Most Recent Developments and Modifications of 14-alkylamino and 14-alkoxy-4,5-epoxymorphinan Derivatives

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Abstract: The 14-position of natural opiates (e.g. morphine) are unsubstituted, however synthetic approaches have uncovered that functionalizing position 14 gives rise to a wide range of diverse activities. This review focuses on SAR of the position, with the aim of aiding in the search for opioid analgesics with improved clinical profiles.

I. INTRODUCTION

The provision of effective pain management is essential in a clinical setting where pain is common in individuals treated for cancer, post-operative patients, or in cases of severe trauma. There are two major classes of drugs that are commonly used in treating moderate to severe clinical pain; opioids and nonsteroidal anti-inflammatory agents [1]. Even though opioids are known to be most problematic [2], they are the mainstay of treatment of severe clinical pain [3, 4]. Undesirable side effects such as tolerance, dependence [5], respiratory depression, constipation and nausea [6] have been the leading cause of under-medication and inadequate pain management [7, 8]. Patients that receive opioid treatment often receive additional medications to treat or prevent some of the undesirable side effects. For example, constipation can be managed with stool softeners and laxatives, but not chronically [9]. More recently, alvimopan and methylnaltrexone have been approved as selective antagonists of gastrointestinal opioid receptors to treat constipation [10]. While additional medication may lessen or even prevent some of the adverse effects, in some cases it may dramatically decrease the effectiveness of the opioid itself due to drug-drug interaction [11]. Another problem associated with taking additional medication is that it adds to the regimen of drugs already taken by the patients.

Opioid receptors are G-protein coupled receptors that contain seven transmembrane domains and are primarily located in the brain and the spinal cord as well as the gastrointestinal tract (GIT) [12]. The three types of opioid receptors that have been cloned and pharmacologically characterized are κ [13], δ [14, 15], and μ [16], and each exhibits unique pharmacological response upon stimulation. μ Agonists produce analgesia, euphoria, respiratory depression, tolerance, and constipation [17]. Agonists of the κ receptor have been shown to produce dysphoria, by
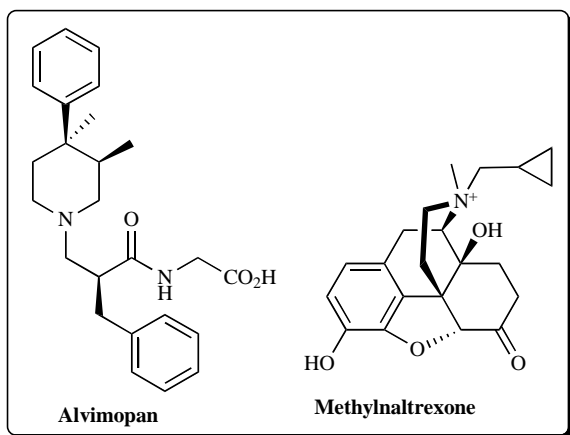
interacting though central nervous system (CNS) mechanisms, tremendously limiting the use of κ agonists in a clinical setting [18]. δ Agonists are not effective against severe pain and are known to produce convulsions [19, 20]. The growing body of evidence concerning the physiological relevance of homo- and heterodimers of opioid receptors [21, 22], leads to the potential of designing ligands that target the dimers and give rise to different effects. However, at present, μ opioid receptors remain the preferred target for more severe pain therapeutics.

