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A selective delta opioid receptor antagonist based on a stilbene core

Alyssa M. Hartung [a], Hernan A. Navarro [b], David F. Wiemer [a], Jeffrey D. Neighbors [a,c,d,*]

[a] Department of Chemistry, The University of Iowa, Chemistry Building, Iowa City, IA 52242-1294, United States
[b] Discovery Sciences, RTI International, Research Triangle Park, NC 27709, United States
[c] Department of Pharmacology, Pennsylvania State University Hershey College of Medicine, Hershey, PA 17033, United States
[d] Penn State Hershey Cancer Institute, Hershey, PA 17033, United States

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ABSTRACT

Studies of directed *ortho* metalation reactions on an aromatic substrate with multiple potential directing groups have identified conditions that favor either of two regioisomers. One of these regioisomers has been converted to an analogue of the stilbene pawhuskin A, and been shown to have high selectivity as an antagonist of the delta opioid receptor. Docking studies have suggested that this compound can adopt a conformation similar to naltrindole, a known delta antagonist.

The development of opioid compounds for treatment of pain is one of the triumphs of modern medicine.[1] These compounds, however, are associated with numerous negative side effects, most prominently including sensitization to chronic treatment leading to development of addiction and the associated societal problems.[2] The canonical opioid receptors kappa (KOP), mu (MOP), and delta (DOP) mediate a variety of key physiological processes, and are involved with the adaptation to chronic opioid analgesic treatment to different degrees.[1,3] The primary analgesic response is attributable to activation of the MOP.[4] The DOP is much less well studied but appears to play an interesting role in the development of learned habitual responses to chronic treatment with these potent analgesics.[5] Because of this role in the addictive effects of the opioid pain medications, selective DOP receptor antagonists are gaining interest in the field of pain management and psychiatry.[6–8]

Our interest in opioids stems from the reported isolation of the pawhuskin family of natural products.[9] These compounds are non-nitrogenous opioid receptor modulators based around a stilbene core, and show significant potential as a scaffold for further exploration aimed at developing novel drug leads. There are several other non-nitrogenous scaffolds that are being studied as leads for opioid receptor modulators with the most prominent being the salvinorins, which have been studied predominantly as KOP agonists.[10–12] Our studies of the pawhuskins have led to the synthesis of pawhuskin A (**1**)[13] and C (**2**)[14] (Fig. 1) as well as several analogues, and to the demonstration that compound **1** is a moderately selective KOP antagonist. During these explorations we synthesized compound **3**,[15] with the prenyl group on the 'left-half' of the molecule (the portion biochemically derived from shikimate) placed in a different orientation than in the parent pawhuskin A. To our surprise, this regioisomer turned out to be an opioid receptor antagonist with high selectivity for the KOP ($\delta/\kappa > 67$ and $\delta/\mu > 67$) and to be a bit more potent than pawhuskin A ($K_e = 0.15$ μM vs 0.20 μM).[15]

In our synthesis of pawhuskin A we employed a directed *ortho* metalation approach (Scheme 1).[13] Lithiation of the ring may be directed by the MOM protecting group and presumably the benzylic alcohol anion of the known starting material (**5**) to afford the intermediate anion. Transmetalation to the copper species followed by treatment with prenyl bromide gave the final product alcohol (**6**) in modest yields as the only easily isolated product. In attempts to improve the yield use of copper iodide and TMEDA was explored because this had been shown in our prior work with halogen metal exchange reactions in similar systems to afford superior yields.[16] The addition of TMEDA and use of copper iodide in ether afforded a mixture of the arene **6** and the isomeric prenylated compound **7** in a 1:1.2 ratio (Table 1, entry 1) and a combined yield of 36%. A more thorough exploration of the conditions showed that either regioisomer could be made with some selectivity. Slightly colder reaction temperatures afforded the best combined yield of products favoring compound **7** (entry 2). Forgoing the transmetalation step improved the ratio of compound **7** to **6**

* Corresponding author.

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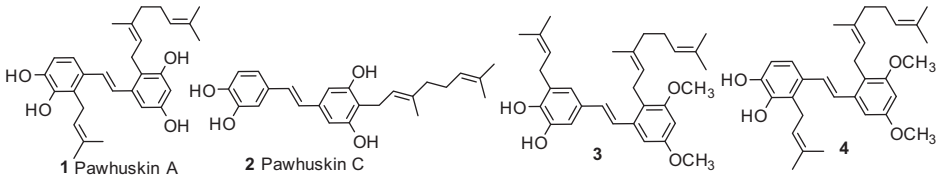
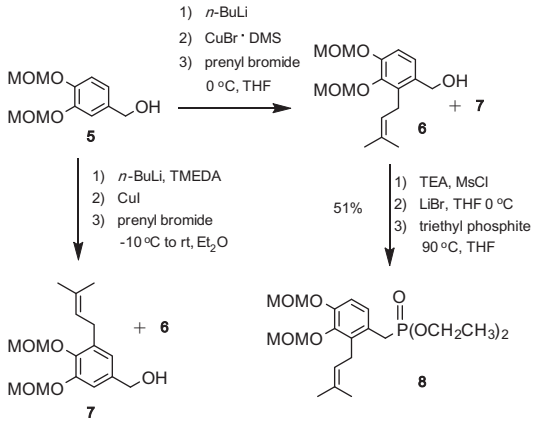
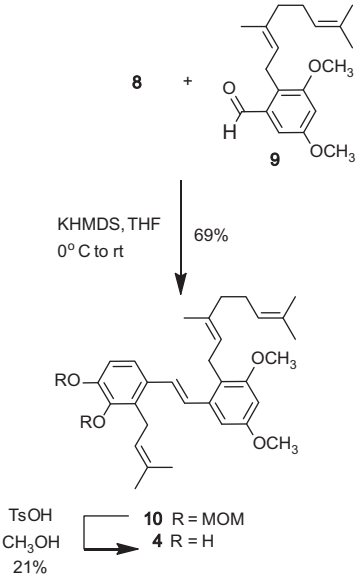


