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Synthesis of potent sigma-1 receptor ligands via fragmentation of dextromethorphan

Mark P. Arrington, Claire Brown and C. Eric Schwartz*

UCB Research, Inc., 840 Memorial Drive, Cambridge, MA 02139, USA

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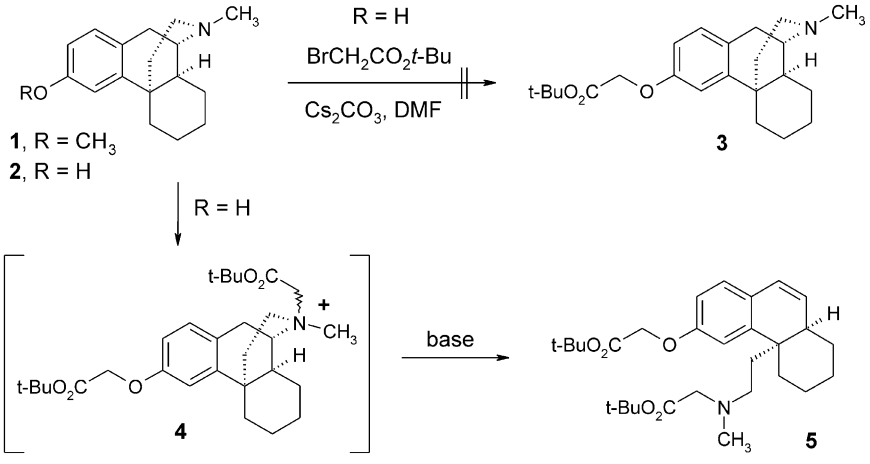
Abstract—Treatment of dextromethorphan **1** with various alkylating agents followed by base treatment led to Hoffman-type elimination reactions to produce a series of tricyclic derivatives, **6**. These derivatives were characterized in vitro as sigma-1 receptor ligands.

Dextromethorphan (**1**, Scheme 1) is one of the most widely used antitussive agents despite the fact that its precise mechanism of action has not been fully elucidated. Dextromethorphan displays antagonist activity at the cationic NMDA receptor channel[1] and agonist activity at sigma receptors,[2] suggesting that the antitussive activity may involve action at either or both of these receptors. Indeed, the antitussive effect of dextromethorphan in animal models of citric acid-induced cough was reversed[3] by rimcazole, a sigma receptor antagonist, suggesting a role for the sigma receptor in modulating the cough response.

While dextromethorphan is a nonnarcotic antitussive with a cleaner profile than codeine,[4] we were interested in preparing zwitterionic derivatives in an attempt to limit CNS penetration and related side effects while maintaining antitussive activity via activity at peripheral sigma receptors.[5] Accordingly, we treated dextrorphan[6] (**2**) with *t*-butyl bromoacetate in the presence of cesium carbonate with the expectation of isolating the glycolate **3** (Scheme 1); subsequent deprotection of the *t*-butyl ester would then provide the desired zwitterion. However, the major product from this reaction was the tricycle **5**, isolated in modest yield (ca. 35%). This product



Scheme 1.

* Corresponding author. Fax: +1-617-547-8481; e-mail: eric.schwartz@ucb-group.com

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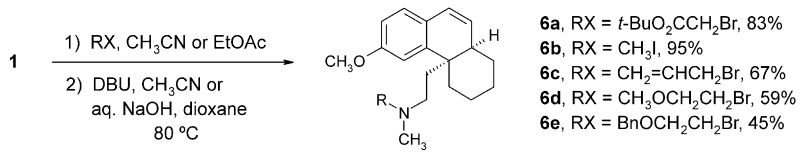
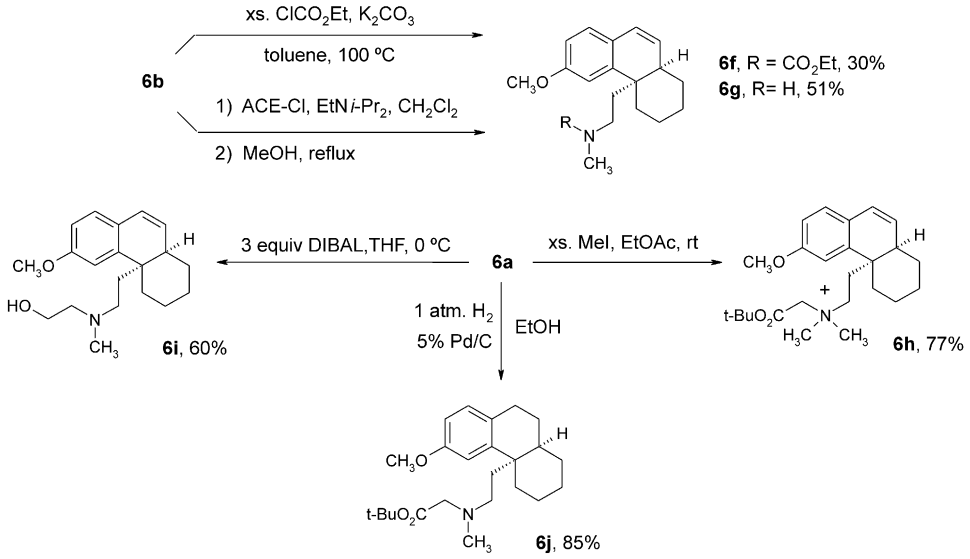


Scheme 2.

