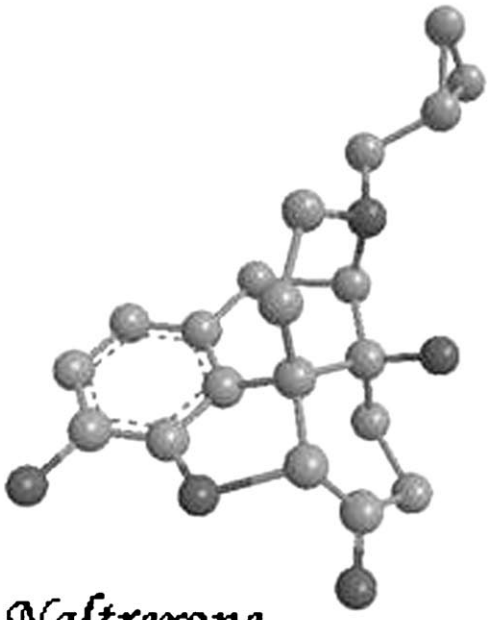
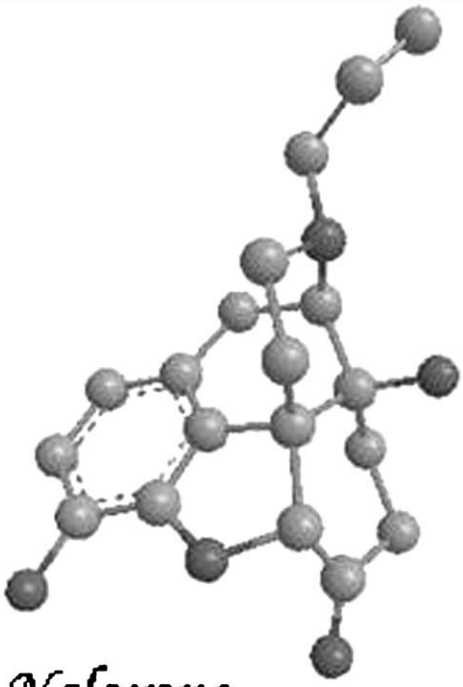


Naltrexone



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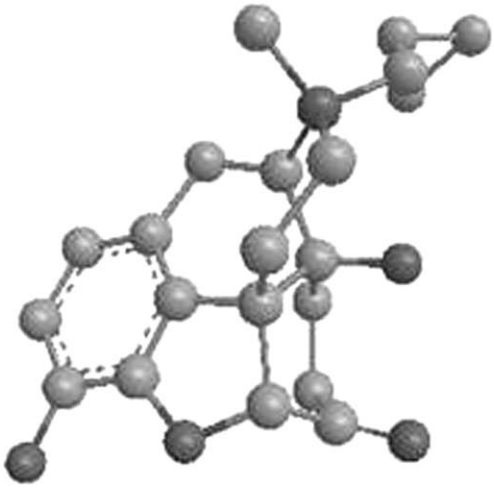
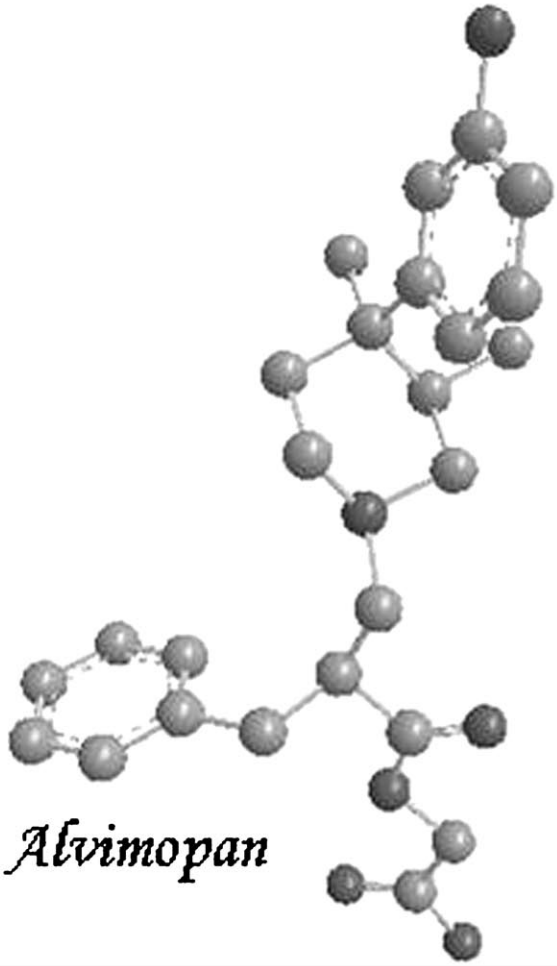


N-Methylnaltrexone



Alvimopan

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# Mu Opioid Receptor Antagonists: Recent Developments

Allan J. Goodman,* Bertrand Le Bourdonnec, and Roland E. Dolle[a]

*For thousands of years mu opioid agonists such as morphine have been utilized for their analgesic properties. Today, morphine and related compounds are still used as a first line therapy in the treatment of moderate to severe pain. However, despite the clear benefits of mu agonists in pain management, severe side effects such as dependence and respiratory depression are associated with use of these drugs. To date, there are only two approved mu opioid antagonists for use in the treatment of these adverse effects, that is, naloxone and naltrexone. However, many other clinical and therapeutic areas have been linked to mu opioid receptor antagonism. These include treatment of opioid induced pruritis of the skin, obesity, and Parkinson-induced tardive dyskinesia. Currently there are two compounds,* N*-methylnaltrexone and alvimopan, under FDA review as possible treatments for opioid induced bowel dysfunction and postoperative ileus. These compounds are of special interest as they are peripherally restricted. This attribute enables treatment of peripheral side effects induced by opioid agonists without reversal of the centrally mediated analgesia of the agonist. In this article we discuss the structural classes of mu opioid antagonists, their potential clinical applications, and review the relevant patents of the last ten years.*

## Introduction

It is well established that the action of endogenous opioid peptides are mediated by a family of G-protein coupled seven transmembrane receptors, designated as mu, kappa, and delta opioid receptors.[1] Activation of the opioid receptors in the central, peripheral, and enteric nervous systems by their endogenous peptides is involved in the regulation of both behavioral and homeostatic functions, such as nociception, food intake, respiration, reward, and gastrointestinal motility. The analgesic properties of opioid agonists such as morphine **1**, oxycodone **2**, meperidine **3**, methadone **4**, fentanyl **5**, and tramadol **6** are well known (Figure 1). The analgesic action of **1**–**6** are predominantly mediated by activation of the mu opioid receptor. Activation of mu opioid receptors has also been associated with a wide range of undesirable side effects. These include dependence, sedation, decreased respiratory function, seizure, constipation, and opioid bowel dysfunction (OBD). Despite these serious and potentially fatal adverse events, the use of opioids such as morphine and oxycodone for moderate to severe pain has increased in recent years. Morphine use in the U.S. increased more than tenfold from 1980 to 1999.[2,3] The use of opioid-based narcotics continues to rise.[4] In addition to research performed by the academic community, more than $2.5 billion has been spent by the pharmaceutical industry over the past two decades to identify new pain medications. Despite these efforts, morphine and related compounds still remain the first-line therapy for moderate to severe pain in the U.S. Furthermore, many new drugs either marketed or in clinical development are alternative dosage forms of classical opioids.[5] Opioid antagonists are commonly used as rescue medications to reverse the severe side effects (respiratory depression, overdose) induced by opioid agonists. These agents are also used clinically to treat dependence induced by opioid use and alcoholism.[6] Other potential therapeutic indications of mu opioid antagonists include obesity,[7] psychosis,[8] and Parkinson's disease.[9]

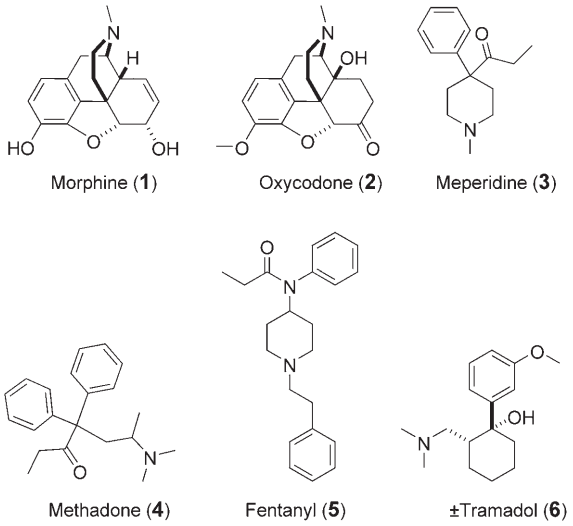


**Figure 1.** Opioid agonists.

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## Chemical Classes of Mu Opioid Antagonists

There has been extensive research carried out over the past 30 years to generate 'pure' mu opioid antagonists.[10,11] A pure mu opioid antagonist is defined as a ligand that shows no in vivo or in vitro agonist effects at high doses (typically 10 μM). Several structural classes have been identified as mu opioid antagonists with varying degrees of selectivity over delta and kappa opioid receptors. These include *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidines, morphinans, phenylmorphans, octahydroquinolizines, and octahydropyridopyrazines. These structural classes will be discussed in detail in the following sections.


Allan Goodman received his degree in chemistry in 1996 from the University of Northumbria at Newcastle in the U.K. Under the supervision of Dr. Stephen Stanforth he received his PhD in organic chemistry from the same university in 1999. He was a postdoctoral researcher at the University of Massachusetts working on molecular recognition processes under the guidance on Professor Vincent Rotello. Allan joined Adolor in 2004 and is a Senior Research Investigator in the Medicinal Chemistry department.

Bertrand Le Bourdonnec obtained his diploma in Chemical engineering from the Ecole Nationale Superieure de Chimie de Lille (ENSCL), France in 1994. He then received his Ph.D. degree in Organic Chemistry in 1997 from the Institute of Pharmaceutical Chemistry (Lille, France). He joined the College of Pharmacy of the University of Minnesota, where he was a postdoctoral fellow from 1997 to 2000 in the laboratory of Professor P. S. Portoghese. He joined Adolor Corporation in 2000 and holds the position of Principal Research Investigator in the Department of Medicinal Chemistry.

Roland E. Dolle is currently the Senior Director of Chemistry at Adolor Corporation having joined the company in its pre-IPO stage in 2000. Research interests are focused on the discovery of novel pain therapeutics and agents to manage the side effects of narcotics. Roland began his career as a drug discovery scientist in medicinal chemistry at SmithKline & French (now GlaxoSmithKline). He completed graduate studies in synthetic organic chemistry in 1985 at the University of Pennsylvania under the direction of Professor K. C. Nicolaou.


