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N-(Trifluoromethyl)benzyl Substituted *N*-Normetazocines and *N*-Norketobemidones

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Abstract—To further investigate the unusual profile of *N*-benzyl substituted opioids, *N*-trifluoromethylbenzyl normetazocines and norketobemidones were prepared. The introduction of trifluoromethyl substituents on the benzyl group of the (−)-metazocines reduced affinity at all three receptors, with the greatest loss at kappa receptors. Surprisingly, some of the (+)-normetazocines actually possessed higher affinity than the corresponding (−)-isomers. In the ketobemidone series, the effects were different—the 4-trifluoromethyl substituted ketobemidone actually possessed 3-fold higher mu affinity than the unsubstituted parent to give a ligand with good mu affinity. In functional in vitro assays, this compound was a weak antagonists, but in apparent contradiction it was inactive in in vivo assays.

The nature of the *N*-substituent dominates the pharmacological profile of many classes of opioids. In the 4,5-epoxymorphinan series (like morphine) *N*-methyl and *N*-phenethyl substituents tend to give rise to agonist activity, whereas *N*-allyl and *N*-cyclopropyl methyl (such as naloxone and naltrexone, respectively) tend to display morphine (mu receptor) antagonism.[1] Many different *N*-substituents have been investigated in a number of opioid skeletons,[1] and we recently reported on the unusual effects of *N*-benzyl substituents.[2] *N*-Benzyl substituted 4,5-epoxymorphinans, morphinans, metazocines (benzomorphans), and ketobemidones were shown to possess little activity in vivo, and most displayed correspondingly low affinity at the three opioid receptors (mu, kappa, and delta). One exception was the (−)-*N*-benzyl-*N*-normetazocine (**1a**) (Fig. 1) which possessed high affinity at mu and kappa receptors ($K_i = 44$ and 6 nM respectively, Table 2), but displayed only weak antinociceptive and morphine antagonist activity in vivo (Table 2). Recently, Neumeyer has also reported that an *N*-benzyl substituted morphinan also possessed high affinity at mu and kappa receptors, although functional data was not given.[3]

The effect of *N*-substituents in non-constrained opioids is often different to that of the constrained opioids,[1] and indeed we showed that *N*-benzyl-*N*-norketobemidone (**3a**) (Fig. 1) possessed low affinity for all three opioid receptors (Table 2), yet gave twice the antinociceptive activity in vivo of **1a** (paraphenylquinone $ED_{50} = 7.5$ mg/kg, Table 2).[2]

The lack of significant in vivo activity of **1a** could be attributed to poor penetration into the CNS, or rapid metabolism of the electron rich system, yet this is not consistent with the greater activity of **3a** which contains a substituent prone to the same metabolic and transport processes. To further study this intriguing problem, we have prepared a range of substituted *N*-benzyl derivatives containing a trifluoromethyl substituent (Fig. 1), which would be expected to increase lipophilicity, and therefore CNS penetration, and also reduce the electron density in the ring due to its electron withdrawing nature, and thus reduce the likelihood of metabolism.

Chemistry

The benzyl compounds **1b**–**1d**, **2b**–**2d**, and **3b**–**3d** (Fig. 1) were prepared from (−)- and (+)-*N*-normetazocines and *N*-Norketobemidone and the appropriate benzyl

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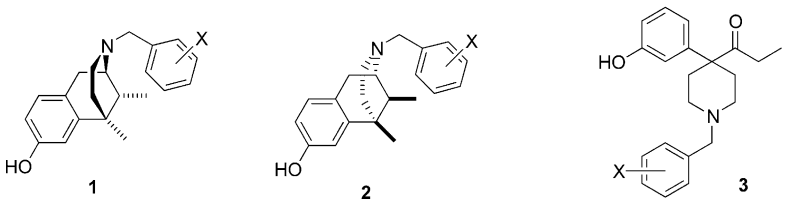

Figure 1. Substituted *N*-benzyl *N*-normetazocines and *N*-norketobemidones (a) X = H, (b) X = 2-CF_3, (c) X = 3-CF_3, (d) X = 4-CF_3.

chlorides. All reactions were refluxed in EtOH or THF/DMF (1–7 h), in the presence of potassium bicarbonate. All were converted into salts, and melting points are shown in Table 1.

