SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME 1-ARYL-1,4-DIHYDRO-4-OXOCINNOLINE-3-CARBOXYLIC ACIDS

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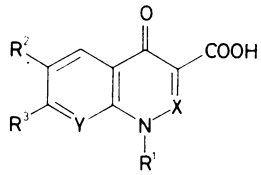
The coupling reaction of corresponding benzene diazonium chlorides with benzoyl acetates *IIIa*–*IIIc* yielded intermediates *IVa*–*IVe*. Their intramolecular nucleophilic cyclization provided 1-aryl-1,4-dihydro-4-oxocinnoline-3-carboxylates *Va*–*Ve*. Compounds *Va*, *Vb*, *Vd*, and *Ve* were hydrolyzed to acids *VIa*–*VIc*. Treatment of these acids with the respective cyclic amines yielded compounds *VIIa*–*VIIg* which were converted to their hydrochlorides. All compounds prepared were tested for their antimicrobial activity in vitro.

Since the discovery of nalidixic acid (*Ia*) as a useful chemotherapeutic agent a large number of its analogs have been studied[1–3]. Oxolinic acid (*Ib*) and its 2-azaanalog cinoxacin (*Ic*) were the first congeners in clinical use. New fluoroquinolones with the increased activity against a wide spectrum of bacteria, e.g. enoxacin (*Id*), norfloxacin (*Ie*), pefloxacin (*If*), and ciprofloxacin (*Ig*), have assumed an important place in antibacterial chemotherapy[2–5]. Similar 2-azaanalogs have also been claimed to be highly active[6,7]. Some very potent 1-aryl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids, e.g. difloxacin (*IIa*), A-56620 (*IIb*), and temafloxacin (*IIc*) have proved to be useful, especially for their activity against anaerobes[8–11]. But no respective cinnoline 1-aryl derivatives have been reported yet. In this paper synthesis and antibacterial activity of such 1-aryl-1,4-dihydro-4-oxocinnoline-3-carboxylic acids is described.

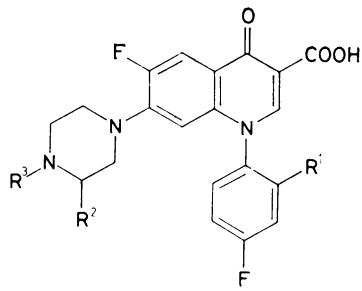
Our synthetic pathway started from benzoylacetates *IIIa*–*IIIc*. Compound *IIIb* was prepared by the known method[12] from 2,4-dichloro-5-fluorobenzoylchloride and diethyl malonate. Similar methyl benzoylacetates *IIIa* and *IIIc* were prepared by the reaction of corresponding acetophenones with magnesium methyl carbonate[13] followed by the acid-catalyzed esterification of primarily formed benzoylacetic acids. For *IIIa* the presence of both enol and keto forms were observed by ^{1}H NMR spectroscopy. In deuterated nitromethane the keto form predominates over the enol form in a 4 : 1 ratio and in deuterated benzene the ratio is quite opposite.

The coupling reaction of corresponding diazonium chlorides with benzoylacetates *IIIa*–*IIIc* provided intermediates *IVa*–*IVe* in good yields. The intramolecular nucleophilic cyclization reaction of *IVa*–*IVe* leading to *Va*–*Ve* was accomplished

by either sodium hydride in N,N-dimethylformamide or potassium carbonate and 18-crown-6 in the same solvent. The latter method has been described for similar cyclization reaction where the leaving group was more reactive fluorine atom[14].



Ia, X = CH ; Y = N ; $R^1 = C_2H_5$; R^2 = H ; $R^3 = CH_3$
Ib, X = Y = CH ; $R^1 = C_2H_5$; $R^2 + R^3$ = O—CH_2—O
Ic, X = N ; Y = CH ; $R^1 = C_2H_5$; $R^2 + R^3$ = O—CH_2—O
Id, X = CH ; Y = N ; $R^1 = C_2H_5$; R^2 = F ; R^3 = 1-piperazinyl
Ie, X = Y = CH ; $R^1 = C_2H_5$; R^2 = F ; R^3 = 1-piperazinyl
If, X = Y = CH ; $R^1 = C_2H_5$; R^2 = F ; R^3 = 4-methyl-1-piperazinyl
Ig, X = Y = CH ; R^1 = cyclopropyl ; R^2 = F ; R^3 = 1-piperazinyl

