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The synthesis of new tricyclic quinolones, resulting from *peri*-annelation of 1,2,4-oxadiazine moiety at the N-1/C-8 position of the pharmacophoric quinolone nucleus, are described. None of the synthesized compounds showed interesting antibacterial activity *in vitro* against the tested strains, with the exception of *Klebsiella pneumoniae* which was susceptible to all the compounds at MIC values of 8 μg/ml.

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Introduction.

Flumequine, containing an all carbocyclic bridge, was the first 1,8-bridged tricyclic quinolone antibacterial to be used clinically [1]. Subsequently, a number of modifications were made on the 1,8-bridge, including replacement of carbon with heteroatoms [2-7], variations of the ring size [8] and substituents [9], as well as stereocontrol of chiral centers within the bridge [10-14]. As a result of these modifications, new 1,8-bridged tricyclic quinolones with high antibacterial potency such as ofloxacin [15], rufloxacin [16], nadifloxacin [17], and levofloxacin [18], have been introduced into clinical practice (Figure 1).

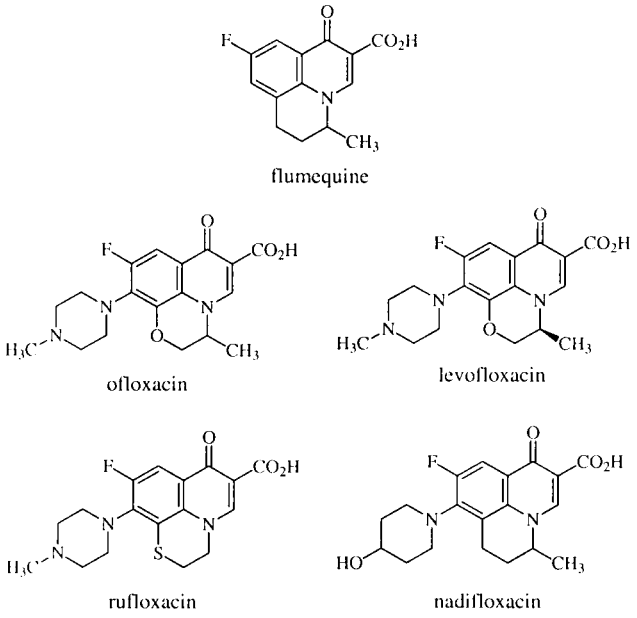


Figure 1

Other new potent 1,8-bridged quinolones, such as pyrido[3,2,1-*ij*]-1,3,4,-benzoxadiazines **1** in which the N-1-α carbon is replaced by a nitrogen atom to give a diazine moiety, have recently been reported [19, 20]. The elimination of the oxygen atom of the oxadiazine ring resulted in the pyrido[3,2,1-*ij*]cinnoline ring system exemplified by WQ-0835 which possesses an extremely potent antibacterial activity and has excellent oral absorbability [21, 22] (Figure 2).

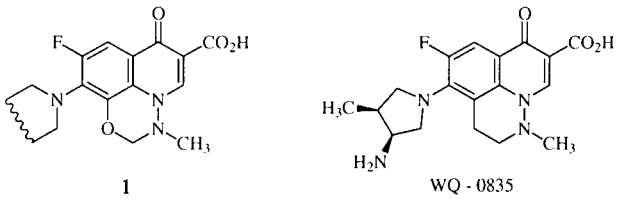
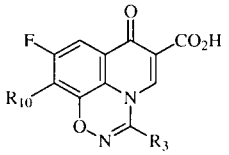


Figure 2

Given the potent activity shown by 1,8-*peri*-annelated tricyclic quinolones and considering that all the quinolone portion opposite the keto-carboxylic moiety (N-1/C-8/C-7) could be involved in the interaction with the enzymatic target DNA-gyrase [23], it was of interest to modify the N-1/C-8 portion by inserting a *peri*-annelated 1,2,4-oxadiazine moiety. In the resulting tricyclic quinolones **2** and **3** (Figure 3), the presence of the third semiflat ring could facilitate the stacking with DNA bases or the self-self aggregation according to the Palumbo [23] or Shen [24] models, respectively, for the quinolone mechanism of action.



