SYNTHESIS OF 6,7-DIHYDRO-8-(4-METHYL-1-PIPERAZINYL)-[1]BENZOXEPINO[4,5-c]QUINOLINE AS POTENTIAL 5-HT$_3$ RECEPTOR LIGAND

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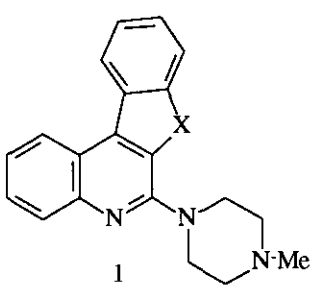
Abstract - Two synthetic routes to the achievement of the title compound are described. The [1]benzoxepino[4,5-c]quinoline nucleus was prepared by nucleophilic aromatic fluoride displacement-cyclization and functionalized with N-methylpiperazine moiety. Alternatively the oxepino ring closure is shifted as the final step. An oxepine ring cleavage occurred in compounds (9) and (3); a mechanistical interpretation is proposed.

We have recently reported on the synthesis[1] of some indeno[2,1-c]quinoline derivatives (1). These conformational constrained derivatives of 2 displayed nanomolar affinity for 5-HT$_3$ sites which appeared much higher than that reported for the parent compound (2). Our structure-affinity relationship studies carried out on these complex arylpiperazines pointed out the importance of the conformation of the phenyl ring in the 4-position of the quinoline nucleus. In order to better understand the role of this structural feature in the interaction with serotonin recognition sites, we were prompted to synthesize [1]benzoxepino[4,5-c]quinoline (3), which could be regarded as a semirigid analogue of 2.



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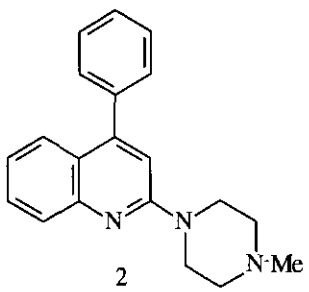

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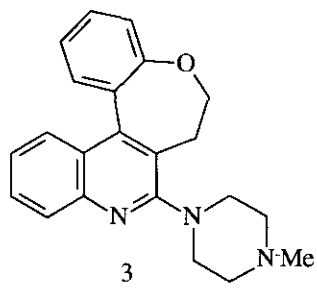


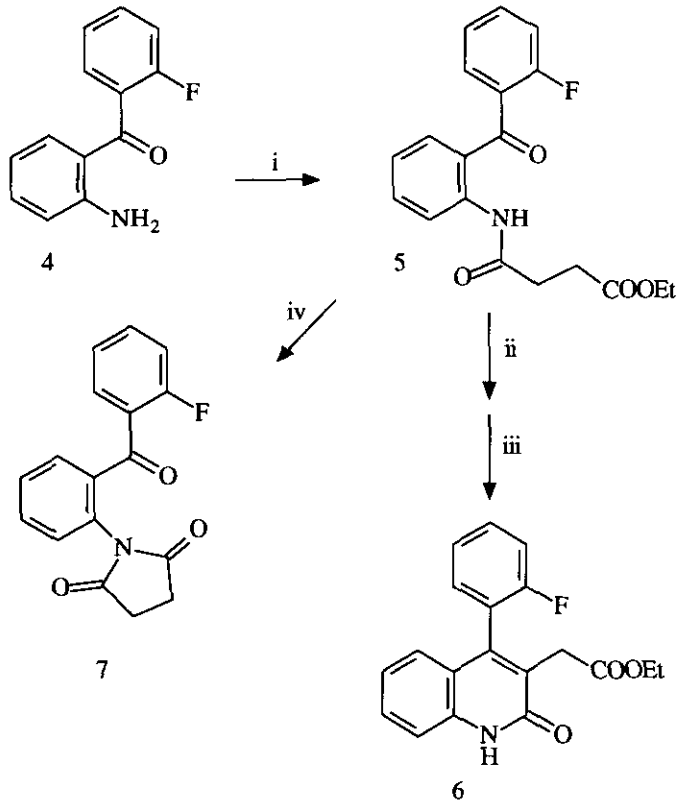
3

X : C=O, CH_2

In this paper we intend to report two different approaches for the synthesis of compound (3); in the first approach the [1]benzoxepino[4,5-c]quinoline ring system was synthesized from the key intermediate (6) and successively

