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Intramolecular 1,3-Dipolar Cycloaddition of Azomethine Ylides Leading to Pyrido[2,3-b]quinolines

Judit Tóth [a], Barbara Somfai [a], Gábor Blaskó [b], András Dancsó [b], László Töke [a] & Miklós Nyerges [a]

[a] Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest, Budapest, Hungary

[b] EGIS Pharmaceuticals Ltd., Budapest, Hungary

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Intramolecular 1,3-Dipolar Cycloaddition of Azomethine Ylides Leading to Pyrido[2,3-*b*]quinolines

Judit Tóth,[1] Barbara Somfai,[1] Gábor Blaskó,[2] András Dancsó,[2] László Töke,[1] and Miklós Nyerges[1]

[1]Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest, Budapest, Hungary
[2]EGIS Pharmaceuticals Ltd., Budapest, Hungary

Abstract: A convenient six-step route to the previously unknown 1*H*-pyrrolo[2,3-*f*]benzo[*b*][1,8]naphthyridine ring system using an intramolecular 1,3-dipolar cycloaddition of nonstabilized azomethine ylides has been described.

Keywords: Cycloadditions, heterocycles, tandem reactions, ylides

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 (**1**) occupy a prominent position because they are intermediates for further [*b*]-annelation of a wide variety of rings and for various functional group interconversions.[3] Beside the large number of quinoline derivatives, the applications of these methodologies have yielded new synthetic approaches for alkaloids such as camptothecin,[4] luotonin A,[5] 22-hydroxyacuminatine,[6] or nothapodytine.[7]

Recently we have described[8] the first [*c*]-annelation of this type of quinoline by 1,5-electrocyclization of azomethine ylides,[9] which gave a direct route to the otherwise hardly accessible pyrrolo[3,4-*c*]quinoline ring system (**2**) (Scheme 1).[10]

The 2-chloro-3-formylquinolines (**1**) remained popular starting compounds for the synthesis of new heterocycles using intramolecular

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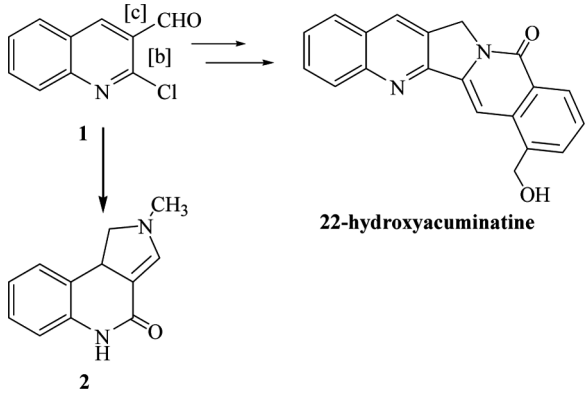
Address correspondence to Miklós Nyerges, Servier Research Institute of Medicinal Chemistry, H-1031 Budapest, Záhony u. 7. Graphisoft Park, Hungary. E-mail: miklos.nyerges@hu.netgrs.com



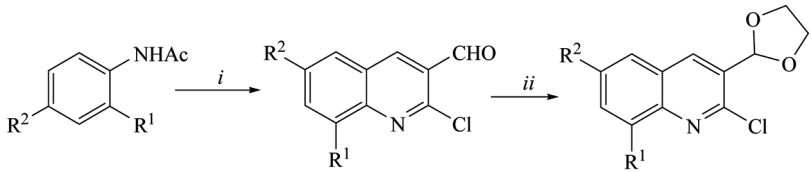
Scheme 1. Synthetic annelations to 2-chloro-3-formylquinolines.

1,3-dipolar cycloadditions of various dipole types.[11] These results prompted us to study the related reactions of azomethine ylides, which gives direct access to the hitherto unknown hexahydro-1*H*-pyrrolo[2,3-*f*]benzo[*b*][1,8]naphthyridin-4-ones.

RESULTS AND DISCUSSION

The starting quinolines (**1a**–**c**) were prepared by the method described by Meth-Cohn and Narine from the corresponding acetanilides (**3a**–**c**) by treatment with the Vilsmeier reagent in a very effective domino reaction (Scheme 2).[12]

The quinoline ketals (**4a**–**c**) were reacted with excess of benzylamine in the absence of any solvent at 180 °C to give the expected 2-benzylamino-quinolines, but at the same time the ketal was also replaced by a



3a $R^1 = R^2 = H$
3b $R^1 = H$, $R^2 = OCH_3$
3c $R^1 = CH_3$, $R^2 = H$

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

4a $R^1 = R^2 = H$
4b $R^1 = H$, $R^2 = OCH_3$
4c $R^1 = CH_3$, $R^2 = H$

Scheme 2. Reagents and conditions: i) $POCl_3$, DMF, 80 °C; and ii) $HOCH_2$-CH_2OH, PTSA, benzene, reflux.

