DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

NEW METHOD FOR THE SYNTHESIS OF METHYL-4-[(3,4-DICHLOROPHENYL)ACETYL]-3-[(1-PYRROLIDINYL)METHYL]-1-PIPERAZINECARBOXYLATE

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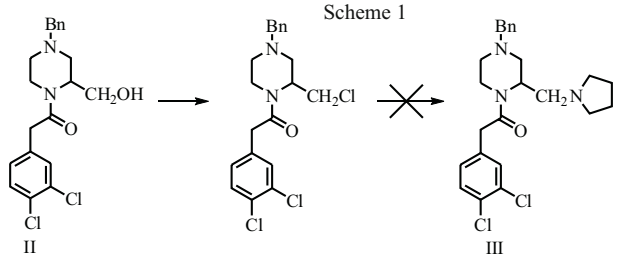
A new simple method involving a reduced number of steps is proposed for the synthesis of methyl-4-[(3, 4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-4-piperazinecarboxylate (GR-89696), which is an agonist of κ-opioid receptors (K_d = 0.41 nM).

Key words: GR-89696, piperazine, κ-agonist.

Medical, biological, and chemical research in the 1970s-1980s identified a large number of opiate receptor subtypes (δ_1, δ_2, μ_1, μ_2, μ_3, κ_1, κ_2, and κ_3) [1 – 3]. Each of these opiate receptor types is involved in the regulation of various functions. Selective ligands must be used to study the mechanisms of ligand-receptor interactions. In particular, various amides of 3,4-dichlorophenylacetic acid such as U-50488, GR-45809, and GR-89696 are used to study the κ-receptors. The most interesting κ-receptor agonist turned out to be methyl 4-[(3, 4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**I**, GR-89696), which has the highest affinity for κ-opioid receptors (K_d = 0.041 nM). However, convenient methods for preparing compounds of this class have not been available. This has limited their broad use. The synthesis of this compound that was developed at Glaxo Res. [4] produces **I** in total yield of less than 7.5% starting from ethyl 3-oxo-1,4-dibenzyl-2-piperazinecarboxylate. Therefore, we investigated the possibility of increasing the yield of **I** and reducing the number of synthetic steps.

For this, we first attempted to synthesize **I** using the known method without the alcohol oxidation step under Swern oxidation conditions. Therefore, alcohol **II** obtained by the known method [1] was treated with thionyl chloride in CH_2Cl_2 and treated without further purification with an excess of pyrrolidine. However, **III** could not be obtained this way (Scheme 1).

Scheme 1



Next we evaluated the possibility of introducing the pyrrolidine moiety by preliminary synthesis of the corresponding pyrrolidide. Several transformations including saponification of starting ester **IV** to the carboxylic acid, synthesis of the acid chloride, and treatment of it with an excess of pyrrolidine did not give the desired amide **V**. Only decarboxylation product **VI** was obtained from **IV**. We also evaluated the possibility of synthesizing **V** by amidation of starting ester **IV** with pyrrolidine using NaOMe as the catalyst. The reaction was carried out in the temperature range from +20 to +70°C. As it turned out, only decarboxylation of starting **IV** occurred during 7 d at 70°C. Under milder conditions, the desired compound was formed extremely slowly. Thus, desired amide **V** was formed in only 3% yield after 30 d at room temperature (Scheme 2).

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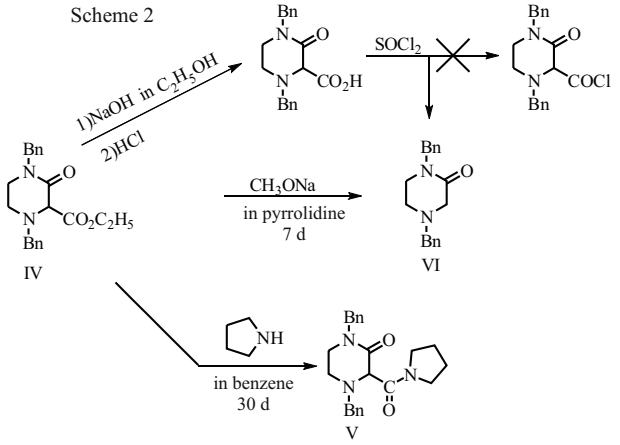
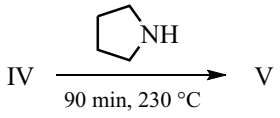
Scheme 2

