A Systematic Review on the Kappa Opioid Receptor and Its Ligands: New Directions for the Treatment of Pain, Anxiety, Depression, and Drug Abuse

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Abstract:
Kappa opioid receptor (KOR) is a member of the opioid receptor system, the G protein-coupled receptors that are expressed throughout the peripheral and central nervous systems and play crucial roles in the modulation of antinociception and a variety of behavioral states like anxiety, depression, and drug abuse. KOR agonists are known to produce potent analgesic effects and have been employed clinically for the treatment of pain, while KOR antagonists have displayed efficacy in the treatment of anxiety and depression. This review summarizes the history, design strategy, discovery, and development of KOR ligands. KOR agonists are categorized into G protein-biased KOR agonists and β-arrestin recruitment-biased KOR agonists, based on their degrees of bias. Mechanisms and associated effects of the G protein signaling pathway and β-arrestin recruitment signaling pathway are also discussed. Meanwhile, KOR antagonists are categorized into three groups, long-acting, intermediate-acting, and short-acting, based on their durations of action. In addition, we have special sections for mixed KOR agonists and selective peripheral KOR agonists. Mechanisms of action and pharmacokinetic, pharmacodynamic, and behavioral studies for each of these categories are also discussed in this review.

Keywords: Kappa opioid receptor, biased and unbiased, agonists and antagonists, pain, anxiety and depression, drug abuse

I. Introduction

Opioid receptors are a group of G protein-coupled receptors (GPCRs) that opioids target and mediate their effects. These opioid receptors are expressed throughout the peripheral and central nervous systems (CNS) and play crucial roles in the modulation of antinociception and a variety of behavioral states like anxiety, depression, and drug abuse. With the impact that opioids have had on our society, interest in opioid receptors has been rising steadily throughout the literature.[1–4] Kappa opioid receptor (KOR) is one of the four receptors in the opioid receptor system. The other three are mu (MOR), delta (DOR), and nociceptin (NOR) opioid receptors.

KOR agonists are known to produce potent analgesic effects and have been employed clinically for the treatment of pain.[5] KOR agonists, such as salvinorin A and salvindolin, have also provided benefits in the treatment of anxiety and depression.[6–8] In addition, KOR agonists can block the rewarding effects of psychostimulants like morphine[9] and cocaine;[9–11] therefore, they possess therapeutic potential in the treatment of drug abuse. Meanwhile, KOR antagonists have also displayed efficacy in the treatment of anxiety and depression.[12] KOR antagonists, such as norbinaltorphimine (nor-BNI), JDTic, and 5'-guanidinonaltrindole (5'-GNTI), have been shown to stop depressive and anxiety-related disorders, which are the common side effects of withdrawal that can lead to the relapse in drug use.[12–17] Mixed KOR agonists/MOR agonists or mixed KOR agonists/MOR antagonists, such as nalbuphine, butorphanol, and levorphanol, have been used as analgesics for a variety of pains, including acute pain, neuropathic pain, and hyperalgesia.[18–23] Nalbuphine has also shown benefits in the alleviation of cocaine withdrawal.[24] Overall, KOR is an important player in the treatment of a variety of illnesses that greatly impact the quality of human health, and the discovery and development of novel KOR ligands will help alleviate the suffering of patients. This review is intended to systematically categorize KOR agonists and antagonists and summarize their therapeutic benefits and important development for pain, anxiety, depression, and drug abuse.

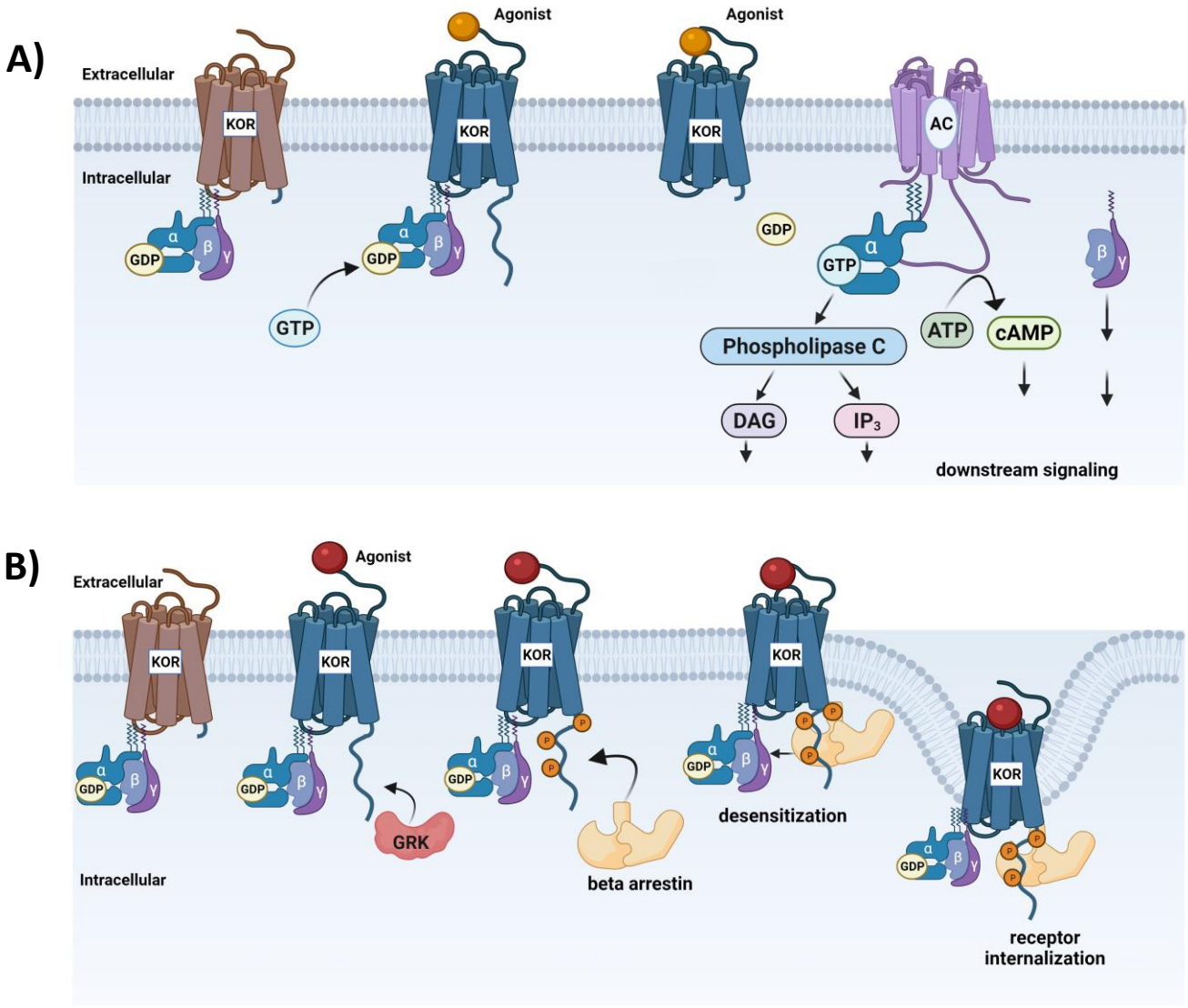


Figure 1. Agonism of kappa opioid receptor: **A)** G protein signaling pathway and **B)** β-arrestin recruitment signaling pathway. KOR, kappa opioid receptor; α, β, γ, three subunits of KOR; GDP, guanosine-5'-diphosphate; GTP, guanosine-5'-triphosphate; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; IP_3, inositol trisphosphate; DAG, diacylglycerol; GRK, G protein-coupled receptor kinase.

II. Nonbiased and Biased KOR Agonists

II.1. G protein Signaling vs. β-Arrestin Recruitment Signaling

Even though they produce their physiological effects through the activation of the same receptor, different KOR agonists have been shown to activate distinct cellular signaling pathways and downstream responses, resulting in different functions of the agonists used and behavioral outcomes. This phenomenon is known as the functional selectivity of KOR agonism. As a GPCR, KOR is exposed to both the extracellular and intracellular environments. At the inactive state, KOR is bound to an intracellular heterotrimeric G protein that consists of three subunits, G_α, G_β, and G_γ (**Figure 1**). This G protein is also bound to GDP.[25] Upon activation of the receptor via binding of an extracellular agonist, in one pathway, GDP is replaced by GTP, which facilitates a dissociation of G_α (bound to

GTP) and $G_{\beta}G_{\gamma}$ from the receptor (**Figure 1A**).[25] Both the resulting G_{α}-GTP and $G_{\beta}G_{\gamma}$ units then activate the formation of downstream secondary messengers, such as cyclic adenosine monophosphate (cAMP), inositol trisphosphate (IP_3), and diacylglycerol (DAG). This pathway is known as G protein-biased agonism.[26]

In another pathway, KOR is phosphorylated by G protein-coupled receptor kinases (GRKs) at the *C*-terminus on the intracellular side of the receptor, which facilitates the recruitment of β-arrestins and prevents the dissociation of G_{α} and $G_{\beta}G_{\gamma}$ from the receptor (**Figure 1B**).[25,26] The overall effects of this β-arrestin recruitment-biased agonism are the desensitization and internalization of KOR.

Biased KOR agonists selectively activate one signaling pathway over the other, so they are categorized into G protein-biased agonists and β-arrestin recruitment-biased agonists. Meanwhile, nonbiased KOR agonists activate both signaling pathways simultaneously. These nonbiased KOR agonists are also known as "unbiased"[27,28] or "balanced";[29–31] however, we believe nonbiased is a more accurate term to describe the nature of these compounds. KOR agonists that display biases towards β-arrestin recruitment have been known to mediate the analgesia with more severe adverse effects, such as anhedonia/dysphoria, sedation, anxiety, and motor incoordination, than the KOR agonists that display biases towards G protein signaling.[30] β-Arrestin recruitment-biased KOR agonists usually recruit both β-arrestin1[32] and β-arrestin2,[33] which regulate different down signaling and trafficking events. The severe adverse effects of β-arrestin recruitment-biased KOR agonists are associated with β-arrestin2 recruitment.[34] Overall, G protein-biased KOR agonists are preferred to both β-arrestin recruitment-biased KOR agonists and nonbiased KOR agonists in the research and in the development of novel GPCR-targeted analgesic therapeutics with minimal undesirable adverse effects. Activations of other opioid receptors, such as MOR and DOR,[35] as well as other CNS-relevant GPCRs, such as cannabinoid receptors 1 and 2 (CB1 and CB2),[36] also undergo G protein-biased signaling and β-arrestin recruitment-biased signaling pathways, and the G protein-biased agonists of these receptors also come with less severe side effects than β-arrestin recruitment-biased agonists or nonbiased agonists.[37,38] Thus, the research and development of G protein-biased agonists are also preferred for these receptors.

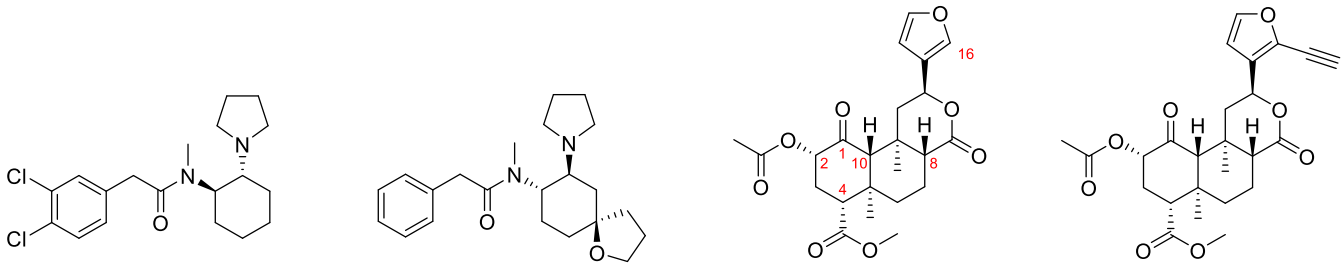


Figure 2. Structures of nonbiased KOR agonists

II.2. Nonbiased KOR Agonists

The majority of known KOR agonists have been observed to be either G protein-biased or β-arrestin recruitment-biased. Only a few known KOR agonists, such as U-50,488, U-69,593, and salvinorin A, are nonbiased. These compounds are often used as the controls in functional assays to determine the functionality of new compounds towards KOR.

II.2.1. U-50,488

In 1981, Voigtlander and coworkers discovered U-50,488 (**Figure 2**) as a highly selective KOR agonist.[39–41] At the time, U-50,488 was a novel non-mu opioid analgesic that was used as a prototype to develop next-generation analgesics, including U-69,593 (**Figure 2**)[42] and spiradoline (**Figure 3**).[43] U-50,488 displayed a high binding affinity and good potency towards KOR (K_i = 0.2

nM, EC_{50} = 9.31 nM).[44] U-50,488 has been shown to activate both the G protein signaling pathway and the β-arrestin recruitment signaling pathway[45] and is considered to be the first nonbiased KOR agonist. Along with U-69,593 and salvinorin A, U-50,488 has been used as a control in assays, including cAMP inhibition and Tango, that determine the signaling pathways and is often normalized to have a bias factor of 1.[38,45] The overall efficacy of U-50,488 on KOR was ~93% compared to that of U-69,593, which currently is the most widely used standard for the selectivity and functional activity towards KOR.[46] U-50,488 also displayed some small activity on MOR (K_i = 370 nM, >30 times more selective for KOR over MOR).[47,48] U-50,488 produced analgesia in a rat model of unilateral peripheral neuropathy through constriction of the common sciatic nerve (0.3 mg, local s.c.), and this low dose was found to not lead to systemic, central nervous system effects and deleterious side effects associated with centrally-mediated KOR agonists.[49] Similarly, in a rat model of acute pain using formalin, U-50,488 was shown to reduce behaviors associated with acute pain (0.05 mg, local s.c., 30–60 min. after formalin injection).[50] Administration of U-50,488 also showed anticonvulsive[51] and anti-inflammatory effects.[52] In rats, pretreatment of U-50,488 (20 mg/kg, i.p.) produced 50% decrease of dopamine level.[53] U-50,488 also decreased self-administration of cocaine in rats[9] and monkeys[10] in a dose-dependent manner. U-50,488 did not produce physical dependence, but showed tolerance to chronic use.[48] U-50,488 did not decrease respiratory function in rhesus monkeys even with a dose as high as 5.6 mg/kg.[54] However, U-50,488 produced serious side effects, such as sedation and diuresis,[40] possibly due to the recruitment of β-arrestin as is its nature as a nonbiased KOR agonist.