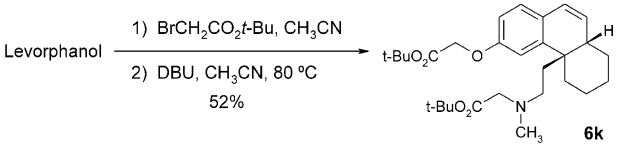


Scheme 3.

presumably arises from *O*- and *N*-alkylation to form the quaternary ammonium salt **4** followed by a based-induced fragmentation to afford **5**.[7] Somewhat surprisingly,[8] **5** was an extremely potent sigma-1 receptor ligand with a $K_i = 14$ nM.[9] This finding prompted us to prepare additional analogues and examine their in vitro affinities for the sigma-1 receptor.

We found that the yield of **5** could be improved to 55% when the transformation was carried out in two steps: alkylation to form the diastereomeric quaternary ammonium salts **4**[10] ($BrCH_2CO_2t$-Bu, EtOAc) followed by base-induced fragmentation (DBU, CH_3CN, 80 °C) to provide **5**. Similar reactions with dextromethorphan, **1**, and various electrophiles allowed easy access to a variety of tertiary amine-substituted tricycles (**6**, Scheme 2).

The dimethylamine **6b** was used to generate two additional analogues, as shown in Scheme 3. Demethylation with ethyl chloroformate[11] afforded the carbamate **6f**, while demethylation using α-chloroethyl chloroformate (ACE-Cl)[12] provided the secondary amine **6g**. Additional analogues were generated from the ester **6a** via *N*-alkylation (**6h**), ester reduction (**6i**), and olefin hydrogenation (**6j**). The last analogue, **6k**, is the enantiomer



Scheme 4.

of **5** and was derived from levorphanol as shown in Scheme 4.

All the tricycles **6** were examined in vitro for their sigma-1 receptor affinity.[9] The results are shown in Table 1, along with the values for **5** and dextromethorphan[13a] (**1**), and some trends are readily observable. The aryl glycolate moiety of **5** is not necessary for high affinity as the aryl methyl ether **6a** retains significant affinity for the receptor. Removal of the ester group from **6a** results in a 6.5-fold loss of affinity (**6b**), but this can be regained by addition of small lipophilic substituents to the nitrogen atom (**6c**,**d**). However, the ethoxybenzyl-substituted analogue **6e** shows a loss of affinity suggesting that the phenyl ring of this substituent is not well accommodated by the receptor.

The nature of the nitrogen atom is also important for receptor binding. The carbamate **6f** is inactive, demonstrating the need for a basic nitrogen atom. The secondary amine **6g** is less potent than the corresponding tertiary amine **6b**, and the quaternary ammonium salt **6h** loses all affinity for the receptor. The tertiary amine

Table 1. Sigma-1 receptor binding affinity

Compd	K_i (nM)	Compd	K_i (nM)
1	348 ($n=5$)	**6f**	>3300 ($n=4$)
5	14 ($n=6$)	**6g**	456 ($n=3$)
6a	37 ($n=8$)	**6h**	>3300 ($n=4$)
6b	245 ($n=5$)	**6i**	161 ($n=4$)
6c	49 ($n=4$)	**6j**	373 ($n=3$)
6d	49 ($n=5$)	**6k**	115 ($n=3$)
6e	241 ($n=4$)		

6i shows that a small, polar *N*-substituent ($HOCH_2CH_2$–) is tolerated but with some loss of affinity (compare to **6c**,**d**).

Saturation of the olefin in **6a** leads to **6j**, with a corresponding 10-fold loss of binding affinity, indicating that conformation and perhaps rigidity are key elements for recognition of this scaffold by the receptor. The interaction is also stereoselective as the enantiomer of **5** (**6k**) is a less potent ligand, albeit only by a factor of eight.

In summary, we have reported the preparation of a novel series of potent sigma-1 receptor ligands and have established an initial SAR for this series. Further analogues as well as functional characterization (agonism versus antagonism) should provide additional insights into the sigma-1 binding site.[13b,14]

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