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# Kappa Opioid Antagonists: Past Successes and Future Prospects

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## ABSTRACT

Antagonists of the kappa opioid receptor were initially investigated as pharmacological tools that would reverse the effects of kappa opioid receptor agonists. In the years following the discovery of the first selective kappa opioid antagonists, much information about their chemistry and pharmacology has been elicited and their potential therapeutic uses have been investigated. The review presents the current chemistry, ligand-based structure activity relationships, and pharmacology of the known nonpeptidic selective kappa opioid receptor antagonists. This manuscript endeavors to provide the reader with a useful reference of the investigations made to define the structure-activity relationships and pharmacology of selective kappa opioid receptor antagonists and their potential uses as pharmacological tools and as therapeutic agents in the treatment of disease states.

**KEYWORDS:** Opioid, Opiate, Receptor, Kappa, Antagonist

## INTRODUCTION

The opioid receptor system consists of 3 types of heterogeneous, G-protein–coupled, opioid receptors mu (μ), delta (δ), and kappa (κ), which have been pharmacologically characterized and cloned.[1-4] Each opioid receptor type has selective agonists and antagonists that bind to and produce effects unique to that individual receptor type. The prototypical agonist acting through opioid receptors is morphine (**1**) (Figure 1), though not selective, it functions as a mu opioid agonist. Mu opioid agonists produce the classic opioid effects: analgesia, euphoria, respiratory depression, constipation, nausea, cough suppression, and the development of tolerance and dependence.[5] The prototypical opioid antagonist naloxone (**2**) (Figure 2) functions as a mu opioid antagonist, though it is also not selective for mu opioid receptors. Selective mu opioid antagonists such as cyprodime (**3**) (Figure 3) reverse the effects of mu opioid agonists only and are used as tools in pharmacological assays.[5,6] Selective delta opioid agonists such as SNC 80 (**4**) (Figure 4) produce weak analgesia, mild convulsions, and immunostimulation.[7] Selective delta antagonists such as naltrindole (**5**) (Figure 5) are being investigated for their potential use as immunosuppressants and modulation of the tolerance effect of mu opioid agonists.[7]

Selective agonists and antagonists for kappa opioid receptors have also been investigated. Selective kappa opioid agonists such as U50,488 (**6**) (Figure 6) produce analgesia, diuresis, dysphoria, and show antipruritic activity,[8] whereas selective kappa opioid antagonists are being explored for their effects in the treatment of a wide variety of areas including cocaine addiction,[9] depression,[10] and feeding behavior,[11] and have been proposed as a treatment for psychosis and schizophrenia.[12] In this manuscript we present currently known chemical classes of selective kappa opioid antagonists, their pharmacology, and ligand-based structure-activity relationships (SAR).

While this manuscript focuses on nonpeptidic selective kappa opioid receptor antagonists, several related issues with peptidic opioids will briefly be addressed. Four different types of endogenous mammalian peptides[13] have been identified that act upon opioid receptors: endorphins, enkephalins, endomorphins, and dynorphins. The dynorphin family of peptides acts predominantly as kappa opioid receptor agonists and peptidic antagonists for the kappa receptor are known.[14,15] Those interested in an excellent discussion of peptidic kappa opioid antagonists should refer to the analgesics chapter in Burger's Medicinal Chemistry.[16] Further, the non-selective kappa opioid antagonist buprenorphine will not be covered due to its mu opioid agonist actions. Those seeking information on buprenorphine should seek John Lewis' excellent book of the same title (Cowan and Lewis[17]). Subtypes of kappa opioid receptors have been proposed through the results of pharmacological assays, but only one type of kappa opioid receptor has been cloned so far.[2] Further, it has been shown that receptor dimerization between the kappa and delta opioid receptors produces a dimer that possesses the pharmacological profile of the kappa-2 subtype,[18] and that the kappa-1 and kappa-2 receptor subtypes may be different affinity

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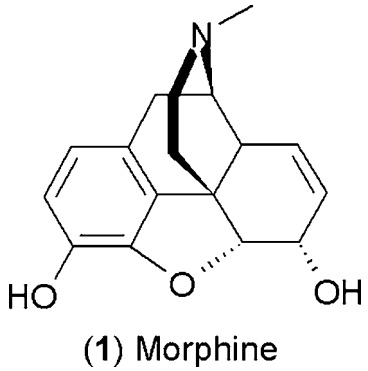



**Figure 1.** Structure of morphine.

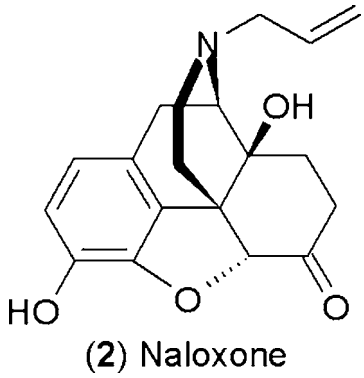



**Figure 2.** Structure of naloxone.

states of the same receptor,[19] which may explain the pharmacological findings of subtypes of kappa opioid receptors.[20] Therefore, this article will not differentiate between subtypes of kappa opioid receptors. Target-based modeling of kappa opioid antagonists has been performed[21-27] and an excellent review is available,[28] however this review will focus on ligand-based SAR. We endeavor herein to cover nonpeptidic, selective kappa opioid antagonists including the most recent chemical and pharmacological developments.

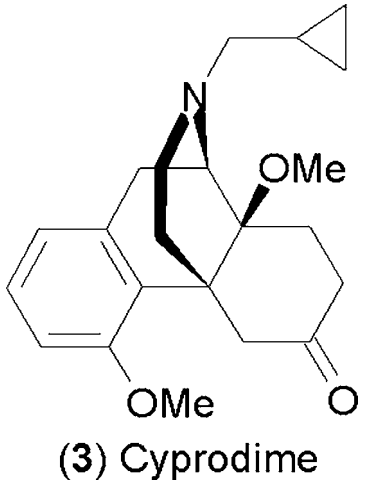



**Figure 3.** Structure of cyprodime.

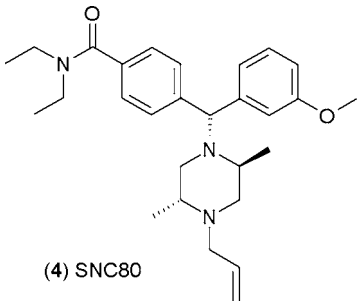



**Figure 4.** Structure of SNC80.

## COMPETITIVE KAPPA OPIOID ANTAGONISTS

Antagonist selectivity for the kappa opioid receptor has been a goal of chemists and pharmacologists since the recognition of the different subtypes of opioid receptors.[20] Early accomplishments in developing kappa opioid antagonists produced Mr 2266 (**7a**) (Figure 7) and WIN 44,441 (quadazocine) (**7b**).[29] While occasionally used[30] for their historical value as kappa opioid antagonists, these compounds are not selective[20] antagonists for the kappa opioid receptor. The first nonpeptide selective kappa opioid antagonist, triethyleneglycolnaltrexamine (TENA) (**8**) (Figure 8), was developed by Erez et al.[31] TENA (**8**), a derivative of β-naltrexamine (**8a**), contains 2 naltrexone (**9**) (Figure 9) pharmacophores linked by a spacer. While superior to Mr 2266 (**7a**) and quadazocine (**7b**), TENA (**8**) possesses only a modest selectivity for kappa receptors over mu and delta opioid receptors[32] (Table 1). Although TENA (**8**) was not an ideal selective kappa opioid antagonist, it was very useful as a lead compound in the development of selective kappa opioid antagonists. Numerous structural modifications of the spacing linker[33-35] involving the substituents, length, flexibility, and conformation

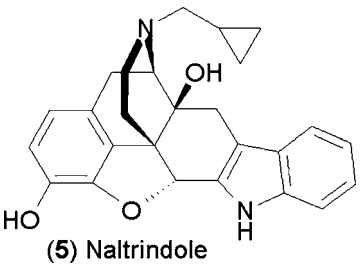



**Figure 5.** Structure of naltrindole.

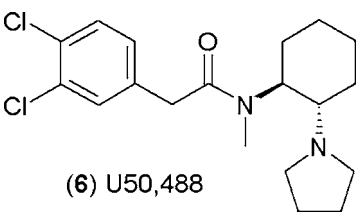



**Figure 6.** Structure of U50,488.

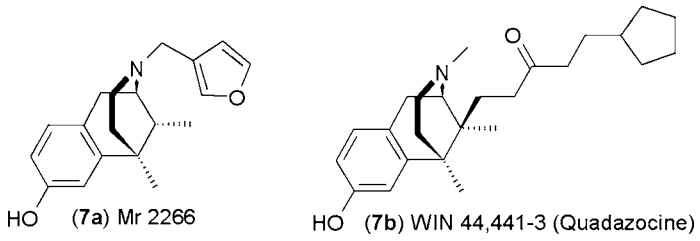



**Figure 7.** Structures of Mr 2266 and WIN 44,441–3.

led to a short, rigid, pyrrole ring between the 2 pharmacophores as the optimal spacer. This spacing linker produced the selective kappa opioid receptor antagonists[36] binaltorphimine (BNI) (**10**) (Figure 10) and norbinaltorphimine (norBNI) (**11**).

