.4, 35.1, 33.6, 32.3, 20.0, 17.9; MS (ESI) *m*/*z* 374.3 $(M + H)^+$. A beige solid was obtained as the dihydrochloride salt of **15**: mp 158–162 °C; $[\alpha]_D^{23}$ = +69.4° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•0.75 H_2O) C, H, N.

(3*R*)-*N*-[(1*S*)-1-{[(3*RS*,4*SR*)-3,4-Dimethylpiperidin-1-yl]methyl}-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (16) Dihydrochloride. Compound **60e** (184 mg, 0.927 mmol) in CH_2Cl_2 (30 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (327 mg, 1.11 mmol) following the protocol described in General Method 1 to provide **Boc-16** (276

mg, 63%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.48 Hz, 1H), 6.53–6.81 (m, 2H), 4.69 (br. s., 1H), 4.49–4.63 (m, 1H), 4.28–4.49 (m, 1H), 3.75–3.91 (m, 0H), 3.50–3.61 (m, 1H), 3.20 (dd, *J* = 3.01, 14.88 Hz, 1H), 2.98 (d, *J* = 14.32 Hz, 1H), 2.07–2.30 (m, 1H), 1.50 (br. s., 9H), 1.40 (d, *J* = 7.16 Hz, 1H), 1.02–1.29 (m, 6H), 0.75–0.97 (m, 7H), 0.64 (br. s., 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 155.6, 134.6, 129.2, 128.9, 124.2, 114.6, 113.0, 81.4, 65.8, 58.3, 56.9, 54.9, 53.5, 50.9, 45.0, 37.5, 37.3, 34.3, 34.4, 30.1, 28.7, 28.4, 19.2, 17.0; MS (ESI) *m*/*z* 474.7 $(M + H)^+$. **Boc-16** (276 mg, 0.584 mmol) in CH_3OH (20 mL) was subjected to Boc cleavage following the General Method 2b to provide **16** (218 mg, 91%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, CD_3OD) δ 6.93 (d, *J* = 8.29 Hz, 1H), 6.61 (dd, *J* = 2.54, 8.19 Hz, 1H), 6.44–6.54 (m, 1H), 3.85–4.06 (m, 2H), 3.44–3.64 (m, 1H), 2.67–3.01 (m, 3H), 2.09–2.63 (m, 4H), 1.74–1.98 (m, 2H), 1.39–1.72 (m, 3H), 1.05–1.37 (m, 2H), 0.81–1.02 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.3, 156.8, 137.4, 130.9, 125.6, 115.0, 113.2, 63.7, 61.5, 58.2, 56.1, 54.8, 54.1, 53.2, 52.5, 38.7, 35.4, 35.1, 33.6, 32.3, 20.0, 17.9; MS (ESI) *m*/*z* 374.3 $(M + H)^+$. A beige solid was obtained as the dihydrochloride salt of **16**: mp 178–183 °C; $[\alpha]_D^{23}$= +82.1° (*c* 0.2, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•1.5 H_2O) C, H, N.

(3*R*)-*N*-{(1*S*)-1-[(3,5-Dimethylpiperidin-1-yl)methyl]-2-methylpropyl}-7-hydroxy-1,2,3,4 tetrahydroisoquinoline-3-carboxamide (17) Dihydrochloride (mixture of isomers). The diamine **60f** (766 mg, 3.57 mmol) and Boc-7-hydroxy-D-Tic-OH (1.26 g, 4.29 mmol) were treated according to the General Method 1 to provide **Boc-17** (1.6 g, 93%) as a mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, *J* = 9.3 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 5.94 (br. s., 1H), 4.70–4.84 (m, 1H), 4.41– 4.58 (m, 2H), 3.79 (br. s., 1H), 3.30 (s, 3H), 3.10–3.22 (m, 2H), 2.95–3.02 (m, 1H), 2.42–2.60 (m, 2H), 1.75–2.28 (m, 6H), 1.50 (s, 9H), 1.21–1.30 (m, 2H), 0.78–0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.7,

134.0, 134.0, 129.1, 124.2, 114.9, 113.3, 81.3, 60.4, 58.8, 55.3, 51.3, 50.8, 44.8, 30.6, 30.4, 30.2, 28.4 (3Cs), 18.9, 17.4; MS (ESI) *m*/*z* 476.6 $(M + H)^+$. **Boc-17** (1.5 g, 2.43 mmol) was treated as described in General Method 2a to remove the Boc-protection and provide 845 mg (93%) of freebase **17** as a mixture of isomers: ^{1}H NMR (300 MHz, CD_3OD) δ 6.94 (d, *J* = 8.4 Hz, 1H), 6.62 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.00–4.05 (m, 1H), 3.91–3.95 (m, 2H), 3.52–3.57 (dd, *J* = 4.8, 10.2 Hz, 1H), 3.37 (s, 1H), 2.74–2.98 (m, 4H), 2.41–2.46 (dd, *J* = 3.7, 12.6 Hz, 1H), 2.24–2.38 (m, 2H), 2.12–2.20 (td, *J* = 2.4, 11.4 Hz, 1H), 1.80–1.95 (m, 1H), 1.44–1.65 (m, 4H), 1.25–1.35(m, 2H), 1.13–1.18 (t, *J* = 7.0 Hz, 1H), 1.07–1.09 (m, 3H), 1.45–1.62 (m, 2H), 0.91–0.96 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.3, 156.8, 137.5, 130.9, 125.6, 115.0, 113.3, 58.2, 57.8, 56.8, 53.2, 52.8, 51.9, 50.0, 48.0, 35.2, 32.8, 32.0, 26.8, 20.1, 18.1, 17.3; MS (ESI) *m*/*z* 374.2 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **17**: mp 158 °C (dec.); $[\alpha]_D^{22}$ = +74.5° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_3$•1.5 H_2O) C, H, N.

(3*R*)-*N*-{(1*S*)-1-[(4,4-Dimethylpiperidin-1-yl)methyl]-2-methylpropyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (18) Dihydrochloride. The diamine **60g** (764 mg, 2.82 mmol) in dichloromethane (50 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (826 mg, 2.82 mmol) following the protocol described in General Method 1 to provide 673 mg (50%) of **Boc-18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.2 Hz, 1H), 6.66 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.54 (s, 1H), 5.92–6.22 (m, 1H), 4.71–4.88 (m, 1H), 4.39–4.57 (m, 2H), 3.79 (br. s., 1H), 3.21 (d, *J* = 14.2 Hz, 1H), 2.99 (dd, *J* = 6.0, 14.6 Hz, 1H), 2.83 (s, 1H), 2.78–2.88 (m, 1H), 2.05–2.27 (m, 4H), 1.00–1.93 (m, 1H), 1.50 (s, 9H), 1.18–1.35 (m, 3H), 0.78–0.88 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 171.4, 155.6, 134.0, 129.2, 124.2, 114.8, 113.0, 81.5, 59.3, 56.5, 54.5, 51.3, 50.0, 44.8, 38.6, 38.5, 30.7, 30.2, 29.6, 28.4 (3Cs), 28.2, 28.1, 19.0, 17.4; MS (ESI) *m*/*z* 474.7 $(M + H)^+$. **Boc-18** (673 mg, 1.42 mmol) in CH_3CN (20 mL) was subjected to Boc cleavage following

the General Method 2a to provide **18** as the freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 6.96 (d, *J* = 8.6 Hz, 1H), 6.65 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.52 (d, *J* = 2.6 Hz, 1H), 4.16–4.21 (m, 1H), 4.09 (d, *J* = 3.3 Hz, 1H), 3.93–4.16 (m, 3H), 3.61–3.76 (m, 2H), 3.36 (s, 1H), 2.74–2.99 (m, 6H), 1.82–1.91 (m, 1H), 1.46–1.63 (m, 4H), 1.14–1.24 (m, 1H), 0.91–1.05 (m, 12H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.2, 157.0, 136.4, 131.0, 125.1, 115.3, 113.4, 61.0, 58.1, 57.1, 51.6, 51.1, 50.0, 47.9, 38.0, 32.6, 31.9, 29.0, 28.3, 20.0, 18.5, 18.3; MS (ESI) *m*/*z* 374.5 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt (390 mg, 73%): mp 192–195 °C; $[\alpha]_D^{25}$ = +73.7° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•1.25 H_2O) C, H, N.

(3*R*)-*N*-{(1*S*)-1-[(4-Ethylpiperidin-1-yl)methyl]-2-methylpropyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (19) Dihydrochloride. The amine **60h** (133 mg, 0.67 mmol) was dissolved in CH_2Cl_2 (5 mL) and added to a solution of 7-hydroxy-Boc-D-Tic-OH (223 mg, 0.75 mmol), EDC•HCl (306 mg, 1.5 mmol) and catalytic HOBt (14 mg, 0.1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight, then was concentrated and purified by chromatography on silica gel eluted with a gradient of 0–35% DMA80 in CH_2Cl_2. The fractions containing the product were concentrated to afford **Boc-19**, which was then treated with and concentrated from CH_3OH (5 mL) and HCl (6 M, 5 mL). The concentrated residue was subjected to chromatography on silica gel eluting with 1:2 DMA80:CH_2Cl_2 to afford 77.5 mg (31%) **19** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.37 (m, 1H), 6.86 (d, *J* = 8.29 Hz, 1H), 6.56 (dd, *J* = 2.35, 8.19 Hz, 1H), 6.44 (d, *J* = 2.07 Hz, 1H), 4.22 (t, *J* = 9.89 Hz, 1H), 3.61 (s, 2H), 3.39 (d, *J* = 10.93 Hz, 1H), 3.25 (dd, *J* = 4.99, 11.59 Hz, 1H), 3.06 (d, *J* = 11.11 Hz, 1H), 2.75–2.94 (m, 2H), 2.30–2.52 (m, 2H), 2.11–2.29 (m, 1H), 1.93–2.10 (m, 1H), 1.62–1.92 (m, 3H), 1.10–1.49 (m, 5H), 0.93 (d, *J* = 6.78 Hz, 6H), 0.77–0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 155.0, 137.0, 130.5, 124.9, 113.8, 112.2, 59.7, 56.8, 55.8, 52.3, 49.5, 48.0, 36.9,

31.7, 30.7, 30.5, 29.6, 28.8, 19.0, 18.1, 11.2; MS (ESI) *m*/*z* 374.2 $(M + H)^+$. The freebase was converted into a white powder as the dihydrochloride salt: mp 176–180 °C (fusion); $[\alpha]_D^{25}$ = +75.0° (*c* 0.20, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2 \bullet H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-[(1*S*)-2-methyl-1-{[4-(trifluoromethyl)piperidin-1-yl]methyl}propyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (20) Dihydrochloride. The diamine **60i** (766 mg, 3.57 mmol) and Boc-7-hydroxy-D-Tic-OH (1.26 g, 4.29 mmol) were treated as described in the General Method 1 to provide **Boc-20** (1.6 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 9.3 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 3.2 Hz, 1H), 5.82–6.17 (m, 1H), 4.70–4.84 (m, 1H), 4.38–4.55 (m, 2H), 3.81 (br. s., 1H), 3.21 (d, *J* = 16.8 Hz, 1H), 2.99 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.62–2.78 (m, 2H), 2.10–2.20 (m, 2H), 1.63–2.02 (m, 6H), 1.51 (s, 9H), 1.21–1.30 (m, 2H), 0.79–0.87 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.3, 155.6, 134.0, 129.1, 127.5 (q, J_{CF} = 272 Hz), 124.1, 114.8, 113.0, 81.1, 60.4, 59.4, 52.6, 52.1, 51.3, 44.9, 40.2 (q, J_{CF} = 23.2 Hz), 39.5 (q, J_{CF} = 27.6 Hz), 29.9, 28.3 (3Cs), 24.5, 19.1, 17.1; MS (ESI) *m*/*z* 514.6 $(M + H)^+$. **Boc-20** (1.6 g, 3.03 mmol) was treated as described in the General Method 2a to remove the Boc protection to provide 1.1 g (88%) of **20** as the freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 3.89–4.03 (m, 3H), 3.59 (dd, *J* = 7.7, 2.9 Hz, 1H), 2.78–3.09 (m, 4H), 2.40–2.47 (m, 2H), 2.04–2.12 (m, 2H), 1.81–1.98 (m, 4H), 1.50–1.65 (m, 2H), 0.89–1.04 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4, 156.8, 137.4, 130.9, 120.9 (J_{CF} = 272 Hz), 125.5, 115.1, 113.3, 61.2, 58.2, 54.2, 53.0, 52.5, 47.8, 41.4 (q, J_{CF} = 26.9 Hz), 32.4, 32.3, 25.7, 20.0, 18.0; MS (ESI) *m*/*z* 376.5 $(M + H)^+$. A beige solid was obtained as the dihydrochloride salt of **20**: mp 200–203 °C; $[\alpha]_D^{22}$ = +67.1° (*c* 2.01, CH_3OH). Anal. ($C_{21}H_{32}Cl_2F_3N_3O_3 \bullet H_2O$) C, H, N.

