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Synthesis of 14-Alkoxymorphinan Derivatives and Their Pharmacological Actions

Helmut Schmidhammer and Mariana Spetea

Abstract Among opioids, morphinans play an important role as therapeutically valuable drugs. They include pain relieving agents such as naturally occurring alkaloids (e.g. morphine, codeine), semisynthetic derivatives (e.g. oxycodone, oxymorphone, buprenorphine), and synthetic analogs (e.g. levorphanol). Currently used opioid analgesics also share a number of severe side effects, limiting their clinical usefulness. The antagonist morphinans, naloxone and naltrexone are used to treat opioid overdose, opioid dependence, and alcoholism. All these opioid drugs produce their biological actions through three receptor types, μ, δ, and κ, belonging to the G-protein-coupled receptor family. Considerable effort has been put forward to understand the appropriate use of opioid analgesics, while medicinal chemistry and opioid pharmacology have been continuously engaged in the search for safer, more efficacious and nonaddicting opioid compounds, with the final goal to reduce complications and to improve patient compliance. Toward this goal, recent advances in chemistry, ligand-based structure activity relationships and pharmacology of 14-alkoxymorphinans are reviewed in this chapter. Current developments of different structural patterns of 14-alkoxymorphinans as research tools and their potential therapeutic opportunities are also summarized.

Keywords 14-Alkoxymorphinans · Opioid agonist · Opioid antagonist · Opioid receptors · Opioids

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Contents

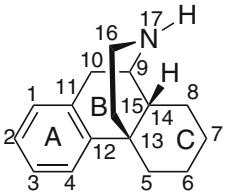
Abbreviations

[^{35}S]GTPγS	Guanosine-5′-O-(3-[^{35}S]thio)-triphosphate
AD_{50}	Analgesic dose necessary to elicit a 50% effect
BBB	Blood–brain barrier
CBE	Colonic bead expulsion test
CHO	Chinese hamster ovary
CNS	Central nervous system
DMF	*N*,*N*-dimethylformamide
ED_{50}	Effective dose necessary to elicit a 50% effect
GPI	Guinea pig ileum bioassay
HP	Hot-plate test
IC_{50}	Concentration necessary to produce a 50% effect
IL-2	Interleukin-2
K_i	Inhibition constant
MeOH	Methanol
MLR	Mixed lymphocyte reaction
MVD	Mouse vas deferens bioassay
NaH	Sodium hydride
NTB	Naltriben
NTI	Naltrindole
PBMC	Peripheral blood mononuclear cells
PPOM	14-Phenylpropoxymetopon
PPQ	Paraphenylquinone writhing test
RVD	Rat vas deferens bioassay
SAR	Structure–activity relationship
s.c.	Subcutaneous
TF	Tail-flick test
TosMIC	Tosylmethylisocyanid

1 Introduction

Although the pain relieving and mood altering effects of extracts of the opium poppy *Papaver Somniferum* have been known for thousands of years, it was only in the twentieth century that there were substantial advances made in understanding the pharmacology of the active constituents of opium, like morphine [1]. Exciting discoveries such as the identification of the endogenous opioid peptides (enkephalins, endorphins, and dynorphins), the existence of specific opioid receptors and cloning of three opioid receptors (μ, δ, and κ) as members of the G-protein coupled receptor (GPCR) family markedly influenced the course of opioid research over the years [2]. Gene cloning and characterization was an important step to evolve the comprehension of opioid receptors, as proteins that operate in the central and peripheral nervous systems (CNS and PNS), and peripheral tissues [3–6] and control nociceptive, hedonic, emotional, autonomic, neuroendocrine, and immune responses [7, 8]. The driving force behind the many years of synthetical efforts in the opioid field has been the search for an alternative to morphine, which would produce powerful analgesia and would be free of undesirable side effects. All the gained knowledge led to viable strategies in exploring the pharmacotherapeutic potential of the opioid system through the discovery of opioid drugs with alternative therapeutic properties. A diversity of opioid ligands was made available through chemical syntheses, which are appraised as valuable research tools or potential therapeutic agents. Such developments resulted in many pharmacologically interesting and clinically useful opioid compounds possessing different degrees of selectivity for each opioid receptor type, agonist or antagonist activity, and central or peripheral site of action [9–19].

Among opioids, morphinans (Fig. 1) play an important role as therapeutically valuable drugs. Representative examples of the morphinan class of compounds (Fig. 2) are μ-opioid analgesic agents for the treatment of moderate-to-severe pain such as naturally occurring alkaloids (e.g. morphine, codeine), semisynthetic derivatives (e.g. oxycodone, oxymorphone, buprenorphine), and synthetic analogs (e.g. levorphanol, butorphanol) [19–21]. Codeine is also an effective antitussive drug. The oxymorphone derivatives naloxone [22] and naltrexone [23] represent



(-)-Morphinan

Morphinans: B/C ring fusion *cis*
Isomorphinans: B/C ring fusion *trans*

Fig. 1 Morphinan

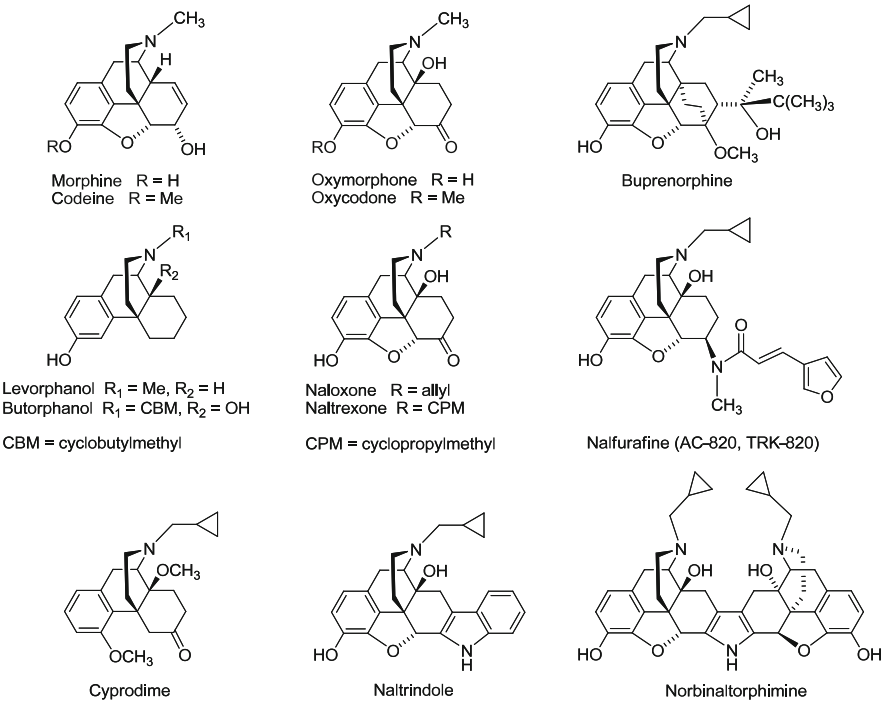


Fig. 2 Examples of opioid morphinans

two opioid antagonists commonly used as rescue medication to reverse severe side effects (respiratory depression, overdose) induced by opioid agonists [18, 19]. They are also used clinically to treat dependence induced by opioid use and alcoholism [18, 19, 24, 25]. The quaternary derivative of naltrexone, methylnaltrexone [26], was recently introduced for clinical use in the therapy of opioid-induced bowel dysfunction [27]. The κ-opioid receptor agonist nalfurafine (AC-820, TRK-820) [28] (Fig. 2) showed efficacy as an antipruritic agent in uremic pruritus patients [29]. Other potential therapeutic indications of opioid morphinans include addiction, depression, feeding behavior, and Parkinson-induced tardive dyskinesia [12, 16, 18, 30–32]. Also, important research tools to investigate opioid receptor multiplicity and function *in vitro* and *in vivo* have come from the development of morphinans, including opioid antagonists cyprodime (μ) [33], naltrindole (δ) [34], and norbinaltorphimine (κ) [35] (Fig. 2).