While developing these compounds, Takemori and Portoghese[37,38] used the "message-address" concept,[39] originally applied to proteins, and his "bivalent-ligand" approach (2 pharmacophores covalently attached to one another) in the development of kappa opioid antagonists TENA (**8**) and norBNI (**11**).[21,40] Later, the message address concept was used in the development of other kappa opioid antagonists.[22,41,42] The "message-address" concept is used to explain the selective binding of ligands to different subtypes of receptors within a general receptor class (here the mu [μ], delta [δ], and kappa [κ] subtypes of the general class of opioid receptors). Briefly, the "message" portion (scaffold) of the ligand provides the affinity for the general class of receptor, and the "address" portion, a chemically specific function, confers specificity for the individual receptor subtype (Figure 11). Examples include the transformation of the nonselective opioid antagonist naltrexone (**9**) to the selective delta opioid antagonist naltrindole (**5**),[37,38] and the transformation of naltrindole (**5**) to the kappa specific antagonist 5′-guanidinonaltrindole (GNTI) (**12**).[22] For an in an in-depth discussion of the "message-address concept" please refer to the eloquently presented argument and discussion in Takemori and Portoghese,[37] Portoghese,[38] and more current, though

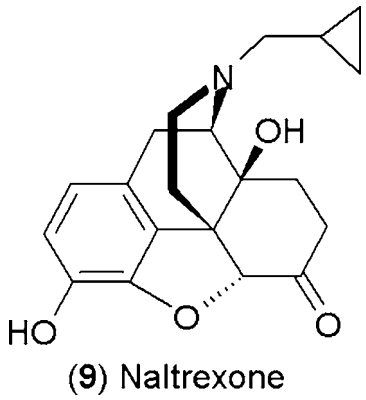



**Figure 9.** Structure of naltrexone.

condensed, discussions by Sharma et al[23] and Thomas et al.[41]

## NorBNI and Analogs

In 1987, Portoghese et al[29,36] reported the selective kappa opioid receptor antagonists binaltorphimine (BNI) (**10**) and norbinaltorphimine (norBNI) (**11**); the latter has become the prototype kappa opioid antagonist ligand. Both ligands displayed high selectivity and potency for kappa opioid receptors (Table 2). A subsequent paper[43] describes (–) norBNI (**11**) compared with its "unnatural" (+) enantiomer (**13**) (Figure 12) and its (±) diasterisomer (**14**) (Figure 13). The difference in the molecules is best appreciated by the perspective drawings in Figures 14 and 15. This series showed that (+)-norBNI (**13**) was inactive while (±)-norBNI (**14**) displayed increased potency, but decreased specificity as a kappa opioid antagonist (Table 2). A series of analogs (**15**–**23**) (Figure 16) of norBNI (**11**) was synthesized to test replacements of the 3, 14, 3′, and 14' hydroxyls, and the N-17 and N-17' substituents[44] (Table 3). Additionally, Schmidhammer's group reported 2 norBNI (**11**) analogs[45] (**24, 25**) (Figure 17) and 2 BNI (**10**) analogs[46] (**26, 27**) (Figure 18) with the 14 and 14' positions occupied by methoxy groups (Table 4). Another study[47] presented data

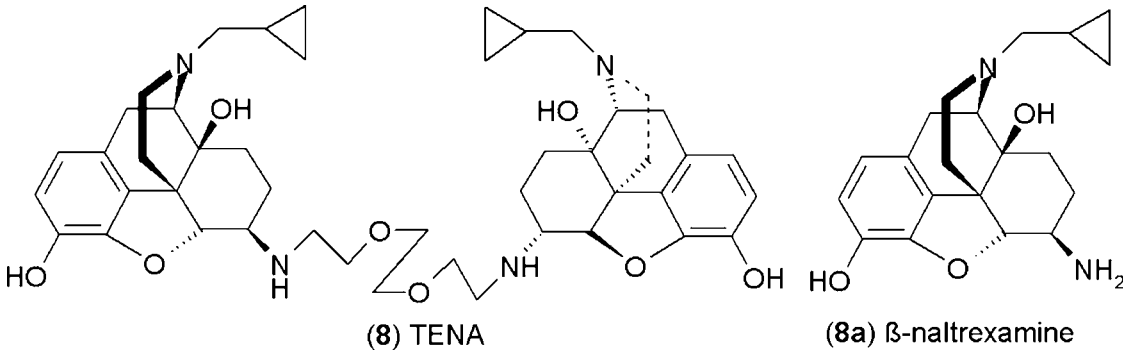



**Figure 8.** Structures of TENA and β-naltrexamine.

**Table 1.** Opioid Antagonist Activities of TENA (**8**) in the GPI and MVD*,32

| | $IC_{50}$ ratio | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **Ethylketozocine (κ)** | **U50,488 (κ)** | **Morphine (μ)** | **DADLE (δ)** | **κ/μ** |
| Naloxone (**2**) | 7.2 | - | 46.8 | | 0.2 |
| TENA (**8**) | 19.6 | 111.5 | 4.2 | 1.2 | 4.7 (26.6) |
| Mr 2266 (**7a**) | 9.6 | 9.9 | 7.9 | 1.5 | 1.2 (1.3) |
| quadazocine (**7b**) | 4.6 | - | 16 | - | 0.3 |

*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay.

on replacements of the nitrogen in the pyrrole ring with the thiophene (**28**) (Figure 19) and pyran (**29**) (Figure 20) analogs of norBNI (Table 5). Also, 2 octahydroisoquinoline BNI (**10**) analogs[40] (**30, 31**) (Figure 21) have been synthesized and tested (Table 6). Another study[48] of norBNI analogs analyzed the results of sequential replacements (**32**–**42**) (Figure 22) of the N-17' substituent (Table 7) and 2 more (**43, 44**) with only binding data.[21] A 3′-dehydroxy analog[49] of norBNI (**45**) (Figure 23) has also been prepared (Table 8). A radio ligand form of norBNI (**46**) (Figure 24) has also been synthesized[50] and possesses high binding affinity and selectivity for kappa receptors.

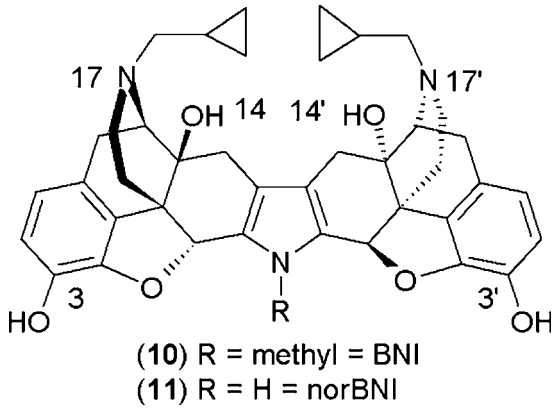



**Figure 10.** Structures of Binaltorphimine and norBinaltorphimine.

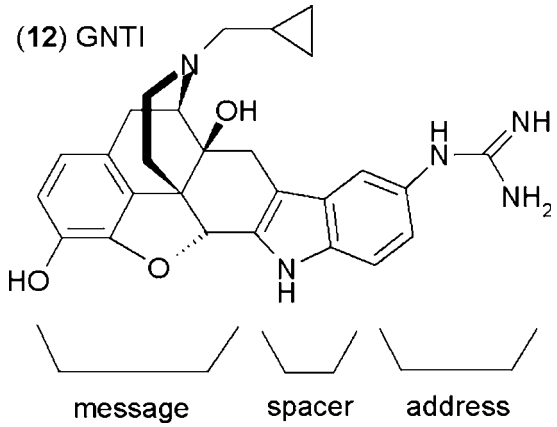



**Figure 11.** Structure of guanidinenaltrindole detailing the message-address concept.

The overall conclusions that can be drawn from these analogs suggest a structure activity relationship as follows. Only one antagonist pharmacophore is necessary for kappa antagonist activity, as suggested by data on compounds **11**, **14, 15**–**18,** and **31**. A second basic nitrogen is necessary for kappa opioid antagonist activity, although the functionality of the nitrogen may vary, suggested by data on compounds **11, 14, 23, 30**–**44**. One phenolic hydroxyl is necessary for activity (although there is loss of potency when the second hydroxyl is masked or eliminated), as suggested by data on compounds **11, 18, 19, 22, 23, 27, 31, 45**. The 14 and 14' hydroxyls can be methylated or acetylated and still retain activity suggested by data on compounds **19, 20, 24, 25**. The pyrrole spacer can have increased size (sulfur) and be functionalized (methylated) and retain activity, as suggested by data on compounds **10, 11, 26, 28, 29**.

**Table 2.** Opioid Antagonist Activities of BNI (2), norBNI (3) and Stereoisomers in the GPI and MVD*,36,43

| | $K_e$ in nM | | | $K_e$ ratio | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| BNI (**10**) | 0.14 | 11 | 5.7 | 79 | 41 |
| (-)-norBNI (**11**) | 0.41 | 13 | 20 | 32 | 49 |
| (±)-norBNI (**14**) | 0.08 | 1.1 | 1.3 | 14 | 16 |
| naltrexone (**9**) | 5.5 | 1.0 | 24 | 0.2 | 4.4 |

*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine.

