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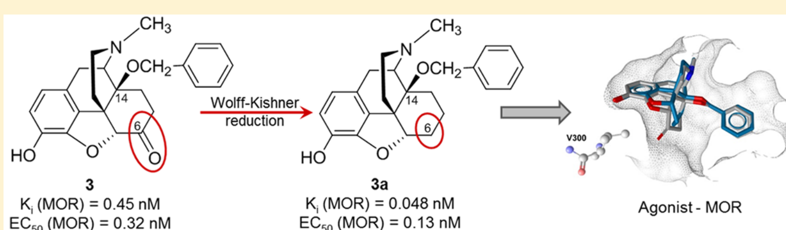
Synthesis, Pharmacology, and Molecular Docking Studies on 6-Desoxo-*N*-methylmorphinans as Potent *μ*-Opioid Receptor Agonists

Maria Dumitrascuta,† Tanila Ben Haddou,† Elena Guerrieri, Stefan M. Noha, Lea Schläfer, Helmut Schmidhammer, and Mariana Spetea*

Department of Pharmaceutical Chemistry, Institute of Pharmacy and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Innrain 80-82, 6020 Innsbruck, Austria

S Supporting Information



ABSTRACT: Position 6 of the morphinan skeleton plays a key role in the *μ*-opioid receptor (MOR) activity in vitro and in vivo. We describe the consequence of the 6-carbonyl group deletion in *N*-methylmorphinan-6-ones **1**−**4** on ligand−MOR interaction, signaling, and antinociception. While 6-desoxo compounds **1a**, **2a**, and **4a** show similar profiles to their 6-keto counterparts, the 6-desoxo-14-benzyloxy substituted **3a** displays significantly increased MOR binding and agonist potency and a distinct binding mode compared with its analogue **3**.

It is more than 90 years ago since the structure of morphine, the naturally occurring alkaloid in the opium poppy *Papaver somniferum*, was clarified.[1] Morphine has a long history of clinical use as an effective analgesic for the treatment of moderate to severe pain. It induces analgesia primarily via activation of the *μ*-opioid receptor (MOR).[2] The morphine skeleton and its conversion to analogues have been continuously explored over the years. The driving force behind the synthetical efforts has been the search for an alternative to morphine that would produce powerful analgesia without its adverse effects (e.g., respiratory depression, sedation, constipation, analgesic tolerance, and addiction).[2,3] Subsequently, the morphinan scaffold has been the basis of new drug developments, and ligands with distinct pharmacological properties are available for patient use or employed as research probes to explore opioid pharmacology in vitro and in vivo.[2,4]

Our laboratory has a long-standing focus in the field of opioid morphinan analgesics. The initial synthetical and pharmacological work led to the generation of *N*-methylmorphinan-6-ones with different substitution patterns at position 14.[2b,4d,5] We established that the introduction of a 14-methoxy group into the clinically used analgesic oxymorphone (**1**),[2a,b] (Figure 1) to yield **2** (14-*O*-methyloxymorphone)[6a] (Figure 1) not only increased MOR affinity by ~9-fold but also produced a significant increase (40-fold) in the antinociceptive potency.[6a,b] However, **2** induces the typical opioid-like side effects (respiratory depression, physical dependence, constipation, and motor dysfunction).[6] Replacement of the 14-methoxy group in **2** with a benzyloxy substituent resulted in **3** (14-*O*-

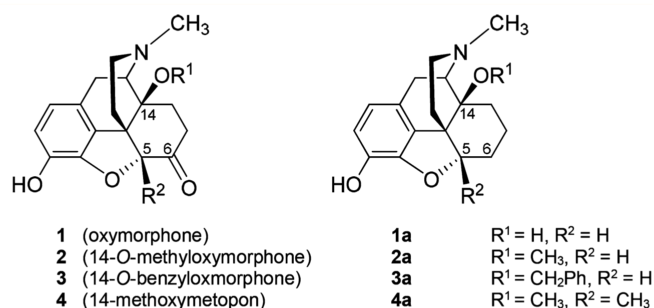


Figure 1. Structures of *N*-methylmorphinan-6-ones **1**−**4** and their 6-desoxo counterparts **1a**−**4a**. Ph, phenyl.