Pharmacolgy

The tail flick (TF), hot plate (HP), phenylquinone (PPQ), and tail flick antagonist (TF versus M) assays were carried out in male Sprague–Dawley mice as previously described,[4,5] and single-dose-suppression (SDS) and precipitated withdrawal (PPtW) assays in Rhesus monkeys employing the standard procedures of the Drug Evaluation Committee, College on Problems of Drug Dependence.[6–8] Binding assays were preformed through displacement of [^{3}H]-diprenorphine from cloned mu, kappa, and delta receptors. In vitro functional assays using the [^{35}S]GTPγS binding assay at cloned mu receptors, again employing the standard procedures of the Drug Evaluation Committee, College on Problems of Drug Dependence.[9] Data are shown in Table 2.

Table 1. Physical data of compounds

	Salt	Mp (°C)	$[\alpha]_D^{20}$	Solvent	Concentration (g/100 mL)
1b	HCl	210–215	−61.0	MeOH	0.277
1c	HCl	279	−74.8	MeOH	0.155
1d	Oxalate	125	−66.6	MeOH	0.308
2b	HCl	210–215	+60.9	MeOH	0.216
2c	HCl	279	+76.0	MeOH	0.171
2d	Oxalate	127	+66.1	MeOH	0.232
3b	HCl	212–214	—	—	–
3c	HCl	203–205	—	—	–
3d	HCl	260–262	—	—	–

Results and Discussion

The (+)-normetazocines (**2a**–**2d**) all displayed low activity in in vitro and in vivo assays, which is consistent with previous findings for opioids with (+)-stereochemistry.[2,10] Surprisingly, the compounds with (+)-stereochemistry sometimes possessed greater affinity for opioid receptors than predicted by comparison with the corresponding (−)-isomers. **2c** Possessed about the same affinity for opioid receptors as **1c**, and **2d** actually possessed higher affinity than **1d** at all three opioid types. These data further suggest that an *N*-benzyl substituent has unusual effects on opioid pharmacology, and that the 'unnatural' (+)-isomers can possess greater affinity than the 'natural' (−)-isomers, though, with the exception of **1a**, all compounds in the series had low affinity.

The ketobemidones also lost affinity when substituted at the 2- and 3-positions (**3b** and **3c**), but when the trifluoromethyl group was introduced into the 4-position (**3d**), the affinity at mu increased three-fold and kappa about two-fold over the unsubstituted **3a** to give a ligand of relatively high affinity. In an apparent contradiction, the increased affinity resulted in decreased in vivo activity. **3d** Was shown to possess no morphine agonist or antagonist activity in the mouse and monkey, even

Table 2. Pharmacological evaluation of compounds

	Binding data: K_i (nM ±SEM)			In vivo data: EC_{50} (mg/kg)[a]					
	Mu	Delta	Kappa	TF	HP	PPQ	TF versus M	SDS	PPtW
1a	43.9±1.5[b]	>10,000[b]	6.0±1.8[b]	I[c]	I[c]	13.4 (4.1–41.0)[c]	20.3 (8.3–49.6)[c]	I[c]	I[c]
1b	335±95	1091±18	149±17	I	I	I	I	I	I
1c	314±75.6	2904±414	704±111	I	I	I	I	I	I
1d	1435±333	>10,000	1872±316	I	I	27.4 (11.30–66.41)	I	I	I
2a	588±16.9	3966±486	75.6±3.1	I[c]	I[c]	I[c]	I[c]	NT[c,d]	NT[c,d]
2b	867±60	3538±936	645±30	I	I	I	I	I	I
2c	598±166	1644±502	528±37	I	I	I	I	I	I
2d	279±35.7	2217±406	564±93	I	I	32.8 (16.4–65.5)	I	I	I
3a	110±4.6[b]	348±41[b]	192±39[b]	I[c]	I[c]	7.5 (2.8–19.9)[c]	I[c]	I[c]	I[c]
3b	546±101	119±18	836±8	I	I	I	I	I	I
3c	118±28	316±32	203±33	I	I	I	I	I	I
3d	32.9±1.1	291±83	118±28	I	I	I	I	I	I

