Synthesis of 4-Hydroxyquinolin-2(1*H*)-one Analogues and 2-Substituted Quinolone Derivatives

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A versatile synthetic method for preparing 4-hydroxyquinolone and 2-substituted quinolone compounds from simple benzoic acid derivatives was demonstrated. The synthetic strategies involve the use of well known ethyl acetoacetate synthesis, malonic ester synthesis and reductive cyclization. The key intermediates were keto esters **4a-e**, which could be transformed to 4-hydroxyquinolones **5a**,**b** or 2-substituted quinolone ethyl esters **6a-c** depending on the reaction conditions. 4-Hydroxyquinolone analogues were prepared and investigated for *N*-methyl-D-aspartate (NMDA) activity *in vitro*. Among these derivatives, 6,7-difluoro-3-nitro-4-hydroxyquinolin-2(1*H*)-one (**9**) exhibited moderate activity.

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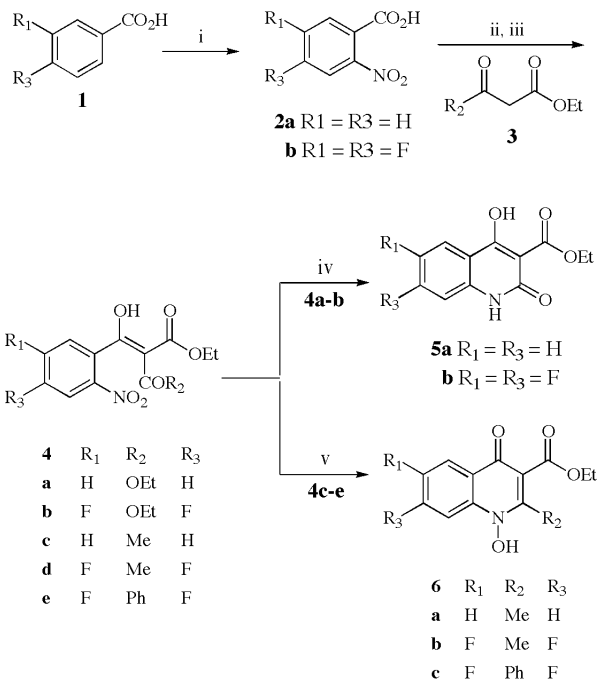
Many 4-hydroxyquinolone compounds are useful intermediates for biologically active substances [1] and many industrial products such as dye stuffs [2] and herbicides [3]. Recent reports [4] describe novel class of 4-hydroxyquinolone derivatives, i.e., 4-hydroxy-3-arylquinolin-2(1*H*)-one and 4-hydroxy-3-nitroquinolin-2(1*H*)-one as potent and selective *N*-methyl-D-aspartate (NMDA) receptor glycine site antagonist after oral administration. Many of these compounds have been derived from the 4-hydroxyquinolin-2(1*H*)-one nucleus.

A variety of routes for the synthesis of 4-hydroxyquinolone compounds have been reported in the literature [5-8]. Most of these methods have been based on the cyclization of malondianilides with aluminium trichloride [9] or poly phosphoric acid [10], which afforded the corresponding 4-hydroxyquinolone compounds in poor to moderate yields and made the product isolation considerably difficult. Our need for rapid access to 4-hydroxyquinolone compounds for large scale syntheses for 2-substituted quinolone compounds, prompted us to explore new methodology for the synthesis of these compounds.

The present paper describes a convenient method for the preparing 4-hydroxyquinolones **5a,b** and 2-substituted quinolone compounds **6a-c**. The synthetic strategies involve the use of well known ethyl acetoacetate synthesis, malonic ester synthesis [11] and reductive cyclization. Several derivatives of 4-hydroxyquinolone and 2-substituted quinolone were also prepared by simple method from 4-hydroxyquinolones **5a,b** and 2-substituted (methyl or phenyl) quinolones **6a-c**. These compounds were evaluated for *N*-methyl-D-aspartate (NMDA) glycine binding site activity and antibacterial activity *in vitro*, respectively.

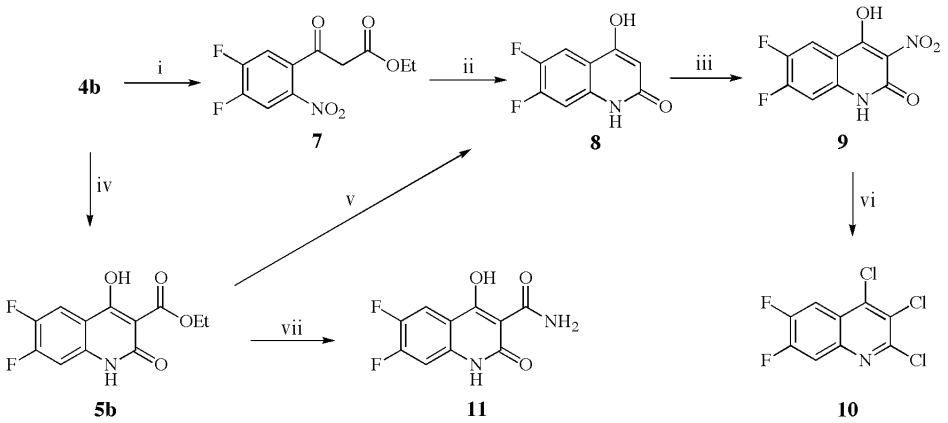
We have used 4,5-difluorobenzoic acid as starting material, which was nitrated to give 4,5-difluoro-2-nitrobenzoic acid (**2b**). Acids **2a,b** were treated with thionyl chloride to give acid chlorides, which were subsequently treated with the anion of diethyl malonate, ethyl acetoacetate or phenyl acetoacetate to give keto esters **4a-e** in excellent yields. In this condensation reaction, we found that magnesium ethoxide was the most effective among bases such as sodium ethoxide, sodium hydride and potassium *t*-butoxide. The keto diesters **4a,b** were smoothly transformed to 4-hydroxyquinolone compounds **5a,b** by reductive ring closure over palladium-on-charcoal with sodium borohydride under akaline reduction condition. Whereas, the diketo esters **4c-e** were converted to *N*-hydroxy-2-substituted quinolone compounds **6a-c** using the mild catalytic hydrogenation over palladium-on-charcoal in ethanol at room temperature (Scheme 1).

