

Discovery and Pharmacological Evaluation of a Diphenethylamine Derivative (HS665), a Highly Potent and Selective κ Opioid Receptor AgonistMariana Spetea,[†] Ilona P. Berzetei-Gurske,[‡] Elena Guerrieri,[†] and Helmut Schmidhammer^{*,†}[†]Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck, University of Innsbruck, Innrain 80-82, A-6020 Innsbruck, Austria[‡]Biosciences Division, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025, United States

S Supporting Information

ABSTRACT: Here we report on the design, synthesis, and biological characterization of novel κ opioid (KOP) receptor ligands of diphenethylamines. In opioid receptor binding and functional assays, the *N*-cyclobutylmethyl substituted derivative **4** (HS665) showed the highest affinity and selectivity for the KOP receptor and KOP agonist potency. Compound **4** inhibited acetic acid induced writhing after subcutaneous administration in mice via KOP receptor-mediated mechanisms, being equipotent as an analgesic to the KOP agonist U50,488.

INTRODUCTION

The κ opioid (KOP) receptor belongs to the family of seven-transmembrane G-protein-coupled receptors (GPCRs), and it plays a significant role in a broad range of physiological functions.^{1,2} Stimulation of the KOP receptor results in significant analgesia, while it is not involved in the unwanted side effects of respiratory depression, inhibition of gastrointestinal motility, dependence, or abuse liability, as in the case of the μ opioid (MOP) receptor.² KOP agonists appear to have some advantages over the widely used MOP analgesics. On the other hand, the therapeutic utility of KOP agonists is associated with dose-limiting effects including dysphoria, sedation, and psychotomimetic effects.^{1,2} Besides the analgesic activity,³ KOP agonists have also shown other beneficial actions such as antipruritic,⁴ antiarthritic,^{5,6} anti-inflammatory,^{5,6} and neuroprotective effects.⁷ At present, the main classes of available chemically distinct KOP receptor agonists include peptides (e.g., dynorphin analogues),⁸ benzomorphans (e.g., bremazocine, pentazocine),⁹ morphinans (e.g., TRK-820),⁹ arylacetamides (e.g., U50,488, U69,593),⁹ diazabicyclononanones (e.g., HZ2),⁹ neoclerodane diterpenes (e.g., salvinorin A),^{9,10} benzodiazepines (e.g., tifluadom).⁹ Several of such compounds are employed as research tools or are in clinical use. Recent reviews on small molecule and peptide ligands as agonists at the KOP receptor and their potential for drug development have been published.^{8–10}

Inhibiting KOP receptors has been proposed to be useful for the treatment of stress-related conditions (e.g., depression and anxiety), drug addiction, and eating disorders.^{1,8,11,12} The first competitive KOP receptor antagonist was norbinaltorphimine (nor-BNI),¹³ followed later by 5'-guanidinonaltrindole (GNTI),¹⁴ both derived from naltrexone. The structurally distinct JD₁Tic, a *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine derivative, was discovered as a highly potent and selective KOP receptor antagonist.¹⁵ Recently, the crystal structure of the human KOP receptor in complex with JD₁Tic

was reported revealing important features of the ligand-binding pocket that contribute to the high affinity and selectivity of JD₁Tic for the human KOP receptor.¹⁶ The pharmacology of currently available selective KOP antagonists shows a delay in onset of action and extremely long-lasting effects in vivo, which might limit their therapeutic utility.^{17,18}

The development of KOP receptor ligands with improved pharmacokinetic and pharmacodynamic properties and safety profile is an important direction in pharmaceutical research toward the discovery of useful clinical agents. Earlier observations were made on the dopamine D₂ receptor agonist **1** (RU 24213, Figure 1),¹⁹ a diphenethylamine derivative,