benzyloxymorphone)[6b] (Figure 1), which displayed a 5-fold increased antinociceptive potency when compared to **2**.[6b] Moreover, this highly potent MOR agonist showed negligible inhibition of gastrointestinal motility, while it was much less constipating than morphine (2.5-fold) and **2** (7-fold).[6b] Chemical derivatization in the class of *N*-methylmorphinan-6-ones using **2** as the lead compound also targeted position 5, by introducing a 5-methyl group and giving rise to **4** (14-methoxymetopon)[7] (Figure 1). Compound **4** is a highly efficacious analgesic in various pain models in animals.[5,7] It was generally described to have an improved side effect profile by

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causing less respiratory depression, bradycardia, constipation, physical dependence, addiction potential, and development of analgesic tolerance in comparison to conventional MOR analgesics.[5,7] Our recent molecular docking and molecular dynamics simulations study[8] using the active structure of the MOR (PDB code 5C1M)[9] in combination with structure–activity relationships (SAR) on *N*-methylmorphinan-6-ones revealed the subtle interplay between substituents at positions 5 and 14 in the morphinan scaffold in the ligand–MOR interaction by enabling identification of key structural elements that determine their distinct pharmacological profiles.[8]

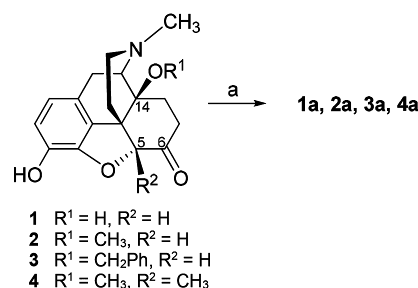
Synthetic approaches have uncovered that functionalizing position 6 in *N*-methylmorphinan-6-ones results in a large diversity of activities.[10−14] The 6-carbonyl group can be easily chemically converted into various functionalities, leading to hydrazones, oximes, carbazones, and semicarbazones,[11] which display antinociceptive efficacies and a favorable side effect profile regarding respiratory depression and gastrointestinal motility.[11] We and others have reported on the incorporation of amino acid residues at position 6 of *N*-methylmorphinan-6-ones.[12] The 6-amino acid zwitterionic conjugates of **2** were established as MOR agonists inducing potent and long-lasting peripherally mediated antinociceptive effects after systemic administration.[4,5a,13] The 6*β*-glycine substituted derivative of **2** was equipotent to fentanyl in the tail-flick assay in rats, acting via activation of peripherally located opioid receptors.[13b] We have also described derivatives of **2** with 6-amino and 6-guanidino substitution that showed high MOR affinity, selectivity, and efficacy and were highly active as antinociceptive agents.[10] By targeting the chemically highly versatile 6-keto function of *N*-methylmorphinan-6-ones, we have reported on a chemically innovative modification giving rise to a novel class of morphinans with acrylonitrile incorporated substructures.[14] The 6-cyano-*N*-methylmorphinans exhibit high affinity and selectivity for the MOR and potent in vitro and in vivo agonism.[14]

The present study was undertaken to evaluate the consequence of the deletion of the 6-carbonyl group of 14-hydroxy and 14-alkoxy substituted *N*-methylmorphinan-6-ones (**1**−**4**, Figure 1) resulting in the respective 6-desoxo-*N*-methylmorphinans **1a**−**4a** (Figure 1) on binding and activation of the MOR and antinociceptive properties. Toward this aim, **1a**−**4a** were prepared using Wolff–Kishner conditions similar to the earlier reported synthesis of 6-desoxonaltrexone[15a] and 6-desoxocyprodime[15b] from their corresponding 6-keto analogues naltrexone and cyprodime, respectively. Additionally, molecular modeling and SAR explorations aided by docking of investigated compounds to the active conformation of the MOR were performed to gain insights into their binding mode and interaction mechanisms.