II.2.2. U-69,593

In 1985, Voigtlander and coworkers developed U-69,593 (**Figure 2**), a close, next-generation analogue of U-50,488, as a selective KOR agonist.[42] U-69,593 was initially developed as a tritiated ligand for research on selective KOR agonists. By adding a tetrahydrofuran ring to the cyclohexane ring in U-50,488 and switching the stereochemistry of the two carbons bearing the tetrahydropyrrole and amide group from (*R*) to (*S*), these researchers discovered that the molecule (U-69,593) had an increase in selectivity and potency towards KOR (K_i = 0.3–3 nM, EC_{50} = 26.1 nM).[42,46] U-69,593 has been the most widely used control in assays for the selective and functional activity towards KOR.[46] U-69,593 activates both the G protein signaling pathway and the β-arrestin recruitment signaling pathway and is often used as a control in assays, including cAMP inhibition (EC_{50} = 0.32 nM) and Tango (EC_{50} = 6.74 nM),[55] that determine the signaling pathways and is often normalized to have a bias factor of 1.[38,45] In rats, intraperitoneal administration of U-69,593 produced greater antinociception in the hot plate test than did U-50,488.[56] U-69,593 was observed to attenuate cocaine self-administration in male Sprague-Dawley rats.[11] A single dose of U-69,593 (0.32 mg/kg, s.c.) decreased the responding maintained by low doses of cocaine (0.015–1 mg/kg) regardless of whether cocaine was administered in an ascending or descending manner.[11] Prior administration of U-69,593 (0.32 mg/kg, s.c.) also attenuated cocaine-seeking behavior in male Sprague-Dawley rats.[11] Similar to U-50,488, U-69,593 produced diuresis in rats.[57] However, unlike U-50,488, which did not decrease respiratory function in rhesus monkeys, U-69,593 decreased respiration in these animals in a dose-dependent manner, producing V_T values (total volumes) that were less than 40% of that of control (no drug).[54]

II.2.3. Salvinorin A

Salvinorin A (**Figure 2**), a *neo*-clerodane diterpene, is the main active ingredient of the hallucinogenic plant *Salvia divinorum* that has been safely used by the Mazatec people for centuries in religious rituals.[58] First isolated from the plant in 1982 by Ortega and coworkers,[59] salvinorin A is one of the most potent, naturally occurring opioid agonists, with high selectivity and affinity towards KOR (K_i = 4 nM, EC_{50} in [^{35}S]GTPγS binding assay = 2.2 nM).[60] In 2002, Roth and coworkers discovered that salvinorin A targeted KORs expressed in both human embryonic kidney-293 cells (K_i = 16 nM) and

guinea pig brain (K_i = 4.3 nM).[61] They also discovered the nonbiased agonistic nature of salvinorin A towards KOR when it was observed to activate both the G protein signaling pathway and β-arrestin recruitment pathway.[61] In the cAMP inhibition assay to determine the G protein signaling, the EC_{50} value of salvinorin A was found to be 4.73 nM, and in the Tango assay to determine the β-arrestin recruitment signaling, the EC_{50} value was found to be 10.5 nM.[62] Salvinorin A has been found to be beneficial in treatment therapies for various central nervous system (CNS) disorders. atai Life Sciences has been developing salvinorin A for treatment-resistant depression, substance use disorder, and pain, with clinical trials expected to begin in the second half of 2022.[7] Due to its high selectivity and potency on KOR, salvinorin A is known to produce hallucinatory side effects that are characterized by vivid visions with eyes closed, changes in dimensionality and time perception, and a complete blockage of external stimuli.[63] However, these side effects usually only last ~10–15 minutes[63] because the C2 ester in the structure of salvinorin A quickly undergoes hydrolysis to yield the inactive metabolite salvinorin B. Nevertheless, salvinorin A has been used as an important prototype for the development of related drug candidates targeting different opioid receptors.[8,64–73]

Since the short-acting activity of salvinorin A has hindered its clinical utility, many efforts have been made to extend its half-life by replacing the ester at C2 with more stable functional groups such as carbamates, ethers, and amides.[64] The two most notable analogues of salvinorin A that are more metabolically stable and have longer durations of action are ethoxymethyl ether salvinorin B[70] and β-tetrahydropyran salvinorin B[69] (2–3 hours); like salvinorin A, these two compounds are also selective KOR agonists with similar binding affinities and potencies towards KOR.[74] Ethoxymethyl ether salvinorin B and β-tetrahydropyran salvinorin B attenuated drug-seeking behavior and cocaine-induced locomotor activities in rats but with reduced adverse effects compared to salvinorin A.[74] β-Tetrahydropyran salvinorin B has been shown to produce analgesic and anti-inflammatory effects in mice.[75] However, the agonism nature of these two salvinorin analogues towards KOR have not been determined.

II.2.4. 16-Ethynyl Salvinorin A

In 2014, Prisinzano and coworkers synthesized and studied a series of salvinorin analogues with various substituents on the furan ring.[76] They discovered 16-ethynyl salvinorin A to be a selective and potent KOR agonist (K_i = 2.5 nM, EC_{50} = 0.019 nM).[31,76] 16-Ethynyl salvinorin A displayed a nonbiased agonistic nature towards KOR when it was observed to activate both the G protein signaling pathway and β-arrestin recruitment pathway.[31] 16-Ethynyl salvinorin A significantly reduced both nociceptive and inflammatory pain-related behaviors in mice (1–2 mg/kg, i.p., warm water tail-withdrawal, hot plate, and intraplantar formaldehyde assays) and reduced side effects compared to salvinorin A (1–2 mg/kg, i.p., elevated zero maze and marble burying tests).[31] A single dose of 16-ethynyl salvinorin A (0.1 mg/kg, i.p.) was observed to attenuate cocaine-seeking behavior in rats without causing sedation or motor incoordination.[76] A higher dose of 16-ethynyl salvinorin A (0.3 mg/kg) also did not cause sedation or motor incoordination.[76]

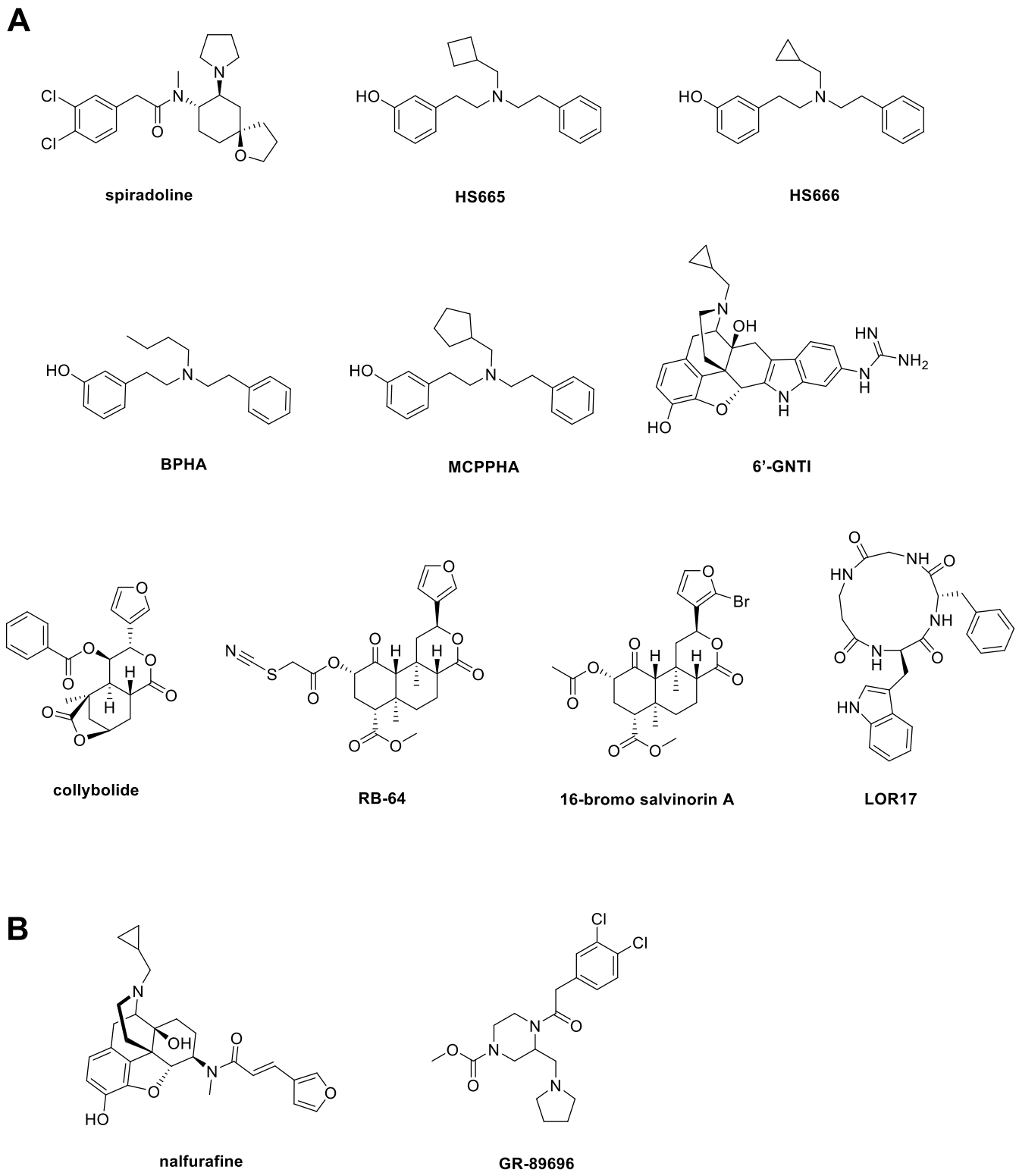


Figure 3. Structures of biased KOR agonists: **A)** G protein-biased KOR agonists and **B)** β-arrestin recruitment-biased KOR agonists.

II.3. Biased KOR agonists

II.3.1. G protein-Biased KOR Agonists

As mentioned above, due to their lack of serious side effects, G protein-biased KOR agonists are the most desired KOR agonists in drug development. Fortunately, the majority of KOR

agonists that have been discovered so far are G protein-biased.

II.3.1.1. Spiradoline

Spiradoline (U-62,006) (**Figure 3A**) is another analogue of U-50,488 that was discovered by Voigtlander and coworkers as a selective KOR agonist (K_i =8.6 nM).[43] Structurally, spiradoline is a hybrid of U-50,488 and U-69,593. The (-) enantiomer of spiradoline displays strong KOR agonistic properties, whereas the (+) enantiomer of spiradoline is a weak MOR agonist.[77] Spiradoline (racemic) showed good potency (agonism) on KOR and displayed a G protein bias with a bias factor of 6 compared to U-69,593 (EC_{50} in GloSensor assay = 1.01 nM, EC_{50} in Tango assay = 6.21 nM).[78] Spiradoline produced analgesic effects in both rat and mouse models.[77,78] Additionally, in rats, spiradoline considerably decreased self-administration of cocaine,[9] while in monkeys, it produced little effect.[79] To date, no studies on cocaine self-administration in humans have been undertaken. Spiradoline also reduced blood pressures, heart rates, and arrhythmia risks.[77] Spiradoline also displayed antitussive and antihistamine activities.[77] However, despite promising analgesic data in animal models, spiradoline only produced analgesia in humans at high doses that often caused serious diuresis,[80,81] sedation,[77] and dysphoria side effects.[77]

II.3.1.2. HS665 and HS666

In 2012, Spetea *et al.* discovered HS665 and HS666 (**Figure 3A**), two *N*-diphenethylamine compounds, as selective KOR agonists.[44,82] HS665 and HS666 share a similar structure and only differ in the *N*-substituted side chain (*N*-methylcyclobutyl for HS665 and *N*-methylcyclopropyl for HS666). HS665 displayed a high binding affinity and potency towards KOR (K_i = 0.49 nM, EC_{50} = 3.62 nM, 90% efficacy compared to U-69,593), whereas HS666 displayed a more moderate binding affinity and potency towards KOR (K_i = 5.90 nM, EC_{50} = 35 nM, 53.4% efficacy compared to U-69,593).[44] Both HS665 and HS666 were biased towards G protein signaling over β-arrestin recruitment with bias factors of 389 and 62, respectively, compared to the normalized bias factor of 1 for U-69,593.[82] In a mouse model for antinociception, HS665 and HS666 displayed both time- and dose-dependence in activity and were two folds greater in potency compared to that of U-50,488.[82,83] Interestingly, HS665 impaired motor coordination in a mouse model, while HS666 did not.[82,83] HS665 also induced aversive-like action in a conditioned place aversion assay, while HS666 did not.[82] Overall, HS666 is a promising KOR-targeting analgesic with reduced liabilities.

II.3.1.3. BPHA

In 2012, Spetea *et al.* also discovered BPHA (**Figure 3A**), another *N*-diphenethylamine compound, as a KOR agonist.[44] However, it has a lower binding affinity and potency towards KOR (K_i = 10.9 nM, EC_{50} = 46.2 nM, 45.5% efficacy compared to U-69,593) compared to those of HS665. BPHA was later discovered to be a full KOR agonist.[83] BPHA is extremely G protein-biased over β-arrestin recruitment with a bias factor of 59.[83] BPHA also displayed significant binding affinity towards MOR (K_i = 360 nM) and DOR (K_i = 2700 nM).[83] In a study in a mouse model, BPHA did not impede nor impair motor coordination, suggesting that its effects are primarily mediated through KOR agonism (instead of MOR agonism) *in vivo*.[83]

II.3.1.4. MCPPHA

In 2017, Spetea and coworkers discovered MCPPHA (**Figure 3A**), also another *N*-diphenethylamine compound, as a KOR agonist.[84] MCPPHA and BPHA share a similar structure and only differ in the *N*-substituted side chain (*N*-methylcyclopentyl for MCPPHA and *N*-*n*-butyl for BPHA). MCPPHA was shown to be a full KOR agonist with a high binding affinity and great potency (K_i = .017 nM, EC_{50} = 3.87 nM, 82.8% efficacy compared to U-69,593). MCPPHA is biased towards G protein signaling over β-arrestin recruitment with a bias factor of 42,[83] which is low compared to other aforementioned G protein-biased KOR agonists, and significantly lower than that of the closely related compound BPHA. Despite its relatively moderate G protein bias, in a mouse model for antinociception, MCPPHA was still three folds

greater in potency compared to U-50,488, which is a nonbiased KOR agonist, and MCPPHA did not impair motor coordination.[84]

II.3.1.5. 6'-Guanidinonaltrindole (6'-GNTI)

