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SAR and biological evaluation of novel *trans*-3,4-dimethyl-4-arylpiperidine derivatives as opioid antagonists

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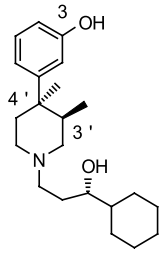
Abstract—The phenolic hydroxy group of opiate-derived ligands is of known importance for biological activity. We have developed a SAR study around LY255582 by comparing the effect of the hydroxy group in the 2- and 4-position of the phenyl ring. Also, we have proved that the 3-position of the phenyl ring is optimal for opioid activity. Furthermore, we have successfully replaced the hydroxy group in LY255582 by carbamate and carboxamide groups. The new analogs have high affinity for the opioid receptors comparable to the corresponding phenol. Carboxamide analog **12** has an improved metabolism profile and proved to be efficacious in in vivo studies.

1. Introduction

Opioid receptors are involved in a multitude of physiological functions, such us GI motility, pain, appetite and emotional state.[1] Thus, selective opioid antagonists may find uses in a number of therapeutic areas. The relative safety of opioid antagonists makes them attractive as a potential drug for the treatment of chronic diseases such as obesity.

Zimmerman[2] described the discovery of opioid antagonist activity in a series of *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines. These 4-phenylpiperidine antagonists were structurally unique since opioid antagonists were generally analogs of morphine. This work led to the discovery of LY255582 (**1**, Fig. 1).[3]

LY255582 is a centrally active antagonist which has a high affinity for μ, κ, and δ receptors (K_i: 0.18, 4.68 and 4.82 nM, respectively). This antagonist has shown exceptional potency and durability in reducing food intake and body weight gain in obese Zucker rats when compared to the standard opioid antagonists naloxone, naltrexone and nalmefene.[4] The bioavailability of parent LY255582 was <1% in both the rat and dog, primarily because of extensive first pass metabolism.[5] Our hypothesis was that the phenol group played an important role in this first pass metabolism. However, our previous SAR in the piperidine scaffold had been based on the 3-phenol substitution by analogy to the morphine-type structures. Traditional structure–activity relationship of morphinans suggests that the phenolic hydroxyl group in the 3-position was a strict requirement for



1, LY255582

Figure 1.

Keywords: Opioid antagonist; *trans*-3,4-Dimethyl-4-arylpiperidine.
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binding to opioid receptors, serving as a H-bonding donor to a complementary site on the protein.[6,7]

We first wanted to know if the 3-position of the phenyl ring was optimal for substitution. In addition, we have studied replacements of the hydroxyl group to improve the ADME profile of LY255582. For these purposes, we synthesized and evaluated different *trans*-3,4-dimethyl-4-arylpiperidine analogs of LY255582.

