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Synthesis of pyrrolo[3,4-*c*]quinolines by 1,5-electrocyclisation of non-stabilised azomethine ylides

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Abstract—A new route to the pyrrolo[3,4-*c*]quinoline ring system has been developed via the 1,5-dipolar electrocyclisation reactions of azomethine ylides derived from easily available 3-formylquinoline derivatives. The intermediacy of azomethine ylides was shown by the trapping of the proposed dipoles with *N*-phenylmaleimide.

1. Introduction

Quinolines and their derivatives are very important in medicinal chemistry because of their wide occurrence in natural products[1] and drugs.[2] Among the quinolines 2-chloro-3-formyl-quinolines occupy a prominent position as they are key intermediates for further [*b*]-annelation of a wide variety of rings and for various functional group interconversions.[3] The applications of these methodologies have yielded beside the huge number of new quinoline derivatives new synthetic approaches for alkaloids such as camptothecin,[4] luotonin A,[5] 22-hydroxyacuminatine[6] or nothapodytine[7] (Fig. 1).

In this paper, we describe[8] the first [*c*]-annelation of this type of quinoline by 1,5-electrocyclisation of azomethine ylides.[9] This conversion gives a direct route to the otherwise hardly accessible pyrrolo[3,4-*c*]quinoline ring system.[10]

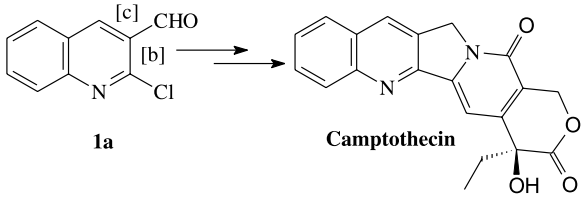

Figure 1.

The starting quinolines (**1a–c**) were prepared by the method described by Meth-Cohn from the corresponding acetanilides by the treatment with the Vilsmeier reagent in a single step.[11] The non-stabilized azomethine ylides **2** were generated from these aldehydes **1a–c** using the decarboxylation method.[12] The reaction of 2-chloro-3-formylquinolines **1a–c** with sarcosine in refluxing xylene gave 2-methyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-ones **4a–c** in acceptable yields via the expected 1,5-electrocyclisation reaction accompanied by hydrolysis of the chlorine function under the applied reaction conditions in the presence of the water formed in the first step (Scheme 1).

The intermediacy of azomethine ylides **2** was shown by trapping the proposed dipoles with *N*-phenylmaleimide to give the two isomeric cycloadducts **5** and **6** (*endo–exo* ratio ≈ 1:1) in quantitative yield (Scheme 1).

After the successful 1,5-electrocyclisation of non-stabilised azomethine ylides, we studied the reactivity of the analogous ester-stabilised system generated from the corresponding Schiff-base **7** by thermal 1,2-prototropy.[13] In contrast, in these cases, no 1,5-electrocyclisation was observed, the **7** imine remained unchanged even after a prolonged reaction time in refluxing xylene (Scheme 2). This result is in good agreement with our earlier observations on the reactivity of azomethine ylides in electrocyclisation reactions.[14]

We performed the next series of experiments with conjugated azomethine ylides derived from 2-phenyl-3-formylquinolines **10a–c**. In these dipoles **11** there is a

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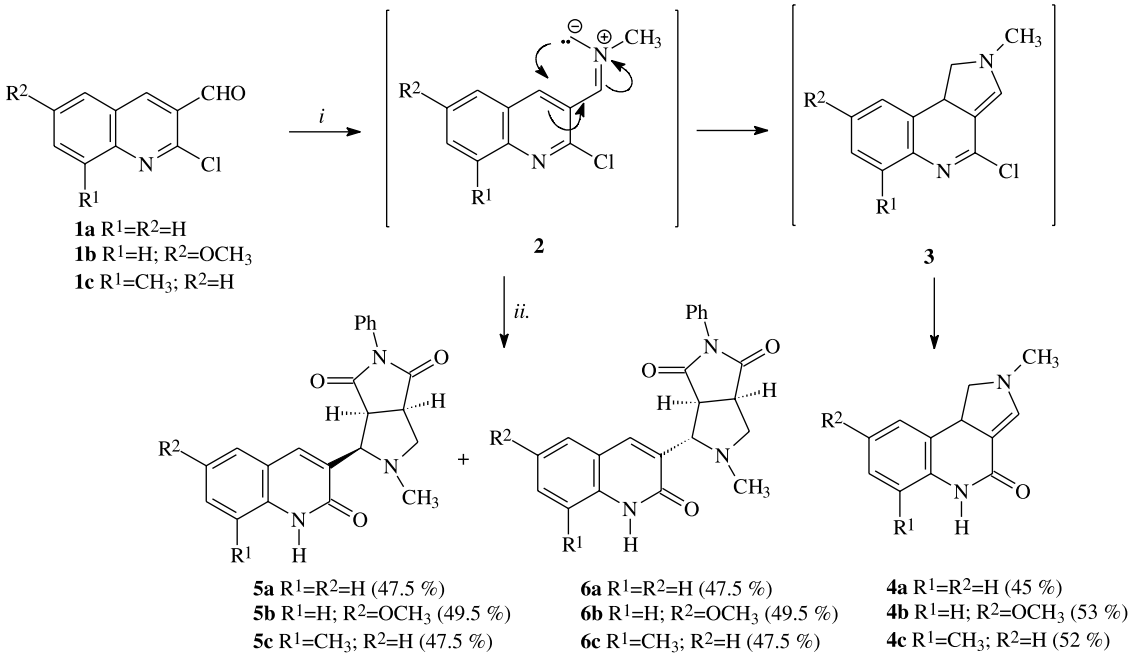


