

PHENANTHRIDONE ANALOGS OF THE OPIATE AGONIST U-47,700 IN THE trans-1,2-DIAMINOCYCLOHEXANE BENZAMIDE SERIES

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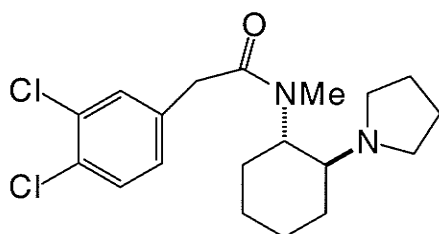
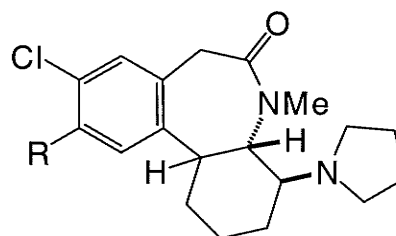
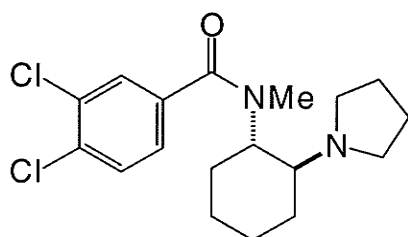
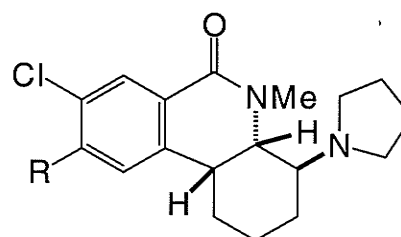
Abstract - The first rigid analog of the opioid trans-1,2-diaminocyclohexane benzamide template was prepared. This analog represented by compound (**4b**), in a phenanthridone analog of the mu agonist U-47,700 which, historically, was the forerunner of the kappa acetamide U-50,488.

INTRODUCTION

The disclosure¹ of the selective κ opiate agonist U-50,488 (**1**) and μ agonist U-47,700 (**2**) has been followed by the preparation of many additional agonists based on this trans-1,2-diaminocyclohexane phenylacetamide template.² The considerable interest in U-50,488 can be seen in 2804 citations to the compound found in the literature thru May 13, 1998. The involvement of the κ receptor, which began simplistically with the analgesic activity, has grown to include diuresis, feeding, neuroendocrine secretions, immune functions, dysphoria^{2d} and also antagonism of μ receptor mediated analgesia.³

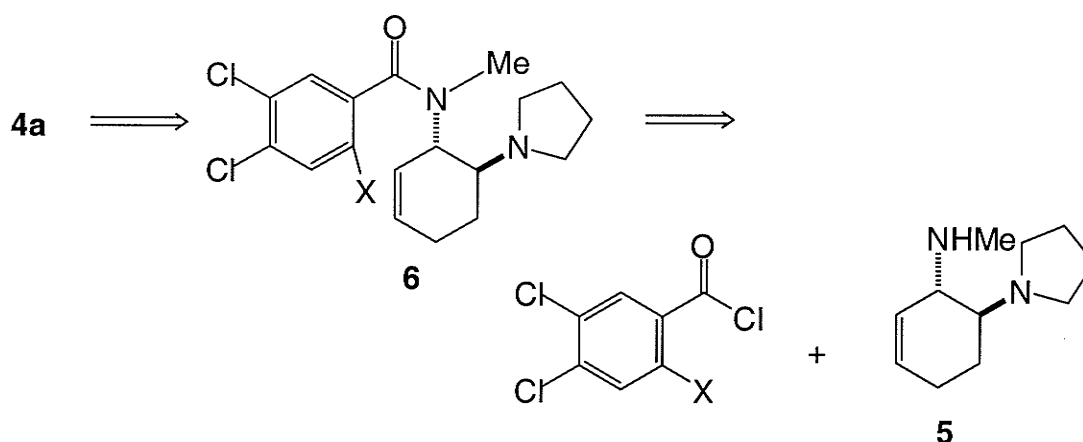
μ , δ and κ Opioid receptors have been cloned and sequenced,⁴ a number of receptor subtypes have been proposed⁵ and site-directed mutagenesis studies performed.⁶ In the κ opioid area there is great need for new templates and more specific ligands.

