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The influence of esters and carboxylic acids as the N-substituent of opioids. 1. Benzomorphans

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Abstract

To investigate the effects of carboxylic ester and acid moieties as the *N*-substituent of opioids, a short series of racemic *N*-substituted normetazocines was prepared. The introduction of both groups as the normetazocine *N*-substituent produced compounds which displayed low potency *in vitro* and *in vivo*, with the esters displaying the greater activity. The pharmacology of the compounds is discussed with implications resulting from potential *in vivo* metabolic hydrolysis.

Keywords

Opioid; Benzomorphan; Normetazocine

1. Introduction

Modification and replacement of the functional group attached to the basic nitrogen in opioids has been the subject of much exploration in opioid chemistry. The nature of the *N*-substituent determines, to a large extent, the pharmacological profile in a majority of classes of opioids, affecting affinity, potency, and efficacy at the three opioid receptor types mu (μ), kappa (κ), and delta (δ).¹ The naturally occurring archetypal opiates morphine and codeine each have an *N*-methyl substituent and, in general, an *N*-methyl substituent produces a compound with opioid agonist activity. Changing from an *N*-methyl group (oxymorphone) to an *N*-allyl group (naloxone) converts a compound which exhibits μ opioid agonist activity to a compound which exerts μ opioid antagonism.¹ Changing the *N*-substituent from an *N*-phenethyl to an *N*-benzyl, in the benzomorphan class of compounds transforms a compound with high agonist potency into a compound without opioid activity.² While not the sole determinant the *N*-substituent is very important for opioid pharmacology, yet the molecular interactions responsible for such an important role are not clear.³

The lipophilicity and hydrophilicity of the *N*-substituent play a large role in the activity of opioids. Generally, lipophilic substituents are required for opioid activity and hydrophilic substituents are not well tolerated.¹ The classic example of the effects of lipophilic and

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hydrophilic *N*-substituent replacement is the development of remifentanyl (*N*-ester) from fentanyl (carfentanyl) (both, *N*-phenethyl) in the 4-anilidopiperidine class of opioids.⁴ When remifentanyl, an *N*-ester, is compared to the corresponding *N*-acid congener, opioid activity is greatly diminished. The change from lipophilic ester to hydrophilic acid results in changes in ED₅₀ from 3.55 nM (*N*-ester, remifentanyl) to 1.95 μM (*N*-acid, metabolite) in the guinea pig ileum (GPI) assay, and from 4.4 μg/kg to 1.6 mg/kg in the rat tail withdraw (RTW) assay.⁴ Outside of this series (remifentanyl) of compounds, few opioid *N*-carboxylic ester or acid substituted compounds have been reported in the literature, fewer still reported with pharmacology. A literature report of an *N*-ester and acid pair (**NME-1** and **NMA-1**) in the *N*-normetazocine (**1**) (benzomorphan) series presented limited data for the two compounds.⁵ The report was investigating the possible metabolites of pentazocine and included both the ester and acid. The data presented showed **NME-1** inactive as an agonist but weakly antagonized the effects of meperidine with an AD₅₀ of 66 (pentazocine AD₅₀ 3.9 from the same study) in the rat tail flick (RTF) assay. The corresponding *N*-acid (**NMA-1**) was devoid of both agonist and antagonist activity in this study.⁵ To further study the effects of *N*-esters and *N*-acids, and the effects of changing the lipophilicity/hydrophilicity of the *N*-substituent we synthesized a series of *N*-substituted-*N*-normetazocine analogs, with the aim of improving the understanding of molecular interactions between the *N*-substituent and the opioid receptors.

2. Results and Discussion

The racemic (±)-*N*-normetazocine-*N*-ester (**NME-1-3**) and -*N*-acid (**NMA-1-3**) analogs (Scheme 1) in this series displayed low potency in both the *in vitro* assays and *in vivo* antinociceptive assays (Table 1). Overall the compounds examined in this series required high (micromolar) concentrations to display significant effects. Since this series of compounds was tested as racemates the activity profiles may display decreased potency, as the greater opioid potency is known to reside in the (-)-isomers.¹ Despite their racemic nature, the compounds in this series present an intriguing profile of *N*-substituent effects.