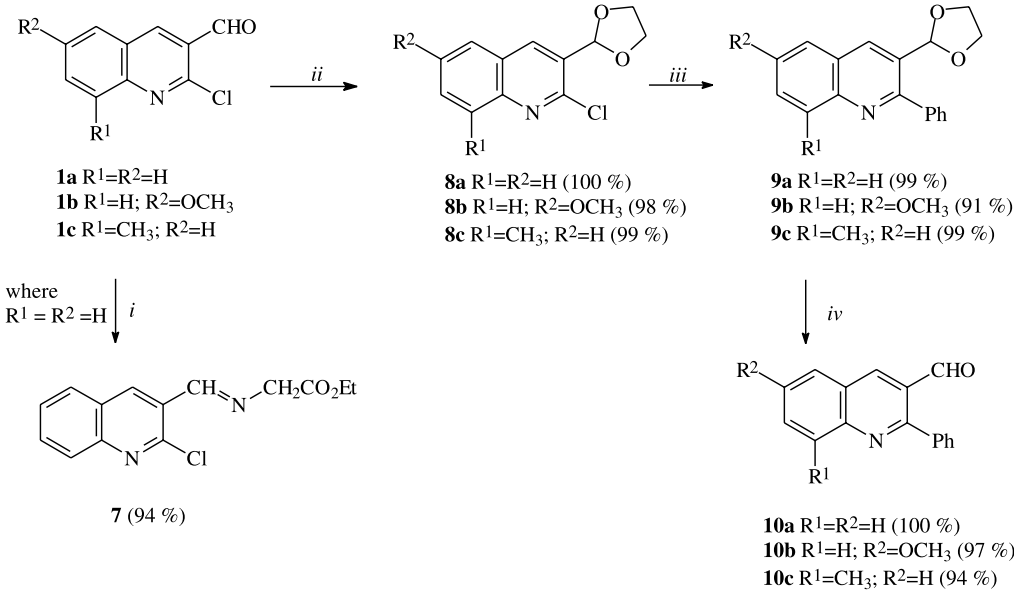
Scheme 1. (i) Sarcosine (2 equiv), xylene, 140 °C; (ii) *N*-phenylmaleimide (1 equiv).

possibility—besides the 1,5-electrocyclisation-of a 1,7-electrocyclic ring closure onto the phenyl group.[15] The starting material was prepared in three simple steps from the 2-chloro-3-formyl-quinolines including a palladium catalysed Suzuki coupling with phenylboronic acid (Scheme 2).

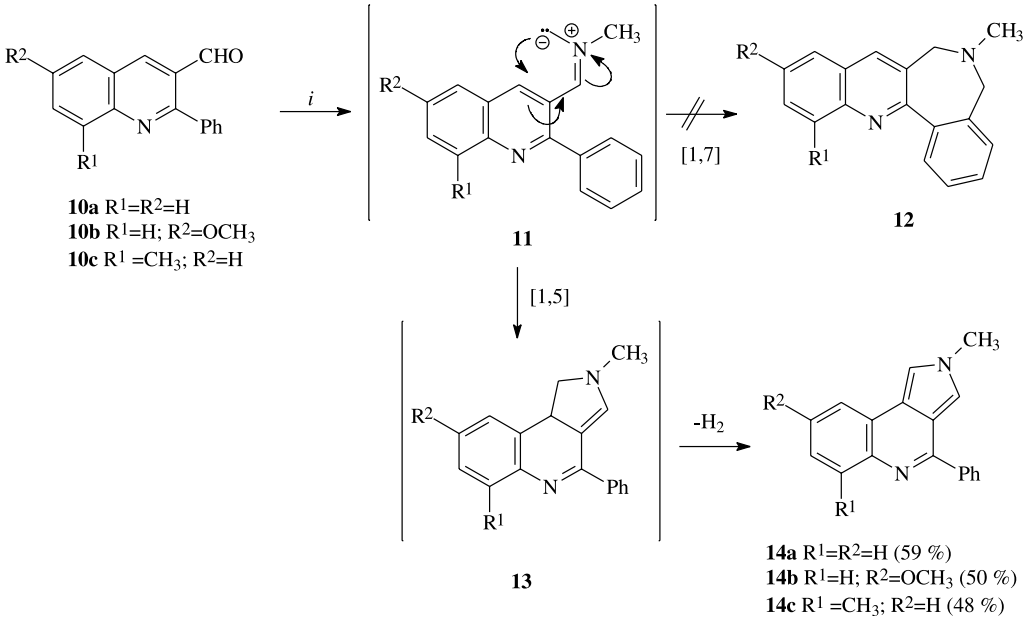
The reaction of the resultant quinolines **10a–c** with sarcosine in refluxing xylene, gave 2-methyl-4-phenyl-1*H*-pyrrolo[3,4-*c*]quinolines **14a–c** as products in moderate yields (Scheme 3). The 1,5-electrocyclisations in these cases were followed by full aromatisation to the tetrahydro-1*H* pyrrolo[3,4-*c*]quinoline **13** ring system. This slightly different result compared to the transformation **1**⇒**4**, may be explained by the delocalisation energy difference between the lactam products **4** and compounds **14** having a more extended conjugation.