functionalized by the introduction of a N-methylpiperazine moiety, while in the other approach the nucleophilic aromatic fluoride displacement-cyclization, which leads to the formation of the oxepine ring, occurred after the introduction of N-methylpiperazine moiety as final step. The key intermediate (6) was prepared as outlined in Scheme 1.

Scheme 1

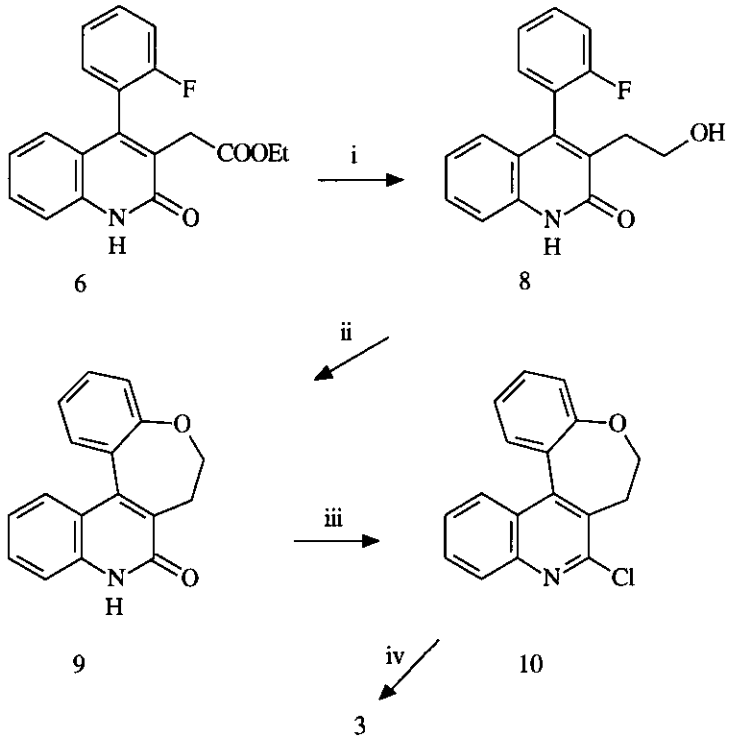


4 5 7 6

Reagents : i = $ClCO(CH_2)_2COOEt/CH_2Cl_2$, ii = t-BuOK/EtOH,
iii = $POCl_3$/EtOH, iv = PPA

The succinanilate (5) was obtained by acylating the benzophenone (4)[2] with ethyl succinyl chloride and cyclized in alkaline conditions; treatment of crude acid material obtained with ethanol and phosphorus oxychloride furnished the expected quinolone (6). Stirring compound (5) in concentrated strong acid (PPA or sulfuric acid) succinimide (7) was the sole product isolated. The first approach to the synthesis of compound (3) is depicted in Scheme 2.