In 2001, Portoghese and coworkers explored different derivatives of 5'-guanidinonaltrindole (5'-GNTI), a KOR antagonist, by varying the position of the guanidinium group on the naltrindole ring.[85,86] Accidentally, they discovered 6'-guanidinonaltrindole (6'-GNTI; **Figure 3A**) as a KOR agonist. This is now one of the classic examples of how an antagonist can be transformed into an agonist, or vice versa, by appropriate structural modifications, sometimes relatively minor modifications. In these cases, the agonists and antagonists bind to the same site but trigger or do not trigger functional responses, respectively, due to their activation of the binding site or prevention of the agonists from reaching the binding site, respectively.[87,88] Besides its activity on KOR (K_i = 1.15 nM), 6'-GNTI also showed activity on MOR (K_i = 20.3 nM) and DOR (K_i = 81.8 nM). The KOR agonism of 6′-GNTI was shown to be blocked by nor-binaltorphimine (nor-BNI), a selective KOR antagonist, in the guinea pig ileum; however, 6′-GNTI displayed no agonistic activity in mouse vas deferens.[89] These results suggested that the receptor target of 6′-GNTI existed in guinea pig ileum but not in mouse vas deferens.[89] In 2005, Portoghese and coworkers proposed that 6′-GNTI targeted opioid receptor heterodimers whose expression varied widely throughout different tissues.[89] 6′-GNTI was more potent and efficacious towards KOR/DOR heterodimers (EC_{50} = ~40 nM) than KOR/MOR heterodimers (EC_{50} = ~100 nM) or KOR homodimers (EC_{50} = ~220 nM). Up until that time, the demonstration of the existence of GPCR heterodimers *in vivo* was challenging, so those results with 6′-GNTI (including *in vitro* activity and tissue-selective *in vivo* analgesia) provided a proof-of-concept for targeting tissue-selective GPCR heterodimers in designing novel analgesic drugs with reduced side effects. In 2012, Javitch and coworkers discovered 6′-GNTI to be a G protein-biased partial KOR agonist (EC_{50} = 1.6 nM, E_{max} = 64%), activating G protein signaling without recruitment of β-arrestin2 or β-arrestin3 to KOR.[86] In 2013, Bohn demonstrated that 6'-GNTI activated Akt but not ERK1/2 in striatal neurons, whereas U-69,593, a nonbiased KOR agonist, activated both kinases.[90] Those results suggested that G protein signaling activated Akt, whereas β-arrestin2 recruitment activated ERK1/2. Identification of KOR agonism's signaling pathways in endogenous systems would aid in the development of KOR-selective agonists. In 2016, 6′-GNTI was shown to not induce condition place avoidance, a measurement of aversive effects, while U-50,488, a nonbiased KOR agonist, was shown to do so.[91]

II.3.1.6. Collybolide

In 1974, Bui *et al.* isolated several sesquiterpene compounds with a furyl-δ-lactone motif from the fungus *Collybia maculate*, including collybolide, isocollybolide, epicollybolide, neocollybolide, and collybolidol.[92] Collybolide (**Figure 3A**) is structurally similar to the natural product salvinorin A from the plant *Salvia divinorum*. While salvinorin A was shown to be a nonbiased KOR agonist (see section **II.2.3.**), collybolide was discovered to be a G protein-biased KOR agonist.[93] While both collybolide and salvinorin A were equipotent in inhibiting the activity of adenylyl cyclase, collybolide exhibited 10–50 fold higher potency in activating the mitogen-activated protein kinase pathway than that of salvinorin A.[93] Collybolide was also shown to preferentially induce phosphorylation of Akt over phosphorylation of ERK.[93] In a direct comparison study to salvinorin A, collybolide showed a higher binding affinity but lower potency towards KOR (collybolide: K_i = 9 nM, EC_{50} = 2 nM; salvinorin A: K_i = 40 nM, EC_{50} = 0.2 nM).[93] Similar to salvinorin A, collybolide also displays high selectivity for KOR over MOR and DOR, and both compounds are thought to mediate their effects via selective and exclusive activation of KOR (K_i for MOR >5,000 nM and K_i for DOR >5,000 nM for both collybolide and salvinorin A).[61,93] In a mouse model, collybolide and salvinorin A displayed similar antinociceptive activity with peak activity at 20 min following i.p. injection.[93] Both compounds also displayed similar activity in the conditioned place

preference/aversion assay with single daily i.p. injections for 4 days leading to significant conditioned place aversion. Collybolide, however, was shown to be significantly better than salvinorin A in blocking pruritus (non–histamine-mediated itch).[93] A 2 mg/kg s.c. injection of collybolide significantly attenuated chloroquine-mediated scratching behavior in mice, while the same dose of salvinorin A did not.[93]

II.3.1.7. RB-64

RB-64 (also known as artasalvin or 22-thiocyanatosalvinorin A, **Figure 3A**) is a semi-synthetic derivative of salvinorin A. RB-64 was first synthesized in 2009 by Roth and coworkers[94] and later discovered to be a highly selective and potent KOR agonist.[78] In 2015, RB-64 was shown to be a G protein-biased KOR agonist, displaying high functional selectivity for G protein over β-arrestin recruitment by a factor of 96.[62] Along with salvinorin A, RB-64 has been widely used in scientific research to study and compare further signaling and specific effects between nonbiased KOR agonists and G protein-biased KOR agonists. For example, salvinorin A was shown to activate the Akt signaling pathway, promote cell survival, and attenuate oxygen-glucose deprivation (OGD)-induced cell injury, while a low concentration of RB-64 (where there was only G protein pathway activation without producing β-arrestin recruitment) did not.[95] These results suggested that KOR internalization through β-arrestin activation and Akt-mediated signaling pathway is a protective mechanism against OGD.[95] In a hot plate assay, administration of RB-64 to wild-type mice (3.0 mg/kg, s.c.) produced analgesia in as little as ten minutes, and the effects lasted for several hours.[62] As a G protein-biased KOR agonist, RB-64 was shown to have fewer side effects, such as motor incoordination and sedation, than the nonbiased KOR agonists U-69,593 and salvinorin A.[62] RB-64 is also famous for being the first and only known salvinorin-based agonist that forms a covalent bond with KOR.[62,94]

II.3.1.8. 16-Bromo Salvinorin A

In 2014, Prisinzano and coworkers synthesized and studied a series of salvinorin analogues with various substituents on the furan ring.[76] They discovered 16-bromo salvinorin A to be a selective and G protein-biased KOR agonist. 16-Bromo salvinorin A showed a similar binding affinity for KOR to those of salvinorin A and U-50,488 (16-bromo salvinorin A K_i = 2.9 ± 0.3 nM; salvinorin A K_i = 2.5 ± 0.6 nM; U-50,488 K_i = 2.2 ± 0.2 nM) and displayed a higher preference for G protein signaling over β-arrestin recruitment with a bias factor of 7.7 compared to that of U-50,488.[31] 16-Bromo salvinorin A displayed modest antinociceptive effects (1–2 mg/kg, i.p., warm water tail-withdrawal, hot plate, and intraplantar formaldehyde assays) and lacked anxiogenic effects (1–2 mg/kg, i.p., elevated zero maze and marble burying tests) in mice.[31] A single dose of 16-bromo salvinorin A (0.3 mg/kg, i.p.) was observed to attenuate cocaine-seeking behavior in rats without causing sedation or motor incoordination.[76] A higher dose of 16-bromo salvinorin A (1.0 mg/kg) also did not cause sedation or motor incoordination in rats.[76]

II.3.1.9. LOR17

Peptide derivatives of endogenous KOR agonists, such as dynorphin, have also been explored. In 2004 and 2016, Spampinato and coworkers synthesized a series of cyclic tetrapeptides and cyclic pentapeptides and studied their activities on different opioid receptors.[96–98] LOR17 (c[Phe-Gly-(β-Ala)-D-Trp], **Figure 3A**) was one of the newly discovered KOR agonists. In 2020, the authors further studied LOR17 and discovered it to be a selective and potent G protein-biased KOR agonist.[96] LOR17 showed higher binding affinity towards KOR (K_i = 1.19 nM) than to MOR (K_i = > 10^5 nM) and DOR (K_i = > 10^5 nM).[96] LOR17 is extremely G protein-biased with a bias factor of 853 over β-arrestin2 recruitment.[96] LOR17 showed antinociception in a dose- and time-dependent manner in mice (0–20 mg/kg, 0–90 min; s.c.) and significantly reduced oxaliplatin-induced thermal hypersensitivity with a single or repeated s.c. administration (1, 10, or 20 mg/kg). Additionally, in rotarod and hole-board tests, LOR17 (10 mg/kg, s.c.) did not show any effects on motor coordination, locomotor, or exploratory activities, and did not induce pro-depressant-like behavior in these mice.[96]

II.3.2. β-Arrestin-Recruitment-Biased KOR Agonists

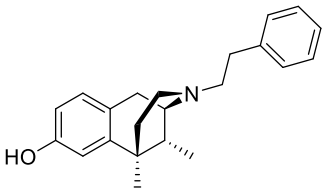
As mentioned above, due to their preference for mediating β-arrestin recruitment signaling, β-arrestin recruitment-biased KOR agonists often come with severe adverse effects, such as anhedonia/dysphoria, sedation, anxiety, and motor incoordination.[99,100] Therefore, they are the least desired KOR agonists in drug development. Fortunately, only a few β-arrestin recruitment-biased KOR agonists have been discovered so far.

II.3.2.1. Nalfurafine (TRK-820)

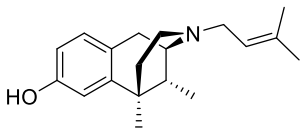
In 1998, Nagase *et al.* applied the "message-address concept" for opioid antagonists and the "accessory site" for general antagonists, both of which were new concepts at the time, and discovered nalfurafine (also known as TRK-820, **Figure 3B**), a 4,5-epoxymorphinan derivative, as a novel KOR agonist.[101] The "message-address concept" was based on the common core structure of several known opioid antagonists, including nor-BNI (KOR), naltrexone (MOR), and naltrindole (DOR). The concept was that the epoxymorphinan part of the structures (message) was responsible for the binding to the opioid receptors, whereas the other parts of the structures, the accessory site (address), were responsible for the selectivity towards specific subtypes of the opioid receptors. Nagase *et al.* used this strategy but to develop opioid receptor agonists and discovered nalfurafine. Nalfurafine showed good agonistic potency in both electrically stimulated guinea pig ileal lonitudinal muscle (IC_{50} = 0.0048 nM) and mouse vas deferens (IC_{50} = 0.036 nM), and good antinociceptive activity in mice in both the acetic acid-induced writhing (ED_{50} = 0.0033 mg/kg) and tail-flick assays (ED_{50} = 0.062 mg/kg).[101] Pretreatment with nalfurafine in male Swiss-Webster mice (0.001–0.03 mg/kg, s.c.) reduced the 5′-GNTI (0.3 mg/kg)-induced scratching in a dose-dependent manner.[102] In a conditioned place preference study in rats, low doses of nalfurafine (10–40 μg/kg) did not produce place preference nor place aversion.[103] Originally, nalfurafine was found to be G protein-biased with a bias factor of 7.73 compared to the nonbiased KOR agonist U-50,488 (GloSensor and Tango assays).[104] However, in another study, nalfurafine was found to be nonbiased with a bias factor of 1 compared to the nonbiased KOR agonist U-50,488 (β-galactosidase complement assay).[105] In 2019, Kreek and coworkers reported nalfurafine to be β-arrestin2-biased compared to the nonbiased KOR agonist U-69,593 (β-galactosidase complement assay). Nalfurafine exhibited a similar potency for KOR activation to that of U-69,593, but its β-arrestin recruitment was ~20-fold greater.[106] In 2009, nalfurafine was approved in Japan for the treatment of uremic pruritis.[107] It was the first selective KOR agonist to be approved for use on the market. Nalfurafine is currently in a phase III clinical trial in the U.S. for treatment-resistant pruritus in hemodialysis patients.[108] Recently, high doses of nalfurafine were found to result in significant place aversion in rats (at 80 μg/kg)[103] and locomotion impairment in mice (at 40 μg/kg).[102] Since the mediated signaling pathway of nalfurafine is still contested, many research groups are investigating the bias nature of this drug.

II.3.2.2. GR-89696

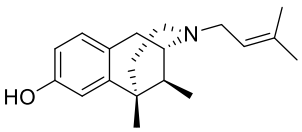
In 1993, Naylor *et al.* synthesized a series of 4-substituted 1-(arylacetyl)-2 [(alkylamino)methyl]piperazines and discovered GR-89696 (**Figure 3B**) as a potent new class of KOR agonists. GR-89696 showed good binding affinity (IC_{50} = 0.041 nM) in KOR-enriched rabbit vas deferens and antinociceptive activity in a mouse model (ED_{50} = 0.52 μg/kg, s.c.).[109] GR-89696 displayed a β-arrestin recruitment bias with a bias factor of 5, whereas the nonbiased KOR agonist U-69,593 displayed a bias factor of 1 (GloSensor and Tango assay).[78] Similar to the G protein-biased KOR agonist 6'-GNTI, GR-89696 also interacts with KOR/DOR heterodimer.[110] However, while 6'-GNTI and GR-89696 both interact with KOR/DOR heterodimers, GR-89696 is weakly β-arrestin recruitment-biased. Experimentally, the difference in bias between the KOR agonists 6'-GNTI and GR-89696 suggested that KOR/DOR heterodimers do not uniformly adopt a G protein-biased conformation.[38]



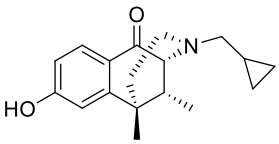
phenazocine



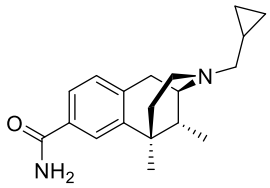
***(R)*-pentazocine**



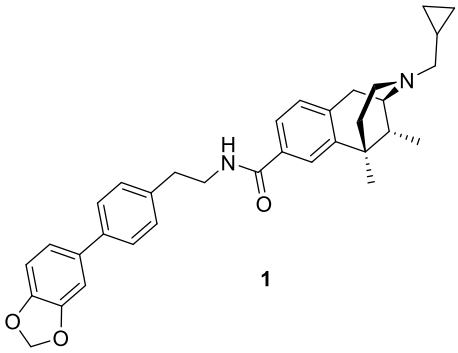
***(S)*-pentazocine**



ketazocine



8-CAC



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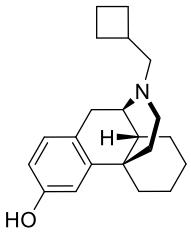
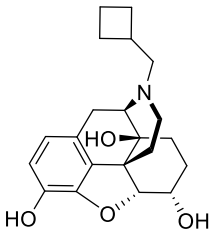
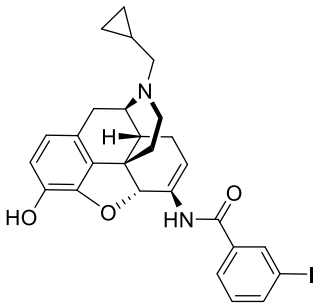


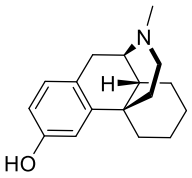
butorphan (MCL-101)



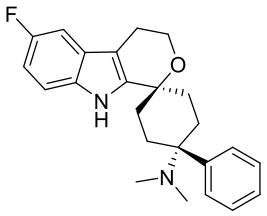
nalbuphine



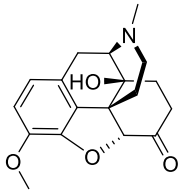
MP1104



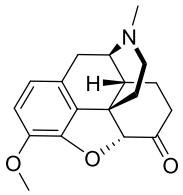
levorphanol



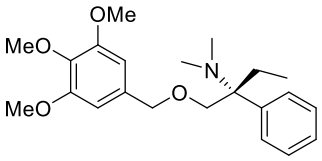
cebranopadol (GRT-60005)



