Pergamon

Tetrahedron 55 (1999) 13233–13250

TETRAHEDRON

Synthesis of Functionalised Quinolines through Tandem Addition/ Annulation Reactions of β-(2-Aminophenyl)-α,β-Ynones

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Received 15 June 1999; revised 25 August 1999; accepted 9 September 1999

Abstract: β-(2-aminophenyl)-α,β-ynones can quickly give functionalized 2,4-disubstituted quinolines through tandem nucleophic addition/annulations reactions. Acid-catalysed cyclization of β-(2-aminophenyl)-α,β-ynones can also occur. The easy entry into 4-iodo-2-substituted-quinolines prompted the development of a one pot procedure for synthesis of 2,4-disubstituted quinolines by further elaboration by means of palladium-catalysed reactions. The exposure to basic conditions of one β-(2-malonylamidophenyl)-α,β-ynone led to a fused quinolone derivative through intramolecular Michael addition /tautomerisation/transesterification cascade reactions. Fused polycyclic quinolines can be viewed as occurring through a tandem concerted Diels-Alder/annulation reactions of β-(2-aminophenyl)-α,β-ynones with enamines, azides and nitrile oxides . © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: quinolines; α,β-ynones; nucleophilic addition; cross coupling; palladium; tandem Diels-Alder/annulation reactions.

INTRODUCTION

The quinoline nucleus occurs in several natural compounds[1] and in some pharmacologically active substances. For instance, a quinoline subunit is present in a new class of peptidoleukotriene LTD4 antagonists developed as antiasthmatic therapeutics,[2] in a series of potent 5-lipoxigenase inhibitors[3] and in some new anti-inflamatory derivatives.[4] Aryl substituted quinolines have also been reported to act as potent inhibitors of tirosyne kinase PDGF-RTK.[5]

Many syntheses of quinolines are known,[6] but due to their importance, the development of new synthetic approaches remains an active research area.[7] It was recently reported that a variety of substituted β-(2-aminophenyl)-α,β-ynones **1** can be obtained through the carbonylative coupling of *o*-trimethylsilylethynylaniline with aryl iodides, and that the palladium-catalysed transfer hydrogenation of these substrates affords 2-aryl quinolines **3** in good yield.[8] Other known syntheses of quinolines from acetylenic ketones include the reaction of secondary amines with α,β-ynones generated *in situ* through the carbonylative

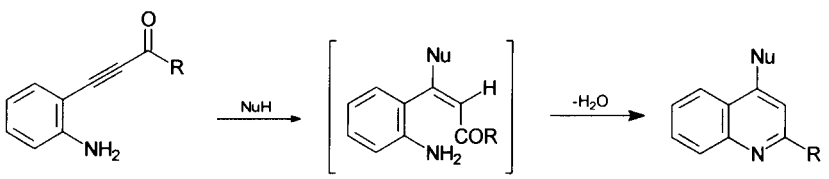
PII: S0040-4020(99)00814-5

coupling of *o*- ethynylaniline with aryl iodides,[9] and the reaction of 2-amino thiophenol with α,β-ynones bearing an acetal group.[10] These last two methods both provide 2,4-disubstituted quinolines in good yields, but are restricted to the synthesis of 4-*N,N*-dialkylamino- and 4-formyl quinolines respectively.

Our ongoing interest in the synthesis of heterocycles[11] has prompted us to further investigate the utilisation of the α,β-ynones **1** as precursors of functionalized quinoline derivatives. We now report that the reaction of substrates **1** with nucleophilic partners may provide a versatile, new approach to 2,4-disubstituted quinolines **3** through a conjugate addition / cyclization tandem reaction. Moreover, electrophilic additions and cycloadditions to **1** have been tested.

RESULTS AND DISCUSSION

The conjugate addition of heteronucleophiles to unsaturated alkynes[12] has not been studied as extensively as the corresponding conjugate addition to unsaturated alkenes.[13] The reactions of sulfur and selenium nucleophiles with alkynones and alkynoic acid derivatives are prominent examples.[14] In view of the considerable potential of heteronucleophilic conjugate addition to alkynone derivatives in the synthesis of heterocycles, we have investigated the reaction of β-(2-aminophenyl)-α,β-ynones **1** with various nucleophiles (Scheme 1) and the results obtained are reported in Table 1.

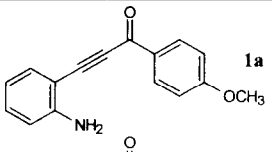
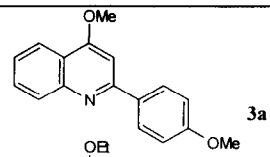
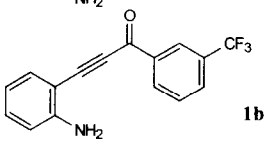
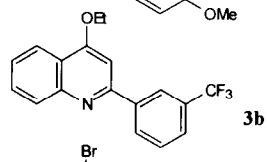
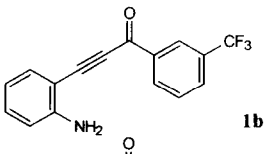
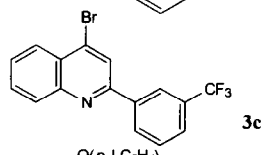
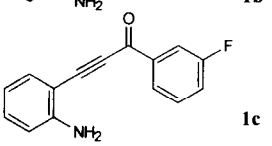
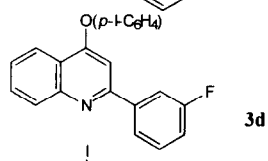
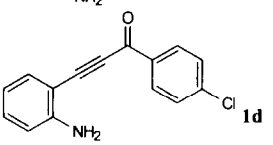
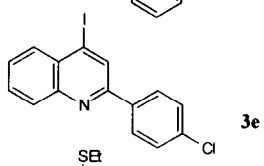
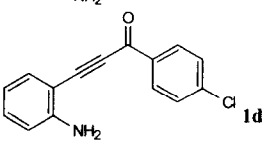
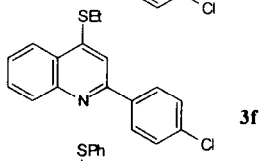
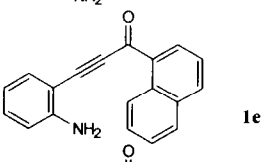
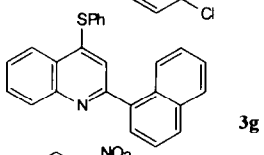
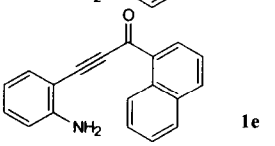
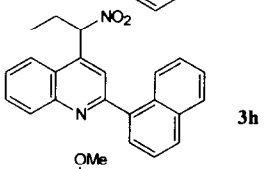
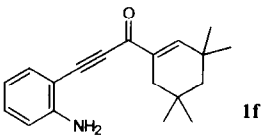
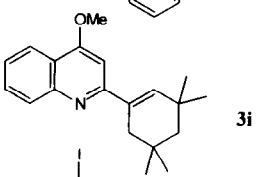
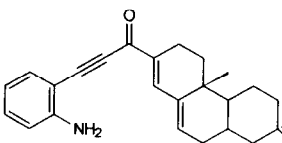
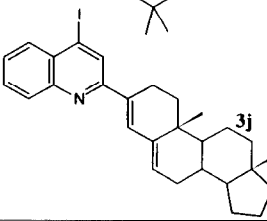


