PHD

Studies towards the synthesis of new irreversible and selective reversible ligands for the kappa opioid receptor

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STUDIES TOWARDS THE SYNTHESIS
OF NEW IRREVERSIBLE AND SELECTIVE REVERSIBLE LIGANDS
FOR THE KAPPA OPIOID RECEPTOR

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A thesis submitted for the degree of Doctor of Philosophy
University of Bath
Department of Pharmacy and Pharmacology
March 2005

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ABSTRACT

There is considerable interest in the synthesis of κ-antagonists as therapeutic agents but also as a means of further understanding the role of the κ-opioid receptor. In the search for irreversible and selective reversible κ-opioid antagonists, it was decided to modify the structures of the two most well-known κ-antagonists, GNTI and norBNI. In particular, two main approaches have been used for the design of novel ligands; these explored the introduction of electrophilic (isothiocyanate) or lipophilic (substituted/unsubstituted benzyl) groups onto the guanidinium moiety of GNTI or at the pyrrolic nitrogen of norBNI.

In the first series of compounds, p-hydroxy-, m-hydroxy-, p-methoxy-, p-methyl- and 3,4-dichlorobenzylGNTI analogues have been prepared. Binding and functional studies of p-hydroxy- and m-hydroxy-derivatives have confirmed the results of molecular modelling studies, which had suggested that the phenolic group of the former should mimic the second phenolic group of norBNI that was previously shown to be crucial for κ-antagonist selectivity. Electrophilic ligands modelled on GNTI have also been prepared and N'- (5-isothiocyanatopentyl)GNTI has been sent for biological evaluation, while the successful synthesis of N'-(4-aminobutyl)GNTI will allow the preparation of the corresponding isothiocyanate to be achieved.

Modification of norBNI followed previous studies where the duration of action of naltrindole was extended by indolic N-benzylation. In-vivo, BnorBNI was a μ-agonist when administered sc and an irreversible κ-antagonist when administered icv. This led us to prepare 17,17'-di-NMe derivatives of norBNI and BnorBNI as potential mixed μ-agonist/κ-antagonist ligands. Binding and functional studies of these analogues showed that replacement of the cyclopropyl methyl groups with methyl groups led to a decrease in κ-antagonist potency and μ-agonist potency with concomitant increase in μ-agonist efficacy. We have also prepared isothiocyanates modelled on BnorBNI, with the electrophilic moiety attached directly to the benzyl group of BnorBNI or linked by a methylene spacer. At the time of submission, pharmacological evaluation of these ligands was still outstanding.

Finally, unexpected reactions with norBNI have led us to investigate whether the p-phthalimidobenzyl group can be used as a general protecting group for indolic and pyrrolic nitrogens. Evaluation on carbazole, tetrahydrocarbazole and an indolomorphinan has shown this is not the case.
ACKNOWLEDGEMENTS

How could I not start this section by acknowledging the Great and Unique Stevey "McManama" Husbands? Of course, I would like to thank Steve for all the precious guidance he gave me during my project, but above all for being such a great friend, always welcoming me in his office, up for a chat and always willing to help. I am truly aware of the luck I had to spend these last three years working for such a great boss and surely one of the funniest and nicest people I've met in my life. I also would like to acknowledge John (Dr Lewis) for his good advice at some crucial points of my PhD and for the entertaining talks we had, especially when it came to sport matters.

All my gratitude goes to a few special people who made my time in Bath all the more enjoyable and help me hang in there during the difficult time: above all, Christiano Millerdonna for introducing me to Bath local population, for inviting me to some memorable parties, for organising the football sessions and camping trips (in beautiful Wedmore), for all the tips on a P&P course, etc... Also Dave and Neil for all the good vital "sessions" and nights we had clubbing and "pubbing" in Bath, Boberto Carlos for being such a permanent entertainment during these 3 years at Bath Uni, whether it was on a football pitch, on a camping trip or in a nightclub. I also particularly appreciated the company of the two wise men that are Koen and my "personal squash coach" Fabrice Jourdan; thank you for all the help and good advice for my project and during my job search.

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Special thanks to my family who have always ranked the financing of my studies as top of the list.

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<tr>
<td>BBB</td>
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<td>BOC</td>
<td>tert-butoxycarbonyl</td>
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<td>BOP</td>
<td>benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate</td>
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<tr>
<td>br</td>
<td>broad</td>
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<tr>
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<td>cyclic adenosine monophosphate</td>
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<tr>
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<td>°C</td>
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<td>CHO</td>
<td>Chinese hamster ovary</td>
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<tr>
<td>CPM</td>
<td>cyclopropyl methyl</td>
</tr>
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<td>CREB</td>
<td>cAMP response element binding protein</td>
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<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
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<td>N,N-dimethylformamide</td>
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<td>electron impact</td>
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<td>EL</td>
<td>extracellular loop</td>
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<td>equi</td>
<td>equivalents</td>
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<td>FAB</td>
<td>fast atom bombardment</td>
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<td>GDP</td>
<td>guanosine diphosphate</td>
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<td>GPCR</td>
<td>G-protein-coupled receptor</td>
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<td>guinea pig ileum</td>
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<td>guanosine triphosphate</td>
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<td>coupling constant</td>
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<td>m</td>
<td>moles per litre</td>
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<td>MHz</td>
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<td>µg</td>
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<td>ml</td>
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</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>MOE</td>
<td>molecular operating environment</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MVD</td>
<td>mouse vas deferens</td>
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<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
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<tr>
<td>NAc</td>
<td>nucleus accumbens</td>
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<tr>
<td>NIDA</td>
<td>National Institute on Drug Abuse</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>ORL</td>
<td>opioid receptor like</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>pentamethylbenzene</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>RAVE</td>
<td>relative activity versus endocytosis</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
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<td>room temperature</td>
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<tr>
<td>s</td>
<td>singlet</td>
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<tr>
<td>SAR</td>
<td>structure/activity relationship</td>
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<td>sc</td>
<td>subcutaneously</td>
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<td>t</td>
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<td>TBDMS</td>
<td>tert-butydimethylsilyl</td>
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<tr>
<td>TEA</td>
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<tr>
<td>THP</td>
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<td>tetrahydrofuran</td>
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<td>thin layer chromatography</td>
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<tr>
<td>TM</td>
<td>transmembrane</td>
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<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>UV</td>
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NUMBERING SYSTEM

Ligands based on the core of naltrindole (indolomorphinans)

Ligands based on the core of norBNI (bimorphinans)
1. INTRODUCTION

1.1 Opioid receptors

Opioid research is not new in that it goes back to early centuries when the experimental use of the poppy, *Papaver somniferum*, proved to confer central analgesic relief to severe pains. However, the exotic origin of the substance together with the euphoric effects experienced upon consumption saw the use of opium drift from therapeutic background to recreational abuse. In 1803, the German pharmacist Sertumer isolated morphine (1), the component responsible for the analgesic and rewarding properties of opium. With the popularisation of morphine, drug addiction became increasingly associated with loss of production, death, delinquency and safer alternatives were urgently required.

In the 1920’s, Gulland and Robinson revealed the structure of morphine\(^1\) and in 1952 its total synthesis was reported.\(^2\) Ironically, initial efforts to produce harmless analogues led to the synthesis of heroin (2) (the diacetyl derivative of morphine), a somewhat more addictive substance. In order to produce opioids free of addictive effects, a better knowledge of the underlying mechanisms involved in opioid activity was therefore necessary.

\[
\begin{align*}
R^1 = R^2 = H & \quad 1 \\
R^1 = R^2 = Ac & \quad 2
\end{align*}
\]

The existence of the opioid receptor was postulated in the 1930’s by two stereochemists Beckett and Casy and later confirmed by the pioneering work of Martin *et al.* in 1976.\(^3,4\) It is now well established that at least three different types of opioid receptors –known as “classical” types– are present within the central nervous system and peripheral sites: \(\mu\) for the receptors that mediate the actions of morphine, \(\kappa\) for the ones that mediate the actions of the synthetic ligand ketocyclazocine and \(\delta\) associated with the actions of the endogenous endorphin and enkephalin.\(^3,4,5\) In 1992, the first opioid receptor (mouse \(\delta\)) was cloned, soon followed by the cloning of the mouse \(\mu\) and \(\kappa\) receptors in 1993,\(^6\) before the cloning of human opioid receptors was achieved.\(^7,8\)
The existence of subtypes within the $\mu$, $\delta$ and $\kappa$ opioid receptors has also been proposed by several research groups. However, there is still a lot of debate on both the nature and existence of these subtypes, as cloning of these receptors has not been achieved yet and it is increasingly believed that they could instead represent posttranslational modification of the 3 classical types. Further confusion arose when additional opioid receptors such as the $\epsilon$ type or opioid receptor-like (ORL) receptors were proposed. Although the latter have been shown to mediate analgesia, they fundamentally differ from opioid receptors in that they do not bind any endogenous or synthetic opioids.

A revolutionary concept for the explanation of additional opioid receptors has recently emerged and relies on the organisation of opioid receptors as dimers/oligomers, a process already known for other receptor systems. The existence of $\delta/\kappa$ heterodimers and $\delta/\mu$ heterodimers has already been proposed, with however some controversy still remaining around the theory; indeed, the bivalent ligands used to prove the existence of these receptors have for long consisted of two pharmacophores linked by a bridge of 20 atom units, a somewhat large spacer (around 22 Å) that could bind two adjacent receptors. Only recently have bivalent ligands with a reduced spacer such as compound 3 been used to probe the existence of dimeric receptors.

![Diagram of compound 3]

However, these ligands still do not constitute irrefutable proof, as it is possible that the observed pharmacological profile stems from the mixture of monomers obtained after metabolism of the drugs. Definite evidence is therefore required but such heterodimeric structural rearrangement of opioid receptors would represent a valuable tool to account for many "odd" pharmacological behaviours that are not consistent with a "classical" monomeric model. Heterodimers should indeed exhibit
different selectivity and signal transduction pathways than monomers, and this could explain, for example, why a highly selective κ-antagonist such as norBNI has been shown to antagonise the activity of highly selective δ-agonists; this is illustrated in figure 1 and explained below.

![Diagram illustrating a heterodimeric opioid receptor](image)

**Figure 1** Schematic model of a heterodimeric opioid receptor; the numbers represent transmembrane domains (TM)

The figure represents a heterodimeric receptor constituted from a κ-opioid receptor (full circles) and a δ-opioid receptor (open circles) presenting a transmembrane (TM) 5,6 interface. Let us suppose for example that the molecular features critical for κ- and δ-selectivity are contained respectively in TM 6 of the κ-receptor and extracellular loop (EL) 3 of the δ-receptor (all these terms will be described later). One might thus also envisage the heterodimeric receptor as constituted of hybrid receptors A and B. An agonist X selective for the δ-receptor will therefore bind to the hybrid receptor B. When a κ-selective antagonist Y binds to hybrid A, it produces a conformational change of both A and B; this might result in the shifting of B to an inactive state and subsequent antagonism of X.

1.2 **The structure of opioid receptors and ligand recognition**

All opioid receptors belong to the superfamily of G-protein-coupled receptors (GPCRs) and are formed with a 7-TM domain, an extracellular N-terminal and an intracellular C-terminal portions as shown on figure 2.
Studies using site directed mutagenesis and mutant opioid receptors have helped in elucidating the role of each portion of the receptor. It is now generally acknowledged that the TM domain is highly conserved between the three different opioid receptor types and is the region involved in the message recognition site (explained further) whereas selectivity may be conferred by the highly divergent EL, mainly through favourable interactions between the ligands and the amino acid residues of the EL and partially by a process of exclusion (unfavourable interactions). It is noteworthy that selectivity observed with very small ligands is still poorly understood, as such molecules are believed to bind exclusively to the TM domain of the receptor, with no interaction with the EL. The region between TM5 and TM6 – third intracellular loop (IL) – is highly conserved among the three types and is the main portion responsible for G-protein activation.

1.3 Pharmacological responses

1.3.1 Analgesic response

Opioid receptors are situated on the neuronal circuit responsible for pain perception (ascending sensory pathway) and modulation (descending inhibitory pathway). In response to the events experienced as painful or stressful, endogenous
opioid ligands are synthesised and released within the central nervous system; binding of these ligands to the EL and/or TM of the opioid receptors causes conformational changes of the IL that act as a switch to activate the G-protein, thereby triggering a whole series of intracellular reactions ultimately leading to analgesia (antinociception).

There is still substantial uncertainty surrounding the mechanisms evoked in G-protein activation and subsequent signaling responses, for example little is known about which conformational changes of the third IL are necessary to obtain the active state of the receptor.\textsuperscript{24,27} The signal transduction process is however now well established and is represented in figure 3.

![Ligand binding and pharmacological responses](image)

**Figure 3** Ligand binding and pharmacological responses

The G-protein coupled to all opioid receptors is heterotrimeric and composed of three different units: $G_{\alpha}$, $G_{\beta}$ and $G_{\gamma}$. Upon activation of the receptor, the $\alpha$ subunit dissociates from GDP and associates with GTP, resulting in dissociation of the G-protein from the receptor (phase a, figure 3) and in separation of the $\alpha$ unit from the
βγ dimer (phase b). Each of these units associates with different effectors and modulates biochemical responses, namely decrease of adenyl cyclase and cAMP, which in turn causes reduction of Ca$^{2+}$ influx and K$^+$ efflux at ion channels (phase c). This results in hyperpolarisation of the cell, reduced excitability and blunting of the “pain” signal. Hydrolysis of GTP to GDP (phase d) leads to the reassociation of the αβγ heterotrimer (phase e) and to a return to the resting state (phase f).

1.3.2 Side effects

Although analgesia is a pharmacological response to activation of all three opioid receptors, each receptor type mediates a unique pattern of biological responses as shown in table 1.

<table>
<thead>
<tr>
<th>μ</th>
<th>κ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>analgesia</td>
<td>analgesia</td>
<td>analgesia</td>
</tr>
<tr>
<td>respiratory depression</td>
<td>diuresis</td>
<td>convulsions</td>
</tr>
<tr>
<td>constipation</td>
<td>sedation</td>
<td>constipation</td>
</tr>
<tr>
<td>euphoria</td>
<td>dysphoria</td>
<td></td>
</tr>
<tr>
<td>urinary retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dependence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1** Pharmacological responses mediated by opioid receptors

The side effects mediated by the opioid receptors are troublesome and, in the case of acute pain, generally leave the practitioner with a dilemma: either the practitioner opts for low analgesic doses free of side effects but the pain is not adequately controlled or the pain is fully controlled but the patient experiences significant debilitating side effects. Of additional and greater concern are however the side effects related to tolerance, dependence and addiction.
1.3.3 Development of tolerance, dependence and addiction

The present project has been sponsored by the National Institute on Drug Abuse from the USA and a large part of our efforts are directed towards a better management of opioid and cocaine abuse. Before emphasising the therapeutic potential of κ-selective ligands as a treatment of addictive behaviours, it seems therefore of interest to give a brief insight into the mechanisms leading to tolerance, dependence and addiction.

Agonist binding to the opioid receptor leads to immediate phosphorylation of the latter by protein kinases, which in turn triggers the recruitment of β-arrestin. This protein has been shown to produce uncoupling of the G-protein from the receptor (desensitisation) and internalisation of the receptor by endocytosis. The receptor can then undergo degradation or be recycled back to the surface. It was originally thought that receptor down-regulation was the cause of tolerance but it has recently been proposed that receptor internalisation would in fact avoid development of tolerance by recycling the receptor back to the surface in a fully active state. With this in mind, drugs might be ranked with a RAVE (relative activity versus endocytosis) value: drugs with a high RAVE value, that is drugs that fail to invoke rapid internalisation and recycling of the receptor (such as morphine), maintain the receptor in an active state and therefore provoke changes at downstream levels, leading to development of tolerance and dependence.

New models are increasingly focussing on the post-receptor level and it is nowadays postulated that opiate activation of the cAMP pathway and CREB in the nucleus accumbens (NAc) represents a "mechanism of motivational tolerance and dependence", resulting in addiction (see figure 4). Depending on whether the addictive behaviour is motivated by the search for euphoric effects or is directed by the willingness to avoid amotivational depressing effects experienced when ceasing the drug, the use of κ-agonists or κ-antagonists appears an attractive solution to the treatment of addiction (see figure 4).

The identity of the genes which cAMP and CREB target to produce this abnormal behaviour remains to be elucidated but one early finding evokes the CREB-mediated regulation of dynorphin (the endogenous κ-agonist). This is interesting since κ-agonists are known to inhibit the release of dopamine and the reinforcing and rewarding effects of morphine, heroin, alcohol and cocaine have been shown to be in part related to the increase of dopamine in the NAc. It seems therefore possible
that CREB activation upon repeated opioid administration leads to change of dynorphin levels, which in turn modifies dopamine levels, thereby triggering anhedonia, depression and drug seeking behaviour.\textsuperscript{34,39}

Figure 4 \textit{\kappa}-Agonists and antagonists in the control of euphoria and dysphoria: a solution to opioid addiction? (adapted from reference 34)
1.4 Significance of the κ-opioid receptor

Since opioid ligands originally disclosed were overwhelmingly μ-selective, the
μ-opioid receptor has been thus far the most intensively investigated and, to the
exception of the two partial agonists nalbuphine (4) and butorphanol (5), all clinically
available opioid drugs are μ-agonists. However, addiction and other side effects
associated with μ-agonists have led to the search for other medications.

The κ-opioid receptor represents a target of particular interest in that its
population is more abundant than μ- and δ-opioid receptors in humans. In addition,
activation of κ-opioid receptors does not elicit constipation, urinary retention,
respiratory depression or euphoria and has been reported to mediate less tolerance
and physical dependence than observed with other opioid receptors. However,
psychotomimetic effects observed in clinical trials have so far impaired the
therapeutic potential of κ-agonists, albeit some studies have nevertheless suggested
that these effects might be circumvented by slow increase in the drug dosage.
Special precaution is therefore required when dosing κ-agonists but further confusion
arises from the lack of consistency on the statement of optimal doses; for instance,
preliminary clinical studies of enadoline (6) showed that diuresis, dizziness, fatigue
and dysphoria were mediated at doses that failed to produce analgesic effects, which
led to the discontinuation of the development of the drug. However, recent
reassessment of enadoline has demonstrated that this κ-agonist can be safely
administered at higher doses than previously used (up to 80 μg/70 kg), with
psychotomimetic effects being only observed at higher doses (160 μg/70 kg). It is
possible that the discrepancy between these results stems from the fact that the second
study was exclusively focussed on patients having drug abuse history.

1.4.1 Significant interest in the synthesis of κ-opioid agonists

Though opioids have been historically associated with pain relief, it has
become increasingly apparent that κ-agonists have a significant role to play in a wider
range of clinical situations.
κ-Agonists have been reported to regulate the gastrointestinal motility in rats, to lower arterial pressure and heart rate, to be involved in the treatment of cerebral oedema of the focal ischemia type and to stimulate food intake. A few patents have recently appeared, claiming therapeutic applications of κ-agonists for the treatment of ocular and otic pains, pruritus, restless leg syndrome, irritable bladder syndrome or septicaemia. Work on the κ₂-selective agonist GR89696 (7) showed that the κ₂-receptor subtype might offer an approach in the control of neuropathic pains (hyperalgesia, allodynia) in patients with chronic or persistent pain. It should be noted however that the implication of the κ-opioid receptor in allodynia needs to be further elucidated; although the κ-antagonist norBNI has been shown to enhance this condition, it is increasingly believed that allodynia could be in fact mediated through non-opioid effects of dynorphin, the endogenous κ-selective agonist. It seems that initiation of the neuropathic pain leads to upregulation of dynorphin, thereby promoting its non-opioid pronociceptive actions, a possible critical factor for the maintenance of abnormal neuropathic pain.

Studies using rhesus monkeys have demonstrated that κ-agonists inhibit many behavioural and neurochemical effects of cocaine related to its reinforcing properties, most probably through their ability to inhibit the cocaine-induced enhancement of extracellular dopamine levels. More recently, it has been suggested that opioids presenting a mixed κ-agonist/μ-agonist profile could represent better drug candidates for the treatment of cocaine addiction in that they should mediate fewer side effects than highly selective κ-agonists. In particular, μ-mediated euphoric effects are expected to counterbalance κ-mediated dysphoria, resulting in dramatically enhanced treatment compliance; this should avoid repeating previous failures with κ-agonists CI-977 (8) and U-50488 (9) which were abandoned as potential treatments against cocaine abuse because of their psychotomimetic effects. Also of significant interest regarding the mixed κ-agonist/μ-agonist profile is that κ-agonists have been suggested to suppress tolerance and rewarding effects experienced upon persistent activation of the μ-opioid receptor.

In the particular cases of somatic and visceral pains (inflammation, abdominal surgery, pancreatitis pain), analgesia might be conferred whilst avoiding centrally-mediated side effects by either administrating small, systemically inactive doses of agonists directly into the injured tissue (useful in the case of localised pain) or by
administering peripheral agonists that have difficulties in crossing the blood/brain barrier (BBB). In this perspective, κ-agonists appear as most useful as it is believed peripheral analgesia might be mediated by peripheral κ-opioid receptors. Early experiments have evoked relief to capsaicin-induced hyperalgesia conferred by the κ-agonist U50,488 (10) in studies using rats and rhesus monkeys.

However, these constitute specific pain models and a better determination of the level at which κ-efficacy leads to dysphoria is required for more general practice. There is a fundamental need for κ-antagonists, as assessment of κ-agonist efficacy is commonly achieved through the use of antagonists as a means of immobilising the receptor reserve in a preparation, thereby placing a higher efficacy demand on agonists to produce a response.

1.4.2 Significant interest in the synthesis of κ-antagonists

Although antagonists are mainly perceived as a tool for blocking a receptor population, κ-antagonists may also present additional pharmacological interest since they have been reported to improve recovery after traumatic brain injury and might prove useful in the treatment of Parkinson's disease; it is indeed suggested that the standard κ-antagonist norBNI might prevent motor fluctuations that normally develop under levodopa therapy.

In feeding studies, administration of norBNI has been shown to attenuate drinking in genetically polydipsic mice and to decrease food intake induced by food
deprivation, electrically-stimulated feeding, nocturnal feeding or exposure to a high-fat diet.\textsuperscript{51}

\(\kappa\)-Antagonists may also help in the treatment of depression, as GNTI (11), ANTI (12) and norBNI (13) have been reported to inhibit immobility in the forced swim test,\textsuperscript{39} an assay commonly used to study depression in rodents.\textsuperscript{65} It is supposed that these drugs mediate antidepressant effects by blocking \(\kappa\)-opioid receptors that normally decrease neurotransmitter release from mesolimbic dopaminergic neurons in the NAc.\textsuperscript{39}

The antidepressant effects of \(\kappa\)-antagonists have also been investigated for the treatment of drug abuse, as dysphoria is a likely condition observed upon drug withdrawal. In post-detoxification treatment of heroin addicts, Rothman and associates have demonstrated that a combination of naltrexone (\(\mu\)-antagonist) and buprenorphine (partial \(\mu\)-agonist/\(\kappa\)-antagonist) produced a greater positive response than naltrexone alone, indicating a possible therapeutic use of \(\kappa\)-antagonists in the treatment of opioid addiction.\textsuperscript{66}

\begin{align*}
\text{GNTI (11)} & \quad \text{ANTI (12)} & \quad \text{norBNI (13)} \\
\text{HO} & \quad \text{HO} & \quad \text{HO}
\end{align*}

On a more general point of view, \(\kappa\)-antagonists might also find therapeutic use as modulatory agents to prevent the tolerance and side effects mediated by \(\mu\)-selective analgesics. With this aim, peripheral antagonists could provide the best alternative since they do not antagonise centrally-mediated analgesia and one single antagonist could prevent several peripherally-mediated side effects.\textsuperscript{67}
1.5 Opioid ligands

1.5.1 General remarks concerning the design of opioid ligands

Pioneering efforts directed towards the synthesis of opioid ligands consisted of bringing slight modifications to the structure of morphine in the hope it would suppress the unwanted effects. These modifications were achieved either through the design of more complex ligands -e.g. orvinol ligands (14)- or via simplification of the morphine structure into diphenylpropylamines (15), 6,7-benzomorphans (aka 2,6-methano-3-benzazocine) (16), morphinans (17), 4-phenylpiperidines (18), 4-anilinopiperidines (19) and N-benzylpiperazines (20). However, regardless of the class of ligands, there still remain strategic choices and obstacles to overcome when designing opioid ligands.

1.5.1.3 Metabolism

High doses of opioids required for the treatment of acute pain might result in high accumulation of metabolites in the body, and consequently in increased risks of toxicity and/or activity. Though appearing a crucial issue, metabolism has for long been disregarded when designing new ligands because of its inconsistent and unpredictable impact on the pharmacological profile of the drug. A good illustration of the problem is provided with opioid drugs containing a hydroxy group (including phenolic) such as morphine (1); morphine is known to give two metabolites, namely morphine-3-glucuronide (21) and morphine-6-glucuronide (22) and the latter has been reported to possess higher potency and toxicity than morphine on an equimolar basis (though interestingly the drug is being developed by the pharmaceutical company...
CeNeS and is now on phase III of clinical trials). In addition, since metabolism of hydroxy groups by glucuronidation and sulfonation causes rapid excretion of the drug,\textsuperscript{20,69} it seems attractive to develop analogues with substituted hydroxy groups.\textsuperscript{70,71} Yet, the diacetyl derivative of morphine, heroin (2), penetrates more easily into the brain because of its higher lipophilicity; it is then quickly hydrolysed into morphine, which on the whole tantamounts to rapid delivery of morphine into the brain and therefore higher abuse liability.

In the case of peptidic ligands, for which biodegradation is a fundamental issue, bioavailability might be increased by the right choice of amino acids; for example, the use of D-amino acids has proved successful with FE200041 (\text{D-Phe-D-Phe-D-Nle-D-Arg-NH\textsubscript{2}}) reported as a peripheral peptidic \(\kappa\)-selective agonist presenting long-lasting bioavailability;\textsuperscript{43} DAMGO (\text{Tyr-D-Ala-Gly-MePhe-Gly-OH}), the \(\mu\)-selective agonist currently used in binding and functional assays, DADLE (\text{Tyr-D-Ala-Gly-Phe-D-Leu-OH}) and DPDPE (\text{Tyr-D-Pen-Gly-Phe-D-Pen-OH}), both used as \(\delta\)-selective agonists in binding assays, constitute other examples.

\begin{align*}
R^1 = R^2 = H & \quad 1 \\
R^1 = \text{Gluc}, R^2 = \text{Ac} & \quad 21 \\
R^1 = R^2 = \text{Ac} & \quad 2 \\
R^1 = H, R^2 = \text{Gluc} & \quad 22
\end{align*}

\textit{1.5.1.b Pharmacokinetic profile}

Although opioid analgesics almost exclusively refer so far to CNS-acting medications, there are encouraging signs that peripherally-acting drugs might prove useful for the treatment of specific pains (discussed above). As a consequence, when designing opioid ligands, medicinal chemists need to consider selectivity issues relating to the site of action. When penetrating into the brain, drugs need to cross the BBB, a very impermeable barrier to lipid-insoluble compounds: therefore, presence of extra basic groups –hence in a protonated state \textit{in-vivo}– might be envisaged as a means to reduce accessibility through the BBB, thus increasing peripheral selectivity.\textsuperscript{39}
In addition, since the transition between adequate pain management to pain might occur through a small variation of the drug blood concentration, it is essential to design drugs with the right pharmacokinetics, hydrophilicity/hydrophobicity ratio, rate of absorption, desired onset and duration of action. For instance, the introduction of ester functional groups in the series of fentanyl-derived ligands has proved judicious for modulating the pharmacokinetic profile of the parent drugs. The outcome was indeed better tissue solubility of the drug (remifentanil (23)) and rapid degradation by plasma esterases, which resulted in rapid onset and short duration of action. This prevents the drug from accumulating in the tissue, thereby alleviating dosing history issues. The other striking example to illustrate the importance of pharmacokinetic properties of opioid ligands is norBNI (13) and this will be discussed in section 1.5.2.b.

1.5.1.c Absence of a well-defined spatial arrangement of the receptor

Although opioid receptor cloning constituted a real advance in ligand design in that binding studies using chimeras and site directed mutagenesis studies allowed the determination of specific amino acids involved in ligand recognition, it is still difficult to predict whether a ligand will target the desired key sites as no three-dimensional (3-D) crystal structure of opioid receptors is currently available. The transmembrane nature of the GPCRs has long proved challenging for crystal structure analysis and only recently has the 3-D structure of bovine rhodopsin, a member of the GPCR family, been elucidated. Based on these data, 3-D computer-generated models of the three opioid receptors have appeared (see figure 5); these models rely on the assumption that the structural organisation of the transmembrane domains should be conserved within the members of the GPCR family because of high amino-acid sequence homology. Such models have since proved reliable and docking studies using these tools have been supported by site directed mutagenesis.
1.5.1.\textit{d} \quad \textit{Structure/Activity Relationship (SAR)}

The difference between an agonist and an antagonist is that an agonist shifts the receptor conformation to an active state. The switch from agonist activity to antagonist activity of opioid ligands is very subtle and can be imparted by a single change in rather complex molecules. For example, replacement of a single amino acid of peptidic ligands has been reported to change their activity (see example in section 1.5.2.a). Regarding the morphine derivatives selective for the \( \mu \)-receptor, it is noteworthy that antagonist ligands are usually obtained when the nitrogen atom is substituted with an allyl or cyclopropyl methyl group whereas substitution with a methyl group leads mainly to pure agonists.\textsuperscript{76} On the contrary, members of the phenylpiperidine class have been shown to retain their antagonist activity irrespective of the N-substituent (discussed below in section 1.5.2.b).

1.5.2 \( \kappa \)-\textit{Antagonists}

1.5.2.a Peptidic antagonists

In the 1970’s, isolation from brain tissue of two opioid peptides,\textsuperscript{77} namely methionine-enkephalin (Met-enkephalin) (24) and leucine-enkephalin (Leu-
enkephalin) (25), spurred pharmaceutical companies to synthesise peptidic ligands, as it was believed they would reveal non-addictive drugs. However, it came quickly apparent that a major challenge with peptidic opioid ligands would be enzymatic cleavage observed in-vivo. Exchange of one or several amino acids of dynorphin A (26) (the endogenous ligand for the κ-receptor) led to the discovery of numerous peptidic κ-agonists with increased selectivity, stability and activity. However, disclosure of peptidic selective κ-antagonists based on the core of 26 remained an elusive goal for many years until Schiller and co-workers disclosed dynantin (27) in 2001. The design of 27 was based on the observation that a positively charged N-terminal amino group seems to be required for signal transduction but not for the binding of peptidic ligands to opioid receptors. This led Schiller and associates to replace the N-terminal Tyr residue with 2',6'-dimethyltyrosine (Dmt), in which the terminal nitrogen was replaced with a methyl group. It is interesting to note that other examples of peptidic opioid antagonists have been reported using this technique and this might represent a general approach to switch from agonist activity to antagonist activity.

\[
\begin{align*}
\text{H-Tyr}^1\text{-Gly}^2\text{-Gly}^3\text{-Phe}^4\text{-Met}^5\text{(OH)} & \quad 24 \\
\text{H-Tyr}^1\text{-Gly}^2\text{-Gly}^3\text{-Phe}^4\text{-Leu}^5\text{(OH)} & \quad 25 \\
\text{Tyr}^1\text{-Gly}^2\text{-Gly}^3\text{-Phe}^4\text{-Leu}^5\text{-Arg}^6\text{-Arg}^7\text{-Ile}^8\text{-Arg}^9\text{-Pro}^{10}\text{-Lys}^{11}\text{-NH}_2 & \quad 26
\end{align*}
\]

1.5.2.b Non-peptidic antagonists

In 1987, Portoghese and co-workers reported the first two non-peptidic ligands selective towards the κ-receptor: binaltorphimine (BNI) (28) and norbinaltorphimine (norBNI) (13). To date, norBNI remains the most widely used κ-selective opioid antagonist since it shows high degree of selectivity for κ-receptors both in-vitro and in-vivo.
NorBNI does not bind irreversibly to the κ-opioid receptor, but the slow onset and very long duration of action of 13 —up to 11 weeks in vivo— are rather a consequence of the drug's bulky nature that impairs both its solubility and diffusion rates into and out of the brain. The disclosure of norBNI led therefore to SAR studies in view of simplifying the drug's structure. These studies revealed that the binding of norBNI with the κ-opioid receptor follows the “message-address” concept introduced by Schwyzer: in a series of bivalent ligands, the message refers to the common molecular features that result in binding to a family of receptors whereas the part of the ligand that provides additional selectivity towards a subsite unique to one of the receptors is called the address. Explicitly, Portoghese showed that only one morphinan pharmacophore (the message) and the basic nitrogen of the second morphinan (the address) were required for norBNI to maintain its activity and selectivity. Of significant importance was the spatial orientation of the second basic nitrogen, as it was supposed to mimic the basic Arg residue of dynorphin A. With this in mind, Portoghese and colleagues developed a series of “smaller” analogues, using rigid scaffolds in order to hold the basic nitrogen in the same position as that occupied in norBNI; this ultimately led to the discovery of GNTI (11) and the octahydroisoquinoline 29, with the former showing higher selectivity towards the κ-opioid receptor.
Subsequent chimera studies have supported Portoghese's intuition and have demonstrated that the second basic nitrogen interacts with an acidic residue Glu297, present in \( \kappa \)-receptors but not in \( \mu \)- or \( \delta \)-receptors, hence conferring \( \kappa \)-selectivity.\textsuperscript{27,83,84} However, there is recent suggestion that the spatial orientation of the second basic nitrogen atom might not be optimal in the structure of norBNI (13) and its derivatives 11 and 29.\textsuperscript{86} Subsequent series of compounds with different spatial arrangement and basicity level conferred to the second basic nitrogen have therefore been synthesised and evaluated in pharmacological assays.\textsuperscript{25,86,87} Although these studies further emphasized the importance of both pKa and position of the nitrogen in the selectivity and activity of the ligands,\textsuperscript{88} no clear conclusion could be reached on the optimal design. It is noteworthy that moving the guanidine group from the 5'-position to the 6'-position resulted in a change of activity of the parent drug (from an antagonist to an agonist),\textsuperscript{25} while moving the guanidine group from the 5'-position to the 7'-position resulted in a predictable change of selectivity (from \( \kappa \) to \( \delta \)).\textsuperscript{89} 

Efforts directed towards the synthesis of "small" \( \kappa \)-antagonists focussed initially on \textit{trans}-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines (30) and 4\( \beta \)-methyl-5-(3-hydroxyphenyl)morphans (31).\textsuperscript{90,91,92,93} Although early antagonists disclosed within the former family did not exhibit \( \kappa \)-selectivity, their discovery nevertheless constituted a major advance in the search for \( \kappa \)-antagonists in that antagonist activity was retained upon modification of the N-substituent.\textsuperscript{94} This then allowed Thomas \textit{et al.} to use a library of compounds based on the general structure 30 and biased for opioid antagonist activity and reduced \( \mu \)-affinity. This led to the discovery of the \( \kappa \)-selective antagonist 32 \textsuperscript{92} and further refinement using the message/address concept culminated in the disclosure of JDTic (33), as a \( \kappa \)-antagonist with remarkable selectivity and potency.\textsuperscript{91}
Despite structural resemblance between the trans-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidine family and the 5-(3-hydroxyphenyl)morphan family, the disclosure of κ-antagonists has proved more difficult in the latter case. However, the discovery of 34, a potent antagonist at the three opioid receptors and application of the message/address concept led to 35, the first potent and selective κ-antagonist within this family.

In addition, it is interesting to note that in a similar way to the trans-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidine family (30) and unlike morphine-based antagonists, there is no evidence of efficacy being introduced when changing the N-substituent. It is believed that the discrepancy in SAR behaviours stems from the fact that, upon binding of the ligands to the receptor, the N-substituent occupies different binding pockets of the receptor and thereby does not play the same role; this is illustrated on figure 6. For opioid antagonists having a piperidine ring in a chair conformation and substituted with an axial 3-hydroxyphenyl group, e.g. morphinones 36 or trans-(3,4)-dimethyl-4-(3-hydroxyphenyl)piperidines 37, the N-substituent is postulated to be in the equatorial position and would therefore represent the trigger for antagonist activity; for opioid antagonists having a piperidine ring in a chair conformation and substituted with an equatorial 3-hydroxyphenyl group, such as 5-(3-hydroxyphenyl)morphans 38 or trans-(3,4)-dimethyl-4-(3-hydroxyphenyl) piperidines 39, it is the axial 3-methyl group of 39 or the 9β-methyl group of 38 that are supposed to be responsible for antagonist activity; in 38 and 39, the N-substituent confers selectivity but not activity.
κ-Antagonists are also known in the arylacetamide class of compounds, a family usually associated with κ-agonists. The rationales behind the two irreversible κ-selective ligands UPHIT (40) and ICI 199411 (41) were identical and explored the introduction of an electrophilic group onto the two κ-selective agonists U50488 (42) and DIPPA (43) with the aim of promoting irreversible binding. However, this approach did not prove completely successful since, in both cases, irreversible antagonism is preceded by agonism. It is believed that 40 and 41 initially mimic 42 and 43, thereby shifting the receptor to an activated state; subsequent nucleophilic attack on the isothiocyanate groups results in conformational change of the receptor and loss of activity. Such tools might be used once their initial agonism has worn off, but it can be inferred that agonist effects of 40 and 41 might alter subsequent antagonist activity. It should be noted that the pharmacological profile of both drugs is however highly debated, including among our collaborators.
1.6 Aim of the present project

The need for κ-antagonists as a means of further understanding the biological processes associated with the κ-opioid receptor and as a means of better characterising κ-agonists has prompted us to develop new selective antagonists and potential irreversible antagonists for the κ-opioid receptor. Since norBNI (13) and GNTI (11) are the two most prominent κ-selective antagonists thus far reported, it was decided to modify their structure with the aim of promoting covalent binding with the κ-opioid receptor or pseudo-irreversible binding. In particular, two main approaches are investigated in the present project, namely introduction of a lipophilic group (substituted/unsubstituted benzyl) or electrophilic group (isothiocyanate) onto the guanidinium group of GNTI (11) or at the pyrrolic nitrogen of norBNI (13).
2. DISCUSSION

2.1 Benzylguanidinyl substituted ligands

2.1.1 Rationale

Since GNTI (11) is a highly selective κ-antagonist, it represented an ideal starting point for the design of potentially irreversible κ-selective antagonists. In particular, the unsubstituted guanidinyl group appeared to provide an ideal position for further structural modification.

In 1992, Lewis and associates reported that the substitution of the 14-hydroxy group of naltrexone (44), a reversible μ-selective antagonist, with a p-chlorocinnamoylamido group afforded C-CAM (45) as an irreversible μ-selective antagonist (scheme 1). The irreversibility in the binding of 45 does not stem from Michael addition on the cinnamoyl group of C-CAM, as originally believed, but is likely due to very strong lipophilic interactions presumably between the styryl group of 45 and a lipophilic pocket of the μ-opioid receptor (pseudo-irreversible binding); studies with strong electron-withdrawing groups on the phenyl ring (e.g. NO₂) have indeed failed to promote covalent binding with the receptor, thus emphasising the prominent contribution of lipophilic interactions in the binding with the receptor.

![Scheme 1 Design of C-CAM (45)](image)

Interestingly, the addition of a lipophilic group (benzyl) onto the indolic nitrogen of NTI has also been reported to result in longer duration of action of the drug (this will be further detailed in section 2.4.1.b). It was thus decided to investigate the effect of similar introduction of a lipophilic group, in particular benzyl, to the reversible κ-antagonist GNTI (11). In the pioneering series of benzylGNTI analogues synthesized by Dr Shannon Black, the p-chlorobenzylGNTI derivative (46) proved particularly promising since the binding in C6(6) and CHO (κ) cells remained after washing, suggesting irreversible binding with the receptors (see scheme 2).
However, it was found in the opioid antagonist functional assay that selectivity towards the \( \kappa \)-receptor (37-fold \( \kappa/\mu \) selectivity and 55-fold \( \kappa/\delta \) selectivity) was modest compared to that exhibited by GNTI (81-fold \( \kappa/\mu \) selectivity and 389-fold \( \kappa/\delta \) selectivity).\(^{101}\) The present project thus explores further modification of benzylGNTI in order to enhance \( \kappa \)-opioid receptor selectivity.

\[
\text{Scheme 2 Pioneering work within our group on benzylGNTI analogues}
\]

2.1.2 Design

As mentioned in the introduction, the phenolic group of the first pharmacophore of norBNI (13) has been reported to be crucial for \( \kappa \)-antagonist activity. To demonstrate this point, Portoghese \textit{et al.} synthesised the 3-O,3'-O-dimethylated and 3'-O-monomethylated norBNI derivatives (47 and 48 respectively).\(^{102}\) Biological evaluation of the opioid antagonist activity showed that the dimethylated analogue 47 was inactive at all three receptors, while the monomethylated derivative 48 exhibited potency and selectivity similar to that of norBNI. It was later concluded that the second phenolic group of norBNI was not important for \( \kappa \)-antagonist selectivity \(^{20,83}\) and this was corroborated by GNTI being a highly selective \( \kappa \)-antagonist.\(^{84}\) However, when disclosing JDTic (33), Thomas \textit{et al.} demonstrated that both amino groups and both phenolic groups were required to maintain \( \kappa \)-opioid potency and selectivity.\(^ {103}\) Intrigued by this point, they decided to synthesise the dehydroxy analogue of norBNI (49).\(^{104}\) Unexpectedly, evaluation of 13 and 49 in the binding assay showed that loss of the hydroxy group had little impact on \( \kappa \)- and \( \delta \)-affinity but entailed a 10-fold increase in \( \mu \)-affinity, which resulted on the whole in no change of \( \kappa/\delta \) selectivity but in a 10-fold decrease of \( \kappa/\mu \) selectivity. In the functional assay, loss of the hydroxy group produced a 3.5-fold loss of \( \kappa \)-antagonist potency with concomitant slight increase in \( \mu \)-antagonist potency and huge
decrease in δ-antagonist potency; this resulted therefore in a decrease of κ/μ selectivity and huge enhancement of κ/δ selectivity, thus demonstrating the importance of the second phenolic group in determining κ-antagonist selectivity. The discrepancy between these findings and Portoghese’s earlier conclusions might be explained by the fact that Portoghese and associates used the monomethylated analogue of norBNI (48) to study the importance of the second phenolic group. It is possible that the oxygen atom of the second phenolic group of 13 unfavourably interacts with a group present in the lipophilic pocket of the μ-receptor. The presence of the hydrogen-bond accepting oxygen atom may therefore be important for κ-antagonist selectivity but not the presence of a hydrogen-bond donor.  

![Chemical structures](image)

We have demonstrated by using the “flexible align” function implemented in MOE that, when in a low energy conformation, the phenolic group of p-hydroxybenzylGNTI (50) can be exactly overlaid on the second phenolic group of norBNI (see figure 7) and therefore could be expected to have a beneficial effect on κ-selectivity, if not affinity.

![Figure 7 Overlay of norBNI (13) and p-hydroxybenzylGNTI (50)](image)
The synthesis and biological evaluation of p-hydroxybenzylGNTI (50), m-hydroxybenzylGNTI (51) and p-methoxybenzylGNTI (52) are therefore reported in the present project. Comparison of 50 and 51 should provide information on the importance of the orientation of the hydroxyl group, while comparison of 50 and 52 will provide evidence of the importance, or not, of hydrogen-bond donating/accepting capability.

\[
\begin{align*}
R^1 &= \text{OH, } R^2 = \text{H} & 50 \\
R^1 &= \text{H, } R^2 = \text{OH} & 51 \\
R^1 &= \text{OCH}_3, R^2 = \text{H} & 52
\end{align*}
\]

2.1.3 Synthesis

The synthesis of 50 and 51 was carried out simultaneously and will be described in section 2.1.3.a, with the synthetic route further exploited for the preparation of 52 (section 2.1.3.b).

2.1.3.a Synthesis of p- and m-hydroxybenzylGNTI analogues (50) and (51)

The synthesis of GNTI (11) is reported in the literature and involves guanidinylation of amine 53 with 1,3-bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (54) (scheme 3).\(^{84,88}\)

\[
\begin{align*}
\text{NBoc}^+ &+ \text{S}^\text{Boc}^- \\ &\rightarrow 53 + 54
\end{align*}
\]

Scheme 3 Synthetic route reported in the literature for the preparation of 11\(^{84,88}\)

With this in mind, two different approaches might be envisaged for the synthesis of 50 and 51, namely guanidinylation of 53 with substituted guanidinylating agents (path A) or direct alkylation of 11 (path B) as shown in scheme 4.\(^{105}\) Since the latter method would require protection and deprotection of the hydroxy groups of 55,
it was decided to synthesise 50 and 51 via guanidinylation of 53 with appropriately N-substituted derivatives of 54.

Scheme 4  Two possible synthetic approaches for the preparation of 50 and 51

The method employed by Portoghese and associates for the preparation of amine 53 involved a Fisher indole reaction between naltrexone hydrochloride (44) and 4-nitrophenylhydrazine, followed by reduction of the nitro group with Raney nickel and hydrazine hydrate (see scheme 5).\(^{88}\)

Scheme 5  Preparation of amine 53 reported in the literature \(^{88}\)
Portoghese and co-workers reported that very harsh conditions were required for the first step because of the strong electron-withdrawing effect of the nitro group on phenylhydrazine; stirring the materials for 7 days at 110°C in a mixture of acetic acid/conc. HCl thus afforded 5'-nitronaltrindole (56) in modest yield (43%).

However, earlier work within our group had suggested that a shorter reaction time, a less tedious workup and a better yield could be obtained when the first step was carried out in ethanol/conc. HCl (50/50) under reflux. Modifications had also been reported for subsequent reduction of the nitro group into the corresponding amine, as Raney nickel-catalysed transfer hydrogenation with cyclohexene was found preferable. While the modified first step proceeded relatively well during this current study (26% yield), the reduction of 56 to 53 using Raney Ni/cyclohexene transfer hydrogenation could not be repeated. Hydrogenation, using Raney Nickel or palladium as catalysts under an atmospheric pressure of hydrogen, also proved unsuccessful. Pd-catalytic hydrogenation, increasing the hydrogen pressure to 5 bars, gave somewhat better results, as the desired product was obtained in 31% yield. It was then decided to reproduce Portoghese’s method (Raney nickel/hydrazine hydrate transfer hydrogenation), which afforded the amine in 47% yield (vs 69% reported in the literature). Reduction using iron(II) sulfate heptahydrate/NH₄OH was also attempted to see if this would allow a more efficient preparation of 53, as this method had been satisfactorily employed within our group for the reduction of aromatic nitro groups; indeed, stirring morphinan 56 and 9 equivalents of iron(II) sulfate heptahydrate at 80°C for 3 hours in a mixture of methanol/H₂O/conc. NH₄OH afforded 53 in 56% yield.

As noted earlier, the synthetic approach used in the present project for the preparation of 50 and 51 required the synthesis of suitable guanidinylating agents. Guanidines are generally commercially synthesised via the nucleophilic displacement of methyl mercaptan from S-methylisothiouronium salts by amines. However, since methyl mercaptan is a highly smelly noxious gas, such a procedure requires subsequent transformation of the byproduct. The synthesis of guanidines has also been achieved by reaction of ammonia derivatives with cyanamides, chloroformamidines, aminoiminomethanesulfonic acids or carbodiimides but these procedures generally involve corrosive, moisture-sensitive starting materials and require high temperatures. More recently, guanidinylation employing protected
guanidinylating agents, such as pyrazole carboxamidine 57 or thiourea derivatives 54 and 58, in presence of Mukaiyama’s reagent (59) or a thiophile (such as mercury, copper or lead salts) \(^{113,114}\) have emerged and this proved more attractive to us as the desired guanidinylating agents could be prepared by direct N-alkylation of these. Such a procedure was also employed by Portoghese and colleagues for the disclosure of GNTI (11), with mercury(II) chloride being used as the catalyst for the coupling of 54 with 53. \(^{84,88}\) Although it is generally agreed that mercury forms a complex with the sulfur atom, resulting in activation of the carbon atom towards nucleophilic attack by the amine, it is not clear however whether the reaction proceeds via formation of a tetrahedral intermediate \(^{115}\) or a carbodiimide intermediate. \(^{116}\)

As N-benzylation of 54 with benzyl bromide derivatives 60 and 61 required the use of sodium hydride, the synthesis of guanidinylating agents 62 and 63 started with the protection of the hydroxy group of 3- and 4-hydroxybenzaldehydes (see scheme 6). Three protecting groups were initially investigated, namely benzyl, O-tetrahydropyranyl and trityl, but it appeared very early in the synthesis that the use of the benzyl group was the most promising. Benzyl-protection of 3- and 4-hydroxybenzaldehydes was achieved following the procedure used by Nicolaou et al., \(^{117}\) which quantitatively afforded 64 and 65 that were subsequently reduced with sodium borohydride into the corresponding alcohols 66 and 67 (93% and 84% respectively). The latter were then converted into their bromide derivatives 60 and 61 according to a general procedure reported by Lange et al. for the conversion of alcohols into alkyl iodides; \(^{118}\) this procedure involved forming iodonitriphenylphosphonium iodide salt before subsequent reaction with 0.83 equivalent of alcohol in the presence of one equivalent of imidazole; in our case, iodonitriphenylphosphonium iodide was replaced by the bromide salt. Deprotonation of 1,3-bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (54) with 1.2 equivalents of sodium hydride and subsequent nucleophilic attack on 1.1 equivalents of 60 and 61,
using a similar procedure to that previously reported within our group,\textsuperscript{106} afforded the guanidinylating agents 62 and 63 in 62\% and 54\% yields respectively.

![Chemical structure](image)

**Scheme 6** Preparation of guanidinylating agents 62 and 63

Coupling of 53 with 62 and 63 was achieved following an analogous HgCl\textsubscript{2}-promoted guanidinylation procedure to that reported in the literature, namely using 0.56 equivalent of mercury(II) chloride and 1.0 equivalent of both triethylamine and 53.\textsuperscript{84} However, since initial attempts showed that some unreacted amine 53 was still present at the end of the reaction, we eventually decided to increase the number of equivalents of mercury(II) chloride, triethylamine and guanidinylating agent (1.5, 2.0 and 2.0 equivalents respectively) (scheme 7). Simultaneous removal of the BOC and benzyl protecting groups of 68 and 69 was then attempted using a large excess of trifluoroacetic acid but this afforded products still bearing the benzyl protecting group. Since it was reported in the literature that debenzylation with TFA might be improved by adding a strong nucleophile (thioanisole) or a benzylic cation scavenger (pentamethylbenzene),\textsuperscript{119,120} the benzyl-protected morphinans were stirred overnight
at 40°C in TFA with 20 equivalents of thioanisole, but this gave only unreacted materials. However, simultaneous benzyl and BOC deprotection was eventually achieved stirring 68 and 69 overnight in a mixture of conc. HCl/MeOH (50/50) at 80°C, which afforded the target compounds 50 and 51 in quantitative yields.

(a) 1.2 equi. 4-nitrophenylhydrazine, EtOH/conc. HCl (50/50), 24 hrs, reflux; (b) 9 equi. FeSO₄·7H₂O, MeOH/H₂O/NH₂OH, 3 hrs, 80°C; (c) 1.5 equi. HgCl₂, 2.0 equi. 62 or 63, 2.0 equiv. NEt₃, dry DMF, 24 hrs, 60°C; (d) conc. HCl/MeOH (50/50), overnight, 80°C

Scheme 7 Synthetic approach used for the preparation of compounds 50 and 51

2.1.3.b Synthesis of p-methoxybenzylGNTI (52)

The synthetic pathway described in section 2.1.3.a was further employed for the preparation of 52. 4-Hydroxybenzaldehyde was reacted with 1 equivalent of
methyl iodide and 1.5 equivalents of potassium carbonate in DMF, which led to the methoxy derivative 70 in 92% yield (scheme 8). 70 was quantitatively reduced with sodium borohydride to the corresponding alcohol 71 before conversion into 4-methoxybenzyl bromide (72), using the same conditions as described above for 60 and 61. It is noteworthy that 72 could not be purified by column chromatography because of decomposition and was subsequently used without any purification. Reaction of 72 with 54 in presence of sodium hydride led to the guanidinylation agent 73 (49% yield) that was in turn coupled with 53 using the same mercury(II) chloride-promoted guanidinylation as used for the preparation of 68 and 69. This afforded a mixture containing the desired di-BOC-protected morphinan 74 and its mono-BOC-protected analogue. Deprotection of the mixture with a large excess of TFA afforded cleanly and quantitatively the target compound 52 (see scheme 8).

Scheme 8  Synthetic route used for the preparation of p-methoxybenzylGNTI (52)
2.2 Further work with benzylGNTI derivatives

2.2.1 Rationale

Still intrigued by the results reported by Thomas et al. relating to the contribution of the second phenolic group towards the binding of norBNI and in our effort to develop antagonists with increased κ-opioid receptor selectivity and activity, we decided to further study the interaction between the benzylic group of benzylGNTI analogues and the lipophilic pocket of the κ-opioid receptor. A Topliss approach was thus implemented in order to investigate which physicochemical parameters of the substituent on the phenyl ring are optimal for κ-antagonist potency and selectivity. The Topliss method requires the synthesis and biological evaluation of a first series of derivatives, namely p-chloro, 3,4-dichloro, p-methyl, p-methoxy and unsubstituted benzyl analogues; according to the rank order of potency of these compounds, one can predict which type of substitution on the phenyl ring is optimal for activity. As Dr Shannon Black had already synthesised p-chlorobenzylGNTI and benzylGNTI, it was decided to prepare and evaluate 3,4-dichlorobenzylGNTI (75) and p-methylbenzylGNTI (76) (see scheme 9).

2.2.2 Synthesis

The preparation of 76 and 75 was achieved using a similar synthetic strategy as used in section 2.1 and started with the synthesis of guanidinylating agents 77 and 78. 1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (54) was thus deprotonated with 1.1 equivalents of sodium hydride in presence of 0.1 equivalent of 15-crown-5; the corresponding base was subsequently reacted with commercially available 4-methylbenzyl bromide (79) or 3,4-dichlorobenzyl chloride (80), stirring the mixture overnight at 70°C, which afforded the desired products 77 and 78 in 74% and 47% yields respectively (see scheme 9). Subsequent HgCl₂-promoted guanidinylation of amine 53 with 77 and 78, using the procedure described in section 2.1, led to 81 and 82 in 68% and 74% yields respectively. It is noteworthy that both 81 and 82 were isolated as a mixture of mono- and di-BOC protected morphinans. Finally, deprotection of the morphinans (mixture of mono- and di-BOC protected derivatives) was accomplished stirring the compounds overnight at room temperature in a large excess of TFA, which led cleanly to the targets 76 and 75.
Scheme 9 Synthetic approach used for the preparation of 75 and 76

2.3 Irreversible guanidinyl substituted ligands

2.3.1 Design

We have explored in sections 2.1 and 2.2 the possibility of promoting irreversible binding with the receptor via additional lipophilic interactions. This resulted in benzylGNTI analogues exhibiting pseudo-irreversible binding with the κ-receptor (see section 2.1.1). During the present project, the possibility of eliciting
covalent binding between GNTI-derived ligands and the κ-opioid receptor was also investigated.

With that aim, it was decided to substitute the guanidinium group of GNTI so as to orientate an electrophilic group in close proximity to a putative nucleophile near or at the active site of the κ-opioid receptor. The use of a wide range of electrophiles has been reported in the literature for promoting covalent binding with opioid receptors, including nitrogen mustard, Michael acceptor and disulfide compounds. However, the isothiocyanate group appeared more attractive to us because of its reactivity profile and fairly small size, the latter generally resulting in little modification in the selectivity of the parent ligand. Isothiocyanates are known to react preferentially with amino and sulphydryl groups while reacting slowly with water and hydroxyl functions, hence limiting non-specific binding. It was therefore decided to substitute the guanidinium group of GNTI with a series of side chains of different length terminating with an isothiocyanate group (targets of type A or B).

\[\text{A} \quad n = 2 \text{ to } 6\]

\[\text{B} \quad \text{NCS}\]

2.3.2 Synthesis

Although the synthesis of isothiocyanates via nucleophilic attack of thiocyanate ions on acyl halides, alkyl halides or aryl diazonium compounds is reported in the literature, these methods did not appear most attractive to us as S-alkylation is also generally observed. We instead sought to prepare the targeted isothiocyanates via the corresponding primary amino precursors, using one of several reagents reported in the literature, including carbon disulfide in combination with BOP or dicyclohexylcarbodiimide, thiophosgene or di-2-pyridyl thionocarbonate.