During the past decade, 14-alkoxymorphinans have emerged as highly interesting and promising substitution patterns to improve potency and selectivity towards single opioid receptor types affording opioid ligands that besides their scientific value as pharmacological tools, may also have the potential of emerging as novel therapeutic agents. This chapter will cover 14-alkoxymorphinan derivatives including recent chemical developments, pharmacology and ligand-based structure–activity relationships (SAR), with a focus on a number of key findings and selected studies.

2 Synthesis

2.1 Synthesis of 14-Alkoxymorphinan-6-ones

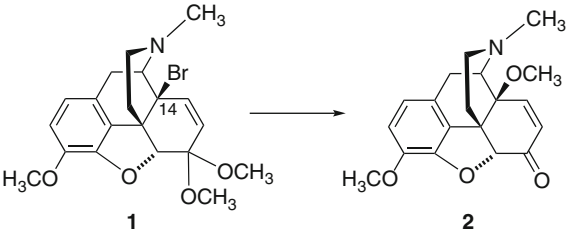
2.1.1 Introduction of a 14-Alkoxy Group

Introduction of a 14-Alkoxy Group into 7,8-Didehydromorphinans

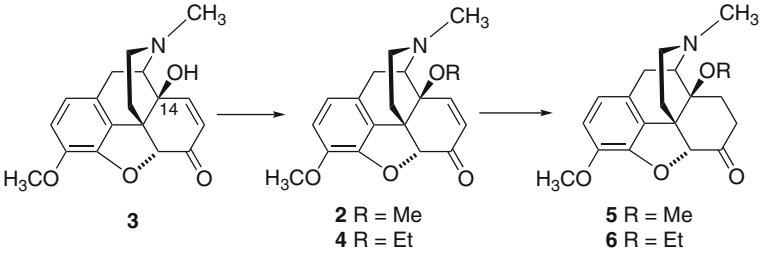
Introduction of a 14-alkoxy group into morphinans was first accomplished by methanolysis of 14-bromocodeinone dimethyl acetale (**1**) to yield 14-methoxycodeinone (**2**) (Scheme 1) [36]. An improved synthesis of 14-methoxycodeinone (**2**) was performed by 14-*O*-methylation of 14-hydroxycodeinone (**3**) using either methyliodide [37] or dimethyl sulfate [38] as the alkylating agent in DMF in the presence of NaH (Scheme 2). 14-Ethoxycodeinone (**4**) was synthesized similarly by alkylation of **2** with diethyl sulfate [38]. Catalytic hydrogenation of **2** and **4** gave the dihydrocodeinones **5** and **6** [38]. Analogously compounds **10** and **11** have been prepared from 7,8-didehydromorphinan **7** via **8** and **9** (using methyliodide or ethyliodide and NaH) (Scheme 3) [39, 40].

Introduction of a 14-Alkoxy Group into Morphinan-6-ones Without 7,8 Double Bond

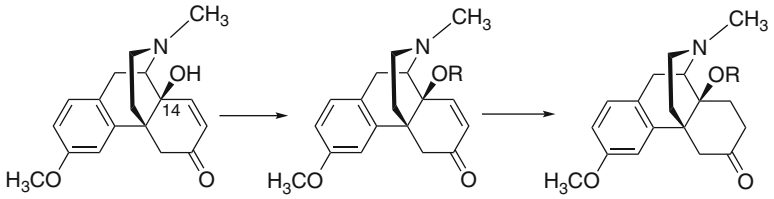
14-*O*-Alkylation can also be achieved using oxymorphone-derived morphinan-6-ones without a 7,8 double bond employing dimethyl or diethyl sulfate under



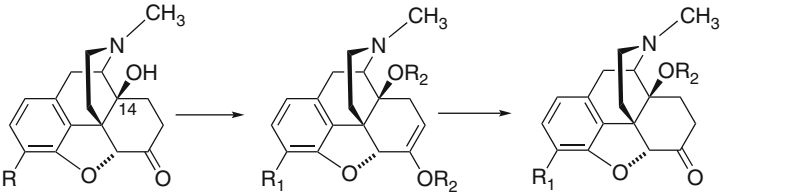
Scheme 1



Scheme 2



Scheme 3

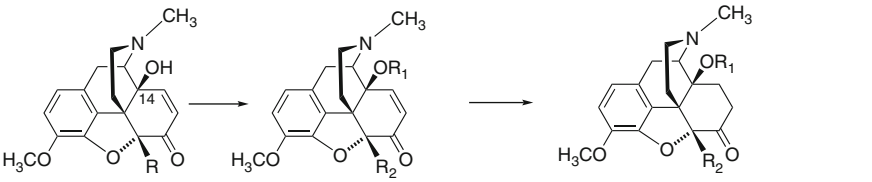


Scheme 4

similar conditions as described above. Thus, 3-deoxygenated oxymorphone (**12**) and the 3-*O*-benzyl-substituted oxymorphone derivative **13** yielded 14-alkoxy-substituted enol ethers **14**–**16**, which were hydrolyzed under mild acidic conditions to give ketones **17**–**19** (Scheme 4) [41, 42].

Introduction of a 14-Alkoxy Group Using Allylic Halides

Because of the low reactivity of the tertiary alcohol, alkylation of the C14-hydroxyl with alkyl halides such as propyl or isoamyl halides was unsuccessful [Schmidhammer H, unpublished observations]. Therefore, allylic halides were employed to introduce 14-*O*-alkenyl substituents using similar conditions as described above [43–46]. Catalytic hydrogenation afforded the corresponding 14-*O*-alkyl derivatives [43–45]. Thus, 14-hydroxy-5-methylcodeinone (**20**) was treated with 3,3-dimethylallyl bromide in DMF in the presence of NaH to give compound **21**, which underwent catalytic hydrogenation to yield 14-*O*-isoamyl-substituted morphinan **24** (Scheme 5) [43]. Similarly 14-phenylpropoxymorphinans **25** and **26** were prepared from 14-hydroxycodeinone (**3**) and **21**, respectively, via intermediates **22** and **23**, which were obtained by alkenylation using cinnamyl bromide (Scheme 5) [44, 45].

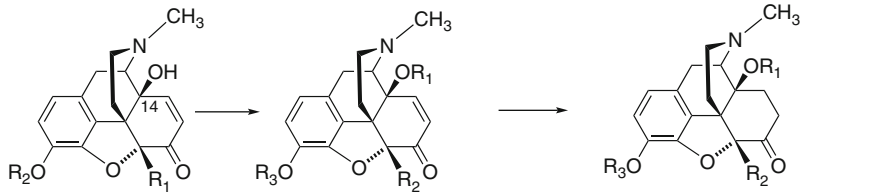


20 R = Me
3 R = H

21 $R_1 = CH_2CH{=}C(CH_3)_2$, R_2 = Me
22 $R_1 = CH_2CH{=}CHPh$, R_2 = H
23 $R_1 = CH_2CH{=}CHPh$, R_2 = Me

24 $R_1 = (CH_2)_2CH(CH_3)_2$, R_2 = Me
25 $R_1 = (CH_2)_3Ph$, R_2 = H
26 $R_1 = (CH_2)_3Ph$, R_2 = Me

Scheme 5



3 R_1 = H, R_2 = Me
27 R_1 = Me, R_2 = H

28 $R_1 = CH_2Ph$, R_2 = H, R_3 = Me
29 $R_1 = R_3 = CH_2Ph$, R_2 = Me

30 $R_1 = CH_2Ph$, R_2 = H, R_3 = Me
31 $R_1 = CH_2Ph$, R_2 = Me, R_3 = H

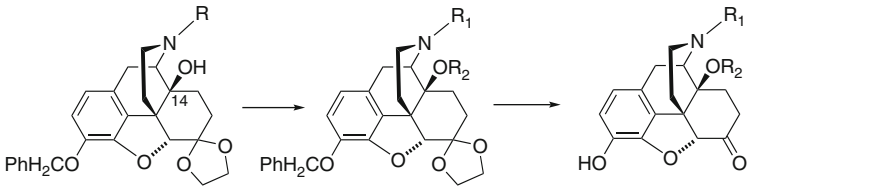
Scheme 6

Introduction of 14-Arylmethoxy Substituents into 7,8-Didehydromorphinans

Introduction of 14-arylmethoxy substituents can be achieved starting from 14-hydroxycodeinones (e.g. **3**) or 14-hydroxymorphinones (e.g. **27**) using arylmethyl bromides (e.g. benzyl bromide) in DMF in the presence of NaH to yield compounds **28** and **29**, respectively (Scheme 6). Catalytic hydrogenation leads to the desired *N*-methylmorphinan-6-ones **30** and **31**, respectively [47].