Scheme 1



i) HNO_3/H_2SO_4; ii)$SOCl_2$, urea/toluene; iii) Mg, EtOH/toluene; iv) $NaBH_4$, Pd-C, NaOH (aq), 1,4-dioxane; v) H_2, Pd-C, EtOH, 1 bar.

Scheme 2



i) *p*-TsOH/H_2O; ii) H_2, Pd-C, EtOH; iii) HNO_3/AcOH; iv) $NaBH_4$, Pd-C, NaOH (aq), 1,4-dioxane; v) 3 N HCl (aq)/EtOH; vi) $POCl_3$/EtN; vii) NH_4OH

The treatment of diethyl 3,4-difluoro-2-nitrobenzoylmalonate (**4b**) with *p*-toluenesulfonic acid gave the ethyl 3,4-difluoro-2-nitrobenzoylacetate (**7**), which was used without further purification for the next step. In this decarboxylation reaction, we found that *p*-toluenesulfonic acid gave the best yield among acids or base such as 10% sulfuric acid, 10% hydrochloric acid or 15% sodium hydroxide. Reductive cyclization of **7** with catalytic hydrogenation over palladium-on-charcoal in ethanol proceeded smoothly to afford 6,7-difluoro-4-hydroxyquinolin-2(1*H*)-one (**8**) in 96% yield. Compound **8** was nitrated with a mixture of nitric acid and acetic acid to produce 6,7-difluoro-3-nitro-4-hydroxyquinolin-2(1 *H*)-one (**9**). Chlorination of compound **9** with phosphoryl chloride in the presence of triethylamine gave 6,7-difluoro-2,3,4-trichloroquinoline (**10**) in good yield. The compound **5b** was treated with concentrated ammonium hydroxide to give the 6,7-difluoro-4-hydroxyquinolin-2(1*H*)-3-carboxamide (**11**) [12a,b] in 75% yield (Scheme 2).

On the other hand, the compounds **6b,c** were readily reduced to ethyl 6,7-difluoro-2-(methyl or phenyl)-4-oxoquinoline-3-carboxylates (**12a,c**) using sodium hydrosulfite in aqueous ethanol in near quantitative yield.

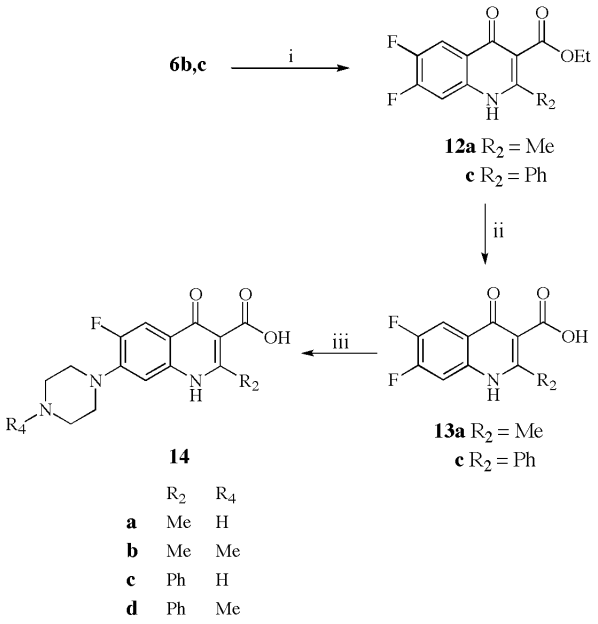
Table

In Vitro Antibacterial Activity of 2-Substituted Quinoline Compounds

	Minimum Inhibitory Concentrations (MICs, μg/ml) [a]				
Organism	14a	14b	14c	14d	NFLX [b]
Streptococcus pyogenes 308 A	1.6	3.2	1.6	3.2	1.6
Streptococcus pyogenes 77 A	6.3	1.6	3.2	3.2	1.6
Streptococcus faccium MD 8b	0.8	0.8	1.6	1.6	3.2
Staphylococcus aureus SG 511	1.6	1.6	6.3	1.6	0.06
Staphylococcus aureus 285	3.2	1.6	0.8	1.6	0.8
Staphylococcus aureus 503	6.3	3.2	3.2	0.8	0.4
Escherichia coli 078	6.3	6.3	6.3	3.2	0.8
Escherichia coli DC 0	6.3	3.2	6.3	6.3	0.01
Escherichia coli DC 2	3.2	1.6	3.3	6.3	0.8
Escherichia coli TEM	3.2	3.2	6.3	3.2	0.16
Escherichia coli 1507 E	1.6	6.3	3.2	6.3	0.4
Pseudomonas aeruginosa 9027	6.3	6.3	3.2	6.3	0.1
Pseudomonas aeruginosa 1592 E	6.3	3.2	6.3	6.3	0.2
Pseudomonas aeruginosa 1771	3.2	6.3	3.2	3.2	0.02
Pseudomonas aeruginosa 1771 M	3.2	6.3	6.3	6.3	0.1
Salmonella typhimurium	6.3	3.2	6.3	6.3	0.02
Klebsiella oxytoca 1082 E	3.2	3.2	6.3	6.3	0.4
Klebsiella aerogenes 1522 E	6.3	3.2	6.3	3.2	0.63
Enterobacter cloacae P 99	6.3	6.3	6.3	6.3	0.4
Enterobacter cloacae 1321 E	6.3	6.3	6.3	3.2	0.8