With this in mind, it was proposed to prepare the target compounds according to the same approach as used in sections 2.1 and 2.2, but using guanidinylating agents bearing a side chain terminating with a protected amino group or a moiety that could be easily transformed into an amino group.
2.3.2. a Synthesis with guanidinylating agents bearing a terminal BOC-protected amino group

Although coupling of amine 53 with derivatives of 54 had proved relatively successful (from 30 to 74% yield, see sections 2.1 and 2.2), we decided to prepare guanidinylating agents modelled on 58 since they have been reported to give best results for the guanidinylation of sterically hindered amines;\textsuperscript{113} for our purpose, guanidinylating agents would therefore be reagents of type C. Although it is reported in the literature that the presence of one proton on each of the nitrogen atoms of 58 is required for the guanidinylation to succeed,\textsuperscript{116} suggesting that the reaction proceeds via the formation of a carbodiimide intermediate, preliminary results within our group with N,N'-disubstituted derivatives of 58 have shown this is not a necessary condition, which suggests the reaction might also evolve via a tetrahedral intermediate.\textsuperscript{106} It is noteworthy that the BOC groups not only play the role of protecting groups but also facilitate the guanidinylating step, a consequence of their electron-withdrawing properties; thus, unprotected N,N'-dialkyl substituted thioureas have been reported not to undergo guanidinylation while di-BOC-protected thioureas have been shown to react more swiftly than mono-BOC derivatives.\textsuperscript{116} Again however, preliminary findings within our group tended to be in disagreement with that stated in the literature, as coupling of mono-BOC protected thioureas with amine 53 had been found to proceed with great facility.\textsuperscript{106}

Since it was intended to utilise BOC protecting groups on the nitrogens of the thiourea moiety, it seemed particularly attractive to use a BOC group for the protection of the terminal amino group of agents C (P = NHBoc) with the view of subsequently removing all protecting groups in one single step (see scheme 10).
Scheme 10  Synthetic route planned for the preparation of 101-103

The route planned for the synthesis of guanidinylating agents of type C is presented in scheme 11 and started with the mono-BOC protection of diaminoalkanes. This was achieved by reacting the diamines with 0.1 equivalent of di-tert-butyl dicarbonate as reported by Muller and co-workers (80-90% yields, based on di-tert-butyl dicarbonate). The free amino group of 83-85 was then converted into an isothiocyanate functional group (compounds 86-88) using two equivalents of thiophosgene in presence of one equivalent of calcium carbonate. Nucleophilic attack of ammonia (aqueous solution) onto 86-88 yielded thioureas 89-91 that were subsequently BOC-protected using two equivalents of both sodium hydride and di-tert-butyl dicarbonate. This afforded a mixture of N mono and N,N'-di-BOC-
protected thioureas 92-94 but no separation was undertaken as it was believed that all products would successfully undergo guanidinylation with 53. The coupling step was achieved using analogous HgCl₂-promoted guanidinylation described in section 2.1, which gave a mixture containing di-BOC-protected morphinans 95-97 and their mono-BOC-protected analogues. These were subsequently stirred overnight at room temperature in a mixture of methanol/conc. HCl (50/50), affording deprotected derivatives 98-100.

\[
\begin{align*}
&H_2N(-\text{R})_nNH_2 \quad \overset{a}{\longrightarrow} \quad \text{Boc}N(-\text{R})_nNH_2 \\
&83 \quad n = 2 \\
&84 \quad n = 4 \\
&85 \quad n = 6 \\
&\overset{b}{\longrightarrow} \quad \text{Boc}N(-\text{R})_nNCS \\
&86 \quad n = 2 \\
&87 \quad n = 4 \\
&88 \quad n = 6 \\
&\overset{c}{\longrightarrow} \quad \text{Boc}N(-\text{R})_nS \quad \overset{d}{\longrightarrow} \quad \text{Boc}N(-\text{R})_nNH\text{Boc} \\
&89 \quad n = 2 \\
&90 \quad n = 4 \\
&91 \quad n = 6 \\
&92 \quad n = 2 \\
&93 \quad n = 4 \\
&94 \quad n = 6 \\
\end{align*}
\]

(a) 0.1 equi. (Boc)₂O, CHCl₃, 24 hrs, room T°; (b) 1.0 equi. CaCO₃, 2.0 equi. CCl₄CHCl₃/H₂O, 24 hrs, room T°; (c) 10 equi. conc. NH₄OH, Acetone, 24 hrs, room T°; (d) 2.0 equi. NaH, 2.0 equi. (Boc)₂O, dry THF, overnight, room T°

Scheme 11 Synthetic route used for the preparation of guanidinylating agents 92-94

The last step of the synthesis involved conversion of 98-100 into the corresponding isothiocyanates. Previously, it has been shown within our group that the preparation of an isothiocyanate from an aniline can be achieved in presence of the hydrochloride salt of an imidazoline ring by using acetone/water as the solvent mixture (see scheme 12).³³³

\[
\begin{align*}
&H_2N(-\text{R})_nNH_2 \quad \overset{\text{CSCl}_2 (1.5 \text{ equi.})}{\longrightarrow} \quad \text{SCN}(-\text{R})_nNH \\
&\overset{\text{H}_2\text{O/Acetone}}{\longrightarrow} \\
\end{align*}
\]

Scheme 12 Previous preparation of an isothiocyanate from the corresponding aniline
Thus, we attempted an equivalent procedure for the preparation of target compounds 101-103 from the hydrochloride salts of 98-100; the free base of the terminal ammonium group was first generated *in-situ* in a mixture of acetone/water by using an excess of sodium hydrogen carbonate and was subsequently reacted with 1.3 equivalents of thiophosgene. However, this procedure failed to give the desired products, probably as a direct consequence of the reacting conditions; a high proportion of water in the acetone/water solvent system was indeed required to dissolve amines 98-100 because of their highly protonated state. It is possible that the tiny amount of thiophosgene used in the reaction (a few μL) was partially destroyed in presence of water before reacting with the amines; this resulted in a complex mixture of materials that could not be purified by column chromatography due to the highly polar nature of the compounds.

Although the synthetic pathway did not lead to the target compounds, it would be interesting to evaluate the pharmacological profile of these amines as they might represent useful peripheral κ-selective antagonists. GNTI (11) has indeed been suggested to penetrate into the brain to a lesser extent than ANTI (12) because of the higher pKa of the guanidinium group compared to that of the amidinium group.\(^{39}\) Thus, systemic administration of GNTI, at doses up to 10 mg/kg, was ineffective in providing anti-depressant effects (forced swim test) whereas administration of an equivalent dose of ANTI proved successful. We believe that the extra ammonium group present in compounds 98-100 will further impair access through the BBB, thus possibly restricting the bioavailability of the drugs to peripheral sites. Amines 98-100 have therefore been sent for pharmacological evaluation.

2.3.2.b Synthesis with guanidinylating agents bearing a terminal phthalimido-protected amino group

Since the preparation of guanidinylating agents modelled on 58 proved more tedious than that modelled on 54, we decided to return to using the latter. It was thus
planned to react the conjugate base of 54 with electrophiles that could be later transformed into amino derivatives. However, attempts employing acrylonitrile or acrolein as such electrophiles proved unsuccessful despite varying the reacting conditions, including time, temperature or amount of base and electrophile (entries 1-5 table 2). The reactivity of 54 was then evaluated with bromobutane and bromo- and chloroacetyl chloride but all attempts proved again unsuccessful (entries 6 to 10). It was finally possible to successfully react 54 by using 3 equivalents of sodium hydride, 2 equivalents of allyl bromide or acetyl chloride and heating the reaction mixture, which afforded compounds 104 and 105 (entries 12 and 15). This led us to react 54 with 1,4-dibromo-2-butene and 4-chlorobutyryl chloride, leading respectively to analogues 106 and 107 that could be further converted into amino derivatives.

Unfortunately, attempts to react the more reactive compound, allyl bromide 106, with potassium cyanide proved unsuccessful despite following a general procedure reported in the literature. Since Itsuno et al. have reported that alkyl halides can be directly converted into protected amines by using potassium 1,1,3,3-tetramethyldisilazide (108), it was hoped that similar treatment of 106 with 108 would lead to 109 (see scheme 13). In our case, 108 was replaced by the sodium salt, prepared from commercially available 1,1,3,3-tetramethyldisilazane with sodium hydride, but subsequent reaction with 106 led unfortunately to the recovery of 106.

\[
\begin{align*}
\text{HN(SiMe}_2\text{)}_2 & \xrightarrow{1.1 \text{ equi. KH}} \text{KN(SiMe}_2\text{)}_2 + \text{H}_2 \\
\text{RX} & \xrightarrow{1 \text{ equi.} \text{108}} \text{RN(SiMe}_2\text{)}_2 + \text{H}^+; \text{NH}_4\text{OH} \\
\text{RX} & = \text{106} \xrightarrow{\text{108}} \text{109}
\end{align*}
\]

\textbf{Scheme 13} Synthetic route planned for the preparation of 109

51
<table>
<thead>
<tr>
<th>Reagents</th>
<th>Conditions used</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylonitrile (1 equi.) Sodium hydride (1 equi.)</td>
<td>reaction at room temperature for 24 hours</td>
<td>unreacted starting materials</td>
</tr>
<tr>
<td>Acrylonitrile (1.1 equi.) Sodium hydride (1.2 equi.)</td>
<td>reaction at room temperature for 5 days</td>
<td>unreacted starting materials</td>
</tr>
<tr>
<td>Acrylonitrile (1 equi.) Sodium hydride (1 equi.)</td>
<td>reaction at 72°C for 40 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Acrylonitrile (2 equi.) Sodium hydride (3 equi.)</td>
<td>reaction at 70°C for 25 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Acrolein (1.1 equi.) Sodium hydride (1.2 equi.)</td>
<td>reaction at 48°C for 24 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Bromobutane (1.1 equi.) Sodium hydride (1.2 equi.)</td>
<td>reaction at 48°C for 24 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Bromobutane (1.1 equi.) Sodium hydride (1.2 equi.)</td>
<td>presence of 18-crown-6 (0.1 equi.) reaction at 48°C for 24 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Chloroacetyl chloride (1.1 equi.) Sodium hydride (1.2 equi.)</td>
<td>reaction at room temperature for 5 days</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Chloroacetyl chloride (2 equi.) Sodium hydride (3 equi.)</td>
<td>presence of 18-crown-6 (0.1 equi.) attempts with heating at 58°C and 86°C</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Bromoacetyl chloride (2 equi.) Sodium hydride (3 equi.)</td>
<td>presence of 18-crown-6 (0.1 equi.) attempts with heating at 58°C and 86°C</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Allyl bromide (1.1 equi.) Sodium hydride (1.2 equi.)</td>
<td>reaction at 80°C for 41 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Allyl bromide (2 equi.) Sodium hydride (3 equi.)</td>
<td>reaction at 70°C for 41 hours</td>
<td>yield = 61 %</td>
</tr>
<tr>
<td>Acetyl chloride (1 equi.) Sodium hydride (1 equi.)</td>
<td>reaction at room temperature for 25 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Acetyl chloride (1 equi.) Triethylamine (1.1 equi.)</td>
<td>reaction at 50°C for 41 hours</td>
<td>no trace of product</td>
</tr>
<tr>
<td>Acetyl chloride (2 equi.) Sodium hydride (3 equi.)</td>
<td>presence of 18-crown-6 (0.1 equi.) reaction at 48°C for 24 hours</td>
<td>yield = 19 %</td>
</tr>
</tbody>
</table>

¹: for one equivalent of 1,3-bis-BOC-2-methyl-2-thiopseudourea

Table 2 Preliminary experiments for the preparation of guanidinylation agents
A Gabriel synthesis, one of the most popular methods used for the preparation of primary amines, was then envisaged to convert the bromo group of 106; however, the small amount of 106 left at this stage required preparing more starting material.

Instead, we decided to react first 1,4-dibromo-2-butene with potassium phthalimide before subsequent reaction with 54; indeed, it seemed more economically sound to proceed in this order since the first attack on 1,4-dibromo-2-butene with one equivalent of nucleophile leads to some disubstituted derivative and potassium phthalimide is much cheaper than 54. Nucleophilic attack of potassium phthalimide on 1,4-dibromo-2-butene was achieved following a similar method reported by Langenbeck et al. but employing one equivalent of potassium phthalimide instead of two (scheme 14).136 The product (110) was isolated in 51% yield and further reacted with 54 according to the same procedure as reported in sections 2.1 and 2.2. 111 was obtained in very good yield (80%) and subsequently coupled with 53 via HgCl₂-promoted guanidinylation, which afforded a mixture containing the desired product 112 and its mono-BOC-protected analogue. It was then proposed to remove the BOC and phthalimido protecting groups in one single step employing acidic conditions (conc. HCl/MeOH (50/50), room temperature, three days), but this afforded 113 still bearing the phthalimido protecting group; the reaction was repeated stirring the mixture at 80°C for 2 days, but this resulted in no further deprotection of 113. Although deprotection of phthalimido groups is reported using hydrolytic (in acidic or alkaline solutions), aminolytic and hydrazinolytic (Ing-Manske) procedures,137,138 the latter is generally the preferred method because of quicker kinetics. This led us to attempt deprotecting phthalimide 113 under hydrazinolytic conditions, first stirring 113 overnight at room temperature with 12 equivalents of hydrazine hydrate, which did not lead to full deprotection of 113, then at 60°C with 28 equivalents of hydrazine hydrate, but this resulted in a complex mixture of materials. It seems that the primary amine was formed but could not be isolated from 2,3-dihydrophthalazine formed during the reaction. The crude product could not be purified by column chromatography because of the extreme polarity of the guanidinium salt and the side product could not be washed out with any solvent. At this stage, there was insufficient quantity of morphinan 113 to allow further work. Since strong lipophilic interactions are possible between the phthalimido group of 113 and the lipophilic pocket of the κ-receptor, in a similar manner as observed with the benzyl group of p-
chlorobenzylGNTI (46), it was instead decided to send 113 for *in-vitro* pharmacological evaluation.

![Chemical structure](image)

(a) 1.0 equi. potassium phthalimide, dry DMF, overnight, room T°; (b) 1.1 equi. NaH, 0.9 equi. 54, dry DMF, overnight, 70°C; (c) 1.5 equi. HgCl₂, 2.0 equi. 111, 2.0 equi. NEt₃, dry DMF, 24 hrs, 60°C; (d) conc. HCl/ MeOH (50/50), 3 days, room T°

**Scheme 14** Synthetic route used for the preparation of 113

The problems encountered with the previous synthetic strategy led us to plan a different chronology for the removal of the protecting groups present on the guanidine moiety and on the terminal amino group, in order to allow purification of the opioid after cleavage of the phthalimido group. Moreover, we decided to use guanidinylating agents bearing a fully saturated side chain in order to afford greater flexibility of the ligand, thereby enhancing the possibility of forming a covalent bond with the receptor. Since reaction of the conjugate base of 54 with alkyl bromide proved unsuccessful (see table 2), we decided to use the synthetic pathway presented in scheme 15 (target compound 114).
Scheme 15 Synthetic route planned for the preparation of 114

Phthalimido-protection of 3-aminopropanol was achieved in 86% yield, following a procedure reported by Li and co-workers, namely by reacting the amine with one equivalent of both N-carbethoxy-phthalimide and triethylamine. The product 3-phthalimidopropanol (115) was then tosylated using p-toluenesulfonyl chloride in presence of either triethylamine or pyridine, both methods giving the
desired tosylate 116 with similar yields (around 60%). 116 was then reacted with the conjugate base of 54, affording the guanidinylating agent 117 that was subsequently coupled with amine 53 according to the procedure previously described in sections 2.1 and 2.2. Unfortunately, phthalimido-deprotection of di-BOC protected morphinan 118 and its mono-BOC-analogue with 1.2 equivalents of hydrazine hydrate did not lead to the expected product 119 but to the recovery of amine 53 as a result of the high nucleophilicity of hydrazine together with the electron-withdrawing effect of the BOC groups. Basic hydrolysis of 118 with NaOH (2M aqueous solution) was then attempted but this resulted in decomposition of the starting material with no useful product being isolated. 118 was instead BOC-deprotected with trifluoroacetic acid and the corresponding salt 120 was sent for in-vitro pharmacological evaluation; comparison of 113 and 120 will provide information on the importance, or not, of the flexibility of the side chain in lipophilic interactions with the opioid receptors.

2.3.2.c Synthesis with guanidinylating agents bearing a terminal dibenzyl-protected amino group

In 1991, Purchase and co-workers reported the synthesis of a pirmenol metabolite (121) and the synthetic route utilised is presented in scheme 16.140

![Scheme 16](image)

Scheme 16 Preparation of a pirmenol metabolite (121) reported in the literature140
Having been unsuccessful in preparing 121 via reaction of phthalimide 122 with 2-pyridyllithium, they decided to replace the phthalimido-protecting group by a dibenzyl-protecting group (compound 123), which ultimately led to the successful synthesis of the target product 121.

Although only two primary amines had been successfully prepared via N,N-didebenzylation at that time, suggesting that the reaction was troublesome, they reported that the didebenzylation proceeded with great facility when catalytic transfer hydrogenation was used (Pd/C 10 wt. %, ammonium formate). We thus investigated whether the use of a dibenzyl-protecting group would resolve the difficulties encountered during the preparation of the irreversible ligand 114. This led us to adopt a similar route as presented in scheme 15, but replacing the phthalimido-group with a N,N-dibenzyl protecting group (see scheme 17).

![Scheme 17](image)

(a) 1.0 equi. benzyl bromide, DCM, overnight, room T°; (b) 1.0 equi. NEt₃, 1.0 equi. p-toluenesulfonyl chloride, DCM, 3 hrs, room T°; (c) 1.0 equi. NaH, 0.1 equi. 15-crown-5, 1.1 equi. 125, dry DMF, overnight, 80°C; (d) 0.7 equi. HgCl₂, 0.5 equi. 53, 1.0 equi. NEt₃, dry DMF, 24 hrs, 60°C; (e) Pd/C (10 wt. %), 20 equi. NH₄HCO₂, EtOH, 6 hrs, reflux or Pd/C (10 wt. %), cyclohexene/EtOH, reflux, overnight

**Scheme 17** Synthetic route planned for the preparation of 119 (route involving a dibenzyl protecting group)
The N,N-dibenzyl protecting group was introduced by stirring overnight 3-aminopropanol with one equivalent of benzyl bromide in DCM. N,N-dibenzylaminopropanol (124) was obtained in 42% yield and subsequently converted into its tosylate derivative 125, using one equivalent of both p-toluenesulfonyl chloride and triethylamine in a similar manner as used for the preparation of 116. Nucleophilic attack of the conjugate base of 1,3-bis-BOC-2-methyl-2-thiopseudourea (54) on 125 afforded the guanidinylating agent 126, which was in turn coupled with amine 53, yielding a mixture of mono- and di-BOC-protected morphinans 127. Unfortunately, attempted debenzylation of the latter by transfer hydrogenation, using Pd/C and ammonium formate, resulted mainly in recovery of the starting material; monitoring of the reaction by thin-layer chromatography (TLC) showed the appearance of a weak spot that was believed to correspond to the mono-benzylated derivative but there was no evidence of formation of the desired primary amine 119.

When preparing 6N-cinnamoyl-β-naltrexamine (128), Derrick et al. reported that while catalytic hydrogenation of the 6N,6N-dibenzyl intermediate 129 led to the didebenzylated intermediate 130 in poor yield, transfer hydrogenation using a suspension of Pd/C in ethanol/cyclohexene afforded the desired product 130 with remarkable ease (83% yield).141

Thus we attempted a similar procedure for the deprotection of 127, but this led to the same concluding remarks as when using Pd/C and ammonium formate. Since the cleavage of the dibenzyl protecting group proved uncannily troublesome, it was instead decided to remove the BOC protecting groups of 127 with an excess of trifluoroacetic acid. The corresponding product 131 was sent for binding studies in order to investigate whether the presence of benzylic groups would lead to pseudo-irreversible binding with the receptor through strong lipophilic interactions.
2.3.2.d Synthesis with guanidinylating agents bearing a nitro precursor to the terminal amino group

A last alternative was explored for the preparation of the targeted isothiocyanates and involved the preparation of guanidinylating agents bearing a side chain terminating with an aliphatic nitro group. It was planned to reduce the nitro group after guanidinylation with 53; the amine would then be converted into the corresponding isothiocyanate and the BOC groups finally removed (see scheme 18).

Scheme 18 Synthetic route used for the preparation of 137

(a) 1.0 equi. NaH, 0.1 equi. 15-crown-5, 3.3 equi. 1,5-diiodopentane, dry DMF, overnight, room T°; (b) 1.7 equi. NaN02, DMF/H2O (5/1), 2 hrs, room T°, (c) 1.4 equi. HgCl2, 2.0 equi. 133, 2.0 equi. NEt3, dry DMF, 24 hrs, 60°C; (d) 9.0 equi. FeSO4.7H2O, MeOH/H2O/NH4OH, 3 hrs, 80°C; (e) 6.0 equi. NaHCO3, 1.1 equi CSeCl2, CHCl3/H2O, 2 hrs, room T°, (f) DCM/TFA, overnight, room T°
54 was deprotonated with one equivalent of sodium hydride and subsequently reacted with three equivalents of 1,5-diiodopentane, yielding the desired product 132.

The conversion of halides into nitro derivatives has been reported in the literature through the use of diverse reagents including sodium nitrite,\textsuperscript{142} silver nitrite \textsuperscript{143} or NaOMe/CH\textsubscript{3}NO\textsubscript{2},\textsuperscript{144} this latter method of course extending the chain by one methylene. Given there was no particular length of side chain, we opted for the former method since the latter was reported to be low yielding; moreover, we believed that decomposition of the starting material \textit{via} elimination was likely to occur when using NaOMe/CH\textsubscript{3}NO\textsubscript{2}. Nucleophilic displacement of iodide by sodium nitrite gave the guanidinylating agent 133; although modest (40%), the yield obtained when stirring both starting materials in DMF/H\textsubscript{2}O (5/1) was substantially better than when stirring both starting materials in pure DMF, probably as a result of higher solubility of sodium nitrite.

133 was subsequently coupled with amine 53 in presence of triethylamine and mercury(II) chloride in a similar way as used in sections 2.1 and 2.2, which gave a mixture of mono- and di-BOC-protected morphinans 134.

The reduction of aliphatic nitro compounds into primary amines has been far less investigated than the reduction of aromatic derivatives and traditionally involved the use of high pressure catalytic hydrogenation.\textsuperscript{145} However, Ram \textit{et al.} reported in 1984 that aliphatic nitro derivatives could be easily reduced into the corresponding amines by catalytic transfer hydrogenation (with ammonium formate as the hydrogen transfer agent) when other methods such as cyclohexene/Pd-C, hydrazine/Raney Ni, Zn/AcOH or FeSO\textsubscript{4}/NH\textsubscript{4}OH had proved unsuccessful.\textsuperscript{145} Other reducing agents have since been successfully used for the reduction of aliphatic nitro groups, including LiAlH\textsubscript{4}, NaBH\textsubscript{4}/BH\textsubscript{3} or more recently NaBH\textsubscript{4}/ZrCl\textsubscript{4}.\textsuperscript{146} However, we decided to reduce 134 using either 9 equivalents of iron(II) sulfate heptahydrate or transfer hydrogenation (palladium 10 wt. % on activated carbon, ammonium formate) since these procedures appeared more convenient to us (easier procedure, quicker reaction time, less tedious workup). In both cases, the product 135 was isolated in modest yield (43\% and 29\% respectively).

Conversion into the corresponding isothiocyanate 136 was accomplished following the procedure reported by Korlipara and associates,\textsuperscript{129} who used an excess of sodium hydrogencarbonate and freshly distilled thiophosgene in a biphasic CHCl\textsubscript{3}/H\textsubscript{2}O solvent system. However, in the current work, only 1.1 equivalents of
thiophosgene were added instead of the two equivalents reported, so as to avoid possible reaction with the oxygen atoms of 135. After two hours, monitoring of the reaction by TLC showed complete conversion of the starting material and purification by column chromatography afforded the desired product 136 in 71% yield. Finally, BOC deprotection using TFA afforded the target compound 137.

The same synthetic strategy was utilised to target analogues of 137 bearing shorter side chains. However, nucleophilic attack of the conjugate base of 54 on 1,2-diiodoethane or 1,2-dibromoethane proved unsuccessful while reaction with 1,3-diiodopropane afforded 1,3-bis-tert-butoxycarbonyl-1-allyl-2-methyl-2-thiopseudourea (138). 1,3-Diiodopropane was then replaced with 1,3-dibromopropane, which led to 1,3-bis-tert-butoxycarbonyl-1-(3'-bromopropyl)-2-methyl-2-thiopseudourea (139). However, subsequent attempts to displace the bromo group by sodium nitrite in DMF or in a mixture of DMF/H2O (5/1) did not give the desired product. A similar two-step sequence using 1,4-dibromobutane gave somewhat better results with 1,3-bis-tert-butoxycarbonyl-1-(4'-bromobutyl)-2-methyl-2-thiopseudourea (140) isolated in 48 % yield and converted into 1,3-bis-tert-butoxycarbonyl-1-(4'-nitrobutyl)-2-methyl-2-thiopseudourea (141) in 36% yield (see scheme 19).

(a) 1.0 equi. NaH, 0.1 equi. 15-crown-5, 3.3 equi. 1,4-dibromobutane, dry DMF, overnight, room T°; (b) 2.0 equi. NaNO2, DMF/H2O (5/1), 16 hrs, room T°; (c) 1.5 equi. HgCl2, 2.0 equi. 141, 2.0 equi. NEt3, dry DMF, 48 hrs, 60°C; (d) 0.6 equi. Pd/C (10 wt. %), 20 equi. NH4HCO2, dry MeOH, 2 hrs, reflux

Scheme 19  Synthetic route employed for the preparation of 143

61
Coupling of 141 with 53 in presence of triethylamine and mercury(II) chloride afforded a mixture containing di-BOC-protected morphinan 142 and its mono-BOC-protected analogue that were subsequently reduced to 143 (mixture of mono- and di-BOC-protected morphinans) by transfer hydrogenation (palladium on activated carbon, ammonium formate). There was however insufficient material left at this stage to undertake the conversion into the corresponding isothiocyanate. However, the successful synthesis of 143 will allow the synthesis to be repeated on a larger scale.

Since the synthesis of the two-carbon analogue 144 had not been possible by the route used for 133 or 141, an alternative approach was envisaged from commercially available nitroethanol (scheme 20).

Scheme 20 Synthetic route planned for the preparation of 144

Unfortunately, tosylation of nitroethanol, using one equivalent of p-toluenesulfonyl chloride in pyridine, proved unsuccessful; it is possible that the product 145 was formed but immediately decomposed in presence of pyridine (scheme 21, reaction a). Similar decomposition was also proposed by Riebsomer who failed to isolate any ester when reacting 2-nitro-1-butanol with benzenesulfonyl chloride in pyridine. He believed that the ester 146 was initially formed but immediately decomposed into benzenesulfonic acid and 2-nitro-1-butene as a consequence of the acidity of the proton attached to the carbon bearing the nitro group (scheme 21, reaction b). This was a plausible explanation since the acidity of such protons had been demonstrated in an experiment reported by Schmidt and Rutz, who found out that heating nitro esters of type 147 in presence of sodium bicarbonate led to the nitro olefin derivatives 148 (scheme 21, reaction c). Of additional support is
the fact that tosylation of 2-nitro-2-methylpropanol (ie a nitro-alcohol lacking a proton attached to the carbon bearing the nitro group) using similar conditions as used in the present project has been reported to lead smoothly to the tosylated derivative 149 (see scheme 21, reaction d).\textsuperscript{148}

\begin{center}
\begin{tikzpicture}
  \node [draw, align=center] (a) {a) \begin{center}\begin{tabular}{c}
\includegraphics[width=2cm]{a.png}
\end{tabular}\end{center}};
  \node [draw, below of=a, align=center] (b) {b) \begin{center}\begin{tabular}{c}
\includegraphics[width=2cm]{b.png}
\end{tabular}\end{center}};
  \node [draw, below of=b, align=center] (c) {c) \begin{center}\begin{tabular}{c}
\includegraphics[width=2cm]{c.png}
\end{tabular}\end{center}};
  \node [draw, below of=c, align=center] (d) {d) \begin{center}\begin{tabular}{c}
\includegraphics[width=2cm]{d.png}
\end{tabular}\end{center}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 21} Decomposition of arylsulfonylesters of nitro alcohols in presence of pyridine: a consequence of acidity?

In summary, one ligand (137), modelled on GNTI (11) and modified by the introduction of a side chain terminating with an isothiocyanate group, has been successfully prepared, while the successful synthesis of 143 should allow the preparation of the corresponding isothiocyanate.

2.4 Benzylnorbinaltorphimine
2.4.1 Rationale and design

Since norBNI (13) is a highly \(\kappa\)-selective opioid antagonist with long lasting but surmountable effects, the present work explores the synthesis of a new irreversible ligand for the \(\kappa\)-opioid receptor modelled upon the structure of norBNI. It is recognised that the already long duration of action of norBNI will make assessment of relative irreversibility of analogues somewhat difficult.
2.4.1. a Modification of norBNI: at which position?

As already mentioned, norBNI (13) is a bivalent ligand, whose binding with the \( \kappa \)-receptor is based upon the "message-address" concept: the first pharmacophore (message component) binds to the region of the \( \kappa \)-receptor responsible for activity whereas the scaffold (pyrrolic spacer) of 13 rigidly holds the second basic nitrogen (address) towards the acidic residue Glu297 present within the \( \kappa \)-receptor. Docking studies of GNTI (11) (whose binding mimics that of 13) into the \( \kappa \)-receptor have also suggested an ion pair interaction between N-17 and the carboxylate group of Asp138 (TM3), which was confirmed by site directed mutagenesis.\(^8\) In addition, it was also demonstrated that the cyclopropyl methyl and phenolic moieties of the first pharmacophore of 13 are prominent in conferring affinity and activity.\(^8\) This was later confirmed by docking studies of GNTI (11), which suggested that the phenolic group might indeed interact with the imidazoline ring of His291.\(^10\) Therefore, it was not appropriate to modify these groups and since the synthesis of unsymmetrical derivatives of norBNI has been reported to be low yielding,\(^10\) it was decided not to modify those groups on the second pharmacophore.

With this in mind, there remain only two viable positions for the modification of 13, namely the 14,14'-hydroxy groups and the pyrrolic nitrogen (see figure 8). It was believed that the pyrrolic group was the more readily accessible and the present project sought to investigate the possibility of conferring irreversible binding to norBNI via substitution of its pyrrolic nitrogen.

Figure 8 The structure of norBNI (13): elements crucial for \( \kappa \)-selectivity and activity
2.4.1.b Modification of norBNI: which substituent?

In 1994, Korlipara et al. explored the modification of the δ-selective antagonist naltrindole (NTI) (150) by benzyl substitution at the indolic nitrogen; this resulted in benzynaltrindole (BNTI) (151) as a δ2-antagonist with longer duration of action (see scheme 22). Although the effects of 151 were still surmountable, true irreversible binding via formation of a covalent bond with the receptor was eventually achieved by subsequent addition of an electrophilic isothiocyanate moiety onto the benzyl group.

Scheme 22 Strategy employed for the design of BNTI (151) and analogues

Since norBNI (13) is already a long-lived κ-antagonist, it was of interest to investigate whether benzylaion of norBNI was sufficient to produce a κ-selective irreversible or pseudo-irreversible antagonist. In addition, and in an analogous approach to that used by Korlipara, subsequent incorporation of an isothiocyanate group into BnorBNI (152) was also planned if necessary (scheme 23).

Scheme 23 Strategy employed for the design of BnorBNI (152)
2.4.2 Synthesis

A synthesis of 152, based on the method reported for the preparation of BNI (28) and modified by the use of N-benzylhydrazine sulfate, had already been developed within our group and is presented in scheme 24.

![Scheme 24](image)

**Scheme 24** A previous synthetic approach for the preparation of BnorBNI (152)

Although straightforward, this route was not satisfactory because of the long reaction time (9 days) and low yield reported (1%). It is noteworthy that azine 153 was isolated as a side product; although 153 could result from debenzylation of the expected intermediate 154, it cannot be ruled out that an alternative complex rearrangement from the reaction mixture had occurred.
Schmidhammer and Schwarz have also reported unexpected reactions when stirring azines 155 and 156 with methanesulfonic acid in dry DMSO. They found out that the main product isolated after reaction was inexplicably not the expected pyrroles 157 and 158 but rather bimorphinan 159 (see scheme 25).

Scheme 25 Unexpected reactions of azines in presence of methanesulfonic acid

In any case, if BnorBNI had to be prepared on a larger scale, another synthetic approach was required. The method employed in the present project explored direct benzylation of norBNI (13). It was believed that in presence of a large excess of strong base, benzylation of the penta-anion of 13 with one equivalent of benzyl bromide should occur at the pyrrolic nitrogen because of its higher reactivity compared to the phenoxide groups and because of less steric hindrance compared with the alkoxide groups at the 14 and 14' positions.
13 was synthesised from naltrexone (44) according to the Piloty procedure used by Ivy Carroll, except that hydrazine hydrochloride was replaced with hydrazine sulfate. Deprotonation of 13 with 10 equivalents of sodium hydride and subsequent benzylation with one equivalent of benzyl bromide led to the quantitative addition of one benzyl group onto the starting material as expected; however, NMR analysis showed that the reaction had not occurred at the targeted pyrrolic site but most probably at one of the hydroxyl groups.

This led us to envisage the formation of BnorBNI (152) in several steps, namely benzylation of 13 with three equivalents of benzyl bromide followed by debenzylation of the phenolic benzyl ethers under acidic conditions, as it was believed that, once formed, the benzylation pyrrolic group should remain stable under such conditions (see scheme 26).

\[
\text{(a) 0.53 equi. NH}_2\text{NH}_2\cdot\text{H}_2\text{SO}_4, \text{ dry DMF, 6 hrs, 100°C then 0.51 equi. CH}_3\text{SO}_3\text{H, DMSO, 3.5 hrs, 130°C; (b) 10.0 equi. NaH, 0.25 equi. 18-crown-6, 3.0 equi. BnBr, DMF, 43 hrs, room T°; (c) HCl/MeOH (50/50), 40 hrs, 90°C}}
\]

**Scheme 26** Total synthesis of BnorBNI (152)
Deprotonation of 13 with ten equivalents of sodium hydride and subsequent benzylation with three equivalents of benzyl bromide afforded a mixture of tri- and pentabenzyl-substituted norBNI. The fact that no starting material was left at the end of the reaction and that some penta-substituted product was obtained when using only three equivalents of benzyl bromide suggested that some decomposition had occurred during the reaction or during the purification. The mixture of tri- and pentabenzyl-substituted norBNI was immediately treated with a mixture of methanol/conc. HCl (50/50) at 90°C; this gave after purification benzynorbinaltorphimine (152) in a 40% overall yield from naltrexone, a hugely improved yield compared to the first method employed within our group for the preparation of 152 (1% yield).

2.5 Irreversible ligands modelled on benzynorbinaltorphimine (152)

2.5.1 Rationale

We decided to investigate whether introduction of an isothiocyanate group onto the benzyl ring of BnorBNI would result in covalent binding with the receptor and whether such modification would have an influence on the selectivity and/or affinity of the parent compound. It was thus proposed to synthesize the \( o \), \( m \), and \( p \) isothiocyanate regioisomers 160, 161, 162, 163, 164, and 165 derived from the equivalent anilines 166, 167 and 168 and benzylamines 169, 170 and 171.

\[
\begin{align*}
R = p \text{NCS} & \quad 160 \quad R = p \text{NH}_2 & \quad 166 \\
R = m \text{NCS} & \quad 161 \quad R = m \text{NH}_2 & \quad 167 \\
R = o \text{NCS} & \quad 162 \quad R = o \text{NH}_2 & \quad 168 \\
R = p \text{CH}_2\text{NCS} & \quad 163 \quad R = p \text{CH}_2\text{NH}_2 & \quad 169 \\
R = m \text{CH}_2\text{NCS} & \quad 164 \quad R = m \text{CH}_2\text{NH}_2 & \quad 170 \\
R = o \text{CH}_2\text{NCS} & \quad 165 \quad R = o \text{CH}_2\text{NH}_2 & \quad 171
\end{align*}
\]

2.5.2 Synthesis of compounds 160-162

Since the synthetic strategy employed for the preparation of BnorBNI (152) gave satisfactory results, we decided to employ a similar route for the synthesis of 160-162, but replacing benzyl bromide with suitable alternatives; the use of nitro groups as precursors to isothiocyanates proving successful for the preparation of irreversible benzylGNTI analogues (section 2.3.2.d), it was planned to benzylate
norBNI (13) with o-, m- and p-nitrobenzyl halides. The synthetic approach is presented in scheme 27.

(a) 10 equi. NaH, 3 equi. NO₂C₆H₄CH₂X, DMF, overnight, 70°C; (b) HCl/MeOH (50/50), overnight, 80°C; (c) 9 equi. FeSO₄·7H₂O, MeOH/H₂O/NH₄OH, 3 hrs, 80°C; (d) 6 equi. NaHCO₃, 1.2 equi. CSCI, CHCl₃/H₂O, room T°

Scheme 27  Synthetic route planned for the preparation of 160, 161 and 162

Deprotonation of norBNI (13) with ten equivalents of sodium hydride, followed by nucleophilic attack on readily-available p-nitrobenzyl chloride (three equivalents, room temperature) led to a mixture of mono- and di-benzylated products 172 and 173 in 10% and 30% yield respectively; no expected product 174 was isolated, probably as a consequence of the low nucleophilicity of the pyrrolic nitrogen together with the low reactivity of p-nitrobenzyl chloride.
$p$-Nitrobenzyl bromide was then utilised due to the better leaving group properties of bromide, though it was acknowledged that the deactivating nitro group might still prevent reaction; this was indeed confirmed since benzylation of 13 using $p$-nitrobenzyl bromide, stirring the reaction mixture at 60°C, led to the same result as before with only phenolic ether products isolated. Reaction of the conjugate base of 13 with $p$-nitrobenzoyl chloride also failed to give the desired product despite several similar benzoylations of pyrrolic nitrogens reported in the literature. Though direct benzylation of 13 did not give the desired product, it was felt desirable to use 173 to confirm whether the necessary 3,3'-O-debenzylation could be achieved before trying to improve the benzylation step. Thus, 173 was stirred overnight at 80°C in a mixture of methanol/conc. HCl (50/50) but this led only to unreacted starting materials.

Since nitro groups are less deactivating in $m$-position, benzylation of the penta-anion of 13 with three equivalents of $m$-nitrobenzyl bromide was carried out, initially stirring at room temperature then warming to 52°C overnight. This gave two fractions, the main one being identified as the di-substituted product 175 and the other as the desired tri-substituted product 176 (28% yield). Unfortunately, stirring 176 overnight in a mixture of methanol/conc. HCl (50/50) at 94°C resulted in recovery of the tri-benzylated starting material.

As the difficulties in both introducing the benzyl group at the pyrrolic nitrogen and its subsequent removal from the phenolic hydroxyls appeared to be due to the electron-withdrawing effect of the nitro group, it was decided to convert the nitro group of the benzyl bromides into a protected amino group before subsequent benzylation of 13. In order to avoid polymerisation of the aminobenzyl bromides,
both reduction and protection would have to be achieved under acidic conditions, which led us to envisage the synthetic route presented in scheme 28.

\[ \text{NO}_2 \quad \text{Fe, CH}_3\text{COOH} \quad \rightarrow \quad \text{NH}_3^+ \quad \rightarrow \quad \text{R=O or NH} \quad \text{CH}_3\text{COOH} \]

**Scheme 28** Synthetic route planned for the preparation of benzyl bromide derivatives

Broggini *et al.* have reported that quantitative reduction of nitrobenzyl derivatives into the corresponding amines can be achieved when refluxing the former for 3 hours with iron powder in ethanol/acetic acid (20% aqueous solution).\(^{153}\) Reduction of \(p\)-nitrobenzyl bromide was thus attempted following an equivalent procedure, first stirring the reaction mixture at room temperature then under reflux, but unfortunately this proved unsuccessful.

The reactivity of the pentaanion of 13 was then evaluated with \(\alpha\)-bromo-\(p\)-tolunitrile. The groups added at 3- and 3'-positions would then be removed before hydrogenating the nitrile moiety. However, stirring 13 with 10 equivalents of sodium hydride before adding three equivalents of \(\alpha\)-bromo-\(p\)-tolunitrile did not afford any useful product.

Although it is acknowledged that the pentaanion of norBNI could be successfully reacted with benzyl bromide, it appeared that the poor solubility of the pentaanion, in combination with other parameters such as low reactivity of the electrophiles, could be prejudicial to the success of the reaction. As we had already shown during the synthesis of 152 that 13 could be readily benzylationed (section 2.4) and that the phenolic benzyl ethers were readily cleaved under acidic conditions, it was decided to first protect the phenolic hydroxyls of 13 with benzyl groups. This was achieved in quantitative yield by stirring 13 overnight in DMF with 1.5 equivalents of potassium carbonate and 2.5 equivalents of benzyl bromide. The product (177) was then deprotonated with 10 equivalents of sodium hydride and reacted with 5 equivalents of \(p\)-nitrobenzyl bromide, but this resulted in recovery of 177.
This led us to envisage the protection of all four hydroxy groups of 13; we opted for an acetate protecting group since this group had been successfully used by Nelson and colleagues for the protection of 3- and 14-hydroxy groups of naltrexone-derived ligands, with its deprotection being achieved with remarkable ease (this will be discussed later).\textsuperscript{154,155} A procedure for the preparation of the tetraacetyl 178 was reported by Portoghese and involved stirring 13 in acetic anhydride and pyridine for 2 days at 24°C.\textsuperscript{102} The esterification was initially postulated to occur via formation of acyloin groups in 17- and 17'-positions of 13 followed by intramolecular transfer to the neighbouring hydroxyls (14- and 14'-positions), hence explaining the remarkable ease of the tetraacylation.\textsuperscript{102} It seems however more likely that the basic nitrogens in 17- and 17'-positions act as hydrogen acceptors from the 14- and 14'-hydroxyls, thereby resulting in higher nucleophilicity of the oxygen atoms.\textsuperscript{156}

However, we instead decided to prepare 178 by refluxing 13 in acetic anhydride since we believed that the reaction would reach completion in a much shorter time; 178 was indeed obtained in quantitative yield after stirring the reaction mixture for only two hours. The tetraacetyl compound was subsequently deprotonated with sodium hydride and reacted with an excess of \(p\)-nitrobenzoyl chloride, \(p\)-nitrobenzyl bromide, \(m\)-nitrobenzyl bromide and \(\alpha\)-bromo-\(p\)-tolunitrile. The results are presented in figure 9: no desired product was isolated in any case while reactions with \(\alpha\)-bromo-\(p\)-tolunitrile and \(m\)-nitrobenzyl bromide afforded the di-substituted products 179 and 180 respectively. These products seem to arise from cleavage of the acetate esters in 3- and 3'-positions before nucleophilic attack of the phenoxide groups onto the benzyl bromide derivatives; it is noteworthy that the acyl group has
moved to the pyrrolic nitrogen in the former case. 180 was further reacted with \textit{m}-nitrobenzyl bromide, which gave the desired tri-substituted product 181. However, the overall yield (11\%) prompted us to find another synthetic route.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Attempted pyrrolic N-substitutions of 178}
\end{figure}

\begin{enumerate}
\item[(a)] 4.0 equi. NaH, then 1.2 equi. \( p\)-\( NO_2 \)C\(_6\)H\(_4\)COCl, dry THF, overnight, 60\(^\circ\)C;
\item[(b)] 4.4 equi. NaH, then 2.0 equi. \( m\)-\( NO_2 \)C\(_6\)H\(_4\)CH\(_2\)Br, dry THF, overnight, 60\(^\circ\)C;
\item[(c)] 10.0 equi. NaH, 0.1 equi. 18-crown-6, then 2.0 equi. \( p\)-\( NC \)(C\(_6\)H\(_4\))CH\(_2\)Br, dry THF, 2 days, room T\(^\circ\) then 6hrs, 70\(^\circ\)C;
\item[(d)] 10.0 equi. NaH, 0.1 equi. 18-crown-6, then 3.0 equi. \( p\)-\( NO_2 \)C\(_6\)H\(_4\)CH\(_2\)Br, dry THF, overnight, 60\(^\circ\)C;
\item[(e)] 10.0 equi. NaH, then 3.0 equi. \( m\)-\( NO_2 \)C\(_6\)H\(_4\)CH\(_2\)Br, dry THF, overnight, 60\(^\circ\)C
\end{enumerate}

Again, it was believed that replacing the deactivating nitro and cyano groups of the benzyl bromides with protected amino groups should result in greater facility of pyrrolic N-benzylation. We opted for a phthalimido-protecting group as it would remove both protons from the nitrogen of the aminobenzyl bromides and therefore alleviate problems likely to be encountered when using sodium hydride for the
subsequent deprotonation and benzylation of 178. We planned to prepare $p$-, $m$- and $o$-phthalimidobenzyl bromides 182, 183 and 184 from the corresponding aminobenzyl alcohols 185, 186 and 187 by protecting first the hydroxy groups, since preliminary attempts to react 187 with phthalimide or phthalic anhydride had failed to give the desired product. The choice of tert-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) protecting groups appeared most attractive for this purpose, as THP- and TBDMS-ethers can be directly converted into the corresponding bromides. Although 185 is commercially available, it is either expensive or of unsatisfactory quality depending on the source; this prompted us to start the synthesis, in this particular case, with the nitro-analogue (see scheme 29).

(a) 1.0 equi. 3,4-dihydro-2H-pyran, 0.01 equi. $p$-toluenesulfonic acid monohydrate, CHCl$_3$, overnight, room T°; (b) 0.03 equi. Pd/C (10 wt. %), EtOH, H$_2$, overnight, room T°; (c) 1.0 equi. phthalic anhydride, xylene (mixed), reflux, overnight; (d) 2.0 equi. PPh$_3$, 2.0 equi. imidazole, 2.0 equi. Br$_2$, dry DCM, 3 hrs, room T°

Scheme 29 Preparation of $p$-phthalimidobenzyl bromide (182)

Tosic acid-catalysed addition of 4-nitrobenzyl alcohol on one equivalent of 3,4-dihydro-2H-pyran gave the THP-protected derivative 188 that was subsequently
reduced to the corresponding aniline 189 via standard catalytic hydrogenation (room temperature, Pd/C, ethanol, hydrogen). Subsequent attempts to react 189 with one equivalent of phthalimide in boiling xylenes (mixed) failed to yield the desired product; however, reaction with phthalic anhydride, using a modified procedure based on reaction of aniline with phthalic anhydride in p-cymene,\textsuperscript{157} proved somewhat successful, with 190 isolated in 16% yield.

Direct conversion of THP ethers into the corresponding bromides is most commonly achieved using PPh\textsubscript{3}/CBr\textsubscript{4}. In some specific cases, such as bromination of THP ethers of secondary alcohols, the use of these reagents has however proved unsuccessful and other reagents such as triphenylphosphine and 2,4,4,6-tetrabromo-2,5-cyclohexadienone were required.\textsuperscript{158} For 190, the standard conditions were sufficient, with the desired product 182 readily obtained in 3 hours when using bromine, triphenylphosphine and imidazole (60% yield).

Surprisingly, o-phthalimidobenzyl bromide could not be prepared by an analogous route as THP-protection of 2-aminobenzyl alcohol with 3,4-dihydro-2H-pyran failed to give the desired product. An alternative protecting group was thus required and the TBDMS protecting group appeared to be suitable; the new synthetic route is presented in scheme 30.

Scheme 30 Preparation of phthalimidobenzyl bromides 182, 183 and 184
(synthetic route using TBDMS protection)
Since the previous route did not provide sufficient p-phthalimido benzyl bromide (182), we decided to repeat the preparation of this compound according to this new strategy. This involved first preparing 4-aminobenzyl alcohol; this was achieved by reducing the nitro analogue via standard hydrogenation procedure (Pd/C, ethanol, hydrogen, room temperature), which afforded the desired product 185 in 67% yield, along with a side-product identified as p-toluidine (17% yield).

The aminobenzyl alcohols 185, 186 and 187 were quantitatively protected into TBDMS ethers 191, 192 and 193 by stirring overnight at room temperature with 1.5 equivalents of tert-butyldimethylsilyl chloride and 2.0 equivalents of imidazole. The anilines were subsequently refluxed in mixed xylenes with one equivalent of phthalic anhydride, which afforded 194, 195 and 196 in 96, 71 and 45% yields respectively. Conversion of these into the corresponding bromides 182, 183 and 184 was achieved following a general procedure reported by Aizpurua et al.,159 with a slight modification of the amount of PPh₃Br₂ complex used (1.2 equivalents vs 1.1 equivalents).

Deprotonation of 178 with three equivalents of sodium hydride and benzylation with 182, 183 and 184 in presence of a catalytic amount of 18-crown-6 gave the desired tetraacetyl N-substituted norBNI-derivatives 197 and 198 (scheme 31). However, it seems that steric hindrance observed with o-phthalimidobenzyl bromide precluded nucleophilic attack of 178 in this case.

(a) 4.0 equi. NaH, 0.1 equi. 18-crown-6, 3.0 equi. 182 or 183, THF, overnight, 70°C

Scheme 31  Benzylaition of 178 with phthalimidobenzyl bromide derivatives
Since the cleavage of acetate protecting groups in the 14-position had been reported in the literature by simply stirring acetyl salts 199 and 200 in methanol (see scheme 32), we attempted to deprotect 197 and 198 using the same procedure, but this resulted only in the recovery of starting materials.

A solution of the tetraacetyl compounds 197 and 198 in ethanol was then treated with sodium hydroxide (2M aqueous solution) but mass spectrometry suggested this had only resulted in formation of N-substituted phthalamic acids 201 and 202 via saponification of the phenolic esters and hydrolysis of the phthalimido-group (see scheme 33).
Though unexpected, ring-opening of phthalimido-protecting groups into stable N-substituted phthalamic acids has been reported in the literature, with subsequent cleavage into the corresponding amines being accomplished using a mild enzymatic approach.\textsuperscript{160} Unfortunately, we were unable to purchase the enzyme used in this experiment (o-phthyl amidase). All four esters were eventually cleaved stirring the acetyl groups overnight in a mixture of methanol/conc. HCl (50/50) at 85°C. This method proved to be somewhat successful for the deprotection of the m-derivative 198, with 203 being isolated in 68% yield (see scheme 34).

\begin{itemize}
  \item \textbf{a} conc. HCl/MeOH (50/50), overnight, 85°C;
  \item \textbf{b} 3 equi. NH$_2$NH$_2$•H$_2$O, 30 hrs, room T\textdegree;
  \item \textbf{c} 6.0 equi. NaHCO$_3$, 1.1 equi CSCl$_2$, CHCl$_3$/H$_2$O, 2hrs, room T\textdegree
\end{itemize}

\textbf{Scheme 34} Deprotection of 197 and 198 and subsequent preparation of 161
However, the result was much less satisfactory with the \( p \)-derivative since it afforded the desired product 204 in only 5% yield. The main product was identified as norBNI, which suggests that the bond between the pyrrolic nitrogen and the benzylic carbon is particularly weak when substituted with a \( p \)-phthalimidobenzyl group. This was corroborated with attempted phthalimido-deprotection of 204, using 1.2 equivalents of hydrazine hydrate, leading exclusively to unsubstituted norBNI (13). This led us to investigate whether the \( p \)-phthalimidobenzyl group could represent a general protecting group for indolic and pyrrolic nitrogens and this will be discussed in another chapter (see section 2.7).

Deprotection of phthalimide 203 with 3 equivalents of hydrazine hydrate afforded the corresponding aniline 205, that was subsequently converted into the corresponding isothiocyanate 161; this was achieved using 6 equivalents of sodium hydrogen carbonate and 1.1 equivalents of freshly distilled thiophosgene according to a similar procedure as employed in section 2.3.2.d for the preparation of 136.

2.5.3 Synthesis of compounds 163, 164, and 165

2.5.3.a Preliminary work

It was decided to prepare the irreversible ligands 163, 164, and 165 using an analogous approach to that employed in section 2.5.2, namely via benzylation of protected norBNI with benzyl bromide derivatives 206, 207 and 208 (see scheme 35). These were obtained through nucleophilic attack of potassium phthalimide on commercially available dibromoxylenes in presence of 18-crown-6 in refluxing toluene (or in DMF) following a similar procedure reported by Fisher and colleagues.\(^{161}\)

Given the earlier difficulties encountered with the use of acetate protecting groups for hydroxyls in 14- and 14'-positions, alternative protecting groups were sought that could be both introduced and removed in a facile manner. We instead elected to protect all four hydroxy groups of norBNI (13) as silyl ethers. Though known to be extremely labile, we initially opted for trimethylsilyl (TMS) ethers rather than TBDMS ethers because of steric hindrance around the hydroxyls in 14- and 14'-positions. 13 was thus reacted with an excess of both trimethylsilyl chloride and imidazole, which led in quantitative yield to the tetrasilyl ether 209. Deprotonation of the latter with sodium hydride and subsequent reaction with 206 led to dissubstitution
of 209, most probably as a result of cleavage of TMS ethers at 3- and 3'-positions before subsequent attack of the phenoxide groups.

\[ \text{A} \xrightarrow{\text{a}} \text{B} \]

(a) 1.0 equi. potassium phthalimide, 0.1 equi. 18-crown-6, toluene, overnight, reflux

**Scheme 35** Synthetic approach planned for the synthesis of 163, 164, and 165

This led us to protect the hydroxyls of 13 as TBDMS ethers, since these are known to be more stable towards base than TMS ethers.\(^{162}\) This was achieved in quantitative yield by reacting 13 at room temperature with tert-butyldimethylsilyl chloride (1.05 equivalents per hydroxy group) and imidazole (1.1 equivalents per hydroxy group). Since \(^1\)H NMR spectrometry of the crude material showed the product 210 to be formed cleanly, 210 was not purified but immediately deprotonated with sodium hydride and reacted with 206 according to the general procedure previously described for pyrrolic N-benzylation. After work-up and subsequent deprotection of the silyl ethers with TBAF, the crude product was shown to be very unclean by TLC. Repeated purification by column chromatography failed to afford definite evidence of the desired product; although the main peak (10 times stronger than secondary peaks) on the mass spectrum corresponded to the correct molecular
weight, $^1$H-NMR showed that the fraction was a complex mixture of different materials.

Since it had not been possible to prepare the irreversible ligands 163, 164, and 165 via an easy route utilising simultaneous protection of the phenolic and hydroxy groups of 13, we investigated preparing the 14,14'-dimethoxy analogue 211. Methylation of the hydroxyl in 14 position of 44 and its 17-N-allyl derivative has indeed been reported to result in little modification of the pharmacological profile of the parent ligands, while methylation of the hydroxyls in the 14- and 14'-positions of 13 has been shown to result in no modification of $\kappa$-affinity. One might thus envisage that the effect of N-benzylation of 211 with 206, 207 and 208 should be equivalent to that of 13 (scheme 36).

Scheme 36 Another approach for the preparation of irreversible ligands modelled on norBNI (13)
The synthesis of 211 from 14-OMe naltrexone (212) has been previously reported by Schmidhammer and associates and involved a two-step synthesis, first reacting 212 with hydrazine hydrate, before heating the product (azine 213) in presence of methanesulfonic acid (20% yield, see scheme 37).\textsuperscript{163} However, it was felt that isolation of the azine intermediate was unnecessary and we instead envisaged preparing 211 using similar reacting conditions as employed for the preparation of norBNI in section 2.4 (scheme 26).

The preparation of 212 has been reported in the literature starting either from 44\textsuperscript{163,164} or from 14-hydroxycodeinone (214).\textsuperscript{165} We opted for the first approach because naltrexone was readily available in our laboratory and also because this method was more straightforward (3 steps instead of 6). These considerations led us to prepare 211 according to the synthetic route presented in scheme 38. Benzylation of naltrexone was achieved using one equivalent of benzyl bromide and an excess of potassium carbonate, which afforded 215 in quantitative yield. The attempted
dimethylation of 215 employed a modified version of the procedure used by Schmidhammer et al.;\textsuperscript{164} thus, 2.1 equivalents of methyl iodide and three equivalents of sodium hydride were used instead of 2.75 equivalents of dimethyl sulfate and an excess of sodium hydride due to the easier removal of excess of methylating agent. The amount of methylating agent was decreased in order to avoid methylation of 17-N that was likely to occur. However, this did not prove successful as the formation of numerous side products was observed and 216 was eventually prepared following Schmidhammer's procedure. It should be noted that monomethylation of 215 at the 14-hydroxyl is not possible because of the propensity of the ketonic group of morphinan-6-ones to exist in the enol form that is susceptible to alkylation.\textsuperscript{156} 216 was immediately refluxed overnight in methanol/conc. HCl (3/2) in accordance with the procedure reported by Schmidhammer's group and this afforded 212 that was purified, carefully dried and converted into its HCl salt (71\% overall yield from naltrexone).

Scheme 38 Synthetic route used for the preparation of 211

\begin{align*}
\text{44} & \xrightarrow{a} \text{215} & & \text{216} \\
& \xrightarrow{c} \text{212} & & \text{211} \\
\end{align*}

(a) 1.3 equi. $K_2CO_3$, 1.0 equi. BnBr, DMF, overnight, room T°; (b) 3.0 equi. NaH, 2.75 equi. dimethyl sulfate, DMF, 2 hrs, 0°C; (c) conc. HCl/MeOH (2/3), overnight, reflux; (d) 0.53 equi. NH$_3$NH$_2$H$_2$SO$_4$, dry DMF, 6 hrs, 100°C then 0.51 equi. CH$_3$SO$_3$H, DMSO, 3.5 hrs, 130°C
Unfortunately, Piloty reaction between the hydrochloride salt of \textbf{212} and hydrazine sulfate, following the procedure used in section 2.4, failed to give the desired bivalent ligand \textbf{211}. It is noteworthy that similar difficulties were encountered for the reaction of hydrazine sulfate with hydromorphone (\textbf{217}) (this will be discussed in section 2.6.2.a). Interestingly, both \textbf{212} and \textbf{217} lack a hydrogen-bond donor in the 14-position (see figure 10). When the 14-position was occupied by a hydroxyl, a group capable of hydrogen-bond donation, the reaction was found to proceed in good yield (62\% yield for reaction with \textbf{44} and 75\% yield for reaction with \textbf{218}, see sections 2.4 and 2.6.2.b respectively). This would suggest that intramolecular hydrogen-bond interactions facilitate the reaction of morphinone-6-ones with hydrazine.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{Substitution in 14-position and facility of pyrrole formation: a coincidence?}
\end{figure}

Interestingly, Nagase et al. have proposed in their study on dihydromorphinone and related opiates that hydrogen-bond donor/acceptor interactions might partly account for the remarkable enolic character of these ketones.\textsuperscript{156} In particular, it seems that the basic nitrogen in 17-position is capable of forming a hydrogen-bond with the hydroxyl in 14-position and that the oxygen atom in 14-position would then remove the axial proton in 7-position, thereby resulting in enolisation of morphinan-6-ones (see figure 11).
Figure 11 Importance of hydrogen-bonding in the enolisation of dihydromorphinone and related opiates \(^1\text{56}\)

The observation that hydromorphone analogues, \(ie\) morphinans lacking a hydrogen-bond donor in 14-position, require much longer reaction time than equivalent oxymorphones (\(ie\) with a 14-hydroxyl) to undergo silylation of their enolic group under mild conditions tend to demonstrate the importance of hydrogen-bonding and anchimeric assistance of 17-N and 14-O in the reactivity of these opioids.\(^1\text{56}\)

However, the fact that hydromorphones still undergo silylation indicates that hydrogen-bonding interactions are not a requisite but only one of many factors influencing enolisation. Of greater importance would be the dipolar interaction between the carbonyl group in 6-position and the nearly eclipsed oxygen of the furan ether; since this unfavourable interaction is greatly reduced in the enolic form due to ring flattening, the enolic form is therefore the most thermodynamically favoured.\(^1\text{56}\)

Since the nitrogen atom is less electronegative than the oxygen atom, it means that this negative dipolar interaction is less marked for imine derivatives than for the corresponding ketones. It is possible that the strong unfavourable dipolar interaction is a sufficient condition for morphinan-6-ones to adopt the enol form but not for an imine to adopt the enamine form. In the latter case, another factor might be required, such as the presence of a hydrogen-bond donor in 14-position. The formation of pyrroles \(via\) the reaction of morphinan-6-ones with hydrazine proceeds through an azine intermediate (see figure 12). In the absence of a hydrogen-bond donor in 14-position, it is possible that the azine intermediate would have difficulty tautomerising to its enamine form (this might require higher energy than provided by the reacting conditions), which would then result in the failure to react morphinan-6-ones with hydrazine (see figure 12).
Figure 12 The formation of pyrroles from the reaction of morphinan-6-ones with hydrazine: azine intermediate

Accordingly, a better approach for the preparation of 211 would be via dimethylation of norBNI (13), which initially requires selective protection of the pyrrolic nitrogen and phenolic groups. Such protection had been reported by Schmidhammer and colleagues in their efforts to develop a series of 14-alkoxy-substituted indolomorphinans and involved a MOM-protecting group. This led us to react 13 with 4 equivalents of both sodium hydride and chloromethyl methyl ether, which afforded the tri-MOM-protected bimorphinan 219 (see scheme 39).

