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Brief Article

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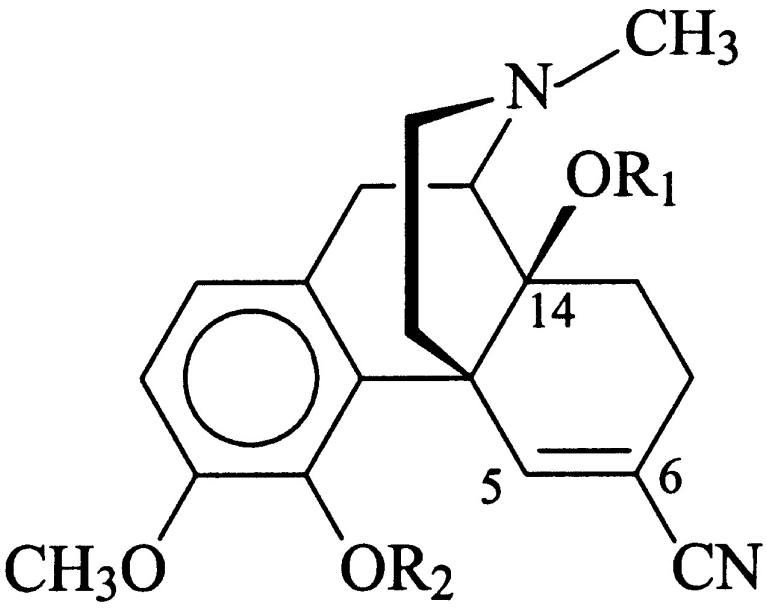

$R_1 = H, CH_3$

$R_2 = H, CH_3$

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Effect of a 6-Cyano Substituent in 14-Oxygenated *N*-Methylmorphinans on Opioid Receptor Binding and Antinociceptive Potency

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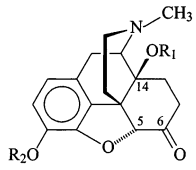
In a continued effort to find new substitution patterns in morphinans that would produce strong antinociception while inducing lesser side effects, 4,5-oxygen bridge-opened 6-cyano-substituted *N*-methylmorphinans (**1**−**3**) were synthesized. All compounds showed high affinities in the low nanomolar range to the μ opioid receptor and decreased interaction with δ and κ receptors, thus being μ selective. When tested in vivo, the 6-cyanomorphinanas acted as potent antinociceptive agents which were either more active or equipotent to their 6-keto analogues **4**−**6**.

Introduction

Today, oxycodone is one of the most frequently used opioid analgesics for the treatment of moderate to severe pain. Like its analogue oxymorphone, it belongs to the chemical class of *N*-methylmorphinan-6-ones. A derivative of oxymorphone, 14-*O*-methyloxymorphone (Figure 1) was developed by our group and described to be about 400- and 40-fold more potent than morphine and oxymorphone, respectively, in the hot-plate test in mice.[1] However, there are a number of serious side effects such as physical dependence and respiratory depression associated with this class of opioids.[1] Identifying new substitution patterns in morphinans that would result in high antinociceptive actions while producing diminished side effects remains an important task in medicinal chemistry and opioid pharmacology.

Results from our previous investigations have shown that 4,5-oxygen bridge-opened 6-ketomorphinans have increased affinities to the μ opioid receptor[1,2] and higher antinociceptive potency[2] than their 4,5-oxygen-bridged analogues. The C-6 carbonyl group of 6-ketomorphinans can be easily chemically modified, and earlier studies have demonstrated that such modifications generally do not affect the opioid character of the ligand.[3−6] For example, hydrazone, oxime and semicarbazone derivatives, and amino acid conjugates of *N*-methyl-6-ketomorphinans display high affinity to the μ opioid receptor,[3−6] and high antinociceptive potencies together with reduced unwanted side effects.[7−10] On the basis of these findings, we have prepared a novel class of acrylonitrile incorporated 4,5-oxygen bridge-opened *N*-methylmorphinans (**1**−**3**) aiming to explore how the combination of a C-6 cyano functionality together with an open 4,5-oxygen bridge will affect the interaction with opioid receptors. Using a modified van Leusen reaction we were able to introduce the cyano group and to open the 4,5-oxygen bridge simultaneously in a convenient, high yield one-pot reaction, leading to the 14-hydroxylated and 14-methoxylated 6-cyanomorphinans **1** and **2**, respectively[11] (Figure 2). In addition, the synthesis of the 4-O-methylated derivative of compound **1**, namely compound **3**, is described in this study. Thus, compounds **1** and **2**[11] and the newly prepared analogue **3** were biologically and pharmacologically characterized. Moreover, in the present study we aimed to investigate to which degree the presence of a 6-cyano group would change opioid receptor binding and in vivo potency



