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Synthesis and pharmacological evaluation of hydrophobic esters and ethers of butorphanol at opioid receptors

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ABSTRACT

We synthesized several hydrophobic esters and ethers of butorphanol and assessed their affinities at opioid receptors in CHO cell membranes. Tested compounds displayed moderate to high affinities to the μ and κ receptors. The findings accord with previous evidence of a lipophilic binding pocket in the opioid receptors that can be accessed to afford good binding affinity without the need for a phenolic hydrogen-bond donor group. The most potent (K_i = 61 pM at μ and 48 pM at κ) novel agent was (−)-*N*-cyclobutylmethylmorphinan-3-yl-14-ol phenoxyacetate (**4d**).

It is generally accepted that two sites within the morphinan skeleton (**1**), the basic nitrogen at position 17 and the A-ring phenol moiety at position 3, are necessary for binding to the μ, δ, and κ opioid receptors and induction of the narcotic analgesic affect.[1,2] The phenolic hydroxyl group has been recognized as requisite for the formation of a hydrogen bond with a dipolar site on the receptor and for good antinociceptive activity.[2,3] Recent studies however call this into question. It was reported that a series of aryl 8-carboxamidocyclazocine (e.g., **2**) have good nM binding affinity to the opiate receptors.[4] This was rationalized as the aryl group (e.g., biphenyl) interacting with a hydrophobic binding pocket in the opioid receptor to such an extent that the increase in hydrophobic binding energy offsets that due to the loss of hydrogen-bonding binding energy (see Image 1).

Reports from our laboratories indicated that bivalent morphinan analogs of butorphan (**3a**) connected by a diacid linker spacer of varying lengths had potent binding affinity to the μ and κ opioid receptors.[5] When the phenol group of these compounds is reacted with the linker group to form an ester, the phenolic group of the resultant compounds loses its ability to act as a hydrogen-bond donor (see Image 2).

Conversion of the phenol group of butorphan into carbamates also retains excellent binding affinity to the opioid receptors.[6] Within the butorphan carbamate series it was found that the phenyl carbamate analogue retained the same high affinity at the κ opioid receptor and had a twofold increase in binding affinity at the μ opioid receptor. A butorphan benzyl carbamate had lower affinity at the μ and κ opioid receptors though the binding affinity was still subnanomolar (K_i μ = 0.70 nM, κ = 0.30 nM).

To gain greater insight into the design of bivalent opioid ligands and to further explore the importance of the phenolic group in the binding of morphinans to the opioid receptors, a series of butrophanol esters and ethers were prepared in which the phenol moiety is converted into a hydrophobic ester or ether. The goal was to determine if the binding affinity and selectivity of butorphanol could be maintained when the ability of the 3-OH group to participate as a hydrogen bond donor is removed.

Butorphanol[7] (**3b**) is an opioid μ partial agonist/κ agonist used commercially as an analgesic in humans (Stadol®) and in animals (Torbugesic®). The analgesic potency of butorphanol in humans is 4–8 times that of morphine, 30–40 times that of meperdine, and 16–24 times that of pentazocine.[8] Butorphanol has been shown to decrease cocaine self-administration in rhesus monkeys without producing a significant change in food-maintained responding.[9]

Esters of butorphanol (**4a–f**) were prepared by reacting acid chlorides or carboxylic acids with butorphanol under suitable condensation conditions as shown in Scheme 1. Ethers of butorphanol (**5a–f**) were prepared by reacting alkyl halides with the sodium salt of butorphanol generated in situ using sodium hydride. Spectral (^{1}H NMR and ^{13}C NMR) data and combustion analysis for the target compounds were consistent with their proposed structures.[10]

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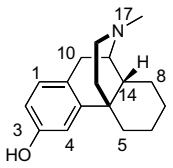

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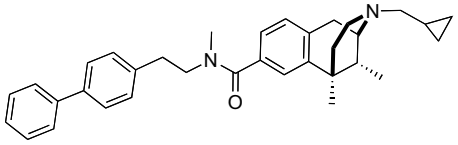

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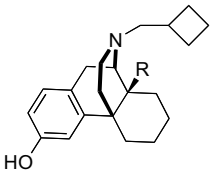
Image 1.



