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Investigation of Phenolic Bioisosterism in Opiates: 3-Sulfonamido Analogues of Naltrexone and Oxymorphone

Christopher R. McCurdy, Robert M. Jones, and Philip S. Portoghese*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

porto001@maroon.tc.umn.edu

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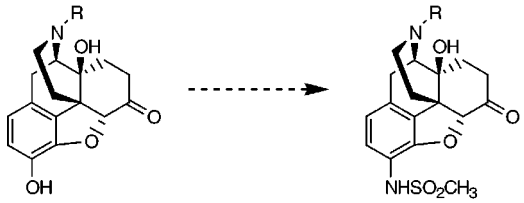
ABSTRACT



The phenolic hydroxy group of opiate-derived ligands is of known importance for biological activity. On the basis of its putative role as a hydrogen-bonding donor in the interaction with opioid receptors, it was replaced with a sulfonamide group because of their similar pK_a values. The first thebaine-derived 3-amino (8a, 8b) and subsequent sulfonamide analogues (10a, 10b) were synthesized from naltrexone (1a) and oxymorphone (1b) in a linear nine-step synthesis. The sulfonamides were tested in vitro and found inactive.

The opioid antagonist, naltrexone (**1a**), and its receptor agonist, oxymorphone (**1b**), are thebaine-derived structures that share a common opiate-type template. It is well-established that the phenolic hydroxy group of these and related opiates is important for recognition by opioid receptors.[1] Indeed, substitution at this position greatly reduces or abolishes activity. Given the putative role of the phenolic hydroxy proton as a hydrogen-bonding donor in enhancing binding, we have investigated the replacement with a group whose pK_a is similar. There is good precedent for such an approach, as replacement of a phenolic hydroxy with a sulfonamide group in catecholamines has been reported to afford ligands which retain the intensity of action and biological profile for adrenergic receptors.[2] This was attributed to the similar pK_a value of the sulfonamide and phenolic hydroxy groups, whose protons were presumed to function as donors in hydrogen bonding to the adrenergic receptor. Since adrenergic receptors, like opioid receptors, interact with G protein-coupled receptors, it seemed reasonable that a smiliar modification of thebaine-derived opiates might afford retention of biological activity. Here we describe the first reported synthesis and biological evaluation of 3-methylsulfonamide-substituted opiates in an effort to obtain ligands that retain affinity for opioid receptors. Such modification was of interest because it would permit the introduction of functionality without eliminating an acidic proton to that region of the opiate.

Direct conversion of a phenol to an aniline usually employs high temperatures that are not suitable for the stability of the opiate structure. The recent reports[3] of palladium-catalyzed amination have opened an efficient route for conversion of phenols to anilines. Indeed, such an approach was very recently utilized in the synthesis of 8-amino-substituted benzomorphan analogues.[4] Although the 8-phenolic hydroxy group of benzomorphans is in an equivalent position to the 3-phenolic hydroxy group of the thebaine-

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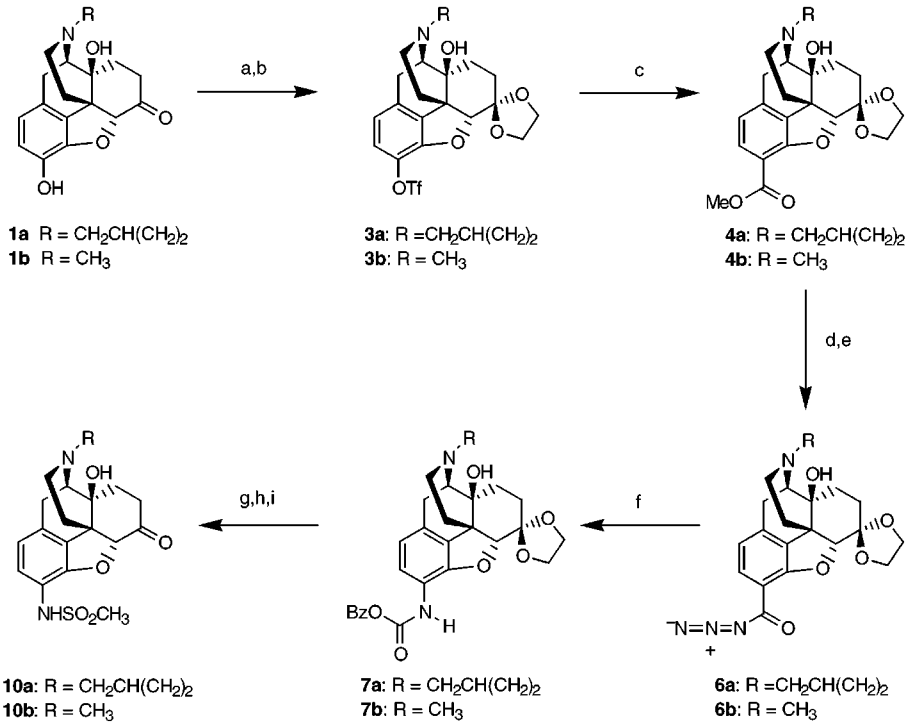
Scheme 1[a]