This was dimethylated into 220, using a similar procedure as employed for the preparation of 216, ie by deprotonating the hydroxy groups with 3 equivalents of sodium hydride before reacting the dianion with an excess of dimethyl sulfate. The yield (22%) was substantially lower than that observed for dimethylation of 215 (72%) and is explained by the presence of monomethylated product and unreacted starting material 219 at the end of the reaction; however, the reaction time could not be extended because of progressive formation of an unidentified side product.

It was not possible to selectively cleave the MOM-protecting group from the pyrrolic nitrogen due to the non-availability of the lone pair of electrons at nitrogen;
indeed, while cleavage of the methoxymethyl group from alcohols is generally achieved under mild conditions, e.g. stirring the protected alcohols in methanol in presence of a sulfonic acid, the cleavage from indolic nitrogens is inconsistent and requires much harsher reagents such as BF$_3$.Et$_2$O. Since Schmidhammer's group had reported that deprotection of the MOM groups from both 3-hydroxyl and indolic-nitrogen could be achieved simultaneously stirring the morphinans in MeOH/1N. HCl under reflux, we also decided to use acidic hydrolysis. We first attempted to remove all three MOM-protecting groups of 220 by stirring overnight at room temperature in a mixture of conc. HCl/MeOH (50/50). However, this afforded 221 still having its pyrrolic nitrogen protected with a MOM group. Complete deprotection into 211 was eventually achieved by treating 221 under similar conditions, but increasing the temperature to 80°C.

Selective reprotction of the phenolic groups of 211 was then required for subsequent benzylation of the pyrrolic nitrogen. Our previous experience with the protection of phenolic groups of norBNI-derived ligands led us to opt for a protecting group that would be stable under strong basic conditions but also very easy to cleave under mild acidic conditions. Since each dimethoxy substitution on the trityl group has been demonstrated to enhance the rate of deprotection by 100-fold, resulting in very facile deprotection, the 4,4'-dimethoxytrityl protecting group appeared a perfect candidate for that aim. 211 was thus reacted with 4,4'-dimethoxytrityl chloride under DMAP-catalysed reacting conditions. Evidence of the formation of the expected intermediate 212 was provided by $^1$H NMR but the product was not purified by column chromatography since its deprotection was likely to occur in presence of silica. 222 was immediately deprotonated with sodium hydride and reacted with 206. Unfortunately, this did not lead to the desired product but to a main product identified as 223.

We then envisaged protecting the phenolic groups of 211 with the more stable benzyl group but there was however insufficient amount of material left at this stage to undertake further work.
(a) 4.0 equi. NaH, 4.0 equi. chloromethyl methyl ether, dry DMF, 2 hrs, room T°; (b) 3.0 equi. NaH, 2.5 equi. dimethyl sulfate, DMF, 3 hrs, 0°C; (c) conc. HCl/MeOH (1/1), overnight, room T°; (d) conc. HCl/MeOH (1/1), overnight, 80°C; (e) 2.0 equi. 4,4′-dimethoxytrityl chloride, 1.6 equi. DMAP, pyridine, overnight, room T°; (f) 4.1 equi. NaH, 3.0 equi. 206, dry DMF, overnight, 70°C

Scheme 39 Preparation of bimorphinan 211 and subsequent pyrrolic N-substitution
2.5.3.b Synthesis

Since studies focusing on the protection of 14- and 14'-hydroxyls of 13 did not lead to any useful alternative to the acetate protecting group, we eventually reverted to using acetates in the synthesis of the potential irreversible ligands 163, 164, and 165 (see scheme 40).

(a) 1.0 equi. potassium phthalimide, 0.1 equi. 18-crown-6, toluene, overnight, reflux;
(b) 4.0 equi. NaH, 0.1 equi. 18-crown-6, 3.0 equi. 206, 207, or 208, dry THF or DMF, overnight, 70°C;
(c) conc. HCl/MeOH (1/1), overnight, 85°C;
(d) 3 equi. NH₂NH₂·XH₂O, 16 to 48 hrs, room T°;
(e) 6.0 equi. NaHCO₃, 1.1 equi CSCI₂, CHCl₃/H₂O, 2hrs, room T°

Scheme 40 Synthetic route used for the synthesis of 163, 164, and 165
In a similar manner as employed in section 2.5.2, the synthetic route thus involved deprotonation of 178 followed by nucleophilic attack onto benzyl bromides 206, 207 and 208, which afforded the desired N-substituted products 224, 225 and 226. As expected, attempts to cleave the acetate esters of 224, stirring in warm methanol, turned out to be unsuccessful. Basic saponification of 224, 225 and 226 in MeOH/H₂O (9/1) - using potassium carbonate (1.2 to 5 equivalents per acetate group), lithium hydroxide (1.4 equivalents) or concentrated aqueous ammonia - resulted in either recovery or decomposition of the starting materials, with no desired product being isolated. Stirring 224 and an excess of sodium methoxide in methanol at room temperature or at 45°C led again to the recovery of unreacted materials while reduction with diisobutylaluminium hydride (2 equivalents per acetate group) did not afford any useful product. Decomposition of the 14,14'-diacetyl analogue of 224 was also observed when stirring overnight at room temperature in an anhydrous mixture of THF/MeOH (50/50) with 1.4 to 16 equivalents of magnesium. Deprotection of the acetyl s 224, 225 and 226 into 227, 228 and 229 was eventually accomplished stirring the compounds overnight in a mixture of MeOH/conc. HCl (50/50) at 85°C; it is noteworthy that amines 169 and 171 were also isolated when using such acidic conditions. Treatment of 227, 228 and 229 with an excess of hydrazine hydrate afforded the desired amines 169, 170 and 171, which were finally converted into the corresponding isothiocyanates 163, 164 and 165, employing the same procedure as used for the preparation of 161.

2.6 Ligands with mixed profile: μ-agonist/κ-antagonist
2.6.1 Rationale and design

As discussed in the pharmacological section, in-vivo biological evaluation of BnorBNI (152) showed that this bivalent ligand exhibits μ-opioid receptor agonist activity with modest potency and duration of action when administered subcutaneously (sc), while it displays κ-opioid receptor antagonism with high potency, selectivity and very long duration of action when administered intracerebroventricularly (icv) (see section 3.2). Since there is an interest in developing mixed μ-agonist/κ-antagonist ligands (see section 1.4.2), we decided to attempt to improve the pharmacological profile of 152, more specifically regarding its μ-agonist effects.
When studying the SAR of BNI-related ligands, Portoghese and associates disclosed three members displaying full agonist activity (230, 231 and 232) in the guinea pig ileum (GPI) and mouse vas deferens (MVD) assays; interestingly, all three ligands were N-Me disubstituted derivatives. Further study with 230 in the GPI assay showed that the agonist effects were mediated through the µ-receptor, with similar selectivity likely for the other members. This suggests that the SAR of norBNI derivatives, in particular regarding substitution at N-17 and N-17', follows that displayed by other series of opioids; N-Me substitution typically leads to µ-agonism, while N-CPM substitution generally results in a decrease in µ-efficacy and a more κ-profile. It was therefore of interest to investigate whether similar N-Me disubstitution would optimise the µ-agonist pharmacological profile of BnorBNI; we here investigate the synthesis and biological evaluation of 233 and 234.

![Chemical structures of compounds 230-234](image)

2.6.2 Synthesis

2.6.2.a Synthesis of 233

Replacement of N-substituents from the 17-position of morphinans has been reported in the literature and involves alkylation of N-noralkaloid intermediates or quaternisation of the starting tertiary amine followed by dealkylation.

In the first approach, the starting tertiary amine is first reacted either with cyanogen bromide (von Braun reaction) or alkyl chloroformates before cleavage of the cyanamide or carbamate product; the N-noralkaloid intermediate is then alkylated with the appropriate alkyl bromide derivative. However, there were potential problems in applying this method for the conversion of BnorBNI (152) into the targeted derivative 233: reaction of a tertiary amine (constituted of three alkyl groups) with cyanoammonium bromide results indeed in cleavage of the smallest alkyl...
bromide. Thus, the method represents an attractive approach for replacing the N-Me group of morphinans, but not for replacing the CPM group of BnorBNI. Of concern was the possible formation of side products arising from cleavage at the 16-position since cyclic amines have been reported to be frequently cleaved through von Braun reaction.

The second approach, i.e. quaternisation of BnorBNI with methyl iodide followed by dealkylation, should lead to the targeted product 233. However, such a method would present some disadvantages when applied to BnorBNI; firstly, protection and deprotection of the hydroxy groups of BnorBNI was required, which we wished to avoid due to our previous experiences. Also tedious purification was predictable: since BnorBNI is a bivalent ligand, the N-Me disubstituted product 233 would have to be isolated from a mixture likely to contain the N-CPM di-substituted starting material, the mono-converted compound, the products arising from mono/di-Hofmann elimination, amongst others. In the light of these considerations, it seemed inappropriate to synthesise 233 from 152.

It was instead decided to prepare 17,17'-di-N-Me-substituted norBNI intermediate 235 reported by Portoghese, before subsequent pyrrolic N-benzylation, in a similar approach as used for BnorBNI (see scheme 41). Demethylation of oxycodone (236) has been reported under various conditions, e.g. heating the morphinan to 110-120°C in aqueous HBr (35% yield) or stirring in aqueous HCl in presence of Pd/C. BBr₃ has also been employed for this purpose, but it was believed that better yields would be achieved with BBr₃.DMS because of the reduced propensity of BBr₃ to complex with the electron-donor groups of oxycodone. We thus decided to utilise this reagent; the experiment was adapted from a general procedure described for dealkylation of aryl ethers and afforded oxymorphone (218) in 63% yield. Similar Piloty reaction as used for the preparation of norBNI, starting with the hydrochloride salt of 218 and hydrazine sulfate, afforded the bivalent ligand 235; this was then deprotonated with sodium hydride and reacted with five equivalents of benzyl bromide, the conditions that had proved successful for the preparation of BnorBNI. This afforded the tri-benzylated product 237, which was immediately reacted with aqueous HBr (50% in methanol) into the target derivative 233.
2.6.2.2 Synthesis of 234

The successful preparation of 233 via multiple benzylation and subsequent selective debenzylation prompted us to use the same strategy for the synthesis of 234, but with hydrocodone (238) as the starting material (see scheme 42).

Although demethylation of hydrocodone (238) using four equivalents of BBr₃.DMS led to the anticipated product hydromorphone (217), the yield turned out to be substantially lower than that observed for the demethylation of oxycodone (218) (33% compared to 63%). This was surprising since replacement of the hydroxyl in 14-position with a hydrogen atom was expected to result in reduced complexation with BBr₃ and consequently in a higher yield. However, as discussed in section 2.5.3.a, intramolecular hydrogen-bond interactions generally exist between the basic nitrogen in 17-position, the hydroxyl in 14-position and the hydrogen atom in 7-position of morphinan-6-ones;¹⁵⁶ 218 is no exception to that rule and this is demonstrated with

Scheme 41 Synthetic pathway used for the preparation of 233
hydromorphone (217) being more polar than oxymorphone (218) (see \( R_f \) values in section 3).\textsuperscript{156} Although it is acknowledged that BBr\(_3\) was used in excess and as its methyl sulfide complex, it still remains that stronger complexation exists between BBr\(_3\) and 238 than between BBr\(_3\) and 236, which might explain why the reaction proceeds better in the latter case. Demethylation of 238 with two equivalents of boron tribromide (from -78°C to room temperature) gave a similar yield (40%). Trimethylsilyl iodide, formed \textit{in-situ} from nucleophilic attack of sodium iodide on trimethylsilyl chloride, was also utilised to see if this would allow a more efficient synthesis of 217, but this procedure failed to give any demethylated product.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {217};
\node (b) at (2,0) {238};
\node (c) at (4,0) {239};
\node (d) at (6,0) {240};
\node (e) at (8,0) {234};
\draw (a) -- (b) node[midway,above] {a};
\draw (b) -- (c) node[midway,above] {b};
\draw (c) -- (d) node[midway,above] {c};
\draw (d) -- (e) node[midway,above] {d};
\end{tikzpicture}
\end{center}

(a) 4.0 equi. BBr\(_3\).DMS, dichloroethane, overnight, 65°C; (b) 0.52 equi. NH\(_2\)NH\(_2\).H\(_2\)SO\(_4\), dry DMF, overnight, 105°C then 0.49 equi. CH\(_3\)SO\(_3\)H, DMSO, 4 hrs, 130°C; (c) 10.0 equi. NaH, 0.38 equi. 18-crown-6, 5.1 equi. BnBr, DMF, 24 hrs, room T\(^\circ\); (d) MeOH/HBr (in AcOH) (1/1), overnight, room T\(^\circ\)

\textbf{Scheme 42} Synthetic route planned for the preparation of 234

Although preparation of the bivalent ligand 239 from 217 has been reported by Portoghese \textit{et al.} using N-aminosuccinimide hydrochloride,\textsuperscript{173} we instead decided to use 1.1 equivalents of hydrazine sulfate in a similar way as used for the preparation of 235. The desired product 239 was isolated in 35% yield; again, the yield was lower.
than that obtained with the 14-OH analogue 235, which is in line with our previous observation that pyrrole formation via reaction between hydrazine and morphinan-6-ones proceeds in much better yield when the 14-position is occupied by a hydrogen-bond donor (see section 2.5.3.a).

Our greatest surprise came however when reacting deprotonated 239 with five equivalents of benzyl bromide. We indeed believed that the reaction would proceed better than when starting with 235 because of the lack of hydroxy groups in 14- and 14'-positions. However, this proved not to be the case and the desired product 240 was obtained in very low yield (19%). Moreover, repeating the reaction several times showed the result not to be reproducible, with highly-benzylated species being routinely formed; unfortunately, it was not possible to characterise these products. This led us to change the reacting conditions, including reducing the amount of sodium hydride and/or benzyl bromide, replacing sodium hydride with potassium tert-butoxide or sodium hydroxide. According to mass spectrometry, use of 4 equivalents of potassium hydroxide and 3.5 equivalents of benzyl bromide afforded a complex mixture of penta-, tetra- and tribenzylated derivatives, while hexa-, penta- and tetrabenzylated products were obtained when using 3.1 equivalents of tert-butoxide and 3.2 equivalents of benzyl bromide. In both cases, no starting material was isolated, suggesting that some decomposition had occurred during the reaction. Accepting the low yield of the original procedure, 240 was then treated with HBr in acetic acid in order to cleave the phenolic benzyl ethers. Unfortunately, no product was obtained and there was insufficient amount of material left to try any other method of debenzylation.

This urged us to explore another approach for the preparation of 234, namely the two-step synthetic pathway presented in scheme 43. The first step involved a Piloty reaction between hydrocodone (238) and benzylhydrazine dihydrochloride; although reaction of morphinan-6-ones with substituted hydrazine seemed to prove difficult in our hands (for example, such a procedure afforded BnorBNI in only 1% yield, see section 2.4.2), we still hoped the reaction would work in this case since Schmidhammer and co-workers had reported that stirring a mixture of hydrocodone (238) and N-methylhydrazine sulfate in acetic acid for 3 hours at room temperature led smoothly to the desired product.174
However, reacting the HCl salt of hydrocodone (238) with benzylhydrazine dihydrochloride in an analogous manner as usually employed within our group for pyrrole formation, *ie* stirring first in DMF at 100°C then in DMSO and methanesulfonic acid at 130°C, failed in giving any desired product 241. Modification of the reacting conditions, namely stirring overnight the free base or the salt of both hydrocodone and benzylhydrazine in refluxing ethanol in presence of molecular sieves before proceeding as described earlier for the second stage, did not afford the desired product. Finally, stirring hydrocodone (238) and benzylhydrazine in acetic acid, following an equivalent procedure to that employed by Schmidhammer and associates, also proved unsuccessful. The reaction mixture was then stirred for one hour at 70°C, but this led to the same conclusion.

Since reaction of morphinan-6-ones with substituted hydrazine had not proved successful in our hands, we instead planned to react 238 with unsubstituted hydrazine before subsequent pyrrolic N-benzylation and 3,3'-demethylation (see scheme 44). This new approach also offered the advantage that both phenolic groups of 242 were

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**Scheme 43** Alternative approach for the preparation of 234
*(via Piloty reaction between 238 and benzylhydrazine)*

(a) 0.52 equi. BnNHNH$_2$.2HCl, dry DMF, overnight, 105°C then 0.49 equi. CH$_3$SO$_3$H, DMSO, 4 hrs, 130°C; (b) 8.0 equi. BBr$_3$.DMS, dichloroethane, overnight, 65°C
"protected" during pyrrolic N-benzylaion, which should reduce extra-benzylaion observed when reacting the 3,3'-dihydroxyl derivative 239.

Scheme 44  Alternative approach for the preparation of 234  
(via Piloty reaction between 238 and hydrazine)

Condensation of hydrocodone hydrochloride with hydrazine sulfate followed by acid-catalysed cyclisation, using an equivalent procedure to that employed for the preparation of norBNI (13), led to the desired product 242 in 71% yield. This suggests that substitution of hydrazine prior to its reaction with morphinan-6-ones is a critical impediment to the success of the reaction; it is possible that steric hindrance inherent to the benzyl substituent shifts the azine intermediate to a conformation unfavourable to subsequent electron transfer.

We then decided to use lithium diisopropylamide for the deprotonation of 242 since it is a hindered base, which might reduce the number of deprotonated sites and result in selective benzylation of the pyrrolic nitrogen. Moreover, using freshly-titrated LDA solution appeared particularly convenient for our purpose, for the scale
we were working on was quite small (less than 0.5 mmol). Unfortunately, all attempts to benzylate 242 using lithium diisopropylamide (from 1.05 equivalents to 1.5 equivalents) and benzyl bromide (from 1.1 equivalents to 3.3 equivalents) led to the decomposition and/or recovery of 242, with no useful product 243 isolated.

2.7 Studies towards a new protecting group for pyrrolic and indolic nitrogens

Since it was found in section 2.5 that N-substitution of norBNI (13) with a p-phthalimidobenzyl group did not survive acidic or hydrazinolytic environment, we decided to investigate whether such a group could find application as a protecting group for pyrrolic and indolic nitrogens. Should the \( p \)-phthalimidobenzyl group be envisaged as a protecting group, a higher-yielding approach for its preparation had also to be achieved. This led us to plan the synthesis of 182 via the two-step route presented in scheme 45.

![Scheme 45 Two-step synthesis of 182](image)

(a) 1.0 equi. phthalic anhydride, AcOH, 2 hrs, reflux
(b) 3.0 equi. NaBrO₃, 3.0 equi. NaHSO₃, EtOAc/H₂O, 6 hrs, room T°

Reaction of \( p \)-toluidine with one equivalent of phthalic anhydride in refluxing acetic acid led to the protected intermediate 244 in 84% yield. With greater and greater environmental concern, new procedures using environmentally-friendly solvents or generating bromine \textit{in-situ} have recently appeared for benzylic brominations,\textsuperscript{175,176} which led us to brominate 244 using a mixture of sodium bromate/sodium hydrosulphite in a similar way as reported by Kikuchi and co-workers.\textsuperscript{176} This led to 182 in 62% yield (52% overall yield from \( p \)-toluidine).
We then evaluated the use of the \( p \)-phthalimidobenzyl group for the protection of indolic nitrogens. To that end, we reacted 182 with the conjugate base of carbazole (245) and tetrahydrocarbazole (246) according to the same procedure as employed for benzylation of 178.

In both cases, monitoring of the reaction by TLC showed the reaction mixture to be surprisingly messy; replacing sodium hydride with potassium tert-butoxide or a milder base such as potassium carbonate did not result in cleaner reactions. It is unclear whether the product and/or starting materials decomposed during the reaction or during the purification; of additional concern, is the fact that both commercially available and freshly ordered carbazole and tetrahydrocarbazole gave similar messy TLCs despite getting very clean NMR spectra. Because of complex purification, the protection of tetrahydrocarbazole with 182 was abandoned, while indolic N-substitution of carbazole afforded the desired product 247 in modest yield (37%) (scheme 46). Deprotection of 247 with three equivalents of hydrazine hydrate also proved to be messy when monitored by TLC but the fact that amine 248 was isolated suggested that the deprotection was not proceeding in an analogous manner to that with norBNI (13).

(a) 2.0 equi. NaH, 1.1 equi. 182, 0.1 equi. 15-crown-5, dry DMF, overnight, 70°C;
(b) 3.0 equi. NH\(_2\)NH\(_2\)\(\cdot\)xH\(_2\)O, EtOH, 2 days, room T°

**Scheme 46** Protection and deprotection of 245 with a \( p \)-phthalimidobenzyl group
Since it was clear that carbazole and tetrahydrocarbazole did not represent ideal candidates for the evaluation of the \( p \)-phthalimidobenzyl group as a nitrogen-protecting group, we further conducted our study with indolomorphinan 249 (scheme 47); this was obtained from esterification of readily available 250 with acetic anhydride, in a similar way as employed for the preparation of 178.

\[
\begin{align*}
&\text{MeO} \quad \text{NMe} \quad \text{OAc} \\
\text{MeO} \quad \text{NMe} \quad \text{OH} \\
&250 \\
&\begin{array}{c}
\text{MeO} \quad \text{NMe} \\
\text{OAc}
\end{array} \\
&251
\end{align*}
\]

(a) acetic anhydride, 3 hrs, 100°C; (b) 4.0 equi. NaH, 0.1 equi. 15-crown-5, 3.0 equi. 182, dry DMF, overnight, 70°C

**Scheme 47** Protection of 249 with a \( p \)-phthalimidobenzyl group

Deprotonation of 249 with an excess of sodium hydride followed by nucleophilic attack on 182 gave the desired N-substituted product 251. 251 was subsequently treated with either a mixture of MeOH/conc. HCl (50/50) at 85°C or with 3 equivalents of hydrazine hydrate at room temperature; in both cases, TLC showed consumption of the starting material with neither 249 or 250 being formed. In the light of these experiments, it seems that the \( p \)-phthalimidobenzyl group cannot be used as a general protecting group for indolic or pyrrolic nitrogens.
3. PHARMACOLOGICAL EVALUATION

3.1 Methods

The initial pharmacological evaluation of all ligands was performed by NIDA-OTDP through a contract to SRI or by Dr. John R. Traynor and colleagues; all ligands were evaluated in binding assays, measuring the affinity at each receptor type, and in-vitro ([35S]GTPγS assay), measuring the antagonist and agonist potency (and efficacy) at each receptor. In some cases, the pharmacological profile of the test compound was also investigated in-vivo. At the time of submission, only pharmacological data related to compounds 13, 152, 233, 235, 50 and 51 were available.

3.1.1 Binding assays

The identification and purification of homogenous populations of opioid receptors has allowed the development of assays that measure the amount of radiolabeled ligand bound to these receptors. By determining the concentration (IC50) of unlabeled test compound required to displace 50% of radiolabeled ligand from the receptor, one can calculate the affinity of the test compound for this receptor using the following formula:

\[ K_i = \frac{IC_{50}}{1 + \frac{[D]}{K_D}} \]

where, \( K_i \) = dissociation constant of test compound

\( [D] \) = concentration of radiolabeled ligand

\( K_D \) = dissociation constant of radiolabeled ligand

3.1.2 Functional assays

In the present project, in-vitro evaluation of the test compounds was based on stimulation of opioid receptor-mediated binding of the GTP analogue guanosine-5'-O-(3-[35S]thio)triphosphate ([35S]GTPγS) to human κ, μ and δ-receptors transfected into Chinese hamster ovary cells (NIDA-OTDP) or rat μ and δ-receptors transfected into C6 cells (Traynor and colleagues). Thus, dose-response curves of [35S]GTPγS binding mediated by selective agonists DAMGO (for μ), SNC80 (for δ, NIDA-OTDP), DPDPE (for δ, Traynor and colleagues) and U69593 (for κ) were recorded in presence or absence of the test compound.

Antagonist potency was determined from the concentration of the test compound required to lower [35S]GTPγS binding by 50% according to the formula:
Ke = [antagonist]/(dose ratio -1), where dose ratio corresponds to the ratio between [antagonist] and the concentration of the radiolabeled ligand required to get 50% of maximal $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding.

Agonist potency at a receptor type was determined from the concentration ($EC_{50}$) of the test compound required to get 50% of the $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding value obtained with the standard agonist. Relative efficacy of agonist test compounds at a receptor type was determined by the percentage of maximal stimulation of $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding obtained with the test ligand compared to that observed with the full agonist selective to that receptor.

3.1.3 In-vivo assays

In-vivo assays are often based upon response of rodents to a wide range of nociceptive stimuli including temperature, chemical irritants or electric shocks. In-vivo pharmacological evaluation of the ligands synthesised in the present project was achieved using the warm-water tail withdrawal assay, in which the temperature was 50°C.

3.2 Pharmacological evaluation of 13, 152, 233 and 235

13, 152, 233 and 235 were evaluated in opioid binding assays and in-vitro stimulation of $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding with BnorBNI (152) further evaluated in-vivo in the tail withdrawal assay (in mice).

The binding affinities are reported in table 3 and showed subnanomolar affinity of both 13 and 152 for $\kappa$-receptors with modest selectivity over $\mu$ and $\delta$ ($\leq$ 15-fold). When compared to 13, 152 had 8-fold lower $\mu$-affinity than norBNI and as a result slightly improved $\kappa/\mu$ selectivity. Although Takemori et al. have reported similar low $\kappa$-selectivity for the closely related analogue 28, it the low selectivity observed with norBNI (13) is surprising and is in disagreement with previous reports (around 160-fold $\kappa$-selectivity over both $\mu$ and $\delta$); it is unclear why the results are divergent but it is noteworthy that the methods used by Takemori et al. differed from that used by our collaborators (different tissue and different radiolabeled ligands). The N-Me analogues 235 and 233 also showed modest $\kappa$-selectivity broadly in line with that seen for 13 and 152. The replacement of the N-CPM substituents by N-Me resulted in similar decreases in $\kappa$ and $\delta$-affinity of around an order of magnitude, but
in contrast the effect on \( \mu \)-affinity was not consistent. While 235 exhibited 50-fold lower \( \mu \)-affinity than 13, replacement of the N-CPM group of 152 resulted in slightly higher \( \mu \)-affinity for 233.

<table>
<thead>
<tr>
<th></th>
<th>( K_i ) (nM)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \mu )</td>
<td>( \delta )</td>
</tr>
<tr>
<td>13</td>
<td>1.2 ± 0.2</td>
<td>5.8 ± 0.7</td>
</tr>
<tr>
<td>152</td>
<td>10.0 ± 2.5</td>
<td>8.6 ± 0.7</td>
</tr>
<tr>
<td>235</td>
<td>63.6 ± 39.1</td>
<td>98.2 ± 25.3</td>
</tr>
<tr>
<td>233</td>
<td>6.4 ± 1.1</td>
<td>207 ± 96</td>
</tr>
</tbody>
</table>

Values are from 3 separate experiments, each performed in duplicate.
Radiolabeled ligand is nonselective antagonist \([3H]diprenorphine\).

**Table 3** Affinities in opioid receptor displacement binding assays

In the *in-vitro* functional assay, 152 exhibited partial \( \mu \)- and \( \kappa \)-agonist activity of modest and low potency respectively (see table 4); its agonists effects showed a 10-fold \( \mu/\kappa \) selectivity and reached respectively 38% and 29% of maximal effect compared with the full agonists at each receptor. 13 showed no opioid agonist activity at any receptor, which is in agreement with literature reports.\(^{81}\)

<table>
<thead>
<tr>
<th></th>
<th>EC(_{50}) (nM) and % Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[(^3)H]DAMGO - ( \mu )</td>
</tr>
<tr>
<td>13</td>
<td>- (^{a})</td>
</tr>
<tr>
<td>152</td>
<td>187 (^{b})</td>
</tr>
<tr>
<td>235</td>
<td>1388 ± 370</td>
</tr>
<tr>
<td>233</td>
<td>526 ± 279</td>
</tr>
</tbody>
</table>

Values are from 3 separate experiments; \(^{a}\) no stimulation up to 10,000 nM; \(^{b}\) 95% CI, 42-844 nM; \(^{c}\) 95% CI, 269-13490 nM.

**Table 4** Opioid agonist effects measured by the [\(^{35}\)S]GTP\(_\gamma\)S assay
Both 235 and 233 possessed weak \(\mu\)-agonist effects with no detectable agonism at \(\kappa\) and \(\delta\)-receptors. Both compounds showed higher efficacy than that exhibited by the corresponding N-CPM derivatives, which is in agreement with general SAR studies related to 17-N substitution of morphine derivatives (see section 2.6.1). It is noteworthy that while pyrrolic benzylation of 13 to 152 had resulted in an increase in \(\mu\)-efficacy, equivalent benzylation of 235 to 233 had resulted in improved \(\mu\)-potency but slightly reduced \(\mu\)-efficacy.

As the compounds displayed little efficacy at opioid receptors, they were evaluated as opioid antagonists, the exception being 235 and 233 at \(\mu\)-receptors where they had too high efficacy. In the opioid antagonist functional assay, 152 exhibited potent \(\kappa\)-antagonism with a 50-fold \(\kappa/\delta\) and 100-fold \(\kappa/\mu\) selectivity (table 5). In both cases, the selectivity was similar or higher than that showed by norBNI (13) (47 and 22-fold respectively). Both N-Me analogues 235 and 233 were weak antagonists at \(\kappa\)-receptors, with a 2-3 order of magnitude lower potency than the corresponding N-CPM derivatives 13 and 152.

<table>
<thead>
<tr>
<th>(\mathrm{K}_e) (nM)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{H}]\text{DAMGO} - \mu)</td>
<td>([\text{H}]\text{SNC80} - \delta)</td>
</tr>
<tr>
<td>13</td>
<td>2.38 ± 0.58</td>
</tr>
<tr>
<td>152</td>
<td>25.5 ± 2.3</td>
</tr>
<tr>
<td>235</td>
<td>NT</td>
</tr>
<tr>
<td>233</td>
<td>NT</td>
</tr>
</tbody>
</table>

Values are from three separate experiments; NT: not tested

**Table 5** Opioid receptor antagonist activity in the \([35S]GTP\gamma S\) assay

Replacement of the N-CPM substituents with N-Me has thus resulted in increased \(\mu\)-agonist efficacy of both 13 and 152; of concomitant effect, was the huge decrease in \(\kappa\)-antagonist potency observed upon such modification. It is difficult to compare this effect with previously reported similar replacement of 17-N-CPM group of GNTI (11) and NTI (150). While such modification has been reported to result in
loss of selectivity and potency in the $\delta$-antagonist activity of 150, with simultaneous appearance of $\delta$-agonism, the N-Me derivative of 11 exhibited no agonist activity but was a $\kappa$-antagonist with decreased $\kappa$-selectivity and potency compared to 11.88,181

The pharmacological profile of BnorBNI (152) was further investigated in vivo; its agonist and antagonists effects on the dose-response curve of the selective $\kappa$-agonist U69593 were evaluated with the drug being either administered sc or icv. The results are presented in tables 6 and 7 respectively (negative shift values reflect a leftward shift on the dose-response curve of the agonist, while positive values reflect a rightward shift).

<table>
<thead>
<tr>
<th>Treatment conditions applied to U69593</th>
<th>EC$_{50}$ mg/kg</th>
<th>Fold shift</th>
<th>Shift significance p value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>U69593</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ vehicle at -1h$^a$</td>
<td>5.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ 10 mg/kg BnorBNI at -1h</td>
<td>2.0</td>
<td>-2.56</td>
<td>0.0002</td>
</tr>
<tr>
<td>+ 10 mg/kg BnorBNI at -3h</td>
<td>2.1</td>
<td>-2.55</td>
<td>0.0145</td>
</tr>
<tr>
<td>+ 10 mg/kg BnorBNI at -18h</td>
<td>9.0</td>
<td>1.73</td>
<td>n.s.</td>
</tr>
<tr>
<td>+ 10 mg/kg BnorBNI at -24h</td>
<td>4.4</td>
<td>-1.17</td>
<td>n.s.</td>
</tr>
<tr>
<td>+ 32 mg/kg BnorBNI at -24h</td>
<td>5.7</td>
<td>1.09</td>
<td>n.s.</td>
</tr>
<tr>
<td>+ 10 mg/kg BnorBNI at -48h</td>
<td>9.9</td>
<td>1.90</td>
<td>n.s.</td>
</tr>
<tr>
<td>+ norBNI vehicle at -1h</td>
<td>5.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ 10 mg/kg norBNI at -24h</td>
<td>8.1</td>
<td>1.47</td>
<td>n.s.</td>
</tr>
<tr>
<td>+ 32 mg/kg norBNI at -24h</td>
<td>22.7</td>
<td>4.12</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

$^a$ vehicle is 10% DMSO in normal saline

$^b$ n.s.: not significant; shift significance represents the significance of difference between vehicle and drug curves

Table 6 Effect of sc administered antagonists on the dose-effect curve of U69593 in the warm water tail withdrawal assay (U69593 administered sc)
<table>
<thead>
<tr>
<th>Treatment conditions</th>
<th>EC&lt;sub&gt;50&lt;/sub&gt; mg/kg</th>
<th>Fold shift</th>
<th>Shift significance p value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>U69593</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ vehicle at -1h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>+ 10 nmol BnorBNI at -1h</td>
<td>26.3</td>
<td>5.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+ 10 nmol BnorBNI at -24h</td>
<td>26.3</td>
<td>5.04</td>
<td>0.0003</td>
</tr>
<tr>
<td>+ 10 nmol BnorBNI at -48h</td>
<td>74.2</td>
<td>14.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+ 10 nmol BnorBNI at -168h</td>
<td>37.0</td>
<td>7.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+ 32 nmol BnorBNI at -24h</td>
<td>—&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>+ 10 nmol norBNI at -24h</td>
<td>31.8</td>
<td>6.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+ 32 nmol norBNI at -24h</td>
<td>—&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ 10 nmol BnorBNI at -1h</td>
<td>5.4</td>
<td>2.00</td>
<td>0.3415</td>
</tr>
<tr>
<td>SNC80&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ 10 nmol BnorBNI at -1h</td>
<td>4.6</td>
<td>-1.41</td>
<td>0.1563</td>
</tr>
</tbody>
</table>

<sup>a</sup> Shift significance represent the significance of difference between vehicle and drug curves;  
<sup>b</sup> Vehicle is 10% DMSO in normal saline; <sup>c</sup> EC<sub>50</sub> could not be calculated because the curve was shifted beyond the agonist dose range; <sup>d</sup> SNC80 was not a full agonist.

Table 7  Effect of centrally (icv) administered antagonists on the dose-effect curve in the warm water tail withdrawal assay (U69593 administered sc)

Subcutaneous administration of BnorBNI (152) (10 mg/kg) at pretreatment times up to 3 hours before U69593 administration sc produced a 2.5-fold shift to the left of the dose-response curve of the agonist, indicating an additive antinociceptive effect of 152 (Table 6). By 24 hours, no significant effect could be observed when 152 (10 or 32 mg/kg) was administered sc. This initial antinociceptive action of 152 could
be antagonised by the selective \(\mu\)-antagonist methocinnamox (M-CAM) as shown on figure 13 but not by norBNI (13) (data not shown), which suggests 152 is a \(\mu\)-agonist when administered sc. In contrast, 13 (32 mg/kg) administered icv 24 hrs before U69593 (sc) produced a 4.1-fold shift to the right of the dose-response curve of the agonist, reflecting an expected antagonist effect of the drug.

**Figure 13** Evaluation of agonist activity of 152 in the tail withdrawal assay

When BnorBNI (152) (10 nmol) was administered icv before administration sc of U69593, no antinociceptive effect was observed at any time (table 7) but instead 152 strongly antagonised the effect of U69593 with pretreatment times up to 168h (at this time, the shift was still 7-fold). After 1h pretreatment, administration (icv) of 152 (10 nmol) did not antagonise the effects of SNC80 and morphine (see table 7), which indicates 152 is a \(\kappa\)-antagonist when administered centrally. It is unclear why 152 did not exhibit any agonist activity when administered icv but it is noteworthy that similar contradicting observations were reported for 14-cinnamoylaminocodeinone, which displays potent \(\mu\)-agonism with high efficacy when administered sc, but is a \(\mu\)-antagonist devoid of any agonist effects when administered icv.\(^{182,183}\)

Finally, we investigated whether the introduction of a benzyl group at the pyrrolic site of norBNI (13) was sufficient to produce an irreversible antagonist. An irreversible antagonist reduces the number of available receptors, rendering the number of receptors insufficient for an agonist to produce maximum response;
therefore, an irreversible antagonist will flatten and shift to the right the dose-response curve of an agonist. As shown on figure 14, both 10 nmol and 32 nmol administrations icv of 152, 24 h before U69593 administration (sc), produced a flattening of the dose-response curve of the agonist, indicating a non-competitive interaction of 152 with κ-opioid receptors.

![Figure 14](image)

**Figure 14** Effect of 152 administration (icv) on the dose-response curve of U69593

The effect of equimolar administration (10 nmol, icv) of BnorBNI (152) and norBNI (13) was then compared (see figure 15); the pretreatment time was set at 24 h, since it represents the optimum time for 13 to be selective.

![Figure 15](image)

**Figure 15** Comparison of the effect of 13 and 152 (administered icv) on the dose-response curve of U69593 (administered sc)

Both compounds produced a rightward shift of the dose-response curve of U69593, with evidence of flattening of the U69593 dose-response curve observed upon administration of BnorBNI (152) but not of norBNI (13); however, irreversible
antagonism upon administration of 13 was observed when higher doses of 13 (32 nmol, icv) were used (not shown on figure 15, but this is reflected by the fact that the U69593 dose-response curve was shifted beyond the agonist dose range, see table 7).

In conclusion, benzylaition of the pyrrolic nitrogen of norBNI (13) has resulted in dramatic modification of the in-vivo pharmacological profile of the ligand; while 13 is a competitive \( \kappa \)-antagonist devoid of agonist effects when administered sc or icv, 152 is a partial \( \mu \)-agonist with short duration of action when administered sc and an irreversible \( \kappa \)-antagonist upon central administration. Moreover, in-vitro pharmacological evaluation of 235 and 233 has revealed that replacement of the CPM groups (at 17- and 17'-N) of 13 and 152 with methyl groups has resulted in lower \( \mu \)-agonist potency/increased \( \mu \)-agonist efficacy than that displayed by the parent ligands with concomitant huge decrease in \( \kappa \)-antagonist potency.

### 3.3 Guanidinyl substituted ligands (50) and (51)

\( p \)-HydroxybenzylGNTI (50) and \( m \)-hydroxybenzylGNTI (51) were evaluated in opioid binding assays and in the in-vitro stimulation of \( [\text{S}] \)GTP\( \gamma \)S binding assay; the results are reported in table 8 and table 9 respectively.

<table>
<thead>
<tr>
<th></th>
<th>( K_i ) (nM) (^{a,b} )</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \mu )</td>
<td>( \delta )</td>
</tr>
<tr>
<td>50</td>
<td>14.67 ± 3.65</td>
<td>41.86 ± 0.93</td>
</tr>
<tr>
<td>51</td>
<td>14.16 ± 4.11</td>
<td>17.58 ± 0.29</td>
</tr>
<tr>
<td>46</td>
<td>29.78 ± 0.50</td>
<td>82.05 ± 5.06</td>
</tr>
<tr>
<td>11</td>
<td>36.9 ± 2.3</td>
<td>70.0 ± 0.3</td>
</tr>
<tr>
<td>13(^c)</td>
<td>21.0 ± 5.0</td>
<td>5.7 ± 0.9</td>
</tr>
</tbody>
</table>

\(^a\) Values are from 2 separate experiments, each performed in triplicate
\(^b\) Radiolabeled ligands are \(^{3}\)H-DAMGO (for \( \mu \)), \(^{3}\)H-C1-DPDPE (for \( \delta \)) and \(^{3}\)H-U69593 (for \( \kappa \)).
\(^c\) Data are from reference 180

**Table 8** Binding affinities to cloned human opioid receptors transfected into Chinese hamster ovary (CHO) cells
In the binding assay, both 50 and 51 displayed modest affinity for the κ-receptor with poor κ/μ selectivity (less than 5-fold for both compounds) and κ/δ selectivity (13-fold for 50 and 6-fold for 51). In particular, the binding assay showed our efforts to recover κ-selectivity unsuccessful since both 50 and 51 exhibited lower κ-selectivity than that displayed by the pioneering ligand p-chlorobenzylGNTI (46) (45-fold κ/μ and 129-fold κ/δ selectivity). In comparison, norBNI (13) and GNTI (11), the two standard κ-antagonists, displayed much higher κ-selectivity than 50 and 51 in this assay (up to 60 times higher).

In the functional assay, both 50 and 51 failed to stimulate [35S]GTPγS binding for any type of opioid receptor (data not shown) and displayed potent and selective κ-antagonist effects (table 9).

![Table 9](image)

Table 9 Antagonist potency in [35S]GTPγS assays performed in cloned human opioid receptors

Interestingly, 50 exhibited a higher κ/μ selectivity than that observed with GNTI (11) (127- and 81-fold respectively) and higher κ/δ selectivity than that displayed by norBNI (13) (183- and 113-fold respectively). The κ-selectivity of 50 was about 4 or 5 times higher than that of the p-chlorobenzylGNTI analogue (46), which shows that substitution with a hydroxy group in p-position has successfully led to recovery of selectivity towards the κ-receptor. In contrast, 51 showed less substantial selectivity (33-fold κ/μ and κ/δ selectivity) and its κ-selectivity was
broadly similar to that observed with 46; these results thus appear to support the molecular modelling studies, which showed the superposition of the phenolic group of norBNI (13) and 50 to be much closer than that of norBNI (13) and 51. It is also noteworthy that the improved $\kappa$-selectivity observed with 50 did not result from enhanced $\kappa$-potency but was rather a consequence of decreased potency at $\mu$ and $\delta$-receptors due to the presence of the hydroxy group in $p$-position. Interestingly, this is in agreement with Thomas's earlier findings, who proposed that the oxygen atom of the second phenolic group of norBNI (13) might unfavourably interact with a group present in the lipophilic pocket of $\mu$ and $\delta$-receptors.104

Finally, 46, 50 and 51 failed to flatten the dose-response curve of the agonist U69593 (data not shown), which suggests they do not bind irreversibly towards the $\kappa$-receptor. It is interesting to note that, at the start of the present project, $p$-chlorobenzylGNTI (46) was believed to bind irreversibly towards the $\kappa$-receptor since its antagonist effects remained after washing the membranes (see figure 16). However, the irreversible character of 46 was not confirmed in further antagonist assays (data not shown), which suggests that wash-resistant binding does not represent a suitable criterion for assessment of irreversibility.

![Figure 16](image)  
**Figure 16**  Binding of [3H]diprenorphine in $\kappa$-membranes (CHO cells) that have been pretreated with naloxone or 46 and extensively washed
4. EXPERIMENTAL

Analytical specifications

All chemicals were purchased from Aldrich, Acros or Lancaster chemical companies. All solvents were GPR grade, purchased from Merck or Fisher Scientific.

Column chromatography was performed under gravity over silica gel 60 (35-70μm) purchased from Merck, except for compounds 136, 161, 163, 164 and 165, which were purified on a pre-packed column of silica gel 60 (10g, 30-90μm, purchased from International Sorbent Technology) using "Flash master personal" equipment ("anti-gravity" elution). Analytical TLC was performed using aluminium-backed plates coated with Kieselgel 60 F_{254}, purchased from Merck. The chromatograms were visualised using either UV light (UVGL-58, short wavelength), ninhydrin (acidic) or PMA.

Infrared spectroscopy was performed on a Perkin-Elmer RX 1 FT-IR Instrument. \( ^1H \) NMR and \( ^{13}C \) NMR spectra were recorded using either JEOL GX 270 (operating at 270 MHz for \( ^1H \) and 67.8 MHz for \( ^{13}C \)) or JEOL EX 400 (operating at 400 MHz for \( ^1H \) and 100.5 MHz for \( ^{13}C \)) spectrometers. Chemical shifts are expressed in ppm. Spectra were referenced internally using either tetramethylsilane as the standard or using the residual solvent resonance. Coupling constants (\( J \)) are reported in Hz and the multiplicities abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). In the particular cases of morphinan-derived compounds, only diagnostic peaks have been recorded for proton NMR. High and low resolution fast atom bombardment (FAB) mass spectra were carried out on a Fisons VG AutoSpec Q instrument, with a matrix of m-nitrobenzylalcohol. High and low resolution electron impact (EI) mass spectra were recorded using EI ionisation at 70eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. All mass spectra were recorded in positive mode. Melting points were evaluated using a Gallenkamp MFB-595 melting point apparatus or a Reichert-Jung hot stage microscope apparatus and are uncorrected.

Microanalyses were performed with a Perkin-Elmer 240C analyser and were recorded by the Microanalysis Laboratory in the Department of Chemistry, University of Bath.
General Procedure A – Guanidinylation of amine 53.
A solution of 53 (1 equi.), mercury(II) chloride (1.5 equi.) and freshly distilled triethylamine (2 equi.) in anhydrous N,N-dimethylformamide (DMF) (15 mL) was cooled to 0°C under a nitrogen atmosphere. A solution of the guanidinylating agent (2 equi.) in anhydrous DMF (5 mL) was added and the mixture allowed to warm to room temperature. Stirring was continued at 60°C for 24 h, after which the reaction mixture was filtered through a short column of celite, eluting with acetate. Sodium bicarbonate (30 mL) was then added, the organic phase isolated and the aqueous phase further extracted with ethyl acetate. The organic phases were combined, washed with water and brine, dried over magnesium sulfate (MgSO₄) and concentrated. Purification by silica gel column chromatography, eluting first with dichloromethane (DCM) until removal of unreacted guanidinylating agent, then with DCM/MeOH/NH₂OH: 250/10/1, afforded the desired product.

A solution of 1,3-bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (54) (1 equi.), sodium hydride (3 equi.) and crown ether (18-crown-6 or 15-crown-5, 0.1 equi.) in dry tetrahydrofuran (THF) or DMF (5 mL) was cooled to 0°C under a nitrogen atmosphere. Stirring was continued for 20 minutes at that temperature before adding the appropriate benzyl bromide derivative (2 equi.). The reaction mixture was then allowed to warm to room temperature and stirring continued for 22-41 hours at 70°C. The reaction was quenched by slow addition of water (5 mL), the organic phase isolated and the aqueous phase further extracted with diethyl ether. The combined organic phases were washed with water and dried (MgSO₄). The crude product was purified by column chromatography, eluting first with dichloromethane (DCM) until removal of unreacted guanidinylating agent, then with DCM/MeOH/NH₂OH: 250/10/1, afforded the desired product.

General Procedure C – Mono-BOC-protection of diamines.
To a solution of the diamine (1 equi.) in chloroform (CHCl₃) (100 mL) at 0°C was added dropwise a solution of di-tert-butyl-dicarbonate (0.1 equi.) in CHCl₃ (45 mL). The ice bath was removed and stirring continued at room temperature for 24 hours. Brine (25 mL) was added, the organic phase isolated and the aqueous phase further
extracted with diethyl ether. The organic phases were combined, dried (MgSO₄) and concentrated. Purification by silica gel column chromatography, eluting with DCM/MeOH/NH₄OH: 85/10/5, afforded the protected diamine.

**General Procedure D – Preparation of isothiocyanates from primary amines.**

To a solution of the primary amine (1 equi.) in CHCl₃ (50 mL) was added a solution of calcium carbonate (1 equi.) in water (4 mL). The mixture was stirred for 5 minutes at room temperature before adding thiophosgene (2 equi.) and stirring continued for a further 24 hours. The organic phase was isolated, washed with water, dried (MgSO₄) and concentrated. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 3/1, afforded the desired isothiocyanate.

**General Procedure E – Preparation of N,N'-disubstituted thioureas from isothiocyanates.**

To a solution of the isothiocyanate (1 equi.) in acetone (30 mL) was added dropwise NH₄OH (concentrated aqueous solution, 10 equi.). The solution was stirred at room temperature for 24 hours, after which the solvents were removed under vacuum. Purification by silica gel column chromatography, eluting first with n-hexanes/ethyl acetate: 3/1 then with n-hexanes/ethyl acetate: 1/1, afforded the desired product.

**General Procedure F – BOC-Protection of N,N'-disubstituted thioureas.**

A solution of the dissubstituted thiourea (1 equi.) and sodium hydride (2 equi.) in dry THF (90 mL) was stirred for 10 min at 0°C under a nitrogen atmosphere. A solution of di-tert-butyl-dicarbonate (2 equi.) in THF (20 mL) was then added, the ice bath removed and stirring continued overnight at room temperature. The reaction was quenched by addition of NaOH (aqueous solution, 0.1 M) and the mixture stirred for a further 20 min. The organic layer was isolated and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried (MgSO₄) and concentrated. Purification by silica gel column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, afforded a mixture of mono and di-BOC-protected N,N'-disubstituted thioureas.
General procedure G – TBDMS-Protection of benzyl alcohols.
To a solution of imidazole (2 equi.) and tert-butyldimethylsilyl chloride (1.5 equi.) in dry THF (20 mL) under a nitrogen atmosphere was added slowly a solution of the alcohol (1 equi.) in dry THF (10 mL). The reaction mixture was stirred overnight at room temperature, then water was added (5mL) and the reaction mixture extracted three times with diethylether. The organic phase was dried (MgSO₄) and the solvent evaporated. The crude oil was then taken up in n-hexanes and filtration of the solid – washing with n-hexanes– afforded the protected alcohol. If no precipitation was observed, the crude oil was purified by column chromatography, eluting with n-hexanes/ethyl acetate: 10/1.

General procedure H – Phthalimido-protection of primary amines.
A solution of the primary amine (1 equi.) and phthalic anhydride (1 equi.) in mixed xylenes was refluxed overnight under a nitrogen atmosphere. The reaction mixture was then cooled to room temperature and water was added. The aqueous phase was extracted several times with CHCl₃, the organic phase was dried (MgSO₄) and the solvent evaporated. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 6/1, afforded the desired phthalimide.

General procedure I – N-Benzylation or N-alkylation of pyrrolic or indolic nitrogen.
To a solution of 13 (or other pyrrole or indole derivative) (1 equi.) in dry THF or DMF (5 mL) under a nitrogen atmosphere were added sodium hydride (60% in oil, 4 equi.) and 18-crown-6 (0.1 equi.). This mixture was stirred for 20 minutes at room temperature before adding a solution of the appropriate benzyl bromide (3 equi.) in dry THF or DMF (2 mL) and stirring continued overnight at 70°C. The reaction was quenched with water (5 mL), the aqueous phase extracted several times with DCM/MeOH: 5/1, the organic phase dried (MgSO₄) and the solvent evaporated. The crude oil was purified by column chromatography, eluting with CHCl₃ until complete removal of unreacted benzyl bromide derivative, then with gradient elution (CHCl₃/MeOH/ NH₄OH: 900/10/1 to CHCl₃/MeOH/NH₄OH: 200/10/1), which afforded the desired product.
General procedure J – Preparation of $\alpha,\alpha'$-phthallimidobromoxylenes.
A mixture of dibromoxylene (1 equi.), potassium phthalimide (1 equi.) and 18-crown-6 (0.1 equi.) in toluene (30 mL) was refluxed overnight under a nitrogen atmosphere. Water was then added, the organic phase isolated, dried (MgSO$_4$) and evaporated. Purification by flash chromatography, eluting with $n$-hexanes/ethyl acetate: 4/1, afforded the desired product.

General procedure K – Preparation of pyrroles from morphinan-6-ones.
A solution of morphinan-6-one (1 equi.) in anhydrous DMF (0.1 M) was heated to 100°C under a nitrogen atmosphere. A solution of hydrazine sulfate (ground into a thin powder, 0.53 equi.) in DMF was added to the solution. The mixture was stirred for 6 hours at 100°C, then cooled to room temperature and the solvent evaporated under vacuum. The residue was dissolved in dry dimethylsulfoxide (DMSO) (0.25 M) and a solution of methanesulfonic acid (0.50 equi.) in dry DMSO (0.6 M) was added. The mixture was stirred at 130°C under a nitrogen atmosphere for 3.5 hours. The solution was then cooled to room temperature, diluted with water (10 mL) and basified to pH = 10 with NH$_4$OH. The solution was extracted with DCM/MeOH:5/1, the organic phase was washed with brine and dried (MgSO$_4$). The solvent was removed by evaporation, yielding a dark brown oil that was purified by column chromatography (gradient elution, 100% DCM then DCM/MeOH/NH$_4$OH: 400/10/1 to DCM/MeOH/NH$_4$OH: 110/10/1).

General procedure L – Conversion of benzyl alcohols into benzyl bromides.
Bromine (1.2 equi.) was added dropwise to a solution of triphenylphosphine (1.2 equi.) and imidazole (1.2 equi.) in dry DCM (20 mL) under a nitrogen atmosphere and stirring continued at room temperature for a further 20 minutes. A solution of the benzyl alcohol (1 equi.) in dry DCM (5mL) was added dropwise and the reaction mixture stirred at room temperature until completion. The solvent was then evaporated and the crude product purified by column chromatography eluting with $n$-hexanes/ethyl acetate: 3/1.
General procedure M – Reduction of benzaldehydes.
A solution of the benzaldehyde (2 equi.) in dry THF (10 mL) was added dropwise to a suspension of sodium borohydride (1 equi.) in dry THF (10 mL) and the reaction mixture was stirred overnight at room temperature. Water (4 mL) and a diluted solution of acetic acid (2.5 mL) were then added, the organic phase isolated and the aqueous phase further extracted with diethyl ether (2x25 mL). The organic phases were combined, washed first with a solution of sodium hydrogencarbonate (2x10 mL) then with water (2x10 mL) and dried (MgSO₄). The solvent was evaporated and the product used without any further purification.

General procedure N – Preparation of isothiocyanates from primary amines in the morphinan series.
To a solution of the amine (1 equi.) in CHCl₃ (2 mL) was added a solution of sodium hydrogencarbonate (6 equi.) in water (0.7 mL). The mixture was stirred for 20 minutes before adding freshly distilled thiophosgene (1.1 equi.) and stirring continued for a further 2 hours. The organic phase was isolated and the aqueous phase extracted with CHCl₃. The organic phase was then dried (MgSO₄) and concentrated under vacuum. Purification of the crude product was performed on silica gel (10 g) using “Flash master personal” equipment and eluting under pressure and against gravity, first with 100% CHCl₃ then with gradient elution (CHCl₃/MeOH: 300/5 to CHCl₃/MeOH: 300/8).

General procedure O – Deprotection of phthalimides.
The protected amine (1 equi.) was dissolved in ethanol (1 mL) and the solution was warmed up when necessary till complete dissolution of the material. Hydrazine hydrate (3 to 5 equi.) was added and the reaction mixture was stirred till complete deprotection (16 to 48 hours). The solvent was then removed under vacuum and the crude product purified by column chromatography, eluting first with CHCl₃/MeOH/NH₄OH: 500/10/1, then with CHCl₃/MeOH/NH₄OH: 250/10/1.

General procedure P – Deprotection of BOC groups with trifluoroacetic acid.
The mixture of mono- and di-BOC-protected morphinans was dissolved in DCM (3 mL) and the solution was cooled to 0°C. Trifluoroacetic acid (2 mL) was added and
the solution stirred for a further 30 minutes at 0°C. The ice bath was then removed and stirring continued overnight at room temperature. After evaporation under vacuum, the oil was precipitated with diethyl ether and the solid washed several times with diethyl ether.

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'- (imino) [7,7'-bimorphinan]-3,3',14,14'-tetrol (norbinaltorphimine) (13)

Naltrexone hydrochloride (1.00 g, 2.65 mmol), hydrazine sulfate (0.18 g, 1.41 mmol) and methanesulfonic acid (0.08 mL, 1.31 mmol) were reacted according to the general procedure K. 13 was isolated as a brown solid (0.54 g, 62%).