2. Chemistry

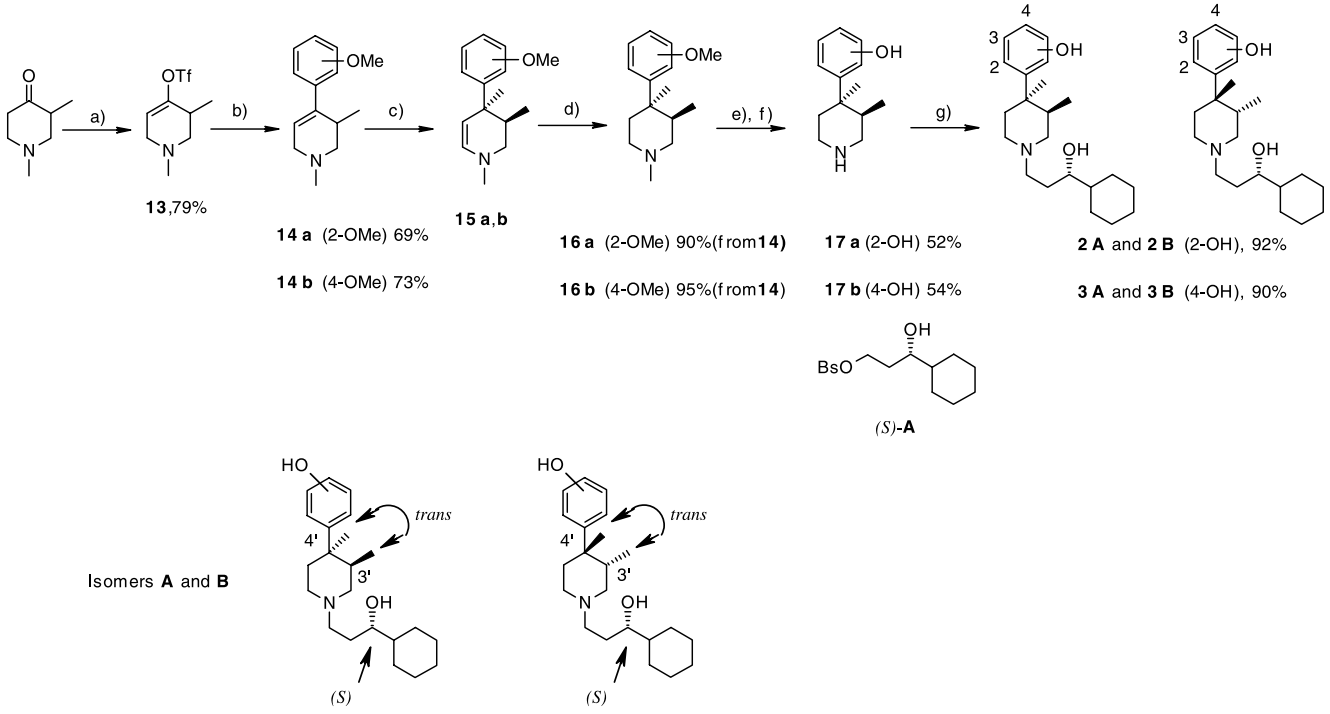
Mitch and co-workers developed a nine-step synthesis for the preparation of these arylpiperidines[8] and a few years later Werner et al.[9] published an improved synthesis of LY255582. However, we desired a new synthetic approach that would allow for the preparation of different 4-arylpiperidines in a more effective way. Thus, we implemented a new chemistry route where the key step involves the Suzuki coupling between the racemic vinyltriflate **13**[10] and the corresponding boronic acid (Scheme 1). After some experimentation we found that the best conditions for the coupling are the ones reported by Fu:[11] $Pd(Ph_3)_4$, K_2CO_3, DMA/THF, rt. The methylation of the allylamine **14** with dimethylsulfate at −50 °C gave the desired 3,4-dimethylenamine **15** in excellent yield. Alkylation of the allylamine is regiospecific at the γ-position and occurs exclusively *trans* to the C3-methyl substituent.[12] The reduction of the enamine using $NaBH_4$ gave piperidine **16**. N-demethylation with phenyl chloroformate in refluxing toluene followed by removal of both N- and O-protecting groups with HBr in refluxing AcOH gave the racemic piperidine **17**. Finally, its alkylation with the enantiomerically pure brosylate (*S*)-**A** afforded compounds **2** and **3** which were separated by chiral chromatography to give enantiomerically pure **2A**, **2B**, **3A** and **3B**. The relative stereochemistry of methyl groups on carbons 3′ and 4′ is *trans*; however, the absolute stereochemistry on these carbons for **2A**, **2B** and **3A**, **3B** was not assigned (see Scheme 1).

The 3-substituted phenyl ring piperidines **4**, **10**–**12** were synthesized from the common intermediate **18**, prepared from LY255582.[13] The reductive elimination of the triflate in a Pd-catalyzed reaction using $NaHCO_2$ as a reducing agent gave compound **4**. On the other hand, the carbonylation of the triflate using the same catalytic system: $Pd(OAc)_2$/dppf in the presence of methanol gives the ester **10** which upon treatment with ammonia leads to the carboxamide **12**. Hydrolysis of **10** in the presence of LiOH gives the carboxylic acid **11**.