The compounds in this series displayed activity in only one of the four *in vivo* assays for activity, the phenylquinone antiwrithing assay (PPQ) (Table 1.). Since the PPQ is an antinociceptive assay which is non-selective for narcotic analgesia (opioid) and can also detect antinflammatory (NSAID type) analgesia, no conclusions can be made from this assay alone as to the type of analgesia detected.⁶ In both the *N*-ester series and the *N*-acid series there is a gain of antinociceptive activity in the PPQ with increasing chain length. This increased potency with increasing chain length is similar to the increase in potency reported for the remifentanyl ester series of compounds.⁴ In the remifentanyl series of esters potency increased from the methyl acetate 39 mg/kg ED₅₀ to the methyl propionate 4.4 μg/kg (remifentanyl), to the methyl butyrate 1.6 μg/kg in the RTW.⁴ The corresponding propionic acid analog of remifentanyl had an ED₅₀ of 1.6 mg/kg in the RTW, no data was presented on the acetic or butyric acid congeners.⁴ While interesting to note this similarity of *in vivo* activity with increasing spacing chain lengths, no direct comparisons can be made due to the differing assay types. Further, the activity of **NMA-2** and **NMA-3** is likely due to non-opioid effects, suggested by the lack of both binding and opioid agonist activity in the *in vitro* experiments.

Another result from the *in vivo* studies presented here which bears comment is the failure of the compound **NME-1** to show antagonist activity in the mouse tail flick antagonism of morphine (TFA) assay. This compound was previously reported to be active though weak (AD₅₀ of 66), as an antagonist.^{5,7} The differences in studies may have contributed to the lack of *in vivo* activity reported here. The use of rats instead of mice, freebase instead of oxalate salt, meperidine instead of morphine, and higher vs. lower tested dosage used in the original vs. experiments presented here could all factor into the lack of antagonist activity reported.

However the *in vitro* experiments presented here argue for the opioid antagonistic effect of **NME-1**.

The ethyl acetate analog (**NME-1**) displayed micromolar binding affinity and weak opioid antagonist activity in the MVD assay. The opioid antagonist activity of **NME-1** in the MVD was, though weaker, similar to that of naltrexone. **NME-1** produced 12 fold, 11.6 fold, and 2.8 fold right shifts in the concentration-effect curves of sufentanil (μ), U50,488 (κ), and DSLET (δ) respectively, without altering the maximum response of any of the agonists (a similar profile as naltrexone in this assay). For a comparison of antagonist potency, if the 2.8 fold shift for **NME-1** vs. DSLET is used as a basis for calculation, pA_2 value of 4.52 was obtained.⁸ Naltrexone has a pA_2 value of 7.41 for DSLET, and the comparison of values indicates that **NME-1** is three orders of magnitude less potent than naltrexone.⁹ These results support the previously reported evidence of the compound's weak *in vivo* antagonist effect on meperidine induced antinociception.⁵ The corresponding acetic acid analog (**NMA-1**), previously reported to be devoid of agonist opioid activity *in vivo* in the RTW or antagonism of meperidine's effects in the RTW, here displayed opioid agonist activity in the *in vitro* MVD assay.

In the *in vitro* tests **NMA-1** displayed μ opioid agonist activity in the MVD, but failed to show binding activity. In the MVD, **NMA-1** exhibited a profile consistent with (μ) opioid agonists (inhibition of the twitch, and reversal of its effects by both naltrexone and β -fulnaltrexamine but not ICI 174864).¹⁰ At no concentration did **NMA-1** inhibit the effects of sufentanil in the MVD. These results suggest **NMA-1** has weak opioid agonist effects in the MVD. The lack of binding activity of **NMA-1** should be noted, and argues against an opioid classification. The binding activity may have been revealed if higher concentrations were tested. Of the remaining analogs, only the ethyl butyrate analog (**NME-3**) exhibited significant binding and either agonist or antagonist activity at the doses tested. **NME-3** displayed micromolar (μ) opioid agonist activity in the MVD (its effects were reversed by naltrexone, and β -fulnaltrexamine, but not ICI 174864), and micromolar binding affinity. Though both compounds (**NMA-1** and **NME-3**) have very weak opioid activity in the MVD, and only **NME-3** displayed significant opioid receptor binding, their profiles are consistent with that of opioid agonists.¹⁰