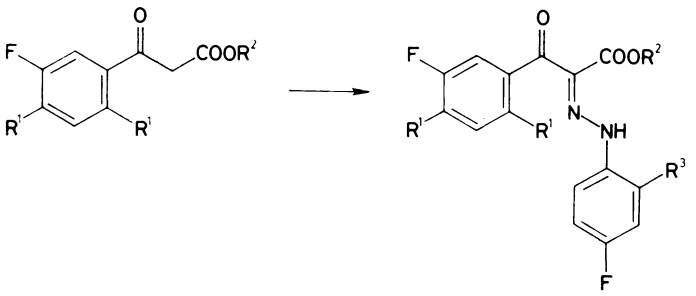


IIa, $R^1 = R^2$ = H ; $R^3 = CH_3$
IIb, $R^1 = R^2 = R^3$ = H
IIc, R^1 = F ; $R^2 = CH_3$; R^3 = H

Esters *Va*, *Vb*, *Vd*, and *Ve* were hydrolyzed to acids *VIa*—*VIc* by aqueous-methanolic solution of potassium hydroxide. The same treatment of *Vc* provided a mixture, apparently due to higher reactivity of the C-7 fluorine atom since the presence of a methoxy group was observed by IR spectroscopy.

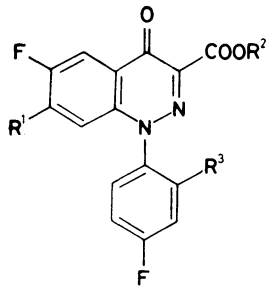
Compounds *VIa*—*VIc* upon a treatment with piperazine or N-methylpiperazine in pyridine yielded compounds *VIIa*—*VIIf*. Similar treatment of *VIc* with 3-ethylaminomethylpyrrolidine[15] yielded *VIIg*. According to the molecular modelling and computer graphics the 3-ethylaminomethylpyrrolidinyl group might mimic the 4-methylpiperazinyl moiety[16] and therefore comparison of antibacterial activity of compounds

having both of these substituents was supposed to be of interest. Since none of the compounds prepared was substantially active no further compounds were prepared.

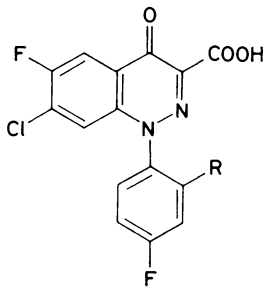


IIIa, R^1 = Cl ; R^2 = CH_3
IIIb, R^1 = Cl ; R^2 = C_2H_5
IIIc, R^1 = F ; R^2 = CH_3

IVa, R^1 = Cl ; R^2 = CH_3 ; R^3 = H
IVb, R^1 = Cl ; R^2 = C_2H_5 ; R^3 = H
IVc, R^1 = F ; R^2 = CH_3 ; R^3 = H
IVd, R^1 = Cl ; R^2 = C_2H_5 ; R^3 = F
IVe, R^1 = Cl ; R^2 = CH_3 ; R^3 = CH_3



Va, R^1 = Cl ; R^2 = CH_3 ; R^3 = H
Vb, R^1 = Cl ; R^2 = C_2H_5 ; R^3 = H
Vc, R^1 = F ; R^2 = CH_3 ; R^3 = H
Vd, R^1 = Cl ; R^2 = C_2H_5 ; R^3 = F
Ve, R^1 = Cl ; R^2 = R^3 = CH_3

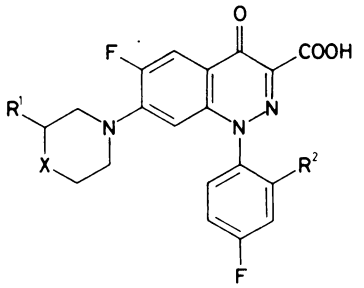


VIa, R = H
VIb, R = F
VIc, R = CH_3

Because of low water-solubility of acids *VIIa*–*VIIg* and their alkaline salts, their water-soluble hydrochlorides were prepared by usual way. Both the 7-(substituted amino) acids *VIIa*–*VIIg* and their hydrochlorides tend to form hydrates.

All prepared compounds were tested for their antibacterial activity in vitro at the Department of Microbiology of the Institute (Dr V. Holá, Head). The minimum inhibitory concentrations (MIC) in mg/l are given unless they exceed 128 mg/l: *Staphylococcus aureus*, *Ve* 64, *VIc* 64, *VIId* 64, *VIIg* 32; *Streptococcus pyogenes*,

VIb 64, *VIId* 64, *VIId*.HCl 64, *VIIg*.HCl 64; *Escherichia coli*, *VIIb* 64, *VIIb*.HCl 64; *Proteus vulgaris*, *VIIb* 32, *VIIb*.HCl 16; *Pseudomonas aeruginosa*, *VIId* 64.