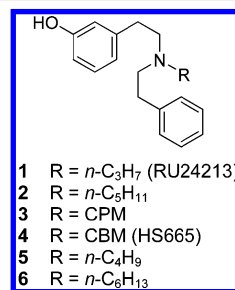


Figure 1. Structures of investigated compounds. CPM, cyclopropylmethyl; CBM, cyclobutylmethyl.

reported to display moderate affinity to KOP receptors and to act as KOP antagonist.²⁰ Moreover, its *n*-pentyl analogue **2** (Figure 1) also exhibited moderate affinity to the KOP receptor and showed KOP antagonist activity in vivo. Compound **2** antagonized diuresis and antinociceptive effects in rats after subcutaneous (sc) administration produced by the KOP receptor agonist U50,488.²¹ Therefore, such simple molecules

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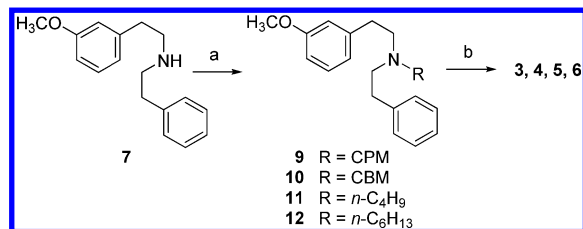
represent useful lead structures for the design of novel ligands for KOP receptors.

In the present study, we describe further chemical derivatization of diphenethylamines by targeting the substitution at the nitrogen. Several *N*-substituted diphenethylamine analogues (3–6) have been synthesized (Figure 1) and biologically characterized. In this work, we have also investigated the character of the *N*-substituent on opioid receptor activities to understand the role of the substitution pattern at the nitrogen on the interaction with the KOP receptor. Additionally, the effect of different substitution patterns on binding and functional activity at dopamine (D_1 , D_2 , and D_3) receptors was examined.

RESULTS AND DISCUSSION

Chemistry. Starting material for the synthesis of 1–6 was 2-(3-methoxyphenyl)-*N*-phenylethaneamine (7), which is readily available from 2-(3-methoxyphenyl)ethaneamine (8) by alkylation with phenethyl bromide.²⁰ Compounds 1 and 2 were prepared from 7 essentially as earlier described.^{20,21} *N*-Alkylation of 7 with the respective alkyl bromide in DMF in the presence of potassium carbonate afforded 9–12, which were in turn transformed by ether cleavage with sodium ethanethiolate in DMF into the respective phenols 3–6 (Scheme 1).

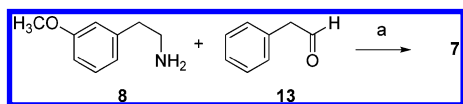
Scheme 1. Synthesis of Compounds 9–12 and 3–6^a



^aReagents and conditions: (a) respective alkyl bromide, K_2CO_3 , DMF, 80 °C; (b) sodium ethanethiolate, DMF, 130 °C.

Two alternative routes have been employed for the synthesis of 4. First, 7 has been prepared from phenylacetaldehyde (13) by reductive amination with 2-(3-methoxyphenyl)ethaneamine (8) using $NaBH_3CN$ in MeOH (Scheme 2), while the following steps remained unchanged to give 4 in an overall yield of 26% in comparison to the lower overall yield of 17% of the original procedure.

Scheme 2. Alternative Synthesis of Compound 7 from Phenylacetaldehyde^a

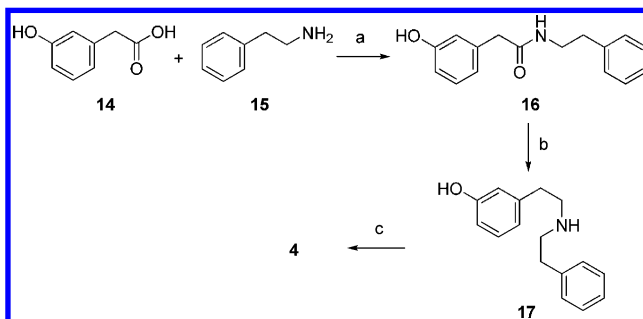


^aReagents and conditions: (a) $NaBH_3CN$, Et_3N , MeOH, rt.

