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Il Farmaco 55 (2000) 47–50

IL FARMACO

Some new 1,2,3,4-tetrahydroquinoline derivatives

Anna Ferranti [a,*], Giuseppe Giovanninetti [a], Francesco Piazza [a], Patrizia Romualdi [b], Annalisa Capobianco [b], Sanzio Candeletti [b]

[a] *Dipartimento di Scienze Farmaceutiche, Università degli Studi di Bologna, via Belmeloro 6, I-40126 Bologna, Italy*
[b] *Dipartimento di Farmacologia, Università degli Studi di Bologna, via Irnerio 48, I-40126 Bologna, Italy*

Received 23 July 1999; accepted 1 May 1999

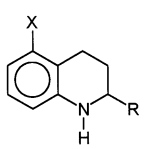
Abstract

Two 1,2,3,4-tetrahydoquinoline-based compounds were synthesized and evaluated for antinociceptive properties. Both compounds displayed no significant analgesic activity and at the higher dose showed no characterized CNS depressant activity. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Antinociceptive compounds; Analgesic agents; Quinoline derivatives; 1,2,3,4-Tetrahydroquinolines; CNS depressant activity

1. Introduction

Analgesic activity was found in 1,2,3,4-tetrahydroquinolines with an oxygenated function in the benzene moiety [1]. Important structural features for the activity were: (a) a hydroxyl group at the five carbon free, as well as the 1-amino function; (b) the introduction of a methyl substituent on the C-atom in the 2-quinoline position so that the 2-methyl-1,2,3,4-tetrahydro-5-quinolinol (**1**) (Fig. 1) was shown to be the most active compound in the short series of 1,2,3,4-tetrahydroquinoline derivatives. The replacement of the phenolic hydroxyl by another weak acid group (carbohydroxamic or carboxylic) led to the decrease and loss of the analgesic activity, respectively [2].



Compound	X	R
1	OH	CH_3
2	CH_2OH	CH_3
3	OH	C_4H_9

Fig. 1. New 1,2,3,4-tetrahydroquinoline derivatives.

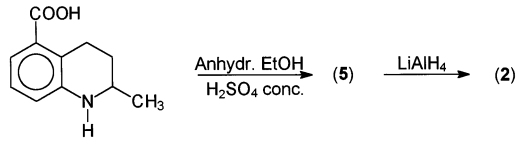
Other possible molecular modifications of compound **1** in order to acquire further information on the structural characteristics enhancing analgesic activity resulted in the removal of the hydroxyl group from the quinoline skeleton and the extension of the alkyl chain at the 2-carbon. This paper reports on the preparation and the preliminary pharmacological tests of the 2-methyl-1,2,3,4-tetrahydroquinoline-5-methanol (**2**) and the 2-butyl-1,2,3,4-tetrahydro-5-quinolinol (**3**) (Fig. 1) obtained to explore the above-mentioned possibilities. Recently, antinociceptive 1,2,3,4-tetrahydroisoquinolines showed the incorporation of the benzene methanol moiety into their molecules [3], and 1,2,3,4-tetrahydroquinolines with hydrophobic substituents appeared to be tachykinin NK_1 receptor–antagonists with analgesic activity [4].

2. Chemistry

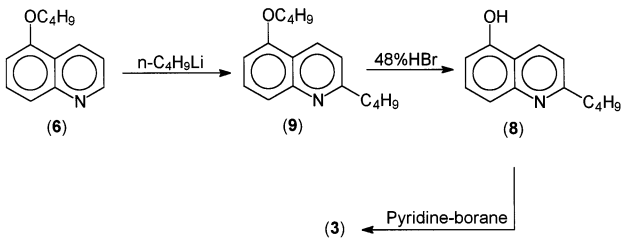
The preparation of 2-methyl-1,2,3,4-tetrahydroquinoline-5-methanol (**2**) was carried out in good yield from 2-methyl-1,2,3,4-tetrahydroquinoline-5-carboxylic acid (**4**) (Scheme 1) [2]. The latter was esterified according to the standard methods [5] to yield ethyl 2-methyl-1,2,3,4-tetrahydroquinoline-5-carboxylate (**5**), which by reduction with pyridine–borane afforded the desired compound.

