ACS Medicinal Chemistry Letters

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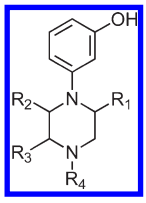
1-Substituted 4-(3-Hydroxyphenyl)piperazines Are Pure Opioid Receptor Antagonists

F. Ivy Carroll,* Juan Pablo Cueva, James B. Thomas, S. Wayne Mascarella, Scott P. Runyon, and Hernán A. Navarro

Center for Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, North Carolina 27709-2194

ABSTRACT This report describes the discovery that 1-substituted 4-(3-hydroxyphenyl)piperazines are pure opioid receptor antagonists. Compounds in this new series include *N*-phenylpropyl (3*S*)-3-methyl-4-(3-hydroxyphenyl)piperazine and (3*R*)-3-methyl-4-(3-hydroxyphenyl)piperazine, both of which display low nanomolar potencies at μ, δ, and κ receptors and pure antagonist properties in a [^{35}S]GTPγS assay.

KEYWORDS Opioid antagonists, 4-(3-hydroxyphenyl)piperazines



The opioid receptors, μ, δ, and κ, and the opioid-like receptor ORL-1 belong to the superfamily of G-protein coupled receptors (GPCRs) that possess seven helical trans-membrane spanning domains in their architecture.[1] These opioid receptors have been extensively studied, and thousands of compounds have been synthesized and evaluated by in vitro binding and functional assays as well as by animal models.[2] An integral part of the effort to characterize the opioid receptor system has been the discovery of potent, pure antagonists. Naloxone (**1a**) and naltrexone (**1b**), both competitive antagonists at μ, δ, and κ opioid receptors,[3] have been used extensively as pharmacological tools to identify and characterize opioid systems. Additionally, naloxone is approved to treat heroin overdose and to reverse respiratory depression caused by morphine.[3] Naltrexone is used to treat heroin and alcohol abuse.[4,5]

In 1978, Zimmerman and co-workers reported the discovery of a structurally unique series of opioid receptor pure antagonists based on *N*-substituted analogues of 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**2a**, LY272922).[6] Unlike naloxone (**1a**) and naltrexone (**1b**) where the antagonist activity is dependent on the *N*-allyl or *N*-cyclopropylmethyl substituent, all *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**) including the *N*-methyl analogue **2b** are opioid receptor pure antagonists.[6−10] A few of the more interesting analogues include alvimopan (**3**), which is an FDA-approved drug for GI motility disorder,[11] LY255,582 (**2d**),[9,12] which was developed to treat obesity, and the selective κ opioid receptor antagonist JDTic (**4**),[13−16] which shows activity in rat models of depression,[17] anxiety,[18] stress-induced cocaine relapse,[17] and nicotine withdrawal.[19]

Given that *N*-substituted analogues of **2a** have been developed as opioid receptor antagonists of clinical relevance, we initiated a program to identify new scaffolds that avoided lengthy chiral syntheses and could be readily functionalized by expanding the SARs surrounding this subset of opioid antagonists. *N*-Substituted 4-(3-hydroxyphenyl)piperazines (**5**) were identified with the expectation that a similarly *N*-functionalized piperazine ring system to that in the piperidine ring of the 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of compounds would provide more synthetically accessible pure opioid antagonists. These prospects were strengthened by a report by Komoto et al.[20] which described arylpiperazines such as **6a**,**b** as having nanomolar binding affinity at μ opioid receptors but did not present information regarding their functional antagonist properties.