Tremendous effort has been put towards the development of novel opioids lacking side effects that are commonly seen in opioid treatment [23]. For example, orvinols (such as bupronorphine) developed by Bentley, exhibit extreme potency but are unsuccessful in elimination of the frequently seen side effects [24]. More recently, several μ-receptor antagonists have been approved for treatment of opioid induced constipation: alvimopan [25], and methylnaltrexone bromide [26]. Alvimopan's large molecular weight, zwitterionic form, and polarity reduce its CNS penetration, thereby allowing the agent to selectively antagonize the effect of opioids on μ receptors in the GI tract. Another significant limitation to prolonged use is the risk of a heart attack. Consequently, alvimopan is only available as a short-term treatment, in hospitals approved by the Entereg Access Support and Education (E.A.S.E.) program, and cannot be dispensed to patients after discharge [25, 27]. Methylnaltrexone bromide is a derivative of naltrexone which has a high peripheral selectivity resulting from the low lipid solubility due to its quaternary salt form. Moreover, methylnaltrexone must be administered subcutaneously as it exhibits poor oral bioavailability [26].
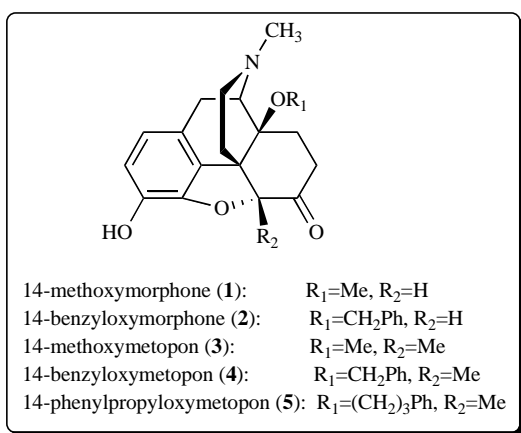
Recent modifications at position 14 have opened a new realm of possibilities. Though natural opiates are unsubstituted at position 14, introduction of 14-OH and $14NH_2$ has been achieved starting from thebaine [28, 29]. Substituents in position 14 have shown to not only improve potency but also selectivity for certain receptor types. For example, Schmidhammer et. al., showed that extremely high potency can be achieved at all three opioid receptors with

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14-alkoxymorphinan derivatives [30]. While, Husbands' group presented modest selectivity with 14-aminodihydromorphinones and 14-aminodihydrocodeinones, clocinnamox analogs [31]. Most recently, studies by Zhang et. al., showed that high binding affinity for the μ opioid receptor with high selectivity over the δ and the κ receptors can be achieved with 14-O-heterocyclic substituted naltrexone [32]. This review will present the most recent developments and modifications in the 14 position of the morphine analogs as potential therapeutic opportunities.

Alvimopan　　　**Methylnaltrexone**

II. 14-ALKOXYMORPHINANS

14-methoxymorphone (**1**):　　　R_1=Me, R_2=H
14-benzyloxymorphone (**2**):　　　R_1=CH$_2$Ph, R_2=H
14-methoxymetopon (**3**):　　　R_1=Me, R_2=Me
14-benzyloxymetopon (**4**):　　　R_1=CH$_2$Ph, R_2=Me
14-phenylpropyloxymetopon (**5**): R_1=(CH$_2$)$_3$Ph, R_2=Me

One of the most promising subclass of opioids with the potential for reduced undesired effects is the 14-alkoxy-morphinans, which was developed by Schmidhammer et. al. [30] During the initial structure-activity relationship (SAR) studies, Schmidhammer's group showed that introduction of a 14-methoxy in oxymorphone (**1**) result in increased binding affinities at all three opioid receptors (0.10 nM at μ receptor; 4.80 nM at δ receptor; and 10.2 nM at κ receptor) [33]. The 14-O-methoxymorphone was reported to possess agonist properties with 400-fold greater potency than morphine and 800-fold greater potency than the parent compound oxymorphone by hot-plate test in mice [34]. Like the parent compound, 14-O-oxymorphone induced res-piratory depression, physical dependence, and constipation [34].
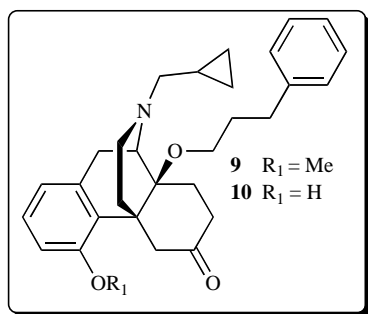
Further studies revealed that introduction of a 14-benzyloxy group (**2**) compared to 14-methoxy group produced similar μ binding affinities (0.12 nM and 0.10 nM respectively), but lower selectivity over δ opioid receptors (2.14 nM and 4.80 nM, respectively) and κ opioid receptors (1.18 nM and 10.2 nM, respectively). Moreover, 14-O-benzyloxymorphone was reported to have 4-fold greater potency than the 14-methoxy analog and 700-fold greater potency than morphine. Most interestingly, 14-O-benzyloxymorphone displayed 2.5-fold less constipative activity as compared to morphine and 7.0-fold less constipation effects than 14-O- methoxymorphone in mice after s.c. administration [33].

