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Synthesis and structure–activity relationships of a new series of 2α-substituted *trans*-4,5-dimethyl-4-(3-hydroxyphenyl)piperidine as μ-selective opioid antagonists

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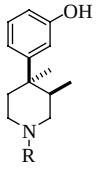
Abstract—Structure–activity relationships at the 2α-position of the piperidine ring of the *trans*-4,5-dimethyl-4-(3-hydroxyphenyl) piperidine μ-opioid antagonist series were investigated. This study showed that only small linear alkyl groups (methyl, propyl) are tolerated at the 2α-position of the piperidine ring of this series.

The series of *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (Formula **A**),[1] exemplified by the *N*-phenethyl derivative **1**[2] (see Table 1), have been widely investigated as opioid receptor antagonists. These 4-phenyl piperidine antagonists were structurally unique since opioid antagonists were generally structural analogs of morphine. Structure–activity relationship (SAR) in this *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine series has been focused largely on the substitution of the piperidine nitrogen,[2–5] and, more recently, on modification of the OH phenolic position.[6,7]



A

Virtually all the opioid ligands feature a basic nitrogen, which is protonated at physiological pH and is thought to interact with a conserved aspartate residue, located inside the receptor transmembrane domain and conserved among all the opioid receptors.[8] Earlier studies demonstrated that both the binding potency and efficacy of the antagonists of Formula **A** were directly related to the structure of the N-substituent, with the most potent compounds incorporating a lipophilic entity.[2] Introduction of substituents at the α-position of the piperidine nitrogen of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine series has not been investigated. We now wish to report the synthesis, opioid receptor binding properties, and in vitro functional activity of a series of 2α-substituted *trans*-4,5-dimethyl-4-(3-substituted-phenyl)piperidines.[9]

The target compounds **2**–**24** were prepared according to Schemes 1 and 2. The key step of the chemistry relied on the addition of Grignard reagents to the nitrone derived from (+)-4(*R*)-(3-benzyloxyphenyl)-3(*R*),4-dimethyl-1-piperidine (**25**).[10] Oxidation of **25** using sodium tungstate and hydrogen peroxide provided a mixture of nitrones **26a**/**26b** (1:4 ratio as determined by ^{1}H NMR) that could not be separated by column chromatography. Addition of allylmagnesium chloride to the mixture **26a**/**26b** provided the hydroxylamine derivative **27** in 56% isolated yield. The other regio- and stereoisomers (i.e., 2β, 6α, and 6β), analogs of **27**, were detected but were of insufficient quantity to be isolated in meaningful amounts. Treatment of **27** with zinc powder in acetic acid under sonication conditions afforded the 2α-allyl piperidine derivative **28**. In order to assign unequivocally the

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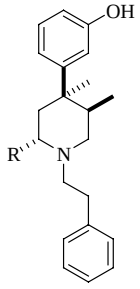
Table 1. Opioid receptor (μ, κ, and δ) binding data and in vitro antagonist activity (μ) of *N*-phenethyl-*trans*-4,5-dimethyl-2α-substituted-4-(3-hydroxyphenyl)piperidines