VII a, X = NH ; $R^1 = R^2 = H$
VII b, X = NCH_3 ; $R^1 = R^2 = H$
VII c, X = NH ; $R^1 = H$; $R^2 = F$
VII d, X = NCH_3 ; $R^1 = H$; $R^2 = F$
VII e, X = NH ; $R^1 = H$; $R^2 = CH_3$
VII f, X = NCH_3 ; $R^1 = H$; $R^2 = CH_3$
VII g, X = single bond ; $R^1 = C_2H_5NHCH_2$; $R^2 = CH_3$

EXPERIMENTAL

The melting points were determined on a Kofler block and were not corrected. IR spectra were taken on a Unicam SP-2006 spectrometer in KBr pellets; wavenumbers are given in cm^{-1}. UV spectra were taken on a Unicam PU 8800 spectrophotometer in ethanol, molar absorption coefficients (ε) are given in $m^2\ mol^{-1}$, wavelengths (λ) in nm. Mass spectra were measured on MCH 1320 and MAT 44 S spectrometers. ^1H NMR spectra were measured on an apparaturs BS-567 A (TESLA Brno) 100 MHz, compound *IIIa* on an apparatus BS-487 (TESLA Brno) at 80 MHz, with tetramethylsilane as internal standard, unless otherwise stated. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz.

Methyl 2,4-Dichloro-5-fluorobenzoylacetate (*IIIa*)

A mixture of 2,4-dichloro-5-fluoroacetophenone[17] (5 g, 24 mmol) and 2·35M solution of methyl magnesium carbonate (41 ml) in N,N-dimethylformamide was stirred at 110°C for 1 h. Then the reaction mixture was cooled to 10°C and carefully poured into the mixture of ice and water (400 g) and concentrated hydrochloric acid (20 ml). When the evolution of carbon dioxide ceased, the separated solid was filtered off, washed with cold water and dried. This crude 2,4-dichloro-5-fluorobenzoylacetic acid (4·8 g) was without further purification dissolved in 3% methanolic solution of hydrogen chloride (20 ml) at 40°C and the mixture was left to stand at room temperature for 20 h. The separated crystals were filtered off, washed with cold methanol (2 ml); yield 2·0 g (31%), m.p. 82—84°C. The filtrate was taken to dryness, the residue was crystallized from methanol yielding another crop of crystals of the quality (m.p., TLC); 0·56 g (9%). For $C_{10}H_7Cl_2FO_3$ (265·1) calculated: 45·31% C, 2·66% H, 26·75% Cl, 7·17% F; found: 45·41% C, 2·65% H, 26·69% Cl, 7·24% F. ^1H NMR spectrum (CD_3NO_2): 3·68 s, 2·4 H (keto CH_3); 3·78 s,

0·6 H (enol CH_3); 4·00 s, 1·6 H (keto CH_2); 5·58 s, 0·2 H (enol CH); 7·52 m, 2 H (H-3, H-6); 12·15 bs, 0·2 H (enol OH). ^{1}H NMR spectrum (C_6D_6): 3·22 s, 0·6 H (keto CH_3); 3·28 s, 2·4 H (enol CH_3); 3·46 s, 0·4 H (keto CH_2); 5·48 s, 0·8 H (enol CH); 6·82 m, 2 H (H-3, H-6); 7·12 bs, 0·8 H (enol OH).

Methyl 2,4,5-Trifluorobenzoylacetate (*IIIc*)

A mixture of 2,4,5-trifluoroacetophenone (5 g, 29 mmol) and 2·5M solution of methyl magnesium carbonate in N,N-dimethylformamide (49 ml) was stirred at 125°C for 2 h. The mixture was cooled to 50°C and under reduced pressure was concentrated to a half of its original volume. Then the mixture was poured into a solution of dry hydrogen chloride (4%) in methanol (150 ml), the formed solution was stirred at 40°C for 4 h and left standing at room temperature for 20 h. The solution was concentrated to 50 ml and then poured onto ice (250 g). The mixture was extracted by dichloromethane (100 ml) and the extract was washed with 5% solution of sodium hydrogen carbonate (20 ml) and water (20 ml). After drying over sodium sulfate the solution was evaporated and crystallized from methanol; yield 1·8 g (27%), m.p. 61–64°C. For $C_{10}H_7F_3O_3$ (232·2) calculated: 51·73% C, 3·04% H, 24·55% F; found: 51·66% C, 3·14% H, 24·36% F.

