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4-Phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives, a novel class of selective δ-opioid agonists

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Abstract—A novel series of 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives has been prepared and their synthesis described herein. In vitro affinities for δ-, μ-, and κ-opioid receptors, as well as the functional activity in the [^{35}S]GTPγS assay are reported. The most potent and selective δ-opioid agonist **18a** exhibited a K_i of 18 nM, and was >258-fold and 28-fold selective over μ- and κ-receptors, respectively; the compound is a full agonist with an EC_{50} value of 14 nM.

Selective non-peptidic δ-opioid agonists have been subject of great interest over the last 20 years as potential analgesic agents that may lack some of the undesired effects of μ-opioid agonists.[1,2] Besides pain conditions, this intensive research has led to the discovery of new potential applications of δ-opioid agonists to treat a wide range of conditions, such as urinary incontinence,[3] depression,[4] neuroprotection,[5] cocaine addiction,[6] cardiac ischemia[7] amongst others.[8]

The discovery of non-peptidic δ-opioid agonists TAN-67 (**1**)[9] and SNC80 (**2**)[10] has contributed to the rapid expansion of the opioid research based on the δ-receptor subtype (Fig. 1).[11,12] We have recently described at Johnson & Johnson PRD, new families of tropane derivatives represented by compounds **3**[13] and **4**,[14] showing impressive potency and selectivity for the δ receptor. One possible drawback of compounds **1**, **2**, **3**, and **4** is their complex stereochemistry which makes their synthesis difficult, requiring either chiral separations or enantiomeric synthesis routes.

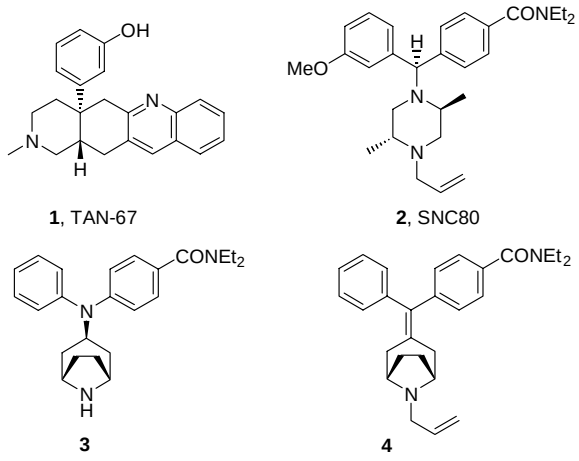

Figure 1. Set of selective non-peptidic δ-opioid agonists **1**–**4**.

High throughput binding screening of our corporate compound collection against the human δ-opioid receptor resulted in the identification of the non-chiral 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivative **5** (Fig. 2) as a weak to moderate δ-opioid ligand (K_i = 81 nM) with selectivity over μ and κ receptors

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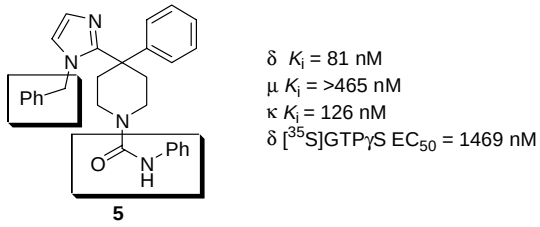


Figure 2. Binding affinities of compound **5**.

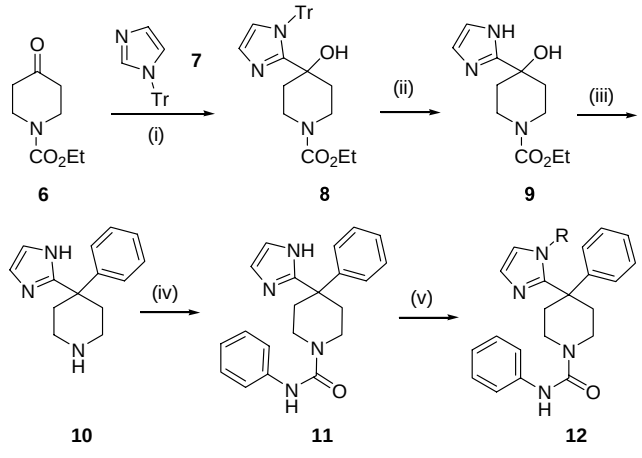
(>5- and 1.5-fold, respectively). The compound was found to be a weak agonist in our functional assays.

