Synthesis and Pharmacological Activity of 4-(4′-(Chlorophenyl)-4-hydroxypiperidine) Derivatives

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A new series of 4-(4′-chlorophenyl)-4-hydroxypiperidine derivatives (2—5), substituted at nitrogen, were synthesized and tested as potential analgesic compounds as well as evaluated for their effect on hypotensive activity. Results showed that all the derivatives exhibit significant analgesic activity in male Wistar rats at a dose of 50 mg/kg of body weight after intramuscular injection, when tested by thermal stimuli (tail flick test). Pethidine was used as reference drug. Compounds 2, 3 and 5 produced reduction in blood pressure in normotensive rat.

Key words piperidine; derivative; activity

The preparation of *N*-phenacyl derivatives of alkylated and arylated piperidinols was reported in 1957, but they were not evaluated for any biological activity.[1)] Later on, a series of 3-alkyl-3-phenylpiperidine derivatives were synthesized and examined for their analgesic activity.[2,3)] Several classes of 4-anilidopiperidine analogues were also synthesized in an attempt to discover potent *ultra* short-acting analgetics.[4)] Some 1-[(3,4-dichlorophenyl)acetyl]-2[(alkylamino)methyl]piperidines were prepared and their activities as potential analgesic agents were studied.[5)] Similarly, a series of *N*-substituted *trans*-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines,[6)] novel 4-phenylpiperidinyl- and (4-phenyl-piperazinyl)alkyl 1-phenylcyclopentanecarboxylates were synthesized and their activities as analgesic agents were evaluated.[7)]

According to recent reports on pharmacological effects of substituted piperidines, there is still an increasing interest in synthesizing and biotesting new pharmacophores based on this skeleton.[8—10)] This initiated us to explore the syntheses as well as selected pharmacological activities of various derivatives of 4-(4′-chlorophenyl)-4-hydyroxypiperidine.

Results and Discussion

In the present studies, four derivatives (**2**—**5**) of 4-(4′-chlorophenyl)-4-hydroxypiperidine (**1**) were prepared and their analgesic and hypotensive activities determined.

The four derivatives were synthesized according to the route given in Chart 1.[10)] In general, 1 mol of **1** was reacted with the corresponding substituted phenacyl halide in ethanol under reflux yielding compounds **2**—**5** in good yield. All compounds were characterized by their elemental analysis, UV, IR, mass and ^{1}H-NMR spectra.

The four derivatives along with the parent compound were tested intramuscularly for analgesic activity at doses of 50 mg/kg body weight by the tail flick test and the results are summarized in Table 1. All compounds except parent compound **1** showed analgesic activity. The highest activity was observed for compound **5** with a substitution of bromine at the benzene ring. The 3′-nitrophenacyl derivative **3** had less analgesic activity compared to **5**, while the propiophenone derivative **4** was found to be the least active one. In the phenacyl moiety compounds **2** and **3** the nitro derivative **3** showed higher activity compared with the dihydroxy derivative **2**.

The 3″,4″-dihydroxyphenacyl derivative **2** revealed significant ($p<0.5$) maximum analgesia at 150 min with a tail flick latency difference (TFLD) value (±S.E.M. in seconds) 2.15±0.10 ($p<0.01$) and at 120 and 180 min TFLD values of 1.61±0.40 and 1.14±0.35 were recorded, respectively. It is

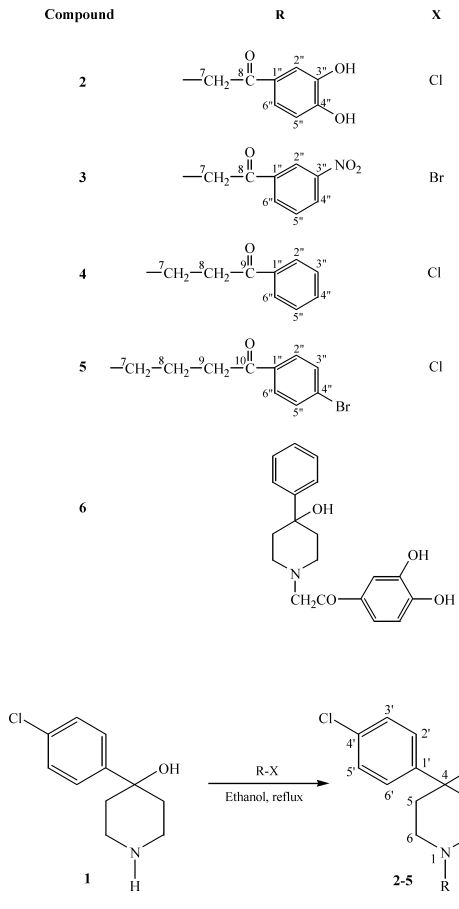

Chart 1

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Table 1. Analgesia Produced by Compounds **1**—**5** against Thermal Stimuli (Tail Flick Method)