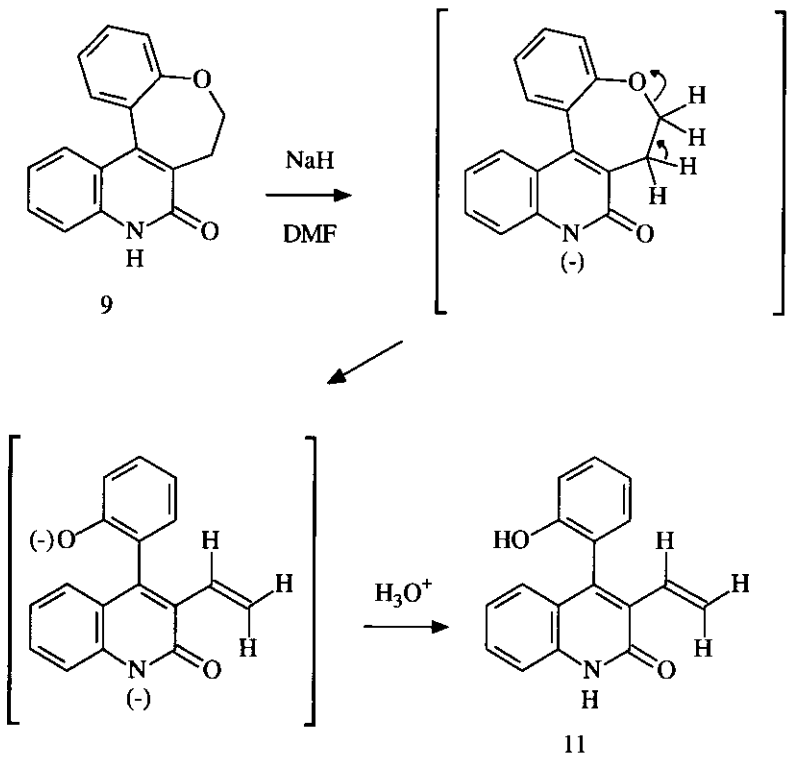
Scheme 2



Reagents : i = $LiAlH_4$/THF, ii = NaH/DMF, iii = $POCl_3$, iv = N-Methylpiperazine

Selective reduction of the ester (6) with lithium aluminum hydride yielded the desired alcohol (8), which was cyclized with nucleophilic aromatic fluoride displacement into 6,7-dihydro[1]benzoxepino[4,5-c]quinolin-8(9H)-one (9). We have discovered that the cyclization reaction, handled in the conditions reported by Walser and co-workers for the synthesis of the lower homologous 11-chloro-6,8-dihydro-7H-[1]benzopyrano[3,4-c]quinolin-7-one,[3] produced, beside the expected compound (9), a little amount of a byproduct which was eliminated from the reaction mixture by washing with ethyl acetate. Spectroscopic studies (ir and ^{1}H-Nmr) and mass spectrometry suggested for this byproduct the structure (11). This structure prompted us to consider 11 as a ring cleavage product of compound (9). This hypothesis appeared substantiated by the observation that the amount of compound (11) in the reaction mixture increased (to detriment of compound (9) as the reaction time increased. Furthermore by heating 9 at 155-160°C in N,N-dimethylformamide in presence of sodium hydride we obtained a total ring cleavage after 20 minutes. In Scheme 3 we proposed a possible mechanistical interpretation of the observed ring cleavage.