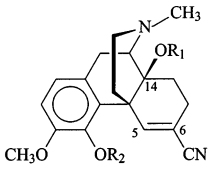
Oxycodone: R_1 = H, R_2 = CH_3

14-*O*-Methyloxycodone: R_1 = R_2 = CH_3

Oxymorphone: R_1 = R_2 = H

14-*O*-Methyloxymorphone: R_1 = CH_3, R_2 = H

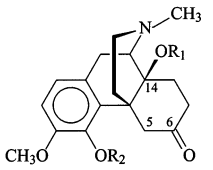
Figure 1.



1: R_1 = R_2 = H

2: R_1 = CH_3, R_2 = H

3: R_1 = H, R_2 = CH_3



4: R_1 = R_2 = H

5: R_1 = CH_3, R_2 = H

6: R_1 = H, R_2 = CH_3

Figure 2.

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Table 1. Opioid Receptor Binding Affinities and Selectivities of Compounds **1**−**6** and Reference Compounds in Rat Brain Membranes

compd	K_i (nM) ± SEM			selectivity ratio	
	[^{3}H]DAMGO (μ)	[^{3}H][Ile^{5,6}]-deltorphin II (δ)	[^{3}H]U69,593 (κ)	δ/μ	κ/μ
1	31.7 ± 2.1	498 ± 79	1648 ± 201	16	52
2	5.38 ± 0.42	197 ± 29	378 ± 155	37	70
3	2.44 ± 0.13	107 ± 5	364 ± 7	44	149
4	32.6 ± 2.6	881 ± 79	763 ± 73	27	23
5	4.65 ± 0.13	180 ± 19	592 ± 67	39	127
6	3.88 ± 0.01	91.6 ± 6.4	693 ± 238	24	179
oxycodone	43.6 ± 1.5	1087 ± 246	2658 ± 367	25	61
morphine[a]	6.55 ± 0.74	217 ± 19	113 ± 9	33	17

[a] Data from ref 26.

compared to their 6-keto analogues **4**−**6** (Figure 2), which have been reported to exhibit high antinociceptive potencies.[1,12−14]

Chemistry. The 6-cyano-substituted morphinans **1** and **2** were obtained by applying the van Leusen reaction to oxycodone and 14-*O*-methyloxycodone,[15] respectively.[11] The 3,4-dimethoxy-substituted compound **3** was prepared from compound **2** by alkylation with phenyltrimethylammonium chloride in *N,N*-dimethylformamide in the presence of potassium carbonate at elevated temperature (Figure 2). Compounds **4**−**6** were prepared as published previously.[1,12]

Results and Discussion

Opioid Receptor Binding. Opioid binding affinities of compounds **1**−**6** were determined in receptor binding assays using rat brain membranes by displacement of [^{3}H][D-Ala^2,Me-Phe^4,Gly-ol^5]enkephalin ([^{3}H]DAMGO, μ), [^{3}H][Ile^{5,6}]deltorphin II (δ), and [^{3}H]U69,593 (κ) as previously described.[16] The binding data expressed as inhibition constant (K_i) values are shown in Table 1. The selectivity for the μ opioid receptor versus δ and κ receptors was defined by the ratio of the K_i values.

An examination of the affinities of the 6-cyano target compounds **1**−**3** reveals that they display high binding affinity in the low nanomolar range to the μ receptor and are μ selective. Their binding affinities at the μ site are 1 to 2 orders of magnitude higher than the affinities to δ and κ receptors. Compounds **2** and **3** showed affinities to μ receptors comparable or higher than that of morphine, but considerably greater than that of oxycodone (Table 1). The 6-cyano derivatives were found to be more μ selective than the reference compounds as indicated by δ/μ and κ/μ selectivity ratios.