Subsequently, the same group showed that introduction of a 14-methoxy in an N-methylmorphinan-6-one series (**3**), produced similar μ binding affinity as 14-O- methoxymor-phone (0.15 nM and 0.10 nM, respectively) with a slightly better selectivity over δ opioid receptors (13.3 nM and 4.80 nM, respectively) and κ opioid receptor (25.2 nM and 10.2 nM, respectively) [35]. Remarkably high antinociceptive activity was reported for 14-methoxymetopon, which exhibited approximately 20,000-fold greater potency than morphine and 1500-fold greater potency than oxymorphone by the acetylcholine-writhing test in rats and mice [36]. Upon supraspinal administration, 14-methoxymetopon can elicit potency of up to one million-fold greater than morphine [37]. Perhaps the most exciting finding was that 14-methoxymetopon lacked tolerance and physical dependence after repeated treatment [38]. Studies also showed that 14-methoxymetopon has reduced constipation [37] and respiratory depression [38] commonly associated with highly potent opioids. These results indicate that a more favorable interaction is possible with the receptor *via* position 14 in the N-methylmorphinan-6-one series.

Furthermore, the 14-alkoxymorphinan series shows that potency can be further magnified by C$_{14}$ arylalkyl substituents as seen with 14-benzyloxy (**4**) [33] and 14-phenylpropyloxymetopon (**5**) [39] derivatives. These 14-arylalkyloxymetapon derivatives displayed enhanced δ and κ affinities while maintaining high μ affinities. Though the 14-phenylpropyloxymetopon derivative exhibited complete loss in μ-selectivity with 0.20 nM at μ receptor, 0.14 nM at δ receptor, and 0.40 nM at κ receptor, it was reported to have extreme potency (24,000-fold higher in the tail flick assay and 8,500-fold higher in the hot plate assay as compared to morphine) [39]. This analog is even more potent than etorphine which makes 14-phenylpropoloxymetapon unsuitable for clinical use due to its extreme potency [39].

6 R_1 = allyl, R_2 = OH
7 R_1 = CPM, R_2 = OH
8 R_1 = CPM, R_2 = H
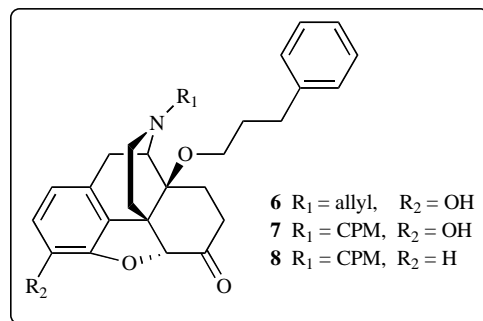
While developing novel μ agonists for the treatment of pain is beneficial, their reinforcing properties make for strong abuse potential [40]. Thus, there has been a growing interest in the development of μ antagonists to block the actions of the abused μ agonists [41]. For many years, it has been generally acknowledged that the introduction of either cyclopropylmethyl or allyl groups on the nitrogen position 17 typically results in antagonism [23]. However, in contrast to the generally accepted antagonist SAR models, 14-O-phenylpropyl derivatives containing *N*-cyclopropylmethyl and *N*-allyl groups (**6-8**) displayed full agonist activity [28]. These results indicate that the nature of the *N*-substituent does not determine the efficacy, but rather the position of the *N*-substituent is important for efficacy [28]. In addition, both analogs **6** and **7** displayed enhanced potency, about 100-400-fold more potent in the hot plate assay than morphine [28]. Moreover, 14-alkoxymorphinans such as 14-O-phenylpro-pyloxy-3-desoxy naltrexone (**8**) was capable of maintaining subnanomolar affinity for μ (0.84 nM) even when there is no C_3 oxygen function [42]. Here it is evident that the substituents in position 3 that were previously considered essential for μ activity are not required in the 14-alkoxymorphinone subclass [42].