The second route started from 3-hydroxyphenylacetic acid (14), which was reacted with 2-phenethylamine 15 in CH_2Cl_2 in the presence of EDCI and HOAt to afford amide 16. BH_3 reduction in THF yielded amine 17, which was *N*-alkylated with cyclobutylmethyl bromide in CH_3CN in the presence of $NaHCO_3$ to give 4 in an overall yield of 21% (Scheme 3).

Biological Evaluation. Diphenethylamine analogues 3–6 (Figure 1) were examined for their affinity and selectivity for KOP, MOP, and DOP receptors in binding assays using

Scheme 3. Alternative Synthesis of Compound 4 via Acetamide 16^a



^aReagents and conditions: (a) EDCI, HOAt, CH_2Cl_2 , rt; (b) 1 M $BH_3 \cdot THF$, THF, reflux; (c) cyclobutylmethyl bromide, $NaHCO_3$, CH_3CN , reflux.

membranes from Chinese hamster ovary (CHO) cells expressing one of the human opioid receptors.²² The lead compounds *N*-*n*-propyl (1) and *N*-*n*-pentyl (2) substituted derivatives showed K_i in the low nanomolar range to KOP receptors while having 2–3 orders of magnitude decreased affinities at MOP and DOP receptors (Table 1). Our findings support earlier observations on the binding to the KOP receptor of the two derivatives (IC_{50} of 57 nM for 1 and 2), based on binding assays in guinea pig brain with [3H]-ethylketocyclazocine as KOP receptor specific radioligand.^{20,21}

Replacement of the *n*-propyl group by an *n*-butyl group at the nitrogen (1 and 5) resulted in comparable affinity to KOP receptors and a minor increase in affinities to MOP and DOP receptors and as a consequence in a 2-fold decrease in KOP receptor selectivity (Table 1). A similar profile was revealed when the *n*-butyl group in 5 was replaced by an *n*-pentyl group in 2. With further extension of the *N*-substituent by one methylene group resulting in the *n*-hexyl analogue 6, a more than 10-fold decrease in KOP receptor affinity and selectivity was observed, paralleled by lower interaction with MOP and DOP receptors.

We also evaluated the effect on opioid receptor binding of cyclopropylmethyl (CPM) and cyclobutylmethyl (CBM) groups at the nitrogen, derivatives 3 and 4 (HS665), respectively. Interestingly, the *N*-CBM substituted analogue 4 showed a remarkable >1100-fold selectivity for KOP vs MOP receptors, and >20000-fold selectivity for KOP vs DOP receptors, being the most selective derivative in the new series of compounds. Compared to analogues 1 and 2 described earlier,^{20,21} compound 4 displayed considerably higher KOP receptor affinity and selectivity (Table 1).

The presence of an *N*-CPM group in 3 also resulted in increased binding at the KOP receptor and greater MOP/KOP and DOP/KOP selectivity ratios than 1 and 2 and also than the other new alkyl derivatives 5 and 6. From the opioid binding data, it is apparent that a CPM or CBM substitution at the nitrogen is more favorable for interaction with KOP receptors than *n*-alkyl groups by causing a notable increase in KOP receptor affinity and selectivity, thus indicating that cycloalkylalkyl groups are superior over *n*-alkyl groups in this respect.