### Morphinans

The morphinan structural series represents the earliest and most extensively investigated class of mu opioid antagonists. These compounds are close analogues of morphine and the antagonist behavior is mediated through changes in the N-substituent. Changing the *N*-methyl group of the agonist oxymorphone **7** to an allyl or cyclopropylmethyl group leads to naloxone **8** and naltrexone **9**, respectively (Figure 2). Compounds **8** and **9** have been shown to display full antagonist activity at the mu opioid receptor. Naloxone and naltrexone, although pure mu antagonists, are only moderately selective for the mu opioid receptor.[12] In 1981, Portoghese described the first selective mu opioid antagonist, β-funaltrexamine (β-FNA) **11** (Figure 3), a site-directed alkylating agent that binds covalently to mu opioid receptors.[13] β-FNA, an analogue of β-naltrexamine **10**, initially binds to all three opioid receptors, but because of very subtle structural differences within the receptor subtypes this compound alkylates, in vitro, only mu opioid receptors. This ability to selectively alkylate the mu receptors leads to a depletion of the mu opioid receptor population. Consequently this then enables study of mu opioid mediated effects, or the non-mu mediated interactions of opioid ligands. Bioisosteric replacement of the 14-hydroxy group of naltrexone with an amino group was found to be well tolerated (Figure 3). Indeed 14-aminonaltrexone **12** displayed potent antagonist activity in in vitro and in vivo studies.[14] Acylation of the 14-amino group led to the mu antagonists clocinnamox (C-CAM) **13** and methocinnamox (M-CAM) **14**[15] which, like β-FNA, also bind to the mu opioid receptor in an irreversible fashion. However, unlike β-FNA which showed potent kappa agonist activity in vitro, the 14-acylamino derivatives displayed potent antagonistic activity at all three opioid receptors.[16] It should be noted that one of the major drawbacks associated with derivatives of 14-acylaminonaltrexone is their complex synthesis.[17,18] Opening of the dihydrofuran ring of the morphinan structures led to another class of opioid antagonists exemplified by cyprodime **15**. In the [$^3$H] naloxone displacement binding assay cyprodime ($IC_{50}$ = 4.5 nM) exhibited good affinity for mu opioid receptors, comparable to the mu binding affinity of naloxone ($IC_{50}$ = 2.0 nM) and naltrexone ($IC_{50}$ = 0.5 nM).[19,20] Furthermore in the mouse vas deferens bioassay, cyprodime exhibited improved mu opioid receptor selectivity in compari-

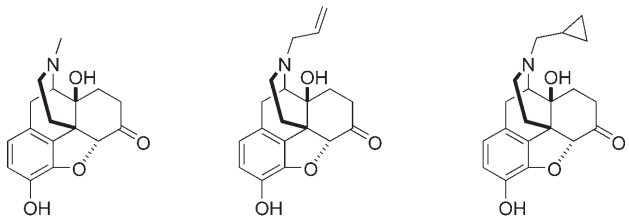



**Figure 2.** Oxymorphone and analogues.

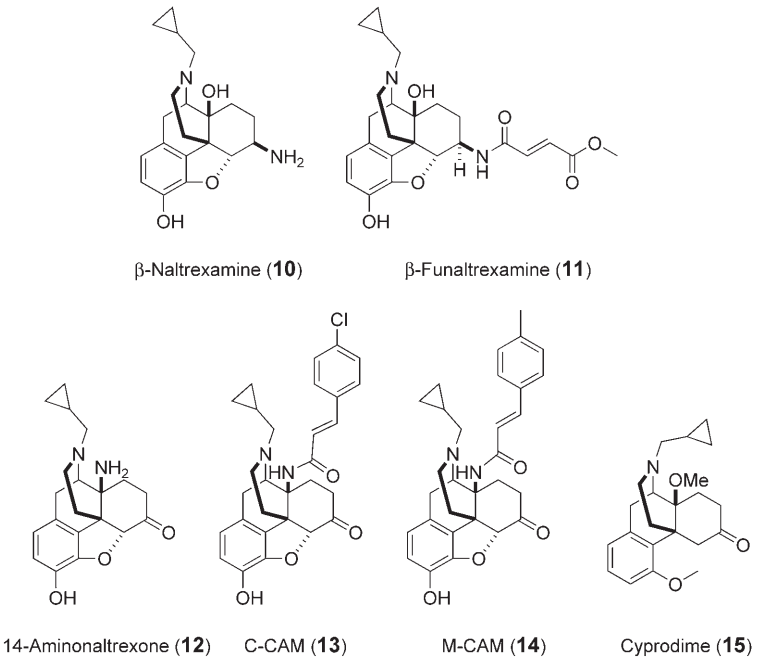



**Figure 3.** Morphinan-based mu opioid receptor antagonists.

son to naloxone (cyprodime: $\kappa/\mu = 28$, $\delta/\mu = 110$; naloxone: $\kappa/\mu = 12$, $\delta/\mu = 7$).[20,21]

### *trans*-3,4-Dimethyl-4-(3-hydroxyphenyl)piperidines and conformationally constrained analogues

In 1978, Zimmerman identified the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines as a novel class of opioid antagonists.[21] Introduction of a methyl substituent at the 3-position of the opioid agonist **16**[23] was investigated (Figure 4). This structural modification led to the identification of compound **17**, which displayed pure antagonist activity in vivo. Interestingly the *cis*-3,4-dimethyl analogue of **17**, that is, **18** exhibited mixed agonist/antagonist behavior and was more than 100 times less potent than **17** in in vivo antagonist activity studies. It is hypothesized that the antagonistic behavior of **17** is mediated through the phenol moiety adopting an equatorial orientation. This configuration is thought to be driven by the *trans* relationship of the 3- and 4-methyl groups on the piperidine ring.[24] This hypothesis was later substantiated through synthesis and pharmacological evaluation of constrained analogues

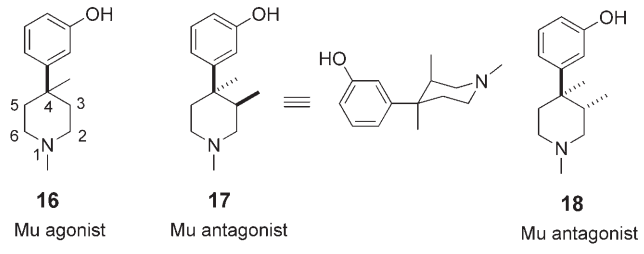



**Figure 4.** Stereochemical effects on functional activity (agonist versus antagonist) in the 3,4-dimethyl-4-(3-hydroxyphenyl)piperidines.

of **17**. Linkage of the 4-methyl substituent and the C2 position of the piperidine ring of **16** using an ethylene moiety (Figure 5), led to the 5-(hydroxyphenyl)-morphan derivatives **19**–**21**.[25–27] As observed in the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines, addition of a methyl group at the 9β position of the morphan skeleton converted the mu opioid agonist **19** to the mu opioid antagonist **20**. However, unlike the *cis*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine **18**, the 9α-isomer **21** displayed pure, albeit weak, antagonist behavior in vitro. These results suggest that the conformational restriction locks the phenol moiety into an equatorial orientation, thereby inducing antagonistic behavior. X-ray crystallographic data for compound **20** confirms this assertion (Figure 6).[26] Carroll also reported a different series of constrained analogues of **17** in which the C4 methyl group is attached to C3 via a benzyl moiety, that is, **22**. As with the morphinans, compound **22** exhibits pure antagonist activity. As these compounds act predominantly at the kappa opioid receptor they will not be discussed in detail in this article.[28]

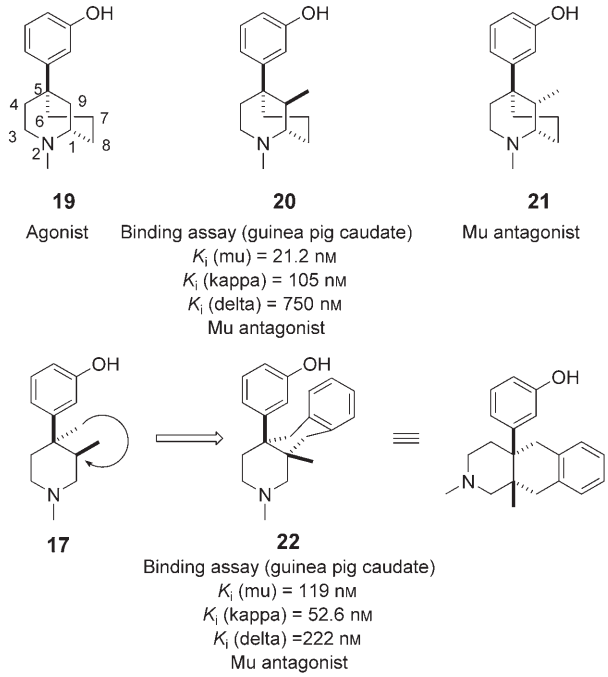



**Figure 5.** Conformational restriction of 3,4-dimethyl-(3-hydroxyphenyl)-piperidines.

### Optimization of the N-substituent

As previously discussed, modification of the N-substituent of potent morphinan agonists leads to potent antagonists. However, the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines were the first class of opioid compounds that did not show modulation of the intrinsic behavior with modification of the N-substituent. Instead the N-substituent was found to modu-

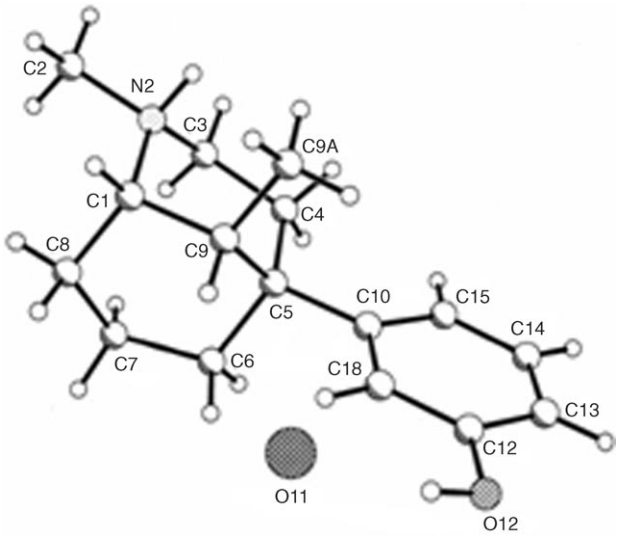



**Figure 6.** X-ray crystallographic representation of compound **20**.

late the binding affinity of the ligand to the opioid receptors. As shown in Figure 7, replacement of the NH moiety of **23** with an *N*-phenethyl **24** or phenpropyl **25** group led to a significant increase in the affinity toward the mu opioid receptor.[27] Hence it was found that the optimal N-substituent consisted of a lipophilic moiety (phenyl or cyclohexyl) attached through a 2–3 atom spacer to the piperidine nitrogen. Similarly, replacement of the *N*-methyl group of the constrained analogues **20** and **22** with an *N*-phenethyl moiety (that is, **26** and **27** respectively) results in a significant increase of the binding affinity toward the mu receptor.[28,29] To gain insight into the bioactive conformation of *N*-substituted *trans*-3,4-dimethyl-(3-hydroxyphenyl)piperidine derivatives, compounds containing rotationally restricted or rigidified N-substituents were prepared **28**–**31**.[30] Comparison of the binding affinities between compound **28** ($K_i$(mu) = 0.74 nM) and its *cis* isomer **29** ($K_i$(mu) = 11.4 nM) strongly suggests that the spatial orientation of the phenyl ring is critical for optimal receptor interaction (Figure 8). Furthermore, comparison of the binding data of the *cis* and *trans*-cyclopropane analogues **30** ($K_i$(mu) = 56.1 nM) and **31** ($K_i$(mu) = 1.75 nM), respectively, supports this hypothesis.