The compounds presented here can be examined for comparisons of the effects of esters and acids. One comparison of the compounds, examined as two series of different functional group types, *N*-esters and *N*-acids, indicates varying activity by chain length. *In vitro*, the *N*-ester series ethyl acetate analog (**NME-1**) displayed an opioid antagonist profile and the ethyl butyrate analog (**NME-3**) displayed an opioid agonist profile. *In vitro*, the *N*-acetic acid analog (**NMA-1**), was the only *N*-acid compound which displayed any opioid efficacy or activity (opioid agonist activity) while the other two acids (**NMA-2** and **NMA-3**) lost all opioid activity. Both *N*-esters and *N*-acids show a change in *in vitro* activity with increasing spacing chain length. *In vivo* both the *N*-ester series and the *N*-acid series gain antinociceptive activity with increasing chain length. While *in vitro* assays show the *N*-esters change from antagonist activity to agonist activity, and the *N*-acids loose activity with increasing chain length. This observation is consistent with other benzomorphans we have studied previously where *in vitro* and *in vivo* activity do not always correlate.^{2, 3} The broad picture gleaned from this *in vitro* based comparison is *N*-esters tend to retain opioid activity (though switching efficacy from antagonism to agonist activity) with increasing chain length, and *N*-acids lost opioid activity with increasing chain length. Non-specific antinociception (*in vivo* PPQ activity) was revealed in both the *N*-ester and the *N*-acid series as chain length increased.

Another comparison examines the compounds in pairs with identical spacing chain lengths, representing the before and after effects of hydrolysis of the ester functional group. An examination of calculated log P (CLogP) values (a model for comparison of lipophilicity), shows a significant decrease in lipophilicity when *N*-esters are compared to their *N*-acid

congeners (hydrolysis product) (Table 2).¹¹ Though each analog pair shows a significant decrease in lipophilicity resulting from the modeled hydrolysis, no consistent effect other than change in activity is seen between the pairs. The ethyl acetate (**NME-1**) acetic acid (**NMA-1**) pair shows an opioid antagonist (**NME-1**) transformed into an opioid agonist (**NMA-1**) in the MVD. In this pair, *in vitro* functional activity is reversed when the before (ester, lipophilic) and after (acid, hydrophilic) components of hydrolysis are compared. The ethyl butyrate (**NME-3**) butyric acid (**NMA-3**) pair shows an opioid agonist (**NME-3**, ester, lipophilic) transformed into a compound devoid of opioid activity (**NMA-3**, acid, hydrophilic) in the MVD. Both pairs show a change in activity when hydrolysis is simulated *in vitro*. However, the *in vivo* data (non-opioid specific antinociception) show little change in activity when comparing the before (**NME-3**) and after (**NMA-3**) components of hydrolysis. These results are again similar to previous observations where *in vitro* and *in vivo* activity does not correlate.^{2, 3}

The broad picture from comparing *N*-ester, *N*-acid congener pairs indicates change in *in vitro* activity. The **NME-3**, **NMA-3** pair compares similarly to the change observed in the remifentanyl series of compounds where an opioid agonist is reduced in potency when changed from an ester to an acid. The **NME-1**, **NMA-1** pair also displays a change in activity but the change is in efficacy instead of potency. It is interesting to speculate that this change may be due to the physical properties of the short chain compounds interacting with receptor.

Overall the results indicate that a combination of both the functional group character (lipophilicity and electronic effects) and the spacing carbon chain *length* between the basic nitrogen and the carbonyl carbon appeared to determine the compound's activity (or lack thereof), and not solely the functional group itself. The opioid antagonist activity of **NME-1** reported here, supports the previous report of the antagonist activity of this compound. The confirmation of antagonist activity for an opioid *N*-ester, an efficacy profile opposite the profile of the *N*-ester remifentanyl, suggests that the ester functional group's effects on efficacy may be dependant upon opioid class. This observation is supported by the analysis of other opioid classes where antagonist activity is dependant upon binding mode, and not solely on the nature of the *N*-substituent.^{12, 13} The potential of this observation is interesting, however additional compounds and data are required to make generalizations.