The intermediacy of azomethine ylides **11** was again shown by the trapping the dipole with *N*-phenylmaleimide to give the two isomeric cycloadducts **15** and **16** (ratio≈1:5) in good yield. The stereochemistry of the major isomer (**16**) was proved by NOE experiments (Scheme 4).

In conclusion, we have developed a new, one-step route from simple starting materials to the challenging pyrrolo[3,4-*c*]quinoline ring system via the 1,5-dipolar electrocyclisation reaction of non-stabilised azomethine ylides.



Scheme 2. (i) $EtO_2CCH_2NH_2 \cdot HCl$, Et_3N, CH_2Cl_2, rt; (ii) $HOCH_2CH_2OH$, PTSA, benzene, reflux; (iii) $PhB(OH)_2$, $Pd(OAc)_2$ (cat.), K_2CO_3, DME, H_2O; (iv) 5% HCl, THF, 80 °C.

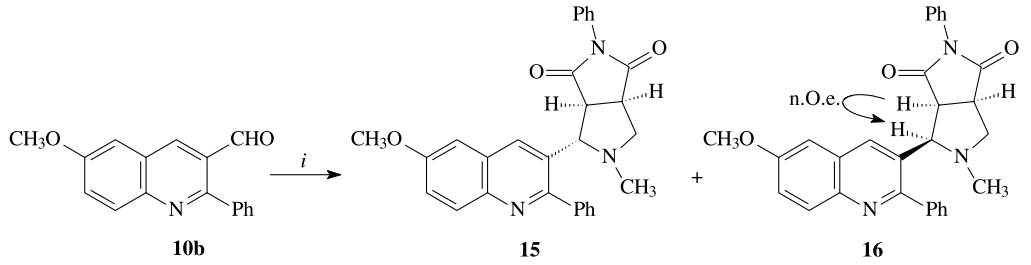


10a $R^1=R^2=H$
10b $R^1=H$; $R^2=OCH_3$
10c $R^1=CH_3$; $R^2=H$

11 **12** **13**

14a $R^1=R^2=H$ (59 %)
14b $R^1=H$; $R^2=OCH_3$ (50 %)
14c $R^1=CH_3$; $R^2=H$ (48 %)

Scheme 3. (i) Sarcosine (2 equiv), xylene, 140 °C.



10b **15** **16**

Scheme 4. (i) *N*-Phenylmaleimide (1 equiv), sarcosine (2 equiv), xylene, 140 °C.

2. Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Column chromatography was performed using Merck Kieselgel 60 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml cc sulphuric acid and 1 ml anisaldehyde) and heated at ca. 150 °C. IR spectra were measured on a NICOLET FT-IR instrument. NMR spectra were obtained on a Brucker 250 instrument. Chemical shifts are given relative to δ_{TMS}. All solvents were purified according to standard procedures and the quinolines **1a–c** were prepared by the method of Meth-Cohn et al.[11]

2.1. The 1,5-electrocyclisation reaction of azomethine ylides 2. General procedure

The corresponding 2-chloro-quinoline-3-carbaldehyde **1a–c** (5.0 mmol), was dissolved in xylene (150 ml) and sarcosine (1.34 g; 15.0 mmol) was added. The reaction mixture was boiled for 4 h. After the reaction was completed all the solvents were removed in vacuo and the residue was purified by column chromatography (eluent: chloroform–methanol 8:1 vol/vol).

2.1.1. 2-Methyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-one (4a).

Pale yellow powder (0.45 g, 45%); mp 145–6 °C; [Found: C, 72.0; H, 5.9; N, 14.0. $C_{12}H_{12}N_2O$ requires C 71.98; H 6.04; N 13.99%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.79 (s, 1H, H-3), 7.66 (d, 1H, $J=8.0$ Hz, H-9), 7.54 (d, 1H, $J=8.0$ Hz, H-6), 7.44 (t, 1H, $J=8.0$ Hz, H-8), 7.14 (t, 1H, $J=8.0$ Hz, H-7), 5.77 (broad s, 1H, NH), 5.17 (broad s, 1H, H-9*b*), 3.69 (t, 1H, $J=9.0$ Hz, H-1), 3.30 (dd, 1H, $J=2.2$, 9.0 Hz, H-1), 2.99 (s, 3H, *N*CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): 160.4 (q), 148.5 (q), 130.8 (CH), 128.9 (q), 128.8 (CH), 128.0 (CH), 125.4 (CH), 123.6 (q), 121.3 (CH), 66.0 (CH), 59.8 (CH_2), 31.2 (CH_3); IR (KBr, cm^{-1}): 2944, 2868, 2790, 1651, 1581, 1541, 1507, 1446, 1408, 1359, 1308, 1286, 1252, 1150, 1106, 1071, 1038, 1002.

2.1.2. 2-Methyl-8-methoxy-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-one (4b).

Pale yellow powder (0.56 g, 53%); mp 157–8 °C; [Found: C, 67.6; H, 6.0; N, 12.1. $C_{13}H_{14}N_2O_2$ requires C 67.81; H 6.13; N 12.17%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.75 (s, 1H, H-3), 7.48 (d, 1H, $J=8.8$ Hz, H-6), 7.17 (d, 1H, $J=2.4$ Hz, H-9), 7.11 (dd, 1H, $J=2.4$, 8.8 Hz, H-7), 5.74 (broad s, 1H, NH), 5.16 (broad s, 1H, H-9*b*), 3.79 (s, 3H, *O*CH_3), 3.65 (dd, 1H, $J=7.8$, 10.5 Hz, H-1), 3.25 (dd, 1H, $J=4.0$, 10.5 Hz, H-1), 2.95 (s, 3H, *N*CH_3);^{13}C NMR (62.5 MHz, DMSO-d_6): 159.5 (q), 154.0 (q), 143.5 (q), 130.2 (CH), 129.1 (q), 126.5 (CH), 124.0 (q), 119.2 (CH), 108.1 (CH), 66.2 (CH), 60.0 (CH_2),

55.3 (CH_3), 34.4 (CH_3); IR (KBr, cm^{-1}): 3160, 3062, 2994, 2939, 2831, 1648, 1618, 1582, 1500, 1453, 1430, 1404, 1336, 1292, 1235, 1204, 1166, 1097, 1062, 1038.

