Synthesis and analgesic–anti-inflammatory activity of certain fluorinated cinchophen analogues*

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(Received September 25, 1991; accepted February 11, 1992)

Abstract

The synthesis of certain fluorinated cinchophen analogues has been achieved. All compounds show analgesic and apparent anti-inflammatory activity comparable to cinchophen and indomethacin but they are toxic at, or close, to the 'active' doses. The structure–activity relationship is discussed.

Introduction

A wide variety of non-steroidal anti-inflammatory drugs are used for the treatment of arthritic diseases [1, 2]. Besides aspirin, phenylbutazone and indomethacin, new compounds have been introduced such as fenoprofen [3], indoprofen [4] and the oxicams [5]. The major mechanism underlying the anti-inflammatory activity is that of inhibition of prostaglandin synthesis [6, 7]. Despite the therapeutic effectiveness of these drugs, serious adverse effects are liable to occur with most of them, e.g. gastrointestinal bleeding with aspirin [8, 9] and gastric and duodenal ulceration with indomethacin [10, 11]. Hepatic injury has been reported to occur in patients receiving long-term salicylate therapy [12–14]. Phenylbutazone is no longer used in therapy because it may suppress the bone marrow if administered for longer than a few days [15].

Cinchophen, 2-phenyl-4-quinolinecarboxylic acid (**I**) was one of the early introduced compounds for the treatment of gout [16]. It possesses analgesic antipyretic, anti-inflammatory and uricosuric activity [17–19], but was found to produce hepatic damage resembling acute viral hepatitis [11, 20].

*Presented before the 13th International Symposium on Fluorine Chemistry, Bochum, Germany, 1–6 September 1991: *J. Fluorine Chem., 54* (1991) 201.

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0022-1139/92/$5.00

The objective of this work was to synthesize new fluorinated cinchophen analogues that might have potent analgesic and/or anti-inflammatory activity but be devoid of, or have mild side-effects, at doses close to the active dose.

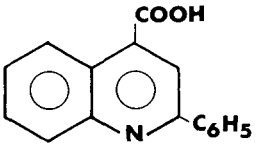
Experimental

General

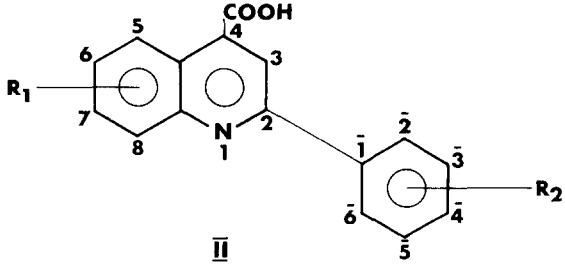
Melting points were determined on a Mettler FP51 instrument and are reported uncorrected. IR data were determined on a Perkin Elmer 567 spectrophotometer from samples prepared as KBr disks. PMR spectra were recorded on Varian T-60 spectrometer at 60 MHz using tetramethylsilane as an internal standard. UV spectra were determined on a Varian DMS-90 instrument; the compounds were dissolved in 5% ethanol. Mass spectra were determined using a Ribermag R-10 quadrupole spectrometer in the EI mode with samples introduced directly into the ion source. The spectra data for all compounds were consistent with the assigned structures. The elemental analyses for C, H and N were within $\pm 0.4\%$ of the theoretical values and were undertaken at Janssen Pharmaceutica, Beerse, Belgium (see Table 1).

Chemistry

Eleven compounds having the general formula **II** (see Table 1) were synthesized by refluxing the appropriate aniline derivative, pyruvic acid and benzaldehyde derivative in absolute ethanol in the presence of air as oxidizing agent as required for the conversion of the starting materials to the aromatic level of oxidation of the products. The solvent was then evaporated and the residue purified and crystallized from aqueous ethanol [20].



I



II

Preparation of substituted 2-phenyl-4-quinolinecarboxylic acid derivatives (II 1–11)

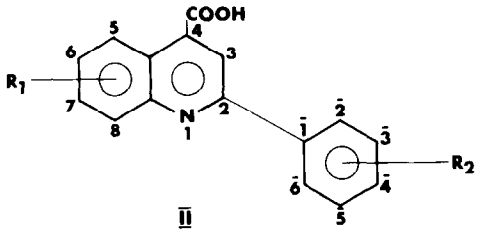
Equimolar amounts (0.01 mol) of pyruvic acid, benzaldehyde derivative and aniline derivative were refluxed for 2 h in 50 ml absolute ethanol. The reaction mixture was cooled, the solvent evaporated under vacuum to dryness, the dark brown solid mass triturated with petroleum ether several times until it became granular, then filtered off and crystallized from aqueous ethanol.