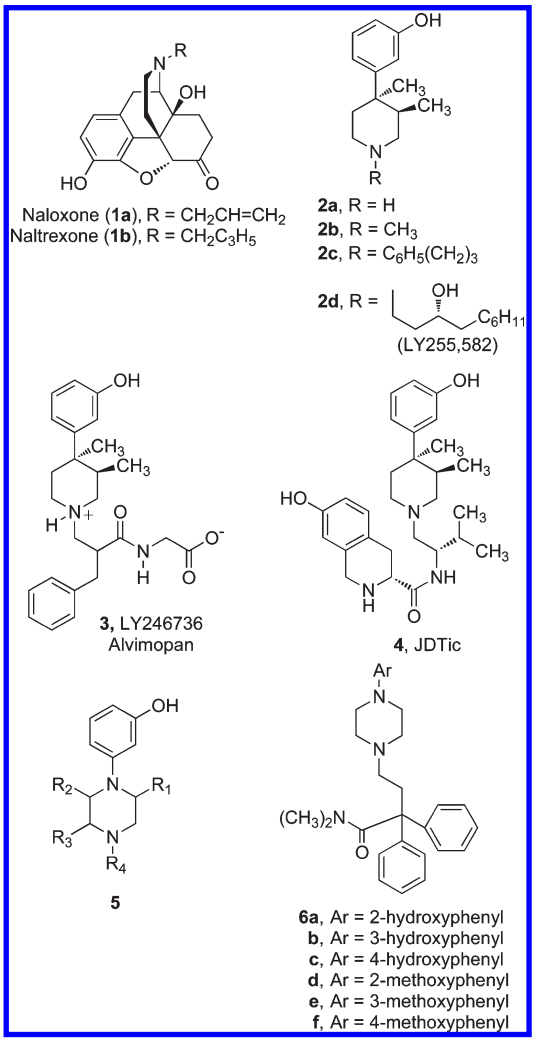
We discovered that 1-substituted 4-(3-hydroxyphenyl)piperazines (**5**) are pure opioid receptor antagonists (see Table 1 for structures of **5a**−**i**). At present, there are few reported classes of pure opioid receptor antagonists; the opiate class, represented by naloxone (**1a**), naltrexone (**1b**), and the *N*-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)piperidines, represented by alvimopan, LY255,582, and JDTic, are the most studied of non-peptide pure opioid receptor antagonists known[21] (see ref 21 for a recent review). Our discovery that 1-substituted 4-(3-hydroxyphenyl)piperazines (**5**) are pure opioid receptor antagonists will add an additional example of this important class of compounds.

Compounds **5a**−**f** were synthesized by the reaction sequence shown in Scheme 1. The *tert*-butoxycarbonyl-protected starting piperazines **7a**−**e** were commercially available, or easily prepared by treating the appropriate piperazine with di-*tert*-butylpyrocarbonate [$(Boc)_2O$] or 2-*tert*-butoxycarbamyloxyimino-2-phenylacetonitrile (Boc-ON) using standard conditions. The piperazine needed for the preparation of **7e** was synthesized according to reported methods.[22,23] *tert*-Butoxycarbonyl-protected piperazines **7b**,**c** were coupled to 3-bromoanisole under palladium-catalyzed conditions to give arylpiperazines **8b**,**c**. Arylation of **7d**,**e** gave higher yields when the arylation conditions reported by Bolliger and Frech[24] using potassium hexamethyldisilazide in dry

Received Date: June 1, 2010
Accepted Date: July 5, 2010
Published on Web Date: July 09, 2010

DOI: 10.1021/ml100126b | *ACS Med. Chem. Lett.* **2010**, *1*, 365–369

1,4-dioxane were employed. Removal of the *tert*-butoxycarbonyl group and demethylation were effected by treatment of



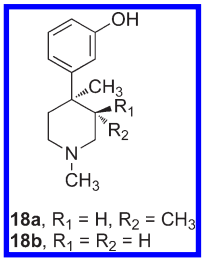
8a−**e** with concentrated HBr or boron tribromide to give **9a**−**e**. Reductive alkylation of **9a**−**e** using 3-phenylpropionaldehyde and sodium triacetoxyborohydride in 1,2-dichloroethane yielded the desired compounds **5a**−**e**. Reductive alkylation of **9b** using formalin and Raney nickel under a hydrogen atmosphere yielded **5f**.