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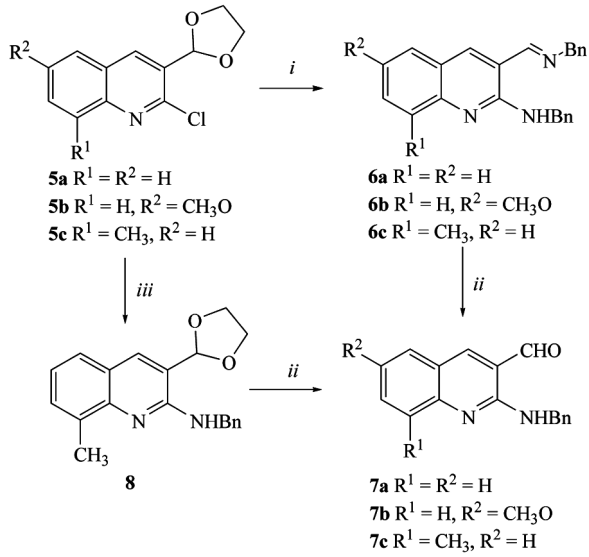

Scheme 3. Reagents and conditions: i) $PhCH_2NH_2$, 180 °C; ii) 5% HCl, THF, rt; and iii) $PhCH_2NH_2$, $NaOBu^t$, $Pd(OAc)_2$, PPh_3, toluene, 180 °C.

benzylimino moiety. The direct reaction of the 3-formyl-quinolines **1a**–**c** with benzylamine under the same conditions proceeded in much lower yield.

The 3-(benzyliminomethyl)quinolines (**6a-c**) were easily hydrolized to the corresponding aldehydes under mild conditions (Scheme 3). Alternatively, in one example, the palladium-catalyzed coupling of benzylamine to ketal-protected quinoline **5c** was also investigated, followed by the hydrolytic removal of the protecting group from **8**, but the overall yield was lower coupled with longer reaction times, so we decided to use the route that applies the neat benzylamine.

The 2-aminoquinolines **7a**–**c** were acylated with acryloyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) in dimethyl formamide solution at 80 °C. The nonstabilized azomethine ylides **10** were generated from the aldehydes **9a**–**c** in refluxing toluene using the method of decarboxylative condensation with sarcosine.[13] The azomethine ylides intermediates reacted via the expected intramolecular 1,3-dipolar cycloaddition[14] to the acrylamide double bond to give the tetracyclic hexahydro-1*H*-pyrrolo[2,3-*f*]benzo[*b*][1,8]naphthyridin-4-ones **11a**–**c** as products, which were isolated in acceptable yields after column chromatography (Scheme 4). The stereochemistry of the isolated cycloadducts (**11**) were proven by nuclear Overhauser effect (NOE) experiments.

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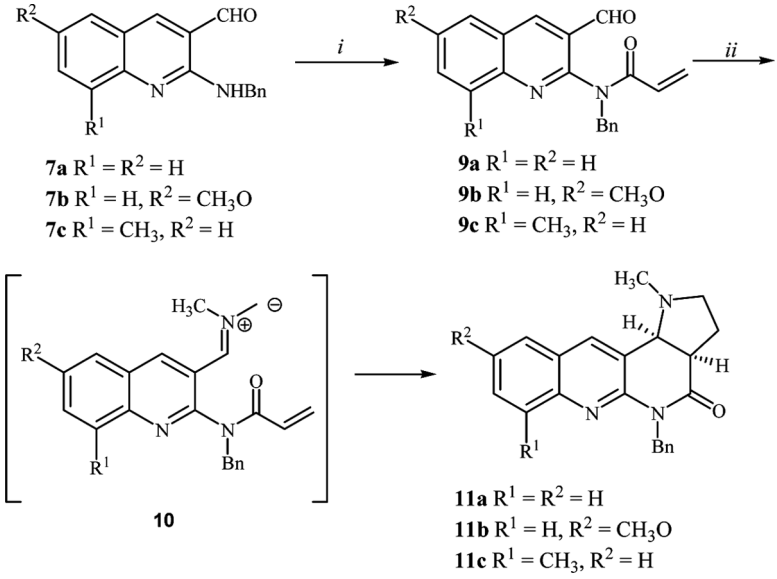

Scheme 4. Reagents and conditions: i) CH_2=CHCOCl, Et_3N, DMF, DMAP, 80°C; ii) CH_3NHCH_2COOH, toluene, 110°C.

