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

Shikai Zhao[a], Michael J. Totleben,[a] Stephen A. Mizsak,[b] Jeremiah P. Freeman,[a] and Jacob Szmuszkovicz[a*]

[a]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556 and [b]Pharmacia and Upjohn, Kalamazoo, MI 49001, U.S.A.

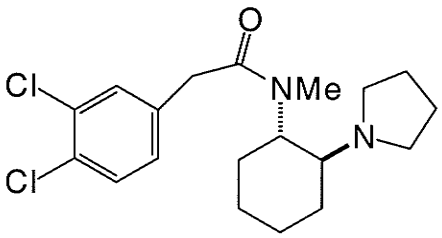
Abstract - The first rigid analog of the opioid trans-1,2-diaminocyclohexane benzamide template was prepared. This analog represented by compound (**4b**), in a phenanthridone analog of the mu agonist U-47,700 which, historically, was the forerunner of the kappa acetamide U-50,488.

INTRODUCTION

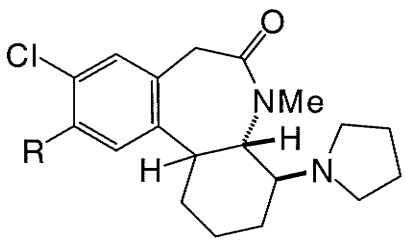
The disclosure[1] of the selective κ opiate agonist U-50,488 (**1**) and μ agonist U-47,700 (**2**) has been followed by the preparation of many additional agonists based on this trans-1,2-diaminocyclohexane phenylacetamide template.[2] The considerable interest in U-50,488 can be seen in 2804 citations 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 proposed[5] and site-directed mutagenesis studies performed.[6] In the κ opioid area there is great need for new templates and more specific ligands.

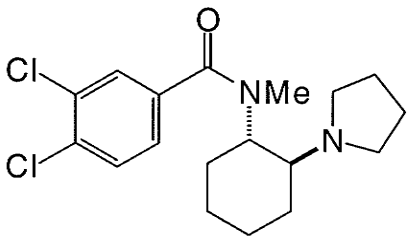
When comparing the formula of morphine, the best drug in the μ agonist class, with the numerous simplified structures based on morphine[7] which are active analgesics, the inevitable conclusion is reached that the five rings of morphine create a very rigid environment in which the ligand finds itself when interacting with the μ receptor. Since morphine also interacts with other receptors[8] 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**).



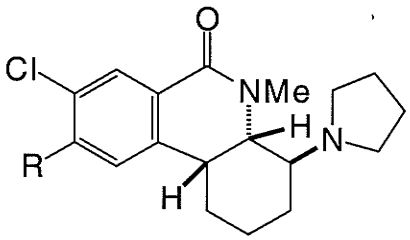
1 (U-50,488)



3 a: R =Cl
b: R =H



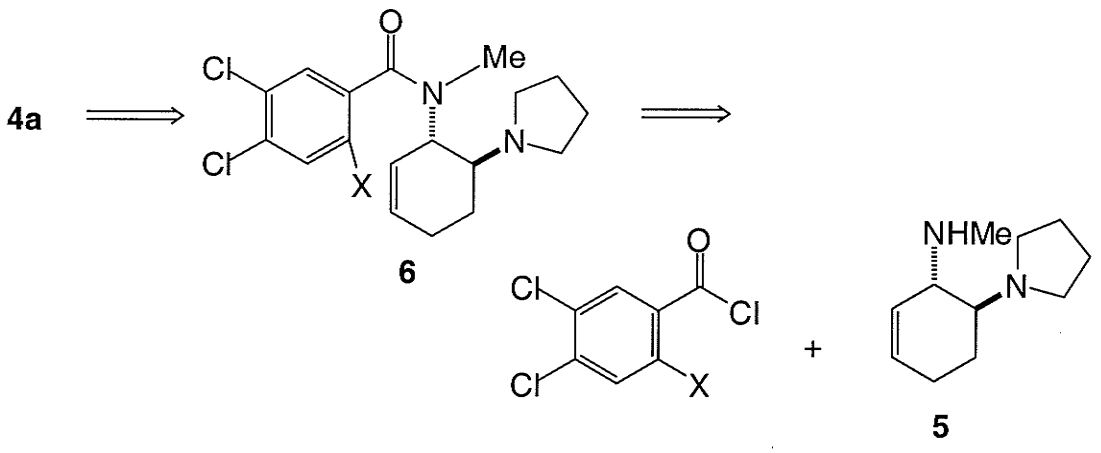
2 (U-47,700)