2 $R_3 = H$
3 $R_3 = CH_3$

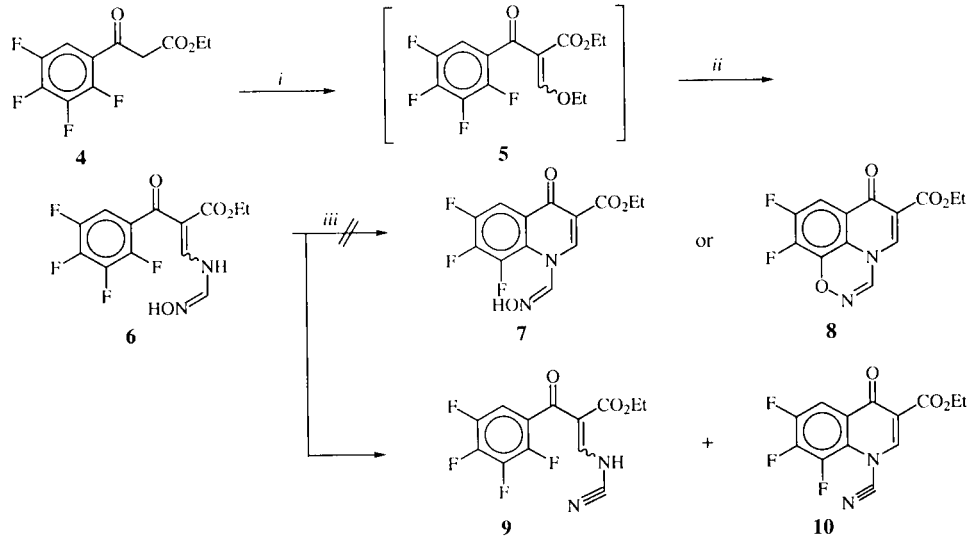
Figure 3

Chemistry.

The synthetic strategy chosen to prepare the new tricyclic derivatives was based on the simultaneous formation of both pyridone and oxadiazine rings by a double intramolecular displacement reaction of ketoester **6**, as depicted in Scheme 1. The employed route is like the procedure of the one pot synthesis of rufloxacin, [25] and differs slightly from that used, in general, to prepare 1,8-bridged tricyclic quinolone antibacterials where the construction of the quinolone ring is followed by the building of the third ring [6, 20].

The requisite ketoester **6** was prepared in 50% yield in a single step by reacting β-ketoester **4** [26, 27] with triethyl orthoformate in acetic anhydride and treating the reaction

Scheme 1 [a]



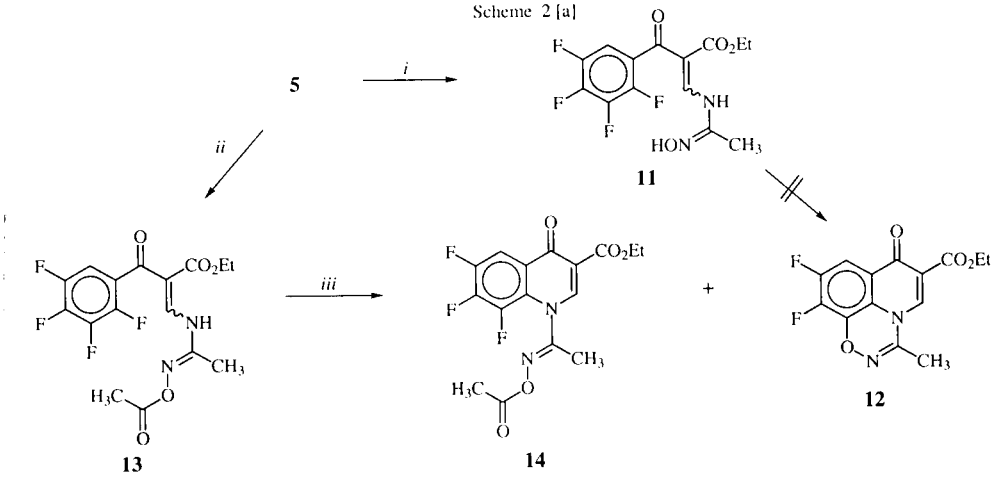
[a] Reagents: (*i*) Ac_2O, $(EtO)_3CH$, 120°; (*ii*) $HONCHNH_2$, THF, 40-55°; (*iii*) DMF, K_2CO_3, 50°

mixture with commercial formamidoxime in dry tetrahydrofuran at 40 °C for 48 hours.