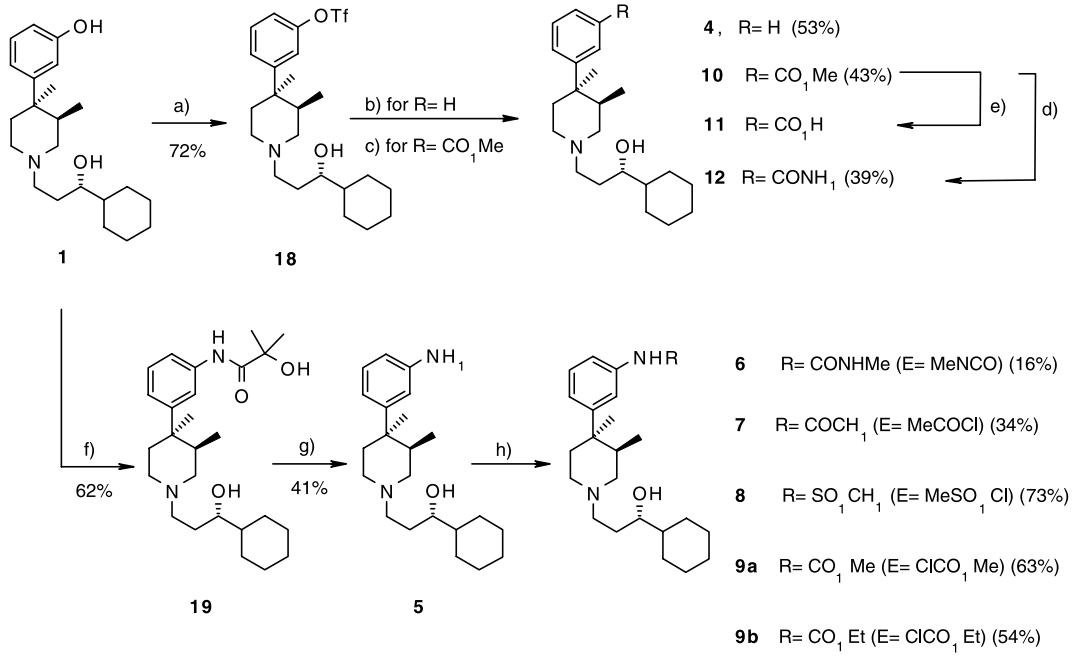
Amine **5** was prepared from phenol **1** by the Smiles rearrangement.[14] The treatment of **1** with 2-bromo-2-methylpropionamide in the presence of sodium hydride and cesium carbonate in a mixture of NMP, DMPU and dioxane at reflux gave **19**, which was treated with acid to give amine **5**. Analogs **6**–**9** were synthesized starting from **5** by reaction with the corresponding electrophile.

3. Results and discussion

Our effort was directed towards the analysis of the structure–activity relationship around the aryl domain by



Scheme 1. Reagents and conditions: (a) i—LDA, THF, −78 °C, ii—*N*-phenyltriflimide, Et_3N, CH_2Cl_2, −78 °C, rt; (b) $(OH)_2BC_6H_4OMe$, $Pd(Ph_3)_4$, K_2CO_3, DMA, THF, rt; (c) i—*n*-BuLi, THF, −10 °C, ii—Me_2SO_4, −50 °C; (d) $NaBH_4$, MeOH, rt; (e) PhO_2CCl, toluene, 100 °C; (f) i—HBr, HOAc, reflux, ii—pH 10.5; (g) $NaHCO_3$, **A**, DME, reflux.

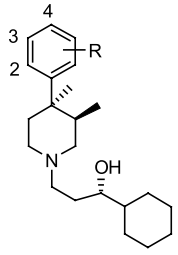


Scheme 2. Reagents and conditions: (a) *N*-phenyltriflimide, Et_3N, CH_2Cl_2, rt; (b) $Pd(OAc)_2$, dppf, Et_3N, $NaHCO_2$, DMSO, 65 °C; (c) $Pd(OAc)_2$, dppf, Et_3N, CO, DMSO, MeOH, 65 °C; (d) MeOH, NH_3, NaCN; (e) LiOH 1 N, 0 °C rt; (f) 2-bromo-2-methylpropionamide, NaH, Cs_2CO_3, NMP, DMPU, dioxane, reflux; (g) 6 N HCl, EtOH, (h) CH_2Cl_2, pyridine, E.

changing the nature of the functional group or by changing the position of the hydroxyl group. For that purpose, we synthesized and evaluated compounds **2**–**12**, which are shown in Table 1.