When comparing the formula of morphine, the best drug in the μ agonist class, with the numerous simplified structures based on morphine⁷ which are active analgesics, the inevitable conclusion is reached that the five rings of morphine create a very rigid environment in which the ligand finds itself when interacting with the μ receptor. Since morphine also interacts with other receptors⁸ it is possible that variations in the rigidification of the structure may provide a clue to specificity. It seemed, therefore, of interest to place some constraints on structures (**1**) and (**2**). We choose to accomplish this by using the phenanthridone ring system. This paper describes the preparation of compound (**4b**), which represents a rigidified analog of the mu agonist U-47,700 (compound **2**) and a model for the future synthesis of the seven-membered ring analog of the kappa agonist U-50,488 (compound **1**) represented by structure (**3**).

**1** (U-50,488)**3 a:** R = Cl
b: R = H**2** (U-47,700)**4 a:** R = Cl
b: R = H

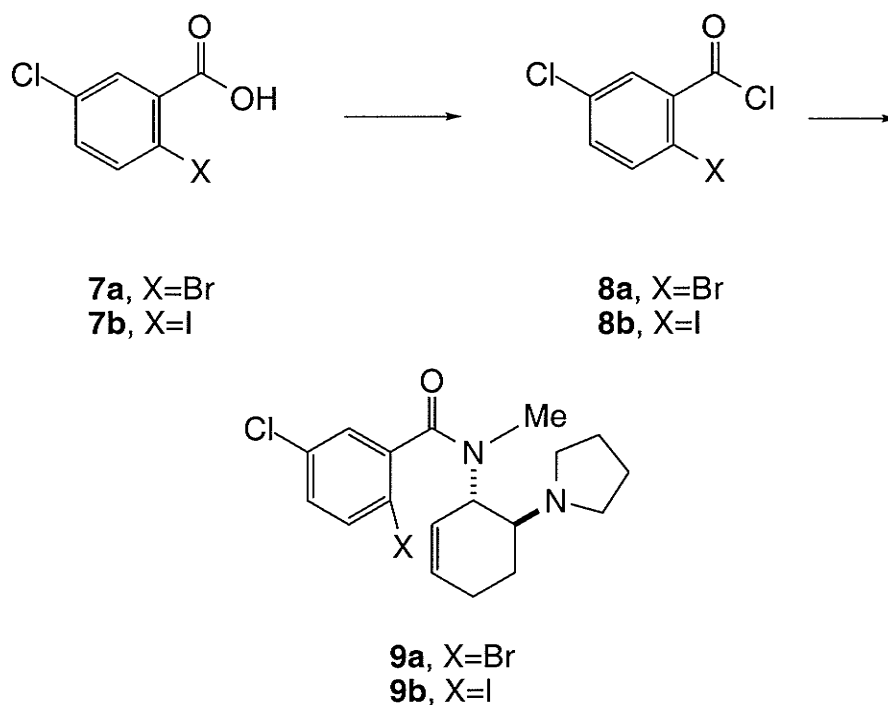
CHEMISTRY

Retrosynthetic analysis based upon a simple examination of structures (**3a**) and (**4a**) suggested joining position 6 of the aromatic ring to position 3 (or 6) of the cyclohexane ring. Formally a Friedel-Crafts alkylation, such a process would require activation of the cyclohexane ring; a possible candidate was the olefinic diamine (**5**), previously reported by us.^{2c} We envisioned a Heck reaction of a suitably substituted amide (**6**) derived from (**5**). The only available candidates for the acid portion of (**6**) were compounds (**7a** and **7b**). They contain only one chlorine in addition to the *o*-bromine or *o*-iodine. A single chlorine would