Introduction of 14-Benzyloxy Substituents into Morphinan-6-ones Without 7,8 Double Bond

14-*O*-Benzylation can also be achieved using oxymorphone and derivatives thereof (e.g. naltrexone). Since 14-*O*-alkylation of morphinan-6-ones without 7,8 double bond does not proceed as smoothly when other alkylating reagents than dimethyl or diethyl sulfate (see above) are used, the 6-keto function was protected by ketalization [47, 48]. For instance, 3-*O*-benzyl-protected ketals **32** and **33** were 14-*O*-alkylated with different benzyl bromides in DMF in the presence of NaH to afford compounds **34** and **35**, respectively. Removal of the protecting groups



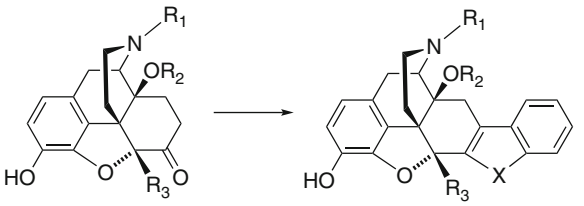
32 R = Me
33 R = CPM

34 R_1 = Me, R_2 = CH_2Ph-2,6-diCl
35 R_1 = CPM, R_2 = CH_2Ph-3-Cl

36 R_1 = Me, R_2 = CH_2Ph-2,6-diCl
37 R_1 = CPM, R_2 = CH_2Ph-3-Cl

CPM = cyclopropylmethyl

Scheme 7



R_1 = Me, allyl, CPM, CBM etc.
R_2 = Me, Et, Pr, benzyl etc.
R_3 = H, Me

Indolomorphinans: X = NH
Benzofuromorphinans: X = O

CPM = cyclopropylmethyl
CBM = cyclobutylmethyl

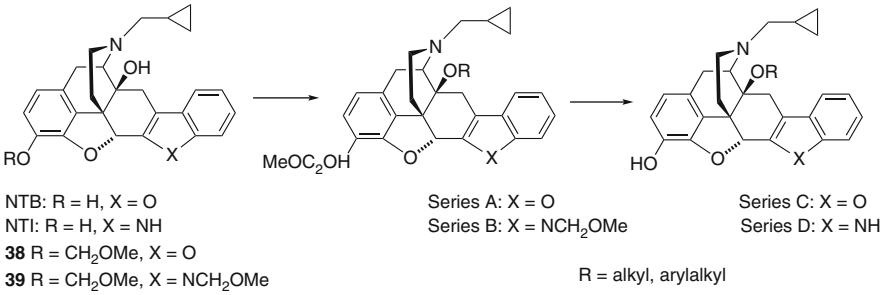
Scheme 8

was accomplished with methanol/HCl to give ketones **36** and **37**, respectively (Scheme 7) [47, 48].

2.2 Synthesis of 14-Alkoxy-Substituted Indolo- and Benzofuromorphinans

2.2.1 Synthesis from 14-Alkoxymorphinan-6-ones

Indolomorphinans can be prepared from their 6-ketomorphinan precursors via Fischer indole synthesis with phenylhydrazine hydrochloride in glacial acetic acid [43, 49, 50], while benzofuromorphinans can be synthesized from the corresponding 6-ketomorphinans using *O*-phenylhydroxylamine hydrochloride and methanesulfonic acid in MeOH (Scheme 8) [43].



Scheme 9

2.2.2 Synthesis Starting from Naltrindole or Naltriben

Naltrindole (NTI) [34, 51] and naltriben (NTB) [52] are prototype δ-opioid receptor antagonists belonging to the indolo- and benzofuromorphinan series of compounds. Starting either from NTI or NTB, a more efficient synthesis of 14-alkoxy-substituted indolo- and benzofuromorphinans in three steps was reported, whereby the 14-*O*-alkyl group is introduced in the penultimate step of the procedure [53]. Thus, protection of the C3-hydroxyl group of NTB and of both the C3-hydroxyl group and indole nitrogen of NTI with methoxymethyl bromide gave methoxymethyl-protected derivatives **38** and **39**, respectively. Subsequent 14-*O*-alkylation with different alkyl bromides in DMF using NaH as the base afforded 14-*O*-alkylated series A and series B, respectively. Acid hydrolysis (MeOH/1 N HCl) yielded the desired benzofuromorphinans (series C) and indolomorphinans (series D) (Scheme 9). Similarly benzofuromorphinans of series C were prepared using the triisopropylsilyl protecting group instead of methoxymethyl [53].

2.3 Introduction of New Functionalities to 14-Alkoxymorphinan-6-ones

Among the most indispensable analgesics, morphinan-6-ones such as oxymorphone, oxycodone, and dihydromorphinone have their main importance in clinical use. As earlier shown, hydrazone, oxime, carbazone, and semicarbazone derivatives of these morphinan-6-ones exhibit high affinity at the μ-opioid receptor [54–56] and exhibit high antinociceptive potency in addition to less pronounced side effects [19, 57–60]. Therefore, it remains a promising synthetic task to convert the carbonyl group into various functionalities.

2.3.1 Incorporation of Acrylonitrile Substructures into Morphinans

An interesting approach to incorporate acrylonitrile substructures into morphinans is the van Leusen homologation reaction in which the standard reagent

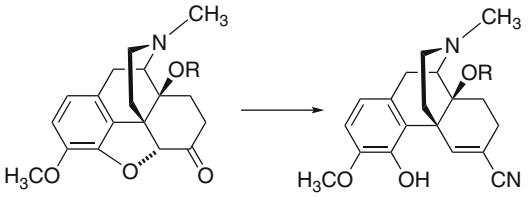
tosylmethylisocyanid (TosMIC) reacts with carbonyl compounds to give the corresponding nitriles with one additional carbon atom [61].

Van Leusen Reaction Applied to Morphinan-6-ones Without 7,8 Double Bond

Applying the van Leusen reaction [61] to oxycodone (**40**) and 14-*O*-methyloxycodone (**41**), the ether bridge between positions 4 and 5 was opened and the respective acrylonitrile derivatives **42** and **43** were formed (Scheme 10) [62].

Van Leusen Reaction Applied to 7,8-Didehydromorphinan-6-ones

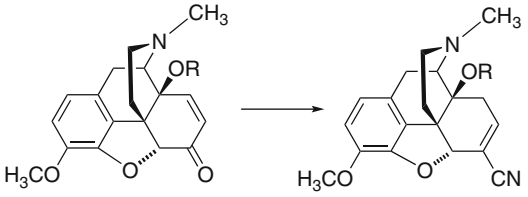
In contrast to the cyanation of oxycodone (**40**) and 14-*O*-methyoxycodone (**41**) with TosMIC (Sect. 2.3.1.1), 7,8-didehydromorphinan-6-ones such as 14-hydroxycodeinone (**3**), 14-methoxycodeinone (**2**), and 14-cinnamyloxycodeinone (**44**) were found to yield 6,7-didehydrocarbonitriles **45**–**47** with retainment of the 4,5-epoxy ring under these conditions (Scheme 11) [63].