[a]I = Inactive— did not reach 50% response at the highest dose (30 mg/kg).
[b]Previously reported in monkey cortex.[2]
[c]Previously reported.[2]
[d]NT = not tested.

though it possessed an affinity at mu receptors of 33 nM. In the [^{35}S]GTPγS binding assay the compound had no agonist activity, but did shift the concentration–effect curve for the mu agonist DAMGO to the right with an affinity (K_e) of 516 ± 166 nM, and in a buffer containing NaCl and GDP the affinity of the compound in binding assays was shifted approximately 3-fold to lower affinity. These data suggest that, even though affinity and activity at opioid receptors can be obtained with an *N*-benzyl substituent in vitro, this is relatively weak and does not translate well to activity in in vivo assays. As the trifluoromethyl groups were introduced in an attempt to reduce the likelihood of metabolism, and also to increase lipophilicity, it appears that these processes are not responsible for the low in vivo activity of *N*-benzyl substituted opioids.

These studies have also clearly demonstrated that (+)-*N*-benzylnormetazocines can possess greater affinity for opioid receptors than the corresponding (−)-isomers, suggesting that *N*-benzyl substituted opioids may be recognized differently at opioid receptors than opioids with other *N*-substituents. Opioids with the (+)-stereochemistry have previously been reported which have significant opioid activity, such as (+)-thebaine[11] and (+)-phenazocine,[12] but they are clearly exceptions to the general rule. Further studies to determine to determine structure activity relationships for (+)-*N*-benzylnormetazocines at opioid receptors are currently underway, with the intention of investigating why they possess affinity for opioid receptors, yet produce no opioid action in in vivo models.

Experimental

Optical rotations were determined employing a Perkin Elmer 141 polarimeter, and infrared spectra on a Beckman Acculab B spectrophotometer. Mass spectral data were consistent with assigned structures. Recrystalization of the salts were performed from acetone or acetone:MeOH mixtures. Elemental analyses were performed for C, H, and N by Atlantic Microlabs, Norcross, GA, and were within ±0.4% of theory.

Typical procedure

(−)-(1*R*,5*R*,9*R*)-2-(2-Trifluoromethyl)benzyl-2′-hydroxy-6,7-benzomorphan (1b). (−)-*N*-Normetazocine (0.5 g, 2.3 mmol), 2-trifluoromethylbenzyl chloride (0.5 g, 2.57 mmol), and $KHCO_3$ (0.7 g, 7.0 mmol) were added to a mixture of THF (7 mL) and DMF (2 mL), and resulting mixture heated at reflux for 7 h. After cooling, the THF was removed under reduced pressure and the residue was partitioned between Et_2O and water. The aqueous layer was further extracted with Et_2O, the organic extracts combined, washed with brine, and dried ($MgSO_4$). Removal of the drying agent by filtration, followed by acidification with HCl (1 M in Et_2O) gave the HCl salt of **1b** (0.87 g, 100%). Mp 210–215 °C (MeOH:acetone).

Elemental analyses

	Calcd			Found		
Compd	C	H	N	C	H	N
1b.HCl	64.15	6.12	3.40	64.08	6.15	3.42
1c.HCl	64.15	6.12	3.40	64.00	6.00	3.33
1d.Oxalate. CH_3COCH_3	61.92	6.18	2.65	61.56	5.98	2.74
2b.HCl	64.15	6.12	3.40	64.00	6.05	3.44
2c.HCl	64.15	6.12	3.40	64.11	6.00	3.36
2d.HCl. CH_3COCH_3	61.92	6.18	2.65	61.83	6.01	2.80
3b.HCl	61.75	5.89	3.28	61.85	5.93	3.25
3c.HCl	61.75	5.89	3.28	61.87	5.93	3.24
3d.HCl	61.75	5.89	3.28	61.33	5.83	3.22

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