Treatment (intramuscular)	Dose mg/kg	Mean increase in latency±S.E.M. (s)					
		30 min	60 min	90 min	120 min	150 min	180 min
1	50	0.32±0.93	0.15±0.04	0.30±0.11	0.31±0.08	0.27±0.03	0.15±0.025
2	50	0.77±0.37	1.14±0.52	1.17±0.51	1.61*±0.40	2.15±0.10**	1.14**±0.35
3	50	0.82±0.29	2.05*±0.36	2.44**±0.31	3.10**±0.26	2.51**±0.42	1.13**±0.19
4	50	0.75±0.34	0.82±0.31	0.88*±0.21	1.44**±0.19	1.57**±0.19	0.53±0.19
5	50	2.32**±0.16	2.60**±0.22	2.70**±0.23	3.72**±0.31	3.18**±0.45	0.56±0.13
Control for **1** and **4**	—	0.31±0.04	0.32±0.03	0.39±0.08	0.36±0.09	0.31±0.05	0.36±0.07
Control for **2** and **3**	—	0.67±0.18	0.70±0.11	0.68±0.21	0.50±0.12	0.23±0.04	0.33±0.14
Control and **5**	—	0.55±0.10	0.66±0.10	0.42±0.14	0.36±0.15	0.38±0.14	0.37±0.08
Pethidine	50	2.26*±0.63	3.52**±0.46	2.82**±0.13	2.57**±0.23	1.92**±0.07	1.57**±0.20

Significant differences by Student "*t*" test * $p<0.05$, ** $p<0.01$ as compared to control.

of interest that the 3″,4″-dihydroxyacetophenone derivative **6** of 4-hydroxy-4-phenylpiperidine shows no analgesic activity,[10] when tested for antinociceptive activity in the tail flick test, but produced significant analgesic effect, when examined by a chemical method (writhing test). The only difference between compounds **2** and **6** is the presence of a chlorine atom located at the phenyl ring. This difference led to exhibit strong analgesia. What can be proven by the fact that the writhing test is a simple and sensitive method for screening weak analgesics, whereas the tail flick test is specifically useful for screening strong narcotic analgesia.[11]

Compound **3** exhibited highly significant ($p<0.01$) activities at time intervals 90, 120, 150 and 180 min showing TFLD values (±S.E.M. in seconds) of 2.44±0.31, 3.10±0.26, 2.51±0.42, and 1.13±0.19, respectively. A significant analgetic response ($p<0.05$) was produced already at 60 min showing a TFLD value of 2.05±0.36 s. Derivative **3** exhibited greater TFLD values than pethidine at 120 and 150 min. Propiophenone derivative **4** demonstrated significant ($p<0.05$) analgetic activity after 90 min of its administration showing a TFLD value (±S.E.M. in seconds) of 0.88±0.21. A significant analgetic response ($p<0.01$) was observed at 120 and 150 min with TFLD values of 1.44±0.19 and 1.57±0.19 s, respectively. This compound produced a comparable analgetic activity with that of pethidine at 150 min, whereas at 30, 60, 90, 120 and 180 min it was lower compared to pethidine. Compound **5** produced pronounced analgetic activity after 30 min of administration, and it was retained till 150 min. Highly significant ($p<0.01$) TFLD values (±S.E.M. in seconds) of 2.32±0.16, 2.60±0.22, 2.70±0.23, 3.72±0.31 and 3.18±0.45 were observed at 30, 60, 90, 120 and 150 min, respectively. The peak analgetic response was observed after 120 min of administration (3.72±0.31). This derivative showed comparable activity with that of pethidine at 30 and 90 min and displayed larger TFLD values at 120 and 150 min compound to pethidine.

Compounds **2**, **3** and **5** were also screened for their effects on the mean arterial blood pressure in anaesthetized rats. The results are summarized in Table 2. All compounds tested at doses of 1 mg/kg of body weight intravenously in normotensive rats produced reduction in blood pressure. The onset of depressor responses occurred immediately after administration and the maximal hypotensive effect was produced within 30 s. The duration of responses was 1—3 min. The hypotensive response produced by each of the derivative regained its normal level after 1 min.

