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4-Phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives as non-peptidic selective δ-opioid agonists with potential anxiolytic/antidepressant properties. Part 2

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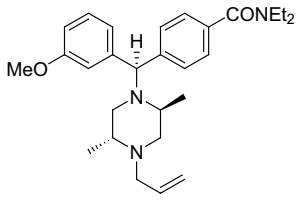
Abstract—Novel 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives have been prepared and their synthesis described herein. In vitro affinities for δ-, μ-, and κ-opioid receptors are reported. Evaluation of some representative compounds from this series in the mouse neonatal ultrasonic vocalization test and the mouse tail suspension test revealed anxiolytic- and antidepressant-like effects, respectively, upon subcutaneous administration.

The presence of at least three populations of opioid receptors, μ, δ, and κ, is well established and documented. All three populations appear to be present in the central and peripheral nervous system of many species, including human beings.[1] There is an increasing rationale suggesting that endogenous opioids are involved in the response to antidepressant treatment and stress-related disorders such as depression and anxiety.[2] Endogenous enkephalins have been hypothesized to diminish the impact of stress, which could be mediated, at least to some extent, via activation of δ-opioid receptors.[3] For example, the psychological stress of housing conditions and rank status has been demonstrated to alter the functional activity of δ-opioid receptors in rats.[4] Moreover, prenatal stress, which functions as an animal model of depression, has been shown to induce a down-regulation of δ-opioid receptors in different hypothalamic regions in rats.[5] In addition, the monoamine oxidase A inhibitor moclobemide, a clinically active antidepressant drug, increased δ-opioid receptor binding in frontal cortex and amygdala after 4 days of treatment in rats.[6] More recently Filliol et al. reported that δ-opioid receptor-knockout mice exhibited depressive-like and anxiogenic-like responses in the forced swimming and elevated plus-maze test, respectively.[7]

SNC80,[8] a non-peptidic selective δ-opioid agonist, has shown both anxiolytic- and antidepressant-like activities in behavioral models in rodents (Fig. 1). Perrine et al. have shown that SNC80 produced dose-dependent anxiolytic effects in two paradigms of anxiety: the elevated plus-maze and defensive burying models.[9] Furthermore, SNC80 suppresses ultrasonic vocalizations in rats in response to air-puff stress,[4] providing further evidence



SNC80

Figure 1. Selective nonpeptidic delta opioid agonist SNC80.

Keywords: Opioid; δ-Agonist; Antidepressant; Anxiolytic.
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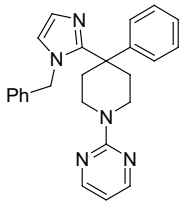
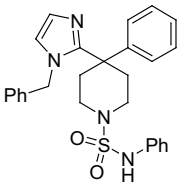


1

δ K_i = 18 nM
μ K_i = >4652 nM
κ K_i = 505 nM
δ [^{35}S]GTPγS EC_{50} = 14 nM



2

δ K_i = 3.2 nM
μ K_i = 980 nM
κ K_i = 346 nM
δ [^{35}S]GTPγS EC_{50} = 832 nM

Figure 2. Compounds **1** and **2** and their binding affinities.

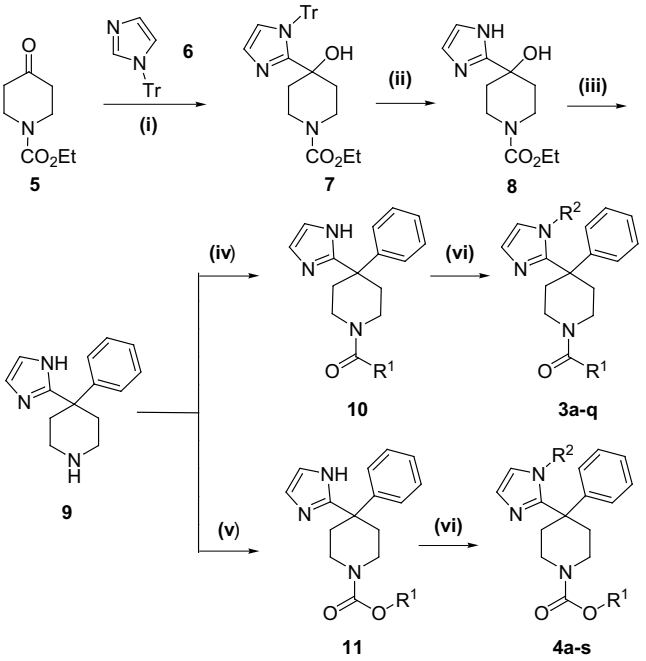
for reduced stress responsivity following δ-agonism. The actions of SNC80 in animal models of depression have been well characterized.[9a,10] Thus SNC80 dose-dependently reduced the duration of immobility in the forced swim test in rats. Both anxiolytic- and antidepressant-like effects could be significantly antagonized by naltrindole, a selective δ-opioid-receptor antagonist.

