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μ-Opioid/5-HT$_4$ dual pharmacologically active agents—Efforts towards an effective opioid analgesic with less GI and respiratory side effects (Part I)

Liming Shao *, Fengjiang Wang, Michael C. Hewitt, Timothy J. Barberich

Sepracor Inc., 84 Waterford Drive, Marlborough, MA 01752, USA

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ABSTRACT

Novel compounds were prepared that united the pharmacologies of the μ-opioid tramadol with the 5-HT4 agonists metoclopramide and norcisapride. The synthesis, chiral separation and in vitro activity of the new compounds is described.

Hundreds of years after the discovery of morphine and its application to pain treatment, opioids remain the most effective and most widely prescribed analgesic class. For many decades scientists around the world have been diligently working to uncouple the analgesic potency from the concomitant side effects that occur after chronic use.

Constipation is the most common adverse effect of chronic opioid therapy,[1] and typically afflicts at least 41% of patients receiving long-term therapy.[2] It is known that opioid-induced constipation is largely peripherally mediated—μ and *delta* opioid receptors located on gut smooth muscle play a large role in gastrointestinal motility, with μ directly affecting the myenteric plexus.[3] Prevention and treatment of opioid-induced constipation includes both non-pharmacologic options such as hydration, diet and exercise, and pharmacologic intervention such as laxatives, opioid-receptor antagonists, and prokinetics.

The idea of combining multiple pharmacologies into a single molecular entity (i.e. polypharmacology) was the common paradigm for drug discovery when animal models of disease were the main drivers of compound selection, but fell out of vogue with the growth of in vitro biology and single target (selective) drugs. The failure of the single target approach to adequately treat psychiatric diseases such as depression and schizophrenia led to drug discovery programs against multiple targets such as the triple (5-HT, Norepinephrine and dopamine) reuptake inhibitors[4] for depression and D$_2$/5-HT$_{2a}$ antagonists[5] for schizophrenia. This general concept has been coined 'designed multiple ligands (DML)'[6] and can be defined as taking two selective ligands and combining them into a single molecular entity with dual activity. There are a number of advantages to the DML approach over multicomponent drugs such as Caudet[7] or Vytorin,[8] including a reduced risk of drug-drug interactions and a less complex PK/PD relationship. Most importantly, the success of marketed dual acting drugs such as the selective serotonin and norepinephrine reuptake inhibitor Duloxetine has validated this approach as a potential solution to patients who are not responding to their current (selective) medications.

(±)-*cis* Tramadol is used for the treatment of moderate to moderately severe pain.[9,10] The analgesic activity of tramadol is thought to be the result of a dual mechanism—the parent (**1**) acts as an inhibitor of norepinephrine and serotonin reuptake and the major *O*-desmethyl metabolite (**2**) is a potent μ-opioid receptor agonist (Fig. 1).[11] Not unlike other opioids, tramadol also causes

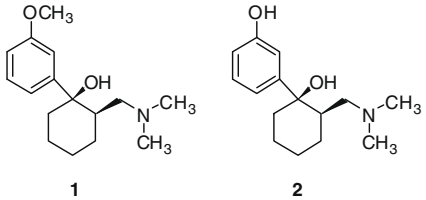

Figure 1. (±)-Tramadol **1** and metabolite (±)-**2**.

* Corresponding author. Tel./fax: +1 5083577467.
E-mail address: liming.shao@sepracor.com (L. Shao).

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a number of side effects including constipation, nausea, dizziness, and somnolence. Sepracor has maintained an active research program targeted toward development of improved version of tramadol for a number of years, and our previous efforts to improve the phamarcokinetics[12] and potency[13] of Tramadol have already been disclosed. While the complex pharmacology of Tramadol presented some difficulties in the development of DMLs, our familiarity with the Tramadol scaffold gave us a competitive advantage and allowed us more rapid entry into analog sets using Tramadol as the μ-opioid component.