Compounds were tested for their affinities (K_i) towards the cloned human μ, κ and δ receptors expressed in Chinese hamster ovary cells as measured by their abilities to displace [^{3}H]diprenorphine (μ- and κ-opioid receptor

Table 1. Binding data (K_i) and antagonist activity (K_b) of compounds **1–12**



	R	K_i (nM)			K_b (nM)		
		μ	κ	δ	μ	κ	δ
1	3-OH	0.1	4.7	4.8	0.04	0.3	1.2
2A	2-OH	410	1340	6993[a]	40.5	559.1	>2038
2B		235	1074	2381[a]	18.8	>1711	747.5
3A	4-OH	30.4	224.3	364.0[a]	1.3	92.2	122.4
3B		376	386	3543[a]	23.1	88.3	>2015
4	H	7.7	749	169	1.6	40.6	47.1
5	3-NH_2	1.9	55.2	44.9	0.7	15.7	24.7
6	3-NHCONHMe	1.8	69.5	51.3	0.3	9.8	14.3
7	3-NHCOMe	2.4	133	64.9	0.4	16.4	25.8
8	3-$NHSO_2$Me	9.4	192	251	nd	nd	nd
9a	3-$NHCO_2$Me	1.0	10.6	14.2	0.1	0.6	1.9
9b	3-$NHCO_2$Et	1.2	12.3	24.6	0.1	0.7	3.2
10	3-CO_2Me	43.3	2326	1635	34.6	984	1242
11	3-CO_2H	143	3015	3507	nd	nd	nd
12	3-$CONH_2$	0.2	12.7	6.4	0.1	1.9	2.8

nd, not done.

[a] K_i affinities were measured using [^{3}H]diprenorphine instead of [^{3}H]bremazocine.

assays) or [^{3}H]bremazocine (δ-opioid receptor assay).[15] Functional antagonist potency (K_b) of the compounds was assessed by their ability to inhibit agonist-stimulated activation of G-proteins using a [^{35}S]GTPγS binding assay in CHO membranes containing each of the cloned opioid receptor subtypes.[16] No agonist activity was detected for these compounds at concentrations up to 10 μM.

Our primary goal for this study was to determine if the phenolic group was mandatory and if its position on carbon 3 of the phenyl ring was optimal. To accomplish this goal, we evaluated aryl piperidines **2**, **3** and **4**.

The activity of both compounds **2A** and**2B** for all three receptors declines precipitously relative to compound **1**. In the case of compound **3**, where the hydroxyl group has been moved to the 4-position of the phenyl ring, isomer **3A** shows higher affinity (for μ and δ receptors) than isomer **3B**; however, 300-fold lower than those observed with LY255582. This activity is similar to that of compound **4**, the deshydroxy derivative. These results suggest that the hydroxyl group in the 3-position is of importance for the molecular interaction of the arylpiperidines with the opioid receptors. Recently, Kim et al. have published similar findings showing the need for a specific phenolic position in 5-phenylmorphans.[17]

Our second goal was to find replacements of the hydroxyl group that would retain the essential H-bond donating properties of the 3-phenol in LY255582 but have an improved ADME profile, thus we prepared compounds **5**–**12** to evaluate this hypothesis.

We first prepared aniline **5**, as the amino group is known to mimic the hydroxy group at the site of some receptors.[18] In fact, Wentland et al. have successfully replaced OH by amino groups in their cyclazocine analogs.[19] In our case, we also found that aniline **5** had significant affinity for μ, κ and δ receptors, however, it was 20-, 11- and 10-fold less potent than LY255582, respectively.

Next, we tested analogs **6**–**9**. Urea **6** shows similar affinity across the three receptors compared to aniline **5**. Amide **7** and sulfonamide **8**,[20] although active at μ, κ and δ receptors, had lower affinity than aniline **5**.

On the other hand, carbamates **9a** and**9b** showed improved potency across the three receptors compared to aniline **5** (**9a**; K_i: 1.0, 10.6 and 14.2 nM for μ, κ and δ, respectively), though these analogs are less potent than LY255582 (10-, 2- and 3-fold less potent) they do retain significant potency. Furthermore, carbamates displayed potent in vitro antagonist activity for the three opioid receptors (**9a**, K_b: 0.1, 0.6 and 1.9 nM for μ, κ and δ, respectively).