In summary, we have explored a convenient reaction sequence that provides a useful route to the previously unknown 1*H*-pyrrolo[2,3-*f*] benzo[*b*][1,8]naphthyridin ring system using an intramolecular 1,3-dipolar cycloaddition of nonstabilized azomethine ylides.

EXPERIMENTAL

General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Column chromatography was performed using Merck Kieselgel 60, 70–230 mesh, and thin-layer chromatography (TLC) on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml conc. sulfuric acid, and 1 ml anisaldehyde) and heated at ca. 150 °C. IR spectra were obtained on a Bruker Vector 22 FT-IR instrument. NMR spectra were obtained on Varian Inova 500, Bruker DRX-500, and Bruker 250 instruments. Chemical shifts are given relative to δ_{TMS}. All solvents were purified according to standard procedures.

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Synthesis of *N*-Benzyl-3-[(benzylimino)methyl]quinolin-2-amines (6a–c)

General Procedure

The corresponding 3-[1′,3′-dioxolane-2′-yl]-2-chloroquinoline (**5a**–**c**, 20 mmol) was suspended in benzylamine (10 ml), and the reaction mixture was heated at 180 °C for 1 h under an argon atmosphere. The excess of benzylamine was removed with vacuum distillation, and the residue was crystallized from ether to yield the yellow product.

Data for 6a–c

N-Benzyl-3-[(benzylimino)methyl]quinolin-2-amine (**6a**)

Yield: 6.46 g (92%); yellow crystals; mp. 123–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 9.72 (1H, br s, NH), 8.46 (1H, s, H-4), 7.82 (1H, s, CH=N), 7.52 (6H, m, Ar-H), 7.33 (4H, m, Ar-H), 7.21 (4H, m, Ar-H), 4.84 (2H, d, $J = 5.5$ Hz, $NHC\underline{H}_2$-), 4.77 (2H, s, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$): 163.0 (CH), 147.7 (q), 142.0 (CH), 140.0 (q), 139.6 (q), 134.7 (q), 129.7 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 127.9 (2 × CH), 127.2 (2 × CH), 126.4 (CH), 126.1 (CH), 125.1 (CH), 121.1 (q), 121.5 (CH), 121.3 (CH), 118.1 (q), 64.8 (CH_2), 44.7 (CH_2); IR (KBr, cm^{-1}): 3220, 3061, 3017, 2859, 1635, 1600, 1571, 1536, 1499, 1451, 1412, 1394, 1164, 1141, 1016. HRMS: calcd. 351.1735 for $C_{24}H_{21}N_3$; found 351.1734. H, 6.02; C, 82.02; N, 11.96.

N-Benzyl-3-[(benzylimino)methyl]-6-methoxyquinolin-2-amine (**6b**)

Yield: 7.31 g (96%); yellow crystals; mp 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 9.56 (1H, br s, NH), 8.47 (1H, s, H-4), 7.81 (1H, s, CH=N), 7.65 (1H, d, $J = 8.0$ Hz, H-8), 7.42 (2H, d, $J = 7.5$ Hz, Ph-H), 7.28 (9H, m, Ar-H), 6.93 (d, 1H, $J = 2.5$ Hz, H-5), 4.86 (2H, d, $J = 5.2$ Hz, $NHC\underline{H}_2$-), 4.78 (2H, s, NCH_2), 3.85 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 162.6 (CH), 154.5 (q), 154.1 (q), 141.7 (CH), 138.9 (q), 128.6 (q), 128.5 (2 × CH), 128.4 (q), 128.3 (2 × CH), 127.8 (2 × CH), 127.7 (2 × CH), 127.5 (CH), 127.0 (CH), 126.8 (CH), 122.9 (CH), 122.4 (q), 116.8 (q), 106.5 (CH), 65.0 (CH_2), 55.5 (CH_3), 45.0 (CH_2); IR (KBr, cm^{-1}): 3221, 3060, 3027, 2895, 2859, 1638, 1602, 1572, 1531, 1495, 1452, 1402, 1373, 1339, 1232, 1166, 1118, 1079, 1033. HRMS: calcd. 381.1841 for $C_{25}H_{23}N_3O$; found: 381.1830. H, 6.08; C, 78.71; N, 11.02; O, 4.19.