Compounds **5g**,**h** were synthesized by the routes shown in Scheme 2. Compound **10**[25] was coupled to 3-bromoanisole under palladium-catalyzed conditions to give **11**. Subjection of **11** to palladium on carbon in refluxing aqueous acetic acid removed the *N*-allyl-protecting group to give **12**. Treatment of **12** with boron tribromide in methylene chloride at −78 °C affected demethylation of **12** to give the phenol **13**. Reductive alkylation of **13** using 3-phenylpropionaldehyde and sodium triacetoxyborohydride in 1,2-dichloroethane yielded **5h**. Treatment of **10** with $(Boc_2)O$ in methylene chloride containing triethylamine gives the *N*-allyl, *N*-Boc-protected piperazine **14**. Subjection of **14** to palladium on carbon in refluxing aqueous acetic acid selectively removed the *N*-allyl group to give **15**. Compound **15** was coupled to 3-bromoanisole under palladium-catalyzed conditions to yield **16**. Treatment of **16** with boron tribromide in methylene chloride at −78 °C effected removal of the *tert*-butoxycarbonyl group and demethylation of the methyl ether to give **17**. Reductive alkylation of **17** using 3-phenylpropionaldehyde and sodium triacetoxyborohydride in 1,2-dichloroethane afforded the desired compound **5g**.

Measures of opioid receptor antagonism and specificity were obtained by monitoring the ability of selected test compounds to inhibit stimulation of [^{35}S]GTPγS binding produced by the selective agonists (D-Ala,^{2}MePhe,^{4}Gly-ol^5)enkephalin (DAMGO, μ receptor), cyclo[D-Pen,^{2}D-Pen^5]enkephalin (DPDPE, δ), and *N*-methyl-*N*-[(5*R*,7*S*,8*S*)-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69,593, κ) in cloned human receptors (Table 1).

The 1-substituted 4-(3-hydroxyphenyl)piperazines (**5a**−**f**) are pure opioid receptor antagonists that differ structurally in two ways from the *N*-substituted 3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**). They have a nitrogen atom in place of carbon atoms at position 4 of the six-membered ring (relative to the piperidine ring) and do not have a 4-methyl substituent. Similar to *N*-methyl-3,4-*trans*-dimethyl-4-(3-hydroxyphenyl)piperidine (**2b**), the *N*-methyl substituted (2*S*)-methyl piperazine analogue **5f** is a pure opioid antagonist. Changing from *N*-methyl to *N*-phenylpropyl gives **5b**, which had K_e values of 0.88, 13.4, and 4.09 nM at the μ, δ, and κ opioid receptors, respectively. These data are similar to the K_e values obtained for *N*-phenylpropyl (3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (**2c**).

The (3*R*)-methyl piperazine analogue **5c** is also a pure opioid receptor antagonist with K_e values of 1.01, 6.99, and 1.57 nM at the μ, δ, and κ opioid receptors, respectively. Somewhat surprisingly, the piperazine analogue **5a**, which does not have a methyl substituent at the 3-position of the piperazine ring, was also a pure opioid receptor antagonist, with K_e values of 8.47, 34.3, and 36.8 nM at the μ, δ, and κ opioid receptors, respectively. These results contrast with the structure−activity information of compounds in the *N*-methyl 4-(3-hydroxyphenyl)piperidine series: the *cis*-3,4-dimethylpiperidine analogue **18a** is reported to be a mixed agonist−antagonist, and the 3-desmethyl analogue **18b** is a morphine-like agonist.[6,26]



The 1-phenylpropyl dimethylpiperazines (**5d,e,g,h**) all had higher K_e values at all three opioid receptors than the 1-phenylpropyl monomethylpiperazines (**5b** and **5c**). All compounds (**5a**−**f**) of this class thus far tested are nonselective opioid receptor antagonists.