IR \( \nu_{\text{max}} / \text{cm}^{-1} \) (KBr): 3382 (br, bonded OH), 3075 and 3001 (C-H aromatic); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 0.12 (m, 4H, 2\( \times \)NCH\(_2\)CH(CH\(_3\)CH\(=\)CH\)), 0.52 (m, 4H, 2\( \times \)NCH\(_2\)CH(CH\(=\)CH\(=\)CH\)), 0.79-0.88 (m, 2H, 2\( \times \)NCH\(_2\)CH(CH\(_3\)CH\(_3\))), 5.69 (s, 2H, 5-H + 5'-H), 6.49 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.66 (d, 2H, J=8.2 Hz, 2-H + 2'-H); \(^{13}\)C NMR (100.5 MHz, CDCl\(_3\)): 4.27 (2\( \times \)NCH\(_2\)CH(CH\(_3\)CH\(_3\))), 4.54 (2\( \times \)NCH\(_2\)CH(CH\(_3\)CH\(_3\))), 9.87 (2\( \times \)NCH\(_2\)CH(CH\(_3\)CH\(_3\))), 23.50 (10-C + 10'-C), 29.27 (8-C + 8'-C), 31.77 (15-C + 15'-C), 44.08 (16-C + 16'-C), 50.60 (13-C + 13'-C), 59.70 (18-C + 18'-C), 62.56 (9-C + 9'-C), 73.34 (14-C + 14'-C), 85.80 (5-C + 5'-C), 116.20 (7-C + 7'-C), 117.76 (2-C + 2'-C), 119.10 (1-C + 1'-C), 124.98 (C), 125.27 (C), 130.80 (12-C + 12'-C), 139.32 (3-C + 3'-C), 143.08 (4-C + 4'-C); MS (FAB): \( m/z = 662 \) (M+H); C\(_{40}\)H\(_{43}\)N\(_3\)O\(_6\) requires 661; mp > 240°C

17-Cyclopropylmethyl-6,7-didehydro-4,5\( \alpha \)-epoxy-5\( \alpha \)-(N\( \alpha \)-4-hydroxybenzyl) guanidinyl-3,14-dihydroxyindolo [2\( \alpha \),3\( \alpha \):6,7]-morphinan (50)

68 (mixture of mono- and di-BOC protected derivatives) (90 mg, 0.10 mmol) was dissolved in a mixture of conc. HCl/MeOH (2.5 mL/2.5 mL) and the solution stirred overnight at room temperature. The solvents were then removed under vacuum, the solid washed several times with diethyl ether and dried under vacuum for several days. 50 (HCl salt) (0.058 g, 97%) was isolated as a brown solid.

IR \( \nu_{\text{max}} / \text{cm}^{-1} \) (KBr): 3363-3234 (br, bonded OH and bonded NH), 1637 (C=N, NH and NH\(_2\)); \(^1\)H NMR (400 MHz, CD\(_3\)OD): 0.48-0.62 (m, 2H, NCH\(_2\)CH(CH\(=\)CHCH\(_=\)CH)), 0.72-
0.93 (m, 2H, NCH₂(CH₂CH₂)), 1.12-1.22 (m, 1H, NCH₂CH₂CH₂)), 4.26 (s, 2H, CH₂), 5.72 (s, 1H, 5-H), 6.64 (d, 1H, J=8.0 Hz, 1-H), 6.68 (d, 1H, J=8.0 Hz, 2-H), 6.94-7.03 (m, 2H, Ar), 7.22-7.50 (m, 5H, Ar); ¹³C NMR (100.5 MHz, CD₃OD): 2.59 (NCH₂(CH₂CH₂)), 5.50 (NCH₂CH₂CH₂)), 6.05 (NCH₂CH₂CH₂)), 24.22 (10-C), 28.75 (CH₂), 29.32 (CH₂), 46.60 (CH₂), 46.97 (CH₂), 48.88 (13-C), 57.88 (18-C), 62.49 (9-C), 72.58 (14-C), 83.78 (5-C), 108.98 (Ar), 112.69 (Ar), 113.55 (Ar), 115.08 (Ar), 116.96 (Ar), 118.17 (Ar), 119.59 (Ar), 120.99 (Ar), 121.53 (Ar), 125.62 (Ar), 127.28 (Ar), 129.08 (Ar), 129.58 (Ar), 131.29 (Ar), 136.92 (Ar), 140.82 (Ar), 143.51 (Ar), 155.44 (Ar), 157.40 (NCNN); MS (FAB): m/z = 578.2743 (M+H); C₃₄H₃₆O₄N₅ requires 578.2767; Anal. (C₃₄H₃₅O₄N₅:2HCl:2H₂O) requires C 56.47 %, H 5.85 %, N 9.68 %, found : C 56.20 %, H 6.01 %, N 9.28 %; mp > 250°C

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-(Nα-3-hydroxybenzyl)guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (51)

69 (mixture of mono- and di-BOC protected derivatives) (78 mg, 0.09 mmol) was dissolved in a mixture of conc. HCl/MeOH (2.5 mL/2.5 mL). A similar workup as used for the synthesis of 50 afforded 51 (HCl salt) as a brown solid (51 mg, 98%).

IR ν_max/cm⁻¹ (KBr): 3348-3231 (br, bonded OH and bonded NH), 1637 (C=N, NH and NH₂); ¹H NMR (400 MHz, CD₃OD): 0.46-0.62 (m, 2H, NCH₂CH(CH₂CH₂)), 0.69-0.95 (m, 2H, NCH₂CH(CH₂CH₂)), 1.08-1.21 (m, 1H, NCH₂CH(CH₂CH₂)), 4.42 (s, 2H, CH₂), 5.70 (s, 1H, 5-H), 6.61-6.84 (m, 5H, Ar), 6.96 (d, 1H, J=8.4 Hz, Ar), 7.18 (t, 1H, J=8.4 Hz, Ar), 7.28-7.34 (m, 1H, Ar), 7.38-7.52 (m, 1H, Ar); ¹³C NMR (67.8 MHz, CD₃OD): 4.25 (NCH₂(CH₂CH₂)), 7.11 (NCH₂CH₂CH₂)), 7.69 (NCH₂CH₂CH₂)), 25.89 (10-C), 30.44 (CH₂), 31.01 (CH₂), 46.72 (CH₂), 48.29 (CH₂), 48.73 (13-C), 59.08 (18-C), 64.29 (9-C), 74.40 (14-C), 85.60 (5-C), 110.91 (Ar), 114.67 (Ar), 115.81 (Ar), 116.61 (Ar), 118.96 (Ar), 120.05 (Ar), 120.12 (Ar), 121.54 (Ar), 123.04 (Ar), 123.50 (Ar), 127.55 (Ar), 129.24 (Ar), 131.03 (Ar), 131.70 (Ar), 132.22 (Ar), 138.86 (Ar), 139.96 (Ar), 142.77 (Ar), 145.49 (Ar), 158.38 (Ar), 159.74 (NCNN); MS (FAB): m/z = 578.2748 (M+H); C₃₄H₃₅O₄N₅:3HCl:2H₂O requires 578.2767; Anal. (C₃₄H₃₅O₄N₅:3HCl:2H₂O) requires C 56.47 %, H 5.85 %, N 9.68 %, found : C 56.80 %, H 5.96 %, N 10.10 %; mp > 250°C
17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-\(N^\prime\)-4-methoxybenzyl
guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (52)

73 (0.67 g, 1.62 mmol), 53 (0.35 g, 0.81 mmol), mercury(II) chloride (0.24 g, 1.34
mmol) and triethylamine (0.23 mL, 1.62 mmol) in DMF (18 mL) were reacted
according to the general procedure A. A mixture containing the desired product 74
and the mono-BOC protected analogue was obtained as a brown solid (0.31 g, 48 %).

No NMR data available as the product collected was a mixture containing 74 and its
mono-BOC protected derivative. MS (FAB): \(m/z = 692\) (M+H, one BOC), 792 (M+H,
two BOC); mono-BOC protected product: \(C_{40}H_{45}N_5O_6\) requires 691; di-BOC
protected product: \(C_{45}H_{53}N_5O_8\) requires 791

A solution of the above mixture (0.15 g, 0.19 mmol) in DCM (3 mL) was treated with
trifluoroacetic acid (2 mL) as described in the general procedure P and 52 (TFA salt)
was isolated as a brown solid (0.17 g, 96%).

IR \(\nu_{\text{max}}\)/cm (KBr): 3200 (br, bonded OH and NH), 1678, 1643 (C=\(N\), NH and NH2);
\(^1\)H NMR (270 MHz, CD\(_3\)OD): 0.43 (d, 2H, \(J=4.9\) Hz, NCH\(_2\)CH(CH\(_2\)CH(HH))), 0.63-
0.80 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH(HH))), 1.01-1.09 (m, 1H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 3.67 (s,
3H, CH\(_3\)), 4.28 (s, 2H, CH\(_2\)), 5.61 (s, 1H, 5-H), 6.53-6.61 (m, 2H, 1-H and 2-H), 6.79-
6.90 (m, 3H, Ar), 6.74-7.21 (m, 3H, Ar), 7.31-7.34 (m, 3H, Ar); \(^{13}\)C NMR (67.8 MHz,
CD\(_3\)OD): 3.34 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 6.17 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 6.73
(NCH\(_2\)CH\(_2\)) (CH\(_2\)CH\(_2\)), 24.95 (10-C), 29.59 (CH\(_2\)), 30.11 (CH\(_2\)), 45.55 (CH\(_2\)), 47.46
(CH\(_2\)), 55.72 (CH\(_2\)), 58.87 (18-C), 63.56 (9-C), 73.51 (14-C), 84.78 (5-C), 110.00 (C),
113.80 (CH), 115.19 (CH), 118.08 (CH), 119.33 (CH), 120.60 (CH), 122.25 (CH),
122.48 (C), 126.83 (C), 128.42 (C), 129.46 (C), 129.68 (CH), 130.15 (C), 132.40 (C),
138.08 (C), 142.01 (C), 144.70 (C), 157.47 (C), 160.80 (CN); MS (FAB): \(m/z =
592.2895\) (M+H), \(C_{35}H_{38}N_5O_4\) requires 592.2923; Anal. (\(C_{35}H_{38}N_5O_4\cdot3\)TFA) requires
C 52.73 %, H 4.32 %, N 7.50 %, found : C 52.50 %, H 4.79 %, N 7.96; mp > 220°
5'-Amino-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14-dihydroxyindolo[2',3':6,7]-morphinan (53) 106

Method A
To a solution of 56 (1.08 g, 2.38 mmol) in methanol (15 mL) were added 2 spatula of Raney nickel. The mixture was stirred at room temperature under a nitrogen atmosphere for 10 minutes, after which hydrazine hydrate (2.3 mL, 47.3 mmol) was slowly added and stirring continued at 55°C for a further 6 hours. The mixture was then filtered through a short column of celite, concentrated and purified by column chromatography, eluting with DCM/MeOH/NH₄OH: 110/10/1. 53 was isolated as a brown solid (0.47 g, 47%).

Method B
A solution of 56 (2.50 g, 5.5 mmol) and iron(II)sulfate heptahydrate (13.62 g, 49.0 mmol) in methanol (120 mL), water (24 mL) and NH₄OH (84 mL) was stirred at 80°C for 3 hours. The reaction mixture was then allowed to cool to room temperature, filtered and extracted, first with DCM then with DCM/MeOH: 5/1. The organic phase was dried (MgSO₄), concentrated under vacuum and the crude oil purified by column chromatography, eluting first with CHCl₃ then with CHCl₃/MeOH/NH₄OH: 250/10/1. 39 was isolated as a brown solid (1.31 g, 56%).

1H NMR (270 MHz, CD₃OD): 0.32-0.38 (m, 2H, NCH₂CH(CHCH₂H)), 0.65-0.76 (m, 2H, NCH₂CH(CHCH₂H)), 0.91-1.02 (m, 1H, NCH₂CH(CH₂CH₂)), 5.74 (s, 1H, 5-H), 6.54 (d, 1H, J=8.3 Hz, 1-H), 6.70 (d, 1H, J=8.3 Hz, 2-H), 7.29 (m, 1H, 7'-H), 7.98 (m, 1H, 6'-H), 8.37 (m, 1H, 4'-H); 13C NMR (67.8 MHz, CD₃OD): 3.42 (NCH₂CH(CH₂CH₂)), 3.89 (NCH₂CH(CH₂CH₂)), 8.63 (NCH₂CH(CH₂CH₂)), 23.31 (10-C), 28.26 (CH₂), 30.64 (CH₂), 43.81 (16-C), 47.28 (13-C), 58.47 (18-C), 62.17 (9-C), 72.48 (14-C), 84.65 (5-C), 104.02 (Ar), 109.23 (Ar), 111.83 (Ar), 113.67 (Ar), 117.01 (Ar), 118.41 (Ar), 124.08 (Ar), 126.48 (Ar), 129.13 (Ar), 130.35 (Ar), 132.61 (Ar), 137.05 (Ar), 139.42 (Ar), 143.10 (Ar); MS (FAB): m/z = 430 (M); C₂₆H₂₈N₃O₃ requires 430; Rₜ (DCM/MeOH/NH₄OH: 110/10/1): 0.33
A solution of naltrexone (3.00 g, 8.8 mmol) and 4-nitrophenylhydrazine (1.61 g, 10.5 mmol) in ethanol/conc. HCl (45 mL/45 mL) was refluxed for 24 h under a nitrogen atmosphere. The solvents were then removed under vacuum and the residue basified to pH = 10 with NH₄OH. The solution was extracted with DCM, the organic phase was dried (MgSO₄) and the solvent removed by evaporation. The dark residue was purified by column chromatography, eluting first with 100% DCM, then with DCM/MeOH/NH₂OH: 300/10/1. 56 was isolated as a brown solid (1.07 g, 26%).

IR \( \nu_{\text{max}}/\text{cm} \) (KBr): 3391 (br, bonded OH and bonded NH), 1156 (C-N); \(^1\)H NMR (270 MHz, CDCl₃): 0.10-0.26 (m, 2H, NCH₂CH(CH₂CH₂)), 0.48-0.61 (m, 2H, NCH₂CH(CH₂CH₂)), 0.86-1.03 (m, 1H, NCH₂CH(CH₂CH₂)), 5.50 (s, 1H, 5-H), 6.45-6.52 (m, 2H, 1-H and 2-H), 7.10-7.18 (m, 1H, Ar), 7.20-7.29 (m, 2H, Ar); \(^1^3\)C NMR (67.8 MHz, CDCl₃): 4.08 (NCH₂CH(CH₂CH₂)), 4.14 (NCH₂CH(CH₂CH₂)), 9.28 (NCH₂CH(CH₂CH₂)), 23.24 (10-C), 27.94 (CH₂), 31.28 (CH₂), 43.51 (16-C), 48.12 (13-C), 59.23 (18-C), 62.08 (9-C), 72.49 (14-C), 84.36 (5-C), 110.08 (Ar), 113.59 (Ar), 114.97 (Ar), 116.87 (Ar), 117.83 (Ar), 119.97 (Ar), 124.72 (Ar), 125.86 (Ar), 130.28 (Ar), 131.87 (Ar), 139.36 (Ar), 139.84 (Ar), 143.02 (Ar); MS (FAB): \( m/z = 460 \) (M); C\(_{26}\)H\(_{26}\)N\(_3\)O\(_5\) requires 460; \( R_f \) (DCM/MeOH/NH₂OH: 89/10/1): 0.54; mp > 230°C (lit.: >230°C)

4-(Benzyloxy)benzyl bromide (60) \(^{184,185}\)

Triphenylphosphine (1.57 g, 6.0 mmol), imidazole (0.408 g, 6.0 mmol), bromine (0.31 mL, 6.0 mmol) and 66 (1.07 g, 5.0 mmol) in dry DCM (25mL) were reacted according to general procedure L. 60 was obtained as a white solid after purification by column chromatography (1.29 g, 93%).

IR \( \nu_{\text{max}}/\text{cm} \) (neat): 3064 and 3030 (C-H aromatic); \(^1\)H NMR (400 MHz, CDCl₃): 4.50 (s, 2H, CH₂Br), 5.06 (s, 2H, CH₂), 6.92-6.96 (m, 2H, Ar), 7.25-7.44 (m, 7H, Ar); \(^1^3\)C NMR (100.5 MHz, CDCl₃): 34.01 (CH₂Br), 70.02 (CH₂O), 114.97 (CH), 127.31 (CH), 127.91 (CH), 128.48 (CH), 130.03 (C), 130.31 (CH), 136.49 (C), 158.61 (C); \( R_f \) (n-hexanes/ethyl acetate: 1/1): 0.93; mp : 82°C (lit.: 78-82°C) \(^{184}\)
3-(Benzyloxy)benzyl bromide (61)\textsuperscript{184,186}

Triphenylphosphine (3.51 g, 13.4 mmol), imidazole (0.91 g, 13.4 mmol), bromine (0.69 mL, 13.4 mmol) and 67 (2.39 g, 11.2 mmol) in dry DCM (15mL) were reacted according to general procedure L. 61 was obtained as a colourless solid after purification by column chromatography (2.73 g, 88%).

IR $\nu_{\text{max}}$/cm (neat): 3063 and 3032 (C-H aromatic); $^1$H NMR (400 MHz, CDCl$_3$): 4.47 (s, 2H, CH$_2$Br), 5.07 (s, 2H, CH$_2$), 6.90-6.93 (m, 1H, Ar), 6.99-7.03 (m, 2H, Ar), 7.24-7.46 (m, 6H, Ar); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 33.56 (CH$_2$Br), 69.99 (CH$_2$O), 114.82 (CH), 115.29 (CH), 121.42 (CH), 127.38 (CH), 127.90 (CH), 128.46 (CH), 129.70 (CH), 136.52 (C), 138.99 (C), 158.71 (C); MS (FAB): $m/z = 276$ (M, $^{79}$Br), 277 (M+H, $^{79}$Br), 278 (M, $^{81}$Br), 279 (M+H, $^{81}$Br); C$_{14}$H$_{13}$OBr requires 277; R$_f$ (n-hexanes/ethyl acetate: 1/1): 0.93; mp : 37°C (lit.: 37-39°C)\textsuperscript{186}

1,3-Bis-\textit{tert}-butoxycarbonyl-1-(4'-benzyloxybenzyl)-2-methyl-2-thiopseudourea (62)

1,3-Bis-\textit{tert}-butoxycarbonyl-2-methyl-2-thiopseudourea (0.79 g, 2.7 mmol), sodium hydride (60% in oil, 0.13 g, 3.3 mmol) and 60 (0.83 g, 3.0 mmol) in dry DMF (11 mL) were reacted according to the procedure B. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 9/2, afforded 62 as a very viscous colourless oil (0.91 g, 62%).

IR $\nu_{\text{max}}$/cm (neat): 2978, 2932 (C-H aromatic), 1742 (carbamate), 1715 (C=N), 1612 (carbamate), 1153 (C-N); $^1$H NMR (270MHz, CDCl$_3$): 1.42 (s, 9H, C(CH$_3$)$_3$), 1.53 (s, 9H, C(CH$_3$)$_3$), 2.27 (s, 3H, SCH$_3$), 4.72 (s, 2H, CH$_2$N), 5.05 (s, 2H, CH$_2$O), 6.91-6.96 (d, 2H, $J$=8.4 Hz, Ar), 7.25-7.43 (m, 7H, Ar); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 15.53 (SCH$_3$), 27.95 (2xC(CH$_3$)$_3$), 51.79 (CH$_2$N), 69.92 (CH$_2$O), 81.71 (C(CH$_3$)$_3$), 82.56 (C(CH$_3$)$_3$), 114.63 (CH), 127.44 (CH), 127.89 (CH), 128.50 (CH), 129.31 (CH), 129.65 (C), 136.89 (C), 152.17 (C), 157.99 (CO), 158.15 (CO), 163.40 (CN); MS (FAB): $m/z = 487$ (M+H); C$_{28}$H$_{34}$N$_2$O$_5$S requires 486; R$_f$ (n-hexanes/ethyl acetate: 9/2): 0.47
1,3-Bis-tert-butoxycarbonyl-1-(3'-benzyloxybenzyl)-2-methyl-2-thiopseudourea (63)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (0.29 g, 1.01 mmol), sodium hydride (60% in oil, 48 mg, 1.21 mmol) and 61 (0.31 g, 1.11 mmol) in dry DMF (5 mL) were reacted according to the procedure B. After purification by column chromatography, eluting with n-hexanes/ethyl acetate: 9/2, 63 was isolated as a very viscous colourless oil (0.29 g, 54%).

IR $\nu_{\max}$/cm (neat): 2978, 2931 (C-H aromatic), 1721 (br, C=N), 1611 (carbamate), 1140 (C-N); $^1$H NMR (400 MHz, CDCl$_3$): 1.39 (s, 9H, C(CH$_3$)$_3$), 1.52 (s, 9H, C(CH$_3$)$_3$), 2.28 (s, 3H, SCH$_3$), 4.76 (s, 2H, CH$_2$N), 5.06 (s, 2H, CH$_2$O), 6.94 (m, 2H, Ar), 7.01 (s, 1H, 2-H), 7.21-7.26 (m, 2H, Ar), 7.29-7.44 (m, 5H, Ar); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 15.72 (SCH$_3$), 28.04 (C(CH$_3$)$_3$), 28.13 (C(CH$_3$)$_3$), 52.40 (CH$_2$N), 69.84 (CH$_2$O), 81.65 (C(CH$_3$)$_3$), 82.71 (C(CH$_3$)$_3$), 113.63 (CH), 114.08 (CH), 120.05 (CH), 127.32 (CH), 127.74 (CH), 128.38 (CH), 129.25 (CH), 136.82 (C), 138.83 (C), 151.66 (3-C), 157.71 (CO), 158.63 (CO), 163.08 (CN); Rf (n-hexanes/ethyl acetate: 9/2): 0.52

4-(Benzyloxy)benzaldehyde (64) $^{187,188}$

To a solution of 4-hydroxybenzaldehyde (1.22 g, 10.0 mmol) and anhydrous potassium carbonate (2.07 g, 15.0 mmol) in dry DMF (5mL) was added dropwise a solution of benzyl bromide (1.71 g, 1.2 mL, 10.0 mmol) in dry DMF (1mL). The mixture was stirred overnight at room temperature under a nitrogen atmosphere. Water (3 mL) was then added and the solution extracted with diethyl ether (2x25 mL). The organic phase was washed with water (2x10 mL), dried (MgSO$_4$) and the solvent removed by evaporation. 64 was isolated as a white solid and used without any further purification (1.94 g, 91%).

IR $\nu_{\max}$/cm (KBr): 3034 and 3071 (C-H aromatic), 2810 and 2727 (C-H aldehyde), 1694 (CO); $^1$H NMR (400 MHz, CDCl$_3$): 5.15 (s, 2H, CH$_2$), 7.07 (d, 2H, $J$=8.6 Hz), 7.32-7.45 (m, 5H, Ph), 7.83 (d, 2H, $J$=8.6 Hz), 9.89 (s, 1H, CHO); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 70.25 (CH$_2$O), 115.01 (CH), 127.34 (CH), 128.19 (CH), 128.58 (CH), 129.93 (C), 131.84 (CH), 135.74 (C), 163.47 (C), 190.51 (CO); MS (FAB): $m/z$ = 213
3-(Benzyloxy)benzaldehyde (65) \(^{188,189}\)

3-Hydroxybenzaldehyde (1.22 g, 10.0 mmol), anhydrous potassium carbonate (2.07 g, 15.0 mmol) and benzyl bromide (1.71 g, 1.2 mL, 10.0 mmol) in dry DMF were reacted as for the synthesis of 64. 65 was isolated as a white solid and used without any further purification (2.02 g, 95 %).

IR \(v_{\text{max}}/\text{cm} (\text{KBr}): 3024\) and 3055 (C-H aromatic), 2829 and 2744 (C-H aldehyde), 1686 (CO); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 5.13 (s, 2H, CH\(_2\)), 7.26 (m, 1H), 7.33-7.49 (m, 8H), 9.97 (s, 1H, CHO); \(^{13}\)C NMR (100.5 MHz, CDCl\(_3\)): 70.19 (CH\(_2\)O), 113.07 (CH), 122.06 (CH), 123.56 (CH), 127.39 (CH), 128.06 (CH), 128.52 (CH), 129.96 (CH), 136.10 (C), 137.61 (C), 159.05 (C), 191.79 (CO); MS (FAB): \(m/z = 213\) (M+H); \(C_{14}H_{12}O_2\) requires 212; \(R_f\) (n-hexanes/ethyl acetate: 1/1): 0.87; mp : 65 °C (lit.: 67-68°C)\(^{188}\)

4-(Benzyloxy)benzyl alcohol (66) \(^{185,187}\)

Sodium borohydride (0.38 g, 5.0 mmol) and 64 (2.12 g, 10.0 mmol) in dry THF (20 mL) were reacted according to the general procedure M. 66 was isolated as a white solid (2.0 g, 93 %).

IR \(v_{\text{max}}/\text{cm} (\text{KBr}): 3329\) (br, bonded OH), 3060 and 3034 (C-H aromatic); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 4.49 (s, 2H, CH\(_2\)OH), 5.05 (s, 2H, CH\(_2\)), 6.93 (d, 2H, \(J=8.4\) Hz, Ar), 7.25-7.45 (m, 7H, Ar); \(^{13}\)C NMR (100.5 MHz, CDCl\(_3\)): 64.74 (CH\(_2\)OH), 69.89 (CH\(_2\)O), 114.66 (CH), 127.23 (CH), 127.74 (CH), 128.36 (CH), 128.41 (CH), 133.16 (C), 136.67 (C), 157.98 (C); MS (FAB): \(m/z = 214\) (M), 215 (M+H); \(C_{14}H_{14}O_2\) requires 214; \(R_f\) (n-hexanes/ethyl acetate: 1/1): 0.64; mp : 52°C (lit.: 52-53°C)\(^{190}\)

3-(Benzyloxy)benzyl alcohol (67) \(^{191}\)

65 (1.06 g, 5.0 mmol) and sodium borohydride (0.19 g, 5.0 mmol) in dry THF (10 mL) were reacted according to the general procedure M. This afforded 67 as a white solid (0.90 g, 84 %).

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IR $\nu_{\text{max}}$/cm (KBr): 3340 (br, bonded OH), 3063 and 3032 (C-H aromatic); $^1$H NMR (400 MHz, CDCl$_3$): 4.64 (s, 2H, CH$_2$OH), 5.07 (s, 2H, CH$_2$), 6.90-7.03 (m, 3H, Ar), 7.25-7.46 (m, 6H, Ar); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 65.15 (CH$_2$OH), 69.89 (CH$_2$O), 113.06 (CH), 113.94 (CH), 119.21 (CH), 126.81 (CH), 127.32 (CH), 127.47 (CH), 127.80 (CH), 128.41 (CH), 129.45 (CH), 136.73 (C), 142.37 (C), 158.77 (C); MS (FAB): $m/z$ = 214 (M), 215 (M+H); C$_{14}$H$_{14}$O$_2$ requires 214; R$_f$ ($n$-hexanes/ethyl acetate: 1/1): 0.72; mp : 44°C (lit.: 44.5-45°C)$^{100}$

17-Cyclopropylmethyl-6,7-didehydro-4,5a-epoxy-5'-bis-tert-butoxycarbonyl-(N'-4-benzoxoxybenzyl)guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (68)

62 (0.35, 0.72 mmol), 53 (0.153 g, 0.36 mmol), mercury(II) chloride (0.158 g, 0.58 mmol) and triethylamine (0.10 mL, 0.72 mmol) in dry DMF (10 mL) were reacted according to the general procedure A. A mixture containing 68 and the mono-BOC protected analogue was obtained as a brown solid (0.11 g, 35%).

Data for di-BOC protected product:
IR $\nu_{\text{max}}$/cm (KBr): 3368 (br, bonded OH and bonded NH), 1671 (C=N); $^1$H NMR (400 MHz, CDCl$_3$): 0.09-0.17 (m, 2H, NCH$_2$CH(CHHCHH)), 0.45-0.58 (m, 2H, NCH$_2$CH(CHHCHH)), 0.80-0.92 (m, 1H, NCH$_2$CH(CH$_2$CH$_2$)), 1.38 (s, 9H, C(CH$_3$)$_3$), 1.46 (s, 9H, C(CH$_3$)$_3$), 4.85 (s, 2H, CH$_2$), 5.03 (s, 2H, CH$_2$O), 5.60 (s, 1H, 5-H), 6.45 (d, 1H, $\beta$=7.8 Hz, 1-H), 6.56 (d, 1H, $\beta$=7.8 Hz, 2-H), 6.64-7.06 (m, 4H, Ar), 7.29-7.43 (m, 8H, Ar); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 4.25 (NCH$_2$CH(CH$_2$CH$_2$)), 4.42 (NCH$_2$CH(CH$_2$CH$_2$)), 9.92 (NCH$_2$CH(CH$_2$CH$_2$)), 23.62 (10-C), 28.04 (C(CH$_3$)), 28.60 (C(CH$_3$)), 29.26 (CH$_2$), 31.90 (CH$_2$), 43.81 (16-C), 48.34 (CH$_2$N), 50.84 (13-C), 59.85 (18-C), 62.75 (9-C), 70.29 (CH$_2$O), 72.75 (14-C), 80.14 (C(CH$_3$)), 82.02 (C(CH$_3$)), 85.29 (5-C), 111.94 (Ar), 112.54 (Ar), 114.64 (Ar), 115.03 (Ar), 117.51 (Ar), 118.57 (Ar), 119.07 (Ar), 124.93 (Ar), 126.97 (Ar), 127.53 (Ar), 127.63(Ar), 128.15 (Ar), 128.73 (Ar), 129.94 (Ar), 130.51 (Ar), 130.89 (Ar), 130.97 (Ar), 135.47 (Ar), 137.09 (Ar), 139.65 (Ar), 143.11 (Ar), 152.64 (Ar), 158.10 (CO), 158.35 (CO), 162.82 (NCNN); MS (FAB): $m/z$ = 868 (M+H); C$_{51}$H$_{57}$N$_5$O$_8$ requires 867; R$_f$ (DCM/MeOH/NEt$_3$: 110/10/1): 0.57

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17-Cyclopropylmethyl-6,7-didehydro-4,5a-epoxy-5'-bis-tert-butoxycarbonyl-(N'-3-benzyloxybenzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (69) 63 (0.52 g, 1.07 mmol), 53 (0.23 g, 0.53 mmol), mercury(II) chloride (0.158 g, 0.88 mmol) and triethylamine (0.15 mL, 1.07 mmol) in dry DMF (12 mL) were reacted according to the general procedure A. A mixture containing 69 and the mono-BOC protected analogue was obtained as a brown solid (0.14 g, 30%).

Data for di-BOC protected product:
IR ν_max/cm⁻¹ (KBr): 3362 (br, bonded OH and bonded NH), 1671 (C=N); ¹H NMR (400 MHz, CDCl₃): 0.12-0.20 (m, 2H, NCH₂CH(CH₂CH₂)), 0.51-0.62 (m, 2H, NCH₂CH(CH₂CH₂)), 0.99-1.12 (m, 1H, NCH₂CH(CH₂CH₂)), 1.37 (s, 9H, C(CH₃)₃), 1.47 (s, 9H, C(CH₃)₃), 4.98 (s, 2H, CH₂N), 5.02 (s, 2H, CH₂O), 5.61 (s, 1H, 5-H), 6.49 (d, 1H, J=8.2 Hz, 1-H), 6.58 (d, 1H, J=8.2 Hz, 2-H), 6.67-7.38 (m, 12H, Ar); ¹³C NMR (100.5 MHz, CDCl₃): 3.92 (NCH₂CH(CH₂CH₂)), 4.11 (NCH₂CH(CH₂CH₂)), 9.53 (NCH₂CH(CH₂CH₂)), 23.18 (10-C), 28.03 (C(CH₃)), 28.15 (C(CH₃)), 28.70 (CH₂), 31.37 (CH₂), 43.46 (16-C), 47.96 (CH₂N), 50.60 (13-C), 59.43 (18-C), 62.41 (9-C), 69.74 (CH₂O), 72.36 (14-C), 81.95 (C(CH₃)), 82.55 (C(CH₃)), 84.97 (5-C), 111.51 (Ar), 112.32 (Ar), 114.27 (Ar), 114.75 (Ar), 117.16 (Ar), 118.11 (Ar), 118.76 (Ar), 121.56 (Ar), 124.62 (Ar), 126.60 (Ar), 127.25 (Ar), 127.42 (Ar), 127.61 (Ar), 128.25 (Ar), 129.21 (Ar), 129.98 (Ar), 130.48 (Ar), 135.00 (Ar), 136.72 (Ar), 136.93 (Ar), 139.12 (Ar), 142.63 (Ar), 143.72 (Ar), 149.32 (Ar), 158.35 (CO), 158.44 (CO), 162.46 (NCNN); MS (FAB): m/z = 868.4294 (M+H+); C₅₁H₅₃N₇O₈ requires 868.4285; Rₕ (DCM/MeOH/NH₄OH: 110/10/1): 0.57

4-Methoxybenzaldehyde (70)¹²
To a mixture of 4-hydroxybenzaldehyde (6.10 g, 50.0 mmol) and anhydrous potassium carbonate (10.35 g, 75.0 mmol) in dry DMF (25mL) was added dropwise methyl iodide (3.1 mL, 50.0 mmol). The mixture was stirred overnight at room temperature under a nitrogen atmosphere. Water (15 mL) was added and the solution extracted with diethyl ether (2x50 mL). The organic phase was washed with brine (2x20 mL), dried (MgSO₄) and concentrated under vacuum. 70 was used without any further purification and isolated as an orange oil (6.26 g, 92%).
IR $v_{\text{max}}$/cm (neat): 2840 and 2740 (C-H aldehyde), 1682 (CO); $^1$H NMR (270 MHz, CDCl$_3$): 3.85 (s, 3H, CH$_3$), 6.98 (d, 2H, $J$=8.8 Hz), 7.81 (d, 2H, $J$=8.8 Hz), 9.86 (s, 1H, CHO); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 55.86 (CH$_3$), 114.47 (CH), 130.02 (C), 132.06 (CH), 164.64 (C), 190.77 (CHO); MS (EI): $m/z$ = 136.0510 (M), C$_8$H$_8$O$_2$ requires 136.0524; R$_f$ (n-hexanes/ethyl acetate: 6/1): 0.44

4-Methoxybenzyl alcohol (71) $^{193}$
A suspension of sodium borohydride (1.52 g, 40.0 mmol) in dry THF (35 mL) and a solution of 70 (5.44 g, 40.0 mmol) in dry THF (35 mL) were reacted according to the general procedure M. 71 was obtained as a yellow oil (5.49 g, 99%).

IR $v_{\text{max}}$/cm (neat): 3338 (br, bonded OH), 3064 and 3033 (C-H aromatic); $^1$H NMR (270 MHz, CDCl$_3$): 2.95 (br, s, 1H, OH), 3.76 (s, 3H, CH$_3$), 4.51 (s, 2H, CH$_2$OH), 6.84 (d, 2H, $J$=8.6 Hz), 7.23 (d, 2H, $J$=8.6 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 55.08 (CH$_3$), 64.40 (CH$_2$), 113.68 (CH), 128.44 (CH), 133.04 (C), 158.83 (C); MS (EI): $m/z$ = 138.0682 (M), C$_8$H$_{10}$O$_2$ requires 138.0680; R$_f$ (n-hexanes/ethyl acetate: 1/1): 0.51

4-Methoxybenzyl bromide (72) $^{194,195}$
Triphenylphosphine (6.25 g, 24.0 mmol), imidazole (1.63 g, 24.0 mmol), bromine (1.22 mL, 24.0 mmol) and 71 (2.76 g, 20.0 mmol) in dry DCM (100mL) were reacted according to the general procedure L. 72 was used with no further purification (only a small quantity of the crude product has been purified on column chromatography for NMR characterisation).

$^1$H NMR (270 MHz, CDCl$_3$): 3.78 (s, 3H, CH$_3$), 4.49 (s, 2H, CH$_2$Br), 6.85 (d, 2H, $J$=8.6 Hz), 7.31 (d, 2H, $J$=8.6 Hz); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 34.50 (CH$_2$Br), 55.70 (CH$_3$), 114.45 (CH), 130.14 (C), 130.67 (CH), 159.78 (C)

1,3-Bis-tert-butoxycarbonyl-1-(4'-methoxybenzyl)-2-methyl-2-thiopseudourea (73) $^{196}$
1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (5.35 g, 18.2 mmol), sodium hydride (60% in oil, 1.41 g, 35.2 mmol), 15-crown-5 (0.2 mL, 1.0 mmol) and 4-methoxybenzyl bromide (72) (4.02 g, 20.0 mmol) in dry DMF (27 ml) were reacted
according to the general procedure B. 73 was isolated as a very viscous colourless oil (4.0 g, 49%).

IR $\nu_{\text{max}}$/cm (neat): 1719 (C=N), 1613 (carbamate), 1141 (C-N); $^1$H NMR (270 MHz, CDCl$_3$): 1.40 (s, 9H, C(CH$_3$)$_3$), 1.50 (s, 9H, C(CH$_3$)$_3$), 2.24 (s, 3H, SCH$_3$), 3.77 (s, 3H, OCH$_3$), 4.69 (s, 2H, CH$_2$), 6.83 (d, 2H, $J$=9.0 Hz), 7.26 (d, 2H, $J$=9.0 Hz); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 15.43 (SCH$_3$), 27.91 (C(CH$_3$)), 27.94 (C(CH$_3$)), 51.74 (CH$_2$), 55.04 (OCH$_3$), 81.49 (C(CH$_3$)), 82.39 (C(CH$_3$)), 113.63 (CH), 129.26 (CH), 151.87 (C), 157.87 (CO), 158.98 (CO), 163.05 (CN); MS (FAB): $m/z$ = 411.1952 (M+H);

$C_{20}H_{31}N_2O_5S$ requires 411.1953; $R_f$ (n-hexanes/ethyl acetate: 5/1): 0.33

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-N'-3,4-dichlorobenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (75)

78 (0.49 g, 1.09 mmol), 53 (0.24 g, 0.55 mmol), mercury(II) chloride (0.22 g, 0.83 mmol) and triethylamine (0.15 mL, 1.10 mmol) in dry DMF (10 mL) were reacted according to the general procedure A. A mixture containing 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-3,4-dichlorobenzyl) guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (82) and the corresponding mono-BOC-protected analogue was obtained as a brown solid (0.34 g, 74%).

No NMR data available. IR (82) $\nu_{\text{max}}$/cm (neat): 3393 (br, bonded OH), 1712 (C=N), 1611 (carbamate); MS (FAB): $m/z$ = 730 (M+H, $^{35}$Cl), 732 (M+H, $^{35}$Cl$^7$Cl), 830 (M+H, $^{35}$Cl$^7$Cl), 832 (M+H, $^{35}$Cl$^7$Cl); mono-BOC protected product: $C_{39}H_{41}^{35}$Cl$_2$N$_2$O$_5$ requires 730; di-BOC protected product: $C_{44}H_{49}^{35}$Cl$_2$N$_2$O$_7$ requires 830; HRMS (di-BOC protected compound): 830.3088 (M+H, $^{35}$Cl$_2$), 832.3080 (M+H, $^{35}$Cl$^7$Cl); $C_{44}H_{50}^{35}$Cl$_2$N$_2$O$_7$ requires 830.3087 and $C_{44}H_{50}^{35}$Cl$^7$ClN$_2$O$_7$ requires 832.3057; $R_f$ (DCM/MeOH/NaOH: 200/12/1): 0.66

The above mixture (0.26 g, 0.31 mmol) was dissolved in DCM (3 mL) and treated with trifluoroacetic acid (2 mL) as described in the general procedure P. 75 (TFA salt) was isolated as a brown solid (0.25 g, 90%).

IR $\nu_{\text{max}}$/cm (KBr): 3193 (br, bonded OH and NH), 1678 and 1633 (C=N, NH and NH$_2$); $^1$H NMR (270 MHz, CD$_3$OD/CDCl$_3$: 6/1): 0.52 (d, 2H, $J$=4.2 Hz,
NCH₂CH(CH₂CH₂H), 0.72-0.88 (m, 2H, NCH₂CH(CH₂CH₂H)), 2.32 (s, 3H, CH₃), 4.45 (s, 2H, CH₂), 5.69 (s, 1H, 5-H), 6.64-6.71 (m, 2H, 1-H and 2-H), 6.97 (d, 1H, J=8.7 Hz, 6'-H), 7.22-7.27 (m, 2H), 7.41 (d, 1H, J=8.7 Hz, 4'-H), 7.47-7.50 (m, 2H);

¹³C NMR (67.8 MHz, CD₂OD/CDCl₃: 6/1): 3.85 (NCH₂CH(CH₂CH₂)), 6.70 (NCH₂CH(CH₂CH₂)), 7.22 (NCH₂CH(CH₂CH₂)), 25.44 (10-C), 30.02 (CH₂), 30.57 (CH₂), 45.18 (CH₂), 48.36 (13-C), 59.33 (18-C), 63.96 (9-C), 73.97 (14-C), 85.24 (5-C), 110.47 (C), 114.37 (CH), 118.49 (CH), 119.82 (CH), 121.15 (CH), 122.65 (CH), 122.92 (C), 127.15 (C), 128.36 (CH), 128.85 (C), 130.67 (CH), 132.27 (CH), 132.85 (C), 133.05 (C), 138.51 (C), 139.09 (C), 142.43 (C), 145.12 (C), 158.11 (NCNN); MS (FAB): m/z = 630.2026 (M+H, ¹³C₁₂), 632.2014 (M+H, ¹³C₁₃), 634.2019 (M+H, ¹³C₁₄), 634.2019 (M+H, ¹³C₁₅), C₃₄H₃₄N₅O₅ requires 630.2038, C₃₄H₃₄N₅Cl₂Cl requires 632.2008, C₃₄H₃₄N₅Cl₂O₂ requires 634.1979; Anal. (C₃₄H₃₄N₅O₅Cl₂:2TFA:2H₂O) requires C 51.01 %, H 4.39 %, N 7.83 %, found : C 50.90 %, H 4.03 %, N 7.78 %; mp: 190°C

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-((N'-4-methylbenzyl)guanidinyl)-3,14-dihydroxyindolo [2',3':6,7]-morphinan (76)

77 (0.43 g, 1.09 mmol), 53 (0.24 g, 0.55 mmol), mercury(II) chloride (0.22 g, 0.83 mmol) and triethylamine (0.15 mL, 1.10 mmol) in dry DMF (10 ml) were reacted according to the general procedure A. A mixture containing 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-4-methylbenzyl)guanidinyl-3,14-dihydroxyindolo [2',3':6,7]-morphinan (81) and the corresponding mono-BOC protected analogue was obtained as a brown solid (0.29 g, 68 %).

No NMR data available as the product collected contained a mixture of di-BOC protected compound (81) and its mono-BOC protected derivative; IR νmax/cm (neat): 3395 (br, bonded OH), 1706 (C=O), 1609 (carbamate); MS (FAB): m/z = 676 (M+H), 776 (M+H); mono-BOC protected product: C₄₀H₄₅N₅O₇ requires 675; di-BOC protected product: C₄₅H₅₄N₅O₇ requires 775; HRMS (FAB) m/z = 776.4037 (M+H), C₄₅H₅₄N₅O₇ requires 776.4023; Rf (DCM/MeOH/NH₄OH: 200/12/1): 0.66
The above mixture (0.19 g, 0.24 mmol) in DCM (3 mL) was deprotected with trifluoroacetic acid (2 mL) as described in the general procedure P and 76 (TFA salt) was isolated as a brown solid (0.22 g, 96%).

IR $\nu_{\text{max}}$/cm (KBr): 3310 (br, bonded OH and NH), 1681 (O=H, NH and NH$_2$); $^1$H NMR (270 MHz, CD$_3$OD/CDCl$_3$: 6/1): 0.53 (d, 2H, $J=4.0$ Hz, NCH$_2$CH(CH$_2$CH$_2$)), 0.74-0.93 (m, 2H, NCH$_2$CH(CH$_2$CH$_2$)), 2.32 (s, 3H, CH$_3$), 4.23 (d, 1H, $J=6.0$ Hz, CH$_2$), 4.41 (s, 2H, CH$_2$), 5.72 (s, 1H, 5-H), 6.64 (d, 1H, $J=8.2$ Hz, 1-H), 6.68 (d, 1H, $J=8.2$ Hz, 2-H), 7.01 (dd, 1H, $J=1.8$ Hz and $J=8.7$ Hz, 6'-H), 7.18 (d, 2H, $J=8.9$ Hz), 7.20 (d, 2H, $J=8.9$ Hz), 7.33 (d, 1H, $J=1.8$ Hz, 7'-H), 7.44 (d, 1H, $J=8.7$ Hz, 4'-H); $^{13}$C NMR (67.8 MHz, CD$_3$OD/CDCl$_3$: 6/1): 3.86 (NCH$_2$CH(CH$_2$CH$_2$)), 6.69 (NCH$_2$CH(CH$_2$CH$_2$)), 7.16 (NCH$_2$CH(CH$_2$CH$_2$)), 21.72 (CH$_3$), 25.39 (10-C), 29.96 (CH$_2$), 30.52 (CH$_2$), 46.19 (CH$_2$), 47.87 (CH$_2$), 48.29 (13-C), 59.30 (18-C), 63.90 (9-C), 73.90 (14-C), 85.18 (5-C), 110.38 (C), 114.27 (CH), 118.52 (CH), 119.77 (CH), 121.04 (CH), 122.66 (CH), 122.74 (C), 127.09 (C), 128.61 (CH), 128.79 (C), 130.47 (C), 130.87 (CH), 134.79 (C), 138.45 (C), 139.19 (C), 142.39 (C), 145.06 (C), 157.90 (NCNN); MS (FAB): $m/z = 575.2952$ (M), 576.3008 (M+H); C$_{35}$H$_{38}$N$_5$O$_3$ requires 576.2974; Anal. (C$_{35}$H$_{37}$N$_5$O$_3$:3TFA:2H$_2$O) requires C 51.62 %, H 4.65 %, N 7.34 %, found : C 51.30 %, H 4.42 %, N 7.28 %; mp > 190°C (decomposition)

1,3-Bis-tert-butoxycarbonyl-1-(4'-methylbenzyl)-2-methyl-2-thiopseudourea (77)
1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (2.90 g, 10.0 mmol), sodium hydride (60% in oil, 0.44 g, 11.0 mmol), 15-crown-5 (0.2 mL, 1 mmol) and 4-methylbenzyl bromide (2.22 g, 12.0 mmol) in dry DMF (20 ml) were reacted according to the general procedure B. 77 was isolated as a colourless oil (2.93 g, 74 %).

IR $\nu_{\text{max}}$/cm (neat): 3350 (br, bonded OH), 1612 (carbamate); $^1$H NMR (270 MHz, CDCl$_3$): 1.40 (s, 9H, C(CH$_3$)$_3$), 1.51 (s, 9H, C(CH$_3$)$_3$), 2.26 (s, 3H, SCH$_3$), 2.31 (s, 3H, CH$_3$), 4.72 (s, 2H, CH$_2$), 7.11 (d, 2H, $J=7.9$ Hz), 7.21 (d, 2H, $J=7.9$ Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 14.79 (SCH$_3$), 20.43 (CH$_3$), 27.26 (C(CH$_3$)), 27.32 (C(CH$_3$)), 51.43 (CH$_2$), 80.76 (C(CH$_3$)), 81.73 (C(CH$_3$)), 127.08 (CH), 128.34 (CH), 133.58 (C), 132
136.27 (C), 151.21 (CO), 157.15 (CO), 162.35 (CN); MS (FAB): m/z = 395.2007 (M+H); C_20H_31N_2O_4S requires 395.2004; R_f (n-hexanes/ethyl acetate: 5/1): 0.42

**1,3-Bis-tert-butoxycarbonyl-1-(3',4'-dichlorobenzyl)-2-methyl-2-thiopseudourea (78)**

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (2.90 g, 10.0 mmol), sodium hydride (60% in oil, 0.44 g, 11.0 mmol), 15-crown-5 (0.2 mL, 1 mmol) and 3,4-dichlorobenzyl chloride (1.66 mL, 12.0 mmol) in dry DMF (20 ml) were reacted according to the general procedure B. 78 was isolated as a colourless oil (2.11 g, 47%).

IR ν_max/cm (neat): 1721 (C=N), 1617 (carbamate); ^1^H NMR (270 MHz, CDCl_3): 1.41 (s, 9H, C(CH_3)_3), 1.50 (s, 9H, C(CH_3)_3), 2.31 (s, 3H, SCH_3), 4.68 (s, 2H, CH_2), 6.94 (m, 2H), 7.19 (dd, 1H, J=8.2 Hz and J=1.9 Hz), 7.38 (d, 1H, J=8.2 Hz), 7.42 (d, 1H, J=1.9 Hz); ^1^C NMR (67.8 MHz, CDCl_3): 15.17 (SCH_3), 27.50 (C(CH_3)), 27.54 (C(CH_3)), 50.72 (CH_2), 81.41 (C(CH_3)), 82.70 (C(CH_3)), 126.82 (CH), 129.43 (CH), 129.92 (CH), 130.99 (C), 131.86 (C), 137.21 (C), 151.28 (CO), 157.21 (CO), 161.82 (CN); MS (FAB): m/z = 449.1051 (M+H, ^3^C_12) and 451.1032 (M+H, ^3^C_37^3^Cl); C_{19}H_{27}^{35}Cl_{2}N_2O_4S requires 449.1067; C_{19}H_{27}^{35}Cl_{2}N_2O_4S requires 451.1037; R_f (n-hexanes/ethyl acetate: 5/1): 0.40

**N-(tert-Butyloxycarbonyl)diaminoethane (83)**

Diaminoethane (12.02 g, 200 mmol) in CHCl_3 (150 mL) and di-tert-butyl-dicarbonate (4.36 g, 20 mmol) in CHCl_3 (70 mL) were reacted according to the general procedure C. Purification by silica gel chromatography, eluting with DCM/MeOH/NH_4OH: 85/10/5, gave 83 (2.57 g, 80%) as a colourless oil.

IR ν_max/cm (neat): 3360 (br, bonded NH), 1693 (carbamate); ^1^H NMR (270 MHz, CDCl_3): 1.28 (s, br, 2H, NH_2), 1.33 (s, 9H, C(CH_3)_3), 2.64-2.73 (m, 2H, CH_2NH_2), 3.00-3.12 (m, 2H, CH_2NH), 5.42 (s, br, 1H, NH); ^1^C NMR (67.8 MHz, CDCl_3): 28.08 (C(CH_3)_3), 41.53 (CH_2NH_2), 43.09 (CH_2NH), 78.61 (C(CH_3)_3), 156.04 (CO); MS (FAB): m/z = 161 (M+H); C_7H_16N_2O_2 requires 160; R_f (DCM/MeOH/NH_4OH: 85/10/5): 0.29
**N-(tert-Butyloxycarbonyl)diaminobutane (84)**

1,4-Diaminobutane (9.0 mL, 90 mmol) in CHCl₃ (90 mL) and di-tert-butyl-dicarbonate (1.95 g, 9 mmol) in CHCl₃ (45 mL) were reacted according to the general procedure C. Purification by silica gel column chromatography, eluting with DCM/MeOH/NH₄OH: 85/10/5, afforded the desired product 84 as a colourless oil (1.51 g, 89%).

IR v_max/cm (neat): 3358 (br, bonded NH), 1694 (carbamate); H NMR (270 MHz, CDCl₃): 1.27 (s, br, 2H, NH₂), 1.44 (s, 9H, C(CH₃)₃), 1.46-1.56 (m, 4H, 2xCH₂), 2.69 (t, 2H, J=6.2 Hz, CH₂NH₂), 3.12 (t, 2H, J=6.2 Hz, CH₂NH), 4.95 (s, br, 1H, NH); C NMR (67.8 MHz, CDCl₃): 27.85 (CH₂), 28.80 (C(CH₃)₃), 31.27 (CH₂), 40.75 (CH₂NH₂), 42.17 (CH₂NH), 79.17 (C(CH₃)₂), 156.13 (CO); MS (FAB): m/z = 189 (M+H), 377 (2M+H); C₉H₂₀N₂O₂ requires 188; Rf (DCM/MeOH/NH₄OH: 85/10/5): 0.33

**N-(tert-Butyloxycarbonyl)diaminohexane (85)**

1,6-Diaminohexane (10.47 g, 90 mmol) in CHCl₃ (90 mL) and di-tert-butyl-dicarbonate (1.95 g, 9 mmol) in CHCl₃ (45 mL) were reacted according to the general procedure C. Purification by silica gel column chromatography, eluting with DCM/MeOH/NH₄OH: 85/10/5, afforded 85 as a colourless oil (1.73 g, 89%).

IR v_max/cm (neat): 3357 (br, bonded NH), 1692 (carbamate); H NMR (270 MHz, CDCl₃): 1.28 (s, br, 2H, NH₂), 1.31-1.37 (m, 4H, 2xCH₂), 1.44 (s, 9H, C(CH₃)₃), 1.48-1.54 (m, 4H, 2xCH₂), 2.68 (t, 2H, J=6.6 Hz, CH₂NH₂), 3.08-3.13 (m, 2H, CH₂NH), 4.77 (s, br, 1H, NH); C NMR (67.8 MHz, CDCl₃): 26.93 (CH₂), 27.02 (CH₂), 28.81 (C(CH₃)₃), 30.42 (CH₂), 34.07 (CH₂), 40.83 (CH₂), 42.45 (CH₂), 79.16 (C(CH₃)₂), 156.11 (CO); MS (FAB): m/z = 217 (M+H); C₁₀H₂₀N₂O₂ requires 216; Rf (DCM/MeOH/NH₄OH: 85/10/5): 0.40

**[(1,1-Dimethylethoxy)carbonyl]amino]ethylisothiocyanate (86)**

83 (2.50 g, 15.6 mmol), calcium carbonate (1.53 g, 15.6 mmol) and thiophosgene (2.40 mL, 31.2 mmol) in CHCl₃ (50 mL) were reacted according to the general procedure D. Purification by column chromatography yielded 86 as a white solid (2.60 g, 82%).
IR \(\nu_{\text{max}}/\text{cm}\) (neat): 3348 (br, bonded NH), 2978 (br, N-H), 2198 and 2113 (isothiocyanate), 1694 (carbamate); 
\(^1^H\) NMR (270 MHz, \(\text{CDCl}_3\)): 1.46 (s, 9H, C(CH\(_3\))\(_3\)), 3.38 (virtual quartet, 2H, \(J=5.5\) Hz, \(\text{CH}_2\text{NH}\)), 3.65 (t, 2H, \(J=5.5\) Hz, \(\text{CH}_2\text{NCS}\)), 5.02 (s, br, 1H, NH); 
\(^{13}\)C NMR (67.8 MHz, \(\text{CDCl}_3\)): 28.41 (C(CH\(_3\))\(_3\)), 40.63 (CH\(_2\)), 43.97 (CH\(_2\)), 80.02 (C(CH\(_3\))\(_3\)), 132.23 (NCS), 155.55 (CO); MS (FAB): 
\(m/z = 203\) (M+H) and 405 (2M+H); \(\text{C}_8\text{H}_m\text{N}_2\text{O}_2\text{S}\) requires 202; 
R\(_f\) (n-hexanes/ethyl acetate:4/1): 0.33; mp : 62°C (lit.: 63-64°C)

\[\text{[(1,1-Dimethylethoxy)carbonyl]amino|butylisothiocyanate (87)}\]
84 (1.73 g, 9.2 mmol), calcium carbonate (0.90 g, 9.2 mmol) and thiophosgene (1.41 mL, 18.4 mmol) in CHCl\(_3\) (50 mL) were reacted according to the general procedure D. After purification by column chromatography, 87 was isolated as a yellowish oil (1.90 g, 90%).

IR \(\nu_{\text{max}}/\text{cm}\) (neat): 3357 (br, bonded NH), 2978 (br, N-H), 2185 and 2107 (isothiocyanate), 1698 (carbamate); 
\(^1^H\) NMR (75.45 MHz, \(\text{CDCl}_3\)): 1.43 (s, 9H, C(CH\(_3\))\(_3\)), 1.35-1.55 (m, 2H, CH\(_2\)), 1.67-1.73 (m, 2H, CH\(_2\)), 3.09 (virtual quartet, 2H, \(J=6.3\) Hz, \(\text{CH}_2\text{NH}\)), 3.53 (t, 2H, \(J=6.3\) Hz, \(\text{CH}_2\text{NCS}\)), 4.84-4.91 (m, br, 1H, NH); 
\(^{13}\)C NMR (67.8 MHz, \(\text{CDCl}_3\)): 27.27 (CH\(_2\)), 27.38 (CH\(_2\)), 28.45 (C(CH\(_3\))\(_3\)), 39.46 (CH\(_2\)), 44.63 (CH\(_2\)), 79.16 (C(CH\(_3\))\(_3\)), 130.05 (NCS), 155.88 (CO); MS (FAB): \(m/z = 231\) (M+H); \(\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2\text{S}\) requires 230; R\(_f\) (n-hexanes/ethyl acetate: 3/1): 0.33

\[\text{[(1,1-Dimethylethoxy)carbonyl]amino|hexylisothiocyanate (88)}\]
85 (1.75 g, 8.1 mmol), calcium carbonate (0.80 g, 8.1 mmol) and thiophosgene (1.22 mL, 16.2 mmol) in CHCl\(_3\) (50 mL) were reacted according to the general procedure D. 88 was isolated as a colourless oil (1.61 g, 77%) after purification by column chromatography (elution with n-hexanes/ethyl acetate: 3/1).

IR \(\nu_{\text{max}}/\text{cm}\) (neat): 3351 (br, bonded NH), 2976 (br, N-H), 2183, 2105 (isothiocyanate), 1693 (carbamate); 
\(^1^H\) NMR (270 MHz, \(\text{CDCl}_3\)): 1.29 (s, 9H, C(CH\(_3\))\(_3\)), 1.41-1.65 (m, 8H, 4xCH\(_2\)), 3.01 (virtual quartet, 2H, \(J=6.4\) Hz, \(\text{CH}_2\text{NH}\)), 3.43 (t, 2H, \(J=6.4\) Hz, \(\text{CH}_2\text{NCS}\)), 4.79-4.86 (m, br, 1H, NH); 
\(^{13}\)C NMR (67.8 MHz, \(\text{CDCl}_3\)): 28.47 (CH\(_2\)), 28.50 (CH\(_2\)), 29.65 (C(CH\(_3\))\(_3\)), 40.80 (CH\(_2\)), 42.00 (CH\(_2\)), 42.13
(CH₂), 46.02 (CH₂), 78.78 (C(CH₃)₃), 129.54 (NCS), 155.74 (CO); MS (FAB): m/z = 259 (M+H); C₁₂H₂₂N₂O₂S requires 258; Rf (n-hexanes/ethyl acetate: 3/1): 0.34

1,1-Dimethylethoxycarbonyl N-(2-(thioureido)ethyl)carbamate (89)
A solution of 86 (2.54 g, 12.6 mmol) in acetone (30 mL) and NH₄OH (14.43 mL, 0.25 mol) were reacted according to the general procedure E. After purification by column chromatography, 89 was isolated as a white solid (2.26 g, 82%).