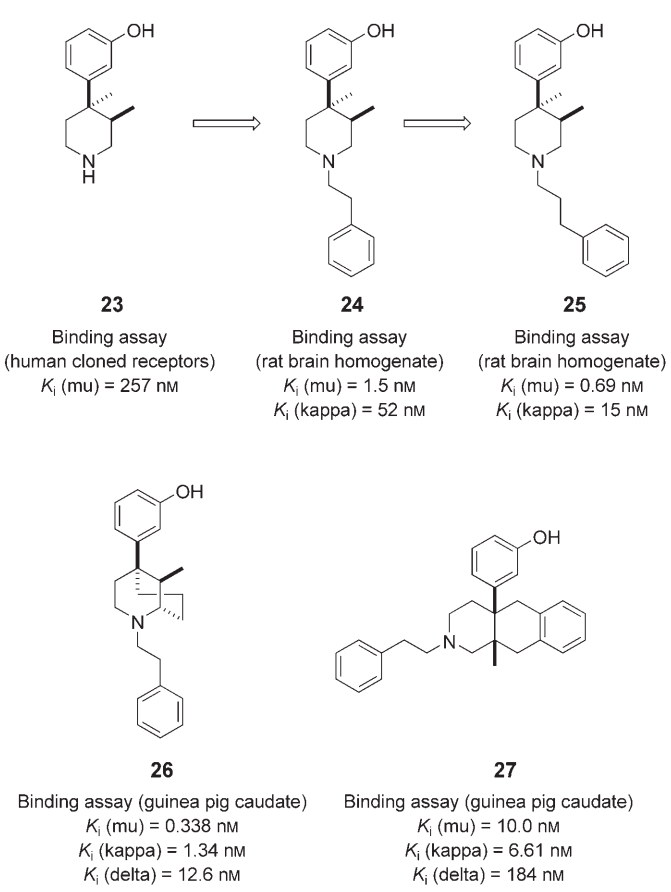



**Figure 7.** Effect of *N*-substituent on opioid receptor binding.

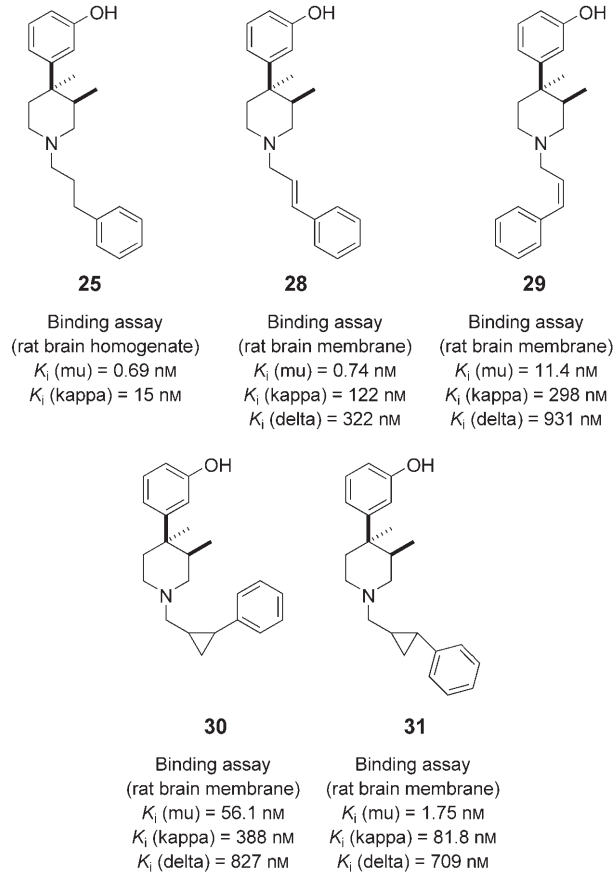



**Figure 8.** Effects of confomationally restricted *N*-substituents on opioid receptor binding.

### Octahydroquinolizines

To provide information on the mu antagonist bioactive conformation, a series of rigid analogues of the potent opioid antagonist **24** were designed and synthesized at Adolor Corporation (Figure 9).[31] Rigidification of the template was achieved by introduction of an ethylene group between the 2- or 6-position of the piperidine ring and the benzylic carbon of the *N*-phe-

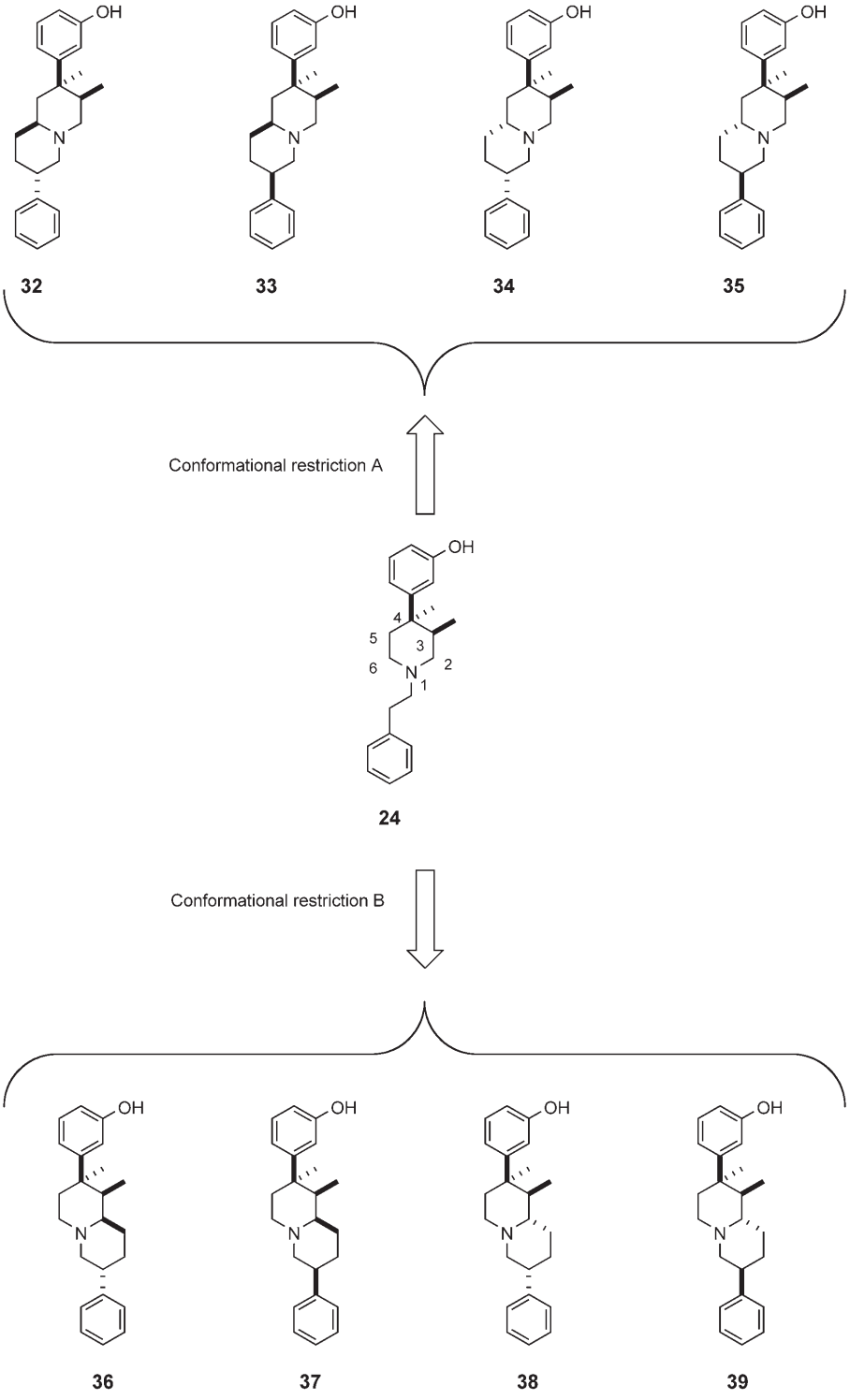
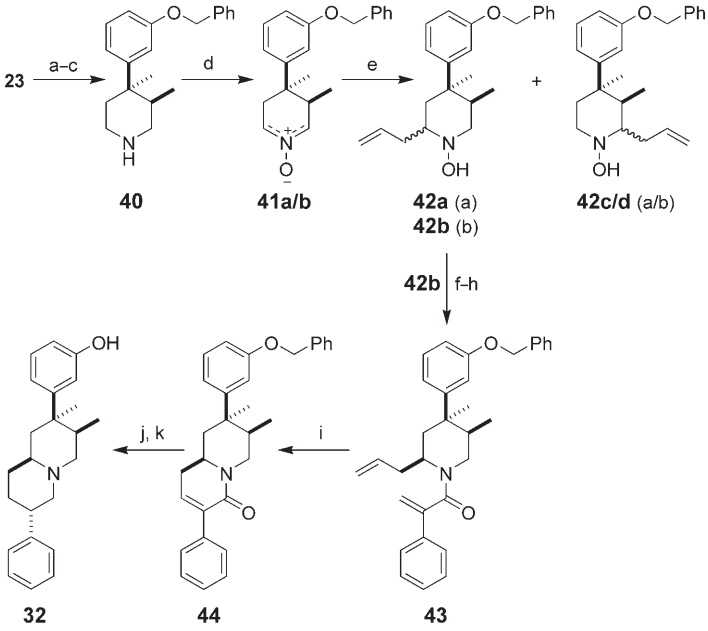



**Figure 9.** Structures of the constrained analogs of **24**.

nethyl moiety. This structural modification gave rise to eight regio- and stereoisomers, **32**–**39**, which were synthesized and tested for their binding affinity at mu, delta, and kappa opioid receptors. Compound **23** was used as starting material for the synthesis of the rigidified structures (Scheme 1). The first key step of the sequence consisted of the addition of allylmagnesium chloride to the nitrones **41a/b**. This afforded the four regio- and stereoisomers **42a**–**d**. Isolation of stereoisomers **42a** and **42b** was achieved through column chromatography. However, stereoisomers **42c** and **42d** were inseparable by column chromatography and were carried forward as a mixture of stereoisomers. Ring closing metathesis (RCM) of the *bis* olefin **43**, obtained in three steps from **42b**, was achieved in high yield using the second generation Grubb's catalyst. Hydrogenation of the RCM product, that is, **44**, followed by reduction of the corresponding lactam using the borane-dimethyl sulfide complex afforded the target compound, that is, **32**. A similar reaction sequence was employed to prepare compounds **33**–**39**. The overall yields of **32**–**39** from **23** ranged from 0.07% to 4%. Of the eight constrained analogues prepared during this study, **32** and **39** displayed potent affinity at the mu opioid receptor (**32**: $K_i = 0.62$ nM; **39**: $K_i = 0.90$ nM), comparable to the mu affinity of the flexible derivative **24** ($K_i = 1.8$ nM). Compound **32** was a highly potent mu opioid antagonist ($IC_{50} = 0.54$ nM) in the [$^{35}$S]GTP$\gamma$S functional assay. Interestingly, compound **39** showed no antagonist activity. Indeed, compound **39** was found to be a potent full agonist at the mu opioid receptor with an $EC_{50}$ of 53 nM (Figure 10). Comparison of the low energy conformers of **24**, **32**, and **39** was conducted to provide some insight into the agonist and antagonist bioactive conformations (see Table 1). These studies showed that the mu opioid antagonist **32** adopts, in its lowest energy conformation, an extended configuration in which the hydroxyphenyl moiety is positioned in an equatorial orientation. A low energy conformation of **24** was found to overlay well with the lowest energy of **32** (Figure 11). On the contrary, the lowest energy conformation of the mu opioid agonist **39** adopts a folded configuration in which the hydroxyphenyl moiety is positioned




**Scheme 1.** Synthesis of octahydroquinolizines. a) $Boc_2O$, $Et_3N$, THF; b) Benzyl bromide, $K_2CO_3$, DMF; c) HCl in dioxane, MeOH; d) $Na_2WO_4$, $H_2O_2$, $H_2O$/$CH_2Cl_2$/$CH_3OH$, 0–25 °C; e) $CH_2=CHCH_2MgCl$, THF, 0–25 °C; f) Zn, $CH_3CO_2H$/$H_2O$, sonication, 25 °C; g) $C_6H_5COCO_2H$, TBTU, i-$Pr_2EtN$, $CH_3CN$, 25 °C; h) $(Ph)_3PCH_3Br$, t-BuOK, THF, $C_6H_6$, reflux; i) Grubbs catalyst (2nd generation), $CH_2Cl_2$, 25 °C; j) $H_2$, Pd/C, $C_2H_5OH$, 25 °C; k) $BH_3{\cdot}S(CH_3)_2$, THF, reflux.