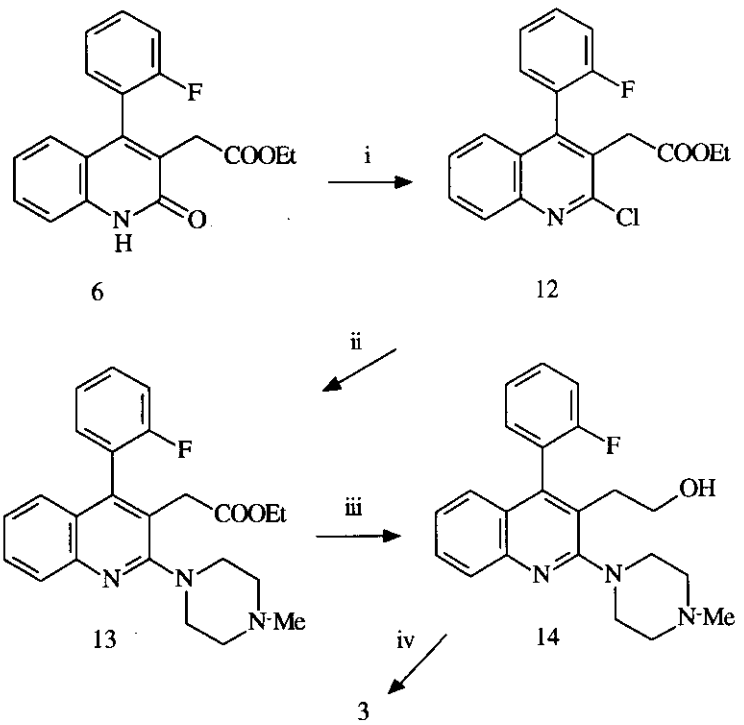
Scheme 3



9 11

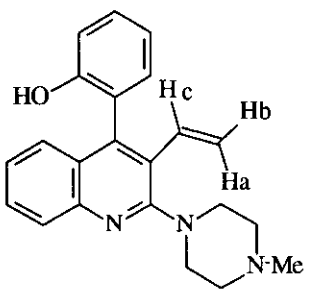
The optimization of the cyclization conditions and purification of compound (9) was rather difficult, but after several attempts it was possible to obtain 9 in 47% yield. Finally, compound (8) was converted, by refluxing in phosphorus oxychloride into 8-chloro-6,7-dihydro[1]benzoxepino[4,5-c]quinoline (10) which was transformed into piperazinyl derivative (3) by reaction with N-methylpiperazine. In order to improve the efficiency of the synthesis of compound (3) we changed strategy shifting the nucleophilic aromatic fluoride displacement-cyclization as final step (Scheme 4).

Scheme 4



Reagents : i = $POCl_3$, ii = N-Methylpiperazine, iii = $LiAlH_4$/THF, iv = NaH/DMF

The key intermediate (6) was easily transformed into the corresponding 2-chloroquinoline (12) which was successively converted into piperazinyl derivative (13). Selective reduction of compound (13) with lithium aluminum hydride furnished the expected alcohol (14). Cyclization of compound (14) was easily optimized by monitoring the reaction trend with thin layer chromatography and compound (3) was obtained in good overall yield.



15

The vinylquinoline (15) was obtained only in trace amount in the optimized cyclization reaction, but it constituted

the sole reaction product when 3 was heated in N,N-dimethylformamide at 155-160°C in presence of sodium hydride for 20 min.

EXPERIMENTAL

Melting points are determined in open capillaries on a Electrothermal 8103 apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240C Elemental Analyzer. Merck silica gel 60, 70-230 mesh, was used for column chromatography and Riedel-de Haen DC-Mikrokarten SI F 37341 were used as tlc. Ir spectra were recorded in nujol mulls with a Perkin-Elmer mod. 397 spectrophotometer. ^{1}H-Nmr spectra were recorded with a Bruker AC 200 spectrometer in the indicated solvents (TMS as internal standard): the values of chemical shifts are expressed in ppm and coupling costants (J) in Hz. Mass spectra (EI, 70 eV) were recorded on a VG 70-250S spectrometer. Ir, nmr spectra and elemental analyses were performed by Dipartimento Farmaco Chimico Tecnologico - Università di Siena. Mass spectra were performed by Centro di Analisi e Determinazioni Strutturali - Università di Siena.