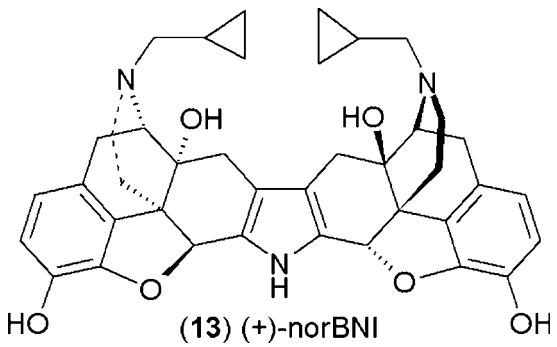



**Figure 12.** Structure of (+)-norBinaltorphimine.

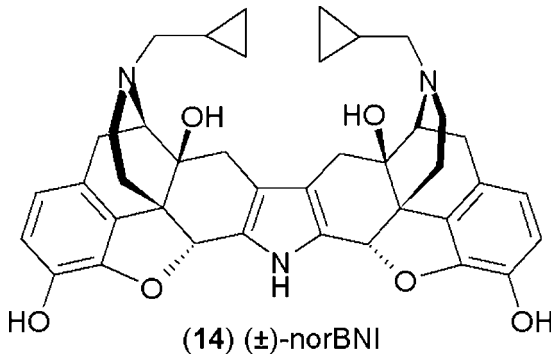



**Figure 13.** Structure of (±)-norBinaltorphimine.

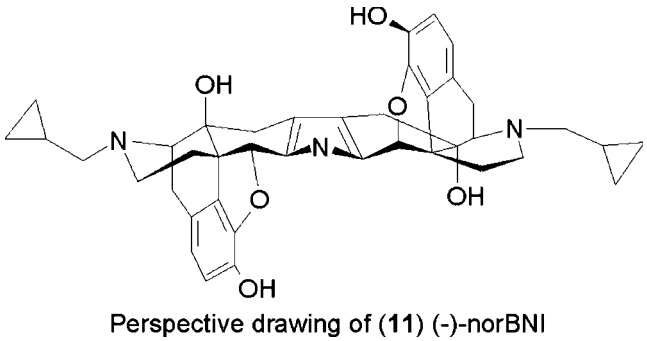



**Figure 14.** Perspective model of (-)-norBinaltorphimine.

## INDOLOMORPHINAN KAPPA OPIOID ANTAGONISTS

In 1993, Portoghese's group (Olmstead et al[51]) presented a series of 3 amidines (**47**–**49**) (Figure 25), based on the naltrindole (NTI) (**5**) pharmacophore, which converted the selective delta opioid antagonist naltrindole (**5**) into selective kappa opioid antagonists (Table 9). Subsequently, the same group reported the preparation of guanidinonaltrindole[22] (GNTI) (**12**); the 5′-guanidinyl derivative of naltrindole. GNTI (**12**) (Figure 11) showed increased affinity, selectivity, and potency over norBNI (**11**); with $pA_2$ values of 10.40, 8.49, and 7.81, respectively, for kappa, mu, and delta cloned human opioid receptors in Chinese hamster ovary (CHO) cells.[52] A series of GNTI analogs[24] (**12, 50**–**71**) (Figure 26) were synthesized with GNTI being the most potent and selective of the series (Table 10). ANTI (**58**) would eventually be tested[10] as a peripherally active GNTI (**12**) derivative. Lewis' group published data (Jales et al[53])

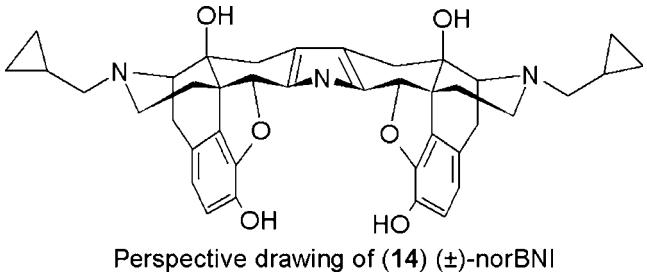
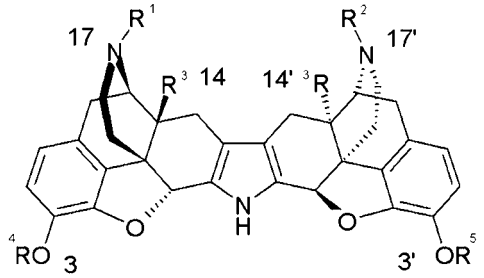



**Figure 15.** Perspective model of (±)-norBinaltorphimine.



| | R¹ | R² | R³ | R⁴ | R⁵ |
|---|---|---|---|---|---|
| **15** | allyl | allyl | OH | H | H |
| **16** | Methyl | Methyl | OH | H | H |
| **17** | Methyl | Methyl | H | H | H |
| **18** | Methyl | Methyl | H | Methyl | Methyl |
| **19** | CPM | CPM | OAc | Ac | Ac |
| **20** | CPM | CPM | OAc | H | H |
| **21** | CPM | CPM | OH | Methyl | Methyl |
| **22** | CPM | CPM | OH | H | Methyl |
| **23** | CPM | Methyl | OH | H | H |

CPM = cyclopropyl methyl, OAc = acetate, Ac = acetyl

**Figure 16.** Structures of norBinaltorphimine analogs.

on a butyl amidine (**72**); similar but less potent than norBNI (**11**), in the [$^{35}$S]GTPγS assay (kappa $K_i$ (nM) = 0.12, 0.17, and 0.039 for compounds **55**, **72**, and **11**, respectively) (Figure 27). Portoghese also presented (Sharma et al[23]) a sequential substitution of the guanidine moiety (**73**–**75**) (Figure 28) at each position of the naltrindole (**5**) scaffold. The results showed the 4' GNTI (**73**) was inactive ($K_e$ >1000 nM at all opioid receptors), 6'-GNTI (**74**) showed selective kappa

**Table 3.** Opioid Antagonist Activities of norBNI (**11**) and analogs in the GPI and MVD*,[44]

| | $K_e$ in nM | | | | $K_e$ ratio | |
|---|---|---|---|---|---|---|
| **Antagonist** | **Conc. nM** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| BNI (**10**) | 20 | 0.14 | 11 | 5.7 | 79 | 41 |
| norBNI (**11**) | 20 | 0.41 | 13 | 20 | 32 | 49 |
| **15** | 100 | 0.91 | ≥250 | ≥143 (pa) | ≥275 | ≥157 |
| **16** | 20 | a | a | | | |
| **17** | 10 | a | a | | | |
| **18** | 100 | a | a | | | |
| **19** | 100 | | | | | |
| **20** | 100 | 0.38 | 42 | 12 | 111 | 32 |
| **21** | 20 | 7.1 | | | | |
| **22** | 200 | 1.3 | 38 | 45 | 29 | 35 |
| **23** | 200 | 1.9 | 21 | 41 | 11 | 22 |
| naltrexone (**9**) | 100 | 5.5 | 1.0 | 24 | 0.2 | 4.4 |

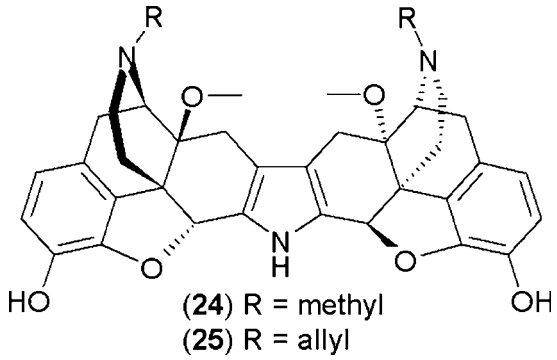



**Figure 17.** Structures of norBinaltorphimine analogs.

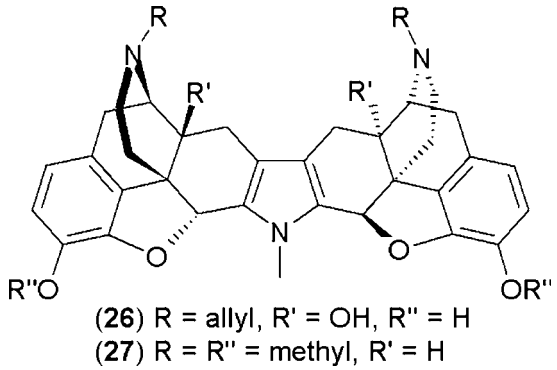



**Figure 18.** Structures of Binaltorphimine analogs.

opioid agonist activity (51-fold greater potency than morphine in the guinea pig ileum assay (GPI) and reversed by norBNI (**11**), and 7'-GNTI (**75**) showed selective delta antagonist activity ($K_e$ = 0.96 in the mouse vas deferens assay [MVD]). Husbands' group presented a series of amides, amidines, and urea analogs of GNTI (Black et al[54]) (**76**–**94**) (Figures 29, 30, 31 and 32) (Table 11). These compounds, especially the ureas, showed less selectivity and potency than norBNI in the [$^{35}$S]GTPγS assay. Following this work, this group presented a series of guanidine-substituted analogs of GNTI[55] (**95**–**109**) (Figures 33, 34, 35 and 36) (Table 12). In 2003, Ananthan et al[56] published a pyridomorphinan kappa opioid antagonist (**110**) (Figure 37); while only slightly preferring [$^{35}$S]GTPγS ($K_i$ = 1.0, 6.1, and 6.5 nM for kappa, mu, and delta, respectively), this compound (**110**) serves as another lead compound in the development of future kappa opioid antagonists.

**Table 4.** Opioid Antagonist Activities of norBNI and two analogs in the GPI and MVD*,[45,46]

| | $K_e$ in nM | | | Selectivity ratio | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.02 | 27 | 22 | 1350 | 1100 |
| **24** | 0.6 | 88 | 4.6 | 147 | 8 |
| **25** | 0.03 | 0.36 | 2.3 | 12 | 77 |
| **26** | 0.11 | 5.7 | 6.1 | 52 | 6 |

*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine, a = agonist; pa = partial agonist.
*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine.

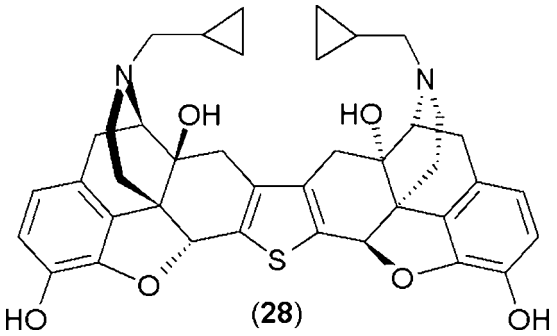



**Figure 19.** Structure of Pyran analog of norBinaltorphimine.

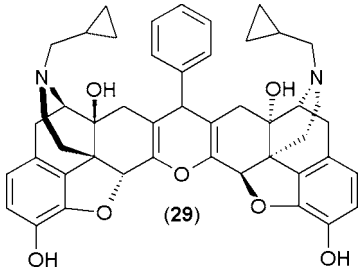



**Figure 20.** Structure of Furan analog of norBinaltorphimine.

The results from the indolomorphinan analogs seem to confirm the SAR found in the norBNI analogs (single pharmacophore, 2 basic nitrogens, spacing ring[s], phenolic hydroxyl), also adding, perhaps, that increasing the basicity of the second basic nitrogen leads to increased potency, as suggested by compounds **12, 58, 67**.

## NON-EPOXYMORPHINANS

In 2001 Carroll's group presented the phenylpiperidine-based, selective kappa opioid antagonist JDTic (**111**) (Figure 38),atrans-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine (Thomas et al[57]). While many 4-phenylpiperidine N-substituted derivatives have been previously prepared,[58,59] none were selective kappa opioid receptor antagonists until JDTic

**Table 5.** Opioid Antagonist Activities in the GPI and MVD*,[47]

| | $K_e$ in nM | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.55 | 14 | 10.6 | 25 | 19 |
| naltrexone (**9**) | 5.5 | 1.0 | 24 | 0.2 | 4.4 |
| **28** | 2.6 | 41 | 33 | 16 | 13 |
| **29** | 2.6 | 39 | 36 | 15 | 14 |

*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine.

