Design, Synthesis, and Biological Evaluation of (3R)-1,2,3,4-Tetrahydro-7-hydroxy-N-[(1S)-1-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-3-isoquinolinecarboxamide (JDTic) Analogues: In Vitro Pharmacology and ADME Profile

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Supporting Information

ABSTRACT: JDTic analogues 4–15 which have the hydroxyl groups replaced with other groups were synthesized and their in vitro efficacy at the μ, δ, and κ opioid receptors determined and compared to JDTic using [35S]GTPγS assays. Compounds 4, 5, 6, 13, 14, and 15 had Kᵦ = 0.024, 0.01, 0.039, 0.02, 0.11, and 0.041 nM compared to the Kᵦ = 0.02 nM for JDTic at the κ receptor and were highly selective for the κ receptor relative to the μ and δ opioid receptors. Unexpectedly, replacement of the 3-hydroxyl substituent of the 4-(3-hydroxyphenyl) group of JDTic with a H, F, or Cl substituent leads to potent and selective KOR antagonists. In vitro studies to determine various ADME properties combined with calculated TPSA, clogP, and logBB values suggests that the potent and selective κ opioid receptors 4, 5, 13, and 14 deserve consideration for further development toward potential drugs for CNS disorders.

INTRODUCTION

The opioid receptors (μ, δ, κ, and the opioid-like receptor ORL-1) belong to the super family of G-protein coupled receptors (GPCRs) that possess seven helical trans-membrane spanning domains in their architecture.1 The majority of research efforts focused upon this group of proteins has been directed toward the μ receptor because it mediates the analgesic actions of opiates such as morphine (Chart 1).2 Over the years, however, it has become increasingly clear that the entire family of opioid proteins are actively involved in a host of important physiological processes.2

Studies with selective κ opioid receptor antagonists have shown that this system is intimately involved in brain processes that relate to stress, fear, and anxiety as well as reward-seeking behavior.3,4 Studies have shown that (3R)-1,2,3,4-tetrahydro-7-hydroxy-N-[(1S)-1-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-3-isoquinolinecarboxamide (JDTic) and nor-binaltorphimine (nor-BNI), another κ opioid selective antagonist, dose-dependently reduce fear and stress-induced responses in multiple behavioral paradigms with rodents (immobility in the forced-swim assay,5 reduction of exploratory behavior in the elevated plus maze, and fear-potentiated startle).6 Further, selective κ opioid receptor antagonists have been shown to reduce stress-induced reinstatement of cocaine self-administration in rats5 to block the stress-induced potentiation of cocaine place preference conditioning,8–10 to decrease dependence-induced ethanol self-administration,11 to attenuate the expression of both the physical (somatic signs hyperalgesia) and effective (anxiety-related behavior conditional place aversion) signs of nicotine-induced withdrawal in mice, to diminish deprivation-induced eating in rats,12 and to prevent prepulse inhibition mediated by US0,488.13 These observations regarding the behavioral consequences of receptor blockade in several animal tests suggest that κ opioid receptor antagonists could be useful for treating anxiety, depression, schizophrenia, addiction, and eating disorders.

Compounds 1 (AZ-MTAB),14,15 2 (PF-4455242),16,17 and 3 (LY2456302)18–20 have been reported as newer selective κ opioid receptor antagonists (Chart 1). See also ref 3 for a review of these studies. These newer κ opioid receptor antagonists show activity in various animal models similar to those reported for nor-BNI and JDTic. In addition, JDTic and compounds 2 and 3 have undergone phase 1 and/or phase 2 studies directed toward various CNS disorders.21–25

No drugs for the treatment of cocaine and methamphetamine abuse, however, are currently available.3 Further, nicotine replacement therapy (NRT), bupropion, and varenicline are used to treat nicotine addiction, but no more than 25% of patients respond to these treatments.26 Naltrexone is used to treat alcoholism but has limited efficacy.27 A number of antidepressants are on the market, but many patients do not...
respond to any of them. In addition, all of these therapeutic agents have undesirable side effects. Accordingly, κ opioid antagonists remain of high interest. In this study, we report the synthesis and in vitro efficacy as determined by [35S]GTP\(_{\gamma}\)S assay of JDTic analogues 4–15 (see Table 2 for structures). These compounds have the hydroxyl group on the 4-(3-hydroxyphenyl) or 7-hydroxy-tetrahydroisoquinoline parts of JDTic replaced with other functional groups. A comparison of their in vitro efficacy properties to those of JDTic show that several of the analogues were potent and selective κ opioid receptor antagonists. Preclinical ADME studies show that some of the antagonists have better drug-like properties than JDTic.
The synthesis of 4 is outlined in Scheme 1. Bis-triflate 17 was prepared by treating 16 with an excess of triflic anhydride at −78 °C. Subjection of 17 to palladium-catalyzed transfer hydrogenation in DMF at 80 °C afforded intermediate 18. Reduction of 18 with lithium aluminum hydride in toluene and tetrahydrofuran mixture cleaved the triflimide to give (3R,4R) -3,4-dimethyl-4-phenylpiperidine (19). Reductive amination of 19 with Boc-L-valinal, prepared according to the procedure reported by Skiles et al., followed by t-butoxycarbonyl (Boc) deprotection with trifluoroacetic acid in dichloromethane afforded 20. Coupling of 20 with (3R)-2-(t-butoxycarbonyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Boc-7-hydroxy-D-Tic) using N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) in dichloromethane followed by Boc deprotection with trifluoroacetic acid in dichloromethane afforded 4.

Scheme 2

Reagents: (a) phthalic anhydride, CHCl₃; (b) PhN(Tf)₂, NEt₃, CH₂Cl₂; (c) BuNH₂, JohnPhos, Pd(OAc)₂, tKBuO, tol; (d) Pd(OH)₂/C, H₂, EtOH; (e) HCl, dioxane; (f) EDC·HCl, NEt₃, Boc-7-hydroxy-D-Tic; (g) HCl, MeOH.