40 R = H
41 R = Me

42 R = H
43 R = Me

Scheme 10



3 R = H
2 R = Me
44 R = cinnamyl

45 R = H
46 R = Me
47 R = cinnamyl

Scheme 11

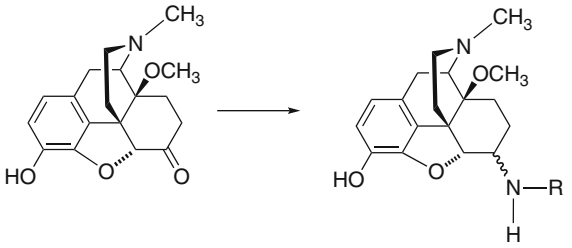
2.3.2 Synthesis of 6-Amino Acid-Substituted 14-Alkoxymorphinans

Morphinans with zwitterionic moieties show greatly reduced access to the CNS without substantially decreased opioid receptor activity [64, 65]. A series of 6-amino acid conjugates (glycine, alanine, and phenylalanine) of the highly potent opioid analgesic 14-*O*-methyloxymorphone (**48**) [41] has been synthesized in an effort to obtain opioid agonists with high potency that would have reduced ability to cross the blood–brain barrier (BBB) [66] (Scheme 12). A novel synthetic approach for the synthesis of 6-amino acid derivatives in the morphinan series was employed. Thus, the *tert*-butyl ester derivatives **49**–**54** were prepared from 14-*O*-methyloxymorphone (**48**) by reductive amination with the respective *tert*-butyl ester hydrochlorides and sodium cyanoborohydride in ethanol. After separating the epimers by column chromatography, esters **49**–**54** were treated with tetrafluoroboric acid to afford compounds **55**–**60** as bis(tetrafluoroborates).

3 Pharmacological Actions

3.1 14-Alkoxymorphinan-6-ones

Introduction of a 14-methoxy group in oxymorphone resulted in 14-*O*-methyloxymorphone (**48**) (Fig. 3) [41] which not only increases affinity to opioid receptors in

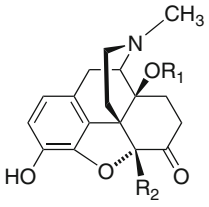


48

49 R = $CH_2COOC(CH_3)_3$, H-6β
50 R = $CH_2COOC(CH_3)_3$, H-6α
51 R = (S)-$CH(CH_3)COOC(CH_3)_3$, H-6β
52 R = (S)-$CH(CH_3)COOC(CH_3)_3$, H-6α
53 R = (S)-$CH(CH_2Ph)COOC(CH_3)_3$, H-6β
54 R = (S)-$CH(CH_2Ph)COOC(CH_3)_3$, H-6α
55 R = CH_2COOH, H-6β
56 R = CH_2COOH, H-6α
57 R = (S)-$CH(CH_3)COOH$, H-6β
58 R = (S)-$CH(CH_3)COOH$, H-6α
59 R = (S)-$CH(CH_2Ph)COOH$, H-6β
60 R = (S)-$CH(CH_2Ph)COOH$, H-6α

Scheme 12

Fig. 3 Oxymorphone derivatives



48 R_1 = Me, R_2 = H
61 R_1 = CH_2Ph, R_2 = H
62 R_1 = Me, R_2 = Me
63 R_1 = CH_2Ph, R_2 = Me
64 R_1 = $(CH_2)_3Ph$, R_2 = Me

Table 1 Opioid receptor binding affinities of oxymorphone derivatives [45, 47]

Compound	K_i μ (nM)	K_i δ (nM)	K_i κ (nM)	Selectivity ratio	
				δ/μ	κ/μ
48	0.10	4.80	10.2	48	102
61	0.12	2.14	1.18[a]	18	10
62	0.15	13.3	25.2	89	168
63	0.18	3.67	2.46[a]	20	14
64	0.20	0.14	0.40[a]	0.7	2
Oxymorphone	0.97	80.5	61.6[a]	83	63
Morphine	6.55	217	113	33	17

[a]Guinea rat or guinea pig brain membranes were used in binding assays
K_i inhibition constant

Table 2 Antinociceptive potencies of oxymorphone derivatives [45, 47]

Compound	HP AD_{50} (nmol/kg)	HP ED_{50} (μg/kg)	TF ED_{50} (μg/kg)	PPQ ED_{50} (μg/kg)
48	53	–	–	–
61	9.6	–	–	–
62	280	30	30	9.0
63	65			
64	–	0.10	0.08	0.16
Morphine	6,690	850	1,920	400

AD_{50} and ED_{50} analgesic and effective dose, respectively, necessary to elicit a 50% effect in mice after *s.c.* administration; *HP* hot-plate test; *TF* tail-flick test; *PPQ* paraphenylquinone writhing test; – not tested

in vitro opioid binding assays, while retaining the μ-receptor selectivity of oxymorphone (Table 1), but also markedly enhances the antinociceptive potency [41, 47, 67]. The presence of the methoxy group at position 14 resulted in a considerable increase in μ-opioid agonist activity in the mouse vas deferens (MVD) bioassay with derivative **48** having over 800-fold increased potency compared to oxymorphone [67]. 14-*O*-Methyloxymorphone (**48**) was characterized by potent agonist properties in the guinea pig ileum (GPI) and rat vas deferens (RVD) bioassays with IC_{50} values of 2 nM and 143 nM, respectively [47, 67]. It was reported to possess about 40-fold higher antinociceptive potency than its parent compound, and was up to 400-fold more potent than the "golden standard" for pain therapy, morphine, in rodent models of acute nociception i.e. hot-plate test in mice (Table 2) [41, 47] and tail-flick test in rats [67, 68] and mice [67], after subcutaneous (s.c.) administration. Compound **48** induces the classical opioid side effects of the conventional μ-opioid

analgesics including respiratory depression [41], physical dependence [41], and constipation [47] after s.c. administration to mice.

Using 14-*O*-methyloxymorphone (**48**) as the lead structure, a series of novel 14-alkoxy-substituted (i.e. allyloxy, benzyloxy, naphthylmethoxy) morphinan-6-one derivatives was prepared and pharmacologically evaluated [47]. The analog having a benzyl group in position 14 (**61**, Fig. 3) preserved the high affinity at the μ-opioid receptor of the parent compound **48** but had significantly increased interaction with the other opioid receptor types, δ and κ (Table 1), thus resulting in a reduction in μ-receptor selectivity. It was a highly potent μ-opioid agonist in the GPI ($IC_{50} = 0.9$ nM) and MVD bioassays ($IC_{50} = 1.5$ nM), showing 2- and 20-fold, respectively, increased agonist potency in comparison to the 14-*O*-methyl analog **48** [47]. Antinociceptive potency in the hot-plate test after s.c. administration in mice was further augmented through the introduction of a 14-benzyloxy group compared to the methoxy group, by about 5-fold increase when compared to the parent compound **48**, and by about 500-fold increase versus morphine (Table 2). Remarkable was the observation that the 14-benzyloxy substitution gave rise to a μ-opioid agonist eliciting negligible constipative activity at the analgesic dose, using the colonic bead expulsion test (CBE) in mice after s.c. administration. Analog **61** was 7-fold less constipating than 14-*O*-methyloxymorphone (**48**) as assessed by the CBE (ED_{50} CBE/AD_{50} hot-plate test = 2.8 and 0.4, respectively [47]).