9   R_1 = Me
10   R_1 = H

Further SAR studies revealed that partial agonism at μ and δ can be attained by introducing a 14-phenylpropyl group into cyprodime [42], a selective μ-antagonist. Although antagonism was observed at κ opioid receptors by GTPγS functional assays, the cyprodime derivatives, **9** and **10** showed no antagonist activity against morphine in the mouse tail flick assay. These results further imply that the overall conformation of the *N*-substituent in relation to its skeleton, rather than the substituent itself, dictates the efficacy [42]. The presence of 14-alkoxy showed an increase in binding affinity at all three opioid receptors and acted as a potent antinociceptive agent *in vivo* with potency similar to that of 14-metoxymetopon [42].

11   R_1 = methyl
12   R_1 = ethyl
13   R_1 = propyl
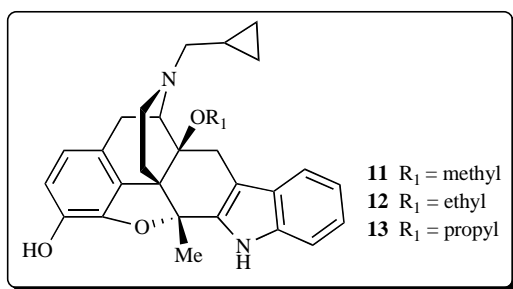
Schmidhammer's group also showed that conversion of a hydroxyl to alkoxy in naltrindole with a methyl moiety

located at position 5 produced lower affinity for δ while increasing δ selectivity when compared to naltrindole. Further studies showed that the nature of the substituent in position 14 determines the binding strength. The 14-ethoxy substituent (**12**) showed increased interaction with the δ receptor (K_i = 0.78 nM) when compared to the 14-methoxy (**11**: K_i = 1.15 nM) and 14-propoxy (**13**: K_i = 5.3 nM) naltrindole derivatives. All 14-alkoxy derivatives possessed antagonist activity in the GTPγS functional assay. Some loss in δ affinity and selectivity was seen with the 14-arylalkoxy naltrindole derivatives (8-30 nM) [43].

Evidence that δ antagonists such as naltrindole and 7-benzylspiroindanylnaltrexone may be involved in allograft survival [44] persuaded Schmidhammer's group to investigate such a phenomena with analog **12**, which was previously shown to be superior to naltrindole [43]. The results showed that **12** inhibited rat lymphocyte proliferation *in vitro* (IC_{50} = 0.54 μM) [45]. Additionally, compound **11** showed immunosuppressive activity *in vitro* and reduced interleukin-2 (IL-2) production in mouse and human lymphocytes [46]. In contrast to the previous finding, these naltrindole derivatives did not exhibit immunosupression *via* δ opioid receptors as seen in the mixed lymphocyte reaction assay that uses μ/δ/κ receptor knock-out mice. Furthermore, it has been suggested that the indolo moiety is involved in immunosuppressive activity [47].
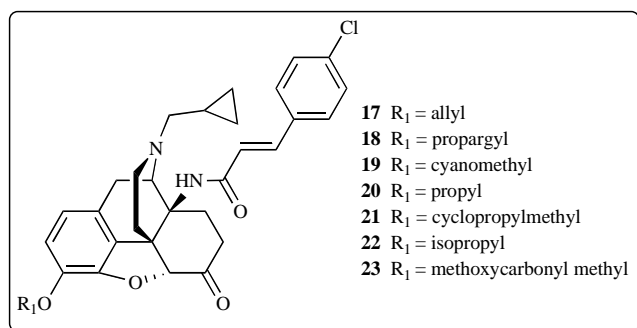
III. 14-AMINOMORPHINONES AND CODEINONES