3a R = H butorphan (MCL-101)
3b R = OH butorphanol

Image 2.

All new compounds were evaluated as their hydrochloride salts for their binding affinity at all three opioid receptors (μ, κ, δ) (Table 1) using a previously reported procedure.[11]

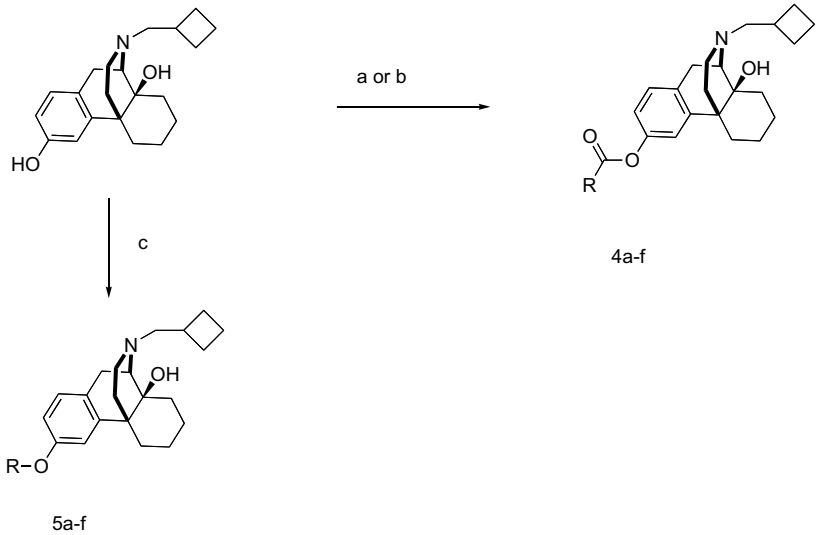
Introduction of hydrophobic groups onto the phenol oxygen maintained binding affinity to the μ and κ opioid receptors. In general the binding affinities were lower than that of butorphanol, especially in the ether series. Affinity to the δ receptor was reduced, as much as by a factor of 16. The energy of interaction of these compounds with the receptors appears to be driven by hydrophobic forces as the introduction of hydrogen bond donor and acceptor groups onto the phenol oxygen (**5a, 5b**) reduced the binding. All the compounds maintained the μ, κ, δ selectivity profile as seen with the parent compound butorphanol. The increase in hydrophobicity tended to increase κ selectivity relative to μ opioid receptor (see Image 4).

There is an inverse linear correlation between hydrophobicity ($C\mathrm{Log}P$)[12] and pK_i for the ester series (**4a**–**f**) at the μ opioid receptor (Fig. 1) and κ opioid receptor. Within this series, as the hydrophobicity of the compound increases the binding potency decreases.

The most potent compound (**4d**) is more hydrophobic than butorphanol by a factor of 140. Despite the loss of the 3-OH group in contributing to intermolecular noncovalent bonding as a hydrogen-bond donor, compound **4d** is about twofold more potent binding at the μ receptor and is a fourfold more potent binder at the κ receptor than butorphanol. It would appear that the loss in hydrogen bond donor binding energy from masking of the phenol oxygen is compensated, in part, by the change in hydrophobicity by addition of a phenyl group. The logarithmic relationship of affinity and partition coefficient indicates that the binding affinity is very sensitive to the hydrophobicity of the compound. The ester series is stable to hydrolysis under the assay conditions used. The stability of **4b** and **4c** was studied at pH 7.4 in 25 mM phosphate buffer at 37 °C by HPLC.[13] No hydrolysis of the esters was observed after 24 h.

The binding affinity of the ether series tended to be much less than with butorphanol though the affinity of two, **5d** and **5f**, are still less than 10 nM at both μ and κ opioid receptors. Within the ether series a similar pK_i/$C\mathrm{Log}P$ relationship is observed at the μ and κ opioid receptors for compounds **5c**–**f**. Compounds **5a** and **5b**, containing more polar substituents, are of approximately the same hydrophilicity as butorphanol yet are much less potent. This indicates that hydrogen bond donor capability in of itself is not necessary for binding.