3. Conclusions

The compounds presented here expand upon the current knowledge of functional group tolerance for opioid carboxylic ester and acid *N*-substituents. Although displaying significantly lower potency than alkyl substituents, esters appear to be tolerated in the benzomorphan class of opioids, and produced both opioid agonist and an opioid antagonist. Acids in the benzomorphan series appeared less well tolerated as they are extended out from the basic nitrogen leading to loss of opioid activity with extension beyond one methylene spacing unit. The data presented in this study show that an *N*-ester can produce opioid antagonism, which is the opposite efficacy of the remifentanyl series of *N*-esters. This finding suggests both an expanded profile of *N*-ester substituent effects upon opioid efficacy, and also supports the observation that *N*-substituent efficacy effects are also dependant upon opioid class. These observations will be incorporated into future models of efficacy at opioid receptors underway in this laboratory.

4. Experimental

4.1 Chemistry

The *N*-ester-normetazocines (**NME-1–3**) were prepared from racemic normetazocine (**1**) and the appropriate halogenated esters, in a suspension of DMF/THF in the presence of sodium

carbonate. The *N*-acid-normetazocine compounds (**NMA-1–3**) were prepared from the corresponding *N*-ester-normetazocine analogs by hydrolysis in potassium hydroxide in water, followed by neutralization with 10% hydrochloric acid (Scheme 1). All were compounds were converted into oxalate or HCl salts.¹⁴

Typical procedures

(±)-2-carbethoxymethyl-5,9- α -dimethyl-2'-hydroxy-6,7-benzomorphan oxalate = *N*-Carboethoxymethyl- α -*N*-normetazocine oxalate $C_{18}H_{25}NO_3 \cdot (COOH)_2 \cdot (H_2O)_{0.5}$ (NME-1**):** (±)-*N*-normetazocine (**1**) (2.0 g), ethylbromoacetate (1.5 g), and K_2CO_3 (2.0 g) were added to a mixture of tetrahydrofuran (6 mL) and dimethylformamide (2 mL) and the resulting mixture stirred under reflux for 5 hours. Solvents were evaporated *in vacuo*. The residue was diluted with water and extracted three times with diethyl ether. The resulting extracts were combined, washed with brine, dried with magnesium sulfate, and concentrated under vacuum which gave 2.8g of base. The acidification of the freebase with oxalic acid in acetone gave the hemihydrated oxalate salt. m.p. 116–118 °C.

α -(±)-2-carboxymethyl-5,9- α -dimethyl-2'-hydroxy-6,7-benzomorphan oxalate = *N*-Carboxymethyl- α -*N*-normetazocine oxalate $C_{16}H_{21}NO_3 \cdot (HCl)_1 \cdot (H_2O)_{0.25}$ (NMA-1**):** **NME-1** (1.0 g, freebase), ethanol (0.1g) and KOH (1.0 g) were refluxed in water (2.5 mL) for 1.5 hours. The ethanol was evaporated *in vacuo* and the residue neutralized to pH7 with 10% HCl. The resulting white solid was collected by filtration, washed with cold water yielding 0.65g of free acid (m.p. 195–200). The free acid was dissolved in a mixture of methanol and ethylacetate and precipitated as the hydrochloride salt by bubbling HCl gas through the solution. m.p. 232–233 °C.