Cyclization of ketoester **6**, in a variety of conditions commonly used in quinolone cyclization such as triethylamine/tetrahydrofuran, potassium hydroxide/tetrahydrofuran, sodium hydride/tetrahydrofuran, potassium carbonate/dimethylformamide and 1,8-diazabicyclo[5.4.0]undec-7-ene/toluene, afforded neither the desired tricyclic derivative **8** nor the bicyclic derivative intermediate **7**, but rather, gave a series of by-products. Among these, only the cyano derivatives **9** and **10** were always isolated and identified (ir, ^{13}C nmr, ^{1}H nmr) as dehydration products. Ease of dehydration made the synthesis of unsaturated oxadiazinoquinoline **2** impossible.

The above synthetic procedure was repeated (Scheme 2) but formamidoxime was replaced by ethanamidoxime [28, 29] in which the presence of a methyl group prevented the formation of undesired dehydration products. Thus, the reaction of intermediate **5** with ethanamidoxime gave ketoester **11** which did not afford the desired tricyclic derivative **12** even when the above cyclization methods were used. However, derivative **12** was obtained when ethanamidoxime was replaced by *O*-acetyl ethanamidoxime [28, 29] to give enolate **13**. The cyclization of **13** in potassium carbonate/dimethylformamide at room temperature gave compound **12** but in a very low yield (< 10%), together with monocyclized intermediate **14**. This cyclization reaction is difficult to monitor by thin layer chromatography because the monocyclized intermediate **14**, and desired tricyclic derivative **12** have very similar ratio front (Rf) values and, if the reaction proceeds for several hours, additional by-products are produced. It was found that the molecular rates of compound **13** and potassium carbonate influence the yield; the yield increased to 15% when the rate ranged from 1:2 to 1:4 and the reaction was carried out at room temperature for

Scheme 2 [a]

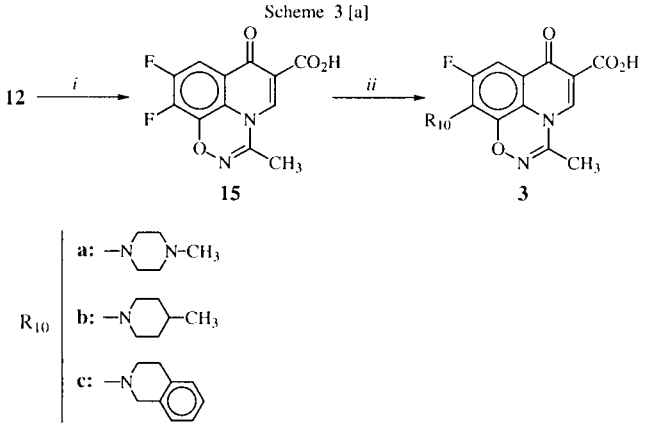


[a] Reagents: (*i*) $HONC(CH_3)NH_2$, THF, 40-50°; (*ii*) $AcONC(CH_3)NH_2$, THF, 40-50°; (*iii*) DMF, K_2CO_3, 50-60°.

24 hours. If the reaction was first conducted at room temperature for 2 hours and then heated at 50-60° for 20 minutes, the yield increased to 22%. Longer heating decreased the yield and decomposition occurred.

Attempts were made to prepare the desired acid **15** (Scheme 3), using hydrolysis methods usually employed in quinolone synthesis, under acid conditions (1*N* hydrochloride acid/tetrahydrofuran, acetic acid/hydrochloride acid, 1*N* hydrochloride acid/ethanol) or basic conditions (1% sodium hydroxide), as well as treatment with trimethylsilyl iodide followed by aqueous hydrolysis under neutral conditions [30]. Acid **15** was obtained in 88% yield only by using fuming sulfuric acid, under ice cooling.

Scheme 3 [a]



[a] Reagents: (*i*) fuming H_2SO_4; (*ii*) $R_{10}H$, DMF, Et_3N, 100°.

Finally, the successive nucleophilic displacement reaction of the C-10 fluorine atom with selected heterocyclic side chains was carried out in dry dimethylformamide and using triethylamine or an excess of the side chain as a hydrofluoric acid scavenger. Thus, the target acids **3a-c** were obtained, even if in low yield which could be due to steric and/or electronic repulsion between the oxadiazine and heterocyclic base ring in agreement with what was already reported for similar tricyclic quinolones [6].