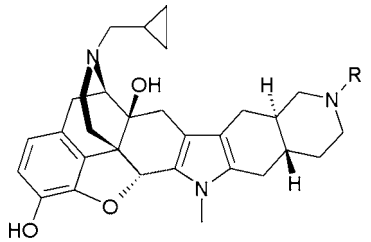



**Figure 21.** Structures of Octahydroisoquinoline analogs of norBinaltorphimine.

(**111**). JDTic (**111**) was based on a previous nonselective compound (**112**) that was kappa preferring (Table 13). The same group followed this discovery with the publication of a series of phenylmorphan kappa opioid antagonists[60] (**113**–**117**) (Figure 39); the best (**113**) was similar, but less potent than norBNI (kappa antagonist $K_e$ = 0.24 and 0.04 nM, respectively, in the [$^{35}$S]GTPγS assay with cloned human opioid receptors). In a follow-up SAR study of the JDTic pharmacophore, a series of compounds[41] (**118**–**126**) (Figures 40 and 41) (Table 14) was presented that highlighted the necessity for 2 basic nitrogens, similar to norBNI (**11**) and GNTI (**12**), and for and 2 phenolic hydroxyls for kappa opioid antagonist activity in the [$^{35}$S]GTPγS assay. In another study, Carroll presented a comparison of the dehydroxy analogs of norBNI (**45**) and JDTic (**111**) (Thomas et al[49]) (Table 15). This analysis showed both compounds lose potency when the second hydroxyl group is deleted from their structure. Husbands recently presented a series of amino tetralin derivatives (Grundt et al[61]) (**127**–**141**) (Figure 42) that produced a nonselective kappa opioid antagonist (**141**) (Table 16). This work is similar to that of Thomas et al,[59] which produced the kappa opioid antagonist (**112**) and led to the development of the selective kappa opioid antagonist JDTic (**111**). These results likely indicate the amino tetralin pharmacophore is poised for development of selective kappa opioid antagonists.

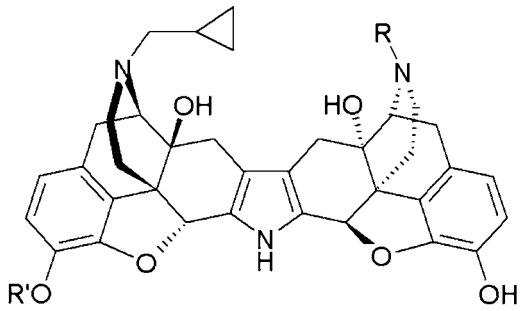
## Irreversible Kappa Opioid Antagonists, UPHIT and DIPPA

In an effort to develop site-directed affinity labels of the kappa opioid receptor, the Rice group (de Costa et al[62]) discovered UPHIT (**142**) (Figure 43). UPHIT (**142**) was based on their previous compound[63] (**143**) that was able to irreversibly inhibit [$^3$H]U69,593 binding to kappa opioid receptors with an $IC_{50}$ of 100 nM, but was unable to irreversibly inhibit kappa opioid receptors when administered intracerebroventricularly (i.c.v.). Based on the design of U50,488 (**144**), a potent selective kappa opioid agonist, UPHIT contains an isothiocyanate acetylating group and was able to irreversibly inhibit 98% specific binding of [$^3$H]U69,593 to guinea pig kappa opioid receptors compared with control when 100 μg was administered i.c.v.[62] Portoghese's group followed UPHIT (**142**) with DIPPA (**145**) (Figure 44) (Chang et al[64,65]), which also contained an isothiocyanate acetylating group, though located on a different portion of the molecule. DIPPA (**145**) displayed irreversible kappa opioid antagonism in vitro, $B_{max}$ (fmol/mg) [$^3$H]U69,593 of 3.55 (87% decrease in number of [$^3$H]U69,593 binding sites) and kappa opioid agonism in the GPI and MVD ($IC_{50}$ = 23.8 and 14.9 nM, respectively). DIPPA (**145**) also displayed kappa opioid agonism in vivo with an $ED_{50}$ ratio of 16.7 at kappa opioid receptors [($ED_{50}$ of DIPPA [1.53 μmol] in

**Table 6.** Opioid Antagonist Activities in GPI and MVD*,[40]

| | $IC_{50}$ ratio | | | Selectivity ratio | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **κ/μ** | **κ/δ** |
| norBNI (**11**) | 181 | 8.3 | 10.4 | 22 | 17 |
| **30** | 1.6 | 1.7 | 9.2 | 0.9 | 0.2 |
| **31** | 40 | 1 | 1.1 | 40 | 36 |

*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine.




| | R | R' |
|---|---|---|
| **32** | H | H |
| **33** | ethyl | H |
| **34** | butyl | H |
| **35** | pentyl | H |
| **36** | phenethyl | H |
| **37** | $(CH_2)_2NHCbz$ | H |
| **38** | $(CH_2)_2NH_2$ | H |
| **39** | $(CH_2)_2NH(C{=}NH)NH_2$ | H |
| **40** | $COCH_3$ | H |
| **41** | $COCH_2NH_2$ | H |
| **42** | $COCH_2NHCOCH_2NH_2$ | H |
| **43** | $CH_3$ | $CH_3$ |
| **44** | $(C{=}NH)NH_2$ | H |

**Figure 22.** Structures of asymmetrical analogs of norBinaltorphimine.

**Table 7.** Opioid Antagonist Activities of norBNI and N-17' substituted analogs in the GPI and MVD*,[48]

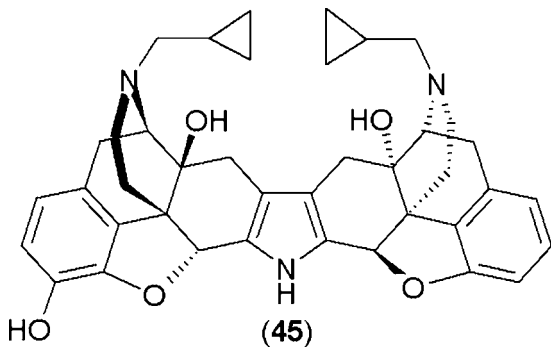
| | $IC_{50}$ ratio | | | Selectivity ratio | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **κ/μ** | **κ/δ** |
| norBNI (**11**) | 181 | 8.3 | 10.4 | 22 | 17 |
| **32** | 41 | 1.9 | 8.5 | 22 | 4.8 |
| **33** | 22 | 1.6 | 6.3 | 14 | 3.5 |
| **34** | 61 | 1.8 | 1.9 | 34 | 32 |
| **35** | 27 | 3.1 | 3.1 | 8.7 | 8.7 |
| **36** | 44 | 1.8 | 2.4 | 24 | 18 |
| **37** | 26 | 4.5 | 4.6 | 5.7 | 5.7 |
| **38** | 20 | 1.6 | 1.9 | 12.5 | 10 |
| **39** | 27 | 1.7 | 1.0 | 15 | 27 |
| **40** | 4.3 | 1.8 | 2.8 | 2.4 | 1.5 |
| **41** | 11.8 | 1.4 | 2.2 | 8.4 | 5.4 |
| **42** | 9.6 | 2.0 | 0.67 | 4.8 | |

*GPI indicates guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine.

norBNI [**11**] treated mice [norBNI dose of 12.25 μmol/kg s.c. 3.5 hours before DIPPA] divided by the control $ED_{50}$) ($ED_{50}$ ratio 1.25 and 3.03 for mu [β-FNA] and delta [NTI] receptors)] in the mouse abdominal stretch assay.[65] However DIPPA (**145**) also displayed kappa opioid antagonism in the tail flick assay with an $ED_{50}$ ratio of 9.1 (U50,488) at kappa receptors compared with 1.8 for mu (morphine) and 1.3 for delta (DPDPE) receptors.[65] The in vivo kappa opioid effects appeared to be short-term agonism (peak at one-half hour, duration less than 4 hours), followed by long-term antagonism (peak at 4 hours, duration of 48 hours).[65] Portoghese notes (Change et al[64]) that β-chlornaltrexamine (β-CNA) (another affinity label, for mu opioid receptors) also displays short-term agonism followed by long-term antagonism.

## Additional Information

While in review, an article was published by the Husbands group detailing additional information about the norBNI




(**45**)

**Figure 23.** Structure of 14'-Desoxy analog of norBinaltorphimine.

**Table 8.** Antagonist Potency in the [$^{35}$S]GTPγS assay in Guinea Pig Caudate Membranes*,[49]

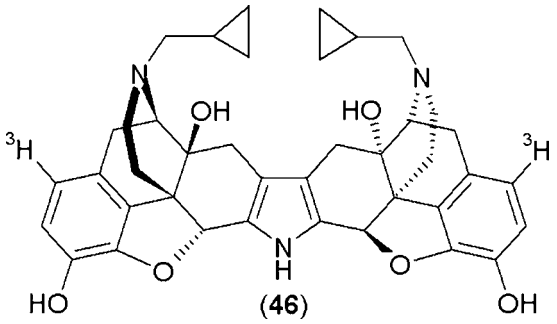
| | $K_i$ (nM) | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.038 | 16.7 | 10.2 | 439 | 268 |
| **45** | 0.13 | 5.55 | >300 | 43 | >2307 |

*NorBNI indicates norbinaltorphimine.

pharmacophore (Chauvignac et al[66]). This work showed that benzylation of the pyrrole nitrogen in norBNI (**11**) and its 17, 17'-diNmethyl analog (**16**) produced compounds with mu opioid partial agonism. This was a change in efficacy for the benzylated norBNI (**146**) (Figure 45), which displayed mu opioid partial agonism in the [$^{35}$S]GTPγS assay ($EC_{50}$ 187 nM, 38% stimulation) and also some kappa opioid partial agonism ($EC_{50}$ 1906 nM, 29% stimulation). The 17, 17'-diNmethyl analog (**147**) had increase potency in the [$^{35}$S]GTPγS assay $EC_{50}$ 526 nM, compared with $EC_{50}$ 1388 nM for compound **16**. These findings represent a significant addition to the pharmacophore of norBNI-based analogs.