4 a: R =Cl
b: R =H

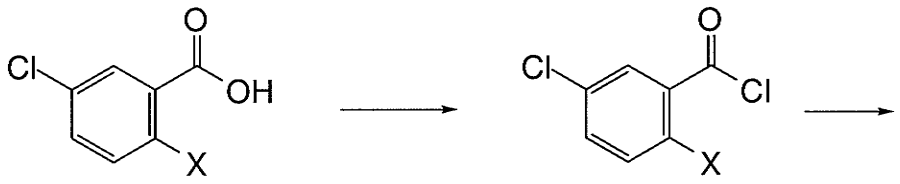
CHEMISTRY

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



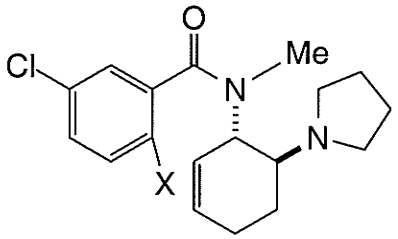
not reduce the activity of the final products, based on the known SAR of U-50,488, but may have some implications in the metabolism of the compound. We proceeded with these two

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**).



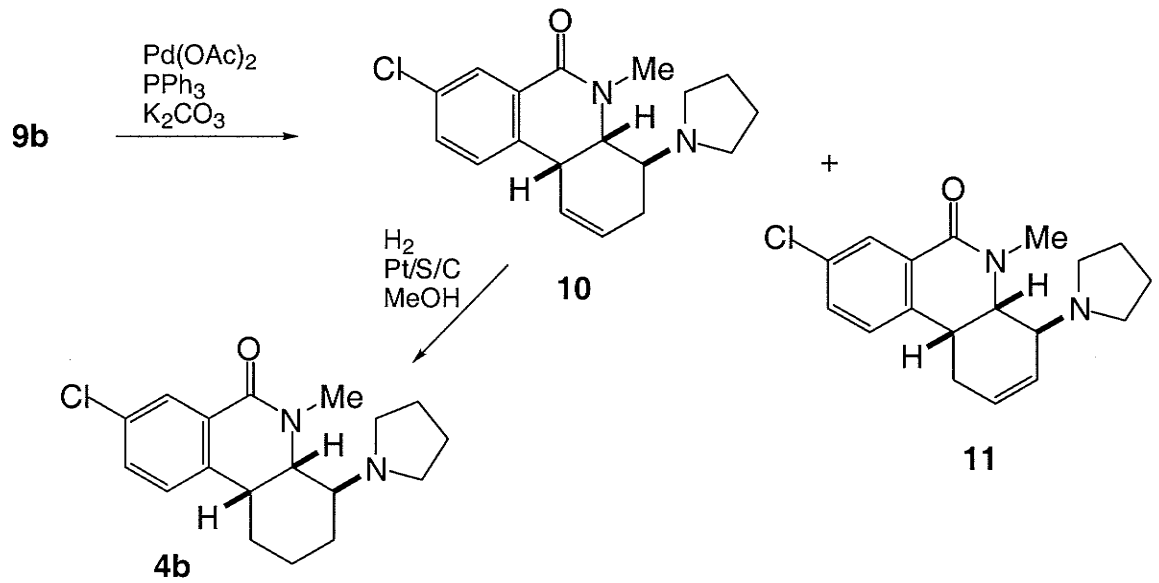
7a, X=Br
7b, X=I

8a, X=Br
8b, X=I



9a, X=Br
9b, X=I

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] Ki 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 $CHCl_3$/MeOH/NH_4OH (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 ($C_{18}H_{22}N_2OBrCl$ + 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 $CHCl_3$/MeOH/H_4OH (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 $C_{18}H_{22}N_2OCII$: 444.0465, found 444.0463.

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

A mixture of amide (**9b**) (759 mg, 1.71 mmol), $Pd(OAc)_2$ (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 ($MgSO_4$) 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; ^{1}H 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, CH_3), 2.88 (dt, J = 10.3, 7.2 Hz, H-4), 2.52 (m, 4 H, $N(CH_2CH_2)_2$), 2.27 (m, 2 H, H-3's), 1.66 (m, 4 H, $N(CH_2CH_2)_2$); ^{13}C 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 ($NC(CH_2CH_2)_2$), 38.02 (C-10b), 36.61 (NCH_3), 27.55 (C-3), 23.44 ($N(CH_2CH_2)_2$); MS (FAB), m/z (rel intensity) 317 (100, M + H), 97 (24), 84 (60); HRMS (FAB) m/z calcd for ($C_{18}H_{21}N_2OCl$ + H): 317.1421, found 317.1419; Anal. Calcd for $C_{18}H_{21}N_2OCl$: 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.

^{1}H and ^{13}C 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	-	-	

[a]In $CDCl_3$ solution to internal TMS.