Another important subclass of opioids contains 14-aminomorphinones and codeinones. Clocinnamox (**14**, C-CAM) and methoclocinnamox (**15**, MC-CAM) were the first analogs developed in their structural class by Lewis *et al.* [48]. MC-CAM and its parent compound C-CAM had very similar affinities (μ = 0.46 nM and 7.2 nM; δ = 29 nM and 7.2 nM; and κ = 4.5 nM and 1.6 nM respectively) [49]. While C-CAM displayed μ antagonism with no agonist activity [50], MC-CAM was reported to have higher efficacy, displaying partial agonism at the μ receptor after peripheral administration *in vivo* [51]. Potentially, the most exciting finding was that MC-CAM had pseudo-irreversible effects with its extremely long duration of antagonist action similar to that of buprenorphine [52]. Initially, MC-CAM was believed to exhibit its delayed long-term antagonist effect *via* its de-methylated metabolite C-CAM [48]. However, it was later shown that MC-CAM was capable of producing μ-antagonist effects after i.c.v. administration [53]. Although long duration of action μ-antagonists can be used to treat drug abuse by blocking the effects of the drug upon subsequent administration [54], MC-CAM does not possess a superior profile to buprenorphine.

Other studies presented by the groups of Husbands and Lewis looked at the effect of the aryl ring substituent orientation (**16**) [55]. In these studies, the μ efficacy decreases in the order: ortho- > meta- > para- for the methyl and chloro substituents while no effect was seen with the fluoro substituent [55]. In contrast, a reduction in μ agonist efficacy and potency was seen when the nitro orientation was changed from the para- to the ortho- position possibly due to the lipophilicity rather than steric or electronic effects [55]. Conclusions drawn from these studies showed that 2'-

14 R$_1$ = H, X = 4'-Cl, **C-CAM**
15 R$_1$ = Me, X = 4'-Cl, **MC-CAM**

16
X = 2'-, 3'-, and 4'-H, Cl, Me, NO$_2$
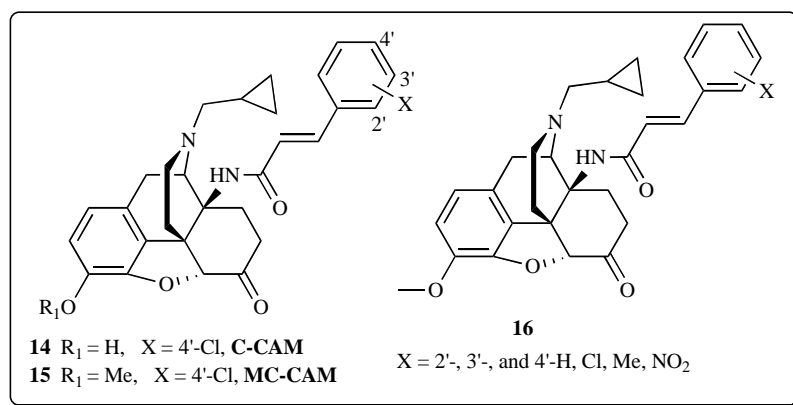
chloro, 2'-methyl, 4'-fluoro and 4'-nitro substituted cinnamylaminomorphinone analogs possessed potent agonist effects, with ED$_{50}$ of 0.003 mg/kg to 0.014 mg/kg compared to morphine's 0.66 mg/kg in the rat tail pressure *in vivo* assay [31]. Interestingly, the 4'-nitro analog acted as a short-term agonist in the mouse hot water tail-withdrawal (TW) assay[53]. However, when pretreated for 24 hours, the 4'-nitro analog had morphine antagonist activity with a long duration of action [55].