The reasons for the differences in binding affinities measured between the ester and ether series are unknown. It is clear that hydrophobicity cannot be the sole determinate variable. The phenethyl ether **5d** is similar in hydrophobicity to the phenoxyacetate ester **4d** yet **5d** has 164-fold less binding affinity at the μ opioid receptor than **4d**. The esters will have more rotational degrees of freedom than the ethers. It is possible that the more flexible ester linkage allows a conformer to be ob-



4a-f

5a-f

Scheme 1. Reagents and conditions: (a) ROCl, Et_3N, CH_2Cl_2, rt; (b) RCOOH, DCC, DMAP, CH_2Cl_2, rt; (c) RBr, NaH, DMF, rt.

Table 1
K_i values for the inhibition of μ, δ, κ opioid binding to CHO membranes

Compound	K_i ± SEM (nM)			Selectivity	*C*Log*P*[12]
	μ([^{3}H]DAMGO)	δ([^{3}H]Naltindole)	κ ([^{3}H]U69,593)	μ/δ/κ	
1[5a] (levorphanol)	0.21 ± 0.017	4.2 ± 0.45	2.3 ± 0.26	1/20/11	3.5
2[4]	6.7 ± 1.7	12 ± 2.4	11 ± 0.44	1/1.8/1.6	7.0
3a[5a] (MCL-101)	0.23 ± 0.01	5.9 ± 0.55	0.079 ± 0.003	3/75/1	4.9
3b (butorphanol)	0.22 ± 0.012	12 ± 1.1	0.12 ± 0.12	2/100/1	3.7
4a (MCL-474)	2.7 ± 0.36	190 ± 12	0.87 ± 0.042	3.1:218:1	7.5
4b (MCL-488)	0.32 ± 0.019	63 ± 1.4	0.48 ± 0.10	1:197:1.5	5.6
4c (MCL-489)	2.3 ± 0.12	96 ± 10	1.3 ± 0.21	1.9:74:1	6.4
4d (MCL-603)	0.061 ± 0.006	22 ± 1.8	0.048 ± 0.003	1.3:458:1	5.2
4e (MCL-601)	15 ± 1.6	690 ± 16	18 ± 1.2	1:46:1	7.8
4f (MCL-602)	0.22 ± 0.003	23 ± 1.7	0.21 ± 0.009	1:110:1	5.5
5a (MCL-486)	55 ± 3.4	760 ± 5.3	67 ± 7.7	1:11:1.2	4.0
5b (MCL-485)	18 ± 1.6	490 ± 13	8.6 ± 1.2	2.1:57:1	3.8
5c (MCL-499)	21	670	28	1:32:1.3	6.1
5d (MCL-600)	10 ± 1.1	500 ± 27	9.0 ± 0.76	1:56:1	5.5
5e (MCL-604)	16	1500	28	1:94:1.8	6.23
5f (MCL-605)	3.9	930	5.2	1:240:1.3	5.26

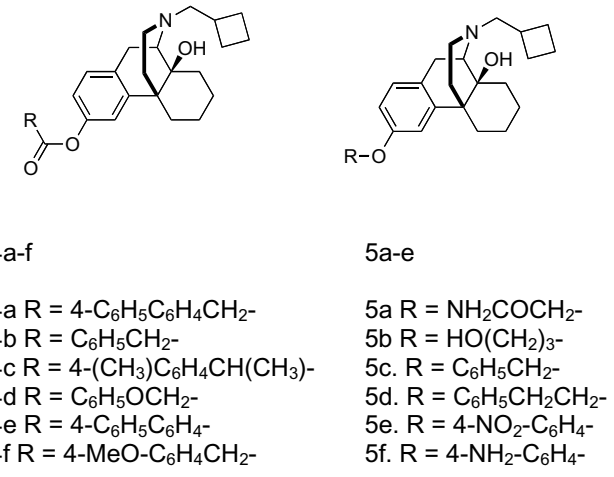


Image 4.