Microbiological Results.

The synthesized compounds were tested for their *in vitro* antibacterial activity against representative Gram-negative (*Escherichia coli*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Hemophilus influenzae*) and Gram-positive (Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Enterococcus faecalis) bacteria, including some clinical isolates, as well as a ciprofloxacin-resistant and methicillin-resistant *Staphylococcus aureus* strains. The control drug ciprofloxacin, was included for comparative purposes. The minimum inhibitory concentrations (MICs, μg/ml) were determined by microdilution technique using nutrient broth, according to the National Committee for clinical Laboratory Standards [31].

The synthesized compounds were inactive (MIC > 16 μg/ml) against the strains assayed with the exception of *Klebsiella pneumoniae* which was susceptible to all compounds at MIC value of 8 μg/ml.

EXPERIMENTAL

Thin layer chromatography (TLC) was performed on precoated sheets of silica gel $60F_{254}$ (Merck) and visualized by using UV. Column chromatography separations were carried out on Merck silica gel 40 (mesh 70-230). Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. Elemental analyses were performed on a Carlo Erba elemental analyzer, Model 1106, and the data for C, H and N are within ± 0.4% of the theoretical values. ^1H nmr spectra were recorded at 200 MHz (Bruker AC-200) with tetramethylsylane as internal standard and chemical shifts are given in ppm (δ). The spectral data are consistent with the assigned structures. Reagents and solvents were purchased from common commercial suppliers and were used as received. Organic solutions were dried over anhydrous sodium sulfate and concentrated with a Büchi rotary evaporator at low pressure. Yields were of purified product and were not optimized. All starting materials were commercially available unless otherwise indicated.

Ethyl 3-[(Hydroxyiminomethyl)amino]-2-(2,3,4,5-tetrafluorobenzoyl)-2-propenoate (**6**).

A mixture of ester **4** [26, 27] (6.16 g, 23.3 mmol), triethyl orthoformate (5.8 ml, 35.0 mmol) and acetic anhydride (8.8 ml, 94.2 mmol) was heated at 120 °C in a flask equipped with a Dean-Stark condenser for 3 hours. After cooling, the mixture was concentrated in vacuum to give a thick residue of the unstable intermediate **5**. It was dissolved in dry tetrahydrofuran (40 ml), added (1.68 g, 27.9 mmol) of formamidoxime and reacted at 40-55 °C for two days. Evaporation *in vacuo* gave an oil, which was purified by column chromatography eluting with a gradient of ethyl acetate/petroleum ether (1:3) to ethyl acetate/petroleum ether (1:2) to give 3.96 g (yield 51%) of **6** as a 1:1 mixture of (*E*) and (*Z*) isomers, mp 73-75 °C; ^1H nmr (deuteriochloroform): δ 1.20-1.36 (m, 3H, CH_2CH_3), 4.20 (q, 2H, J = 7 Hz, CH_2CH_3), 7.10 (d, 1H, J = 13 Hz, CHNOH), 7.20-7.25 (1H, m, Ar-H), 7.90 and 8.15 (each d, 0.5H, J = 13 Hz, vinyl H), 8.30 (1 H, bs, OH), 11.15 and 12.0 (each t, 0.5H, J = 13 Hz, NH).

Anal. Calcd. for $C_{13}H_{10}F_4N_2O_4$: C, 46.72; H, 3.02; N, 8.38. Found: C, 46.38; H, 3.12; N, 8.40.

Ethyl 3-[(1-Hydroxyiminoethyl)amino]-2-(2,3,4,5-tetrafluorobenzoyl)-2-propenoate (**11**).

Using a procedure similar to that used to prepare compound **6**, derivative **11** was prepared from ester **4** replacing formamidoxime with ethanamidoxime [28, 29]. It was obtained in 55% yield as a 1:1 mixture of (*E*) and (*Z*) isomers, mp 84-86 °C; ^1H nmr (deuteriochloroform): δ 1.05-1.30 (m, 3H, CH_2CH_3), 2.20 (s, 3H, CH_3), 4.15 (q, 2H, J = 7 Hz, CH_2CH_3), 7.00-7.28 (1H, m, Ar-H), 7.90 and 8.10 (each d, 0.5H, J = 13 Hz, vinyl H), 8.40 and 8.70 (each bs, 0.5H, OH), 11.50 and 12.40 (each d, 0.5H, J = 13 Hz, NH).