* Corresponding author. Fax: +39-051-259 700.

PII: S0014-827X(99)00120-2



Scheme 1.



Scheme 2.

The synthesis of 2-butyl-1,2,3,4-tetrahydro-5-quinolinol was performed starting from commercial 5-quinolinol, which was converted with 1-bromobutane into 5-butoxyquinoline (**6**) (Scheme 2). This last treatment with butyllithium in tetrahydrofuran produced 5-butoxy-2-butyl-quinoline (**7**), which by hydrolysis with 48% hydrobromic acid gave 2-butyl-5-quinolinol (**8**). The reduction of **8** with pyridine–borane yielded the desired compound **3**.

3. Pharmacology

3.1. Materials and methods

Male Sprague–Dawley rats (Charles River, Calco, Italy) weighing 200–220 g were used. They were caged individually with a 12 h light–dark cycle and allowed free access to food and water.

Rats were implanted with a permanent catheter consisted of polyethylene tubing (PE 10, Becton Dickinson, 0.28 mm o.d.) with a small bead of dental cement placed 0.4 cm from the tip, preventing it from entering further into the brain under sodium pentobarbital anesthesia.

Prior to insertion, the catheter was sterilized by immersion in a solution of benzalkonium chloride and flushed with a sterile, osmotically balanced solution adopted as a vehicle (NaCl, 7.46 g; KCl, 0.19 g; $MgCl_2$, 0.19 g; $CaCl_2$, 0.14 g in 1000 ml distilled water). Rats were anaesthetized with sodium pentobarbital (35 mg/kg intraperitoneally (i.p.) and a permanent plastic cannulae was implanted into the right brain ventricle (1.5 mm from the sagittae suture, 1.5 mm posterior to bregma) at a depth of 4.5 mm below the skull surface. Cannulae were fixed in place with acrylic dental cement and one skull screw. At the end of surgery, 5 μl of the sterile vehicle were injected to clear the catheter, then the upper tip was closed with a stylet that was easily removed to allow injection of the substances employed. All animals were allowed to recover for 5 days before they were used in the experiment and those rats that showed neurological or motor deficits were discarded. Each animal was used only once. At the end of the experiments, the rats were injected randomly with 10 μl of blue dye (Evans blue) and sacrificed to verify the correct position of the catheter.

3.2. Compounds

Drugs were dissolved in the drug vehicle solution and injected either i.p. or intracerebroventricularly (i.c.v.) in a volume of 0.2 ml/100 g b.w. or 5 μl/rat, respectively. The catheter was cleared by the subsequent injection of the 8 μl vehicle solution.

3.3. Evaluation of antinociceptive activity

The response to nociceptive stimuli was determined in conscious unrestrained animals by the tail-flick test [6] before and at appropriate times after administration of drugs or vehicle alone (control). The mean of two trials was recorded. In preliminary experiments, no apparent interaction was observed using this order of testing. In the tail-flick test, the strength of a radiant heat source was adjusted to produce a baseline tail-flick of 2–3 s. A cut-off time of 10 s was used in order to avoid tissue damage. Each rat was used only once and observation and scoring were carried out by two observers, unaware of the drug treatment. In all the experiments, attention was paid to the ethical guidelines of investigations of experimental pain in conscious animals.

4. Results

2-Methyl-1,2,3,4-tetrahydroquinoline-5-methanol (**2**) and 2-butyl-1,2,3,4-tetrahydro-5-quinolinol (**3**) failed to produce an elevation of nociceptive threshold as measured by means of the tail-flick test when injected i.p. or i.c.v. at doses of 10 or 50 mg and 10 or 50 μg/ml, respectively. At the higher doses of both compounds i.c.v. injected, rats showed few signs of depressed CNS activity, accompanied with a reduction of spontaneous locomotor activity.

The last observations together with the well-known importance of the homologous series in medicinal chemistry [7], appear to stimulate a deeper research into the relationship between the length of the alkyl chain substituent and the CNS depressant activity in these 1,2,3,4-tetrahydroquinoline-based compounds.

