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SYNTHESIS AND OPIATE RECEPTOR BINDING PROPERTIES OF 17-METHYL-6,7-DEHYDRO-3,14-DIHYDROXY-4,5α-EPOXY-6,7:4',5'-PYRIMIDINOMORPHINANS

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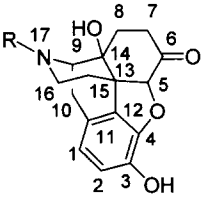
Abstract: A class of opioid receptor active derivatives of oxymorphone has been synthesized using a common enaminone intermediate. The derivatives have heterocyclic groups fused to the 6,7-positions of the morphinan system and all were synthesized in high yield. A pyrazolo derivative is an agonist for the μ and δ receptors and an antagonist for the κ receptor.

Opiates have been used by man for ages to treat a variety of maladies but only recently has there been an understanding, although fragmented, of how they induce their pharmacological effects. The opioid receptor was one of the first human receptors hypothesized in 1954.[1] Approximately 20 years later, opiate-specific receptors were demonstrated to exist in mammalian brain[2,3] and shortly after this, types of the opioid receptor were proposed.[4] These are now widely referred to as the μ, δ and κ types and subtypes of each have been proposed.[5] The opioid receptors are all G-protein coupled receptors and their endogenous peptide ligands have been identified.

Opioid receptors are widely distributed in mammalian systems, both in the central nervous system, CNS, and in the periphery.[6] It is generally thought that stimulation of μ receptors leads to analgesic effects, respiratory depression, euphoria and physical dependence[7,8] while κ receptors, when stimulated, produce analgesia.[9] δ Receptors play a role in spinal analgesia[9] but are involved in other biological processes as well. Cells of the immune system have been shown to have δ receptors on their surface.[10] Immune response is stimulated by δ agonists[11] and suppressed by δ antagonists.[12] For a detailed discussion of the various, nonpeptide ligands used to study the opioid receptors see reference 6.

Naltrexone, **1a**, is a nonselective antagonist of moderate affinity for the μ, δ and κ receptors and has served as a template for derivatization at the 6,7-positions. Recently, we reported the synthesis and opioid receptor binding properties of a series of 6,7:4',5' fused pyrimidino derivatives and the 6,7:4',5' pyrazolo derivative of **1a.**[13] Oxymorphone, **1b**, is a nonselective agonist for the μ, δ and κ receptors, and in an



1a; R = cyclopropylmethyl
1b; R = methyl

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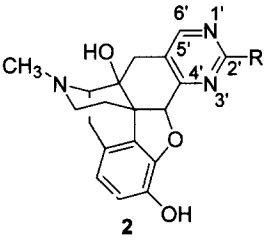
extension of this work, we have used it as a template for designing a similar series of 6,7:4',5'-fused heterocyclic derivatives of **1b**. The structures are given as **2a-e**. By introducing fused, heterocyclic substituents, the effect of variation in hydrogen bonding potential, pKa and lipophilicities on affinity and selectivity can be realized. For example, **2a,d** have hydrogen bond acceptor and donor sites which are weakly basic or acidic while **2e** has both hydrogen bond donor and acceptor sites and the acceptor site is expected to be highly basic and protonated in aqueous solution. Compound **2b** has a small, moderately lipophilic substituent in the 2'-position, and **2c** has a large, highly lipophilic group in the 2'-position of the pyrimidine. While this paper was in review, the N-cyclopropylmethyl, N-CPM, derivatives of **2b** and **2c** were reported.[14]