[a] Legend: (a) ethylene glycol, *p*-TSA, 65 °C, 1 mmHg; (b) *N*-phenyltrifluoromethylsulfonimide, TEA, CH_2Cl_2, 0 °C; (c) $Pd(OAc)_2$, CO, DPPF, MeOH, DMSO, 65 °C, CO atm; (d) $H_2NNH_2-H_2O$, 50 °C; (e) THF/H_2O, 2 N HCl, t-$BuNO_2$, 0 °C; (f) (1) benzene, TEA, reflux, (2) $PhCH_2OH$; (g) Pd/C, H_2, MeOH; (h) CH_3SO_2Cl, TEA, CH_2Cl_2, 0 °C; (i) HCl(aq), EtOH, reflux, 8 h.

derived opiates, under several conditions, including those employed in the synthesis of the 8-aminobenzomorphans, the palladium-catalyzed amination of **3a** and **3b** was unsuccessful. Since the 8-position of the benzomorphan structure does not contain an ortho epoxy group, it is possible that this may be a reason for the failure of this reaction with the thebaine-derived opiates. Consequently, we embarked on an alternate route involving carbon−carbon palladium cross-coupling chemistry in order to generate the 3-carbomethoxy opiates, which could subsequently be converted to amines via the Curtius rearrangement.

The desired target compounds (**10a**, **10b**) were synthesized as outlined in Scheme 1. The 6-keto group of **1a** and **1b** was protected by forming the ethylene glycol derived dioxolanes (**2a**, **2b**). Compounds **2a** and **2b** were converted to the corresponding triflates **3a (**96%) and **3b** (79%) using equivalent amounts of *N*-phenyltrifluoromethanesulfonimide and triethylamine. To a solution of triflate (**3a** or **3b**) containing DMSO−methanol (1.5:1) was added palladium acetate (0.1 equiv), diphenylphosphoferrocene (0.21 equiv), and triethylamine (2.2 equiv). Carbon monoxide gas was bubbled into this solution for 10 min, and the entire reaction mixture was sealed under a carbon monoxide atmosphere and heated to 65 °C for 3 h to afford the carboxymethyl esters[5] (**4a**, 78%; **4b**, 81%). Hydrolysis of **4a** and **4b** with lithium hydroxide in a mixture of THF and water afforded the free acids (not shown). One-pot Curtius rearrangements were attempted utilizing sodium azide or DPPA in either *tert*-butyl alcohol or benzyl alcohol with no success, presumably due to decomposition of the azide prior to reaction with the ester. Therefore, it was determined that the azide moiety would need to be synthesized on the opiate scaffold itself. The esters (**4a** and **4b**) were converted to the hydrazides (**5a**, 60%; **5b**, 55%) in neat hydrazine monohydrate. Treatment of a solution of **5a** or **5b** in a mixture of tetrahydrofuran and 2 N HCl with *tert*-butyl nitrite yielded the acyl azides **6a** (99%) and **6b** (92%). The azides were dissolved in benzene and in the presence of triethylamine were heated to reflux to form the isocyanate Curtius rearrangement[6] products which, without isolation, were converted to the benzyloxycarbamates (**7a**, 38%; **7b**, 24%) by refluxing with benzyl alcohol. Catalytic hydrogenolysis of the carbamates afforded the corresponding anilines (**8a**, 98%; **8b**, 98%). Subsequent conversion of **8a** or **8b** to the methyl sulfonamides (**9a**, 50%; **9b**, 49%) followed by deprotection of the 6-dioxolane afforded the desired sulfonamides **10a** (68%) and **10b** (70%).

The opiate sulfonamides (**10a**, **10b**) were tested on the electrically stimulated guinea pig ileum[7] and mouse vas deferens[8] preparations at a concentration of 1 μM and were

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found to be devoid of agonist or antagonist activity. Similarly, they exhibited no significant binding ($K_i > 1\ \mu M$) to cloned μ, κ, or δ opioid receptors transiently expressed in HEK293 cells. The absence of significant binding or function may be due to the bulky nature of the sulfone moiety.

In conclusion, this is the first reported synthesis of 3-sulfonamide-substituted derivatives of thebaine-derived opiates. In addition, this report provides a nontrivial synthetic route to 3-amino opiates via the Curtius rearrangement. These compounds were synthesized to determine whether a sulfonamide group could replace the phenolic 3-hydroxy group of an opiate in view of their similar pK_a values. Unlike catecholamines, where activity was retained when one of the phenolic groups was replaced by a sulfonamide group, similar modification in the opiates abolishes activity. The reason for this is unclear, but in contrast to the catecholamines, it appears likely that the steric bulk of the sulfone moiety makes the sulfonamide group an unsuitable substitution in opiate ligands.

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Supporting Information Available: Experimental procedures and spectral data of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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