A second approach to obtaining μ-opioid analgesics in the *N*-methylmorphinan-6-one class exhibiting more favorable pharmacological features was based on the introduction of a methyl group in position 5 of 14-*O*-methyloxymorphone, leading to 14-methoxymetopon (**62**) (Fig. 3). Following its first description in 1990 [69], a number of reports on *in vitro* and *in vivo* activities of 14-methoxymetopon (**62**) were published in the past years [47, 67, 70–78]. The presence of the 5-methyl substituent had no major effect on affinity to the μ-opioid receptor compared to 14-*O*-methyloxymorphone (**48**), while a slight decrease in binding to δ- and κ-receptors was observed, thus, maintaining the μ-receptor selectivity (Table 1). The 5-methyl-substituted derivative **62** showed high agonist activity and comparable potency to the 5-unsubstituted derivative **48** in the GPI, MVD, and RVD bioassays [47, 67]. The high agonist potency of compound **62** was also established using [^{35}S]GTPγS functional assay in rat brain [74], calf striatum [77], and Chinese hamster ovary (CHO) cells expressing mouse μ-receptor splice variants [77]. A tritium-labeled form of 14-methoxymetopon, [^{3}H]14-methoxymetopon, has also been prepared [74] and possesses high affinity and selectivity for native and recombinant μ-opioid receptors [74, 77].

In vivo, introduction of a methyl group in position 5 in 14-*O*-methyloxymorphone (**48**) resulted in somewhat of a decrease in antinociceptive potency, i.e. 5-fold in the hot-plate test (Table 2) and 2-fold in the tail-flick test in mice after s.c. administration for compound **62** [67]. Pharmacological studies consistently reported on the high antinociceptive activity of the μ-opioid agonist **62** ranging between 24- and 20,000-fold in comparison to morphine in diverse models of acute nociception (i.e. hot-plate test [44, 47, 71], tail-flick test [44, 67, 73, 76, 79] and tail electrical stimulation test [72]), and visceral pain (acetic acid- [69, 79], and

paraphenylquinone (PPQ)-induced writhing test [44]) in rodents (mice, rats) after systemic administration. It was equipotent to sufentanil in eliciting analgesia in the skin-twitch test in canines after intravenous administration [70]. Antinociceptive effects of compound **62** after s.c. administration were also reported in inflammatory pain using a rat model of carrageenan-induced hindpaw inflammation [75]. The μ-agonist **62** at a dose of 20 μg/kg showed comparable efficacy to morphine (2 mg/kg) in inhibiting nociceptive behavior in inflamed hindpaws, thus being 100-fold more potent than morphine in experimental inflammatory pain.

Despite its high analgesic potency, 14-methoxymetopon (**62**) was reported to display little respiratory depression, hypotension, bradycardia, or sedation compared to sufentanil in canines [70]. It decreases gastrointestinal transit far less than morphine and reportedly develops lower levels of tolerance [76, 79], physical dependence [79], and a diminished propensity to cause convulsions in mice [79]. Behavioral studies showed that compound **62** is far more effective than morphine in reducing the emotive/affective component of pain and in producing an anxiolytic effect in rats [72]. Therefore, it was depicted as a highly potent μ-opioid analgesic with a pharmacological profile distinct from that of traditional μ-opioid agonists such as morphine.

Physicochemical properties are often an important consideration for understanding the behavior of bioactive molecules and their correlation with pharmacological activities. Experimentally determined liphophilicity of oxymorphone derivatives, 14-*O*-methyloxymorphone (**48**) and 14-methoxymetopon (**62**), have been recently reported [67]. 14-*O*-Methyloxymorphone (**48**) displays comparable lipophilicity to its parent compound oxymorphone (log*P* values of 0.60 and 0.67, respectively), but shows greater μ-opioid receptor affinity (Table 1) and behaves as a more potent agonist *in vitro* and *in vivo* [67]. Introduction of a methyl group in position 5 in 14-*O*-methyloxymorphone (**48**) leads to a more liphophilic molecule **62** (log*P* = 1.12), while showing comparable antinociceptive potency *in vivo* and similar activities i.e. μ-opioid affinity and agonist potency *in vitro*.

Further chemical derivatization having 14-methoxymetopon (**62**) as the lead, resulted in a series of 14-arylalkyloxymetopon derivatives i.e. benzyloxymetopon [47] and phenylpropoxymetopon [45]. Replacement of the 14-methoxy substituent by benzyloxy or phenylpropoxy gave rise to analogs **63** and **64** (Fig. 3) displaying markedly enhanced binding affinities to both δ- and κ-opioid receptors, while the high affinity at the μ-receptor remains unchanged. This resulted in a decrease in selectivity for the μ-receptor of derivative **63** and a complete loss of μ-selectivity for 14-phenylpropoxymetopon (PPOM, **64**) (Table 1). Both analogs were potent antinociceptive agents in mice after s.c. administration (Table 2). The most striking finding was that compound **64** acted as an extremely potent opioid agonist *in vivo*, showing considerable increased antinociceptive potency (60- to 400-fold) compared to 14-methoxymetopon (**62**) in different nociceptive tests (i.e. hot-plate, tail-flick, and PPQ writhing tests) in mice after s.c. administration (Table 2). PPOM (**64**) was 8,500- and 24,000-fold more active in the hot-plate and tail-flick tests, respectively, than morphine. It was reported that the 14-phenylpropoxy-substituted analog **64** is even more potent as an antinociceptive agent than etorphine, a well-known

opioid morphinan used in veterinary medicine [80, 81]. The 3-*O*-methyl ether of PPOM (**26**) showed unexpectedly high antinociceptive potency after s.c. administration in mice although its potency was about 10- to 55-fold lower than that of PPOM (**64**) [45]. On the basis of SAR studies, it was evident that the nature of the substituent at position 14 in *N*-methylmorphinan-6-ones has a major impact on their abilities to interact with opioid receptors leading to profound alteration in the pharmacological profile in this class of opioid compounds. A 14-phenylpropoxy substituent would also increase liphophilicity of 14-methoxymetopon (**62**) which might broaden the therapeutic scope, for example use in transdermal systems.

Established and generally accepted SAR models have assigned critical importance in defining the pharmacological profile of agonist/antagonist of morphinan-6-ones to the substituent at the morphinan nitrogen [82, 83]. Substituents such as cyclopropylmethyl or allyl at the nitrogen have been commonly associated with an antagonist character. Well-known examples are the nonselective opioid receptor antagonists, naloxone and naltrexone (Fig. 2). The introduction of a 14-*O*-methyl or ethyl group into naloxone and naltrexone, respectively, did not significantly alter the *in vitro* and *in vivo* potencies of these two antagonists [12, 38]. A 14-phenylpropoxy substitution in naloxone and naltrexone afforded derivatives **65** and **66**, respectively (Fig. 4) [44] having high affinity at all three opioid receptor types, with low K_i values in the subnanomolar range (Table 3). Surprisingly, they acted as opioid agonists *in vivo*, inducing potent antinociceptive effects in different nociceptive tests (i.e. hot-plate, tail-flick and PPQ-writhing tests) in mice after s.c. administration (Table 3). Both 14-phenlypropxy analogs **65** and **66** were several folds more potent than morphine (100- and 300-fold in the hot-plate and tail-flick tests, respectively for compound **65**, and 400-, 600- and 60-fold in the hot-plate, tail-flick and PPQ-writhing tests, respectively, for compound **66**). They even

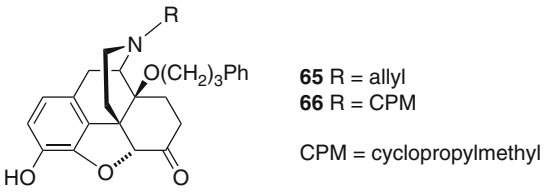


Fig. 4 14-Phenylpropoxy-substituted derivatives of naloxone and naltrexone

Table 3 *In vitro* and *in vivo* opioid activities of 14-phenylpropoxy derivatives of naloxone and naltrexone [44]