Methyl 2,4-Dichloro-5-fluoro-α-(4-fluorophenylhydrazono)benzoylacetate (*IVa*)

A solution of sodium nitrite (0·21 g, 3 mmol) in water (2 ml) was added dropwise during 30 min to a stirred solution of 4-fluoroaniline (0·34 g, 3 mmol) in concentrated hydrochloric acid (1 ml) cooled to 0°C in an outher bath. The solution was stirred for additional 30 min at this temperature and then was added dropwise during 30 min to a stirred supspension of benzoylacetate *IIIa* (0.80 g, 3 mmol) and potassium acetate (0·9 g, 9 mmol) in methanol (10 ml) and dioxane (5 ml) at 0°C. The reaction mixture was stirred at room temperature for 2 h and then extracted with dichloromethane, the extract was washed with water and dried over sodium sulfate. The solution was evaporated under reduced pressure yielding 1·12 g (97%) of *IVa* (brown oil) which was used for the further reaction without purification.

Ethyl 2,4-Dichloro-5-fluoro-α-(4-fluorophenylhydrazono)benzoylacetate (*IVb*)

This was prepared from benzoylacetate *IIIb* (ref.[12]), adhering to the procedure described for the preparation of *IVa*; yield 1·15 g (96%), brown oil which was used for the further reaction without purification.

Methyl 2,4,5-Trifluoro-α-(4-fluorophenylhydrazono)benzoylacetate (*IVc*)

A solution of the diazonium chloride prepared from 4-fluoroaniline (0·49 g, 4·3 mmol) was added dropwise during 30 min to a solution of benzoylacetate *IIIc* (1·0 g, 4·3 mmol) and potassium acetate (1·25 g, 13 mmol) in a mixture of methanol (6 ml), dioxane (6 ml) and water (3 ml) and the mixture was stirred at 5°C for 30 min and at room temperature for 2 h. The yellow precipitate was filtered off, washed with water and crystallized from methanol; yield 1·43 g (93%), m.p. 112–117°C. For $C_{10}H_{10}F_4N_2O_3$ (354·3) calculated: 54·25% C, 2·85% H, 21·45% F, 7·91% N; found: 53·85% C, 2·87% H, 21·29% F, 8·11% N. UV spectrum, λ_{max} (log ε): 361 (3·29), 278 (2·84), 239 (3·06), 202 (3·16).

Ethyl 2,4-Dichloro-5-fluoro-α-(2,4-difluorophenylhydrazono)-benzoylacetate (*IVd*)

This was prepared from benzoylacetate *IIIb* and 2,4-difluoroaniline according to the procedure described for the preparation of *IVc*; yield 80%, m.p. 86–89°C (ethanol). For $C_{17}H_{11}Cl_2F_3N_2O_3$

(419·2) calculated: 48·71% C, 2·64% H, 16·92% Cl, 13·60% F, 6·68% N; found: 48·61% C, 2·65% H, 16·97% Cl, 13·36% F, 6·66% N. UV spectrum, λ_{max} (log ε): 350 (3·29), 202 (3·43).

Methyl 2,4-Dichloro-5-fluoro-α-(4-fluoro-2-methylphenylhydrazono)-benzoylacetate (*IVe*)

This was prepared from benzoylacetate *IIIa* and 4-fluoro-2-methylaniline according to the procedure described for the preparation of *IVc*; yield 73%, m.p. 140—144°C (methanol). For $C_{17}H_{12}Cl_2F_2N_2O_3$ (401·2) calculated: 50·89% C, 3·01% H, 17·67% Cl, 9·47% F, 6·98% N; found: 51·01% C, 3·03% H, 17·84% Cl, 9·64% F, 7·65% N. UV spectrum, λ_{max} (log ε): 368 (3·27) 284 (2·38), 243 (3·04).

General Procedure for Preparation of *Va—Ve*

A mixture of the respective phenylhydrazonobenzoylacetate *IVa—IVe* (20 mmol), anhydrous potassium carbonate (2·8 g, 20 mmol), 18-crown-6 (40 mg), and N,N-dimethylformamide (60 ml) was stirred at 100°C for 1 h. The reaction mixture was cooled down and poured onto ice (150 g), the formed precipitate was filtered off, dried and crystallized.

Methyl 7-chloro-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxocinnoline-3-carboxylate (Va). Yield 79%, m.p. 199—201°C (methanol). For $C_{16}H_9ClF_2N_2O_3$ (350·7) calculated: 54·80% C, 2·59% H 10·11% Cl, 10·83% F, 7·99% N; found: 54·42% C, 2·67% H, 10·09% Cl, 10·71% F, 7·80% N. IR spectrum: 1 710 (COO); 1 640 (C=O); 1 610, 1 510, 1 490 (arom. system). UV spectrum, λ_{max} (log ε): 351 (3·14), 269 (3·14), 223 (3·37), 208 (3·37). ^{1}H NMR spectrum ($CDCl_3$): 3·96 s, 3 H (CH_3); 7·20—7·60 m, 5 H (H-8, phenyl H); 8·13 d, 1 H (H-5, J(H-5, F-6) = 9).

