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N-SUBSTITUTED OCTAHYDRO-4a-(3-HYDROXYPHENYL)-10a-METHYL-BENZO[*g*]ISOQUINOLINES ARE OPIOID RECEPTOR PURE ANTAGONISTS

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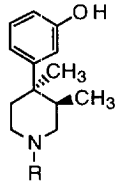
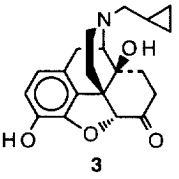
Abstract: N-Methyl- and N-phenylethyl-(±)-1,2,3,4,4a,5,10,10a-octahydro-4a-(3-hydroxyphenyl)-10a-methyl-benzo[*g*]isoquinolines (**4** and **5**, respectively) were found to be pure opioid antagonists. These compounds were shown to share many of the characteristics identified with the N-methyl- and N-phenylethyl *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**1** and **2**, respectively) including N-substituent mediated potency and a lack of N-substituent mediated antagonism. These data suggest that compounds **4** and **5** and the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**1** and **2**) may interact with opioid receptors similarly.

Introduction

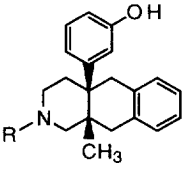
Reports from previous studies on the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine opioid antagonists such as **1** and **2** identified the 3-methyl substituent and its *trans* relative relationship to the 4-methyl substituent as being both necessary and sufficient to impart antagonist activity to the agonist 4-(3-hydroxyphenyl)piperidine.[1–4] In addition, these studies also demonstrated that the N-substituent on the piperidine ring controlled their potency and antagonist efficacy.[4] This feature distinguished the 3,4-dimethylphenylpiperidines from the oxymorphones like naltrexone (**3**), which relies on particular N-substituents (i.e., cyclopropylmethyl) for expression of opioid antagonist activity.[5] In this study, we report the synthesis of N-methyl and N-phenylethyl (±)-1,2,3,4,4a,5,10,10a-octahydro-4a-(3-hydroxyphenyl)-10a-methylbenzo[*g*]isoquinolines (**4** and **5**, respectively) and show that these compounds are opioid pure antagonists with properties similar to those of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of opioid antagonists.



1, R = CH_3
2, R = CH_2CH_2Ph



3



4, R = CH_3
5, R = CH_2CH_2Ph

Chemistry

The N-methyl and N-phenylethyl derivatives of (±)-1,2,3,4,4a,5,10,10a-octahydro-4a-(3-hydroxyphenyl)-10a-methylbenzo[*g*]isoquinoline (**4** and **5**, respectively) were prepared starting from tetrahydropyridine (**6**) according to the method illustrated in the Scheme.[6] Accordingly, **6** was deprotonated with *sec*-butyl lithium

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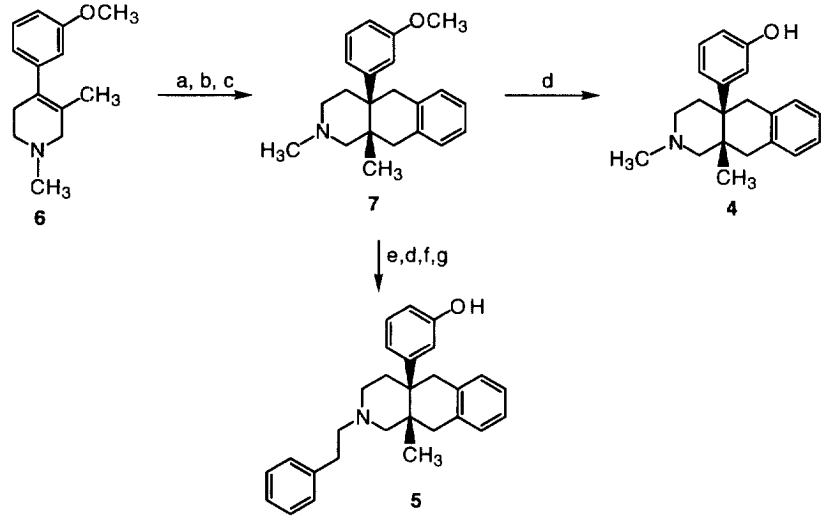
followed by alkylation with α,α'-dichloroxylene. This material was not isolated but was immediately cyclized with sodium iodide in refluxing acetonitrile followed by reduction with sodium borohydride to provide intermediate **7** in 23% yield. The N-methyl derivative (**4**) was prepared via O-demethylation employing refluxing HBr in acetic acid. The N-phenylethyl derivative (**5**) was prepared from **7** by N-demethylation using phenylchloroformate in refluxing toluene followed by subjecting the crude carbamate to refluxing HBr in acetic acid to cleave the urethane and deprotect the phenol. Conversion of this material to the desired N-phenylethyl analog **5** was accomplished by coupling with phenylacetic acid using benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) followed by reduction of the resulting amides using borane in tetrahydrofuran.