IR v_max/cm (KBr): 3404-3190 (br, bonded NH), 2980 (br, N-H), 1686 (carbamate), 1243 (C=S), 1152 (C-N); ¹H NMR (270 MHz, CDCl₃): 1.44 (s, 9H, C(CH₃)₃), 3.23-3.31 (m, 2H, CH₂), 3.44-3.48 (m, 2H, CH₂), 3.64 (s, br, 1H, NH), 5.57-5.90 (m, br, 2H, 2xNH), 6.43 (s, br, 1H, NH); ¹³C NMR (67.8 MHz, CDCl₃): 28.37 (C(CH₃)₃), 40.18 (CH₂), 45.27 (CH₂), 80.06 (C(CH₃)₃), 157.24 (CO), 184.09 (CS); MS (FAB): m/z = 220 (M+H); C₈H₁₇N₃O₂S requires 219; Rf (ethyl acetate: 100%): 0.57; mp: 127°C

1,1-Dimethylethoxycarbonyl N-(4-(thioureido)butyl)carbamate (90)
A solution of 87 (2.50 g, 10.8 mmol) in acetone (30 mL) and NH₄OH (12.46 mL, 0.22 mol) were reacted according to the general procedure E. After purification by column chromatography, 90 was isolated as a white solid (2.35 g, 88%).

IR v_max/cm (neat): 3305 (br, bonded NH), 2977, 2932 (br, N-H), 1682 (carbamate), 1252 (C=S), 1169 (C-N); ¹H NMR (270 MHz, CDCl₃): 1.43 (s, 9H, C(CH₃)₃), 1.49-1.68 (m, 6H, 3xCH₂), 3.06-3.18 (m, 2H, CH₂), 3.53 (s, br, 1H, NH), 5.09 (s, br, 1H, NH), 6.52 (s, br, 1H, NH), 6.75 (s, br, 1H, NH); ¹³C NMR (100.5 MHz, CDCl₃): 26.67 (CH₂), 27.97 (CH₂), 28.87 (C(CH₃)₃), 40.61 (CH₂), 45.21 (CH₂), 79.82 (C(CH₃)₃), 156.88 (CO), 183.21 (CS); MS (FAB): m/z = 248 (M+H); C₁₀H₂₁N₃O₂S requires 247; Rf (n-hexanes/ethyl acetate: 1/1): 0.26; mp: 152°C (lit. : 157-159°C)

1,1-Dimethylethoxycarbonyl N-(6-(thioureido)hexyl)carbamate (91)
A solution of 88 (3.07 g, 11.9 mmol) in acetone (30 mL) and NH₄OH (13.55 mL, 0.24 mol) were reacted according to the general procedure E. After purification by column chromatography, 91 was isolated as an off-white solid (3.21 g, 98%).
IR $\nu_{\text{max}}$/cm (neat): 3305 (br, bonded NH), 2977, 2933 (br, N-H), 1687 (carbamate), 1529 (N-H), 1252 (C=S), 1170 (C-N); $^1$H NMR (270 MHz, CDCl₃): 1.31-1.38 (m, 6H, 3xCH₂), 1.43 (s, 9H, C(CH₃)₃), 1.45-1.50 (m, 2H, CH₂), 1.56-1.63 (m, 2H, CH₂), 3.06-3.10 (m, 2H, CH₂), 3.52 (s, br, 1H, NH), 4.85 (s, br, 1H, NH), 6.36 (s, br, 2H, NH₂); $^{13}$C NMR (100.5 MHz, CDCl₃): 26.45 (CH₂), 28.87 (C(CH₃)₃), 29.12 (CH₂), 30.23 (CH₂), 40.61 (CH₂), 45.28 (CH₂), 60.78 (CH₂), 79.69 (C(CH₃)₃), 156.67 (CO), 183.33 (CS); MS (FAB): $m/z = 276$ (M+H); C₁₀H₂₁N₃O₂S requires 275; Rᵣ (n-hexanes/ethyl acetate: 1/1): 0.37; mp : 77°C

17-Cyclopropylmethyl-6,7-didehydro-4,5a-epoxy-5'-bis-tert-butoxycarbonyl-(N'-2-tert-butoxycarbonylamino-ethyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (95)

A solution of the disubstituted thiourea 89 (2.13 g, 9.7 mmol), sodium hydride (0.776 g, 19.4 mmol) and di-tert-butyl-dicarbonate (2.33 g, 10.7 mmol) in dry THF (110 mL) were reacted according to the general procedure F. After purification, a mixture containing 92 and the mono-BOC protected analogue was isolated. Rᵣ (n-hexanes/ethyl acetate: 3/1): 0.5

53 (0.269 g, 0.63 mmol), mercury(II) chloride (0.255 g, 0.94 mmol), triethylamine (0.17 mL, 1.25 mmol) and 92 (mixture of mono and di-BOC-protected thioureas) (0.40 g, 1.25 mmol) were reacted according to the general procedure A. After purification, a mixture containing 95 and the mono-BOC protected analogue was isolated as a brown solid (0.09 g, 20%).

$^1$H NMR (270 MHz, CDCl₃, di-BOC protected derivative): 0.16 (d, 2H, $J=4.8$ Hz, NCH₂CH(CHHCHH)), 0.57 (d, 2H, $J=8.1$ Hz, NCH₂CH(CHHCHH)), 0.85-0.96 (m, 1H, NCH₂CH(CH₂CH₂)), 1.30 (s, 9H, C(CH₃)₃), 1.50 (s, 9H, C(CH₃)₃), 4.87 (s, br, 1H, NH), 5.25 (s, br, 1H, NH), 5.63 (s, 1H, 5'-H), 6.50 (d, 1H, $J=7.8$ Hz, 1-H), 6.63 (d, 1H, $J=7.8$ Hz, 2-H), 6.82 (m, 1H, 6'-H), 7.12 (m, 1H, 7'-H), 7.21 (m, 1H, 4'-H), 8.89 (s, br, 1H, NH); $^{13}$C NMR (67.8 MHz, CDCl₃, mono-BOC protected derivative): 3.89 (NCH₂CH(CH₂CH₂)), 4.04 (NCH₂CH(CH₂CH₂)), 9.69 (NCH₂CH(CH₂CH₂)), 22.86 (10-C), 28.44 (C(CH₃)₃), 28.97 (CH₂), 31.62 (CH₂), 39.49 (CH₂), 42.56 (CH₂), 43.84 (CH₂), 48.24 (13-C), 59.76 (18-C), 62.68 (9-C), 72.90 (14-C), 79.80 (C(CH₃)₃), 85.52
17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-
4-tert-butoxycarbonylamino-butyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-
morphinan (96)

A solution of the disubstituted thiourea 90 (0.54 g, 2.18 mmol), sodium hydride
(0.174 g, 4.36 mmol) and di-/er/-butyl-dicarbonate (0.95 g, 4.36 mmol) in dry THF
(25 mL) were reacted according to the general procedure F. After purification, a
mixture containing 93 and the mono-BOC protected analogue was isolated (0.49 g,
65%). Rf (n-hexanes/ethyl acetate: 3/1): 0.5

53 (0.278 g, 0.65 mmol), mercury(II) chloride (0.263 g, 0.97 mmol), triethylamine
(0.18 mL, 1.30 mmol) and 93 (mixture of mono and di-BOC-protected thioureas)
(0.45 g, 1.30 mmol) were reacted according to the general procedure A. After
purification, a mixture containing 96 and the mono-BOC protected analogue was
isolated as a brown solid (0.19 g, 39%).

Data for di-BOC protected product:
IR \( \nu_{\text{max}} / \text{cm} \) (neat): 3319 (br, bonded OH and NH), 2976 (br, N-H), 1697 (C=\( \text{N}, \text{NH} \) and \( \text{NH}_2 \)), 1149 (C-N); \(^1\text{H} \) NMR (400 MHz, CDC\(_3 \)): 0.13-0.18 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 0.52-0.61 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 0.83-0.95 (m, 1H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 1.10-1.22 (m, 2H, CH\(_2\)), 1.40 (s, 9H, C(CH\(_3\))\(_3\)), 1.46 (s, 9H, C(CH\(_3\))\(_3\)), 1.49 (s, 9H, C(CH\(_3\))\(_3\)), 4.52 (s, br, 1H, NH), 4.93 (s, br, 1H, NH), 5.68 (s, 1H, 5-H), 6.49 (d, 1H, \( J=7.8 \text{ Hz}, 1\)-H), 6.63 (d, 1H, \( J=7.8 \text{ Hz}, 2\)-H), 6.70 (s, 1H, 6'-H), 7.09 (m, 1H, 7'-H),
7.17 (m, 1H, 4'-H), 9.83 (s, br, 1H, NH); \(^{13}\text{C} \) NMR (100.5 MHz, CDC\(_3 \)): 4.33
(NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 4.53 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 9.89 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 23.54
(CH\(_2\)), 27.26 (CH\(_2\)), 28.53 (CH\(_2\)), 28.62 (C(CH\(_3\))\(_3\)), 28.87 (C(CH\(_3\))\(_3\)), 29.10 (CH\(_2\)),
31.90 (CH\(_2\)), 40.29 (CH\(_2\)), 40.77 (CH\(_2\)), 44.01 (CH\(_2\)), 48.31 (13-C), 59.81 (18-C),
62.60 (9-C), 73.10 (14-C), 78.75 (C(CH\(_3\))\(_3\)), 79.40 (C(CH\(_3\))\(_3\)), 85.18 (5-C), 111.15
(C), 113.06 (CH), 117.37 (CH), 117.58 (CH), 119.14 (CH), 121.52 (CH), 124.88 (C),
126.78 (C), 127.35 (C), 130.92 (C), 131.29 (C), 136.41 (C), 139.97 (C), 143.38 (C),
156.28 (CO), 159.91 (CO), 162.84 (NCNN); MS (FAB): \( m/z = 743 \) (M+H); 
\( \text{C}_{41}\text{H}_{54}\text{N}_{6}\text{O}_{7} \) requires 742; \( R_f \) (DCM/MeOH/NH\(_2\)OH: 200/10/1): 0.40

17-Cyclopropylmethyl-6,7-didehydro-4,5a-epoxy-5'-bis-\( \text{tert} \)-butoxycarbonyl-(N'-6-\( \text{tert} \)-butoxycarbonylamino-hexyl)guanidiny-1-3,14-dihydroxyindolo[2',3':6,7]-morphinan (97)

A solution of the disubstituted thiourea 91 (0.83 g, 3.01 mmol), sodium hydride (0.24 g, 6.02 mmol) and di-\( \text{tert} \)-butyl-dicarbonate (1.31 g, 6.02 mmol) in dry THF (45 mL) were reacted according to the general procedure F. After purification, a mixture containing 94 and the mono-BOC protected analogue was isolated (0.82 g, 72%). \( R_f \) (n-hexanes/ethyl acetate: 3/1): 0.45

53 (0.24 g, 0.55 mmol), mercury(II) chloride (0.22 g, 0.82 mmol), triethylamine (0.15 mL, 1.1 mmol) and 94 (mixture of mono and di-BOC-protected thioureas) (0.41 g, 1.10 mmol) were reacted according to the general procedure A. After purification, a mixture containing 97 and the mono-BOC protected analogue was isolated as a brown solid (0.12 g, 28%).

Data for mono-BOC protected product:
IR \( \nu_{\text{max}}/\text{cm} \) (neat): 3389 (br, bonded OH and NH), 2976 (br, N-H), 1697 (C=N, NH and NH\(_2\)), 1149 (C-N); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 0.11-0.21 (m, 2H, NCH\(_2\)(CH\(_2\)CH\(_3\))), 0.50-0.61 (m, 2H, NCH\(_2\)(CH\(_2\)CH\(_2\)H)), 0.83-0.93 (m, 1H, NCH\(_2\)CH\((\text{CH}\_2\text{CH}2\text{H})\)), 1.01-1.12 (m, 2H, CH\(_2\)), 1.18-1.30 (m, 2H, CH\(_2\)), 1.44 (s, 9H, C(CH\(_3\))\(_3\)), 1.46-1.51 (m, 2H, CH\(_2\)), 4.67 (s, br, 1H, NH), 5.71 (s, 1H, 5-H), 6.52 (d, 1H, J=8.1 Hz, 1-H), 6.65 (d, 1H, J=8.1 Hz, 2-H), 6.81 (m, 1H, 6'-H), 7.12 (m, 1H, 7'-H), 7.26 (m, 1H, 4'-H), 9.30 (s, br, 1H, NH); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)): 3.72 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 3.98 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 9.33 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 23.05 (CH\(_2\)), 25.97 (CH\(_2\)), 26.15 (CH\(_2\)), 27.97 (CH\(_2\)), 28.41 (C(CH\(_3\))\(_3\)), 29.25 (CH\(_2\)), 29.51 (CH\(_2\)), 31.49 (CH\(_2\)), 40.27 (CH\(_2\)), 40.77 (CH\(_2\)), 43.62 (CH\(_2\)), 47.85 (13-C), 59.40 (18-C), 62.18 (9-C), 72.74 (14-C), 78.38 (C(CH\(_3\))\(_3\)), 85.06 (5-C), 110.74 (C), 113.38 (CH), 116.93 (CH), 117.57 (CH), 118.78 (CH), 121.13 (CH), 124.36 (C), 126.37 (C), 127.11 (C), 130.62 (C), 131.11 (C), 136.41 (C), 140.28 (C), 143.33 (C), 159.87 (CO), 164.05 (NCNN); MS (FAB): \( m/z = 671 \) (M+H); \( \text{C}_{38}\text{H}_{50}\text{N}_{6}\text{O}_{5} \) requires 670; \( R_f \) (DCM/MeOH/NH\(_2\)OH: 200/10/1): 0.41
17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(N′-2-aminoethyl)guanidinyl-3,14-dihydroxyindolo [2′,3′:6,7]-morphinan (98)

95 (mixture of mono and di-BOC-protected products) (108 mg, 0.15 mmol) was dissolved in a mixture of conc. HCl/methanol (2.5 mL/2.5 mL). The solution was stirred overnight at room temperature then the solvent was removed until dryness. The solid was washed several times with diethyl ether then dried under vacuum, yielding 98 (HCl salt) as a brown solid (70 mg, 95%).

IR \( \nu_{\text{max}}/\text{cm} \) (KBr): 3400 (br, bonded OH and NH), 1623 (O=N, NH and NH\(_2\)); \(^1\)H NMR (270 MHz, CD\(_3\)OD): 0.46 (d, 2H, \( J=4.7 \text{ Hz} \), NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 0.69-0.79 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 1.01-1.12 (m, 1H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 5.64 (s, 1H, 5-H), 6.56 (d, 1H, \( J=8.1 \text{ Hz} \), 1-H), 6.60 (d, 1H, \( J=8.1 \text{ Hz} \), 2-H), 6.92-6.98 (m, 1H, 6′-H), 7.25-7.38 (m, 2H, 7′-H and 4′-H); \(^13\)C NMR (100.5 MHz, CD\(_3\)OD): 3.38 (NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 6.29 (NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 6.87 (NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 25.04 (CH\(_2\)), 29.69 (CH\(_2\)), 30.26 (CH\(_2\)), 39.59 (CH\(_2\)N), 40.23 (CH\(_2\)N), 47.57 (16-C), 48.02 (13-C), 58.86 (18-C), 63.52 (9-C), 73.62 (14-C), 84.85 (5-C), 110.17 (C), 113.85 (CH), 118.43 (CH), 119.31 (CH), 120.65 (CH), 122.33 (CH), 122.66 (C), 126.54 (C), 128.55 (C), 130.28 (C), 132.52 (C), 138.25 (C), 142.08 (C), 144.76 (C), 157.81 (NCNN); MS (FAB): \( m/z = 515 \) (M+H); \( \text{C}_{29}\text{H}_{34}\text{N}_{6}\text{O}_{3} \) requires 514; Anal. (\( \text{C}_{29}\text{H}_{34}\text{N}_{6}\text{O}_{3} \cdot 4\text{HCl} \cdot 2\text{H}_{2}\text{O} \)) requires C 50.0 %, H : 6.0 %, N : 12.0 %, found C 50.6 %, H : 5.7 %, N : 11.5 %; mp > 225°C

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(N′-4-aminobutyl)guanidinyl-3,14-dihydroxyindolo [2′,3′:6,7]-morphinan (99)

96 (mixture of mono and di-BOC-protected products) (93 mg, 0.13 mmol) was dissolved in a mixture conc. HCl/methanol (2.5 mL/2.5 mL). The solution was stirred overnight at room temperature then the solvent was removed until dryness. The solid was washed several times with diethyl ether then dried under vacuum, yielding 99 (HCl salt) as a brown solid (64 mg, 99%).

IR \( \nu_{\text{max}}/\text{cm} \) (KBr): 3401 (br, bonded OH and NH), 1635 (C=N, NH and NH\(_2\)); \(^1\)H NMR (270 MHz, CD\(_3\)OD): 0.43-0.62 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 0.69-0.92 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 1.07-1.23 (m, 1H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 1.59-1.90 (m,
17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5′-(N′-6-aminohexyl)guanidinyl-3,14-dihydroxyindolo[2′,3′:6,7]-morphinan (100)

97 (mixture of mono and di-BOC-protected products) (140 mg, 0.18 mmol) was dissolved in a mixture conc. HCl/methanol (2.5 mL/2.5 mL). The solution was stirred overnight at room temperature then the solvent was removed until dryness. The solid was washed several times with diethyl ether then dried under vacuum, yielding 100 (HCl salt) as a brown solid (95 mg, 96%).

IR ν_{max}/cm (KBr): 3400 (br, bonded OH and NH), 2936 (br, N-H), 1634 (C=O, NH and NH₂); \(^1\)H NMR (270 MHz, CD₃OD): 0.49-0.63 (m, 2H, NCH₂CH(CH₂CH₂CH₂)), 0.71-0.91 (m, 2H, NCH₂CH(CH₂CH₂CH₂)), 1.09-1.23 (m, 1H, NCH₂CH(CH₂CH₂)), 1.34-1.49 (m, 4H, 2xCH₂), 1.57-1.76 (m, 4H, 2xCH₂), 2.94 (t, 2H, J=7.3 Hz, CH₂), 4.27 (s, br, 1H, NH), 5.71 (s, 1H, 5-H), 6.68 (d, 1H, J=8.4 Hz, 1-H), 6.75 (d, 1H, J=8.4 Hz, 2-H), 6.95-6.99 (m, 1H, 6′-H), 7.29-7.34 (m, 1H, 7′-H), 7.46 (d, 1H, J=8.4 Hz, 4′-H), 7.92 (s, br, 1H, NH); \(^13\)C NMR (67.8 MHz, CD₃OD): 3.45 (NCH₂CH(CH₂CH₂)), 6.33 (NCH₂CH(CH₂CH₂)), 6.91 (NCH₂CH(CH₂CH₂)), 25.10 (CH₂), 26.97 (CH₂), 27.08 (CH₂), 28.30 (CH₂), 29.64 (CH₂), 30.22 (CH₂), 40.61 (CH₂), 42.58 (CH₂), 47.51 (16-C), 47.95 (13-C), 58.86 (18-C), 63.46 (9-C), 73.66 (14-C), 84.85 (5-C), 110.12 (C), 113.97 (CH), 118.25 (CH), 119.32 (CH), 120.76 (CH), 122.32 (CH), 122.77 (C), 126.85 (C), 128.47 (C), 130.28 (C), 132.42 (C), 138.04 (C), 141.95 (C), 144.69 (C), 157.46 (NCNN); MS (FAB): m/z = 571 (M+H); C₃₃H₄₂N₆O₃

\[\text{C₃₁H₃₈N₆O₃}\] requires 542; Anal. (C₃₁H₃₈N₆O₃·4HCl·3H₂O) requires C 50.14 %, H : 6.51 %, N : 11.31 %, found C 50.15 %, H : 6.39 %, N : 11.25 %; mp > 220°C
requires 570; Anal. (C_{33}H_{42}N_{6}Cl_{3}:H_{2}O) requires C 51.43 %, H : 6.80 %, N : 10.90 %, found C 51.40 %, H : 6.56 %, N : 11.00 %; mp > 220°C

1,3-Bis-tert-butoxycarbonyl-1-acetyl-2-methyl-2-thiopseudourea (104)
1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (0.87 g, 3.0 mmol), sodium hydride (0.36 g, 9.0 mmol), 18-crown-6 (50 mg) and acetyl chloride (0.51 mL, 6.0 mmol) in dry THF (5 mL) were reacted according to the general procedure B. After purification by silica gel column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, 104 was isolated as a white solid (0.17 g, 19%).

IR $\nu_{\text{max}}$/cm (neat): 1750 (carbamate), 1727 (C=N), 1629 (carbamate); $^1$H NMR (400 MHz, CDCl$_3$): 1.44 (s, 9H, C(CH$_3$)$_3$), 1.49 (s, 9H, C(CH$_3$)$_3$), 2.42 (s, 3H, CH$_3$), 2.44 (s, 3H, CH$_3$); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 14.95 (SCH$_3$), 24.80 (CH$_3$), 27.08 (C(CH$_3$)$_3$), 27.18 (C(CH$_3$)$_3$), 81.81 (C(CH$_3$)$_3$), 84.36 (C(CH$_3$)$_3$), 149.35 (COCH$_3$), 152.81 (CN), 162.04 (CO), 170.82 (CO); $R_f$ (n-hexanes/ethyl acetate: 9/1): 0.22; mp : 54°C

1,3-Bis-tert-butoxycarbonyl-1-allyl-2-methyl-2-thiopseudourea (105)
1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (0.87 g, 3.0 mmol), sodium hydride (0.36 g, 9.0 mmol), 18-crown-6 (50 mg) and allyl bromide (0.51 mL, 6.0 mmol) in dry THF (5 mL) were reacted according to the general procedure B. After purification by silica gel column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, 105 was isolated as a colourless oil (0.60 g, 61%).

IR $\nu_{\text{max}}$/cm (neat): 1722 (C=N), 1619 (carbamate); $^1$H NMR (400 MHz, CDCl$_3$): 1.46 (s, 9H, C(CH$_3$)$_3$), 1.50 (s, 9H, C(CH$_3$)$_3$), 2.37 (s, 3H, SCH$_3$), 4.12 (d, 2H, $J$=5.8 Hz, CH$_2$), 5.16-5.26 (m, 2H, CH=CH$_2$), 5.83-5.93 (m, 1H, CH=CH$_2$); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 15.48 (SCH$_3$), 27.97 (2xC(CH$_3$)$_3$), 51.19 (CH$_2$), 81.66 (C(CH$_3$)$_3$), 82.42 (C(CH$_3$)$_3$), 117.83 (CH=CH$_2$), 132.95 (CH=CH$_2$), 151.63 (CN), 157.81 (CO), 162.84 (CO); MS (FAB): $m/z$ = 331 (M+H); C$_{15}$H$_{26}$N$_2$O$_4$S requires 330; $R_f$ (n-hexanes/ethyl acetate: 9/1): 0.15
1,3-Bis-tert-butoxycarbonyl-1-(4'-bromo-2-butenyl)-2-methyl-2-thiopseudourea (106)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (1.74 g, 6.0 mmol), sodium hydride (0.29 g, 7.2 mmol) and 1,4-dibromo-2-butene (1.41 g, 6.6 mmol) in anhydrous DMF (20 mL) were reacted according to the general procedure B. The crude product was purified by flash column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, yielding 106 as a colourless oil (1.25 g, 49%).

IR νmax/cm⁻¹ (neat): 1743 (C=N); ¹H NMR (400 MHz, CDCl₃): 1.44 (s, 9H, C(CH₃)₃), 1.48 (s, 9H, C(CH₃)₃), 2.35 (s, 3H, CH₃), 3.91 (t, 2H, J=6.6 Hz, CH₂), 4.10 (t, 2H, J=5.5 Hz, CH₂), 5.76-5.92 (m, 2H, CH=CH); ¹³C NMR (67.8 MHz, CDCl₃): 15.50 (SCH₃), 27.86 (2xC(CH₃)₃), 31.68 (CH₂Br), 49.56 (NCH₂), 81.57 (C(CH₃)₃), 82.59 (C(CH₃)₃), 129.70 (CH=CH), 129.80 (CH=CH), 151.34 (CN), 157.62 (CO), 162.42 (CO); MS (FAB): m/z = 423 (M+H, ⁷⁹Br) and 425 (M+H, ⁸¹Br); C₁₆H₂₇N₂O₄S⁷⁹Br requires 422 and C₁₆H₂₇N₂O₄S⁸¹Br requires 424; Rₕ (n-hexanes/ethyl acetate: 9/1): 0.37

1,3-Bis-tert-butoxycarbonyl-1-(4'-chlorobutyryl)-2-methyl-2-thiopseudourea (107)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (0.87 g, 3.0 mmol), sodium hydride (0.36 g, 9.0 mmol) and 4-chlorobutyryl chloride (0.67 mL, 6.0 mmol) in anhydrous DMF (7 mL) were reacted according to the general procedure B. The crude product was purified by column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, and 107 was isolated as a colourless oil (0.40 g, 34%).

IR νmax/cm⁻¹ (neat): 1750 (carbamate), 1728 (C=N), 1629 (carbamate); ¹H NMR (270 MHz, CDCl₃): 1.47 (s, 9H, C(CH₃)₃), 1.52 (s, 9H, C(CH₃)₃), 2.13 (virtual quintet, 2H, J=6.4 Hz, CH₂), 2.46 (s, 3H, CH₃), 3.04 (t, 2H, J=6.4 Hz, COCH₂), 3.63 (t, 2H, J=6.4 Hz, CH₂Cl); ¹³C NMR (67.8 MHz, CDCl₃): 16.07 (SCH₃), 27.55 (CH₂), 28.15 (C(CH₃)₃), 28.27 (C(CH₃)₃), 34.62 (COCH₂), 44.48 (CH₂Cl), 82.86 (C(CH₃)₃), 85.48 (C(CH₃)₃), 149.00 (CN), 157.18 (CO), 159.97 (CO), 172.18 (COCH₂); MS (FAB): m/z = 395 (M+H, ³⁵Cl) and 397 (M+H, ³⁷Cl); C₁₆H₂₇N₂O₄S³⁵Cl requires 394 and C₁₆H₂₇N₂O₄S³⁷Cl requires 396; Rₕ (n-hexanes/ethyl acetate: 9/1): 0.25
**N-(4-Bromo-2-butenyl)phthalimide (110)**

A mixture of 1,2-dibromo-2-butene (2.56 g, 12.0 mmol) and potassium phthalimide (2.22 g, 12.0 mmol) in anhydrous DMF (30 mL) was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was quenched by addition of water (10 mL). The precipitate was filtered, washed with water and dried under vacuum. The crude product was purified by column chromatography, eluting with n-hexanes/ethyl acetate: 3/1, affording 110 as a white solid (1.72 g, 51%).

IR \(\nu_{\text{max}}/\text{cm} \) (neat): 2926 (C-H aromatic), 1715 (amide); \(^1\text{H} \) NMR (270 MHz, CDCl\(_3\)): 3.90 (d, 2H, \(J=6.3 \) Hz, CH\(_2\)Br), 4.30 (d, 2H, \(J=5.6 \) Hz, NCH\(_2\)), 5.78-6.02 (m, 2H, CH\(=CH\)), 7.71-7.77 (m, 2H), 7.84-7.89 (m, 2H); \(^{13}\text{C} \) NMR (100.5 MHz, CDCl\(_3\)): 31.40 (CH\(_2\)Br), 38.98 (NCH\(_2\)), 123.49 (CH), 128.54 (CH=CH), 130.21 (CH=CH), 132.30 (C), 134.13 (CH), 167.17 (CO); MS (FAB): \(m/z = 280 \) (M\(^+\)H, \(^{79}\text{Br}\)), 282 (M\(^+\)H, \(^{81}\text{Br}\)), \(C_{12}H_{10}NO_2^{79}\text{Br}\) requires 279 and \(C_{12}H_{10}NO_2^{81}\text{Br}\) requires 281; \(R_f \) (n-hexanes/ethyl acetate: 3/1): 0.45; mp: 95°C (lit.: 95-96°C).

1,3-Bis-tert-butoxycarbonyl-1-(4-phthalimido-2-butenyl)-2-methyl-2-thiopseudourea (111)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (1.93 g, 6.6 mmol), sodium hydride (0.32 g, 8.0 mmol) and 110 (2.05 g, 7.3 mmol) in anhydrous DMF (20 mL) were reacted according to the general procedure B. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, afforded 111 as a colourless oil (2.62 g, 80%).

IR \(\nu_{\text{max}}/\text{cm} \) (neat): 2979, 2932 (C-H aromatic), 1717 (C=\(\equiv\)N), 1615 (CO); \(^1\text{H} \) NMR (270 MHz, CDCl\(_3\)): 1.43 (s, 9H, C(CH\(_3\))\(_3\)), 1.48 (s, 9H, C(CH\(_3\))\(_3\)), 2.34 (s, 3H, SCH\(_3\)), 4.09 (d, 2H, \(J=4.6 \) Hz, CH\(_2\)), 4.28 (d, 2H, \(J=4.3 \) Hz, CH\(_2\)), 5.75-5.82 (m, 2H, CH\(=CH\)), 7.70-7.77 (m, 2H), 7.81-7.88 (m, 2H); \(^{13}\text{C} \) NMR (100.5 MHz, CDCl\(_3\)): 15.90 (SCH\(_3\)), 28.38 (2xC(CH\(_3\))\(_3\)), 39.21 (CH\(_2\)Nphtha), 50.14 (CH\(_2\)N), 81.92 (C(CH\(_3\))\(_3\)), 82.71 (C(CH\(_3\))\(_3\)), 123.36 (CH), 127.73 (CH=CH), 128.87 (CH=CH), 132.37 (C), 134.01 (CH), 151.64 (CN), 157.80 (CO), 162.63 (CO), 167.71 (CO); MS (FAB): \(m/z = 490 \) (M\(^+\)H); \(C_{24}H_{31}N_3O_6\) requires 489; \(R_f \) (n-hexanes/ethyl acetate: 3/1): 0.41
17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-4'-phthalimido-2-butenyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (112)

53 (0.43 g, 1.0 mmol), mercury(II) chloride (0.41 g, 1.5 mmol), triethylamine (0.27 mL, 2.0 mmol) and 111 (0.98 g, 2.0 mmol) were reacted according to the general procedure A. After purification, a mixture containing 112 and the mono-BOC protected analogue was obtained as a brown solid (0.23 g, 13%).

Data for 112:

$^1$H NMR (400 MHz, CDCl$_3$): 0.17 (d, 2H, $J$=4.7 Hz, NCH$_2$CH(CH$_3$CH$_2$)), 0.51-0.62 (d, 2H, $J$=7.4 Hz, NCH$_2$CH(CH$_3$CH$_2$)), 0.84-0.94 (m, 1H, NCH$_2$CH(CH$_2$CH$_2$)), 1.36 (s, 9H, C(CH$_3$)$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 3.94-4.32 (m, 4H, CH$_2$CH=CHCH$_2$), 5.67 (s, 1H, 5-H), 5.72-5.95 (m, 2H, CH=CH), 6.43-6.58 (m, 2H, 1-H and 2-H), 6.77 (m, 1H, 6'-H), 7.02-7.27 (m, 2H, 4'-H and 7'-H), 7.46-7.68 (m, 4H, Ar); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 4.31 (NCH$_2$CH(CH$_2$CH$_2$)), 4.38 (NCH$_2$CH(CH$_2$CH$_2$)), 9.85 (NCH$_2$CH(CH$_2$CH$_2$)), 23.57 (10-C), 28.24 (C(CH$_3$)$_3$), 28.49 (C(CH$_3$)$_3$), 29.19 (CH$_2$), 31.82 (CH$_2$), 39.18 (CH$_2$), 39.31 (CH$_2$), 44.07 (16-C), 48.41 (13-C), 59.93 (18-C), 62.81 (9-C), 73.01 (14-C), 82.30 (C(CH$_3$)$_3$), 82.85 (C(CH$_3$)$_3$), 85.60 (5-C), 111.64 (C), 112.37 (CH), 112.92 (CH), 117.97 (CH), 119.43 (CH), 123.44 (CH), 123.56 (CH), 125.24 (C), 127.29 (C), 127.41 (CH), 127.75 (CH), 130.62 (C), 131.11 (C), 132.33 (C), 134.10 (CH), 134.25 (C), 135.78 (C), 139.88 (C), 143.36 (C), 150.08 (CN), 153.39 (CO), 153.81 (CO), 168.27 (CO); R$_f$ (DCM/MeOH/NH$_4$OH: 110/10/1): 0.41

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-4'-phthalimido-2-butenyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (113)

The above mixture (0.16 g, 0.18 mmol) was dissolved in a mixture of MeOH/conc. HCl (5 mL/5mL) and the solution was heated at 80°C overnight. The solvents were removed by evaporation until dryness. The solid was washed several times with diethyl ether then dried under vacuum to give 113 (HCl salt) as a brown solid (0.12 g, 97%).

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IR v max/cm (KBr): 3393 (br, bonded OH and bonded NH), 1707 (C=N, NH and NH2),
1610 (CO); 1 H NMR (270 MHz, CD3OD): 0.50-0.61 (m, 2H, NCH2CH(CH=CH2)), 0.73-0.95 (m, 2H, NCH2CH(CH=CH2)), 1.11-1.24 (m, 1H, NCH2CH(CH2CH2)), 3.82-3.91 (m, 2H, CH2Nguan), 4.23-4.33 (m, 2H, CH2Nphtha), 5.73 (s, 1H, 5-H), 5.73-5.86 (m, 2H, CH=CH), 6.62 (d, 1H, J=8.1 Hz, 1-H), 6.66 (d, 1H, J=8.1 Hz, 2-H), 6.94-7.02 (d, 1H, J=8.4 Hz, 6'-H), 7.33 (s, 1H, 4'-H), 7.39 (d, 1H, J=8.4 Hz, 7'-H), 7.75-7.87 (m, 4H, Ar); 13C NMR (67.8 MHz, CD3OD): 3.75 (NCH2CH(CH2CH2)), 6.64 (NCH2CH(CH2CH2)), 7.25 (NCH2CH(CH2CH2)), 25.43 (10-C), 30.09 (CH2), 30.66 (CH2), 40.03 (CH2Nphtha), 43.72 (16-C), 47.99 (CH2), 49.05 (13-C), 59.25 (18-C), 63.91 (9-C), 73.98 (14-C), 85.19 (5-C), 110.53 (C), 114.26 (CH), 118.67 (CH), 119.83 (CH), 121.12 (CH), 122.78 (CH), 123.10 (C), 124.17 (CH), 127.27 (C), 128.30 (CH), 129.00 (C), 129.38 (CH), 130.74 (C), 132.99 (C), 133.26 (C), 135.49 (CH), 138.69 (C), 142.60 (C), 145.23 (C), 158.00 (CN), 169.74 (CO); MS (FAB): m/z = 671 (M+H); C39H38N6O5 requires 670; mp > 250°C

3-Phthalimidopropanol (115)\textsuperscript{139,203,204}
A solution of 3-aminopropanol (3.2 mL, 41.5 mmol), N-carbethoxy-phthalimide (9.1 g, 41.5 mmol) and triethylamine (5.8 mL, 41.5 mmol) in THF (100 mL) was stirred overnight at room temperature. The solvent was removed by evaporation and the crude oil purified by column chromatography, eluting with n-hexanes/ethyl acetate: 1/1. 115 was isolated as a white solid (7.35 g, 86%).

IR v max/cm (KBr): 3413 (br, bonded OH), 1722 (C=N), 1604 (carbamate); 1 H NMR (270 MHz, CDCl3): 2.15 (virtual quintuplet, 2H, J=6.7 Hz, CH2), 3.56 (t, 2H, J=6.6 Hz, CH2N), 3.83 (t, 2H, J=6.8 Hz, CH2O), 7.69-7.72 (m, 2H), 7.82-7.85 (m, 2H); 13C NMR (100.5 MHz, CDCl3): 31.10 (CH2), 34.23 (CH2N), 58.96 (CH2O), 123.06 (CH), 131.70 (C), 133.86 (CH), 168.59 (CO); MS (FAB): m/z = 206.0814 (M); C11H12NO3 requires 206.0817; Rf (n-hexanes/ethyl acetate: 1/1): 0.45; mp : 65 °C

3-Phthalimidopropyl p-toluenesulfonate (116)\textsuperscript{205}
Method A
To a solution of 115 (1.08 g, 5.25 mmol) and pyridine (1.41 mL, 17.5 mmol) in DCM (5 mL) at 0°C was added a solution of p-toluenesulfonfyl chloride (1.00 g, 5.25 mmol)
in DCM. The reaction mixture was stirred overnight at room temperature. Water was then added and the mixture acidified with conc. HCl (1.0 mL, 12.3 mmol). The aqueous phase was extracted several times with DCM and the organic phase dried over MgSO₄ and concentrated under vacuum. Further purification by column chromatography, eluting with DCM, afforded 116 as a white solid (1.18 g, 63%).

**Method B**

To a solution of 115 (2.16 g, 10.5 mmol) and triethylamine (1.46 mL, 10.5 mmol) in DCM (5 mL) at 0°C was added a solution of p-toluenesulfonyl chloride (2.00 g, 10.5 mmol) in DCM. The reaction mixture was stirred at room temperature for 3 hours; water was added, the aqueous phase then extracted several times with DCM and the organic phase dried over MgSO₄ and evaporated under vacuum. Similar purification than used in method A afforded 116 as a white solid (2.07 g, 55%).

IR v_max/cm (KBr): 3104-2970 (C-H aromatic), 1698 (C=N), 1615 (carbamate); H NMR (270 MHz, CDCl₃): 2.03 (virtual quintuplet, 2H, J=6.6 Hz, CH₂), 2.41 (s, 3H, CH₃), 3.71 (t, 2H, J=6.9 Hz, CH₂N), 4.08 (t, 2H, J=6.4 Hz, CH₂O), 7.30 (d, 2H, J=8.4 Hz), 7.67-7.72 (m, 2H), 7.75 (d, 2H, J=8.4 Hz), 7.78-7.81 (m, 2H); C NMR (100.5 MHz, CDCl₃): 21.68 (CH₃), 27.98 (CH₂), 34.61 (CH₂N), 67.78 (CH₂O), 123.34 (CH), 127.98 (CH), 129.88 (CH), 131.97 (C), 134.07 (CH), 144.87 (C), 168.12 (CO); MS (FAB): m/z = 360.0915 (M+H); C₁₈H₁₇NO₅S requires 359.0826; Rf (n-hexanes/ethyl acetate: 3/1): 0.31; mp : 164 °C

1,3-Bis-tert-butoxycarbonyl-1-(3'-phthalimidopropyl)-2-methyl-2-thiopseudourea (117)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (0.74 g, 2.56 mmol), sodium hydride (60% in oil, 92 mg, 2.30 mmol) and 116 (0.92 g, 2.56 mmol) in dry DMF (5 mL) were reacted according to the general procedure B. The crude oil was purified by column chromatography, eluting with n-hexanes/ethyl acetate: 9/1. 117 was isolated as a colourless oil (0.60 g, 49%).

IR v_max/cm (neat): 2974, 2933 (C-H aromatic), 1737 (CO), 1716 (br, C=N), 1621 (carbamate), 1146 (C-N); H NMR (270 MHz, CDCl₃): 1.41 (s, 9H, C(CH₃)₃), 1.46
9H, C(CH$_3$)$_3$), 2.04 (m, 2H, CH$_2$), 2.34 (s, 3H, CH$_3$), 3.54-3.60 (m, 2H, CH$_2$NPhtha), 3.70 (t, 2H, $J$=7.1 Hz, CH$_2$N), 7.66-7.69 (m, 2H), 7.79-7.82 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 15.64 (CH$_3$), 28.06 (2x(C(CH$_3$)$_3$), 28.23 (CH$_2$), 35.67 (CH$_2$), 46.71 (CH$_2$), 81.93 (C(CH$_3$)$_3$), 82.59 (C(CH$_3$)$_3$), 123.30 (CH), 132.14 (C), 134.02 (CH), 151.70 (CO), 162.82 (NCN), 168.28 (CO); R$_f$ (n-hexanes/ethyl acetate: 1/1): 0.48

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-3'-phthalimido-propyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (118)

53 (0.24 g, 0.55 mmol), mercury(II) chloride (0.17 g, 0.60 mmol), triethylamine (0.16 mL, 1.18 mmol) and 117 (0.54 g, 1.13 mmol) were reacted according to the general procedure A. After purification, a mixture containing 118 and the mono-BOC protected analogue was isolated as a brown solid (0.11 g, 23%).

Data for 118:
$^1$H NMR (270 MHz, CDCl$_3$): 0.15 (d, 2H, $J$=4.2 Hz, NCH$_2$CH(CHHCHH)), 0.55 (d, 2H, $J$=7.4 Hz, NCH$_2$CH(CHHCHH)), 0.82-0.93 (m, 1H, NCH$_2$CH(CH$_2$CH$_2$)), 1.35 (s, 9H, C(CH$_3$)$_3$), 5.62 (s, 1H, 5-H), 6.48 (d, 1H, $J$=8.0 Hz, 1-H), 6.56 (d, 1H, $J$=8.0 Hz, 2-H), 6.57-6.59 (m, 1H), 7.03-7.17 (m, 1H), 7.52-7.73 (m, 5H); R$_f$ (DCM/MeOH/NH$_3$OH: 200/10/1): 0.31

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-3'-phthalimido-propyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (120)

The above mixture (40 mg, 47 pmol) in DCM (2 mL) was treated with trifluoroacetic acid (0.2 mL) as described in the general procedure P. The desired product 120 (TFA salt) was recrystallised from ethanol/diethyl ether and isolated as a brown solid (27 mg, 58%).

$^1$H NMR (270 MHz, CD$_3$OD): 0.54 (d, 2H, $J$=4.7 Hz, NCH$_2$CH(CHHCHH)), 0.72-0.89 (m, 2H, NCH$_2$CH(CHHCHH)), 1.11-1.21 (m, 1H, NCH$_2$CH(CH$_2$CH$_2$)), 1.88-2.00 (m, 2H, CH$_2$), 3.73 (t, 2H, $J$=6.5 Hz, CH$_2$N), 4.24 (d, 1H, $J$=5.9 Hz), 5.73 (s, 1H, 5-H), 6.63 (d, 1H, $J$=8.3 Hz, 1-H), 6.67 (d, 1H, $J$=8.3 Hz, 2-H), 7.04 (dd, 1H, $J$=2.0 Hz and $J$=8.6 Hz, 6'-H), 7.39 (d, 1H, $J$=2.0 Hz, 4'-H), 7.44 (d, 1H, $J$=8.6 Hz, 7'-H), 148
7.76-7.84 (m, 4H); $^{13}$C NMR (67.8 MHz, CD$_3$OD): 3.40 (NCH$_2$CH(CH$_2$CH$_2$)), 6.24 (NCH$_2$CH(CH$_2$CH$_2$)), 6.88 (NCH$_2$CH(CH$_2$CH$_2$)), 25.04 (CH$_2$), 28.93 (CH$_2$), 29.74 (CH$_2$), 30.29 (CH$_2$), 35.95 (CH$_2$), 40.07 (CH$_2$), 47.60 (16-C), 49.84 (13-C), 58.90 (18-C), 63.60 (9-C), 73.63 (14-C), 84.89 (5-C), 110.11 (C), 113.87 (CH), 118.26 (CH), 119.36 (CH), 120.61 (CH), 122.38 (CH), 122.63 (C), 124.16 (CH), 126.91 (C), 128.57 (C), 130.30 (C), 132.50 (C), 133.29 (C), 135.43 (CH), 138.20 (C), 142.11 (C), 144.80 (C), 157.60 (NCNN), 169.90 (CO); Anal. (C$_{38}$H$_{38}$N$_6$O$_5$·3TFA·6H$_2$O) requires C 47.7 %, H : 4.8 %, N : 7.6 %, found C 47.7 %, H : 5.3 %, N : 8.2 %; mp > 220 °C

$N,N$-Dibenzylaminopropanol (124) 206

To a solution of aminopropanol (3.06 mL, 40 mmol) in DCM (5 mL) was added a solution of benzyl bromide (4.75 mL, 40 mmol) in DCM (5 mL). The reaction mixture was stirred overnight at room temperature, then the solution was basified to pH=10 with NH$_4$OH; water was added, the organic phase separated and the aqueous phase further extracted with DCM. The organic phase was washed with brine, dried over MgSO$_4$ and concentrated. Purification by flash chromatography eluting first with $n$-hexanes, then with $n$-hexanes/ethyl acetate: 6/1, afforded 124 as a colourless oil (2.14 g, 42 %).

IR $\nu_{\text{max}}$/cm (neat): 3339 (br, bonded OH), 2945 (C-H aromatic); $^1$H NMR (270 MHz, CDCl$_3$): 1.73-1.79 (m, 2H, CH$_2$), 2.64 (t, 2H, $J$=5.8 Hz, CH$_2$N), 3.56 (s, 4H, 2xCH$_2$Ph), 3.64 (t, 2H, $J$=5.3 Hz, CH$_2$O), 4.67 (s, 1H, OH), 7.23-7.36 (m, 10H); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 28.02 (CH$_2$), 53.21 (CH$_2$), 58.64 (CH$_2$), 63.91 (CH$_2$), 127.33 (CH), 128.52 (CH), 129.21 (CH), 138.33 (C); $R_f$ ($n$-hexanes/ethyl acetate: 3/1): 0.43

$N,N$-Dibenzylaminopropyl-$p$-toluenesulfonate (125)

124 (1.28 g, 5.0 mmol), triethylamine (0.70 mL, 5.0 mmol) and $p$-toluenesulfonyl chloride (0.95 g, 5.0 mmol) in DCM (5 mL) were reacted according to a similar way as employed for the preparation of 116 (method B). 125 (0.84 g, 39%) was isolated as an off-white solid.
IR $\nu_{\text{max}}/\text{cm (neat)}$: 3442 (br, bonded OH), 2922 (C-H aromatic), 1187 (C-N); $^1$H NMR (270 MHz, CDCl$_3$): 1.78 (virtual quintuplet, 2H, $J$=6.7 Hz, CH$_2$), 2.41 (s, 3H, CH$_3$), 2.43 (t, 2H, $J$=6.7 Hz, CH$_2$N), 3.46 (s, 4H, 2xCH$_2$Ph), 4.03 (t, 2H, $J$=6.8 Hz, CH$_2$O), 7.21-7.31 (m, 12H), 7.72 (d, 2H, $J$=8.4 Hz); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 14.35 (CH$_2$), 21.34 (CH$_3$), 59.23 (CH$_2$), 64.65 (CH$_2$), 126.00 (CH), 128.73 (C), 128.76 (CH), 129.36 (CH), 130.42 (CH), 132.59 (CH), 139.40 (C), 143.79 (C); mp > 220 °C

1,3-Bis-tert-butoxycarbonyl-1-((N,N-dibenzyaminopropyl)-2-methyl-2-thiopseudourea (126)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (0.64 g, 2.21 mmol), sodium hydride (60% in oil, 88 mg, 2.20 mmol), 15-crown-5 (40 µL, 0.22 mmol) and 125 (1.04 g, 2.44 mmol) in dry DMF (5 mL) were reacted according to the general procedure B. 126 was isolated as a colourless oil (0.82 g, 71%).

$^1$H NMR (270 MHz, CDCl$_3$): 1.42 (s, 9H, C(CH$_3$)$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 1.83-1.94 (m, 2H), 2.32 (s, 3H, CH$_3$), 2.42 (t, 2H, $J$=6.8 Hz, CH$_2$N), 3.53 (s, 4H, 2xCH$_2$Ph), 3.53 (m, 2H, CH$_2$NCN), 7.18-7.36 (m, 10H); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 15.53 (CH$_3$), 26.36 (CH$_2$), 28.04 (C(CH$_3$)$_3$), 28.09 (C(CH$_3$)$_3$), 47.53 (CH$_2$), 50.78 (CH$_2$), 58.18 (2xCH$_2$), 81.69 (C(CH$_3$)$_3$), 82.20 (C(CH$_3$)$_3$), 126.85 (CH), 128.21 (CH), 128.85 (CH), 139.60 (C), 151.79 (CO), 157.87 (CO), 163.11 (NCN); R$_f$ (n-hexanes/ethyl acetate: 3/1): 0.64

17-Cyclopentylmethyl-6,7-didehydro-4,5a-epoxy-5'-(N',3'-dibenzylamino propyl)guanidinyl-3,14-dihydroxyindolo[2',3',6,7]-morphinan (131)

53 (0.13 g, 0.30 mmol), mercury(II) chloride (0.12 g, 0.43 mmol), triethylamine (0.08 mL, 0.56 mmol) and 126 (0.31 g, 0.59 mmol) were reacted according to the general procedure A. After purification, a mixture containing 127 and the mono-BOC protected derivative was isolated as a brown solid (0.13 g, 48%). MS (FAB): $m/z$ = 909 (M+H); C$_{54}$H$_{64}$N$_6$O$_7$ requires 908; R$_f$ (DCM/MeOH/NH$_3$OH: 200/10/1): 0.31

The above mixture (66 mg, 73 µmol) in DCM (3 mL) was treated with trifluoroacetic acid (0.2 mL) as described in the general procedure P and 131 (TFA salt) was isolated as an off-white solid (70 mg, 82%).
\( ^1 H \) NMR (270 MHz, CD\(_3\)OD): 0.54 (d, 2H, \( J=4.2 \) Hz, NCH\(_2\)CH(CH\(_2\)CH\(_2\)CHH)), 0.74-0.91 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)H)), 1.11-1.21 (m, 1H, NCH\(_2\)CH(CH\(_2\)CH\(_2\)), 4.37 (s, 4H, 2xCH\(_2\)Ph), 5.73 (s, 1H, 5-H), 6.65 (d, 1H, \( J=8.2 \) Hz, 1-H), 6.67 (d, 1H, \( J=8.2 \) Hz, 2-H), 6.93 (dd, 1H, \( J=1.9 \) Hz and \( J=8.6 \) Hz, 6'-H), 7.29 (d, 1H, \( J=1.9 \) Hz, 4'-H), 7.44 (d, 1H, \( J=8.6 \) Hz, 7'-H); \( ^{13} C \) NMR (67.8 MHz, CD\(_3\)OD): 3.34 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 6.20 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 6.81 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 24.49 (CH\(_2\)), 24.99 (CH\(_2\)), 29.68 (CH\(_2\)), 30.23 (CH\(_2\)), 39.61 (CH\(_2\)), 47.56 (16-C), 50.68 (CH\(_2\)), 58.48 (2xCH\(_2\)Ph), 58.90 (18-C), 63.62 (9-C), 73.57 (14-C), 84.86 (5-C), 110.05, 113.84, 118.26, 119.36, 120.63, 122.32, 122.57, 126.71, 128.54, 130.27, 130.47, 130.83, 131.20, 132.18, 132.53, 138.21, 142.13, 144.78, 157.56 (NCN); mp : 188 °C; Anal. (C\(_{44}\)H\(_{48}\)N\(_6\)O\(_3\)).3TFA:2H\(_2\)O) requires C 55.25 %, H 5.10 %, N 7.73 %, found: C 55.3 %, H 4.92 %, N 7.60 %

**1,3-Bis-tert-butoxycarbonyl-1-(5'-iodopentyl)-2-methyl-2-thiopseudourea (132)**

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (2.95 g, 10.1 mmol), sodium hydride (60% in oil, 0.41 g, 10.2 mmol), 15-crown-5 (0.2 mL, 1 mmol) and 1,5-diiodopentane (4.5 mL, 33.5 mmol) in dry DMF (5 mL) were reacted according to the general procedure B, but the reaction mixture was stirred at room temperature overnight. 132 was isolated as a colourless oil (2.50 g, 51%).

IR \( \nu_{max}/cm \) (neat): 2977, 2932 (C-H aromatic), 1719 (C=\(_N\)), 1618 (carbamate), 1143 (C-N); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 1.30-1.40 (m, 2H), 1.46 (s, 9H, C(CH\(_3\))\(_3\)), 1.48 (s, 9H, C(CH\(_3\))\(_3\)), 1.61-1.72 (m, 2H), 1.83 (virtual quintuplet, 2H, \( J=7.2 \) Hz), 2.37 (s, 3H, SCH\(_3\)), 3.16 (t, 2H, \( J=6.9 \) Hz, CH\(_2\)), 3.48 (m, 2H, CH\(_2\)N); \( ^{13}C \) NMR (67.8 MHz, CDCl\(_3\)): 6.59 (CH\(_2\)), 15.55 (CH\(_3\)), 27.60 (CH\(_2\)), 27.70 (CH\(_2\)), 27.98 (C(CH\(_3\))\(_3\)), 28.05 (C(CH\(_3\))\(_3\)), 32.93 (CH\(_2\)), 48.56 (CH\(_2\)N), 81.79 (C(CH\(_3\))\(_3\)), 82.25 (C(CH\(_3\))\(_3\)), 151.85 (CO), 157.83 (CO), 162.79 (NCN); MS (FAB): \( m/z = 486.9 \) (M); \( C_{17}H_{31}lN_2O_4S \) requires 486.410; \( Rf(n\)-hexanes/ethyl acetate: 5/1): 0.65

**1,3-Bis-tert-butoxycarbonyl-1-(5'-nitropentyl)-2-methyl-2-thiopseudourea (133)**

A solution of sodium nitrite (2.16 g, 3.08 mmol) and 132 (0.90 g, 1.86 mmol) in a mixture of DMF (5 mL) and water (1 mL) was stirred for 2 hrs at room temperature.
Water was added and the aqueous solution extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO₄ and the solvent removed under vacuum. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, afforded 133 as a colourless oil (0.30 g, 40%).

IR ν_max/cm⁻¹ (neat): 2978, 2934 (C-H aromatic), 1719 (C=O), 1617 (carbamate), 1143 (C-N); ¹H NMR (270 MHz, CDCl₃): 1.36-1.46 (m, 2H), 1.46 (s, 9H, C(CH₃)₃), 1.49 (s, 9H, C(CH₃)₃), 1.65-1.76 (m, 2H), 2.03 (virtual quintuplet, 2H, J=7.3 Hz), 2.37 (s, 3H, SCH₃), 3.47-3.53 (m, 2H, CH₂NBoc), 4.37 (t, 2H, J=6.9 Hz, CH₂NO₂); ¹³C NMR (67.8 MHz, CDCl₃): 15.60 (CH₃), 23.39 (CH₂), 26.89 (CH₂), 28.00 (C(CH₃)₃), 28.07 (C(CH₃)₃), 48.22 (CH₂NCN), 75.42 (CH₂NO₂), 81.93 (C(CH₃)₃), 82.45 (C(CH₃)₃), 151.85 (CO), 157.85 (CO), 162.67 (NCN); Rf (n-hexanes/ethyl acetate: 3/1): 0.64

17-Cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-5'-nitropentyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (134) 53 (0.30 g, 0.71 mmol), mercury(II) chloride (0.28 g, 0.99 mmol), triethylamine (0.20 mL, 1.41 mmol) and 133 (0.57 g, 1.41 mmol) were reacted according to the general procedure A. After purification, a mixture containing 134 and its mono-BOC protected analogue was isolated as a brown solid (0.18 g, 32%).

IR ν_max/cm⁻¹ (neat): 3394 (br, bonded OH and NH), 2976, 2931 (C-H aromatic), 1707 (C=O), 1614 (carbamate), 1148 (C-N); ¹H NMR (270 MHz, CDCl₃) (data for di-BOC protected derivative): 0.14 (d, 2H, J=4.3 Hz, NCH₂CH(CHHCHH)), 0.54 (d, 2H, J=7.9 Hz, NCH₂CH(CHHCHH)), 0.83-0.92 (m, 1H, NCH₂CH(CH₂CH₂)), 1.37 (s, 9H, C(CH₃)₃), 1.48 (s, 9H, C(CH₃)₃), 5.64 (s, 1H, 5-H), 6.48 (d, 1H, J=8.0 Hz, 1-H), 6.53-6.59 (m, 1H), 6.76-6.81 (m, 1H), 7.02-7.16 (m, 2H); ¹H NMR (270 MHz, CDCl₃) (data for mono-BOC protected derivative): 0.14 (d, 2H, J=4.2 Hz, NCH₂CH(CHHCHH)), 0.55 (d, 2H, J=7.6 Hz, NCH₂CH(CHHCHH)), 0.81-0.93 (m, 1H, NCH₂CH(CH₂CH₂)), 1.13 (s, 9H, C(CH₃)₃), 5.59 (s, 1H, 5-H), 6.46 (d, 1H, J=8.2 Hz, 1-H), 6.56 (d, 1H, J=8.2 Hz, 2-H), 6.74-6.85 (m, 1H), 7.02-7.10 (m, 2H); MS (FAB): m/z = 687 (M+H), 787 (M+H); P (mono-BOC protected derivative) C₃₇H₄₆N₆O₇ requires 686; P (di-BOC protected derivative) C₄₂H₅₄N₆O₉ requires 786; Rf (DCM/MeOH/NH₄OH: 100/16/1.6): 0.46
**17-Cyclopropylmethyl-6,7-didehydro-4,5β-epoxy-5'-bis-tert-butoxycarbonyl-(N'-5'-aminopentyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (135)**

**Method A**

The above mixture (50 mg, 64 µmol) and iron(II)sulfate heptahydrate (0.16 g, 0.58 mmol) in methanol (2 mL), water (0.5 mL) and concentrated ammonia (1 mL) were reacted according to the same procedure as employed for the preparation of 53. After purification by column chromatography, eluting first with CHCl₃ then with CHCl₃/MeOH/NH₄OH: 250/10/1, a mixture containing 135 and its mono-BOC protected analogue was isolated as a brown solid (21 mg, 43 %).