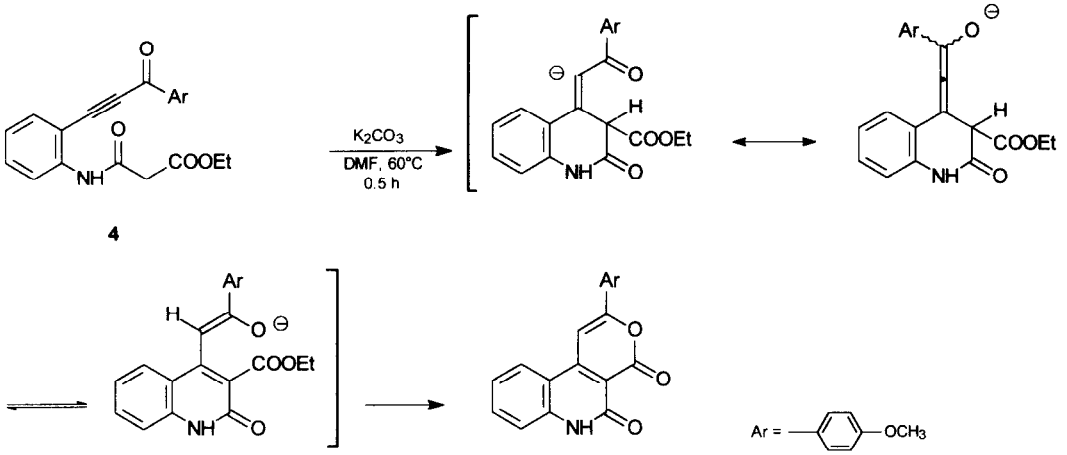
SCHEME 1 **1a-g** **2** **3a-j**

The reactions were generally carried out at 60-80 °C, in the presence of an excess of nucleophile or pronucleophile, and the 2,4-disubstituted quinolines **3** were isolated in good yields as sole products. This protocol represents a versatile approach to 4-heterosubstituted 2-aryl-quinolines (Table 1, entries 1-7); of course the carbonucleophile addition reaction can give 4-alkyl-2-arylquinolines[15] (Table 1, entry 8). Moreover the nucleophilic addition reaction to readily available vinyl α,β-ynones[16] allows the synthesis of 4-substituted-2-vinylquinolines (Table 1, entries 9, 10).

Interestingly, the exposure of the β-(2-malonylamidophenyl)-α,β-ynone[17] **4** to K_2CO_3 accomplished the synthesis of the fused quinolone **5** through an intramolecular Michael addition /tautomerisation/transesterification cascade reaction (Scheme 2).

Table 1. Synthesis of 2,4-disubstituted quinolines **3** trough nucleophilic addition to β-(*o*-aminophenyl)α,β-ynones **1**.

Entry	β-(*o*-aminophenyl)α,β-ynones 1	Nucleophile (solvent)	Temp. (°C) (time, h)	Product	Yield (%)
1	 **1a**	MeONa (MeOH)	60 (3)	 **3a**	84
2	 **1b**	EtONa (EtOH)	25 (2.5)	 **3b**	92
3	 **1b**	NaBr (CH_3COOH)	60 (17)	 **3c**	62
4	 **1c**	4-iodophenol/K_2CO_3 (CH_3CN)	80 (3)	 **3d**	90
5	 **1d**	NaI (CH_3COOH)	60 (8)	 **3e**	85
6	 **1d**	EtSNa (DMSO)	60 (2)	 **3f**	88
7	 **1e**	$PhSH/K_2CO_3$ (CH_3CN)	80 (24)	 **3g**	98
8	 **1e**	NO_2/K_2CO_3 (CH_3CN)	reflux (24)	 **3h**	61
9	 **1f**	MeONa (MeOH)	60 (4)	 **3i**	80
10	 **1g**	NaI (CH_3COOH)	60 (16)	 **3j**	32

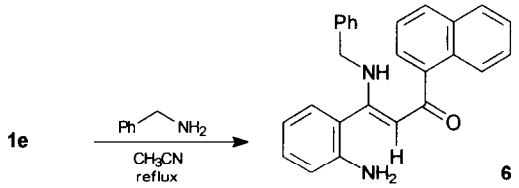


4

5 (80%)

SCHEME 2

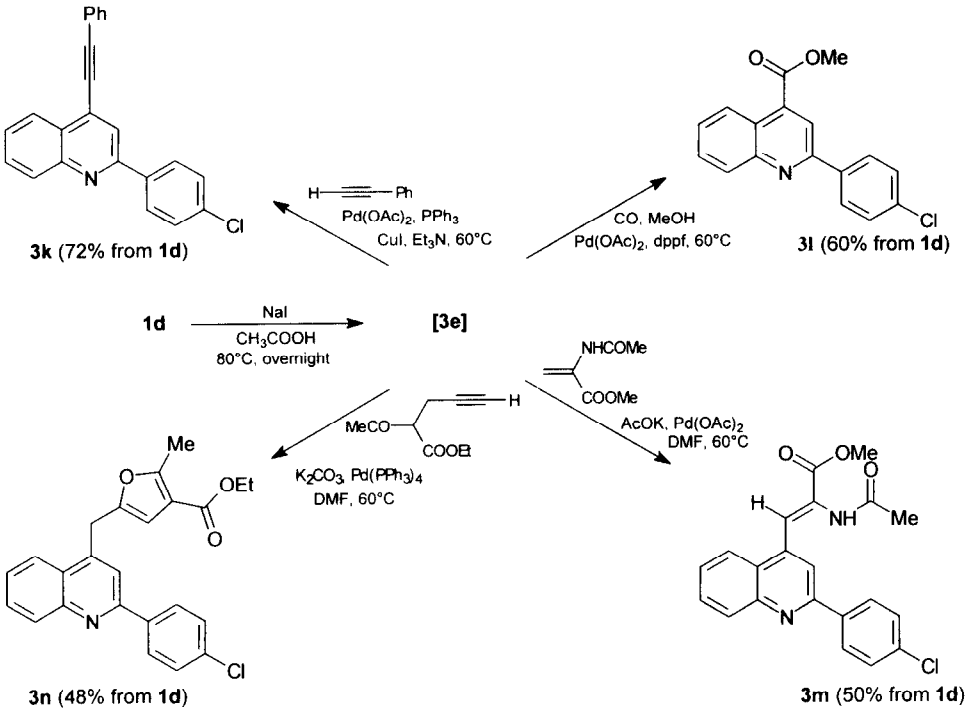
The nucleophilic addition reactions to α,β-ynones **1** proceed with high stereoselectivity and, the stereochemical outcome allows tandem annulation reactions. Only the reaction of α,β-ynone **1f** with benzylamine failed to afford the corresponding quinoline derivative, and the Z-enamine **6** was isolated as the main product (Scheme 3). The structure of **6** was deduced on the basis of literature data concerning the nucleophilic additions of primary amines to acetylenic esters and ketones,[18] and confirmed by NOESY spectroscopy.



6

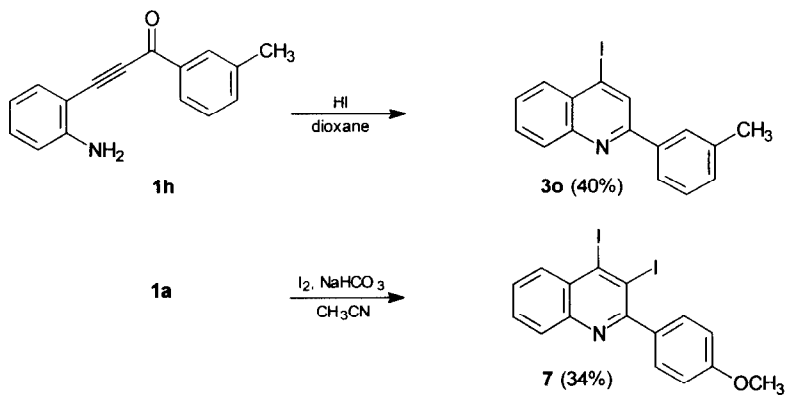
SCHEME 3

The successful synthesis of 2-(4'-chlorophenyl)-4-iodoquinoline **3e** through the addition of sodium iodide in acetic acid[19] to **1d** (Table 1, entry 5) prompted us to investigate further elaboration by means of Pd-catalysed coupling reactions. To keep the methodology as simple as possible, we briefly investigated the development of a one pot procedure starting from **1**. Thus, crude **3e,** obtained after usual work-up of the reaction mixture of sodium iodide and **1d** in acetic acid stirred overnight at 60 C°, underwent a variety of palladium catalysed-reactions including hydroxymethyl carbonylation,[20] coupling with phenylacetylene,[21] Heck reaction with α-acetamidoacrylate[22] and reaction with 4- acetyl -ethyl -1-pentynoate[23] (Scheme 4).