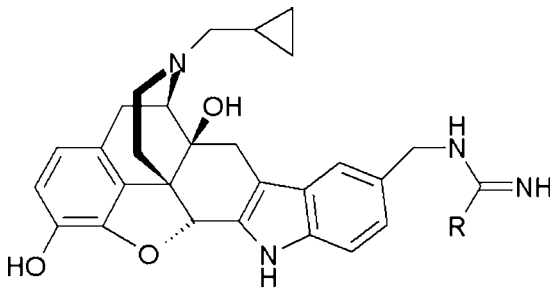
## Time Course of Kappa Opioid Receptor Antagonists

Two interesting characteristics of currently described kappa opioid receptor antagonists are their delay in onset of action




(**46**)

**Figure 24.** Structure of tritiated analog of norBinaltorphimine.




(**47**) R = ethyl
(**48**) R = propyl
(**49**) R = butyl

**Figure 25.** Structures of amidine kappa opioid antagonists.

**Table 9.** Opioid Antagonist Activities of NTI and 5′ substituted analogs in the GPI and MVD*,[51]

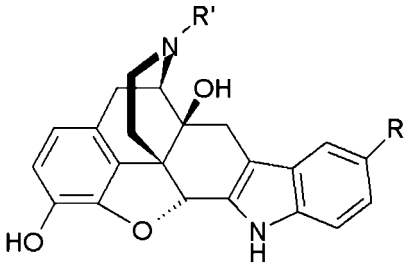
| | $IC_{50}$ ratio | | | Selectivity ratio | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **κ/μ** | **κ/δ** |
| NTI (**5**) | 1.3 | 11.2 | 459 | | |
| norBNI (**11**) | 181 | 8.3 | 10.4 | 22 | 17 |
| **47** | 159 | 11.3 | 2.28 | 14 | 69 |
| **48** | 185 | 19.3 | 3.00 | 10 | 62 |
| **49** | 439 | 15.7 | 4.71 | 28 | 93 |

*NTI indicates naltrindole; GPI, guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine.

and their long duration of action. Both norBNI and GNTI display these characteristics, and recently JDTic has been confirmed as having a similarly long duration of action and delayed onset of action.

All 3 kappa opioid antagonists (norBNI, GNTI, JDTic) show a delay in the onset of their effects as kappa opioid antagonists. The slow onset of kappa opioid antagonists is discussed by Negus et al[67] as "unusual among opioid antagonists…For comparison, the mu-[and kappa] selective opioid antagonist quadazocine and the delta-selective opioid antagonist naltrindole produce their peak effects in less than one hour, and these antagonist effects lasted less than one day." Citing other articles,[68,69] GNTI,[67] JDTic,[70] and norBNI[71] all produce their peak effects after 24 hours. GNTI did not alter the $ED_{50}$ of morphine after 1 hour or 1 day[67] and norBNI is not selective for kappa antagonism over mu opioid antagonism until after 24 hours.[72,73]

NorBNI has been reported to have various long durations of action when administered peripherally and centrally in several different species. In peripheral administration, norBNI produced the following results. In one study[72] male ddY mice were administered norBNI subcutaneously (s.c.) and retained kappa antagonistic actions in the tail pinch test for as long as 4 and 8 days (no end time limit reported). In another study,[71] rhesus monkeys were administered norBNI s.c. and experienced kappa opioid antagonism as long as 14 and 21 days in the tail withdrawal assay. A third study[73] reports after administration of norBNI s.c., male NIH mice experienced kappa opioid antagonism for at least 4 weeks in the writhing assay, but did not retain kappa opioid antagonist effects at 8 weeks. In a fourth study, administration of norBNI s.c. to rhesus monkeys significantly blocked U-50,488 (kappa opioid agonist) attenuation of morphine-induced scratching through 21 days after norBNI administration.[74] Upon central administration, norBNI also displays a long duration of action. One study[75] showed that Sprague-Dawley rats experienced




| | R | R' |
|---|---|---|
| **50** | -NH(C=NH)$NH_2$ | Methyl |
| **51** | -(C=NH)$NH_2$ | CPM |
| **52** | -$CH_2$(C=NH)$NH_2$ | CPM |
| **53** | -$NH_2$ | CPM |
| **54** | -$CH_2NH_2$ | CPM |
| **55** | -$CH_2CH_2NH_2$ | CPM |
| **56** | -NH(C=NH)$CH_3$ | CPM |
| **57** | -$CH_2$NH(C=NH)$CH_3$ | CPM |
| ANTI (**58**) | -$CH_2CH_2$NH(C=NH)$CH_3$ | CPM |
| GNTI (**12**) | -NH(C=NH)$NH_2$ | CPM |
| **59** | -$CH_2$NH(C=NH)$NH_2$ | CPM |
| **60** | -$CH_2CH_2$NH(C=NH)$NH_2$ | CPM |
| **61** | -NH(C=NH)NH(C=NH)$NH_2$ | CPM |
| **62** | -$N(CH_3)_2$ | CPM |
| **63** | -$CH_2N(CH_3)_2$ | CPM |
| **64** | -$CH_2CH_2N(CH_3)_2$ | CPM |
| **65** | -$N^+(CH_3)_3I^-$ | CPM |
| **66** | -$CH_2N^+(CH_3)_3I^-$ | CPM |
| **67** | -$CH_2CH_2N^+(CH_3)_3I^-$ | CPM |
| **68** | -NH(C=N-CN)$NH_2$ | CPM |
| **69** | -$CH_2$NH(C=N-CN)$NH_2$ | CPM |
| **70** | -NH(C=S)$NH_2$ | CPM |
| **71** | -NH(C=NH)$SCH_3$ | CPM |

CPM = cyclopropyl methyl

**Figure 26.** Structures of guanidinenaltrindole analogs.

kappa antagonism, after intracisternal (i.c.) administration of norBNI, at 1, 7, and 21 days in the paw-lick and hot-plate tests. Another study[76] reports kappa opioid antagonism after i.c.v. administration of nor-BNI in male ICR mice for up to 28 days in the tail flick test. A study in

**Table 10.** Opioid Antagonist Activities of GNTI and analogs in the GPI and MVD*,[24]

| | $K_e$ in nM | | | $K_e$ ratio | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.4[a] | 13 | 11 | 31 | 33 κ/δ |
| **50** | 17 | | | 6.3 κ/μ | 41 κ/δ |
| **51** | 0.7 | 16 | | 22 | 142 κ/δ |
| **52** | 2.2 | | | 22 κ/μ | 26[i] |
| **53** | | 57 | | 1.5 κ/μ | 0.4 κ/δ |
| **54** | 34 | 61 | 18 | 1.8 | 0.5 |
| **55** | 2.1 | | | 15 κ/μ | 21 κ/δ |
| **56** | 1.0 | 16 | | 15 | 52 κ/δ |
| **57** | 6.1 | 8.8 | | 1.4 | 17.3 κ/δ |
| ANTI (**58**) | 0.3[a] | 7.6 | 18 | 27 | 65 |
| GNTI (**12**) | 0.2[a] | 30 | | 193 | 366 κ/δ |
| **59** | 0.6 | 11 | | 19 | 172 κ/δ |
| **60** | 1.7 | 12 | 3.4 | 7.3 | 2.0 |
| **61** | 0.2 | 14 | | 74 | 512 κ/δ |
| **62** | 6.8 | 36 | | 5.3 | 6.6 κ/δ |
| **63** | 0.8 | 9.8 | | 12 | 87 κ/δ |
| **64** | 3.2 | | | 13 κ/μ | 18 κ/δ |
| **65** | 3.1 | | | 13 κ/μ | 9.1 κ/δ |
| **66** | 0.7 | 4.0 | | 6.2 | 154 κ/δ |
| **67** | 0.4[a] | 5.7 | | 13 | 96 κ/δ |
| **68** | 3.1 | 16 | 9.1 | 5.1 | 2.9 |
| **69** | 2.9 | 18 | 5.9 | 6.2 | 2.0 |
| **70** | 7.2 | 38 | | 5.3 | 12 κ/δ |
| **71** | 0.5[a] | 16 | | 33 | 115 κ/δ |

All compounds tested at 100nM except [a]Tested at 20nM.
*GNTI indicates guanidinonaltrindole; GPI, guinea pig ileum assay; MVD, mouse vas deferens assay; norBNI, norbinaltorphimine; ANTI, 5'-acetamidinoethylnaltrindole.

Sprague-Dawley rats[10] showed that i.c.v. norBNI had antidepressant-like activity in the forced swim test at 48 and 72 hours after administration, which was similar to and directly compared with GNTI. A third study[77] reports that rhesus monkeys administered norBNI i.c. experienced kappa opioid antagonism 49 days after administration in the tail withdrawal assay. In a study conducted with pigeons, norBNI was ineffective at 1 hour, displayed a

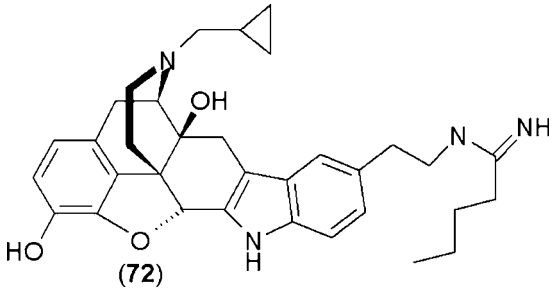
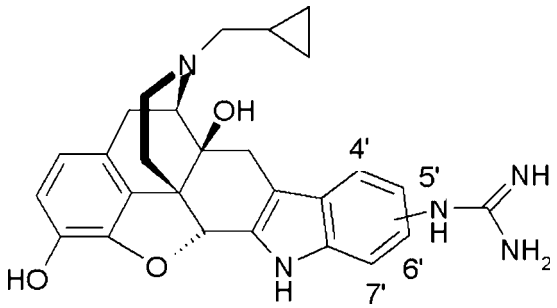
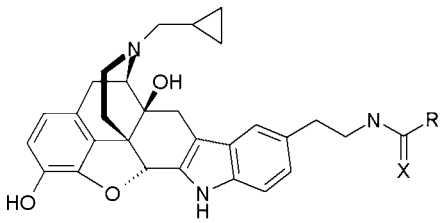