Compound	Receptor binding assay					Antinociception		
	K_i μ (nM)	K_i δ (nM)	K_i κ (nM)	Selectivity ratio		ED_{50} (mg/kg s.c.)		
				δ/μ	κ/μ	HP	TF	PPQ
65	0.20	0.26	0.11	0.55	1.30	0.006	0.006	–
66	0.34[a]	0.48[a]	0.41[a]	1.96	1.84	0.002	0.003	0.006

C6 rat glioma cells or [a]rat brain membranes were used in binding assays

K_i inhibition constant; *ED_{50}* effective dose necessary to elicit a 50% effect in mice after s.c. administration; *HP* hot-plate test; *TF* tail-flick test; *PPQ* paraphenylquinone writhing test; – inconsistent dose response

surpassed 14-methoxymetopon (**62**) in analgesic potency and were essentially inactive as antagonists in the tail-flick test in mice versus morphine [44]. This observation is in contrast to the findings upon 14-*O*-methylation and ethylation of naloxone and naltrexone which did not significantly alter binding affinities and agonist potency. These derivatives of naloxone and naltrexone were reported to be essentially devoid of agonist activities in the MVD bioassay and nociceptive assays (i.e. hot-plate and tail-flick tests) in rats and were pure opioid antagonists [12, 38].

Another study [84] reported on the effect of introduction of a 14-phenylpropoxy group in cyprodime and analogs (Fig. 5) on *in vitro* and *in vivo* opioid activities. The presence of a 14-phenylpropoxy substituent in cyprodime, a selective μ-opioid receptor antagonist (Fig. 2) markedly improved the interaction with the μ-receptor, noted as a considerable increase in μ-binding affinity (K_i values of 10.6 nM for cyprodime, 0.34 nM for the analog **67**, and 0.40 nM for analog **68**) and similar or higher μ-receptor selectivity compared to cyprodime (Table 4). In the [^{35}S]GTPγ functional assay, both derivatives **67** and **68** were low efficacy partial agonists at μ- and δ-opioid receptors while at the κ-receptor, antagonist activity was shown by the 14-phenylpropoxy analog **67** and some partial activity by the derivative **68**. Compound **67** was tested for antagonism at human κ-receptors and showed a K_e value of 2.52 nM in the [^{35}S]GTPγS functional assay [84]. *In vivo*, it was found that cyprodime was converted into potent antinociceptive agents through the introduction of a 14-phenylpropoxy group (Table 4). When tested in mice after s.c. administration using hot-plate, tail-flick and PPQ-induced writhing tests, derivatives **67** and **68** were considerably more potent than morphine, with phenol **68** showing the highest antinociceptive potency (21-, 38- and 300-fold in the hot-plate, tail-flick and PPQ-writhing tests, respectively). It also showed similar potency to 14-methoxymetopon (**62**) in all three nociceptive assays. Both 14-phenylpropoxy-

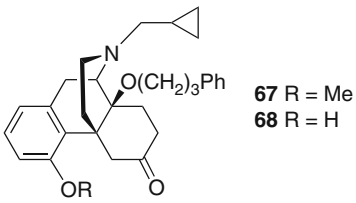


Fig. 5 14-Phenylpropoxy-substituted derivatives of cyprodime

Table 4 *In vitro* and *in vivo* opioid activities of 14-phenylpropoxy derivatives of cyprodime [84]

Compound	Receptor binding assay					Antinociception		
	K_i μ (nM)	K_i δ (nM)	K_i κ (nM)	Selectivity ratio		ED_{50} (mg/kg s.c.)		
				δ/μ	κ/μ	HP	TF	PPQ
67	0.34	16.9	7.36	55	20	0.30	0.28	0.06
68	0.40	5.06	5.84	13	15	0.04	0.05	0.0014
Cyprodime	10.6	414	109	39	10	–	–	–

Rat brain membranes were used in binding assays

K_i inhibition constant; *ED_{50}* effective dose necessary to elicit a 50% effect in mice after s.c. administration; *HP* hot-plate test; *TF* tail-flick test; *PPQ* paraphenylquinone writhing test; – not applicable

substituted derivatives of cyprodime where inactive as antagonists against morphine in the tail-flick test in mice [84].

The SAR studies and pharmacological findings reported in the two studies [44, 84] provide evidence that not necessarily the nature of the substituent at the nitrogen in morphine-like compounds but rather residues occupying a defined position in the vicinity to the morphinan nitrogen seem to be responsible for the agonist/antagonist action. This observation seems to revise the traditionally established SAR models [82, 83]. In the series of morphinan-6-ones with a 14-phenylpropoxy group, even with *N*-substituents such as cyclopropylmethyl and allyl that are usually associated with distinct antagonist properties, agonists and highly potent analgesics were obtained.

3.2 6-Cyanomorphinans

The C6 carbonyl group of morphinan-6-ones can be easily chemically modified, and pharmacological studies have shown that such modifications generally do not affect the opioid character of the ligand [54–56], while the resulting compounds have high antinociceptive potencies, together with reduced unwanted side effects such as respiratory depression and gastrointestinal inhibition [57, 58]. These included for example hydrazones, oximes, and semicarbazone derivatives of *N*-methyl-6-ketomorphinans. On the basis of the pharmacological findings that 4,5-oxygen bridge-opened morphinan-6-ones (*N*-methyl substituted [41] and *N*-cycloproplymethyl substituted [84]) have increased affinities at the μ-opioid receptor and higher antinociceptive potency than their 4,5-oxygen-bridged analogs, it was investigated how and to what degree the presence of a 6-cyano group would affect the opioid receptor binding profile and *in vivo* antinociceptive potency compared to their 6-keto analogs.

The report [85] on acrylonitrile incorporated 4,5-oxygen bridge-opened *N*-methylmorphinans (Fig. 6) described that a 6-cyano substituent leads to compounds (**42**, **43**, and **69**) with high affinity at the μ-opioid receptor and decreased interaction with δ- and κ-receptors, thus being μ-selective (Table 5). Also, the replacement of the 6-keto group by a 6-cyano group did not significantly affect μ-opioid receptor affinity and retained the low binding to the δ- and κ-sites. *In vivo*, the 6-cyanomorphinans (**42**, **43**, and **69**) acted as potent antinociceptive agents in three nociceptive

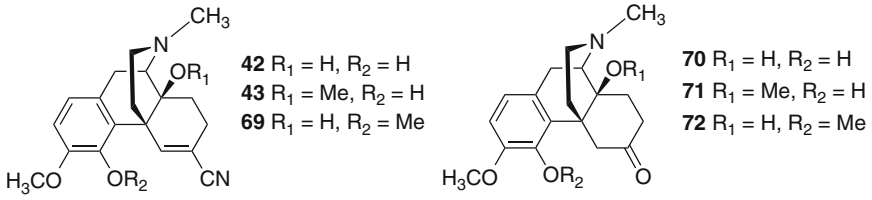


Fig. 6 6-Cyanomorphinans and their 6-keto analogs

Table 5 *In vitro* and *in vivo* opioid activities of 6-cyanomorphinans and their 6-keto analogs [85]

Compound	Receptor binding assay					Antinociception		
	K_i μ (nM)	K_i δ (nM)	K_i κ (nM)	Selectivity ratio		ED_{50} (mg/kg s.c.)		
				δ/μ	κ/μ	HP	TF	PPQ
42	31.7	498	1648	16	52	0.50	1.88	0.18
43	5.38	197	378	37	70	0.25	0.21	0.11
69	2.44	107	364	44	149	0.15	0.018	0.026
70	32.6	881	763	27	23	2.60	–	–
71	4.65	180	592	39	127	0.29	–	–
72	3.88	91.6	693	24	179	0.14	–	–
Oxycodone (**40**)	43.6	1087	2658	25	61	1.37	0.94	0.38

Rat brain membranes were used in binding assays

K_i inhibition constant; ED_{50} effective dose necessary to elicit a 50% effect in mice after s.c. administration; *HP* hot-plate test; *TF* tail-flick test; *PPQ* paraphenylquinone writhing test; – not tested

tests (i.e. hot-plate, tail-flick and PPQ-writhing tests) in mice after s.c. administration. They were either more active or equipotent to their 6-keto counterparts (**70**–**72**), and also to oxycodone (**40**) (Table 5). The presence of a 14-methoxy substituent (compound **43**) instead of a hydroxy group in 6-cyanomorphinan **42** not only increases *in vitro* binding affinity at the μ-receptor, but also enhances the antinociceptive potency (Table 5), a similar observation being made for the morphinan-6-ones [44, 47, 84]. The chemically highly versatile acrylonitrile substructure allows for further conversion into various and more polar derivatives, and, therefore bears the potential to open up a new field in morphinan chemistry and opioid pharmacology.