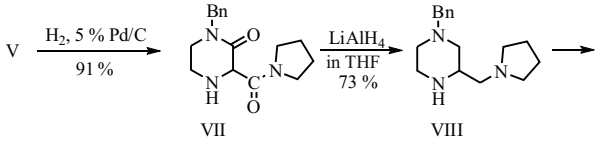


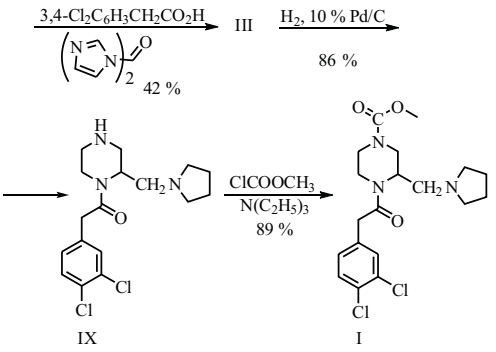
Based on the results, several experiments were performed to evaluate the potential for large-scale preparation of **V**. Variation of the temperature (from +20 to +300°C) and time (from 15 min to 8 h) established the conditions for preparing **V** in the greatest yield (Table 1). The highest yield (85%) of amide was achieved for the reaction at +230°C for 90 min. Side product **IV** was decarboxylated to form **VI** (yield less than 10%). The reaction mixture was saponified at higher temperatures. Lowering the reaction temperature increased the time for conversion of starting **IV** and the yield of side product **VI**.



Thus, a synthetic method for the desired compound was developed by adding the pyrrolidine moiety without oxidizing the alcohol under Swern reaction conditions. This reduced the number of synthetic steps. Compound **I** was synthesized according to Scheme 3.

Scheme 3





Compounds **V**, **VII**, and **VIII** have not been previously reported. Starting **IV** was prepared by the literature method [4]. All other steps were developed or optimized by us.

Thus, the newly developed method for preparing **I** that involves six steps can increase the product yield to 17.6%.

EXPERIMENTAL PART

Mass spectra were obtained on a HP-6890 spectrometer at ionizing potential 70 eV. Melting points were measured on a Buchi B-545 instrument.

3-Oxo-1,4-dibenzyl-2-piperazinecarboxylic acid pyrrolidide (V). Compound **IV** (12 g, 34.1 mmol) and pyrrolidine (40 mL) were placed in a 150-mL steel autoclave, hermetically sealed, heated to 230°C, held at that temperature for 90 min, and cooled to room temperature. The mixture of pyrrolidine and ethanol was evaporated. The solid was purified using column chromatography (eluent $CHCl_3$:CH_3OH:NH_4OH, 100:10:1; silica gel sorbent). Yield of **V**, 10.92 g (85%). Mass spectrum (m/z, I_{rel}): 377 (9), 279 (43), 91 (100).

3-Oxo-4-benzyl-2-piperazinecarboxylic acid pyrrolidide (VII). Anhydrous ethanol (250 mL), pyrrolidide **V** (10 g, 26.5 mmol), and Pd on activated C (2 g, 5%) were placed in a 500-mL three-necked flask equipped with a magnetic stirrer (Teflon-coated bar), capillary for adding H_2, and a reflux condenser with an outlet tube; saturated with Ar; stirred vigorously; treated with H_2 for 24 h; and filtered to remove catalyst. The ethanol and toluene were evaporated.