(*3R*)-*N*-[(*1S*)-1-{[4-(Difluoromethyl)piperidin-1-yl]methyl}-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (21) Dihydrochloride. Compound **60j** (994 mg, 4.66 mmol) in CH_2Cl_2 (40 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (1.0 g, 3.41 mmol) following the protocol described in General Method 1 to provide 1.22 g (73%) of the Boc-protected **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.29 Hz, 1H), 6.67 (dd, *J* = 2.07, 8.10 Hz, 1H), 6.54 (br. s., 1H), 5.52 (d, *J* = 4.71 Hz, 1H), 4.76 (br. s., 1H), 4.37–4.60 (m, 2H), 3.74–3.87 (m, 1H), 3.24 (dd, *J* = 3.01, 15.45 Hz, 1H), 2.96 (dd, *J* = 5.84, 15.26 Hz, 1H), 2.67 (br. s., 2H), 1.98–2.27 (m, 2H), 1.82 (dd, *J* = 6.12, 11.40 Hz, 2H), 1.55–1.73 (m, 3H), 1.50 (s, 9H), 1.18–1.43 (m, 2H), 0.95–1.16 (m, 1H), 0.83 (dd, *J* = 6.69, 16.67 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 155.6, 133.8, 129.2, 124.1, 118.8, 114.7, 113.0, 81.6, 59.4, 56.3, 53.2, 52.0, 51.1, 44.8, 39.7, 30.3, 28.4, 24.7, 19.1, 17.4; MS (ESI) *m*/*z* 496.6 $(M + H)^+$. Boc-deprotection was accomplished following the General Method 2b to provide compound **21** (873 mg, 90%) as the freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 9.61 Hz, 1H), 6.85 (d, *J* = 8.29 Hz, 1H), 6.57 (d, *J* = 7.35 Hz, 1H), 6.42 (s, 1H), 5.23–5.73 (m, 1H), 4.04 (td, *J* = 4.52, 9.04 Hz, 1H), 3.74 (s, 2H), 3.06 (d, *J* = 10.55 Hz, 1H), 2.81–3.01 (m, 2H), 2.38–2.65 (m, 2H), 2.24–2.37 (m, 1H), 2.02 (t, *J* = 11.11 Hz, 1H), 1.54–1.90 (m, 4H), 1.17–1.53 (m, 2H), 0.62–0.99 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 155.1, 136.6, 130.1, 124.7, 118.6, 114.1, 112.3, 59.8, 56.7, 53.8, 51.6, 50.5, 50.0, 47.4, 39.6, 30.9, 30.2, 24.5, 19.2, 17.7; MS (ESI) *m*/*z* 396.4 $(M + H)^+$. A beige solid was obtained as dihydrochloride salt, **21**•2HCl. mp 186–188 °C; $[\alpha]_D^{20}$ = +154° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{33}Cl_2F_2N_3O_2$•$H_2O$) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methoxypiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (22) Dihydrochloride. The diamine **60k** (766 mg, 3.57 mmol) and Boc-7-hydroxy-D-Tic-OH (1.26 g, 4.29 mmol) were treated according to the General

Method 1 to provide **Boc-22** (1.6 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, *J* = 9.3 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 5.94 (br s, 1H), 4.70–4.84 (m, 1H), 4.41–4.58 (m, 2H), 3.79 (br. s., 1H), 3.30 (s, 3H), 3.10–3.22 (m, 2H), 2.95–3.02 (m, 1H), 2.42–2.60 (m, 2H), 1.75–2.28 (m, 6H), 1.50 (s, 9H), 1.21–1.30 (m, 2H), 0.78–0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.7, 134.0, 134.0, 129.1, 124.2, 114.9, 113.3, 81.3, 60.4, 58.8, 55.3, 51.3, 50.8, 44.8, 30.6, 30.4, 30.2, 28.4 (3Cs), 18.9, 17.4; MS (ESI) *m*/*z* 476.6 $(M + H)^+$. **Boc-22** (1.2 g, 2.4 mmol) was treated as described in General Method 2a to remove the Boc-protection to provide 731 mg (80%) of **22** as the freebase: ^{1}H NMR (300 MHz, CD_3OD) δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 3.92–4.0 (m, 3H), 3.56–3.58 (m, 1H), 3.33 (s, 3H), 3.21–3.26 (m, 1H), 2.70–2.98 (m, 4H), 2.41–2.44 (m, 2H), 2.08–2.27 (m, 2H), 1.81–1.90 (m, 3H), 1.45–1.62 (m, 2H), 0.91–0.96 (m, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.4 156.8, 137.4, 130.9, 125.6, 115.0, 113.3, 77.7, 61.1, 58.2, 55.8, 52.5, 52.1, 50.0, 48.0, 32.6, 32.4, 31.8, 20.0, 18.0; MS (ESI) *m*/*z* 376.5 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **22**: mp 184–186 °C; $[\alpha]_D^{20}$ = +75.1° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_3 \bullet H_2O$) C, H, N.

(*3R*)-*N*-[(*1S*)-1-{[4-(Dimethylamino)piperidin-1-yl]methyl}-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (23) Trihydrochloride. Compound **60l** (994 mg, 4.66 mmol) in CH_2Cl_2 (40 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (1.4 g, 1.0 equiv) following the protocol described in General Method 1 to provide 1.94 g, (85%) of the Boc-protected **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.10 Hz, 1H), 6.53–6.71 (m, 2H), 4.72 (br. s., 1H), 4.33–4.56 (m, 2H), 3.78 (br. s., 1H), 3.11–3.28 (m, 1H), 2.95 (dd, *J* = 6.03, 15.26 Hz, 1H), 2.25 (br. s., 5H), 1.61–1.84 (m, 5H), 1.47 (s, 9H), 1.22 (t, *J* = 7.16 Hz, 1H), 0.80 (dd, *J* = 6.69, 17.99 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.6, 133.9, 129.1, 124.0,

121.8, 114.7, 112.9, 81.6, 60.4, 58.6, 56.6, 54.9, 51.6, 50.1, 44.9, 33.7, 30.7, 30.2, 28.3, 21.0, 19.2, 17.3; MS (ESI) *m*/*z* 489.7 $(M + H)^+$. Removal of the Boc protection following the General Method 2b furnished freebase **23** (1.38 g, 72%): ^{1}H NMR (300 MHz, CD_3OD) δ 6.76 (d, *J* = 8.29 Hz, 1H), 6.44 (d, *J* = 8.10 Hz, 1H), 6.34 (s, 1H), 3.73–3.87 (m, 3H), 3.42 (dd, *J* = 4.80, 9.89 Hz, 1H), 2.83–3.05 (m, 3H), 2.58–2.83 (m, 3H), 2.20–2.40 (m, 2H), 2.00–2.15 (m, 2H), 1.82–1.98 (m, 2H), 1.60–1.81 (m, 4H), 1.44–1.59 (m, 1H), 1.22–1.42 (m, 2H), 1.08 (t, *J* = 7.16 Hz, 1H), 0.93 (t, *J* = 7.16 Hz, 1H), 0.77 (t, *J* = 6.12 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.3, 156.9, 137.3, 130.9, 125.6, 115.1, 113.4, 63.8, 61.0, 58.2, 54.7, 53.5, 52.6, 47.9, 45.3, 41.8, 39.1, 35.9, 32.3, 28.9, 20.1, 18.2; MS (ESI) *m*/*z* 389.5 $(M + H)^+$. A beige solid was obtained as the trihydrochloride salt of **23**: mp 184 °C (dec); $[\alpha]_D^{20}$ = +91.6° (*c* 0.14, CH_3OH). Anal. ($C_{22}H_{39}Cl_3N_4O_2$•1.75 H_2O) C, H, N.

(*3R*)-*N*-{[(*1S*)-1-[4,4-Difluoropiperidin-1-yl]methyl]-2-methylpropyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (24) Dihydrochloride. Compound **60m** (992 mg, 4.807 mmol) in CH_2Cl_2 (40 mL) was coupled with Boc-7-hydroxy-D-Tic-OH (1.41 g, 1.0 equiv) following the protocol described in General Method 1 to provide 1.73 g, (75%) of the Boc-protected **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.10 Hz, 1H), 6.53–6.71 (m, 2H), 4.72 (br. s., 1H), 4.33–4.56 (m, 2H), 3.78 (br. s., 1H), 3.11–3.28 (m, 1H), 2.95 (dd, *J* = 6.03, 15.26 Hz, 1H), 2.25 (br. s., 5H), 1.61–1.84 (m, 5H), 1.47 (s, 9H), 1.22 (t, *J* = 7.16 Hz, 1H), 0.80 (dd, *J* = 6.69, 17.99 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.6, 133.9, 129.1, 124.0, 121.8, 114.7, 112.9, 81.6, 60.4, 58.6, 56.6, 54.9, 51.6, 50.1, 44.9, 33.7, 30.7, 30.2, 28.3, 21.0, 19.2, 17.3; MS (ESI) *m*/*z* 482.4 $(M + H)^+$.A solution of **Boc-24** (1.733 g, 4.77 mmol) in CH_3OH (20 mL) was subjected to Boc cleavage following the General Method 2b to provide freebase **24** (1.25 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 9.61 Hz, 1H), 6.90 (d, *J* = 8.29 Hz,

1H), 6.54–6.72 (m, 1H), 6.46–6.53 (m, 1H), 3.95–4.16 (m, 1H), 3.72–3.88 (m, 2H), 3.47 (dd, *J* = 5.18, 10.27 Hz, 1H), 3.02 (dd, *J* = 4.99, 16.29 Hz, 1H), 2.60–2.75 (m, 3H), 2.39–2.53 (m, 3H), 1.78–1.99 (m, 5H), 0.70–0.97 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 155.1, 136.6, 130.1, 124.8, 121.8, 114.1, 112.3, 58.9, 56.7, 51.0, 50.2, 47.3, 33.7, 30.6, 30.3, 19.3, 17.7; MS (ESI) *m*/*z* 382.8 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **24**: mp 195–197 °C; $[\alpha]_D^{20}$ = +67.9° (*c* 0.5, CH_3OH). Anal. ($C_{20}H_{31}Cl_2F_2N_3O_2 \bullet H_2O$) C, H, N.

(*3R*)-*N*-{(*1S*)-1-[(4-Cyanopiperidin-1-yl)methyl]-2-methylprolyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (25) Dihydrochloride. Diamine **60n** (470 mg, 2.41 mmol) and Boc-7-hydroxy-D-Tic-OH (705 mg, 2.41 mmol) were treated according to the General Method 1 to provide **Boc-25** (558 mg, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (br. s., 1H), 6.93–7.06 (m, 1H), 6.60–6.78 (m, 2H), 4.76 (br. s., 1H), 4.37–4.59 (m, 2H), 3.82 (br. s., 1H), 3.23 (d, *J* = 17.71 Hz, 2H), 2.88–3.03 (m, 1H), 2.05–2.60 (m, 6H), 1.57–1.82 (m, 4H), 1.38–1.56 (m, 9H), 0.66–0.91 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.5, 142.9, 134.0, 129.2, 124.2, 121.6, 114.8, 113.2, 81.0, 59.5, 51.1, 50.9, 44.8, 33.8, 30.6, 28.4, 28.4, 28.3, 28.1, 25.6, 24.9, 21.0, 19.2, 17.2; (ESI) *m*/*z* 471.4 $(M + H)^+$. A solution of **Boc-25** (300 mg, 0.64 mmol) in methylene chloride was treated with trifluoroacetic acid (1 ml) and stirred at room temperature overnight to remove the Boc-protection. The reaction mixture was concentrated, neutralized by addition of DMA80 and concentrated down again and the remaining residue was subjected to silica gel chromatography eluting with a gradient of DMA80 in CH_2Cl_2 to afford 213 mg (90%) of the freebase **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.85 Hz, 1H), 6.82–6.97 (m, 1H), 6.54–6.70 (m, 1H), 6.38–6.52 (m, 1H), 5.47 (br. s., 2H), 3.94–4.08 (m, 1H), 3.77–3.91 (m, 2H), 3.54 (dd, *J* = 5.09, 9.80 Hz, 1H), 2.88–3.02 (m, 1H), 2.43–2.85 (m, 5H), 2.30–2.42 (m, 1H), 1.72–1.94 (m, 4H), 0.82–1.06 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 155.0,

135.7, 130.1, 124.7, 121.6, 114.3, 112.4, 59.9, 56.5, 51.4, 50.5, 46.9, 31.0, 30.8, 30.0, 28.3, 25.8, 19.3, 17.7; (ESI) *m*/*z* 371.3 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **25**: mp 182 °C (dec); $[\alpha]_D^{20}$ = +82.2° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{32}Cl_2N_4O_2$•0.75 H_2O) C, H, N.

(*3R*)-*N*-{(*1S*)-1-[(4-Carbamoylpiperidin-1-yl)methyl]-2-methylprolyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (26) Dihydrochloride. Diamine **60o** (526 mg, 2.47 mmol) and Boc-7-hydroxy-D-Tic-OH (796 mg, 2.71 mmol) were reacted according to the General Method 1 to provide **Boc-26** (882 mg, 73% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–8.47 (m, 1H), 6.85–7.12 (m, 1H), 6.56–6.79 (m, 2H), 5.78–6.46 (m, 1H), 4.26–5.34 (m, 4H), 3.50–3.95 (m, 1H), 3.39 (d, *J* = 15.82 Hz, 1H), 3.10–3.31 (m, 2H), 2.74–3.07 (m, 2H), 2.64 (d, *J* = 17.14 Hz, 1H), 2.16–2.45 (m, 3H), 1.85 (dd, *J* = 26.56, 44.27 Hz, 1H), 1.38–1.56 (m, 11H), 1.12–1.31 (m, 3H), 0.69–1.05 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 180.9, 161.2, 157.5, 141.8, 136.2, 129.9, 125.1, 115.4, 114.0, 82.1, 61.5, 57.9, 54.3, 52.9, 49.9, 47.5, 45.2, 43.5, 39.0, 35.9, 32.2, 29.9, 28.8 (3C's), 19.9; MS (ESI) *m*/*z* 489.5 $(M + H)^+$. **Boc-26** (730 mg, 1.5 mmol) was treated according to the General Method 2a to provide 462 mg (80%) of the freebase **26**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.94 (d, *J* = 8.29 Hz, 1H), 6.62 (d, *J* = 8.10 Hz, 1H), 6.52 (d, *J* = 2.07 Hz, 1H), 3.95 (d, *J* = 6.22 Hz, 2H), 3.62 (q, *J* = 6.97 Hz, 2H), 2.74–3.23 (m, 5H), 2.34–2.56 (m, 2H), 1.56–2.12 (m, 4H), 1.19 (t, *J* = 7.06 Hz, 3H), 1.10 (t, *J* = 7.25 Hz, 3H), 0.80–1.04 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.1, 156.9, 136.5, 131.0, 125.3, 115.3, 113.4, 65.0, 61.3, 58.0, 55.2, 53.8, 52.0, 50.0, 47.8, 47.7, 45.4, 36.7, 32.1, 29.9, 19.9; MS (ESI) *m*/*z* 388.5 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **26**: mp 184–186 °C; $[\alpha]_D^{25}$ = +62.2° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{34}Cl_2N_4O_3$•1.5 H_2O) C, H, N.