Ethyl 7-chloro-6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxocinnoline-3-carboxylate (Vb). Yield 94%, m.p. 196—199°C (ethanol). For $C_{17}H_{11}ClF_2N_2O_3$ (364·7) calculated: 55·98% C, 3·04% H, 9·72% Cl, 10·42% F, 7·68% N; found: 55·88% C, 3·10% H, 9·78% Cl, 10·23% F, 7·50% N. IR spectrum: 1 710 (COO); 1 640 (C=O); 1 610, 1 510, 1 500 (arom. system). UV spectrum, λ_{max} (log ε): 349 (3·14), 257 (3·14), 221 (3·36), 205 (3·38). ^{1}H NMR spectrum ($CDCl_3$): 1·20 t, 3 H (CH_3, J = 7); 4·44 q, 2 H (CH_2, J = 7); 7·20—7·60 m, 5 H (H-8, phenyl H); 8·15 d, 1 H (H-5, J(H-5, F-6) = 9·5).

Methyl 6,7-difluoro-1-(4-fluorophenyl)-1,4-dihydro-4-oxocinnoline-3-carboxylate (Vc). Yield 82%, m.p. 172—174°C (methanol). For $C_{16}H_9F_3N_2O_3$ (334·3) calculated: 57·49% C, 2·71% H, 17·05% F, 8·38% N; found: 57·50% C, 2·79% H, 16·49% F, 8·15% N. IR spectrum: 1 715 (COO); 1 640 (C=O); 1 620, 1 585, 1 510 (arom. system). UV spectrum, λ_{max} (log ε): 341 (3·15), 249 (3·09), 206 (3·37). ^{1}H NMR spectrum ($CDCl_3$): 3·99 s, 3 H (CH_3); 7·20—7·60 m, 4 H (phenyl H); 7·00 dd, 1 H (H-8, J(H-8, F-7) = 10; J(H-8, F-6) = 6); 8·22 dd, 1 H (H-5, J(H-5, F-6) = 10; J(H-5, F-7) = 8).

Ethyl 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxocinnoline-3-carboxylate (Vd). Yield 87%, m.p. 237—240°C (methanol). For $C_{17}H_{10}ClF_3N_2O_3$ (382·7) calculated: 53·35% C, 2·63% H, 9·26% Cl, 14·89% F, 7·32% N; found: 53·11% C, 2·69% H, 9·45% Cl, 14·99% F, 7·22% N. ^{1}H NMR spectrum ($CDCl_3$): 1·40 t, 3 H (CH_3); 4·44 q, 2 H (CH_2); 7·00—7·60 m, 4 H (H-8, phenyl H); 8·13 d, 1 H (H-5, J(H-5, F-6) = 8).

Methyl 7-chloro-6-fluoro-1-(4-fluoro-2-methylphenyl)-1,4-dihydro-4-oxocinnoline-3-carboxylate (Ve). Yield 91%, m.p. 144—146°C (methanol). For $C_{17}H_{11}ClF_2N_2O_3$ (364·7) calculated: 55·98% C, 3·04% H, 9·72% Cl, 10·42% F, 7·68% N; found: 55·78% C, 3·23% H, 9·64% Cl, 10·40% F, 7·43% N. IR spectrum: 1 725 (COO); 1 640 (C=O); 1 610, 1 590, 1 500 (arom. system). UV spectrum, λ_{max} (log ε): 347 (3·14), 258 (3·11), 210 (3·44), λ_{infl}243 (3·11). ^{1}H NMR

spectrum ($(CD_3)_2SO$, pentadeuterated 3-trimethylsilylpropionic acid): 2·08 s, 3 H (CH_3-2′); 4·86 s, 3 H (CH_3); 7·26 d, 1 H (H-8, J(H-8, F-6) = 5); 7·40 m, 2 H (H-3′, H-5′); 7·70 dd, 1 H (H-6′, J(H-6′, H-5′) = 9); 8·16 d, 1 H (H-5, J(H-5, F-6) = 9).

General Procedure for Preparation of Acids *VIa*—*VIc*

A 1M methanolic solution of potassium hydroxide (25 ml) was added to a stirred suspension of the respective esters *Va*, *Vb*, *Vd*, or *Ve* (15 mmol) in methanol (150 ml) and water (50 ml). The solid was dissolved at 50°C and the solution formed was left to stand at room temperature for 2 h. Then the solution was filtered with a small amount of charcoal, the filtrate was acidified with hydrochloric acid and left to stand overnight in a refrigerator. The separated solid was filtered off and washed with water, dried and crystallized from 95% aqueous methanol.