■ RESULTS AND DISCUSSION

Chemistry. The 6-desoxomorphinans **1a**−**4a** reported herein were prepared from **1**, **2**,[6a] **3**,[6b] and **4**,[7] respectively, by Wolff–Kishner reduction as depicted in Scheme 1.

Scheme 1. Synthesis of Compounds 1a−4a[a]



[a]Reagents and conditions: (a) hydrazine hydrate, triethylene glycol, 180 °C, 1.5 h; then KOH pellets, 180 °C, 2 h.

Pharmacology. Binding affinities at the human MOR, *δ*-opioid (DOR) and *κ*-opioid (KOR) receptors of *N*-methylmorphinan-6-ones **1**−**4** and their 6-desoxo counterparts **1a**−**4a** (Figure 1) were first determined in competition binding assays using membranes from Chinese hamster ovary (CHO) cells stably transfected with one of the recombinant human opioid receptors (CHO-hMOR, CHO-hDOR, and CHO-hKOR cells) according to the described procedures.[16] Binding affinities expressed as inhibition constant (K_i) values are shown in Table 1. All compounds displayed high potency to inhibit [^{3}H][D-Ala^2,Me-Phe^4,Gly-ol^5]enkephalin ([^{3}H]DAMGO) binding to the human MOR in a concentration-dependent manner (Figure S1) with K_i values in the subnanomolar range (Table 1). The high binding affinities to the human MOR expressed in CHO cells showed by **1**−**4** corroborates our earlier findings at the rat MOR in brain tissue.[6b] Evaluation of *N*-methylmorphinan-6-ones and their 6-desoxo analogues revealed that the removal of the 6-keto function does not significantly affect binding affinity at the MOR when comparing **1** vs **1a**, **2** vs **2a**, and **4** vs **4a**. In the case of **3** vs **3a** only, a significant increase up to 9-fold in the MOR affinity was noticed. Generally, the 6-desoxo derivatives showed a similar binding affinity to the DOR as their 6-ketomorphinan counterparts, the exception being the pair **1a** and **1**, where a ∼3-fold decrease in affinity to the DOR was observed for **1a** (Table 1). We also found that KOR affinities of **1a**−**4a** were in the range of their parent compounds **1**−**4**. The removal of the 6-keto group in **1** increased selectivity for MOR vs DOR of **1a**, but it did not affect selectivity vs KOR. In the case of the 14-methoxy substituted **2** and **2a**, a slight decrease in MOR vs KOR selectivity ratios was found, while selectivity for MOR vs DOR was not changed. The same observation on somewhat reduced MOR selectivity vs KOR was made when comparing 5-methyl substituted **4** and its 6-deoxo analogue **4a**, while a decrease was also noticed vs DOR (Table 1). Interesting was the observation of the increase in MOR selectivity upon deletion of the 6-keto function in the 14-benzyloxy substituted **3** leading to **3a**. We found that the nonselective **3** was converted into a MOR selective compound, **3a**, which displayed about 9- and 6-fold higher MOR/DOR and MOR/KOR selectivity ratios, respectively, than **3** (Table 1).

Functional opioid activity of *N*-methylmorphinan-6-ones **1**−**4** and their 6-desoxo counterparts **1a**−**4a** at the human MOR receptor was next evaluated, where ligand-induced stimulation of guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate ([^{35}S]GTPγS) binding to membranes from CHO cells expressing the human MOR receptor was measured (Table 1) as described earlier.[14c] Efficacies are presented as percentage stimulation (% stim) relative to the prototypical MOR full agonist DAMGO (EC_{50} = 27.8 ± 3.7 nM and % stim = 221 ± 13%). While we have reported previously on the potent MOR agonism of **2**−**4** in bioassays using isolated organs (mouse vas deferens, guinea pig ileum)[6b,7] and ligand-stimulated [^{35}S]GTPγS binding in rat brain membranes,[6c] herein the first data on G protein activation upon ligand binding to the human MOR are presented. On the basis of in vitro functional activities, all test compounds