5. Experimental

5.1. Chemistry

Melting points were taken on an electrothermal open capillary apparatus and are uncorrected. IR spectra (Nujol mull technique), recorded on a Perkin–Elmer 177 spectrometer, agree with the proposed structures. ^{1}H NMR spectra were taken on Gemini 200 MHz NMR spectrometer (DMSO-d_6 or $CDCl_3$ solvent; TMS: internal standard). n_D^{20} measurements were carried out using an Able refractometer. Elemental analyses were within $\pm 0.4\%$ of theoretical values. TLC on silica gel plates (Baker Flex IB2-F precoated 0.2 mm) was usually used to follow the reaction and to check the purity of the products; eluents: 6:4 petroleum ether 60–80°C–EtOAc, 8:2 toluene–acetone, methanol.

5.1.1. Ethyl 2-methyl-1,2,3,4-tetrahydoquinoline-5-carboxylate (5)

A mixture of 2-methyl-1,2,3,4-tetrahydroquinoline-5-carboxylic acid (2 g, 10.46 mmol) in dry ethanol (100 ml) containing a few drops of concentrated sulfuric acid was refluxed for 6 h. After cooling and the addition of water (30 ml), the solution was alkalinized with 2 M NaOH, evaporated under reduced pressure to remove ethanol and extracted with ethyl acetate (3×15 ml). The collected organic layers, washed with water, were dried on anhydrous sodium sulfate and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel eluting with 8:2 toluene–acetone to give the desired compound. Yield: 74%; $n_D^{20} + 0.05$: 1.584. *Anal.* ($C_{13}H_{17}NO_2$) C, H, N; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 1.23$ (3H, d, $J = 6.30$), 1.37 (3H, t, $J = 7.13$), 1.65 (1H, m), 1.8 (1H, m), 2.00 (1H, m), 3.20 (1H, m), 3.51 (1H, m), 4.32 (2H, quart, $J = 7.14$), 6.62 (1H, d, $J = 7.58$), 6.99 (1H, t, $J = 7.72$), 7.14 (1H, d, 7.64).

5.1.2. 2-Methyl-1,2,3,4-tetrahydroquinoline-5-methanol (2)

To a solution of the previous ester (0.489, 4.56 mmol) in 30 ml dry tetrahydrofuran, diisobutylaluminum hydride was added dropwise (1 M in THF, 6.68 ml, 6.68 mmol) and the mixture was stirred at 0°C for 2 h. The reaction was quenched with methanol; then the mixture was evaporated to dryness and partitioned between water and EtOAc. The organic phase was washed three times with water, dried and evaporated to give a solid residue, which was crystallized from 8:2 EtOAc–petroleum ether 60–80°C to afford the desired alcohol (**2**) as white crystals. Yield 91%; m.p. 115–118°C. *Anal.* ($C_{11}H_{15}NO$) C, H, N; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 1.26$ (3H, d, $J = 6.37$), 1.64 (1H, m), 1.77 (1H, m), 2.10 (1H, m), 2.90 (1H, m), 3.12 (1H, m), 4.71 (2H, s), 6.48 (1H, d, $J = 7.41$), 6.71 (1H, d, $J = 7.71$), 7.03 (1H, t, $J = 7.58$).

5.1.3. 5-Butoxyquinoline (6)

To a stirred suspension of 5-quinolinol (0.285 g, 1.96 mmol) and anhydrous K_2CO_3 (0.270 g, 1.96 mmol) in dry acetone (20 ml), butyl bromide (0.6 ml, 5.6 mmol) was added dropwise and the reaction mixture was refluxed for 9 h, then cooled and evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was washed three times with water, dried over Na_2SO_4 and evaporated under reduced pressure to give a solid residue which was purified by column chromatography on silica gel, eluting with 8:2 petroleum ether 60–80°C–ethyl acetate. White crystals from EtOAc–petroleum ether 60–80°C. Yield: 92%; m.p. 45–47°C. *Anal.* ($C_{13}H_{15}NO$) C, H, N; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 1.05$ (3H, t, $J = 7.35$), 1.63 (2H, m), 1.92 (2H, m), 4.18 (2H, t, $J = 6.06$), 6.81 (1H, d, $J = 7.62$), 7.36 (1H, t, $J = 4.26$), 7.58 (1H, t, $J = 7.59$), 7.67 (1H, d, $J = 7.56$), 8.61 (1H, d, $J = 7.47$).