7-*Chloro*-6-*fluoro*-1-(4-*fluorophenyl*)-1,4-*dihydro*-4-*oxocinnoline*-3-*carboxylic acid* (VIa). Yield 82% from *Va* and 78% from *Vb*, m.p. 288—291°C. For $C_{15}H_7ClF_2N_2O_3$ (336·7) calculated: 53·51% C, 2·10% H, 10·53% Cl, 11·29% F, 8·32% N; found: 53·13% C, 2·11% H, 10·55% Cl, 11·04% F, 8·24% N. IR spectrum: 3 438 (OH); 2 890, 2 660 (COOH); 1 762, 1 739 (C=O); 1 588, 1 508 (arom. system). ^{1}H NMR spectrum ($(CD_3)_2SO$, pentadeuterated 3-trimethylsilylpropionic acid): 7·40—7·90 m, 5 H (H-8, phenyl H); 8·20 d, 1 H (H-5, J(H-5, F-6) = 9·5).

7-*Chloro*-1-(2,4-*difluorophenyl*)-6-*fluoro*-1,4-*dihydro*-4-*oxocinnoline*-3-*carboxylic acid* (VIb). Yield 96%, m.p. 273—276°C. For $C_{15}H_6ClF_3N_2O_3$ (354·7) calculated: 50·80% C, 1·71% H, 10·00% Cl, 16·07% F, 7·90% N; found: 50·55% C, 1·94% H, 10·06% Cl, 15·68% F, 7·73% N. IR spectrum: 3 320 (OH); 1 735 (COOH); 1 615 (C=O); 1 590, 1 510, 1 490 (arom. system). UV spectrum, λ_{max} (log ε): 348 (3·17), 258 (3·16), 245 (3·15), 210 (3·40), λ_{infl} 216 (3·39).

7-*Chloro*-6-*fluoro*-1-(4-*fluoro*-2-*methylphenyl*)-1,4-*dihydro*-4-*oxocinnoline*-3-*carboxylic acid* (VIc). Yield 90%, m.p. 244—246°C. For $C_{16}H_9ClF_2N_2O_3$ (350·7) calculated: 54·80% C, 2·59% H, 10·11% Cl, 10·83% F, 7·99% N; found: 54·59% C, 2·72% H, 10·12% Cl, 10·93% F, 7·82% N, IR spectrum: 3 300 (OH); 1 750 (COOH); 1 600 (C=O); 1 490 (arom. system). UV spectrum, λ_{max} (log ε): 355 (3·11), 257 (3·26), 210 (3·46). ^{1}H NMR spectrum ($(CD_3)_2SO$, pentadeuterated 3-trimethylsilylpropionic acid): 2·09 s, 3 H (CH_3); 7·34 d, 1 H (H-8, J(H-8, F-6) = 6); 7·40—7·60 m, 2 H (H-3′, H-5′); 7·70 dd, 1 H (H-6′, J(H-6′, H-5′) = 9); 8·24 d, 1 H (H-5, J(H-5, F-6) = 9).

General Procedure for Preparation of Acids *VIIa*—*VIIg*

A mixture of the respective acid *VIa*—*VIc* (3 mmol), anhydrous cyclic amine (15 mmol of piperazine for *VIIa*, *VIIc*, *VIIe*; 15 mmol of N-methylpiperazine for *VIIb*, *VIId*, *VIIIf*; 6 mmol of 3-ethylaminomethylpyrrolidine for *VIIg*), and pyridine (30 ml) was stirred at 100°C for 5—25 h. The reaction was monitored by TLC (pre-coated plates Merck Kieselgel 60 F_{254}, chloroform, methanol, acetic acid (80 : 15 : 5)). When no starting acid was present, the mixture was evaporated to dryness under reduced pressure and the residue was triturated with water. The solid portion was filtered off, washed with water and crystallized from aqueous methanol yielding *VIIa*—*VIIg*. Amount of 100 mg of each compound was dissolved in concentrated hydrochloric acid (0·5 ml), cooled to 0°C and then methanol (5 ml) was added. The crystaline hydrochloride was filtered off and dried.

6-*Fluoro*-1-(4-*fluorophenyl*)-1,4-*dihydro*-4-*oxo*-7-(1-*piperazinyl*)-*cinnoline*-3-*carboxylic acid* (VIIa). Yield 89%, m.p. 223—226°C (50% equeous methanol). For $C_{19}H_{16}F_2N_4O_3.H_2O$ (404·4)

calculated: 56·44% C, 4·49% H, 9·40% F, 13·86% N; found: 56·61% C, 4·81% H, 8·75% F, 13·66% N. IR spectrum: 3 340 (NH, OH); 1 740 (COOH); 1 620 (C=O); 1 600, 1 575, 1 520 (arom. system). UV spectrum, λ_{max} (log ε): 350 (3·19), 279 (3·43), 202 (3·39). Mass spectrum, m/z: 386 (M^+).