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Table 1. Opioid Receptor Binding, Functional Activities, Antinociceptive Potencies, and Physicochemical Properties of N-Methylmorphinan-6-ones 1–4 and Their 6-Desoxo Counterparts 1a–4a

	opioid receptor binding, K_i (nM)[a,c]					functional activity[b,c] $[^{35}S]GTP\gamma S$ MOR		antinociceptive activity[d] hot-plate assay	
	affinity			selectivity					
compd	MOR	DOR	KOR	DOR/MOR	KOR/MOR	EC_{50} (nM)	% stim	ED_{50} (μg/kg, sc) (95% CI)	clogP[e]
1	1.79 ± 0.34	70.0 ± 4.1	25.3 ± 8.4	39	14	7.80 ± 1.61	91.5 ± 5.0	382 (186–785)	0.88
1a	1.65 ± 0.5	201 ± 80	21.6 ± 3.9	122	13	8.99 ± 2.19	104 ± 7	383 (209–802)	1.24
2	0.32 ± 0.08	8.80 ± 0.35	10.1 ± 3.1	28	32	1.45 ± 0.32	96.4 ± 5.0	14.2 (7.75–26.1)	1.45
2a	0.24 ± 0.08	8.64 ± 2.25	3.99 ± 0.63	36	17	1.37 ± 0.26	105 ± 6	17.3 (8.68–34.4)	1.82
3	0.45 ± 0.10	1.05 ± 0.42	1.27 ± 0.24	2.3	2.8	0.32 ± 0.16	101 ± 5	2.38 (1.29–4.38)	3.23
3a	0.048 ± 0.011	0.89 ± 0.29	0.85 ± 0.05	21	18	0.13 ± 0.03	103 ± 8	2.41 (1.39–4.17)	3.60
4	0.25 ± 0.04	19.8 ± 1.3	15.1 ± 0.9	79	60	3.28 ± 0.81	99.2 ± 2.8	27.1 (12.7–58.1)	1.66
4a	0.34 ± 0.08	12.9 ± 1.6	7.92 ± 4.47	38	23	2.95 ± 0.54	104 ± 3	25.1 (13.0–48.5)	1.90

[a]Determined in competition binding assays using membranes from CHO cells expressing human opioid receptors. [b]Determined in the $[^{35}S]GTP\gamma S$ binding assay using CHO-hMOR cell membranes. Percentage stimulation (% stim) relative to the MOR full agonist DAMGO. [c]Values are the mean ± SEM of at least three independent experiments. [d]Determined in the hot-plate assay in mice at peak effect (30 min) after sc drug administration (n = 5–6 mice per group). [e]Calculated logP (clogP) using MarvinSketch 17.10 (ChemAxon, www.chemaxon.com).

produced a concentration-dependent increase in $[^{35}S]GTP\gamma S$ binding (Figure S2) and showed high efficacy at the human MOR acting as full agonists (≥85% of the response to DAMGO), with the most potent agonists being **3** and **3a** (Table 1). Our present data indicate that the removal of the 6-keto function did not largely influence the MOR agonism of **1** vs **1a**, **2** vs **2a**, and **4** vs **4a**. However, an increase of ~2.5-fold in the EC_{50} of **3a** compared to **3** was observed (Table 1).