Scheme 3

Reagents: (a) BF₃·OEt₂, C₆H₅ONO, CH₂Cl₂, then heat, neat; (b) NaNO₂, HCl, then CuCl₂; (c) NaNO₂, HBr; then CuBr; (d) hydrazine, EtOH; (e) HBTU, CH₃CN, NEt₃, Boc-7-hydroxy-D-Tic; (f) EDC·HCl, NEt₃, Boc-7-hydroxy-D-Tic, CH₂Cl₂, HOBt; (g) HCl.
followed by removal of the Boc protecting group with hydrochloric acid in aqueous methanol, afforded the desired final product 8.

The compounds 5, 6, and 7 where the phenolic group of the 4-(3-hydroxyphenyl) group in JDTic has been replaced by a fluoro, chloro, and bromo substituent, respectively, were prepared as described in Scheme 3. The diazotization of 25 followed by Schiemann fluorination afforded 27. Alternatively, Sandmeyer halogenation of the diazo intermediate afforded the chloro and bromo intermediates 28 and 29. Subsequent deprotection of the phthaloyl protected amines present in 27, 28, and 29 using hydrazine in ethanol afforded 30, 31, and 32, respectively. These intermediates were coupled with Boc-7-fluoro-\(\alpha\)-Tic using HBTU or EDC·HCl and a catalytic amount of N-hydroxybenzotriazole (HOBt) in dichloromethane followed by treatment with hydrogen chloride to afford 10 and 12, respectively.

The synthesis of 13, 14, and 15 is illustrated in Scheme 5. The methyl ester of Boc-7-hydroxy-\(\alpha\)-Tic (33) prepared using trimethylsilyldiazomethane in methanol and toluene was converted to the intermediate aryl triflate with triflic anhydride,31 which was transformed to the benzonitrile (35) via palladium-catalyzed cyanation.32 Careful hydrolysis of the methyl ester using lithium hydroxide in aqueous dioxane, followed by addition of hydrogen peroxide to the cooled solution, resulted in a very rapid hydrolysis of the benzonitrile to the benzamide 36. The appropriate amine (21, 3-{(3R,4R)-1-[(2S)-2-amino-3-methylbutyl]-3,4-dimethylpiperidin-4-yl}benzamide, 33 or 20) could then be coupled with 36 using HBTU or EDC·HCl to afford the intermediate amides which yielded the desired compounds 13, 14, and 15 upon deprotection of the Boc group with trifluoroacetic acid in dichloromethane or hydrochloric acid in aqueous methanol.

Pharmacology. Because \(^{35}\text{S}\)GTP\(\gamma\)S binding strongly correlates with animal behavior studies of previously reported \(\kappa\) antagonists, measures of opioid receptor antagonism and specificity for the compounds in the study were obtained by monitoring the ability of selected test compounds to inhibit stimulation of \(^{35}\text{S}\)GTP\(\gamma\)S binding produced by the selective agonists (\(\beta\)-Ala\(^2\) MePhe\(^4\) Gly-ol\(^5\))enkephalin (DAMGO, \(\mu\)
receptor) cyclo[D-Pen²,D-Pen⁵]encephalin (DPDPE, δ) and 5,7,8-(−)-N₉-methyl-N₉-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]benzeneacetamide (U69,593, κ) in cloned human receptors using previously reported methods. Ke values were calculated as previously reported.

In Vitro ADME Studies. Several in vitro studies were conducted to characterize κ opioid receptor antagonists 4, 5, 13, and 14 and compared to the results from JDTic and previously reported 37 (Chart 2), which like compounds 13 and 14 has its phenol groups replaced by a carboxamido group. An in vitro model using MDCK-MDR1 cells was used to predict brain penetration. Plasma and S9 stability of each compound was determined using procedures similar to those previously reported. Compounds that interact with the human ether-a-go-go gene hERG product (which is a potassium channel) are cardiotoxic. Thus, the affinity of synthesized κ opioid receptor antagonists toward the hERG channel was determined. The interaction of these test compounds with the hERG channel was analyzed using a radioligand displacement assay based on a protocol developed by Chiu et al. For these studies, [³H]astemizole was used as the high-affinity hERG radioligand (Kᵵ ~ 20 nM). See Experimental Section for details.

Solubility of the compounds was determined using a kinetic 96-well plate assay essentially as described by Zhu et al. See Experimental Section for details.

The parallel artificial membrane permeability assay (PAMPA) was used to predict oral absorption in a 96-well format as has been described previously and detailed in the Experimental Section.

RESULTS AND DISCUSSION

In the late 1970s, Zimmerman and co-workers reported that N-methyl-trans-4-phenylpiperidine 38 (LY83577) (Chart 2) was an opioid receptor pure antagonist whose potency was significantly increased by adding a phenolic group to the aromatic ring to give the N₉-methyl-trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine 39 (LY99335) (Chart 2). In a study directed toward determining if the 3-hydroxy group present on the aromatic ring in 40 (LY255582) was required for potent antagonist efficacy, it was found that removal of the 3-hydroxy group led to 40-, 135-, and 39-fold reduction in the Ke value at the μ, δ, and κ receptors relative to 40 using [³S]GTPγS assays (Table 1). In addition, replacement of the 3-hydroxy group in 40 with 10 other functional groups all led to much reduced in vitro antagonist efficacy relative to 40, suggesting that the phenolic group was essential for the high potency of 40.