**Figure 27.** Structure of amidine guanidinenaltrindole analog.




(**12**) 5'-guanidine = 5'-GNTI = GNTI
(**73**) 4'-guanidine = 4'-GNTI
(**74**) 6'-guanidine = 6'-GNTI
(**75**) 7'-guanidine = 7'-GNTI

**Figure 28.** Structures of guanidinenaltrindole positional isomers.

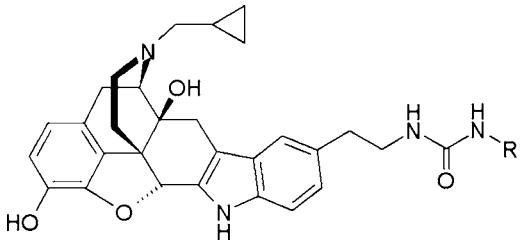



(**76**) X = O, R = Ethyl
(**77**) X = O, R = Propyl
(**78**) X = O, R = Butyl
(**79**) X = NH, R = Methyl
(**80**) X = NH, R =Ethyl
(**81**) X = NH, R =Propyl
(**82**) X = NH, R =*n*-butyl
(**83**) X = NH, R =*iso*-butyl

**Figure 29.** Structures of amide and amidine guanidinenaltrindole analogs.

3-fold reduction in kappa agonist potency at 8 days, a 10-fold reduction in agonist potency between 2 and 3 weeks, with control sensitivity returning only at 112 days.[78] These studies show that the duration of a single, smallest effective dose of norBNI is on the order of weeks in rats, mice, and monkeys, and months in pigeons.

GNTI and JDTic also demonstrate long durations of action. A study[67] showed rhesus monkeys receiving intramuscular (i.m.) GNTI experienced significant kappa antagonism at 2 days, lasted as long as 10 days in some of the monkeys, and returned to control in 14 days in the schedule controlled behavior assay. GNTI also displays a long duration of action when administered centrally. A study in Sprague-Dawley rats[10] showed that i.c.v. GNTI had antidepressant like activity in the forced swim test at 48 and 72 hours after administration, which was similar to and directly compared with




(**84**) R = ethyl
(**85**) R = *n*-butyl
(**86**) R = *n*-hexyl

**Figure 30.** Structures of urea guanidinenaltrindole analogs.

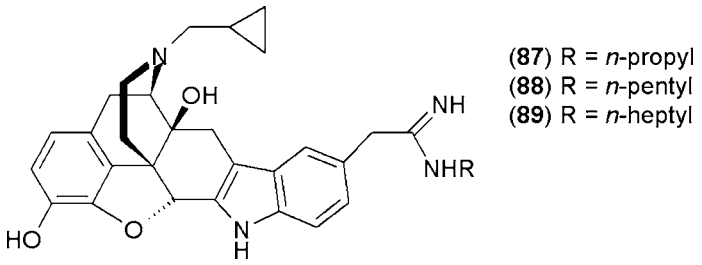



**Figure 31.** Structures of amidine guanidinenaltrindole analogs.

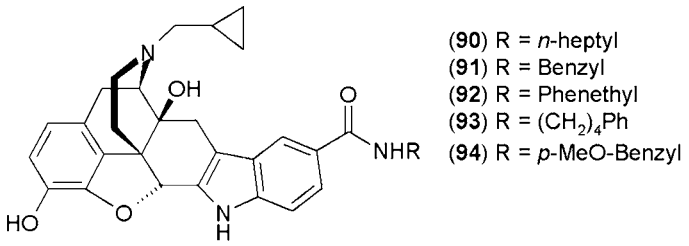



**Figure 32.** Structures of amide guanidinenaltrindole analogs.

nor-BNI. JDTic (Figure 2) was reported to have a long duration of action, which is comparable with GNTI.[67] This initial report[67] was confirmed in a recent study[70] that showed JDTic (p.o. or s.c.) had kappa opioid antagonist effects at 24 hours, 7 days, and 28 days in male ICR mice in the tail flick test. In the same study, JDTic showed that when given to squirrel monkeys i.m., they displayed a right shift in the antinociceptive (shock titration) $ED_{50}$ of U50,488 (a kappa opioid agonist) up to 10 days after administration. Also in this same paper, JDTic and norBNI both showed significant reduction of U50,488-induced diuresis in Sprague-Dawley rats up to 3 weeks.

**Table 11.** Antagonist Activities in the [$^{35}$S]GTPγS assay in Human Recombinant Receptors in CHO cells*,[54]

| | $K_i$ (nM) | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.04 | 18.9 | 4.42 | 484 | 113 |
| **76** | 0.48 | 4.94 | 0.38 | 10 | 1 |
| **77** | 0.35 | 3.17 | 0.30 | 9 | 1 |
| **78** | 0.46 | 3.37 | 0.23 | 7 | 0.5 |
| **79** | 0.21 | 3.78 | 1.79 | 18 | 9 |
| **80** | 0.24 | 4.70 | 1.77 | 20 | 7 |
| **81** | 0.18 | 4.21 | 1.89 | 23 | 11 |
| **82** | 0.17 | 5.33 | 3.31 | 31 | 20 |
| **83** | 0.32 | 14.73 | 5.23 | 46 | 16 |
| **84** | 2.47 | 1.60 | 0.65 | 0.6 | 0.3 |
| **85** | 1.52 | 1.63 | 0.53 | 1 | 0.3 |
| **86** | 1.71 | 1.79 | 1.04 | 1 | 0.6 |
| **87** | 0.05 | 3.19 | 4.41 | 64 | 88 |
| **88** | 0.21 | 5.61 | 3.83 | 27 | 18 |
| **89** | 0.37 | 2.04 | 5.83 | 6 | 16 |
| **90** | 0.29 | 6.86 | 6.95 | 24 | 24 |
| **91** | 0.73 | 4.40 | 2.99 | 6 | 4 |
| **92** | 0.17 | 2.70 | 1.21 | 16 | 7 |
| **93** | 0.26 | 2.78 | 5.15 | 10 | 20 |
| **94** | 0.28 | 0.94 | 6.20 | 3 | 22 |

*CHO indicates Chinese hamster ovary; norBNI, norbinaltorphimine.

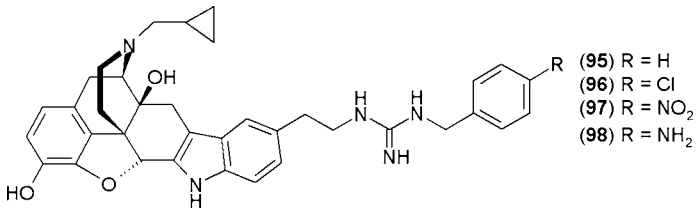



**Figure 33.** Structures of substituted guanidinenaltrindole analogs.

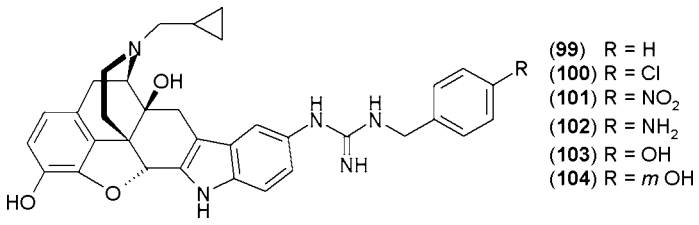



**Figure 34.** Structures of substituted guanidinenaltrindole analogs.

## In Vivo Effects

NorBNI has demonstrated selective kappa opioid antagonism of antinociceptive responses in the tail flick assay in mice i.c.v.[76,79] and s.c,[79] in the mouse antiwrithing assay i.c.v[72,79] and s.c,[73] in the tail withdraw assay in rhesus

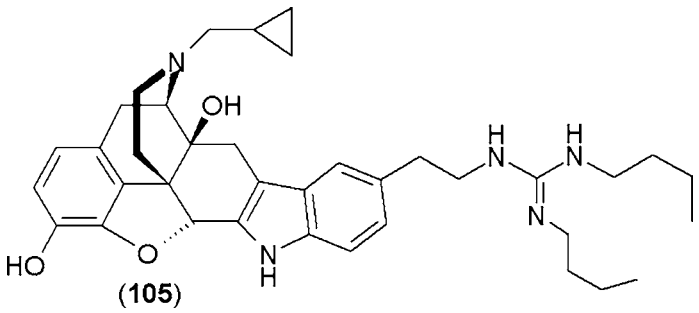



**Figure 35.** Structures of di-substituted guanidinenaltrindole analogs.

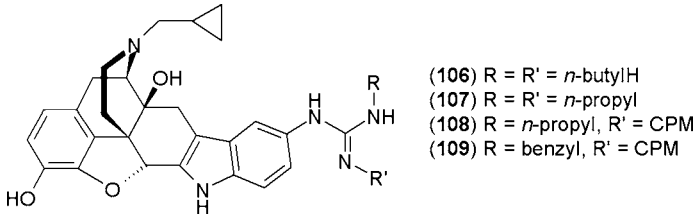



**Figure 36.** Structures of di-substituted guanidinenaltrindole analogs.

**Table 12.** Antagonist Potency in the [$^{35}$S]GTPγS assay in Cloned Human Opioid Receptors*,[55]

| | $K_i$ (nM) | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.04 | 18.9 | 4.42 | 484 | 113 |
| GNTI (**12**) | 0.04 | 3.23 | 15.49 | 81 | 389 |
| **60** | 0.40 | 1.25 | 0.88 | 3 | 2 |
| **95** | 0.13 | 2.94 | 1.36 | 23 | 10 |
| **96** | 0.23 | 2.61 | 1.48 | 11 | 6 |
| **97** | 0.17 | 2.20 | 1.34 | 13 | 8 |
| **98** | 0.25 | 1.57 | 0.95 | 6 | 4 |
| **99** | 0.06 | 1.41 | 4.09 | 24 | 68 |
| **100** | 0.14 | 5.24 | 7.67 | 37 | 55 |
| **101** | 0.18 | 3.71 | 16.66 | 21 | 93 |
| **102** | 0.09 | 1.22 | 10.80 | 14 | 120 |
| **103** | 0.10 | 12.66 | 18.31 | 127 | 183 |
| **104** | 0.13 | 4.28 | 4.35 | 33 | 33 |
| **105** | 0.39 | 4.62 | 1.05 | 12 | 3 |
| **106** | 0.44 | 5.66 | 5.24 | 13 | 12 |
| **107** | 0.26 | 4.59 | 2.43 | 18 | 9 |
| **108** | 0.08 | 3.26 | 6.31 | 41 | 79 |
| **109** | 0.17 | 2.75 | 3.28 | 16 | 19 |

*norBNI indicates norbinaltorphimine; GNTI, guanidinonaltrindole.

monkeys i.c.[77] and s.c[71], in the hot plate test in rats i.c,[75] and in the tail pinch assay in mice s.c.[72] NorBNI has also suppressed kappa opioid agonist–induced diuresis in the rat s.c.[80] and i.c.[81] BNI demonstrated selective kappa opioid antagonist activity in the mouse writing assay 90 minutes pretreatment time.[29]

JDTic has demonstrated[70] selective kappa opioid antagonism of antinociceptive responses in the mouse tail flick test p.o. or s.c., shock titration assay in squirrel monkeys i.m., and also suppressed kappa opioid agonist–induced diuresis s.c. in rats.