Comparison of 6-cyanomorphinans to their 6-keto analogues, **1** vs **4**, **2** vs **5**, and **3** vs **6**, indicate that introduction of a 6-cyano group does not significantly affect μ opioid receptor affinity. As shown in Table 1, the affinities of 6-cyanomorphinans **1**, **2**, and **3** at the μ site were comparable or slightly higher than those of their 6-keto counterparts **4**, **5**, and **6**, respectively. On the other hand, like their corresponding 6-keto analogues, they also retained the low binding affinities to δ and κ sites.

The observed differences in receptor binding affinities and selectivities of the investigated compounds are related to specific structural features. Among the tested compounds, the 6-cyano-3,4-dimethoxy derivative **3** displayed the highest μ affinity (K_i of 2.44 nM). When comparing the binding affinity to the μ receptor of compounds **3** and **6** to their 4-hydroxy analogues **1** and **4**, respectively, it is apparent that methylation of the 4-hydroxy group increases considerably μ affinity but also μ selectivity (Table 1).

In the present study, 14-methoxylated 6-cyanomorphinan **2** and its 6-keto analogue **5** were noted to interact with higher affinity to μ opioid receptors (K_i of 5.38 and 4.65 nM) than their 14-hydroxy analogues **1** and **4** (K_i of 31.7 and 32.6 nM). In our earlier studies on *N*-methyl-6-ketomorphinans, we found that enhancement in the binding affinity of μ opioid receptor agonists can be achieved with different substituents in position 14. It has been shown that replacement of a 14-hydroxy group with an alkoxy group (e.g. methoxy, ethoxy) results in compounds with improved μ receptor affinity.[1,8] In addition, we have recently found that in the series of C-14-substituted morphinan-6-ones, the presence of larger groups such as 14-phenlypropoxy markedly increases binding affinities to δ and κ opioid receptors while retaining the high affinity to the μ receptor.[17]

When comparing opioid receptor affinities of the 14-hydroxy-6-cyanomorphinan **1** and the 14-hydroxy-6-ketomorphinan **4** with oxycodone, it is evident that they show comparable affinities to μ, δ, and κ binding sites (Table 1). On the other hand, the 4-methoxy derivatives **3** and **6** had about 11- and 18-fold, respectively, higher μ affinity than oxycodone, followed by improved selectivities to the μ opioid receptor. This indicates that opening of the 4,5-oxygen bridge produces a modest increase in binding affinity and selectivity, while methylation of the phenolic group in position 4 leads to a significant increased μ affinity and μ selectivity. Similar observations have been reported in other series of *N*-methylmorphinans-6-ones.[1,13,14]

It was previously shown that hydrazone, oxime, or semicarbazone derivatives of *N*-methylmorphinan-6-ones such as dihydromorphinone and oxymorphone have comparable opioid binding affinities to the parent compound.[4] Recently, we reported on the replacement of the 6-keto group in *N*-methylmorphinans-6-ones with amino acid residues at position C-6 which does not seem to have a major effect on the in vitro biological activities, i.e., μ affinity and agonist potency.[6,18] On the basis of previous[1,3−6] and present observations, a 6-keto group is not a requirement for high affinity to the μ opioid receptor in the class of *N*-methylmorphinan opioids.

Antinociception. The 6-cyanomorphinans **1**−**3** were further evaluated in vivo for the analgesic effects. Antinociceptive potencies of these compounds were assessed in the hot-plate (HP), tail-flick (TF), and *p*-phenylquinone writhing (PPQ) tests in mice. The results of the in vivo pharmacological findings are in qualitative agreement with the in vitro binding data.

As shown in Table 2, compounds **1**−**3** when administered subcutaneously (sc) showed potent antinociceptive effects in all three in vivo assays. The 6-cyano-3,4-dimethoxy derivative **3** displayed the highest antinociceptive potency of the three 6-cyanomorphinans, being in the HP about 9- and 6-fold, in the TF about 52- and 106-fold, and in the PPQ about 14- and 15-fold more potent than oxycodone and morphine, respectively. Compound **3** was about 3-, 100-, and 7-fold more potent than derivative **1** in the HP, TF, and PPQ, respectively.