N-Benzyl-3-[(benzylimino)methyl]-8-methylquinolin-2-amine (**6c**)

Yield: 6.57 g (90%); yellow crystals; mp 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 9.67 (1H, br t, $J = 5.4$ Hz, NH), 8.47 (1H, s, H-4), 7.84 (1H, s, CH=N), 7.42 (4H, m, Ar-H), 7.26 (8H, m, Ar-H), 7.06 (1H, t, $J = 7.3$ Hz, H-6), 4.87 (2H, d, $J = 5.4$ Hz, $NHCH_2$-), 4.79 (2H, s, NCH_2), 2.62 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 162.8 (CH), 154.2 (q), 147.4 (q), 142.9 (CH), 140.2 (q), 139.1 (q), 134.1 (q), 131.1 (CH), 128.5 ($2 \times$ CH), 128.3 ($2 \times$ CH), 127.8 ($2 \times$ CH), 127.6 ($2 \times$ CH), 127.0 (CH), 126.6 (CH), 125.9 (CH), 121.9 (q), 121.3 (CH), 116.3 (q), 64.9 (CH_2), 44.9 (CH_2), 17.9 (CH_3); IR (KBr, cm^{-1}): 3201, 3028, 2941, 2906, 2869, 1641, 1618, 1579, 1531, 1494, 1469, 1452, 1415, 1397, 1375, 1335, 1250, 1176, 1077, 1026. HRMS: calcd. 365.1891 for $C_{25}H_{23}N_3$; found: 365.1901. H, 6.34; C, 82.16; N, 11.50.

Synthesis of 2-(Benzylamino)quinoline-3-carbaldehydes (7a–c)

General Procedure

The corresponding *N*-benzyl-3-[(benzylimino)methyl]quinolin-2-amine (**6**, 10 mmol) was dissolved in tetrahydrofurane (50 ml), and 5% aqueous hydrochloric acid (10 ml) was added. The reaction mixture was stirred at room temperature for 2 h and then water (50 ml) and ether (50 ml) were added. The organic phase was washed with water (2×50 ml) and brine (50 ml), dried over $MgSO_4$, and evaporated in vacuo. The residue was crystallized from aqueous ethanol.

Data for 7a–c

2-(Benzylamino)quinoline-3-carbaldehyde (**7a**)

Yield: 1.44 g (55%); yellow crystals; mp 144 °C; ^{1}H NMR (300 MHz, $DMSO_{d6}$): 10.05 (1H, s, CHO), 8.81 (1H, s, H-4), 8.72 (1H, br s, NH), 7.91 (1H, d, $J = 7.8$ Hz, H-5), 7.74 (1H, d, $J = 7.5$ Hz, Ph-2′ and 6′H), 7.45 (4H, m, Ph-H and H-6 and H-7), 7.28 (1H, d, $J = 7.8$ Hz, H-8), 4.89 (2H, br s, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): 194.2 (CH), 153.3 (q), 150.1 (q), 139.0 (q), 134.2 (q), 130.0 (CH), 128.8 (q), 128.6 ($2 \times$ CH), 127.9 (CH), 127.7 ($2 \times$ CH), 127.2 (CH), 123.3 (CH), 121.6 (CH), 117.6 (CH), 44.3 (CH_2); IR (KBr, cm^{-1}): 3351, 2963, 2851, 1672, 1622, 1601, 1568, 1536, 1493, 1451, 1416, 1393, 1164, 1143, 1026. HRMS: calcd. 262.1106 for $C_{17}H_{14}N_2O$; found: 262.1111. H, 5.38; C, 77.84; N, 10.68; O, 6.10.