The functional activity of all diphenethylamine analogues 1–6 was evaluated using the guanosine 5'-*O*-(3-[^{35}S]thio)-triphosphate ([^{35}S]GTP γ S) binding assays with membranes from CHO expressing human KOP receptors.²² It was observed that the overall rank order of potencies (EC_{50}) in

Table 1. Binding Affinities and [³⁵S]GTPγS Stimulation at Human Opioid Receptors

compd	binding (<i>K_i</i> , nM) ^a			selectivity		stimulation of [³⁵ S]GTPγS binding ^a	
	KOP	MOP	DOP	MOP/KOP	DOP/KOP	EC ₅₀ (nM)	% stim ^b
1	8.13 ± 0.32	594 ± 101	3713 ± 1266	73	457	49.1 ± 8.8	21.2 ± 0.1
2	12.6 ± 1.9	325 ± 26	1315 ± 364	26	104	86.4 ± 4.6	36.2 ± 2.7
3	5.90 ± 3.00	826 ± 98	>10000	140	>1700	35.0 ± 5.3	53.4 ± 8.1
4	0.49 ± 0.20	542 ± 239	>10000	1106	>20000	3.62 ± 1.87	90.0 ± 3.7
5	10.9 ± 2.4	412 ± 19	2429 ± 837	38	223	46.2 ± 11.4	45.5 ± 5.9
6	141 ± 42	788 ± 175	3572 ± 222	5.6	25	647 ± 88	24.0 ± 1.3
U50,488 ^c	0.2 ± 0.05	290 ± 14	>10000	1450	>50000	9.31 ± 2.54	93 ± 11
U69,593 ^c	0.3 ± 0.0	1145 ± 335	>10000	3817	>30000	26.1 ± 10.7	100

^aData are the mean ± SEM. ^bPercentage stimulation (% stim) relative to U69,593 (KOP). ^cFrom ref 23.

Table 2. Binding Affinities and Activities in Stimulation of Mitogenesis at Human Dopamine Receptors

compd	binding (<i>K_i</i> , nM) ^a			stimulation of mitogenesis ^a					
	D ₁	D ₂	D ₃	D ₂ , EC ₅₀ (nM)	D ₂ , % stim ^b	D ₂ , IC ₅₀ (nM)	D ₃ , EC ₅₀ (nM)	D ₃ , % stim ^b	D ₃ , IC ₅₀ (nM)
1	>10000	64.4 ± 7.5	21.8 ± 0.4	39.0 ± 9.8	99.7 ± 4.7		5.32 ± 0.2	74.2 ± 8.6	
2	>10000	1420 ± 13	1098 ± 161						
3	>10000	118 ± 16	168 ± 30	181 ± 8	63.8 ± 1.1		32.2 ± 8.2	84.5 ± 3.7	
4	>10000	450 ± 28	282 ± 34	>10000		1647 ± 297	>10000		953 ± 74
5	>10000	1233 ± 433	1148 ± 273						
6	>10000	831 ± 18	1147 ± 32	>10000		1252 ± 25			
dopamine ^c	4470 ± 1598	422 ± 9.2	20.0 ± 1.2	65 ± 15	90		6.1 ± 0.4	100	
quinpirole ^c	>10000	1185 ± 265	43.0 ± 19.7	19 ± 16	100		8.4 ± 5.7	100	

^aData are the mean ± SEM. ^bPercentage stimulation (% stim) relative to quinpirole. ^cFrom ref 23.

the functional assays correlated with affinities (*K_i*) at the KOP receptor derived from the binding studies (Table 1). At human KOP receptors, derivatives **1** and **2** showed moderate potency and low efficacy, acting as weak partial agonists with only 21% and 36% stimulation relative to U69,593. Examination of the chemical structure and functional activities revealed certain SAR in this series of differently *N*-substituted diphenethylamine analogues. The targeted alkyl modifications at the nitrogen, i.e., *n*-butyl and *n*-hexyl, resulted in partial agonists at the KOP receptor with efficacies roughly similar to those of the parent compounds **1** and **2**. The *n*-butyl substituted **5** exhibited a potency comparable to that of the *n*-propyl **1**, while the *n*-hexyl derivative **6** had substantially reduced potency at the KOP receptor compared with the *n*-pentyl **2**, observations that are in line with the binding data (Table 1). Replacement of the *n*-alkyl groups with cycloalkylalkyl substituents resulted in increased potency and efficacy at the KOP receptor, especially for the CBM derivative **4**. This compound was 14- and 24-fold more potent than derivatives **1** and **2**, respectively, and was up to 179-fold more potent than the diphenethylamine analogues **3**, **5**, and **6**. It also had significantly higher efficacy (90%) acting as a full KOP receptor agonist compared to all compounds in the series. The highly selective KOP ligand **4** was 2.5- and 7-fold more potent than the prototypical KOP receptor agonists. Compounds **3** and **5** did not antagonize U69,593-stimulated [³⁵S]GTPγS binding, indicating that they are low efficacy agonists.