These results prompted us to start a limited chemical exploration around **5** to evaluate its hit potential. The synthesis and preliminary pharmacological evaluation of these analogues are reported.

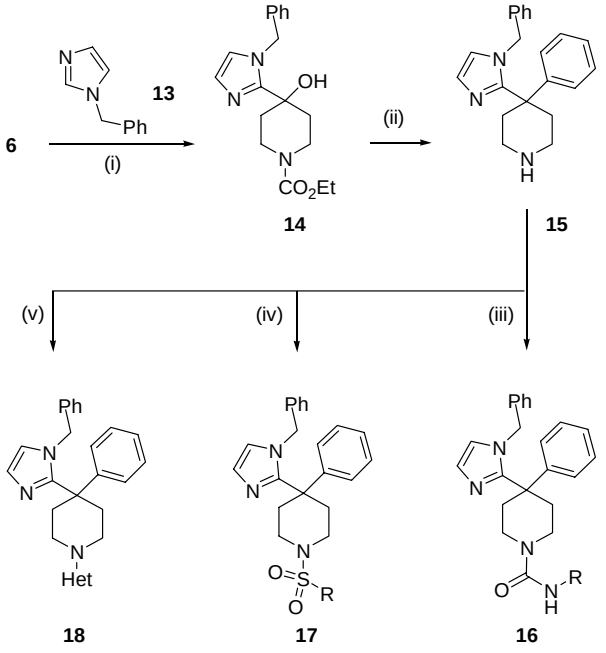
The preparation of analogues of compound **5** in which the substitution of the imidazole nitrogen is different than benzyl (**12**) is shown in Scheme 1. Thus, reaction of the 2-lithium salt of the commercially available 1-tritylimidazole (**7**) with 1-carbethoxy-4-piperidone (**6**) led to the corresponding addition product **8** in moderate yield. The trityl-protecting group was removed under acidic conditions to give the unprotected imidazole derivative **9**. The Friedel–Crafts reaction of **9** with benzene occurred with simultaneous hydrolysis of the carbamate function affording the key intermediate **10** in good yield (77%).

Selective reaction of **10** with phenylisocyanate gave **11** in almost quantitative yield. The alkylation of the imidazole nitrogen in **11** was carried out by reaction with different alkyl halides in THF, using sodium hydride as base. The targeted compounds **12** were obtained in moderate to good yields.

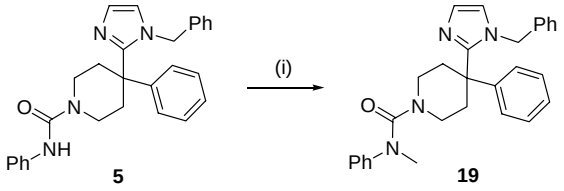
For the synthesis of modified analogues on the piperidine nitrogen a similar synthetic strategy, starting from 1-benzyl imidazole, was followed. First, addition of the corresponding lithiated heterocycle to 1-carbethoxy-4-piperidone (**6**) gave the hydroxy derivative **14** in 56% yield. Then, Friedel–Crafts reaction with benzene led to the 4-phenyl substituted piperidine **15**. This piperidine intermediate (**15**) was transformed into the final compounds **16**, **17**, and **18** under the standard reaction conditions shown in Scheme 2.