[a] Standard microdilution techniques, [13a,b]. [b] Norfloxacin.

Scheme 3



i) $Na_2S_2O_4$, EtOH/H_2O; ii) 2 *N* NaOH (aq) or LiOH/THF; ii) piperazine or *N*-methylpiperazine/pyridine

Compounds **12a,c** were hydrolyzed with aqueous sodium hydroxide or lithium hydroxide in tetrahydrofuran and then acidified with 2*N* hydrochloric acid to give the 6,7-difluoro-2-methyl or phenyl-4-oxoqinoline-3-carboxylic acids **13a,c**. Acids **13a,c** were treated with anhydrous piperazine or *N*-methylpiperazine in pyridine according to the reported method [14-15] to yield 6-fluoro-2-(methyl or phenyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl or *N*-methyl-piperazinyl)quinoline-3-carboxylic acids **14a-d**, respectively (Scheme 3). Spectral data (^{1}H nmr, ^{13}C nmr, ir, ms) of all the prepared compounds are in accordance with the proposed compounds.

The minimum inhibitory concentrations (MICs) of **14a-d** against six Gram-positive bacteria and fourteen Gram-negative bacteria compared to those of norfloxacin, *in vitro* are listed in Table. Interestingly, these compounds showed better antibacterial activities against Gram-positive bacteria than Gram-negative bacteria. The affinity of the prepared 4-hydroxyquinolone analogues such as **5b**, **6b**, **8-10** and **11** for the *N*-methyl-D-aspartate receptor glycine binding site was measured by inhibition of [^{3}H]MDL 105,519 binding to rat brain cortical membranes. Among these compounds, 6,7-difluoro-3-nitro-4-hydroxyquinolin-2(1*H*)-one (**9**) exhibited the most potent activity (IC_{50} : 3.9 μM).

In conclusion, the operational simplicity, inexpensive and readily available materials and high yields can make this procedure a useful and alternative to the currently available methods. It is also applicable to industrial scale preparation.

EXPERIMENTAL

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (tlc) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with 254-nm uv light or ceric sulfate-ammoniummolybdate-sulfuric acid spray. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040~0.063 mm, 230~400 mesh ASTM). ^{1}H nmr and ^{13}C nmr spectra were recorded on a Brucker DPX 300 at 300 MHz and 76 MHz, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and J-values were in Hz. Infrared spectra (ir) were obtained on a Jasco FT/IR-300E spectrometer. Mass spectra (ms) were recorded on a Shimadzu-LKB 9000 GC/MS system. High resolution mass spectra (hrms) were obtained on a JEOL JMS-HX-110A/110A high resolution mass spectrometer. Elemental analyses were performed on a CE instruments Model 1110 elemental analyzer. All compounds has analytical results within ±0.4% of their theoretical values. All mps were uncorrected. When necessary, chemicals were purified according to the reported procedure [16].

All cultures were stored as frozen stock. The MICs determinations; a broth microdilution method [13a,b] was used to quantitate antibacterial activity for these compounds. The antibacterial activity was determined by agar dilution assay using a multipoint inoculator. The test compounds were dissolved and incorporated by the two fold dilution method in the agar medium. Bacterial inocula, coming from overnight broth and containing 10^7 colony-forming units per point, were inoculated by multipoint inoculator. Bacterial growth was observed after 18 hours of incubation at 37°. The lowest concentration of test compounds that completely inhibited growth was considered to be the minimum inhibitory concentrations (MICs).

4,5-Difluoro-2-nitrobenzoic Acid (**2b**).

A solution of nitric acid (70%, 9.9 g, 110 mmoles) in concentrated sulfuric acid (11.4 g, 110 mmoles) was added dropwise to a solution of 3,4-difluorobenzoic acid (15.8 g, 100 mmoles) in 60 ml of concentrated sulfuric acid at 10° for 1 hour. The reaction mixture was stirred at room temperature for 3 hours and diluted with 120 ml of ice water in an ice-salt bath. The product was collected by filtration, washed with water and cold ethanol. The pale yellow solid was dried at 40° for 16 hours to give 17.5 g (86%) of **2b**, mp 158-159° (ref [17a,b], 152-154°); ir (potassium bromide); 3310, 1716, 1540, 1438, 1196, 660 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 10.05 (br s, 1H), 8.14 (dd, 1H, J = 7.19, Hz, J = 3.66 Hz), 7.93 (dd, 1H, J = 8.00 Hz, J = 4.34 Hz); ^{13}C nmr (acetone-d_6): δ 164.3, 152.8, 152.0, 146.1, 125.7, 120.2, 115.5.

