Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 831–834

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Ring Constrained Analogues of the Orvinols: The Furanomorphides.

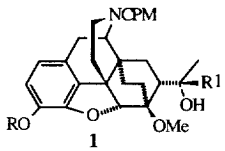
Stephen M. Husbands, Simon W. Breeden, Konstantinos Grivas, John W. Lewis*.

School of Chemistry, Cantock's Close, University of Bristol, Bristol, BS8 1TS, England.

Received 14 December 1998; accepted 8 February 1999

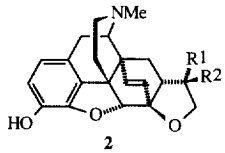
Abstract: A series of furanomorphides were synthesised as ring-constrained analogues of buprenorphine and related orvinols. Evaluation in binding and functional assays has shown that the furanomorphides have reduced efficacy at the μ opioid receptor compared to the orvinols.

Buprenorphine (**1a**) is a potent opioid analgesic that is being developed as a treatment for opiate abuse and dependence. Its opioid receptor profile - μ-partial agonist and κ, δ-antagonist - is unique among clinically used opioid analgesics and is also unique in the series of orvinols of structure **1** which normally show some agonist activity at κ as well as μ opioid receptors.[1] In order to more closely define the structural requirements for activation of all opioid receptor types in orvinols related to buprenorphine particularly the nature and conformation of C20, several series of ring-constrained analogues have been synthesised and evaluated.[2,3,4,5]



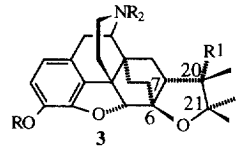
1

a: R = H, R^1 = ^{t}Bu
b: R = H, R^1 = Me
c: R = R^1 = Me



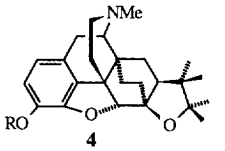
2

a: R^1 = H, R^2 = ^{n}Bu
b: R^1 = ^{n}Bu, R^2 = H
c: R^1 = H, R^2 = Me
d: R^1 = Me, R^2 = H



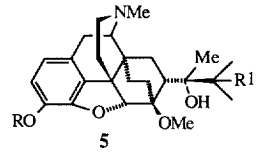
3

a: R = R^1 = R^2 = Me
b: R = R^2 = Me, R^1 = H
c: R = H, R^1 = R^2 = Me
d: R = R^1 = H, R^2 = Me
e: R = H, R^1 = Me, R^2 = CPM



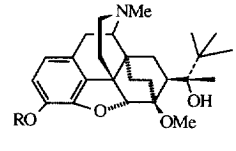
4

a: R = Me
b: R = H



5

a: R = H, R^1 = Me
b: R = Me, R^1 = H
c: R = H, R^1 = H



6: R = H

Hutchins and Rapoport[6] synthesised two pairs of furanomorphides (**2**) and reported the activity of **2a** and **2b**

* e-mail: J.Lewis@bristol.ac.uk and fax: (UK) 117 929 8611

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00085-2

in the rat tail flick antinociceptive assay. The 20[*S*]-diastereomer **2b** was about ten times more potent than the [*R*]-diastereomer from which it was concluded that a lipophilic site on the receptor was available for binding the butyl group in **2b**. We here report investigation of a series of methyl-substituted furanomorphides (**3c**, **3d**, **3e**, **4b**) related to the C20 branched orvinols such as buprenorphine.

Synthesis

The tri- and tetramethyl-substituted furanomorphides (**3c**, **3d**, **4b**) were synthesised by O-demethylation of the equivalent furanocodides (**3a**, **3b**, **4a**)[7,8] with sodium propane thiolate. The furanomorphide (**3e**) derived from buprenorphine (**1a**) was prepared directly from the orvinol by formic acid promoted rearrangement.[7] The epimeric monomethyl-substituted analogues (**9a**, **9b**) were prepared from diprenorphine methyl ether (**3c**)(Figure 1) by brief treatment with formic acid to afford the isopropenyl derivative (**7**)[9] which was hydroborated and oxidised with H_2O_2 to afford a mixture of the two diastereomeric primary alcohols (**8a**, **8b**). These were separated by silica gel chromatography, eluting with hexane: ethyl acetate, then converted to the mesylates and treated with lithium aluminium hydride to effect ring closure.[6] The yields of furanocodides (**9c**, **9d**) were only 24% and 22%, with the major product being the thevinan (**10**) formed by hydrogenolysis of the mesylates.[6] The furanocodides were demethylated with sodium propane thiolate to afford **9a** and **9b**.