Lead compound **1** was initially described as a potent dopamine agonist showing high selectivity for the D₂ receptor.¹⁹ We also found that **1** displays binding affinity comparable to that of dopamine to the D₃ receptor (Table 2). The corresponding *n*-pentyl analogue **2** was reported to be devoid of dopaminergic activity,²⁰ which was confirmed in our study. The diphenethylamine analogues **3–6** were evaluated for binding to dopamine receptors in radioligand binding assays

using membranes from LHD₁ cells expressing human D₁ receptors and CHOp cells expressing human D₂ and D₃ receptors.²³ None of the compounds showed any specific binding to the D₁ receptor, and much reduced binding to D₂ and D₃ receptors was displayed by the derivatives **3–6** in comparison to the parent molecule **1** (Table 2). These data indicate that the nature of the substituent at the nitrogen in diphenethylamines is an important determinant for affinity to the dopamine receptors and to the KOP receptor. In particular, the presence of the *N*-CBM group appears to be favorable for KOP receptor binding and leads to reduced interaction with dopamine receptors.

Diphenethylamines **1**, **3**, **4**, and **6** were evaluated for functional activity at D₂ and D₃ receptors by determination of stimulation of mitogenesis in CHOp cells expressing human D₂ and D₃ receptors.²³ Compound **1** was a full agonist at the D₂ receptor and a partial agonist at the D₃ receptor (Table 2). Substitution of the *n*-propyl group in **1** with cycloalkylalkyl groups in **3** and **4** or a longer *n*-alkyl group in **6** was also found to largely influence the activity at dopamine receptors. The *N*-CPM substituted analogue **3** was a partial to full agonist at D₂ and D₃ receptors, having lower potency than **1**, while the *N*-CBM derivative **4** was a weak antagonist. Compound **6** also displayed a low potency D₂ antagonism.

Compound **4** was evaluated in vivo for analgesic activity (Figure 2). Antinociceptive potency was assessed after sc administration in mice in the acetic acid induced writhing test.²⁴ Dose-dependent inhibition of writhing was produced by derivative **4** with an antinociceptive ED₅₀ of 1.91 mg/kg, which was comparable to the analgesic potency of the KOP agonist U50,488 (ED₅₀ = 1.54 mg/kg). Antinociceptive effects of compound **4** were blocked by the selective KOP receptor antagonist nor-BNI (Figure 2).

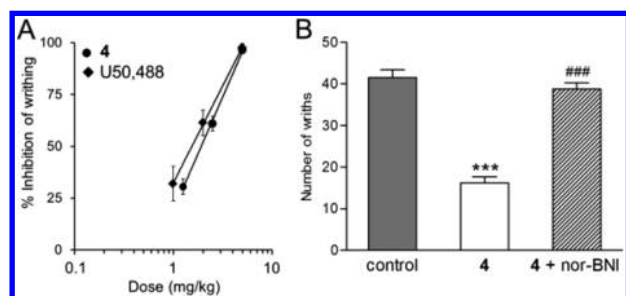


Figure 2. Antinociceptive effects of derivative 4 and U50,488 after sc administration to mice in the acetic acid induced writhing test: (A) dose–response effect; (B) antagonism of compound 4 (2.5 mg/kg, sc) by nor-BNI (20 mg/kg, sc). Values are the mean \pm SEM ($n = 5$ –6 mice per group): (***) $p < 0.001$ vs control group; (###) $p < 0.001$ vs 4-treated animals (Student's t -test).