3.3 6-Amino Acid-Substituted 14-Alkoxymorphinans

The important function of opioid receptors outside of the CNS in different pathophysiological conditions has gained considerable attention during the past decades, and nowadays opioid researchers and physicians are beginning to appreciate the new "peripheral" paths for improved and innovative therapy [6, 8, 86]. Medicinal chemistry and opioid pharmacology focuses increasingly on exploring the potential of peripheral opioid receptors through the development of peripherally acting opioid compounds as therapeutic agents in the treatment of disease states such as pain, inflammatory diseases, and gastrointestinal disorders [14, 18, 27, 87–89]. Approaches to limit access to the CNS and as a consequence also to reduce the occurrence of unwanted CNS side effects include chemical modifications at opioid compounds that increase their hydrophilicity such as incorporation of highly polar substituents. Earlier works to develop peripherally selective opioids have primarily focused on the quaternization of the nitrogen in known opioid morphinans such as morphine, oxymorphone, or naloxone [14, 26, 90]. Although quaternary compounds show reduced ability to cross the BBB relative to their tertiary amine

precursors, they have considerably lower affinity to opioid receptors [26, 90]. Quaternization also trends to reduce potency *in vivo*. In order to avoid these limitations, opioids with hydrophilic groups attached at the C6 position of the morphinan skeleton have been synthesized from β-oxymorphamine [64], β-naltrexamine [64], and β-funaltrexamine [91]. Such opioids with zwitterionic moieties showed reduced penetration to the CNS, without substantially decreased opioid receptor activity [64, 65].

The study [66] reported on the incorporation of an amino acid residue into the highly potent centrally acting μ-opioid analgesic 14-*O*-methyloxymorphone leading to zwitterionic 6-amino acid-substituted derivatives (glycine, alanine, and phenylalanine) (**55**–**60**) of 14-*O*-methyloxymorphone (**48**) (Scheme 12) as potent μ-opioid receptor agonists with limited access to the CNS. In binding studies with rat brain membranes [92], all 6-amino acid conjugates **55**–**60** displayed high affinities ($K_i = 0.77$–2.58 nM) at the μ-opioid receptor (Table 6). They were potent μ-opioid agonists in the MVD bioassay ($IC_{50} = 5.52$–26.8 nM). While the α-amino acid epimers were favored by μ-opioid receptors, the β-epimers have increased interaction with δ-binding sites (Table 6). Only the 6β-phenylalanine **60** conjugate showed some preference for δ- over μ-opioid receptors, and δ-opioid receptor agonist activity in the MVD bioassay (Table 6). The μ- and δ-receptor affinities remained somewhat similar to the parent compound 14-*O*-methyloxymorphone (**48**), whereas affinities at the κ-receptor were significantly decreased independent of α- or β-substitution (Table 6).

A number of *in vivo* pharmacological studies reported that amino acid substitution in position 6 of 14-*O*-methyloxymorphone (**48**) afforded derivatives **55**–**60** that produce potent antinociceptive actions via peripheral mechanisms after s.c. administration in different pain models such as acute nociception i.e. tail-flick test [68], inflammatory pain i.e. formalin test [68] and carrageenan-induced hindpaw inflammation [75] and visceral pain i.e. acetic acid-induced writhing test [93]. In the tail-flick test in the rat, the 6-amino acid derivatives were 19- to 209-fold more potent than morphine (Table 7) and showed similar potency to fentanyl after s.c

Table 6 Opioid receptor binding affinities and agonist potencies of 6-amino acid-substituted derivatives of 14-*O*-methyloxymorphone (**48**) [92]

Compound	Receptor binding assay					MVD bioassay
	K_i μ (nM)	K_i δ (nM)	K_i κ (nM)	Selectivity ratio		IC_{50} (nM)
				δ/μ	κ/μ	
55	0.89	15.4	43.2	17	49	26.8
56	0.83	7.86	44.8	9.5	54	7.00
57	0.77	26.9	142	35	184	12.2
58	1.90	7.71	63.7	4.1	34	19.6
59	0.95	3.67	28.5	3.9	30	5.52
60	2.58	1.03	151	0.40	59	6.07
48	0.10	4.80	10.2	48	102	7.76

Rat brain membranes were used in binding assays

K_i inhibition constant; *MVD* mouse vas deferens; IC_{50} agonist concentration necessary to produce a 50% effect

Table 7 Antinociceptive potencies of 6-amino acid-substituted derivatives of 14-*O*-methyloxymorphone (**48**) [68]

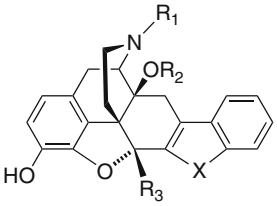
Compound	ED_{50} (nmol/kg s.c.)		
	Tail-flick test	Formalin test	
		I phase	II phase
55	58.5	72	110
56	29.0	125	204
57	68.9	–	–
58	53.4	–	–
59	315	171	292
60	>3,600	79	107
48	14.9	–	–
Morphine	6,053	1,613	1,472
Fentanyl	38.6	–	–

ED_{50} effective dose necessary to elicit a 50% effect in rats after s.c. administration; – not tested

administration [68]. Both s.c. (Table 7) and local intraplantar administration [94] of the zwitterionic compounds **55**, **56**, **59**, and **60** produced antihyperalgesic effects in the formalin test in the rat showing greater potencies than morphine. Potent and significant antinociceptive behavior was also reported after s.c. administration of the 6β-glycine conjugate **56**, using a rat model of prolonged inflammatory pain, i.e. unilateral carrageenan-induced hindpaw inflammation [75] and a mouse model of abdominal visceral pain [93]. Antihyperalgesic and antiallodynic effects of compounds **55**, **56**, **59**, and **60** were also described in rats with neuropathic pain after local intraplantar administration [94]. Generally, antinociceptive actions of the 6-amino acid-substituted derivatives of 14-*O*-methyloxymorphone **55–60** were considerably longer-lasting (2–3 h in the tail-flick and writhing tests and up to 4 h in carrageenan-induced inflammatory pain) compared to the clinically relevant μ-opioid analgesics, morphine and fentanyl, and the structurally related and centrally acting μ-opioids, 14-*O*-methyloxymorphone (**48**) and 14-methoxymetopon (**62**) (30–60 min) [68, 75, 93]. Also, a significant and long-lasting antinociceptive effect (up to 4 h) was reported after oral administration of the 6β-glycine conjugate **56** (10 mg/kg) to rats with carrageenan-induced inflammatory pain [75]. Opioid analgesics with limited access to the CNS that could be administered systemically or orally are of high relevance for clinical use.