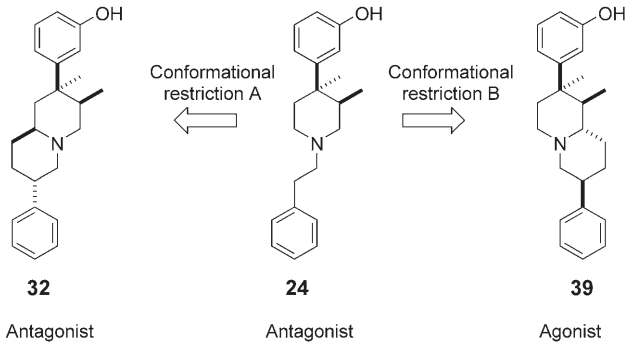



**Figure 10.** Conformational restriction effects on intrinsic behavior.

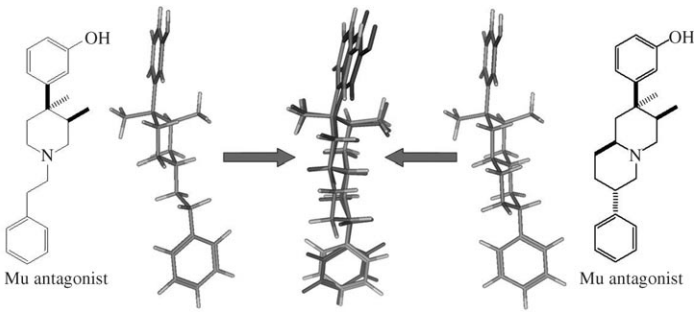



**Figure 11.** Lowest energy conformations and favourable overlay of mu antagonists **24** and **32**.

**Table 1.** In vitro data for compounds **24**, **32**, and **39**.

| Assay | Parameter | 24 | 32 | 39 |
|---|---|---|---|---|
| Mu receptor binding | $K_i$ | 1.9 nM | 0.62 nM | 0.90 nM |
| Mu [$^{35}$S]GTPγS, human cloned (antagonism) | $IC_{50}$ | 1.1 nM | 0.54 nM | – |
| Mu [$^{35}$S]GTPγS, human cloned (agonism) | $EC_{50}$ | – | – | 53 nM |
| Kappa receptor binding | $K_i$ | 17 nM | 9 nM | 65 nM |
| Delta receptor binding | $K_i$ | 33 nM | 31 nM | 2.1 nM |

in an axial orientation. The lowest energy conformation of **39** does not overlay well with a low energy conformation of **24** (Figure 12). The pendant phenyl moiety of antagonist **32** was shown to be a crucial component for optimal binding (Figure 13a). Replacement of the pendant phenyl group of **32** with a hydrogen atom **45** led to a substantial decrease in affinity for the mu opioid receptor. Furthermore, the difference in affinity between **32** and its diastereomer **33** showed that spatial orientation of the phenyl ring is also of crucial importance for good affinity toward the mu opioid receptor. Similar SAR was observed in the agonist series (Figure 13b).

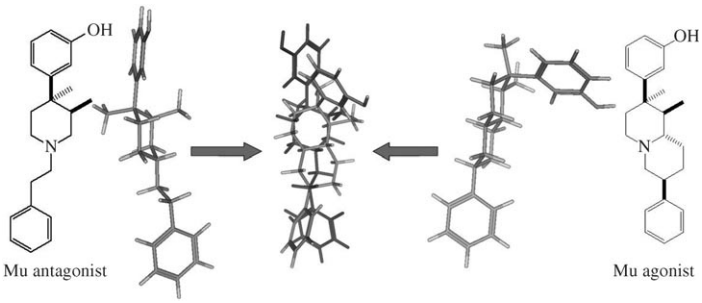



**Figure 12.** Lowest energy conformations and poor overlay of mu agonist **39** and antagonist **24**.

### Octahydropyridopyrazines

The complexity of the synthesis of the octahydroquinolizine class of compounds prevents further SAR exploration at positions 8 and 9 of the template (Figure 14). Therefore, the authors investigated the bioisosteric replacement $CH_2 \rightarrow NH$ at position 8 of the octahydroquinolizine scaffold.[32] Synthesis of the octahydropyridopyrazine scaffold is shown in Scheme 2. The key step of the synthetic sequence was the introduction of the carboxylic acid moiety at the 6β-position of the piperidine ring of **48**. This was achieved with high stereo- and regioselectivity. Coupling of **49** with various amino acid methyl esters provided the amides **50** which were converted to the subsequent diketopiperazine derivatives **51** under standard conditions. Reduction of **51** afforded the amines **52** which could be further derivatized to **53**. As shown in Figure 15, bicycle **54**, the bioisosteric analogue of **32**, displays potent mu opioid antagonist activity. As anticipated from previous studies removal of the pendant phenyl moiety in **54** led to a signifi-

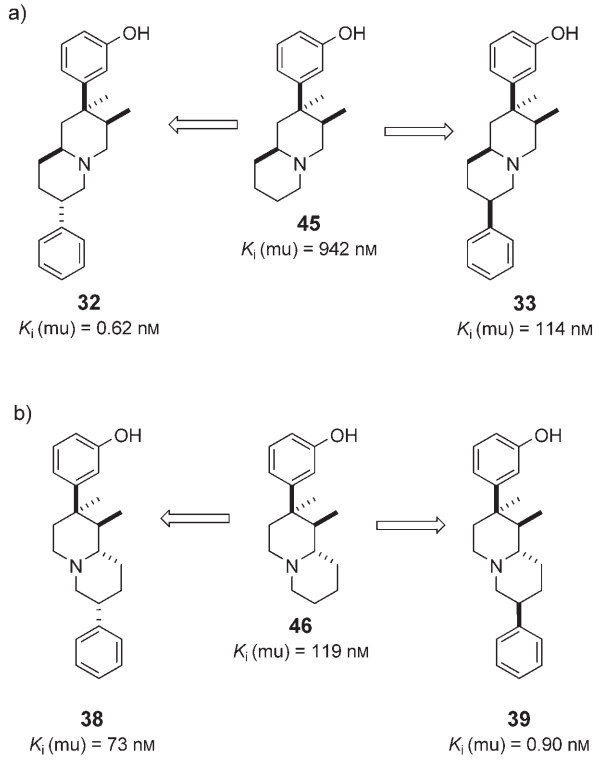



**Figure 13.** Importance of the pendant phenyl ring for optimal mu binding affinity in the octahydroquinolizine series.

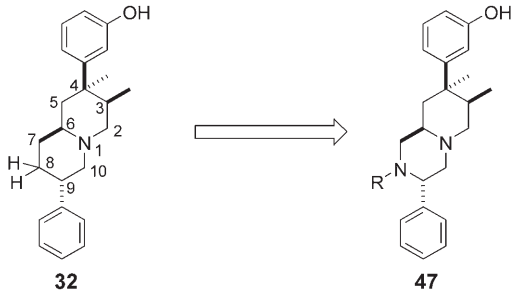
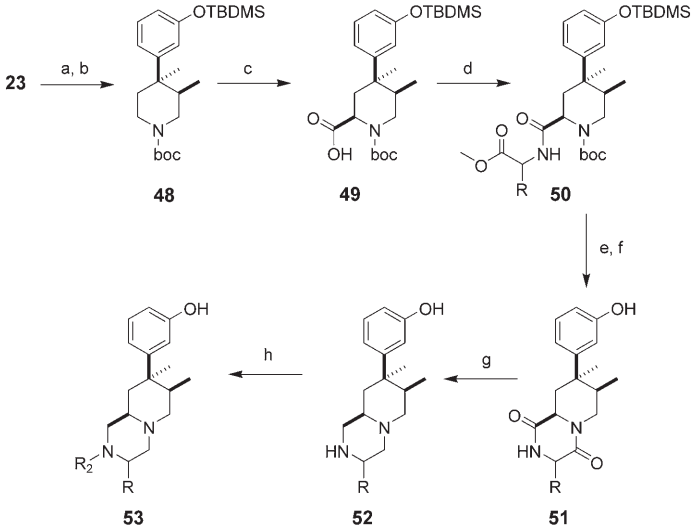



**Figure 14.** Octahydropyridopyrazines—design rationale.

cant loss of the affinity toward the opioid receptors. However, substitution of the N-position of **55** with benzoyl or benzyl moieties produced potent mu opioid receptor antagonists (Figures 16 and 17).

### Phenol bioisostere

Cyclazocine **58** is a partial mu agonist with a short duration of action due to extensive glucuronidation during first pass metabolism. In an attempt to improve the pharmacokinetic properties of cyclazocine, research designed to identify bioisosteres of the 8-OH substituent was conducted.[33] Results from this study identified the carboxamido derivative **59** as a suitable bioisostere of the phenolic hydroxyl group of cyclazocine (Figure 18). This interesting and unexpected finding initiated similar studies with the mu opioid antagonist naltrexone **9**. As




**Scheme 2.** Preparation of octahydropyridopyrazines. a) $Boc_2O$, $Et_3N$, THF; b) $(CH_3)_3Si(CH_3)_2Cl$, imidazole, DMAP, DMF; c) s-BuLi, TMEDA, $CO_2$, $Et_2O$; d) amino acid methyl ester, TBTU, $iPr_2NEt$, $CH_3CN$; e) 4M HCl in dioxane; f) for R = H, $Et_3N$, reflux; for R > H, toluene or xylene, reflux; g) $BH_3{\cdot}S(CH_3)_2$, THF; h) $R_2COCl$ or $R_2COOH$ and coupling agent or $R_2CHO$, [H-].

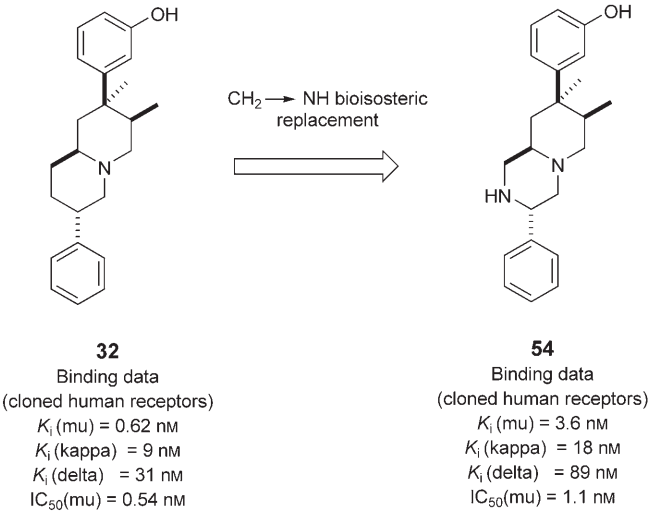



**Figure 15.** Bioisosteric replacement effects on receptor binding.

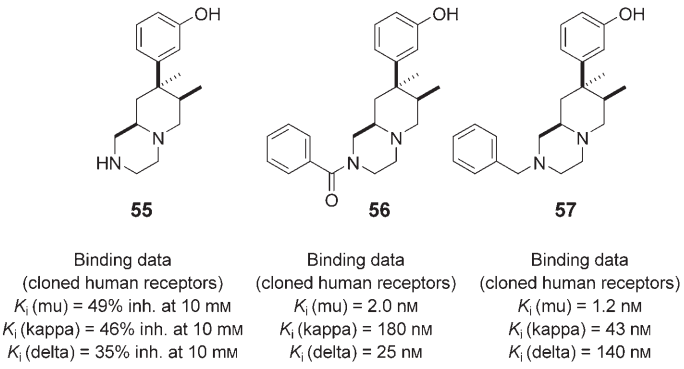
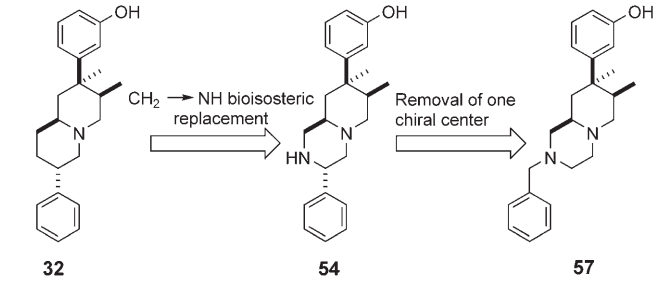



**Figure 16.** Structures and in vitro profile of **55**–**57**.




**32**

No. steps: 11
Overall yield: 0.07%
No. chiral centers: 4
Stereoselective control: No
Regioselective control: No
$K_i$ (mu) = 0.62 nM
$IC_{50}$ (mu) = 0.54 nM