General Procedure for the Preparation of Keto Esters (**4a-e**).

Thionyl chloride (60.3 mmoles) was added to a well stirred suspension of compound **2** (50.2 mmoles) and urea (0.3 g) in 40 ml of anhydrous toluene. The reaction mixture was heated in an oil bath at 100° for 3 hours, then cooled to room temperature. The mixture of compound **3** (50.2 mmoles), magnesium (53.4 mmoles), ethanol (165.0 mmoles), carbon tetrachloride (1.1 ml) and 80 ml of anhydrous toluene was stirred at room temperature for 1 hour and refluxed for 1 hour. The reaction

mixture was cooled to 5°. The former solution was cannulated into the latter. The resulting reaction mixture was stirred at room temperature for 30 minutes and then 20 ml of 10% hydrochloric acid was added. The mixture was extracted with ether, and the combined organic extracts were washed with brine, dried and concentrated at reduced pressure.

Diethyl 2-nitrobenzoylmalonate (**4a**).

This compound was obtained in 99% yield as a beige liquid (ref [18]), ir (chloroform); 3428, 2964, 1726, 1702, 1455, 1196 cm^{-1}; ^1H nmr (deuteriochloroform): δ 14.53 (br s, 1H), 7.82-7.46 (m, 3H), 7.38 (d, 1H, J = 7.06 Hz), 4.18 (q, 2H, J = 7.12 Hz), 4.10 (q, 2H, J = 7.14 Hz), 1.26 (t, 3H, J = 7.12 Hz), 1.11 (t, 3H, J = 7.14 Hz); ^{13}C nmr (deuteriochloroform): δ 176.1, 169.7, 166.2, 152.3, 133.9, 130.6, 126.8, 125.1, 119.2, 97.4, 62.4, 61.8, 14.2, 14.0.

Diethyl 4,5-difluoro-2-nitrobenzoylmalonate (**4b**).

This compound was obtained in 95% yield as a yellow liquid, ir (chloroform); 3390, 1703, 1687, 1460, 1080, cm^{-1}; ^1H nmr (deuteriochloroform): δ 13.26 (br s, 1H), 8.11 (dd, 1H, J = 7.09 Hz, J = 6.93 Hz), 7.33 (dd, 1H, J = 8.69 Hz, J = 7.92 Hz), 4.24 (q, 2H, J = 7.13 Hz), 4.16 (q, 2H, J = 7.12 Hz), 1.26 (t, 3H, J = 7.13 Hz), 1.18 (t, 3H, J = 7.12 Hz); ^{13}C nmr (deuteriochloroform): δ 169.4, 168.9, 166.2, 158.1, 152.9, 148.2, 120.3, 118.6, 113.8, 95.7, 62.0, 61.9, 14.0, 13.8; ms (fab$^+$) 346 (M^++1), 274, 186 (base peak), 154, 137; hrms: calcd. for 346.0738, found 346.0734 (M^++1).

Ethyl 2-nitrobenzoylacetoacetate (**4c**).

This compound was obtained in 98% yield as a yellow liquid (ref [18]), ir (chloroform); 3368, 2951, 1726, 1706, 1454, 1088 cm^{-1}; ^1H nmr (deuteriochloroform): δ 13.84 (br s, 1H), 7.69-7.40 (m, 3H), 7.32 (d, 1H, J = 6.98 Hz), 4.22 (q, 2H, J = 7.13 Hz), 2.43 (s, 3H), 1.28 (t, 3H, J = 7.13 Hz); ^{13}C nmr (deuteriochloroform): δ 192.5, 174.8, 173.2, 150.6, 133.4, 128.9, 126.8, 125.7, 120.1, 100.6, 61.2, 21.4, 14.1.

Ethyl 4,5-difluoro-2-nitrobenzoylacetoacetate (**4d**).

This compound was obtained in 97% yield as a yellow liquid, ir (chloroform); 3405, 1712, 1639, 1437, 1014 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.55 (br s, 1H), 8.47 (dd, 1H, J = 6.99 Hz, J = 6.95 Hz), 7.83 (dd, 1H, J = 7.77 Hz, J = 7.75 Hz), 3.90 (q, 2H, J = 7.09 Hz), 2.45 (s, 3H), 0.86 (t, 3H, J = 7.09 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 192.3, 173.6, 165.8, 157.2, 155.0, 149.8, 119.6, 118.5, 113.4, 100.3, 58.9, 24.2, 13.4; ms (fab$^+$) 316 (M^++1, base peak), 270, 186, 137; hrms: calcd. for 316.0633, found 316.0632 (M^++1).

Ethyl 2-benzoyl-3-(4,5-difluoro-2-nitrophenyl)-3-oxopropanonate (**4e**).

This compound was obtained in 98% yield as a beige liquid, ir (chloroform); 3378, 1711, 1604, 1541, 1411, 1148 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.60 (br s, 1H), 8.62 (dd, 1H, J = 7.16 Hz, J = 7.13 Hz), 8.15-8.05 (m, 3H), 7.95 (dd, 1H, J = 7.93 Hz, J = 7.92 Hz), 7.67-7.60 (m, 2H), 3.94 (q, 2H, J = 7.15 Hz), 0.89 (t, 3H, J = 7.15 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 193.6, 173.1, 170.7, 158.0, 152.5, 150.2, 136.4, 133.8, 133.3, 129.8, 129.1, 127.6, 120.2, 118.7, 112.9, 95.8, 60.0, 13.9; ms (fab$^+$) 378 (M^++1, base peak), 332, 274, 193, 105, 77; hrms: calcd. for 378.0789, found 378.0789 (M^++1).