We have recently disclosed a series of non-chiral/non-peptidic 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives as δ-opioid ligands with good selectivity over μ- and κ-receptors.[11,12] This family of compounds has the advantage of having no chiral centers and can be easily synthesized from relatively cheap commercially available reagents.

Compounds **1** and **2** were identified as the most promising representatives among the first set of analogues prepared (Fig. 2). Thus, compound **1** was found to be the most potent agonist found among all tested compounds (EC_{50} = 14 nM), despite having only moderate binding activity (K_i = 18 nM). Conversely, compound **2** showed good binding affinity (K_i = 3.2 nM) but weak agonism (EC_{50} = 832 nM).[12]

These results prompted us to start a chemical exploration around 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine scaffold to further evaluate its potential. In order to expand our previous exploration around the piperidine nitrogen a series of amides **3a**–**q** and carbamates **4a**–**s** were prepared. The synthesis, binding affinities to μ-, δ-, and κ-opioid receptors, and preliminary pharmacological evaluation of these analogues in two in vivo anxiety and depression paradigms are reported.

The route for the synthesis of compounds **3a**–**q** and **4a**–**s** is outlined in Scheme 1 and is similar to the one previously reported by our group.[12] Thus, reaction of the 2-lithium salt of 1-tritylimidazole (**6**) with the N-protected piperidone **5** led to the corresponding addition product **7** in moderate yield. The trityl protecting group was removed under acidic conditions to give the unprotected imidazole derivative **8**. The Friedel–Crafts reaction of **8** with benzene occurred with simultaneous hydrolysis of the carbamate function affording the key intermediate **9** in good yield (77%). This compound was easily obtained in 50–100 gram scale.



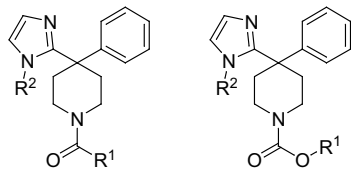
Scheme 1. Reagents and conditions: (i) *n*-BuLi, 1-tritylimidazole (**6**), THF, −78 °C to rt, 2 h, 48%; (ii) AcOH (5% in MeOH), reflux, 6 h, 85%; (iii) $AlCl_3$, benzene, 60 °C, 1 h, 77%; (iv) R^1COCl, Et_3N, DMF, THF, rt, 2 h; (v) R^1OCOCl, Et_3N, CH_2Cl_2, rt, 2 h; (vi) NaH, THF, rt, 10 min, then R^2Hal, reflux, 8 h, 56–87%.

Selective reaction of **9** with the corresponding acid chlorides or chloroformates gave compounds **10** and **11**, respectively. The alkylation of the imidazole nitrogen in **10** and **11** was carried out by reaction with different alkyl halides in THF, using sodium hydride as a base. The targeted compounds **3a**–**o** and **4a**–**o** were obtained in moderate to good yields.[13]

The pharmacological profile of the compounds was determined in radioligand binding studies and functional GTPγS assays. The binding affinities (K_i) of the compounds against cloned human δ-, μ-, and κ-receptors were determined. The opioid binding affinities of analogues of **3a**–**q** and **4a**–**s** are listed in Table 1.

As it can be deduced from the data shown in Table 1, in general both chemical subseries, amides **3** and carbamates **4**, showed affinities in the nanomolar range for the δ-opioid receptor and selectivities over μ and κ receptors in the range of 10- to 100-fold. Regarding the exploration of R^1 a wide range of different groups was tolerated in classes (**3a**–**k** and **4a**–**h**) keeping a reasonably good affinity and selectivity for the δ-opioid target. Due to their high potency and good selectivity, compounds **3f** (R^1 = methoxymethyl), **3h** (R^1 = phenyl), and **4b** (R^1 = ethyl) were selected as good representatives to further study the influence of the R^2 substituent. Thus the introduction of a methyl substituent in the benzylic position of **3f**, **3h**, and **4b** resulted in compounds with equal or slightly better affinity for the δ-receptor (**3l**, **3n**, and **4i**, respectively). A similar trend was also observed when the benzyl substituent was replaced by 4-methoxycarbonylbenzyl. Thus, **3m**, **3p** and **4o** showed higher affinities for the δ-opioid receptor than their