Anal. Calcd. for $C_{14}H_{12}F_4N_2O_4$: C, 48.28; H, 3.47; N, 8.04. Found: C, 47.98; H, 3.45; N, 8.10.

Ethyl 3-[(1-Acetoxyiminoethyl)amino]-2-(2,3,4,5-tetrafluorobenzoyl)-2-propenoate (**13**).

Using a procedure similar to that used to prepare compound **6**, derivative **13** was prepared from ester **4** by replacing formamidoxime with *O*-acetyl ethanamidoxime [28, 29]. It was obtained in 64% yield as a 1:1 mixture of (*E*) and (*Z*) isomers, mp 76-78 °C; ^{1}H nmr (deuteriochloroform): δ 1.05-1.18 (m, 3H, CH_2CH_3), 2.30-2.40 (m, 6H, $COCH_3$ and CH_3), 4.19 (q, 2H, J = 7 Hz, CH_2CH_3), 7.15 and 7.30 (each m, 0.5H, Ar-H), 7.94 and 8.17 (each d, 0.5H, J = 13 Hz, vinyl H), 11.61 and 12.41 (each d, 0.5H, J = 13 Hz, NH).

Anal. Calcd. for $C_{16}H_{14}F_4N_2O_5$: C, 49.24; H, 3.62; N, 7.18. Found: C, 49.50; H, 3.75; N, 7.20.

Ethyl 1-(1-Acetoxyiminoethyl)-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**14**) and Ethyl 9,10-Difluoro-3-methyl-7-oxo-7*H*-[1,2,4]oxadiazino[6,5,4-*ij*]quinoline-6-carboxylate (**12**).

A solution of **13** (0.30 g, 0.86 mmol) in dry dimethylformamide (3 ml) was treated with powdered, anhydrous potassium carbonate (0.37 g, 2.6 mmol) and stirred at room temperature for 2 hours and then at 50-60 °C for 20 minutes. After cooling, the reaction mixture was poured into ice-water (20 ml), and extracted with chloroform (10 ml x 3). The combined organic layers were dried, and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a gradient of petroleum ether/chloroform (3:1) to petroleum ether/chloroform (2:1) to give 58 mg (22%) of pure tricyclic ester **12** as white needle, mp 194-195 °C and 40 mg (14%) of bicyclic product **14** as white solid, mp 178-179 °C.

14: ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.35 (t, 3H, J = 7 Hz, CH_2CH_3), 1.95 (s, 3H, $COCH_3$), 2.65 (s, 3H, CH_3), 4.25 (q, 2H, J = 7 Hz, CH_2CH_3), 8.00-8.15 (m, 1H, H-5), 8.70 (s, 1H, H-2); ^{13}C nmr (deuteriodimethyl sulfoxide) δ 170.3 (C-4), 166.4 ($OCOCH_3$), 163.3 ($CO_2C_2H_5$), 151.7 (CN), 147.8 (ddd, J = 241.5, 10.7 and 6.0 Hz, C-8), 145.6 (C-2), 142.6 (dt, J = 275.1 and 15.3 Hz, C-7), 141.5 (ddd, J = 255.0, 13.3 and 6.0 Hz, C-6), 125.3 (dd, J = 14.0 and 5.8 Hz, C-8a), 123.1 (t, J = 5.8 Hz, C-4a), 111.8 (C-3), 108.5 (dd, J = 18.4 and 6.5 Hz, C-5), 60.5 (CH_2CH_3), 19.1 ($OCOCH_3$), 18.6 (CH_3), 14.1 (CH_2CH_3).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_5$: C, 51.90; H, 3.54; N, 7.57. Found: C, 51.56; H, 3.74; N, 7.55.