Table 2. Effect of 4-(4′-Chlorophenyl)-4-hydroxy Piperidine Derivatives **2**, **3** and **5** on Blood Pressure Level in Normotensive Anaesthetized Rats

Compound	Dose, mg/kg (i.v.)	% Decrease in systolic/diastolic pressure
2	1	11/12
3	1	15/18
5	1	11/ 6

Among them, derivative **3** showed maximum hypotensive activity at a dose of 1 mg/kg. Lowering in blood pressure started immediately after intravenous injection and after 20 s, the systolic and diastolic pressures were reduced by 15% and 18%, respectively. Compound **2** also exhibited hypotensive activities at similar levels as compound **3**. Minimal blood pressure was recorded at 20 s after administration where the systolic and diastolic pressures decreased by 11% and 12%, respectively. Compound **5** produced the larger falls of systolic pressure (11%) as compared to diastolic pressure (6%). The onset of hypotensive response was immediate and retained for about 3 min.

Conclusion

The present series of compounds were prepared to assess the feasibility of piperidine derivatives with special reference to pethidine as potential analgetic agents.

Experimental

General Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet (UV) spectra were recorded in methanol on a Hitachi U-3200 spectrophotometer. Infrared (IR) spectra were measured on a Shimadzu IR 460 spectrophotometer using KBr discs. Mass spectra (MS) were determined on a MAT 311A spectrophotometer. Elemental analyses were carried out on a Perkin Elmer 2400 CHN elemental analyzer. Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 on a Bruker AM-300 spectrophotometer operating at 300 MHz. Reactions were monitored by TLC using silica gel type 60 F_{254} of E. Merck for preparing TLC plates and visualized with iodine vapours.

Analgesic Assay (Tail Flick Test) The analgesic activity of the compounds was tested as antinociceptive effect against thermal stimuli (tail flick test). White male albino mice, weighing 20—30 g, were used for the thermal test. The animals were kept under standard colony condition (12 h light and 12 h dark, temperature: 21±2 °C) and fed with balanced diet and water *ad libitum*.[10] Analgetic activity of the compounds was assessed according to di-Stasi *et al.*[12] Test compounds were dissolved in water or DMSO (vehicle) for injection and administered intramuscularly at a dose of 50 mg/kg body weight. Pethidine (50 mg/kg) was used as a standard drug and the control groups received only the vehicle. Readings were taken at 30, 60, 90, 120, 150 and 180 min after administration of the compounds. The tail flick latency difference (TFLD) after compound administration was used to mea-

sure the analgesia produced by the test compounds and the standard drug.

Determination of Mean Arterial Blood Pressure Male Wistar rats (200—250 g) were used for the determination of mean arterial blood pressure (MABP).[13,14] The animals were anesthetized with an intraperitoneal injection of thiopentone (pentothal, 70—90 mg/kg body weight). The right carotid artery was cannulated with heparinized polyethylene tubing (PE-50) connected to a pressure transducer coupled with a Grass 7D model polygraph. The left jugular vein was cannulated with a similar tubing to facilitate the intravenous injection of the drugs and test compounds. The rats were injected with heparin (1000 μg/kg body weight) to prevent blood clotting. After a 20 min period of equilibrium, the rats were injected intravenously with 0.2 ml saline (NaCl 0.9%) or with the same volume of test substance. Arterial blood pressure was allowed to return to the resting level between injections. Changes in blood pressure were recognized as the differences between the steady state values before and the lowest readings after injection. Mean blood pressure was calculated as the diastolic blood pressure plus one-third-pulse width.

General Procedure for the Preparation of Compounds 2—5 Equimolar quantities of 4-(4′-chlorophenyl)-4-hydroxypiperidine (**1**) and various substituted phenacyl halides were dissolved in approximately 50 ml ethanol in separate conical flasks and mixed together. The reaction mixture was stirred at room temperature for 4—8 h, followed by refluxing on a water bath until completion of the reaction. The solid precipitate was filtered and washed with appropriate solvents to remove the unreacted starting materials. The product was recrystalized from appropriate solvents to give the purified product.

1-(3″,4″-Dihydroxyphenacyl)-4-(4′-chlorophenyl)-4-hydroxypiperidinium Hydrochloride (**2**): Colorless crystalline powder (300 g, 83%). mp 250 °C (ethanol). UV λ_{max} (MeOH) nm (log ε): 274 (4.9). IR ν_{max} (KBr) cm^{-1}: 3311, 2912, 1719, 1573, 1305, 821, 742, 613. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 9.05 (1H, s, N–H), 7.49 (2H, d, J=8.6 Hz, H-2′/H-6′), 7.41 (1H, dd, J=8.4, 1.7 Hz, H-6″), 7.36 (2H, d, J=8.6 Hz, H-3′/H-5′), 7.01 (1H, d, J=1.7 Hz, H-2″), 6.87 (1H, d, J=8.4 Hz, H-5″), 5.54 (1H, s, H-4), 3.32 (2H, s, H-7), 3.23—3.11 (4H, m, H_2-2/H_2-6), 2.27—2.08 (4H, m, H_2-3/H_2-5). EI-MS *m/z*: 362 (M^+−Cl), 213, 193, 158, 139, 111, 82. *Anal.* Calcd for $C_{19}H_{21}ClNO_4$ (362.83): C, 62.90; H, 5.83; N, 3.86; Found: C, 62.94; H, 5.78; N, 3.91.