Ethyl 2-(2-fluorobenzoyl)succinanilate (5)

To a solution of 4 (4.3 g, 20 mmol) in dichloromethane (50 ml), ethyl succinyl chloride (3.4 ml, 23.9 mmol) was added dropwise at 0°C with stirring. The reaction mixture was allowed to warm to room temperature, stirred for 3 h and then a saturated sodium bicarbonate solution was added within 20 min at 0-5°C with vigorous stirring. The organic layer was separated, dried over sodium sulfate and evaporated. Crystallization of the residue from cyclohexane gave 5 in 85% yield (5.85 g). An analytical sample recrystallized from the same solvent melted at 94-95°C. Ir: 3260, 1735, 1700, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.26 (t, J=7.0, 3H, CH_3), 2.71-2.86(m, 4H, $2CH_2$), 4.17 (q, J=7.0, 2H, OCH_2), 7.01-7.62 (m, 7H, Ar-H), 8.74 (d, J=8.6, 1H, Ar-H), 11.43 (bs, 1H, NH). Anal. Calcd for $C_{19}H_{18}NO_4F$: C, 66.46; H, 5.28; N, 4.08. Found: C, 66.73; H, 5.32; N, 4.12.

Ethyl 4-(2-fluorophenyl)quinolin-2(1H)-one-3-acetate (6)

A mixture of 5 (5.6 g, 16.3 mmol) in absolute ethanol (80 ml) with potassium tert-butoxide (1.6 g, 14.3 mmol) was refluxed for 1 h and then other potassium tert-butoxide (1 g, 8.9 mmol) was added and the mixture was refluxed for 10 min. The solvent was concentrated in vacuo and the residue was dissolved in water. The filtrate was cautiously acidified with 3N hydrochloric acid and the precipitate was collected by filtration, washed and dried. To a mixture of this crude acid in absolute ethanol (50 ml), phosphorus oxychloride (3 ml, 32.8 mmol) was added and the reaction mixture was allowed to cool to room temperature. Afterwards the solvent was removed in vacuo the residue was treated with ice-water and collected by filtration. By washing the yellow solid with ether pure 6 was obtained as white crystals (1.75-2.44 g, yield 33-46%). Crystallization from ethyl acetate furnished an analytical sample melting at 219-221°C. Ir: 1740, 1650 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.22 (t, J=7.0, 3H, CH_3), 3.54 (ABq, J=16.5, 2H, CH_2CO,), 4.05-4.21 (m, 2H, OCH_2), 7.05-7.56 (m, 8H, Ar-H), 12.66 (bs, 1H, NH). Anal. Calcd for $C_{19}H_{16}NO_3F$: C, 70.14; H, 4.96; N, 4.31. Found: C, 70.42; H, 4.98; N, 4.37.

N-[2-(2-Fluorobenzoyl)phenyl]succinimide (7)

A mixture of 5 (0.5 g, 1.5 mmol) in polyphosphoric acid (10 g) was stirred at 90-100°C for 20 h, then cooled, and ice-water was added. The aqueous mixture was basified with 10% sodium hydroxide and extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo to give a gummy solid. Purification by chromatography eluting with dichloromethane-ethyl acetate (8:2) gave 7 which was further purified by crystallization from benzene-cyclohexane (0.308 g, yield 69%, mp 134-135°C). Ir: 1720, 1670 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 2.73 (s, 4H, $2CH_2$), 7.09-7.35 (m, 3H, Ar-H), 7.50-7.67 (m, 5H, Ar-H). Ms: m/z 297 (M^+, 87). Anal. Calcd for $C_{17}H_{12}NO_3F$: C, 68.68; H, 4.07; N, 4.71. Found: C, 68.86; H, 4.24; N, 4.71.

4-(2-Fluorophenyl)-3-(2-hydroxyethyl)quinolin-2(1H)-one (8)