Continuing with the effort of looking for suitable replacements for the phenolic group we prepared and evaluated analogs **10**–**12**, where the OH was replaced by a carbon attachment. There are very few papers that describe any type of carbon attachment at the position of the prototypic phenolic OH. For example, when 3-OH group of morphine[21] and naltrindole[22] was replaced by alkyl, acetyl, aryl and/or heteroaryl groups; these molecules had substantially lower affinity for opioid receptors. Very recently, Neumeyer et al. reported the successful replacement of the phenolic hydroxyl moiety of morphinans by a 2-aminothiazole.[23]

Wentland et al. had reported the only carbon attachment that has successfully replaced the prototypic hydroxyl group. They found unexpectedly high affinity for opioid receptors in cyclazocine analogs, where the OH– was replaced by a carboxamide group[24] (though a significant decrease was observed on replacement of hydroxy by carboxamide in morphine and naltrexone).[25]

We prepared and tested the carboxamide derivative **12**. Carboxymethoxy analog **10** and carboxylic acid **11**, which were intermediates in the synthesis of the carboxamide, were also tested. While the ester and acid **10** and **11** had substantially diminished affinity for opioid receptors relative to their 3-OH counterpart, compound **12** showed high affinity at the three opioid receptors, comparable to its OH– counterpart (K_i: 0.18, 12.73 and 6.38 nM, respectively). Compound **12** displayed potent in vitro μ, κ and δ antagonist activity (K_b: 0.1, 1.9 and 2.8 nM, respectively), which was similar to the antagonist potency of **1** (K_b: 0.04, 0.3 and 1.2 nM, respectively).

During the preparation of this paper, Bourdonnec et al.[26] published that the carboxamide group was an effective isostere in vitro of the phenolic OH moiety in this *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine scaffold.

4. Pharmacology and metabolism

We next wanted to study if carboxamide **12** was active in vivo and if it could provide us with a better profile than LY255582 (**1**).

Opioid antagonist activity in vivo was measured in the tail-flick assay, measuring the compound's ability to block morphine-induced analgesia.[27] Phenol **1** exhibited higher potency ($ED50_{sc}$: 0.017 mg/kg) than **12** ($ED50_{sc}$: 0.024 mg/kg) when administered by the subcutaneous route. However, carboxamide **12** showed better oral potency ($ED50_{po}$: 0.15 mg/kg) than **1** ($ED50_{po}$: 0.26 mg/kg). This result might be due to an improved metabolism of compound **12**.

In fact, the studies of the metabolism in rat liver slices after 24 h show that carboxamide **12** was 27% metabolized while phenol **1** was 98% metabolized. The decreased metabolism of compound **12** was found to correspond to an improved oral bioavailability (%*F*)[28] in rats compared to compound **1** (%F = 32% and 2.5%, respectively)

Compound **12** was evaluated for its effect on food consumption in fasted male Long–Evans rats.[29] Oral administration of a 3 mg/kg dose of **12** resulted in a statistically significant reduction of the cumulative amount

of food consumed, as measured over 1- and 2-h time periods. In contrast, oral administration of a 3 mg/kg dose of LY255582 was inactive over the same time periods.

5. Conclusions

From these early SAR findings, it seems reasonable to conclude that the hydroxyl group on carbon 3 of the aromatic ring of **1** plays an important role in binding to opioid receptors. We have been successful in the bioisosteric replacement of the hydroxyl group by a carboxamide group (analog **12**). Carbamates **8** also show high receptor affinity. We have demonstrated that carboxamide **12** improved the pharmacokinetic properties of LY255582 and also was efficacious in reducing food consumption in rats. Further evaluation of carboxamide **12** is on going.

Acknowledgments

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27. The tails of mice ($n = 5$/group) were immersed in a water bath maintained at 55 °C and the latency to removal was measured. A baseline response latency was determined, followed by administration of vehicle or a dose of drug either sc or po then 30 min later a postinjection latency was determined. If an animal did not flick its tail within 10 s (cut-off time), it was removed and assigned a response time of 10 s. For each animal, the percentage maximum possible effect was calculated using the following formula: [(postdrug latency − predrug latency)/(cutoff time − predrug latency)] × 100. ED50 values were determined using a four-parameter logistic equation.
28. The bioavailability was determined using Long–Evans rats ($n = 3$). It was a crossover study (po −10 mg/kg to iv −1 mg/kg). Formulation for oral arm: 1% CMC, 0.5% SLS, 0.085% Povidone. Formulation for iv arm: 50% PEG, 1% ethanol in saline.
29. The male Long–Evans rats had been fasted for 18 h prior to testing. The weight of food consumed was measured for groups of six rats treated with test substance and compared to the food consumed by an untreated control group of six animals.