Table 2. In Vivo Potencies of Compounds **1**−**6** and Reference Compounds in Mice

compd	ED_{50} (sc, mg/kg)[a]		
	HP[b]	TF[c]	PPQ[d]
1	0.50 (0.12−2.02)	1.88 (1.25−2.83)	0.18 (0.076−0.42)
2	0.25 (0.11−0.59)	0.21 (0.11−0.40)	0.11 (0.072−1.64)
3	0.15 (0.054−0.41)	0.018 (0.061−0.23)	0.026 (0.012−0.055)
4[e]	2.60 (2.10−3.40)	-	-
5[f]	0.29 (0.22−0.36)	-	-
6[e]	0.14 (0.10−0.18)	-	-
oxycodone[g]	1.37 (0.48−3.92)	0.94 (0.40−2.30)	0.38 (0.19−0.75)
morphine[h]	0.85 (0.39−1.86)	1.90 (0.89−4.14)	0.40 (0.20−0.80)

[a] Effective dose 50% (95% confidence limits). [b] HP = hot-plate test. [c] TF = tail-flick test. [d] PPQ = *p*-phenylquinone writhing test. [e] Data from ref 13. [f] Data from ref 1, converted from μmol/kg to mg/kg. [g] Data from ref 27. [h] Data from ref 28.

The 14-methoxy derivative **2** showed about 2- to 11-fold lower potency than compound **3**. These results indicate that 4-O-methylation leads to higher antinociceptive potency compared to a 14-O-methylation.

Remarkably, the 6-cyanomorphinan **1** showed about 5-fold greater antinociceptive potency than its 6-keto analogue **4** in the HP in mice (Table 2). The 6-cyano derivatives **2** and **3** exhibited similar potencies compared to their 6-keto analogues **5** and **6**, respectively. It is evident that the introduction of a 6-cyano group in *N*-methylmorphinans gives rise to potent antinociceptive agents which are either more active or equipotent to their 6-keto analogues **4**−**6**.

When comparing the potency in the HP of compounds **3** and **6** to their 4-hydroxy congeners **1** and **4**, respectively, it became apparent that introduction of a 4-methoxy group increases antinociceptive potency in both classes of compounds (Table 2). The observed enhancement in the in vivo potency correlates very well with the increase in affinities to μ opioid receptors for the 4-methoxy derivatives **3** and **6** as determined in binding assays (Table 1). Introduction of a methoxy group in position 14, as in the case of the 6-cyanomorphinan **2** and its 6-keto analogue **5**, leads to increased analgesic potency in the HP compared to their 14-hydroxy counterparts **1** and **4**. In the TF, the 14-methoxy analogue **2** was about 9-fold more potent than the 14-hydroxy-substituted derivative **1**, while in the PPQ they were equipotent (Table 2). The present results are in line with our previous studies on the improved analgesic potencies of 14-alkoxy-substituted *N*-methylmorphinans compared to the corresponding 14-hydroxy analogues.[1,8,13] It is evident that the 14-methoxy group not only increases the affinity to the μ opioid receptor in binding assay but also enhances the antinociceptive potency as earlier described.[1]

While the 14-hydroxy-6-cyanomorphinan **1** and the 14-hydroxy-6-ketomorphinan **4** showed analgesic effects overall comparable to oxycodone, the 4-methoxy derivatives **3** and **6** were found to be much more active. The greater potency of compounds **3** and **6** is due to increased interaction with the μ sites achieved by opening of the 4,5-oxygen bridge and methylation of the phenolic group in position 4.

The potent antinociceptive effect of the *N*-methylmorphinan class of opioids might be attributed to the substitution pattern in position C-6 of the morphinan skeleton. It was reported that opioids bearing various substituents in position C-6, e.g. azido[9] and 6-*O*-glucuronide[19,20] in morphine, amino in oxymorphamine,[21] amino acid residues in 14-*O*-methyloxymorphone,[10] hydrazones, oximes, and semicarbazones in oxycodone,[7,9] and a 6-cyano group in 4,5-oxygen bridge-opened *N*-methylmorphinans of the present study induce strong analgesic actions.