(3*R*)-*N*-[(1*S*)-1-(3,6-dihydropyridin-1(2*H*)-ylmethyl)-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (27) Dihydrochloride. 7-Hydroxy-Boc-D-Tic-OH

(285 mg, 0.97 mmol), EDC•HCl (305 mg, 1.6 mmol), catalytic HOBt (53 mg, 0.4 mmol) and the amine **68a** (156 mg, 0.93 mmol) in CH_2Cl_2 (15 mL) were treated with NEt_3 (0.42 mL, 3.0 mmol) and reacted for 4h at room temperature. The reaction mixture was then concentrated in vacuo and purified by chromatography on silica gel eluted with a gradient of 0–35% DMA80 in CH_2Cl_2. The Boc-intermediate containing fractions were concentrated, and the residue was dissolved in CH_3OH (5 mL) and HCl (6 M, 5 mL). After 1 h, the reaction mixture was concentrated. The resulting residue was purified by chromatography on silica gel, eluting with a gradient of 0–25% DMA80 in CH_2Cl_2 to afford freebase **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, *J* = 10.36 Hz, 1H), 6.67 (d, *J* = 8.29 Hz, 1H), 6.34 (dd, *J* = 2.45, 8.10 Hz, 1H), 6.27 (d, *J* = 2.26 Hz, 1H), 5.62–5.79 (m, 2H), 4.13–4.31 (m, 1H), 3.54–3.68 (m, 1H), 3.36–3.54 (m, 2H), 3.12 (dd, *J* = 5.09, 11.87 Hz, 1H), 2.63–2.87 (m, 4H), 2.24–2.50 (m, 3H), 1.84–2.06 (m, 2H), 1.62–1.79 (m, 1H), 0.78–0.95 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 154.9, 137.4, 130.7, 125.7, 125.1, 124.1, 113.8, 111.9, 59.5, 56.6, 51.3, 50.8, 49.3, 48.6, 32.2, 29.3, 24.7, 19.3, 18.0; MS (ESI) *m*/*z* 344.4 $(M + H)^+$. The freebase was converted into 75.6 mg (20% from **68a**) of a white powder as the dihydrochloride salt: m.p ~175 °C (dec.); $[\alpha]_D^{25}$ = +75° (*c* 0.10, CH_3OH). Anal. ($C_{20}H_{31}Cl_2N_3O_2$•H_2O) C, H, N.

(3*R*)-7-hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methyl-3,6-dihydropyridin-1(2*H*)-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (28) Dihydrochloride. A solution of Boc-7-hydroxy-D-Tic-OH (78 mg, 0.25 mmol), EDC•HCl (95 mg,0.5 mmol), catalytic HOBt and the amine **68b** (33 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was treated with NEt_3 (0.21 mL, 1.5 mmol). After 12 h, the reaction mixture was concentrated and purified by chromatography on silica gel eluting with a gradient of 0–40% DMA80 in CH_2Cl_2. The Boc-intermediate containing fractions were dissolved in CH_3OH (5 mL) and HCl (6 M, 5 mL). After

1 h, the reaction mixture was concentrated. The residue was purified by chromatography on silica gel, eluting with a gradient of 0–50% DMA80 in CH_2Cl_2 to afford the freebase **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.19 (m, 1H), 6.72 (d, *J* = 8.29 Hz, 1H), 6.39 (dd, *J* = 2.54, 8.19 Hz, 1H), 6.33 (d, *J* = 2.26 Hz, 1H), 5.47 (br. s., 1H), 4.19–4.36 (m, 1H), 3.65 (s, 1H), 3.57 (s, 1H), 3.39–3.51 (m, 1H), 3.19 (d, *J* = 6.97 Hz, 1H), 2.70–2.94 (m, 4H), 2.44–2.57 (m, 1H), 2.37 (dd, *J* = 3.20, 12.43 Hz, 2H), 1.85–2.04 (m, 2H), 1.69–1.84 (m, 1H), 1.66 (s, 3H), 0.83–1.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 154.9, 137.4, 133.4, 130.8, 125.0, 118.0, 113.4, 111.8, 59.1, 56.6, 51.6, 50.8, 50.7, 49.4, 48.7, 32.2, 29.4, 22.6, 19.3, 18.0; MS (ESI) *m*/*z* 358.2 $(M + H)^+$. The freebase was converted into 32.5 mg (40%) of a white powder as the dihydrochloride salt: m.p 184–188 °C (fusion); $[\alpha]_D^{25}$ = +80° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}Cl_2N_3O_2$•1.25 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(5-methyl-3,6-dihydropyridin-1(2*H*)-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (29) Dihydrochloride. A solution of Boc-7-hydroxy-D-Tic-OH (290 mg, 1 mmol), EDC•HCl (380 mg, 2 mmol), catalytic HOBt (14 mg, 0.1 mmol) and the amine **68c** (167 mg, 0.91 mmol) in CH_2Cl_2 (10 mL) was treated with NEt_3 (0.2 mL, 1.4 mmol). After 12 h, the reaction mixture was concentrated and purified by chromatography on silica gel eluting with a gradient of 0–50% DMA80 in CH_2Cl_2. The Boc-intermediate containing fractions were concentrated, and the residue dissolved in CH_3OH (5 mL) then treated with HCl (6 M, 5 mL). After 1 h, the reaction mixture was concentrated. The residue was purified by reverse-phase chromatography on C-18 silica gel, eluting with 25% CH_3CN in water (0.1 % TFA). The product containing fraction was evaporated then applied to silica gel and eluted with 25% DMA80 in CH_2Cl_2 to afford 17.7 mg (5% from **67c**) of the freebase **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 10.17 Hz, 1H), 6.75 (d, *J* =

7.91 Hz, 1H), 6.26–6.38 (m, 2H), 5.49 (br. s., 1H), 4.29 (t, *J* = 11.49 Hz, 1H), 3.61–3.75 (m, 1H), 3.51–3.61 (m, 1H), 3.12–3.30 (m, 2H), 2.65–2.95 (m, 4H), 2.26–2.54 (m, 3H), 1.92–2.18 (m, 2H), 1.66–1.88 (m, 4H), 0.84–1.04 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 154.9, 137.4, 131.0, 130.6, 125.1, 119.9, 113.6, 111.9, 59.0, 56.6, 55.1, 49.4, 48.6, 32.1, 29.3, 24.4, 21.0, 19.2, 18.1; MS (ESI) *m*/*z* 358.3 $(M + H)^+$. The freebase was converted to a white powder as the dihydrochloride salt: mp 86–90 °C (fusion), $[\alpha]_D^{25}$ +77° (*c* 0.10, CH_3OH). Anal. ($C_{21}H_{33}Cl_2N_3O_2 \bullet H_2O$) C, H, N.

(3*R*)-*N*-{(1*S*)-1-[(4,5-dimethyl-3,6-dihydropyridin-1(2*H*)-yl)methyl]-2-methylpropyl}-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (30) Dihydrochloride. A solution of Boc-7-hydroxy-D-Tic-OH (106 mg, 0.36 mmol), EDC•HCl (112 mg, 0.59 mmol), catalytic HOBt (12 mg) and the amine **68d** (55 mg, 0.28 mmol) in CH_2Cl_2 (6 mL) was treated with NEt_3 (0.3 mL, 2.2 mmol). After 12 h, the reaction mixture was concentrated and purified by chromatography on silica gel eluting with a gradient of 0–40% DMA80 in CH_2Cl_2. The Boc-intermediate containing fractions were concentrated then the residue dissolved in CH_3OH (5 mL) and aq HCl (6 M, 5 mL). After 1 h, the reaction mixture was concentrated. The residue was purified by reverse-phase chromatography on C-18 silica gel, eluting with 20% CH_3OH in water (0.1 % TFA). The product containing fraction was evaporated then applied to silica gel and eluted with a gradient of 0–40% DMA80 in CH_2Cl_2 to afford 36.8 mg (35% over two steps) of the freebase **30**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 10.17 Hz, 1H), 6.72 (d, *J* = 8.29 Hz, 1H), 6.32 (d, *J* = 2.26 Hz, 1H), 6.26 (dd, *J* = 2.35, 8.19 Hz, 1H), 4.20–4.37 (m, 1H), 3.62–3.75 (m, 1H), 3.50–3.62 (m, 1H), 3.12–3.30 (m, 2H), 2.65–2.93 (m, 4H), 2.26–2.56 (m, 3H), 1.87–2.01 (m, 2H), 1.71–1.87 (m, 1H), 1.63 (d, *J* = 19.97 Hz, 6H), 0.82–1.05 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 155.1, 137.4, 130.6, 125.1, 125.0, 122.8, 113.3, 111.9, 58.9, 56.6, 56.0,

51.6, 49.5, 48.6, 32.1, 30.5, 29.5, 19.2, 18.1, 18.1, 16.7; MS (ESI) *m*/*z* 372.1 $(M + H)^+$. The freebase was converted into a white powder as the dihydrochloride salt: m.p. 135–139 °C (fusion); $[\alpha]_D^{25} = +74°$ (c 0.10, CH_3OH). Anal. ($C_{22}H_{35}Cl_2N_3O_2$•1.5 H_2O) C, H, N.

(3*S*)-7-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (31) Dihydrochloride. The diamine **60a** (401 mg, 2.18 mmol) and Boc-7-hydroxy-L-Tic-OH (491 mg, 1.67 mmol) were treated according to the General Method 1 to provide **Boc-31** (727 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.64 (s, 1H), 5.90–6.30 (m, 1H), 4.69–4.79 (br. s., 1H), 4.40–4.58 (m, 2H), 3.83 (br. s., 1H), 3.21 (dd, *J* = 2.5, 15.3 Hz, 1H), 2.95–3.02 (m, 1H), 2.74–2.82 (m, 2H), 2.20–2.25 (m, 2H), 1.85–1.92 (m, 2H), 1.51 (s, 9H), 1.40–1.60 (m, 3H), 1.10–1.36 (m, 6H), 0.82–0.95 (m, 4H), 0.45–0.59 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.2, 134.0, 129.1, 123.9, 114.7, 113.2, 81.1, 65.8, 59.5, 57.9, 54.3, 53.8, 51.2, 45.1, 34.1, 31.4, 30.8, 30.5, 29.6, 28.4 (3Cs), 21.8, 18.5, 16.6; MS (ESI) *m*/*z* 460.4 $(M + H)^+$. **Boc-31** (696 mg, 1.5 mmol) was treated according to the General Method 2a for removal of the Boc-protection to provide 479 mg (88%) of the freebase **31**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.90 (d, *J* = 8.3 Hz, 1H), 6.60 (dd, *J* = 8.4, 2.4 Hz, 2.91–2.98 (m, 2H), 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 3.90–4.03 (m, 3H), 3.54 (dd, *J* = 5.3, 4.4 Hz, 1H), 3.37 (s, 1H), 3.31–3.39 (m, 1H), 2.72–2.82 (m, 2H), 2.37–2.51 (m, 2H), 2.09 (td, *J* = 13.6, 2.8 Hz, 1H), 1.77–2.13 (m, 3H), 1.49–1.65 (m, 3H), 1.11–1.40 (m, 4H), 0.88–0.95 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.6, 156.9, 135.3, 137.2, 125.7, 115.1, 113.4, 61.6, 58.3, 55.9, 54.5, 51.1, 52.4, 48.3, 35.3, 32.5, 31.9, 28.9, 22.4, 19.9, 18.1; MS (ESI) *m*/*z* 360.3 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **31**: mp >230 °C; $[\alpha]_D^{22} = -37.0°$ (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2$•1.25 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-{(1*R*)-2-methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (32) Dihydrochloride. The diamine **69** (377 mg, 2.04 mmol) and Boc-7-hydroxy-D-Tic-OH (599 mg, 2.04 mmol) were treated according to the General Method 1 to provide **Boc-32** (689 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 8.1 Hz, 1H) 6.67 (d, J = 8.3 Hz, 1H), 6.65 (s, 1H), 5.97–6.41 (m, 1H), 4.71–4.80 (br. s., 1H), 4.40–4.58 (m, 2H), 3.83 (br. s., 1H), 3.18–3.24 (dd, J = 2.5, 15.3 Hz, 1H), 2.95–3.02 (m, 1H), 2.74–2.82 (m, 2H), 2.20–2.25 (m, 2H), 1.85–1.92 (m, 2H), 1.51 (s, 9H), 1.40–1.60 (m, 3H), 1.12–1.33 (m, 6H), 0.85–0.95 (m, 3H), 0.45–0.59 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.2, 134.0, 129.1, 123.9, 114.7, 113.2, 81.1, 65.8, 59.5, 57.9, 54.3, 53.8, 51.2, 45.1, 34.1, 31.4, 30.8, 30.5, 29.6, 28.4 (3Cs), 21.8, 18.5, 16.6; MS (ESI) m/z 460.4 $(M + H)^+$. **Boc-32** (689 mg, 1.5 mmol) was treated according to the General Method 2a for removal of the Boc-protection to provide 348 mg (64%) of the freebase **32**: ^{1}H NMR (300 MHz, CD_3OD) δ 6.90 (d, J = 8.3 Hz, 1H), 6.60 (dd, J = 8.4, 2.4 Hz, 1H), 6.50 (d, J = 2.5 Hz, 1H), 3.90–4.03 (m, 3H), 3.54 (dd, J = 5.3, 4.4 Hz, 1H), 3.37 (s, 1H), 3.31–3.39 (m, 1H), 2.91–2.98 (m, 2H), 2.72–2.82 (m, 2H), 2.37–2.51 (m, 2H), 2.09 (td, J = 13.6, 2.8 Hz, 1H), 1.77–2.13 (m, 3H), 1.49–1.65 (m, 3H), 1.11–1.40 (m, 4H), 0.88–0.95 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.6, 156.9, 135.3, 137.2, 125.7, 115.1, 113.4, 61.6, 58.3, 55.9, 54.5, 51.1, 52.4, 48.3, 35.3, 32.5, 31.9, 28.9, 22.4, 19.9, 18.1; MS (ESI) m/z 360.3 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **32**: mp >228 °C; $[\alpha]_D^{22}$ = +36.6° (c 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2 \bullet H_2O$) C, H, N.