Combining SAR studies of the *N*-substituted 4-(3-hydroxyphenyl)piperidine class of compounds with their ^{1}H and

DOI: 10.1021/ml100126b | ACS Med. Chem. Lett. 2010, 1, 365–369

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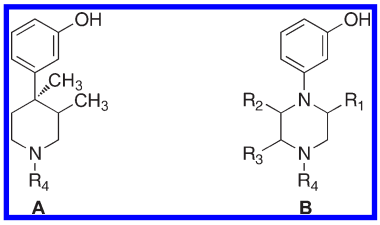
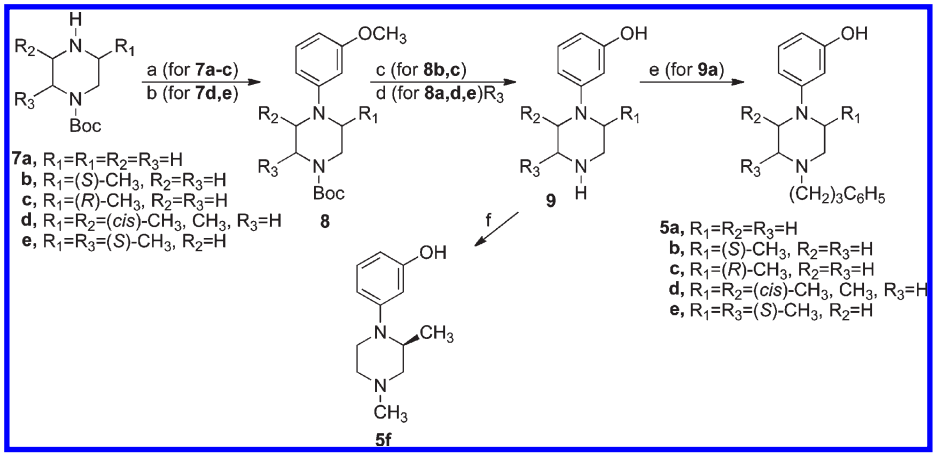
Table 1. Comparison of Inhibition of Agonist Stimulated [^{35}S]GTPγS Binding in Cloned Human μ, δ, and κ Opioid Receptors for **1b**, **2b,c**, and **5a**−**h**.



						K_e[a] (nM)		
compd	structure	R_1	R_2	R_3	R_4	μ, DAMGO	δ, DPDPE	κ, U69,593
1b						3.6 ± 1.0	61 ± 11	4.6 ± 1.5
2b	A				CH_3	29.3 ± 3.4	681 ± 241	134 ± 27.1
2c	A				$C_6H_5(CH_2)_3$	0.1 ± 0.02	0.9 ± 0.32	0.88 ± 0.17
5a	B	H	H	H	$C_6H_5(CH_2)_3$	8.47 ± 1.42	34.3 ± 5.8	36.8 ± 16.8
5b	B	(*S*)−CH_3	H	H	$C_6H_5(CH_2)_3$	0.88 ± 0.03	13.4 ± 4.2	4.09 ± 0.79
5c	B	(*R*)−CH_3	H	H	$C_6H_5(CH_2)_3$	1.01 ± 0.24	6.99 ± 2.3	1.57 ± 0.34
5d	B	(*S*)−CH_3	(*S*)−CH_3	H	$C_6H_5(CH_2)_3$	1650[b]	9000 ± 3200[c]	123 ± 58
5e	B	(*S*)−CH_3	H	(*S*)−CH_3	$C_6H_5(CH_2)_3$	17.9 ± 7.7	23.4 ± 6.0[c]	19.5 ± 7.9
5f	B	(*S*)−CH_3	H	H	CH_3	508 ± 26	NA[d]	194 ± 32.3
5g	B	(*S*)−CH_3	H	(*R*)−CH_3	$C_6H_5(CH_2)_3$	6.14 ± 1.7	55.3 ± 3.2	4.25 ± 0.82
5h	B	(*R*)−CH_3	H	(*S*)−CH_3	$C_6H_5(CH_2)_3$	18.0 ± 3.9	180 ± 68	22.9 ± 5.6

[a] Data are from the mean ± SE from at least three experiments. [b] Data from one experiment. [c] Data from two experiments. [d] NA = >10 μM.