Metoclopramide (Reglan, Fig. 2) is used clinically to induce gastric emptying; cisapride (Prepulsid) was on the market as a prokinetic agent before it was voluntarily withdrawn by Janssen in 2000 because of reports of QT prolongation. Both compounds are thought to work via 5-HT_4 agonism; it is known that (+)-norcisapride, one of the primary de-alkylated metabolites of the parent drug,[14] is a potent 5-HT_4 agonist/5-HT_3 antagonist and has activity in animals models of constipation such as $MgSO_4$ induced intestinal lavage.[15] Furthermore, norcisapride is devoid of inhibitory activity at the potassium hERG channel in vitro. Our idea was to combine the pharmacophores of Tramadol with Metoclopramide or norcisapride to create a novel analgesic that would cause less constipation after chronic treatment (Fig. 2). It is also worth mentioning that BIMU8, a selective 5-HT_4 agonist, was shown to

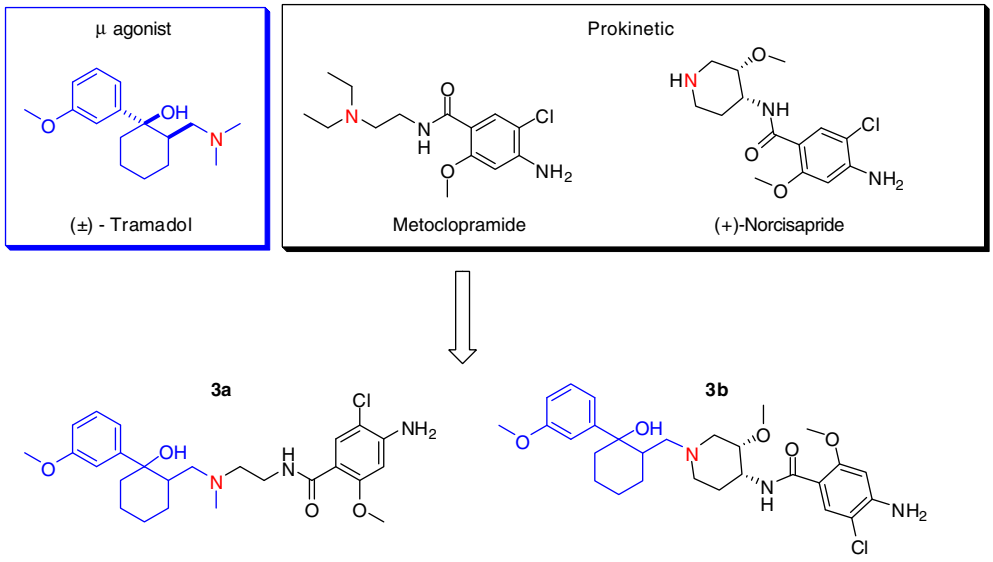
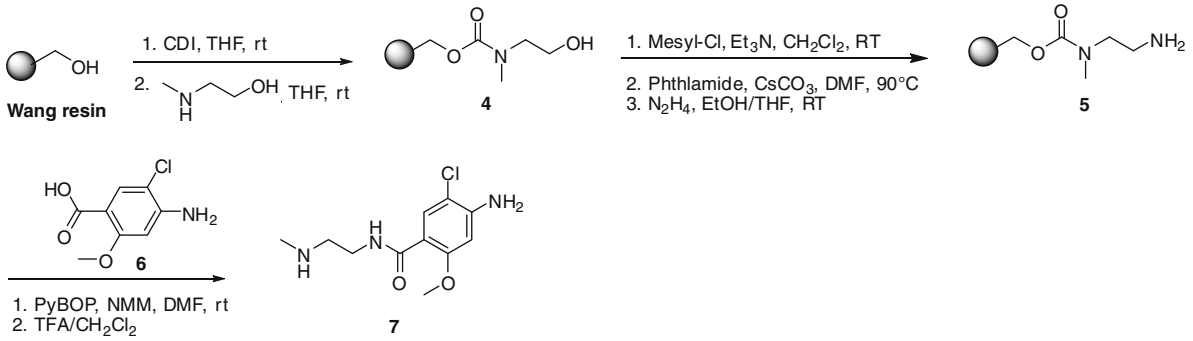
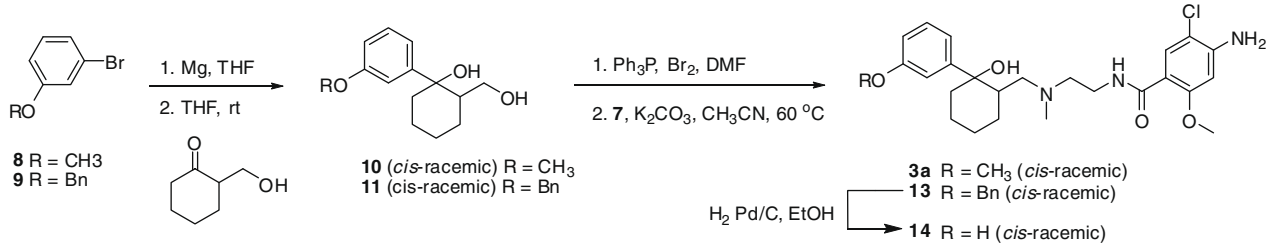