1-(3″-Nitrophenacyl)-4-(4′-chlorophenyl)-4-hydroxypiperidinium Hydrobromide (**3**): Colorless needles (267 g, 71%). mp 231 °C (ethanol). UV λ_{max} (MeOH) nm (log ε): 383 (5.3). IR ν_{max} (KBr) cm^{-1}: 3392, 2917, 1762, 1581, 1379, 821, 718. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 9.08 (s, 1H, N–H), 8.01 (1H, dd, J=1.6, 1.6 Hz, H-2″), 7.83 (1H, dt, J=8.3, 1.6 Hz, H-6″), 7.79 (1H, dd, J=8.3, 1.6 Hz, H-4″), 7.47 (2H, d, J=8.1 Hz, H-2′/H-6′), 7.41 (1H, t, J=8.3 Hz, H-5″), 7.32 (2H, d, J=8.1 Hz, H-3′/H-5′), 5.57 (1H, s, H-4), 3.35 (2H, s, H-7), 3.21—3.10 (4H, m, H_2-2/H_2-6), 2.27—2.16 (4H, m, H_2-3/H_2-5). EI-MS *m/z*: 376 (M^+−Br), 212, 195, 164, 158, 111, 80, 58. *Anal.* Calcd for $C_{19}H_{20}ClN_2O_4$ (375.82): C, 60.72; H, 5.36; N, 7.45; Found: C, 60.67; H, 5.41; N, 7.52.

1-(Propiophenone)-4-(4′-chlorophenyl)-4-hydroxypiperidinium Hydrochloride (**4**): Colorless crystalline powder (285 g, 83%). mp 214 °C (ethanol). UV λ_{max} (MeOH) nm (log ε): 389 (5.1). IR ν_{max} (KBr) cm^{-1}: 3317, 2911, 1678, 1324, 823, 745, 687. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 9.02 (1H, s, N-H), 8.03—8.01 (2H, m, H-2″/H-6″), 7.70—7.65 (1H, m, H-4″), 7.58—7.54 (2H, m, H-3″/H-5″), 7.49 (2H, d, J=7.9 Hz, H-2′/H-6′), 7.41 (2H, d, J=7.9 Hz, H-3′/H-5′), 5.56 (1H, s, H-4), 3.72 (2H, t, J=7.2 Hz, H-8), 3.41 (2H, t, J=7.2 Hz, H-7), 3.32—3.23 (4H, m, H_2-2/H_2-6), 2.58—2.31 (4H, m, H_2-3/H_2-5). EI-MS *m/z*: 343 (M^+−HCl), 223, 205, 138, 105, 105, 83, 56. *Anal.* Calcd for $C_{20}H_{23}ClNO_2$ (344.85): C, 69.66; H, 6.72; N, 4.06; Found: C, 69.71; H, 6.67; N, 4.09.

1-(4″-Bromobutyrophenone)-4-(4′-chlorophenyl)-4-hydroxypiperidinium Hydrochloride (**5**): Colorless needles (252 g, 71%). mp 252 °C (ethanol). UV λ_{max} (MeOH) nm (log ε): 263 (4.8). IR ν_{max} (KBr) cm^{-1}: 3311, 2921, 1719, 1573, 1392, 732, 559. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 8.55 (1H, s, N–H), 7.93—7.89 (2H, m, H-2″/H-6″), 7.69—7.61 (1H, m, H-4″), 7.57—7.52 (2H, m, H-3″/H-5″), 7.48 (2H, d, J=8.1 Hz, H-2′/H-6′), 7.41 (2H, d, J=8.1 Hz, H-3′/H-5′), 5.53 (1H, s, *H*-4), 3.36 (2H, t, J=7.1 Hz, H-7), 3.27—3.13 (4H, m, H_2-2/H_2-6), 2.52—2.48 (4H, m, H_2-3/H_2-5), 2.14 (2H, t, J=7.1 Hz, H-9), 1.75 (2H, m, H-8). EI-MS *m/z*: 437 (M^+−HCl), 223, 205, 138, 105, 105, 83, 56. *Anal.* Calcd for $C_{21}H_{24}BrClNO_2$ (437.77): C, 57.61; H, 5.53; N, 3.20; Found: C, 57.68; H, 5.47; N, 3.25.

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