(3*S*)-7-Hydroxy-*N*-{(1*R*)-2-methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (33) Dihydrochloride. The diamine **69** (353 mg, 1.92 mmol) and Boc-7-hydroxy-L-Tic-OH (511 mg, 1.74 mmol) were treated according to the General Method 1 to provide **Boc-33** (428 mg, 53.5% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96

(d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.60 (s, 1H), 6.00–6.29 (m, 1H), 4.70–4.85 (br. s., 1H), 4.40–4.61 (m, 2H), 3.86 (br. s., 1H), 3.20 (dd, *J* = 2.5, 15.3 Hz, 1H), 2.94–3.02 (m, 1H), 2.50–2.61 (m, 1H), 2.20–2.23 (m, 2H), 1.70–1.85 (m, 2H), 1.50 (s, 9H), 1.40–1.60 (m, 3H), 1.01–1.25 (m, 2H), 0.78–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 156.0, 134.0, 129.1, 124.0, 114.7, 113.1, 81.1, 59.3, 58.1, 54.3, 53.4, 51.2, 45.1, 34.1, 31.4, 34.0, 30.5, 30.3, 28.4 (3Cs), 21.8, 19.0, 17.4; MS (ESI) *m*/*z* 460.4 $(M + H)^+$. **Boc-33** (428 mg, 0.935 mmol) was treated as described in General Method 2a for removal of the Boc-protection to provide 266 mg (79%) of the freebase **33**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 11.2, Hz, 1H), 6.49 (s, 1H), 5.20–5.40 (m, 3H), 4.11–4.23 (br. s., 1H), 3.65–3.73 (m, 2H), 3.35–3.42 (m, 2H), 3.12–3.16 (d, *J* = 11.6 Hz, 1H), 2.80–2.87 (dd, *J* = 3.8, 15.8 Hz, 1H), 2.53–2.68 (m, 2H), 2.39 (t, *J* = 10.9 Hz, 1H), 2.20 (t, *J* = 10.9 Hz, 1H), 1.77–1.88 (m, 1H), 1.60–1.72 (m, 2H), 1.31–1.53 (m, 3H), 0.86–0.95 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 155.1, 136.0, 130.2, 124.4, 114.1, 112.3, 59.5, 58.0, 57.0, 55.2, 52.3, 49.4, 47.4, 32.1, 31.4, 30.0, 29.8, 21.3, 19.2, 18.1; MS (ESI) *m*/*z* 360.3 $(M + H)^+$. A pale-yellow solid was obtained as the dihydrochloride salt of **33**: mp >230 °C; $[\alpha]_D^{22}$ = –77.0° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{35}Cl_2N_3O_2$•0.5 H_2O) C, H, N.

(3*R*)-7-Hydroxy-*N*-(2-piperidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (34) Dihydrochloride. The amine 2-(1-piperidinyl)ethanamine (**70**) (0.825 g, 6.5 mmol) was added to a solution of dicyclohexylcarbodiimide (DCC) (1.36 g, 6.6 mmol), HOBt (891 mg, 6.6 mmol) and 7-hydroxy-Boc-D-Tic-OH (1.94 g, 6.6 mmol) in THF (20 mL) at 0 °C. The solution was allowed to warm to room temperature overnight, forming a suspension. The solids were filtered, and the filtrate concentrated to a residue which was partitioned between CH_2Cl_2 and satd. aq. $NaHCO_3$. The organic layer was separated and

dried (Na_2SO_4), then concentrated and the residue subjected to chromatography on silica gel eluting with a gradient of 0–50% DMA80 in CH_2Cl_2 to afford 1.62 g (62%) of the Boc-protected intermediate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.10 Hz, 1H), 6.49–6.79 (m, 1H), 6.42 (br. s., 1H), 4.64 (br. s., 1H), 4.32–4.58 (m, 1H), 3.06–3.41 (m, 2H), 2.79–3.06 (m, 1H), 2.05–2.53 (m, 4H), 1.28–1.72 (m, 11H). The Boc-protected intermediate (1.00 g, 2.6 mmol) was dissolved in MeOH (10 mL) and treated with aq HCl (6 N, 10 mL) at room temperature. After 2 h, the solution was concentrated. The residue was subjected to chromatography on silica gel eluting with a gradient of 0–50% DMA80 in CH_2Cl_2 to afford 0.35 g (44%) of the **34** freebase: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (br. s., 1H), 7.78 (t, *J* = 5.46 Hz, 1H), 6.87 (d, *J* = 8.29 Hz, 1H), 6.53 (dd, *J* = 2.54, 8.19 Hz, 1H), 6.42 (d, *J* = 2.45 Hz, 1H), 3.71–3.90 (m, 2H), 3.33 (dd, *J* = 4.80, 10.08 Hz, 1H), 3.15–3.25 (m, 3H), 2.79 (dd, *J* = 4.71, 15.82 Hz, 1H), 2.59 (dd, *J* = 10.17, 15.82 Hz, 1H), 2.19–2.45 (m, 6H), 1.44–1.58 (m, 4H), 1.39 (d, *J* = 4.90 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.4, 155.2, 136.8, 129.5, 124.3, 113.3, 111.8, 57.5, 56.2, 53.9, 46.8, 35.8, 30.1, 25.5, 24.0. The free base was converted into a pale yellow powder as the dihydrochloride salt: MS (ESI) *m*/*z* 304.5 $(M + H)^+$; mp 129–133 °C (fusion); $[\alpha]_D$ = +57° (*c* 1.2, CH_3OH). Anal. ($C_{17}H_{27}Cl_2N_3O_2 \cdot 0.5H_2O$) C, H, N.

(*3R*)-*N*-[(*1S*)-1-Cyclopropyl-2-(4-methylpiperidine-1-yl)ethyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (35) Dihydrochloride. Compound **73a** (1.24 g, 2.67 mmol) in CH_3CN (20 mL) was subjected to Boc cleavage following the General Method 2b to provide **35** (626 mg, 65%). ^{1}H NMR (300 MHz, CD_3OD) δ 6.66 (d, *J* = 8.29 Hz, 1H), 6.36 (dd, *J* = 2.07, 8.29 Hz, 1H), 6.24 (d, *J* = 1.70 Hz, 1H), 3.57–3.75 (m, 1H), 3.38 (q, *J* = 7.22 Hz, 2H), 3.24 (q, *J* = 7.03 Hz, 2H), 2.34–2.75 (m, 3H), 2.13–2.32 (m, 1H), 1.76–1.91 (m, 1H), 1.52–1.74

(m, 1H), 1.36 (td, *J* = 2.80, 5.51 Hz, 2H), 0.86–1.15 (m, 7H), 0.59–0.76 (m, 3H), -0.03–0.32 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) d 175.1, 156.8, 137.4, 130.9, 125.6, 115.1, 113.4, 66.9, 63.8, 62.9, 58.4, 56.0, 54.5, 51.7, 35.2, 31.9, 30.3, 22.5, 18.6, 16.2, 15.7; MS (ESI) *m*/*z* 358.3 $(M + H)^+$. A white solid was obtained as dihydrochloride salt of **35**: mp 162–164 °C; $[\alpha]_D^{24}$ = +62.7° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{33}Cl_2N_3O_2$•1.25 H_2O) C, H, N.

***N*-{(1*S*)-2-Methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-D-tyrosinamide 36 Dihydrochloride**. A solution of Boc-D-tyrosine (928 mg, 3.3 mmol), HOBt (0.45 g, 3.3 mmol) and dicyclohexylcarbodiimide (0.68 g, 3.3 mmol) in THF (10 mL) was stirred for 1 h, forming a suspension. A solution of (2*S*)-3-methyl-1-(4-methylpiperidin-1-yl)butan-2-amine (**60a**) (735 mg, 3.7 mmol) in THF (1.5 mL) was added then the suspension was stirred overnight at room temperature. The solids were separated by filtration and the filtrate concentrated. The residue was partitioned between EtOAc and sat. $NaHCO_3$. The organic layer was concentrated to a residue which was dissolved in CH_3OH (25 mL) and 6 N HCl (25 mL). After 12 h, the solution was concentrated by approximately half. Sodium hydroxide (5 M) was used to adjust the solution to pH 9. The aqueous was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to a residue which was subjected to chromatography on silica gel eluting with a gradient of 0–50% DMA80 in CH_2Cl_2 to afford 83 mg (7% over two steps) of the desired **36** freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.23 Hz, 1H), 7.00 (d, *J* = 8.29 Hz, 2H), 6.78 (d, *J* = 8.48 Hz, 2H), 4.02 (td, *J* = 4.36, 9.18 Hz, 1H), 3.48 (dd, *J* = 4.33, 9.42 Hz, 1H), 3.14 (dd, *J* = 4.14, 13.75 Hz, 1H), 2.78 - 2.99 (m, 2H), 2.49 (dt, *J* = 9.42, 13.75 Hz, 2H), 2.26 - 2.39 (m, 1H), 2.00–2.15 (m, 1H), 1.78–1.98 (m, 2H), 1.58 (d, *J* = 11.49 Hz, 2H), 1.10–1.43 (m, 2H), 0.79–0.94 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 155.9, 130.3, 128.8, 115.9, 59.5, 57.0, 54.8, 53.3, 50.8, 40.3, 34.0, 33.9, 30.6, 30.5, 21.8, 19.1, 17.6. The freebase was converted into a

white powder as the dihydrochloride salt: MS (ESI) *m/z* 348.0 $(M + H)^+$; mp 161–165 °C (fusion); $[\alpha]_D^{25} = -20°$ (*c* 0.10, CH_3OH). Anal. ($C_{20}H_{35}Cl_2N_3O_2$•0.75 H_2O) C, H, N.

6-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methylpipieridine-1-yl)methyl]propyl}naphthalene-2-carboxamide (37) Hydrochloride. A solution of 6-hydroxynapthalene-2-carboxylic acid (233 mg, 1.24 mmol), **60a**, (220 mg, 1.24 mmol) and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (367.1 mg, 1.48 mmol) in DMF was heated at 100 °C for 3 h then transferred to a rotovap and heated for an additional 1 hour under reduced pressure until all the solvent was evaporated. The residue was purified on silica gel eluted with ethyl acetate in hexanes to provide 96 mg (22%) of **37** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.47 (dd, *J* = 1.60, 8.57 Hz, 1H), 7.15–7.25 (m, 1H), 7.10 (d, *J* = 8.67 Hz, 1H), 6.74 (dd, *J* = 2.26, 8.85 Hz, 1H), 6.46–6.58 (m, 1H), 4.29–4.42 (m, 1H), 3.26 (d, *J* = 11.49 Hz, 1H), 2.89 (d, *J* = 11.49 Hz, 1H), 2.77 (t, *J* = 12.24 Hz, 1H), 2.36 (dd, *J* = 3.86, 12.72 Hz, 1H), 2.13 (t, *J* = 10.93 Hz, 1H), 1.85–2.03 (m, 2H), 1.69 (d, *J* = 12.62 Hz, 1H), 1.44–1.61 (m, 1H), 1.10–1.40 (m, 3H), 0.74–1.00 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 155.9, 135.9, 130.5, 128.5, 126.5, 126.4, 123.6, 118.8, 109.0, 58.7, 55.6, 51.9, 50.7, 33.6, 33.4, 31.9, 30.4, 29.7, 21.6, 19.0, 18.3; MS (ESI) *m/z* 355.4 $(M + H)^+$. A beige solid was obtained as the hydrochloride salt of **37**: mp 128–132 °C; $[\alpha]_D^{21} = +33°$ (*c* 0.11, CH_3OH). Anal. ($C_{22}H_{31}ClN_2O_2$•0.75 H_2O) C, H, N.

6-Hydroxy-*N*-{(1*S*)-2-methyl-1-[(4-methylpipieridine-1-yl)methyl]propyl}-1,2,3,4-tetrahydronaphthalene-2-carboxamide (38) Hydrochloride. A solution of 6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**74a**)[22] (378 mg, 1.833 mmol) in aqueous HBr (48%) (10 mL) and acetic acid (10 mL) was heated at reflux for 5 h then cooled. Solvent was removed in vacuo to provide 6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**74b**) which was carried on to the next step without further purification. A solution of **74b**, **60a**, (220 mg, 1.24

mg), BOP (973 mg, 2.2 mmol, 1.2 equiv), and NEt_3 (0.880 mL, 5.5 mmol, 3 equiv) in THF (20 mL) was stirred at room temperature overnight. A saturated aqueous solution of $NaHCO_3$ (50 mL) was then added to the mixture, followed by extraction using EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered over Celite and concentrated in vacuo. The residue was purified on silica gel eluted with 10% CH_3OH in CH_2Cl_2 to provide a clear oil 563 mg (86% over two steps) of **38** as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (t, *J* = 8.48 Hz, 1H), 6.48–6.70 (m, 2H), 6.02–6.22 (m, 1H), 4.02 (dt, *J* = 4.99, 9.28 Hz, 1H), 2.94–3.07 (m, 1H), 2.70–2.93 (m, 2H), 2.44–2.70 (m, 6H), 2.08–2.44 (m, 3H), 1.83–1.95 (m, 2H), 1.59–1.79 (m, 3H), 1.12–1.48 (m, 3H), 0.77–1.01 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 154.9, 136.9, 129.8, 126.0, 115.3, 113.5, 58.6, **55**.2, 52.6, 50.5, 42.2, 36.8, 33.7, 32.1, 30.7, 30.4, 28.6, 26.0, 23.3, 18.7, 17.9; MS (ESI) *m*/*z* 359.5 $(M + H)^+$. A beige solid was obtained as the hydrochloride salt of **38**: mp 118–122 (fusion) °C; $[\alpha]_D^{20}$ = +40.3° (*c* 0.3, CH_3OH). Anal. ($C_{22}H_{35}ClN_2O_2$•1.25 H_2O) C, H, N.

(*3R*)-3-[({(*1S*)-2-Methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}amino)methyl]-1,2,3,4-tetrahydroisoquinolin-7-ol (39) Trihydrochloride. A solution of **12** (113 mg, 0.314 mmol) in anhydrous THF was treated with borane dimethylsulfide (3 mmol, 0.3 mL) and heated at reflux overnight. After cooling, the mixture was quenched with CH_3OH (10 mL) and stirred at room temperature for 1 h. The mixture was treated with an aqueous 2 M HCl solution (5 mL) and heated at reflux for an additional 2 hours. The solvent was removed in vacuo and resultant crude material was purified on silica gel, eluted with CMA80 (or DMA80) in CH_2Cl_2 to provide 81.2 mg (75%) of the reduced desired product. ^{1}H NMR (300 MHz, CD_3OD) δ 6.83 (d, *J* = 8.29 Hz, 1H), 6.53 (dd, *J* = 2.45, 8.29 Hz, 1H), 6.43 (d, *J* = 2.26 Hz, 1H), 3.91 (s, 1H), 3.42–3.54 (m, 1H), 3.24 (s, 1H), 2.82–3.10 (m, 4H), 2.38–2.73 (m, 6H), 2.32 (t, *J* = 10.93 Hz, 1H), 1.66 (d, *J* =

13.00 Hz, 2H), 1.32–1.56 (m, 2H), 1.06–1.30 (m, 2H), 0.76–0.99 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.8, 135.6, 131.1, 125.2, 115.5, 113.5, 60.4, 59.3, 55.7, 55.5, 53.2, 51.8, 48.0, 33.6, 33.4, 31.9, 30.8, 30.2, 21.8, 19.6, 17.5; MS (ESI) *m*/*z* 346.4 $(M + H)^+$. The freebase was converted to the trihydrochloride salt of **39** as a white solid: mp 172 °C (sublimes); $[\alpha]_D^{20}$ = +27.3° (*c* 0.2, CH_3OH). Anal. ($C_{21}H_{38}Cl_3N_3O$•0.75 H_2O) C, H, N.