In the present studies, we demonstrate that 4, which has the hydroxyl group of the 4-(3-hydroxyphenyl) group in JDTic replaced by a hydrogen (Table 2), is a potent and selective κ opioid receptor antagonist. Compound 4 has Ke values of 8.9,
Table 2. Inhibition of Agonist-Stimulated $[^{35}S]$GTPyS Binding in Cloned Human $\mu$, $\delta$, and $\kappa$ Opioid Receptors

| compd    | $R_1$ | $R_2$ | $K_\mu$ (nM) | $K_\delta$ (nM) | $K_\kappa$ (nM) | $\mu/k$ | $\delta/k$ |
|----------|-------|-------|--------------|----------------|----------------|---------|----------|
| JDTic    | OH    | OH    | 25 ± 4       | 74 ± 2         | 0.02 ± 0.01    | 1250    | 3700     |
| 4        | OH    | H     | 8.9 ± 3      | 442 ± 130      | 0.024 ± 0.01   | 370     | 18400    |
| 5        | OH    | F     | 14.8 ± 5     | 249 ± 44       | 0.01 ± 0.004   | 1480    | 24900    |
| 6        | OH    | Cl    | 6.81 ± 2.6   | 685 ± 99       | 0.039 ± 0.001  | 175     | 17600    |
| 7        | OH    | Br    | 6.56 ± 0.44  | 594 ± 160      | 0.268 ± 0.01   | 25      | 2200     |
| 8        | OH    | NH$_2$| 10.6 ± 3.6   | 1899 ± 657     | 0.25 ± 0.09    | 42      | 7600     |
| 9        | H     | OH    | 16 ± 5       | 158 ± 49       | 4.3 ± 2        | 3.7     | 37       |
| 10       | F     | OH    | 7.7 ± 0.9    | b              | 2.20 ± 0.47    | 3.5     |          |
| 11       | H     | H     | 724 ± 146    | >3 $\mu$M      | 16 ± 7         | 45      | >188     |
| 12       | F     | F     | 360 ± 63     | b              | 2.22 ± 0.47    | 162     |          |
| 13       | CONH$_2$ | OH | 7.09 ± 2.58 | 131 ± 23       | 0.02 ± 0.005   | 355     | 6550     |
| 14       | CONH$_3$ | CONH$_2$ | 25.3 ± 7.58 | 517 ± 52       | 0.11 ± 0.02    | 230     | 4700     |
| 15       | CONH$_2$ | H   | 6.70 ± 2.1   | 111 ± 29       | 0.041 ± 0.006  | 163     | 2700     |
| 37$^a$   | OH    | CONH$_2$ | 21 ± 3       | 478 ± 75       | 0.12 ± 0.03    | 175     | 4000     |

$^a$The data represents the mean (SE) from at least three independent experiments. $^b$These compounds are weak inverse agonists at the $\delta$ opioid receptor. $^c$Data taken from ref 33.

442, and 0.024 nM at the $\mu$, $\delta$, and $\kappa$ receptors, respectively, compared to $K_e$ values of 25, 74, and 0.02 nM for JDTic. Compound 4 with 370- and 18400-fold selectivity for the $\kappa$ receptor relative to the $\mu$ and $\delta$ receptors was more selective than JDTic for the $\delta$ receptor but a little less selective than JDTic for the $\mu$ receptor. Both compounds, however, are highly selective for the $\kappa$ receptor relative to both the $\mu$ and $\delta$ receptors. This discovery is in contrast to previously reported structural activity studies of 40 as well as other compounds in this class of compounds.

Compound 5, which has a fluoro group in place of the hydrogen present in 4 or the hydroxyl group in JDTic, with $K_e$ values of 14.8, 249, and 0.01 nM at the $\mu$, $\delta$, and $\kappa$ receptors, respectively, and 1480- and 24900-fold $\kappa$ selectivity relative to the $\mu$ and $\delta$ receptors, is both a more potent and more selective $\kappa$ opioid receptor antagonist than JDTic or 4. Compounds 6 and 7 have a chloro and bromo group, respectively, in place of the hydroxyl group in JDTic. Compound 6 has a $K_e$ = 0.039 nM at the $\kappa$ receptor, with 175- and 17600-fold selectivity for the $\kappa$ relative to the $\mu$ and $\delta$ receptors and thus has good $\kappa$ potency and selectivity. Compound 7, which has the larger bromo group in place of the hydroxyl in JDTic, has a weaker $K_e$ value of 0.268 nM at the $\kappa$ receptor and only a 25-fold selectivity for the $\kappa$ receptor relative to the $\mu$ receptor. Replacement of the hydroxyl group in JDTic with the amino electron donating amino group to give 8 results in a decrease in potency at the $\kappa$ receptor ($K_e$ = 0.25 nM) and increased potency at the $\mu$ receptor ($K_e$ = 10.6 nM). This results in only 42-fold selectivity for the $\kappa$ relative to the $\mu$ receptor. Compound 8 has 7600-fold selectivity for the $\kappa$ relative to the $\delta$ receptor and thus is more selective than JDTic for the $\kappa$ relative to the $\delta$ receptor.

In a previous report, we compared the opioid receptor antagonist efficacy of compounds 41–45 (Chart 2) using the same conditions as that used in this study. The nitro (41), acetylamino (42), methanesulfonylamino (43), and amino (44) analogues were 320-, 70-, 200-, and 10-times less potent as a $\kappa$ antagonist than JDTic and were not as selective for the $\kappa$ receptor relative to the $\mu$ and $\delta$ receptors as JDTic. The methoxy (45) analogue was only 3-fold less potent than JDTic as a $\kappa$ antagonist. Compound 45 was selective for the $\kappa$ receptor relative to the $\mu$ and $\delta$ but was not as selective as JDTic.

The critical importance of a methoxy or hydroxyl group in the tetrahydroisouquinoline carbamidine (Tic) part of JDTic is further shown by the results with 9 and 10, where the Tic hydroxyl group in JDTic is replaced by a hydrogen or fluoro substituent, respectively. Compound 9 has $K_e$ values of 16, 158, and 4.3 nM at the $\mu$, $\delta$, and $\kappa$ receptors, respectively, with only 3.7- and 37-fold selectivity for the $\kappa$ relative to the $\mu$ and $\delta$ receptors. Thus, 9 is much less potent and selective as a $\kappa$ opioid antagonist than JDTic or 4 (compound 9 was previously characterized as the free base but was not evaluated for opioid antagonist efficacy under conditions used in this study). Compound 10 with $K_e$ values of 7.7 and 2.20 nM at the $\mu$ and $\kappa$ receptors, respectively, is also much less potent and selective as a $\kappa$ opioid receptor antagonist. Surprisingly, 10 behaved as a weak inverse agonist at the $\delta$ receptor.
Compound 11 can be viewed as a compound having both hydroxyl groups in JDTic replaced by a hydrogen or by replacement of the Tic hydroxyl group in 4 with a hydrogen. Viewing the change either way again shows the importance of the Tic hydroxyl group to the high κ potency and selectivity. Compound 11 with a $K_e$ value of 16 nM at the κ receptor has low potency for this receptor.