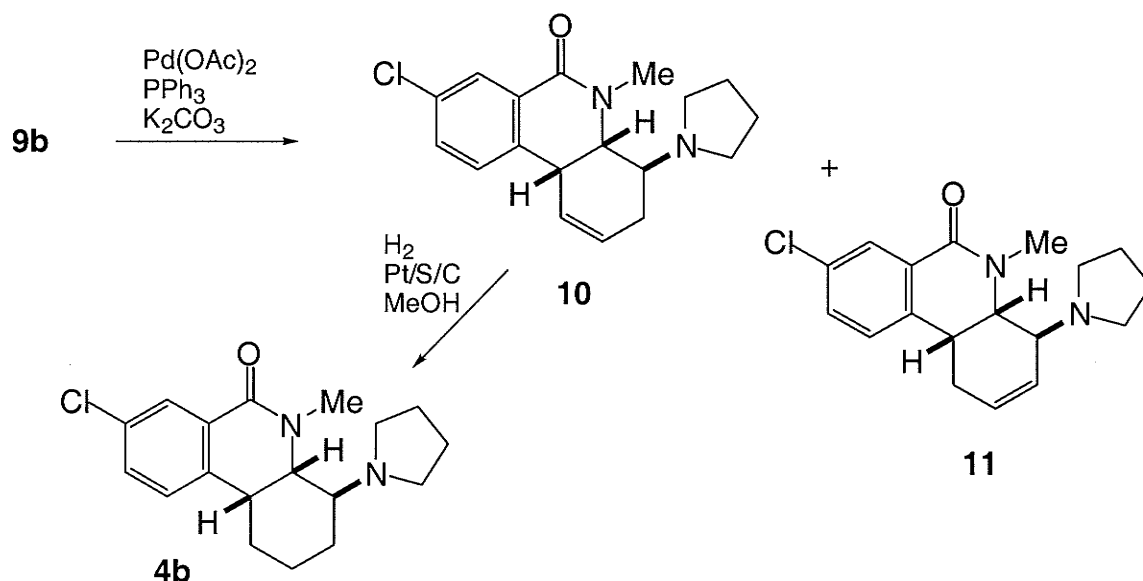


not reduce the activity of the final products, based on the known SAR of U-50,488, but may have some implications in the metabolism of the compound. We proceeded with these two

acids. Both acids (**7a**) and (**7b**) were converted to the corresponding acid chlorides (**8a**) and (**8b**) and allowed to react with olefinic *trans*-diamine (**5**) to give the *trans*-amino amides (**9a**) and (**9b**).



Both amides were subjected to the intramolecular Heck reaction catalyzed by palladium acetate and triphenylphosphine. The bromo amide did not cyclize, but iodo compound (**9b**) indeed gave cyclized products, compounds (**10**) and (**11**) in a ratio of ~2:1. NMR analysis indicates that both compounds have the same stereochemistry and differ only in the location of the double bond.



Compound (**10**) was hydrogenated to give the desired compound (**4b**).

BIOLOGICAL STUDIES

Compounds (**4b**) and (**10**) were inactive in μ , δ and κ binding assays.¹⁰ K_i in each case was $>10,000$ nM.

The lack of mu agonist opioid activity in **4b** may be ascribed to undesirable stereochemistry at ring junction adjacent to the aromatic ring and difficulties in the ligand-receptor interactions with mu specific amino acid residues.¹¹ Further research is mandatory to resolve these problems.

EXPERIMENTAL SECTION

N-Methyl-*N*-3-[*trans*-2-(1-pyrrolidinyl)cyclohexenyl]-2-bromo-5-chlorobenzamide (**9a**).