2.1.3. 2,6-Dimethyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4-one (4c). Pale yellow powder (0.55 g, 52%); mp 151 °C; [Found: C, 72.9; H, 6.4; N, 13.0. $C_{13}H_{14}N_2O$ requires C 72.87; H 6.59; N 13.07%]; ^{1}H NMR (250 MHz, DMSO-d_6): 7.77 (s, 1H, H-3), 7.49 (d, 1H, J=7.5 Hz, H-9), 7.32 (d, 1H, J=7.5 Hz, H-7), 7.04 (t, 1H, J=7.5 Hz, H-8), 5.80 (broad s, 1H, NH), 5.09 (broad s, 1H, H-9*b*), 3.66 (dd, 1H, J=7.7, 10.2 Hz, H-1), 3.29 (dd, 1H, J=3.9, 10.2 Hz, H-1), 3.01 (s, 3H, NCH_3), 2.56 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): 159.7 (q), 147.1 (q), 132.5 (q), 131.1 (CH), 129.1 (CH), 128.3 (q), 126.0 (CH), 123.1 (q), 120.8 (CH), 66.1 (CH), 59.8 (CH_2), 31.1 (CH_3), 17.8 (CH_3); IR (KBr, cm^{-1}): 2942, 2860, 1653, 1583, 1543, 1511, 1442, 1361, 1318, 1256, 1151, 1111, 1071, 1032, 1012.

2.2. The 1,3-dipolar cycloaddition of azomethine ylides 2 to *N*-phenyl-maleimide. General procedure

The corresponding 2-chloro-quinoline-3-carbaldehyde **1a–c** (1.0 mmol), was dissolved in xylene (50 ml) and *N*-phenyl-maleimide (0.17 g; 1 mmol), sarcosine (0.36 g; 4.0 mmol) was added. The reaction mixture was boiled for 2 h. After the reaction was completed all the solvents were removed in vacuo and the residue was purified by column chromatography (eluent: hexanes–acetone 3:1 vol/vol).

2.2.1. 5-(2-Chloroquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (5a and 6a). White powder (0.35 g, 95%); 1:1 mixture of two diastereomers; ^{1}H NMR (250 MHz, $CDCl_3$): 8.27 (s, ½H, Ar-4′H), 8.16 (s, ½H, Ar-4′H), 8.03 (d, ½H, J=8.2 Hz, Ar-5′H), 7.83 (d, ½H, J=8.2 Hz, Ar-5′H), 7.77–7.27 (m, 8H, Ar-6′, 7′ and 8′H, Ph–H), 4.37 (d, ½H, J=6.0 Hz, H-5), 4.09 (d, ½H, J=8.5 Hz, H-5), 3.90 (t, ½H, J=8.5 Hz, H-5*a*), 3.79–3.55 (m, 3½H, H-2*a*, H-5*a*, H-3), 2.29 (s, 1½H, NCH_3), 2.23 (s, 1½H, NCH_3); IR (KBr, cm^{-1}): 3060, 2972, 2940, 2836, 2780, 1708, 1619, 1591, 1560, 1496, 1456, 1388, 1320, 1188, 1172, 1158, 1043, 1010; HRMS: Calcd: 373.1426 for $C_{22}H_{19}N_3O_3$; Found: 373.1434.

2.2.2. 5-(2-Chloro-6-methoxyquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (5b and 6b). White powder (0.40 g, 99%); 1:1 mixture of two diastereomers; ^{1}H NMR (250 MHz, $CDCl_3$): 8.17 (s, ½H, Ar-4′H), 8.08 (s, ½H, Ar-4′H), 7.93 (d, ½H, J=8.2 Hz, Ar-8′H), 7.90 (d, ½H, J=8.2 Hz, Ar-8′H), 7.51–7.26 (m, 5H, Ar-6′ and 7′H, Ph–H), 7.17–6.95 (m, 3H, Ar-5′H and Ph–H), 4.35 (d, ½H, J=6.0 Hz, H-5), 4.08 (d, ½H, J=8.5 Hz, H-5), 3.93 (s, 1½H, OCH_3), 3.91 (s, 1½H, OCH_3), 3.87–3.41 (m, 4H, H-2*a*, H-5*a*, H-3), 2.24 (s, 3H, NCH_3); IR (KBr, cm^{-1}): 2964, 2794, 1714, 1621, 1589, 1498, 1453, 1498, 1385, 1326, 1262, 1231, 1183, 1096, 1025; HRMS: Calcd: 403.1532 for $C_{23}H_{21}N_3O_4$; Found: 403.1534.

