Bioorganic & Medicinal Chemistry Letters, Vol.3, No.12, pp. 2641-2646, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

PHENALENE ANALOGS OF THE KAPPA OPIATE AGONIST, U-50,488

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(*Received in USA* 7 *July* 1993; *accepted* 3 *September* 1993)

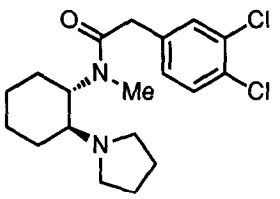
Abstract

Analogs of the kappa opiate agonist, U-50,488, a trans-1,2-cyclohexane-aminoamide, incorporating a phenalene unit have been prepared.

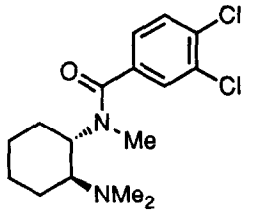
The disclosure[1] of the selective kappa opiate agonist U-50,488 (**1**) and mu agonist U-47,700 (**2**) has been followed by the preparation of many additional agonists based on this 1,2-amino-phenylacetamide template[2].

We[3] and others[4] have reported syntheses of the benzo- and naphtho- analogs of U-50,488, their interaction with the mu and kappa receptors and their analgesic activity.

In the present paper we extended the SAR to the preparation of the corresponding phenalene analogs. The phenalene system has attracted our attention previously because of its interesting chemical properties[5] and its potential as a template in drug design.[6] Phenalene derivatives of 1,2-amino amides offer an interesting extension of the aromatic analogs mentioned above and present candidates to further explore the interaction of 1,2-cyclohexanediamine analogs with kappa and mu receptors.



U-50,488 (**1**)



U-47,700 (**2**)

The syntheses started with the preparation of a pyrrolidinyl alcohol **6**, which was obtained in a three step sequence starting from 1-hydroxyphenalene (**3**).[7] Alcohol **3** was dehydrated using p-toluenesulfonic acid to give 1*H*-phenalene (**4**)[8] which, without purification, was oxidized to epoxide **5** with MCPBA.[9] The subsequent reaction of **5** with pyrrolidine gave the amino alcohol **6** (Scheme 1). The regiospecific formation of **6** arose from the attack of pyrrolidine at the benzylic carbon as observed in other cases[3].

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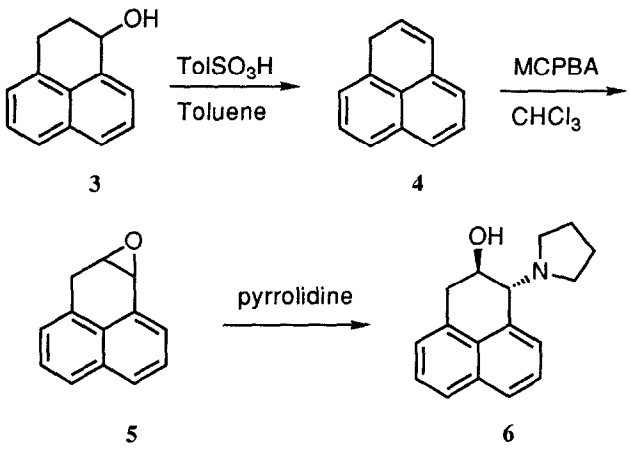
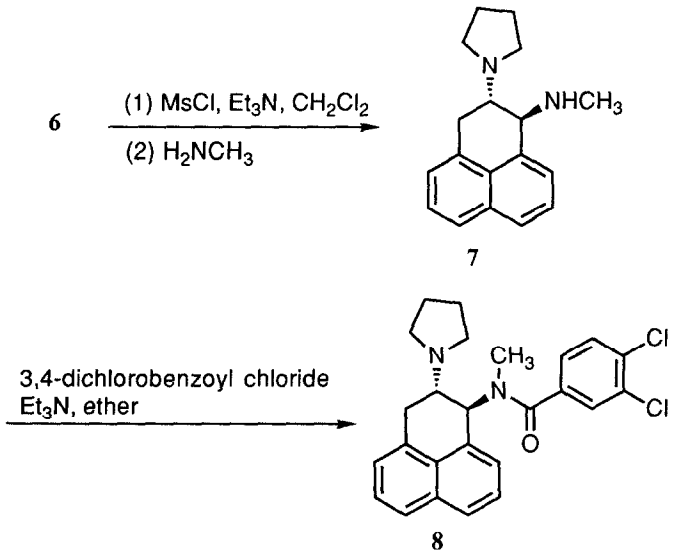
Scheme 1