Ethyl 4-hydroxyquinolin-2(1*H*)-3-carboxylate (**5a**).

To a solution of keto diester **4a** (3.1 g, 10.0 mmoles) in dioxane (45 ml) was added 20% aqueous sodium hydroxide (10 ml) and 10% palladium-on-charcoal (0.4 g) at room temperature. The mixture was stirred for 20 minutes and then added dropwise to a solution of sodium borohydride (0.7 g, 18 mmoles) in water (5 ml). The reaction mixture was stirred at room temperature under hydrogen gas for 30 minutes and filtered through Celite. The filtrate was concentrated to remove dioxane and then the residue was acidified with 10% hydrochloric acid to give a pale yellow solid, which was recrystallized from ethanol to give 1.6 g (70%) of **5a**, mp 300° (dec, ref [19], 304°); ir potassium bromide); 3320-3084, 1711, 1412, 1144 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.64 (br s, 1H), 8.22-8.01 (m, 3H), 7.95 (d, 1H, J = 6.97 Hz), 4.26 (q, 2H, J = 7.11 Hz), 1.30 (t, 3H, J = 7.11 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 172.3, 171.4, 164.2, 151.1, 129.2, 126.3, 125.7, 120.2, 105.1, 99.0, 59.8, 13.9.

According to the same procedure, ethyl 6,7-difluoro-4-hydroxyquinolin-2(1*H*)-one-3-carboxylate (**5b**) was prepared. Compound **5b** was obtained in 72% yield from **4b**, mp 280° (dec); ir (potassium bromide); 3270-3030, 1649, 1579, 1188 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.86 (br s, 1H), 8.10 (dd, 1H, J = 9.34 Hz, J = 9.17 Hz), 7.71 (dd, 1H, J =7.01 Hz, J = 6.79 Hz), 4.44 (q, 2H, J = 7.13 Hz), 1.40 (t, 3H, J = 7.13 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 168.2, 165.6 162.8, 152.0, 148.5, 143.9, 117.2, 112.9, 109.8, 101.9, 61.8, 14.3; ms (m/e) 269 (M^+), 239 (base peak), 171, 143, 115.

Anal. Calcd. for $C_{12}H_9N$: C, 53.54; H, 3.37; N, 5.20. Found C, 55.36; H, 3.51; N, 5.39.

Ethyl 1-hydroxy-2-methyl-4-oxoquinoline-3-carboxylate (**6a**).

A solution of the diketo ester **4c** (2.8 g, 10.2 mmoles) in 80 ml of ethanol was hydrogenated over 10% palladium-on-charcoal (0.5 g) under atmospheric pressure at room temperature for 2 hours. The reaction mixture was filtered through Celite and evaporated to give a pale yellow solid, which was recrystallized from ethanol to give 1.9 g (77%) of **6a**, mp 198°; ir (potassium bromide); 3508, 1713, 1588, 1246, 1096 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.43 (br s, 1H), 12.25 (br s, 1H), 8.29 (d, 1H, J = 7.94 Hz), 7.64-7.40 (m, 3H), 4.23 (q, 2H, J = 7.12 Hz), 2.32 (s, 3H), 1.30 (t, 3H, J = 7.12 Hz); ^{13}C nmr (dimethyl sulfoxide d_6): δ 171.2, 166.5, 154.1, 150.8, 135.4, 128.1, 126.4, 120.9, 110.3, 101.7, 57.8, 14.1, 12.7.

Ethyl 6,7-difluoro-1-hydroxy-2-methyl-4-oxoquinoline-3-carboxylate (**6b**).

A solution of the diketo ester **4d** (3.2 g, 10.2 mmoles) in 80 ml of ethanol was hydrogenated over 10% palladium-on-charcoal (0.6 g) under atmospheric pressure at room temperature for 6 hours. The reaction mixture was filtered through Celite and evaporated to give a pale yellow solid, which was recrystallized from ethanol to give 2.2 g (78%) of **6b**, mp 202°; ir (potassium bromide); 3450, 1717, 1605, 1475, 1110 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.33 (br s, 1H), 8.04 (dd, 1H, J = 10.07 Hz, J = 8.44 Hz), 7.91 (dd, 1H, J = 7.09 Hz, J = 6.77 Hz), 4.26 (q, 2H, J = 7.10 Hz), 2.42 (s, 3H), 1.30 (t, 3H, J = 7.10 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 168.0, 164.8, 152.5, 149.1, 147.3, 143.6, 135.2, 119.8, 110.9, 102.3, 58.9, 13.6, 12.1; ms (m/e) 283 (M^+), hrms: calcd. for 283.0707, found 283.0727 (M^+).

According to the same procedure, ethyl 6,7-difluoro-1-hydroxy-2-phenyl-4-oxoquinoline-3-carboxylate (**6c**) was prepared. Compound **6c** was obtained in 71% yield from **4e**, mp

194-195°; ir (potassium bromide); 3414, 1720, 1608, 1477, 1102 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.26 (br s, 1H), 8.17 (dd, 1H, J = 8.61 Hz, J = 8.59 Hz), 7.63-7.53 (m, 5H), 3.96 (q, 2H, J = 7.11 Hz), 0.90 (t, 3H, J = 7.11 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 169.8, 164.4, 154.5, 150.8, 150.4, 148.6, 145.3, 136.8, 130.1, 129.4, 128.5, 127.6, 121.7, 115.1, 112.5, 104.4, 59.9, 13.0; ms (m/e) 345 (M^+), hrms: calcd. for 329.0863, found 329.0847 (M^+).