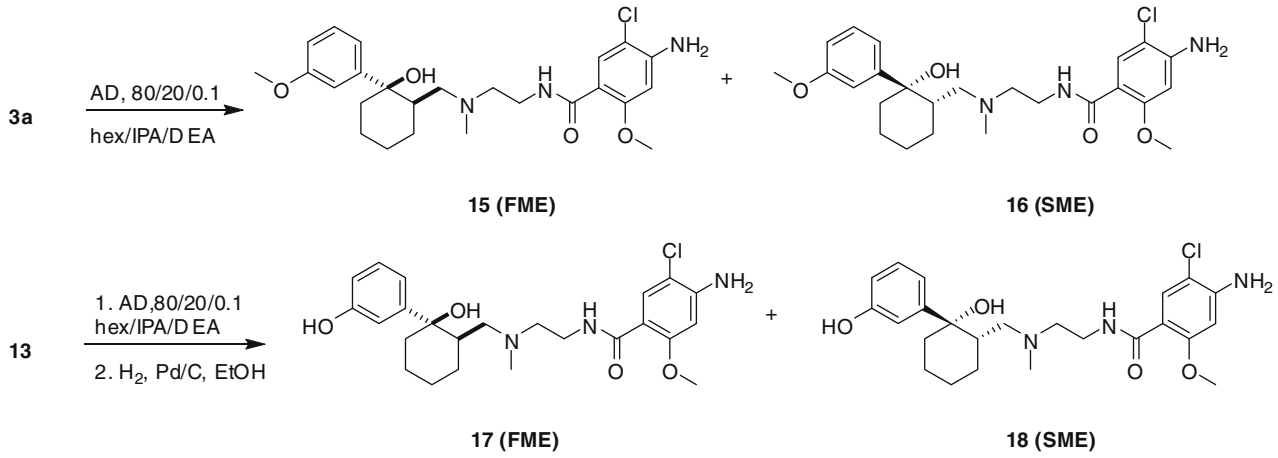
Figure 2. Designed dual μ-opioid agonist/prokinetic compounds **3a** and **3b**.



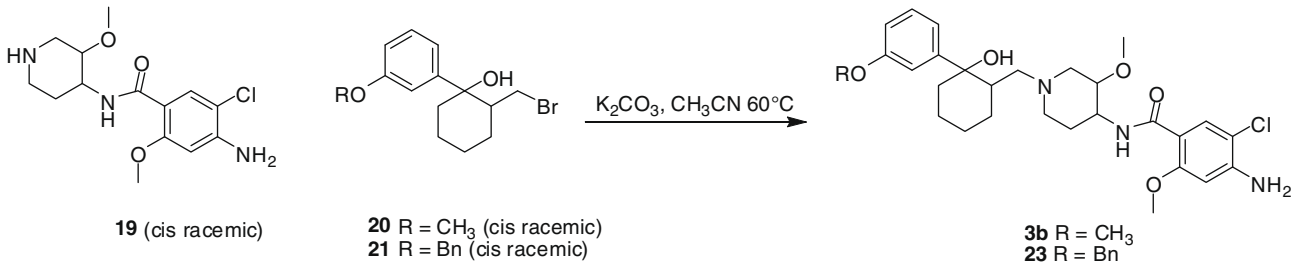
Scheme 1. Synthesis of methyl amine **7**.