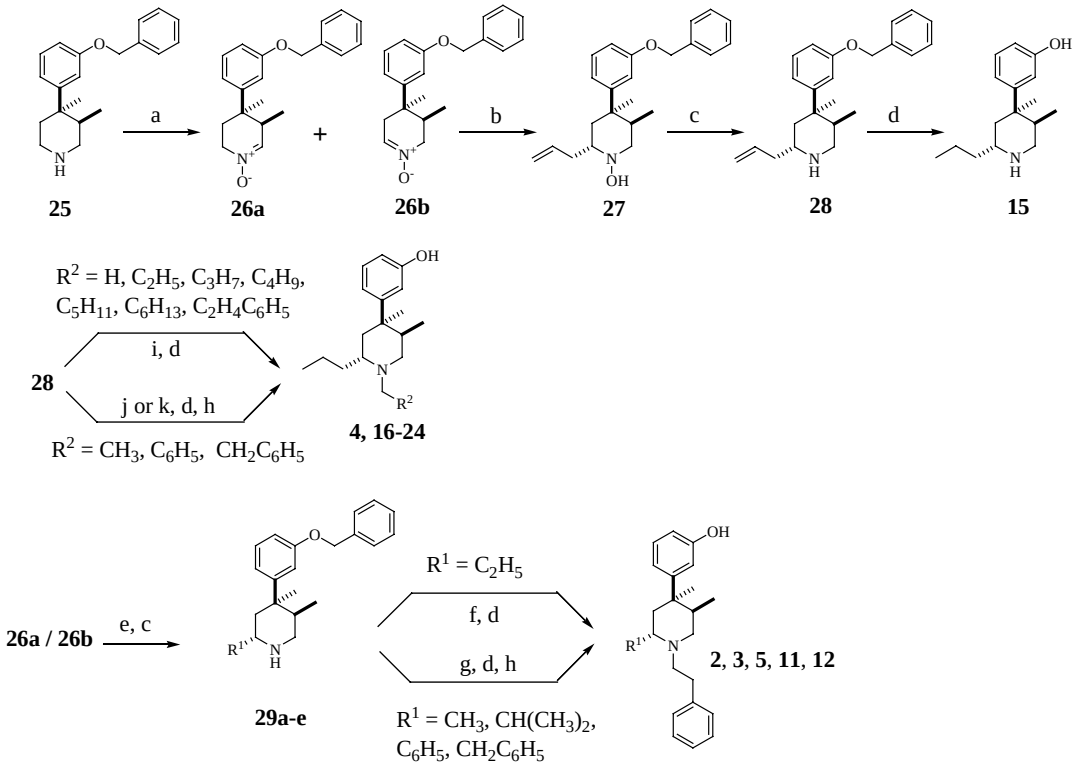


Compound	R	K_i (μ) (nM)[a]	IC_{50} (μ) (nM)[b]	K_i (κ) (nM)[a]	K_i (δ) (nM)[a]
1	H	1.9	2.0	17	33
2	––	15	50	100	65
3		75	90	710	680
4		20	15	110	120
5		270	620	>1000	>1000
6		110	120	200	580
7		780	390	510	>1000
8		190	130	620	>1000
9		59	130	200	710
10		>1000	>1000	>1000	>1000
11		280	>1000	290	260
12		290	280	920	800
13		160	210	790	610
14		230	360	260	320

[a] The potencies of the compounds were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the non-selective opioid antagonist, [^{3}H]diprenorphine, to cloned human μ-, κ-, and δ-opioid receptors, expressed in separate cell lines. K_i values are geometric means computed from at least three separate determinations.

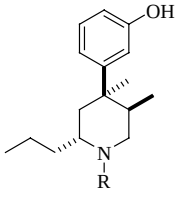
[b] The potencies of the antagonists were assessed by their abilities to inhibit agonist (loperamide)-stimulated [^{35}S]GTPγS binding to membranes containing the cloned μ-opioid receptor.

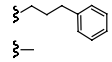
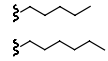
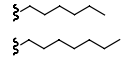
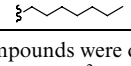
absolute regio- and stereochemistry of **28**, X-ray crystallography was conducted on the piperidine derivative **15**, obtained from **28** by hydrogenation. The crystal structure of **15**,[11] shown in Figure 1, indicates that the propyl side chain is positioned at the 2α-substitution of the piperidine ring. Condensation of **28** with the desired aldehydes under reductive amination conditions afforded the corresponding tertiary amines, which were converted to the compounds **17**, **18**, and **20**–**24** by hydrogenation. Alternatively, coupling of **28** with the desired acyl chloride derivatives provided the corresponding amides, which were converted to the compounds **16**, **19**, and **4** in two steps. Addition of various Grignard reagents to the nitrones **26a**/**26b**, followed by de-hydroxylation of the resulting hydroxylamine derivatives, provided the corresponding 2α-substituted piperidine derivatives **29a**–**e**, using the reaction conditions similar to the ones described for the synthesis of **28**. The *N*-phenethyl derivatives **2**, **3**, **5**, **11**, and **12** were then obtained from **29a**–**e** in two or three steps (Scheme 1). Oxidative cleavage of the olefinic bond of **30** using osmium tetroxide and sodium periodate provided the aldehyde **31** (Scheme 2). Treatment of **31** with phenylmagnesium chloride gave the alcohol **32** (diastereomeric mixture), which was converted to **33** in three steps. Hydrogenation of **33** followed by borane reduction of the resulting amide provided the derivative **13**. Condensation of **31** with pyrrolidine under reductive amination conditions afforded the corresponding pyrrolidine derivative, which was converted to the target compound **10** in four steps. The primary amine **34**, obtained from **31** under reductive amination conditions, was converted to the *N*-phenethyl derivative **7**. Acylation of **7** with acetyl chloride or benzoyl chloride provided the amides **8** and **9**, respectively. Treatment of **31** with ethyltriphenylphosphonium iodide or benzyltriphenylphosphonium chloride provided the Wittig