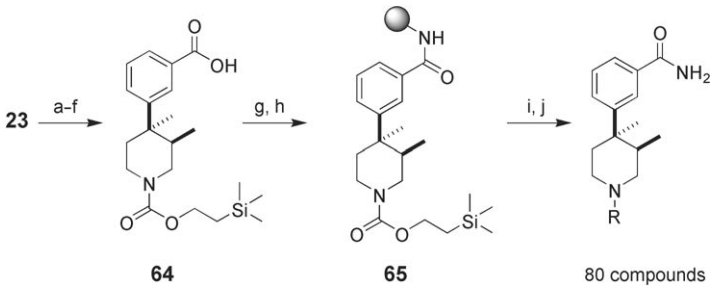
**54**

No. steps: 7
Overall yield: 14%
No. chiral centers: 4
Stereoselective control: Yes
Regioselective control: Yes
$K_i$ (mu) = 3.6 nM
$IC_{50}$ (mu) = 1.1 nM

**57**

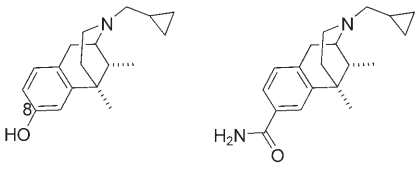
No. steps: 8
Overall yield: 25%
No. chiral centers: 3
Stereoselective control: Yes
Regioselective control: Yes
$K_i$ (mu) = 1.2 nM
$IC_{50}$ (mu) = 0.73 nM

**Figure 17.** Comparison of binding profile and chemistry of **32**, **54** and **57**.




**64** **65** 80 compounds

**Scheme 3.** Solid-phase synthesis of *trans*-3,4-dimethyl-4-(3-carboxamidophenyl)piperidines. a) $Boc_2O$, $Et_3N$, THF; b) $C_6H_5N(SO_2CF_3)_2$, $Et_3N$, $CH_2Cl_2$; c) CO(g), $Pd(OAc)_2$, DPPF, $Et_3N$, DMSO/MeOH; d) HCl/$Et_2O$, MeOH; e) 2-(trimethylsilyl)ethyl-p-nitrophenyl-carbonate, $(iPr)_2EtN$, $CH_3CN$; f) LiOH, $H_2O$/THF; g) Fmoc-deprotected Rink amide resin, HATU, HOBt, $(iPr)_2EtN$, $CH_2Cl_2$/DMF; h) TBAF, THF; i) aldehyde or ketone, NMP/EtOH, $BH_3/C_5H_5N$; j) TFA/$CH_2Cl_2$.

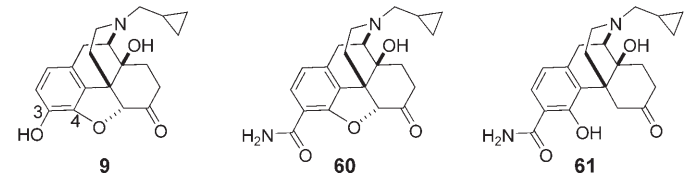



**58**

Binding data
(human cloned receptors)
$K_i$ (mu) = 0.10 nM
$K_i$ (kappa) = 0.052 nM
$K_i$ (delta) = 0.58 nM

**59**

Binding data
(human cloned receptors)
$K_i$ (mu) = 0.17 nM
$K_i$ (kappa) = 0.28 nM
$K_i$ (delta) = 2.6 nM




**9**

Binding data
(human cloned receptors)
$K_i$ (mu) = 0.11 nM
$K_i$ (kappa) = 0.19 nM
$K_i$ (delta) = 60 nM

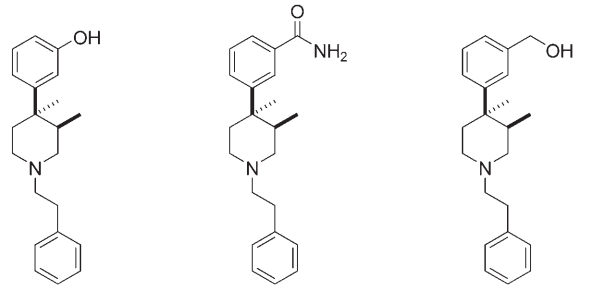
**60**

Binding data
(human cloned receptors)
$K_i$ (mu) = 0.71 nM
$K_i$ (kappa) = 11 nM
$K_i$ (delta) = 550 nM

**61**

Binding data
(human cloned receptors)
$K_i$ (mu) = 0.052 nM
$K_i$ (kappa) = 0.23 nM
$K_i$ (delta) = 2.6 nM

**Figure 18.** Opioid binding of **9**, **58**–**61**.




**24**

Binding data
(human cloned receptors)
$K_i$ (mu) = 1.9 nM
$K_i$ (kappa) = 17 nM
$K_i$ (delta) = 33 nM

**62**

Binding data
(human cloned receptors)
$K_i$ (mu) = 4.7 nM
$K_i$ (kappa) = 95 nM
$K_i$ (delta) = 72 nM

**63**

Binding data
(human cloned receptors)
$K_i$ (mu) = 11 nM
$K_i$ (kappa) = 840 nM
$K_i$ (delta) = 270 nM

**Figure 19.** Bioisosteres of **24**.

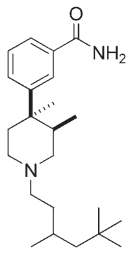
anticipated, the carboxamido analogue of naltrexone, that is, **60**, retained high affinity for the mu opioid receptor.[34] Ring opening of the dihydrofuran portion of **60**, led to compound **61** which binds to the mu opioid receptor with picomolar affinity.[35] It is hypothesized that intramolecular hydrogen bonding between the carbonyl oxygen of the carboxamide moiety and the adjacent hydroxyl group locks the molecule into its active conformation.[35] Bioisosteric replacement of the phenolic moiety of the (+)-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine derivatives was also investigated (Scheme 3).[36] This study showed that the carboxamido and hydroxymethyl moieties were effective bioisosteres of the hydroxyl phenolic group (Figure 19). Having identified the carboxamido group as a suitable bioisostere for the phenolic moiety, SAR studies at the *N*-position of **62** were explored. Using solid-phase chemistry a library of 80 compounds was prepared. This led to the identification of compound **66** (Figure 20), the most potent derivative reported in this study.

## Clinical Indications of Mu Opioid Antagonists

### Centrally acting mu antagonists

#### *Marketed mu antagonists*

The mu opioid antagonists naloxone and naltrexone are used clinically as rescue medications for opioid related intoxication. These compounds have also been studied for the treatment of many other CNS disorders. Tables 2 and 3 highlight some therapeutic indications studied or treated with naloxone and naltrexone, respectively. Some of the potential indications




**66**

Binding data
(human cloned receptors)
$K_i$ (mu) = 0.7 nM
$K_i$ (kappa) = 8.1 nM
$K_i$ (delta) = 19 nM

**Figure 20.** Structure and opioid binding data of compound **66**.

**Table 2.** Clinical and potential therapeutic uses of Naloxone.

| Indication | FDA approved | Notes | Reference |
|---|---|---|---|
| Antidiarrheal overdose, Diphenoxylate | No | Naloxone has proven effective in reversing toxic overdose symptoms secondary to Lomotil (diphenoxylate and atropine) | [39–41] |
| Drug detoxification—Opioid abuse | No | Several studies have indicated that naloxone can be used effectively for the rapid detoxification of narcotic addicts | [42, 43] |
| Drug-induced constipation—Opioid analgesic adverse reaction | No | Naloxone has been shown to be effective in treating opioid-induced constipation | [44–46] |
| Methadone overdose | Yes | Naloxone is useful in treating symptoms resulting from methadone overdose; repeated doses of naloxone may be necessary to prevent recurrence of symptoms | [47, 48] |
| Opioid abuse | No | Naloxone therapy has been shown to be effective in the treatment of opioid-addicted patients in methadone treatment programs | [49–51] |
| Opioid analgesic adverse reaction—Respiratory depression | Yes | Naloxone is indicated for the complete or partial reversal of narcotic depression including respiratory depression, induced by natural and synthetic opioids | [52–59] |
| Opioid dependence; Diagnosis | No | Naloxone is effective in diagnosing physical dependence in opiate addicts | [60–62] |
| Overdose of opiate, known or suspected; Diagnosis | Yes | Naloxone is indicated for the complete or partial reversal of opioid depression including respiratory depression, induced by natural and synthetic opioids | [63–68] |
| Pruritus of skin | No | Naloxone has been effective in narcotic-induced and cholestatic pruritus | [69–71] |
| Reversal of opiate activity, Postoperative | Yes | Naloxone can be used to partially reverse opioid-induced respiratory or circulatory depression following surgery | |
| Septic shock; Adjunct | Yes (Adult) | Naloxone is indicated as an adjunct agent to increase blood pressure in the management of septic shock | [72–76] |
| Simple obesity | No | Naloxone was shown to be effective in one study | [77] |
| Tardive dyskinesia | No | Improvements with naloxone in tardive dyskinesia may be related to interactions between brain dopaminergic activity and the endogenous opioid system | [78, 79] |

**Table 3.** Clinical and potential therapeutic uses of Naltrexone.

| Indication | FDA approved | Notes | Reference |
|---|---|---|---|
| Alcoholism | Yes (Adult) | Effective as adjunctive therapy in the treatment of alcohol dependence<br>Did not increase time to relapse or decrease the percentage of drinking days in Veterans Affairs outpatients with chronic severe alcohol dependence ($n = 627$)<br>May cause withdrawal symptoms in manic patients<br>Has favorable effect on plasma lipids in abstinent alcoholics | [80–84] |
| Drug withdrawal syndrome | No | | [85, 86] |
| Gilles de la Tourette's syndrome | No | Naltrexone was effective in decreasing tics and improving attention and visuomotor sequencing and planning in patients with Tourette's syndrome. | [87] |
| Morphine adverse reaction; Prophylaxis | No | The incidence of adverse effects was significantly lower when patients were pretreated with naltrexone. | [88, 89] |
| Opioid dependence | Yes (Adult) | Available data suggest that naltrexone is an effective and safe narcotic antagonist for the treatment of narcotic addiction. | [90–123] |
| Pruritus of skin | No | Efficacy in uremia-associated pruritus controversial<br>Effective for pruritus caused by other etiologies such as dermatological diseases, liver cirrhosis, or diabetes | [124–128] |
| Self-injurious behavior | No | Effective in treating self-injurious behaviors in autistic and mentally retarded patients<br>Reduces dissociation symptoms and flashbacks in borderline personality disorder | [129–133] |

include alcohol, cocaine and nicotine dependence, obesity and eating disorders, obsessive compulsive disorder (OCD) spectrum and impulse control disorders, self-injurious behavior, and schizophrenia.[37] Naltrexone has been approved as a treatment for alcohol addiction for more than a decade, although oral administration leads to poor patient compliance.[38] A contributing factor for this may be due to elevated plasma concentrations of the first pass metabolite 6β-naltrexol **67** (Figure 21). Increased incidence of side effects and treatment dropout have been linked with the presence of this metabolite.[36] Collaborative research between Alkemes Inc. and Cephalon Inc. led to the identification of an extended release formu-

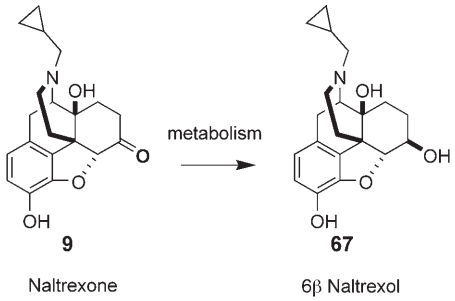


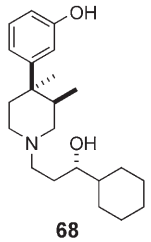

**Figure 21.** Structure of naltrexone and its metabolite 6β-naltrexol.

lation of naltrexone, Vivitrol.[38] Administered intramuscularly, this once-a-month treatment was recently approved by the FDA for the treatment of alcohol addiction. Administration of Vivitrol results in lower plasma concentrations of 6β-naltrexol. This leads to better patient compliance and a reduced side-effect profile.