Thionyl chloride (0.146 mL, 2.00 mmol) was added to a solution of acid (**7a**) (235 mg, 1.00 mmol) in CHCl_3 (10 mL) and the solution was refluxed for 2 h. The solvent was removed *in vacuo* to give a colorless solid. Methylene chloride (10 mL) was added followed by the addition of Et_3N (0.279 mL, 2.00 mmol). Diamine (**5**)^{2c} (180 mg, 1.00 mmol) in CH_2Cl_2 (21 mL) was added at rt and the mixture was stirred at rt for 18 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with Na_2CO_3 (sat., 10 mL), brine, (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel column eluting with $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ (95/4/1) to give **9a** as a yellow oil (101 mg, 26%): ^1H NMR (300 MHz) δ 7.20-7.50 (m, 3 H), 5.35-6.00 (m, 2.5 H), 3.85 (m, 0.5 H), 1.40-3.00 (m, 16 H); MS (FAB), m/z (rel intensity) 397 (40, M), 326 (12), 217 (15), 149 (20), 97 (100); HRMS (EI) m/z calcd for $(\text{C}_{18}\text{H}_{22}\text{N}_2\text{OBrCl} + \text{H})$: 397.0683, found 397.0690.

N-Methyl-*N*-3-[*trans*-2-(1-pyrrolidinyl)cyclohexenyl]-2-iodo-5-chlorobenzamide (**9b**).

Similarly acid (**7b**) (472 mg, 1.67 mmol) in CHCl_3 (15 mL) was converted to its acid chloride with thionyl chloride (0.244 mL, 3.34 mmol) and to benzamide (**9b**) with Et_3N (0.465 mL, 3.34 mmol) and diamine (**5**)^{2c} (301 mg, 1.67 mmol). The residue was chromatographed on silica gel column eluting with $\text{CHCl}_3/\text{MeOH}/\text{H}_4\text{OH}$ (95/4/1) to give **9b** as a yellow oil (581 mg): ^1H NMR (300 MHz) δ 7.73 (d, $J = 9.3$ Hz, 0.5 H), 7.70 (d, $J = 8.5$ Hz, 0.5 H), 7.26 (d, $J = 2.6$ Hz, 0.5 H), 7.14 (m, 0.5 H), 7.04 (dd, $J = 8.5, 2.5$ Hz, 0.5 H), 7.02 (dd, $J = 8.5, 2.5$ Hz, 0.5 H), 5.35-6.00 (m, 2.5 H), 3.87 (m, 0.5 H), 1.30-3.00 (m, 16 H); MS (EI), m/z (rel intensity) 444 (6, M), 237 (6), 149 (15), 133 (9), 97 (100); HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{OClI}$: 444.0465, found 444.0463.

3,4,4a,5,6,10b-Hexahydro-4-(1-pyrrolidinyl)-5-methyl-8-chlorophenanthridin-6(2H)-one (**10**).

A mixture of amide (**9b**) (759 mg, 1.71 mmol), $\text{Pd}(\text{OAc})_2$ (38 mg, 0.17 mmol), PPh_3 (90 mg, 20 mmol) and Li_2CO_3 (252 mg, 3.42 mmol) in DMF (20 mL) was degassed under vacuum for 10 min and then heated at 80 °C for 24 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with H_2O (3 x 20 mL). The combined aqueous phase was then extracted

with EtOAc (3 x 20 mL). The combined organic phase was dried (MgSO₄) and concentrated. The residue was chromatographed on silica gel column (EtOAc/Hexanes: 1/1 to 10/1) to give **10** as a yellow solid (264 mg) and **11** as a brown solid (126 mg). Both compounds were recrystallized from EtOAc/MeOH.