Scheme 1[a]



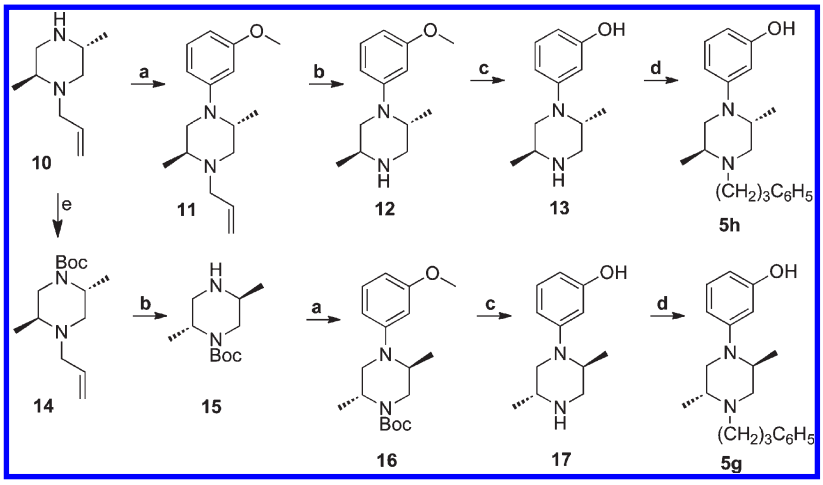
[a] (a) 3-Bromoanisole, $Pd_2(dba)_3$, KOtBu, $P(tBu)_3$, toluene, 100 °C, 18 h; (b) $KN(Si(CH_3)_3)_2$, 3-bromoanisole, 1,4-dioxane 100 °C, 2 h; (c) BBr_3, CH_2Cl_2, −78 °C, 4 h; (d) HBr (48%) reflux; (e) $C_6H_5(CH_2)_2CHO$, $Na(OAc)_3BH$, Et_3N, DCE; (f) Raney Ni, H_2CO, H_2, EtOH.

^{13}C NMR properties and conformational energy analyses, Zimmerman et al. concluded that the opioid antagonist activity of this class of compounds is mediated through the equatorial phenyl low-energy conformation.[27] Conformational energy analysis of the 4-(3-hydroxyphenyl)piperizines **5a** and **5c** shows that the phenyl equatorial conformers are favored by ca. 2 kcal/mol.

In summary, 1-substituted 4-(3-hydroxyphenyl)piperizines were found to be pure opioid receptor antagonists with potencies at the μ, δ, and κ opioid receptors in a [^{35}S]GTPγS assay similar to the potencies of *N*-substituted 4-(3-hydroxyphenyl)piperidines. Comparison of the SAR data of compounds in the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine series with the activities of compounds **5a**−**h** makes evident that, despite the isosteric resemblance between these two templates, there are significant differences between the respective manners in which ligands from these classes interact with opioid receptors to produce antagonist effects. The relatively simple synthesis of this new class of opioid receptor antagonists will allow efficient production of analogues.

DOI: 10.1021/ml100126b | *ACS Med. Chem. Lett.* **2010**, *1*, 365–369

Scheme 2[a]



[a] (a) 3-Bromoanisole, $Pd_2(dba)_3$, KOtBu, $P(tBu)_3$, toluene, 110 °C, sealed vessel; (b) Pd/C, CH_3CO_2H, H_2O, reflux; (c) BBr_3, CH_2Cl_2, −78 °C; (d) $C_6H_5(CH_2)_3CHO$, $Na(OAc)_3BH$, Et_3N, DCE; (e) $(Boc)_2O$, CH_2Cl_2, Et_3N.

Efforts in our laboratories are currently being directed toward a more comprehensive understanding of the structure−activity relationships of compounds in this new series.

SUPPORTING INFORMATION AVAILABLE

Experimental procedures for the synthesis and elemental analysis data for **5a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author: *To whom correspondence should be addressed. Phone: (919) 541-6679. Fax: (919) 541-8868. E-mail: fic@rti.org.

Funding Sources: This research was supported by the National Institute on Drug Abuse, Grant DA 09045.

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DOI: 10.1021/ml100126b | *ACS Med. Chem. Lett.* **2010,** *1*, 365–369

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DOI: 10.1021/ml100126b | *ACS Med. Chem. Lett.* **2010,** *1*, 365–369