(3*R*)-*N*^{3}-{(1*S*)-2-Methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxamide (41) Dihydrochloride. Compound **73b** (993.4 mg, 2.04 mmol) was treated according to the General Method 2b for removal of the Boc-protection to provide 795 mg (100% yield) of the freebase amine **41**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (d, *J* = 9.2 Hz, 1H), 7.61 (s, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 4.04–4.21 (m, 2H), 3.76 (br. s., 1H), 3.40–3.53 (m, 2H), 3.12–3.29 (m, 2H), 2.92–3.10 (m, 2H), 2.80–2.90 (m, 1H), 1.95–1.98 (m, 2H), 1.85–1.93 (m, 2H), 1.62–1.74 (m, 1H), 1.35–1.55 (m, 3H), 0.98–1.01 (m, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 176.1, 175.3, 171.6, 138.6, 135.6, 130.1, 126.4, 118.0, 111.1, 66.5, 60.6, 58.1, 57.0, 55.0, 53.2, 50.9, 47.3, 32.0, 31.8, 21.9, 19.3, 18.0; MS (ESI) *m*/*z* 387.4 $(M + H)^+$. An off-white solid was obtained as the dihydrochloride salt of **41**: mp 185–187 °C; $[\alpha]_D^{22}$ = +69.2° (*c* 1.1, CH_3OH) Anal. ($C_{22}H_{36}Cl_2N_4O_2$•2 H_2O) C, H, N.

(*3R*)-7-Methoxy-*N*-{(*1S*)-2-methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (43) Dihydrochloride. A solution of **73c** (365 mg, 0.793 mmol) and diisopropylethylamine (1 mL, 5.00 equiv) in 5 mL CH_3CN:CH_3OH (4:1) was treated with trimethylsilyl diazomethane (1.7 mL, 2M in Et_2O, 3 equiv.) and stirred at room temperature overnight. The excess reagent was quenched with AcOH and solvent was removed in vacuo. The residue was extracted from $NaHCO_3$ with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered over Celite and concentrated in vacuo. The residue

was purified over silica gel, eluted with EtOAc in hexanes to furnish compound **Boc-43** (290 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90–7.21 (m, 1H), 6.58–6.84 (m, 2H), 5.89–6.27 (m, 1H), 4.36–4.76 (m, 3H), 3.79 (s, 1H), 3.51–3.67 (m, 1H), 3.14–3.40 (m, 1H), 2.90–3.14 (m, 1H), 2.60 (br. s., 2H), 2.00–2.28 (m, 2H), 1.63–1.97 (m, 2H), 1.39–1.60 (m, 13H), 0.91–1.34 (m, 4H), 0.76–0.89 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.6, 155.6, 134.0, 129.2, 123.7, 114.5, 113.2, 81.5, 59.3, 56.9, 56.5, 54.3, 53.5, 51.3, 45.1, 44.5, 34.2, 34.0, 30.5, 30.2, 28.3 (3C's), 21.8, 18.9, 17.4; MS (ESI) *m*/*z* 474.6 $(M + H)^+$. **Boc-43** (290 mg, 0.62 mmol) was subjected to Boc-cleavage according to General Method 2a to provide **43** (155 mg, 63%) as the freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89–7.15 (m, 2H), 6.72 (dd, *J* = 2.64, 8.29 Hz, 1H), 6.56 (d, *J* = 2.45 Hz, 1H), 3.89–4.06 (m, 2H), 3.70–3.81 (m, 3H), 3.43–3.58 (m, 1H), 3.11 (dd, *J* = 5.09, 16.20 Hz, 1H), 2.69–2.94 (m, 4H), 2.23–2.51 (m, 2H), 1.95–2.08 (m, 1H), 1.72–1.94 (m, 2H), 1.42–1.62 (m, 2H), 1.20–1.37 (m, 2H), 0.95–1.16 (m, 2H), 0.83–0.93 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 157.9, 136.8, 130.1, 126.4, 112.5, 110.5, 59.8, 56.9, 55.2, 55.1, 53.2, 50.7, 47.7, 34.4, 34.2, 30.7, 30.6, 30.3, 21.8, 19.2, 17.7; MS (ESI) *m*/*z* 374.6 $(M + H)^+$. A beige solid was obtained as the dihydrochloride salt of **43**: mp 116–120 °C; $[\alpha]_D^{25}$ = +69.8° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•0.75 H_2O) C, H, N.

(*3R*)-7-Fluoro-*N*-{(*1S*)-2-methyl-1-[(4-methylpiperidin-1-yl)methyl]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (45) Dihydrochloride. Compound **73d** (1.15 g, 2.48 mmol) was subjected to Boc-cleavage according to General Method 2b to provide **45** (588 mg, 66%) as the freebase: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97–7.23 (m, 2H), 6.83 (dt, *J* = 2.26, 8.48 Hz, 1H), 6.67–6.76 (m, 1H), 3.89–4.08 (m, 3H), 3.56 (dd, *J* = 5.27, 9.42 Hz, 1H), 3.10 (dd, *J* = 5.18, 16.29 Hz, 1H), 2.62–2.93 (m, 3H), 2.16–2.51 (m, 2H), 1.72–2.08 (m, 4H), 1.53 (t, *J* = 12.90 Hz, 2H), 1.29 (dt, *J* = 3.58, 6.97 Hz, 1H), 1.16 (dt, *J* = 3.20, 11.77 Hz, 1H), 0.97–1.10 (m,

1H), 0.83–0.95 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 161.0 (J_{CF} = 244.7 Hz), 137.6 (J_{CF} = 6.5 Hz), 130.5 (J_{CF} = 7.7 Hz), 129.8 (J_{CF} = 2.4 Hz), 113.4 (J_{CF} = 21.4 Hz), 112.0 (J_{CF} = 21.0 Hz), 59.8, 56.3, 55.0, 53.2, 50.8, 47.0, 34.5, 34.2, 30.6, 30.5, 30.2, 21.8, 19.2, 17.7; MS (ESI) *m*/*z* 362.4 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **45**: mp 172–175 °C; $[\alpha]_D^{24}$ = +68.9° (*c* 1.1, CH_3OH). Anal. ($C_{21}H_{34}Cl_2FN_3O$•1.25 H_2O) C, H, N.

(3*R*)-7-Hydroxy-2-methyl-*N*-{(1*S*)-2-methyl-1-[(4-methylpiperidin-1yl)methy]propyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide (47) Dihydrochloride. A solution of **12** (446 mg, 1.24 mmol) in dichloroethane (5 mL) was treated with formalin (0.11 mL, 1.2 equiv) followed by $NaBH(OAc)_3$ (1.2 g, 5.6 mmol). The reaction mixture was stirred at room temperature for 24 h, then partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic portion was extracted three times (3 × 30 mL), combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified on silica gel eluted with ethyl acetate/ hexanes to furnish 232 mg (50% yield) of the desired freebase **47**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 9.23 Hz, 1H), 6.91 (d, *J* = 8.10 Hz, 1H), 6.66 (dd, *J* = 2.35, 8.19 Hz, 1H), 6.56 (d, *J* = 2.26 Hz, 1H), 3.93–4.05 (m, 1H), 3.78 (d, *J* = 15.07 Hz, 1H), 3.56 (d, *J* = 15.07 Hz, 1H), 3.15–3.26 (m, 1H), 2.86–3.05 (m, 2H), 2.62–2.84 (m, 2H), 2.37–2.50 (m, 3H), 2.23–2.36 (m, 2H), 1.73–2.03 (m, 3H), 1.52 (td, *J* = 3.18, 6.64 Hz, 2H), 1.00–1.38 (m, 4H), 0.83–0.96 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 155.2, 135.4, 128.9, 124.2, 114.3, 113.1, 64.6, 59.8, 55.7, 54.8, 53.2, 51.0, 42.3, 34.4, 34.2, 30.6, 28.5, 21.9, 19.3, 17.7; MS (ESI) *m*/*z* 374.3 $(M + H)^+$. A white solid was obtained as the dihydrochloride salt of **47**: mp 186–188 °C; $[\alpha]_D^{25}$ = +61.7° (*c* 1.1, CH_3OH). Anal. ($C_{22}H_{37}Cl_2N_3O_2$•H_2O) C, H, N.

[^{35}S]GTPγS Binding Assay. The [^{35}S]GTPγS assays were conducted using the methods previously reported.[15] Briefly, the binding of the GTP analogue [^{35}S]GTPγS to membranes was

determined in a volume of 500 μL. The assay mixture contained 50 mM HEPES (pH 7.4), 100 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA·$2H_2O$, 1 mM dithiothreitol, 0.1% BSA, 10 μM GDP, test compounds, and approximately 132,000 cpm of [^{35}S]-GTPγS (0.1 nM). Human kappa (20 μg), mu (10 μg), or delta (7 μg) opioid receptor-expressing CHO cell membranes was added to each tube. For the kappa receptor assays, eight-point concentration response curves of the agonist U69,593 (31.6 μM, 10 μM, 3.16 μM, 316 nM, 100 nM, 31.6 nM, 3.16 nM, 0.316 nM final) were prepared and the dilutions were co-incubated with a single concentration of each test compound. For the mu and delta receptors, the agonists were DAMGO (31.6 μM, 10 μM, 3.16 μM, 316 nM, 100 nM, 31.6 nM, 3.16 nM, 0.316 nM final) and DPDPE (10 μM, 3.16 μM, 1 μM, 100 nM, 10 nM, 1 nM, 0.1 nM, 0.01 nM final), respectively. Following a 60 min shaking incubation at 22 °C, the assay was terminated by filtration under vacuum on a Brandel (Gaithersburg, MD, USA) 96-well harvester using pre-soaked Perkin-Elmer GF/B glass fiber filters. The filters were rinsed three times with 1 mL washes of 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 final unlabeled GTPγS. Percent specific bound (SB) was calculated using the equation % SB = (SB/MB) × 100 where maximal binding (MB) 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.

Pharmacokinetic Studies

In Vivo Study. Pharmacokinetic studies were conducted at Mispro Biotech Services (RTP, NC) and were approved by the 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" (National Research Council 2011). Male Sprague Dawley CD rats (Crl:CD(SD)) 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 Picolab 5053 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 **12** at 5 mg/kg was administered in saline (5 mg/mL) at a dose volume of 1 mL/kg. Three rats per timepoint were euthanized at 1, 4, 24, 72, and 168 h post dose by asphyxiation with CO_2 and blood was collected via cardiac puncture using K_3EDTA as anticoagulant. Plasma was prepared from blood by centrifugation at 2000g 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 were 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. Aliquots

(50 μL) of supernatant were mixed with 50 μL of mobile phase B in a new plate and analyzed by LC/MS-MS.

Standard Curve preparation. Stock solutions of **12** were prepared and diluted serially to generate standard curve and quality control spiking solutions. The concentrations in plasma were 1, 10, 50, 100, 500, and 1000 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, 5, 10, and 50 ng/mL, and 2 and 20 ng/mL for quality control samples.

LC/MS-MS conditions. Chromatography was conducted using an Agilent 1100 binary 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 CH_3CN:H_2O 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 **12** was quantitated by monitoring the transition of m/z 360.231 → 148.2, and the internal standard, buspirone, was monitored by m/z 386.243 → 122.1. MS 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. The limit of quantitation for plasma was 1.0 ng/mL, and for brain was 0.6 ng/g.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publication Website at doi: .

Experimental Details for the Synthesis of Intermediate Compounds, 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

PWO and CMK 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 manuscript, FIC overall study design, data evaluation and compilation of the final manuscript.

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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-Ala2,MePhe4,Gly-ol5]enkephalin; DPDPE, [D-Pen2,D-Pen5]enkephalin; U69,593, (5α,7α,8β)-(—)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]dec-8-yl]benzeneacetamide; EDC, 1-ethyl-3(-3-dimethylaminopropyl)carbodiimide; HOBt, hydroxybenzotriazole; AUC_{last} Area Under the Curve from the time zero to time of last measurable concentration.