Table 1. Binding affinity of 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives **3a**–**q** and **4a**–**o** to δ-, μ- and κ-receptors[a,b]



Compound	R^1	R^2	δ K_i (nM)	μ K_i (nM)	κ K_i (nM)	μ/δ	κ/δ
3a	Methyl	Benzyl	37	>465	1008	>12	27
3b	Ethyl	Benzyl	29	>465	n.t.	>52	—
3c	Isopropyl	Benzyl	48	>465	621	>10	13
3d	Cyclopropyl	Benzyl	23	>465	n.t.	>20	—
3e	*tert*-Butyl	Benzyl	37	>4652	n.t.	>126	—
3f	Methoxymethyl	Benzyl	7.4	>465	622	>63	84
3g	Benzyl	Benzyl	23	>465	n.t.	>20	—
3h	Phenyl	Benzyl	2.3	>4652	124	>2023	54
3i	3,5-Dimethylphenyl	Benzyl	37	>465	284	>13	7.7
3j	2,4,6-Trimethylphenyl	Benzyl	125	>4652	n.t.	>37	—
3k	3,5-Trifluoromethylphenyl	Benzyl	29	>465	n.t.	>16	—
3l	Methoxymethyl	α-Methylbenzyl	3.7	>4652	>4652	>1257	>1257
3m	Methoxymethyl	4-Methoxycarbonylbenzyl	5.9	>4652	65	>788	11
3n	Phenyl	α-Methylbenzyl	2.3	>4652	334	>2022	145
3o	Phenyl	3-Methoxycarbonylbenzyl	85	>465	n.t.	>5.5	—
3p	Phenyl	4-Methoxycarbonylbenzyl	0.93	>4652	88	>5002	95
3q	Phenyl	4-(*N*,*N*-Diethylaminocarbonyl)benzyl	158	>4652	n.t.	>29	—
4a	Methyl	Benzyl	19	>4652	n.t.	>245	—
4b	Ethyl	Benzyl	3.7	2763	171	747	46
4c	*n*-Propyl	Benzyl	2.9	>465	>4652	>160	>1064
4d	*n*-Butyl	Benzyl	9.3	>465	188	>50	20
4e	Isopropyl	Benzyl	1.8	>465	201	>258	112
4f	Cyclohexyl	Benzyl	7.4	>465	121	>63	16
4g	*tert*-Butyl	Benzyl	9.3	>465	84	>50	9.0
4h	Benzyl	Benzyl	12	>465	121	>39	10
4i	Ethyl	α-Methylbenzyl	1.2	>465	62	>378	52
4j	Ethyl	3-Methoxybenzyl	29	>4652	366	>160	13
4k	Ethyl	4-Methoxybenzyl	12	>4652	201	>388	17
4l	Ethyl	3-Fluorobenzyl	5.9	>465	>4652	>79	>788
4m	Ethyl	4-Fluorobenzyl	51	>465	n.t.	>6.5	—
4n	Ethyl	4-Hydroxybenzyl	4.6	>465	108	>101	23
4o	Ethyl	4-Methoxycarbonylbenzyl	0.74	>465	25	>628	34
4p	Ethyl	2-Naphthylmethyl	642	>465	3116	>0.7	4.8
4q	Ethyl	2-Pyridylmethyl	173	>465	n.t.	>2.7	—
4r	Ethyl	Cyclohexylmethyl	147	>465	n.t.	>3.2	—
4s	Ethyl	Cynnamyl	280	>465	n.t.	>1.6	—

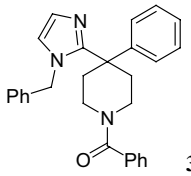
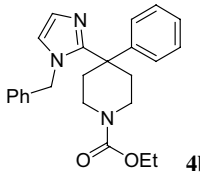
[a] The binding activity of compounds is represented as means of two-independent and confirmatory experiments. Only differences in pIC_{50} up to 0.6 (SD < 0.5) were considered as reproducible and were maintained. The K_i values represent the concentration giving half-maximal inhibition of [^{3}H]DPDPE (δ), [^{3}H]DAMGO (μ), [^{3}H]U69593 (κ) to cloned human receptors.