Scheme 1. Reagents and conditions: (i) *n*-BuLi, 1-tritylimidazole (**7**), 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) phenylisocyanate, CH_2Cl_2, rt, 3 h, 95%; (v) NaH, THF, rt, 10 min, then RHal, reflux, 8 h, 56–87%.



Scheme 2. Reagents and conditions: (i) *n*-BuLi, 1-benzylimidazole (**13**), THF, −78 °C to rt, 2 h, 56%; (ii) $AlCl_3$, benzene, 60 °C, 1 h, 54%; (iii) RNCO, CH_2Cl_2, rt, 3 h, 80–90%; (iv) RSO_2Cl or $(RSO_2)_2O$, Et_3N, CH_2Cl_2, −78 °C to rt, 8 h, 57–89%; (v) HetHal, Et_3N, DMSO, 180 °C, 20 min, microwaves, 55–84%.

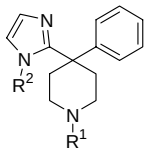


Scheme 3. Reagents and conditions: (i) NaH, DMF, rt, 1 h, then MeI, 60 °C, 6 h, 49%.

The preparation of the disubstituted urea **19** is shown in Scheme 3 and was carried out by direct alkylation of **5** with methyl iodide.

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. Agonist potency values (EC_{50}) were obtained by monitoring the ability of test compounds to activate [^{35}S]GTPγS binding in comparison to the selective δ agonist DPDPE in C6-Glioma cells expressing cloned human δ-opioid receptors. The opioid binding affinities of analogues of **5** are listed in Table 1. Functional data for a set of selected analogues of compound **5** are shown in Table 2.

Table 1. Binding affinity of 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine derivatives 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
5	*N*-Phenylaminocarbonyl	Benzyl	81	>465	126	5.7	1.6
12a	*N*-Phenylaminocarbonyl	2-Fluorobenzyl	72	428	116	5.9	1.6
12b	*N*-Phenylaminocarbonyl	3-Fluorobenzyl	128	>4652	1877	>36	15
12c	*N*-Phenylaminocarbonyl	4-Fluorobenzyl	203	>4652	2156	>23	11
12d	*N*-Phenylaminocarbonyl	3-Methoxybenzyl	217	3246	2059	15	9
12e	*N*-Phenylaminocarbonyl	2-Pyridylmethyl	3074	1417	46	0.46	0.015
12f	*N*-Phenylaminocarbonyl	α-Methylbenzyl	43	497	>465	12	11
12g	*N*-Phenylaminocarbonyl	Benzoyl	3696	>4652	1185	>1.2	0.32
12h	*N*-Phenylaminocarbonyl	H	>465	>465	>4652	—	—
19	*N*,*N*-Methylphenylaminocarbonyl	Benzyl	9	>4652	397	>516	44
16a	Aminocarbonyl	Benzyl	99	>4652	334	>51	3.4
16b	*N*-Ethylaminocarbonyl	Benzyl	39	>4652	242	>47	6.2
16c	*N*-Methylpiperazinylcarbonyl	Benzyl	161	>4652	858	>29	5.3
16d	*N*-(2-fluorophenyl)Aminocarbonyl	Benzyl	29	2520	318	87	11
16e	*N*-(3-fluorophenyl)Aminocarbonyl	Benzyl	29	>4652	>4652	>160	>160
16f	*N*-(4-fluorophenyl)Aminocarbonyl	Benzyl	97	1206	148	12	1.5
16g	*N*-(2-methoxyphenyl)Aminocarbonyl	Benzyl	31	>4652	782	>150	25
16h	*N*-(3-methoxyphenyl)Aminocarbonyl	Benzyl	46	1385	152	30	3.3
16i	*N*-(4-methoxyphenyl)Aminocarbonyl	Benzyl	44	>465	n.t.	>10	—
17a	Methylsulfonyl	Benzyl	46	>4652	2012	>101	44
17b	Aminosulfonyl	Benzyl	106	>4652	>4652	>44	>44
17c	*N*-Phenylaminosulfonyl	Benzyl	3.2	980	346	306	108
18a	2-Pyrimidyl	Benzyl	18	>4652	505	>258	28
18b	2-Thiazolyl	Benzyl	79	>4652	2533	>58	32
18c	2-Benzothiazolyl	Benzyl	73	>4652	n.t.	>63	—
18d	2-*N*-Methylbenzimidazolyl	Benzyl	138	235	40	1.7	0.29

[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.