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2-(Benzylamino)-6-methoxyquinoline-3-carbaldehyde (**7b**)

Yield: 1.96 g (67%); yellow crystals; mp 153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 9.89 (1H, s, CHO), 8.20 (1H, br s, NH), 8.05 (1H, s, H-4), 7.59 (1H, d, $J = 8.0$ Hz, H-8), 7.30 (6H, m, Ph-H and H-7), 6.91 (1H, s, H-5), 4.83 (s, 2H, NCH_2), 3.83 (3H, s, OMe); ^{13}C NMR (125 MHz, $CDCl_3$): 192.9 (CH), 154.7 (q), 153.3 (q), 146.8 (CH), 139.3 (q), 128.3 (2 × CH), 127.9 (q), 127.8 (CH), 127.6 (2 × CH), 126.9 (CH), 125.7 (CH), 121.9 (q), 116.9 (q), 106.4 (CH), 55.3 (CH_3), 44.4 (CH_2); IR (KBr, cm^{-1}): 3417, 3268, 2965, 2676, 1682, 1615, 1588, 1514, 1479, 1461, 1400, 1378, 1347, 1292, 1236, 1209, 1171, 1134, 1024. HRMS: calcd. 292.1211 for $C_{18}H_{16}N_2O_2$; found: 292.1214. H, 5.52; C, 73.95; N, 9.58; O, 10.95.

2-(Benzylamino)-8-methylquinoline-3-carbaldehyde (**7c**)

Yield: 1.60 g (58%); yellow crystals; mp 139–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 9.74 (1H, s, CHO), 8.32 (1H, t, $J = 5.5$ Hz, NH), 7.88 (1H, s, H-4), 7.38 (1H, t, $J = 7.1$ Hz, Ph-4′H), 7.36 (2H, t, $J = 7.1$ Hz, Ph-2′ and 6′H), 7.22 (3H, m, H-5, Ph-3′ and 5′H), 7.14 (1H, d, $J = 8.0$ Hz, H-7), 6.99 (1H, t, $J = 8.0$ Hz, H-6), 7.00 (1H, t, $J = 7.7$ Hz, H-6), 4.78 (2H, d, $J = 5.5$ Hz, CH_2), 2.53 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 192.8 (CH), 153.1 (q), 149.4 (q), 148.2 (CH), 139.5 (q), 134.3 (q), 133.1 (CH), 128.2 (2 × CH), 127.7 (2 × CH), 126.8 (2 × CH), 121.9 (CH), 121.4 (q), 116.6 (q), 44.4 (CH_2), 17.8 (CH_3); IR (KBr, cm^{-1}): 3375, 3027, 2915, 1663, 1618, 1534, 1466, 1451, 1416, 1408, 1397, 1375, 1360, 1303, 1167, 1155, 1077. HRMS: calcd. 276.1262 for $C_{18}H_{16}N_2O$; found: 276.1241. H, 5.84; C, 78.24; N, 10.14; O, 5.79.

N-Benzyl-3-(1,3-dioxolan-2-yl)-8-methylquinolin-2-amine (8)

3-[1′,3′-Dioxolane-2′-yl]-8-methyl-2-chloroquinoline (**4c**, 2.50 g, 10 mmol) was dissolved in dry toluene (50 ml) and benzylamine (1.18 g, 1.21 ml, 11 mmol); sodium *tert*-butoxide (0.96 g, 11 mmol) and triphenylphosphine (0.39 g, 1.5 mmol) were added. The reaction was flushed with argon and kept under an argon atmosphere. Then, palladium(II) acetate (0.18 g, 0.8 mmol) was added, and the reaction mixture was heated under reflux for 8 h. Palladium was filtered off using a pad of Celite®. The remaining solution was washed with water (2 × 25 ml) and brine (25 ml), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (eluent hexane–ethyl acetate 1:1) to yield the title product (1.50 g, 47%).

^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (1H, s, H-4), 7.37 (3H, m, Ar-H), 7.28 (4H, m, Ar-H), 7.23 (1H, t, $J = 7.2$ Hz, H-5), 6.05 (1H, br s, NH), 5.81 (1H, s, CH), 4.82 (2H, d, $J = 5.5$ Hz, NHC_2), 3.95 (4H, m, OCH_2-CH_2O), 2.61 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 153.2 (q), 146.6 (q), 140.3 (q), 135.0 (CH), 134.0 (q), 129.7 (CH), 128.4 ($2 \times$ CH), 127.7 ($2 \times$ CH), 126.7 (CH), 125.9 (CH), 122.3 (q), 121.7 (CH), 118.6 (q), 101.9 (CH), 64.7 ($2 \times CH_2$), 45.2 (CH_2), 17.8 (CH_2); IR (KBr, cm^{-1}): 3442, 3061, 2980, 2891, 1628, 1598, 1571, 1526, 1491, 1412, 1368, 1330, 1262, 1208, 1179, 1136, 1100, 1037; HRMS: Calcd: 320.1524 for $C_{20}H_{20}N_2O_2$; found: 320.1544. H, 6.29; C, 74.98; N, 8.74; O, 9.99.