3.4 14-Alkoxy-Substituted Indolo- and Benzofuromorphinans

The δ-opioid receptor was the first opioid receptor type to be cloned in 1992 [2], and its molecular and functional characterization was largely based on the use of the δ-selective indolomorphinan NTI (Fig. 2) and its benzofuran analog naltriben (NTB). SAR studies on series of NTI and NTB analogs focusing on the introduction of alkoxy groups at position 14 were reported [43, 50] (Fig. 7). Further chemical modifications, SAR and biological investigations on 14-alkoxy analogs of NTI and



73 R_1 = CPM, R_2 = Me, R_3 = H, X = NH
74 R_1 = CPM, R_2 = Et, R_3 = H, X = NH
75 R_1 = allyl, R_2 = Me, R_3 = H, X = NH
76 R_1 = allyl, R_2 = Et, R_3 = H, X = NH
77 R_1 = CPM, R_2 = Me, R_3 = Me, X = NH
78 R_1 = CPM, R_2 = Et, R_3 = Me, X = NH
79 R_1 = CPM, R_2 = Pr, R_3 = Me, X = NH
80 R_1 = allyl, R_2 = Me, R_3 = H, X = N-Me
81 R_1 = allyl, R_2 = allyl, R_3 = H, X = N-allyl
82 R_1 = CPM, R_2 = Et, R_3 = H, X = O
83 R_1 = allyl, R_2 = Et, R_3 = H, X = O

CPM = cyclopropylmethyl

Fig. 7 14-Alkoxy-substituted indolo- and benzofuromorphinans

Table 8 Opioid receptor binding affinities of 14-alkoxy-substituted indolo- and benzofuromorphinans [43, 50, 95]

Compound	K_i δ (nM)	K_i μ (nM)	K_i κ (nM)	Selectivity ratio	
				μ/δ	κ/δ
73	1.44	68.7	103	48	72
74	0.40	97.0	313	242	783
75	3.8	869	233	229	134
76	2.6	1368	349	526	134
77	1.15	284	421	247	366
78	0.78	340	134	436	172
79	5.3	555	504	105	95
80	1.97	731	149	371	76
81	7.3	1001	763	137	105
82	1.18	185	94	157	80
83	1.20	22.8	68	19	57
NTI	0.14	13.0	15.8	93	113
NTB	0.15	27.1	23.4	180	156

Rat brain membranes were used in μ- and δ-receptor binding assays and guinea pig brain membranes were used in the κ-receptor binding assay
K_i inhibition constant

NTB differently substituted in position 5 and 17 and at the indole nitrogen were described [43, 50, 95–98].

The introduction of a 14-alkoxy instead of the 14-hydroxy group present in NTI resulted in somewhat lower binding affinity at the δ-receptor, while δ-receptor selectivity was considerably increased (compounds **74**–**81**) (Table 8). The nature of the substituent in position 14 was reported to be an important determinant for the interaction with δ-receptors. A 14-ethoxy group in indolomorphinans seems to be superior to 14-methoxy and 14-propoxy substitution concerning δ-affinity and selectivity. The presence of a 14-ethoxy group (compounds **74**, **76**, and **78**) resulted in higher affinity and selectivity for the δ-receptor compared to their 14-methoxy-substituted derivatives **73**, **75**, and **77**, respectively, and 14-propoxy analog **79**

(Table 8). Arylalkoxy substituents in position 14 reduced δ-affinity and selectivity [50]. The introduction of a 5-methyl group in the 14-methoxy indolomorphinan **73** did not significantly change δ-receptor affinity, but decreased affinities at μ- and κ-receptors, resulting in higher μ/δ and κ/δ selectivity ratios (247 and 366, respectively) for compound **77**. Substitution at the indole nitrogen with methyl (compound **80**) or allyl groups (compounds **81**) does not have much influence on δ-receptor affinity and selectivity when compared to the unsubstituted analogs (Table 8). The nature of X (O-, NH-, or N-substituted) did not largely affect δ-receptor affinity and selectivity. Also, replacement of the 17-cyclopropylmethyl group by an allyl substituent has little influence on binding at the δ-receptor [43, 50].

The higher δ-receptor selectivity of the 14-ethoxy-substituted indolomorphinans **76** and **78** compared to NTI based on opioid receptor binding assays was also reported in [^{35}S]GTPγS functional assays [43, 95]. Potent antagonist activities at the δ-receptor were described for other 14-alkoxy-substituted indolo- and benzofuromorphinans compared to NTI and NTB [43, 50, 97]. The interesting opioid receptor activity profile of derivative **78** makes this compound a useful tool to selectively antagonize δ-opioid receptor agonist-induced effects or to assess receptor specificity of opioid ligands *in vitro* and *in vivo* [74, 99–101].

Highly interesting was the observation reported in several studies [102–104] that the indolomorphinan δ-opioid receptor antagonist NTI significantly prolongs renal allograft survival in the rat and inhibits allogenic mixed lymphocyte reaction (MLR) *in vitro*, similar to the clinically used immunosuppressant cyclosporin A. This remarkable finding brought attention to this class of δ-opioid antagonists as potential immunosuppressive agents in organ transplantation and inflammatory diseases. The 14-ethoxy-5-methyl-substituted derivative of NTI (**78**), which showed higher selectivity and antagonist potency towards the δ-opioid receptor than NTI, was reported to inhibit rat lymphocyte proliferation *in vitro* (IC_{50} = 0.54 μM), being more active than NTI (IC_{50} = 6.93 μM) [95]. Other structurally related selective δ-opioid antagonists **73**, **75**, **77**, and **83** were also found to possess immunosuppressive activity *in vitro* in human peripheral blood mononuclear cells (PBMC) at a concentration of 10 μM [96]. Similar to NTI, they reduce interleukin-2 (IL-2) production in mouse and human lymphocytes [96]. The immunosuppressive action of NTI and close derivatives was reported not to be mediated through the δ-opioid receptor or any of the other opioid receptor types (μ and κ) using *in vitro* MLR with splenocytes from δ and triple μ/δ/κ opioid receptor knockout mice [105]. These observations have shed new light on the immunoregulatory mode of action of this class of opioids. It has been postulated that structural determinants of the indolo moiety in NTI and derivatives **73**, **75**, **77**, and **78** or the corresponding benzofuran group in **83** (Fig. 7) appear to be required for the immunosuppressive activity, since naltrexone was inactive in the MLR suppression [105]. Recently, NTI and 14-alkoxy-substituted indolomorphinan derivatives **77** and **78** have been reported to suppress tryptophan degradation and neopterin formation (markers for diseases that are associated with inflammation or altered immune function [106]), in mitogen-induced human PBMC, with derivatives **77** and **78** exhibiting slightly higher potency than NTI [98]. Thus, there is evidence that such opioid indolomorphinans

besides their significant scientific value as pharmacological tools might also have potential for therapeutic use in immunopathological disorders.

4 Conclusions

In recent years, numerous amounts of synthetical efforts have resulted in the development of new 14-alkoxymorphinans together with a significant expansion of knowledge on their pharmacology and ligand-based structure–activity relationships. The nature of the substituent at position 14 in this class of compounds has a major impact on the ability of morphinans to interact with opioid receptors, leading to qualitative and quantitative differences in biological and pharmacological activities. Targeting position 14 represents a viable approach for tuning the pharmacological properties of this class of opioids. Additional substitution patterns in positions 5, 6, and 7 in 14-alkoxymorphinans results in compounds with distinct opioid activities and provided further understanding of structural requirements and functional selectivity. Appropriate molecular manipulations of the morphinan template can afford novel opioid ligands, which besides their scientific value as pharmacological tools, may also have the potential of emerging as novel therapeutic agents for the treatment of human disease states. These advances may lead to strategies in investigating the pharmacotherapeutic potential of the opioid system through the discovery of novel and innovative opioid drugs from the 14-alkoxymorphian class. They will provide a continued infusion of new scientific input into the drug discovery process for identification of safer, more efficacious drugs with improved side effect profiles than the conventional therapies.

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