Scheme 1. Reagents and conditions: (a) Na_2WO_4, H_2O_2, $H_2O/CH_2Cl_2/CH_3OH$, 0–25 °C, 76%; (b) $CH_2{=}CHCH_2MgCl$, THF, 0–25 °C, 56%; (c) Zn, CH_3CO_2H/H_2O, sonication, 25 °C, 84–100%; (d) H_2, Pd/C, C_2H_5OH, 25 °C, 26–100%; (e) R^1MgCl, THF, 0–25 °C, 18–53%; (f) $C_6H_5CH_2CHO$, $BH_3 \cdot C_5H_5N$, C_2H_5OH, 25 °C, 6%; (g) $C_6H_5CH_2COOH$, *i*-Pr_2EtN, TBTU, CH_3CN, 25 °C, 64–77%; (h) $BH_3 \cdot S(CH_3)2$, THF, reflux, 33–64%; (i) R^2CHO, $BH_3 \cdot C_5H_5N$, C_2H_5OH, 25 °C, 53–100%; (j) CH_3COCl or $C_6H_5CH_2COCl$, Et_3N, DMAP, CH_2Cl_2, 61–87%; (k) $C_6H_5CO_2H$, *i*-Pr_2EtN, TBTU, CH_3CN, 25 °C, 64%.

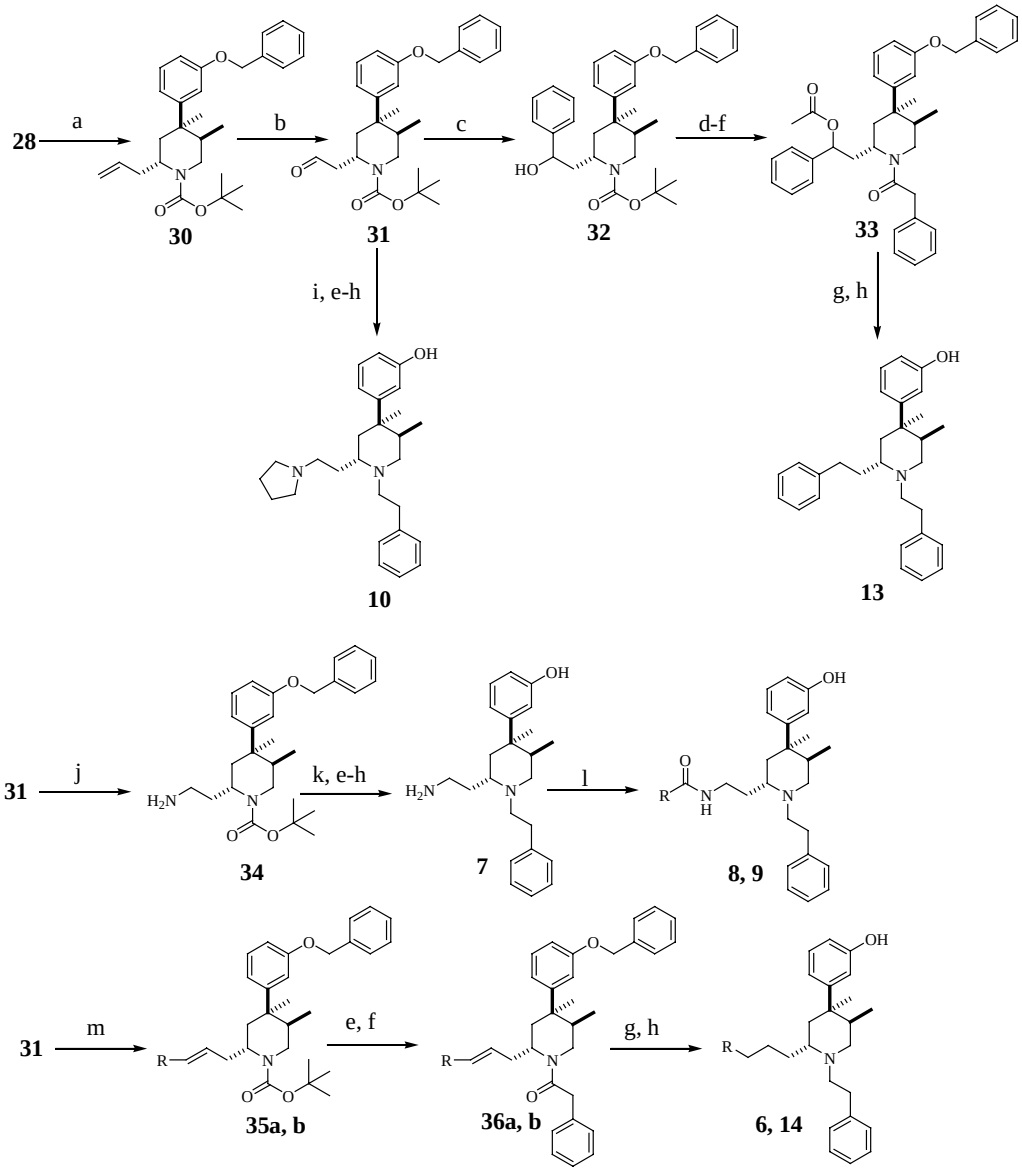
Table 2. Opioid receptor (μ, κ, and δ) binding data and in vitro antagonist activity (μ) of N-substituted-*trans*-4,5-dimethyl-2α-propyl-4-(3-hydroxyphenyl)piperidines