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2e

2a, R = NH_2
2b, R = CH_3
2c, R = C_6H_5
2d, R = OH

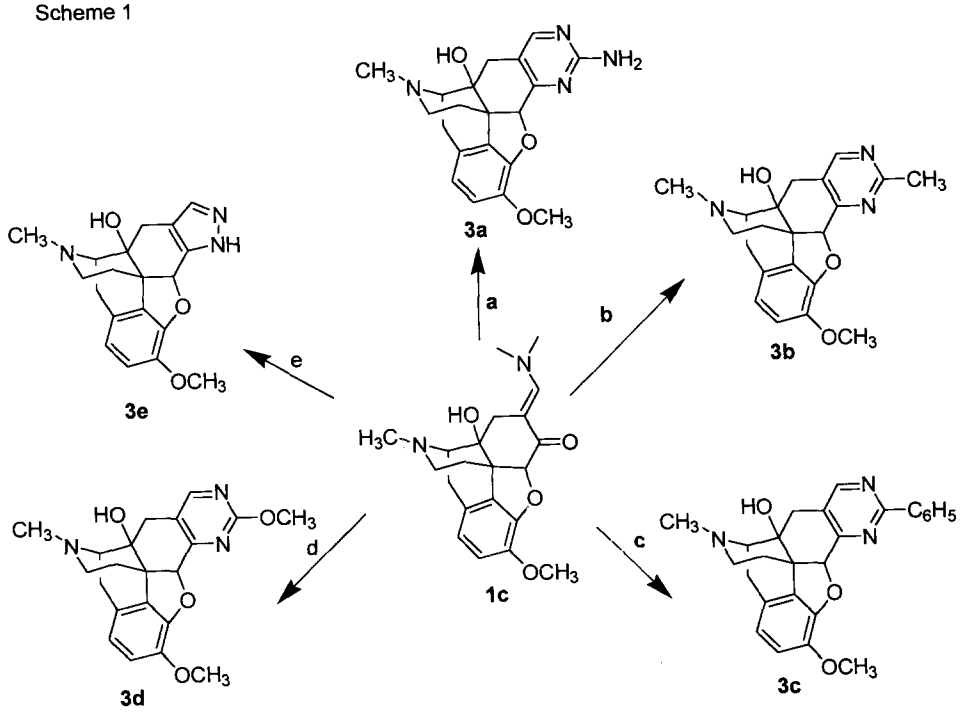
Methylation of **1b** with trimethylsilyldiazomethane[15] gave the *3-O*-Me derivative which was converted to the enaminone, **1c**, by refluxing in DMF-DMA as described by Kotick, et al.[16] The enaminone, which was isolated and characterized, was transformed to the heterocyclic derivative by the appropriate amidine or hydazine (Scheme 1).

Reaction of **1c** with *O*-methylisourea (urea did not react) gave the 2'-methoxy pyrimidine, **3d**, and, in the case of **3e**, the enaminone was converted to the pyrazole by reaction with hydrazine hydrate. With the exception of **3d**, deprotection by BBr_3 in anhydrous CH_2Cl_2 afforded the final products. Deprotection of **3d** with BBr_3 gave the 3-hydroxy-2'-methoxy analog which was converted to **2d** by refluxing the 2'-methoxy pyrimidine intermediate in conc HCl. All structures were consistent with ^1H, ^{13}C nmr and MS. Purity was indicated by a single spot by TLC.

The opioid receptor activities reported were carried out by the Opiate Treatment Discovery Program of the National Institutes of Health. Receptor binding studies were conducted on human opioid receptor transfected into Chinese hamster ovary (CHO) cells. Routine binding assays were conducted using [^{3}H]DAMGO, [^{3}H]Cl-DPDPE and [^{3}H]U69,593 as labelling ligands specific for μ, δ, and κ receptors, respectively. For binding, cell membranes were incubated with the appropriate radio ligand and unlabeled drug in a total volume of 200 μL in 96-well plates, usually for 1 h at 25 °C. For routine experiments, membranes are incubated with the test compounds at concentrations ranging for 10^{-10} to 10^{-5} M. K_i values are calculated using the Cheng-Prusoff transformation.

In order to determine agonist/antagonist properties, membranes prepared as described above are incubated

Scheme 1



(a) $H_2NC(=NH)NH_2$; (b) $CH_3C(=NH)NH_2$; (c) $C_6H_5C(=NH)NH_2$;
(d) $CH_3OC(=NH)NH_2$; (e) $H_2N\text{-}NH_2$

with [^{35}S]GTPγS (50pM), GDP (usually 10 μM) and the desired compound in a total volume of 200 μL for 60 min at 25 °C. Agonist activity at μ, δ and κ receptors is reported as % stimulation relative to the respective agonists DAMGO, Cl-DPDPE and U69,593. High affinity compounds that demonstrate no agonist activity were tested as antagonists. The receptor binding data are given in Table 1 and agonist/antagonist data are given in Table 2.