Compound 12 can be viewed as a compound having both hydroxyl groups in JDTic replaced by fluoro groups or by replacement of the Tic hydroxyl group in 5 with a fluoro group. Regardless of how 12 is viewed, its low κ potency ($K_e = 2.22$ nM compared to 0.02 nM for JDTic) shows the importance of Tic hydroxyl to the κ potency and selectivity of JDTic, 4, and 5. Similar to 10, 12 also behaved as a weak inverse agonist in the δ opioid receptor assay. Of all the JDTic analogues synthesized and evaluated herein, these are the only two compounds that are inverse agonists in the δ receptor assay.

One interesting finding from the X-ray crystallographic structure of the human κ opioid receptor is that the interaction of ligand hydroxyls with the receptor is mediated by intervening structured water molecules (Figure 1a, receptor pocket waters indicated by blue—green spheres). As illustrated in the two-dimensional KOR-JDTic interaction diagram of the 7-hydroxy-D-Tic, hydroxyl participates in hydrogen bonds with two structured water molecules which in turn interact with residues Lys227 and Tyr139 (Figure 1b). This binding arrangement suggested that replacing the ligand hydroxyls with a substituent, which could replace the structured water in the X-ray structure, both in location and hydrogen bonding capacity, would result in direct ligand-to-receptor hydrogen bonding interactions. Removing the dependency on water molecules in the receptor pocket might result in enhanced or altered properties. Three of the compounds, 13, 14, and 15, were prepared to test this hypothesis by replacing one or both of the JDTic hydroxyls with carboxamide substituents. The feasibility of this bioisosteric equivalence of a hydroxyl—water pair with a carboxamide group was tested by computational docking studies of compound 13 (in which the 7-hydroxy of 7-hydroxy-D-Tic is replaced by a carboxamide). As anticipated, the overall binding pose of compound 13 is identical to that observed for JDTic, with the 13 carboxamide group directly providing a hydrogen-bond interaction with Lys227 (Figure 2a). This two-dimensional KOR-13 interaction diagram of the docking result (Figure 2b) illustrates that 13 carboxamide interaction with Lys227 may not require an intervening water molecule.

In this study, we found that 13 had a $K_e = 0.02$ nM and thus was as potent a κ opioid receptor antagonist as JDTic (Table 2). Compound 14, which has both phenolic groups in JDTic replaced by a carboxamide group, has a $K_e = 0.11$ nM at the κ opioid receptor. All three compounds are highly selective for the κ relative to the μ and δ receptors. Compound 15 can be viewed as an analogue of 4, where the hydroxyl group in the Tic portion of 7 has been replaced by a carboxamide group. This compound with a $K_e = 0.041$ nM at the κ receptor and 163- and 2700-fold selectivity for the κ receptor relative to the μ and δ receptors, respectively, is slightly less κ potent and selective than compound 4. In previous studies, we reported that 37, which has a carboxamide group replacing the hydroxyl of the 4-(3-hydroxyphenyl) group, has a $K_e = 0.12$ nM at the κ receptor, which was only 6 times less potent than JDTic as a κ opioid receptor (KOR) antagonist (Table 2).

Calculated physiochemical properties such as topological polar surface area (TPSA), lipophilicity (clogP), and derived values such as logBB are useful indicators of a compound’s potential to penetrate the brain. These molecular descriptors were calculated for JDTic, previously reported 37, as well as 4, 5, 13, and 14 (Table 3). In general, CNS drugs have clogP in the range 2—4, TPSA less than 76 Å², and logBB greater than $-1$. The lead compound, JDTic, which proceeded through phase 1 clinical studies, has a TPSA = 84.83, which is larger than 76 Å². Compounds 13, 14, and 37, with TPSA values of 107.69, 130.55, and 107.69, respectively, are also above the 76 Å². Compounds 4 and 5 both have TPSA values of 64.6, which is less than 76 Å². JDTic and all of the analogues except 5 had clogP values of less than 4. Even 5 had a clogP = 4.15, just above the recommended threshold. JDTic, 4, and 5 have logBB values of $-0.57$, $-0.23$, and $-0.19$ and thus are greater than $-1$, predicting good brain penetration. Compounds 13, 14, and 37 with logBB values of $-0.98$, $-1.39$, and $-1.02$, are predicted to have poorer brain penetration.

Compounds that interact with the human ether-a-go-go gene (hERG) product, which is a potassium channel, can produce QT
Conclusions: These studies provide the unexpected finding that replacement of the 3-hydroxyl substituent of the 4-(3-hydroxyphenol) group of JDTic with either a hydrogen, fluoro, or chloro group leads to \( \kappa \) opioid receptor antagonists that are as highly potent and selective as JDTic. This finding is in contrast to what would have been predicted based on structure–activity relationship studies of other \( N \)-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)piperidines such as 40 (LY255582),42 as well as much of the SAR studies reported for opioid ligands in general. The high \( \kappa \) opioid receptor potency and selectivity relative to the \( \mu \) and \( \delta \) opioid receptors of 4, 5, and 14 combined with their favorable hERG, MDCK, PAMPA, solubility, and plasma and S9 stability in vitro preclinical studies and calculated TPSA, cLogP, and logBB values suggest that the compounds should be considered for further development as potential drugs for treating depression, anxiety, schizophrenia, and addiction (cocaine, nicotine, methamphetamine, alcohol, and eating disorders).