CONCLUSIONS

We report on the design, synthesis, and biological evaluation of diphenethylamines bearing different substituents at the nitrogen as new KOP receptor ligands. An *N*-CPM or *N*-CBM substitution is more favorable for interaction with KOP receptors than *n*-alkyl groups by causing a significant increase in KOP receptor affinity and selectivity. In addition, an *N*-CBM group leads to reduced interaction with dopamine receptors. The *N*-CBM substituted derivative 4 was identified as a novel highly selective KOP receptor agonist with potent antinociceptive action. Moreover, the *N*-CPM substituted analogue 3, a selective KOR partial agonist, might have the potential for the treatment of addiction and stress-related disorders.

EXPERIMENTAL SECTION

General Methods. Melting points were determined on a Kofler melting point microscope and are uncorrected. ^1H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer and ^{13}C NMR spectra on a Bruker Avance DPX-300 (75.47 MHz). IR spectra were taken on a Mattson Galaxy FTIR series 3000 (in cm^{-1}). Mass spectra were recorded on a Varian MAT 44 S apparatus. Elemental analyses were performed at the Microanalytic Laboratory of the University of Vienna, Austria. For column chromatography (MPLC), silica gel 60 (0.040–0.063 mm, Fluka, Switzerland) was used. Compounds 1–4 were used as hydrochloride salts, and 5 and 6 were used as bases. Purities of tested compounds were determined by elemental analysis and were $\geq 95\%$.

General Procedure for the Synthesis of Phenols 3–6 (4 as Example). A mixture of 10 (300 mg, 0.93 mmol), sodium ethanethiolate (623 mg, 7.42 mmol), and anhydrous DMF (7 mL) was stirred under N_2 at 130°C for 20 h. After cooling, the mixture was poured on saturated NH_4Cl solution. The resulting mixture was slightly acidified with 2 N HCl and then alkalized with diluted NH_4OH solution and extracted with CH_2Cl_2 (3×15 mL). The organic phase was washed with H_2O (5×15 mL), brine (15 mL), dried over Na_2SO_4 , and evaporated. The resulting oil was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$, 97.5:1.5:1) to give 247 mg (86%) of 4 as a transparent oil. ^1H NMR (CDCl_3) δ 7.28–7.10 (m, 6 arom H); 6.70–6.23 (m, 3 arom H); 2.96–2.48 (m, 10 H); 2.10–1.57 (m, 7 H).

3-[2-[(Cyclobutylmethyl)(phenethyl)amino]ethyl]phenol Hydrochloride (4-HCl). A part of the obtained oil of 4 was dissolved in Et_2O and treated with HCl/ Et_2O . The precipitate was isolated and recrystallized from acetone/ Et_2O to afford 4-HCl. Mp 153 – 155°C ; IR (KBr) 3134 (OH, ^+NH); ^1H NMR ($\text{DMSO}-d_6$) δ 10.73 (br s, ^+NH), 9.45 (s, OH), 7.39–7.08 (m, 6 arom H), 6.72–6.64 (m, 3 arom H), 3.10–2.78 (m, 10 aliph H), 2.11–1.82 (m, 7 aliph H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 157.66, 138.32, 136.99, 129.53, 128.76, 128.58,

126.77, 119.21, 115.67, 113.74, 56.42, 52.96, 29.96, 29.04, 26.76, 18.17; MS (EI) m/z 309 [M^+]. Anal. ($\text{C}_{21}\text{H}_{27}\text{NO}\cdot\text{HCl}$) C, H, N, Cl.