We have earlier reported on the replacement of the 6-keto group in *N*-methylmorphinans-6-ones with other functionalities (i.e., amino acids, cyano, amino, and guanidino) at C-6, which produced subtle alterations in the in vitro biological activities, i.e., MOR affinity and agonist potency. On the basis of previous and present findings, a 6-keto group is not a requirement for high affinity to the MOR of *N*-methylmorphinans displaying agonist activity. Earlier observations in the class of morphinans with opioid antagonism, including naltrexone and *N*-cyclopropylmethyl-4,14-dimethoxymorphinan (cyprodime), revealed that deletion of the 6-keto group maintains the MOR antagonism while MOR selectivity is unchanged or decreased.[15] The 6-desoxo-*N*-methylmorphinans **1a–4a** were further assessed for antinociceptive properties after sc adminstration in a mouse model of acute thermal nociception, the hot-plate assay.[6b,c] Antinociceptive potencies expressed as ED_{50} values (and 95% confidence intervals) were calculated at the peak of action and compared to those of the 6-ketomorphinans **1–4** (Table 1). All test compounds significantly increased latencies to heat stimulation in a time- and dose-dependent manner (Figures S3 and S4), with the peak of antinociception generally occurring at 30 min after sc administration to mice. Compared to morphine (ED_{50} = 2428 μg/kg, 95% CI of 1382–4268 in the hot-plate assay),[14c] all compounds were considerably more efficacious in inducing an antinociceptive response in mice, being up to 1020-fold more potent than morphine. Within the series, the 14-benzyloxy substituted **3** and **3a** were the most active as antinociceptive agent, a finding that correlates well with their in vitro opioid activity profile (Table 1). Overall, as shown in Table 1 and Figure S5, the 6-desoxo compounds **1a–4a** exhibit very similar antinociceptive potencies to their analogue **1–4** indicating that the absence of a 6-carbonyl group does not significantly affect the in vivo agonism (two-way ANOVA, $P > 0.05$ when comparing **1–4** to **1a–4a** counterparts). In both series of *N*-methylmorphinan-6-ones **1–4** and 6-desoxo-*N*-methylmorphinans **1a–4a**, it was apparent that compounds carrying a 14-methoxy (**2**, **4**, **2a**, and **4a**) and a 14-benzyloxy (**3** and **3a**) group have enhanced affinity and in vitro and in vivo agonist potency to the MOR than the 14-hydroxy substituted **1** and **1a** (Table 1).

Assessment of physicochemical properties has gained considerable importance over the past years, emerging as a significant aspect in drug development, especially for understanding of the behavior of bioactive molecules and correlation with pharmacological activities.[17] The calculated log *P* (clogP) values of *N*-methylmorphinans **1–4** and **1a–4a** are indicative of good capability to enter the CNS (Table 1).

Molecular Modeling. The X-ray crystal structure of the active MOR conformation (PDB code 5C1M)[9] provides nowadays novel prospects in the drug discovery process.[18] In order to further understand the effect of a 6-carbonyl group deletion in *N*-methylmorphinan-6-ones, we performed molecular docking using the active conformation of the MOR. Docking studies were carried out to unravel potential differences in receptor interactions of **1–4** and their 6-desoxo counterparts **1a–4a** using GOLD[19] as outlined in the Supporting Information. Differences and similarities in the experimentally determined binding affinities to the MOR (Table 1) are likely to emerge from the type and number of receptor contacts formed by these morphinans in those particularly similar docked orientations. Accounting for pharmacophore models inferred within LigandScout,[20] receptor side chains in putative contact with the bound ligands are depicted in Figure 2 and listed in Table 2. In line with our recent findings from molecular docking,[8] the aromatic ring of targeted morphinans was deduced to be embedded by hydrophobic residues (e.g., M151, V236, I296, and V300), which are responsible for hydrophobic interactions (Table 2 and Figures 2). The participation of the phenolic hydroxyl group at position 3 in a water-mediated hydrogen-bonding network with H297 was shown by all ligands. This is recognized as a conserved interaction between morphinan ligands and the binding pocket.[8,9] In addition, the basic nitrogen forms a charge-enhanced hydrogen bond to the key residue D147. This observation is supported by earlier experimental data derived from site-directed mutagenesis studies demonstrating the crucial role of D147 for binding of small molecule agonists to the MOR.[21] When comparing the

