Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Quinolinone and Pyridopyrimidinone Inhibitors of DNA-dependent Protein Kinase

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Supplementary Information

Experimental procedures for compounds 2b-2g and 3b-3f

Crystal structures of compounds 10a and 16

Experimental Procedures

8-Substituted 2-morpholin-4-yl-quinolin-4-ones 2b-2g

These compounds were prepared using the typical procedure described in the Experimental Section of the paper and exemplified there for **2a**.

2-Morpholin-4-yl-8-thiophen-3-yl-1*H*-quinolin-4-one (2b)

Thiophen-3-ylboronic acid (62 mg, 0.49 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (100 mg; 0.32 mmol) gave crude product that was purified by HPLC (aqueous methanol as eluent). The title compound was obtained as a red solid (37 mg, 37%): R_f = 0.10 (ethyl acetate); mp: 115 °C (dec.); λ_{max} (EtOH)/nm 254; IR (cm^{-1}) 3409, 3086, 2964, 2846, 1611, 1576, 1496, 1427, 1227, 1111, 1002, 825, 781, 757, 681; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.11 (4H, m, 2 x NCH_2-morpholine), 3.69 (4H, m, 2 x OCH_2-morpholine), 5.68 (1H, s, H-3), 7.12-7.21 (2H, m), 7.48-7.72 (3H, m), 8.06 (1H, s), 8.17-8.19 (1H, m, H-6); ^{13}C NMR, (75

MHz, $CDCl_3$) δ 46.6, 66.4, 92.9, 123.4, 124.2, 124.8, 125.9, 128.3, 128.9, 132.5, 135.8, 137.4, 154.2; MS (ES+) *m/z* 312.97; Anal. Calcd for 0.87 mol $C_{17}H_{16}N_2O_2S$ + 0.13 mol H_2O: C, 63.12, H, 5.10, N, 8.48. Found: C, 63.10, H, 4.70, N, 8.60.

8-Benzo[*b*]thiophen-2-yl-2-morpholin-4-yl-1*H*-quinolin-4-one (2c)

Benzothiophen-2-ylboronic acid (87 mg, 0.49 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (100 mg; 0.32 mmol) gave crude product that was purified by medium pressure chromatography using DCM-methanol (95:5 v/v) as eluent. The resulting material was further purified by medium pressure chromatography using ethyl acetate-DCM (80:20 v/v) as eluent. The title compound was obtained as a green solid (48 mg, 41%): R_f = 0.33 (ethyl acetate); mp: 120 °C (dec.); λ_{max} (EtOH)/nm 265; IR (cm^{-1}) 3386, 2908, 2851, 1613, 1578, 1481, 1423, 1373, 1226, 1159, 1113, 1016, 978, 903, 801, 720; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.33 (4H, m, 2 x NCH_2-morpholine), 3.62 (4H, dd, *J* = 5.1 and 4.5 Hz, 2 x OCH_2-morpholine), 6.09 (1H, s, H-3), 7.17-7.39 (3H, m), 7.40-7.62 (2H, m) 7.72-7.82 (3H, m), 8.19 (1H, d, *J* = 7.0 Hz, H-5); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.6, 66.7, 92.6, 122.6, 123.61, 124.04, 125.04, 129.0, 129.2, 131.5, 132.4, 132.6, 132.7, 132.7, 132.9, 140.1, 141.2; MS (ES+) *m/z* 363.00; Anal. Calcd for 0.75 mol $C_{21}H_{18}N_2O_2S$ + 0.25 mol DCM: C, 65.49, H, 4.82, N, 7.16. Found: C, 65.85, H, 4.78, N, 6.56.

8-Biphenyl-3-yl-2-morpholin-4-yl-1*H*-quinolin-4-one (2d)

Biphenyl-3-ylboronic acid (96 mg, 0.49 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (100 mg; 0.32 mmol) gave crude product that was purified by medium pressure chromatography using ethyl acetate-DCM (90:10 v/v) as eluent. The title compound was obtained as a yellow solid (87 mg, 70%): R_f = 0.10 (ethyl acetate); mp: 120 °C (dec.); λ_{max} (EtOH)/nm 252; IR (cm^{-1}) 3409, 2959, 2848, 1612, 1576, 1481, 1431, 1296, 1224, 1113, 1069,