10: mp 140-142 °C; ¹H NMR (400 MHz) δ 8.03 (d, J = 2.3 Hz, H-7), 7.38 (dd, J = 8.2, 2.3 Hz, H-9), 7.11 (dd, J = 8.2, 0.9 Hz, H-10), 6.04 (m, H-1), 5.86 (m, H-2), 3.94 (t, J = 5.4 Hz, H-10b), 3.55 (dd, J = 10.4, 5.5 Hz, H-4a), 3.27 (s, CH₃), 2.88 (dt, J = 10.3, 7.2 Hz, H-4), 2.52 (m, 4 H, N(CH₂CH₂)₂), 2.27 (m, 2 H, H-3's), 1.66 (m, 4 H, N(CH₂CH₂)₂); ¹³C NMR (75 MHz) δ 162.51 (C-6), 139.41, 132.85, 131.62, 129.86 (C-9), 127.95 (C-2 and C-7), 127.86 (C-10), 124.81 (C-1), 62.75 (C-4a), 57.15 (C-4), 50.25 (NC(CH₂CH₂)₂), 38.02 (C-10b), 36.61 (NCH₃), 27.55 (C-3), 23.44 (N(CH₂CH₂)₂); MS (FAB), m/z (rel intensity) 317 (100, M + H), 97 (24), 84 (60); HRMS (FAB) m/z calcd for (C₁₈H₂₁N₂OCl + H): 317.1421, found 317.1419; Anal. Calcd for C₁₈H₂₁N₂OCl: C, 68.24, H, 6.68; N, 8.84; Cl, 11.19. Found: C, 67.93; H, 6.57; N, 8.69; Cl, 10.85.

¹H and ¹³C NMR Spectral Assignments for Compound (**10**)

Assignments	¹³ C Chemical Shifts ^a	Multiplicity ^b	¹ H Chemical Shifts	Multiplicity
C-12	23.49	T	1.67	M
C-3	27.57	T	2.28	M
NCH ₃	36.63	Q	3.27	S
C-10b	38.06	D	3.94	T J = 5.5
C-11	50.25	T	2.52	M
C-4	57.16	D	2.88	DT J = 10.3, 7.2
C-4a	62.81	D	3.55	DD J = 10.3, 5.5
C-1	124.87	D	6.02	M
C-10	127.88	D	7.11	DD J = 8.2, 0.9
C-7	128.00	D	8.03	D J = 2.3
C-2	128.00	D	5.86	DT J = 9.7, 3.6
C-9	131.64	D	7.38	DD J = 8.2, 2.3
C-6a	132.05	S	-	-
C-8	132.90	S	-	-
C-10a	139.44	S	-	-
C-6	162.54	S	-	-

^aIn CDCl₃ solution to internal TMS.

^bS = singlet, D = doublet, T = triplet, Q = quartet, and M = multiplet.

The COSY spectrum gave the connectivity of the 6-membered ring.

The HETCOR spectrum showed that the CH groups C-4a and C-4 were at 62.81 and 57.16, indicating that their carbons are attached to nitrogens. Protons H-4a is in the bridge head position due to its proton shift of 3.55 ppm compared to proton H-4 at 2.88 ppm. The proton spectrum showed $J_{4,4a} = 10.4$ Hz; therefore, H-4 and H-4a are axial (or *trans*). The coupling $J_{4a,10b} = 5.5$ Hz; therefore, H-10b is equatorial (or *cis*).

1,4,4a,5,6,10b-Hexahydro-4-(1-pyrrolidinyl)-5-methyl-8-chlorophenanthridin-6(2H)-one (11):

mp 175-178 °C (EtOAc/MeOH); ^1H NMR (500 MHz) δ 8.07 (d, $J = 2.4$ Hz, H-7), 7.39 (dd, $J = 8.3, 2.4$ Hz, H-9), 7.12 (d, $J = 8.3$ Hz, H-10), 5.89 (ddt, $J = 10.3, 4.9, 2.5$ Hz, H-2), 5.58 (br d, $J = 10.3$ Hz, H-3), 3.57 (m, H-10b), 3.55 (m, H-4a), 3.32 (s, CH_3), 3.18 (m, H-4), 2.71 (br dd, $J = 18.5, 5.1$ Hz, H-1), 2.65 (m, 2 H, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.57 (m, 2 H, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.53 (br d, $J = 18.5$ Hz, H-1), 1.71 (m, 4 H, $\text{N}(\text{CH}_2\text{CH}_2)_2$); ^{13}C NMR (75 MHz) δ 162.83 (C-6), 137.64, 133.02, 131.88, 131.39 (C-9), 128.46 (C-7), 127.08 (C-2), 126.06 (C-3), 125.67 (C-10), 59.60 (C-4a), 59.50 (C-4), 48.27 ($\text{N}(\text{CH}_2\text{CH}_2)_2$), 36.02 (C-10b), 35.70 (NCH_3), 26.13 (C-1), 24.11 ($\text{N}(\text{CH}_2\text{CH}_2)_2$); Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{OCl}$: C, 68.24, H, 6.68; Cl, 11.19; N, 8.84. Found: C, 67.84; H, 6.55; Cl, 10.90; N, 8.62.