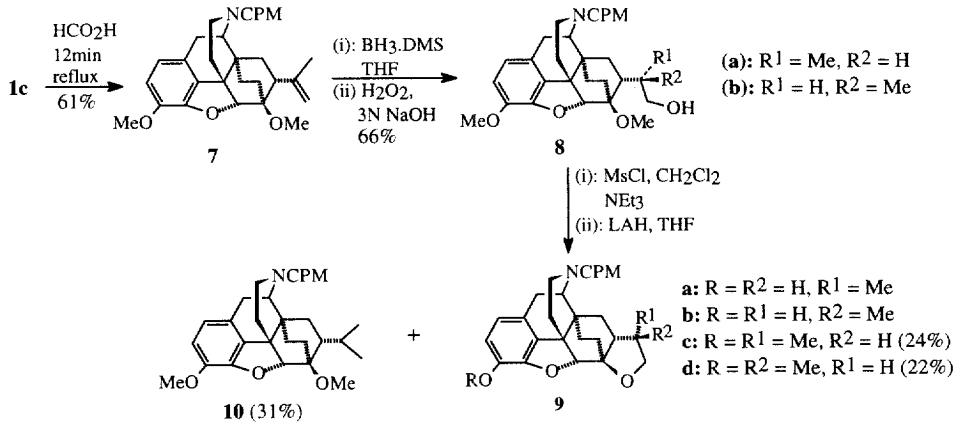


Figure 1: Synthesis of furanomorphides **9a** and **9b**.

Results and Discussion

Opioid receptor affinities were determined in receptor binding assays in guinea pig brain homogenates (Table 1).[10] All of the furanomorphides had subnanomolar affinity for the μ receptor but only the N-CPM (cyclopropylmethyl) derivatives (**3e**, **9a**, **9b**) had this level of affinity for the κ and δ receptors. As a result the N-Me furanomorphides (**3c**, **3d**, **4b**) showed some μ selectivity. For the ring junction isomers **3c** and **4b** there were only small differences of affinity. Similarly, the orvinols from which the furanomorphides are derived showed opioid receptor binding profiles qualitatively similar to the furanomorphides *i.e.* high affinity with modest μ selectivity.

In the electrically stimulated guinea pig *ileum* preparation (GPI) the two N-Me furanomorphides (**3c**, **3d**) and the corresponding orvinols (**5a**, **5c**) showed agonist activity with low nanomolar potency (Table 2). These responses was reversed by the μ-selective antagonist CTAP but not by the κ-antagonist nor-BNI (data not shown). These furanomorphides and orvinols (**3c**, **3d**, **5a**, **5c**) were all agonists in the mouse *vas*

deferens (MVD) but the orvinols were 40-80 times more potent than the furanomorphides (Table 2). This may have resulted from the furanomorphides having limited μ-efficacy giving shallow dose-response curves. In the case of **3c** it appears that the μ response was inferior to low potency δ-agonism which was identified by naltrindole (NTI) antagonism. The N-CPM analogue (**3e**) was a partial agonist in GPI of lower efficacy than its parent, buprenorphine but had no agonist activity in MVD. It potently antagonised selective agonists for μ, δ, κ-receptors in this preparation (Table 2). Like buprenorphine, the agonist response of **3e** could not be reversed by selective μ and κ antagonists and it could not be washed out of the *in vitro* preparations.

Table 1: Opioid receptor binding affinities of furanomorphides and orvinols in guinea pig brain membranes.

	Ki (nM)		
	[^{3}H] DAMGO	[^{3}H] Cl-DPDPE	[^{3}H] U69593
structure	μ	δ	κ
3c	0.2±0.05	4.4±0.1	3.4±1.8
3d	0.5±0.2	4.4±0.8	2.6±1.8
4b	0.6±0.08	6.1±1.6	4.4±0.02
9a[b]	0.7±0.04	1.2±0.005[b]	1.1±0.8
9b[b]	0.3±0.08	0.7±0.2[b]	0.6±0.2
3e	0.2±0.1	0.8±0.3	0.7±0.3
5b	0.4±0.1	1.3±0.5	0.7±0.2
5c	0.1±0.01	0.6±0.1	2.2±0.5
6[a]	0.6±0.2	1.1±0.6	2.4±1.3
1b	0.2±0.06	0.3±0.05	0.4±0.2
1a	1.3±0.15	1.6±0.07	1.5±0.3

a: In cloned human receptors transfected in CHO cells. b: Data from Dr A.L. Hudson, University of Bristol. c: vs [^{3}H] DPDPE.