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2-(Benzylamino)-8-methylquinoline-3-carbaldehyde (7c)

Amine (**8**, 0.64 g, 2 mmol) was dissolved in tetrahydrofuran (10 ml), and 5% aqueous hydrochloric acid (2 ml) was added. The reaction mixture was stirred at room temperature for 2 h, and then water (10 ml) and ether (10 ml) were added. The organic phase was washed with water (2×10 ml) and brine (10 ml), dried over $MgSO_4$, and evaporated in vacuo. The residue was purifed by flash chromatography (eluent hexane–ethyl acetate 1:1) to yield the title product (**7c**, 0.29 g, 52%).

Synthesis of Acrylamides (9a–c), General Procedure

The corresponding 2-(benzylamino)quinoline-3-carbaldehyde (7, 3.5 mmol) was dissolved in dry DMF (10 ml), and 4-dimethylaminopyridine (10 mg) and triethylamine (0.38 g, 0.54 ml, 3.8 mmol) were added. The resulting solution was heated to 80 °C under an argon atmosphere, and acryloyl chloride (0.34 g, 0.31 ml, 3.8 mmol) was added dropwise. The reaction mixture was kept at 80 °C for 15 h, then water (20 ml) and ethyl acetate (25 ml) were added. The organic phase was washed by further portions of water (3×10 ml) and brine (15 ml), dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography (eluent hexane–ethyl acetate 1:1) to yield the title products.

Data for 9a–c

N-Benzyl-*N*-(3-formylquinolin-2-yl)prop-2-enamide (**9a**)

Yield: 0.49 g (44%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): 8.67 (1H, s, CHO), 8.11 (1H, s, qui-H-4), 7.96 (1H, d, $J = 8.0$ Hz, qui-H-8),

7.67 (1H, t, $J = 8.0$ Hz, qui-H-7), 7.23 (8H, m, Bn-H, H-1, qui-H-5 and 6), 6.47 (1H, d, $J = 16.5$ Hz, H-2), 5.83 (1H, br m, $PhCH_2$), 5.36 (2H, br m, H-2 and $PhCH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): 187.7 (CH), 172.0 (q), 161.1 (q), 152.8 (q), 140.1 (CH), 132.8 (q), 130.7 (CH_2), 130.4 (CH), 129.3 (CH), 128.9 ($2 \times$ CH), 128.8 ($2 \times$ CH), 128.0 (CH), 127.7 (CH), 126.5 (CH), 124.1 (q), 122.2 (CH), 120.2 (q), 53.3 (CH_2); IR (KBr, cm^{-1}): 3063, 3031, 2927, 1698, 1618, 1586, 1536, 1495, 1408, 1191, 1080, 1029. HRMS: calcd. 316.1211 for $C_{20}H_{16}N_2O_2$; found: 316.1211. H, 5.10; C, 75.93; N, 8.85; O, 10.11.

N-Benzyl-*N*-(3-formyl-6-methoxyquinolin-2-yl)prop-2-enamide (**9b**)

Yield: 0.63 g (52%); pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): 9.42 (1H, s, CHO), 8.47 (1H, s, qui-H-4), 7.94 (1H, d, $J = 7.5$ Hz, qui-H-8), 7.46 (1H, d, $J = 7.5$ Hz, qui-H-7), 7.19 (1H, s, qui-H-5), 7.15 (6H, m, Bn-H and H-1), 6.36 (1H, d, $J = 17$ Hz, H-2), 5.69 (2H, br m, H-2 and $PhCH_2$), 5.47 (1H, br s, $PhCH_2$), 3.82 (3H, s, OMe); ^{13}C NMR (125 MHz, $CDCl_3$): 187.9 (CH), 171.2 (q), 166.0 (q), 159.0 (q), 150.6 (q), 146.2 (q), 138.8 (CH), 132.7 (CH), 130.8 (CH), 129.8 (CH_2), 129.9 ($2 \times$ CH), 128.3 ($2 \times$ CH), 127.3 (q), 126.8 (CH), 126.7 (q), 126.5 (CH), 106.0 (CH), 55.7 (CH_3), 52.2 (CH_2); IR (KBr, cm^{-1}): 3352, 2998, 2924, 2879, 1697, 1665, 1613, 1542, 1464, 1412, 1257, 1192, 1112, 1084, 1055, 1025. HRMS: calcd: 346.1317 for $C_{21}H_{18}N_2O_3$; found: 346.1319. H, 5.24; C, 72.82; N, 8.09; O, 13.86.