Conclusions

The present study on acrylonitrile incorporated 4,5-oxygen bridge-opened *N*-methylmorphinans shows that a 6-cyano substituent leads to compounds with high affinity to the μ opioid receptor and decreased interaction with δ and κ receptors, thus being μ selective. In vivo, the 6-cyanomorphinans acted as potent antinociceptive agents which were either more active or equipotent to their 6-keto analogues.

The presence of a methoxy substituent instead of a hydroxy group in position 4 increases analgesic potency in both classes of compounds. Replacement of the hydroxyl group in position 14 with a methoxy group enhanced both in vitro opioid activity and in vivo potency. It appears that substitution in positions 4 and 14 causes significant changes in interaction with opioid receptors in both the 6-cyano and the 6-ketomorphinan series of 4,5-oxygen bridge-opened compounds, with 4-O-methylation resulting in higher μ selectivity and antinociceptive potency compared to 14-O-methylation.

The chemically highly versatile acrylonitrile substructure allows for easy conversion into various and more polar derivatives and thus bears the potential to open up a new field in morphinan chemistry and opioid pharmacology.

Experimental Section

The required reagents as well as anhydrous *N*,*N*-dimethylformamide were purchased from Fluka, Switzerland, in the highest purities available. The solvents were distilled before usage. Melting points were determined on a Kofler melting point microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer. Chemical shifts (δ) are reported in ppm (relative to $SiMe_4$ as internal standard), coupling constants (*J*) in Hz. Mass spectra were recorded on a Finnigan Mat SSQ 7000 apparatus. Elemental Analyses were performed at the Institute of Physical Chemistry at the University of Vienna, Austria. For TLC, POLYGRAM SIL G/UV_{254} precoated plastic sheets (Macherey-Nagel, Germany) were used (eluent: CH_2Cl_2/MeOH/concentrated NH_4OH solution, 90:9:1), and for column chromatography, silica gel 60 (230−400 mesh ASTM, Fluka, Switzerland) was used.

5,6-Didehydro-14β-hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile (3). A mixture of **2** (2.00 g, 6.13 mmol), potassium carbonate (3.74 g, 27.06 mmol), phenyltrimethylammonium chloride (3.34 g, 19.46 mmol), and *N*,*N*-dimethylformamide (30 mL) was stirred at 80 °C (bath temperature) under N_2 for 5 h. After addition of H_2O (80 mL),

the mixture was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over Na_2SO_4, and evaporated. The residue (3.21 g brown oil) was purified by column chromatography (silica gel, elution with CH_2Cl_2/MeOH/concentrated ammonia 250:2:0.5) to afford a yellow oil which was crystallized from MeOH to yield 1.77 g (85%) of **3** as yellowish crystals. Mp 132−134 °C; ^{1}H NMR (DMSO-d_6) δ 6.98 (t, J = 2 Hz, 1 olef. H), 6.90 and 6.85 (2 d, J = 8.4, 8.4 Hz, 2 arom. H), 4.48 (s, OH), 3.76 and 3.68 (2 s, 2 OCH_3), 2.30 (s, NCH_3); CI-MS *m/z* (M^++1) 341. Anal. ($C_{20}H_{24}N_2O_3$·0.2 H_2O) C, H, N.

Opioid Receptor Binding Assays. Rat brain membrane preparations and binding assays were performed as previously described.[16]

In Vivo Assays. General Methods. ICR male mice (Harlan-Sprague−Dawley, Inc., Indianapolis, IN) weighing 20−30 g were used, and each animal was tested only once. All drugs were given by the sc route. At least three doses were tested, and 6−10 animals/dose were used. All animals received care according to the *Guide for the Care and Use of Laboratory Animals*, U.S. Department of Health and Human Services, 1985. These studies were approved by the Institutional Animal Care and Use Committee at Virginia Commonwealth University.

Hot-Plate Test (HP). A modified method previously described was used.[22]

Tail-Flick Test (TF). The procedures[23,24] and their modifications were previously described.[18]

***p*-Phenylquinone Writhing Test (PPQ).** The original procedures and their modifications have been previously described.[24,25]

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Supporting Information Available: Elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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