Potentially the most exciting work with kappa opioid antagonists has been their effects on the behaviors induced by the administration of cocaine. Experimentally naive rats pretreated (48 hours) with s.c. norBNI had decreased intake of cocaine when offered at reinforcement threshold level, but not when cocaine was presented at higher, double-threshold level, doses.[9] In one study, the aversive effects of cocaine-conditioned place preference were blocked in rats pretreated with norBNI, which had also been given herpes simplex virus vector delivering cAMP response element binding protein (HSV-CREB).[82] In a following study,[83] rats given HSV-CREB and treated with norBNI displayed increased

**Table 13.** Antagonist Potency in the [$^{35}$S]GTPγS assay in Guinea Pig Caudate Membranes[57]

| | $K_i$ (nM) | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.038 | 16.7 | 10.2 | 439 | 268 |
| JDTic (**111**) | 0.02 | 2.16 | >300 | 108 | >15000 |
| **112** | 4.7 | 7.25 | 450 | 1.5 | 96 |

**Table 14.** Antagonist Potency in the [$^{35}$S]GTPγS assay in Guinea Pig Caudate Membranes*,[29]

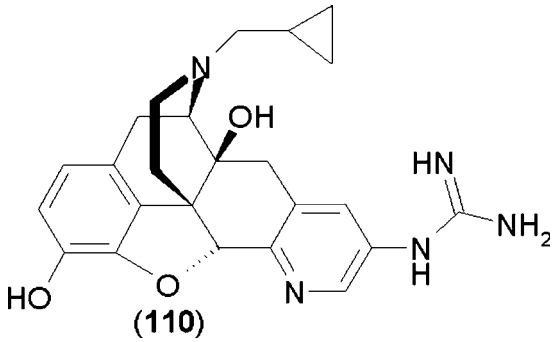
| | $K_e$ (nM) | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.038 | 16.7 | 10.2 | 440 | 268 |
| JDTic (**111**) | 0.02 | 2.16 | >300 | 108 | >15000 |
| **112** | 4.7 | 7.25 | 450 | 1.5 | 96 |
| **118** | 4.2 | 11 | 327 | 2.6 | 78 |
| **119** | 11.5 | 68.6 | 147 | 5.9 | 12.8 |
| **120** | 44.6 | 12 | 334 | 0.3 | 7.5 |
| **121** | 30 | 16.5 | 452 | 0.55 | 15 |
| **122** | 0.20 | 12.8 | >300 | 64 | >15000 |
| **123** | 0.37 | 12.7 | >300 | 34 | 810 |
| **124** | 19.6 | 17.4 | >300 | 0.9 | 15 |
| **125** | 0.16 | 29 | 628 | 181 | 3925 |
| **126** | 16.7 | 178 | >300 | 10.7 | >18 |

*norBNI indicates norbinaltorphimine.

**Table 15.** Antagonist Potency in the [$^{35}$S]GTPγS assay in Guinea Pig Caudate Membranes*,[49]

| | $K_i$ (nM) | | | | |
|---|---|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** | **μ/κ** | **δ/κ** |
| norBNI (**11**) | 0.038 | 16.7 | 10.2 | 439 | 268 |
| **45** | 0.13 | 5.55 | >300 nM | 43 | >2307 |
| JDTic (**111**) | 0.02 | 2.16 | >300 | 108 | >15000 |
| **110** | 11.5 | 68.6 | 213 | 6 | 18 |
| **119** | 4.7 | 7.25 | 450 | 1.5 | 96 |

*norBNI indicates norbinaltorphimine.




(**110**)

**Figure 37.** Structure of pyridomorphinan guanidinenaltrindole analog.

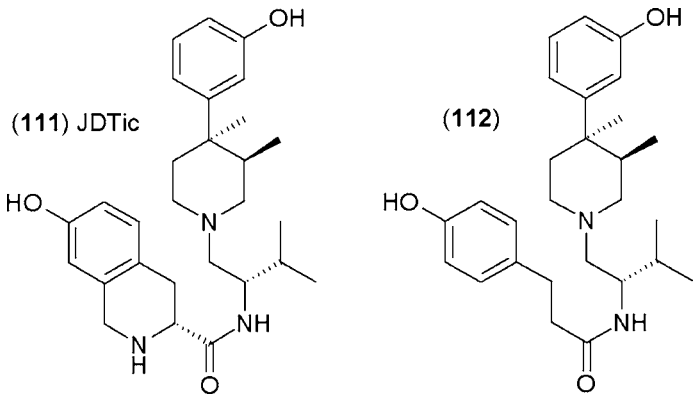



**Figure 38.** Structures of JDTic and its lead compound.

latencies to become immobile in the forced swim test, which were similar to rats given HSV-mCREB, which downregulates dynorphin production, and sham surgery (indicating an antidepressant effect of norBNI). Another study presented data that demonstrated mice pretreated with norBNI and exposed to stress via the forced swim test did not develop increased sensitivity to cocaine-conditioned place preference testing, which non-norBNI–treated mice developed,[84] again indicating an antidepressant-like effect of norBNI.

Another exciting area where kappa opioid antagonists are being explored as therapeutic agent is their potential use in the treatment of depression. The kappa opioid antagonists norBNI i.c.v., GNTI i.c.v., and ANTI intraperitoneal (i.p.) all displayed antidepressant-like activity in the forced swim test.[10] A recent study[85] of norBNI, administered s.c. in male CD1 mice, showed no effect in the forced swim test, however, it must be noted that norBNI was administered only 30 minutes before the test, a time when norBNI is not effective as a selective kappa opioid antagonist.[71-73] A study of norBNI in Sprague-Dawley rats showed an antidepressant-like effect in the learned helplessness model when norBNI was injected i.c.v., and intra-accumbens, but not when injected into the hippocampus (all trials conducted 3 days after injection).[86] Another study of norBNI showed an antidepressant effect in the learned helplessness model when injected into the hippocampus and the nucleus accumbens of male Sprague-Dawley rats.[87]

Scratching behavior has also been attributed to administration of kappa opioid antagonists. In one study,[88] norBNI administered s.c. produced dose-dependant scratching behavior (at the injection site) in IRC mice beginning within 5 minutes of injection and disappeared within 2 hours. This effect was dose-dependently reversed with both a histamine antagonist (chlorpheniramine) and a kappa agonist (U-50,488).[88] In another study,[89] GNTI administered s.c. to male Swiss mice precipitated frenzied scratching (at the site of injection) within 5 minutes, which tapered off between 40 and 80 minutes. This behavior was decreased by pretreatment with both centrally active (enadoline) and peripherally active (ICI 204448) kappa opioid agonists. Additionally the study indicated that i.c.v. and intrathecal (i.t.) administration of GNTI did not produce the scratching behavior. Other studies indicate that norBNI did not affect scratching behavior. When norBNI was administered s.c. to