Experimental Section:
Melting points were determined using a MEL-TEMP II capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (\(^1\)H NMR and \(^{13}\)C NMR) spectra were obtained on a Varian spectrometer.
Avance DPX-500 MHz NMR spectrometer or a Bruker Unity Inova 300 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) with reference to internal solvent. Mass spectra (MS) were conducted on a PerkinElmer Mass Spec API 150 EX mass spectrometer equipped with ESI (turbospray) source. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. The purity of the compounds (>95%) was established by elemental analysis. Optical rotations were measured on an AutoPolarimeter, purchased from Rudolf Research. Analytical thin-layer chromatography (TLC) was carried out using EMD silica gel 60 F254 TLC plates. TLC visualization was achieved with a UV lamp or in an iodine chamber. Flash column chromatography was done on a CombiFlash Companion system using ISCO prepacked silica gel columns or using EM Science silica gel 60A (230–400 mesh). Solvent system: CMA80 18:2 CHCl3:MeOH:conc NH4OH. Unless otherwise stated, reagent-grade chromatography was done on a CombiFlash Companion system using CHCl3:MeOH. Analytical thin-layer chromatography (TLC) was conducted on a PerkinElmer Sciex AP1 150 EX mass spectrometer. Chemical shifts are reported in parts per million (M). 1H NMR and 13C NMR (75 MHz, CDCl3) δ 173.3, 154.9, 136.6, 130.2, 128.1, 125.7, 125.5, 125.4, 121.2, 112.3, 59.6, 57.1, 51.5, 50.7, 47.9, 38.8, 38.4, 30.9, 30.7, 30.4, 27.7, 19.1, 17.8, 16.3. MS (EI) m/z 450.7. The free base was converted to dihydrochloride salt (100 mg, 34% over two steps) as a white powder. 19F NMR (282 MHz, DMSO-d6) δ −112.97; mp 219–223 °C (fusion); [α]D 25° = +174 (c 0.4, CH3OH). Anal. (C32H43Cl2N3O2·2H2O) C, H, N.

### Table 4. In Vitro ADME Data

| compd      | hERG (Kₐ, μM) | MDCCK (%) | solubility (μM) | plasma stability (% of parent) | S9 stability (% of parent) | PAMPA (%) |
|------------|---------------|------------|-----------------|-------------------------------|----------------------------|------------|
| JTDC      | 8.820         | 11         | 11              | 11                            | 11                         | 26.8       |
| 4          | 7.05          | 27         | 11              | 42                            | 59                         | 76         |
| 5          | 6.25          | 6          | 10              | 47                            | 35                         | 92         |
| 13 > 10   | 10            | 18         | 38              | 77                            | 84.7                       | 91.5       |
| 14 > 10   | 10            | 14         | 81              | 100                           | 53.3                       | 92.6       |
| 37 > 10   | 10            | 2          | 54              | 36                            | 85                         | 82         |

"Percent transported from the optical to basal side."
2.10, 2.27 (d, J = 8.1 Hz, 1H), 2.64–2.66 (m, 6H), 2.58–2.59 (m, 3H), 2.54 (d, J = 4.7 Hz, 2H), 2.26 (m, 1H), 1.98 (s, 1H), 1.87 (s, 2H), 2.27 (d, J = 12.2 Hz, 1H), 2.17 (s, br, 1H), 1.98 (s, 1H), 1.87 (s, 2H), 1.49 (d, J = 12.2 Hz, 1H), 0.97–1.38 (m, 3H), 0.70–0.91 (m, 6H), 0.62 (d, J = 6.8 Hz, 3H). 13C NMR (CDCl3, δ = 173.1, 154.5, 152.5, 136.8, 130.2, 129.7, 128.9, 128.5, 125.6, 124.4, 124.2, 114.0, 112.2, 59.4, 56.8, 55.3, 51.2, 50.7, 55.2, 51.1, 50.6, 49.7, 38.7, 38.6, 30.6, 30.3, 27.5, 19.2, 17.6. MS (ESI) m/z 528.6 (M + H)⁺. The free base was converted to the dihydrochloride salt: [α]D = +98.0 (c 0.61, MeOH). Anal. (C23H31BrCl2O3SiH2O) C, H, N.

(3R)-N-[1-(115)-1-[(3R,4R)-4-(3-Aminophenyl)-3,4-dimethylpiperidin-1-yl]-methyl]-2-methylpropyl]-7-hydroxy-1,2,3,4-tetrahydroquinoline-3-carboxamide (8) Trihydrochloride. To a solution 26 (125 mg, 0.43 mmol) in CH2Cl2 (10 mL) was added Boc-7-hydroxy-n-Tic (125 mg, 0.43 mmol), HOBT (10 mg, 0.01 mmol), and EDG-HCl (191 mg, 1.0 mmol), followed by the addition of diisopropylethylamine (0.15 mL, 0.88 mmol). The resulting white MS was stirred at room temperature for 12 h then washed with saturated aqueous NaHCO3 (5 mL). The aqueous layer was extracted once with EtOAc (15 mL). The combined organic layers were washed with brine (5 mL), dried (Na2SO4), and concentrated. The resulting residue was purified by chromatography on silica gel using a gradient up to 50% CMA80 in CH2Cl2 as the eluent. The product containing fractions were combined and concentrated to afford 174 mg (72%) of the Boc-protected intermediate. The intermediate was then dissolved in CH2OH (10 mL) to which aq HCl (6 N, 10 mL) was added. The resulting solution was stirred for 12 h then concentrated. The concentrated residue was subjected to chromatography on silica gel using a gradient up to 50% CMA80 in CH2Cl2 as the eluent to afford 8 free base. 1H NMR (300 MHz, CDCl3) 6.89–7.18 (m, 2H), 6.85 (d, J = 8.3 Hz, 1H), 6.41–6.72 (m, 5H), 4.02 (dt, J = 4.6, 9.1 Hz, 1H), 3.82 (s, 2H), 3.38–3.48 (m, 2H, 3.02 (d, J = 4.7, 16.2 Hz, 1H), 2.51–2.79 (m, 3H), 2.36–2.51 (m, 3H), 2.10–2.35 (m, 2H), 1.79–2.00 (m, 2H, 1.50 (d, J = 12.6 Hz, 1H), 1.16–1.31 (m, 3H), 0.83–0.98 (m, 6H, 0.66 (d, J = 6.8 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ = 173.1, 154.9, 151.3, 148.5, 136.0, 134.8, 128.8, 124.9, 116.4, 114.2, 112.9, 112.4, 59.4, 56.8, 55.3, 51.2, 50.7, 47.6, 38.7, 38.2, 30.7, 30.5, 30.1, 27.3, 19.7, 17.6. The free base was then converted to the dihydrochloride salt (suspended in 32 mg, 124 mg, 0.86 mmol), according to two steps of two powder. MS (ESI) m/z 468.5 (M + H)⁺. The free base was converted to the dihydrochloride salt (90.7 mg, 15% over two steps) as a white powder: mp 202–206 °C (fusion); [α]D = +93 (c 0.1, CH3OH). Anal. (C23H31BrCl2O3SiH2O) C, H, N.