### *Mu antagonists as potential antiobesity agents*

Obesity is a chronic disease reaching epidemic proportions in the United States and in most developed countries. Incidence of obesity in the United States has increased ~50% in the past ten years. In the United States alone, 64.5% adults are overweight (BMI > 25). Of these 30.5% are obese (BMI > 30) and 4.7% are severely obese (BMI > 40). Incidence of childhood obesity and resulting comorbidities is also reaching epidemic proportions.[134,135] Despite a tremendous amount of research in both academia and industry over the past 20 years, pharmacological treatment of obesity still remains a difficult challenge. Many pharmaceutical companies have large programs directed at the development of new modulators of neuropeptide receptors, antagonists of appetite enhancing peptides, and agonists of appetite suppressing peptides, including neuropeptide Y receptors and melanocortin receptors. Extensive work indicates that the opioid system plays a role in the regulation of appetite. Indeed, opioid receptors and peptides are expressed in sites of CNS that play a role in regulating feeding behavior. Opioids play a role in modulating the palatable aspects of food, making food more rewarding.[136] It has been demonstrated that intake of high-fat food is selectively enhanced by mu opioid receptor stimulation and that mu receptors are upregulated in diet-induced obese rats.[137] Elevated concentrations of the naturally occurring opiate beta-endorphin were also found in the pituitaries of genetically obese mice (ob/ob) and rats (fa/fa) and in the blood plasma of the obese rats.[138] When MOR−/− and MOR+/+ mice raised on a regular diet were switched to a high-fat diet, the MOR−/− mice showed a dramatically smaller increase in weight and adiposity.[139] In summary, there is strong evidence that the mu opioid pathway might be a potential target for pharmacological intervention in the treatment of obesity associated with the intake of fatty diets. This is also supported by preclinical and clinical studies assessing the role of opioid agonists and antagonists on food intake and weight change. For example, administration of opioid agonists in rodents, including morphine and endogenous peptides, has been shown to increase food intake. Numerous studies using opioid receptor antagonists report reduced food intake and body weight in a variety of rodent animal models.[140] The inhibitory effects of opioid receptor antagonists on food intake and body weight appear most pronounced in obese animals or when animals are fed a highly palatable diet.[141] Phenylpiperidine opioid antagonists exhibit efficacy that is greater and longer lasting than antagonists of the morphinan class (for example, naltrexone) in animal models of obesity.[7,142–145] Hence, LY255582 **68** (15 mg kg$^{-1}$ s.c per day) decreased food intake significantly from the first day of treatment, the effect lasting the entire 30 day treatment. In contrast to amphetamine, fenfluramine, and naltrexone, the obese Zucker rat did not develop tolerance to the effects of LY255582 administered chronically; similar results were obtained during a 68 day treatment.[146] LY255582 (0.2–20 mg kg$^{-1}$, p.o.) also decreases 24 h consumption of high-energy diet in dietary induced obese (DIO) Long-Evans rats in a dose-dependent manner.[142]




**68**

LY255582

Naltrexone has been tested for weight loss in humans, but the results have been inconsistent. Reduction in food consumption after acute treatment has been reported. However, weight loss efficacy in chronic studies has been largely inconsistent with positive effects in some studies and no effects in others.[135] There could be several explanations for the disparity between the acute effects and chronic effects of naltrexone. First, naltrexone may display partial agonist activity at delta and kappa receptors and this activity could partially offset the positive effects of mu antagonism. Second, data generated from Eli Lilly suggest that inverse agonists (that is, LY255582), rather than antagonists (that is, naltrexone) may have more robust effects in the animal models of food consumption and weight gain.[7] Based on these limitations, naltrexone might not be the ideal drug to study the effect of mu opioid antagonist for the treatment of obesity in the clinic. Eli Lilly first reported that a phenylpiperidine opioid antagonist had appetite suppressant activity in animals in 1988. They appear to have continued interest in the use of opioid antagonists as a potential treatment of obesity.[147] However the clinical status of this program has not been reported.

### Peripherally acting mu antagonists

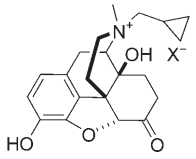
Postoperative ileus (POI), which is a disruption of normal coordinated movements in the gastrointestinal (GI) tract, affects almost all patients who undergo abdominal surgery and is exacerbated by opioid use during and following surgery.[148] Other surgeries, especially those performed around the abdomen are also reported to lead to POI. Although POI is a transient condition generally lasting 3–5 days after surgery there is currently no treatment available to patients. Adverse effects associated with POI include vomiting, nausea, delayed passage of flatus or stool and distension, bloating, cramping, and pain of the abdomen. This can lead to further adverse events such as delayed wound healing and infection, caused by impedance in the resumption of normal food and fluid intake. Aspiration of vomit induced by POI in severely weakened patients can lead to pneumonia and death.[149] Postoperative ileus is the leading contributor of patient morbidity and prolonged hospitalization. Morphine and its analogues are often the drugs of choice in the treatment of postoperative pain and are well documented to disrupt GI function, thereby contributing to POI. Administration of a peripherally restricted mu opioid antagonist was shown to reduce or reverse the effects of morphine and other

opioids on POI without affecting analgesia produced by the opioid agonists.

### N-*Methylnaltrexone*[150–152]

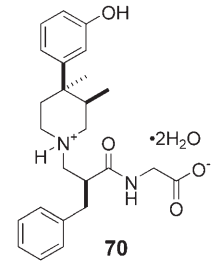
*N*-Methylnaltrexone **69** is a peripherally restricted, pure mu opioid antagonist, currently under clinical evaluation for the treatment of opioid induced gastrointestinal disorders. As in the case of *N*-methylmorphine, *N*-methylnaltrexone is peripheralized because of a quaternary nitrogen atom.[153] Initially developed by University of Chicago faculty, *N*-methylnaltrexone was out-licensed to UR labs in 1985. In 2001 Progenics pharmaceuticals sublicensed *N*-methylnaltrexone from UR labs and in 2005 Progenics formed a collaboration with Wyeth to develop and market the compound. To address the needs of specific applications three different dosage forms and routes of administration of *N*-methylnaltrexone are being investigated. The drug is being evaluated, as a subcutaneous injection, for the treatment of opioid-induced constipation in patients receiving palliative care for advanced cancer, AIDS, cardiopulmonary disease, and other painful terminal illnesses. An oral formulation is under development for the treatment of opioid-induced constipation in patients with chronic pain, whereas administration by intravenous infusion is being evaluated for the treatment of postoperative ileus. *N*-Methylnaltrexone is a relatively potent mu opioid antagonist ($IC_{50}$ = 70 nM) and is moderately selective versus the kappa opioid receptor ($IC_{50}$ = 575 nM), with no interaction observed at delta opioid receptors. In vivo demethylation of *N*-methyl-naltrexone to naltrexone is a major consideration as release of naltrexone by this process could lead to antagonism of analgesic effects produced by coadministered agonists. Studies gave mixed results on this potential issue and indicated species dependence. Metabolism studies in rats and mice with $^{14}$C-methyl enriched *N*-methylnaltrexone indicated demethylation over time, but this effect was not observed in dogs, primates, or humans. An NDA of the subcutaneous formulation of *N*-methylnaltrexone bromide for the treatment of opioid-induced constipation (OIC) was recently submitted for FDA review.



**69**

### *Alvimopan*[148,154–159]

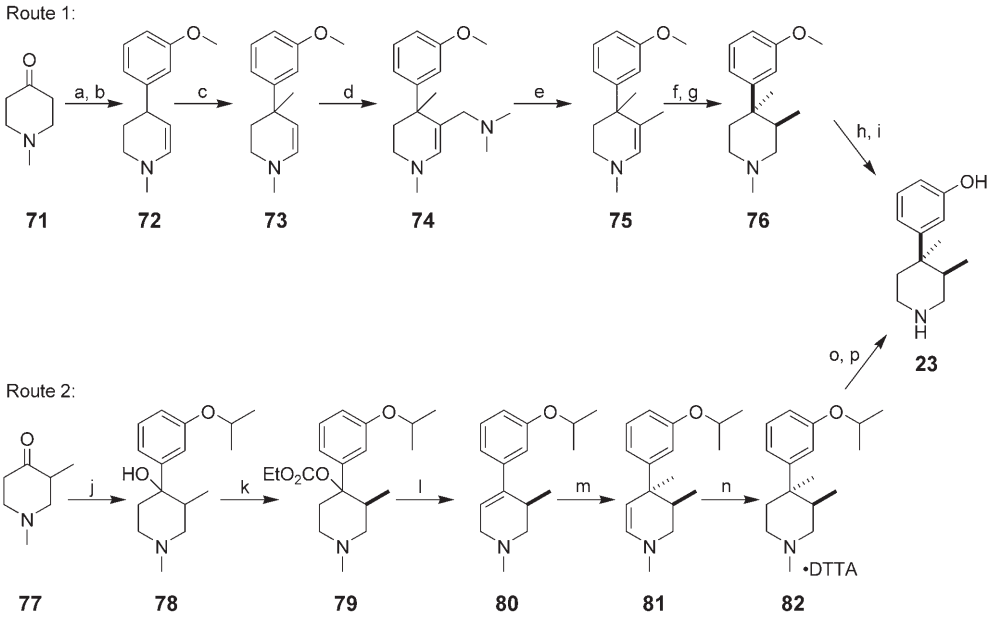
Alvimopan (Entereg) **70** is an orally administered peripherally restricted mu opioid antagonist (Figure 22). Alvimopan attains its peripheral restriction through a relatively large molecular weight (460.1 KDa) and zwitterionic form. First reported by Eli Lilly[160,161] and subsequently licensed to Roberts, alvimopan is being co-developed by Adolor Corporation and GlaxoSmithKline Ltd. Alvimopan is synthesized in 12 steps and 6.2% overall yield from 1,3-dimethyl-4-piperidone. Optimization of the synthesis of this compound has been reported in the literature.[157,158] Optically pure (+)-*trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidine **23** is used as the key starting material for the synthesis of alvimopan (Scheme 4). Two approaches were devised for the synthesis of this key intermediate. The first route to **23** consisted of a nine-step process in which compound **23** was obtained from 1-methyl-4-piperidinone in 5.5% yield.[162] Five years later an alternative synthesis of **23** was reported from the same laboratories. In this approach **23** was prepared in a seven-step process and 14.4% yield, using a different starting material, that is, 1,3-dimethylpiperidinone.[163] The second route was found to be superior for the following reasons: a) the overall yield of **23** was improved from 5.5% to



**70**

Binding assay
(cloned human receptors)
$K_i$ (mu) = 0.77 nM
$K_i$ (kappa) = 40 nM
$K_i$ (delta) = 4.4 nM

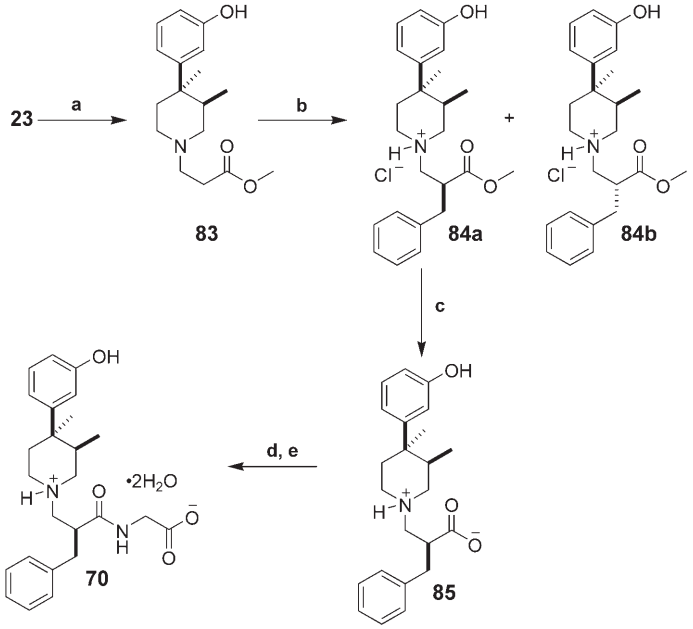
**Figure 22.** Alvimopan.