Ethyl 3,4-difluoro-2-nitrobenzoylacetate (**7**).

A solution of diethyl 4,5-difluoro-2-nitrobenzoylmalonate **4b** (7.0 g, 20.3 mmoles) and *p*-toluenesulfonic acid (0.2 g) in 80 ml of water was refluxed for 12 hours. The reaction mixture was cooled at room temperature and extracted with 120 ml of ethyl acetate. The organic layer was washed with 2% sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give a yellow oil 5.0 g (91%) of **7**, ir (chloroform); 3280-3045, 1738, 1605, 1070 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.07 (dd, 1H, J = 6.71 Hz, J = 6.69 Hz), 7.45 (dd, 1H, J = 7.39 Hz, J = 7.37 Hz), 4.18 (q, 2H, J = 7.14 Hz), 3.88 (s, 1H), 2.54 (s, 1H), 1.28 (t, 3H, J = 7.14 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 182.9, 168.2, 159.1, 158.7, 153.5, 133.2, 117.4, 115.6, 61.4, 44.8, 14.1; ms (fab^+) 274 (M^++1, base peak), 186, 137, 89; hrms: calcd. for 274.0527, found 274.0528 (M^++1).

6,7-Difluoro-4-hydroxyquinolin-2(1*H*)-one **(8)**.

Method A The keto ester **7** (5.5 g, 20.1 mmoles) in ethanol (120 ml) was hydrogenated over 10% palladium-on-charcoal (1.0 g) at 36 psi for 1 hour. The mixture was filtered through Celite and evaporated. A dark yellow solid was obtained, which was recrystallized from ethanol to give 3.8 g (96%) of **8**, mp 310° (dec); ir (potassium bromide); 3200-2230, 1685, 1486, 1173 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.65 (br s, 1H), 11.34 (br s, 1H), 7.69 (dd, 1H, J = 8.69 Hz, J = 8.69 Hz), 7.21 (dd, 1H, J = 6.99 Hz, J = 6.99 Hz), 5.76 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 163.4, 152.8, 149.5, 146.3, 143.1, 136.3, 110.5, 103.3, 98.4; ms (m/e) 197 (M^+); hrms: calcd. for 197.0288, found 197.0291 (M^+).

Anal. Calcd. for $C_9H_5N_1$: C, 54.83; H, 2.55; N, 7.10. Found C, 54.89; H, 2.51; N, 7.23.

Method B A mixture of ethyl 6,7-difluoro-4-hydroxyquinolin-2(1*H*)-one-3-carboxylate **5b** (2.6 g, 7.5 mmoles), 3*N* hydrochloric acid (30 ml) and ethanol (12 ml) was refluxed for 6 hours. The reaction mixture was cooled to 10° and filtered. The product was washed with water, dried in the air to afford 1.7 g (92%) of **8** as a white solid. Analyses same as *Method A.*

6,7-Difluoro-3-nitro-4-hydroxyquinolin-2(1*H*)-one (**9**).

A solution of **8** (1.1 g, 5.6 mmoles), nitric acid (70%, 12 ml, 8 mmoles) and glacial acetic acid (8 ml) was heated at 90° for 1 hour. The reaction mixture was cooled to room temperature and then diluted with 12 ml of ice water. The product was filtered and washed with water, and dried to give 1.0 g (77%) of **9** as a yellow crystal, mp 193-194°; ir (potassium bromide); 3280-2160, 1658, 1420, 1188 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.93 (br s, 1H), 7.80 (dd, 1H, J = 8.44 Hz, J = 8.42 Hz), 7.11 (dd, 1H, J = 6.89 Hz, J = 6.88 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 156.4, 154.7, 151.4, 147.6, 144.3, 135.9, 127.1, 112.8, 104.5; ms (m/e) 242 (M^+); hrms: calcd. for 242.0139, found 242.0142 (M^+).

Anal. Calcd. for $C_9H_4N_2$: C, 44.64; H, 1.66; N, 11.57. Found C, 44.73; H, 1.71; N, 11.80.

6,7-Difluoro-2,3,4-trichloroquinolin (**10**).

A solution of **9** (2.5 g, 10.3 mmoles), phosphoryl chloride (14 ml) and triethylamine (2 ml) was heated at 100° for 2 hours. The excess solvent was evaporated *in vacuo* and the residue was poured on 33 ml of ice water. The solution was brought to pH 6 with 2*N* sodium hydroxide and then the precipitated solid was filtered, washed with water, and dried to afford 2.4 g (86%) of **10** as a white solid, mp 96°; ir (potassium bromide); 3390, 1509, 1252, 1196, 660 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.03 (dd, 1H, J = 8.00 Hz, J = 7.98 Hz), 7.00 (dd, 1H, J = 7.44 Hz, J = 7.33 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 156.2, 153.9, 152.9, 150.5,134.1, 130.6, 122.2, 116.5, 111.8; ms (m/e) 268 (M^+), 232, 220, 197 (base peak), 171, 136, 112.

Anal. Calcd. for C_9H_2N: C, 40.27; H, 0.75; N, 5.22. Found C, 41.23; H, 0.75; N, 5.41.