5.1.4. 2-Butoxy-2-butylquinoline (7)

A solution of *n*-BuLi (1 M in *n*-hexane; 1.125 ml, 1.8 mmol) was added under natrium to a stirred and cooled (ice-water) solution of 5-butoxyquinoline (0.363 g, 1.8 mmol) in 10 ml dry tetrahydrofuran. After allowing the reaction to proceed for 12 h at room temperature (r.t.), it is quenched by adding to H_2O (100 ml) and extracted with $EtOA_c$ (3×30 ml). The combined organic layer is dried (Na_2SO_4) and evaporated under reduced pressure. The resulting product was an oil, which was purified by column chromatography on silica gel eluting with 8:2 petroleum ether 60–80°C–EtOAc. Yield: 61%; $n_D^{20} +$ 0.05:1.638. *Anal.* ($C_{17}H_{23}NO$) C, H, N; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 0.96$ (3H, t, $J = 7.32$), 1.03 (3H, t, $J = 7.35$), 1.46 (2H, m), 1.59 (2H, m), 1.79 (2H, m), 1.89 (2H, m), 2.97 (2H, t, $J = 6.01$), 4.17 (2H, t, $J = 6.05$), 6.72 (1H, d, $J = 7.42$), 7.24 (1H, d, $J = 7.54$), 7.65 (2H, m), 8.41 (1H, d, 7.57).

5.1.5. 2-Butyl-5-quinolinol (8)

A mixture of 5-butoxy-2-butylquinoline (0.204 g, 0.79 mmol) in 48% aqueous hydrobromic acid (10 ml, 59 mmol) was refluxed for 32 h. After cooling and the addition of water (30 ml), the solution was neutralized with dilute NH_4OH and extracted with ethyl acetate (3×30 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography on silica gel eluting with 7:3 petroleum ether 60–80°C–EtOAc and crystallized from ethyl acetate–petroleum ether 60–80°C. Yield: 84%; m.p. 150–152°C. *Anal.* ($C_{13}H_{15}NO$) C, H, N; ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 0.95$ (3H, t, $J = 7.31$), 1.48 (2H, m), 1.81 (2H, m), 3.00 (2H, $J = 7.74$), 6.82 (1H, d, $J = 7.42$), 7.35 (1H, d, $J = 7.52$), 7.42 (1H, t, $J = 7.44$), 7.68 (1H, d, $J = 7.54$), 8.55 (1H, d, $J = 7.43$).

*5.1.6. 2-Butyl-1,2,3,4-tetrahydro-5-quinolinol hydrochloride (**3**)*

A mixture of 2-butyl-5-quinolinol (0.126 g, 0.63 mmol), pyridine:borane (0.25 ml, 2.45 mmol) and AcOH (1 ml) was stirred for 36 h at r.t. After the addition of water (30 ml) and the neutralization with dilute NH_4OH, the mixture was extracted with EtOAc (3×15 ml). The organic layers dried on anhydrous Na_2SO_4 were evaporated under reduced pressure. The addition of 10% HCl to the oily residue to decompose excess pyridine–borane afforded a solid product, which was collected by filtration and crystallized from MeOH–acetone. Yield: 63%; m.p. 210–211°C. *Anal.* ($C_{13}H_{20}ClNO$) C, H, N; ^1H NMR (200 MHz, DMSO-d_6, ppm): $\delta = 0.72$ (3H, t, $J = 7.26$), 1.25 (4H, m), 1.62 (3H, m), 2.17 (1H, m), 2.51 (1H, m), 2.72 (1H, m), 3.32 (1H, m), 6.65 (1H, d, $J = 7.39$), 6.72 (1H, d, $J = 7.49$), 7.08 (1H, t, 7.54).

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