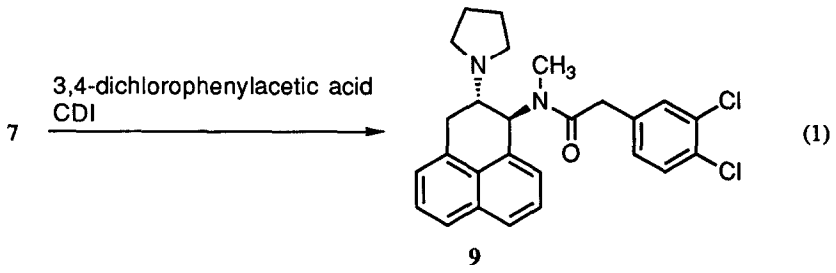


In the usual way, compound **6** was allowed to react with methanesulfonyl chloride and then methylamine to furnish diamine **7**. As expected,[3] the pyrrolidine group underwent 1,2 transposition in going from **6** to **7**. Diamine **7** was allowed to react with 3,4-dichlorobenzoyl chloride in the presence of triethylamine to give the amide **8** (Scheme 2).

Scheme 2



The corresponding homolog **9** was also prepared by the reaction of diamine **7** with 3,4-dichlorophenylacetic acid in the presence of carbonyldiimidazole (equation 1).



In summary, two phenalene derivatives (**8** and **9**) of 1,2-diaminoamides were synthesized, and subjected to preliminary biological evaluation.[9a]

Experimental Section

^{1}H NMR spectra were obtained at 300 MHz unless otherwise stated and ^{13}C NMR spectra were obtained at 75 MHz with $CDCl_3$ as a solvent.

***Trans*-2,3-dihydro-1-pyrrolidinyl-2-hydroxyphenalene (6):** Toluenesulfonic acid hydrate (54 mg) was added to the toluene solution (10 mL) of compound **3** (204 mg, 1.1 mmol)[10]. After the mixture was heated at reflux temperature for 1 h, it was concentrated to about 5 mL by rotary evaporation. Hexanes (10 mL) were added to the mixture. The mixture was filtered though celite, and rinsed with hexanes. The filtrate was concentrated in vacuo to give **4** as a red solid.

Compound **4** was dissolved in $CHCl_3$ (10 mL) and cooled to 0 °C. MCPBA (66%, 300 mg, 1.1 mmol) was then added in portions to the cooled solution. The resulting suspension was stirred at r.t. for 40 min. The reaction mixture was then washed with 5% aqueous K_2CO_3 (3 x 10 mL). The organic phase was dried with sodium sulfate. After the mixture was filtered, pyrrolidine (5 mL) was added to the filtrate, and the filtrate was concentrated in vacuo. Another portion of pyrrolidine (5 mL) was added to the residue, which was transferred to a bomb. The bomb was heated at 85 °C for 18 h and then cooled to r.t. The reaction mixture was dissolved in ether (100 mL), and the solution was washed with saturated Na_2CO_3 (20 mL), and then extracted with 10% HCl (2 x 50 mL). The acidic solution was basified by the addition of solid Na_2CO_3 to basic (pH>8) and extracted with ether (3 x 50 mL). The ether extract was dried with $MgSO_4$ and concentrated in vacuo to give **6** as a red oil (198 mg, 71%): ^{1}H NMR δ 7.78 (d, J = 7.8 Hz), 7.70 (d, J = 8.2 Hz), 7.42 (t, J = 7.5 Hz), 7.41 (t, J = 7.6 Hz), 7.37 (d, J = 6.9 Hz), 7.30 (d, J =