SCHEME 4

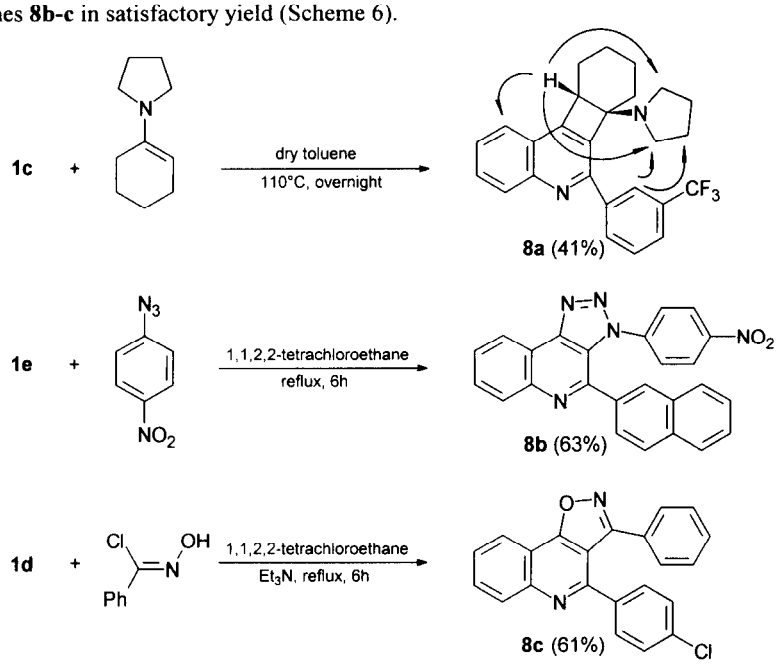
It is worthwhile pointing out that α,β-ynones **1** may also undergo electrophilic addition, and acetylenic ketones are versatile synthetic precursors of various heterocycles by acid-catalysed cyclization reactions.[24] In this way, the reaction of **1h** with HI gave the expected 4-iodoquinoline **3o** in moderate yield (40%) (Scheme 5). Very surprisingly, the reaction of **1a** with iodine/$NaHCO_3$ in CH_3CN gave the 2-(4'-methoxyphenyl)-3,4-diiodoquinoline 7. The outcome of this reaction is remarkably different from the regio-controlled iodoaminocyclization reaction[25] of related derivatives.



SCHEME 5

Furthermore, we investigated the sequential addition/cyclization of 1-(cyclohexen-1-yl)pyrrolidine to **1c**: according to literature data concerning the reactions of enamines with acetylenic esters[26] the polycyclic derivative **8a** was isolated in 41% yield. This compound can be viewed as occurring through a tandem [2+2] cycloaddition/annulation reaction. Regio and diastereoselectivity for the cycloaddition reaction was demonstrated by ^{1}H-NMR spectra analysis and 2D-NOESY experiment. Diagnostic NOE interactions for **8a** are reported in Scheme 6.

Analogously, tandem 1,3-dipolar cycloaddition/annulation reactions of both **1e** with *p*-nitrophenyl azide[27] and **1d** with the phenyl nitrile oxide[28] (generated in *situ* from the corresponding chlorooxime) gave the fused quinolines **8b-c** in satisfactory yield (Scheme 6).



SCHEME 6

In conclusion, the results reported here show that β-(2-aminophenyl)-α,β-ynones **1** can quickly give functionalized 2,4-disubstituted quinolines through tandem nucleophilic addition/annulations reactions. Acid-catalysed cyclization of β-(2-aminophenyl)-α,β-ynones **1** can also occur. Very surprisingly, the reaction of one β-(2-aminophenyl)-α,β-ynones **1** with iodine/$NaHCO_3$ in CH_3CN gave a 2-substituted-3,4-diiodoquinoline derivative. The ready access to 4-iodo-2-substituted-quinolines prompted the development of a versatile one pot procedure of synthesis of 2,4-disubstituted quinolines by further elaboration by means of palladium-catalysed reactions. The exposure to basic conditions of β-(2-malonylamidophenyl)-α,β-ynones may give fused quinolone derivatives through an intramolecular Michael addition /tautomerisation/transesterification

cascade reaction. Thus, fused polycyclic quinolines can be viewed as occurring through a tandem concerted Diels-Alder/annulation reaction of β-(2-aminophenyl)-α,β-ynones with enamines, azides and nitrile oxides.

EXPERIMENTAL

Mps are uncorrected and were measured with a Buchi apparatus. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded with a Bruker AC 200 E or with a Varian Gemini 200 spectrometer. EI (70eV) mass spectra were recorded with a TSQ 700 Finnigan/Mat instrument. I. R. were recorded with a Perkin-Elmer 683 spectrometer. All starting materials, catalysts, ligands, bases, and solvents (anhydrous solvents included) if not otherwise stated, are commercially available and were used as purchased, without further purification.

β-(2- Aminophenyl) α,β-ynones **1a-h** and the malonamide **4** were prepared as reported in Ref. 8 and 17 respectively. The products, after usual work-up, were purified by flash chromatography on silica gel eluting with *n*-hexane/ethylacetate mixtures. All the isolated new compounds gave satisfactory microanalyses.

1a: m.p. 109-111°C; [Found: C, 76.44; H, 5.17; N, 5.60; $C_{16}H_{13}O_2N$ requires C, 76.48; H, 5.57; N, 5.57%]; IR (KBr, cm^{-1}): 3400, 3340, 2180, 1600.; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.17 (d, J = 9.0, 2H, arom., AA' part of an AA'BB 'system), 7.46 (bd, J= 8, 1H, arom.), 7.28-7.19 (m, 1H, arom.), 6.98 (d, J = 9.0, 2H, arom., BB' part of an AA'BB 'system), 6.75-6.68 (m, 2H, arom.), 4.53 (bs, 2H, -N$\underline{H}_2$), 3.88 (s, 3H, -OC$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 176.5, 164.4, 150.3, 133.6, 132.4, 131.9, 130.4, 117.9, 114.7, 113.9, 104.1, 93.2, 90.3, 55.6.

1b: m.p. 135-136°C; [Found: C, 66.48; H, 3.15; N, 4.81; $C_{16}H_{10}F_3ON$ requires C, 66.42; H, 3.49; N, 4.84%]; IR (KBr, cm^{-1}): 3460, 3360, 2180, 1650; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.48 (s, 1H, arom.), 8.39 (d, J = 8, 1H, arom.), 7.89-7.85 (m, 1H, arom.), 7.71-7.63 (m, 1H, arom.), 7.50-7.46 (m, 1H, arom.), 7.32-7.24 (m, 1H, arom.), 6.78-6.71 (m, 2H, arom.), 4.53 (bs, 2H, -N$\underline{H}_2$); ^{13}C-NMR ($CDCl_3$, δ): 176.2, 150.7, 137.5, 133.9, 133.1, 132.5, 130.7(q), 130.3, 130.2, 129.4, 126.2, 118.1, 114.8, 103.2, 93.0, 92.8.

1c: m.p. 127-129°C; [Found: C, 75.35; H, 4.19; N, 6.63; $C_{15}H_{10}FON$ requires C, 75.29; H, 4.22; N, 6.69%]; (KBr, cm^{-1}): 3490, 3400, 2200, 1630; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.02 (dt, J = 7, 1.4, 1H, arom.), 7.89-7.83 (m, 1H, arom.), 7.55-7.45 (m, 2H, arom.), 7.36-7.22 (m, 2H, arom.), 6.77-6.70 (m, 2H, arom.), 4.54 (bs, 2H, -N$\underline{H}_2$); ^{13}C-NMR ($CDCl_3$, δ): 176.4, 162.7(d), 150.6, 133.8, 132.9, 130.4, 130.3, 125.4, 121.0(d), 118.0, 115.8(d), 114.8, 103.4, 93.2, 92.0.