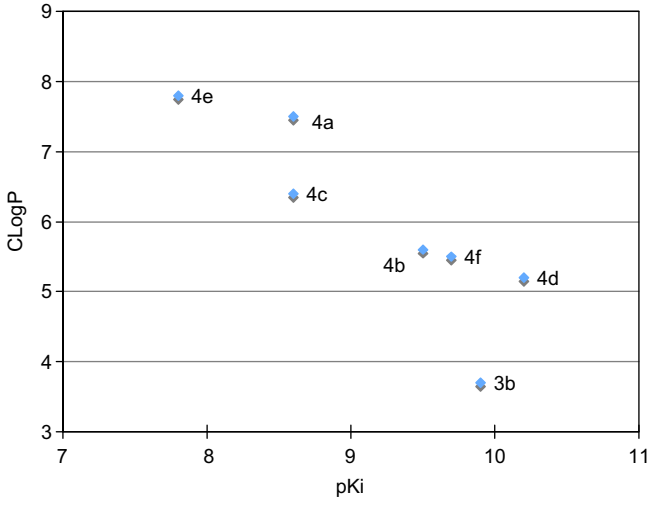


Figure 1. Relationship between hydrophobicity of esters **4a**–**4f** and binding affinity at the μ opioid receptor in comparison with butorphanol (**3b**).

tained that maximizes hydrophobic interactions of the ester side chain with hydrophobic groups in the binding pocket of the opioid receptors. It has been suggested that Phe152, Phe237, and Phe241 in the μ opioid receptor may be able to create a hydrophobic pocket complementary to the ester/ether aryl substituents at position 3 of butorphanol.[4]

Acknowledgments

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10. Phenoxyacetyl chloride (49 mg, 0.29 mmol) in 1 mL of dichloromethane was added to a solution of butorphanol (80 mg, 0.24 mmol) and triethylamine (50 μL, 0.37 mmol) in 5 mL of dichloromethane at room temperature. The resultant solution was allowed to stir overnight at room temperature under nitrogen. The reaction mixture was quenched with water, and extracted twice with dichloromethane. The organic layers were combined and washed twice with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (1:1:0.1 ethyl acetate/hexane/triethylamine) gave 99 mg (89% yield) of the pure ester **4d** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.30 (m, 2H), 7.1 (d, J = 8.3 Hz, 1H), 7.05–6.96 (m, 4H), 6.89 (dd, J = 2.6, 8.3 Hz, 1H), 4.87 (s, 2H), 3.03 (d, J = 18.3 Hz, 1H), 2.74, (dd, J = 6.6, 18 Hz, 1H), 2.62 (d, J = 5.7 Hz, 1H), 2.47 (m, 3H), 2.34 (dd, J = 2, 11.7 Hz, 1H) 2.14–1.8 (m, 9H), 1.67 (m, 2H), 1.52–1.37 (m, 5H), 0.98 (d, J = 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7, 157.7, 148.7, 143.2, 134.3, 129.6, 128.4, 122.0, 118.4, 118.1, 114.7, 69.3, 65.4, 61.1, 60.5, 44.5, 41.6, 36.9, 33.8, 31.6, 30.1, 26.9, 26.7, 25.2, 21.6, 18.7; Anal. ($C_{29}H_{35}NO_4 \cdot 0.5H_2O$) C, H, N.
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12. *C*Log*P* was calculated using the ChemProp feature in CambridgeSoft ChemDraw Ultra, version 9.0.1.
13. Hydrolysis was determined by the procedure described in: Mathews,J. L.; Fulton,B. S.; Negus, S. S.; Neumeyer, J. L.; Bidlack, J. M. Invivo characterization of(−)(−)MCL-144 and (+)(−)MCL-193: isomeric, bivalent ligands with mu/kappa agonist properties. *Neurochemical Research*, **2008**doi:10.1007/s11064-008-9752-3.