VIIa. $HCl.H_2O$; not melting up to 360°C. For $C_{19}H_{16}F_2N_4O_3.HCl.H_2O$ (440·8) calculated: 51·76% C, 4·34% H, 8·04% Cl, 8·62% F, 12·71% N; found: 51·88% C, 4·07% H, 8·21% Cl, 8·18% F, 12·18% N. UV spectrum, λ_{max} (log ε): 352 (3·11), 279 (3·36), 202 (3·34).

6-*Fluoro*-1-(4-*fluorophenyl*)-1,4-*dihydro*-7-(4-*methyl*-1-*piperazinyl*)-4-*oxocinnoline*-3-*carboxylic acid* (VIIb). Yield 59%, not melting up to 360°C (50% aqueous methanol). For $C_{20}H_{18}F_2N_4O_3$ (400·6) calculated: 60·00% C, 4·53% H, 9·49% F, 13·99% N; found: 59·79% C, 4·54% H, 9·23% F, 13·86% N. IR spectrum: 3 340 (OH); 2 780 (NCH_3); 1 620 (C=O); 1 510, 1 500 (arom. system). UV spectrum, λ_{max} (log ε): 348 (3·19), 278 (3·41), 202 (3·33). Mass spectrum, m/z: 400 (M^+).

VIIb. HCl; not melting up to 360°C. For $C_{20}H_{18}F_2N_4O_3.HCl$ (436·8) calculated: 54·99% C, 4·38% H, 8·12% Cl, 8·70% F, 12·83% N; found: 54·57% C, 4·32% H, 8·32% Cl, 8·70% F, 12·41% N, IR spectrum: 3 360 (OH); 2 800 (NCH_3); 1 735 (COOH); 1 620 (C=O); 1 600, 1 570, 1 510 (arom. system). UV spectrum, λ_{max} (log ε): 347 (3·24), 279 (3·47), 202 (3·38).

1-(2,4-*Difluorophenyl*)-6-*fluoro*-1,4-*dihydro*-4-*oxo*-7-(1-*piperazinyl*)*cinnoline*-3-*carboxylic acid* (VIIc). Yield 49%, m.p. 241—246°C (50% aqueous methanol). For $C_{19}H_{15}F_3N_4O_3.H_2O$ (422·4) calculated: 54·03% C, 4·06% H, 13·50% F, 13·27% N; found: 53·75% C, 4·14% H, 13·15% F, 13·51% N. IR spectrum: 3 310 (OH); 3 200 (NH); 1 610 (C=O); 1 500 (arom. system). UV spectrum, λ_{max} (log ε): 347 (3·09), 276 (3·13), 204 (3·21).

VIIc. $HCl.H_2O$; not melting up to 360°C. For $C_{19}H_{15}F_3N_4O_3.HCl.H_2O$ (458·8) calculated: 49·73% C, 3·95% H, 7·73% Cl, 12·42% F, 12·21% N; found: 49·81% C, 3·87% H, 7·05% Cl, 12·07% F, 12·47% N. IR spectrum: 3 330 (OH, NH); 1 720 (COOH); 1 620 (C=O); 1 610, 1 590, 1 510 (arom. system). UV spectrum, λ_{max} (log ε): 347 (3·08), 277 (3·32), 202 (3·29).

1-(2,4-*Difluorophenyl*)-6-*fluoro*-1,4-*dihydro*-7-(4-*methyl*-1-*piperazinyl*)-4-*oxocinnoline*-3-*carboxylic acid* (VIId). Yield 48%, not melting up to 360°C. For $C_{20}H_{17}F_3N_4O_3.H_2O$ (436·4) calculated: 55·05% C, 4·38% H, 13·06% F, 12·84% N; found: 54·90% C, 4·21% H, 12·49% F, 12·72% N. IR spectrum: 3 370 (OH); 2 760 (NCH_3); 1 620 (C=O); 1 580, 1 510, 1 500 (arom. system). UV spectrum, λ_{max} (log ε): 346 (3·17), 276 (3·37), 202 (3·27). Mass spectrum, m/z: 418 (M^+).