1d: m.p. 138-140°C; [Found: C, 70.55; H, 4.00; N, 5.40; $C_{15}H_{10}ClON$ requires C, 70.58; H, 3.95; N, 5.49%];

IR (KBr, cm^{-1}): 3450, 3390, 2210, 1650; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.14 (d, J = 8.6, 2H, arom., AA' part of an AA'BB 'system), 7.52-7.44 (m, 3H, arom.+ BB' part of an AA'BB 'system), 7.31-7.22 (m, 1H, arom.), 6.78-6.70 (m, 2H, arom.), 4.52 (bs, 2H, N$\underline{H}_2$); ^{13}C-NMR ($CDCl_3$, δ): 176.8, 150.9, 141.0, 136.0, 134.2, 133.3, 131.2, 129.5, 118.5, 115.2, 104.1, 93.6, 92.2.

1e: m.p. 121-123°C; [Found: C, 84.20; H, 4.83; N, 5.20; $C_{19}H_{13}ON$ requires C, 84.11; H, 4.83; N, 5.16%]; IR (KBr, cm^{-1}): 3460, 3360, 2180, 1650; ^{1}H-NMR ($CDCl_3$, δ, Hz): 9.18 (d, J = 8.6, 1H, arom.), 8.57 (dd, J = 7.3, 1.2, 1H, arom.), 8.06 (d, J = 8.2, 1H, arom.), 7.90 (d, J = 6.6, 1H, arom.), 7.70-7.45 (m, 4H, arom.), 7.28-7.19 (m, 1H, arom.), 6.75-6.68 (m,2H, arom.), 4.51 (bs, 2H, N$\underline{H}_2$); ^{13}C-NMR ($CDCl_3$, δ): 179.6, 150.4, 134.8, 133.8, 133.7, 132.5, 128.8, 128.6, 126.7, 125.9, 124.5, 117.9, 114.7, 104.0, 95.1, 90.0.

1f: m.p. 97-99°C; [Found: C, 81.20; H, 8.19; N, 5.05; $C_{19}H_{23}ON$ requires C, 81.10; H, 8.24; N, 4.98%]; IR (KBr, cm^{-1}): 3440, 3340, 2180, 1640; ^{1}H-NMR ($CDCl_3$, δ, Hz): 7.39 (bd, J = 8, 1H, arom.), 7.25-7.17 (m, 1H, arom.), 7.11 (s, 1H, -C=C$\underline{H}$), 6.74-6.66 (m, 2H, arom.), 4.46 (bs, 2H, N$\underline{H}_2$), 2.09 (d, J = 1.1, 2H, -C=C-C$\underline{H}_2$-), 1.41 (s, 2H, -C$\underline{H}_2$-), 1.16 (s, 6H, two -C$\underline{H}_3$), 0.98 (s, 6H, two -C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 160.0, 154.6, 150.0, 136.9, 133.4, 132.0, 117.8, 114.6, 104.3, 92.4, 88.8, 49.5, 35.7, 34.1, 30.6, 30.2, 29.6.

1g: m.p. > 240°C (dec); [Found: C, 81.25; H, 7.60; N, 3.35; $C_{28}H_{31}O_2N$ requires C, 81.32; H, 7.56; N, 3.39%]; IR (KBr, cm^{-1}): 3460, 3350, 2160, 1750, 1610; ^{1}H-NMR ($CDCl_3$, δ, Hz): 7.42-7.37 (m, 2H, arom. + -C=C$\underline{H}$), 7.26-7.18 (m, 1H, arom.), 6.74-6.69 (m, 2H, arom.), 6.05 (bs,1H, -C=C$\underline{H}$), 4.43 (bs, 2H, -N$\underline{H}_2$), 2.75-1.10 (m, 17H, -C$\underline{H}_2$- + -C$\underline{H}$-), 0.96 (s, 3H, -C$\underline{H}_3$), 0.93 (s,3H, -C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 220.2, 178.9, 149.9, 143.8, 142.2, 136.3, 133.9, 133.4, 132.0, 117.9, 114.6, 92.8, 88.8, 51.9, 48.3, 47.7, 35.8, 35.5, 33.1, 31.6, 31.4, 21.8, 20.5, 20.3, 19.2, 13.7.

1h: m.p. 108-110°C; [Found: C, 81.69; H, 5.50; N, 5.89; $C_{16}H_{13}ON$ requires C, 81.67; H, 5.57; N, 5.96%]; IR (KBr, cm^{-1}): 3410, 3310, 2160, 1650; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.03-7.99 (m, 2H, arom.), 7.49-7.38 (m, 3H, arom.), 7.25-7.19 (m, 1H, arom.), 6.75-6.67 (m, 2H, arom.), 4.58 (bs, 2H, -N$\underline{H}_2$), 2.43 (s, 3H, -C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 178.0, 150.5, 138.5, 137.0, 134.8, 133.7, 132.6, 129.7, 128.5, 127.0, 117.9, 114.7, 103.8, 93.4, 91.1, 21.3.

4: m.p. 94-96°C; [Found: C, 69.38; H, 4.73; N, 3.84; $C_{21}H_{37}O_5N$ requires C, 69.41; H, 4.72; N, 3.85%]; IR (KBr, cm^{-1}): 3250, 2200, 1750, 1660, 1610; ^{1}H-NMR ($CDCl_3$, δ, Hz): 9.85 (bs,1H, N$\underline{H}$), 8.42 (d, J = 8.4, 1H, arom.), 8.21 (d, J = 6.9, 2H, arom., AA' part of an AA'BB 'system), 7.66-7.62 (m, 1H, arom.), 7.53-7.45 (m, 1H, arom.), 7.19-7.11 (m, 1H, arom.), 6.98 (d, J = 6.9, 2H, arom., BB' part of an AA'BB 'system), 4.17 (q, J =

7.1, 2H, -C<u>H</u>$_2$CH$_3$), 3.90 (s, 3H, -OC<u>H</u>$_3$), 3.54 (s, 2H, -C<u>H</u>$_2$), 1.25(t, J = 7.1, 3H, -CH$_2$C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 176.1, 169.1, 164.6, 163.5, 133.3, 132.2, 131.8, 129.1, 124.1, 123.4, 120.6, 114.1, 113.9, 94.1, 87.1, 62.0, 55.6, 42.0, 14.0.

2-(4'-Methoxyphenyl)-4-methoxyquinoline 3a. To a well stirred solution of sodium methoxide in methanol (30% w/w, 7 mL) **1a** (0.1 g, 0.4 mmol) was added. The mixture was stirred at 60°C under nitrogen for 3h, poured into NH_4Cl saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography. Elution with hexane/ethyl acetate 95:5 afforded pure **3a** (0.089g, 84 %); m.p. 66-68°C; [Found: C, 76.99; H, 5.69; N, 5.31; $C_{17}H_{15}O_2N$ requires C, 76.96; H, 5.70; N, 5.28%]; IR (KBr, cm^{-1}): 1600, 1510; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.17-8.04 (m, 4H, arom.), 7.71-7.63 (m,1H, arom.), 7.48-7.39 (m,1H, arom.), 7.10 (s, 1H, arom,), 7.02 (d, J = 8.9, 2H, arom., BB' part of an AA'BB 'system), 4.06 (s, 3H, -OC<u>H</u>$_3$), 3.86 (s, 3H, -OC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 162.7, 160.7, 158.3, 149.2, 132.9, 129.9, 129.0, 128.8, 125.0, 121.6, 120.2, 114.1, 97.4, 55.5, 55.4; EI-MS m/z (relative intensity): 265 (M^+, 100), 250 (6), 235 (52).