**Method B**

To a suspension of palladium (10 wt. % on activated carbon) (40 mg, 38 µmol) in dry methanol (1.5 mL) were added 134 (and its mono-BOC protected derivative) (60 mg, 76 µmol) and ammonium formate (60 mg, 0.95 mmol). The solution was refluxed for 2 hrs, after which the solid was removed by filtration and the solvent evaporated. The crude product was purified by column chromatography, eluting first with CHCl₃: 100%, then with gradient elution (CHCl₃/MeOH/NH₄OH: 500/10/1 to CHCl₃/MeOH/NH₄OH: 250/10/1). A mixture containing 135 and its mono-BOC protected analogue was isolated as a brown solid (17 mg, 29%).

**IR v_max/cm (neat):** 3529 (br, bonded OH and NH), 2926 (C-H aromatic), 1717 (C=N), 1611 (carbamate), 1145 (C-N); **¹H NMR (270 MHz, CDCl₃):** 0.14 (d, 2H, J=4.7 Hz, NCH₂CH(CH₂/CH₂)), 0.55 (d, 2H, J=8.4 Hz, NCH₂CH(CH₂/CH₂)), 0.84-0.96 (m, 4H), 3.77 (t, 1H), 5.63 (s, 1H, 5-H), 6.42-6.60 (m, 3H, 1-H + 2-H + Ar), 6.89-6.92 (m, 1H), 7.08-7.14 (m, 1H), 7.97-8.02 (br, m, 1H); **MS (FAB):** m/z = 757 (M+H); C₄₂H₅₆N₆O₇ requires 756; R_f (DCM/MeOH/NH₄OH: 100/16/1.6): 0.43

**17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tert-butoxycarbonyl-(N'-5'-isothiocyanatopentyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (136)**

135 and its mono-BOC protected analogue (12 mg, 16 µmol), sodium hydrogencarbonate (8.0 mg, 95 µmol) and thiophosgene (1.3 µL, 17 µmol) were
reacted according to the general procedure N. After purification, a mixture containing 136 and the mono-BOC analogue was isolated as a white solid (9 mg, 71%).

Data for 136:
IR $\nu_{max}/cm$ (neat): 3329 (br, bonded OH and NH), 2183 and 2106 (isothiocyanate), 1704 (C=\(\equiv\)N, NH and NH$_2$), 1644 and 1613 (carbamate); $^1$H NMR (270 MHz, CDCl$_3$):
0.14 (d, 2H, $J$=4.7 Hz, NCH$_2$CH(CH$_2$CH$_2$H)), 0.55 (d, 2H, $J$=7.9 Hz, NCH$_2$CH(CH/H/CH)), 0.83-0.94 (m, 1H, NCH$_2$CH(CH$_2$CH$_2$H)), 1.37 (s, 9H, C(CH$_3$_3), 1.49 (s, 9H, C(CH$_3$_3), 5.65 (s, 1H, 5-H), 6.51 (d, 1H, $J$=8.0 Hz, 1-H), 6.57 (d, 1H, $J$=8.0 Hz, 2-H), 6.80 (s, 1H, 6'-H), 6.99-7.18 (m, 2H, 4'-H + 7'-H), 9.13 (s, br, 1H, NH); $R_f$ (DCM/MeOH: 10/1): 0.51

17-Cyclopropylmethyl-6,7-didehydro-4,5a-epoxy-5'-N'-5'-isothiocyanatopentyl guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (137)
The above mixture (136 and its mono-BOC protected analogue) (12.7 mg, 15.9 pmol) in DCM (2 mL) was treated with trifluoroacetic acid (0.2 mL) as described in the general procedure P. 137 (TFA salt) was isolated as a white solid (6.9 mg, 46%).

IR $\nu_{max}/cm$ (neat): 3342 (br, bonded OH and NH), 2184 and 2105 (isothiocyanate), 1704 (C=\(\equiv\)N, NH and NH$_2$); $^1$H NMR (270 MHz, CD$_3$OD): 0.54 (d, 2H, $J$=3.7 Hz, NCH$_2$CH(CH/H/CH/H)), 0.76-0.92 (m, 2H, NCH$_2$CH(CH/H/CH/H)), 1.11-1.22 (m, 1H, NCH$_2$CH(CH$_2$CH$_2$H)), 1.93-2.02 (m, 2H, CH$_2$), 3.58 (t, 2H, $J$=6.5 Hz, CH$_2$), 4.23 (d, 1H, $J$=6.1 Hz, CH$_2$), 5.73 (s, 1H, 5-H), 6.64 (d, 1H, $J$=8.2 Hz, 1-H), 6.68 (d, 1H, $J$=8.2 Hz, 2-H), 7.01-7.06 (m, 1H, 6'-H), 7.34-7.36 (m, 1H, 4'-H), 7.46 (dd, 1H, $J$=2.2 Hz and $J$=8.6 Hz, 7'-H); MS (FAB): $m/z$ = 599.2822 (M+H); C$_{33}$H$_{39}$N$_6$O$_3$S requires 599.2804; mp > 250°C

1,3-Bis-tert-butoxycarbonyl-1-allyl-2-methyl-2-thiopseudourea (138)
1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (3.86 g, 13.3 mmol), sodium hydride (60% in oil, 0.52 g, 12.9 mmol), 15-crown-5 (0.26 mL, 13 mmol) and diiodopropane (4.58 mL, 39.9 mmol) were reacted according to the general procedure B, but the reaction mixture was stirred overnight at room temperature. 138 was isolated as a colourless oil (2.04 g, 47%)
IR $v_{\text{max}}$/cm (neat): 3084 (CH, alkene), 1722 (C=N), 1618 (carbamate), 1144 (C-N); $^1$H NMR (270 MHz, CDCl$_3$): 1.44 (s, 9H, C(CH$_3$)$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 2.35 (s, 3H, SCH$_3$), 4.11 (td, 2H, $J$=1.4 and $J$=5.9 Hz, CH$_2$NBOC), 5.13-5.26 (m, 2H), 5.79-5.93 (m, 1H); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 15.55 (CH$_3$), 28.02 (C(CH$_3$)$_3$), 28.04 (C(CH$_3$)$_3$), 51.26 (CH$_2$), 81.74 (C(CH$_3$)$_3$), 82.51 (C(CH$_3$)$_3$), 117.90 (CH$_2$), 133.01 (CH), 151.59 (CO), 157.86 (CO), 162.98 (CN); MS (FAB): $m/z$ = 331.1695 (M+H); C$_{15}$H$_{27}$N$_2$O$_4$S requires 331.1691; R$_f$ (n-hexanes/ethyl acetate: 5/1): 0.57

1,3-Bis-tert-butoxycarbonyl-1-(4'-bromobutyl)-2-methyl-2-thiopseudourea (140)

1,3-Bis-tert-butoxycarbonyl-2-methyl-2-thiopseudourea (2.95 g, 10.2 mmol), sodium hydride (60% in oil, 0.41 g, 10.2 mmol), 15-crown-5 (0.2 mL, 1.0 mmol) and 1,4-dibromobutane (4.0 mL, 33.5 mmol) in dry DMF (5 mL) were reacted according to the general procedure B, but the reaction mixture was stirred overnight at room temperature. 140 was isolated as a colourless oil (2.07 g, 48%).

IR $v_{\text{max}}$/cm (neat): 2979, 2932 (C-H aromatic), 1720 (C=N), 1648 (carbamate), 1139 (C-N); $^1$H NMR (270 MHz, CDCl$_3$): 1.45 (s, 9H, C(CH$_3$)$_3$), 1.48 (s, 9H, C(CH$_3$)$_3$), 1.76-1.90 (m, 4H), 2.36 (s, 3H, SCH$_3$), 3.39 (t, 2H, $J$=6.4 Hz, CH$_2$Br), 3.52 (t, 2H, $J$=7.2 Hz, CH$_2$NBOC); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 15.17 (SCH$_3$), 27.20 (CH$_2$), 27.61 (C(CH$_3$)$_3$), 27.66 (C(CH$_3$)$_3$), 29.52 (CH$_2$), 32.64 (CH$_2$), 47.47 (CH$_2$N), 81.30 (C(CH$_3$)$_3$), 81.92 (C(CH$_3$)$_3$), 151.35 (CO), 157.34 (CO), 162.15 (NCN); R$_f$ (n-hexanes/ethyl acetate: 3/1): 0.69

1,3-Bis-tert-butoxycarbonyl-1-(4'-nitrobutyl)-2-methyl-2-thiopseudourea (141)

A solution of sodium nitrite (2.74 g, 4.70 mmol) and 140 (1.00 g, 2.35 mmol) in DMF (5 mL) was stirred for 16 hrs at room temperature. Water was then added and the solution extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO$_4$ and the solvent removed under vacuum. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, afforded 141 (0.17 g, 19%). The reaction was repeated with DMF/H$_2$O: 5/1 as the solvent mixture and the yield improved to 36%.
\(^1\)H NMR (270 MHz, CDCl\(_3\)): 1.45 (s, 9H, C(CH\(_3\))\(_3\)), 1.47 (s, 9H, C(CH\(_3\))\(_3\)), 1.65-1.78 (m, 2H), 1.95-2.06 (m, 2H), 2.36 (s, 3H, S\(_2\)CH\(_3\)), 3.55 (t, 2H, J=7.2 Hz, CH\(_2\)NBOC), 4.39 (t, 2H, J=6.9 Hz, CH\(_2\)NO\(_2\)); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)): 15.46 (SCH\(_3\)), 24.31 (CH\(_2\)), 25.53 (CH\(_2\)), 27.85 (C(CH\(_3\))\(_3\)), 27.90 (C(CH\(_3\))\(_3\)), 47.47 (CH\(_2\)NCN), 74.89 (CH\(_2\)NO\(_2\)), 81.85 (C(CH\(_3\))\(_3\)), 82.54 (C(CH\(_3\))\(_3\)), 151.71 (CO), 157.67 (CO), 162.29 (NCN)

17-Cyclopropylmethyl-6,7-didehydro-4,5\(a\)-epoxy-5'-bis-tert-butoxycarbonyl-(N\(^{4'}\)-4'-nitrobutyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (142)

53 (0.17 g, 0.43 mmol), mercury(II) chloride (0.18 g, 0.65 mmol), triethylamine (0.12 mL, 0.86 mmol) and 141 (0.18 g, 0.43 mmol) were reacted according to the general procedure A. The reaction mixture was stirred at 60°C for 48 hours. After purification, a mixture containing 142 and its mono-BOC protected derivative was isolated as a yellowish solid (91 mg, 27%).

\(^1\)H NMR (270 MHz, CDCl\(_3\)): 0.15 (d, 2H, J=4.2 Hz, NCH\(_2\)CH(CHHCHH)), 0.56 (d, 2H, J=8.2 Hz, NCH\(_2\)CH(CHHCHH)), 0.84-0.93 (m, 1H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 1.36 (s, 9H, C(CH\(_3\))\(_3\)), 1.48 (s, 9H, C(CH\(_3\))\(_3\)), 3.80 (t, 2H, J=7.3 Hz, CH\(_2\)NBOc), 4.14 (s, br, 1H, NH), 4.38 (t, 2H, J=6.6 Hz, CH\(_2\)NO\(_2\)), 5.63 (s, 1H, 5'-H), 6.50 (d, 1H, J=7.7 Hz, 1-H), 6.54-6.60 (m, 1H, 2-H), 6.78-6.82 (m, 1H, 6'-H), 7.04-7.18 (m, 2H, 7'-H and 4'-H), 8.66 (s, br, 1H, NH); R\(_f\) (DCM/MeOH/NH\(_2\)OH: 100/16/1.6): 0.46

17-Cyclopropylmethyl-6,7-didehydro-4,5\(a\)-epoxy-5'-bis-tert-butoxycarbonyl-(N\(^{4'}\)-4'-aminobutyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]-morphinan (143)

A suspension of the above mixture (142 and its mono-BOC protected derivative) (40 mg, 52 \(\mu\)mol), palladium (10 wt. % on activated carbon) (33 mg, 31 \(\mu\)mol) and ammonium formate (64 mg, 1.01 mmol) in dry methanol (5 mL) were reacted according to the same procedure as used for the preparation of 135 (method B). A mixture containing 143 and its mono-BOC protected analogue was isolated as a brown solid (8 mg, 21%).

IR \(\nu\)\(_{\text{max}}\)/cm (neat): 3320 (br, bonded OH and NH), 2926 (C-H aromatic), 1700 (C=\(\equiv\))

\(^1\)H NMR (270 MHz, CDCl\(_3\) for 143): 0.15 (d, 2H, J=4.7 Hz, NCH\(_2\)CH(CHHCHH)),
17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'-(benzylimino) [7,7'-bimorphinan]-3,3',14,14'-tetrol (152)

NorBNI (13) (0.30g, 0.45 mmol), sodium hydride (0.18g, 4.52 mmol), 18-crown-6 (30 mg, 0.11 mmol) and benzyl bromide (0.16 mL, 1.36 mmol) were treated according to the general procedure I, the reaction being carried out however at room temperature and for 43 hours. The crude oil was purified by column chromatography, eluting with DCM/MeOH/NH₄OH: 400/10/1 to 290/10/1, to yield a mixture of tri- and pentabenzyl-substituted norBNI (0.33g). This mixture was dissolved in MeOH/conc. HCl (20 mL, 1/1) and heated to 90°C for 40 h. Cooling, basification (NH₄OH) and removal of the precipitate by filtration, was followed by evaporation of the filtrate to dryness. Column chromatography, eluting with DCM/MeOH/NH₄OH: 200/10/1, yielded BnorBNI (152) as an off-white solid (0.21g, 63%).

IR v max/cm⁻¹ (KBr): 3401 (br); ¹H NMR (400 MHz, CDCl₃): 0.09 (d, 4H, J=5.1 Hz, 2xNCH₂CH(CH₃CH₂)), 0.49 (d, 4H, J=8.2 Hz, 2xNCH₂CH(CH₃CH₂)), 0.78-0.83 (m, 2H, 2xNCH₂CH(CH₂CH₂)), 3.02 (d, 2H, J=18.3 Hz, 10-H + 10'-H), 3.16 (d, 2H, J=5.9 Hz, 9-H + 9'-H), 5.27 (d, 1H, J=15.8 Hz, NCH₇/H), 5.33 (s, 2H, 5-H + 5'-H), 5.51 (d, 1H, J=15.8 Hz, NCH₇/H), 6.42 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.49 (d, 2H, J=8.2 Hz, 2-H + 2'-H), 6.88-6.90 (m, 2H, Ar), 7.22-7.29 (m, 3H, Ar); ¹³C NMR (67.8 MHz, CDCl₃): 3.79 (2xNCH₂CH(CH₃CH₂)), 3.90 (2xNCH₂CH(CH₂CH₂)), 9.40 (2xNCH₂CH(CH₃CH₂)), 22.99 (10-C + 10'-C), 28.98 (8-C + 8'-C), 31.44 (15-C + 15'-C), 43.55 (16-C + 16'-C), 47.27 (CH₂), 48.06 (13-C + 13'-C), 59.34 (18-C + 18'-C), 62.37 (9-C + 9'-C), 72.72 (14-C + 14'-C), 85.00 (5-C + 5'-C), 116.44 (7-C + 7'-C), 116.76 (2-C + 2'-C), 118.61 (1-C + 1'-C), 125.29 (11-C + 11'-C), 125.50 (CH), 125.63 (6-C + 6'-C), 126.81 (CH), 128.62 (CH), 130.72 (12-C + 12'-C), 138.63 (3-C + 3'-C), 140.33 (C), 142.89 (4-C + 4'-C); MS (FAB): m/z = 752.3715 (M+H), C₄₇H₅₀N₅O₆ requires 752.3698; Rf (DCM/MeOH/NH₄OH: 110/10/1): 0.76; mp >
240°C; Anal. (C_{47}H_{49}N_{3}O_{6}:2HCl:5H_{2}O) requires C 61.73 %, H 6.72 %, N 4.59 %, found: C 62.06 %, H 6.95 %, N 4.76 %

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'-{(3-

isothiocyanatomethyl)benzylimino}{7,7'-bimorphinan}-3,3',14,14'-tetrol (161)

205 (15 mg, 20 pmol), sodium hydrogencarbonate (9.8 mg, 117 pmol) and

thiophosgene (1.6 µL, 21 pmol) were reacted according to the general procedure N.

After purification, 161 was isolated as a white solid (7 mg, 44%).

IR ν_{max}/cm (neat): 3294 (br, bonded OH), 3111 (isothiocyanate); ^1H NMR (270 MHz, CDCl₃): 0.10 (d, 4H, J=4.2 Hz, NCH₂CH(CH/H/C/H)), 0.47-0.52 (m, 4H, NCH₂CH(CH/H/C/H)), 0.76-0.88 (m, 2H, NCH₂CH(CH₂CH₂)), 1.58 (d, 2H, J=8.6 Hz), 3.03 (d, 2H, J=18.5 Hz), 3.16 (d, 2H, J=5.2 Hz), 5.24 (d, 1H, J=17.1 Hz, NCH/HPh), 5.27 (s, 2H, 5-H + 5'-H), 5.41 (d, 1H, J=17.1 Hz, NCH/HPh), 6.48 (d, 2H, J=8.3 Hz, 1-H + 1'-H), 6.58 (d, 2H, J=8.3 Hz, 2-H + 2'-H), 6.69-6.74 (m, 1H), 7.01 (s, 1H), 7.09-7.14 (m, 1H), 7.21-7.27 (m, 1H); ^13C NMR (67.8 MHz, CDCl₃): 3.79 (2xNCH₂CH(CH₂CH₂)), 3.91 (2xNCH₂CH(CH₂CH₂)), 9.32 (2xNCH₂CH(CH₂CH₂)), 23.03 (10-C + 10'-C), 28.94 (8-C + 8'-C), 31.40 (15-C + 15'-C), 43.53 (16-C + 16'-C), 46.85 (CH₂), 48.06 (13-C + 13'-C), 59.30 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.61 (14-C + 14'-C), 84.83 (5-C + 5'-C), 116.78 (CH), 118.74 (CH), 123.25 (CH), 124.45 (CH), 124.84 (CH), 125.26 (C), 125.57 (C), 129.82 (CH), 130.54 (C), 131.50 (C), 135.06 (NCS), 138.62 (C), 141.52 (C), 142.71 (C); MS (FAB): m/z = 808.3351 (M), 809.3359 (M+H); C_{48}H_{49}N_{4}O_{6}S requires 809.3372; R_{f} (DCM/MeOH: 10/1): 0.44; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'-(3-

isothiocyanatomethyl)benzylimino){7,7'-bimorphinan}-3,3',14,14'-tetrol (163)

169 (16 mg, 21 µmol), sodium hydrogencarbonate (10.3 mg, 122 µmol) and

thiophosgene (1.7 µL, 21 µmol) were reacted according to the general procedure N.

After purification, 163 was isolated as a white solid (15 mg, 89%).

IR ν_{max}/cm (neat): 3385 (br, bonded OH), 2179 and 2096 (isothiocyanate); ^1H NMR (270 MHz, CDCl₃): 0.09 (d, 4H, J=4.3 Hz, 2xNCH₂CH(CH/H/H)), 0.49 (d, 4H,
$J=7.9 \text{ Hz, } 2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$, 0.75-0.88 (m, 2H, $2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 3.02 (d, 2H, $J=18.5 \text{ Hz}$), 3.15 (d, 2H, $J=5.9 \text{ Hz}$), 4.67 (s, 2H, CH$_2$NCS), 5.27 (d, 1H, $J=17.1 \text{ Hz, NCH}_2\text{HPh}$), 5.29 (s, 2H, 5-H + 5'-H), 5.47 (d, 1H, $J=17.1 \text{ Hz, NCH}_2\text{HPh}$), 6.47 (d, 2H, $J=8.1 \text{ Hz, 1-H + 1'-H}$), 6.56 (d, 2H, $J=8.1 \text{ Hz, 2-H + 2'-H}$), 6.90 (d, 2H, $J=8.2 \text{ Hz, Ar}$), 7.23 (d, 2H, $J=8.2 \text{ Hz, Ar}$); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 3.77 ($2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 3.89 ($2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 9.31 ($2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 23.01 (10-C + 10'-C), 28.95 (8-C + 8'-C), 31.37 (15-C + 15'-C), 43.51 (16-C + 16'-C), 47.02 (NCH$_2$), 48.02 (13-C + 13'-C), 48.29 (CH$_2$NCS), 59.29 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.66 (14-C + 14'-C), 84.87 (5-C + 5'-C), 116.59 (C), 116.72 (CH), 118.67 (CH), 125.21 (C), 125.60 (C), 126.20 (CH), 127.17 (CH), 130.67 (C), 131.98 (NCS), 132.85 (C), 138.63 (C), 140.19 (C), 142.75 (C); MS (FAB): $m/z = 822.3418$ (M), 823.3495 (M+H); $C_{49}H_{50}N_4O_6S$ requires 822.3451; $R_f$ (DCM/MeOH: 10/1): 0.43; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxy-6,6'-((3-(isothiocyanatomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (164) 170 (11 mg, 14 µmol), sodium hydrogen carbonate (7.1 mg, 84 µmol) and thiophosgene (1.2 µL, 15 µmol) were reacted according to the general procedure N. After purification, 164 was isolated as a white solid (8 mg, 70%).

IR $v_{\text{max}}$/cm (neat): 3303 (br, bonded OH), 2165 and 2096 (isothiocyanate); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 3.80 ($2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 3.91 ($2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 9.33 ($2\text{xNCH}_2\text{CH(CH}_2\text{CH)}$), 23.06 (10-C + 10'-C), 28.95 (8-C + 8'-C), 31.43 (15-C + 15'-C), 43.50 (16-C + 16'-C), 47.09 (NCH$_2$), 48.01 (13-C + 13'-C), 48.44 (CH$_2$NCS), 59.31 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.74 (14-C + 14'-C), 84.92 (5-C + 5'-C), 116.62 (CH), 116.68 (C), 118.74 (CH), 124.07 (CH), 125.32 (C), 125.43 (CH), 125.62 (C), 125.68 (CH), 129.13 (CH), 130.74 (C), 131.14 (NCS), 135.06 (C), 138.55 (C), 140.87 (C), 142.77 (C); $R_f$ (DCM/MeOH: 10/1): 0.43; mp (oxalate salt) > 220°C

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**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-(2-(isothiocyanatomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (165)**

171 (20 mg, 26 µmol), sodium hydrogen carbonate (19 mg, 226 µmol) and thiophosgene (2.1 µL, 28 µmol) were reacted according to the general procedure N. After purification, 165 was isolated as a white solid (7.4 mg, 35%).

**IR νmax/cm (neat):** 3370 (br, bonded OH), 2161 and 2094 (isothiocyanate); **1H NMR (270 MHz, CDCl3):** 0.09 (d, 4H, J=4.4 Hz, 2xNCH2CH(CH2CH2)), 0.46-0.52 (m, 4H, 2xNCH2CH(CH2CH2)), 0.75-0.87 (m, 2H, 2xNCH2CH(CH2CH2)), 3.02 (d, 2H, J=18.3 Hz), 3.15 (d, 2H, J=6.4 Hz), 4.84 (d, 1H, J=16.2 Hz, CHNCS), 4.92 (d, 1H, J=16.2 Hz, CHNCS), 5.23 (d, 1H, J=17.3 Hz, NCHHPh), 6.50 (s, 2H, 5-H + 5'-H), 5.52 (d, 1H, J=17.3 Hz, NCHHPh), 6.35 (d, 1H, J=6.9 Hz), 6.50 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.57 (d, 2H, J=8.2 Hz, 2-H + 2'-H), 7.21-7.41 (m, 3H); **13C NMR (67.8 MHz, CDCl3):** 3.79 (2xNCH2CH(CH2CH2)), 3.90 (2xNCH2CH(CH2CH2)), 9.38 (2xNCH2CH(CH2CH2)), 23.03 (10-C + 10'-C), 28.97 (8-C + 8'-C), 31.43 (15-C + 15'-C), 43.52 (16-C + 16'-C), 44.49 (CH2), 46.73 (CH2), 48.10 (13-C + 13'-C), 59.33 (18-C + 18'-C), 62.34 (9-C + 9'-C), 72.64 (14-C + 14'-C), 84.80 (5-C + 5'-C), 116.74 (CH), 116.88 (C), 118.77 (CH), 125.28 (C), 125.68 (C), 126.23 (CH), 127.46 (CH), 128.01 (CH), 129.48 (CH), 130.18 (C), 130.60 (C), 132.48 (NCS), 137.69 (C), 138.57 (C), 142.71 (C); **MS (FAB):** m/z = 823.3449 (M), 823.3537 (M+H); C49H51N4O6S requires 823.3529; Rf (DCM/MeOH: 10/1): 0.44; mp > 220°C

**17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-(3-aminobenzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (167)**

198 (60 mg, 56 µmol) was dissolved in a mixture of conc. HCl/MeOH (5mL, 1/1) and the reaction was stirred overnight at 85°C. The solvents were then removed and water was added. The aqueous phase was basified to pH=8 with diluted NH4OH and extracted with DCM/MeOH: 5/1. The organic phase was dried (MgSO4) and the solvent evaporated. Purification by column chromatography, eluting first with CHCl3/MeOH/NH4OH: 450/10/1, then with CHCl3/MeOH/NH4OH: 300/10/1, afforded 203 (34 mg, 68%). 203 (29 mg, 32 µmol) and hydrazine hydrate (3.0 µL, 96 µmol) in ethanol (1 mL) were reacting according to the general procedure O. 167 was isolated as a brown solid (22 mg, 90%).
IR $\nu_{\text{max}}$/cm (neat): 3368 (br, bonded OH and NH); $^1$H NMR (270 MHz, CDCl$_3$): 0.08-0.10 (m, 4H, NCH$_2$CH(CHOHCH)$_2$), 0.48-0.51 (m, 4H, NCH$_2$CH(CHOHCH)$_2$), 0.79-0.88 (m, 2H, NCH$_2$CH(CH$_2$CH$_2$)), 3.02 (d, 2H, $J$=18.3 Hz), 3.15 (d, 2H, $J$=6.1 Hz), 5.17 (d, 1H, $J$=17.0 Hz, NCHH), 5.35 (s, 2H, 5-H + 5'-H), 5.39 (d, 1H, $J$=17.0 Hz, NCHH), 6.09 (s, 1H), 6.44 (d, 2H, $J$=8.0 Hz, 1-H + 1'-H), 6.46-6.57 (m, 2H), 6.55 (d, 2H, $J$=8.0 Hz, 2-H + 2'-H), 7.08 (t, 1H, $J$=7.8 Hz); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 3.76 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.90 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.35 (2xNCH$_2$CH (CH$_2$CH$_2$)), 23.00 (10-C + 10'-C), 28.94 (8-C + 8'-C), 31.41 (15-C + 15'-C), 43.54 (16-C + 16'-C), 47.28 (NCH$_2$), 48.01 (13-C + 13'-C), 59.31 (18-C + 18'-C), 62.30 (9-C + 9'-C), 72.75 (14-C + 14'-C), 84.88 (5-C + 5'-C), 112.76 (CH), 113.84 (CH), 116.08 (CH), 116.17 (C), 117.30 (CH), 118.55 (CH), 125.37 (C), 125.71 (C), 129.20 (CH), 130.80 (C), 138.62 (C), 140.84 (C), 143.28 (C), 146.72 (C); MS (FAB): m/z = 767 (M+H); C$_{47}$H$_{50}$N$_4$O$_6$ requires 766; R$_f$ (DCM/MeOH/NH$_4$OH: 100/10/1): 0.25; mp > 250°C

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-([4-aminomethyl]benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (169) 227 (39 mg, 43 µmol) in ethanol (1 mL) and hydrazine hydrate (6.3 µL, 202 µmol) were reacted according to the general procedure O. 169 was isolated as a brown solid (18 mg, 54%).

$^1$H NMR (270 MHz, CDCl$_3$): 0.05 (d, 4H, $J$=5.0 Hz, 2xNCH$_2$CH(CHOHCH)$_2$), 0.39-0.50 (m, 4H, 2xNCH$_2$CH(CHOHCH)$_2$), 0.68-0.79 (m, 2H, 2xNCH$_2$CH(CHOHCH)$_2$), 3.00 (d, 2H, $J$=18.3 Hz), 3.15 (d, 2H, $J$=6.2 Hz), 3.62 (s, 2H, CH$_2$NH$_2$), 3.72-4.18 (br, s, 2H, NH$_2$), 5.22 (d, 1H, $J$=16.8 Hz, NCHH), 5.27 (s, 2H, 5-H + 5'-H), 5.43 (d, 1H, $J$=16.8 Hz, NCHH), 6.46 (d, 2H, $J$=8.0 Hz, 1-H + 1'-H), 6.57 (d, 2H, $J$=8.0 Hz, 2-H + 2'-H), 6.80 (d, 2H, $J$=7.6 Hz), 7.12 (d, 2H, $J$=7.6 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 3.62 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.96 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.32 (2xNCH$_2$CH(CH$_2$CH$_2$)), 22.98 (10-C + 10'-C), 28.97 (8-C + 8'-C), 31.46 (15-C + 15'-C), 43.65 (16-C + 16'-C), 45.32 (CH$_2$NH$_2$), 47.06 (NCH$_2$), 48.01 (13-C + 13'-C), 59.29 (18-C + 18'-C), 62.22 (9-C + 9'-C), 72.73 (14-C + 14'-C), 84.56 (5-C + 5'-C), 116.40 (C), 117.24 (CH), 118.66 (CH), 124.56 (C), 125.57 (C), 126.15 (CH), 127.62 (CH), 130.66 (C), 138.30 (C), 139.32 (C), 140.76 (C), 142.94 (C); MS (FAB): m/z =
781.3952 (M+H); C_{48}H_{53}NaO_{6} requires 781.3864; Rf (DCM/MeOH/NH_{4}OH: 100/16/1.6): 0.34; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-((aminomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (170)

228 (32 mg, 35 µmol) in ethanol (1 mL) and hydrazine hydrate (4.4 µL, 141 µmol) were reacted according to the general procedure O. 170 was isolated as a brown solid (13 mg, 47%).

IR ν_{max}/cm (neat): 3419 (br, bonded OH and NH), 1640 (N-H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 3.73 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.91 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.34 (2xNCH$_2$CH(CH$_2$CH$_2$)), 23.01 (10-C + 10'-C), 28.96 (8-C + 8'-C), 31.57 (15-C + 15'-C), 43.59 (16-C + 16'-C), 45.30 (CH$_2$), 47.66 (CH$_2$), 47.99 (13-C + 13'-C), 59.30 (18-C + 18'-C), 62.31 (9-C + 9'-C), 72.73 (14-C + 14'-C), 84.63 (5-C + 5'-C), 116.14 (C), 118.10 (CH), 118.46 (CH), 125.00 (C), 125.86 (CH), 125.91 (CH), 126.44 (CH), 128.29 (CH), 130.76 (C), 139.14 (C), 141.81 (C), 143.92 (C); Rf (DCM/MeOH/NH$_4$OH: 100/16/1.6): 0.35; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-((aminomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (171)

229 (30 mg, 33 µmol) in ethanol (1 mL) and hydrazine hydrate (5.0 µL, 160 µmol) were reacted according to the general procedure O. 171 was isolated as a brown solid (22 mg, 86%).

IR ν_{max}/cm (neat): 3353 and 3076 (br, bonded OH and NH); $^{1}$H NMR (270 MHz, CDCl$_3$): 0.04 (d, 4H, $J$=4.4 Hz, 2xNCH$_2$CH(CH/H/H)), 0.44 (d, 4H, $J$=8.0 Hz, 2xNCH$_2$CH(CH/H/H)), 0.68-0.80 (m, 2H, 2xNCH$_2$CH(CH$_2$CH$_2$)), 3.06 (d, 2H, $J$=6.2 Hz), 3.29 (d, 1H, $J$=14.1 Hz, CH/H/NH$_2$), 3.77 (d, 1H, $J$=14.1 Hz, CH/H/NH$_2$), 4.95 (s, 2H, 5-H + 5'-H), 5.24 (d, 1H, $J$=15.0 Hz, NCH/H), 5.44 (d, 1H, $J$=15.0 Hz, NCH/H), 6.38 (d, 2H, $J$=8.1 Hz, 1-H + 1'-H), 6.50 (d, 2H, $J$=8.1 Hz, 2-H + 2'-H), 7.10 (d, 1H, $J$=7.2 Hz), 7.21-7.32 (m, 2H), 7.49 (d, 1H, $J$=7.2 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$/CD$_3$OD: 8/1): 3.64 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.73 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.18 (2xNCH$_2$CH(CH$_2$CH$_2$)), 22.81 (10-C + 10'-C), 28.70 (8-C + 8'-C), 31.43 (15-C
+ 15'-C), 42.14 (CH₂), 43.36 (16-C + 16'-C), 47.50 (CH₂ or 13-C + 13'-C), 47.60 (CH₂ or 13-C + 13'-C), 59.19 (18-C + 18'-C), 62.14 (9-C + 9'-C), 72.59 (14-C + 14'-C), 84.19 (5-C + 5'-C), 116.20 (C), 117.56 (CH), 118.57 (CH), 124.04 (C), 126.03 (C), 127.39 (CH), 128.64 (CH), 129.74 (CH), 130.57 (C), 131.93 (CH), 134.13 (C), 139.64 (C), 141.31 (C), 142.84 (C); MS (FAB): m/z = 781 (M+H); C₄₈H₅₂N₄O₆ requires 780; Rf (DCM/MeOH/NH₄OH: 100/16/1.6): 0.37; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-3-(4-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-{imino}[7,7'-bimorphinan]-3,14,14'-triol (172)

NorBNI (13) (0.66 g, 1.0 mmol), sodium hydride (60% in oil, 0.40 g, 10.0 mmol), 18-crown-6 (20 mg, 0.08 mmol) and 4-nitrobenzyl chloride (0.51 g, 3.0 mmol) in dry THF (20 mL) were reacted according to the general procedure I. 172 (0.08 g, 10 %) and 173 (0.28 g, 30 %) were isolated as brown solids, but no desired product could be isolated.

H NMR (270 MHz, CDCl₃): 0.07-0.12 (m, 4H, 2xNCH₂CH(CH₂CH₂)), 0.51-0.53 (m, 4H, 2xNCH₂CH(CH₂CH₂)), 0.79-0.91 (m, 2H, 2xNCH₂CH(CH₂CH₂)), 5.04 (d, 1H, J=13.2 Hz, OCH₂), 5.18 (d, 1H, J=13.2 Hz, OCH₂), 5.52 (s, 1H, 5-H or 5'-H), 5.62 (s, 1H, 5-H or 5'-H), 6.47-6.55 (m, 3H, 1-H + 1'-H + 2-H or 2'-H), 6.64 (d, 1H, J=8.2 Hz, 2-H or 2'-H), 7.44 (d, 2H, J=8.6 Hz), 8.11 (d, 2H, J=8.6 Hz), 8.82 (br, s, 1H, NH); Rf (DCM/MeOH/NH₄OH: 200/20/1): 0.29

17,17'-Bis(cyclopropylmethyl)-3,3'-{4-nitrobenzyloxy}-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-{imino}[7,7'-bimorphinan]-14,14'-diol (173)

Obtained as a side product from the reaction that gave 172 (brown solid).

H NMR (270 MHz, CDCl₃): 0.08 (d, 4H, J=4.7 Hz, 2xNCH₂CH(CH₂CH₂)), 0.49 (d, 4H, J=7.9 Hz, 2xNCH₂CH(CH₂CH₂)), 0.73-0.88 (m, 2H, 2xNCH₂CH(CH₂CH₂)), 5.07 (d, 2H, J=13.4 Hz, 2xOCH₂), 5.24 (d, 2H, J=13.4 Hz, 2xOCH₂), 5.45 (s, 2H, 5-H + 5'-H), 6.45 (d, 2H, J=8.1 Hz, 1-H + 1'-H), 6.54 (d, 2H, J=8.1 Hz, 2-H + 2'-H), 7.42 (d, 4H, J=8.1 Hz), 8.14 (d, 4H, J=8.1 Hz), 8.32 (br, s, 1H, NH), C NMR (67.8 MHz, CDCl₃): 3.56 (2xNCH₂CH(CH₂CH₂)), 3.76 (2xNCH₂CH(CH₂CH₂)), 9.21 (2xNCH₂CH(CH₂CH₂)), 22.93 (10-C + 10'-C), 28.66
(8-C + 8'-C), 31.34 (15-C + 15'-C), 43.30 (16-C + 16'-C), 47.49 (13-C + 13'-C), 58.97 (18-C + 18'-C), 61.84 (9-C + 9'-C), 69.66 (2xOCH2), 72.27 (14-C + 14'-C), 85.19 (5-C + 5'-C), 116.26 (C), 116.39 (CH), 118.40 (CH), 123.38 (CH), 124.59 (C), 126.91 (C), 127.74 (CH), 131.50 (C), 141.06 (C), 144.65 (C), 147.14 (C); \( R_f \) (DCM/MeOH/NH4OH: 200/12/1): 0.16

17,17'-Bis(cyclopropylmethyl)-3,3',(3-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan]-14,14'-diol (175)
Isolated as a side product from the reaction that afforded 176 (brown solid).

\(^1\)H NMR (270 MHz, CDCl3): 0.13 (d, 4H, \( J=4.2 \) Hz, 2xNCH2CH(CH2CH2)), 0.48-0.55 (m, 4H, 2xNCH2CH(CH2CH2)), 0.77-0.90 (m, 2H, 2xNCH2CH(CH2CH2)), 3.04 (d, 2H, \( J=18.5 \) Hz, 10-H + 10'-H), 3.18 (d, 2H, \( J=5.7 \) Hz, 9-H + 9'-H), 5.05 (d, 2H, \( J=11.9 \) Hz, 2xOCH2), 5.12 (d, 2H, \( J=11.9 \) Hz, 2xOCH2), 5.15 (s, 2H, 5-H + 5'-H), 6.48 (d, 2H, \( J=8.2 \) Hz, 1-H + 1'-H), 6.66 (d, 2H, \( J=8.2 \) Hz, 2-H + 2'-H), 7.24-7.42 (m, 8H), 8.10 (br, s, 1H); MS (FAB): \( m/z = 932 \) (M); C\(_{54}\)H\(_{53}\)N\(_5\)O\(_{10}\) requires 932

17,17'-Bis(cyclopropylmethyl)-3,3',(3-nitrobenzyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-nitrobenzylimino)[7,7'-bimorphinan]-14,14'-diol (176)
NorBNI (13) (0.10 g, 0.15 mmol), sodium hydride (60% in oil, 66 mg, 1.65 mmol) and 3-nitrobenzyl bromide (0.108 g, 0.50 mmol) in dry DMF (5 mL) were reacted according to the general procedure I. 176 (45 mg, 28 %) was isolated as a brown solid.

\(^1\)H NMR (270 MHz, CDCl3): 0.10 (d, 4H, \( J=4.2 \) Hz, 2xNCH2CH(CH2CH2)), 0.51 (d, 4H, \( J=7.9 \) Hz, 2xNCH2CH(CH2CH2)), 0.77-0.89 (m, 2H, 2xNCH2CH(CH2CH2)), 4.96 (s, 4H, OCH2), 5.26 (s, 2H, 5-H + 5'-H), 5.44 (d, 1H, \( J=17.3 \) Hz, NCHH), 5.54 (d, 1H, \( J=17.3 \) Hz, NCHH), 6.54 (d, 2H, \( J=8.2 \) Hz, 1-H + 1'-H), 6.64 (d, 2H, \( J=8.2 \) Hz, 2-H + 2'-H), 7.11-7.25 (m, 2H), 7.45-7.58 (m, 4H), 7.71 (d, 1H, \( J=8.4 \) Hz), 7.93 (s, 1H), 8.15 (d, 2H, \( J=7.9 \) Hz), 8.19 (s, 2H); MS (FAB): \( m/z = 1067 \) (M); C\(_{61}\)H\(_{58}\)N\(_6\)O\(_{12}\) requires 1067; \( R_f \) (DCM/MeOH/NH4OH: 200/12/1): 0.18
17,17'-Bis(cyclopropylmethyl)-3,3'-(benzyloxoy)-6,6',7,7'-tetrahydro-4,5:4',5'-
diepoxy-6,6'-(imino)[7,7'-bimorphinan]-14,14'-dil (177)

A solution of norBNI (13) (0.15 g, 0.23 mmol), benzyl bromide (0.14 mL, 1.13
mmol) and potassium carbonate (0.10 g, 0.68 mmol) in dry DMF (2 mL) was stirred
at room temperature for 22 hrs. Water (3 mL) was then added, the organic phase
isolated and the aqueous phase further extracted with DCM. The combined organic
phase was dried over MgSO₄ and concentrated under vacuum. The crude product was
purified by column chromatography, eluting first with 100% DCM, then with
DCM/MeOH/NH₄OH: 450/10/1, which afforded 177 as a brown solid (0.18 g, 94 %).

¹H NMR (400 MHz, CDCl₃): 0.12 (d, 4H, J=4.3 Hz, 2xNCH₂CH(CHOCH₂)), 0.52
(d, 4H, J=8.2 Hz, 2xNCH₂CH(CH₂CH₂)), 0.83-0.90 (m, 2H, 2xNCH₂CH(CH₂CH₂)), 3.05 (d, 2H, J=18.8 Hz), 3.18 (d, 2H, J=6.2 Hz), 5.07 (d, 2H, J=11.9 Hz, 2xOCHH), 5.12 (d, 2H, J=11.9 Hz, 2xOCHH), 5.46 (s, 2H, 5-H + 5'-H),
6.48 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.65 (d, 2H, J=8.2 Hz, 2-H + 2'-H), 7.27-7.42 (m,
10 H), 8.11 (br, s, 1H, NH); MS (FAB): m/z = 842 (M); C₅₄H₅₅N₃O₆ requires 842; Rf
(DCM/MeOH/NH₄OH: 290/10/1): 0.49

17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-tetraacetoxy-6,6',7,7'-tetrahydro-
4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (178)¹⁰²

NorBNI (13) (0.62 g, 0.93 mmol) was dissolved in acetic anhydride (15 mL) and the
solution was stirred for two hours at 100°C under a nitrogen atmosphere. Excess of
acetic anhydride was then removed under vacuum and the residual oil was basified to
pH=7 with NH₄OH. The aqueous phase was extracted with DCM and the organic
phase washed with brine, dried over MgSO₄ and concentrated under vacuum.
Purification by column chromatography, eluting first with CHCl₃ then with
CHCl₃/MeOH/NH₄OH: 450/10/1, afforded 178 as an off-white solid (0.75 g, 97%).

IR νmax/cm (KBr): 3348 (br, bonded NH), 1770 and 1729 (CO); ¹H NMR (270 MHz,
CDCl₃): 0.01-0.06 (m, 4H, NCH₂CH(CH₂CH₂)), 0.42-0.45 (m, 4H, NCH₂CH(CH₂CH₂)), 0.68-0.76 (m, 2H, NCH₂CH(CH₂CH₂)), 1.88 (s, 6H, 2xCH₃),
2.19 (s, 6H, 2xCH₃), 3.09 (d, 2H, J=18.8 Hz, 10-H and 10'-H), 3.17 (d, 2H, J=16.6
Hz, 8-H and 8'-H), 4.43 (d, 2H, J=5.9 Hz, 9-H and 9'-H), 5.48 (s, 2H, 5-H and 5'-H),
6.61 (d, 2H, J=8.2 Hz, 1-H and 1'–H), 6.75 (d, 2H, J=8.2 Hz, 2-H and 2'–H), 8.39 (br, s, 1H, NH); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)): 3.53 (2xNCH\(_2\)CH(CH\(_2\)CH\(_2\))), 3.68 (2xNCH\(_2\)CH(CH\(_2\)CH\(_2\))), 9.40 (2xNCH\(_2\)CH(CH\(_2\)CH\(_2\))), 20.49 (2xCH\(_3\)), 22.40 (2xCH\(_3\)), 23.79 (10-C + 10'–C), 24.37 (8-C + 8'–C), 30.91 (15-C + 15'–C), 43.49 (16-C + 16'–C), 48.05 (13-C + 13'–C), 55.77 (9-C + 9'–C), 59.44 (18-C + 18'–C), 84.04 (14-C + 14'–C), 85.81 (5-C + 5'–C), 115.44 (7-C + 7'–C), 118.36 (1-C + 1'–C), 121.98 (2-C + 2'–C), 124.21 (6-C + 6'–C), 130.86 (12-C + 12'–C), 132.00 (11-C + 11'–C), 132.45 (3-C + 3'–C), 146.89 (4-C + 4'–C), 168.58 (CO), 170.97 (CO); MS (FAB): m/z = 830.3638 (M+H); C\(_{48}\)H\(_{52}\)N\(_3\)O\(_{10}\) requires 830.2652; R\(_f\) (DCM/MeOH/NH\(_4\)OH: 200/12/1): 0.26; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-3,3'-{4-cyanobenzyloxy}-14,14'-diacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (179)

178 (0.25 g, 0.30 mmol), sodium hydride (60% in oil, 0.12 g, 3.00 mmol), 18-crown-6 (10 mg, 0.04 mmol) and \(\alpha\)-bromo-\(\beta\)-tolunitrile (0.12 g, 6.12 mmol) in dry THF (10 mL) were reacted according to the general procedure I. 179 (0.10 g, 33 %) was isolated as a brown solid, but no desired product could be isolated.

\(^{1}\)H NMR (270 MHz, CDCl\(_3\)): 0.02–0.07 (m, 4H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 0.44–0.47 (m, 4H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 0.67–0.81 (m, 2H, NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 1.95 (s, 6H, 2xCH\(_3\)), 4.43 (d, 2H, J=5.7 Hz, 9-H and 9'–H), 5.10 (d, 2H, J=13.1 Hz, 2xOCH\(_2\)H), 5.21 (d, 2H, J=13.1 Hz, 2xOCH\(_2\)H), 5.90 (s, 2H, 5-H and 5'–H), 6.57 (d, 2H, J=8.2 Hz, 1-H and 1'–H), 6.69 (d, 2H, J=8.2 Hz, 2-H and 2'–H), 7.45 (d, 4H, J=8.3 Hz), 7.63 (d, 4H, J=8.3 Hz); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)): 3.53 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 3.90 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 9.55 (NCH\(_2\)CH(CH\(_2\)CH\(_2\))), 22.58 (2xCH\(_3\))), 23.47 (10-C + 10'–C), 24.78 (8-C + 8'–C), 26.08 (CH\(_3\)), 31.55 (15-C + 15'–C), 43.55 (16-C + 16'–C), 47.90 (13-C + 13'–C), 55.56 (9-C + 9'–C), 59.59 (18-C + 18'–C), 71.39 (2xOCH\(_2\)), 82.57 (14-C + 14'–C), 85.23 (5-C + 5'–C), 111.57 (C), 118.16 (CH), 118.72 (C), 118.98 (CH), 121.41 (C), 126.93 (C), 127.69 (4xCH), 128.14 (C), 130.83 (C), 132.22 (4xCH), 141.19 (C), 143.02 (C), 144.56 (C), 169.81 (NCO), 170.87 (2xCO); MS (FAB): m/z = 1018 (M); C\(_{62}\)H\(_{59}\)N\(_3\)O\(_{9}\) requires 1018; R\(_f\) (DCM/MeOH/NH\(_4\)OH: 250/5/1): 0.27
17,17'-Bis(cyclopropylmethyl)-3,3'-(3-nitrobenzyloxy)-14,14'-diacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-nitrobenzylimino)[7,7'-bimorphinan] (180)

180 (0.20 g, 0.24 mmol), sodium hydride (60% in oil, 41 mg, 1.03 mmol) and 3-nitrobenzyl bromide (0.10 g, 0.48 mmol) in dry THF (6 mL) were reacted according to the general procedure I. 180 (70 mg, 29%) was isolated as a brown solid, but no desired product could be isolated.

$^1$H NMR (270 MHz, CDCl$_3$): 0.01-0.08 (m, 4H, NCH$_2$CH(CH/HCH/CH)), 0.68-0.78 (m, 2H, NCH$_2$CH(CH$_2$CH$_2$)), 1.56 (d, 2H, $J$=10.7 Hz), 1.79 (s, 3H, CH$_3$), 1.80 (s, 3H, CH$_3$), 3.04 (d, 2H, $J$=18.5 Hz), 3.24 (d, 2H, $J$=16.6 Hz), 4.43 (d, 2H, $J$=5.7 Hz), 4.81-5.02 (m, 4H, 2xOCH$_2$), 5.33 (s, 2H, 5-H and 5'-H), 6.39 (d, 2H, $J$=8.3 Hz, 1-H and 1'-H), 6.44 (d, 2H, $J$=8.3 Hz, 2-H and 2'-H), 7.40 (virtual double triplet, 2H, $J$=1.5 and 7.9 Hz), 7.64 (d, 2H, $J$=7.4 Hz), 8.09 (d, 2H, $J$=8.2 Hz), 8.21-8.24 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 3.45 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.87 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.52 (2xNCH$_2$CH(CH$_2$CH$_2$)), 22.42 (2xCH$_3$), 23.56 (10-C + 10'-C), 24.62 (8-C + 8'-C), 31.19 (15-C + 15'-C), 43.50 (16-C + 16'-C), 48.07 (13-C + 13'-C), 55.85 (9-C + 9'-C), 59.51 (18-C + 18'-C), 70.13 (2xOCH$_2$), 83.99 (14-C + 14'-C), 84.93 (5-C + 5'-C), 115.76 (C), 116.08 (CH), 118.48 (CH), 122.70 (CH), 122.77 (CH), 124.65 (C), 127.88 (C), 129.27 (CH), 130.51 (C), 133.73 (CH), 139.29 (C), 141.14 (C), 144.47 (C), 148.15 (C), 170.68 (CO); R$_f$(DCM/MeOH/NH$_3$OH: 500/10/1): 0.22

17,17'-Bis(cyclopropylmethyl)-3,3'-(3-nitrobenzyloxy)-14,14'-diacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(3-nitrobenzylimino)[7,7'-bimorphinan] (181)

180 (70 mg, 69 µmol), sodium hydride (60% in oil, 29 mg, 0.72 mmol) and 3-nitrobenzyl bromide (47 mg, 0.22 mmol) in dry THF (5 mL) were reacted according to the general procedure I. 181 (32 mg, 40%) was isolated as a brown solid.

IR $\nu_{max}$/cm (neat): 1762 and 1731 (CO); $^1$H NMR (270 MHz, CDCl$_3$): 0.01-0.07 (m, 4H, NCH$_2$CH(CH/HCH/CH)), 0.43 (d, 4H, $J$=6.9 Hz, NCH$_2$CH(CH/HCH/CH)), 0.67-0.77 (m, 2H, NCH$_2$CH(CH$_2$CH$_2$)), 1.87 (s, 6H, 2xCH$_3$), 4.44 (d, 2H, $J$=5.9 Hz), 4.86 (s, 4H, 2xOCH$_2$), 5.19 (s, 2H, 5-H and 5'-H), 5.40 (d, 1H, $J$=17.6 Hz, NCH/H), 5.48 (d, 1H, $J$=17.6 Hz, NCH/H), 6.57 (d, 2H, $J$=7.9 Hz, 1-H + 1'-H), 6.61-6.64 (m, 2H, 2-H +
2'-H), 7.23-7.27 (m, 2H), 7.42-7.68 (m, 6H), 8.06-8.15 (m, 4H); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)): 3.47 (2xNCH\(_2\)CH(CH\(_2\)CH\(_2\))), 3.93 (2xNCH\(_2\)CH(CH\(_2\)CH\(_2\))), 9.58 (2xNCH\(_2\)CH(CH\(_2\)CH\(_2\))), 22.42 (2xCH\(_3\)), 23.67 (10-C + 10'-C), 24.77 (8-C + 8'-C), 31.28 (15-C + 15'-C), 43.49 (16-C + 16'-C), 46.80 (NCH\(_2\)PhNO\(_2\)), 48.18 (13-C + 13'-C), 55.99 (9-C + 9'-C), 59.56 (18-C + 18'-C), 70.46 (2xOCH\(_2\)), 83.93 (14-C + 14'-C), 84.30 (5-C + 5'-C), 116.51 (C), 117.01 (CH), 118.86 (CH), 120.62 (CH), 121.70 (CH), 122.21 (CH), 122.76 (CH), 125.48 (C), 128.24 (C), 128.81 (CH), 129.30 (CH), 130.75 (C), 131.57 (CH), 133.15 (CH), 139.41 (C), 141.19 (C), 141.64 (C), 144.61 (C), 148.26 (C), 148.57 (C), 170.82 (CO); \(R_f\) (DCM/MeOH/NH\(_2\)OH: 250/5/1): 0.33

4-Phthalimidobenzyl bromide (182)

Method A

A solution of imidazole (80 mg, 1.16 mmol) and triphenylphosphine (0.30 g, 1.16 mmol) in DCM (5 mL) was cooled down to 0°C under a nitrogen atmosphere. Bromine (60 \(\mu\)L, 1.16 mmol) was added dropwise and the reaction mixture was stirred for 10 minutes. A solution of 190 (0.18 g, 0.53 mmol) in DCM (1 mL) was then added and the reaction mixture allowed to warm up to room temperature and stirred for a further 3 hrs. Water was added and the aqueous phase extracted several times with DCM. The organic phase was dried (MgSO\(_4\)) and the solvent evaporated. Purification by flash chromatography, eluting with \(n\)-hexanes/ethyl acetate: 4/1, gave 182 as a white solid (0.10 g, 60%).

Method B.

Bromine (0.18 mL, 3.51 mmol), triphenylphosphine (0.95 g, 3.62 mmol) and 194 (1.14 g, 3.10 mmol) were treated as described for the preparation of 184, which afforded 182 (0.53 g, 54%) as a white solid.

Method C.

To a solution of NaBrO\(_3\) (6.75 g, 45 mmol) in water (22.5 mL) was added 244 (3.55 g, 15 mmol) in ethyl acetate (30 mL). Stirring was continued for 10 minutes after which a solution of NaHSO\(_3\) (4.65 g, 45 mmol) in water (45 mL) was added dropwise. The reaction mixture was stirred for 6 hours at room temperature then poured into 200
mL of diethyl ether. The organic phase was collected and the aqueous phase further extracted with diethyl ether. The combined organic phase was washed with a solution of sodium hydrogensulfite, dried (MgSO₄) and concentrated under vacuum. 182 was isolated as a white solid after recrystallisation in acetone (2.94 g, 62%).

IR νₘₐₓ/cm (KBr): 2920, 2859 (C-H aromatic), 1707 (CO); ¹H NMR (270 MHz, CDCl₃): 4.52 (s, 2H, CH₂), 7.43 (d, 2H, J=8.5 Hz), 7.52 (d, 2H, J=8.5 Hz), 7.77-7.80 (m, 2H), 7.93-7.96 (m, 2H); ¹³C NMR (100.5 MHz, CDCl₃): 32.63 (CH₂), 123.89 (CH), 126.73 (CH), 129.88 (CH), 131.68 (C), 134.58 (CH), 137.52 (C), 167.15 (CO); MS (FAB): m/z = 315.9960 (M+H, ⁷⁹Br) and 317.9945 (M+H, ⁸¹Br); C₁₅H₁₁⁷⁹BrN₀₂ requires 315.9972; C₁₅H₁₁⁸¹BrN₀₂ requires 317.9952; Rₐ (n-hexanes/ethyl acetate: 4/1): 0.17, (n-hexanes/ethyl acetate: 1/1): 0.70; mp : 205°C

3-Phthalimidobenzyl bromide (183)
Bromine (0.15 mL, 2.81 mmol), triphenylphosphine (0.77 g, 2.93 mmol) and 195 (0.85 g, 2.45 mmol) were treated as described for the preparation of 182, affording 183 as a white solid (0.58 g, 75%).

¹H NMR (270 MHz, CDCl₃): 4.52 (s, 2H, CH₂), 7.36-7.50 (m, 4H), 7.77-7.80 (m, 2H), 7.93-7.96 (m, 2H); ¹³C NMR (67.8 MHz, CDCl₃): 32.53 (CH₂), 123.74 (CH), 126.29 (CH), 126.90 (CH), 128.55 (CH), 129.44 (CH), 131.53 (C), 131.97 (C), 134.46 (CH), 138.74 (C), 166.98 (CO); MS (FAB): m/z = 315.9971 (M+H, ⁷⁹Br) and 317.9954 (M+H, ⁸¹Br); C₁₅H₁₁⁷⁹BrNO₂ requires 315.9972; C₁₅H₁₁⁸¹BrNO₂ requires 317.9952; Rₐ (n-hexanes/ethyl acetate: 4/1): 0.33

2-Phthalimidobenzyl bromide (184)
A solution of triphenylphosphine (0.145 g, 55 μmol) in DCM (1 mL) was cooled to 0°C under a nitrogen atmosphere. Bromine (30 μL, 55 μmol) was added dropwise and the reaction mixture stirred for 10 minutes. A solution of 196 (0.160 g, 46 μmol) in DCM (1 mL) was added and the reaction mixture allowed to warm up to room temperature and stirred for a further 3 hrs. Water was then added, and the aqueous phase extracted several times with DCM. The organic phase was dried (MgSO₄) and
the solvent evaporated. Purification by flash chromatography, eluting with n-hexanes/ethyl acetate: 4/1, gave 184 as a white solid (0.10 g, 69 %).