Figure 1. Structures of pawhuskins and analogues.



Scheme 1.



Scheme 2.

but the overall yield was particularly disappointing (entry 3). Reaction at room temperature in THF with copper bromide but without TMEDA afforded the alternate regioisomer **6** as the predominant product (**6**:**7** 2.9:1 entry 4) in a combined yield of 47%. Variation of the reaction temperature and the scale, which also might afford better control of the reaction temperature, did not improve this ratio (entries 5–7).

With a viable route to compound **6** in hand we set about preparation of the pawhuskin A analogue **4**. Treatment of the benzylic alcohol **6** with methanesulfonyl chloride in trimethylamine gave the mesylate which was converted into the bromide without isolation. An Arbuzov reaction was carried out by heating the bromide with triethyl phosphite to give the desired phosphonate **8** in moderate yield. Horner–Wadsworth–Emmons coupling of phosphonate **8** and the known aldehyde **9**[15] afforded the protected stilbene **10** (Scheme 2). Global deprotection of the methoxymethyl ether groups by treatment with *p*-toluenesulfonic acid in methanol gave the desired analogue **4**.

Analogue **4** was tested for opioid receptor activity by first assessing if intrinsic agonist activity was present. After finding no agonist activity, this compound was tested for antagonist selectivity against the mu, delta and kappa opioid receptors (MOP, DOP, and KOP). To our surprise the analogue **4** displayed strong antagonist activity that was very selective for the DOP (K_e = 25 nM, κ/δ > 400, MOP/DOP μ/δ > 400, Fig. 2). This was an intriguing

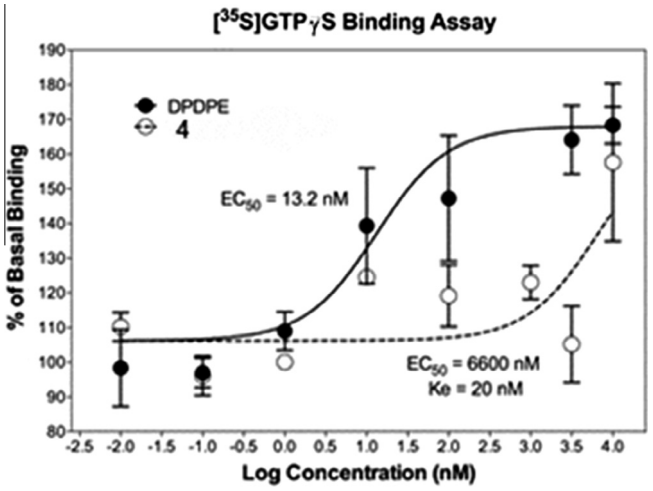


Figure 2. Antagonist activity of pawhuskin analogue **4** at the DOP.

Table 1
Effect of temperature and other parameters on directed *ortho* metalation of compound **5**

Trial	Scale (mmol)	TMEDA (mmol)	*n*-BuLi (mmol)	CuBi·DMS (mmol)	Prenyl bromide (mmol)	Solvent [concd]	*T*	**6**:**7**	Yield (%)
1	6.51	14.01	14.25	6.53[a]	7.16	Et_2O [0.07 M]	−10 °C to rt	1.0:1.2	36
2	7.97	16.67	17.5	7.98[a]	11.93	Et_2O [0.06 M]	−20 to 0 °C to rt	1.0:1.9	25
3	4.18	8.67	9.2	NA	6.31	Et_2O [0.06 M]	−20 to 0 °C to rt	1.0:4.0	10
4	4.46	NA	9.52	4.91	4.94	THF [0.13 M]	rt	2.9:1.0	47
5	0.92	NA	1.95	1.02	1.11	THF [0.13 M]	rt	1.1:1.0	25
6	1.31	NA	2.75	1.11	1.53	THF [0.13 M]	0 °C	1.0:1.0	39
7	4.53	NA	9.52	4.98	4.94	THF [0.13 M]	0 °C	1.8:1.0	51

[a] In these experiments, copper iodide was used.