Table 2. Functional activity data for **5** and a set of selected analogues[a]

Compound	δ GTPγS EC_{50} (nM)
5	1479
19	776
16b	117
16g	117
16h	436
17c	832
18a	14
18b	98
18c	26

[a] Agonism values (pEC_{50}s) were measured in membranes expressing human δ receptors from three-parameter logistic curve fits of percent stimulated [^{35}S]GTPγS binding vs log(molar ligand).

To investigate the structure–activity relationship of this series, the following structural modifications were made: (a) substitution on the benzyl group of **5**; (b) replacement of the benzyl substituent; (c) modifications of the urea substituents of compound **5**; (d) substitution of the urea functionality in **5** by sulfonamides and 2-aminoheterocyclic groups.

As it can be deduced from the data shown in Table 1, in general, most of the new analogues showed affinities in the nanomolar range for the δ-opioid target. Most compounds were highly selective over μ and κ receptors in the region of 10- to 100-fold. The introduction of electron-withdrawing (**12a**–**c**) or electron-donating (**12d**) groups on the benzyl group of the hit **5** was well tolerated and led to compounds with comparable or slightly lower affinity for the δ receptor but, in general, higher selectivity with respect to the other opioid receptors. The attempts to replace the benzyl substituent in **5** by other groups such as 2-pyridylmethyl (**12e**), benzoyl (**12g**) or hydrogen (**12h**) resulted in a complete loss of affinity for the δ receptor. Surprisingly, the pyridyl derivative **12e** showed moderate binding affinity (K_i = 46 nM) and selectivity (κ/δ 67-fold) for the κ-opioid receptor. Compound **12f**, that presents a methyl substituent at the benzylic position, showed higher affinity for the δ-opioid receptor, with selectivity versus μ and κ receptors being slightly better than that of **5**.

Regarding the influence of the substitution on the urea functionality compound **19**, a tetrasubstituted urea, showed the highest affinity and selectivity for the δ recep-

tor among all the ureas prepared. In general, alkyl (**16b**,**c**) and aryl groups (**16d**–**i**) proved to be good substituents in terms of affinity and selectivity. Moreover, both electron-withdrawing and electron-donating groups have a positive influence on the binding affinity for the δ receptor regardless of their substitution position (*ortho*-, *metha*- or *para*-). Interestingly, sulfonamides (**17a**–**c**) and aromatic heterocycles (**18a**–**d**) were good replacements for the urea moiety. The phenylsulfonamide derivative **17c** and the pyrimidyl analogue **18** were the most potent and selective compounds found in this preliminary exploration.

A small set of compounds was selected to evaluate their functional activity in the [^{35}S]GTPγS assay, the results obtained are listed in Table 2. All the compounds tested were found to be full agonists within a range of nanomolar activities and were found to have no potential to antagonize DPDPE-induced [^{35}S]GTPγS incorporation. Compounds **18a** and **18c** were the most potent agonists, EC_{50} = 14 and 26 nM, respectively, despite having only moderate binding activity. Conversely, compounds **19** and **17c** showed good binding affinity but weak agonism.

In summary, we have shown the viability and potential of a new chemical class of selective δ-opioid agonists based on the 4-phenyl-4-[1*H*-imidazol-2-yl]-piperidine scaffold. Further pharmacological characterization and chemical exploration of the series in order to broaden the SAR around its structure are currently in progress.

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