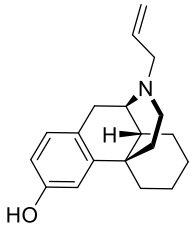
oxycodone



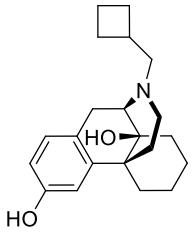
hydrocodone



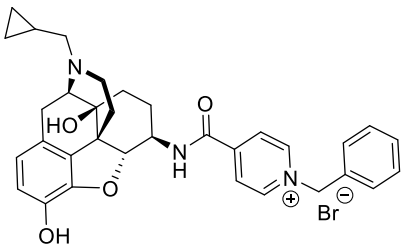
fedotozine



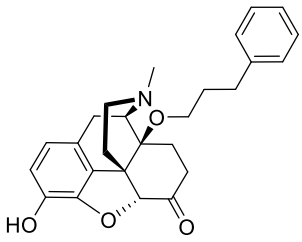
levallorphan



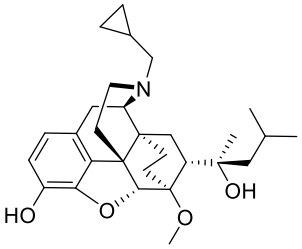
butorphanol



BNAP



POMO



2

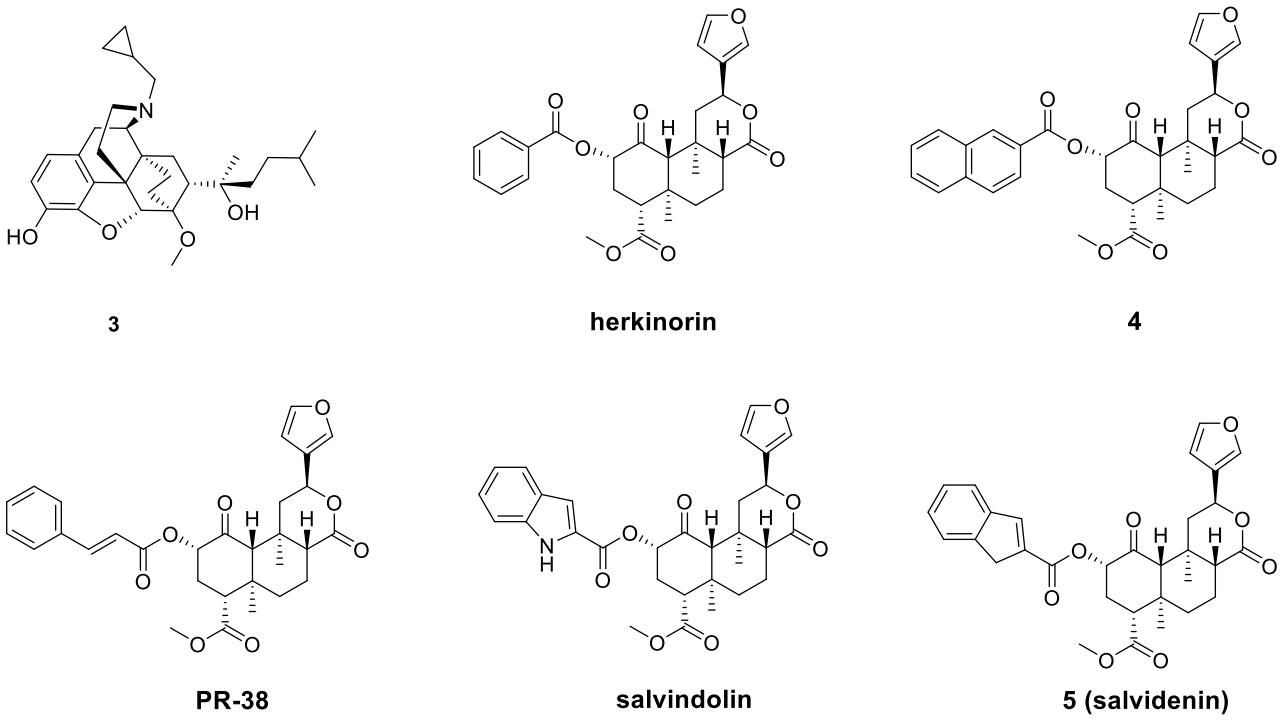


Figure 4: Structures of mixed KOR agonists

III. Mixed KOR Agonists

Besides their activity on KOR, many of the above KOR agonists, such as 6'-GNTI, collybolide, and nalfurafine, also displayed moderate activity on other opioid receptors. Thus, their overall behavioral effects could be a combination of the biased agonism on KOR and the mixed activity on other opioid receptors. There are other known KOR agonists whose functional biases on KOR have not been identified, but they display mixed agonism on KOR and agonism/antagonism on other opioid receptors. For example, recent studies have shown that mixed KOR agonists/MOR partial agonists have therapeutic potential in psychostimulant abuse, including cocaine,[111] whereas mixed KOR agonists/partial MOR antagonists are being developed as analgesics with balanced side-effect profiles and reduced tolerance.[112] Several dual KOR/MOR agonists and triple KOR/MOR/DOR agonists have produced strong antinociception and blocked cocaine-conditioned place preference in mice, while lacking the typical dysphoric or addictive properties of pure KOR or pure MOR agonists, respectively.[65,113–115]

III.1. Phenazocine

Phenazocine (**Figure 4**) is a first-generation benzomorphan-based analgesic. It was first synthesized by Eddy, May, and Ager in 1959.[116–118] Phenazocine was 20 times more potent than morphine and 70 times more potent than its (+)-isomer in eliciting analgesia in mice in a hot plate test.[116] The racemic mixture of phenazocine was shown to have only one-sixth the physical dependence potency of morphine in monkeys and produced a similar result for the relief of both acute and chronic pains in humans but at only about one-seventh the optimal dose of morphine.[116] The racemic mixture of phenazocine also came with fewer and less objectionable side effects than those of morphine.[116] Unfortunately, just like morphine, phenazocine still caused respiratory depression at higher doses, which was a concern for its clinical use.[119] In 1964, Harris and Pierson showed that the racemic mixture of phenazocine alleviated pain in an acetic acid-induced writhing assay in mice with an ED_{50} of 6.3 mg/kg (s.c.).[120] Additionally, researchers also showed that racemic phenazocine had efficacy in humans to treat postoperative pain, and was as efficacious as 10 mg/kg of morphine at a 0.25

mg/kg dose, although higher dosages of phenazocine led to excessive sedation and dysphoria.[120,121] In 1971, Hopton reported that the negative isomer, (-)-phenazocine was four times more potent than morphine at eliciting analgesia[122] and lacked considerable respiratory depression as a side effect.[123] In 2008, Wentland and coworkers determined phenazocine to be a potent KOR agonist with some moderate activity on MOR and DOR (K_i for KOR = 0.2 nM, K_i for MOR = 2 nM, K_i for DOR = 5 nM).[124] Due to its higher selectivity towards KOR, phenazocine causes dysphoria and hallucinations;[125] however, due to its moderate activity on MOR, phenazocine possesses fewer side effects than morphine.[122] Unlike morphine, usage of phenazocine does not result in negative mood effects.[120] Phenazocine has been used as a pain medication in the United States since the late 1970s, but it is now not commonly prescribed.[126] Phenazocine (brand name Narphen) was withdrawn from the United Kingdom market in 2001.[127]

III.2. Pentazocine

Pentazocine (**Figure 4**) is also a first-generation benzomorphan-based analgesic. Pentazocine was also first synthesized as a racemic mixture by Eddy, May, and Ager in 1959.[116–118] The mixture of pentazocine was determined to be two to six times less potent than morphine in eliciting analgesia in humans and was shown to be effective at mitigating postoperative pain in male patients within twenty minutes of i.m. injection in dosages from 20–40 mg.[128] Specifically (-)-pentazocine showed strong binding affinities towards KOR and MOR, but weaker binding affinity towards DOR (K_i for KOR = 7.6 nM, K_i for MOR = 3.2 nM, K_i for DOR = 62 nM), and was determined to be a potent dual KOR/MOR agonist with weak DOR agonism (EC_{50} for KOR = 40 nM, EC_{50} for MOR = 43 nM, EC_{50} for DOR = 255 nM).[129–131] Due to its strong preference for both KOR and MOR, the analgesic effects of pentazocine are thought to be mediated through both kappa and mu opioid receptor subtypes.[129,132] An apparent upper limit of analgesia or "ceiling effect" to the dose-response of pentazocine has been observed.[132,133] At higher dosages, pentazocine administration causes both typical side effects of KOR agonists (dysphoria and hallucination) and MOR agonists (sedation, respiratory depression, confusion, euphoria, agitation, itching, sweating, abdominal bloating, nausea, addiction liability, vomiting, and constipation).[134] An upper limit of side effects, such as respiratory depression, to the dose-response of pentazocine has also been observed.[120,134] Pentazocine was approved by the Food and Drug Administration (FDA) in June 1967 as a "nonaddictive" painkiller and has been sold under various brand names, including Talwin, Fortral, Sosegon, Fortwin, and Talacen.[135–139] The initial "nonaddictive" evaluation of pentazocine was later found to be incorrect, and it was scheduled to be a level IV controlled substance by the United States Drug Enforcement Administration (DEA) in 1979.[140] Pentazocine is currently prescribed to patients older than twelve years for moderate to severe pain and may also be used as a surgical anesthetic in some cases.[139]

III.3. Ketazocine (a.k.a. ketocyclazocine)

Ketazocine (a.k.a. ketocyclazocine) (**Figure 4**) is also a first-generation benzomorphan-based analgesic. Ketazocine was also first synthesized by Eddy, May, and Ager in 1959.[116–118] However, it was not further studied until 1976 when Gilbert and coworkers discovered that administration of ketazocine caused behavioral changes in canines that were markedly different from the behavioral changes caused by MOR or DOR agonists, but rather more consistent with the characteristics of a KOR agonist.[141] Administration of the MOR antagonist naltrexone was found to attenuate the effects of the potent MOR agonist morphine, but not those of ketazocine.[141] In 1980, Pasternak showed that a single dose of ketazocine at low concentrations inhibited acetic acid-induced writhings in naloxazone- and naloxone-treated mice (ED_{50} = 0.47 and 0.077 mg/kg, respectively).[142] In 2002, Holzgrabe and coworkers found that ketazocine was ~2.5–3 times more selective towards KOR than MOR or DOR (K_i for KOR = 0.21 nM, K_i for MOR = 0.6 nM, K_i for DOR = 0.5 nM).[143] The activity of ketazocine is lowest on DOR, which is consistent with other benzomorphans as benzomorphans

often have lower activities on DOR than on KOR and/or MOR.[144] Due to its higher preference for KOR than MOR, ketocyclazocine produced antinociceptive effects but avoided substantial addiction liability and severe respiratory depression,[141] which are common concerning characteristics of potent MOR agonists like morphine. However, ketazocine is not devoid of all adverse side effects; at dosages that elicited antinociception in rats, sedation and diuresis were also observed.[143]

III.4. 8-Carboxamidocyclazocine (8-CAC)

In 2001, Wentland, Bidlack, and coworkers explored different cyclazocine-based benzomorphan compounds by substituting the C8-hydroxyl group with different carboxamido groups and discovered 8-carboxamidocyclazocine (8-CAC, **Figure 4**) as a dual KOR/MOR agonist.[145] 8-CAC displayed equally strong binding affinity and efficacy towards KOR (K_i = 0.42 nM, EC_{50} = 8.8 nM) and MOR (K_i = 0.34 nM, EC_{50} = 4.9 nM), and slightly weaker binding affinity towards DOR (K_i = 0.42 nM, EC_{50} = 8.8 nM).[146] 8-CAC displayed antinociceptive effects in both tail flick (ED_{50} = 0.21 nmol, i.c.v.) and acetic acid-induced writhing tests (single dose of 1 mg/kg, i.p.) in mice.[146] 8-CAC displayed a notably longer antinociceptive duration of action in mice (~15 hours) compared to that of cyclazocine (~2 hours).[146] In addition to eliciting potent analgesia in mice, 8-CAC also decreased chronic self-administration of cocaine in rhesus monkeys with a single dose of 0.032–0.56 mg/kg, i.m.[147] Unfortunately, daily intramuscular injections of 8-CAC led to tolerance, and the dosages that decreased cocaine self-administration also decreased food-maintained responding.[147] The development of tolerance to 8-CAC and the decrease of food-maintained responding may limit the therapeutic potential of this mixed KOR agonist. In 2012, Wentland, Bidlack, and coworkers synthesized and studied many analogues of 8-CAC, specifically oxygenated *N*-(2-[1,1'-biphenyl]-4-ylethyl) analogues of 8-CAC.[148] Several of these analogues were discovered to be triple KOR/MOR/DOR agonists. However, most of these compounds showed a much higher preference for MOR (single-digit pM binding affinity) to KOR or DOR. The most potent compound of this series was the 3',4'-methylene-dioxy analogue **1** (**Figure 4**, K_i = 1.6 pM).[148] The analgesic effects of these compounds, which are likely mediated through MOR agonism, have not been studied.

III.5. Butorphan (MCL-101)

In 1999, Neumeyer and coworkers discovered butorphan (a.k.a. MCL-101, **Figure 4**) as a mixed KOR agonist.[149] It has higher binding affinity towards KOR than MOR or DOR (K_i for KOR = 0.079 nM, K_i for MOR = 0.23 nM, K_i for DOR = 5.9 nM).[144] Butorphan showed dual agonism on KOR and DOR but antagonism on MOR.[149] Butorphan displayed antinociception in both tail flick (ED_{50} = 7.3 nmol) and acetic acid-induced writhing tests (ED_{50} = 0.79 nmol) in mice. In rhesus monkeys, 7 days of chronic treatment of butorphan (0.0032–0.032 mg/kg/h) was observed to decrease cocaine self-administration and cocaine-maintained responding in a dose-dependent manner.[19]

III.6. Nalbuphine

In 1968, Pachter and Zaven synthesized and patented a series of *N*-substituted-14-hydroxydihydro-normorphines, one of which was nalbuphine (**Figure 4**).[20,150] Nalbuphine was later shown to be a mixed KOR agonist with strong binding affinity and potency towards KOR (K_i = 2.2 nM, EC_{50} = 27 nM) and MOR (K_i = 0.89 nM, EC_{50} = 14 nM), but low binding affinity towards DOR (K_i = 240 nM).[151] Nalbuphine showed strong antinociceptive effects in humans (ED_{50} = 5.85 mg and 0.5 mg for early phase pain and late phase pain, respectively)[152] and attenuated cocaine abuse in both rhesus monkeys and male humans.[24] In 1979, nalbuphine was approved in the United States as a pain medication.[20] Recently, in 2019, nalbuphine-6-glucuronide, a metabolite of nalbuphine, was found to exhibit a stronger analgesic response than that of nalbuphine in both Randall-Selitto and cold ethanol tests in rats.[153]