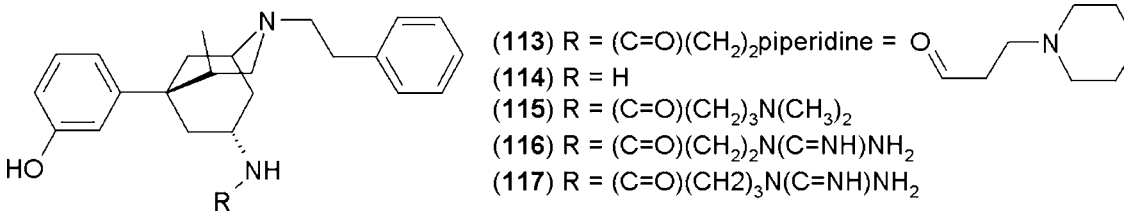



**Figure 39.** Structures of phenylmorphan JDTic analogs.

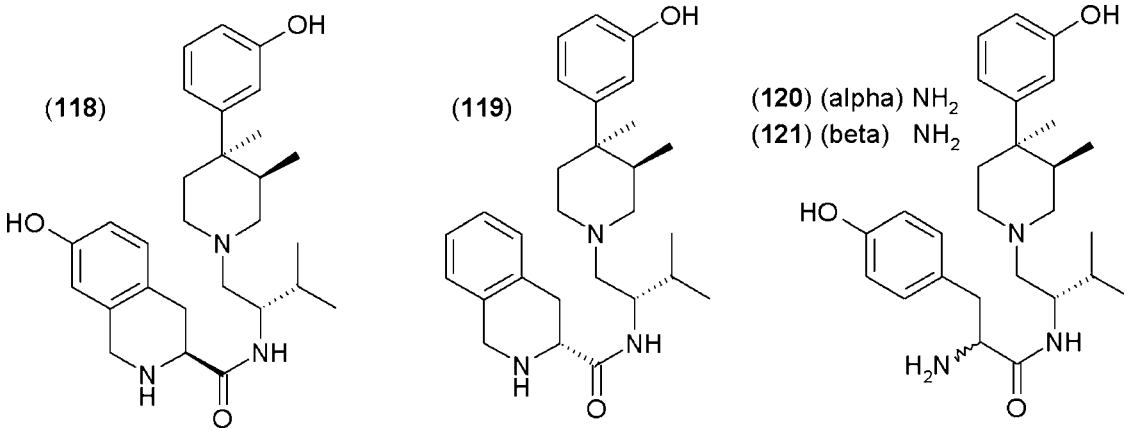



**Figure 40.** Structures of JDTic analogs.

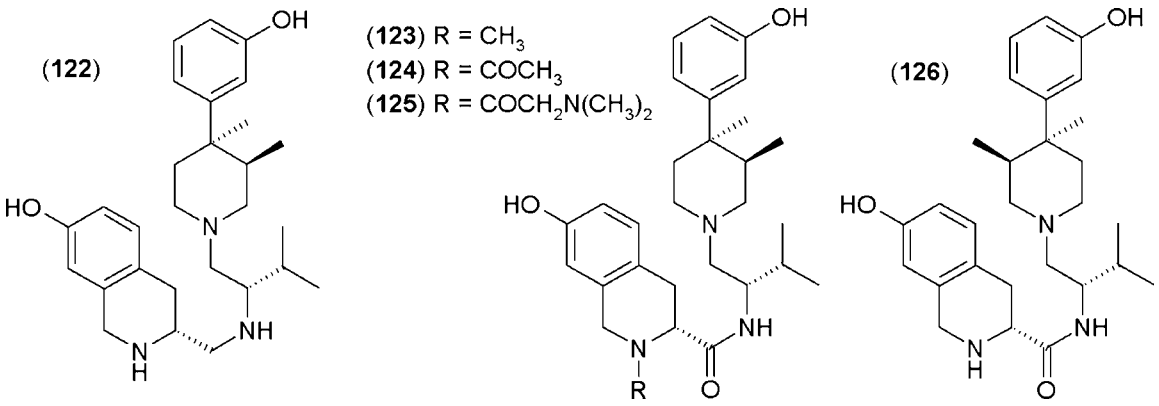
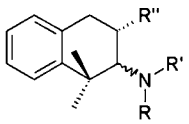



**Figure 41.** Structures of JDTic analogs.

male ICR mice there was no scratching effect noted after 24 hours,[90] but no description was given for the prior 24-hour time period immediately following the injection of norBNI. When norBNI was administered to rhesus monkeys s.c. there were no scratching responses detected in the 3 hours following injection and also none 24 hours after administration.[91] This administration of s.c. norBNI significantly blocked U-50,488 attenuation of morphine-induced scratching for a period 21 days after norBNI administration.[91] Another study in which norBNI was administered i.c.v. to male ddY mice, notes that norBNI treatment did not affect scratching behavior.[92] Taken together, these studies suggest that administration of a s.c. dose of kappa opioid antagonist may produce scratching behavior, however this behavior occurs during a time period (immediately following injection) when kappa opioid antagonist effects are inconsistent. After a time period of 24 hours or more after administration, when kappa opioid antagonists display kappa opioid antagonistic effects, there has been no induction of scratching behavior reported.




| | R | R' | R'' |
|---|---|---|---|
| **127** | $CH_3$ | $CH_3$ | H |
| **128** | *n*-propyl | H | H |
| **129** | *n*-propyl | $CH_3$ | H |
| **130** | *n*-propyl | *n*-propyl | H |
| **131** | cyclopropylmethyl (CPM) | H | H |
| **132** | CPM | $CH_3$ | H |
| **133** | CPM | CPM | H |
| **134** | allyl | H | H |
| **135** | allyl | $CH_3$ | H |
| **136** | allyl | allyl | H |
| **137** | Cinnamyl | H | H |
| **138** | Cinnamyl | $CH_3$ | H |
| **139** | Cinnamyl | Cinnamyl | H |
| **140** | (N is β) H | (N is β) H | $OCH_3$ |
| **141** | (N is β) H | (N is β) Cinnamyl | $OCH_3$ |

CPM = cyclopropyl methyl

**Figure 42.** Structures of aminotetralins.

Feeding behavior is another area where kappa opioid antagonists have been studied for their impact. NorBNI has produced the following: reduction of butorphanol-induced feeding in male Sprague-Dawley rats,[93] reduction in weight and food intake in lean and obese Zucker rats,[94] reduction of deprivation-induced food intake in rats,[95] reduction of sucrose intake in sham-fed rats,[96] reduction of GABA agonist– induced feeding in male Sprague-Dawley rats,[97] reduction of NPY-induced feeding in male Sprague-Dawley rats,[98] reduction of glucose solution intake in female Long-Evans rats.[99] GNTI has been shown to reduce U50,488-, DAMGO-, and deprivation-induced feeding behavior in rats.[11]

Both norBNI and GNTI have been explored in various other pharmacological models. NorBNI has also been studied for various other effects on systems including enhancement of morphine-induced sensitization in the rat,[100] the hypothalamic

**Table 16.** Antagonist Potency in the [$^{35}$S]GTPγS assay in Human Cloned Opioid Receptors*,[61]

| | $K_i$ (nM) | | |
|---|---|---|---|
| **Antagonist** | **(κ)** | **(μ)** | **(δ)** |
| norBNI (**11**) | 0.039 | 18.9 | 4.42 |
| NTX (**9**) | 1.86 | 0.59 | 5.44 |
| NTI (**5**) | 4.95 | 4.26 | 0.11 |
| **137** | 42.7 | 67.7 | NT |
| **140** | 49.3 | agonist | NT |
| **141** | 2.12 | 2.62 | 26.3 |

*norBNI indicates norbinaltorphimine; NTI, naltrindole; NTX, naltrexone.

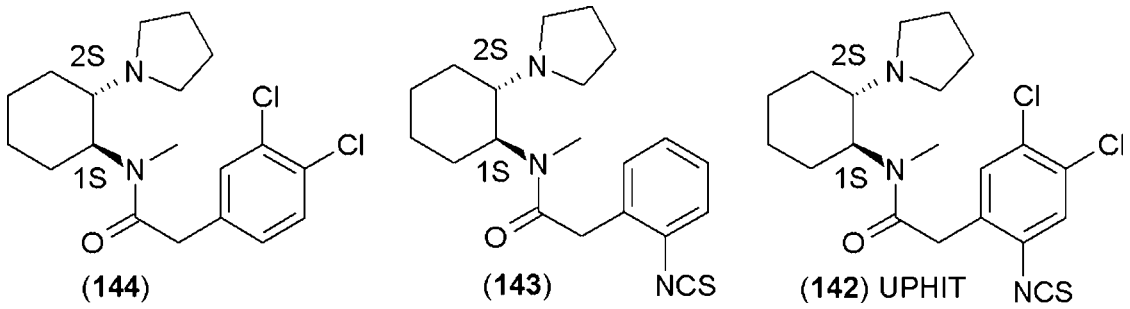



**Figure 43.** Structures of UPHIT and analogs.

pituitary-axis,[101] modulation of morphine-induced reward,[102] instrumental learning in the spinal cord,[103] decrease of THC-induced place aversion,[104] reversal of kappa opioid agonist–induced increases of [$^{35}$S]GTPγS binding,[105] enhanced binding in butorphanol-dependent rats,[106] enhancement of noradrenalin release,[107] kappa opioid inhibitory tone,[108] the enhancement of allodynia,[109] antagonism of kappa opioid agonist induced hypothermia,[110] antagonism of the effects of kappa agonist anticonvulsant effects in the maximum electroshock seizure model,[111] increases in the activity of tuberohypophysial dopamine neurons in male Long-Evans rats,[112] effects on the heart,[113-115] attenuation of the discriminative stimulus effects of kappa agonists in squirrel monkeys,[116] and attenuation of kappa agonist–induced food-reinforced responding in pigeons[78,117] and rats.[118]

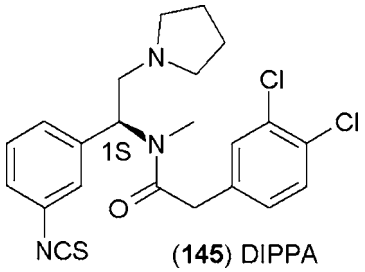



**Figure 44.** Structure of DIPPA.

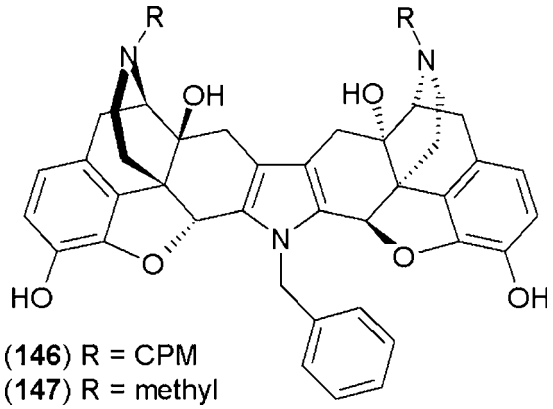



**Figure 45.** Structures of benzylated norBinaltorphimine analogs.

GNTI has been studied for its effects on systems including: the enhancement of allodynia,[109] antagonism of the effects of kappa opioid agonists in schedule controlled behavior in rhesus monkeys,[67] and antagonism of the discriminative stimulus effects of salvinorin A (a kappa opioid agonist) in rhesus monkeys.[30]

## Conclusions

Selective kappa opioid antagonists have been sought since the discovery of multiple opioid receptor types in the 1970s. Several compounds with kappa opioid selective pharmacology are now available for further research and numerous lead compounds have been presented that provide excellent candidates for future development. The structure activity relationships of the currently known selective kappa opioid antagonists indicate the need for a traditional antagonist pharmacophore that contains a second basic nitrogen. The pharmacology of the selective kappa opioid antagonists shows a delay in onset of action, a very long duration of action, and presents various possibilities for the treatment of human disease states.

## Acknowledgments

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