(3R)-N-[1-(115)-1-[(3R,4R)-3,4-Dimethylphenylpiperidin-1-yl]-methyl]-2-methylpropyl]-1,2,3,4-tetrahydroquinoline-3-carboxamide (11) Dihydrochloride. The amine 20 (137 mg, 0.50 mmol), Boc-7-n-Tic (152 mg, 0.55 mmol), HBTU (208 mg, 0.55 mmol), and NEt3 (280 µL, 2.2 mmol) were stirred in CH2Cl2 (1 mL) for 12 h. The concentrated residue was subjected to chromatography on silica gel using a step gradient up to 50% CMA80 in CH2Cl2; the eluent to afford 11 free base. 1H NMR (300 MHz, CDCl3) δ = 7.06–7.22 (m, 2H), 7.01 (dd, J = 5.8, 8.3 Hz, 1H), 6.61–6.86 (m, 5H, 4.9H), 4.09 (s, 2H, 3.95, 3.52 (dd, J = 4.9, 10.6 Hz, 1H, 3.14 (dd, J = 4.8, 16.5 Hz, 1.2H, 2.61–2.82 (m, 3H), 2.27–2.55 (m, 4H), 2.11–2.27 (m, 1H), 1.80–1.98 (m, 2H, 1.52 (d, J = 12.8 Hz, 1H, 1.25 (s, 3H, 0.92 (J = 7.7 Hz, 6H), 0.66 (d, J = 6.8 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ = 172.9, 161.2 (d, J = 245 Hz), 156.9, 151.4, 157.4 (J = 6.5 Hz, 1H), 150.7 (J = 7.8 Hz, 129.7 (J = 2.9 Hz, 129.1, 117.3, 113.6 (J = 12.2 Hz, 113.1, 112.6, 112.1, 10.21 (J = 2.1 Hz, 111.6, 59.6, 56.7, 55.7, 51.3, 50.6, 47.6, 38.8, 38.4, 30.8, 30.7, 30.3, 27.5, 19.6). MS (ESI) m/z 468.5 (M + H)⁺. The free base was converted to the dihydrochloride salt (90.7 mg, 15% over two steps) as a white powder: mp 202–206 °C (fusion); [α]D = +93 (c 0.1, CH3OH). Anal. (C23H31BrCl2O3SiH2O) C, H, N.

(3R)-7-Fluoro-N-[1-(115)-1-[(3R,4R)-4-(3-Fluorophenyl)-3,4-dimethylpiperidin-1-yl]-methyl]-2-methylpropyl]-1,2,3,4-tetrahydroquinoline-3-carboxamide (12) Dihydrochloride. The amine 30 (24.2 mg, 0.083 mmol) and acid 7-fluoro-Boc-n-Tic (55.7 mg, 0.19 mmol) were combined in CH2Cl2 (8 mL) and treated with EDG-HCl (40 mg, 0.2 mmol) then NEt3 (0.10 mL, 0.72 mmol). After 12 h, the concentrated residue was subjected to chromatography on silica gel using a gradient up to 50% CMA80 in CH2Cl2; the product containing fractions were concentrated then treated with MeOH (5 mL) and aq HCl (6 N, 5 mL). After 1 h, the concentrated residue was subjected to chromatography on silica gel using a gradient up to 75% CMA80 in CH2Cl2, as the eluent to afford 12 free base. 1H NMR (300 MHz, CDCl3) δ = 7.19–7.29 (m, 1H), 6.98–7.14 (m, 3H, 6.93 (J = 2.1, 11.3 Hz, 1H, 6.84 (tt, J = 2.8, 8.3 Hz, 2H, 6.73 (dd, J = 2.6, 9.0 Hz, 1H), 3.94–4.10 (m, 3H, 3.51 (dd, J = 4.9, 10.6 Hz, 1H), 3.15 (dd, J = 5.0, 16.5 Hz, 1H), 2.58–2.85 (m, 3H, 2.06–2.54.
2.94 (m, 2H), 2.73 (m, 1H), 2.51 (m, 5H), 1.89 (dd, J = 7.72 Hz, 6H), 0.53 (d, J = 12.06 Hz, 1H), 2.23 (m, J = 13.36 Hz, 1H), 2.12–2.51 (m, 1H), 1.89 (dd, J = 6.97, 12.24 Hz, 1H), 1.58 (d, J = 12.06 Hz, 1H), 1.19–1.33 (m, 3H), 0.92 (t, J = 7.72 Hz, 6H), 0.53 (d, J = 6.78 Hz, 3H).

13C NMR (75 MHz, CDCl3) δ 172.2, 172.1, 170.2, 169.4, 151.1, 138.8, 136.2, 133.2, 131.1, 129.4, 128.3, 125.1, 125.0, 124.7, 124.1, 59.9, 55.9, 55.0, 51.3, 50.8, 46.9, 38.7, 38.5, 30.7, 30.6, 27.4, 19.2, 17.9, 16.2. MS (ESI) m/z 470.9 (M + H)+. The free base was converted to the dihydrochloride salt as a pale-yellow powder: mp 210–215 °C (fusion), [α]D +101 (c 0.50, CH0H). Anal. (C20H22Cl2N6O4·2H2O) C, H, N.