Table 1
Receptor binding data for **2a-e**
K_i(SEM)(nM)

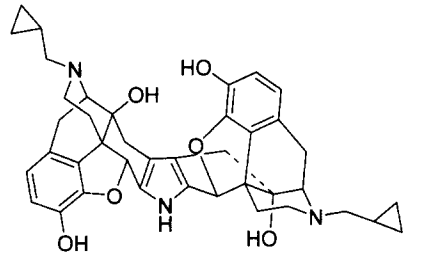
	μ	δ	κ
Compound	[^{3}H]-DAMGO	[^{3}H]-Cl-DPDPE	[^{3}H]-U69,593
2a	7.32(0.67)	18.99(2.78)	21.08(10.60)
2b	5.26(0.94)	24.04(3.94)	68.50(34.60)
2c	7.34(1.40)	6.48(0.40)	45.14(22.80)
2d	3.75(0.71)	19.06(1.17)	12.29(6.20)
2e	1.72(0.42)	12.23(2.22)	11.92(6.00)

Table 2
Agonist/Antagonist Data for **2a-e**
EC_{50}(nM)(SEM)(% Stimulation)

Compound	μ-CHO membrane	δ-CHO membrane	κ-CHO membrane
2a	75.20(14.49)(83.8)	66.09(23.95)(78.7)	1075(555.5)(34.3)
2b	71.95(26.60)(109.2)	95.92(19.19)(60.05)	2729.5(1029.5)(96.95)
2c	58.42(6.27)(89.40)	24.00(11.32)(92.50)	1421.0(270)(49.45)
2d	110.25(110.25)(87.70)	61.49(18.02)(96.95)	1021.0(322.0)(40.70)
2e	19.26(0.54)(80.30)	25.02(4.67)(75.20)	K_e=59.33(18.85)

All compounds have high affinity for the three opioid receptors with, however, little receptor selectivity. All are full or partial agonists for the receptors with the exception of **2e**, the pyrazolo derivative, which is an agonist for the μ and δ receptors and an antagonist for the κ receptor.

While there are a number of κ antagonists, compounds with this receptor profile rare. A peptide derivative of dynorphin A-(1-11) has recently been reported to be a κ antagonist but was also a partial κ agonist.[17] norBNI, **4**, is a nonpeptide κ antagonist of moderate selectivity[18] and [(-)-1*R*,5*R*,9*R*)-(5,9-diethyl-2-(3-furyl-methyl)-2'-hydroxy-6,7-benzomorphan], **5**, is a nonselective κ antagonist.[6]



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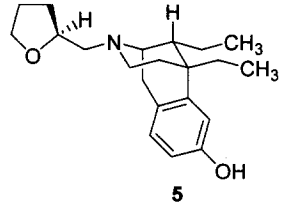

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The structural requirements for κ antagonism are unclear. Based on the SAR of **2e**, **4** and **5**, there are inconsistencies. Generally, the 17-N-Me morphinan derivatives are agonists while

the 17-N-CPM derivatives are antagonists. Consistent with this, the 17-N-CPM derivative of **2e** is a high affinity, nonspecific antagonist at all opioid receptors[13] as are the 17-N-CPM derivatives of **2b** and **2c**. Thus the opioid receptor agonist/antagonist profile of **2e** is unusual if not unique.

Because of the only recent discovery of κ specific antagonists, the pharmacological effects of κ agonists/antagonists are only now being determined. It has recently been reported that κ agonists reduce blood pressure in the rat[19] and, in humans, a κ agonist **increased** pain when used as a postoperative analgesic.[20] The κ antagonist, **4**, has been shown to significantly reduce self-administration of cocaine in mice suggesting the involvement of the endogenous κ receptor system in the mechanisms of self-administration of cocaine.[21] Herein may lie the ultimate utility of these compounds. Further work on the SAR and factors which lead to κ receptor selectivity of **2e** and its derivatives is underway.

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