4-Ethoxy-2-(3'-trifluoromethylphenyl)-quinoline 3b. A mixture of **1b** (0.140 g, 0.48 mmol) and sodium ethoxide (0.165 g, 2.42 mmol) in absolute ethanol (12 mL) was stirred under nitrogen at room temperature for 2.5 h. The mixture was then poured into NH_4Cl saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography. Elution with hexane/ethyl acetate 95:5 afforded pure **3b** (0.141 g, 92%); m.p.104-106°C; [Found: C, 68.15; H, 4.50; N, 4.39; $C_{18}H_{14}F_3ON$ requires C, 68.13; H, 4.45; N, 4.41%]; IR (KBr, cm^{-1}): 1590, 1430, 1320; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.36 (s, 1H, arom.), 8.26-8.17 (m, 2H, arom.), 8.10-8.05 (m, 1H, arom.), 7.73-7.43 (m, 4H, arom.), 7.06 (s, 1H, arom.), 4.28 (q, J = 6.9, 2H, -C<u>H</u>$_2$CH$_3$), 1.57 (t, J = 6.9, 3H, -CH$_2$C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 162.4, 156.9, 149.1, 141.1, 131.4, 130.8, 131.0(q), 130.2, 129.2, 125.8, 125.7, 124.4, 124.3, 121.8, 120.6, 96.1, 64.2, 14.5; EI-MS m/z (relative intensity): 317 (M^+, 100), 302 (21), 289 (60).

4-Bromo-2-(3'-trifluoromethylphenyl)-quinoline 3c. A mixture of **1b** (0.16g, 0.55 mmol) and NaBr (0.114 g, 1.1 mmol) in acetic acid (5 mL) was stirred at 60 °C for 17h. Then the mixture was poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethyl ether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography. Elution with hexane/ethyl acetate 97: 3 afforded pure **3c** (0.121 g, 62 %); m.p. 63-65°C; [Found: C, 54.54; H, 2.60; N, 3.98; $C_{16}H_9BrF_3N$ requires C, 54.57; H, 2.58; N, 3.98%]; IR (KBr, cm^{-1}): 1590, 1500; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.43 (s, 1H), 8.30 (bd, J = 8, 1H), 8.20-8.14 (m, 3H), 7.82-7.59 (m, 4H); ^{13}C-NMR ($CDCl_3$, δ): 155.3, 148.6, 139.0, 135.1, 130.9, 130.6,

130.2, 129.4, 128.0, 126.9, 126.6, 126.4, 126.3, 124.4, 124.3, 122.5; EI-MS m/z (relative intensity): 353 (M^++ 2, 89), 351 (M^+, 89), 272 (100).

2-(3'-Fluorophenyl)-4-(4''-iodophenoxy)-quinoline 3d. A mixture of **1c** (0.084 g, 0.35 mmol), 4-iodophenol (0.093 g, 0.42 mmol) and K_2CO_3 (0.145g, 1.05mmol) in dry CH_3CN (5 mL) was stirred under nitrogen at 80 °C for 3h. Then the mixture was poured into NH_4Cl saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 95:5 afforded pure **3d** (0.139g, 90%); m.p. 110-112°C; [Found: C, 57.20; H, 2.99; N, 3.18; C21H13FION requires C, 57.16; H, 2.97; N, 3.17%]; IR (KBr, cm^{-1}): 1600, 1480, 1230; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.31-8.26 (m, 1H), 8.18-8.13 (m, 1H), 7.81-7.67 (m, 5H), 7.60-7.51 (m, 1H), 7.40 (dt, J = 8.1, 5.8, 1H), 7.15-7.06 (m, 1H), 7.00 (s, 1H), 6.88 (d, J = 8.8, 2H,); ^{13}C-NMR ($CDCl_3$, δ): 163.1(d), 161.9, 156.9, 154.5, 149.7, 141.9, 139.4, 130.6, 130.3, 130.1, 129.5, 126.3, 122.9, 121.5, 120.5, 116.3(d), 114.4(d), 102.4, 89.1; EI-MS m/z (relative intensity): 441 (M^+, 100).

2-(4'-Chlorophenyl)-4-iodoquinoline 3e. A solution of **1d** (0.138 g, 0.54 mmol) and NaI (0.162 g, 1.08 mmol) in acetic acid (5 mL) was stirred at 60 °C for 17h. Then the mixture was poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethyl ether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 97: 3 afforded pure **3e** (0.168 g, 85%); m.p. 115-116°C; [Found: C, 49.30; H, 2.48; N, 3.80; $C_{15}H_9ClIN$ requires C, 49.28; H, 2.48; N, 3.83%]; IR (KBr, cm^{-1}): 1600, 1510; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.40 (s, 1H), 8.10-7.97 (m, 4H), 7.78-7.70 (m, 1H), 7.63-7.55 (m, 1H), 7.48 (d, J = 8.5, 2H.); ^{13}C-NMR ($CDCl_3$, δ): 155.5, 147.6, 136.2, 135.9, 131.4, 130.6, 130.2, 129.9, 129.1, 129.0, 128.7, 127.9, 112.7; EI-MS m/z (relative intensity): 367 (M^+ + 2, 32), 365 (M^+, 100), 238 (46).

2-(4'-Chlorophenyl)-4-ethylthioquinoline 3f. A mixture of **1d** (0.138 g, 0.54 mmol) and sodium ethanthiolate (0.059 g, 0.702 mmol) in dry DMSO (3 mL) was stirred at 60°C, under nitrogen, for 2h. Then the mixture was poured into HCl 0.1N (150 mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 80: 20 afforded pure **3f** (0.142 g, 88%); m.p. 98-99°C; [Found: C, 68.12; H, 4.74; N, 4.63; $C_{17}H_{14}ClNS$ requires C, 68.10; H, 4.71; N, 4.67%]; IR (KBr, cm^{-1}): 1570, 1540, 1490, 1410; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.14-8.02 (m, 4H, arom.), 7.76-7.68 (m, 1H, arom.), 7.51 (s, 1H, arom.), 7.50-7.45 (m, 3H, arom.), 3.18 (q, J = 7.4, 2H, -$SC\underline{H}_2CH_3$), 1.51 (t, J = 7.4, 3H, -$SCH_2C\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 155.6, 148.7, 148.0, 138.7, 136.0, 130.7, 130.5, 129.6, 129.3, 126.7, 126.1, 123.9, 114.1, 26.0, 13.9; EI-MS m/z

(relative intensity): 301 (M^+ + 2, 36), 299 (M^+, 100).

2-(1'-Naphthyl)-4-phenylthioquinoline 3g. A mixture of **1e** (0.1 g, 0.37 mmol), thiophenol (0.049 g, 0.44 mmol) and K_2CO_3 (0.254 g, 1.84 mmol) in dry CH_3CN (5 mL) was stirred under nitrogen at 80 °C for 3h. Then the mixture was poured into $NaHCO_3$ saturated solution (150mL) and extracted twice with ethyl acetate. The organic layer, dried over anhydrous Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 98:2 afforded pure **3g** (0.131 g, 98%); m.p. 137-139°C; [Found: C, 82.64; H, 4.58; N, 3.80; $C_{25}H_{17}NS$ requires C, 82.61; H, 4.71; N, 3.85%]; IR (KBr, cm^{-1}): 1570, 1480, 1390; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.34 (bd, J= 8, 2H), 7.98-7.70 (m, 4H), 7.67-7.41 (m, 10H), 7.13 (s, 1H); ^{13}C-NMR ($CDCl_3$, δ): 158.3, 150.4, 147.1, 137.8, 135.5, 134.3, 131.4, 131.1, 130.6, 130.2, 130.0, 129.96, 129.90, 128.9, 128.6, 127.3, 127.1, 126.5, 125.81, 125.77, 125.3, 123.9, 120.6; EI-MS m/z (relative intensity): 362 (M^+, 100), 254 (32).

