RESEARCH PAPER

Accepted 19 March 1999
Received 5 October 1998
Indian J. Pharm. Sci. 1999, 61 (3) 158-161

Synthesis and Evaluation of Antiinflammatory Activity of Ibuprofen Analogs

A. RAJASEKARAN*, P. SIVAKUMAR AND B. JAYAKAR
Periyar College of Pharmaceutical Sciences for Girls, Trichy-21

N-hydroxy methyl derivative of 2(4-isobutyl phenyl) propionamide was synthesised and condensed with seven different active hydrogen containing compounds (antipyrine, pyrrolidine, piperidine, phthalimide, morpholine, piperazine and hydrazine). These compounds were characterised by their analytical and spectral data. The antiinflammatory activity of the synthesised compounds was evaluated by carrageenan-induced rat paw oedema method and the compounds with pyrrolidine, phthalimide and hydrazine showed potent antiinflammatory activity.

Ibuprofen, chemically 2(4-isobutyl phenyl) propionic acid (I) is a well known non steroidal antiinflammtory drug[1]. As with other non steroidal antiinflammatory drugs, this drug also suffers from gastrointestinal complications ranging from mild dyspesia, gastric discomfort to gastric bleeding[2-5]. The gastric irritation and other gastrointestinal disturbances are mainly due to the presence of free carboxylic acid group[6]. Hence, efforts have been made to synthesise derivatives of ibuprofen by blocking the carboxylic acid moiety to have better pharmacological action with minimum side effects.

EXPERIMENTAL

All melting points were determined by open capillary method and are uncorrected. The purity of the compounds were ascertained by TLC on silica gel G plates of 0.25 mm thickness using the solvent system; ethylacetate:methanol:strong ammonia solution(detecting agent-5% ferric chloride solution). Ultraviolet spectral measurements were performed with a Elico SL 159 single beam spectrophotometer. IR spectra were taken using the KBr disc technique on a Perkin Elmer-6000 Fourier transform spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were obtained using Joel 90 MHZ spectrophotometer with TMS as internal standard. Ibuprofen was a gift sample from Pharm Products Ltd, Thanjavur. All other chemicals used were of analytical grade.

*For Correspondence

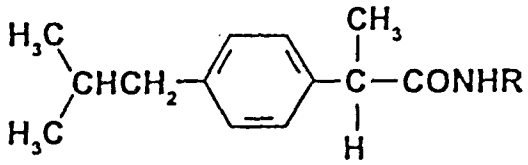
2-(4-Isobutyl Phenyl) Propionyl Chloride Ia

Ibuprofen (0.1 mol) was placed in a 500 ml round bottomed flask fitted with a reflux condenser and a guard tube and 100 ml of redistilled thionyl chloride was added and refluxed for 1 h on a heating mantle at 70-80°. Excess thionyl chloride was then distilled off. The residue left in the flask was the acid chloride. IR spectra of Ia showed absorption band (in Cm^{-1}) at 1785 (C=O) and 1611 (C=C), while ^{1}H NMR of Ia revealed the presence of signals (in ppm) at δ 0.9 (6H, d, $(CH_3)_2$), 1.48 (3H, d, CH_3), 1.8 (1H, m, $(CH_3)_2$), 2.45 (2H, d, CH_2), 3.7 (1H, q, CH) and 7 (4H, m, aromatic protons).

2-(4-Isobutyl Phenyl) Propionamide Ib

The acid chloride was added dropwise with stirring to concentrated ammonia solution kept in a beaker surrounded by freezing mixture and allowed to stand for about half an hour. The amide which separated out was filtered using the pump and the product was recrystallised from 50% (v/v) ethanol and dried. IR spectra of Ib showed absorption band (in Cm^{-1}) at 3358 (NH), 1651 (C=O), 1501 (C=C) and 1390 (C-N-C), while ^{1}H NMR of Ia revealed the presence of signals (in ppm) at δ 0.9 (6H, d, $(CH_3)_2$), 1.48 (3H, d, CH_3), 1.8 (1H, m, $(CH_3)_2$), 2.45 (2H, d, CH_2), 3.7 (1H, q, CH), 6.3 (2H, s, NH_2) and 7 (4H, m, aromatic protons).