12: ^{1}H nmr (deuteriochloroform): δ 1.40 (t, 3H, J = 7 Hz, CH_2CH_3), 2.50 (s, 3H, CH_3), 4.40 (q, 2H, J = 7 Hz, CH_2CH_3), 7.60 (dd, 1H, J = 10.5 and 7.7 Hz, H-8), 8.40 (s, 1H, H-5). ^{13}C nmr (deuteriodimethyl sulfoxide) δ 170.6 (C-7), 163.6 ($CO_2C_2H_5$), 149.6 (dd, J = 249.4 and 11.0 Hz, C-9), 147.5 (C-3), 140.0 (d, J = 14.5 Hz, C-10a), 137.1 (dd, J = 251.3 and 18.3 Hz, C-10), 138.9 (C-5), 122.0 (C-10b), 120.9 (C-7a), 112.3 (C-6), 104.0 (dd, J = 19.4 and 5.5 Hz, C-8), 60.7 (CH_2CH_3), 15.2 (CH_3), 14.1 (CH_2CH_3).

Anal. Calcd. for $C_{14}H_{10}F_2N_2O_4$: C, 54.55; H, 3.27; N, 9.09. Found: C, 54.78; H, 3.20; N, 9.13.

Ethyl 3-(Cyanoamino)-2-(2,3,4,5-tetrafluorobenzoyl)-2-propenoate (**9**) and Ethyl 1-Cyano-6,7,8-trifluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**10**).

When **6** was put to cyclize by the similar procedure for preparing **12**, dehydration products **9** in 21% yield, mp 145-146 °C and **10** in 26 % yield mp 173-175 °C were obtained.

9: ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.35 (t, 3H, J = 7 Hz, CH_2CH_3), 4.25 (q, 2H, J = 7 Hz, CH_2CH_3), 7.80 (s, 1H, vinyl H), 7.85-7.95 (m, 1H, Ar-H), 9.75 (bs, 0.5H, NH), 12.80 (s, 0.5H, OH); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 173.2 (CO), 167.7 ($CO_2C_2H_5$), 156.9 (ddt, J = 255.8, 20.3 and 5.2 Hz, C-4'), 148.1 (ddd, J = 255.8, 21.1 and 4.9 Hz, C-5'), 147.6 (ddd, J = 255.0, 18.0 and 5.2 Hz, C-2'), 145.7 (ddt, J = 245.1, 18.0 and 5.0 Hz, C-3'), 121.4 (C-3), 120.9 (CN), 120.1 (dt, J = 28.1 and 6.0 Hz, C-1'), 116.7 (dt, J = 28.0 and 6.0 Hz, C-6'), 94.6 (C-2), 59.4 (CH_2CH_3), 14.3 (CH_2CH_3); ir (potassium bromide): ν 1630, 1726, 2225 cm^{-1}.

Anal. Cald. For $C_{13}H_8F_4N_2O_3$: C, 49.38; H, 2.55; N, 8.86. Found: C, 49.50; H, 2.35; N, 8.66.

10: ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.35 (t, 3H, J = 7 Hz, CH_2CH_3), 4.25 (q, 2H, J = 7 Hz, CH_2CH_3), 7.80-7.90 (m, 1H, H-5), 8.50 (s, 1H, H-2); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 174.0 (C-4), 164.0 ($CO_2C_2H_5$), 155.5 (dt, J = 260 and 28 Hz, C-7), 142.5 (dd, J = 260 and 28 Hz, C-6), 143.0 (dd, J = 260 and 7 Hz, C-8), 129.5 (dd, J = 28 and 7 Hz, C-8a), 127.0 (d, J = 7 Hz, C-4a), 120.3 (C-2), 112.5 (dd, J = 28 and 6 Hz, C-5), 111.2 (C-3), 110.6 (CN), 59.51 (CH_2CH_3), 14.3 (CH_2CH_3); ir (potassium bromide): ν 1625, 1730, 2230 cm^{-1}.

Anal. Calcd. for $C_{13}H_7F_3N_2O_3$: C, 52.71; H, 2.38; N, 9.46. Found: C, 52.87; H, 2.15; N, 9.35.

9,10-Difluoro-3-methyl-7-oxo-7*H*-[1,2,4]oxadiazino[6,5,4-*ij*]-quinoline-6-carboxylic Acid (**15**).