2-(1'-Naphthyl)-4-(1-nitro-1-propyl)-quinoline 3h. A mixture of **1e** (0.144 g, 0.53 mmol), 1-nitropropane (0.190 ml, 2.13 mmol) and K_2CO_3 (0.293g, 2.13 mmol) in dry CH_3CN (5 mL) was stirred under nitrogen at reflux for 24 h. Then the mixture was poured into NH_4Cl saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 95:5 afforded pure **3h** (0.111g, 61%); oil; IR ($CHCl_3$, cm^{-1}): 1610, 1560, 1360; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.33 (bd, J = 8, 1H, arom.), 8.18 (bd, J = 8, 1H, arom.), 8.10-8.06 (m, 1H, arom.), 8.00-7.92 (m, 2H, arom.), 7.90 (s, 1H, arom.), 7.84-7.48 (m, 6H, arom.), 6.31(dd, J = 9, 6, 1H, -O_2NC<u>H</u>-), 2.80-2.60 (m, 1H, -O_2NCHC<u>H_2</u>-), 2.40-2.20 (m, 1H, -O_2NCHC<u>H_2</u>-), 1.12(t, J = 7.3, 3H, -O_2NCHCH_2C<u>H_3</u>); ^{13}C-NMR ($CDCl_3$, δ): 159.3, 148.5, 139.4, 134.0, 131.0, 130.9, 130.2, 129.7, 128.6, 128.0, 127.9, 126.9, 126.2, 125.4, 125.3, 124.6, 121.9,121.2, 87.3, 30.9, 27.1, 10.9; EI-MS m/z (relative intensity): 342 (M^+, 25), 296 (100).

4-Methoxy-2-(3',3',5',5'-tetramethyl-cyclohex-1-en-1-yl)-quinoline 3i. To a well stirred solution of sodium methoxide 5.4 M in methanol (7 mL) **1f** (0.102 g, 0.36 mmol) was added. The mixture was stirred at 60°C under nitrogen for 4h, poured into NH_4Cl saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography. Elution with hexane/ethyl acetate 98:2 afforded **3i** (0.085g, 80% yield); m.p. 142-143°C; [Found: C, 81.30; H, 8.56; N, 4.75; $C_{20}H_{25}ON$ requires C, 81.30; H, 8.54; N, 4.74%];IR (KBr, cm^{-1}): 1620, 1600, 1510; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.11 (d, J = 8,1H, arom.), 7.99 (d, J = 8.3, 1H, arom.), 7.63 (m,1H, arom.), 7.40 (m,1H, arom.), 6.93 (s, 1H, arom.), 6.39 (s, 1H, -C=C<u>H</u>-), 4.07 (s, 3H, -OC<u>H_3</u>), 3.47 (s, 2H,

C=C-C$\underline{H}_2$-), 1.46 (s, 2H, -C$\underline{H}_2$-), 1.16 (s, 6H, two C$\underline{H}_3$), 1.08 (s, 6H, two C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 162.5, 160.9, 148.7, 138.4, 134.7, 129.5, 129.0, 124.8, 121.4, 120.4, 96.8, 55.5, 49.7, 39.7, 33.4, 31.5, 30.7, 30.1; EI-MS m/z (relative intensity): 295 (M^+, 32), 280 (100), 264 (32).

4-Iodo-2-(17'-oxo-androsta-3',5'-dien-3'-yl)-quinoline 3j. A solution of **1g** (0.100g, 0.24 mmol) and NaI (0.072g, 0.48 mmol) in acetic acid (20 mL) was stirred at 60 °C for 17h. Then the mixture was poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethyl ether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 97: 3 afforded **3j** (0.040g, 32% yield); m.p. 145-147°C; [Found: C, 64.23; H, 5.80; N, 2.69; $C_{28}H_{30}ION$ requires C, 64.25; H, 5.78; N, 2.68%];IR (KBr, cm^{-1}): 1750, 1570, 1490; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.26 (s,1H, arom.); 8.01-7.91 (m, 2H, arom.); 7.72-7.65 (m,1H, arom.); 7.56-7.48 (m, 1H, arom.); 7.02 (s, 1H, -C=C$\underline{H}$); 5.80 (bs,1H, -C=C$\underline{H}$); 3.10-1.25 (m, 17H, -C$\underline{H}_2$- + -C$\underline{H}$-), 1.03 (s, 3H, -C$\underline{H}_3$); 0.92 (s, 3H, -C$\underline{H}_3$); ^{13}C-NMR ($CDCl_3$, δ): 220.9, 157.6, 147.0, 142.2, 136.3, 131.6, 131.4, 130.4, 129.7, 129.4, 128.8, 127.7, 127.3, 111.8, 51.8, 48.2, 47.7, 35.8, 35.1, 33.8, 31.4, 31.2, 29.7, 23.1, 21.8, 20.4, 19.2,13.7; EI-MS m/z (relative intensity): 523 (M^+, 100).

4-Penten-5(*p*-methoxyphenyl)-5-olide[3,4-c]quinolin-2-one 5. A mixture of **4** (0.230 g, 0.63 mmol) and K_2CO_3 (0.435 g, 3.15 mmol) in DMF (4 mL) was stirred at 60 °C for 0.5h. After cooling, CH_2Cl_2 (150 mL) and 0.1N HCl (100 mL) were added. At this point, part of **5** precipitated and was filtered. The organic, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel eluting with ethyl acetate. The total amount of **5** was 0.160 g (80%); m.p.> 240°C (dec); [Found: C, 71.71; H, 3.81; N, 4.41; $C_{19}H_{12}O_4N$ requires C, 71.69; H, 3.80; N, 4.40%]; IR (KBr, cm^{-1}): 1780, 1610; ^{1}H-NMR (DMSO-d_6, 80°C, δ, Hz): 11.74 (bs, 1H, N$\underline{H}$), 8.53 (d, J = 8.2, 1H, arom.), 8.12 (d, J = 9.1, 2H, arom., AA' part of an AA'BB 'system), 7.85 (s, 1H, arom.), 7.68-7.64 (m, 1H, arom.), 7.36-7.25 (m, 2H, arom.), 7.13 (d, J = 9.1, 2H, arom., BB' part of an AA'BB 'system), 3.88 (s, 3H, -OC$\underline{H}_3$); ^{13}C-NMR (DMSO-d_6, 40°C; very low solubility; δ): 162.1, 161.1, 158.2,151.5, 140.8, 133.9, 128.2, 126.5, 123.2, 122.1, 115.7, 114.5, 55.6; EI-MS m/z (relative intensity): 319 (M^+, 63), 291 (87).

3-(2'-Aminophenyl)-3-benzylamino-1-(α-naphthyl)-propen-1-one 6. A mixture of **1e** (0.150 g, 0.55 mmol) and benzylamine (0.077 g, 0.72 mmol) in dry CH_3CN (5 mL) was heated at reflux, under nitrogen, for 20 h. Then the mixture was poured into HCl 0.1N (150 mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 90: 10 afforded pure **6** (0.172 g, 82%); m.p. 54-56; [Found: C,

82.48; H, 5.87; N, 7.41; $C_{26}H_{22}ON_2$ requires C, 82.50; H, 5.86; N, 7.41%]; IR (KBr, cm^{-1}): 3460, 3340, 1600, 1560; ^{1}H-NMR ($CDCl_3$, δ, Hz): 11.6 (bs, 1H, NH), 8.58-8.54 (m, 1H, arom.), 7.88-7.83 (m, 2H, arom.), 7.70 (dd, J = 7.0, 1.0, 1H, arom.), 7.54-7.11 (m, 10H, arom.), 6.81-6.73 (m, 2H, arom.), 5.68 (s, 1H, -C=CH); 4.45-4.39 (m, 2H, $PhCH_2NH$-), 3.98 (bs, 2H, $-NH_2$); ^{13}C-NMR ($CDCl_3$, δ): 194.0, 164.5, 144.0, 140.3, 138.7, 134.4, 131.0, 130.9, 130.6, 129.3, 129.2, 128.7, 128.0, 127.9, 127.1, 126.7, 126.4, 126.3, 125.3, 120.9, 118.7, 116.2, 98.7, 48.9; EI-MS m/z (relative intensity): 378 (M^+, 9), 223 (86), 155 (100).