Pharmacology

The analgesic activity was evaluated by a modified Randall–Selitto method [5]. Yeast (5 mg) was injected into the hind paw of male rats. After 3 h

TABLE 1

Fluorinated cinchophen analogues



II

Compound No.	Substituents		Melting point (°C)	Yield (%)	Formula	Analysis					
	R_1	R_2				Calcd.			Found		
						C	H	N	C	H	N
1	8-F	H	161–163	70	$C_{16}H_{10}FNO_2$	71.90	3.77	5.24	70.93	3.71	5.22
2	7-F	H	157–158	72	$C_{16}H_{10}FNO_2$	71.90	3.77	5.24	71.39	3.75	5.19
3	6-F	H	173–174	72	$C_{16}H_{10}FNO_2$	71.90	3.77	5.24	71.63	3.69	5.23
4	8-CF_3	H	211–213	81	$C_{17}H_{10}F_3NO_2$	64.35	3.18	4.42	64.15	3.15	4.43
5	7-CF_3	H	207–208	80	$C_{17}H_{10}F_3NO_2$	64.35	3.18	4.42	64.31	3.09	4.40
6	6-CF_3	H	213–215	69	$C_{17}H_{10}F_3NO_2$	64.35	3.18	4.42	64.23	3.18	4.38
7	H	2′-F	181–183	70	$C_{16}H_{10}FNO_2$	71.90	3.77	5.24	71.87	3.74	5.18
8	H	2′-CF_3	163–165	79	$C_{17}H_{10}F_3NO_2$	64.35	3.18	4.42	64.33	3.14	4.39
9	H	4′-F	149–150	68	$C_{16}H_{10}FNO_2$	71.90	3.77	5.24	71.38	3.66	5.22
10	H	4′-CF_3	170–172	78	$C_{17}H_{10}F_3NO_2$	64.35	3.18	4.42	64.17	3.12	4.38
11	H	3′-CF_3	186–187	70	$C_{17}H_{10}F_3NO_2$	64.35	3.18	4.42	63.96	3.14	4.41

the degree of hyperalgesia was determined by applying a force of increasing magnitude to the hind limb by means of an air-driven plunger and the pain threshold determined.

Compounds under investigation as well as cinchophen were dissolved in the least possible quantities of sodium bicarbonate and the pH adjusted to about 7.0. Drugs to be tested were administered orally 2 h after yeast injection in a dose of 30 mg kg^{-1} (control rats were given saline) and measurements of the pain threshold were undertaken 1 h later.

The anti-inflammatory activity was evaluated by the cotton-pellet granuloma method [21]. Male rats weighing 180–200 g were anesthetized with ether and a cotton pellet was implanted under sterile conditions into the subcutaneous tissues of axillae of the rats. The tested compounds were dissolved in the minimum quantities of sodium bicarbonate solution and the pH adjusted to about 7.0. Drugs were given orally to groups of 10 rats in a dose of 0.50 mg kg^{-1} daily for 7 d starting 24 h after implantation of the cotton pellets. Control animals were given saline. One day after the last dose, the animals were killed with ether, the granulomas were removed, freed from extraneous tissues and dried in a hot air oven for 24 h at 60 °C. The granulomas were then individually weighed.

Determination of gastrointestinal lesions was made by sacrificing the rats 3 h after the analgesic dose (acute effect) and soon after the removal of granuloma chronic effect. Stomach and duodenum were isolated and examined thoroughly for ulceration or lesion.

Results and discussion

All compounds showed analgesic activity. Substituted quinoline derivatives (compounds 1–6) exhibited about double the activity of cinchophen on a weight basis, while substituted phenyl (compounds 7–11) were less active. The enhancement of the biological activity of the fluorinated analogues (compounds 1–6) may be due to an increase in the lipophilicity of these derivatives, as well as other physico-chemical properties, and to factors presented in a recently published review by Aboul-Enein [22].

Fluorine substitution on the phenyl ring of the quinoline ring system (compounds 1–6) improved the analgesic activity contrary to fluorine substitution on the phenyl group at C2 (compounds 7–11). This improvement in biological activity may be due to better binding of compounds 1–6 to the analgesic receptor site.

As regards the anti-inflammatory activity, most of the synthesized compounds possessed activity comparable to that of indomethacin. However, compounds 2 and 5 (Table 1) were more potent. The average granuloma weight was 12.4 ± 0.3 mg and 14.1 ± 0.4 mg for compounds 2 and 5, respectively, while that of indomethacin-treated animals was 16.3 ± 0.2 mg.

Postmortem examination revealed no ulceration in the stomach and duodenum of animals used in analgesic tests, i.e. no acute ulceration happened,

but prominent inflammation and lesions were found in the stomach and duodenum of animals used in the anti-inflammatory tests. This was not the case in indomethacin-treated animals.

In summary, the results of the present study indicate that the introduction of a fluorine or trifluoromethyl group into the quinoline ring of cinchophen appears to potentiate the biological activity of the parent drug, while substitution in the phenyl ring decreases the activity. However, severe intestinal inflammatory effects may mediate most of the anti-granuloma response, and, at best, the very small therapeutic ratios for the analgesic effects leaves this work still far short of its objective.

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