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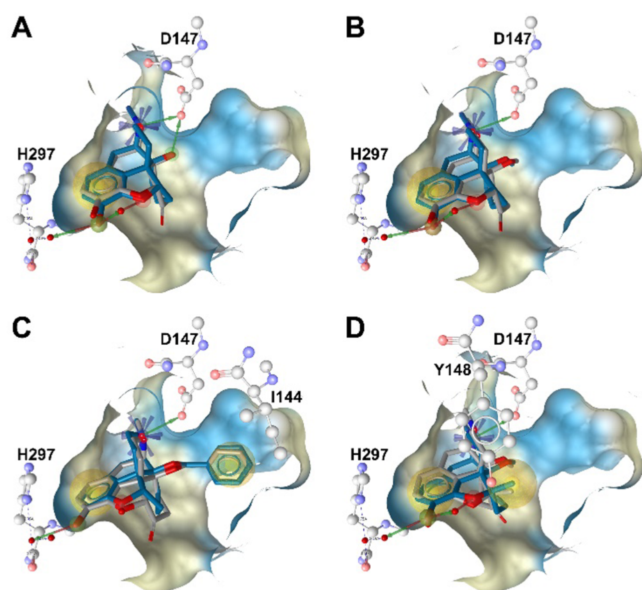

Figure 2. Docking of *N*-methylmorphinans-6-ones **1**-**4** (gray) and corresponding 6-desoxo counterparts **1a**−**4a** (blue) to the active structure of the MOR: (A) overlay of **1** and **1a**; (B) overlay of **2** and **2a**; (C) overlay of **3** and **3a**; (D) overlay of **4** and **4a**. The key residues D147 and H297, involved in a hydrogen-bonding network, and residues I144 and Y148, involved in hydrophobic interactions, are depicted. Chemical features are color-coded: red/green arrow, hydrogen bond acceptor/donor; yellow sphere, hydrophobic interaction; blue asterisk, positively ionizable. Binding pocket surface is shown, colored according to aggregated hydrophilicity/hydrophobicity (blue/ochre).

Table 2. Ligand−MOR Interaction Pharmacophores Inferred from Molecular Docking Solutions of *N*-Methylmorphinan-6-ones 1−4 and Their 6-Desoxo Counterparts 1a−4a

	hydrophobic interactions		hydrogen bonds	
compd	inferred from phenol	inferred from introduced group	charge-enhanced hydrogen bond	interactions mediated by water molecules
1	M151, V236, I296, V300	ND[a]	D147	H297
1a	M151, V236, I296, V300	ND[a]	D147	H297
2	M151, V236, I296, V300	ND[a]	D147	H297
2a	M151, V236, I296, V300	ND[a]	D147	H297
3	M151, V236, I296, V300	I144[b]	D147	H297
3a	M151, V236, I296, V300	I144[b]	D147	H297
4	M151, V236, I296, V300	ND[a]	D147	H297
4a	M151, V236, I296, V300	Y148[c]	D147	H297

[a]ND, not deduced. [b]Formed by the 14-benzyloxy group. [c]Formed by the 5-methyl group.

retrieved docking poses of the 6-desoxo compounds **1a**−**4a** to their corresponding 6-keto analogues **1**−**4**, the observed differences were more or less subtle regarding critical noncovalent interactions, which are required for the recognition of these potent agonists by the MOR (Figure 2). We observed that **1** and **2** and their 6-desoxo analogues **1a** and **2a**, respectively, exhibit a similar binding mode regarding the orientation of these agonists relative to the receptor (Figure 2A and Figure 2B). Differences were noted when evaluating the binding mode of **3** along with its 6-desoxo counterpart **3a**, as well as to the other morphinans (Figure 2C). Docking analysis showed that **3** and **3a** adopt an orientation relative to the receptor distinct from the other analogues, represented by an additional hydrophobic interaction between I144 and the 14-*O*-benzyl group of **3** and **3a** (Figure 2C and Table 2). As a consequence, this modified relative orientation in the binding pocket may be responsible for a steric clash, surmised between the 6-keto group of **3** and residue V300, which is essentially orientated in close proximity to the phenol of targeted morphinans (vide supra). However, in the case of **3** the side chain of V300 is getting rather close to the 6-keto substituted cyclohexane ring. This interaction was not observed for the 6-desoxo-14-benzyloxy substituted **3a**, as the docking pose indicated that the corresponding methylene bridge at position 6 is nicely accommodated in the binding pocket (Figure 3).