(3R)-N1-[[151-1]-(3R,4R)-4-(3-Hydroxyphenyl)-3,4-dimethyl-piperidin-1-yl)methyl]-2-methylpropyl]-1,2,3,4-tetrahydroisoquinoline-3,7-dicarboxamide (15) Dihydrochloride. To a solution of 20 (100 mg, 0.3 mmol) in CH2Cl2 (10 mL) was added 36 (100 mg, 0.3 mmol), HOBt (10 mg, 0.1 mmol), and EDC-HCl (75 mg, 0.4 mmol), followed by the addition of diisopropyl ethylamine (0.26 mL, 1.5 mmol). The cloudy solution was filtered. The resulting residue was washed with saturated aqueous NaHCO3 (10 mL). The aqueous layer was extracted with CH2Cl2·THF (2:1, 20 mL x 2). The combined organic layers were dried with brine (5 mL), filtered through silica gel, and concentrated up to 40% CMA80 in CH2Cl2 as the eluent. The product containing fractions were concentrated and added 134 mg of the Boc-protected intermediate. The intermediate was then dissolved in CH2OH (10 mL) to which aq HCl (6 N, 10 mL) was added. The resulting solution was stirred 1 h, and the resulting residue was subjected to chromatography on silica gel using a gradient up to 75% CMA80 in CH2Cl2 to afford 15 free base. 1H NMR (300 MHz, CDCl3) δ 7.38–7.51 (m, 2H), 6.95–7.28 (m, 9H), 5.93–6.34 (m, 2H), 3.84–4.04 (m, 1H, 2.94 (dd, J = 5.0, 10.3 Hz, 1H), 3.11 (dd, J = 4.8, 17.1 Hz, 1H), 2.62–2.83 (m, 2H), 2.55 (d, J = 10.7 Hz, 1H), 2.30–2.46 (m, 3H), 2.08–2.29 (m, 2H), 1.75–1.99 (m, 2H), 1.51 (d, J = 12.2 Hz, 1H), 1.13–1.28 (m, 3H), 0.74–0.94 (m, 6H), 0.56 (d, J = 6.8 Hz, 3H). 13C NMR (75 MHz, CDCl3) δ 172.2, 169.3, 150.1, 138.8, 136.2, 131.1, 129.4, 128.0, 125.4, 125.3, 125.0, 59.5, 56.3, 55.2, 51.6, 50.9, 47.4, 38.6, 38.4, 31.0, 25.7, 27.5, 17.1, 16.7, MS (ESI) m/z 477.5 (M + H)+. The free base was converted to the dihydrochloride salt, which was sonicated in EtOAc. The solvent was decanted and the solids dried under nitrogen to afford 43 mg (24% over two steps) as a white powder: mp 218–222 °C (fusion), [α]D +105 (c 0.195, CH0H). Anal. (C18H16ClN2O2·2H2O) C, H, N.

3-(3R,4R)-3,4-Dimethyl-1-(trifluoromethane-sulfonyl)piperidin-4-yl)phenyl trifluoromethanesulfonate (17). The title compound was prepared by the addition of trifluoromethanesulfonic anhydride (3.4 mL, 20 mmol) to 3-(3R,4R)-3,4-dimethyl-piperidin-4-yl)phenol (16) (1.0 g, 4.9 mmol) and diisopropyl ethylamine (5.1 mL, 29 mmol) in CH2Cl2 (30 mL) at −78 °C. The solution was allowed to warm to room temperature, quenched with a brine wash, and concentrated. The resulting residue was dissolved in diethyl ether. The ether layer was washed with 1 M HCl, aq NaHCO3 or brine, and then dried. After drying (NaSO4), concentration afforded 17 in quantitative yield. 1H NMR (300 MHz, CDCl3) δ 7.41–7.48 (m, 1H), 7.24–7.32 (m, 1H), 7.11–7.19 (m, 2H), 4.01 (d, J = 13.2 Hz, 1H), 3.54–3.71 (m, 2H), 3.31–3.45 (m, 1H), 2.36 (dt, J = 5.0, 13.1 Hz, 1H), 2.06–2.20 (m, 1H), 1.74 (d, J = 13.6 Hz, 1H), 1.42 (s, 3H), 0.75 (d, J = 7.0 Hz, 3H). This material was used without further purification.

(3R,4R)-3,4-Dimethyl-4-phenyl-1-(trifluoromethane-sulfonyl)piperidin-4-yl)benzamide (18). A solution of the trilate 17 (2.3 g, 4.9 mmol) in DMF (10 mL) was treated with NBOs (3.5 mL, 15 mmol), PdCl2(PPh3)2 (170 mg, 0.25 mmol), and pyridine (0.4 mL, 11 mmol). The solution was heated to 80 °C for 5 h, then concentrated and purified by rapid elution of the product through silica gel using 20% EtOAc in hexanes as eluent to afford 1.4 g (98% of 18). 1H NMR (300 MHz, CDCl3) δ 7.30–7.39 (m, 2H), 7.20–7.28 (m, 3H), 3.98 (d, J = 13.0 Hz, 1H), 3.62 (bs, 2H), 3.30–3.46 (m, 1H), 2.38 (dt, J = 5.1, 13.1 Hz, 1H), 2.08–2.22 (m, 1H), 1.68–1.79 (m, 1H), 1.40 (s, 3H), 0.75 (d, J = 7.0 Hz, 3H). This material was used without further purification.

(3R,4R)-3,4-Dimethyl-4-phenylpiperidine (19). A sample of trilate 18 (520 mg, 1.6 mmol) was dissolved in toluene (10 mL) and THF (5 mL) and treated with LiAlH4 (320 mg, 8.3 mmol) and heated with a microwave to 150 °C in a sealed tube for 10 min. The cooled solution was diluted with ether, washed in an ice bath, and quenched with the sequential addition of water (0.3 mL), 15% NaOH (0.3 mL), then water (0.6 mL). The resulting suspension was filtered through Celite and concentrated to afford 226 mg of an oil. The 1H NMR suggested 19 contained about 15% unreacted starting material 18. 1H NMR (300 MHz, CDCl3) δ 7.08–7.38 (m, 3H), 3.26 (dd, J = 3.3, 13.1 Hz, 1H), 2.91–3.07 (m, 2H), 2.67–2.78 (m, 1H), 2.07–2.23 (m, 1H), 1.83–2.00 (m, 2H), 1.49–1.62 (m, 1H), 1.39 (s, 3H), 0.71 (d, J = 7.2 Hz, 3H). The material was used without further purification.