Table I - N-substituted 2-(4-Isobutyl Phenyl) Propionyl derivatives



Compound	Molecular formula	Melting Point	Percentage Yield	Rf Value
Ib	$C_{13}H_{19}NO$	101-104	60.9	0.830
Ic	$C_{14}H_{23}NO_2$	106-110	25.5	0.958
II	$C_{25}H_{31}N_3O_2$	105-110	72.1	0.953
III	$C_{18}H_{28}N_2O$	90-93	67.5	0.892
IV	$C_{19}H_{30}N_2O$	105-112	64.1	0.969
V	$C_2H_{24}NO_3$	102-106	68.6	0.940
VI	$C_{18}H_{28}N_2O_2$	95-98	83.7	0.852
VII	$C_{18}H_{29}N_3O$	90-93	72.6	0.920
VIII	$C_{14}H_{23}N_3O$	105-110	80.3	0.880

Ibuprofen (I); Ibuprofen acid chloride (Ia); R-Hydrogen (Ib); Hydroxy methyl (Ic); 2,3 dimethyl 1-phenyl 5-pyrazolone methyl (II); pyrrolidino methyl (III); piperidino methyl (IV); phthalimido methyl (v); morpholino methyl (VI); piperazino methyl (VII)I hydrazino methyl (VIII).

Compound Ib and IC were recrystallised from 50% ethanol, where as compounds II to VIII were recrystallised from dimethyl formamide.

Satisfactory elemental (C, H, N) analysis were obtained for all the compounds.

2-(4-Isobutyl Phenyl) N-hydroxy methyl Propionamide Ic[9]

2-(4-Isobutyl Phenyl) Propionamide (0.1 mol), 5 g of paraformaldehyde and 10 ml of potassium carbonate solution (20% w/v) were taken in a round bottom flask and refluxed for an hour. The contents were cooled and kept in a refrigerator overnight. The crystals of the N-hydroxy methyl compound which separated out were washed with distilled water to remove potassium carbonate and excess paraformaldehyde. The product was recrystallised from ethanol and dried. IR spectra of IC showed absorption band (in cm^{-1}) at 3600-3200 (OH, NH), 1658 (C=O), 1511(C=C) and 1390 (C-N-C), while ^1H NMR of Ia revealed the presence of signals (in ppm) at δ 0.9 (6H, d, $(CH_3)_2$), 1.48 (3H, d, CH_3), 1.8 (1H, m, $(CH_3)_2$), 2.4 (2H, d, CH_2, CH_2), 2.8 (1H, d, NH), 3.5 (1H, m, OH), 3.7 (1H, q, CH) and 7 (4H, m, aromatic protons).

Synthesis of Derivatives II-VIII[10]

The active hydrogen containing compounds such as antipyrine, pyrrolidine, piperidine, phthalimide,morpholine, piperazine and hydrazine (0.1 mol) were dissolved in about 50 ml concentrated sulphuric acid (A.R.). N-hydroxy methyl derivative of ibuprofen (0.1 mol) was then added and the reaction mixture was left at room temperature for 48 h. The mixture was then poured on to crushed ice. The product which separates out was washed with ethanol and then with distilled water. The products were purified by dissolving in minimum quantity of dimethylformamide and adding distilled water slowly to precipitate the compounds.

Table II - Antiinflammatory and Ulcerogenic activity of synthesised compounds

Compound	Antiinflammatory activity	Ulcerogenic activity	
	Difference in paw volume (ml) Mean±S.E	% inhibition	Ulcer index
Control	0.06±0.0063	—	—
I	0.02±0.0063	66.7	13.8±1.2
II	0.02±0.0063	66.7	15.4±1.0
III	0.01±0.00387*	83.4	15.6±1.8
IV	0.02±0.00816	66.7	10.2±0.9
V	0.01±0.006*	83.4	15.0±1.2
VI	0.02±0.0142	66.7	14.6±1.3
VII	0.02±0.00186	66.7	15.8±1.2
VIII	0.01±0.00186*	83.4	10.4±1.2

$P<0.001$ Vs control

IR spectra of all the compounds II-VIII showed characteristic absorption band (in Cm^{-1}) at 2275 (NH), 2960.1 (CH), 1650 (C=O), 1585 (C=C) and 1390 (C-N-C str) confirming the structures. ^1H NMR spectra of all synthesised compounds II-VIII exhibited proton signals (in ppm) at δ 0.9 (6H, d, $(CH_3)_2$), 1.48 (3H, d, CH_3), 1.8 (1H, m, CH), 2.45 (4H, d, CH_2, CH_2), 3.7 (1H, q, CH) and 7 (4H, m, aromatic protons).