TABLE 1. Reaction Conditions for **I** and Pyrrolidine

Expt. No.	Temperature, °C	Time	Catalyst	Reagent ratio	Yield of **V**, %	Yield of **VI**, %
1	20	24 h	CH_3ONa	I : pyrrolidine = 1:1	–	–
2	50	24 h	CH_3ONa	I : pyrrolidine = 1:1	–	1
3	70	24 h	CH_3ONa	I : pyrrolidine = 1:1	–	4
4	70	7 d	CH_3ONa	I : pyrrolidine = 1:10	–	58
5	20	30 d	–	I : pyrrolidine = 1:10	3	6
6	70	90 min	–	I : pyrrolidine = 1:10	–	–
7	170	90 min	–	I : pyrrolidine = 1:10	32	5
8	200	120 min		I : pyrrolidine = 1:10	60	9
9	230	90 min	–	I : pyrrolidine = 1:10	85	10
10	300	60 min	–	I : pyrrolidine = 1:10	32	24

Yield of **VII**, 6.92 g (91%). Mass spectrum (m/z, I_{rel}): 287 (14), 270 (7), 189 (94), 91 (100).

4-Benzyl-2-[(1-pyrrolidinyl)methyl]piperazine (VIII). A 250-mL four-necked round-bottomed flask equipped with a mechanical stirrer, dropping funnel, tube for carrying out the reaction under Ar (or N_2), and a funnel for adding friable reagents was charged with anhydrous THF (125 mL). Small portions of $LiAlH_4$ (2.28 g, 60 mmol) were added under a stream of Ar (or N_2). The reaction mixture was stirred, treated dropwise with **VII** (6.0 g, 20.9 mmol) in anhydrous THF (75 mL) over 1 h, stirred for another 2 h, treated carefully dropwise with water (2.30 mL) and NaOH solution (6.67 mL, 2 N) and water (2.40 mL), left for 30 min, and filtered. The filtrate was evaporated to afford **VIII** (3.95 g, 73%). Mass spectrum (m/z, I_{rel}): 259 (1), 189 (21), 175 (79), 168 (29), 91 (100), 84 (93).

1-[(3,4-Dichlorophenyl)acetyl]-4-benzyl-2-[(1-pyrrolidinyl)methyl]piperazine (III). A 250-mL Ehrlenmeyer flask was equipped with a magnetic stirrer and charged with 3,4-dichlorophenylacetic acid (3.28 g, 16 mmol) in CH_2Cl_2 (150 mL). The mixture was stirred vigorously under Ar, treated with 1,1′-carbonyldiimidazole (2.43 g, 15 mmol) and dropwise over 1 h with **VIII** (3.89 g, 15 mmol) in CH_2Cl_2 (50 mL), stirred for 24 h, transferred to a separatory funnel (500 mL), treated with CH_2Cl_2 (100 mL), and washed with Na_2CO_3 solution (2 M, 3 × 120 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated to afford **III** (2.8 g, 42%). Mass spectrum (m/z, I_{rel}): 445 (10), 368 (24), 300 (51), 91 (100).

1-[(3,4-Dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine (IX). Compound **III** (1.2 g) in THF (50 mL), water (50 mL), conc. HCl (5 mL), and Pd on activated C (400 mg, 10%) were placed in a 250-mL three-necked round-bottomed flask equipped with a mechanical stirrer, tube for carrying out the reaction under H_2, and a funnel for adding friable reagents.

The mixture was stirred, purged with Ar for 15 min and then H_2 for 6 h, and filtered. The filtrate was evaporated. The solid was washed with Na_2CO_3 solution (20%) and extracted with CH_2Cl_2 (2 × 30 mL) to afford **IX** (0.8 g, 83.6%).

Mass spectrum (m/z, I_{rel}): 355 (6), 257 (32), 182 (69), 91 (100).

Methyl-4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (I). Compound **IX** (2 g, 5.63 mmol) and triethylamine (0.79 mL, 5.63 mmol) in CH_3CN (30 mL) were placed in a 50-mL Ehrlenmeyer flask equipped with a magnetic stirrer, stirred vigorously, treated dropwise with methylchloroformate (0.53 g, 5.6 mmol), stirred for 12 h, transferred to a separatory funnel (125 – 150 mL), treated with Na_2CO_3 solution (30 mL, 2 M), and extracted with CH_2Cl_2 (2 × 60 mL) to afford **I** (2.07 g, 89%). Mass spectrum (m/z, I_{rel}): 413 (2), 382 (13), 268 (43), 91 (100).

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