[b]S = 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(2*H*)-one (11):

mp 175-178 °C (EtOAc/MeOH); ^{1}H 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, $N(CH_2CH_2)_2$), 2.57 (m, 2 H, $N(CH_2CH_2)_2$), 2.53 (br d, J = 18.5 Hz, H-1), 1.71 (m, 4 H, $N(CH_2CH_2)_2$); ^{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 ($N(CH_2CH_2)_2$), 36.02 (C-10b), 35.70 (NCH_3), 26.13 (C-1), 24.11 ($N(CH_2CH_2)_2$); Anal. Calcd for $C_{18}H_{21}N_2OCl$: 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.

^{1}H 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 carbamine 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%): ^{1}H 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 ($C_{18}H_{23}N_2OCl$ + H): 319.1577, found 319.1562.

ACKNOWLEDGMENT

We thank The Upjohn Company for partial support of this research. The biological testing

was done under NIDA Contract No NO1DA-4-8307. We thank Dr. L. Toll and collaborators of SRI International for performing these tests.

^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	-	-	

[a]In $CDCl_3$ solution to internal TMS.

[b]S = singlet, D = doublet, T = triplet, Q = quartet , and M = multiplet.

REFERENCES

1. (a) J. Szmuszkovicz and P. F. Von Voigtlander, *J. Med. Chem.*, 1982, **25**, 1125; (b) P. F. Von Voigtlander, R. A. Lahti, and J. H. Ludens. *J. Pharmacol. Exp. Ther.*, 1983, **224**, 7.
2. (a) V. Sabin, D. C. Horwell, A. T. McKnight, and P. Broqua, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 291; (b) G. Giardina, G. D. Clarke, M. Grugni, M. Sbacchi, and V. Vechietti, *11 Pharmaco*, 1995, **50**, 405 and references cited therein; (c) S. Zhao, J. P. Freeman, P.

F. Von Voigtlander, W. J. Howe, and J. Szmuszkovicz, *Bioorg. Med. Chem. Lett.*, 1994, **4,** 2139 and references cited therein; (d) B. N. Dhawan, F. Cesselin, R. Raghubir, T. Reisine, P. B. Bradley, P. S. Portoghese, and M. Hamon, *Pharmacol. Rev.*, 1996, **48**, 567; (e) A. Cappelli, M. Anzini, S. Vomero, M. C. Menziani, P. G. De Benedetti, M. Sbacchi, G. D. Clarke, and L. Mannuni, *J. Med. Chem.,* 1996, **39**, 860; (f) For recent reviews of non-peptide kappa-opioid receptor agonists see: D. IC. Scopes, *Exp. Opin. Invest. Drugs*, 1994, **3**, 369; T. Reisine and G. Pasternak, 'Goodman & Gilman's the Pharmacological Basis of Therapeutics,' 9th Ed. McGraw-Hill, 1996, Chapter 23, p. 521; A. Barber and R. Gottschlich, *Exp. Opin. Invest. Drugs*, 1997, **6**, 1351.

3. Z. Z. Pan, S. A.Tershner, and H. L. Fields, *Nature*, 1997, **389**, 382.
4. T. Reisine, *Neuropharmacology*, 1995, **34**, 463.
5. R. M. Caudle, A. J. Mannes, and M. J. Iadarola, *J. Pharmacol. Exp. Ther.*, 1997, **283**, 1342.
6. A. D. Blake, G. Bot, and T. Reisine, *Chemistry & Biology*, 1996, **3**, 967.
7. 'Opiates', ed. by G. R. Lenz, D. E. Walters, S. M. Evans, and A. J. Hopfinger, Academic Press, Inc., 1986.
8. E. G. Anderson in 'The Pharmacologic Basis of Anesthesiology,' ed. by T. A. Bowdle, A. E. Horita, and D. Kharasch, Churchill Livingstone, 1994, 24.
9. T. Izumi, Y. Nishimoto, K. Kohei, and A. Kasahara, *J. Heterocycl. Chem.,* 1990, **27**, 1419.
10. L. Toll, I. P. Berzetei-Gurske, W. E. Polgar, S. R. Brandt, I. D. Adapa, L. Rodriguez, R. W. Schwartz, D. Haggart, A. O'Brien, A. White, J. M. Kennedy, K. Craymer, L. Farrington, and J. S. Auh, 'The College on Problems of Drug Dependence, NIDA Res. Monograph 178, 59th Annual Meeting, 1997, pp. 440-466.
11. G. Subramanian, M. Germana Paterlini, D. L. Larson, P. S. Portoghese, and D. M. Ferguson, *J. Med. Chem.*, 1998, **41**, 4777.

Received, 29th March, 1999