To a suspension of lithium aluminum hydride (0.7 g, 18.5 mmol) in tetrahydrofuran (10 ml), a solution of 6 (1 g, 3.1 mmol) in tetrahydrofuran (20 ml) was added. After stirring for 30 min at -20° to 0°C, the hydride was hydrolyzed by addition of water and the mixture was partitioned between chloroform and 3N hydrochloric acid. The organic layer was washed with water, dried over sodium sulfate and evaporated. The residue crystallized with ethanol-ethyl acetate yielded 0.71g (81%) of 8 as a white solid with mp 229-232°C. Ir: 3310-3240, 1660 cm^{-1}. ^{1}H-Nmr (DMSO-d_6): 2.42-2.69 (m, 2H, CH_2-CH_2OH), 3.38-3.49 (m, 2H, CH_2OH), 4.61 (t, J=5.4, 1H, OH), 6.85 (d, J=8.0, 1H, Ar-H), 7.10 (t, J=7.4, 1H, Ar-H), 7.38-7.68 (m, 6H, Ar-H), 12.03 (bs, 1H, NH). Anal. Calcd for $C_{17}H_{14}NO_2F$: C, 72.07; H, 4.98; N, 4.95. Found: C, 72.36.; H, 4.84; N, 4.68.

6,7-Dihydro-[1]benzoxepino[4,5-c]quinolin-8(9H)-one (9)

To a solution of 8 (0.2 g, 0.7 mmol) in dry N,N-dimethylformamide (10 ml) sodium hydride (0.05 g, 2.13 mmol) was added and the reaction mixture was heated at 155-160°C in a nitrogen atmosphere for 5 min and then poured into ice-water. The aqueous mixture was acidified with 3N hydrochloric acid and the precipitate was collected by filtration, washed with water and dried. Washing the dry crude product with ethyl acetate, pure 9 (0.087 g, 47% yield) was obtained as white crystals. An analytical sample crystallized from ethanol-N,N-dimethylformamide melted at 292-294°C. Ir: 3160, 1660 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 2.36-2.54 (m, 1H, H-7), 3.46-3.55 (m, 1H, H-7), 4.51-4.70 (m, 2H, OCH_2), 7.14-7.55 (m, 7H, Ar-H), 7.75 (d, J=8.9, 1H, Ar-H), 11.08 (bs, 1H, NH). Ms: m/z 263 (M^+, 52). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.43; H, 4.83; N, 5.03.

3-Ethenyl-4-(2-hydroxyphenyl)quinolin-2(1H)-one (11)

Compound (11) was isolated, as a byproduct of the above described reaction in washing mother liquor and purified by chromatography eluting with chloroform-ethyl acetate (7:3) (0.018 g, yield 10%). An analytical sample crystallized from benzene-ethyl acetate melted at 226-228°C. Ir: 3340, 3160, 1660 cm^{-1}. ^{1}H-Nmr (DMSO-d_6): 5.28 (dd, J=3.8 and 11.6, 1H, X-part of an ABX system, H_X), 6.29 (dd, J=11.6 and 17.5, 1H, H_B), 6.44 (dd, J=3.8 and 17.5, 1H, H_A), 6.92-7.11 (m, 5H, Ar-H), 7.31-7.52 (m, 3H, Ar-H), 9.47 (s, 1H, OH), 11.91 (bs, 1H, NH).[4] Ms: m/z 263 (M^+, 100). Anal. Calcd for $C_{17}H_{13}NO_2$: C,77.55; H, 4.98; N, 5.32. Found: C, 77.76; H, 4.85; N, 5.06.

8-Chloro-6,7-dihydro[1]benzoxepino[4,5-c]quinoline (10)

A mixture of 9 (0.9 g, 3.4 mmol) in phosphorus oxychloride (10 ml, 109.2 mmol) was refluxed for 50 min and then poured into ice-water. The precipitate was extracted with chloroform and the organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo. Purification by chromatography of the residue, eluting with chloroform gave pure 10 as white solid (0.89 g, yield 93%). An analytical sample crystallized from n-hexane melted at 141-142°C. ^{1}H-Nmr ($CDCl_3$): 2.78-2.96 (m, 1H, H-7), 3.38-3.47 (m, 1H, H-7), 4.51-4.69 (m, 2H, CH_2O), 7.26-7.57 (m, 5H, Ar-H), 7.71 (t, J=8.0, 1H, Ar-H), 8.00-8.10 (m, 2H, Ar-H). Ms: m/z 281 (M^+, 100). Anal. Calcd for $C_{17}H_{12}NOCl$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.69; H, 4.44; N, 5.03.