17 R$_1$ = allyl
18 R$_1$ = propargyl
19 R$_1$ = cyanomethyl
20 R$_1$ = propyl
21 R$_1$ = cyclopropylmethyl
22 R$_1$ = isopropyl
**23** R$_1$ = methoxycarbonyl methyl

Subsequently, the groups of Lewis and Husbands studied the effect of a variety of 3-alkyl ether to further investigate the possibility of the MC-CAM's delayed long duration of action antagonism to be a result of the C-CAM metabolite. Interestingly, higher efficacy was achieved with 3-alkyl ether C-CAM analogs [41, 56]. Specifically, 3-allyl (**17**), 3-propargyl (**18**), cyanomethyl (**19**), and propyl (**20**) ethers displayed higher efficacy than MC-CAM, with 3-propargyl ether analog having the greatest activity by TW assay [56]. The 3-propargyl ether analog was reported to have similar potency to morphine with higher efficacy than buprenorphine in mice, meanwhile a lack of change in efficacy was seen in rhesus monkeys [56]. Other substituents like cyclopropylmethyl, isopropyl and methoxycarbonyl methyl ether were reported to have antagonist activity by the TW assay in mice. All the ether analogs were reported to have long-term antagonism effects in the TW assay when administered 24 hours prior to morphine administration [56]. In this series, the propagyl ether analog had the preferred long-lived μ-antagonist effects in mice and rhesus monkeys in addition to the increased efficacy when compared to buprenorphine [56]. These results further indicate that the delayed antagonist activity of MC-CAM is not related to its metabolism [56].
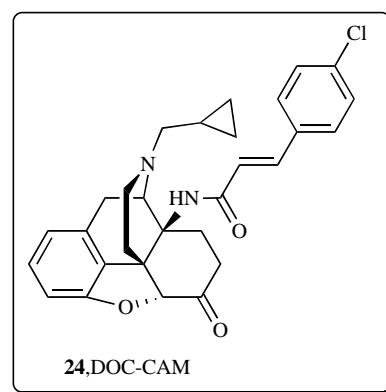
24,DOC-CAM

Similar to Schmidhammer's compounds, [42] the removal of the 3-hydroxy group from C-CAM to give DOC-CAM, **24** resulted in similar μ- affinity as its parent compounds MC-CAM and C-CAM (K$_i$= 0.54 nM, 0.46 nM, and 0.25 nM, respectively). Although DOC-CAM was reported to qbe an antagonist, it did not exhibit irreversible effects as its parent compound *in vivo*. Therefore, even though it is evident that the 3-hydroxyl substituent is not required for μ-opioid activity, it is essential for the irreversible μ antagonist activity in the 14-cinnamoylamino series [31, 57].

25 R$_1$ = Me, TAMO
26 R$_1$ = CPM, *N*-CPM-TAMO
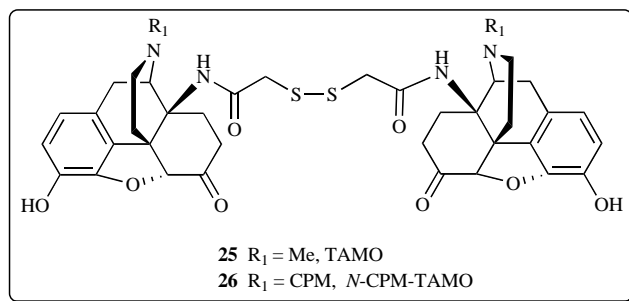
Studied by Archer *et al*. were the 14-aminomorphinone derivatives containing sulfhydryl group, which can form covalent disulfide bonds with the receptor *via* oxidative coupling [58-60]. One such compound is TAMO which displays moderate selectivity for the μ-receptor over δ and κ [58]. This compound was shown to have antinociceptive effects immediately after i.p. and i.c.v. administration for up to 5 h and 2.5 h, respectively [59, 60]. These effects appeared to be mediated *via* the μ opioid receptor as they