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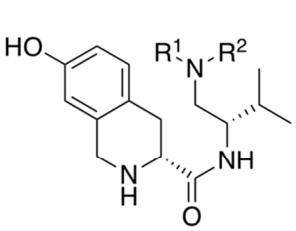
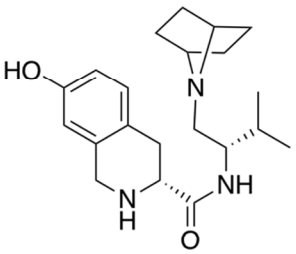
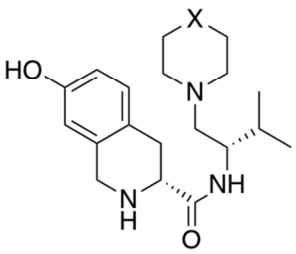
Table 1. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of the piperidine ring



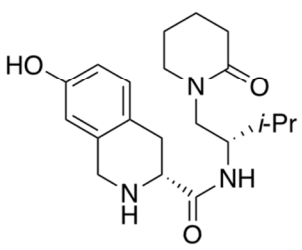
3, **4**, **8**, **9**, **10**



5



6 X=O
7 X=NCH$_3$

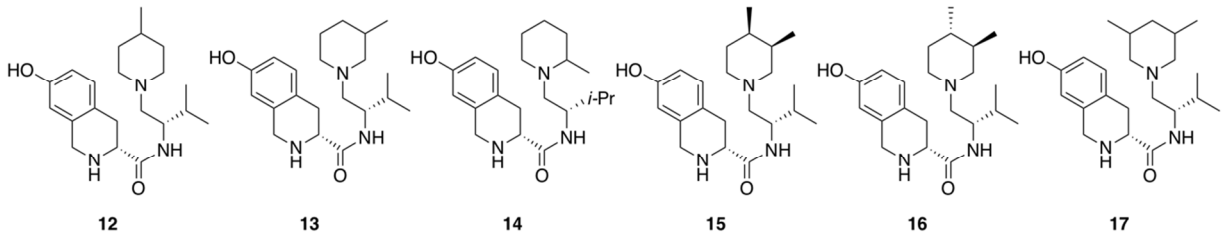


11

		K_e (nM)[a]				
compound	R^1, R^2	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
1	-$(CH_2)_5$-	144 ± 37	>3000	6.80 ± 2.1	21	>441
3	-$(CH_2)_6$-	701 ± 37	>3000	17.0 ± 4.7	41	>177
4	-$(CH_2)_4$-	702 ± 120	>3000	48.5 ± 12	14	>62
5	–	749 ± 59	>3000	2.53 ± 0.6	296	>1186
6	–	>3000	>3000	396 ± 140	>8	>8
7	–	915 ± 303	>3000	98.8 ± 28	9	>30
8	C_2H_5, C_2H_5	690 ± 110	>3000	41.8 ± 12	16.5	>72
9	C_3H_7, C_3H_7	300 ± 27	>3000	14.5 ± 0.5	20.7	>207
10	*i*-Bu, *i*-Bu	>3000	>3000	137 ± 24	>22	>22
11	–	916 ± 130	>3000	61.5 ± 9.3	>15	>49

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

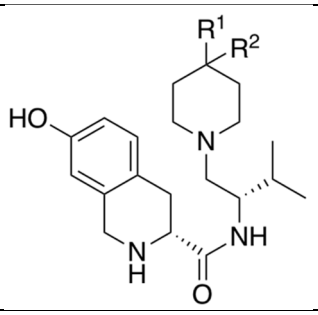
Table 2. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of methyl substituent of **1**.



	K_e (nM)[a]				
compound	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
1	144 ± 37	>3000	6.80 ± 2.1	21	>441
12	239 ± 22	>3000	0.37 ± 0.09	646	>8100
13[b]	139 ± 1.0	>3000	15.6 ± 2.3	9	>192
14[b]	44.9 ± 11	>3000	15.1 ± 4.2	3	>199
15[b]	108 ± 26	>3000	1.26 ± 0.08	86	>2381
16[b]	50.9 ± 7.7	2350 ± 390	2.3 ± 0.64	22	1022
17[b]	30.3 ± 1.0	>3000	3.46 ± 0.54	9	>867

[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] These compounds are mixtures of isomers.

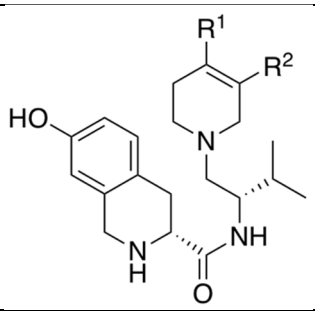
Table 3. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of the piperidine 4-methyl group



compound	R^1	R^2	K_e (nM)[a] μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
12	CH_3	H	239 ± 22	>3000	0.37 ± 0.09	645	>8100
18	CH_3	CH_3	142 ± 25	847 ± 180	3.57 ± 1.5	40	>237
19	CH_2CH_3	H	74.8 ± 23	2490 ± 620	2.48 ± 0.70	30	1004
20	CF_3	H	67.9 ± 12	>3000	4.69 ± 0.29	14	>640
21	CHF_2	H	70.9 ± 9.4	>3000	3.45 ± 1.2	21	>870
22	OCH_3	H	198 ± 48	>3000	6.53 ± 1.8	30	>459
23	$N(CH_3)_2$	H	318 ± 8.4	>3000	8.08 ± 1.2	39	>371
24	F	F	604 ± 83	>3000	11.8 ± 3.0	51	>254
25	CN	H	647 ± 150	>3000	12.7 ± 3.1	51	>236
26	$CONH_2$	H	129 ± 26	>3000	3.22 ± 0.78	40	>932

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

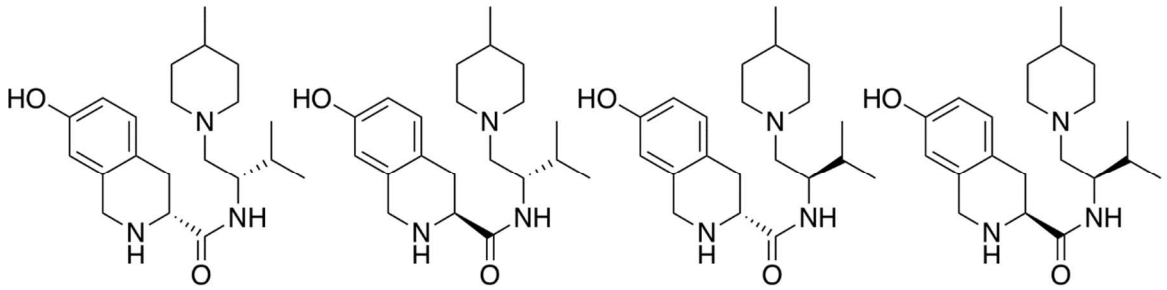
Table 4. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, effects of adding a 3,4-double bond



compound	R^1	R^2	K_e (nM)[a] μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
27	H	H	37.7 ± 7.9	>3000	1.07 ± 0.11	35	>2804
28	CH_3	H	11.8 ± 1.2	>3000	0.88 ± 0.18	13.4	>3410
29	H	CH_3	28.9 ± 3.7	>3000	9.43 ± 2.9	3	>318
30	CH_3	CH_3	1.09 ± 0.11	1930 ± 330	1.81 ± 0.27	0.6	1066

[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 for **12** and three isomers

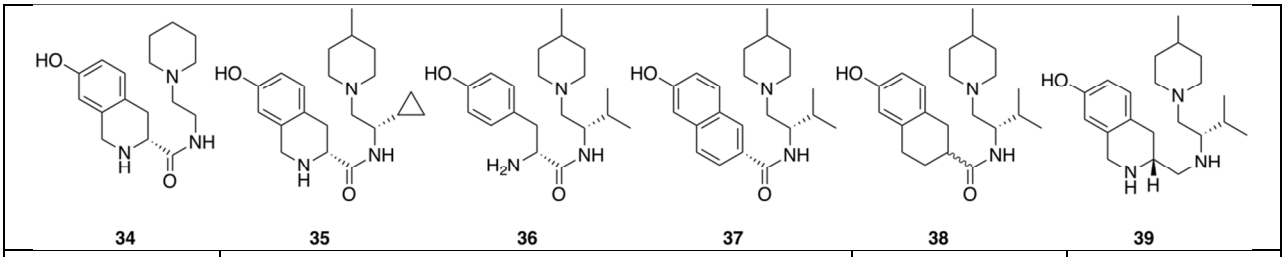


12 **31** **32** **33**

	K_e (nM)[a]				
compound	μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
12	239 ± 22	>3000	0.37 ± 0.09	645	>8100
31	955 ± 280	>3000	9.29 ± 3.2	103	>323
32	479 ± 150	>3000	11.5 ± 1.9	42	>261
33	>3000	>3000	42.8 ± 4.0	>70	>70

[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 6. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, importance of the isopropyl and 7-hydroxy-D-Tic groups

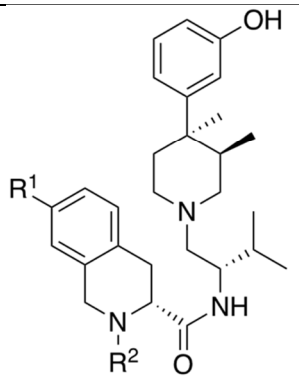


34 35 36 37 38 39

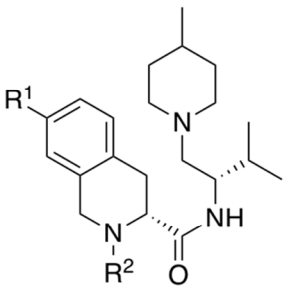
compound	K_e (nM)[a]			μ/κ	δ/κ
	μ, DAMGO	δ, DPDPE	κ, U69,593		
34	>3000	>3000	113 ± 21	>27	>27
35	586 ± 130	>3000	5.58 ± 1.6	105	>538
36	>3000	>3000	387 ± 89	>8	>8
37	431 ± 110	>3000	20.5 ± 4.6	21	>146
38	153 ± 37	>3000	11.1 ± 2.9	14	>270
39	569 ± 110	>3000	17.2 ± 5.8	33	>174

[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 7. Inhibition of agonist-stimulated [^{35}S]GTPγS binding in cloned human μ, δ, and κ opioid receptors, comparison of structural changes in JDTic to similar changes in **12**.



A



B

compound	structure	R^1, R^2	K_e (nM)[a] μ, DAMGO	δ, DPDPE	κ, U69,593	μ/κ	δ/κ
JDTic	A	OH, H	25 ± 0.01	74 ± 2	0.02 ± 0.01	1255	3800
12	B	OH, H	239 ± 22	>3000	0.37 ± 0.09	645	>8100
40[b]	A	$CONH_2$, H	7.09 ± 2.58	131 ± 23	0.02 ± 0.01	355	6550
41	B	$CONH_2$, H	41.3 ± 11	>3000	1.37 ± 0.32	30	>2190
42[b]	A	OCH_3, H	51.4 ± 15	118 ± 45	0.06 ± 0.01	857	1970
43	B	OCH_3, H	1200 ± 140	>3000	25.6 ± 6.3	47	>117
44[b]	A	F, H	7.7 ± 0.9	[c]	2.20 ± 0.47	3.5	–
45	B	F, H	>3000	>3000	182 ± 19	>17	>17
46[d]	A	OH, CH_3	210 ± 60	491 ± 120	0.16 ± 0.06	1313	3070
47	B	OH, CH_3	752 ± 140	>3000	36.7 ± 5.6	20	>82

[a] Data are mean ± SEM of at least three independent experiments conducted in duplicate. [b] Taken from ref 21. [c] This compound was an inverse agonist at the δ opioid receptor with an IC_{50} of 97 ± 7 nM and percent basal binding of 78 ± 3% (data are mean ± SEM of three independent experiments conducted in duplicate). [d] Taken from ref 25.

Table 8. Summary of calculated physiochemical properties for compounds **12, 15,** and JDTic

compound	TPSA	cLogP	logBB[a]	CNS MPO	MW
JDTic	84.83	3.60	–0.57	3.1	465.6
12	64.60	2.32	–0.46	4.5	359.5
15	64.60	2.49	–0.44	4.1	373.5

[a] Equation 6 from ref 29. [Log BB = –0.0148 × TPSA + 0.152 × log *P* + 0.139] was used for calculations of logBB values.

Table 9. Pharmacokinetic parameters for **12** in male Sprague Dawley rats

Parameter	Plasma	Brain
$t_{1/2}$ (h)	30.7	57.2
C_{max} (ng/mL or ng/g)	333	239
Tmax (h)	1	4
Clearance (mL/h/kg)	2625	234
AUC_{last} (h*ng/mL or h*ng/g)	1864	18765
AUC_{Total} (h*ng/mL or h*ng/g)	1905	21400
Ratio of Brain/Plasma AUC_{last}	10.07	

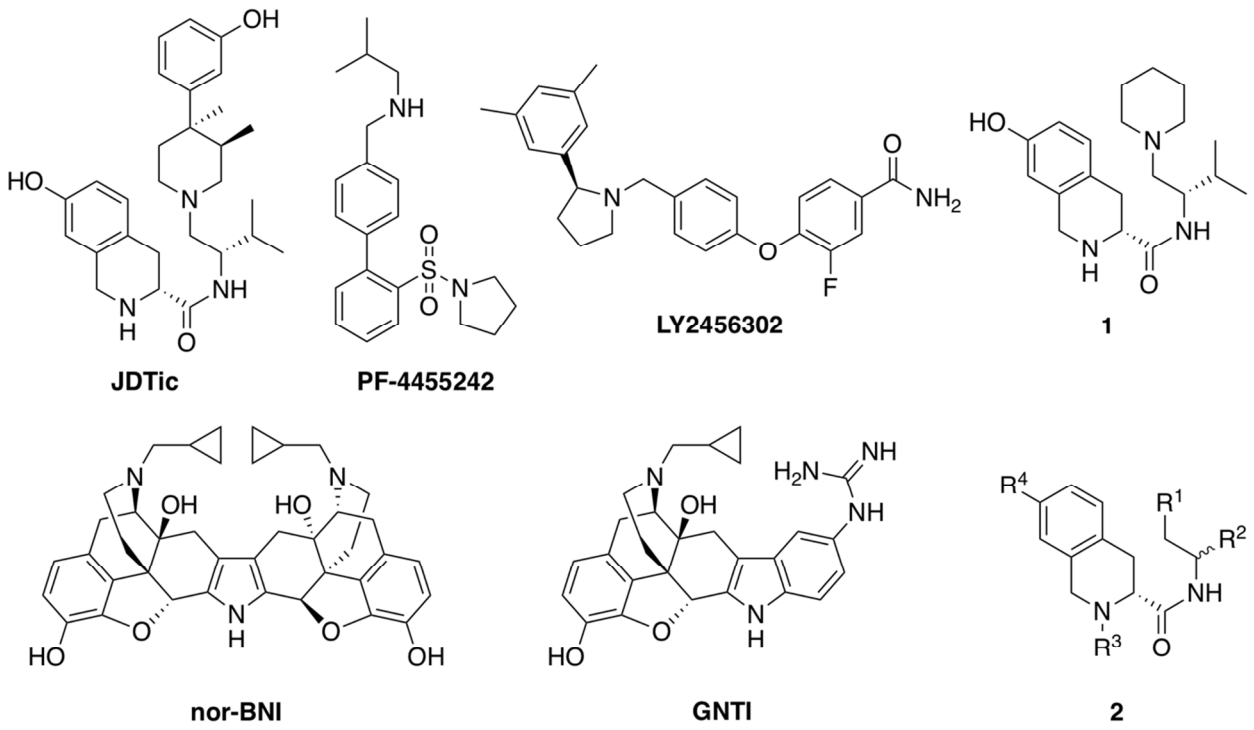


Figure 1. Structures of JDTic, PF-4455242, LY2456302, nor-BNI, GNTI, **1** and **2**