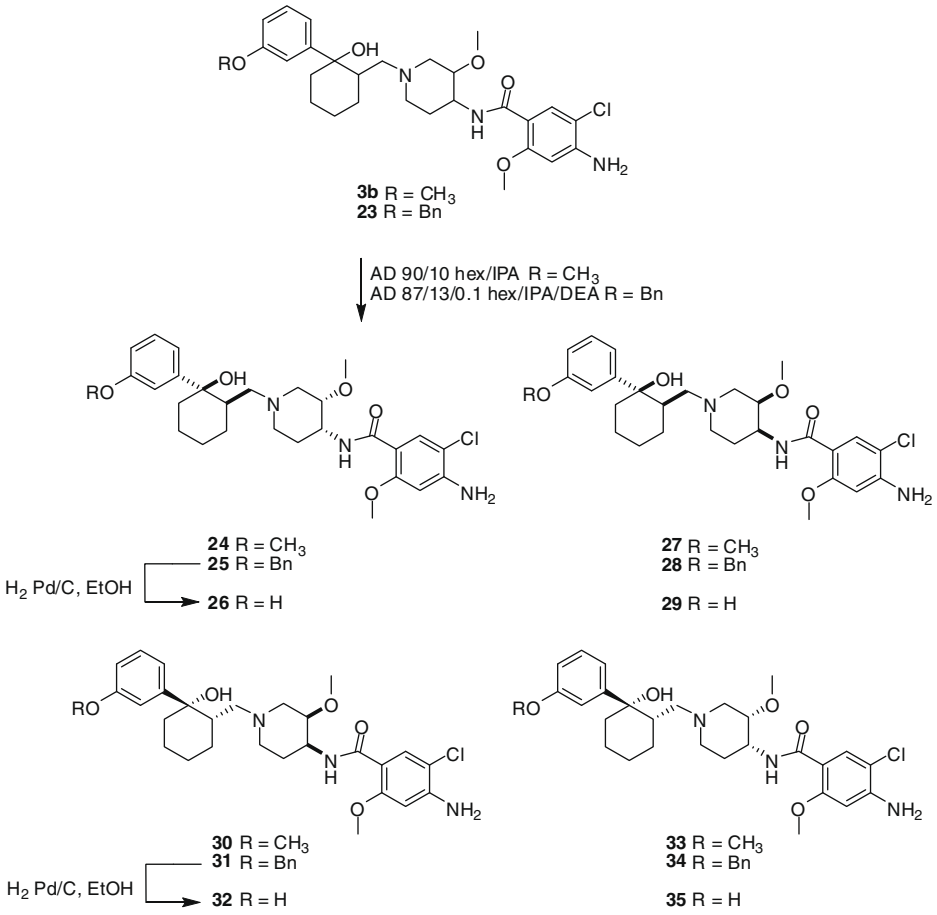
Scheme 2. Synthesis of DML **3a** and **14**.



Scheme 3. Separation of enantiomers of **3a** and **13**.



Scheme 4. Preparation of racemic DMLs **3b** and **23**.



Scheme 5. Chiral separation of piperdines.

Table 1
In vitro binding and functional data for DMLs at 5-HT_3, 5-HT_4 and μ-opioid receptors

	Binding			Functional	
	5-HT_4 (IC_{50}, μM)	5-HT_3 (IC_{50} μM)	μ(IC_{50}, μM)	5-HT_4 (EC_{50}, μM)	5-HT_3 (EC_{50} μM)
19 Norcisapride	1.6	0.019	NT	0.290 (ag)	2.3 (antag)
33	0.159	3.9	>10	0.120 (ag)	>10
32	0.018	9.9	0.41	0.090 (ag)	NT
12	3.3	3.5	>10		
15	3.5	5	4.5		
16	4.9	>10	>10		
14	2.8	>10	0.19		
17	3.1	>10	0.34		
18	2.5	>10	5.1		
24	2.8	>10	>10		
27	0.79	6.1	>10		
30	1.70	4.6	>10		
26	1.6	>10	>10		
29	0.39	>10	>10		
35	1.4	>10	>10		

reverse opioid-induced respiratory depression without loss of analgesia.[16] That made the μ-5-HT_4 combination even more attractive.