2.2.3. 5-(2-Chloro-8-methylquinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (5c and 6c). White powder (0.37 g, 95% 1:1 mixture of two diastereomers); ^{1}H NMR (250 MHz, $CDCl_3$): 8.21 (s, ½H, Ar-4′H), 8.11 (s, ½H, Ar-4′H), 7.55–7.25 (m, 8H, Ar-5′, 6′and 7′H, Ph–H), 4.39 (d, ½H, J=6.0 Hz, H-5), 4.09 (d, ½H, J=8.5 Hz, H-5); 3.89 (t, ½H, J=8.5 Hz, H-5*a*), 3.78–3.39 (m, 3½H, H-2*a*, H-5*a*, H-3), 2.77 (s, 1½H, CH_3), 2.75 (s, 1½H, CH_3), 2.28 (s, 1½H, NCH_3), 2.22 (s, 1½H, NCH_3); IR (KBr, cm^{-1}): 2944, 2846, 1708, 1596, 1497, 1483, 1389, 1323, 1185, 1140, 1089, 1027, 941; HRMS: Calcd: 387.1582 for $C_{23}H_{21}N_3O_3$; Found: 387.1588.

2.2.4. Ethyl-(2-chloroquinolin-3-yl)methyleneamino-acetate (7). The 2-chlorquinoline-3-carbaldehyde **1a** (0.38 g; 2.0 mmol) was dissolved in dry dichloromethane (40 ml). Ethyl glycinate hydrochloride (0.28 g; 2.0 mmol), and triethylamine (0.29 ml, 0.2 g; 2.0 mmol) and approximately 2 g anhydrous magnesium sulfate was added. The reaction mixture was stirred at room temperature overnight. After filtration the reaction mixture was evaporated in vacuo. The resulted solid was suspended in ether and filtered again. The etheral solution was evaporated in vacuo to yield the title product as a pale yellow solid (0.52 g, 94.0%); mp 121–2 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.88 (s, 1H, CH=*N*), 8.78 (s, 1H, H-4), 7.99 (d, 1H, J=8.3 Hz, H-5), 7.87 (d, 1H, J=8.3 Hz, H-6), 7.76 (t, 1H, J=8.3 Hz, H-8), 7.56 (t, 1H, J=8.3 Hz, H-7), 4.53 (s, 2H, NCH_2), 4.29 (q, 2H, J=7.8 Hz, OCH_2), 1.33 (t, 2H, J=7.8 Hz, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 169.6 (q), 161.1 (CH), 148.4 (q), 137.8 (CH), 131.7 (CH), 130.7 (q), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.9 (q), 126.6 (q), 62.0 (CH_2), 61.2 (CH_2), 14.1 (CH_3); IR (KBr, cm^{-1}): 2981, 2877, 1743, 1646, 1596, 1488, 1373, 1268, 1187, 1087, 1029; HRMS: Calcd: 276.0665 for $C_{14}H_{13}N_2O_2Cl$; Found: 276.0660.

2.3. Synthesis of 3-[1,3-dioxolane-2-yl]-2-chloroquinolines (8a–c). General procedure

The corresponding 2-chlorquinoline-3-carbaldehyde **1a–c** (60 mmol) was suspended in benzene (600 ml), and ethylene glycol (4.5 ml, 5.0 g; 80.0 mmol) and *p*-toluene-sulphonic acid (0.57 g; 3.0 mmol) was added. The reaction mixture was refluxed for 4 h with the continous removal of the formed water by the aid of a Dean–Stark trap. After the reaction was completed saturated aq sodium hydrogen carbonate solution (150 ml) was added. The organic layer was separated, and washed with water (2×100 ml) and brine (100 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give the title products.

2.3.1. 3-(1,3-Dioxolane-2-yl)-2-chloroquinoline (8a). Pale yellow solid (14.12 g, 100%); mp 59–60 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.58 (s, 1H, H-4), 8.26 (d, 1H, J=8.0 Hz, H-5), 7.58–7.41 (m, 2H, H-8 and H-6), 7.17 (t, 1H, J=8.0 Hz, H-7), 6.08 (s, 2H, CH), 4.13–4.06 (m, 4H, OCH_2CH_2O); ^{13}C NMR (62.5 MHz, $CDCl_3$): 148.5 (q), 137.3 (CH), 131.4 (CH), 130.9 (q), 128.8 (CH), 128.0 (CH), 127.1 (CH), 126.5 (q), 126.2 (q), 100.2 (CH), 65.3 (2×CH_2); IR (KBr, cm^{-1}): 2894, 1619, 1599, 1568, 1493, 1456, 1368, 1327, 1138, 1101, 1037; HRMS: Calcd: 235.0400 for $C_{12}H_{10}NO2Cl$; Found: 235.0402.

2.3.2. 3-(1,3-Dioxolane-2-yl)-2-chloro-6-methoxy-quinoline (8b). Pale yellow solid (15.74 g, 98%); mp 79–80 °C; ^{1}H NMR (250 MHz, DMSO-d_6): 8.20 (s, 1H, H-4), 7.81 (d,

1H, J=9.2 Hz, H-8), 7.28 (dd, 1H, J=2.8, 9.2 Hz, H-7), 6.97 (d, 1H, J=2.8 Hz, H-5), 6.12 (s, 1H, CH), 4.11–4.08 (m, 2H, OCH_2), 4.05–4.00 (m, 2H, OCH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (62.5 MHz, DMSO-d_6): 159.5 (q), 145.8 (q), 142.7 (q), 135.7 (CH), 129.0 (q), 128.9 (CH), 128.0 (q), 123.5 (CH), 106.3 (CH), 99.7 (CH), 65.0 (2×CH_2), 55.5 (CH_3); IR (KBr, cm^{-1}): 3015, 2960, 2903, 1622, 1596, 1498, 1333, 1225, 1179, 1107, 1043, 1022. HRMS: Calcd: 265.0505 for $C_{13}H_{12}NO_3Cl$; Found: 265.0501.