^1H and ^{13}C NMR spectra showed 23 protons and 18 carbons. The multiplicities of the carbons were the same as in **10** suggesting a closely related analog or diastereoisomer.

A HETCOR spectrum showed that the carbon bearing proton H-10b is at 36.02 ppm while protons H-4a and H-4 are on carbamate carbons at 59.60 ppm and 59.50 ppm, respectively. Proton H-4a is a triplet suggesting that it is between two other CH groups. Its chemical shift is 3.55 ppm (the same as in **10**) while proton H-4 has a shift of 3.18 ppm; this places the amide nitrogen on the carbon bearing proton H-4a and the pyrrolidine ring nitrogen on the carbon bearing proton H-4.

An NOE can be seen between protons H-10 and H-1. An NOE can also be seen between both H-3 and H-4 and the pyrrolidine ring CH_2N protons confirming the pyrrolidine placement. An HMBC experiment confirmed structure **11** as being correct.

No diaxial couplings can be seen for protons H-10b, H-4a and H-4, thus, H-10b must be equatorial. A long range coupling cross peak from H-4 to H-2 can be seen in the COSY spectrum indicating proton H-4 is equatorial also (planar w configuration).

4b: A mixture of **10** (10 mg, 0.32 mmol) and platinum on sulfide carbon (19 mg) in MeOH (2 mL) was hydrogenated (1 atm.) for 4 h. The product was filtered and concentrated *in vacuo* to give **4b**, as a colorless solid (6 mg, 60%): ^1H NMR (300 MHz) δ 8.09 (d, $J = 2.4$ Hz, 1 H), 7.41 (dd, $J = 8.3, 2.4$ Hz, 1 H), 7.17 (d, $J = 8.1$ Hz, 1 H), 3.53 (m, 1 H), 3.42 (dd, $J = 9.8, 5.0$ Hz, 1 H), 3.24 (s, CH_3), 2.66 (td, $J = 10.1, 3.3$ Hz, 1 H), 2.25-2.60 (m, 6 H), 0.82-1.70 (m); HRMS (FAB) m/e calcd for $(\text{C}_{18}\text{H}_{23}\text{N}_2\text{OCl} + \text{H})$: 319.1577, found 319.1562.

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^1H and ^{13}C NMR Spectral Assignments for Compound (11)

Assignments	^{13}C Chemical Shifts ^a	Multiplicity ^b	^1H Chemical Shifts	Multiplicity
C-12	24.11	T	1.71	M
C-1	26.13	T	2.53	DDM J = 18.5, 5.1
			2.72	DDQ J = 18.5, 5.6, 2.8
NCH ₃	35.70	Q	3.32	S
C-10b	36.02	D	3.56	M
C-11	48.27	T	2.57, 2.65	M
C-4	59.50	D	3.18	M
C4a	59.60	D	3.55	T J = 4.6
C-10	125.67	D	7.11	D J = 8.3
C-3	126.06	D	5.58	DM J = 10.3
C-2	127.08	D	5.89	DDT J = 10.3, 4.9, 2.5
C-7	128.40	D	8.06	D J = 2.4
C-9	131.39	D	7.38	DD J = 8.2, 2.4
C-6a	131.88	S	-	-
C-8	133.02	S	-	-
C-10a	137.64	S	-	-
C-6	162.83	S	-	-

^aIn CDCl₃ solution to internal TMS.

^bS = singlet, D = doublet, T = triplet, Q = quartet, and M = multiplet.

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