Compound	**R**	K_i (μ) (nM)[a]	IC_{50} (μ) (nM)[b]	K_i (κ) (nM)[a]	K_i (δ) (nM)[a]
15	H	560	>1000	690	>1000
16		700	170	360	880
17		19	16	74	180
18		520	170	220	>1000
19		410	100	270	>1000
20		430	320	360	>1000
21		550	290	610	>1000
22		380	210	570	>1000
23		47	39	150	340
24		13	9	57	80

[a] The potencies of the compounds were determined by testing the ability of a range of concentrations of each compound to inhibit the binding of the non-selective opioid antagonist, [^{3}H]diprenorphine, to cloned human μ-, κ-, and δ-opioid receptors, expressed in separate cell lines. K_i values are geometric means computed from at least three separate determinations.

[b] The potencies of the antagonists were assessed by their abilities to inhibit agonist (loperamide)-stimulated [^{35}S]GTPγS binding to membranes containing the cloned μ-opioid receptor.



Scheme 2. Reagents and conditions: (a) Boc_2O, Et_3N, THF, 0–25 °C, 79%; (b) OsO_4, NMO, $NaIO_4$, THF/H_2O, 25 °C, 87%; (c) C_6H_5MgCl, THF, 0–25 °C, 87%; (d) $(CH_3CO)_2O$, Et_3N, DMAP, CH_2Cl_2, 0–25 °C, 100%; (e) HCl/dioxane, CH_3OH, 25 °C, 75–100%; (f) $C_6H_5CH_2CO_2H$, *i*-Pr_2EtN, TBTU, CH_3CN, 25 °C, 48–73%; (g) H_2, Pd/C, C_2H_5OH, 25 °C, 40–100%; (h) $BH_3 \cdot S(CH_3)_2$, THF, reflux, 5–62%; (i) pyrrolidine, $BH_3 \cdot C_5H_5N$, C_2H_5OH, 25 °C, 70%; (j) $CH_3CO_2NH_4$, $NaBH_3CN$, CH_3OH, reflux, 100%; (k) $C_6H_5CH_2OCOCl$, Et_3N, THF, 25 °C, 37%; (l) CH_3COCl or C_6H_5COCl, Et_3N, THF, 0–25 °C, 68–69%; (m) $C_2H_5P(C_6H_5)_3I$ or $C_6H_5CH_2P(C_6H_5)_3Cl$, KO*t*-Bu, THF, C_6H_6, 25 °C reflux, 62–99%.

products **35a**,**b** (*E*/*Z* mixture), which were converted to the *N*-phenethyl derivatives **6** and **14**, respectively (see Table 2).

Opioid receptor binding data are found in Table 1.[12] Compounds **1**–**24** were tested for their affinities toward the cloned human μ-, δ-, and κ-opioid receptors as measured by their abilities to displace [^{3}H]diprenorphine from its specific binding sites.[12] The antagonist potencies of compounds **1**–**24** are assessed by their abilities to inhibit agonist (loperamide)-stimulated guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding to membranes containing μ-opioid receptors.[12] The antagonist potencies of compounds **1**–**24** were expressed as IC_{50} values. No agonist activity was detectable for compounds **1**–**24** at concentrations up to 10 μM. On the basis of the structure of **1**, the 2α-hydrogen of the piperidine ring was replaced by various moieties (Table 1) in order to define the SAR at this position. Introduction of a methyl group at the 2α position of the piperidine ring of **1** (compound **2**) resulted in an 8-fold decrease in μ-binding. Changing the methyl group of **2** to an ethyl (compound **3**), propyl (compound **4**), isopropyl (compound **5**), or butyl (compound **6**) moiety resulted in a further decrease in the affinity toward the μ receptor. Similarly, introduction of additional lipophilic functionalities (compounds **11**–**14**) or alkyl chain containing polar substituents (**7**–**10**) at the 2α-postion resulted in a marked decrease in μ binding affinity. Interestingly, compound **4**, which binds to the μ receptor with a K_i of 20 nM, displayed good in vitro antagonist activity ($IC_{50}(\mu)$ = 15 nM). The SAR at the piperidine