7.1 Hz), 4.37 (td, J = 6.0, 3.6 Hz), 3.87 (d, J = 5.9 Hz), 3.63 (dd, J = 16.2, 3.4 Hz), 3.12 (dd, J = 16.1, 6.1 Hz), 2.89 (m, 2 H), 2.71 (m, 2 H), 1.80 (m, 4 H); ^{13}C NMR δ 133.74, 132.61, 132.04, 129.43, 127.78, 126.48, 126.30, 125.95, 125.87, 125.09, 68.01 (d), 67.37 (d), 50.78 (t, $NC\underline{H}_2CH_2$) 35.37 (t, C-3), 23.92 (t, $NCH_2C\underline{H}_2$); MS (EI), m/e (rel intensity) 253 (54, M^+), 181 (52), 165 (100), 153 (61), 72 (100); HRMS *m/e* calcd for $C_{17}H_{19}NO$ 253.1467, found 253.1467.

***Trans*-2,3-dihydro-1-methylamino-2-pyrrolidinylphenalene (7)**: The compound **6** (213 mg, 0.84 mmol) was diluted with methylene chloride (3 mL) and cooled to 0 °C under nitrogen. Triethylamine (139 uL, 1.0 mmol) was added all at once. Methanesulfonyl chloride (77 uL, 1 mmol) in methylene chloride (0.5 mL) was added in 2 min. The mixture was stirred at 0 °C for 1.5 h, and then the solvent was removed by rotary evaporation at 25 °C. The residue was transferred to a bomb with CH_3NH_2 (3 mL, condensed from lecture bottle). The bomb was then sealed and heated to 70 °C for 20 h. After the bomb was cooled with dry ice, it was opened and the dark-red mixture was diluted with ether (100 mL). The ether solution was extracted with saturated potassium hydroxide and brine, dried over magnesium sulfate, concentrated in vacuo to give **7** as a red oil (129 mg, 58%): ^{1}H NMR δ 7.73 (d, J = 7.9 Hz, 1 H), 7.67 (d, J = 8.2 Hz, 1 H), 7.32-7.45 (m, 3 H), 7.23 (1 H, overlapped with $CHCl_3$), 3.92 (d, J = 4.7 Hz, H-1), 3.42 (dd, J = 16.6, 3.2 Hz, 1 H, H-3), 3.17 (dd, J = 16.9, 4.4 Hz, 1 H, H-3), 3.01 (q, J = 4.1 Hz, 1 H, H-2), 2.62 (m, 4 H), 2.52 (s, 3 H, CH_3), 1.62 (m, 4 H); ^{13}C NMR δ 140.65, 135.56, 133.50, 129.29, 127.12, 125.86, 125.52, 125.34, 124.96, 124.46, 62.32, 61.77, 50.74 ($NC\underline{H}_2CH_2$), 34.29, 29.61, 23.41 ($NCH_2C\underline{H}_2$); MS (EI), m/e (rel intensity) 266 (19, M^+), 235 (6), 196 (10), 166 (100), 165 (93), 84 (65), 72 (54), 70 (72);