Furanomorphide **4b** having the 7,8-cis ring junction was evaluated in the [^{35}S]GTPγS assay in cloned human μ, δ and κ opioid receptors transfected into chinese hamster ovary (CHO) cells;[10] it was compared with the parent orvinol (**6**) and with buprenorphine (**1a**). This assay allows the measurement of both potency and efficacy for each opioid receptor type. The furanomorphide **4b** displayed predominant μ partial agonist activity. It's μ potency was more that tenfold higher than δ and κ though its efficacy as a δ receptor agonist was significantly

Table 2: Activity of Furanomorphides and Orvinols in Isolated Tissues

	Guinea Pig Ileum (GPI)		Mouse Vas Deferens (MVD)	
Structure	IC_{50} (nM)	K_e(CTAP: nM)	IC_{50} (nM)	K_e(NTI; nM)
3e	52.6%[a]	NR[b]	[c]	
3c	2.26±0.99	80.4±5.7	308±83	0.037±0.015
3d	3.47±0.75	37.6±6.0	237±60	1.31±0.5
1a	8.13±3.55	NR	21.14±14.3	NR
5a	1.25±0.53	33.1±2.2	7.17±2.11	2.37±2.3
5c	0.49±0.12	49.8±7.6	3.11±1.08	2.34±0.23
DAMGO	8.25±2.0	25.3±2.54	178±134	NR
DPDPE	-	-	4.11±1.32	0.021±0.007

a: Partial Agonist; maximum response. b: Not reversed. c: No agonist activity. Antagonist: Ke (μ) 0.25±0.07nM, Ke (δ) 1.80±0.22 nM, Ke (κ) 0.95±0.27nM

higher than the μ and κ effects. The equivalent orvinol (**6**) had similar μ potency but possibly higher efficacy than **4b**. Its δ and κ potency was substantially higher than that of the furanomorphide. In the GTPγS assay buprenorphine showed μ partial agonist activity but very low δ and κ efficacy; this profile is consistent with its *in vivo* activity.[1]

Table 3: Activity of Furanomorphide **4b** and orvinols **6** and **1a** (buprenorphine) in [^{35}S]GTPγS assays in human opioid receptors transfected in Chinese hamster ovary (CHO) cells.

	μ		δ		κ	
Structure	EC_{50} (nM)	%Stim	EC_{50} (nM)	%Stim	EC_{50} (nM)	%Stim
4b	1.90±0.1	67.5±8.5	28.4±0.7	88.0±5.0	20.9±11	59.0±11
6	1.20±0.34	86.5±13.5	5.0±2.3	79±8.0	2.4±1.25	50.0±14
1a	2.3±1.7	66±36	flat		flat	

These data suggest that the primary effect of constraining the branched 20-alkyl group and masking the hydroxyl group in buprenorphine and related orvinols is to reduce μ efficacy. The location of C21 in the furanomorphides, corresponding to the ^{t}Bu group in buprenorphine and **5a** does not allow substantial binding to Hutchins and Rapoport's proposed lipophilic binding site.[9] The energy minimised conformation for buprenorphine locates the ^{t}Bu group in the least hindered space above and away from C7 allowing an intramolecular hydrogen bond between the 20-hydroxyl and 6-methoxyl groups.[11] If this location of the ^{t}Bu group is of prime importance for the μ agonist binding of buprenorphine and **5a**, its displacement and modification would account for the observed loss of μ efficacy in the furanomorphides.

In conclusion, the furanomorphides derived from branched chain orvinols like buprenorphine have lower μ efficacy than the orvinols but in other respects show similar opioid receptor profiles. The 20-OH is thus not critical for the activity of the orvinols and some support is offered for their active conformation having an intramolecular hydrogen bond.

Acknowledgements: This work was supported by NIDA (OTDP Medications Development Division) grant no. DA 07315.

References

1. Lewis, J.W. in Buprenorphine, Cowen, A and Lewis, J.W editors, New York, Wiley-Liss, 1995, 3-18.
2. Barton, J.W; Coop, A and Lewis, J.W. *Tetrahedron Lett.*, **1993**, *34*, 6777-6778.
3. Coop. A; Grivas, K.; Husbands, S.; Lewis, J.W. and Porter J. *Tetrahedron Lett.*, **1995**, *36*, 1689-1692.
4. Coop, A.; Grivas, K.; Husbands, S.; Lewis, J.W. *Tetrahedron*, **1995**, *35*, 9681-9698.
5. Coop, A.; Lewis, J.W.; Traynor, J.R. And Guo, L. *NIDA Res. Monog.* **1995**, *153*, 128.
6. Hutchins, C.W. And Rapoport, H. *J. Med. Chem.* **1984**, *27*, 521-527.
7. Bentley, K.W.; Hardy, D.G.; Meek, B.; Taylor, J.B.; Brown, J.J. And Morton, G.O. *J. Chem. Soc (C)*, **1969**, 2229-2232.
8. Grivas, K; Breeden, S.W.; Ganter, C; Husbands S.M and Lewis, J.W. *Tetrahedron Lett.*, accepted.
9. Bentley, K.W.; Hardy, D.G. and Meek, B. *J. Am. Chem. Soc.*, **1967**, *89*, 3272-3280.
10. Traynor, J.R and Nahorski, S.R. *Mol. Pharmacol.* **1995**, *47*, 848-854.
11. Loew, G.H and Berkowitz, D.S. *J. Med. Chem.*, **1979**, *22*, 603-607.