N-Benzyl-*N*-(3-formyl-8-methylquinolin-2-yl)prop-2-enamide (**9c**)

Yield: 0.67 g (58%); pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): 8.65 (1H, s, CHO), 7.85 (1H, s, qui-H-4), 7.77 (2H, m, H-1 and qui-H-4), 7.51 (2H, m, H-5 and H-6), 7.28 (5H, m Bn-H), 6.47 (1H, d, $J = 16.6$ Hz, H-2), 5.60 (2H, br m, H-2 and $PhCH_2$), 5.37 (1H, br s, $PhCH_2$), 2.76 (3H, s, Me); ^{13}C NMR (125 MHz, $CDCl_3$): 182.9 (CH), 165.2 (q), 164.0 (q), 145.6 (q), 143.6 (q), 142.0 (CH), 131.6 (q), 130.4 (CH), 128.9 (CH), 128.6 ($2 \times$ CH), 128.2 (CH_2), 127.8 ($2 \times$ CH), 127.2 (CH), 126.8 (CH), 125.4 (CH), 122.5 (q), 121.2 (q), 52.3 (CH_2), 17.5 (CH_3); IR (KBr, cm^{-1}): 3364, 3031, 2924, 2869, 1697, 1668, 1615, 1539, 1487, 1467, 1410, 1254, 1192, 1081, 1056, 1029. HRMS: calcd. 330.1368 for $C_{21}H_{18}N_2O_2$; found: 330.1360. H, 5.49; C, 76.34; N, 8.48; O, 9.69.

Intramolecular 1,3-Dipolar Cycloaddition, General Procedure

The corresponding aldehyde (**9**, 1 mmol) was dissolved in toluene (25 ml), and sarcosine (0.18 g, 2 mmol) was added. The reaction mixture was

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refluxed for 6 h under an argon atmosphere. The water formed was removed by the aid of a Dean–Stark trap. After completion of the reaction, the reaction mixture was filtered through a pad of Celite® and the solvent was evaporated in vacuo. After column chromatography (eluent hexane–ethyl acetate 1:1), the product was crystallized from ether.

Data for 11a–c

5-Benzyl-1-methyl-2,3,3a,4,5,11b-hexahydro-1*H*-pyrrolo[2,3-*f*] benzo[*b*][1,8]naphthyridin-4-one (**11a**)

White powder (0.23 g, 66%), mp 194–195 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 7.83 (1H, d, $J = 9.2$ Hz, H-7), 7.81 (1H, s, H-11), 7.63 (1H, d, $J = 9.2$ Hz, H-10), 7.55 (1H, t, $J = 9.2$ Hz, H-8), 7.45 (2H, d, $J = 7.6$ Hz, Bn-2′ and 6′H), 7.33 (1H, t, $J = 9.2$ Hz, H-9), 7.12 (3H, m, Bn-CH), 5.49 (2H, s, $PhCH_2$), 3.15 (2H, m, H-11*b* and H-3*a*), 3.01 (1H, m, H-2), 2.70 (1H, m, H-2), 2.26 (2H, m, H-3), 2.14 (3H, s, NMe); ^{13}C NMR (125 MHz, $CDCl_3$): 169.5 (q, C-4), 148.7 (q, C-5*a*), 145.8 (q, C-6*a*), 139.0 (q, Bn-1′C), 138.5 (q, C-7), 129.7 (CH, C-11), 128.3 (2 × CH, CH, Bn-CH), 127.9 (2 × CH, Bn-CH and H-9), 126.9 (CH, H-7), 126.5 (CH, H-8), 124.9 (CH, H-6), 120.2 (q, C-10*a*), 64.7 (CH, C-11b), 53.8 (CH_2, Bn), 44.4 (CH_2, C-2), 44.0 (CH, C-3*a*), 39.2 (NCH_3), 25.6 (CH_2, C-3); IR (KBr, cm^{-1}): 3061, 3030, 2957, 2926, 2854, 1668, 1623, 1573, 1496, 1441, 1409, 1385, 1294, 1218, 1168, 1128, 1087, 1028. HRMS: calcd. 343.1684 for $C_{22}H_{21}N_3O$; found: 343.1672. H, 6.16; C, 76.94; N, 12.24; O, 4.66.