2.3.3. 3-(1,3-Dioxolane-2-yl)-2-chloro-8-methyl-quinoline (8c). Pale yellow solid (14.80 g, 99%); mp 71–2 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.31 (s, 1H, H-4), 7.61 (d, 1H, J=8.0 Hz, H-5), 7.51 (d, 1H, J=8.0 Hz, H-7), 7.38 (t, 1H, J=8.2 Hz, H-6), 6.20 (s, 1H, CH), 4.09 (m, 4H, OCH_2CH_2O), 2.72 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 146.9 (q), 136.8 (CH), 136.4 (q), 131.0 (CH), 129.1 (q), 128.5 (q), 127.7 (q), 126.8 (CH), 125.9 (CH), 100.5 (CH), 65.5 (2×CH_2), 17.8 (CH_3); IR (KBr, cm^{-1}): 2954, 2884, 1615, 1598, 1577, 1490, 1466, 1364, 1331, 1182, 1101, 1074, 1021; HRMS: Calcd: 249.0556 for $C_{13}H_{12}NO_2Cl$; Found: 249.0549.

2.4. Suzuki coupling. General procedure

The corresponding acetal (20 mmol) and phenylboronic acid (2.93 g; 24.0 mmol) was dissolved in DME (75 ml) under argon atmosphere. Potassiom carbonate (8.3 g; 60 mmol) dissolved in water (75 ml) was added followed by palladium(II) acetate (49 mg; 0.2 mmol) and triphenyl phosphine (0.21 g; 0.8 mmol). The reaction mixture was refluxed for 1 h. After the reaction was completed it was filtered through a pad of Celite and washed with ethyl acetate. The organic layer was separated and the aqueous phases was extracted with ethyl acetate (2×50 ml). The combined organic extracts were washed with saturated aq sodium hydrogen carbonate solution (50 ml), water (2×50 ml) and brine (50 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give the crude product, which was purified by flash vacuum chromatography (eluent: hexanes–ethyl acetate 3:1 vol/vol).

2.4.1. 3-(1,3-Dioxolane-2-yl)-2-phenylquinoline (9a). White powder (5.50 g, 99%); mp 88–90 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.58 (s, 1H, H-4), 8.21 (d, 1H, J=8.1 Hz, H-5), 7.87 (d, 1H, J=8.1 Hz, H-8), 7.81–7.72 (m, 3H, H-6 and Ph–H), 7.54–7.41 (m, 4H, H-7 and Ph–H), 5.88 (s, 1H, CH), 4.18–4.07 (m, 2H, OCH_2), 4.00–3.90 (m, 2H, OCH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$): 158.8 (q), 147.7 (q), 139.1 (q), 135.5 (CH), 130.2 (CH), 129.5 (2×CH), 129.0 (CH), 128.4 (q), 128.3 (CH), 127.9 (2×CH), 127.7 (CH), 126.7 (q), 126.4 (CH), 100.7 (CH), 65.3 (2×CH_2); IR (KBr, cm^{-1}): 3058, 2953, 2889, 1621, 1599, 1558, 1489, 1442, 1368, 1267, 1169, 1128, 1082, 1018; HRMS: Calcd: 277.1102 for $C_{18}H_{15}NO_2$; Found: 277.1100.

2.4.2. 3-(1,3-Dioxolane-2-yl)-6-methoxy-2-phenylquinoline (9b). White powder (5.60 g, 91%); mp 102–3 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.42 (s, 1H, H-4), 8.04 (d, 1H, J=7.6 Hz, H-8), 7.75 (d, 2H, J=7.5 Hz, Ph-2′ and 6′H), 7.41–7.28 (m, H-7 and Ph–H), 7.01 (s, 1H, H-5), 5.81 (s, 1H, CH), 4.02 (m, 2H, OCH_2), 3.82 (m, 2H, OCH_2), 3.70 (s, 3H, OCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 157.7 (q), 156.5 (q), 144.0 (q), 139.4 (q), 134.3 (CH), 130.4 (CH), 129.6 (2×CH), 129.3 (q), 128.3 (CH), 128.0 (2×CH), 123.3 (CH), 115. 5 (q), 104.9 (CH), 100.8 (CH), 65.4 (2×CH_2), 55.3 (OCH_3); IR (KBr, cm^{-1}): 3056, 2999, 2964, 2888, 2861, 1622, 1602, 1492, 1462, 1364, 1223, 1168, 1085, 1029; HRMS: Calcd: 307.1208 for $C_{19}H_{17}NO_3$; Found: 307.1212.

2.4.3. 3-(1,3-Dioxolane-2-yl)-8-methyl-2-phenylquinoline (9c). White powder (5.79 g, 99%); mp 98–9 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.51 (s, 1H, H-4), 7.84 (d, 2H, J=7.8 Hz, Ph-2′ and 6′H), 7.69 (d, 1H, J=8.1 Hz, H-9), 7.53–7.35 (m, 6H, H-8, H-7 and Ph–H), 5.90 (s, 1H, CH), 4.16 (m, 2H, OCH_2), 3.95 (m, 2H, OCH_2), 2.81 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 157.3 (q), 147.0 (q), 139.8 (q), 137.3 (q), 135.7 (CH), 130.1 (CH), 130.0 (2×CH), 128.3 (q), 128.2 (CH), 127.9 (2×CH), 126.7 (q), 126.2 (CH), 125.8 (CH), 101.0 (CH), 65.5 (2×CH_2), 17.8 (CH_3); IR (KBr, cm^{-1}): 2953, 2892, 1615, 1599, 1568, 1481, 1463, 1365, 1170, 1084, 1072, 1062, 1009; HRMS: Calcd: 291.1259 for $C_{19}H_{17}NO_2$; Found: 291.1265.