Scheme



Reagents: (a) *s*-BuLi, THF; α,α'-dichloroxylene; (b) NaI, CH_3CN; (c) $NaBH_4$, EtOH; (d) HBr, HOAc; (e) PhOCOCl, toluene; (f) phenyl acetic acid, BOP, TEA, THF; (g) borane/THF.

Results and Discussion

Previous studies have provided strong evidence that the antagonist activity of N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines is expressed via a phenyl equatorial piperidine chair receptor–ligand interaction as illustrated in Figure 1b.[2] This is in contrast to the phenyl axial piperidine chair conformation exhibited by naltrexone (Figure 1a). The benzoisoquinoline system (Figure 1c) was selected for synthesis as this fused ring system locks the piperidine substructure into the phenyl equatorial conformation proposed to be responsible for antagonist activity.

Figure 1a

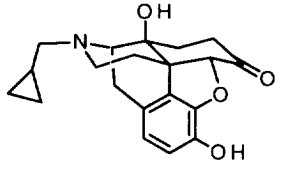


Figure 1b

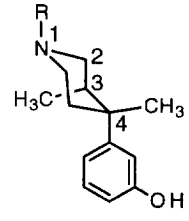
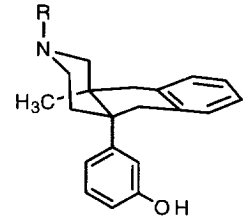


Figure 1c



The binding affinities for the N-methyl and N-phenylethyl derivatives of (±)-1,2,3,4,4a,5,10,10a-octahydro-4a-(3-hydroxyphenyl)-10a-methylbenzo[*g*]isoquinolines (**4** and **5**, respectively) were determined using competitive

binding assays following previously reported procedures (Table 1).[7] For comparison, the radioligand binding assay data for the reference compounds **1** and **2** are given in Table 2.[4] As these data sets are from different assays, the binding data obtained for naltrexone (**3**) are provided as a reference standard from both sets of assays. Inspection of the data reveals a shift in the receptor binding preference of the benzoisoquinolines in favor of the kappa receptor relative to the *trans*-3,4-dimethyl-4-phenylpiperidines, which typically show greater potency at the mu receptor. However, the overall preference for mu/kappa binding relative to delta binding is preserved (the 3,4-dimethyl-4-phenylpiperidines typically show the least preference for the delta receptor; data not shown). Increasing the size of the N-substituent (conversion of **4** to **5**) provides an overall increase in potency at all three receptors, a feature shared by the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines **1** to **2**. The latter information together with the general receptor binding preferences suggests that the benzoisoquinoline antagonists probably interact with the same subsites within the opioid receptors as do the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines. However, the addition of the bridging rings at positions 3 and 4 of the piperidine in **4** and **5** leads to both an increase in affinity for the kappa receptor as well as a loss of affinity for the mu receptor relative to the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine antagonists.