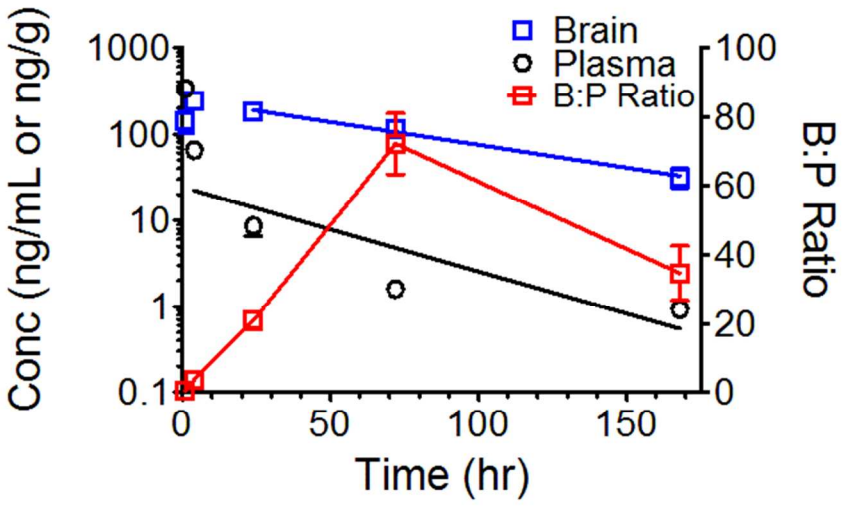
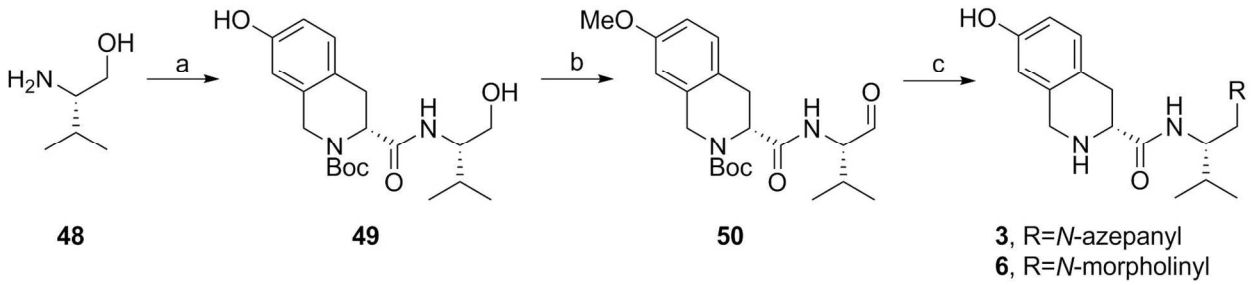


Figure 2. Concentration-time and brain to plasma ratio (B/P) plots for **12** in Sprague Dawley rats after a 5 mg/kg s.c. dose. Values represent Mean ± S.D., N = 3 for all data. Where no error bars are visible, the range is smaller than the dimension of the data point. The solid lines showing brain and plasma concentrations (left axis) are the best-fit lines to an apparent terminal elimination phase.

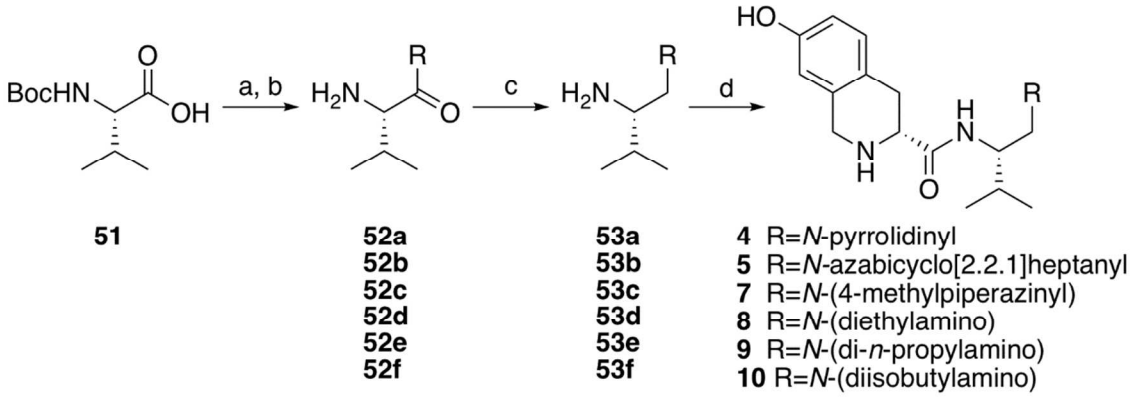
Scheme 1.[a] Synthesis of analogues **3** and **6**



48 **49** **50**

[a] Reagents and conditions: a) Boc-7-hydroxy-D-Tic-OH, DCC, HOBt, NEt_3, THF, rt, 72 h; b) i. $TMSCHN_2$, *N*,*N*-diisopropylethlamine, CH_3CN, CH_3OH, rt, overnight; ii. Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; c) i. azepane or morpholine, $NaBH(OAc)_3$; ii. BBr_3, CH_2Cl_2, –78 °C to rt overnight; iii. NH_4OH aq, reflux.

Scheme 2.[a] Synthesis of analogues **4**, **5**, and **7**–**10**



51

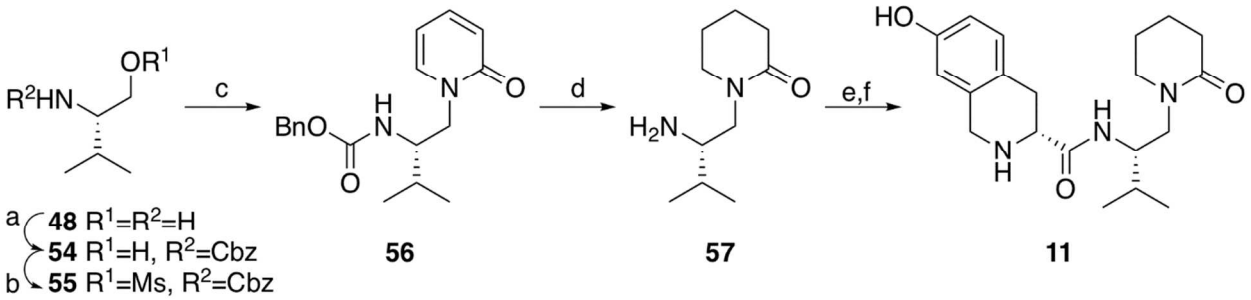
52a **52b** **52c** **52d** **52e** **52f**

53a **53b** **53c** **53d** **53e** **53f**

4 R=*N*-pyrrolidinyl
5 R=*N*-azabicyclo[2.2.1]heptanyl
7 R=*N*-(4-methylpiperazinyl)
8 R=*N*-(diethylamino)
9 R=*N*-(di-*n*-propylamino)
10 R=*N*-(diisobutylamino)

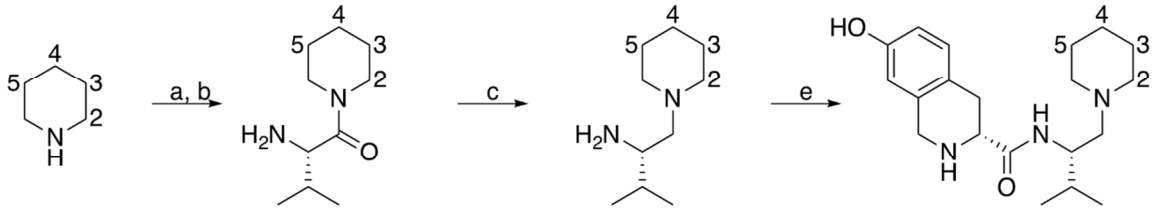
[a] Reagents and conditions: a) Appropriate amine [pyrrolidine (for **52a**), azabicyclo[2.2.1]heptane (for **52b**), 1-methylpiperazine (for **52c**), diethylamine (for **52d**), dipropylamine (for **52e**), diisobutylamine (for **52f**)], HBTU, CH_3CN, rt, overnight; b) TFA in CH_2Cl_2 (for **52a**–**52b**) or HCl (4 N in dioxane) in CH_3CN (for **52c**–**52f**); c) BH_3•SMe_2, THF, reflux, 3 h; d) i. Boc-7-hydroxy-D-Tic-OH, EDC•HCl, HOBt, NEt_3, CH_2Cl_2, rt, overnight; ii. HCl (aq) in CH_3OH (for **4**–**7**) or HCl (4 N in dioxane) in CH_3CN (for **8**–**10**).

Scheme 3.[a] Synthesis of analogue **11**



[a] Reagents and conditions: a) Benzyl chloroformate, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 0 °C to rt, overnight; b) MsCl, pyridine, CH_2Cl_2, 0 °C to rt, overnight; c) 2-Hydroxypyridine, K_2CO_3, TBAB, toluene, H_2O, reflux, overnight; d) H_2, Pd/C, CH_3OH, 40 psi, rt, 24 h; e) Boc-7-hydroxy-D-Tic-OH, EDC•HCl, HOBt, NEt_3, CH_2Cl_2, rt, overnight; f) HCl (4 N in dioxane) in CH_3CN.

Scheme 4.[a] Synthesis of analogues **12**–**26**

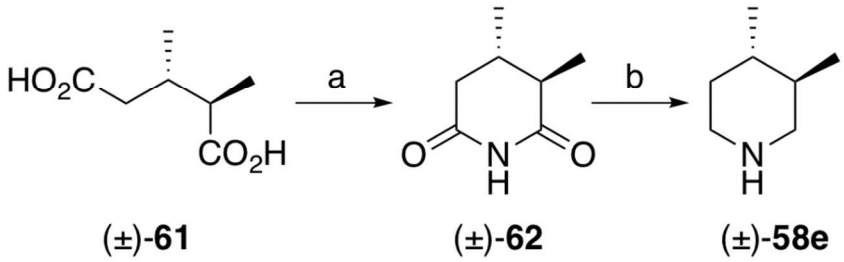


58a, 4-methyl	**59a**, 4-methyl	**60a**, 4-methyl
(±)-**58b**, 3-methyl	**59b**, 3-methyl	**60b**, 3-methyl
(±)-**58c**, 2-methyl	**59c**, 2-methyl	**60c**, 2-methyl
(±)-**58d**, 3,4-*cis*-dimethyl	**59d**, 3,4-*cis*-dimethyl	**60d**, 3,4-*cis*-dimethyl
(±)-**58e**, 3,4-*trans*-dimethyl	**59e**, 3,4-*trans*-dimethyl	**60e**, 3,4-*trans*-dimethyl
58f, 3,5-dimethyl (mixture)	**59f**, 3,5-dimethyl (mix)	**60f**, 3,5-dimethyl (mix)
58g, 4,4-dimethyl	**59g**, 4,4-dimethyl	**60g**, 4,4-dimethyl
58h, 4-ethyl	**59h**, 4-ethyl	**60h**, 4-ethyl
58i, 4-triflouromethyl	**59i**, 4-triflouromethyl	**60i**, 4-triflouromethyl
58j, 4-(difluoromethyl)	**59j**, 4-(difluoromethyl)	**60j**, 4-(difluoromethyl)
58k, 4-methoxy	**59k**, 4-methoxy	**60k**, 4-methoxy
58l, 4-(dimethylamino)	**59l**, 4-(dimethylamino)	**60l**, 4-(dimethylamino)
58m, 4,4-difluoro	**59m**, 4,4-difluoro	**60m**, 4,4-difluoro
58n, 4-cyano	**59n**, 4-cyano	**60n**, 4-cyano
		60o, 4-carboxamide

12, 4-methyl
13, 3-methyl
14, 2-methyl
15, 3,4-*cis*-dimethyl
16, 3,4-*trans*-dimethyl
17, 3,5-dimethyl (mix)
18, 4,4-dimethyl
19, 4-ethyl
20, 4-triflouromethyl
21, 4-(difluoromethyl)
22, 4-methoxy
23, 4-(dimethylamino)
24, 4,4-difluoro
25, 4-cyano
26, 4-carboxamide

[a] Reagents and conditions: a) *N*-Boc-L-valine (**51**), HBTU, CH_3CN, rt, overnight; b) HCl (4 N in dioxane) in CH_3CN, (for **59a**–**59c**, **59g**, **59i**, **59k**, **59n**) / HCl (aq) in CH_3OH (for **59e**–**59f**, **59h**, **59j**)) / TFA in CH_2Cl_2 (for **59l**–**59m**) ; c) BH_3•SMe_2 (or BH_3•THF), THF, reflux, 3 h; d) i. H_2SO_4, H_2O, at 0 °C then rt for 24 h; ii. NaOH; e) i. Boc-7-hydroxy-D-Tic-OH, EDC•HCl, HOBt, NEt_3, CH_2Cl_2, rt, overnight; ii. HCl (4 N in dioxane) in CH_3CN (for **12**–**15**, **17**–**18**, **20**–**22**, **26**) / HCl (aq) in CH_3OH (for **16**, **19**, **23**–**24**) / TFA in CH_2Cl_2 (for **25**).

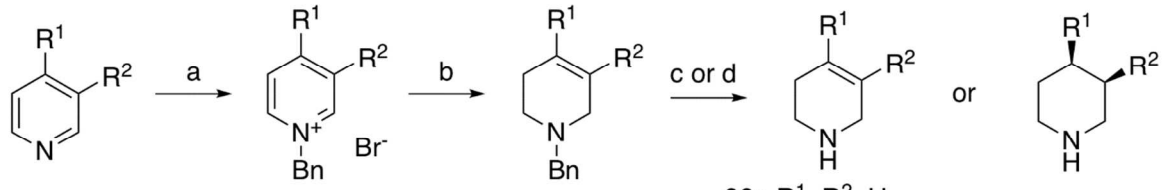
Scheme 5.[a] Synthesis of (±)-**58e**



(±)-**61** (±)-**62** (±)-**58e**

[a] Reagents and conditions: (a) Urea, 180 °C, 3 h; (b) i. BF_3•OEt_2, $NaBH_4$, THF, 2 h, at rt then at reflux, 2h; ii. piperazine, H_2O, reflux, overnight.