III.7. MP1104

In 2015, Majumdar and cowokers studied a series of 3-iodobenzoyl naltrexamine and discovered MP1104 (**Figure 4**) as a triple KOR/MOR/DOR

agonist.[113] Naltrexamine, a 6β-amido 14-OH epoxymorphinan derivative, is a highly potent MOR agonist.[113] MP1104 displayed strong binding affinity and potency towards all three classical opioid receptors KOR (K_i = 0.0064 nM), MOR (K_i = 0.021 nM), and DOR (K_i = 0.08 nM).[113] MP1104 produced 15-fold greater antinociception (ED_{50} = 0.33 mg/kg) than morphine in a tail flick test in mice.[113] In a place-conditioning paradigm, MP1104 (ED_{50} = 1 mg/kg) did not display place preference or aversion.[113] MP1104 (0.3 and 1 mg/kg, i.p.) also attenuated self-administration of cocaine in male Sprague-Dawley rats while lacking the typical dysphoric or addictive properties of pure KOR or pure MOR agonists, respectively.[154] Unlike pure MOR agonists, MP1104 did not produce respiratory depression, physical dependence, or cross tolerance to morphine.[154]

III.8. Levorphanol

Levorphanol (**Figure 4**) was first developed in the 1940s as an alternative to morphine as a pain killer and has been on the market in the United States since 1953.[21] Levorphanol was later discovered to be a triple KOR/MOR/DOR agonist (K_i for KOR = 2.3 nM, K_i for MOR = 0.21 nM, and K_i for DOR = 4.2 nM)[21–23] and has been used to treat acute and neuropathic pains as well as hyperalgesia.[21–23] The antinociceptive activity of levorphanol is likely the result of its activity on MOR rather than its activity on KOR or DOR; however, due to its activity on the latter opioid receptors, levorphanol displayed less respiratory depression compared to morphine.[21–23] Levorphanol has shown KOR agonism-mediated side effects, such as hallucination and delirium.[155]

III.9. Cebranopadol (GRT-60005)

In 2014, Schunk and coworkers discovered a series of spiro[cyclohexanepyrano[3,4-b]indole]-amines as nociceptin opioid receptor (NOR) and MOR agonists with strong efficacy in preclinical rat models of acute and neuropathic pains.[156] In the same year, the authors optimized the lead compound of the series to develop dual NOR/MOR agonists and discovered cebranopadol (also known as GRT-60005, **Figure 4**).[157] Cebranopadol showed activity on all three of the classical opioid receptors KOR, MOR, and DOR, as well as the more recently discovered opioid receptor NOR.[157] It showed partial agonism on KOR (K_i = 2.6 nM, EC_{50} = 17 nM), full agonism on MOR (K_i = 0.7 nM, EC_{50} = 1.2 nM), full agonism on DOR (K_i = 18 nM, EC_{50} = 110 nM), and "near-full" agonism on NOR (K_i = 0.9 nM, EC_{50} = 13 nM).[157,158] Cebranopadol displayed strong potency in mouse models of acute and neuropathic pains with minimal side effects.[157–160] It is currently in clinical development to treat severe chronic,[157] neuropathic,[157] lower back,[161] and cancer pains.[162]

III.10. Oxycodone and Hydrocodone

There are other mixed KOR agonists that only show weak activity on KOR, compared to their activities on other opioid receptors. For example, oxycodone and hydrocodone (**Figure 4**), two famous morphinan-based compounds, are considered selective and potent MOR agonists, despite their partial agonism on KOR. One of the most famous stories that involved MOR agonists is the lawsuit against the Sackler family for the false advertisement of oxycodone.[163] Oxycodone[164] (brand name OxyContin) and hydrocodone[165] are often prescribed as pain killers with analgesic effects lasting up to six hours. Unfortunately, the increase in oxycodone prescription and false advertisement as nonaddictive have directly initiated and fueled the ongoing opioid epidemic in the United States. The Sackler family, owners of Purdue Pharma LP, recently agreed to pay $6 billion to settle Purdue opioid lawsuits and filed bankruptcy, avoiding personal accountability for the opioid crisis.[166] As we now know, potent and selective MOR agonists are not considerably advantageous for research and clinical uses, particularly due to their problematic side effects.[167]

III.11. Other Mixed KOR Agonists in Development

Besides the aforementioned compounds, there are other more recently discovered mixed KOR agonists that are currently in basic research and clinical development:

Fedotozine (**Figure 4**), a triple KOR/MOR/DOR agonist,[168] effectively reduced

postprandial fullness and nausea in nonnuclear dyspepsia patients.[169] It reduced abdominal pain and bloating in both nonnuclear dyspepsia and irritable bowel syndrome (IBS) patients.[169,170] Fedotozine also relieved hypersensitivity to colonic distention in IBS patients.[171]

Levallorphan (**Figure 4**), a mixed KOR agonist/MOR antagonist, has been used to as an opioid analgesic and opioid antagonist/antidote.[172] Levallorphan can prevent or reverse the side effects of opioids, including respiratory depression, sedation, and hypotension.[172] Levallorphan can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine.[172] Currently, naloxone, a nonselective and competitive opioid receptor antagonist, is more commonly used than levallorphan to reverse the effects of opioids.[173] Levallorphan is often used in combination with opioid analgesics to reduce their side effects, and a very small dose of levallorphan used alongside a full MOR agonist can produce greater analgesia than the full MOR agonist alone.[174] Levallorphan is also used in combination with pethidine for labor pain.[175,176]

Butorphanol (**Figure 4**), a weak partial KOR agonist/partial MOR antagonist, has been used for the treatment of labor pain.[177] However, it caused hallucinations, dysphoria, and sedation.[178] Butorphanol (0.03–1 mg/kg/day) has also been shown to decrease cocaine self-administration in rhesus monkeys.[179] Several ester and ether analogues of butorphanol have also been developed and were found to have higher binding affinities towards KOR and MOR than those of butorphanol.[180] However, functionalities of these analogues at KOR and MOR have not been determined, and no further studies have been reported on these molecules.

6β-N-Heterocyclic substituted naltrexamine derivative BNAP (**Figure 4**), a derivative of naltrexamine, is a partial KOR agonist/MOR antagonist.[181] BNAP displayed higher binding affinities towards KOR (K_i = 3.46 nM) and MOR (K_i = 0.76 nM) than DOR (K_i = 722 nM).[181] BNAP reversed morphine-induced antinociception when administered intracerebroventricularly and antagonized morphine-induced contractions of the circular muscle in mice colon.[181] BNAP also inhibited acetic acid-induced abdominal stretching in chronic morphine-treated mice.[181] Due to its nature of a dual KOR agonist/MOR antagonist, BNAP may have a functional use in IBS patients.[181] No further studies have been reported on BNAP.

14-*O*-phenylpropyloxymorphone (POMO, **Figure 4**), an analogue of 14-*O*-methyloxymorphone (14-OMO), is a potent triple KOR/MOR/DOR agonist.[182] POMO showed partial agonism on KOR (K_i = 0.3 nM, EC_{50} = 0.38 nM), full agonism on MOR (K_i = 0.073 nM, EC_{50} = 0.082 nM), and full agonism on DOR (K_i = 0.13 nM, EC_{50} = 0.28 nM).[182] POMO produced antinociception (AD_{50} = 0.7 μg/kg) in a hot plate test in mice.[182] The antinociceptive activity of POMO is thought to be mediated via activation of MOR rather than KOR or DOR.[182] No further studies have been carried out on POMO.

Husbands and coworkers investigated a series of orvinols and discovered many compounds that were KOR agonists/MOR partial agonists.[111] However, these compounds showed a wide range of selectivity towards all classical opioid receptors.[111] Two compounds in this series, **2** and **3** (**Figure 4**), showed antinociceptive activity (ED_{50} = 0.02 mg/kg, s.c) in a *para*-phenylquinone (PPQ)-induced abdominal stretch assay.[111] Husbands and coworkers also discovered various 6β-cinnamoylamino derivatives of naltrexamine that were KOR agonists/MOR partial agonists.[183] These compounds may be of interest as treatment agents for cocaine abuse,[183] but no further research has been done on them.

Several analogues of salvinorin A have shown dual agonism on KOR and MOR, all of which are esters with a conjugated ring, an aromatic ring, or fused rings at C2. These compounds include herkinorin,[184] compound **4**,[185] PR-38,[71] salvindolin,[8] and compound **5**[65] (now known as salvidenin) (**Figure 4**). Herkinorin, discovered by Prisinzano and coworkers, showed an 8-fold preference towards MOR over KOR (K_i for KOR = 90 nM; K_i for MOR =12 nM)[184] and was found to produce antinociceptive effects in the rat formalin paw withdrawal test, a model for peripheral antinociception in inflammatory pain.[186] Compound **4**, also discovered by

Prisinzano and coworkers, showed a great decrease in binding affinities to both KOR and MOR (K_i for KOR = 5490 nM; K_i for MOR = 180 nM) compared to those of herkinorin.[185] No further studies have been done on compound **4**. Both PR-38 and salvindolin were discovered by Zjawiony and coworkers; PR-38 showed a 5-fold preference towards KOR over MOR, while salvindolin showed a 100-fold preference towards MOR over KOR.[8,71] Administration of PR-38 (10 mg/kg, twice daily, i.p.; or 10 mg/kg, twice daily, i.c.; or 20 mg/kg, once daily, p.o.) significantly attenuated trinitrobenzene sulfonic acid (TNBS)- and dextran sodium sulfate (DSS)-induced colitis in mice.[71] PR-38 also attenuated compound 48/80-induced itch responses in mice.[187] Salvindolin was evaluated in mouse models of nociception (acetic acid-induced writhing, formalin, and hot plate tests), depression (forced swim and tail suspension tests), and locomotor activity levels and anxiety (open field test). These experimental results showed that salvindolin had good oral bioavailability, antinociceptive, and antidepressive-like effects in mice, but without locomotor incoordination.[8] Salvidenin was recently discovered by Le and coworkers and demonstrated supraspinal thermal analgesic activity while avoiding anxiogenic effects in male C57BL/6NHsd mice.[65] Mice treated with salvidenin showed a significant increase in the latency to paw response in a hot plate test (single dose 2 mg/kg, i.p.) compared to vehicle-treated mice, which indicated antinociception, and showed a significant increase in the amount of time spent on the open arms in an elevated plus maze test (single dose 5 mg/kg, i.p.), which indicated anxiolysis.[65] Overall, these salvinorin-based dual KOR/MOR agonists have provided further strong evidence in support of the therapeutic advantages of mixed KOR agonists over selective ones.

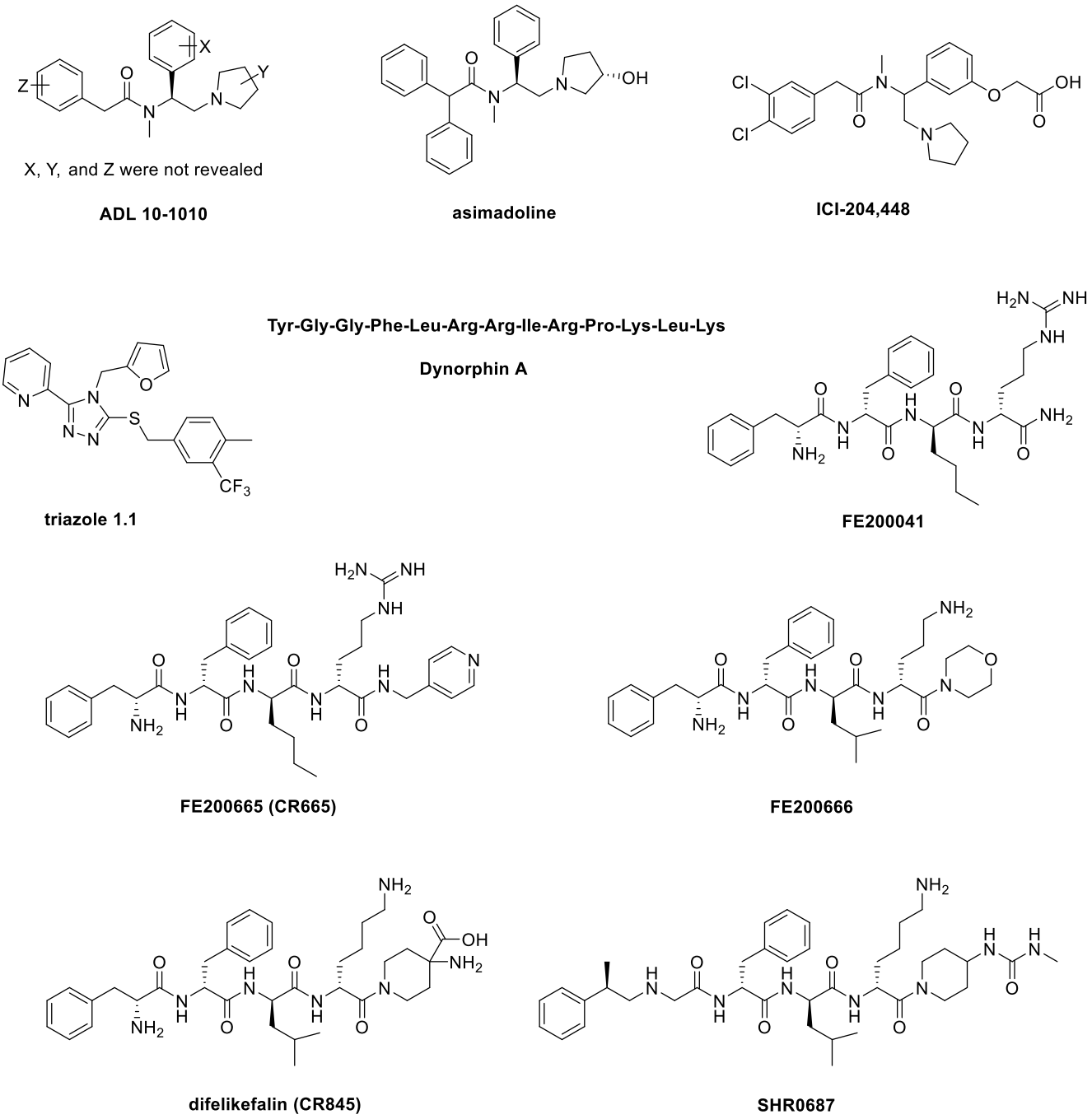


Figure 5: Structures of selective peripheral KOR agonists

IV. Selective Peripheral KOR Agonists (a.k.a. Peripherally Restricted KOR Agonists)

One strategy to avoid the sedative and dysphoric side effects of KOR agonists, which are mediated by the agonism of the receptors in the CNS, is to design and develop compounds that selectively target peripheral KOR. These compounds are often known as peripherally restricted KOR agonists,[188–194] but more accurately, selective peripheral KOR agonists.[195,196]

IV.1. ADL 10-0101

In 1999, Gottshall *et al.* discovered ADL 10-0101 (**Figure 5**) as a selective peripheral KOR agonist with a strong binding affinity and full agonism towards KOR (K_i and EC_{50} values on KOR, MOR, and DOR were not published).[188,193] ADL

10-0101 was shown to reduce visceral nociception induced by uterine cervical distension in rats.[193] In a randomized double-blind study, ADL 10-0101 or placebo was infused into six patients with chronic pancreatitis and ongoing abdominal pain despite being treated with MOR agonists.[197] The results showed that ADL 10-0101 reduced pain score from 63±7.6 (mean±SE) prior to infusion to 23±15 4 h after infusion.[197] ADL 10-0101 entered a phase II clinical trial; however, the initial data showed that patients, following treatment with ADL 10-0101, did not report statistically significant decreases in pain.[198] This result was attributed to the insufficient dose of ADL 10-0101 in the clinical trial.[198]

IV.2. Asimadoline (EMD-61753)

In 1994, Gottschlich *et al.* discovered asimadoline (a.k.a EMD-61753, **Figure 5**) as a novel diarylacetamide selective peripheral KOR agonist.[189,190] It has high binding affinity and selectivity towards KOR [IC_{50} values = 5.6 nM (guinea pig) and 1.2 nM (human recombinant), KOR:MOR:DOR binding ratio is 1:501:498 in human recombinant receptors].[189] Asimadoline has a low blood-brain barrier (BBB) penetration, which contributes to its lack of typical CNS KOR agonists' psychotomimetic effects,[190] such as sedation, putative aversion, diuresis, and antinociception.[199] Asimadoline was shown to reduce visceral pain and abnormal motility in mice[200] and in patients with diarrhea-predominant form of IBS (D-IBS).[200,201] Asimadoline is currently in a phase III clinical trial to treat patients with D-IBS.[200,201] In another study, Granados-Soto and coworkers found that a subcutaneous, intrathecal, and periaqueductal grey administration of asimadoline reduced tactile allodynia in rats.[202] These authors also performed the experiments to evaluate ICI-204,448 (**Figure 5**), which is another selective peripheral KOR agonist,[203] and the results showed that ICI-204,448 also reduced tactile allodynia in rats.[202] No further studies have been done on ICI-204,448.