Table 1. Radioligand Binding Results at the Mu, Delta, and Kappa Opioid Receptors for N-Methyl- and N-Phenylethyl-1,2,3,4,4a,5,10,10a-octahydro-4a-(3-hydroxyphenyl)-10a-methylbenzo[*g*]isoquinolines

	K_i (nM±SD)		
Compound	μ, [^{3}H]DAMGO	δ, [^{3}H]DADLE	κ, [^{3}H]U69,593
4	297 ± 23	>5710	166 ± 15
5	11.2 ± 2.7	1270 ± 106	9.8 ± 1.7
3, naltrexone	1.39 ± 0.40	94.9 ± 6.6	4.71±0.12

Table 2. Affinities of the N-Substituted *trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidine Antagonists for the Mu and Kappa Opioid Receptors

	K_i (nM)[a]	
Compound	μ, [^{3}H]Naltrexone	κ, [^{3}H]Ethylketocyclazocine
1	80	833
2	1.5	52
3, naltrexone	0.56	3.9

[a]Data taken from ref. 4.

Results from the GTP binding functional assay,[7] which are listed in Table 3, show that compounds **4** and **5** display a pattern of activity consistent with the radioligand binding assay. Inhibition of agonist stimulated [^{35}S]GTPγS binding in guinea pig caudate by **4** and **5**, a measure of functional antagonist activity,[8] was greatest against U69,593 (kappa receptor) with the potency demonstrated against DAMGO (mu receptor) being only slightly less. The ability to inhibit SNC80 (delta receptor) stimulated [^{35}S]GTPγS binding was significantly lower. As in the previous assay, increasing the size of the N-substituent lead to an increase in potency. The fact that neither the N-methyl derivative **4** nor the N-phenylethyl (a classical agonist N-substituent) derivative **5** stimulated [^{35}S]GTPγS binding at concentrations as high as 1 μM shows that these compounds are opioid receptor pure antagonists. Since all N-phenylethyl substituted opioids possessing the 3-hydroxyphenyl in an axial position relative to the piperidine ring are opioid agonists,[5] these results further support the notion that **5** interacts with the

Table 3. Inhibition by Antagonists of [^{35}S]GTPγS Binding in Guinea Pig Caudate Stimulated by the Opioid Receptor Subtype-Selective Agonists, DAMGO (μ), SNC80 (δ), and U69,593 (κ).

	K_i (nM±SD) (N)		
Compound	DAMGO	SNC80[a]	U69,593
4	119 ± 7.93	222 ± 30.7	52.60 ± 6.38
5	10 ± 0.91	184 ± 24.3	6.61 ± 0.57
3, naltrexone	0.930 ± 0.21	19.3 ± 2.25	2.05 ± 0.21

[a]SNC80 ([(+)-4-[(αR)-α-(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide]). Agonist selective for delta opioid receptor.

opioid receptors in a phenyl equatorial piperidine chair conformation relative to the phenylpiperidine. A single crystal X-ray analysis of the hydrochloride salt of **5** showed that this compound indeed possessed a phenyl equatorial conformation in the solid state.[9]

In summary, retention of potent, opioid receptor pure antagonist activity was demonstrated for (±)-1,2,3,4,4a,5,10,10a-octahydro-4a-(3-hydroxyphenyl)-2-phenethyl-10a-methylbenzo[*g*]isoquinoline (**5**). Compounds **4** and **5** share many of the characteristics identified with the 3,4-dimethyl-4-phenylpiperidine antagonists like **1** and **2** including N-substituent mediated potency and a lack of N-substituent mediated antagonism. Also, these ligands display a strong preference for mu and kappa versus delta binding. Unlike the 3,4-dimethyl-4-phenylpiperidines, the benzoisoquinolines display a stronger preference for the kappa versus the mu receptor and a lower overall potency, as a racemic mixture, relative to typical *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine antagonists. Together this data suggests both a common site of action within the opioid receptors for compounds **4** and **5** and the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines as well as a probable lack of activity for one of the enantiomers of **5**. Studies to determine enantiospecific binding of compound **5** to the opioid receptors are currently underway and will be reported in due course.

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9. Atomic coordinates may be obtained from the Cambridge Crystallographic Data Centre (Cambridge University, Cambridge, CB2 1EW, UK).