4.2 pharmacology

Hot plate (HP), tail flick (TF), antagonism of morphine in the tail-flick (TFA), and phenylquinone antiwrithing (PPQ) assays were carried out in mice as previously described at doses of 0.25, 1, 10, and 30 mg/Kg.^{15, 16} Binding was determined in rat cerebrum membrane preparations, and EC_{50} determinations by displacement of 0.5nM [3H]-etorphine from rat brain homogenates using the standard procedures of the Drug Evaluation Committee (DEC), College on Problems of Drug Dependence (CPDD).^{17, 18} This assay measures binding at all three opioid receptors, and does not differentiate between the opioid receptor types (μ , κ , δ). Functional activity in the Mouse Vas Deferens (MVD) was determined by suppression of electrically stimulated twitch using 25–30 g NIH Swiss mice, in the presence and absence of antagonists to determine the specific receptor responsible for the actions, again following standard procedures of DEC.¹⁷ Briefly, in the MVD assay, opioid agonists are characterized by the suppression of twitch height and inhibition by naltrexone. If the compound suppresses twitch height but is not inhibited by naltrexone the compound's effect is non-opioid in nature. Compounds are evaluated for opioid antagonist activity in the MVD by their ability to reverse the effects of morphine's suppression of twitch height. A compound, opioid agonist or antagonist, can be further evaluated for receptor specific effects with the use of receptor specific agonists and antagonists replacing naltrexone (for agonists) or morphine (for antagonists). Full details for these standard protocols and procedures are presented in the work of Smith.¹⁰ The *in vitro* experiments (binding and MVD assays) were carried out with concentrations ranging from 10^{-7} to 10^{-5} M. Results are listed in Table 1.

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References

1. Casy, AF.; Parfitt, RT. Opioid Analgesics. New York and London: Plenum Press; 1986.
2. May EL, Jacobson AE, Mattson MV, Coop A, Aceto MD, Bowman ER, John R, Traynor JR, Woods JH, Harris LS. *Med Chem Res* 1998;8:311.
3. May EL, Coop A, Woods JH, Aceto MD, Bowman ER, Harris LS, Traynor JR. *Bioorg Med Chem* 2003;11:31. [PubMed: 12467704]
4. Feldman PL, James MK, Brackeen MF, Bilotta JM, Schuster SV, Lahey AP, Lutz MW, Johnson MR, Leighton HJ. *J Med Chem* 1991;34:2202. [PubMed: 2066993]
5. Albertson NF, McKay FC. *J Med Chem* 1977;20:602. [PubMed: 850250]
6. Taber RI. *Adv Biochem Psychopharmacol* 1973;8:191. [PubMed: 4604927]
7. Defined by the authors of the study (ref 5) as the dose causing a 50% decrease in effect of an approximate ED80 dose of meperidine.
8. $pA_2 = -\log[\text{antagonist}]$ which causes a 2 fold shift to the right in dose response curve of agonist.
9. Due to testing protocols employed; pA_2 values for NME-1 for sufentanil and U50,488 were not calculated.
10. Smith CB. NIDA Research Monograph 1986;76:288. [PubMed: 2830524]
11. CLogP values calculated from structures using ChemDraw Ultra 10.0, CambridgeSoft.
12. Carroll FI, Melvin MS, Nuckols MC, Mascarella SW, Navarro HA, Thomas JB. *J Med Chem* 2006;49:1781. [PubMed: 16509593]
13. Carroll FI. *J Med Chem* 2003;46:1775. [PubMed: 12723940]
14. Spectra were consistent with the assigned structures; the salts gave satisfactory microanalyses ($\pm 0.4\%$).
15. May EL, Jacobson AE, Mattson MV, Traynor JR, Woods JH, Harris LS, Bowman ER, Aceto MD. *J Med Chem* 2000;43:5030. [PubMed: 11150174]
16. Pearl J, Harris LS. *J Pharmacol Exp Ther* 1966;154:319. [PubMed: 4380744]
17. Woods JH, Traynor JR. Problems of Drug Dependence 2000, NIDA Research Monograph 2001;181:141.
18. Negus SS. *Drug Alcohol Depend* 2006;82:182. [PubMed: 16703677]
19. Feldman PL, James MK, Brackeen MF, Bilotta JM, Schuster SV, Lahey AP, Lutz MW, Johnson MR, Leighton HJ. *J Med Chem* 1991;34:2202. [PubMed: 2066993]

Scheme 1.

Reagents and conditions: a. DMF/THF, K_2CO_3 , reflux 3–6 h; b. EtOH, H_2O , KOH, reflux 1–2 h.