Cmpd	R-	Cmpd	R-
27		31	
28		32	
29		33	
30		34	
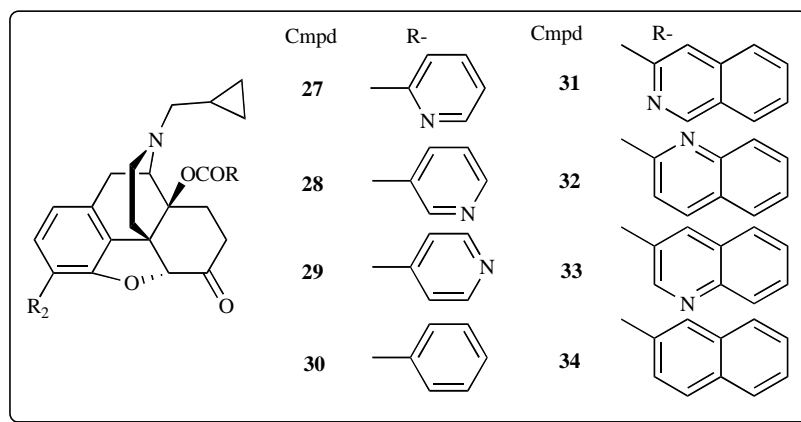
were antagonized by the β-funaltrexamine [60]. Additionally, TAMO was found to act as a selective μ opioid receptor antagonist with long duration of action (from 8h to 48h after administration) against morphine [60]. Interestingly, *N*-cyclopropylmethyl analog of TAMO (*N*-CPM-TAMO) had no antinociceptive activity but acted as a selective μ antagonist with long duration of action [61].

IV. 14-O-HETEROCYCLIC NALTREXONES

Antagonists such as naloxone and naltrexone are the approved drugs used for treatment of opiate overdose [62]. Since there is no crystal structure of the μ receptor in existence to date, these μ antagonists play an important role in the study of opioid receptors [32]. More recently, studies showed that μ antagonists can be used to treat obesity, psychosis, and Parkinson's disease [63], making the development of novel μ antagonists a valuable tool not only for studying the structure of opioid receptors, but also for the development of the much needed therapeutics. 14-O-heterocyclic substituted naltrexone derivatives were most recently developed by Guo et. al. [32], using a constructed homology model based on bovine rhodopsin. This model contained transmembrane helical domains with extracellular and intracellular loops, and was further optimized in a membrane-aqueous system using molecular dynamic simulations. The model revealed that the non-conserved residues, Tyr212 and Trp320, may interact with the receptor *via* hydrogen bonding interactions with the ligand [32]. Thus, a new series of compounds were developed to incorporate a hetero-aromatic moiety on position 14 of naltrexone enabling hydrogen bonding and/or aromatic stacking interactions with Tyr212 and Trp320 [32].

Zhang's group further investigated the effect of the pyridyl nitrogen position and bulkiness *via* additional aromatic moieties on the 14-O-heterocyclic naltrexone derivatives. Almost all compounds were reported to have antagonist activity in GTPγS assays except for compound **33** [32]. When compared to previously reported compounds by Schmidhammer and Husbands [30, 31] this series had similar binding affinities; however, compound **27** had higher selectivity, approximately 800-fold selectivity for the μ over δ and 200-fold selectivity for the μ over κ [32]. Introduction of an additional aromatic moiety (compounds **31-34**) did not improve the interaction with the μ receptor but rather lowered their selectivity [32].

V. CONCLUSION

Advances in the development of highly potent and selective opioid agonists and antagonists *via* position 14 in 14-alkoxymorphinan, 14-aminomorphinone, and 14-O-heterocyclic naltrexone series provide valuable insights into opioid ligand-receptor interaction. It is evident that the nature of the substituent on position 14 and its orientation has a strong influence on receptor binding and post-receptor mechanisms. The advances in SAR illustrated in this review serve as a valuable tool for designing novel molecules with optimal configuration that may aid in identification of ideal opioid medications.

ACKNOWLEDGEMENTS

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