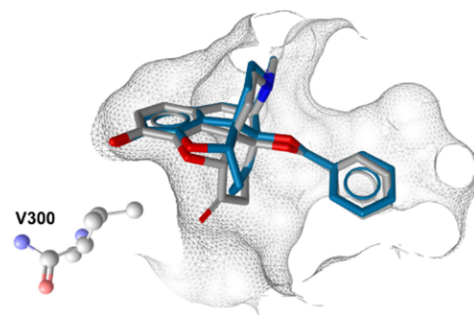

Figure 3. Overlay of molecular docking solutions for **3** (gray) and **3a** (blue) at the active structure of the MOR, illustrating the steric clash inferred to represent the interaction of the 6-keto group of **3** with V300, orientated in close proximity, and the absence of this interaction for **3a**. Residue V300 is presented, along with the binding pocket surface shown in wireframe representation.

These features may contribute to the improved binding affinities to the MOR of **3a** compared to **3** (K_i = 0.048 nM for **3a** vs 0.45 nM for **3**) experimentally determined in radioligand binding assays. The projected orientation in the binding pocket was only slightly different when comparing 5-methyl-14-methoxy-*N*-methylmorphinans **4** and **4a**. Interestingly, the 6-desoxo analogue **4a** was predicted to form an additional hydrophobic interaction by the 5-methyl group targeting the nearby Y148 as counterpart (Figure 2D and Table 2). Overall, the docking analysis pointed toward a subtle interplay of the substituents introduced to this series in positions 14 and 5, and in silico results are in accordance with pharmacological data.

■ CONCLUSIONS

The present study, combining synthetical, pharmacological, and molecular modeling approaches, established that the deletion of the 6-carbonyl group in targeted *N*- methylmorphinan-6-ones **1**, **2**, and **4** did not fundamentally affect binding, post-receptor-signaling, and antinociceptive activities, with the resulting 6-desoxo analogues evolving as potent MOR agonists. Notable was the observation that the 6-desoxo-14-benzyloxy **3a** displays significantly increased MOR binding and agonist potency than its 6-keto counterpart **3**. At the in silico level, the absence of the 6-carbonyl function in **3a** depleted the steric clash shown by the 6-keto group of **3** with residue V300, thus explaining the

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improved binding affinities to the MOR of **3a** compared to **3**. These results expand the understanding on the impact of the 6-carbonyl to 6-CH_2 conversion in *N*-methylmorphinans on ligand−MOR interaction and molecular mode of action and may aid in identifying new leads for development of opioid analgesics devoid of adverse effects for treatment of pain.

■ EXPERIMENTAL SECTION

Chemistry. General Methods. All chemicals were of reagent grade and obtained from standard commercial sources. Melting points were determined on a Kofler melting point microscope and are uncorrected. ^{1}H NMR (200 MHz) spectra were recorded on a Varian Gemini 200 spectrometer using tetramethylsilane (TMS) as internal standard for $CDCl_3$. IR spectra were taken on a Bruker Alpha FT-IR spectrometer (for detection, an ATR sensor was used). Mass spectra were recorded on a Varian MAT 44 S apparatus. Elemental analyses were performed at the Microanalytic Laboratory of the University of Vienna, Austria. For column chromatography (MPLC), silica gel 60 (0.040−0.063 mm, Fluka, Switzerland) was used. Compounds **1a**−**4a** were used as bases for testing. The elemental analysis values were found to be within ±0.4% of the calculated values, indicating a purity of the tested compounds of >95%.