6,7-Dihydro-8-(4-methyl-1-piperazinyl)[1]benzoxepino[4,5-c]quinoline (3)

Method A

A solution of 10 (0.2 g, 0.7 mmol) in N-methylpiperazine (8 ml) was heated overnight at 120°C under nitrogen atmosphere, cooled and then poured into ice-water. The precipitate was extracted with chloroform and the organic layer was washed with water, dried over sodium sulfate and evaporated. The residue was quickly purified by column chromatography eluting with ethyl acetate-triethylamine (8:2) and 3 was obtained in 93% yield (0.225 g) as white solid. An analytical sample crystallized from n-hexane melted at 132-133°C.

Method B

To a solution of 14 (0.3 g, 0.8 mmol) in dry N,N-dimethylformamide (10 ml), sodium hydride (0.06 g, 2.46 mmol) was added and the reaction mixture was heated at 75-80°C under a nitrogen atmosphere. The reaction, monitored by tlc, was stopped when 14 disappeared (1.5 h) and then the reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate. The evaporation of organic phase gave an oily residue which was purified by chromatography eluting with ethyl acetate-triethylamine (8:2) gave pure 3 as white solid (0.196 g, yield 71%). Crystallization from n-hexane yielded an analytical sample melting at 132-133°C. ^{1}H-Nmr ($CDCl_3$): 2.38 (s, 3H, CH_3), 2.64 (t, J=4.7, 4H, piperazine), 2.72-2.85 (m, 1H, H-7), 3.07-3.16 (m, 1H, H-7), 3.35 (t, J=4.7, 4H, piperazine), 4.55-4.62 (m, 2H, OCH_2), 7.23-7.59 (m, 6H, Ar-H), 7.85-7.96 (m, 2H, Ar-H). Anal. Calcd for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found: C, 76.76; H, 6.86, N, 12.15.

Ethyl 2-chloro-4-(2-fluorophenyl)quinoline-3-acetate (12)

A mixture of 6 (1 g, 3.1 mmol) in phosphorus oxychloride (7 ml, 76.5 mmol) was refluxed for 2 h and then poured into ice-water. The precipitate was extracted with dichloromethane and the organic layer was washed with water, dried over sodium sulfate and evaporated. Purification by chromatography of the residue, eluting with chloroform furnished pure 12 (0.97 g, yield 91%) as white solid. Crystallization from n-hexane gave an analytical sample melting at 102-103°C. Ir: 1730 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.19 (t, J=7.3, 3H, CH_3), 3.72 (ABq, J=17.2, 2H, CH_2CO), 4.04-4.19 (m, 2H, OCH_2), 7.22-7.58 (m, 6H, Ar-H), 7.67-7.75 (m, 1H, Ar-H), 8.07 (d, J=8.5, 1H, Ar-H). Anal. Calcd for $C_{19}H_{15}NO_2ClF$: C, 66.38; H, 4.40; N, 4.07. Found: C, 66.28; H, 4.39; N, 4.09.

Ethyl 4-(2-fluorophenyl)-2-(4-methyl-1-piperazinyl)quinoline-3-acetate (13)

A solution of 12 (0.9 g, 2.6 mmol) in N-methylpiperazine (10 ml) was heated for 8 h at 125-130°C under nitrogen atmosphere and then poured into ice-water. The precipitate was collected by filtration, washed with water and dried. Purification by chromatography eluting with ethyl acetate-triethylamine (8:2) gave 13 as a white solid (0.9 g, yield 85%) which was crystallized from n-hexane giving an analytical sample with mp 108-109°C. Ir: 1730 cm^{-1}. ^{1}H-Nmr ($CDCl_3$): 1.12 (t, J=7.3, 3H, CH_2-CH_3), 2.37 (s, 3H, NCH_3), 2.61 (t, J=4.7, 4H, piperazine), 3.30 (t, J=4.7, 4H, piperazine), 3.66 (ABq, J=17.2, 2H, CH_2CO), 3.99 (q, J=7.3, 2H, OCH_2), 7.17-7.33 (m, 5H, Ar-H), 7.42-7.65 (m, 2H, Ar-H), 7.96 (d, J=8.6, 1H, Ar-H). Anal. Calcd for $C_{24}H_{26}N_3O_2F$: C, 70.74; H, 6.43; N, 10.31. Found: C, 70.96; H, 6.58; N, 10.49.