IV.3. Triazole 1.1

In 2012, Aubé and coworkers performed a high-throughput screening on a library of ~290,000 compounds in the NIH Molecular Libraries Program on KOR and discovered many different sets of scaffolds that acted as either KOR agonists or KOR antagonists.[204] The authors called these sets of scaffolds chemotypes.[204] Further SAR studies on four of these chemotypes provided promising results for their future development into lead candidates or chemical tools targeting KOR.[204] One compound, triazole probe 1, was one of the newly discovered KOR agonists with a high binding affinity towards KOR (K_i = 2.4 nM) and very weak binding affinities towards MOR (K_i = 1900 nM) and DOR (K_i = 5351 nM).[100] Aubé and coworkers initially did not determine its binding efficacy; however, in 2013, the authors reported a series of five triazole analogues that activated KOR with a bias towards G protein signaling and minimal effects on β-arrestin2 recruitment and downstream ERK1/2 activation.[100] Triazole 1.1 (**Figure 5**) was the lead compound of this triazole series (EC_{50} in [^{35}S]GTPγS assay = 31 nM, EC_{50} in a β-arrestin2 enzyme fragment complementation assay = 4129 nM).[100] Compared to U-50,488, a nonbiased KOR agonist, triazole 1.1 is 28 times more biased towards G protein signaling.[29,100,205] In a mouse model, triazole 1.1 displayed antinociceptive and antipruritic effects without inducing sedation or dysphoria.[29,100] In male rhesus monkeys, triazole 1.1 did not induce motor coordination impairment or sedation.[206] In male rats, triazole 1.1 reduced oxycodone self-administration while enhancing oxycodone-induced thermal antinociception.[207] In male rhesus monkeys, triazole 1.1 produced weak sedative-like effects and reduced oxycodone-induced scratch.[208] Triazole 1.1 also had a reduced side-effect profile, both alone and in combination with oxycodone, in male rhesus monkeys.[208] While the analgesic effects and the lack of side effects of triazole 1.1 have been widely believed due to its G protein-biased agonistic activity on CNS KOR, in a recent letter, Beck *et al.* used the "Brain Or IntestinaL EstimateD" permeation method (BOILED-Egg), a highly accurate predictive model that works by computing the lipophilicity and polarity of small molecules to estimate biological barrier penetration, and found that triazole 1.1 had a limited capacity to cross the BBB.[209] Thus, these authors argued that the

analgesic activity of triazole 1.1 may be predominantly peripherally mediated.[209]

IV.4. Dynorphin A

Besides the aforementioned small molecules, there are many known peptides that act as selective peripheral KOR agonists. For example, dynorphin A (Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys, **Figure 5**) is a dynorphin, an endogenous opioid peptide that primarily acts as a KOR agonist, but also has some agonism at MOR, DOR, and *N*-methyl-D-aspartic acid (NMDA)-type glutamate receptor.[210,211] Dynorphin A exhibits both anti- and pro-nociceptive properties via activation of either KOR or NMDA receptor, respectively.[195] Dynorphin-(1-9), a truncated fragment of dynorphin A, also produced analgesic effects in a dose-dependent manner in mice (10–100 μg, administered into the spinal subarachnoid space).[212]

IV.5. FE200041

In 1998, Houghten and coworkers at Torrey Pines Institute for Molecular Studies conducted a high-throughput screening of a combinatorial library of 6,250,000 tetrapeptides using KOR, MOR, and DOR binding assays and discovered a lead tetrapeptide that showed high binding affinity and selectivity towards KOR (K_i for KOR <1 nM, MOR/KOR and DOR/KOR ratios = >3000).[213] In 2004, Riviere and coworkers further characterized this tetrapeptide, now called FE200041 (D-Phe-D-Phe-D-Nle-D-Arg-NH_2, **Figure 5**), by radioligand binding and functional assays and revealed FE200041 to be a selective peripheral KOR agonist.[214] In both rat and mouse models, this tetrapeptide displayed full antinociceptive effects (single dose 1 mg/kg, i.v.) without causing CNS KOR agonism-mediated side effects, such as sedation and motor impairment.[214] When FE200041 and the CNS KOR antagonist nor-BNI were coadministered (10 μg nor-BNI, i.c.v., right before systemic administration of FE-200041), the effects of FE200041 were not observed to be antagonized by nor-BNI.[214] Additionally, an intraplantar administration of FE200041 into the paw (10 μg/rat) in a radiant heat paw withdrawal assay resulted in full antinociceptive effects, whereas contralateral administration of FE200041 into the paw (10 μg/rat) did not have any effects on paw withdrawal latency.[214] These results have suggested that FE200041 acted as a selective peripheral KOR agonist *in vivo*.

IV.6. FE200665 (a.k.a. CR665)

In 1999, at the fourth international congress of the Polish Neuroscience Society, Houghten and coworkers reported data for two tetrapeptides from the above library, FE200665 (D-Phe-D-Phe-D-Nle-D-Arg-NH-4-picolyl, now known as CR665) and FE200666 (D-Phe-D-Phe-D-Leu-D-Orn-morpholine amide) (**Figure 5**), that displayed high affinity and selectivity towards KOR (K_i of FE200665 for KOR = 0.24 nM, K_i of FE200666 for KOR = 0.08 nM, MOR/KOR and DOR/KOR ratios for both = >85,000).[191,215,216] In 2001, Rivière and coworkers further studied these two tetrapeptides and discovered them to be selective peripheral KOR agonists (EC_{50} of FE200665 = 0.08 nM, EC_{50} of FE200666 = 0.03 nM).[191,192] Both compounds demonstrated dose-related antinociception in a mouse acetic acid-induced writhing test [median effective antinociceptive dose (A_{50} value) for FE200665 = 0.007 mg/kg, A_{50} value for FE200666 = 0.013 mg/kg, i.v.].[192] Only at very high doses would FE200665 and FE200666 induce centrally mediated effects, such as motor impairment in a rotarod assay (548 and 182 times higher doses, respectively) and antinociception in a tail flick test (>1429 and 430 times higher doses, respectively) after peripheral administration, thus supporting the peripheral mechanism of action of these two compounds. FE200665 was later shown to reduce visceral pain in humans[217] and is currently being developed in clinical trials by Cara Therapeutics as a pain drug candidate.[192] In a small blinded study in healthy humans, FE200665 (CR665) showed analgesic effects at 0.36 mg/kg i.v. dose, which was comparable to a 15 mg oral dose of oxycodone.[217] CR665 was observed to reduce visceral pain, but conversely also increased pain sensitivity to a skin pinch test.[217]

IV.7. Difelikefalin (a.k.a. CR845 or FE202845)

In 2008, Cara Therapeutics presented a poster, titled “Preclinical Profile of CR845: A Novel,

Long-Acting Peripheral Kappa Opioid Receptor Agonist" at the International Association for the Study of Pain (IASP).[218] CR845 (D-Phe-D-Phe-D-Leu-D-Lys-[γ-(4-*N*-piperidinyl)amino carboxylic acid], **Figure 5**), now known as difelikefalin, was presented as a highly selective peripheral KOR agonist (K_i for KOR = 0.32 nM, K_i values for MOR and DOR = >10,000 nM). In male CD1 mice, CR845 was shown to reduce pain in an acetic acid-induced writhing test (ED_{50} = 0.07 mg/kg, i.v.), a dibutyltin dichloride (DBTC)-induced pancreatitis test (ED_{50} = 0.3 mg/kg, i.p. or i.v.), complete Freund's adjuvant (CFA)-induced inflammatory pain test (ED_{50} = 0.3 mg/kg, i.p. or i.v.), and neuropathic pain Chung model (ED_{50} = 0.38 mg/kg, i.v.). CR845 also significantly inhibited scratch behavior in a 48/80- or 5'-GNTI-induced pruritus itch mouse model (ED_{50} = 0.08 mg/kg, i.v.). However, these results presented in the poster have not been peer-reviewed.[218] CR845 has been in multiple phase 2/3 clinical trials for postoperative analgesia and uremic pruritus (intravenous formulation)[219] and chronic osteoarthritis pain (oral formulation).[220] In 2021, CR845 was approved in the United States under the brand name Korsuva for the treatment of moderate-to-severe pruritus in patients with hemodialysis.[221]

IV.8. SHR0687

In 2020, Li and coworkers performed an SAR study on the structure of difelikefalin (CR845) and discovered SHR0687 (**Figure 5**) as a highly potent and selective peripheral KOR agonist (EC_{50} for KOR = 0.53 pM, EC_{50} values for MOR and DOR = >50,000 nM).[222] SHR0687 displayed favorable pharmacokinetic (PK) profiles across different species (mice, rats, canines, and humans) and exhibited negligible BBB penetration. SHR0687 also reduced pain in a rat carrageenan-induced inflammatory pain model even with a single dose as low as 0.03 mg/kg, i.v.[222] Overall, SHR0687 has high potential as a pain therapeutic with marginal CNS-related side effects.

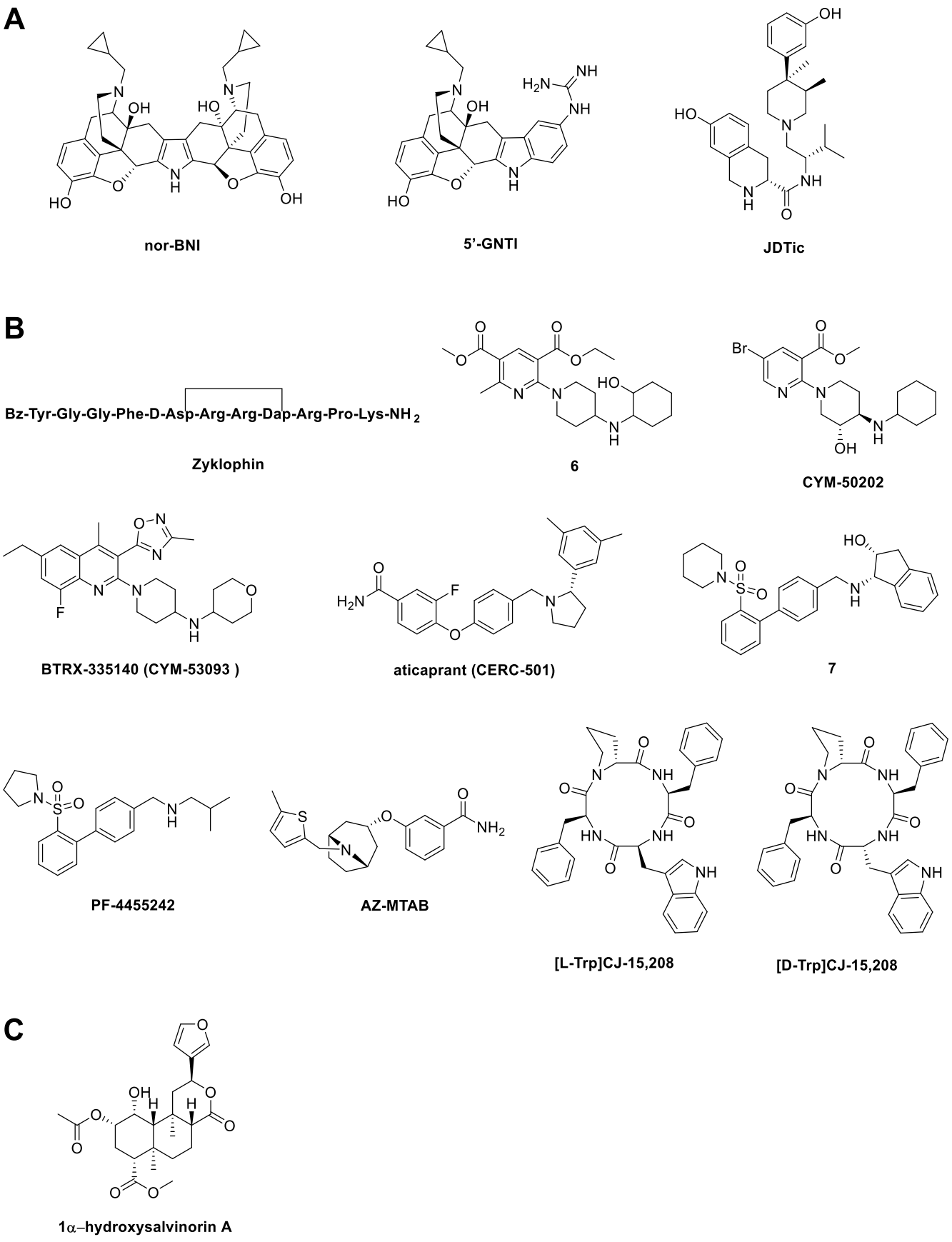


Figure 6. Structures of long-acting KOR antagonists (**A**), intermediate-acting KOR antagonists (**B**), and a short-acting KOR antagonist (**C**)

V. KOR Antagonists

V.1. Long-Acting KOR Antagonists (a.k.a. Receptor-Inactivating KOR Antagonists)

Norbinaltorphimine (nor-BNI), JDTic, and 5'-guanidinonaltrindole (5'-GNTI) are prototypical KOR antagonists and have been studied for the treatment of various neuropsychiatric conditions, including depression, anxiety, substance abuse disorders,[12–16] and anhedonia in the absence of substance use disorders.[223] Unfortunately, these KOR antagonists induce KOR antagonism that is delayed by hours and extremely prolonged. These antagonists can remain in the brain for up to 21 days[224] and their pharmacodynamic activities can persist long after the compounds were eliminated from the body. A single injection of nor-BNI in humans can block the effects of KOR agonists for a couple of months.[12,225] Therefore, these long-acting KOR antagonists are often considered KOR inactivators due to their long-term effects, even though they do not chemically alter KOR. While the reasons for the extraordinarily long duration of action of these KOR antagonists have not yet been understood, there are serious safety concerns about the use of these compounds in humans because they possess a large window for potential drug-drug interactions.[12] In addition, these compounds promote desensitization and potential tolerance in the treatment of drug abuse, and complications in preclinical assessment in paradigms that require multiple administrations.[12] Furthermore, since their persistent pharmacodynamic activities can hinder the ability to instantly reverse unanticipated side effects, the use of these compounds can lead to detrimental results when serious side effects occur.[12]