[b] n.t., not tested.

corresponding unsubstituted analogues **3f**, **3h** and **4b**. The variation in the position of the methoxycarbonyl substituent in **3p** from position 4 to position 3 (**3o**) resulted in a substantial decrease in affinity. The corresponding 4-*N*,*N*-diethylcarboxamide derivative **3q** was also 170-fold less active than **3p**. Attempts to replace the benzyl group by other subtituents led to poorly active compounds (**4p**–**s**). Compounds **3p** and **4o** stand as the most potent compounds prepared within this series so far, their binding affinities for the δ-opioid receptor being in the sub-nanomolar range.

Many compounds underwent functional testing in ([^{35}S]GTPγS) and almost all showed agonistic activity.[11] A representative compound of each subseries (amides **3** and carbamates **4**) was tested in several in vivo paradigms predictable for anxiolytic and antidepressant activities. Preliminary results for the amide **3h** and carbamate **4b** are shown in Table 2. Thus, compounds **3h** and **4b** showed a statistically significant reduction in both the number and duration of calls when tested in the mouse neonatal ultrasonic vocalization test,[14] as a paradigm predictable for anxiolytic activity. Remarkably, the benzamide derivative **3h** showed activity at a dose of 1 mg/kg. Additionally **3h** and **4b** were tested in the mouse tail suspension test.[15] Both compounds decreased the duration of immobility in this test at 10 mg/kg and 30 mg/kg, respectively (lowest active dose), therefore demonstrating antidepressant-like effects.

Table 2. Effects of δ-opioid agonists **3h** and **4b** on mice neonatal ultrasonic vocalization and tail suspension tests[a,b]

Compound	Ultrasonic vocalization (LAD, mg/kg)	Tail suspension (LAD, mg/kg)
 **3h**	<1	10
 **4b**	10	30

[a] LAD, lowest active dose tested.
[b] All compounds were dosed subcutaneously.

In summary, we have shown the potential of a new chemical class of selective δ-opioid agonists based on the 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine scaffold. These compounds have shown for the first time anxiolytic- and antidepressant-like effects in two behavioral paradigms. Further pharmacological characterization and chemical exploration of the series in order to broaden the SAR around its structure are currently in progress.

Acknowledgments

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13. Compound **3h**: white solid; mp 122.7 °C;. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.26 (m, 6H), 7.23–7.20 (m, 5H), 7.15 (br d, J = 7.6, Hz, 2H), 7.08 (br s, 1H), 6.70 (br s, 1H), 6.59 (dd, J = 8.3, 1.6 Hz, 2H), 4.59 (s, 2H), 4.48 (br d, J = 12.7 Hz, 1H), 3.86 (br t, J = 12.4 Hz, 1H), 3.61 (br d, J = 12.8 Hz, 1H), 3.18 (br t, J = 11.6 Hz, 1H), 2.57 (br d, J = 12.9 Hz, 1H), 2.42 (br d, J = 12.7 Hz, 1H), 2.31 (br t, J = 11.1 Hz, 1H), 1.85 (br t, J = 10.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 150.3, 145.9, 136.4, 135.7, 132.4, 130.0, 129.5, 128.8, 128.6, 127.9, 127.6, 127.5, 127.4, 126.3, 122.1, 49.7, 45.8, 44.0, 39.6, 39.1, 35.1; HRMS Calcd for $C_{28}H_{28}N_3O$ (M+1): 422.2232. Found 422.2291; Anal. Calcd for $C_{28}H_{27}N_3O$: C, 79.78; H, 6.46; N, 9.97. Found: C, 79.56; H, 6.57; N, 9.85. Compound **4b**: white solid; mp 164.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.27 (m, 3H), 7.23–7.19 (m, 3H), 7.15 (br d, J = 7.9 Hz, 2H), 7.07 (s, 1H), 7.01–6.97 (m, 2H), 6.68 (s, 1H), 4.59 (s, 2H), 4.12 (q, J = 7 Hz, 2H), 4.08–3.71 (m, 2H), 3.52 (br s, 1H), 3.22 (br s, 1H), 2.71–2.64 (m, 2H), 2.13 (br s, 1H), 1.99 (br s, 1H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CDCl3, 100 MHz) δ 156.0, 150.4, 146.4, 133.9, 129.4, 128.6, 128.5, 127.4, 126.3, 121.9, 120.3, 61.6, 49.6, 43.8, 41.4, 41.2, 15.1; HRMS Calcd for $C_{24}H_{28}N_3O_2$ (M+1): 390.2182. Found 390.2206; Anal. Calcd for $C_{24}H_{27}N_3O_2$: C, 74.01; H, 6.99; N, 10.79. Found: C, 74.19; H, 6.98; N, 10.81.
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