4-(2-Fluorophenyl)-3-(2-hydroxyethyl)-2-(4-methyl-1-piperazinyl)quinoline (14)

To a suspension of lithium aluminum hydride (0.34 g, 9 mmol) in tetrahydrofuran (10 ml), a solution of 13 (0.6 g, 1.5 mmol) in tetrahydrofuran (10 ml) was added. After stirring for 30 min at -20° to 0°C, the hydride was hydrolyzed by addition of water and the inorganic material was filtered off and washed with tetrahydrofuran and ether. The filtrate was dried and evaporated and pure 14 was obtained as a white solid (0.515 g, yield 94%). Crystallization from cyclohexane-ethyl acetate gave an analytical sample melting at 188-189°C. ^{1}H-Nmr (DMSO-d_6): 2.30 (s, 3H, CH_3), 2.57 (t, J=4.7, 4H, piperazine), 2.69-2.92 (m, 2H, CH_2-CH_2OH), 3.25 (t, J=4.7, 4H, piperazine), 3.30-3.46 (m, 2H, CH_2OH), 4.60 (t, J=5.0, 1H, OH), 7.07 (d, J=8.4, 1H, Ar-H), 7.31-7.50 (m, 4H, Ar-H), 7.59-7.67 (m, 2H, Ar-H), 7.85 (d, J=8.2, 1H, Ar-H). Anal. Calcd for $C_{22}H_{24}N_3OF$: C, 72.31; H, 6.62; N, 11.50. Found: C, 72.54; H, 6.57; N, 11.54.

3-Ethenyl-4-(2-hydroxyphenyl)-2-(4-methyl-1-piperazinyl)quinoline (15)

To a solution of 3 (0.07 g, 0.2 mmol) in dry N,N-dimethylformamide (10 ml), sodium hydride (0.015 g, 0.6 mmol) was added and the reaction mixture was heated at 155-160°C under a nitrogen atmosphere for 20 min and then poured into ice-water. The aqueous mixture was extracted with chloroform and the organic layer was washed with water, dried over sodium sulfate and concentrated in vacuo. Purification of the residue by washing with ether gave 0.06 g of pure 15 (yield 87%, mp 215-217°C). ^{1}H-Nmr (DMSO-d_6): 2.27 (s, 3H, CH_3), 2.54 (bs, 4H, piperazine), 3.37 (bs, 4H, piperazine), 5.25 (dd, J=1.6 and 11.7, 1H, Hb), 5.41 (dd, J=1.6 and 18.0, 1H, Ha), 6.57 (dd, J=11.7 and 18.0, 1H, Hc), 6.90-7.36 (m, 6H, Ar-H), 7.59 (t, J=7.2, Ar-H), 7.78 (d, J=8.2, H-8), 9.38 (s, 1H, OH). Ms: m/z Calcd for $C_{22}H_{23}N_3O$: 345.1841. Found: 345.1843. Anal. Calcd for $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found: C, 76.32; H, 6.74, N, 12.25.

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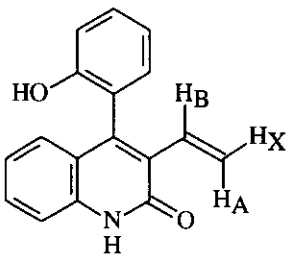

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