Ester **12** (2.1 g, 6.8 mmol) was added portionwise to fuming sulfuric acid (2 ml) cooled in ice-water bath. The mixture was then reacted at room temperature overnight and then poured into ice water. The obtained solid was filtered off, washed with water and crystallized from methanol to provide 1.67 g (88.%) of acid **15** as white needle product, mp 280-283 °C dec; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.55 (s, 3H, CH_3), 7.70 (dd, 1H, J = 10.4, 7.6 Hz, H-8), 8.65 (s, 1H, H-5), 13.80 (bs, 1H, CO_2H).

Anal. Calcd. for $C_{12}H_6F_2N_2O_4$: C, 51.44; H, 2.16; N, 10.00. Found: C, 51.68; H, 2.25; N, 10.12.

9-Fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-[1,2,4]oxadiazino[6,5,4-*ij*]quinoline-6-carboxylic Acid (**3a**).

A mixture of acid **15** (0.18 g, 0.64 mmol), *N*-methylpiperazine (0.28 ml, 2.5 mmol) and dry triethylamine (0.35 ml, 2.5 mmol) in dry dimethylformamide (3 ml) was heated at 95-100 °C for 1 hour. The reaction mixture was cooled to room temperature and then poured into ice-water. The solution was made neutral by adding of 2 *N* hydrochloric acid. The obtained precipitate was collected by filtration, washed with water and ethanol then crystallized from ethyl acetate/methanol to provide 66 mg (29%) of **3a** as yellow-green powder, mp 270-271 °C dec; ^{1}H nmr (deuteriochloroform): δ 2.35 (s, 3H, NCH_3), 2.50 (s, 3H, CH_3), 2.50-2.60 and 3.35-3.45 (each m, 4H, piperazine CH_2), 7.55 (d, 1H, J = 12 Hz, H-8), 8.60 (s, 1H, H-5).

Anal. Calcd. for $C_{17}H_{17}FN_4O_4$: C, 56.66; H, 4.76; N, 15.55. Found: C, 56.80; H, 4.85; N, 15.23.

9-Fluoro-3-methyl-10-(4-methyl-1-piperidinyl)-7-oxo-7*H*-[1,2,4]oxadiazino[6,5,4-*ij*]quinoline-6-carboxylic Acid (**3b**).

This compound was prepared starting from acid **15** by using 1-methylpiperidine as the nucleophile, in the same procedure as for **3a**. The yield was 17%, as green powder, mp > 284 °C dec;

^{1}H nmr (deuteriodimethyl sulfoxide): δ 0.95 (bs, 3H, piperidine CH_3), 1.10-1.35 (m, 2H, piperidine CH_2), 1.40-1.80 (m, 4H, piperidine CH_2), 2.50 (s, 3H, CH_3), 3.00-3.35 (m, 3H, piperidine CH and CH_2), 7.45 (d, 1H, J = 12 Hz, H-8), 8.55 (s, 1H, H-5), 14.25 (bs, 1H, CO_2H).

Anal. Calcd. for $C_{18}H_{18}FN_3O_4$: C, 61.90; H, 2.31; N, 12.03. Found: C, 61.98; H, 2.50; N, 12.12.

9-Fluoro-3-methyl-7-oxo-10-[1,2,3,4-tetrahydro-2-isoquinolinyl]-7*H*-[1,2,4]oxadiazino[6,5,4-*ij*]quinoline-6-carboxylic Acid (**3c**).

A mixture of acid **15** (0.10 g, 0.36 mmol), and 1,2,3,4-tetrahydroisoquinoline (0.22 ml, 1.43 mmol) in dry dimethylformamide (3 ml) was heated at 85 °C for 40 minutes. After cooling, the reaction mixture was poured into water and the precipitated solid was collected by filtration and purified by crystallization from EtOH to give 65 mg (46%) of **3c** as yellow powder, mp 295-298 °C. ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.30 (s, 3H, CH_3), 3.40-3.50 and 3.45-3.65 (each m, 2H, isoquinoline CH_2), 4.10-4.20 (2H, m, isoquinoline CH_2), 7.10 (m, 4H, isoquinoline Ar-H), 7.55 (d, 1H, J = 12 Hz, H-8), 8.60 (s, 1H, H-5), 13.20 (bs, 1H, CO_2H).

Anal. Calcd. for $C_{21}H_{16}FN_3O_4$: C, 64.12; H, 4.10; N, 10.68. Found: C, 64.38; H, 4.21; N, 10.72.

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