25-[1-(3R,4R)-3,4-Dimethyl-4-phenylpiperidin-1-yl]-3-methylbutan-2-amine (20). The amine (19) (226 mg, 0.92 mmol) was combined with Boc-ε-valin (355 mg, 1.8 mmol) in trifluoroethanol (5 mL) and treated with NaCNBH3 (3 mL, 1 M in THF). After 1 h,
The benzyl aniline used without further purification (13.8 mmol) was dissolved in CH2Cl2 (150 mL) containing triethylamine (5.4 g, 15 mmol). After 12 h, the solution was filtered, dried (Na2SO4), and concentrated. The residue was subjected to chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to recover 202 mg of starting material, followed by 50% EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a. 

A solution of 3-(4,4'-difluorophenyl)-3,4-dimethylpiperidin-1-yl)methyl)-2-methylpropyl)-1H-isoindole-1,3(2H)-dione (22). A solution of 25 (55 mg, 0.13 mmol) was dissolved in CH2Cl2 (1 mL) and treated with BF3·OEt2 (32 µL, 0.26 mmol) then isomyl nitrite (26 µL, 0.20 mmol). After stirring 15 min, the solution was cooled and diethyl ether was added. The resulting crystalline solids were collected by filtration, dried, and heated. The resulting residue was subjected to chromatography on silica gel eluting with EtOAc as the eluent to afford 36 mg (66%) of 27. 

The aniline (29). A solution of 25 (340 mg, 0.81 mmol) inaq HCl (37%, 3 mL) was cooled to −5 °C and stirred for 10 min. A solution of NaNO2 (65 mg, 0.89 mmol) in water (1.5 mL) was added dropwise to the reaction mixture, which was then stirred for 1 h. A cold solution of copper(I) chloride (92 mg, 0.93 mmol) in water (1.5 mL) was then added dropwise. The reaction mixture was stirred for 30 min and allowed to warm to rt then was heated to 65 °C for 3 h. The resulting suspension was poured in to a mixture of conc NH2OH (20 mL) and ice (6 g). The resulting solution with water (4 x 20 mL). The combined organic layers were dried (Na2SO4) and evaporated to a residue, which was subjected to chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a chromatography on silica gel using a gradient of EtOAc in hexanes with 1% NH3 as the eluent to a.
(1,3,4,5-tetrahydro-2(1H)-pyrimidinone-3-carboxylic acid (36). A sample of 35 (320 mg, 1.0 mmol) was dissolved in dioxane (2 mL) and THF (1 mL) then treated with aq LiOH (1 M, 3 mL) overnight. The resulting solution was cooled in an ice bath and treated cautiously with H2O2 (30%, 1 mL). After filtering, the reaction mixture was acidified with HCl (2 M) and diluted with water. The resulting solids were separated by filtration and dried to afford 230 mg of 36 (72%). 1H NMR (300 MHz, DMSO-d6) δ 12.72 (s, 1H), 7.90 (br s, 1H), 7.61–7.74 (m, 1H), 7.21–7.37 (m, 1H), 4.89 (br s, 1H), 4.68 (s, 1H), 4.55–4.64 (m, 1H), 4.52 (d, J = 5.7 Hz, 1H), 4.36–4.48 (m, 1H), 3.06–3.26 (m, 2H), 1.33–1.53 (m, 9H). This material was used without further purification.

hERG Assay. Preparations of membranes overexpressing human hERG were purchased from PerkinElmer. The binding assays were performed for 60 min using 4 nM hERG expressing membranes, ~5 nM [1H]Astemizole, and various concentrations of the test agent in a binding buffer (10 mM HEPES, pH 7.4, 130 mM NaCl, 5 mM KCl, 0.8 mM MgCl2, 1 mM NaEDTA, 10 mM glucose, 0.1% BSA). Binding was terminated by rapid filtration onto GF/B fiber filters, presoaked in 0.3% polyethyleneimine, followed by rapid washing 6 times (2 mL) with ice-cold solution containing 25 mM Tris-HCl, pH 7.4, 130 mM NaCl, 5 mM KCl, 0.8 mM MgCl2, 0.05 mM CaCl2, and 0.1% BSA using a Brandel harvester. Filters were dried and counted after addition of a scintillant. Data were analyzed using nonlinear regression (GraphPad Prism), and Ki values were determined as described before. All experiments were performed at least twice in duplicate, and data reported are mean values.

Solubility Determination. For these experiments, 10 mM DMSO stocks of compounds were directly diluted into 10 mM phosphate buffer at pH 7.4 or 3 and shaken for 90 min at room temperature. The final concentration of DMSO was 1%. After the incubation, samples were filtered through a 0.45 μm filter (Millipore). Filters were carefully collected. Analysis of compounds was performed by LC/MS using previously available methods and concentrations determined. Data are reported as mean values from three determinations.

PAMPA Assay. A commercially available PAMPA assay system was used (BD Gentest Precocoated PAMPA System). Assays were performed in duplicate at 10 μM final concentration at pH 7.4 and 5.5 as has been described previously in PBS buffer.13 The donor plate was on top and the receiver plate on the bottom. Samples were incubated for 4 h and then collected carefully from each plate. Quantification was performed using LC/MS.

Docking Studies and Calculation. The ligand preparation, receptor preparation, and docking calculations were conducted under our previously reported methods.14 The two-dimensional interaction diagrams were generated using LigPics.53

ASSOCIATED CONTENT

Supporting Information
Elemental analysis data for compounds 4–15. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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ABBREVIATIONS USED

GPCRs, G-protein-coupled receptors; SAR, structure–activity relationship; [35S]GTPyS, sulfur-35 guanosine-5′-O-(3-thio)-triposophate; DAMGO, [δ-Ala²,MePhe³,Gly-ol⁴]enkephalin; DPDPE, [δ-Pen⁶,δ-Pen⁷]enkephalin; U69,593, (S)-6-[1-(3-hydroxy-2-methyl-3-buten-2-yl)oxy]benzamides as selective antagonists of the kappa opioid receptor. Part 1. Bioorg. Med. Chem. Lett. 2010, 20, 5847–5852.

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