6,7-Difluoro-4-hydroxyquinolin-2(1*H*)-3-carboxamide **(11)**.

A solution of **5b** (1.6 g, 5.9 mmoles) in 14 ml of ammomium hydroxide (28%) was heated at 90° for 6 hours. The reaction mixture was poured into 16 ml of water and then acidified (pH = 4.0-4.5) with 10% hydrochloric acid. The precipitated solid was filtered, which was recrystallized from ethanol to give 1.1 g (75%) of **11** as a beige solid, mp 268° (dec); ir (potassium bromide); 3367, 3154, 1647, 1579, 1211 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 11.69 (br s, 1H), 9.52 (br s, 1H), 8.83 (br s, 1H), 8.08 (dd, 1H, J = 7.46 Hz, J = 7.44 Hz), 7.96 (dd, 1H, J = 6.83 Hz, J = 6.81 Hz), 7.78 (br s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 172.8, 168.4, 164.1, 158.4, 155.6, 147.2, 144.0, 136.8, 112.6, 102.2; ms (fab^+) 241 (M^++1, base peak), 195, 83; hrms: calcd. for 241.0425, found 241.0420 (M^++1).

Ethyl 6,7-difluoro-2-methyl-4-oxoquinoline-3-carboxyl-ate (**12a**).

The mixture of **6b** (1.4 g, 5.0 mmoles) was dissolved in 16 ml of 80% v/v aqueous ethanol and the solution treated with sodium hydrosulfite (1.0 g, 6.0 mmoles). The reaction mixture was heated at 60° for 3 hours, then cooled to room temperature and then the mixture was neutralized with 10% hydrochloric acid. The pale yellow solid was collected by filtration, washed with water and recrystallized from ethanol to give 1.2 g (90%) of **12a**, mp 212-213°; ir (potassium bromide); 3387, 1692, 1584, 1178 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.13 (d, 1H, J = 7.91 Hz), 7.92 (d, 1H, J = 7.65 Hz), 4.26 (q, 2H, J = 7.14 Hz), 2.31 (s, 3H), 1.28 (t, 3H, J = 7.14 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 176.3, 168.0, 152.5, 149.1, 147.3, 143.8, 135.3, 119.8, 110.9, 102.3, 58.9, 16.6, 12.3; ms (m/e) 267 (M^+), 221 (base peak), 165; hrms: calcd. for 267.0707, found 267.0728 (M^+).

According to the same procedure, ethyl 6,7-difluoro-2-phenyl-4-oxoquinoline-3-carboxylate (**12c**) was prepared. Compound **12c** was obtained in 81% yield from **6c**, mp 202-204°; ir (potassium bromide); 3362, 1702, 1681, 1565, 1106 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.41 (d, 1H, J = 8.02 Hz), 8.03 (d, 1H, J = 8.02 Hz), 7.91-7.69 (m, 5H), 4.20 (q, 2H, J = 7.13 Hz), 1.13 (t, 3H, J = 7.13 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 179.8, 164.4, 154.5, 150.8, 150.4, 148.6, 145.3, 136.8, 130.8, 129.4, 128.5, 127.6, 121.7, 115.1, 112.5, 104.4, 59.9, 13.9; ms (m/e) 329 (M^+); hrms: calcd. for 329.0864, found 329.0848 (M^+).

Anal. Calcd. for $C_{18}H_{13}N$: C, 65.65; H, 3.98; N, 4.25. Found C, 65.33; H, 3.89; N, 4.23.

6,7-Difluoro-2-methyl-4-oxoquinoline-3-carboxylic Acid (**13a**).

A suspension of **12a** (1.2 g, 4.5 mmoles) in 50 ml of 2*N* aqueous sodium hydroxide was refluxed for 3 hours. The reaction mixture was cooled and acidified with 10% hydrochloric acid. The white solid was collected by filtration, washed with water and dried to give 1.0 g (94%) of **13a**, mp 310∞ (dec); ir (potassium bromide); 3447, 1636, 1465, 1227, 697 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.48 (br s, 1H), 8.25 (dd, 1H, J = 7.76 Hz, J = 7.76 Hz), 8.03 (dd, 1H, J = 7.31 Hz, J = 7.30 Hz) , 2.45 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 173.1, 167.4, 158.2, 149.6, 146.1, 144.8, 127.1, 115.6, 113.7, 110.2, 16.7; ms (m/e) 239 (M^+); hrms: calcd. for 239.0394, found 239.0403 (M^+).

Anal. Calcd. for $C_{11}H_7N_1$: C, 55.24; H, 2.95; N, 5.86. Found C, 56.63; H, 3.02; N, 5.68.

6,7-Difluoro-2-phenyl-4-oxoquinoline-3-carboxylic Acid (**13c**).

To a solution of **12c** (0.6 g, 1.8 mmoles) in tetrahydrofuran/-water (v/v, 3:1, 30 ml) was added lithium hydroxide (0.2 g , 9.0 mmoles) in tetrahydrofuran (8 ml). The mixture was stirred at room temperature for 18 hours. The reaction mixture was acidified with 10% hydrochloric acid. The white solid was collected by filtration, washed with water and dried to give 0.5 g (92%) of **13c**, mp 310∞ (dec); ir (potassium bromide); 3447, 1636, 1465, 1227, 697 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.02 (br s, 1H), 8.12 (dd, 1H, J = 7.91 Hz, J = 7.86 Hz), 8.96 (dd, 1H, J = 7.55 Hz, J = 7.49 Hz), 7.51-7.40 (m, 5H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 172.8, 167.3, 166.1, 158.4, 149.8, 147.2, 131.6, 130.8, 129.1, 128.5, 127.6, 126.9, 124.0, 116.7, 112.8, 105.9.