V.1.1. Norbinaltorphimine (nor-BNI or nBNI)

In 1982, Portoghese and coworkers developed a series of opioid antagonists using a bivalent design approach in which two β-naltrexamine units were connected to each other via an oxyethylene linker[226] (see section VII for other bivalent KOR ligands). The results indicated that bivalent ligands with different linker lengths exhibited different selectivities towards KOR, MOR, and DOR.[226] In 1984, the authors further evaluated triethyleneglycolnaltrexamine (TENA), one of the above bivalent β-naltrexamine ligands, along with other opioid antagonists for their selectivity in antagonizing the effects of KOR, MOR, and DOR agonists in guinea pig ileum and mouse vas deferens tissues.[227] The results showed that TENA was the most selective KOR antagonist reported at the time. From their studies, Portoghese and coworkers observed that very short linkers increased the selectivity of the bivalent opioid antagonists towards KOR.[228] In 1987, the authors synthesized binaltorphimine (BNI) and norbinaltrophimine (nor-BNI, **Figure 6A**), two bivalent ligands that contained two naltrexone units connected to each other via a pyrrole linker.[228–230] Both of these compounds were shown to be highly selective and potent KOR antagonists, exhibiting even higher selectivities towards KOR than that of TENA.[228–230] Until now, nor-BNI has been used as a prototypical selective KOR antagonist. It showed slow onset and long duration of action (~weeks) *in vivo* models including pigeons,[231] mice,[232–234] and rhesus monkeys.[235,236] nor-BNI (3.2 or 10.0 mg/kg, intramuscular) did not significantly alter cocaine choice or extended-access cocaine intake in rhesus monkeys.[237] However, nor-BNI was shown to reduce spontaneous cocaine withdrawal behaviors in mice[17] and attenuate the development of depressive-like behaviors induced by cocaine withdrawal in rats.[238] nor-BNI also decreased morphine withdrawal and the resulting conditioned place aversion in rats.[239]

V.1.2. 5'-Guanidinonaltrindole (5'-GNTI)

In 1993, Portoghese and coworkers applied the "message-address concept" for opioid antagonists and reported a dramatic and unprecedented change in the selectivity from DOR to KOR by simply modifying NTI with a basic alkylamidino group, which functioned as a KOR address.[240] They discovered several 5′-[(N^2-alkylamidino)methyl]naltrindole derivatives as a novel class of KOR antagonists.[240] 5'-GNTI (**Figure 6A**), the best compound of the series,[240] exhibited >500 times higher selectivity and 5 times greater potency in antagonizing the effects of KOR agonists than those of nor-BNI in smooth muscle preparations, including guinea pig ileal longitudinal muscle and mouse vas deferens

tissues.[241] Similar to nor-BNI, 5′-GNTI showed slow onset and long duration of action in rhesus monkeys (up to 10 days for nor-BNI and up to 14 days for 5′-GNTI).[242–244] Unlike nor-BNI, 5′-GNTI also acts as a positive allosteric modulator of the α_{1A}-adrenergic receptor.[244]

V.1.3. JDTic

In 2003, Carroll and coworkers applied the "message-address concept" and discovered (3*R*)-7-hydroxy-*N*-{(1*S*)-1-{[(3*R*,4*R*)-4-(3-hydroxyphenyl)-3,4-dimethyl-1 piperidinyl]methyl}-2- methylpropyl}-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide (JDTic, **Figure 6A**) as the first potent KOR antagonist that was not derived from the opiate class of compounds.[245,246] The (3*R*,4*R*)-3,4-dimethyl-4-(hydroxyphenyl)piperidinyl group in JDTic represented the message, and the basic amino and phenol groups in the *N*-substituent constituted the address.[246] The authors also performed an SAR study of JDTic analogues, which suggested that the potency and selectivity towards KOR were the results of a combination of (a) the isoquinoline amino group and 7-hydroxy group held in a rigid orientation by the 1,2,3,4-tetrahydroisoquinoline structure in its 3*R* attachment to the amide carboxyl, (b) an *S* configuration of the 2-methylpropyl group in the linker between the piperidine ring and the D-hydroxy Tic acyl group, and (c) the lack of a substituent on the amide nitrogen.[246] Functional assay and *in vivo* studies showed that JDTic was a potent long- and orally-acting selective KOR antagonist.[246,247] A time-course study of JDTic, p.o., versus enadoline revealed that JDTic produced significantly long antagonistic activity, up to 28 days.[247] Meanwhile, JDTic, s.c., did not antagonize the analgesic effects of the selective MOR agonist sufentanil.[247] JDTic has demonstrated therapeutic potential for the treatment of depression,[248] stress,[249,250] morphine addiction,[251] and cocaine addiction.[250] JDTic entered phase I clinical trial for cocaine use; however, the clinical trial was later discontinued due to adverse effects.[15,252]

V.2. Intermediate-Acting KOR Antagonists

KOR antagonists that have shorter durations of action (~days) than those of nor-BNI, JDTic, or 5'-GNTI are currently being developed and studied as they possess more favorable drug profiles. These compounds, including aticaprant, PF-4455242, and AZ-MTAB (**Figure 6B**), have shown promising results for the treatment of depression and substance use disorders in various preclinical models.[12,253]

V.2.1. Zyklophin

Dynorphin A is a dynorphin, an endogenous opioid peptide that primarily acts as a KOR agonist, but also has some agonism at MOR, DOR, and *N*-methyl-D-aspartic acid (NMDA)-type glutamate receptor.[210,211] The C-terminal domain of dynorphin A is known to have a marked effect on the efficacy of the peptide on KOR.[210,211] In 2005, Aldrich and coworkers applied the "message-address concept", exploring modifications in the C-terminal domain of dynorphin A to assess the modification-efficacy relationships, and discovered zyklophin (**Figure 6B**), a cyclic analogue of dynorphin A, as a selective KOR antagonist.[254,255] Zyklophin is metabolically stable and has a good BBB permeability.[256] The antagonistic activity of zyklophin (3 mg/kg, s.c.) against the KOR agonist U-50,488 lasted less than 12 h in mice, which contrasted sharply with the exceptionally long duration of antagonism reported for long-acting KOR antagonists, such as nor-BNI, that lasted weeks after a single administration.[256] Zyklophin (3 mg/kg, s.c.) also prevented stress-induced reinstatement of cocaine-seeking behavior in a conditioned place preference (CPP) assay.[256]

V.2.2. BTRX-335140 (a.k.a. CYM-53093)

In 2014, Roberts, Rosen, and coworkers performed a high-throughput screening using the Molecular Libraries−Small Molecule Repository (MLSMR) to identify novel selective KOR antagonists with desirable pharmacokinetic and pharmacodynamic properties.[257] They discovered compound **6** (**Figure 6B**) as a weak KOR antagonist (IC_{50} = 410 nM) with an 11-fold preference of selectivity for KOR over MOR (IC_{50} for MOR = 4590 nM).[257] In 2019, the authors carried out SAR investigations of compound **6** to increase the potency and selectivity and discovered CYM-50202 (**Figure 6B**) as a potent

KOR antagonist (IC_{50} = 12.6 nM) with a 27-fold preference of selectivity for KOR over MOR and a 278-fold preference of selectivity for KOR over DOR.[258] Further optimization led to the discovery of CYM-53093 (a.k.a. BTRX-335140, **Figure 6B**) as a potent and selective KOR antagonist (IC_{50} = 0.8 nM) with a 138-fold preference of selectivity for KOR over MOR and >8,000-fold preference of selectivity for KOR over DOR.[258] BTRX-335140 displayed favorable *in vitro* ADMET and *in vivo* pharmacokinetic profiles.[258] Unlike nor-BNI, BTRX-335140 showed a shorter duration of action in blocking KOR agonism *in vivo*.[258] A single dose of BTRX-335140 (1 mg/kg, i.p.) blocked the antinociceptive effects of the KOR agonist U-50,488 in mice with 1 h pretreatment time, but not with 24 h pretreatment time.[258] Oral administration of BTRX-335140 showed robust efficacy in antagonizing the effects of the KOR agonist U-69,593 in prolactin secretion and in tail-flick analgesia in mice.[258] BTRX-335140 has also shown benefits for the treatment of several neuropsychiatric disorders. For instance, BTRX-335140 has entered a Phase II clinical trial for major depressive disorder (MDD).[259]

V.2.3. Aticaprant (a.k.a. CERC-501, LY2456302, or JNJ-67953964)

In 2009, scientists at Eli Lilly patented a series of novel selective KOR antagonists.[260] In 2011, they reported the synthesis and biological evaluation of these compounds, one of which was aticaprant (a.k.a CERC-501, LY2456302, or JNJ-67953964, **Figure 6B**).[261] Aticaprant, an aminobenzyloxyarylamide, showed a high potency in antagonizing the effects of the KOR agonist U-69,593 in [^{35}S]GTPγS binding assay (K_b = 0.813 nM) with a 21-fold preference of selectivity for KOR over MOR and a 135-fold preference of selectivity for KOR over DOR. In 2013, the scientists at Eli Lilly further studied aticaprant in animal models and demonstrated it to be a novel, potent, and orally bioavailable KOR antagonist with therapeutic potential for mood and addictive disorders.[262] Aticaprant showed good oral bioavailability (F = 25%), rapid absorption (t_{max} = 1–2 h), great efficacy (ED_{50} = 0.33 mg/kg), and excellent selectivity towards KOR.[262] Aticaprant blocked KOR agonist-mediated analgesia but did not block MOR agonist-mediated effects at doses >30-fold higher than that of aticaprant.[262] Notably, one week after administration, aticaprant did not block KOR-agonist-induced analgesia, which indicated a lack of long-lasting pharmacodynamic effects.[262] In a mouse forced swim test, aticaprant showed antidepressant-like effects and enhanced the effects of the antidepressants imipramine and citalopram.[262] Aticaprant also reduced ethanol self-administration in alcohol-preferring rats and did not produce significant tolerance after 4 days of repeated dosing.[262] Aticaprant (an oral dose of 10 mg) was studied for cocaine dependence in a stress-minimized inpatient setting, but the results showed no significant changes in measures of depression or cocaine craving.[263] In a human laboratory model of smoking behavior, aticaprant did not affect cigarette craving, mood, anxiety, nicotine withdrawal, or subjective effects of smoking.[264] Nevertheless, aticaprant entered a clinical trial for mood and anxiety spectrum disorder[265] and a clinical trial for stress precipitated smoking lapse;[266] the results of these two clinical trials have not been reported. Aticaprant also advanced to phase II clinical trials as an augmentation of antidepressant therapy for treatment-resistant depression; unfortunately, the clinical trials were later terminated due to slow enrollment.[267] Besides aticaprant, several other aminobenzyloxyarylamides were also found to have high binding affinity and selectivity for KOR.[261]

V.2.4. PF-4455242

In 2011, scientists at Pfizer reported a high-throughput screening that resulted in a novel biphenylamine KOR antagonist (compound **7**, **Figure 6B**) with favorable potential drug-like properties.[268] Parallel chemistry coupled with physicochemical property design was performed to study the SARs of **7**, and a series of selective KOR antagonists was discovered.[268] One of those compounds was PF-4455242 (**Figure 6B**), which displayed a >20-fold selectivity for KOR over MOR.[268] In a mouse tail flick test, PF-4455242 was observed to block the analgesic effects of the KOR agonist U-50,488 (ED_{50} = 0.67 mg/kg, s.c.) and the MOR agonist morphine (ED_{50} = 12

mg/kg, s.c.).[268] PF-4455242 displayed good BBB penetration in rats ($AUC_{0–4h}$ free brain/free plasma = ∼1) with no evidence of impairment for the compound to cross the BBB.[268] PF-4455242 showed high clearance in rats and moderate clearance in both dogs and monkeys.[268] PF-4455242 also showed moderate clearance *in vitro* human hepatocytes.[268] In a mouse forced swim test, PF-4455242 demonstrated antidepressant-like efficacy with a minimal effective dose of 3.2 mg/kg, s.c.[269] In a social defeat stress assay, mice pretreated with PF-04455242 showed a day-dependent reduction in time spent in socially defeated immobile postures compared with vehicle-pretreated animals.[269] PF-4455242 also showed benefits in preventing cocaine-seeking behavior in a CPP assay in mice (pretreated with 1 mg/kg PF-4455242, s.c.).[269] Because of these promising data, PF-4455242 entered a phase I clinical trial for the treatment of bipolar disorder and was studied as a treatment for depression and substance abuse.[270] However, its development was later stopped due to toxicology findings in animals that had been exposed to the drug for three months.[270]

V.2.5. AZ-MTAB

In 2010, Brugel and coworkers discovered a series of novel bisamide alkoxypiperidines as highly potent and selective KOR antagonists via virtual and biological assay screenings.[271] AZ-MTAB (**Figure 6B**) was the lead compound of the series (IC_{50} = 20 nM) with 37 times more selectivity towards KOR than MOR and 415 times more selectivity towards KOR than DOR.[271] AZ-MTAB displayed a favorable pharmacokinetic profile with clearance being 113 mL/min/kg, half-life being 1h, and brain:plasma distribution ratio being 1.7.[271] AZ-MTAB was observed to reverse the diuresis (ID_{50} = 6.0 μmol/kg, s.c.) stimulated by the KOR agonist U-50,488 (2.5 mg/kg, s.c.) in rats.[271] Prior administration of AZ-MTAB (30 μmol/kg, s.c.) was observed to reverse behavior deficits in rats caused by prenatal stress in an elevated plus maze assay.[272] These results suggested the anti-anxiety potential of AZ-MTAB.[272]

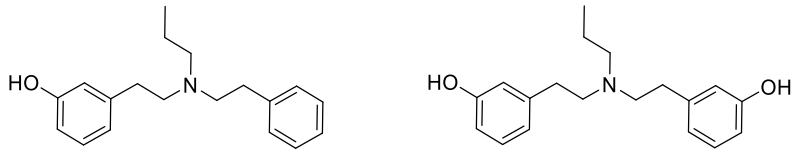
V.2.6. CJ-15,208

Besides small molecule KOR antagonists, such as those mentioned above, there are several known peptides that displayed antagonistic activity towards KOR. One of such peptides is CJ-15,208, which was isolated by Saito and coworkers from the fungus *Ctenomyces serratus* in 2002.[273] CJ-15,208 (**Figure 6B**) is a macrocyclic tetrapeptide that acts as a potent and selective KOR antagonist.[273] The *L*- (natural product) and *D*-Trp (unnatural product) stereoisomers of CJ-15,208 have been synthesized by different research groups.[274–276] Interestingly, in one study in 2012, the [*D*-Trp]CJ-15,208 isomer produced the expected selective KOR antagonism in mice, while the [*L*-Trp]CJ-15,208 isomer demonstrated mixed agonistic activity mediated by both KOR and MOR in addition to selective KOR antagonism.[277] The [*D*-Trp]CJ-15,208 isomer also blocked stress-induced reinstatement of extinguished cocaine CPP in mice, consistent with the results with other selective KOR antagonists, including arodyn and zyklophin.[277] However, in another study in 2013, the [*D*-Trp]CJ-15,208 isomer displayed weak KOR agonistic activity in addition to the short-duration KOR antagonism.[278] Pretreatment with [*D*-Trp]CJ-15,208 (s.c. or p.o.) in mice antagonized the antinociception induced by U-50,488 (10 mg/kg, i.p.) in a dose-dependent manner.[278]