Functionality analysis showed that both μ agonist pharmacophore (tramadol) and prokinetics pharmacophore (metaclopramide and (+)-norcisapride) contained a basic amine critical for activity. Our approach was to use this nitrogen as a merge point (Fig. 2). Following this principal, we could not only preserve the basic amine functionality for both but also allow the pharmacophores to be a substitution group for the other. This would offer us the best chance to obtain all desired activities.

Synthesis of metoclopramide DML **3a** was conducted on solid phase and began with functionalization of Wang resin with CDI followed by 2-methylamino methanol to give resin bound **4** (Scheme 1). Mesylation, displacement with phthlamide and deprotection with hydrazine in EtOH/THF gave primary amine **5**, which was coupled to substituted benzoic acid **6**. Treatment of the resin with TFA in CH_2Cl_2 gave pure **7**.

DML **3a** was synthesized starting from 3-bromo anisole or 1-(benzyloxy)-3-bromobenzene, which were converted to Grignard reagents and added to 2-hydroxymethylcyclohexanone (Scheme 2). *Cis*-racemic diols **10** and **11** were selectively brominated and condensed with amine **7** to give racemic DML **3a** and **13**. Benzyoxy DML **13** could be converted to phenol **14** via hydrogenation over Pd/C.

Racemic **3a** was separated into enantiomers **15** (Fast Moving Enantiomer) and **16** (Slow Moving Enantiomer) using a Chiral Technologies AD column and a solvent system of 80/20/0.1 hexanes/IPA/diethylamine. Benzyl-oxy protected **13** could be similarly separated; hydrogenation on Pd/C gave enantiomeric phenols **17 FME** and **18 SME** (Scheme 3).

Norcisapride was the starting point for DML **3b** (Scheme 4). Coupling of norcisapride with tramadol-derived bromides **20** and **21** gave tertiary amines **3b** and **23**, which could be separated by chiral HPLC (Scheme 5).

The enantiomers of **3b** and **23** could be obtained using an AD column (Scheme 5) - the absolute configuration of the pure chiral compounds was not determined, but was arbitrarily assigned. Hydrogenation on Pd/C of benzyl ethers **25**, **28**, **31** and **34** provided the pure phenols **26**, **29**, **32** and **35** (Scheme 5).

The designed single enantiomer DMLs were tested initially for binding potency at 5-HT_3,[17] 5-HT_4[18] and μ-opioid receptors (Table 1).[19] Several of the most potent ligands were also tested in a functional assay to determine if the compounds were agonists or antagonists at the given receptor. It was clear from the data in Table 1 that the norcisapride series of compounds were much more potent against the 5-HT_4 receptor and provided the two compounds tested in the functional assay, methoxy substituted **33** and phenol **32**. Both compounds were shown to be potent agonists at the 5-HT_4 receptor, with EC_{50}'s of 120 and 90 nM, respectively. Phenol **32** also showed reasonable potency against the μ-opioid receptor (410 nM), and may provide a reasonable starting point for further optimization efforts. The metoclopromide scaffold did not provide significant 5-HT_4 and 5-HT_3 potency when linked to the tramadol scaffold, although the DML phenols such as single enantiomer **17** provided nanomolar μ-opioid potency (340 nM).

Our DMLs based on the μ-opioid agonist tramadol and the prokinetic agent norcisapride were designed to combine 5-HT_4/5-HT_3 and mu activity into a single compound. We succeeded in uniting the 5-HT_4 and μ activity with **32**, which showed potent 5-HT_4 agonist activity and nanomolar potency for the μ-opioid receptor. Future efforts will be focused on incorporating 5-HT_3 antagonist activity and determining the in vivo profile of **32** in models of pain and constipation.

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