5-Benzyl-9-methoxy-1-methyl-2,3,3a,4,5,11b-hexahydro-1*H*-pyrrolo[2,3-*f*]benzo[*b*][1,8]naphthyridin-4-one (**11b**)

White powder (0.27 g, 72%), mp 201–203 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.79 (1H, s, H-11), 7.53 (2H, d, $J = 7.2$ Hz, Bn-2′ and 6′H), 7.30 (dd, 1H, J 3.0 and 9.0 Hz, H-8), 7.29 (3H, m, Bn-H), 7.17 (1H, d, $J = 9.0$ Hz, H-7), 7.5 (1H, d, $J = 3.0$ Hz, H-10), 5.54 (2H, s, $PhCH_2$), 3.90 (3H, s, OMe), 3.22 (2H, m, H-11*b* and H-3*a*), 3.15 (1H, m, H-2), 2.78 (1H, m, H-2), 2.30 (2H, m, H-3), 2.24 (3H, s, NMe); ^{13}C NMR (125 MHz, $CDCl_3$): 172.0 (q, C-4), 156.8 (q, C-9), 148.4 (q, C-5*a*), 142.3 (q, C-6*a*), 138.6 (q, Bn-1′C), 136.7 (q, C-10*a*), 129.5 (CH. C-11), 128.5 (2 × CH, Bn-C), 128.0 (2 × CH, Bn-C), 126.6 (CH, Bn-4′C), 125.6 (CH, C-7), 122.0 (CH, C-8), 118.3 (q, C-11*a*), 105.3 (CH, C-10), 65.0 (CH, C-11*b*), 55.5 (OCH_3), 54.1 (CH_2, Bn), 44.5 (CH_2, C-2), 44.2 (CH, C-3*a*), 39.6 (NCH_3), 25.8 (CH_2, C-3); IR (KBr, cm^{-1}): 3056,

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2925, 2834, 2808, 2771, 1666, 1609, 1504, 1458, 1436, 1398, 1374, 1262, 1232, 1214, 1201, 1163, 1100, 1078, 1029. HRMS: calcd. 373.1790 for $C_{23}H_{23}N_3O_2$; found: 373.1792. H, 6.21; C, 73.97; N, 11.25; O, 8.57.

5-Benzyl-1,7-dimethyl-2,3,3a,4,5,11b-hexahydro-1*H*-pyrrolo[2,3-*f*] benzo[*b*][1,8]naphthyridin-4-one (**11c**)

White powder (0.15 g, 41%), mp 194–195 °C; ^{1}H NMR (250 MHz, $CDCl_3$): 7.83 (1H, s, H-11), 7.45 (5H, m, Ar-H), 7.20 (3H, m, Ar-H), 5.60 (1H, d, $J = 14.2$ Hz, $PhCH_2$), 5.53 (1H, d, $J = 14.2$ Hz, $PhCH_2$), 3.19 (1H, d, $J = 5.6$ Hz, H-11*b*), 3.09 (1H, m, H-3*a*), 3.74 (2H, m, H-2), 2.66 (3H, s, Ar-CH_3), 2.28 (2H, m, H-3), 2.17 (3H, s, NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 172.3 (q, C-4), 148.9 (q, C-5*a*), 145.3 (q, C-6*a*), 138.5 (q, Bn-1′C), 138.0 (CH, C-11), 136.1 (q, C-7), 130.0 (CH, C-8), 128.1 (2 × CH, Bn-CH), 128.0 (2 × CH, Bn-CH), 126.6 (CH, Bn-4′C), 124.9 (CH, C-10), 124.7 (CH, C-9), 117.6 (q, C-10*a*), 64.8 (CH, C-11b), 54.0 (CH_2, Bn), 44.8 (CH_2, C-2), 44.1 (CH, C-3*a*), 39.4 (*N*CH_3), 25.7 (CH_2, C-3), 18.1 (CH_3); IR (KBr, cm^{-1}): 3027, 2938, 2835, 2778, 1666, 1622, 1497, 1476, 1449, 1433, 1411, 1381, 1362, 1337, 1289, 1237, 1221, 1160, 1104, 1077, 1035. HRMS: calcd. 357.1841 for $C_{23}H_{23}N_3O$; found: 357.1850. H, 6.49; C, 77.28; N, 11.76; O, 4.48.

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