IR $v_{\text{max}}$/cm (KBr): 3049-2995 (C-H aromatic), 1714 (CO); $^1$H NMR (270 MHz, CDCl$_3$): 4.35 (s, 2H, CH$_2$), 7.17-7.21 (m, 1H), 7.37-7.41 (m, 1H), 7.43-7.50 (m, 1H), 7.79-7.82 (m, 2H), 7.95-7.98 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 29.43 (CH$_2$), 123.89 (CH), 129.74 (CH), 129.79 (CH), 130.81 (C), 131.07 (CH), 131.82 (C), 134.45 (CH), 135.76 (CN), 167.16 (CO); MS (FAB): $m/z =$ 315.9970 (M+H, $^{79}$Br) and 317.9959 (M+H, $^{81}$Br); C$_{15}$H$_{10}$BrNO$_2$ requires 314.9894 and C$_{15}$H$_{10}$BrNO$_2$ requires 316.9874; $R_f$ (n-hexanes/ethyl acetate: 8/1): 0.14; mp : 168°C (lit. 157-162°C)

4-Aminobenzyl alcohol (185)
A solution of 4-nitrobenzyl alcohol (4.54 g, 30 mmol) and palladium (10 wt. % on activated carbon) (1.03 g, 10 mmol) in ethanol (50 mL) was stirred overnight at room temperature under a hydrogen atmosphere. The reaction mixture was then filtered through a short column of celite and the filtrate concentrated under vacuum. Purification by column chromatography, eluting first with DCM, then with DCM/MeOH/NH$_4$OH: 300/10/1, gave two main fractions, one containing p-toluidine (0.54 g, 17 %) and the other containing the desired product 185 as a light-brown solid (2.46 g, 67 %).

$^1$H NMR (270 MHz, CDCl$_3$): 1.65 (br, s, 1H, NH or OH), 2.15 (br, s, 1H, NH or OH), 3.66 (br, s, 1H, NHH), 4.50 (s, 2H, CH$_2$), 6.64 (d, 2H, $J$=8.4 Hz), 7.12 (d, 2H, $J$=8.4 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 65.05 (CH$_2$), 115.09 (CH), 128.67 (CH), 131.04 (C), 145.86 (C); MS (FAB): $m/z =$ 123 (M); C$_7$H$_9$NO requires 123

Side product: p-toluidine
$^1$H NMR (270 MHz, CDCl$_3$): 2.30 (s, 3H, CH$_3$), 3.58 (br, s, 2H, NH$_2$), 6.63 (d, 2H, $J$=8.1 Hz), 7.02 (d, 2H, $J$=8.1 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 21.12 (CH$_3$), 115.37 (CH), 128.52 (C), 129.88 (CH), 145.12 (C); MS (EI): $m/z =$ 165.0790 (M); C$_7$H$_9$N requires 165.0789; $R_f$ (DCM/MeOH/NH$_4$OH: 100/10/1): 0.65

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4-Amino-O-(tetrahydropyran)benzyl alcohol (189)

A solution of 4-nitrobenzyl alcohol (1.53 g, 10.00 mmol), 3,4-dihydro-2H-pyran (0.84 g, 0.91 mL, 10.00 mmol) and p-toluenesulfonic acid monohydrate (20 mg, 0.11 mmol) was stirred overnight at room temperature in CHCl₃, then washed several times with water and brine, dried (MgSO₄) and finally concentrated under vacuum. Purification by column chromatography, eluting with n-hexanes/ethyl acetate: 9/1, afforded 188 (2.06 g, 87 %). Palladium (10 wt. % on activated carbon) (0.29 g, 0.27 mmol) was added to a solution of 188 (2.00 g, 8.43 mmol) in ethanol (20 mL). The reaction mixture was stirred overnight at room temperature under a hydrogen atmosphere and then filtered through a short column of celite. The solvent was evaporated and the crude product purified by column chromatography, eluting with n-hexanes/ethyl acetate: 5/1, which gave 189 as an orange oil (0.80 g, 46 %).

IR νₘₐₓ/cm (neat): 3446, 3360 (br, bonded NH), 1625 (N-H); ¹H NMR (270 MHz, CDCl₃): 1.42-1.89 (m, 6H), 3.47-3.55 (m, 1H), 3.68 (br, s, 2H, NH₂), 3.86-3.95 (m, 1H), 4.36 (d, 1H, J=11.3 Hz, CH(OH)), 4.64 (d, 1H, J=11.3 Hz, CH(OH)), 4.64-4.67 (m, 1H, OCHO), 6.60 (d, 2H, J=8.4 Hz), 7.12 (d, 2H, J=8.4 Hz); ¹³C NMR (67.8 MHz, CDCl₃): 19.02 (CH₂), 25.06 (CH₂), 30.18 (CH₂), 61.59 (CH₂), 68.29 (CH₂Ph), 96.78 (CH), 114.29 (CH), 126.98 (C), 129.10 (CH), 145.97 (C); MS (FAB): m/z = 207.1266 (M) and 208.1337 (M+H); C₁₂H₁₄NO₂ requires 208.1337; Rₜ (n-hexanes/ethyl acetate: 8/1): 0.66

4-Phthalimido-O-(tetrahydropyran)benzyl alcohol (190)

A solution of 189 (0.40 g, 1.93 mmol) and phthalic anhydride (0.28 g, 1.93 mmol) in mixed xylenes (6 mL) was reacted according to the general procedure H, giving 190 (0.10 g, 16 %) as a white solid.

IR νₘₐₓ/cm (neat): 1707 (CO); ¹H NMR (270 MHz, CDCl₃): 1.47-1.91 (m, 6H), 3.50-3.59 (m, 1H), 3.86-3.95 (m, 1H), 4.54 (d, 1H, J=12.5 Hz, CH(OH)), 4.72 (t, 1H, J=3.2 Hz, OCHO), 4.81 (d, 1H, J=12.5 Hz, CH(OH)), 7.42 (d, 2H, J=8.6 Hz), 7.48 (d, 2H, J=8.6 Hz), 7.73-7.79 (m, 2H), 7.90-7.96 (m, 2H); ¹³C NMR (67.8 MHz, CDCl₃): 19.21 (CH₂), 25.38 (CH₂), 30.45 (CH₂), 62.02 (CH₂), 68.04 (CH₂Ph), 97.62 (CH), 123.69 (CH), 126.43 (CH), 128.30 (CH), 130.75 (C), 131.70 (C), 134.34 (CH), 138.36 (C), 167.24 (CO); MS (FAB): m/z = 337.1315 (M) and 338.1396 (M+H);
C_{20}H_{20}NO_4 requires 338.1382; R_f (n-hexanes/ethyl acetate: 4/1): 0.12, R_f (n-hexanes/ethyl acetate: 1/1): 0.64; mp : 125°C

4-Amino-O-(tert-butyldimethylsilyl)benzyl alcohol (191) \textsuperscript{209,210}

4-Aminobenzyl alcohol (1.17 g, 9.5 mmol), tert-butyldimethylsilyl chloride (2.15 g, 14.2 mmol) and imidazole (1.29 g, 19.0 mmol) were reacted according to the general procedure G. After purification by column chromatography, eluting with n-hexanes/ethyl acetate: 8/1, 191 was isolated as an orange oil (1.82 g, 81%).

IR ν_{max}/cm$^\text{-1}$ (neat): 3445, 3363 (br, bonded NH), 1622 (N-H); $^1$H NMR (270 MHz, CDCl$_3$): 0.13 (s, 6H, 2xCH$_3$), 0.97 (s, 9H, C(CH$_3$)$_3$), 3.62 (br, NH$_2$), 4.66 (s, 2H, CH$_2$), 6.66 (d, J=8.0 Hz), 7.14 (d, J=8.0 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): -5.22 (2xCH$_3$), 18.34 (C(CH$_3$)$_3$), 25.91 (C(CH$_3$)$_3$), 64.91 (CH$_2$), 114.83 (CH), 127.57 (CH), 131.28 (C), 145.33 (C); MS (FAB): m/z = 237.1555 (M), 238.1614 (M+H); C$_{13}$H$_{24}$NOSi requires 238.1626; R_f (n-hexanes/ethyl acetate: 8/1): 0.17, R_f (n-hexanes/ethyl acetate: 1/1): 0.73

3-Amino-O-(tert-butyldimethylsilyl)benzyl alcohol (192) \textsuperscript{210,211}

3-Aminobenzyl alcohol (1.85 g, 15 mmol), tert-butyldimethylsilyl chloride (3.39 g, 22.5 mmol) and imidazole (2.04 g, 30 mmol) were reacted according to the general procedure G. 192 was isolated as a dark oil (2.89 g, 81%).

IR ν_{max}/cm$^\text{-1}$ (neat): 3449, 3361 (br, bonded NH), 1620 (N-H); $^1$H NMR (270 MHz, CDCl$_3$): 0.12 (s, 6H, 2xCH$_3$), 0.97 (s, 9H, C(CH$_3$)$_3$), 3.65 (br, 2H, NH$_2$), 4.68 (s, 2H, CH$_2$), 6.65-6.60 (m, 1H), 6.67-6.75 (m, 2H), 7.12 (t, 1H, J=7.7 Hz), 7.89-7.95 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): -5.31 (2xCH$_3$), 18.37 (C(CH$_3$)$_3$), 25.91 (C(CH$_3$)$_3$), 64.83 (CH$_2$), 112.67 (CH), 113.61 (CH), 116.17 (CH), 129.01 (CH), 142.61 (C), 146.30 (C); MS (FAB): m/z = 237.1537 (M), 238.1622 (M+H); C$_{13}$H$_{24}$NOSi requires 238.1626; R_f (n-hexanes/ethyl acetate: 4/1): 0.38, R_f (n-hexanes/ethyl acetate: 1/1): 0.54
2-Amino-O-(tert-butyldimethylsilyl)benzyl alcohol (193) \(^{212}\)

2-Aminobenzyl alcohol (1.23 g, 10 mmol), tert-butyldimethylsilyl chloride (2.26 g, 15 mmol) and imidazole (1.36 g, 20 mmol) were reacted according to the general procedure G. 193 was isolated as a brown oil (2.32 g, 98%).

IR \(\nu_{\text{max}}/\text{cm} (\text{neat})\): 3461, 3373 (br, bonded NH), 1621 (N-H); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 0.08 (s, 6H, 2xCH\(_3\)), 0.91 (s, 9H, C(CH\(_3\))\(_3\)), 4.69 (s, 2H, CH\(_2\)), 6.65-6.75 (m, 2H), 7.02-7.15 (m, 2H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)): -5.29 (2xCH\(_3\)), 18.17 (C(CH\(_3\))\(_3\)), 25.84 (C(CH\(_3\))\(_3\)), 64.84 (CH\(_2\)), 115.64 (CH), 117.80 (CH), 125.13 (C), 128.39 (CH), 146.06 (C); MS (FAB): \(m/z = 238.1607\) (M), 238.1673 (M+H); \(C_{13}H_{24}NOSi\) requires 238.1626; Rf (n-hexanes/ethyl acetate: 4/1): 0.65

4-Phthalimido-O-(tert-butyldimethylsilyl)benzyl alcohol (194)

A solution of 191 (3.96 g, 16.7 mmol) and phthalic anhydride (2.42 g, 16.3 mmol) in mixed xylenes (40 mL) was reacted according to the general procedure H, which afforded 194 as colourless crystals (2.72 g, 45%).

IR \(\nu_{\text{max}}/\text{cm} (\text{neat})\): 2942-2857 (C-H aromatic), 1714 (CO); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 0.09 (s, 6H, 2xCH\(_3\)), 0.94 (s, 9H, C(CH\(_3\))\(_3\)), 4.79 (s, 2H, CH\(_2\)), 7.39 (d, 2H, \(J=8.5\) Hz), 7.45 (d, 2H, \(J=8.5\) Hz), 7.72-7.79 (m, 2H), 7.89-7.95 (m, 2H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)): -5.37 (2xCH\(_3\)), 18.27 (C(CH\(_3\))\(_3\)), 25.82 (C(CH\(_3\))\(_3\)), 64.28 (CH\(_2\)), 123.53 (CH), 126.21 (CH), 126.39 (CH), 130.12 (C), 131.62 (C), 134.20 (CH), 141.35 (C), 167.16 (CO); MS (FAB): 368.1673; \(C_{21}H_{26}NO_3\)Si requires 368.1681; Rf (n-hexanes/ethyl acetate: 4/1): 0.41; mp : 114°C

3-Phthalimido-O-(tert-butyldimethylsilyl)benzyl alcohol (195)

A solution of 192 (1.29 g, 5.43 mmol) and phthalic anhydride (0.77 g, 5.43 mmol) in mixed xylenes (30 mL) was reacted according to the general procedure H. 195 was isolated as a white solid (1.33 g, 71%).

IR \(\nu_{\text{max}}/\text{cm} (\text{neat})\): 1721 (CO); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 0.10 (s, 6H, 2xCH\(_3\)), 0.93 (s, 9H, C(CH\(_3\))\(_3\)), 4.79 (s, 2H, CH\(_2\)), 7.24-7.52 (m, 4H), 7.76-7.79 (m, 2H), 7.93-7.96 (m, 2H); \(^13\)C NMR (67.8 MHz, CDCl\(_3\)): -5.45 (2xCH\(_3\)), 18.17 (C(CH\(_3\))\(_3\)), 25.75
(C(CH₃)₃), 64.22 (CH₂), 123.40 (CH), 123.84 (CH), 124.76 (CH), 125.34 (CH), 126.67 (CH), 131.42 (C), 131.47 (C), 134.11 (CH), 142.47 (C), 166.93 (CO); MS (FAB): m/z = 367.1572 (M) and 368.1672 (M+H); C₂₁H₂₅NO₃Si requires 367.1603; Rₙ (n-hexanes/ethyl acetate: 4/1): 0.42; mp : 87°C

2-Phthalimido-0-(tert-butylidimethylsilyl)benzyl alcohol (196)
A solution of 193 (0.20 g, 0.84 mmol) and phthalic anhydride (0.12 g, 0.84 mmol) in mixed xylenes (5 mL) was reacted according to the general procedure H. 196 was isolated as a white solid (0.28 g, 96 %).

IR νmax/cm⁻¹ (neat): 1716 (CO); ¹H NMR (270 MHz, CDCl₃): -0.06 (s, 6H, 2xCH₃), 0.79 (s, 9H, C(CH₃)₃), 4.65 (s, 2H, CH₂), 7.22 (dd, 1H, J=1.3 and 7.5 Hz), 7.39 (virtual double triplet, 1H, J=1.7 and 7.4 Hz), 7.46 (virtual double triplet, 1H, J=1.5 and 7.4 Hz), 7.58 (dd, 1H, J=1.4 and 7.3 Hz), 7.75-7.79 (m, 2H), 2.92-2.96 (m, 2H); ¹³C NMR (67.8 MHz, CDCl₃): -5.60 (2xCH₃), 18.17 (C(CH₃)₃), 25.69 (C(CH₃)₃), 62.39 (CH₂), 123.66 (CH), 127.91 (CH), 128.12 (CH), 128.89 (CH), 129.07 (C), 129.28 (CH), 132.06 (C), 134.20 (CH), 139.15 (C), 167.18 (CO); MS (FAB): 368 (M+H); C₂₁H₂₅NO₃Si requires 367; Rₙ (n-hexanes/ethyl acetate: 4/1): 0.42; mp : 122-123°C

17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-tetraacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-4-phthalimidobenzylimino][7,7'-bimorphinan] (197)
178 (0.34 g, 0.41 mmol), sodium hydride (60% in oil, 66 mg, 1.65 mmol), 18-crown-6 (23 mg, 0.09 mmol) and 182 (0.38 g, 1.20 mmol) in dry THF (5 mL) were reacted according to general procedure I. After purification, 197 was obtained as a brown solid (0.23 g, 53%).

¹H NMR (270 MHz, CDCl₃): 0.04 (d, 4H, J=4.5 Hz, NCH₂CH(CHHCHH)), 0.43 (d, 4H, J=8.0 Hz, NCH₂CH(CHHCHH)), 0.66-0.78 (m, 2H, NCH₂CH(CH₂CH₂)), 1.56 (d, 2H, J=10.9 Hz), 1.90 (s, CH₃), 2.05 (CH₃), 4.44 (d, 2H, J=5.9 Hz), 5.29 (s, 2H, 5-H + 5'-H), 5.32 (d, 1H, J=16.8 Hz, NCHHPh), 5.44 (d, 1H, J=16.8 Hz, NCHHPh), 6.62 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.75 (d, 2H, J=8.2 Hz, 2-H + 2'-H), 6.87 (d, 2H, J=8.4 Hz), 7.34 (d, 2H, J=8.4 Hz), 7.75-7.79 (m, 2H), 7.89-7.92 (m, 2H); ¹³C NMR
17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-[(4-
phthalimidobenzylimino)]7,7'-bimorphinan]-3,3',14,14'-tetrol (204)

197 (0.20 g, 0.19 mmol) was dissolved in conc. HCl/methanol (3 mL, 1/1) and the
solution was stirred for 72 hours at 80°C. The solvents were then removed by
evaporation, water was added and the aqueous phase basified to pH = 8 (NH₄OH) and
extracted with DCM/MeOH: 5/1. The organic phase was dried (MgSO₄) and
concentrated under vacuum. The crude material was purified by column
chromatography, eluting first with CHCl₃/MeOH/NH₄OH: 500/10/1 then with
CHCl₃/MeOH/NH₄OH: 250/10/1. 204 was isolated as an off-white solid (9 mg, 5%).

1H NMR (270 MHz, CDCl₃): 0.11 (d, 4H, J=4.4 Hz, NCH₂CH(CH₂CH₂)), 0.51 (d,
4H, J=7.7 Hz, NCH₂CH(CH₂CH₂)), 0.78-0.89 (m, 2H, NCH₂CH(CH₂CH₂)), 1.59
(d, 2H, J=9.7 Hz), 3.02 (d, 2H, J=18.3 Hz), 3.17-3.25 (m, 2H), 5.31 (d, 1H, J=17.8
Hz, NCH₂Ph), 5.36 (s, 2H, 5-H + 5'-H), 5.55 (d, 1H, J=17.8 Hz, NCH₂Ph), 6.47 (d,
2H, J=8.3 Hz, 1-H + 1'-H), 6.59 (d, 2H, J=8.3 Hz, 2-H + 2'-H), 6.94 (d, 2H, J=8.2
Hz), 7.30 (d, 2H, J=8.2 Hz), 7.77-7.80 (m, 2H), 7.93-7.96 (m, 2H); MS (FAB): m/z =
897 (M); C₅₅H₅₂N₄O₈ requires 897; Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.44; mp >
200°C

4-(Phthalimidomethyl)benzyl bromide (206)
A mixture of dibromo-p-xylene (1.0 g, 3.8 mmol), potassium phthalimide (0.7 g, 3.8
mmol) and 18-crown-6 (0.1 g, 0.4 mmol) in toluene (10 mL) was reacted according to
the general procedure J. 206 was isolated as a white solid (0.60 g, 48 %).
IR $\nu_{\text{max}}$/cm (KBr): 3049-2938 (C-H aromatic), 1720 (CO); $^1$H NMR (270 MHz, CDCl$_3$): 4.42 (s, 2H, CH$_2$Br), 4.81 (s, 2H, CH$_2$N), 7.31 (d, 2H, $J=8.2$ Hz), 7.39 (d, 2H, $J=8.2$ Hz), 7.67-7.70 (m, 2H), 7.81-7.84 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 32.96 (CH$_2$Br), 41.09 (CH$_2$N), 123.28 (CH), 128.99 (CH), 129.28 (CH), 131.94 (C), 133.96 (CH), 136.51 (C), 137.29 (C), 167.83 (CO); MS (FAB): $m/z = 330.0125$ (M+H, $^{79}$Br) and 332.0125 (M+H, $^{81}$Br); C$_{16}$H$_{13}$BrNO$_2$ requires 330.0129 and C$_{16}$H$_{13}$BrNO$_2$ requires 332.0108; $R_f$ (n-hexanes/ethyl acetate: 4/1): 0.23; mp : 137°C

3-(Phthalimidomethyl)benzyl bromide (207)

A mixture of dibromo-m-xylene (2.0 g, 7.6 mmol), potassium phthalimide (1.4 g, 7.6 mmol) and 18-crown-6 (0.20 g, 0.76 mmol) in toluene (20 mL) was reacted according to the general procedure J, affording 207 as colourless crystals (1.35 g, 54%).

IR $\nu_{\text{max}}$/cm (KBr): 3042-2931 (C-H aromatic), 1709 (CO); $^1$H NMR (270 MHz, CDCl$_3$): 4.44 (s, 2H, CH$_2$Br), 4.82 (s, 2H, CH$_2$N), 7.27-7.38 (m, 3H), 7.44 (s, 1H), 7.67-7.71 (m, 2H), 7.80-7.85 (m, 2H); $^{13}$C NMR (100.5 MHz, CDCl$_3$): 33.54 (CH$_2$Br), 41.71 (CH$_2$N), 123.62 (CH), 128.83 (CH), 128.94 (CH), 129.38 (CH), 129.40 (CH), 132.22 (C), 134.23 (CH), 137.09 (C), 138.42 (C), 168.08 (CO); MS (FAB): $m/z = 330.0118$ (M+H, $^{79}$Br) and 332.0127 (M+H, $^{81}$Br); C$_{16}$H$_{13}$BrNO$_2$ requires 330.0129 and C$_{16}$H$_{13}$BrNO$_2$ requires 332.0108; $R_f$ (n-hexanes/ethyl acetate: 4/1): 0.24; mp : 124°C

2-(Phthalimidomethyl)benzyl bromide (208) \(^{213}\)

A mixture of dibromo-o-xylene (3.0 g, 11.3 mmol), potassium phthalimide (2.1 g, 11.3 mmol) and 18-crown-6 (0.30 g, 1.13 mmol) in toluene (30 mL) was reacted according to the general procedure J. 208 was isolated as a white solid (1.77 g, 47%).

IR $\nu_{\text{max}}$/cm (KBr): 1712 (CO); $^1$H NMR (400 MHz, CDCl$_3$): 4.82 (s, 2H, CH$_2$Br), 4.97 (s, 2H, CH$_2$N), 7.21-7.27 (m, 2H), 7.31-7.39 (m, 1H), 7.42-7.45 (m, 1H), 7.68-7.70 (m, 2H), 7.81-7.84 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 31.38 (CH$_2$Br), 38.18 (CH$_2$N), 123.29 (CH), 128.38 (CH), 129.13 (CH), 130.34 (CH), 130.57 (CH), 131.90 (C), 134.02 (CH), 134.84 (C), 136.02 (C), 168.03 (CO); MS (FAB): $m/z = 330.0110$
and 332.0120 (M+H, 81Br); C16H1379BrNO2 requires 330.0129 and C16H1381BrNO2 requires 332.0108; Rf (n-hexanes/ethyl acetate: 4/1): 0.25; mp : 144°C

17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-dimethoxy-6,6',7,7'-tetrahydro-4,5:4,5'-diepoxy-6,6'-imino[7,7'-bimorphinan] (209)
To a solution of norBNI (13) (0.33 g, 0.50 mmol) and imidazole (0.27 g, 4.0 mmol) in dry DMF (5 mL) was added trimethylsilyl chloride (0.38 mL, 3.0 mmol). The reaction mixture was stirred for two hours at room temperature, after which water (3 mL) was added and the aqueous phase extracted with DCM/MeOH: 5/1. The organic phase was washed with brine, dried (MgSO4) and concentrated under vacuum. 209 was isolated as a brown solid and used without any further purification (0.45 g, 95%).

IR v_max/cm (neat): no specific peak; 1H NMR (270 MHz, CDCl3): -0.23 (s, 18H, 6xCH3), 0.08 (s, 18H, 6xCH3), 0.03-0.18 (m, 4H, 2xNCH2CH(CH2CH(H)), 0.44-0.54 (m, 4H, 2xNCH2CH(CH2CH2H)), 0.78-0.94 (m, 2H, 2xNCH2CH(CH2CH2)), 5.24 (s, 2H, 5-H + 5'-H), 6.41 (d, 2H, J=8.0 Hz, 1-H + 1'-H), 6.50 (d, 2H, J=8.0 Hz, 2-H + 2'-H)

17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-(tert-butyldimethylsilyloxy)-6,6',7,7'-tetrahydro-4,5:4,5'-diepoxy-6,6'-(imino)[7,7'-bimorphinan] (210)
To a solution of norBNI (13) (0.66 g, 1.0 mmol) and imidazole (0.30 g, 4.4 mmol) in dry DMF (5 mL) was added tert-butyldimethylsilyl chloride (0.63 g, 4.2 mmol). The reaction mixture was stirred for two hours at room temperature, after which water (3 mL) was added and the aqueous phase extracted with DCM/MeOH: 5/1. The organic phase was washed with brine, dried (MgSO4) and concentrated under vacuum. 210 was isolated as a brown solid and used without any further purification (1.08 g, 97%).

IR v_max/cm (neat): no specific peak; 1H NMR (270 MHz, CDCl3): 0.01-0.10 (m, 4H, 2xNCH2CH(CH2CH2H)), 0.08 (s, 12H, 3-COSi(CH3)2 + 3'-COSi(CH3)2), 0.09 (s, 6H, 14-COSi(CH3CH3) + 14'-COSi(CH3CH3)), 0.10 (s, 6H, 14-COSi(CH3CH3) + 14'-COSi(CH3CH3)), 0.49 (d, 4H, J=8.2 Hz, 2xNCH2CH(CH2CH2H)), 0.90 (s, 18H, 6xCH3), 0.94 (s, 18H, 6xCH3), 5.36 (s, 2H, 5-H + 5'-H), 6.43 (d, 2H, J=8.1 Hz, 1-H +
1'-H), 6.53 (d, 2H, J=8.1 Hz, 2-H + 2'-H), 7.94 (s, br, 1H, NH); Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.42

17,17'-Bis(cyclopropylmethyl)-14,14'-dimethoxy-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'-(imino)[7,7'-bimorphinan]-3,3'-dil (211) 163

A solution of 221 (63 mg, 86 μmol) in conc. HCl/MeOH (3 mL, 1/1) was stirred overnight at 80°C. Similar workup and purification as employed for the preparation of 204 afforded 211 (47 mg, 79%) as an off-white solid.

1H NMR (270 MHz, CDCl₃): 0.12 (d, 4H, J=4.0 Hz, 2xNCH₂CH(CH₂CH₂)), 0.41-0.53 (m, 4H, 2xNCH₂CH(CH₂CH₂)), 3.09 (s, 6H, OCH₃), 5.55 (s, 2H, 5-H + 5'-H), 6.46 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.61 (d, 2H, J=8.2 Hz, 2-H + 2'-H); 13C NMR (100.5 MHz, CDCl₃): 3.08 (2xNCH₂CH(CH₂CH₂)), 4.30 (2xNCH₂CH(CH₂CH₂)), 8.76 (2xNCH₂CH(CH₂CH₂)), 22.28 (CH₂), 23.23 (CH₂), 29.82 (15-C + 15'-C), 48.88 (16-C + 16'-C), 48.10 (CH₃ or 13-C + 13'-C), 48.68 (CH₃ or 13-C + 13'-C), 55.32 (9-C + 9'-C), 59.24 (18-C + 18'-C), 78.79 (14-C + 14'-C), 85.31 (5-C + 5'-C), 114.92 (7-C + 7'-C), 117.15 (CH), 118.53 (CH), 124.81 (C), 124.97 (C), 130.81 (C), 139.19 (C), 142.63 (C); Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.39; mp > 215°C

4,5α-Epoxy-3-benzyloxy-14-methoxy-17-cyclopropylmethyl-morphinan-6-one (212) 164

A mixture of 215 (6.97 g, 16.2 mmol) and sodium hydride (1.94 g, 48.5 mmol) in dry DMF (20 mL) was stirred for 20 minutes at 0°C. Dimethyl sulfate (4.21 mL, 44.5 mmol) was then added dropwise. After complete addition, the temperature was maintained at 0°C for another 2 hours before quenching the reaction with water (5 mL). The aqueous phase was extracted with DCM/MeOH: 5/1, the organic phase dried (MgSO₄) and concentrated. The crude product was purified by column chromatography, eluting first with CHCl₃: 100%, then with CHCl₃/MeOH/NH₄OH: 400/5/1. The product was immediately dissolved in MeOH/conc. HCl: 3/2, and the solution was refluxed overnight. The solvents were then removed under vacuum, and recrystallisation in ethanol afforded 212 (HCl salt) as a white solid (4.15 g, 72%).

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IR ν<sub>max</sub>/cm (KBr, HCl salt): 3391 (br, bonded OH), 1730 (CO); <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>, free base): 0.13 (d, 2H, J=5.3 Hz, NCH<sub>2</sub>CH(CHHCHH)), 0.81-0.95 (m, 1H, NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 3.11 (d, 1H, J=18.3 Hz, 10-CHH), 3.37 (s, 3H, OCH<sub>3</sub>), 3.63 (d, 1H, J=5.3 Hz, 9-CHH), 4.65 (s, 1H, 5-H), 6.55 (d, 1H, J=8.2 Hz, 1-H), 6.69 (d, 1H, J=8.2 Hz, 2-H); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>, free base): 3.16 (NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 4.29 (NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 9.12 (NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 22.63 (10-C), 25.04 (8-C), 29.15 (15-C), 35.46 (7-C), 44.88 (16-C), 47.98 (OCH<sub>3</sub>), 51.02 (13-C), 54.43 (9-C), 59.24 (18-C), 75.59 (14-C), 90.49 (5-C), 117.85 (2-C), 119.81 (1-C), 124.94 (11-C), 129.42 (12-C), 138.76 (3-C), 143.45 (4-C), 210.28 (CO); MS (FAB): m/z = 355.1771 (M), 356.1850 (M+H); C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub> requires 356.1861; R<sub>f</sub> (DCM/MeOH/NH<sub>2</sub>OH: 100/10/1, free base): 0.45; mp (HCl salt) > 220 °C

4,5α-Epoxy-3-benzyloxy-17-cyclopropylmethyl-morphinan-6-one (215)<sup>164</sup>

To a solution of naltrexone (5.80 g, 17.01 mmol) and potassium carbonate (3.52 g, 22.47 mmol) in DMF (20 mL) was added benzyl bromide (2.04 mL, 17.1 mmol). The reaction mixture was stirred overnight at room temperature. Water (7 mL) was added, the aqueous phase extracted with DCM/MeOH: 5/1 and the organic phase was dried (MgSO<sub>4</sub>) and concentrated. 215 was isolated as a brown solid (7.26 g, 99%) and used with no further purification.

<sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>): 0.10-0.15 (m, 2H, NCH<sub>2</sub>CH(CHHCHH)), 0.51-0.57 (m, 2H, NCH<sub>2</sub>CH(CHHCHH)), 0.78-0.91 (m, 1H, NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 5.19 (d, 1H, J=12.3 Hz, OCHH), 5.27 (d, 1H, J=12.3 Hz, OCHH), 5.28 (s, 1H, 5-H), 6.54 (d, 1H, J=8.1 Hz, 1-H), 6.70 (d, 1H, J=8.1 Hz, 2-H), 7.26-7.36 (m, 3H, Ar), 7.41-7.46 (m, 2H, Ar); <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>): 3.77 (NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 3.96 (NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 9.38 (NCH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>2</sub>)), 22.63 (10-C), 30.68 (CH<sub>2</sub>), 31.45 (CH<sub>2</sub>), 36.18 (7-C), 43.53 (16-C), 50.71 (13-C), 59.16 (18-C), 61.96 (9-C), 70.10 (14-C), 72.04 (OCH<sub>3</sub>), 90.38 (5-C), 117.87 (CH), 119.37 (CH), 125.55 (C), 127.72 (CH), 128.34 (CH), 129.76 (C), 137.41 (C), 141.74 (C), 145.46 (C), 162.47 (CH), 208.49 (CO); MS (FAB): m/z = 431.2093 (M), 432.2171 (M+H); C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub> requires 432.2174
4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one (217) 214

Method A.
A solution of hydrocodone (4.00 g, 13.4 mmol) in DCM (80 mL) was cooled to -78°C under a nitrogen atmosphere before adding slowly boron tribromide (1 mol/L in DCM, 26.6 mL, 26.6 mmol). The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction was then quenched by the addition of methanol (50 mL) and the solvents were removed under vacuum. Methanol (50 mL) was added a second time and removed by evaporation. Water (50 mL) was added and the pH adjusted to pH=12 (NH₄OH). The aqueous phase was extracted several times with DCM/MeOH: 5/1. The organic phase was dried over MgSO₄, concentrated under vacuum and the brown oil was purified by column chromatography, eluting with CHCl₃/MeOH/NH₄OH: 500/10/1. 217 was obtained as a brown solid (1.50 g, 40%).

Method B.
A solution of hydrocodone (2.10 g, 7.0 mmol) in dichloroethane (10 mL) was added slowly to a solution of boron tribromide-methyl sulfide complex (8.74 g, 28.0 mmol) in dichloroethane (40 mL). The reaction mixture was stirred overnight at 65°C. Similar workup and purification as employed for method A afforded 217 as a brown solid (0.66 g, 33%).

IR νmax/cm (neat): 3380 (br, bonded OH), 1724 (CO); ¹H NMR (270 MHz, CDCl₃): 2.44 (NMe), 4.59 (5-H), 6.53 (d, 1H, J=8.1 Hz, 1-H), 6.64 (d, 1H, J=8.1 Hz, 2-H); ¹³C NMR (67.8 MHz, CDCl₃): 19.94 (10-C), 25.21 (8-C), 34.61 (15-C), 40.00 (7-C), 41.27 (14-C), 42.17 (N-Me), 46.50 (13-C), 46.68 (16-C), 58.74 (9-C), 90.81 (5-C), 118.28 (CH), 119.87 (CH), 123.80 (C), 126.56 (C), 139.95 (C), 144.36 (C), 208.77 (CO); MS (FAB): m/z = 286.1431 (M+H); C₁₇H₂₀NO₃ requires 286.1442; Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.30; mp > 220°C

4,5α-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one (218) 215
Oxycodone (0.58 g, 1.84 mmol) in dichloroethane (10 mL) was added slowly to a solution of boron tribromide-methyl sulfide complex (2.29 g, 7.33 mmol) in dichloroethane (20 mL). The reaction mixture was stirred overnight at 65°C, water was then added, before stirring for another 30 minutes. The aqueous phase was
washed several times with DCM, adjusted to pH=12 with diluted NH₄OH and extracted several times with DCM/MeOH: 5/1. The organic phase was dried over MgSO₄, concentrated under vacuum and the brown oil was purified by column chromatography, eluting with CHCl₃/MeOH/NH₄OH: 220/10/1. 218 was obtained as a brown solid (0.35 g, 63 %).

^1^H NMR (270 MHz, CDCl₃): 2.39 (s, 3H, CH₃), 2.88 (d, 1H, J=5.7 Hz), 3.02 (td, 1H, J=14.6 Hz and 5.2 Hz), 3.12 (d, 1H, J=18.6 Hz), 4.70 (s, 1H, 5-H), 6.58 (d, 1H, J=8.2 Hz, 1-H), 6.70 (d, 1H, J=8.2 Hz, 2-H); ^13^C NMR (100.5 MHz, CDCl₃): 21.99 (10-C), 30.39 (CH₂), 31.30 (CH₂), 36.15 (7-C), 42.76 (N-Me), 45.28 (16-C), 50.46 (13-C), 64.56 (9-C), 70.60 (14-C), 90.51 (5-C), 118.15 (CH), 120.00 (CH), 124.12 (C), 128.85 (C), 138.97 (C), 143.57 (C), 210.21 (CO); Rf (DCM/MeOH/NH₄OH: 100/101): 0.47; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-3,3'-(methoxymethyloxy)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(methoxymethylimino)[7,7'-bimorphinan]-14,14'-diol (219)

A mixture of norBNI (13) (0.80 g, 1.20 mmol) and sodium hydride (192 mg, 4.80 mmol) in dry DMF (10 mL) was stirred for 20 minutes at room temperature before adding chloromethyl methyl ether (0.36 mL, 4.80 mmol) and stirring continued for a further 2 hrs at room temperature. Water (4 mL) was added and the aqueous phase extracted with DCM/MeOH: 5/1. The organic phase was dried (MgSO₄) and concentrated under vacuum. The product was purified by column chromatography, eluting first with CHCl₃: 100%, then with CHCl₃/MeOH/NH₄OH: 800/5/1, which afforded 219 as a brown solid (0.72 g, 76%).

IR v_max/cm (KBr): 3295 (br, bonded OH); ^1^H NMR (270 MHz, CDCl₃): 0.10 (d, 4H, J=4.2 Hz, 2xNCH₂CH(CH₂CH₂)), 0.50 (d, 4H, J=6.9 Hz, 2xNCH₂CH(CH₂CH₂)), 0.75-0.87 (m, 2H, 2xCH₂OCH₂), 3.37 (s, 3H, NCH₂OCH₃), 3.44 (s, 6H, 2xOCH₂OCH₃), 5.06 (d, 2H, J=6.5 Hz, OCHHOCH₃), 5.16 (d, 2H, J=6.5 Hz, OCHHOCH₃), 5.19 (d, 1H, J=10.3 Hz, NC/H/OC/H), 5.62 (s, 2H, 5-H + 5'-H), 5.78 (d, 1H, J=10.3 Hz, NC/H/OC/H), 6.50 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.82 (d, 2H, J=8.2 Hz, 2-H + 2'-H); ^13^C NMR (67.8 MHz, CDCl₃): 3.67 (2xNCH₂CH(CH₂CH₂)), 3.85 (2xNCH₂CH(CH₂CH₂)), 9.29 (2xNCH₂CH(CH₂CH₂)), 22.93 (2xCH₂), 28.76

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(2xCH₂), 31.42 (2xCH₂), 43.50 (16-C + 16'-C), 47.61 (13-C + 13'-C), 55.51 (NCH₂OCH₃), 56.09 (3-COCH₂OCH₃ + 3'-COCH₂OCH₃), 59.21 (18-C + 18'-C), 62.14 (14-C + 14'-C), 72.35 (14-C + 14'-C), 75.02 (NCH₂OCH₃), 84.22 (5-C + 5'-C), 95.66 (3-COCH₂OCH₃ + 3'-COCH₂OCH₃), 116.60 (C), 117.67 (CH), 118.19 (CH), 125.89 (C), 126.99 (C), 131.21 (C), 140.35 (C), 145.25 (C); Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.54; mp : 114 °C

17,17'-Bis(cyclopropylmethyl)-3,3'-{methoxymethylene}-14,14'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-{methoxymethylimino}[7,7'-bimorphinan] (220)

219 (0.65 g, 0.83 mmol), sodium hydride (0.10 g, 2.50 mmol) and dimethyl sulfate (0.2 mL, 2.1 mmol) were reacted according to the same procedure as used for the preparation of 212, but the reaction time was increased to 3hrs. After purification by column chromatography, eluting first with CHCl₃: 100%, then with CHCl₃/MeOH/NH₄OH: 400/5/1, 220 was isolated as a brown solid (0.15 g, 22%).

IR νmax/cm (neat): 2913 (C-H aromatic); 1H NMR (270 MHz, CDCl₃): 0.11 (d, 4H, J=4.2 Hz, 2xNCH₂CH(CH₂CH₂)), 0.46-0.51 (m, 4H, 2xNCH₂CH(CH₂CH₂O)), 0.82-0.92 (m, 2H, 2xNCH₂CH(CH₂CH₂)), 3.13 (s, 6H, 14-OCH₃ + 14'-OCH₃), 3.33 (s, 3H, NCH₂OCH₃), 3.43 (s, 6H, 2xOCH₂OCH₃), 5.08 (d, 2H, J=6.5 Hz, OCH₃OCH₃), 5.16 (d, 1H, J=10.3 Hz, NCH²OCH₃), 5.18 (d, 2H, J=6.5 Hz, OCH₃OCH₃), 5.59 (s, 2H, 5-H + 5'-H), 5.72 (d, 1H, J=10.3 Hz, NCH²OCH₃), 6.52 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.82 (d, 2H, J=8.2 Hz, 2-H + 2'-H); 13C NMR (67.8 MHz, CDCl₃): 3.01 (2xNCH₂CH(CH₂CH₂)), 4.20 (2xNCH₂CH(CH₂CH₂)), 9.03 (2xNCH₂CH(CH₂CH₂)), 22.17 (8-C + 8'-C), 23.09 (10-C + 10'-C), 29.99 (15-C + 15'-C), 44.77 (16-C + 16'-C), 48.12 (13-C + 13'-C), 48.53 (14-COCH₃ + 14'-COCH₃), 55.13 (9-C + 9'-C), 55.30 (NCH₂OCH₃), 56.18 (3-COCH₂OCH₃ + 3'-COCH₂OCH₃), 59.32 (18-C + 18'-C), 75.05 (NCH₂OCH₃), 77.99 (14-C + 14'-C), 84.44 (5-C + 5'-C), 95.68 (3-COCH₂OCH₃ + 3'-COCH₂OCH₃), 116.11 (7-C + 7'-C), 117.61 (2-C + 2'-C), 117.91 (1-C + 1'-C), 125.88 (6-C + 6'-C), 127.82 (11-C + 11'-C), 131.80 (12-C + 12'-C), 140.19 (3-C + 3'-C), 145.17 (4-C + 4'-C); MS (FAB): m/z = 821 (M), C₄₈H₉₉N₉O₉ requires 821; Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.45; mp > 200°C
17,17'-Bis(cyclopropylmethyl)-14,14'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepox-6,6'-((methoxymethylimino)[7,7'-bimorphinan]-3,3'-diol (221)

A solution of 220 (0.11 g, 0.13 mmol) in conc. HCl/MeOH (3 mL, 1/1) was stirred at room temperature overnight. The mixture was evaporated to dryness, water was added and the pH adjusted to pH=10 with diluted NH₄OH. The aqueous phase was extracted with DCM/MeOH: 5/1, the organic phase dried over MgSO₄ and concentrated by evaporation. Purification by column chromatography, eluting first with CHCl₃: 100%, then with CHCl₃/MeOH/NH₄OH: 500/10/1 and finally with CHCl₃/MeOH/NH₄OH: 250/10/1, afforded 221 (70 mg, 71%) as an off-white solid.

IR νmax/cm (neat): 3370 (br, bonded OH); ¹H NMR (270 MHz, CDCl₃): 0.02-0.10 (m, 4H, 2xNCH₂CH(CH₃CH₂)); 0.42-0.52 (m, 4H, 2xNCH₂CH(CH₃CH₂)), 0.86-0.98 (m, 2H, 2xNCH₂CH(CH₃CH₂)), 2.56 (s, 6H, 14-OCH₃ + 14'-OCH₃), 3.30 (s, 3H, NCH₂OCH₃), 5.34 (d, 1H, J=9.7 Hz, NCHHOCH₃), 5.58 (s, 2H, 5-H +5'-H), 5.81 (d, 1H, J=9.7 Hz, NCHHOCH₃), 6.42 (d, 2H, J=7.8 Hz, 1-H + 1'-H), 6.53 (d, 2H, J=7.8 Hz, 2-H + 2'-H); ¹³C NMR (67.8 MHz, CDCl₃): 3.71 (2xNCH₂CH(CH₃CH₂)), 4.37 (2xNCH₂CH(CH₃CH₂)), 8.56 (2xNCH₂CH(CH₃CH₂)), 23.26 (CH₃), 24.49 (CH₃), 29.47 (15-C + 15'-C), 44.54 (16-C + 16'-C), 47.89 (13-C + 13'-C), 50.21 (14-COCH₃ + 14'-COCH₃), 55.18 (OCH₃), 58.69 (9-C + 9'-C), 59.88 (18-C + 18'-C), 70.56 (NCH₂O), 78.25 (14-C + 14'-C), 84.07 (5-C + 5'-C), 116.20 (7-C + 7'-C), 116.68 (CH), 117.98 (CH), 124.41 (C), 126.17 (C), 131.04 (C), 140.02 (C), 142.50 (C); MS (FAB): m/z = 733 (M), C₄₄H₅₁N₃O₇ requires 733; Rf (DCM/MeOH/NH₄OH: 100/10/1): 0.15; mp > 200°C

17,17'-Bis(cyclopropylmethyl)-3,3'-(4-phthalimidomethyl)benzyloxy-14,14'-dimethoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepox-6,6'-(4-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan] (223)

To a solution of 211 (96 mg, 0.14 mmol) and DMAP (28 mg, 0.23 mmol) in pyridine (5 mL) was added 4,4'-dimethoxytrityl chloride (95 mg, 0.28 mmol) and the reaction mixture was stirred overnight at room temperature. Water was added and the aqueous phase extracted with CHCl₃. The organic phase was dried (MgSO₄) and concentrated. 222 was isolated as a brown solid and used without any further purification.
\textsuperscript{1}H NMR (270 MHz, CDCl\textsubscript{3}): 0.05-0.07 (m, 4H, 2xNCH\textsubscript{2}CH(CHHCHH)), 0.41-0.45 (m, 4H, 2xNCH\textsubscript{2}CH(CHHCHH)), 0.74-0.82 (m, 2H, 2xNCH\textsubscript{2}CH(CH\textsubscript{2}CH\textsubscript{2})), 2.99 (s, 6H, 2xOCH\textsubscript{3}), 3.70 (s, 12H, 4xOCH\textsubscript{3}), 5.53 (s, 2H, 5-H +5'-H), 6.41 (d, 2H, J=8.1 Hz, 1-H + 1'-H), 6.63 (d, 2H, J=8.1 Hz, 2-H + 2'-H), 6.75 (d, 8H, J=8.9 Hz), 7.09 (d, 8H, J=8.9 Hz), 7.17-7.22 (m, 10H); R\textsubscript{f} (DCM/MeOH/NH\textsubscript{4}OH: 100/10/1): 0.72

222 (0.14 mmol), sodium hydride (23 mg, 0.57 mmol) and 206 (0.14 g, 0.42 mmol) were reacted according to the general procedure I. After purification, 223 was isolated as a brown solid (41 mg, 20%).

IR \nu_{\text{max}}/\text{cm}^{-1} (neat): 2916 (C-H aromatic), 1715 (CO); \textsuperscript{1}H NMR (270 MHz, CDCl\textsubscript{3}): 0.10 (d, 4H, J=4.6 Hz, 2xNCH\textsubscript{2}CH(CHHCHH)), 0.41-0.53 (m, 4H, 2xNCH\textsubscript{2}CH(CHHCHH)), 0.77-0.91 (m, 2H, 2xNCH\textsubscript{2}CH(CH\textsubscript{2}CH\textsubscript{2})), 3.11 (s, 6H, 2xOCH\textsubscript{3}), 4.76 (d, 2H, J=12.3 Hz, 2xOCH\textsubscript{2}CH\textsubscript{2})), 4.81 (s, 6H, 3xNCH\textsubscript{2}), 4.86 (d, 2H, J=12.3 Hz, 2xOCH\textsubscript{2}CH\textsubscript{2})), 5.23 (s, 2H, 5-H + 5'-H), 5.24 (d, 1H, J=16.8 Hz, NCH\textsubscript{2}H), 5.31 (d, 1H, J=16.8 Hz, NCH\textsubscript{2}H), 6.44 (d, 2H, J=8.2 Hz, 1-H + 1'-H), 6.58 (d, 2H, J=8.2 Hz, 2-H + 2'-H), 6.86 (d, 2H, J=8.2 Hz), 7.13 (d, 2H, J=8.2 Hz), 7.23 (d, 2H, J=8.2 Hz), 7.37 (d, 2H, J=8.2 Hz), 7.61-7.75 (m, 6H), 7.70-7.74 (m, 2H), 7.77-7.81 (m, 4H); \textsuperscript{13}C NMR (67.8 MHz, CDCl\textsubscript{3}): 3.15 (2xNCH\textsubscript{2}CH(CH\textsubscript{2}CH\textsubscript{2})), 4.22 (2xNCH\textsubscript{2}CH(CH\textsubscript{2}CH\textsubscript{2})), 9.18 (2xNCH\textsubscript{2}CH(CH\textsubscript{2}CH\textsubscript{2})), 22.43 (CH\textsubscript{2}), 23.18 (CH\textsubscript{2}), 30.25 (15-C + 15'-C), 40.86 (PhthaNCH\textsubscript{2}), 41.32 (2xPhthaNCH\textsubscript{2}), 44.72 (16-C + 16'-C), 47.28 (NCH\textsubscript{2}Ph), 48.15 (13-C + 13'-C), 48.67 (14-COCH\textsubscript{3} + 14'-COCH\textsubscript{3}), 55.36 (9-C + 9'-C), 59.44 (18-C + 18'-C), 71.16 (2xOCH\textsubscript{2}CH\textsubscript{2}), 78.31 (14-C + 14'-C), 84.53 (5-C + 5'-C), 115.38 (C), 116.66 (CH), 117.76 (CH), 123.19 (CH), 123.25 (CH), 125.75 (C), 126.39 (CH), 126.82 (C), 127.75 (CH), 128.53 (CH), 128.69 (CH), 131.97 (C), 132.05 (C), 133.65 (CH), 133.87 (CH), 134.81 (C), 135.56 (C), 137.43 (C), 138.24 (C), 141.93 (C), 144.62 (C), 167.77 (CO), 167.94 (CO); MS (FAB): m/z = 1437 (M); C\textsubscript{90}H\textsubscript{80}N\textsubscript{6}O\textsubscript{12} requires 1437; R\textsubscript{f} (DCM/MeOH/NH\textsubscript{4}OH: 110/10/1): 0.75 ; mp : 122°C
17,17'-Bis(cyclopropylmethyl)-3,3',14,14'-tetraacetoxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-(4-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan]
(224)

178 (0.17 g, 0.20 mmol), sodium hydride (60% in oil, 24 mg, 0.60 mmol), 18-crown-6 (20 mg, 0.08 mmol) and 206 (0.20 g, 0.60 mmol) were reacted according to the general procedure I. 224 was isolated as a brown solid (0.08 g, 37%).

\[^1{}H\] NMR (270 MHz, CDCl\textsubscript{3}): 0.01-0.05 (m, 4H, 2\times\textit{NCH}_2\textit{CH(CM/CM)}), 0.43 (d, 4H, \textit{J}=7.4 Hz, 2\textit{XNCH}_2\textit{CH(CHOHCHOH)}), 0.66-0.78 (m, 2H, 2\times\textit{NCH}_2\textit{CH(CHOHCHOH)}), 1.85 (s, 3H, \textit{CH}_3), 1.97 (s, 3H, \textit{CH}_3), 4.42 (d, 2H, \textit{J}=5.7 Hz), 4.60-4.98 (m, 2H, NCH\textsubscript{2}Ph), 4.83 (s, 2H, CH\textsubscript{2}NPhtha), 5.21 (s, 2H, 5-H +5'-H), 6.61 (d, 2H, \textit{J}=8.2 Hz, 1-H + 1'-H), 6.73 (d, 2H, \textit{J}=8.2 Hz, 2-H + 2'-H), 7.20-7.38 (m, 4H), 7.64-7.71 (m, 2H), 7.78-7.86 (m, 2H); MS (FAB): \textit{m/z} = 1079.4450 (M+H); \textit{C}_{64}\textit{H}_{63}\textit{N}_{4}\textit{O}_{12} \text{ requires 1079.4442}; \text{Rf (DCM/MeOH/NH}_{4}\text{OH: 200/12/1): 0.55}

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxo-6,6'-(4-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (227)

224 (0.15 g, 0.14 mmol) was dissolved in a mixture of conc. HCl/MeOH (2 mL, 1/1) and the reaction was stirred overnight at 85°C. The mixture was evaporated to dryness and water was added. The aqueous phase was basified to pH=8 with diluted NH\textsubscript{4}OH and extracted with DCM/MeOH: 5/1. The organic phase was dried (MgSO\textsubscript{4}) and the solvent evaporated. Purification by column chromatography (gradient elution, CHCl\textsubscript{3}/MeOH/NH\textsubscript{4}OH: 450/10/1 to CHCl\textsubscript{3}/MeOH/NH\textsubscript{4}OH: 100/10/1) afforded 227 (66 mg, 52%) and 230 (23 mg, 21%) as brown solids.

Data for 227:
IR \textit{v}_{\text{max}}/\text{cm} (neat): 3404 (br, bonded OH), 1713 (CO); \[^1{}H\] NMR (270 MHz, CDCl\textsubscript{3}): 0.09 (d, 4H, \textit{J}=4.9 Hz, 2\times\textit{NCH}_2\textit{CH(CHOHCHOH)}), 0.49 (d, 4H, \textit{J}=8.0 Hz, 2\times\textit{NCH}_2\textit{CH(CHOHCHOH)}), 0.75-0.85 (m, 2H, 2\times\textit{NCH}_2\textit{CH(CHOHCHOH)}), 3.00 (d, 2H, \textit{J}=18.4 Hz), 3.14 (d, 2H, \textit{J}=6.3 Hz), 3.64-4.20 (br, s, 4H, OH), 4.82 (s, 2H, CH\textsubscript{2}NPhtha), 5.19 (d, 1H, \textit{J}=17.2 Hz, NCH\textsubscript{2}H), 5.29 (s, 2H, 5-H +5'-H), 5.44 (d, 1H, \textit{J}=17.2 Hz, NCH\textsubscript{2}H), 6.41-6.48 (m, 4H, 1-H + 1'-H + 2-H + 2'-H), 6.79 (d, 2H, \textit{J}=8.0 Hz, Ar), 7.32 (d, 2H, \textit{J}=8.0 Hz, Ar), 7.66-7.69 (m, 2H, Ar), 7.82-7.85 (m, 2H, Ar);
$^{13}$C NMR (67.8 MHz, CDCl$_3$): 3.74 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.83 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.34 (2xNCH$_2$CH(CH$_2$CH$_2$)), 22.98 (10-C + 10'-C), 28.91 (8-C + 8'-C), 31.34 (15-C + 15'-C), 41.15 (CH$_2$NPhtha), 43.50 (16-C + 16'-C), 47.05 (NCH$_2$), 47.96 (13-C + 13'-C), 59.29 (18-C + 18'-C), 62.34 (9-C + 9'-C), 72.66 (14-C + 14'-C), 84.74 (5-C + 5'-C), 116.45 (C), 116.66 (CH), 118.45 (CH), 123.26 (CH), 124.99 (C), 125.60 (C), 125.75 (CH), 128.61 (CH), 130.66 (C), 132.19 (C), 133.87 (CH), 134.77 (C), 138.68 (C), 139.61 (C), 142.79 (C), 168.12 (CO); MS (FAB): m/z = 911.4004 (M+H); C$_{56}$H$_{55}$N$_4$O$_8$ requires 911.4019; R$_f$ (DCM/MeOH/NH$_4$OH: 110/10/1): 0.31; mp > 220 °C

$^{17}$,17',-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'- (3-(phthalimidomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (228)

178 (0.33 g, 0.40 mmol), sodium hydride (60% in oil, 64 mg, 1.60 mmol), 18-crown-6 (20 mg, 0.08 mmol) and 207 (0.40 g, 1.20 mmol) were reacted according to the general procedure I, affording 225 as a brown solid (0.18 g, 42%).

225 (80 mg, 74 μmol) was immediately dissolved in a mixture of conc. HCl/MeOH (2mL, 1/1) and the solution was stirred overnight at 86°C. The solvents were then removed by evaporation and water was added. The aqueous phase was basified to pH=10 with diluted NH$_4$OH and extracted with DCM/MeOH: 5/1. The organic phase was dried (MgSO$_4$) and concentrated under vacuum. Purification by column chromatography, eluting first with CHCl$_3$/MeOH/NH$_4$OH: 450/10/1, then with CHCl$_3$/MeOH/NH$_4$OH: 300/10/1, afforded 228 as a brown solid (47 mg, 70%).

$^1$H NMR (270 MHz, CDCl$_3$): 0.09 (d, 4H, J=4.9 Hz, 2xNCH$_2$CH(CHHCHH)), 0.49 (d, 4H, J=7.9 Hz, 2xNCH$_2$CH(CHHCHH)), 0.73-0.85 (m, 2H, 2xNCH$_2$CH(CH$_2$CH$_2$)), 1.54 (d, 2H, J=8.5 Hz), 3.02 (d, 2H, J=18.4 Hz), 3.14 (d, 2H, J=6.1 Hz), 4.80 (d, 2H, J=14.9 Hz, CHHNPhtha), 4.87 (d, 2H, J=14.9 Hz, CHJNPhtha), 5.25 (d, 1H, J=16.5 Hz, NCHH), 5.31 (s, 2H, 5-H + 5'-H), 5.37 (d, 1H, J=16.5 Hz, NCHH), 6.45 (d, 2H, J=8.1 Hz, 1-H + 1'-H), 6.57 (d, 2H, J=8.1 Hz, 2-H + 2'-H), 6.84-6.86 (m, 1H), 7.17-7.39 (m, 3H), 7.65-7.71 (m, 2H), 7.80-7.85 (m, 2H); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 3.71 (2xNCH$_2$CH(CH$_2$CH$_2$)), 3.90 (2xNCH$_2$CH(CH$_2$CH$_2$)), 9.34 (2xNCH$_2$CH(CH$_2$CH$_2$)), 22.98 (10-C + 10'-C), 28.91
(8-C + 8'-C), 31.42 (15-C + 15'-C), 41.58 (CH$_2$NPhtha), 43.56 (16-C + 16'-C), 47.47 (NCH$_2$), 47.99 (13-C + 13'-C), 59.27 (18-C + 18'-C), 62.28 (9-C + 9'-C), 72.67 (14-C + 14'-C), 84.86 (5-C + 5'-C), 116.34 (C), 116.89 (CH), 118.50 (CH), 123.48 (CH), 125.07 (C), 125.74 (C), 125.94 (CH), 126.73 (CH), 127.14 (CH), 128.95 (CH), 130.72 (C), 132.00 (C), 134.04 (CH), 136.46 (C), 138.79 (C), 139.51 (C), 143.03 (C), 168.31 (CO); C$_{56}$H$_{54}$N$_4$O$_8$ requires 910.3941; R$_f$ (DCM/MeOH/NH$_4$OH: 100/10/1): 0.38; mp > 220°C

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxy-6,6'-((2-phthalimidomethyl)benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (229)

178 (0.33 g, 0.40 mmol), sodium hydride (60% in oil, 64 mg, 1.60 mmol), 18-crown-6 (20 mg, 0.08 mmol) and 208 (0.40 g, 1.20 mmol) were reacted according to the general procedure I, but the reaction mixture was stirred at 90°C for 14 hrs then at room temperature for 48 hrs. The desired product 226 was obtained as a brown solid (0.18 g, 42%).