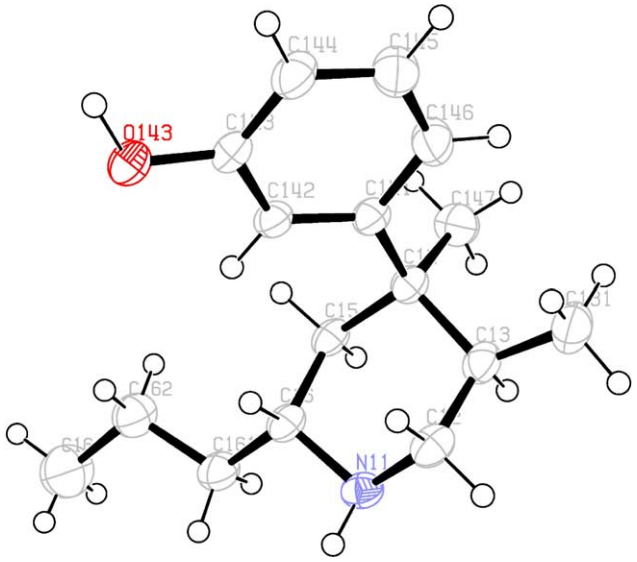


Figure 1. Crystal structure of **15**.

nitrogen of **4** was then investigated. It has been previously determined in the phenolic series that maximum potency and selectivity for the μ-opioid receptor were achieved when the N-substituent incorporated a lipophilic entity (phenyl ring or cyclohexyl) separated from the piperidine nitrogen by three atoms.[2] In this series, the *N*-phenpropyl derivative **17** bound with a comparable affinity (K_i = 19 nM) to μ-opioid receptors than its *N*-phenethyl analog (compound **4**). However, the benzyl derivative **16** binds very weakly to the μ-opioid receptor (K_i = 700 nM). With regard to N-alkylation, increase in the size of the chain length results in an increase in the affinity toward the μ-opioid receptor. In particular, the most active compound in this series, the 1-heptyl-2α-propyl piperidine derivative **24**, displayed potent μ in vitro antagonist activity ($IC_{50}(\mu)$ = 9 nM).

In summary, we have varied the substituent pattern at the 2α-position of the piperidine ring of the *trans*-4,5-dimethyl-4-(3-hydroxyphenyl)piperidine series and examined the resultant effects on μ-opioid receptor binding affinity. This study showed that only small linear alkyl groups (methyl, propyl) are tolerated at the 2α-position of the piperidine ring of this series. The 2α-substitution also led to decreased selectivity for μ versus δ and κ receptors. The highest μ in vitro antagonist activity was observed in the 1-heptyl-2α-propyl piperidine derivative **24**. Further SAR studies are in progress.

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11. Crystal structure data (SR-200307034.02) for **15**: $C_{16}H_{25}NO$, M_r = 247.38, crystal dimensions 0.40 × 0.23 × 0.10 mm^3, T = 150 K, monoclinic, space group $C2$(#5), a = 21.2960 (13), b = 8.7501 (3), c = 25.2605 (15) Å, β = 101.101 (3)°, Z = 12, V = 4619.0 (4) $Å^3$, ρ_{calcd} = 1.067 g cm^{-3}, MoK_α radiation (λ_0 = 0.71073 Å), μ = 0.061 mm^{-1}, $2\theta_{max}$ = 50.02°; of 13643 reflections collected 7383 were independent (R_{int} = 0:060); refinement method: full-matrix least squares on F^2, 521 refined parameters, GOF = 1.018, R = 0:049, R_w = 0:098. Full crystallographic details of **15** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC288363.
12. For a full description of the biological methods, see: Schlechtingen, G.; DeHaven, R. N.; Daubert, J. D.; Cassel, J. A.; Chung, N. N.; Schiller, P. W.; Taulane, J. P.; Goodman, M. *J. Med. Chem.* **2003**, *46*, 2104.