Anal. Calcd. for $C_{16}H_9N$: C, 63.79; H, 3.01; N, 4.65. Found C, 63.99; H, 3.12; N, 4.51.

General Procedure for the Preparation of 6-Fluoro-2-(methyl or phenyl)-1,4-dihydro-7-(1-piperazinyl or 1-methylpiperazinyl)-4-oxoquinoline-3-carboxylic Acids (**14a-d**).

A mixture of **13a,c** (3.3 mmoles) and piperazine or *N*-methylpiperazine (10.0 mmoles) in 20 ml of pyridine was heated at 90° for 6-36 hours under nitrogen atmosphere. The reaction mixture was evaporated under reduced pressure. The residue was treated with water, and then the resulting precipitate was collected by filtration, washed with water and recrystallized from ethanol or *N*,*N*-dimethylformamide to afford **14a-d**, respectively.

6-Fluoro-2-methyl-1,4-dihydro-7-(1-piperazinyl)-4-oxo-quinoline-3-carboxylic Acid (**14a**).

This compound was obtained in 78% yield as a beige crystal, mp 216-217°; ir (potassium bromide); 1702, 1656, 1432, 1091 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.62 (br s, 1H), 8.25 (dd, 1H, J = 7.22 Hz, J = 7.20 Hz), 8.03 (dd, 1H, J = 7.01 Hz, J = 7.04 Hz), 3.64-3.33 (m, 4H), 2.91-3.24 (m, 4H), 2.38 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 174.0, 167.2, 161.9, 156.3, 149.7, 143.7, 123.1, 115.6, 113.8, 107.1, 51.3, 50.9, 45.8, 44.9, 16.5.

Anal. Calcd. for $C_{15}H_{16}N_3$: C, 59.01; H, 5.28; N, 13.76. Found C, 60.30; H, 5.13; N, 13.89.

6-Fluoro-2-methyl-1,4-dihydro-7-(1-methylpiperazinyl)-4-oxoquinoline-3-carboxylic Acid (**14b**).

This compound was obtained in 71% yield as a colorless crystal, mp 246º (dec); ir (potassium bromide); 1710, 1650, 1411, 1105 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.81 (br s, 1H), 8.28 (dd, 1H, J = 7.90 Hz, J = 7.88 Hz), 8.17 (dd, 1H, J = 7.67 Hz, J = 7.67 Hz) , 3.81-3.55 (m, 4H), 3.30-2.86 (m, 4H), 2.44 (s, 3H), 2.29 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 173.1, 166.1, 161.2, 156.7, 148.7, 144.2, 122.1, 116.3, 113.9, 108.1, 55.2, 54.9, 50.2, 49.8, 41.7, 16.7.

Anal. Calcd. for $C_{16}H_{18}N_3$: C, 60.18; H, 5.68; N, 13.16. Found C, 62.35; H, 5.59; N, 12.98.

6-Fluoro-2-phenyl-1,4-dihydro-7-(1-piperazinyl)-4-oxoquinoline-3-carboxylic Acid (**14c**).

This compound was obtained in 80% yield as a pale yellow solid, mp 204∞; ir (potassium bromide); 1698, 1636, 1460, 1121 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.66 (br s, 1H), 9.66 (s, 1H), 8.12 (dd, 1H, J = 8.09 Hz, J = 8.05 Hz), 8.09 (dd, 1H, J = 7.92 Hz, J = 7.92 Hz) , 7.73-7.48(m, 5H), 3.68-3.45 (m, 4H), 3.21-2.98 (m, 4H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 172.5, 165.9, 165.1, 155.0, 149.3, 143.2, 141.9, 130.1, 129.6, 127.9, 127.0, 123.8, 122.7, 116.0, 111.5, 107.3, 52.4, 51.9, 46.5, 45.8;

Anal. calcd. for $C_{20}H_{18}N_3$: C, 65.39; H, 4.94; N, 11.44. found C, 63.90; H, 5.03; N, 11.27.

6-Fluoro-2-phenyl-1,4-dihydro-7-(1-methylpiperazinyl)-4-oxoquinoline-3-carboxylic Acid (**14d**).

This compound was obtained in 76% yield as a colorless crystal, mp 209-210∞; ir (potassium bromide); 1714, 1644, 1420, 1105 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 13.93 (br s, 1H), 8.06 (dd, 1H, J = 7.78 Hz, J = 7.78 Hz), 7.90 (dd, 1H, J = 7.65 Hz, J = 7.62 Hz) , 7.68-7.42 (m, 5H), 3.72-3.49 (m, 4H), 3.28-3.04 (m, 4H), 2.29 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 172.9, 166.6, 165.1, 154.6, 143.7, 142.5, 132.9, 130.1, 129.8, 128.3, 127.9, 127.1, 122.7, 116.4, 111.9, 107.3, 55.6, 54.1, 49.0, 48.6, 41.1;

Anal. Calcd. for $C_{21}H_{20}N_3$: C, 66.13; H, 5.29; N, 11.02. Found C, 65.28; H, 5.42; N, 11.34.

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