**Scheme 4.** Strategies devised for the synthesis of **23**. Route 1: a) (3-Methoxyphenyl)lithium, THF, -70 °C; b) p-TsOH, PhMe, reflux; c) n-BuLi, MeI; d) $CH_2O$, $NMe_2$; e) $H_2$, $Pd/Ba_2SO_4$; f) $NaBH_3CN$; g) dibenzoyl L-tartrate; h) vinyl chloroformate, HCl, MeOH; i) HBr, AcOH; Route 2: j) 1) (3-isopropoxyphenyl)lithium, THF, -70 °C, 2) recryst. from heptane; k) 1) ethyl chloroformate, EtOAc, 2) (+)-DTTA, EtOH, 3) OH-; l) decalin, 190 °C; m) 1) n-BuLi, THF, -10 °C, 2) $Me_2SO_4$, -50 °C; n) 1) $NaBH_4$, MeOH, 2) (+)-DTTA, EtOH; o) 1) OH-, 2) phenylchloroformate, PhMe, 100 °C; p) 1) HBr, AcOH, reflux, 2) pH = 10.5.

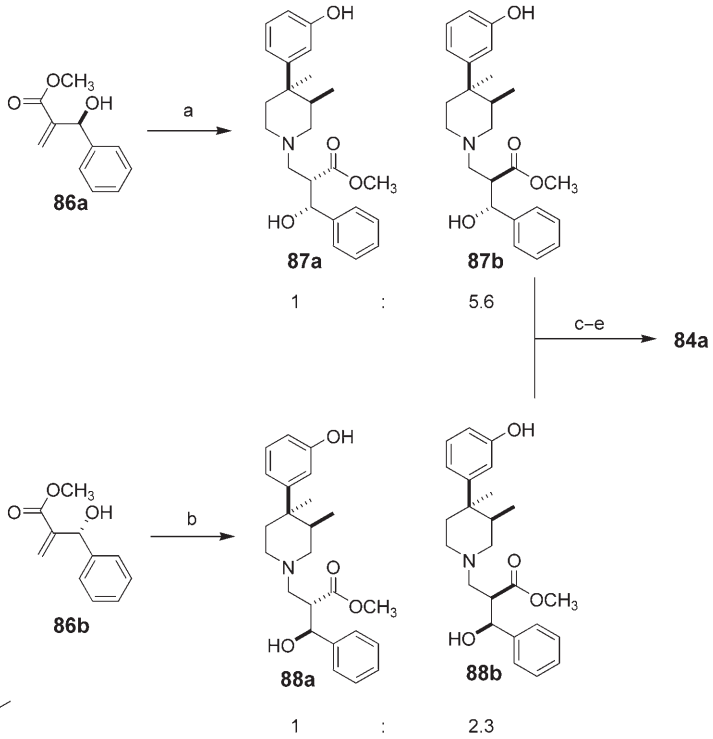
  

14.4%; b) in the original route it was found that intermediate **72** caused neurotoxicity. This was likely to be a major concern for cGMP synthesis. In contrast, none of the intermediates in the improved route have any obvious toxicological liabilities; c) reduction of **75** (step f) yields racemic **76** as a 93:7 mixture of *trans*:*cis* diastereomers respectively. Separation of the diastereomers by recrystallization of the HBr salt is followed by a chiral resolution with dibenzoyl-D-tartaric acid (step g) to afford optically pure **76**. In the improved route two key steps were identified to streamline this process. The first step was the regioselective thermal elimination of the carbonate ester **79** that leads to **80**. The second step was the stereoselective alkylation of enamine **80** using methodology developed previously by Evans.[164] In the procedure described by Lilly, alvimopan was then prepared from **23** in a five-step procedure (Scheme 5). Michael addition of **23** to methyl methacrylate




**Scheme 5.** Synthesis of Alvimopan from compound **23**. a) methyl acrylate, THF; b) 1) LDA, BnBr, -30 to -20 °C, 2) HCl, MeOH; c) 1) NaOH, $H_2O$-MeOH (1:1); 2) HCl, pH = 6; d) DCC, HOBt, $Et_3N$, TsO-$NH_3$ + $CH_2CO_2$-i-Bu; e) 1) NaOH, EtOH/$H_2O$(2:1), 2) HCl, pH = 6.

provided the methyl ester **83**. Treatment of **83** with LDA generates the corresponding dianion which was reacted with benzyl bromide to provide a mixture of **84a**/**84b** in ~1:1 ratio. The temperature of this step must be carefully maintained as no reaction occurs below −30 °C and the material undergoes a retro-Michael at temperature above −15 °C. The separation of the diastereomers was easily achieved by recrystallization of the hydrochloride salt in methanol. By epimerization and recycling of the undesired stereoisomer the yield of the benzylation step was improved from 34% to 55%. The synthesis of alvimopan was then completed in three steps from **84a**. Using this strategy alvimopan was synthesized in an overall yield of 6.2% over a 12 step sequence from 1,3-dimethyl-4-piperidone (**77**). Scientists at Adolor investigated an alternative synthetic strategy to improve the yield of **84a** from **23** (Scheme 6). Their approach was to utilize a chiral electrophile to promote asym-




**Scheme 6.** Alternative synthesis of intermediate **84a**. a) **23**, MeOH, 25 °C; b) **23**, THF, 25 °C; c) $(CH_3CO)_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 25 °C; d) $H_2$, $Pd(OH)_2$, MeOH, 70 psi, 25 °C; e) $K_2CO_3$, MeOH, 25 °C.

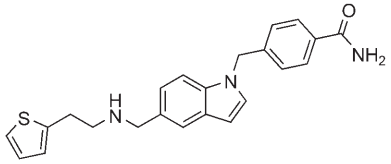
metric induction.[165] Through solvent selection, using a methodology previously developed by Perlmutter and Tabone, a diastereoselective addition of compound **23** to enantiomerically pure methyl 2-(hydroxy(phenyl)methyl)acrylate was performed (Scheme 6).[166,167] The conjugate addition of **23** to the (*S*)-enantiomer, **86a**, in MeOH gave predominately *anti* product **87b** (**87b**:**87a** = 5.6:1). When the 1,4-addition was performed in THF the *syn* addition product, that is, **87a** was the major diastereomer formed. Addition of **23** to the (*R*)-enantiomer (**86b**) in THF gave a mixture of **88a**/**88b** in a 1:2.3 ratio. However, despite the low stereoselectivity of the addition, the diastereomers **88a** and **88b** were easily separated by trituration in methanol. Conversion of **87b** or **88b** to **84a** was achieved in a three-step process: that is, acetylation of the secondary hydroxyl group, removal of the corresponding acetate by hydrogenation, and hydrolysis of the phenyl ester under basic conditions. Overall this strategy represents an attractive alternative to the current process employed, as all reactions are performed at ambient temperature, thereby eliminating the requirement for careful temperature control. Additionally, choice of solvent allows the reaction sequence to be completed using either of the acrylate enantiomers (**86a** or **86b**). In vitro binding data shows alvimopan to have high potency and greater affinity for the mu ($K_i$ = 0.77 nM) versus kappa ($K_i$ = 40 nM) and delta ($K_i$ = 4.4 nM) opioid receptors.[161] In animal studies, only very high doses (that is, 100 times those required for reversal of GI effects) of alvimopan led to antagonism of morphine-induced analgesia. Even after i.v. administration, alvimopan shows a selectivity of 200-fold for peripheral over central mu opioid receptors. With an oral bioavailabity of only 0.03% after

dosing at 100 mg kg$^{-1}$ p.o. the poor systemic absorption of the compound is clearly demonstrated. However, the low bioavailability of the compound is by no means an indication of poor efficacy, as studies performed with [$^{14}$C]alvimopan showed the drug to be concentrated within the GI tract (largely within the gut wall) after oral administration. Further studies of drug distribution, following intravenous administration, showed that the drug was present in all areas of the body except the spinal cord or brain, indicative of peripheralization of the compound. A comparative study in mice of alvimopan and *N*-methylnaltrexone reported alvimopan to be 200 times more effective than *N*-methylnaltrexone at antagonizing the inhibitory effects of morphine on gastrointestinal transit and secretion.[168] Alvimopan is currently under FDA review for treatment of opioid complications associated with POI and is also being developed as a potential therapy for opioid-induced bowel dysfunction (OBD) in chronic opioid users.

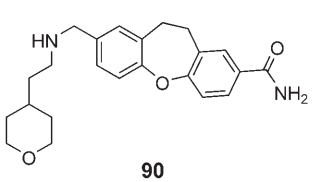
## Mu opioid antagonist patent overview 1997–2007

Eli Lilly recently reported new chemical classes of opioid antagonists. These include the 4-(5-(aminomethyl)-indole-1-ylmethyl)-benzamides, diarylethers, arylalkyloxybenzamide, and 6-substituted nicotinamides, exemplified by compounds **89**–**97** (Figure 23). These compounds are claimed to be potentially useful for the treatment of obesity and related disorders, including diabetes, diabetic complications (including retinop-



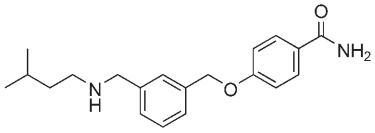
**89**

WO2005090303
GTPgS functional assay:
$K_b$ (mu) = 2 nM
$K_b$ (kappa) = 50 nM
$K_b$ (delta) = 15 nM



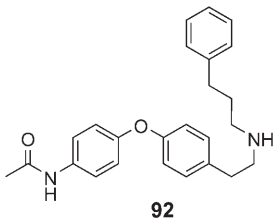
**90**

WO2005090337
GTPgS functional assay:
$K_b$ (mu) = 0.7 nM
$K_b$ (kappa) = 2.2 nM
$K_b$ (delta) = 2.1 nM



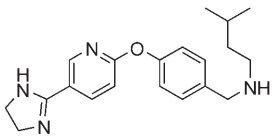
**91**

WO2005090286
GTPgS functional assay:
$K_b$ (mu) = 13 nM
$K_b$ (kappa) = 14 nM
$K_b$ (delta) = 194 nM



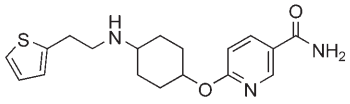
**92**

*WO2005092836*
GTPgS functional assay:
$K_b$ (mu) = 5 nM
$K_b$ (kappa) = 731 nM
$K_b$ (delta) = 62 nM



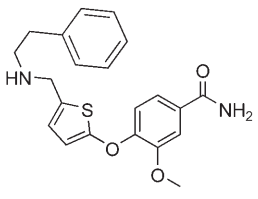
**93**

WO200506616
GTPgS functional assay:
$K_i$ (mu) = 9.5 nM
$K_i$ (kappa) = 34 nM
$K_i$ (delta) = 119 nM



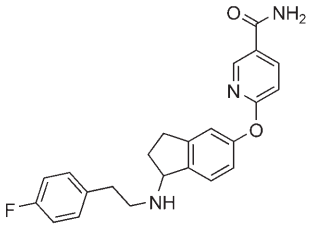
**94**

WO2005061442
Binding assay (rat brain homogenates):
$K_i$ (mu) = 0.13 nM
$K_i$ (kappa) = 2.5 nM
$K_i$ (delta) = 0.35 nM



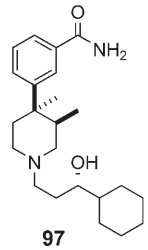
**95**

WO2004080996
GTPgS functional assay:
$K_b$ (mu) = 0.3 nM
$K_b$ (kappa) = 4.0 nM
$K_b$ (delta) = 1.3 nM



**96**

WO2004080968
GTPgS functional assay:
$K_b$ (mu) = 0.4 nM
$K_b$ (kappa) = 9.2 nM
$K_b$ (delta) = 14.6 nM



**97**

WO2003101963
Binding assay (rat brain homogenates):
$K_i$ (mu) = 0.2 nM
$K_i$ (kappa) = 12.7 nM
$K_i$ (delta) = 6.4 nM
F = 32% (rat)