2-(4'-Chlorophenyl)-4-(phenylethynyl)-quinoline 3k. A mixture of **1d** (0.158 g, 0.62 mmol) and NaI (0.185 g, 1.24 mmol) in acetic acid (5 mL) was stirred at 60 °C for 17h. The mixture was then poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethy lether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and crude **3e** dissolved in DMF (4 mL) and Et_3N (1 mL). Diphenylacetylene (0.088 ml, 0.80 mmol), $Pd(OAc)_2$ (0.007g, 0.03 mmol), PPh_3 (0.016g, 0.06 mmol) and CuI (0.006g, 0.03 mmol) were then added to the solution. The mixture was stirred under nitrogen for 18 h at 60 °C, poured into HCl 0.1M (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethylacetate 98:2 afforded pure **3k** (0.151g, 72%); m.p. 122-123°C; [Found: C, 81.30; H, 4.17; N, 4.15; $C_{23}H_{14}ClN$ requires C, 81.29; H, 4.15; N, 4.12%]; IR (KBr, cm^{-1}): 2200, 1590, 1510; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.32 (bd, J = 8, 1H), 8.17-8.01 (m, 3H), 7.98 (s,1H), 7.78-7.54 (m, 4H), 7.48-7.39 (m, 5H); ^{13}C-NMR ($CDCl_3$, δ): 155.4, 148.0, 137.4, 135.7, 132.0, 130.6, 130.2, 130.0, 129.4, 129.0, 128.7, 128.6, 127.1, 126.6, 125.7, 122.2, 121.1, 98.4, 85.3; EI-MS m/z (relative intensity): 341 (M^+ + 2, 35), 339 (M^+, 100), 304 (40).

4-Carboxymethyl-2-(4'-chlorophenyl)-quinoline 3l. A mixture of **1d** (0.158 g, 0.62 mmol) and NaI (0.185 g, 1.24 mmol) in acetic acid (5 mL) was stirred at 60 °C for 17h. The mixture was then poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethyl ether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and crude **3e** dissolved in DMF (4 mL) and CH_3OH (2 mL). Then triethylamine (0.174 mL, 1.24 mmol), $Pd(OAc)_2$ (0.007g, 0.03 mmol), and 1,1'-bis(diphenylphosphino) ferrocene (0.017g, 0.03 mmol) were added. The mixture was stirred under a balloon of CO at room temperature for 18h, poured in HCl 0.1M (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 98:2 afforded pure **3l** (0.110g, 60% yield); m.p. 86-88 °C. [Found: C, 68.55; H, 4.08; N, 4.72; $C_{17}H_{12}ClO_2N$ requires C, 68.58; H, 4.06; N, 4.70%]; IR (KBr, cm^{-1}): 1730, 1600, 1500; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.72 (bd, J = 8.5, 1H, arom.), 8.33 (s, 1H, arom.), 8.20-8.10 (m, 3H, arom.), 7.79-7.71 (m, 1H, arom.), 7.65-7.57 (m, 1H, arom.), 7.48 (d, J = 8.7, 2H, arom., BB' part of an AA'BB 'system), 4.06 (s, 3H, $-OCH_3$); ^{13}C-NMR ($CDCl_3$, δ): 166.6, 155.2, 149.1, 137.0, 136.0, 135.7, 130.2, 130.1, 129.1, 128.7, 128.0, 125.4, 124.0, 119.8, 52.8; EI-MS

m/z (relative intensity): 299 (M^+ + 2, 30.4), 297 (M^+, 84.6), 240 (100).

***(Z)*-2-(4'-Chlorophenyl)-4-(1-acetamido-1-carboxymethyl-ethen-2-yl)-quinoline 3m.** A mixture of **1d** (0.158 g, 0.62 mmol) and NaI (0.185 g, 1.24 mmol) in acetic acid (5 mL) was stirred at 60 °C for 17h. The mixture was then poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethyl ether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and crude **3e** dissolved in DMF (5 mL).Then methyl-α-acetamido acrylate (0.176g, 1.23 mmol), potassium acetate (0.242 g, 2.47 mmol) and $Pd(OAc)_2$ (0.007g, 0.03 mmol) were added. The mixture was stirred under N_2 at 80 °C for 20h, poured into HCl 0.1M (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 80:20 afforded pure **3m** (0.118g, 50% yield); m.p. 208-209°C; [Found: C, 66.21; H, 4.57; N, 7.35; $C_{21}H_{17}ClO_3N_2$ requires C, 66.30; H, 4.51; N, 7.37%]; IR (KBr, cm^{-1}): 1740, 1660, 1600, 1500; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.15 (bd, J = 8, 1H, arom.), 8.04 (d, J = 8.6, 2H, arom., AA' part of an AA'BB 'system), 7.90-7.88 (m, 1H, arom.), 7.76 (s, 1H, -C=C<u>H</u>), 7.73-7.69 (m, 2H, arom.), 7.58-7.50 (m, 1H, arom.), 7.47 (d, J = 8.6, 2H, arom., BB' part of an AA'BB 'system), 7.40 (bs, 1H, -N<u>H</u>), 3.93 (s, 3H, -COOC<u>H</u>$_3$), 1.89 (s, 3H, -COC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 166.1, 164.8, 155.4, 148.4, 141.1, 137.6, 135.7, 130.3, 130.0, 129.0, 128.6, 126.9, 126.5, 125.2, 124.7, 124.0, 117.1, 53.1, 23.1; EI-MS m/z (relative intensity): 382 (M^+ + 2, 14), 380 (M^+, 39), 338 (92), 279 (100).

2-(4'-Chlorophenyl)-4-(4''-carboxyethyl-5''-methyl-furan-2''-yl)methylquinoline 3n. A mixture of **1d** (0.158 g, 0.62 mmol) and NaI (0.185 g, 1.24 mmol) in acetic acid (5 mL) was stirred at 60 °C for 17h. The mixture was then poured into $NaHCO_3$ solution (5%) (200mL) and extracted twice with diethyl ether. The organic layer, dried over Na_2SO_4, was evaporated to dryness and crude **3e** dissolved in DMF (6 mL). Then K_2CO_3 (0.427g, 3.09 mmol), 2-acetyl-ethyl-4-pentynoate (0.156g, 0.927 mmol) and $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) were added. The mixture was stirred under N_2 at 60 °C for 3h, poured into NH_4Cl saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 90:10 afforded pure **3n** (0.121g, 48%yield) m.p. 97-99°C; [Found: C, 71.07; H, 5.00; N, 3.44; $C_{24}H_{20}ClNO_3$ requires C, 71.02; H, 4.97; N, 3.45%]; IR (KBr, cm^{-1}): 1710, 1600, 1500; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.20 (bd, J = 8, 1H, arom.), 8.08 (d, J = 8.6, 2H, arom., AA' part of an AA'BB 'system), 8.04-7.99 (m, 1H, arom.), 7.77-7.69 (m, 1H, arom.), 7.66 (s, 1H, arom.), 7.58-7.50 (m, 1H, arom.), 7.48 (d, J = 8.6, 2H, arom., BB' part of an AA'BB 'system), 6.29 (s, 1H, arom.), 4.39 (s, 2H, -C<u>H</u>$_2$-), 4.23 (q, J = 7.1, 2H, -OC<u>H</u>$_2$CH$_3$), 2.53 (s, 3H, -C<u>H</u>$_3$), 1.30 (t, J = 7.1, 3H, -OCH$_2$C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 164.0, 158.6, 155.8, 149.9, 148.3, 144.1, 137.7, 135.6, 130.3, 129.8, 129.0, 128.8, 128.7, 126.2, 123.3, 119.2, 114.3, 108.2, 60.1, 31.2, 14.3, 13.8; EI-MS m/z (relative

intensity): 407 (M^+ + 2, 36), 405 (M^+, 100), 271 (70).