2.5. Hydrolysis of ketal 9a–c—General procedure

The corresponding ketal **9a–c** (20 mmol) was dissolved in tetrahydofuran (300 ml), water (50 ml) and concentrated hydrochloric acid (10 ml) was added. The reaction mixture was refluxed for an hour under argon atmosphere. After the reaction was completed saturated aq sodium hydrocarbonate solution (150 ml) was added. The tetrahydrofurane was removed in vacuo and the residue was extracted with ethyl acetate (3×50 ml). The combined organic extracts were washed with water (2×50 ml), brine (50 ml), dried over magnesium sulfate, and evaporated under reduced pressure to give the product.

2.5.1. 2-Phenyl-quinoline-3-carbaldehyde (10a). White powder (3.50 g, 100%); mp 105–6 °C; [Found: C, 82.5; H, 4.8; N, 6.0. $C_{16}H_{11}NO$ requires C 82.38; H 4.75; N 6.00%]; ^{1}H NMR (250 MHz, $CDCl_3$): 10.15 (s, 1H, CHO), 8.79 (s, 1H, H-4), 8.19 (d, 1H, J=8.2 Hz, H-8), 7.96 (d, 1H, J=8.2 Hz, H-5); 7.83 (t, 1H, J=8.2 Hz, H-7), 7.68 (m, 2H, Ph–H), 7.52 (m, 4H, H-6 and Ph–H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.3 (CH), 160.1 (q), 149.4 (q), 138.0 (CH), 137.5 (q), 132.5 (CH), 130.1 (2×CH), 129.4 (CH), 129.3 (CH), 129.25 (CH), 128.6 (2×CH), 127.5 (q), 127.3 (CH), 126.2 (q); IR (KBr, cm^{-1}): 2861, 1693, 1614, 1584, 1552, 1485, 1370, 1156, 1121, 1075, 1008.

2.5.2. 6-Methoxy-2-phenylquinoline-3-carbaldehyde (10b). White powder (3.82 g, 97%); mp 125–6 °C; [Found: C, 77.3; H, 4.8; N, 5.2. $C_{17}H_{13}NO_2$ requires C 77.55; H 4.98; N 5.32%]; ^{1}H NMR (250 MHz, $CDCl_3$): 10.14 (s, 1H, CHO), 8.66 (s, 1H, H-4), 8.15 (d, 1H, J=8.3 Hz, H-8), 7.64 (m, 2H, Ph–H), 7.51 (m, 4H, H-7 and Ph–H), 7.16 (d, 1H, J=1.8 Hz, H-5), 3.93 (s, 3H, OCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.7 (CH), 158.3 (q), 158.0 (q), 145.9 (q), 137.8 (q), 136.4 (CH), 130.9 (CH), 130.3 (2×CH), 129.4 (CH), 128.7 (2×CH), 127.7 (q), 127.4 (q), 125.8 (CH), 125.9 (CH), 55.6 (OCH_3); IR (KBr, cm^{-1}): 3452, 3057, 2955, 2855, 1686, 1618, 1585, 1563, 1492, 1446, 1416, 1367, 1349, 1226, 1169, 1130, 1027.

2.5.3. 8-Methyl-2-phenylquinoline-3-carbaldehyde (10c).

White powder (3.48 g, 94%); mp 109–11 °C; [Found: C, 82.7; H, 5.4; N, 5.7. $C_{17}H_{13}NO$ requires C 82.57; H 5.30; N 5.66%]; ^{1}H NMR (250 MHz, $CDCl_3$): 10.16 (s, 1H, CHO), 8.71 (s, 1H, H-4), 7.76–7.40 (m, 8H, Ar-H), 2.81 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 191.7 (CH), 158.5 (q), 148.5 (q), 138.2 (CH), 137.7 (q), 132.4 (CH), 132.3 (q), 130.6 (2×CH), 129.2 (CH), 128.5 (2×CH), 128.4 (q), 127.2 (CH), 127.1 (CH), 126.1 (q), 17.8 (CH_3); IR (KBr, cm^{-1}): 2861, 2844, 1692, 1611, 1580, 1555, 1485, 1371, 1152, 1119, 1075, 1011.

2.6. 1,5-Electrocyclization reactions of azomethine ylides 11 generated from 2-phenyl-quinoline-3-carbaldehydes 10a–c. General procedure

The corresponding 2-phenyl-quinoline-3-carbaldehyde **10a–c** (3.0 mmol) was dissolved in xylene (50 ml) and sarcosine (0.54 g; 6.0 mmol) was added. The reaction mixture was refluxed until the starting aldehyde completely disappeared (judged by TLC). All the solvent was removed in vacuo and the residue purified by flash chromatography (eluent: petroleum ether–acetone 3:1) to give the crystalline product.