**Figure 23.** Mu opioid antagonists specifically claimed in Eli Lilly's patent applications (1997–2008).

athy), atherosclerosis, hyperlipidemia, hypertriglyceridemia, hyperglycemia, and hyperlipoproteinemia. Additional indications claimed for these compounds include irritable bowel syndrome, nausea, vomiting, obesity-related depression, substance abuse (including smoking and alcohol addiction), sexual dysfunction, drug overdose, addictive behavior disorders, compulsive behaviors, and stroke. Scientists at Eli Lilly applied the bioisosteric replacement strategy—hydroxyl to carboxamide—to their lead compound LY255582 **68** to yield carboxamide **97**. Carboxamide **97** displayed potent mu opioid receptor affinity and better bioavailability when compared to **68** ($F = 32\%$ versus 2.5%).[169] Compound **97**, specifically claimed in the WO2003101963 patent application was efficacious after oral administration (3 mg kg$^{-1}$) in a rat model of obesity. In contrast, **68**, administered at the same dose of 3 mg kg$^{-1}$ p.o. was inactive in this assay. Therefore the improved ADME properties of **97**, when compared to **68** are translating to better in vivo efficacy. Adolor Corporation published, over the past 5 years, several patent applications disclosing novel 3,4-disubstituted-4-aryl-piperidine derivatives. The claims include their compositions, their use as opioid receptor binders, particularly mu and kappa receptor binders, and their use, either alone or with other opioid agents, for the treatment of gastrointestinal dysfunction, ileus, side effects of other opioid agents, for example, constipation, nausea, and emesis (Figure 24). As previously described in this article, conformationally restricted analogues of the N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines have been recently reported. Peripheralization of these scaffolds led to the opioid antagonists **98** and **99**, closely related analogues of alvimopan. Based on their chemical structure, these compounds would be expected to distribute selectively to mu peripheral receptors. A series of N-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)-piperidines, mu opioid receptor antagonist analogues of alvimopan, were also reported by Adolor. These compounds were prepared using solid phase methodology. This study led to the identification of compound **100**, a lysine analogue of alvimopan, which binds with subnanomolar affinity to the mu receptor. This compound displayed high selectivity for mu over delta (1275-fold) and kappa (500-fold) opioid receptors. As indicated previously research conducted at Adolor Corporation demonstrated that the $CONH_2$ group is an effective isostere of the phenolic OH moiety of the *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine class of mu opioid antagonist.[35] This was further confirmed by the identification of **101**, the carboxamide analogue of alvimopan, as a potent mu opioid receptor antagonist. The carboxylic acid analogue **102** was found to display good affinity and antagonist activity at the mu opioid receptors. This contrasts with previous SAR studies demonstrating that the replacement of the phenolic hydroxyl of the *N*-phenethyl *trans*-3,4-dimethyl-4-(3-

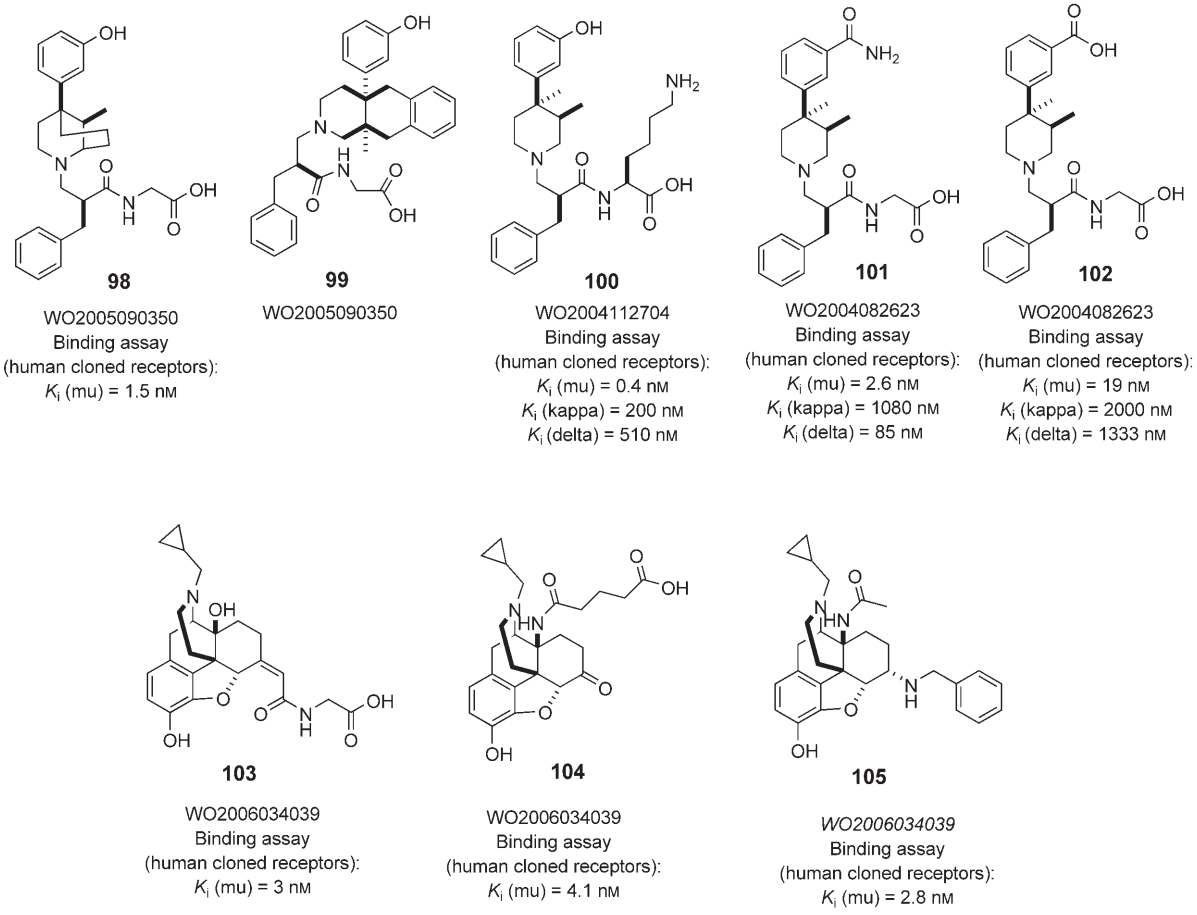
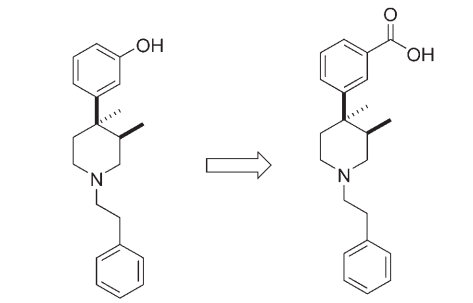



**Figure 24.** Mu opioid antagonists specifically claimed in Adolor's patent applications (1997–2008).

hydroxyphenyl)piperidine **24** by a $CO_2H$ functionality (compound **106**) (Figure 25) results in a complete loss of binding at all three opioid receptors.[35] Adolor also disclosed novel morphinan derivatives exemplified by compounds **103**, **104**, and **105** that displayed potent affinity and antagonist activity at the mu opioid receptors. Pfizer disclosed in the patent literature novel mu opioid antagonists containing, as a central template, a 3-azatricyclo-[3.1.0]hexane **107**–**110**, a 3-azatricyclo-[3.2.1]octane **111**, or a 2-azatricyclo[3.2.1]octane **112** heterocycle (Figure 26). However, no biological data was reported within these patent applications.




**24**

Binding assay
(human cloned receptors):
$K_i$ (mu) = 1.9 nM
$K_i$ (kappa) = 33 nM
$K_i$ (delta) = 17 nM

**106**

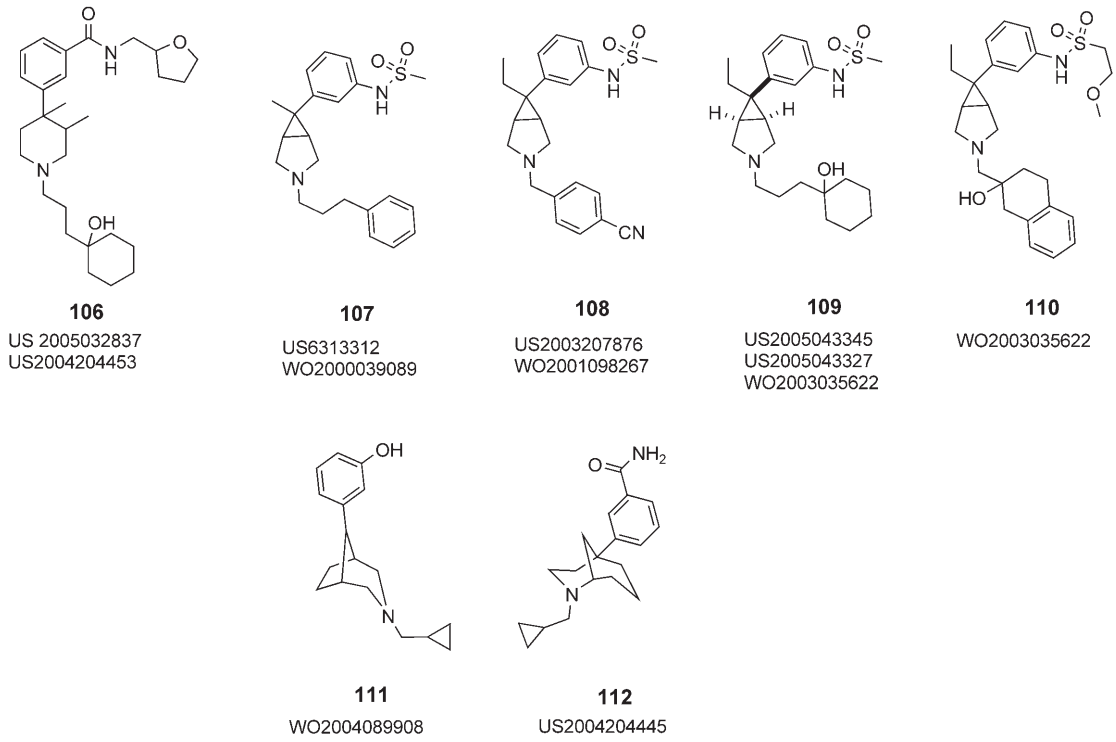
Binding assay
(human cloned receptors):
mu: 25% inh. at 10 mM
kappa: 8% inh. at 10 mM
delta: 9% inh. at 10 mM

**Figure 25.** Structure and in vitro profile of **24** and **106**.

## Conclusions

Mu opioid antagonists have potential use in the treatment of a multitude of physiological disorders. Despite more than 30 years of research naloxone and naltrexone remain the only FDA approved mu opioid antagonists. Currently approved as treatments for only a handful of conditions they are undergoing evaluation as potential treatments for a large number of CNS related disorders. Although effective treatments, naloxone and naltrexone have pharmacokinetic issues associated with them. Naloxone has very poor oral bioavailability and a short half-life, whereas naltrexone is associated with poor compliance, possibly due to elevated levels of the metabolite 6β-naltrexol. Clearly a large window of opportunity exists for centrally acting mu opioid antagonists exhibiting an improved pharmacological profile. Also, there remains an unmet need for reversal of adverse effects induced by activation of peripheral mu opioid receptors by centrally active mu opioid receptor agonists. In an attempt to address this important clinical issue two peripherally restricted mu opioid antagonists, *N*-methylnaltrexone, and alvimopan, are under evaluation in the treatment of opioid induced gastrointestinal disorders.

**Keywords:** mu agonists · mu antagonists · opioids · receptors




**106**
US 2005032837
US2004204453

**107**
US6313312
WO2000039089

**108**
US2003207876
WO2001098267

**109**
US2005043345
US2005043327
WO2003035622

**110**
WO2003035622

**111**
WO2004089908

**112**
US2004204445

**Figure 26.** Mu opioid antagonists specifically claimed in Pfizer's patent applications (1997–2007).

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