3-[2-[(Cyclopropylmethyl)(phenethyl)amino]ethyl]phenol Hydrochloride (3-HCl). A part of the obtained oil of 3 (1.03 g, 91%) was dissolved in Et_2O and treated with HCl/ Et_2O . The precipitate was isolated and recrystallized from acetone/ Et_2O to yield 3-HCl. Mp 134 – 136°C ; IR (KBr) 3434 (OH); ^1H NMR ($\text{DMSO}-d_6$) δ 10.81 (br s, ^+NH), 9.47 (s, OH), 7.39–7.08 (m, 6 arom H), 6.73–6.65 (m, 3 arom H), 3.18–2.96 (m, 10 aliph H), 1.20 (m, 1 aliph H), 0.71–0.42 (m, 4 aliph H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 157.59, 138.45, 137.12, 129.55, 128.78, 128.61, 126.78, 119.22, 115.69, 113.75, 56.18, 52.59, 29.06, 5.37, 4.16; MS (EI) m/z 295 [M^+]. Anal. ($\text{C}_{20}\text{H}_{25}\text{NO}\cdot\text{HCl}\cdot 0.3\text{Et}_2\text{O}$) C, H, N.

3-[2-[Butyl(phenethyl)amino]ethyl]phenol (5). After column chromatography 50% of 5 was obtained as colorless crystals. Mp 79 – 82°C ; IR (KBr) 3434 (OH); ^1H NMR (CDCl_3) δ 7.32–7.11 (m, 6 arom H), 6.74–6.65 (m, 3 arom H), 2.82–2.79 (m, 8 aliph H), 2.60 (m, NCH_2), 1.54–1.25 (m, 4 aliph H), 0.91 (t, $J = 7.0$ Hz, $\text{CH}_2\text{--CH}_3$); ^{13}C NMR ($\text{DMSO}-d_6$) δ 157.73, 142.12, 140.49, 129.90, 128.94, 128.64, 126.27, 120.66, 115.95, 113.82, 55.92, 55.85, 53.70, 33.43, 32.93, 29.49, 21.00, 14.25; MS (CI) m/z 298 [$\text{M}^+ + 1$]. Anal. ($\text{C}_{20}\text{H}_{27}\text{NO}$) C, H, N.

3-[2-[Hexyl(phenethyl)amino]ethyl]phenol (6). After column chromatography 66% of 6 was obtained as colorless crystals. Mp 70 – 72°C ; IR (KBr) 3432 (OH); ^1H NMR (CDCl_3) δ 7.29–7.10 (m, 6 arom H), 6.74–6.65 (m, 3 arom H), 2.60 (m, NCH_2), 1.50 (m, 2 aliph H), 1.27 (m, 6 aliph H), 0.88 (t, $J = 6.4$ Hz, $\text{CH}_2\text{--CH}_3$); ^{13}C NMR ($\text{DMSO}-d_6$) δ 156.48, 142.39, 140.68, 129.88, 128.64, 126.25, 120.84, 115.92, 113.68, 55.99, 54.07, 33.53, 33.13, 32.00, 27.52, 26.51, 22.87, 14.26; MS (CI) m/z 326 [$\text{M}^+ + 1$]. Anal. ($\text{C}_{22}\text{H}_{31}\text{NO}$) C, H, N.

ASSOCIATED CONTENT

Supporting Information

Additional information on syntheses and methods and elemental analysis results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

CBM, cyclobutylmethyl; CHO, Chinese hamster ovary; CPM, cyclopropylmethyl; D_1 , D_2 , D_3 , dopamine receptor subtypes; DOP, δ opioid; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide; HOAt, 1-hydroxy-7-azabenzotriazole; KOP, κ opioid; MOP, μ opioid; U50,488, 2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[(1*R*,2*R*)-2-pyrrolidin-1-ylcyclohexyl]acetamide; U69,593, *N*-methyl-2-phenyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5]dec-8-yl]-acetamide

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