4-Iodo-2-(*m*-tolyl)-quinoline 3o. A mixture of **1f** (0.150g, 0.64 mmol) and aqueous HI (57%, 0.7 ml) in dioxane (4 mL) was stirred at room temperature for 2h. Then the mixture was poured into Na_2CO_3 saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 95:5 afforded pure **3o** (0.088g, 40%); oil; IR (neat, cm^{-1}): 1610, 1490; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.42 (s, 1H); 8.10-8.05 (m, 1H), 8.00-7.85 (m, 3H), 7.76-7.67 (m, 1H), 7.59-7.54 (m, 1H), 7.39 (t, J = 7.5, 1H), 7.28-7.25 (m, 1H), 2.46 (s, 3H, -C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 157.2, 147.8, 138.6, 137.9, 131.4, 130.6, 130.5, 130.4, 130.2, 129.1, 128.8, 128.2, 127.7, 124.7, 112.5, 21.5; EI-MS m/z (relative intensity): 345 (M^+, 56), 218 (100).

3,4-Diiodo-2-(4'-methoxyphenyl)-quinoline 7. A mixture of **1a** (0.163 g, 0.65 mmol), I_2 (0.495 g, 1.95 mmol) and $NaHCO_3$ (0.163 g, 1.95 mmol) in CH_3CN (8 mL) was stirred at room temperature for 4h. Then the mixture was poured into $Na_2S_2O_3$ saturated solution (200mL) and extracted twice with ethyl acetate. The organic layer, dried over Na_2SO_4, was evaporated to dryness and the crude purified by flash chromatography over silica gel. Elution with hexane/ethyl acetate 90:10 afforded pure **7** (0.108 g, 34%); m.p. 197-199°C; [Found: C, 39.47; H, 2.29; N, 2.82; $C_{16}H_{11}I_2NO$ requires C, 39.45; H, 2.28; N, 2.88%]; IR (KBr, cm^{-1}): 1640, 1590, 1540; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.17-8.13 (m, 1H, arom.), 8.03-7.98 (m, 1H, arom.), 7.78-7.70 (m, 1H, arom.), 7.58-7.48 (m, 3H, arom.), 7.00 (d, J = 6.7, 2H, arom., BB' part of an AA'BB 'system), 3.88 (s, 3H, -OC<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$, δ): 159.9, 146.2, 143.8, 137.6, 135.0, 131.5, 130.7, 130.4, 130.1, 129.2, 113.3, 110.3, 55.4; EI-MS m/z (relative intensity): 487 (M^+, 45), 360 (42), 233 (33), 180 (100).

1(1'-Pyrrolidino)bicyclo[4.2.0]-octan[7,8-*c*]-2-(*m*-trifluoromethyl)quinoline 8a. A mixture of **1b** (0.104 g, 0.36 mmol) and 1-(cyclohexen-1-yl)pyrrolidine (0.064 ml, 0.40 mmol) in dry toluene (8 mL) was stirred at 110 °C under nitrogen for 17h. The solvent was then evaporated under vacuum and the crude, purified by flash chromatography (hexane/ethyl acetate 70:30), afforded **8a** (0.062g, 41%); m.p. 94-96°C; [Found: C, 73.85; H, 5.99; N, 6.68; $C_{26}H_{25}F_3N_2$ requires C, 73.90; H, 5.97; N, 6.63%];IR (KBr, cm^{-1}): 1600, 1500; ^{1}H-NMR ($CDCl_3$, δ, Hz): 9.17 (s,1H, arom.) 8.86 (bd, J = 7, 1H, arom.), 8.20 (bd, J = 8, 1H, arom.), 7.79-7.51 (m, 5H, arom.), 4.13 (t, J = 1.8, 1H, -C<u>H</u>-), 2.93-2.89 (m, 2H, -NC<u>H</u>$_2$), 2.59-2.55 (m, 2H, -NC<u>H</u>$_2$), 2.36-2.34 (m, 2H, -C<u>H</u>$_2$-), 2.07-1.95 (m, 2H, -C<u>H</u>$_2$-), 1.81-1.75 (m, 4H, two -C<u>H</u>$_2$-), 1.55-0.90 (m, 4H, two -C<u>H</u>$_2$-); ^{13}C-NMR ($CDCl_3$, δ): 153.0, 151.1, 147.8, 141.4, 138.1, 131.4, 131.1, 129.1, 126.6, 126.4, 126.5, 126.0, 125.9, 124.7, 122.7, 69.4 (C), 47.3 (CH_2), 40.7 (CH), 29.5 (CH_2), 25.2 (CH_2), 23.9 (CH_2), 19.3 (CH_2), 18.6 (CH_2); EI-MS m/z (relative intensity): 422 (M^+, 100).

1-*p*-Nitrophenyl3H-[1,2,3]triazol[4,5-*c*]2-(2'-naphthyl)quinoline 8b. A solution of **1e** (0.150 g, 0.55 mmol) and 4-nitrophenylazide[28] (0.108 g, 0.66 mmol) in dry 1,1,2,2-tetrachloroethane (7 mL) was heated under reflux for 6h. The solvent was then evaporated under vacuum and the crude, purified by flash chromatography (hexane/ethyl acetate 95:5), afforded **8b** (0.145 g, 63%); m.p. 220-222°C; [Found: C, 71.91; H, 3.64; N, 16.80; $C_{25}H_{15}N_5O_2$ requires C, 71.92; H, 3.62; N, 16.79%]; IR (KBr, cm^{-1}): 1600, 1510, 1310; ^{1}H-NMR (C_6D_6, δ, Hz): 8.93 (d, J = 8.2, 1H, arom.), 8.55-8.47 (m, 2H, arom.), 7.90 (d, J = 9.1, 1H, arom.), 7.83-7.75 (m, 2H, arom.), 7.69 (d, J = 9.0, 2H, arom., AA' part of an AA'BB 'system), 7.55-7.35 (m, 3H, arom.), 7.17-7.07 (m, 2H, arom.), 6.88 (d, J = 9.0, 2H, arom., BB' part of an AA'BB 'system); ^{13}C-NMR (C_6D_6, δ): 154.4, 149.3, 146.5, 142.5, 134.8, 134.7, 133.8, 132.0, 131.8, 131.1, 131.0, 130.2, 129.0, 128.0, 127.87, 127.83, 127.76, 126.6, 126.2, 125.9, 125.7, 121.8, 114.7; EI-MS m/z (relative intensity): 417 (M^+, 56), 388 (40), 342 (100).

3-phenylisoxazole[4,5-*c*]-2-(4'-chlorophenyl)quinoline 8c. A solution of **1d** (0.1 g, 0.391 mmol), benzaldehyde chlorooxime[29] (0.08 g, 0.508 mmol) and Et_3N (0.06 g, 0.586 mmol) in dry 1,1,2,2-tetrachloroethane (5 mL) was heated under reflux for 6h. The solvent was then evaporated under vacuum and the crude, purified by flash chromatography (hexane/ethyl acetate 98:2), afforded **8c** (0.086 g, 61%); m.p. 186-188°C; [Found: C, 74.20; H, 3.65; N, 7.82; $C_{22}H_{13}ClN_2O$ requires C, 74.16; H, 3.68; N, 7.87%];IR (KBr, cm^{-1}): 1650, 1630, 1590, 1090; ^{1}H-NMR ($CDCl_3$, δ, Hz): 8.48 (dd, J = 8.1, 1.1, 1H, arom.), 8.31 (d, J = 8.3, 1H, arom.), 7.91 (m, 1H, arom.), 7.76 (m, 1H, arom.), 7.42 (m, 1H, arom.), 7.26 (m, 4H, arom.), 7.34 (d, J = 8.5, 2H, arom., AA' part of an AA'BB 'system), 7.15 (d, J = 8.5, 2H, arom., BB' part of an AA'BB 'system); ^{13}C-NMR ($CDCl_3$, δ): 167.9, 159.2, 154.9, 147.7, 136.5, 135.9, 132.0, 131.3, 130.3, 130.2, 129.9, 128.7, 128.5, 128.3, 128.1, 121.9, 114.7, 112.2; EI-MS m/z (relative intensity): 358 (M^+ + 2, 37), 356 (M^+, 100).

Financial support from MURST (Roma) and CNR (Roma) is gratefully acknowledged.

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