V.3. Short-Acting KOR Antagonists

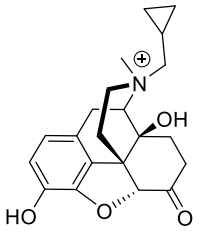
There are many examples in the literature, such as those of histamine and epinephrine analogues, where many agonists and antagonists (often, competitive antagonists) share similar structures.[87] Without eliciting a biological response, an antagonist can simply bind to a site near enough to the agonist's binding site and physically block the agonist from reaching the binding site. By appropriate structural modifications, sometimes relatively minor modifications, an agonist can be transformed into an antagonist.[87] As mentioned above, salvinorin A is an interesting non-opiate KOR agonist that has been used as an important prototype for the development of related drug candidates targeting different opioid receptors. In 2007, Prisinzano and coworkers synthesized many salvinorin compounds with modifications at the C1 ketone to explore the effects at this position.[73]

They discovered six compounds that showed antagonistic activity on opioid receptors, five of which were antagonists at KOR, MOR, and DOR, and one of which was an antagonist at MOR and DOR, but a partial agonist at KOR. Until now, these compounds are the only salvinorin-based antagonists of opioid receptors; all other reported salvinorin-based compounds are agonists. In 2022, Le and coworkers studied the most potent and selective KOR antagonist of these compounds, 1α-hydroxysalvinorin A (**Figure 6C**), on C57BL/6N mice for spontaneous cocaine withdrawal and compared it with the long-acting KOR antagonist nor-BNI.[65] Their studies showed that administration of 1α-hydroxysalvinorin A (5 mg/kg, i.p.) reduced spontaneous cocaine-withdrawal behaviors comparable to nor-BNI (5 mg/kg, i.p.).[65] Notably, 1α-hydroxysalvinorin A produced anti-anxiety-like effects in the light-dark transition test that was not observed with nor-BNI (both 5 mg/kg, i.p.).[65] Assessment of pharmacokinetics showed 1α-hydroxysalvinorin A to be a short-acting compound with an average half-life of 3.75 h across different compartments (brain, spinal cord, liver, and plasma).[65] In-depth computational studies, including induced-fit docking, computational mutagenesis, and molecular dynamics simulations, suggested alteration at C1 and C10 or concurrent modification at C2 of the salvinorin structure could provide a novel strategy for the design and development of selective short-acting KOR antagonists.[65]



RU 24213 RU 24926

Figure 7. Structures of mixed KOR antagonists



methylnaltrexone

Figure 8. Structure of methylnaltrexone, a selective peripheral MOR antagonist

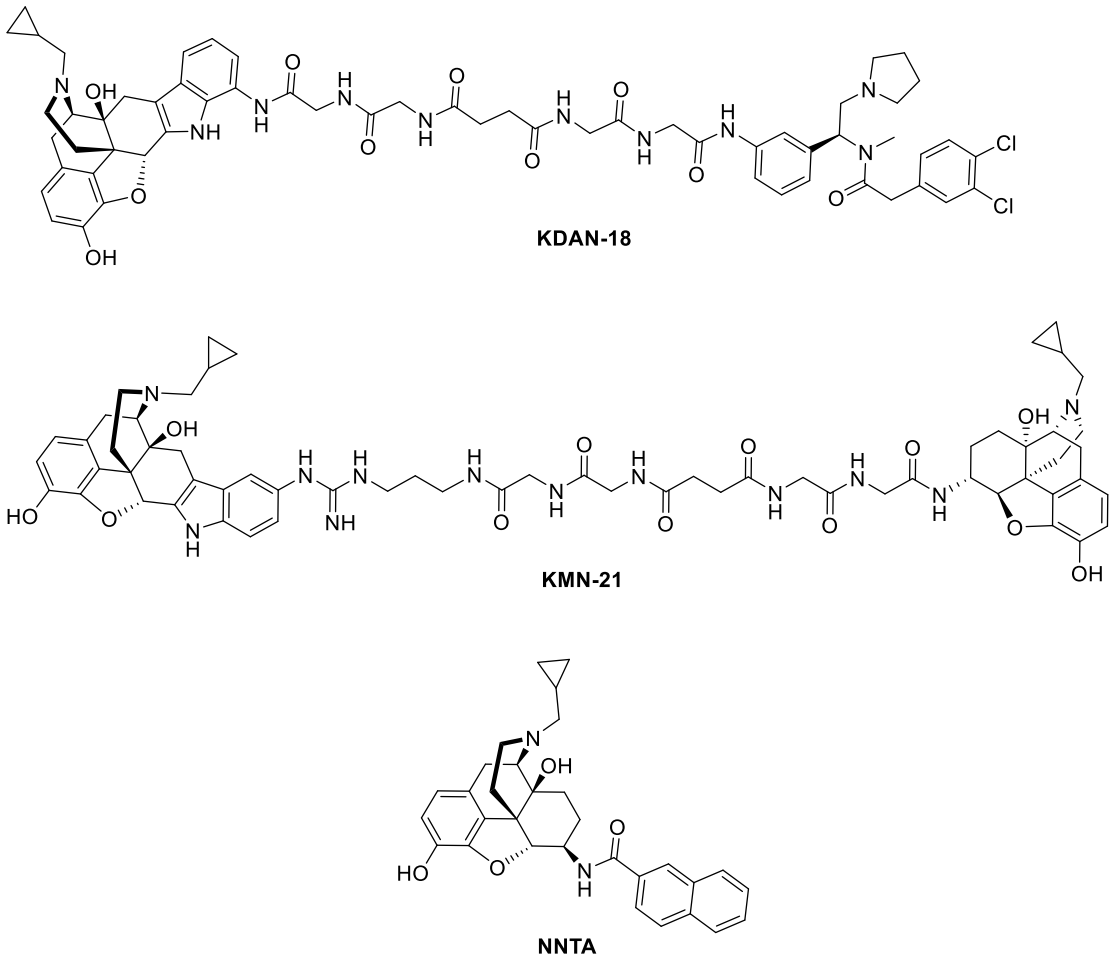


Figure 9. Structures of representative bivalent KOR ligands. KDAN-18 is a bivalent ligand that targets KOR (agonistic) and DOR (antagonistic). KMN-21 is a bivalent ligand that targets KOR (antagonistic) and MOR (antagonistic). *N*-naphthoyl-β-naltrexamine (NNTA) is a selective heteromeric KOR/MOR agonist.

V.4. Mixed KOR Antagonists

Until now, only a small number of mixed KOR antagonists have been discovered. RU 24213 and RU 24926 (**Figure 7**), two *N*-diphenethylamine compounds, were initially known and widely used as selective dopamine D_2 receptor agonists from the early 1980s.[279] Later, in the early 1990s, these two compounds were reported to also display antagonistic activity at KOR.[280] RU 24926 also showed low binding affinity and weak antagonistic activity at MOR.[280] Additionally, RU 24926 displayed analgesic effects in mice (starting from 0.125 mg/kg) in a dose-dependennt manner.[281] No further studies have been done on these two compounds.

VI. Selective Peripheral KOR Antagonists (a.k.a. Peripherally Restricted KOR Antagonists)

Until now, there have been no reports on selective peripheral KOR antagonists. However, there are a few known selective peripheral MOR antagonists, such as methylnaltrexone (**Figure 8**). Methylnaltrexone displayed some moderate antagonistic activity on KOR and was 3 times more selective for MOR than for KOR (K_i for KOR = ~30 nM, K_i for MOR = 10 nM).[282] Methylnaltrexone was highly efficacious at antagonizing agonized guinea pig ileum MOR receptors (IC_{50} = 6.7 nM).[282] Methylnaltrexone was observed to reverse some of the peripherally mediated side effects of MOR opioid analgesics,

including morphine and oxycodone.[283] In 2002, Yuan and coworkers demonstrated that a single dose of methylnaltrexone (0.1 mg/kg, s.c.) co-administered with morphine (0.05 mg/kg, i.v.) significantly reduced the morphine-induced delay in gastrointestinal transit time in patients—an opioid side effect related to constipation—while a higher dose of methylnaltrexone (0.3 mg/kg, s.c.) co-administered morphine (0.05 mg/kg, i.v.) decreased gastrointenstinal transit time below the baseline level in patients.[283] Therefore, methylnatrexone can be used in the treatment of constipation without significantly affecting pain relief or precipitating opioid withdrawals.[284] Since there are no known pure selective peripheral KOR antagonists, their therapeutic potential is unrealized, and their development is an enticing and unexplored area of medical research.

VII. Bivalent KOR Ligands

Besides the design and discovery of small molecules that target multiple opioid receptors, there have been many studies into the design and development of bivalent ligands aiming at specific opioid receptor subtypes. These bivalent ligands consist of two different pharmacophores targeting two different receptors; the two pharmacophores are connected via a linker (also called a spacer).[285] The pharmacophores could be agonists or antagonists of these receptors.[285] For example, KDAN-18 (**Figure 9**) is a bivalent ligand that targets KOR (agonistic) and DOR (antagonistic)[286] and KMN-21 (**Figure 9**) is a bivalent ligand that targets KOR (antagonistic) and MOR (antagonistic).[287] Additionally, there are other bivalent ligands that selectively target opioid heteromers. For example, *N*-naphthoyl-β-naltrexamine (NNTA, **Figure 9**) was discovered to selectively activate heteromeric KOR/MOR in HEK-293 cells and induced potent antinociception in mice through both intrathecal (i.t.) and intracerebroventricular (i.c.v.) routes when tested using the tail flick test (ED_{50} =18.7 (10.3–32.8) pmol for the i.t. route and 2.06 (1.09–3.27) nmol for the i.c.v. route).[288] NNTA did not produce significant physical dependence nor place preference in the above ED_{50} dose ranges.[288] Thus, targeting heteromeric KOR/MOR could be an approach to potent analgesics with fewer deleterious side effects.[288]

VII. Conclusions and Future Directions

The κ-opioid receptor (KOR) is expressed throughout the peripheral and central nervous systems (CNS). In the brain, KOR is expressed in the amygdala, hippocampus, hypothalamus, nucleus accumbens, and striatum, which are involved in the reward, emotional function, stress, and pain processes.[1,112] Dynorphin, the endogenous KOR ligand, is known to be released rapidly in times of stress or after the use of drugs of abuse, activating CNS and peripheral KOR.[249] Thus, KOR plays a crucial role in the modulation of antinociception and a variety of behavioral states like anxiety, depression, and drug abuse.

KOR agonists can elicit antinociceptive effects, but also generate aversive effects, such as dysphoria, hallucination, sedation, and negative moods.[1,112] Different KOR agonists have been shown to activate distinct cellular signaling pathways and downstream responses, resulting in different functions of the drugs used and behavioral outcomes. KOR agonists that display biases towards G protein signaling are known to mediate analgesia with less detrimental adverse effects, such as anhedonia/dysphoria, sedation, anxiety, and motor incoordination, than KOR agonists that display biases towards β-arrestin recruitment. Overall, G protein-biased KOR agonists are preferred to both β-arrestin recruitment-biased KOR agonists and nonbiased KOR agonists in the development of novel analgesics with minimal undesirable adverse effects. Up until now, some specific compounds were observed to produce specific signaling pathways in biased vs. nonbiased KOR agonism. However, the exact molecular level as to why these specific compounds produce specific signaling pathways has not been fully understood. Researchers have looked into establishing SARs for the G protein signaling pathway vs. β-arrestin recruitment pathway, but these SARs still need validation. This is a cutting-edge area of research. It is very crucial to identify the correct biased signaling of new KOR agonists as G protein-biased agonists and β-arrestin recruitment-biased

agonists produce different effects and possess different side effect profiles.

Meanwhile, KOR antagonists can produce antidepressant and anxiolytic effects and alleviate withdrawal symptoms, but they generally possess unfavorable pharmacokinetic and pharmacodynamic liabilities. Current prototypical KOR antagonists are known to induce KOR antagonism that is delayed by hours and extremely prolonged. The brain uptake of these compounds is very slow, and their presence in the brain is persistent and still detectable for weeks. Their activities also persist long after the compounds are eliminated from the body. The use of these compounds in humans raises serious safety concerns because they possess a large window for potential drug-drug interactions.[12] These compounds also promote desensitization in drug abuse treatment, potentially promoting tolerance, and complicate preclinical evaluations in paradigms that require multiple administrations (such as self-administration). Short-acting KOR antagonists may provide the therapeutic benefits of the long-acting KOR antagonists but with more favorable pharmacokinetic and pharmacodynamic profiles. This is also a cutting-edge area of research.

In many cases, compounds display activity on multiple opioid receptors. Thus, their overall behavioral effects could be a combination of their mixed activity. Recent studies have shown that mixed KOR agonists/MOR partial agonists have the potential to treat psychostimulant abuse, including cocaine,[111] whereas mixed KOR agonists/partial MOR antagonists are being developed as analgesics with balanced side effect profiles and reduced tolerance.[112] Several dual KOR/MOR agonists and triple KOR/MOR/DOR agonists have produced strong antinociception and blocked cocaine conditioned place preference in mice, while lacking the typical dysphoric or addictive properties of pure KOR or pure MOR agonists, respectively.[65,113] In addition, many bivalent ligands aiming at different opioid receptors have been designed and developed.[285] These bivalent ligands consist of two different pharmacophores (agonists or antagonists, connected via a linker) targeting two different receptors. The bivalent ligands targeting KOR can produce similar potential therapeutic benefits to those of mixed KOR agonists while also lacking the typical side effects of pure KOR agonists. The development of novel mixed KOR agonists and bivalent KOR agonists in basic and clinical research has intensified.

Since the sedative and dysphoric adverse effects are mediated by the agonism of CNS KOR, another strategy to avoid these side effects is to design and develop compounds that selectively target peripheral KOR. These selective peripheral KOR agonists are known to produce analgesia without producing dysphoria, sedation, and motor impairment. The majority of selective peripheral KOR agonists are peptides that have low BBB penetration. Difelikefalin is currently on the market (it was approved for medical use in the United States in August 2021), while a few other selective peripheral KOR agonists are in clinical development. This is also a hot ongoing research area.

This review has systematically categorized past and current KOR ligands and summarized their discovery, design, and development as therapeutics agents, as well as their potential side effects. Our review has highlighted the utilities, drawbacks, and future directions of compounds in each category to aid in the development of future generations of KOR agonists and antagonists.

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Conflict of Interest

The authors declare no competing financial interest.

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