226 (0.13 g, 0.12 mmol) was immediately dissolved in a mixture of conc. HCl/MeOH (2 mL, 1/1) and the reaction was stirred overnight at 85°C. The solvents were then removed and water was added. The aqueous phase was basified to pH=8 with diluted NH$_4$OH and extracted with DCM/MeOH: 5/1. The organic phase was dried (MgSO$_4$) and concentrated. Purification by column chromatography, eluting first with CHCl$_3$/MeOH/NH$_4$OH: 450/10/1, then with CHCl$_3$/MeOH/NH$_4$OH: 300/10/1, afforded 229 (46 mg, 42%) and 231 (29 mg, 31%) as brown solids.

Data for 229:
1H NMR (270 MHz, CD$_3$OD): 0.03 (d, 4H, J=4.9 Hz, 2xNCH$_2$CH(CH$_2$NHPhtha)), 0.37-0.44 (m, 4H, 2xNCH$_2$CH(CH$_2$NHPhtha)), 0.70-0.78 (m, 2H, 2xNCH$_2$CH(CH$_2$NHPhtha)), 2.97 (d, 2H, J=18.6 Hz), 3.14 (d, 2H, J=6.2 Hz), 5.05 (d, 1H, J=15.6 Hz, CH$_2$NPhtha), 5.12 (d, 1H, J=15.6 Hz, CH$_2$NPhtha), 5.12 (s, 2H, 5-H + 5'-H), 5.45 (d, 1H, J=16.6 Hz, NCH$_2$H), 5.72 (d, 1H, J=16.6 Hz, NCH$_2$H), 6.39 (d, 2H, J=8.0 Hz, 1-H + 1'-H), 6.43 (d, 2H, J=8.0 Hz, 2-H + 2'-H), 6.81-6.84 (m, 1H), 7.03-7.14 (m, 2H), 7.22-7.26 (m, 1H), 7.65-7.68 (m, 2H), Phtha), 7.75-7.78 (m, 2H, Phtha), 13C NMR (67.8 MHz, CD$_3$OD): 4.09 (2xNCH$_2$CH(CH$_2$NHPhtha)), 4.61
17,17'-Dimethyl-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'- (benzylimino)[7,7'-bimorphinan]-3,3',14,14'-tetrol (233)

237 (0.17 g, 0.20 mmol) was dissolved in a mixture of MeOH/conc. HBr (6 mL, 1/1) and the solution was stirred overnight at room temperature. The solvents were removed by evaporation, water was added and the pH adjusted to pH=12 with diluted NH₄OH. The aqueous phase was extracted with DCM/MeOH: 5/1 and the organic phase was dried (MgSO₄) and concentrated. The crude product was purified by column chromatography, eluting with CHCl₃/MeOH/NH₄OH: 250/10/1, which gave 233 as an off white solid (0.125 g, 93 %).

IR νmax/cm⁻¹ (KBr): 3400 (br); ¹H NMR (270 MHz, CDCl₃): 2.35 (s, 6H, 2xNMe), 5.25 (d, 1H, J=16.9 Hz, CH/H), 5.33 (s, 2H, 5-H + 5'-H), 5.50 (d, 1H, J=16.9 Hz, CH/H), 6.50 (d, 2H, J=8.1 Hz, 1-H + 1'-H), 6.58 (d, 2H, J=8.1 Hz, 2-H + 2'-H), 6.88 (d, 2H, J=6.7 Hz), 7.24-7.37 (m, 3H); ¹³C NMR (100.5 MHz, CDCl₃): 22.34 (CH₂), 28.97 (CH₂), 31.23 (CH₂), 42.94 (NMe), 45.28 (CH₂), 47.35 (CH₂), 47.43 (13-C + 13'-C), 64.92 (9-C + 9'-C), 73.02 (14-C + 14'-C), 84.89 (5-C + 5'C), 116.32 (C), 116.88 (CH), 118.71 (CH), 125.23 (C), 125.61 (CH), 125.67 (C), 126.85 (CH), 128.65 (CH), 130.56 (C), 138.75 (C), 140.02 (C), 142.91 (C); MS (FAB): m/z = 672.3063 (M+H); C₄₁H₄₂N₂O₆ requires 672.3073; R₇ (DCM/MeOH/NH₄OH: 110/10/1): 0.27; Anal. (C₄₁H₄₂N₂O₆·2HCl·4H₂O) requires C 60.32 %, H 6.29 %, N 5.14 %, found: C 60.30 %, H 6.05 %, N 4.81 %; mp > 240°C
17,17'-Dimethyl-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-iminobimorphinan]-3,3',14,14'-tetrol (235)

218 (0.66 g, 2.21 mmol), hydrazine sulfate (0.15 g, 1.15 mmol) and methanesulfonic acid (0.07 mL, 1.08 mmol) were reacted according to the general procedure K, the reaction being however stirred in DMF at 105°C overnight. After purification, 235 was isolated as a brown solid (0.48 g, 75%).

IR \( \nu_{\text{max}}/\text{cm} (\text{KBr}) \): 3413 (br, bonded OH); \(^1\text{H} \) NMR (270 MHz, CDCl\(_3\)): 2.36 (s, 3H, N-Me), 5.60 (s, 2H, 5-H and 5'-H), 6.52 (d, 2H, \( J=8.0 \) Hz, 1-H and 1'-H), 6.67 (d, 2H, \( J=8.0 \) Hz, 2-H and 2'-H); \(^{13}\text{C} \) NMR (100.5 MHz, CDCl\(_3\)): 22.35 (CH\(_2\)), 28.78 (CH\(_2\)), 31.37 (CH\(_2\)), 42.96 (2xN-Me), 45.27 (CH\(_2\)), 47.27 (13-C + 13'-C), 64.88 (9-C + 9'-C), 73.11 (14-C + 14'-C), 85.59 (5-C + 5'-C), 116.46, 117.56, 118.97, 125.03, 125.15, 130.34, 138.81, 142.83; MS (FAB): \( m/z = 582.2583 \) (M+H); \( \text{C}_{34}\text{H}_{36}\text{N}_{3}\text{O}_{6} \) requires 582.2608; \( R_f \) (DCM/MeOH/NH\(_4\)OH: 100/10/1): 0.19; mp \( > 220^\circ \text{C} \)

17,17'-Dimethyl-3,3'-dibenzyloxy-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'- (benzylimino)[7,7'-bimorphinan]-14,14'-diol (237)

235 (0.16 g, 0.31 mmol), sodium hydride (0.12 g, 3.0 mmol), 18-crown-6 (33 mg, 0.12 mmol) and benzyl bromide (0.19 mL, 1.59 mmol) were reacted according to the general procedure I, but the reaction was carried out at room temperature. The crude oil was purified by column chromatography (gradient elution, with 100% CHCl\(_3\) then CHCl\(_3\)/MeOH/NH\(_4\)OH: 400/10/1 to 400/25/1) to yield 237 as a brown solid (0.23 g, 87%).

\(^1\text{H} \) NMR (270 MHz, CDCl\(_3\)): 2.35 (s, 6H, 2xNMe), 4.95 (s, 4H, 2xOCH\(_2\)), 5.29 (s, 2H, 5H + 5'-H), 5.31-5.42 (m, 2H, NCH\(_2\)), 6.52 (d, 2H, \( J=8.3 \) Hz, 1-H + 1'-H), 6.66 (d, 2H, \( J=8.3 \) Hz, 2-H + 2'-H), 6.97-7.06 (m, 1H), 7.13 (d, 4H, \( J=4.5 \) Hz), 7.24-7.35 (m, 10H); \(^{13}\text{C} \) NMR (67.8 MHz, CDCl\(_3\)): 22.26 (CH\(_2\)), 28.94 (CH\(_2\)), 31.45 (CH\(_2\)), 42.88 (NMe), 45.23 (CH\(_2\)), 47.05 (13-C + 13'-C), 47.61 (CH\(_2\)), 64.86 (9-C + 9'-C), 71.42 (OCH\(_2\)), 72.82 (14-C + 14'-C), 84.41 (5-C + 5'-C), 115.79 (C), 116.46 (CH), 118.17 (CH), 125.84 (C), 126.09 (C), 126.72 (CH), 127.56 (CH), 128.26 (CH), 131.22 (C), 137.63 (C), 138.33 (C), 142.19 (C), 144.87 (C); MS (FAB): \( m/z = 852 \) (M); \( \text{C}_{55}\text{H}_{53}\text{N}_{3}\text{O}_{6} \) requires 852; mp \( > 240^\circ \text{C} \)

189
17,17'-Dimethyl-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'-(imino)[7,7'-bimorphinan]-3,3'-dion (239) 102

217 (1.45 g, 4.51 mmol), hydrazine sulfate (0.31 g, 2.38 mmol) and methanesulfonic acid (0.14 mL, 2.16 mmol) were reacted according to the general procedure K. After purification by column chromatography, 239 was isolated as a brown solid (0.43 g, 35%).

IR \( \nu_{\text{max}}/\text{cm} (\text{KBr}) \): 3380 (br, bonded OH); \(^1\text{H} \) NMR (270 MHz, \( \text{CDCl}_3 \)): 1.57-1.79 (m, 3H), 1.97 (dd, 1H, \( J=14.7 \) Hz and 5.6 Hz), 2.10-2.40 (m, 5H), 2.22 (s, 3H, NMe), 2.82 (d, 1H, \( J=18.5 \) Hz), 2.98-3.01 (m, 1H), 5.20 (s, 2H, 5H and 5'-H), 6.33 (d, 2H, \( J=8.2 \) Hz, 1-H and 1'-H), 6.39 (d, 2H, \( J=8.2 \) Hz, 2-H and 2'-H); \(^{13}\text{C} \) NMR (67.8 MHz, \( \text{CDCl}_3 \)): 20.26 (2xCH2), 20.93 (2xCH2), 34.99 (15-C + 15'-C), 40.58 (14-C + 14'-C), 42.11 (2xNMe), 42.97 (13-C + 13'-C), 46.40 (16-C + 16'-C), 59.56 (9-C + 9'-C), 85.44 (5-C + 5'-C), 116.29 (CH), 116.86 (C), 118.39 (CH), 124.99 (C), 125.09 (C), 128.44 (C), 139.21 (C), 143.25 (C); MS (FAB): \( m/z = 550.2702 \) (M+H); \( C_{34}H_{36}N_3O_4 \) requires 550.2705; \( R_f (\text{DCM/MeOH/NH}_4\text{OH}: 100/16/1.6) : 0.13; \) mp > 240°C

17,17'-Dimethyl-3,3'-dibenzyloxy-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxo-6,6'-(benzylimino)[7,7'-bimorphinan] (240)

239 (0.13 g, 0.24 mmol), sodium hydride (90 mg, 2.25 mmol), 18-crown-6 (30 mg, 0.11 mmol) and benzyl bromide (0.14 mL, 1.18 mmol) were reacted according to the general procedure I, but the reaction was carried out at room temperature. The crude oil was purified by column chromatography (gradient elution with 100% \( \text{CHCl}_3 \) then \( \text{CHCl}_3/\text{MeOH/NH}_4\text{OH}: 400/10/1 \) to 400/25/1) to yield 240 as a brown solid (37 mg, 19%).

\(^1\text{H} \) NMR (270 MHz, \( \text{CDCl}_3 \)): 2.39 (s, 6H, 2xNMe), 3.00 (d, 2H, \( J=18.5 \) Hz), 3.14-3.19 (m, 2H), 4.96 (s, 4H, 2xOCH2), 5.26 (s, 2H, 5-H and 5'-H), 5.29 (d, 1H, \( J=16.3 \) Hz, NCHH), 5.37 (d, 1H, \( J=16.3 \) Hz, NCHH), 6.55 (d, 2H, \( J=8.2 \) Hz, 1-H and 1'-H), 6.69 (d, 2H, \( J=8.2 \) Hz, 2-H and 2'-H), 7.04-7.13 (m, 5H), 7.24-7.33 (m, 10H); \(^{13}\text{C} \) NMR (67.8 MHz, \( \text{CDCl}_3 \)): 20.46 (CH2), 21.45 (CH2), 35.83 (15-C + 15'-C), 41.18 (C), 42.88 (2xNMe), 43.33 (C), 46.65 (CH2), 47.63 (CH2), 59.77 (9-C + 9'-C), 71.65 (OCH2), 85.08 (5-C + 5'-C), 116.65 (CH), 117.65 (C), 118.51 (CH), 126.69 (CH),
126.96 (CH), 127.57 (CH), 127.62 (CH), 128.24 (CH), 128.35 (CH), 129.68 (C), 137.58 (C), 138.27 (C), 141.87 (C), 145.08 (C); MS (FAB): \( m/z = 820 \) (M);
\( \text{C}_{55}\text{H}_{53}\text{N}_{3}\text{O}_{4} \) requires 820; \( R_f \) (DCM/MeOH/NH\(_4\)OH: 100/10/1): 0.43

17,17'-Dimethyl-3,3'-dimethoxy-6,6',7,7'-tetrahydro-4,5:4',5'-diepoxy-6,6'-
(imo)[7,7'-bimorphinan] (242)

Hydrocodone hydrochloride (1.81 g, 5.39 mmol), hydrazine sulfate (0.31 g, 2.84 mmol) and methanesulfonic acid (0.34 mL, 5.26 mmol) were reacted according to the general procedure K. After purification by column chromatography, 242 was isolated as a brown solid (1.10 g, 71 %).

\(^1\)H NMR (270 MHz, CDCl\(_3\)): 2.39 (s, 6H, 2xNCH\(_3\)), 3.79 (s, 6H, 2xOCH\(_3\)), 5.39 (s, 2H, 5-H and 5'-H), 6.59 (d, 2H, J=8.3 Hz, 1-H and 1'-H), 6.66 (d, 2H, J=8.3 Hz, 2-H and 2'-H), 8.09 (br, s, 1H, NH); \(^{13}\)C NMR (100.5 MHz, CDCl\(_3\)): 19.82 (2xCH\(_2\)), 20.73 (2xCH\(_2\)), 35.37 (15-C + 15'-C), 40.74 (14-C + 14'-C), 42.45 (2xNCH\(_3\)), 42.86 (13-C + 13'-C), 46.11 (16-C + 16'-C), 55.48 (2xOCH\(_3\)), 59.22 (9-C + 9'-C), 85.35 (5-C + 5'-C), 112.28 (CH), 117.00 (C), 117.79 (CH), 125.13 (C), 126.72 (C), 128.67 (C), 142.22 (C), 144.10 (C)

4-Phthalimidotoluene (244) \(^{216}\)

A solution of toluidine (4.28 g, 40 mmol) and phthalic anhydride (5.91 g, 40 mmol) in acetic acid (80 mL) was refluxed for two hours. The reaction mixture was then cooled down to room temperature and poured into water. The precipitate was filtered off, washed with water, dissolved in DCM and dried over MgSO\(_4\). The solvent was removed by evaporation to yield 244 (8.0 g, 84 %) as an off-white solid.

IR \( \nu_{\text{max}}/\text{cm} \) (KBr): 1709 (CO); \(^1\)H NMR (400 MHz, CDCl\(_3\)): 2.39 (s, 3H, CH\(_3\)), 6.78-7.30 (m, 4H), 7.73-7.75 (m, 2H), 7.90-7.92 (m, 2H); \(^{13}\)C NMR (100.5 MHz, CDCl\(_3\)): 21.10 (CH\(_3\)), 123.54 (CH), 126.35 (CH), 128.89 (C), 129.66 (CH), 131.69 (C), 134.21 (CH), 138.03 (C), 167.30 (CO); MS (FAB): \( m/z = 238.0860 \) (M+H); \( \text{C}_{15}\text{H}_{12}\text{NO}_2 \) requires 238.0867; \( R_f \) (n-hexanes/ethyl acetate: 4:1): 0.22; mp : 193-194\(^\circ\)C (lit.: 201-203\(^\circ\)C) \(^{216}\)
N-(4-Phthalimidobenzyl)carbazole (247)
Carbazole (167 mg, 1.0 mmol), sodium hydride (80 mg, 2.0 mmol), 15-crown-5 (0.02 mL, 0.1 mmol) and 182 (0.35 g, 1.1 mmol) in dry DMF (5 mL) were reacted according to the general procedure I. After purification by column chromatography, 247 was isolated as a brown solid (0.15 g, 37%).

$^1$H NMR (270 MHz, CDCl$_3$): 5.51 (s, 2H, CH$_2$), 7.17-7.20 (m, 4H), 7.25-7.29 (m, 2H), 7.31 (d, 2H, $J$=7.9 Hz), 7.35-7.41 (m, 2H), 7.69-7.72 (m, 2H, Pthta), 7.84-7.88 (m, 2H, Pthta); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 46.19 (CH$_2$), 108.93 (CH), 119.45 (CH), 120.49 (CH), 123.14 (C), 123.85 (CH), 126.03 (CH), 126.93 (CH), 127.12 (CH), 131.72 (C), 134.53 (CH), 140.61 (C), 167.33 (CO); mp : 187 °C

N-(4-Aminobenzyl)-carbazole (248)
To a solution of 247 (49 mg, 0.12 mmol) in ethanol (1 mL) was added DCM until the solution became completely clear. Hydrazine hydrate (11.6 μL, 0.37 mmol) was added and the reaction mixture stirred for two days. The solvent was then removed under vacuum and the crude product purified by column chromatography. 248 was isolated as a brown solid (19 mg, 57%).

$^1$H NMR (270 MHz, CDCl$_3$): 3.50 (br, s, 2H, NH$_2$), 5.32 (s, 2H, CH$_2$), 6.48 (d, 2H, $J$=6.5 Hz), 6.88 (d, 2H, $J$=6.5 Hz), 7.12-7.18 (m, 2H), 7.28-7.38 (m, 2H), 8.04 (d, 2H, $J$=7.9 Hz); $^{13}$C NMR (67.8 MHz, CDCl$_3$): 46.15 (CH$_2$), 108.96 (CH), 115.24 (CH), 118.95 (CH), 120.27 (CH), 122.89 (C), 125.70 (CH), 127.01 (C), 127.63 (CH), 140.61 (C), 145.63 (C)

17-Methyl-6,7-didehydro-4,5α-epoxy-3-methoxy-14-acetoxy-indolo[2',3':6,7]-morphinan (249)
A solution of 17-methyl-6,7-didehydro-4,5α-epoxy-3-methoxy-14-hydroxy-indolo[2',3':6,7]-morphinan (0.13 g, 0.33 mmol) in acetic anhydride (10 mL) was treated according to the same method as used for the preparation of 178. Purification by column chromatography, eluting first with CHCl$_3$ then with CHCl$_3$/MeOH/NH$_4$OH: 400/5/1, afforded 249 as an off-white solid (0.142 g, 98%).
IR \(\nu_{\text{max}}/\text{cm} (\text{KBr})\): 1705 (CO); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 1.92 (s, 3H, OCOCH\(_3\)), 2.34 (s, 3H, NCH\(_3\)), 3.25 (d, 1H, \(J=18.6\) Hz), 3.74 (s, 3H, 3-COCH\(_3\)), 3.75 (d, 1H, \(J=16.8\) Hz), 4.40 (d, 1H, \(J=6.2\) Hz), 5.64 (s, 1H, 5-H), 6.58-6.64 (m, 2H, 1-H and 2-H), 6.99-7.05 (m, 1H, 5'-H), 7.12-7.18 (m, 1H, 6'-H), 7.30 (d, 1H, \(J=8.1\) Hz, 7'-H), 7.39 (d, 1H, \(J=7.4\) Hz, 4'-H), 8.17 (br, s, 1H, NH); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)): 22.37 (OCOCH\(_3\)), 22.69 (CH\(_2\)), 24.48 (CH\(_2\)), 30.85 (CH\(_2\)), 42.83 (NMe), 45.52 (16-C), 47.63 (13-C), 55.92 (OMe), 58.02 (9-C), 83.93 (14-C), 84.91 (5-C), 110.58 (C), 111.25 (CH), 113.06 (CH), 118.60 (CH), 118.92 (CH), 119.26 (CH), 122.73 (CH), 126.52 (C), 126.55 (C), 129.08 (C), 129.76 (C), 136.89 (C), 143.10 (C), 143.95 (C), 170.72 (CO); mp > 210°C

17-Methyl-6,7-didehydro-4,5a-epoxy-3-methoxy-14-acetoxy-(4-(phthalimido methyl)benzylindolo)[2',3':6,7]-morphinan (251)

249 (72 mg, 0.17 mmol), sodium hydride (60% in oil, 27 mg, 0.67 mmol), 15-crown-5 (0.01 mL, 0.05 mmol) and 182 (0.17 g, 0.51 mmol) in dry DMF (5 mL) were reacted according to the general procedure I. After purification by column chromatography, eluting first with CHCl\(_3\) then with CHCl\(_3\)/MeOH/NH\(_4\)OH: 400/5/1, 251 was obtained as a brown solid (34 mg, 31%).

IR \(\nu_{\text{max}}/\text{cm} (\text{KBr})\): 1760, 1715 (CO); \(^1\)H NMR (270 MHz, CDCl\(_3\)): 1.91 (s, 3H, OCOCH\(_3\)), 2.34 (s, 3H, NCH\(_3\)), 3.26 (d, 1H, \(J=18.3\) Hz), 3.72 (s, 3H, 3-COCH\(_3\)), 3.80 (d, 1H, \(J=16.5\) Hz), 4.41 (d, 1H, \(J=5.7\) Hz), 5.56 (d, 1H, \(J=17.3\) Hz, NCH\(_2\)H), 5.63 (d, 1H, \(J=17.3\) Hz, NCH\(_2\)H), 5.64 (s, 1H, 5-H), 6.60 (d, 1H, \(J=8.2\) Hz, 1-H), 6.64 (d, 1H, \(J=8.2\) Hz, 2-H), 7.00-7.07 (m, 1H, 5'-H), 7.12-7.15 (m, 3H, 6'-H + 2Ar), 7.31-7.34 (m, 3H, 7'-H + 2Ar), 7.43 (d, 1H, \(J=7.6\) Hz, 4'-H), 7.74-7.79 (m, 2H), 7.90-7.94 (m, 2H); \(^{13}\)C NMR (67.8 MHz, CDCl\(_3\)): 22.42 (OCOCH\(_3\)), 22.77 (CH\(_2\)), 24.72 (CH\(_2\)), 31.02 (CH\(_2\)), 42.88 (NMe), 45.56 (16-C), 46.76 (NCH\(_2\)Ph), 47.87 (13-C), 56.23 (OMe), 58.08 (9-C), 84.02 (14-C), 84.07 (5-C), 110.03 (CH), 110.35 (C), 113.74 (CH), 118.68 (CH), 119.17 (CH), 119.40 (CH), 122.83 (CH), 123.75 (CH), 126.49 (C), 126.56 (C), 126.65 (CH), 126.85 (CH), 130.05 (C), 130.40 (C), 130.66 (C), 131.71 (C), 134.42 (CH), 137.32 (C), 138.05 (C), 143.26 (C), 144.06 (C), 167.27 (CO), 170.69 (CO); mp > 210°C

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ANNEXE

- PUBLICATIONS
Guanidino N-Substituted and N,N-Disubstituted Derivatives of the \( \kappa \)-Opioid Antagonist GNTI

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Derivatives of the highly selective \( \kappa \)-opioid receptor antagonist GNTI (2a) have been prepared. Binding and functional studies conducted on cloned human opioid receptors expressed in Chinese hamster ovarian (CHO) cells suggested that adding a benzyl or a substituted benzyl group to the guanidino moiety led, in general, to a retention of high \( \kappa \)-affinity and antagonist potency. Disubstitution of the guanidino moiety led to reduced \( \kappa \)-selectivity.

Introduction

One of the principal goals for medicinal chemists within the field of drug abuse, and in particular opioid abuse, has been the development of selective antagonists for each of the opioid receptors \( (\mu, \kappa, \text{and} \ \delta) \). The availability of such agents greatly facilitates the study of the physiological function of these receptors. Though the role of opioids in the treatment of pain has long been recognized, it has become increasingly apparent that they have a significant role to play in a wider range of clinical situations and thus there is a continuing need for the development of selective ligands, both as tools for basic research and as leads for potential pharma­cotherapies. Of the three opioid receptor types, the \( \mu \)-receptor has been the most thoroughly investigated due to its involvement in the treatment of pain and opiate abuse. It is, however, becoming increasingly apparent that both the \( \kappa \)- and \( \delta \)-receptors represent viable molecular targets for a number of indications. Of particular interest to us are reports on the role of \( \kappa \)-opioid agonists in cocaine abuse, and in particular, the findings that \( \kappa \)-agonists can block many of cocaine’s behavioral effects.\(^{1-6} \) Thus \( \kappa \)-agonists may be of use in the development of a treatment for cocaine abuse.

\( \kappa \)-Antagonists have also been studied in the preclinical setting with reports of their utility in improving recovery after traumatic brain injury in rats,\(^{7} \) for determining the underlying mechanisms that cause the motor fluctuations that develop during the treatment of Parkinson’s disease,\(^{8} \) and as antidepressants in the forced swim test in rats.\(^{9} \) In feeding studies, administration of the \( \kappa \)-antagonist norBNI (1) significantly reduced deprivation intake and suppressed other forms of food intake in rats\(^{10} \) and has also been shown to attenuate drinking in genetically polydipsic mice.\(^{11} \)

At present, norBNI, discovered by Portoghese and co-workers, is the \( \kappa \)-antagonist of choice.\(^{12-14} \) Extensive investigation of the structural requirements for \( \kappa \)-antagonist selectivity has led to GNTI (2a), a simplified structure based on the indolomorphinan naltrindole.\(^{15,16} \) Initial reports suggest that 2a has comparable, or better, \( \kappa \)-antagonist selectivity than I\(^{15,16} \) and shares with 1 an extended duration of action.\(^{17} \) We were interested in the possibilities that the guanidine group provided for further structural elaboration. Introduction of a lipophilic group into the side chain of \( \mu \)- and \( \delta \)-opioid antagonists can have a profound effect on the selectivity, efficacy, and reversibility of the ligands. For example, introduction of arylalkyl groups to the 14-position in a series of \( \delta \)-antagonists related to naltrindole resulted in a \( \mu \)-agonist/low-­efficacy \( \delta \)-partial agonist profile.\(^{18} \) In addition, the indole \( N \)-benzyl derivative of naltrindole, BNTI (3, \( R = H \))\(^{19,20} \) has no means of forming a covalent bond to the receptor and yet is reported to have an in vivo profile very similar to that of the isothiocyanate-containing BNTII (3, \( R = \text{p-NCS} \)), with antagonist effects lasting up to 5 days. A similar effect has been observed with the well-known \( \mu \)-receptor irreversible antagonist C-CAM (4).\(^{21-23} \) The available evidence does not suggest that 4 forms a covalent bond with the receptor, yet it displays a pharmacological profile consistent with nonsurmountable binding to the receptor. Presumably, in these cases noncompetitive binding is a result of extremely tight binding involving the benzyl and cinnamoyl groups. If such an effect were replicated in the GNTI (2a) series at the \( \kappa \)-receptor, it would result in the first nonsurmountable \( \kappa \)-antagonist based on a...
κ-antagonist, and not κ-agonist, structure. For these reasons benzyl-substituted analogues of 2 were targeted along with a small number of disubstituted aliphatic analogues to extend the SAR.

Chemistry

The synthesis of guanidines 2a and 2b has been previously reported by Stevens et al.24 They were obtained by mercury-assisted condensation of amines 6a,6b with bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea. To access the related N-benzyl guanidines it was decided to utilize TV, Af-bis (ferf-butoxycarbonyl)-/V-benzyl-2-methylthiopseudourea and substituted benzyl analogues (8), in an analogous reaction. The guanidinylation agents (8) were prepared by reaction of the appropriately substituted benzyl bromide with 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea in the presence of sodium hydride. Coupling with amine 6b, to give 9a–c, was carried out at 50 °C in the presence of mercuric chloride, with the less reactive aniline 6a requiring extended reaction time at 60 °C to yield 9e–g. Removal of the tert-butoxycarbonyl protecting group was accomplished using standard conditions of trifluoroacetic acid to give the products (10a–c,e–g) as their trifluoroacetic acid salts. The nitro analogues 9c,g were also converted to their amino counterparts 9d,h by Raney Ni catalyzed transfer hydrogenation in 50% MeOH/cyclohexene before removal of the protecting groups with trifluoroacetic acid to yield 10d,h.

The p- and m-hydroxy analogues (10i,j) were prepared in similar fashion (Scheme 1), the appropriate guanidinylation agents being synthesized from the m- and p-benzoxybenzyl bromides reported previously.25-26 Simultaneous removal of the tert-butoxycarbonyl and benzyl protecting groups of 10i and 10j was found to proceed most efficiently in HCl/MeOH to give 10i and 10j as their hydrochloride salts.

Disubstituted thioureas 15 were prepared by coupling of 6a and 6b with symmetric and unsymmetric N,N-disubstituted thioureas (13), themselves prepared from the appropriate amines and thiophosgene (Scheme 2). The coupling would not take place directly with thioureas (12), in agreement with literature precedent,27 and required the presence of a tert-butoxycarbonyl group on one of the nitrogens. Interestingly, in the same report27 it is suggested that the thiourea group should have one proton on each of the nitrogens in order for the coupling reaction to be successful. This does not
Table 1. Antagonist Potency in [35S]GTPyS Assays Performed in Cloned Human Opioid Receptors

| compd | n | R1       | R2       | Kd (nM) ± SEM
|-------|---|----------|----------|-----------------
| 2b    | 2 | H        | H        | 1.25 ± 0.12    |
| 10a   | 2 | H        | benzy1   | 2.94 ± 0.31    |
| 10b   | 2 | H        | p-chlorobenzyl | 2.61 ± 0.41   |
| 10c   | 2 | H        | p-nitrobenzyl | 2.20 ± 0.60   |
| 10d   | 2 | H        | p-aminobenzyl | 1.57 ± 0.13   |
| 10e   | 2 | H        | benzyl   | 1.41 ± 0.17    |
| 10f   | 2 | H        | p-chlorobenzyl | 5.24 ± 1.13    |
| 10g   | 2 | H        | p-nitrobenzyl | 3.71 ± 0.59    |
| 10h   | 2 | H        | p-aminobenzyl | 1.22 ± 0.06    |
| 10i   | 2 | H        | p-hydroxybenzyl | 12.65 ± 0.84   |
| 10j   | 2 | H        | m-hydroxybenzyl | 4.29 ± 0.52    |
| 15a   | 2 | butyl    | butyl    | 4.62 ± 0.59    |
| 15b   | 2 | butyl    | butyl    | 5.66 ± 0.39    |
| 15c   | 2 | propyl   | propyl   | 4.59 ± 0.80    |
| 15d   | 2 | propyl   | cyclopropylmethyl | 3.26 ± 0.32   |
| 15e   | 2 | benzyl   | cyclopropylmethyl | 2.75 ± 0.24   |
| 1    | H | norBNI   | H        | 18.9 ± 1.8     |
| 2a   | 2 | GNTI     | H        | 3.23           |

* Values are means from five or six experiments. * Converted from pA2 values from ref 16.

Table 2. Binding Affinities to Cloned Human Opioid Receptors Transfected into Chinese Hamster Ovary (CHO) Cells

| compd | n | R1       | R2       | Kd (nM) ± SEM
|-------|---|----------|----------|-----------------
| 2b    | 2 | H        | H        | 5.69 ± 1.28    |
| 10a   | 2 | H        | benzy1   | 3.54 ± 0.25    |
| 10b   | 2 | H        | p-chlorobenzyl | 7.74 ± 1.98    |
| 10c   | 2 | H        | p-nitrobenzyl | 9.21 ± 3.73    |
| 10d   | 2 | H        | p-aminobenzyl | 7.78 ± 2.71    |
| 10e   | 2 | H        | benzyl   | 10.47 ± 1.87   |
| 10f   | 2 | H        | p-chlorobenzyl | 23.78 ± 5.00   |
| 10g   | 2 | H        | p-nitrobenzyl | 26.28 ± 3.82   |
| 10h   | 2 | H        | p-aminobenzyl | 7.89 ± 2.45    |
| 10i   | 2 | H        | p-hydroxybenzyl | 14.67 ± 3.65   |
| 10j   | 2 | H        | m-hydroxybenzyl | 14.16 ± 4.11   |
| 15a   | 2 | butyl    | butyl    | 7.89 ± 0.57    |
| 15b   | 2 | butyl    | butyl    | 18.27 ± 0.34   |
| 15c   | 2 | propyl   | propyl   | 9.83 ± 0.09    |
| 15d   | 2 | propyl   | cyclopropylmethyl | 22.44 ± 7.27   |
| 15e   | 2 | benzyl   | cyclopropylmethyl | 17.73 ± 0.30   |
| 1    | H | norBNI   | H        | 21.0 ± 5.0     |
| 2a   | 2 | GNTI     | H        | 36.9 ± 2.3     |

* Data are the average from two experiments, each carried out in triplicate. * Data from ref 16.

Opioid agonist and antagonist activity was determined using the [35S]GTPyS assay in cloned human opioid receptors transfected into Chinese hamster ovary (CHO) cells (Table 1). None of the compounds stimulated [35S]GTPyS binding for any type of opioid receptor but were found to be antagonists of the selective agonists DAMGO (κ), Cl-DPDPE (δ), and U69,593 (μ) (Table 1). The ligands were also evaluated in competition binding assays in CHO cells transfected with cloned human opioid receptors (Table 2). The displaced radioligands were [3H]DAMGO (κ), [3H]Cl-DPDPE (δ), and [3H]U69,593 (μ).

Each of the compounds was found to be a potent κ-antagonist with varying selectivity over the μ- and δ-receptors (Table 1). κ-Antagonist potency was consistent throughout the series with little variation between compounds (Kd = 0.06–0.44 nM). Those ligands lacking the ethylene spacer group were consistently more selective for the κ-receptor than those with the spacer group 10e–h vs 10a–d and 15a vs 15b. This effect was particularly prominent for κ/δ-selectivity but less so for κ/μ. This appears to confirm earlier reports suggesting that in the majority of cases a spacer group was not beneficial for κ-selectivity. In neither series (n = 0, 2) was there any evidence of consistent effects of the substituents on the benzyl ring, with the unsubstituted, p-amin, p-nitro, p-chloro, and m-hydroxy all having similar κ-antagonist potency and selectivity. The one compound that stood out was 10i, having a p-hydroxy substituent. While 10i retained antagonist potency at κ-receptors, it was less potent than the other ligands at δ- and μ-receptors, leading to increased κ-selectivity (183-fold over δ and 127-fold over μ). These results are intriguing as the p-hydroxy group of 10i can exactly overlay the second phenolic group of norBNI (1) and thus may be interacting unfavorably with the same site/residues on the μ- and δ-receptors. While GNTI (2a) was...
not evaluated in this current study, data from the same source and using the same assays as in the present study have been reported previously. Thus, some comparison can be made between 2a and the current series of compounds with reasonable confidence. 101 appears similar to both 1 and 2a in these assays. Of the three, 1 is the most selective for \( \kappa / \mu \); the least selective for \( \delta \). 2a is the opposite, with the greatest selectivity over \( \delta \) and the least over \( \mu \), while 101 displays a balance, with good selectivity over both \( \delta \) and \( \mu \) receptors.

The dialkylguanidines (15a–e) were again selective antagonists for the \( \kappa \)-receptor, but in general with somewhat reduced selectivity as compared to the benzyl guanidines (Table 1). The most direct comparison is between 10e, having a benzyl group, and 15e, having benzyl and cyclopropylmethyl groups. 10e showed higher selectivity, particularly with respect to \( \delta \). That 15d also displayed higher selectivity than 15e suggests that the increase in steric bulk on having both cyclopropylmethyl and benzyl groups is detrimental for selectivity.

This is a result of slightly reduced \( \kappa \)-antagonist potency and slightly increased \( \mu \)- and \( \delta \)-antagonist potencies for 15e compared to 15d.

In the binding assays, all of the ligands bound with highest affinity at the \( \kappa \) receptor (Table 2) with Hill slopes approximating unity, indicating competitive binding. Selectivity varied considerably, but with the broad trends comparable to those noted in the functional assay. Thus, benzyl guanidines 10a–d had substantially lower \( \kappa \)-selectivity than their analogues 10e–h; this was particularly evident for \( \kappa / \delta \) selectivity. There again appears to be no consistent SAR relating to the ring substituent within this series. Whereas in the functional assays 10i was most selective, in the binding assays it was the \( \delta \)-chloro analogue 10f. GNTI (2a) and its benzyl analogues (15a) each had higher selectivity for \( \kappa / \delta \) than \( \kappa / \mu \), whereas, as found in the functional assays, norBNI (1) was more selective for \( \kappa / \mu \) than \( \kappa / \delta \).

The difference between the disubstituted guanidines (15a–e) and the monosubstituted benzyl guanidines was even more pronounced in the binding assays than in the functional assays, with 15a–e displaying little or no \( \kappa \)-selectivity against the other two opioid receptors.

In the [35S]GTPyS assays, while the ligands caused a shift in the agonist dose–response curves, there was no indication of flattening of the dose–response curve that would be expected if the compounds were acting in a nonsurmountable manner. However, in C6(\( \delta \)) and CHO(\( \kappa \)) cells, the compounds tended to display wash-resistant binding that could be indicative of pseudo-irreversibility (data not shown). As norBNI (1) also displayed similar binding characteristics in these cell lines, it was felt that further studies in the mouse vas deferens (mvd) would provide a more accurate assessment of their reversibility. To this end, two compounds, 10b and 10f, were evaluated for \( \kappa \)-agonist activity in the mvd.

For 10f the antagonism study was conducted in more detail, and the effects were found to be dose-dependent. A Schid plot of the antagonist activity of 10f indicates a linear relationship with a slope approximating unity (0.7), again indicating competitive binding characteristics (Figure 1). It was noted that the \( K_\text{D} \) of 0.2 nM obtained in this mvd assay is considerably higher than the value suggested by the binding and GTPyS data.

Conclusions

The addition of benzyl and substituted-benzyl groups to the guanidino moiety of GNTI (2a) results in ligands that retain high affinity and selectivity for the \( \kappa \)-opioid receptor. Disubstituted guanidines displayed reduced selectivity compared to their monosubstituted counterparts, primarily as a result of lower \( \kappa \)-affinity. That the benzyl group of these ligands may interact with the same site on the receptor as the second phenolic group of norBNI (1) seemed to be confirmed by the substantial selectivity displayed by the \( \rho \)-hydroxy analogue (10i) in the functional assays. The discrepancy between wash-resistant binding in the C6(\( \delta \)) and CHO(\( \kappa \)) cell lines, yet fully reversible binding in the mvd, may suggest that wash-resistance is not a suitable definition of irreversibility.

Experimental Section

Column chromatography was performed under gravity, over silica gel 60 (35–70 \( \mu \)) purchased from Merck. Preparative TLC was performed on plates made with Kieselgel 60 F254, 0.25 mm for preparative TLC, obtained from Merck. The thickness of the silica layer was approximately 1 mm. Analytical TLC was performed using aluminum-backed coated plates with Kieselgel 60 F254, from Merck. The chromatograms were visualized using either UV light (UVG 254 nm), ninhydrin (acidic), or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopf block or a Gallenkamp MFB 595 melting point apparatus and are uncorrected. High- and low-resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument, with a matrix of m-nitrobenzyl alcohol. High- and low-resolution electron impact (EI) mass spectra were recorded using EI ionization at 70 eV, on a VG AutoSpec Q instrument, equipped with a Fisons autosampler. 1H NMR and 13C NMR spectra were recorded using either JEOL 270 (operating at 270 MHz for 1H and 67.8 MHz for 13C), JEOL Lambda 300 (operating at 300 MHz for 1H and 75.4 MHz for 13C), or JEOL EX 400 (operating at 400 MHz for 1H and 100.5 MHz for 13C) spectrometers. Chemical shifts (\( \delta \)) are measured in ppm. Spectra were referenced internally using the residual solvent resonance. Coupling constants (\( J \)) are expressed in hertz, and the multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Only diagnostic peaks have been quoted for proton NMR. Microanalysis was performed with a Perkin-Elmer 240C analyzer. Analytical RP-HPLC was performed with a Beckman System Gold 125 solvent module, equipped with a Beckman System Gold 166 detector (\( \lambda = 254 \) nm). The column stationary phase was Beckman ultraspHERE ODS 5 \( \mu \)m (15 cm x 4.6 mm).

A mobile phase of [MeOH/0.3% NH4C03 (80:20)] was used at a flow rate of 1 mL/min. Infrared spectroscopy was performed.
on either a Perkin-Elmer 782 Instrument or a Perkin-Elmer RM-FTI Instrument. Anhydrous THF, DCM, and MeOH were purchased from Aldrich. HPLC solvent grade chloroform and MeOH were purchased from Merck. All other solvents used were GPR grade, purchased from Merck or Fisher Scientific. Chemicals were purchased from Aldrich, Fluka, or Sigma-Aldrich. Derivatives of the Full experimental details for all compounds are provided as Supporting Information.

17-Cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10d) was isolated by vacuum filtration. Further purification was achieved by recrystallization (methanol/diethyl ether) to give 17-cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10d).

All chemicals were purchased from Aldrich, unless otherwise indicated, and solvents used were GPR grade, purchased from Merck or Fisher Scientific. Derivatives of the Full experimental details for all compounds are provided as Supporting Information.

17-Cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10f) (0.103 g, 0.13 mmol, 44%): mp 186-189 °C; Rf = 0.13 (CH3OH/CH2Cl2/NH4OH (85:10:1)); IR νmax/cm (KBr) 3630-2475 (br, bonded OH and NH) and 1678 (br, C=O, NH and NH2); 1H NMR (400 MHz, CDCl3) δ 0.48-0.59 (m, 2H, CH2), 7.39-7.91 (m, 5H, CH2), 8.19-8.32 (m, 2H, NH), 8.36 (s, 1H, NH), 10.84 (s, 1H, NH), 12.86 (s, 1H, NH). HRMS (FAB) m/z 596.2416 (M+1)+, C31H31N5O5S requires 596.2428. Anal. (C31H31N5O5S) requires 596.2428.

17-Cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10f) was dissolved in dichloromethane (4 mL) and allowed to stir for 10 min at 0 °C. Trifluoroacetic acid (2 mL) was added and the solution allowed to warm to room temperature. Stirring was continued for 12 h, after which the solution was concentrated under reduced pressure. Washing the resultant oil with diethyl ether afforded a precipitate that could be isolated by vacuum filtration. Further purification was achieved by recrystallization (methanol/diethyl ether) to give 17-cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10f).

Details are given for representative examples 10f and 15d. Full experimental details for all compounds are provided as Supporting Information.

17-Cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10f) was dissolved in dichloromethane (4 mL) and allowed to stir for 10 min at 0 °C. Trifluoroacetic acid (2 mL) was added and the solution allowed to warm to room temperature. Stirring was continued for 12 h, after which the solution was concentrated under reduced pressure. Washing the resultant oil with diethyl ether afforded a precipitate that could be isolated by vacuum filtration. Further purification was achieved by recrystallization (methanol/diethyl ether) to give 17-cyclopentylmethyl-6,7-didehydro-4,5α-epoxy-5'-bis-tetrahydroisoindolo[2',3':6,7]benzyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (10f).
Butoxycarbonyl-(3-propyl-7-cyclopropylmethyl)guanidinyl-3,14-dihydroxyindolo[2',3':6,7]morphinan (M + 1)+, C34H45N6O6 requires 568.3812.


Acknowledgment. This work was supported by NIDA Grants DA 07315 and DA00254, and ligand binding and [3H]GTPyS assays were provided by NIDA–ODTP.

Supporting Information Available: Spectra and experimental procedures for all compounds. This material is available free of charge via the Internet at https://pubs.acs.org.

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Derivatives of the κ-Opioid Antagonist GNTI


JM0309203
Major Effect of Pyrrolic N-Benzylion in Norbinaltorphimine, the Selective κ-Opioid Receptor Antagonist

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Indolic N-benzylation of naltrindole reportedly extends the duration of δ-opioid receptor (DOR) antagonism. Similar modification of the κ-opioid receptor (KOR) antagonist norBNI (1a) and its 17,17'-diNMe analogue (1d), a low potency μ-opioid receptor (MOR) partial agonist, was found to affect predominantly their MOR activity. When administered systemically in mouse antinociceptive assays, N-benzyl-norBNI (1b) had only MOR agonist activity of relatively short duration whereas on central administration it had only a KOR-antagonist action of extremely long duration.

Introduction

For the past 30 years there has been considerable interest in the development of nonpeptidic ligands for κ (KOR) and δ (DOR) opioid receptors. Discovery of antagonists with selectivity for KOR1-3 and DOR14 has enabled the function of these receptor systems to be explored. The prototype KOR antagonist norBNI (1a) was designed on the message-address principle in which the address component which confers KOR selectivity is the basic nitrogen of the second N-cyclopropylmethyl (CPM) group.6 The follow-up to norBNI was GNTI (2b) in which the guanidino KOR address component was introduced into the selective DOR-antagonist, naltrindole (NTI, 2a).6 The effect of benzyl substitution at the indole N-atom in NTI to give BNTI (2c) was to bring selectivity for the putative DOR subtype in an antagonist of substantially longer duration than NTI.7 It was thus of interest to investigate the effect of equivalent N-benzylation of norBNI (1a) and its 17,17'-diNMe analogue (1d). Herein we report the results of the in vitro (binding and [35S]GTPyS) pharmacological evaluation of 1b and analogues, plus the further evaluation of 1b in vivo.

Chemistry. Two complimentary methods were utilized for the synthesis of BnorBNI (1b). In the first, the reported method for the synthesis of BNI (lc) from naltrexone (4) and N-methylhydrazine sulfate8 was modified by the use of N-benzylhydrazine sulfate and extending the reaction time to one week, then at elevated temperature for 2 days. Unfortunately, under these conditions only 1% of 1b could be isolated with the major identifiable material appearing to be hydrazone (5) in 20% yield (Scheme 1). The alternative method, direct benzylation of 1a (prepared from naltrexone in 62% yield)9 using excess sodium hydride and benzyl bromide, yielded a mixture of tri- and pentabenzyl-substituted norBNI, that was hydrolyzed immediately in hydrochloric acid/methanol to yield 1b in 63% yield (39% from naltrexone). Similar treatment of 1d, prepared from oxymorphone (4b), with benzyl bromide yielded the tribenzyl-substituted compound that was hydrolyzed to 1e with HBr/Methanol.

Results and Discussion

Affinities of the compounds for opioid receptors were measured using radioligand binding assays in membranes from C6μ, C6δ, and CHO cells and competition for the nonselective antagonist [3H]diprenorphine as previously described.10 BnorBNI (1b) had subnanomolar affinity for KOR with modest selectivity over MOR and DOR (Table 1). When compared with norBNI (1a), the prototypic KOR-antagonist 1b was as, or slightly more, selective under these conditions. The modest selectivity observed for these compounds was not surprising since Takemori et al.2 showed that binaltorphimine (BNI, 1c) had very little KOR selectivity in binding assays. The 17-NMe analogues (1d, 1e) had at least an order of
Scheme 1

\[ \begin{align*}
4a: R &= \text{CH}_2\text{C}_6\text{H}_5 \\
4b: R &= \text{CH}_3 \\
1b: R &= \text{CH}_2\text{C}_6\text{H}_5 \\
1d: R &= \text{CH}_3 \\
\end{align*} \]

*Reagents and conditions: (i) BuHNNH$_2$, H$_2$SO$_4$, AcOH, 100 °C then MeSO$_2$H, DMSO, 130 °C (iii) NaH, 18-crown-6, BuBr then methanol, 12 N HCl, 90 °C (for 1b), HBr, r.t. (for 1e).

**Table 1. Binding Affinities for Ligand Binding to Opioid Receptors**

<table>
<thead>
<tr>
<th>Compound</th>
<th>MOR</th>
<th>DOR</th>
<th>KOR</th>
<th>MOR/KOR</th>
<th>DOR/KOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>la, norBNI</td>
<td>1.20 ± 0.2</td>
<td>5.8 ± 0.645</td>
<td>0.4 ± 0.06</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>1b, BnorBNI</td>
<td>10.0 ± 2.5</td>
<td>8.6 ± 0.7</td>
<td>0.7 ± 0.1</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>1d</td>
<td>63.6 ± 38.1</td>
<td>98.2 ± 25.3</td>
<td>7.7 ± 1.0</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>1e</td>
<td>6.4 ± 1.1</td>
<td>207 ± 96</td>
<td>24.9 ± 5.6</td>
<td>24.9 ± 5.6</td>
<td>8</td>
</tr>
</tbody>
</table>

* Rat MOR or DOR receptors in C6 cells and human KOR receptors in CHO cells. * Values are the mean of three experiments, each performed in duplicate. Experiments were performed as described in ref 10 using [3H]diprenorphine.

**Table 2. Agonist Effects of Ligands at Opioid Receptors Measured by the \[^{[35S]}\text{GTPyS Binding Assay}\]**

<table>
<thead>
<tr>
<th>Compd</th>
<th>EC$_{50}$/nM, % stim</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOR*</td>
</tr>
<tr>
<td>la</td>
<td>187</td>
</tr>
<tr>
<td>1b</td>
<td>1358 ± 370</td>
</tr>
<tr>
<td>1d</td>
<td>526 ± 279</td>
</tr>
<tr>
<td>1e</td>
<td>526 ± 279</td>
</tr>
</tbody>
</table>

* Compared to the full agonist DAMGO. * Compared to the full agonist SNC80. * Compared to the full agonist U69593 (K$_e$ = 0.26 nM) was 50-fold greater than its potency determined against the selective DOR agonist SNC80 and nearly 100-fold greater than its potency against the MOR agonist DAMGO (Table 3). Once again these data for BnorBNI (1b) compare favorably with those obtained for norBNI (1a) (50- and 22-fold selective for KOR over DOR and MOR respectively) under the same assay conditions. Thus, the selectivity of the KOR antagonist action of both norBNI and BnorBNI is substantially greater in this functional assay than their KOR-selectivity in binding assays. The 17-NMe analogues (1d, 1e) were very much less potent KOR antagonists than norBNI and BnorBNI to the extent of 2–3 orders of magnitude (Table 3).

It is of interest to compare the binding and in vitro effects of 17-N-Me versus 17-N-CPM substitution in the
Table 3. Antagonist Effects of Ligands at Opioid Receptors Measured by the \(^{[35]S}GTP\gamma S\) Binding Assay*  

<table>
<thead>
<tr>
<th>compd</th>
<th>MOR(^a)</th>
<th>DOR(^a)</th>
<th>K(_{a}) (± SEM) nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2.38 ± 0.58</td>
<td>5.17 ± 0.73</td>
<td>0.11 ± 0.01</td>
</tr>
<tr>
<td>1b</td>
<td>25.5 ± 2.3</td>
<td>13.3 ± 4.5</td>
<td>0.26 ± 0.085</td>
</tr>
<tr>
<td>1d</td>
<td>NT</td>
<td>NT</td>
<td>27.0 ± 4.3</td>
</tr>
<tr>
<td>1e</td>
<td>NT</td>
<td>NT</td>
<td>311 ± 30</td>
</tr>
</tbody>
</table>

* K\(_{a}\) values were determined from dose-response curves for DAMGO (MOR), SNC80 (DOR), and U69593 (KOR) in the presence or absence of test ligand according to the formula: K\(_{a}\) = (agonist)/(dose-ratio – 1). * Experiments were performed using membranes from Rat MOR or DOR receptors in C\(_6\) cells and human KOR receptors in CHO cells as described in ref 11. Values are from 3 separate experiments.

Table 4. Effect of Ligands on the Dose—Effect Curve for U69593 Administered sc in the Warm Water Tail Withdrawal Assay (TW) after Systemic (sc) or Central (icv) Administration  

<table>
<thead>
<tr>
<th>route of admin</th>
<th>treatment conditions</th>
<th>EC(_{50}) (mg/kg)</th>
<th>shift</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>+vehicle at -1 h</td>
<td>sc +10 mg/kg 1b at -1 h</td>
<td>2.0 ± 0.26</td>
<td>-5.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>+10 mg/kg l a at -1 h</td>
<td>sc +10 mg/kg 1b at -3 h</td>
<td>2.1 ± 0.55</td>
<td>-5.6</td>
<td>0.0146</td>
</tr>
<tr>
<td>+vehicle at -1 h</td>
<td>sc +10 mg/kg 1b at -18 h</td>
<td>9.0 ± 1.73</td>
<td>-1.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>+10 mg/kg 1b at -24 h</td>
<td>sc +10 mg/kg 1b at -24 h</td>
<td>4.4 ± 1.17</td>
<td>-4.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>+vehicle at -1 h</td>
<td>sc +32 mg/kg 1b at -24 h</td>
<td>6.7 ± 1.09</td>
<td>-6.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>+10 mg/kg 1b at -18 h</td>
<td>sc +10 mg/kg 1b at -18 h</td>
<td>9.9 ± 1.90</td>
<td>-9.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>+vehicle at -1 h</td>
<td>sc +32 mg/kg 1a at -24 h</td>
<td>22.7 ± 4.12</td>
<td>-22.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>+32 mg/kg 1a at -24 h</td>
<td>icv +10 nmol 1b at -1 h</td>
<td>49.1 ± 9.41</td>
<td>-49.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+vehicle at -1 h</td>
<td>icv +10 nmol 1b at -24 h</td>
<td>26.3 ± 5.04</td>
<td>-26.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>+10 nmol 1b at -48 h</td>
<td>icv +10 nmol 1b at -48 h</td>
<td>74.2 ± 14.22</td>
<td>-74.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+vehicle at -1 h</td>
<td>icv +10 nmol 1b at -168 h</td>
<td>37.0 ± 7.09</td>
<td>-37.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>+10 nmol 1a at -24 h</td>
<td>icv +10 nmol 1a at -24 h</td>
<td>31.8 ± 6.10</td>
<td>-31.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Assays were performed as previously described in ref 12. Negative shift values reflect a leftward shift; positive values reflect a rightward shift. Significance of the shifts in agonist effect was determined by 2-way ANOVA. * Vehicle is 10% DMSO in normal saline. n.s. = not significant.

Figure 1. Agonist activity of BnorBNI (1b) in the tail withdrawal assay.

BnorBNI (1a) has no antinociceptive activity in the AS antinociceptive assay when administered sc but is an effective and selective KOR antagonist.  

When administered icv, BnorBNI (1b) had no agonist effect in the TW test but was an effective and selective KOR antagonist lasting at least 168 h, with the peak effect around 48 h (Table 4). The antagonist selectivity of BnorBNI (1b) (icv) was assessed after 1 h pretreatment by comparison of its ability to antagonize U69593 (KOR) compared with its antagonism of SNC80 (DOR) and morphine (MOR). In the case of SNC80 the water temperature in TW was set at 48 °C since DOR agonists have very little antinociceptive effect at higher temperatures. Compared with the 9-fold shift in the U69593 dose–effect curve there was no inhibition of the agonist effects of SNC80 and morphine in the presence of 10 nmol of BnorBNI (1b) (data not shown). This confirms that BnorBNI (1b) is a substantially selective KOR antagonist under these conditions, in accord with its selectivity as a KOR antagonist in the \(^{[35]S}GTP\gamma S\) assay. At 24 h pretreatment the shift in the U69593 dose–response curve produced by 10 nmol of BnorBNI (1b) icv was similar to that of 10 nmol of BnorBNI (1a) (Table 4). The lack of agonist action on direct central administration of BnorBNI (1b) is surprising, but there

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are other examples of opioid ligands with agonist and antagonist effects that exhibit agonism only when administered systemically. The 14-cinnamoylamo-
codine (3b) when administered ac showed very potent and efficacious MOR-mediated antinociceptive effects in TW with no evidence of delayed antagonism.18 In contrast on icv administration this same compound was without antinociceptive effects, but was a potent, delayed morphine antagonist.19

In conclusion, the effect of introducing a benzyl substituent to the pyrrole-N of norBNI (1a) and its 17-NMe analogue (1d) was predominantly on their MOR pharmacology. In the former case, the effect was to increase MOR efficacy, but not potency, while in the latter, MOR potency was increased but with no effect on efficacy. Unlike norBNI (1a), BnorBNI (1b) acts as a partial MOR agonist in vitro that shows an antino-
ciceptive effect of relatively short duration when administered systemically. However, when administered centrally the compound lacks this effect and instead is a selective KOR antagonist of very long duration, comparable to norBNI (1a).

Experimental Section

Chemistry. Reagents and solvents were purchased from Aldrich or Lancaster. Melting points were recorded on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High and low resolution fast atom bombardment (FAB) mass spectra were recorded on a Piasac VG Autospec Q instrument, with a matrix of m-nitrobenzyl alcohol. Micro-
analyses were performed on a Perkin-Elmer 240C analyzer.

4',5'-Diepoxy-6,6'- ( benzylimino) [7,7'-bimorphin]-3,3',14,14'-tetrol (1b). To a solution of norBNI (0.30 g: 0.45 mmol) in dry THF under a N2 atmosphere were added NaH (0.18 g: 4.52 mmol) and 18-crown-6 (30 mg: 0.11 mmol). This mixture was stirred for 20 min at rt before adding BNBr (0.16 mL: 1.36 mmol) and stirring continued for a further 43 h. The reaction was quenched by the addition of H2O, the organic layer collected and dried (MgSO4), and solvent removed in vacuo.

17,17-Bis(cyclopropylmethyl)-6,6,7,7'-tetrahydro-4,5:
4',5'-diepoxy-6,6'- (benzylimino) [7,7'-bimorphin]-
3,3',14,14'-tetrol (1b). To a solution of norBNI (0.30 g: 0.45 mmol) in dry THF under a N2 atmosphere were added NaH (0.18 g: 4.52 mmol) and 18-crown-6 (30 mg: 0.11 mmol). This mixture was stirred for 20 min at rt before adding BNBr (0.16 mL: 1.36 mmol) and stirring continued for a further 43 h. The reaction was quenched by the addition of H2O, the organic layer collected and dried (MgSO4), and solvent removed in vacuo.

Acknowledgment. This work was supported by NIDA Grant DA 07315.

Supporting Information Available: Full spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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