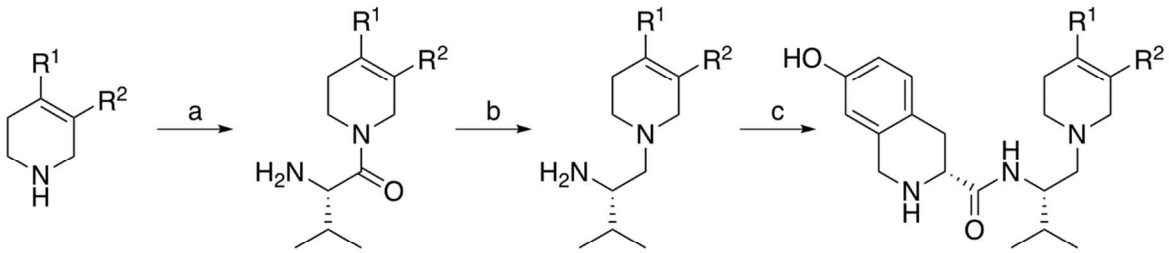
Scheme 6.[a] Synthesis of compounds (±)-**58d**, **58h** and **66a–66d**



63a R^1=CH_3, R^2=H	**64a** R^1=CH_3, R^2=H	**65a** R^1=CH_3, R^2=H	**66a** R^1=R^2=H	
63b R^1=H, R^2=CH_3	**64b** R^1=H, R^2=CH_3	**65b** R^1=H, R^2=CH_3	**66b** R^1=CH_3, R^2=H	
63c R^1=R^2=CH_3	**64c** R^1=R^2=CH_3	**65c** R^1=R^2=CH_3	**66c** R^1=H, R^2=CH_3	
63d R^1=Et, R^2=H	**64d** R^1=Et, R^2=H	**65d** R^1=Et, R^2=H	**66d** R^1=R^2=CH_3	(±)-**58d** R^1=R^2=CH_3
				58h R^1=Et, R^2=H

[a] Reagents and conditions: a) Benzyl bromide, acetone, reflux, 1 h or in a microwave, 100 °C for 5–10 minutes; b) $NaBH_4$, CH_3OH, H_2O, 0 °C then rt, overnight; c) 1-chloroethyl chloroformate, dichloroethane, reflux 12 h, then reflux with CH_3OH for 1 h (for **66b**–**66d**); d) 10% Pd/C, CH_3OH, CH_2Cl_2, H_2, rt, 50 psi, 48 h (for (±)-**58d** and **58h**).

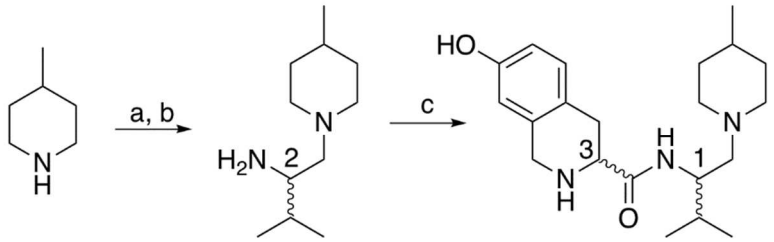
Scheme 7.[a] Synthesis of analogues **27–30**



66a $R^1=R^2=H$	**67a** $R^1=R^2=H$	**68a** $R^1=R^2=H$	**27** $R^1=R^2=H$
66b $R^1=CH_3$, $R^2=H$	**67b** $R^1=CH_3$, $R^2=H$	**68b** $R^1=CH_3$, $R^2=H$	**28** $R^1=CH_3$, $R^2=H$
66c $R^1=H$, $R^2=CH_3$	**67c** $R^1=H$, $R^2=CH_3$	**68c** $R^1=H$, $R^2=CH_3$	**29** $R^1=H$, $R^2=CH_3$
66d $R^1=R^2=CH_3$	**67d** $R^1=R^2=CH_3$	**68d** $R^1=R^2=CH_3$	**30** $R^1=R^2=CH_3$

[a] Reagents and conditions: a) i. *N*-Boc-L-Valine (**51**), HBTU, CH_3CN, rt, overnight; ii. TFA, CH_2Cl_2 (for **67a**, **67d**) / aq HCl, CH_3OH (for **67b**–**67c**); b) BH_3•SMe_2, THF, reflux, 3 h or LAH, THF, 1 h; c) i. Boc-7-hydroxy-D-Tic-OH, EDC•HCl, HOBt, NEt_3, CH_2Cl_2, rt, overnight; ii. aq HCl, CH_3OH.

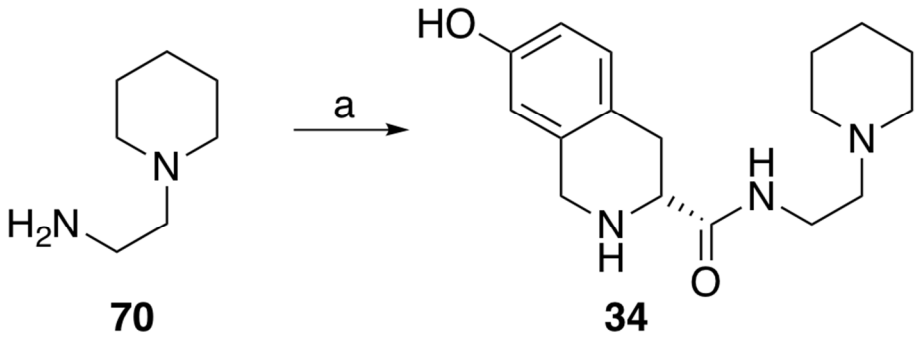
Scheme 8.[a] Synthesis of diastereomers **12** and **31–33**



58a **60a** (2*S*) **69** (2*R*) **12** (+)-(3*R*,1*S*) **31** (−)-(3*S*,1*S*) **32** (+)-(3*R*,1*R*) **33** (−)-(3*S*,1*R*)

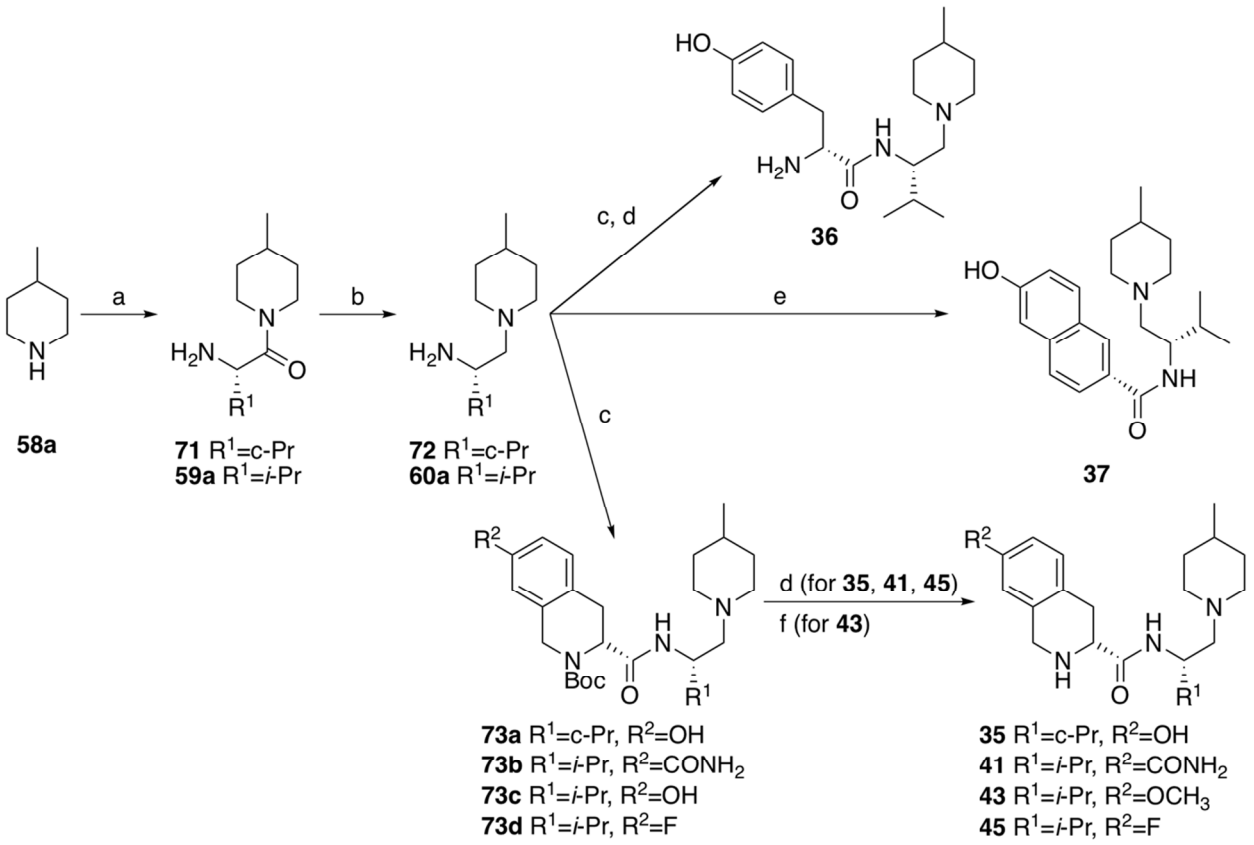
[a] Reagents and conditions: a) i. *N*-Boc-L-Valine (for **60a**) or *N*-Boc-D-Valine (for **69**), HBTU, CH_3CN, rt, overnight; ii. HCl (4 N in dioxane) in CH_3CN; b) BH_3•SMe_2, THF, reflux, 3 h; c) i. Boc-7-hydroxy-D-Tic-OH (for **12** and **32**) or Boc-7-hydroxy-L-Tic-OH (for **31** and **33**), EDC•HCl, HOBt, NEt_3, CH_2Cl_2, rt, overnight; ii. HCl (4 N in dioxane) in CH_3CN.

Scheme 9.[a] Synthesis of analogue **34**



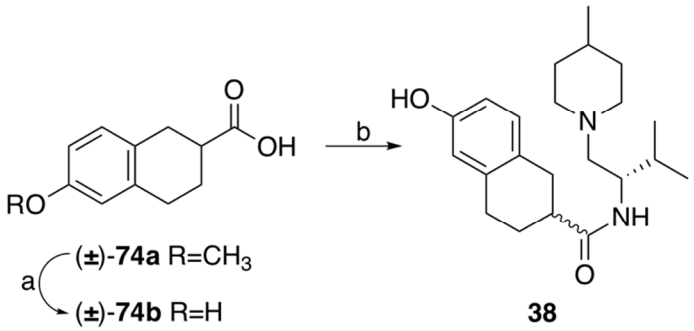
[a] Reagents and conditions: a) i. Boc-7-hydroxy-D-Tic-OH, DCC, HOBt, THF, rt, overnight; ii. aq HCl, CH_3OH.

Scheme 10.[a] Synthesis of analogues **35**–**37**, **41**, **43**, and **45**



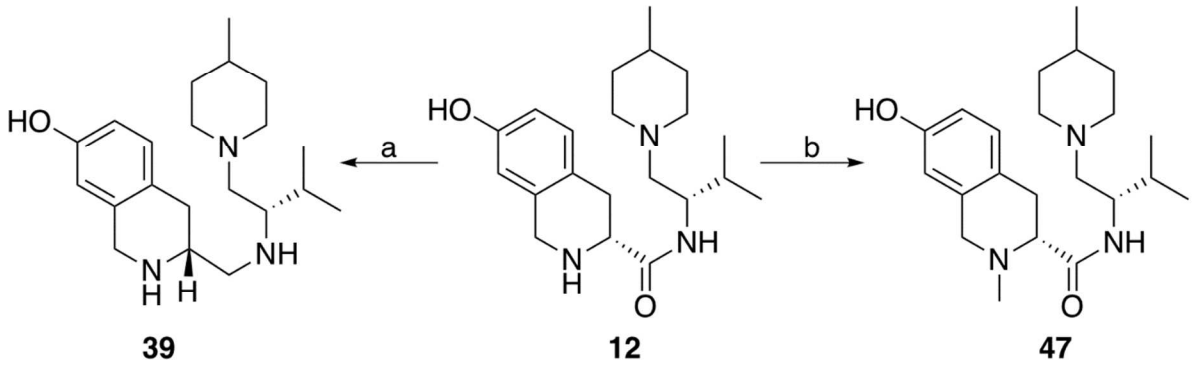
[a] Reagents and conditions: a) i. *N*-Boc-L-cyclopropylglycine (for **71**) or *N*-Boc-L-valine (for **59a**), HBTU, CH_3CN, rt, overnight; ii. HCl (4 N in dioxane) in CH_3CN; b) BH_3•SMe_2, THF, reflux, 3 h; c) Appropriate acid [Boc-D-Tyrosine (for **36**) or Boc-7-hydroxy-D-Tic-OH (for **73a** and **73c**) or Boc-7-carbamoyl-D-Tic-OH (for **73b**) or Boc-7-fluoro-D-Tic-OH (for **73d**)], DCC (for **36**) or EDC•HCl (for **73a**, **73c**–**d**) or HBTU (for **73b**), HOBt, NEt_3, DCM, rt, overnight; d) aq HCl, CH_3OH; e) 6-hydroxynaphathalene-2-carboxylic acid, EEDQ, DMF, 100 °C, 3 h; f) i. $TMSCHN_2$ (2 M in $E_{t2}O$), DIPEA, CH_3CN:CH_3OH (4:1), rt; ii. HCl (4 N in dioxane) in CH_3CN, rt, overnight.

Scheme 11.[a] Synthesis of analogue **38**



[a] Reagents and conditions: a) HBr (48% aq), AcOH, 105 °C, 5 h; b) **60a**, BOP, NEt_3, THF, rt, overnight.

Scheme 12.[a] Synthesis of analogues **39** and **47**



39 **12** **47**

[a] Reagents and conditions: a) BH_3•SMe_2, THF, reflux, overnight; b) 37% aq CH_2O, $NaBH(OAc)_3$, DCE, rt, 24 h.

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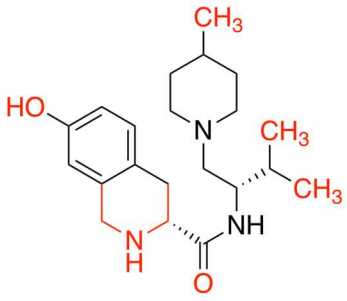
Potent and Selective Kappa Opioid Receptor Antagonists



4Me-PDTic (**12**)

KOR: K_e = **0.37** nM
MOR: K_e = **239** nM
DOR: $K_e \geq$ **3000** nM