Table 1
The Pharmacological Effects of *N*-ester and *N*-acid substituted-*N*-normetazocines

Compound	R	In Vivo ED ₅₀ (mg/kg, sc)				In Vitro EC ₅₀ (M)	
		PPQ	TF	TFA	Binding	MVD	
NME-1	CH ₂ COOEt	I	I	I, *	2.08 μM	NE, ANT ^d	
NME-2	CH ₂ CH ₂ COOEt	I	I	I	NT	NT	
NME-3	CH ₂ CH ₂ CH ₂ COOEt	I	I	I	1.02 μM	17.9 μM, ^{bc}	
NMA-1	CH ₂ COOH	I	I	I	>6 μM ^d	9.79 μM, ^{bc}	
NMA-2	CH ₂ CH ₂ COOH	I	I	I	>6 μM ^e	NE ^f	
NMA-3	CH ₂ CH ₂ CH ₂ COOH	I	I	I	>6 μM ^g	NE ^f	
Morphine	---	0.98	5.8	---	23.6 nM	395 nM	
(-) Metazocine	CH ₃	0.62	0.81	I			
Nalorphine	---	9.9	I	2.6	20.0 nM ^h		
Naloxone	---	I	I	0.03	6.26 nM	ANT ⁱ	
Naltrexone	---	I	I	0.007	0.63 nM	ANT ^j	

^aWeak antagonist [30 μM] of sufentanil (μ), U50,488 (κ), and DSLET (δ);

^bNeither altered or reversed the effects of sufentanil;

^cAntagonized by 10⁻⁷ M naltrexone and 10⁻⁷ M β-fulnaltrexamine but not 10⁻⁷ M ICI-174864;

^d7.0% inhibition at 6 μM;

^e26% inhibition at 6 μM;

^fDid not block or reverse the effects of sufentanil (μ), U50,488 (κ), or DSLET (δ);

^g27% inhibition at 6 μM;

^hconcentration of etorphine for displacement of this ligand was 3.0 nM (compare to codeine 34.7 μM, morphine 142nM, naloxone 9.1nM, and naltrexone 2.0nM when etorphine employed at 3.0nM);

ⁱpA₂ values 7.99, 6.90, 7.35 for sufentanil, U50,488, and DSLET;

^jpA₂ values 8.76, 7.74, 7.41 for sufentanil, U50,488, and DSLET.

I = inactive, did not reach 50% at highest dose (≥30 mg); NE = No Effect at any concentration tested (10⁻⁷ to 10⁻⁵ M); NT = Not Tested; ANT = Antagonist

MVD = Mouse Vas Deferens. Inhibition of electrically driven twitch, Inhibitory EC₅₀ (M); Binding = Displacement of specific [³H]-etorphine binding (0.5 nM) from rat cerebrum homogenates, in presence of 150 mM NaCl; *previous report showed activity as an antagonist of meperidine in rats.⁴

Table 2Effects of *N*-substituents on lipophilicity

Compound	<i>N</i> -substituent	Opioid class	ClogP
Fentanyl [*]	Phenylethyl	Anilidopiperidine	3.621
Carfentanil [*]	Phenylethyl	Anilidopiperidine	3.686
Remifentanil [*]	Ethylpropionate (Carbethoxyethyl)	Anilidopiperidine	1.956
Hydrolyzed Remifentanil [*]	Propionic acid (Carboxyethyl)	Anilidopiperidine	-0.777
Metazocine	Methyl	Benzomorphan	2.965
NME-1	Ethylacetate (Carbethoxymethyl)	Benzomorphan	3.751
NME-2	Ethylpropionate (Carbethoxyethyl)	Benzomorphan	3.992
NME-3	Ethylbutyrate (Carbethoxypropyl)	Benzomorphan	4.229
NMA-1	Acetic Acid (Carboxymethyl)	Benzomorphan	0.459
NMA-2	Propionic acid (Carboxyethyl)	Benzomorphan	0.598
NMA-3	Butyric Acid (Carboxypropyl)	Benzomorphan	0.852

^{*} Compound data from Feldman et al¹⁹; Calculated log P values (CLogP) were calculated using ChemDraw Ultra 10.0, CambridgeSoft;