VIId. $HCl.2\,H_2O$; not melting up to 360°C. For $C_{20}H_{17}F_3N_4O_3.HCl.2\,H_2O$ (490·9) calculated: 48·94% C, 4·52% H, 7·22% Cl, 11·61 % F, 11·41% N; found: 49·63% C, 3·96% H, 7·11% Cl, 11·73% F, 11·43% N. IR spectrum: 3 340 (OH); 2 760 (NCH_3); 1 725 (COOH); 1 620 (C=O); 1 580, 1 510 (arom. system). UV spectrum, λ_{max} (log ε): 346 (3·19), 277 (3·42) 202 (3·36).

6-*Fluoro*-1-(4-*fluoro*-2-*methylphenyl*)-1,4-*dihydro*-4-*oxo*-7-(1-*piperazinyl*)*cinnoline*-3-*carboxylic acid* (VIIe). Yield 84%, m.p. 222—224°C (70% aqueous methanol). For $C_{20}H_{18}F_2N_4O_3.H_2O$ (436·4) calculated: 55·04% C, 5·08% H, 8·71% F, 12·84% N; found: 55·17% C, 4·82% H, 8·32% F, 12·63% N. IR spectrum: 3 320 (OH, NH); 1 620 (C=O); 1 590 (arom. system). UV spectrum, λ_{max} (log ε): 344 (3·13), 279 (3·36), 202 (3·33). Mass spectrum, m/z: 400 (M^+).

VIIe. $HCl.H_2O$; m.p. 228—231°C. For $C_{20}H_{18}F_2N_4O_3.HCl.H_2O$ (454·9) calculated: 52·81% C, 4·65% H, 7·79% Cl, 8·35% F, 12·32% N; found: 53·55% C, 4·51% H, 7·61% Cl, 8·79% F, 12·35% N. IR spectrum: 3 340 (OH, NH); 1 720 (COOH); 1 620 (C=O); 1 590 (arom. system). UV spectrum, λ_{max} (log ε ε): 345 (3·21), 279 (3·45), 203 (3·42).

6-Fluoro-1-(4-fluoro-2-methylphenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxocinnoline-3-carboxylic acid (VIIf). Yield 34%, m.p. 137–140°C (70% aqueous methanol). For $C_{21}H_{20}F_2N_4O_3.H_2O$ (432·4) calculated: 58·33% C, 5·13% H, 8·79% F, 12·96% N; found: 58·60% C, 4·68% H, 8·83% F, 13·02% N. IR spectrum: 3 360 (OH); 2 790 (NCH_3); 1 620 (C=O); 1 610, 1 580, 1 500 (arom. system). UV spectrum, λ_{max} (log ε): 346 (3·20), 278 (3·45), 203 (3·39). Mass spectrum, *m/z*: 414 (M^+).

VIIf. HCl.0.5 H_2O; m.p. 228–231°C. For $C_{21}H_{20}F_2N_4O_3.HCl.0.5\ H_2O$ (459·9) calculated: 54·85% C, 4·82% H, 7·71% Cl, 8·26% F, 12·18% N; found: 55·33% C, 4·63% H, 7·90% Cl, 8·41% F, 12·26% N. IR spectrum: 3 350 (OH); 2 780 (NCH_3); 1 735 (COOH); 1 620 (C=O); 1 585, 1 570, 1 510 (arom. system). UV spectrum, λ_{max} (log ε): 347 (3·25), 279 (3·46), 204 (3·36).

7-(3-Ethylaminomethyl-1-pyrolidinyl)-6-fluoro-1-(4-fluoro-2-methyphenyl)-1,4-dihydro-4-oxocinnoline-3-carboxylic acid (VIIg). Yield 57%, m.p. 251–253°C (95% aqueous methanol). For $C_{23}H_{24}F_2N_4O_3.2\ H_2O$ (478·5) calculated: 57·73% C, 5·90% H, 7·94% F, 11·71% N; found: 57·89% C, 5·57% H, 7·69% F, 11·70% N. IR spectrum: 3 340 (OH); 3 210 (NH), 1 620 (C=O); 1 570, 1 525, 1 495 (arom. system). UV spectrum, λ_{max} (log ε): 351 (3·15), 280 (3·55), 205 (3·34). Mass spectrum, *m/z*: 442 (M^+).

VIIg. HCl; m.p. 252–255°C. For $C_{23}H_{24}F_2N_4O_3.HCl$ (478·9) calculated: 57·68% C, 5·26% H, 7·40% Cl, 7·93% F, 11·70% N; found: 57·44% C, 5·34% H, 8·02% Cl, 7·53% F, 11·34% N. IR spectrum: 3 340 (OH); 3 290 (NH); 1 730 (COOH); 1 620 (C=O); 1 590, 1 575, 1 520, 1 490 (arom. system). UV spectrum, λ_{max} (log ε): 351 (3·05), 289 (3·48), 205 (3·34).

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