General Procedure for the Synthesis of 6-Desoxomorphinans 1a−4a. A mixture of **1**, **2**, **3**, or **4** (0.60 mmol), hydrazine hydrate (27 mmol), and triethylene glycol (3 mL) was stirred at 130 °C for 1.5 h. After cooling, KOH pellets (6 mmol) were added and the mixture was stirred at 180 °C for 2 h. After cooling, the mixture was acidified with 2 N HCl, washed with Et_2O (2 × 10 mL), rendered alkaline with NH_4OH_{conc}, and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with H_2O (3 × 10 mL), dried over Na_2SO_4, and evaporated to provide a solid which was purified by column chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 98:1:1) to yield the final compounds.

3,14-Dihydroxy-4,5*α*-epoxy-17-methylmorphinan (1a). Yield 11% as beige solid. Mp: 90−92 °C. IR (ATR) 3119 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$): δ 6.71 (d, *J* = 8.0 Hz, *H*-C(1)), 6.58 (d, *J* = 8.0 Hz, *H*-C(2)), 4.72 (t, *J* = 8 Hz, *H*-C(5)), 2.37 (s, CH_3N). MS (ESI) *m*/*z* 288.1 [M + 1]$^+$. Anal. ($C_{17}H_{21}NO_3$·0.2MeOH) C, H, N.

4,5*α*-Epoxy-3-hydroxy-14*β*-methoxy-17-methylmorphinan (2a). Yield 22% as beige solid. Mp 82−86 °C. IR (ATR) 2935 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$): δ 6.70 (d, *J* = 8.0 Hz, *H*-C(1)), 6.57 (d, *J* = 8.0 Hz, *H*-C(2)), 4.73 (t, *J* = 7.8 Hz, *H*-C(5)), 3.22 (s, CH_3O), 2.37 (s, CH_3N). MS (ESI) *m*/*z* 302.01 [M + 1]$^+$. Anal. ($C_{18}H_{23}NO_3$·0.6CH_2Cl_2) C, H, N.

14*β*-Benzyloxy-4,5*α*-epoxy-3-hydroxy-17-methylmorphinan (3a). Yield 10% as white solid. Mp 79−83 °C. IR (ATR) 2923 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$): δ 7.44−7.25 (m, 5 arom H), 6.70 (d, *J* = 7.4 Hz, *H*-C(1)), 6.58 (d, *J* = 8.0 Hz, *H*-C(2)), 4.76 (t, *J* = 7.6 Hz, *H*-C(5)), 4.63 (d, *J* = 11 Hz, CH_2-phenyl), 4.30 (d, *J* = 11 Hz, CH_2-phenyl), 2.36 (s, CH_3N). MS (ESI) *m*/*z* 378.2 [M + 1]$^+$. Anal. ($C_{24}H_{27}NO_3$·0.2CH_2Cl_2) C, H, N.

5*β*,17-Dimethyl-4,5*α*-epoxy-3-hydroxy-14*β*-methoxymorphinan (4a). Yield 16% as white solid. Mp 90−95 °C. IR (ATR) 2933 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$): δ 6.68 (d, *J* = 8.0 Hz, *H*-C(1)), 6.55 (d, *J* = 8.0 Hz, *H*-C(2)), 3.19 (s, CH_3O), 2.37 (s, CH_3N), 1.58 (s, CH_3-C(5)). MS (ESI) *m*/*z* 316.2 [M+1]$^+$. Anal. ($C_{19}H_{25}NO_3$·0.1CH_2Cl_2) C, H, N.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.7b01363.

Additional pharmacological and molecular modeling information (PDF)

Molecular formula strings (CSV)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Mariana.Spetea@uibk.ac.at. Phone: +43-512 507 58277.

ORCID

Mariana Spetea: 0000-0002-2379-5358

Author Contributions

†M.D. and T.B.H. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

CHO, Chinese hamster ovary; DOR, δ-opioid receptor; KOR, κ-opioid receptor; MOR, μ-opioid receptor; PDB, Protein Data Bank

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