3,4-Dichloro-N-methyl-N-[trans-2,3-dihydro-2-pyrrolidinylphenalenyl]benzamide (8): Into the solution of the diamine compound **7** (3.30 mmol, 827 mg) in ether (20 mL), was added 3,4-dichlorobenzoyl chloride (3.63 mmol, 759 mg) and triethylamine (3.63 mmol, 505 uL). After the white suspension was stirred at room temperature for 20 h, it was diluted with ether (200 mL) and washed with saturated sodium carbonate (30 mL x 2) and brine (30 mL x 2). The ether solution was dried with sodium sulfate and concentrated in vacuo to give a thick yellow oil. The oil was crystallized with THF to give **8** as a pale yellow solid (535 mg, 37%): mp 200-201 °C (dec.); ^{1}H NMR δ 7.22-7.85 (m), 6.25 (d, J = 11.2 Hz), 5.12 (d, J = 10.7 Hz), 2.86 (s, CH_3), 2.73 (s, CH_3); ^{13}C NMR[11] δ 171.07 (CO), 170.65 (CO), 63.92, 57.75, 56.14, 55.69, 48.25, 47.63, 32.71, 29.24, 29.07, 27.67, 24.03, 23.67; MS (EI), m/e (rel intensity) 438 (4, M^+), 367 (16), 352 (15), 235 (100), 165 (29); Anal. Calcd for $C_{25}H_{24}Cl_2N_2O$: C, 68.34; H, 5.51; Cl, 16.14; N, 6.38. Found: C, 68.00; H, 5.58; Cl, 16.13; N, 6.22.

3,4-Dichloro-N-methyl-N-[trans-2,3-dihydro-2-pyrrolidinylphenalenyl]benzenacetamide (9): After the solution of 3,4-dichlorophenylacetic acid (2.32 mmol, 476 mg) and 1,1'-carbonyldiimidazole (2.40 mmol, 389 mg) in THF (10 mL) was stirred at room temperature for 2.5 h, a solution of the compound **7** (2.19 mmol, 550 mg) in THF (5 mL) was added in 5 min by cannulation. The yellow solution was stirred at room temperature for 40 h. The THF solvent was removed in vacuo. The residue was dissolved with ether (150 mL). The ether solution was washed with saturated sodium carbonate (20 mL x 2) and extracted with aqueous HCl (10%, 30 mL x 3). The acidic solution was neutralized by the addition of solid sodium carbonate and was extracted with ether (50 mL x 3). The extract was dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel column ($CHCl_3$/MeOH/NH4OH = 95/4/1) to furnish **9** as a red oil (420 mg, 42%): ^{1}H NMR[11] δ 7.71 (br t, J = 9.1 Hz, 2 H), 7.37-7.48 (m, 4 H), 7.27 (m, 2 H), 7.12 (dt, J = 7.2, 2.6 Hz), 6.21 (d, J = 10.5 Hz), 5.21 (d, J = 10.1 Hz), 3.92 (d, J = 15.3 Hz, 1 H, $PhCH_2$), 3.83 (d, J = 15.3 Hz, 1 H, $PhCH_2$), 3.33 (m, 1 H), 3.22 (m, 2 H), 2.88 (m, 2 H, NCH_2), 2.74 (s, CH_3), 2.67 (m, 2 H, NCH_2), 1.74 (m, 4 H, NCH_2CH_2); ^{13}C NMR[11] δ 171.13, 57.28, 56.00, 47.75, 40.42, 31.06, 27.80, 23.95; MS (FAB), m/e (rel intensity) 453 (35, M + H1), 382 (18), 236 (66), 235 (77), 165 (100), 70 (21); HRMS *m/e* calcd for ($C_{26}H_{26}Cl_2N_2O$ + H1) 453.1500, found 453.1509.

Acknowledgment. We thank the Upjohn Company for support of this research.

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(a) Compounds **8** and **9** failed to display significant affinity for the opiate and D_2 receptors. The methodology for opiate and D_2 bonding has been described.[1b,12] Likewise, in vivo observation failed to detect any analgesic activity at 100 mg/kg in the mouse tail flick test and the pinch assay.[1b] Compounds **8** and **9** also did not dispaly morphine antagonism activity,[1b] and kappa antagonist activity. The last assay was performed as follows: 1.6 mg/kg of the kappa agonist U-63,640, the active enantiomer of U-62,066, is administered subcutaneously to six mice 30 min. after dosing with the test compound. The flick assay was run 15 min. after dosing with the kappa agonist.

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