2.6.1. 2-Methyl-4-phenyl-pyrrolo[3,4-*c*]quinoline (14a). White powder (0.46 g, 59%); mp 182–3 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.10 (dd, 1H, J=1.9, 7.9 Hz, H-9), 7.97 (dd, 2H, J=2.0, 8.1 Hz, Ph-2′ and 6′H), 7.92 (dd, 1H, J=1.9, 7.9 Hz, H-6), 7.53–7.38 (m, 5H, H-7, H-8 and Ph–H), 7.27 (d, 1H, J=1.8 Hz, H-3), 7.20 (d, 1H, J=1.8 Hz, H-1), 3.77 (s, 3H, NCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 155.6 (q), 142.8 (q), 140.3 (q), 129.7 (CH), 129.0 (CH), 128.5 (2×CH), 128.4 (2×CH), 126.0 (CH), 125.8 (CH), 122.9 (q), 122.2 (CH), 121.9 (q), 117.6 (CH), 117.5 (q), 112.8 (CH), 37.4 (CH_3); IR (KBr, cm^{-1}): 3139, 2942, 1572, 1538, 1521, 1481, 1467, 1454, 1443, 1413, 1357, 1332, 1234, 1220, 1192, 1143, 1078, 1028; HRMS: Calcd: 258.1156 for $C_{18}H_{14}N_2$; Found: 258.1156.

2.6.2. 8-Methoxy-2-methyl-4-phenyl-pyrrolo[3,4-*c*]quinoline (14b). White powder (0.43 g, 50%); mp 188 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.01 (d, 1H, J=9.0 Hz, H-6), 7.96 (m, 2H, Ar-H), 7.49 (m, 3H, Ar-H), 7.30 (m, 2H, Ar-H), 7.22 (d, 1H, J=1.8 Hz, H-1), 7.09 (dd, 1H, J=2.5, 9.0 Hz, H-7), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, NCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 157.6 (q), 157.5 (q), 153.2 (q), 140.3 (q), 137.5 (q), 131.0 (CH), 128.8 (CH), 128.4 (2×CH), 128.3 (2×CH), 122.9 (q), 122.7 (q), 117.4 (CH), 114.9 (CH), 112.8 (CH), 103.8 (CH), 55.4 (OCH_3), 37.4 (NCH_3); IR (KBr, cm^{-1}): 3142, 3058, 2933, 2832, 1706, 1616, 1531, 1485, 1474, 1452, 1434, 1369, 1250, 1210, 1165, 1141, 1104, 1030; HRMS: Calcd: 288.1262 for $C_{19}H_{16}N_2O$; Found: 288.1263.

2.6.3. 2,6-Dimethyl-4-phenyl-pyrrolo[3,4-*c*]quinoline (14c). White powder (0.39 g, 48%); mp 176–7 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 8.10 (d, 2H, J=7.7 Hz, Ph-2′ and 6′H), 7.81 (dd, 1H, J=2.3, 6.7 Hz, H-9), 7.54–7.25 (m, 7H, Ar-H), 3.92 (s, 3H, NCH_3), 2.82 (s, 3H, CH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$): 152.4 (q), 140.2 (q), 139.8 (q), 136.4 (q), 128.2 (CH), 127.7 (2×CH), 127.6 (2×CH), 126.1 (CH), 124.6 (CH), 122.6 (q), 120.7 (q), 119.3 (CH), 116.5 (CH), 116.1 (q), 112.2 (CH), 36.7 (NCH_3), 17.8 (CH_3); IR (KBr, cm^{-1}): 3025, 2951, 1528, 1473, 1446, 1428, 1356, 1329, 1216, 1140, 1089, 1073, 1059, 1020; HRMS: Calcd: 272.1313 for $C_{19}H_{16}N_2$; Found: 272.1313.

2.6.4. 5-(2-Phenyl-6-methoxy-quinolin-3-yl)-1,4-diaza-2,6-dioxo-4-methyl-1-phenyl-bicyclo[3.3.0]octane (16). 2-(6-Methoxyphenyl)-quinoline-3-carbaldehyde **10b** (0.26 g; 1 mmol) was dissolved in xylene (50 ml) and *N*-phenylmaleimide (0.17 g; 1.0 mmol) and sarcosine (0.36 g; 4.0 mmol) was added. The reaction mixture was refluxed for 1 h. On cooling the solvent was removed in vacuo and the residue was purified by flash chromatography (eluent: petroleum ether–acetone 3:1) to give the main isomer as a crystalline product as a white powder (0.30 g, 65%); mp 172–3 °C; ^{1}H NMR (250 MHz, DMSO-d_6): 8.32 (s, 1H, Ar-4′H), 8.06 (d, 1H, J=9 Hz, Ar-8′H), 7.52–7.37 (m, 9H, Ar-H, Ph–H), 7.10 (m, 3H, Ar-H, Ph–H), 3.93 (s, 3H, OCH_3), 3.84 (d, 1H, J=7.3 Hz, H-5), 3.65–3.50 (m, 4H, H-2*a*, H-3, H-5*a*), 2.07 (s, 3H, *N*Me); ^{13}C NMR (63 MHz, DMSO-d_6): 176.2 (q), 175.5 (q), 158.4 (q), 157.9 (q), 143.4 (q), 139.9 (q), 134.7 (CH), 131.4 (q), 131.0 (q), 130.8 (CH), 129.8 (2×CH), 129.1 (2×CH), 128.6 (CH), 128.1 (2×CH), 127.9 (CH), 127.8 (q), 126.4 (2×CH), 123.1 (CH), 104.5 (CH), 68.0 (CH), 57.3 (CH_2), 55.5 (CH_3), 54.8 (CH), 44.2 (CH), 38.6 (CH_3). HRMS: Calcd: 463.1895 for $C_{29}H_{25}N_3O_3$; Found: 463.1898.

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