In addition to the above signals, compound **II** exhibited proton signals at δ 0.8 (3H,s, CH_3) 2.8 (3H, s, NCH_3), compound **III** at δ 3 (8H, s, N $(CH_2)_4$), compound **IV** at δ 3.1 (10H, s, N $(CH_2)_5$), compound **V** at δ 7.2 (4H, m, aromatic protons), compound **VI** at δ 4 (8H, s, N $(CH_2)_2$), **VII** at δ 3.4 (8H, s, N $(CH_2)_2$) and compound **VIII** at 6.3 (2H, s, NH_2).

Antiinflammatory activity

Carrageenan-induced hind paw oedema method[7] was used. Albino rats of either sex (150-200 g) were taken in groups of six animals each. The synthesised compounds were suspended in 0.5% (w/v) hydroxy methyl cellulose in distilled water. The compounds (25 mg/kg) were administered orally. For control 0.5% (w/v) hydroxy methyl cellulose in distilled water was given orally (5 ml/kg). Ibuprofen (25 mg/kg) was used as a reference drug. Thirty minutes after the drug administration 0.1 ml of 1% (w/v) carrageenan solution was injected in the plantar region of the left hind paw of the animals. The inflammation was determined plethysmometically 3 h after phlogogenic agent injection and compared with that of the control. The data was analysed using students "t" test and the level of significance was defined at $P<0.001$. The results are given in table 2.

Ulcerogenic activity

Albino rats of either sex (150-200 g) were taken into groups of six each. They were fasted for 36 h. Control and synthesised compounds (**II-VIII**) were given orally (75 mg/kg) as a suspension in 0.5% (w/v) of hydroxy methyl cellulose. Six h after the administration of the compounds, the rats were sacrifised and the stomach excised out. The stomach was opened along with the greater curvature and mounted on a board. It was examined for the severity of ulcer and the ulcer scores was ascertained by Gupta et al.[8] method. The results are given in table 2.

RESULTS AND DISCUSSION

A perusal of table-2 shows compounds III, V and VIII possess highly potent antiinflammatory effect, where the antiinflammatory activity of other synthesised compounds II, IV, VI and VII are comparable to Ibuprofen. It is also evident from the table-2 that the compounds IV and VIII produced less ulceration when compared to the parent drug Ibuprofen. The other derivatives did not produced any marked reduction in ulcerogenic action. The present investigation showed that the chemical modification of 2(4-isobutyl phenyl) propionic acid with pyrrolidine, phthalimide and hydrazine increases the antiinflammatory activity, where decrease in ulcerogenic activity was observed only for the hydrazine substituted compound.

REFERENCES

1. Busson, M.J., **J. Int. Med. Res.,** 1986, 14, 54.
2. Beck, W.S., Schnineder, B., Nuernverg, K. and Brune, K., **Arch. Toxicol.,** 1990, 64, 210.
3. Garson, J.L., **J. Rheumatol.,** 1988, 15, 24.
4. Coler, L.S., Fries, J.F., Krainer, R.G. and Roth, S.H., **Am. J. Med.,** 1985, 74, 820.
5. Dandonna, P. and Geremy, J.Y., **Drugs.,** 1990, 40, 16.
6. Todd, P.A. and Berestord, R., **Drugs,** 1986, 32, 509.
7. Winter, C.A., Rosley, E.A. and Nuss, G.W., **Proc. Soc. Exp. Biol.,** New york, 1962, 111, 544.
8. Gupta, M.B., Nath, R., Gupta, G.P. and Bhargava, K.P., **Clin. Exp. Pharm. Physio.,** 1985, 12, 61.
9. Singh, G.B., Dixit, B.B. and Vijjan, V.K., **J. Ind. Chem. Soc.,** 1968, 45, 262.
10. Tscherniac, J., German Patent, 1902, 134979; **J. Ind. Chem. Soc.** 1968, 45, 263.

ERRATUM

The title of the Research Paper published in March-April 1999 issue, 'Cenftriaxone-induced Lipid Peroxidation and its Inhibition with Various Antioxidants' by K. Roy, A.U.Dey and Chandana Sengupta, should read as :

'Ceftriaxone-induced Lipid Peroxidation and Its Inhibition with Various Antioxidants'. The typographical error is regretted.

Editor