997, 908, 754; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.13 (4H, m, 2 x NCH_2-morpholine), 3.70 (4H, m, 2 x OCH_2-morpholine), 5.78 (1H, s, H-3), 7.28-7.47 (5H, m), 7.47-7.72 (6H, m), 8.14 (1H, m), 8.32 (1H, m, H-5); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.7, 66.3, 92.9, 122.7, 123.6, 124.2, 125.9, 127.4, 127.5, 127.8, 128.0, 128.5, 129.0, 129.2, 129.4, 129.8, 130.5, 132.7, 135.6, 137.4, 140.3, 143.2, 154.3, 178.9; MS (ES+) *m/z* 383.09; Anal. Calcd for 0.79 mol $C_{25}H_{22}N_2O_2$ + 0.21 mol DCM: C, 74.94, H, 5.68, N, 6.84. Found: C, 75.06, H, 5.51, N, 6.82.

8-Dibenzofuran-4-yl-2-morpholin-4-yl-1*H*-quinolin-4-one (2e)

Dibenzofuran-4-ylboronic acid (103 mg, 0.49 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (100 mg; 0.32 mmol) gave crude product that was purified by HPLC (aqueous methanol as eluent). The title compound was obtained as a red solid (49 mg, 38%): R_f = 0.06 (ethyl acetate); mp: 117-118 °C (dec.); λ_{max} (EtOH)/nm 288; IR (cm^{-1}) 3419, 2852, 1610, 1578, 1497, 1442, 1405, 1226, 1184, 1112, 998, 795, 722; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.93 (4H, m, 2 x NCH_2-morpholine); 3.50 (4H, m, 2 x OCH_2-morpholine), 5.69 (1H, s, H-3), 7.19-7.45 (6H, m), 7.64 (1H, m), 7.95 (3H, m), 8.30 (1H, d, *J* = 6.1 Hz, H-5); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.9, 66.3, 92.2, 112.1, 121.4, 121.8, 123.4, 123.9, 124.4, 125.8, 126.7, 128.5, 129.1, 133.8, 136.0, 153.3, 154.4, 156.3, 178.9; MS (ES+) *m/z* 396.98; HRMS calcd for $C_{25}H_{20}N_2O_3$ $[M+H]^+$ 397.1547, found 397.1549.

8-Dibenzothiophene-4-yl-2-morpholin-4-yl-1*H*-quinolin-4-one (2f)

Dibenzothiophen-4-ylboronic acid (53 mg, 0.23 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (65 mg, 0.21 mmol) gave crude product that was purified by medium pressure chromatography using DCM-methanol (95:5 v/v) as eluent to remove the phosphines. The resulting material was further purified by HPLC (aqueous methanol as eluent). Starting material (11 mg, 16%) was recovered and the title compound was obtained as a white solid

(20 mg, 27%): R_f = 0.28 (MeOH-DCM 1:19); mp: 151-152 °C (dec.); λ_{max} (EtOH)/nm 233; IR (cm^{-1}) 2362, 2331, 1612, 1576, 1496, 1435, 1227, 1116, 997; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.93 (4H, dd, *J* = 4.7 and 4.8 Hz, 2 x CH_2N-morpholine), 3.57 (4H, dd, *J* = 4.7 and 4.8 Hz, 2 x CH_2O-morpholine), 5.68 (1H, s, H-3), 7.31-7.76 (7H, m), 8.14-8.35 (3H, m); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.9, 66.2, 93.4, 122.4, 122.5, 123.3, 123.4, 124.6, 125.3, 125.8, 126.9, 127.7, 127.9, 131.2, 132.6, 135.6, 135.8, 137.4, 139.8, 140.7, 154.2, 178.8; MS (ES+) *m/z* 413.10; Anal. Calcd for 2.0 mol $C_{25}H_{20}N_2O_2S$ + 0.3 mol H_2O: C, 68.32, H, 5.27, N, 6.37. Found: C, 68.11, H, 4.70, N, 6.21.

8-(4-Hydroxymethylphenyl)-2-morpholin-4-yl-1*H*-quinolin-4-one (2g)

4-Hydroxymethylphenylboronic acid (74 mg; 0.49 mmol) and 8-bromo-2-morpholin-4-yl-1*H*-quinolin-4-one (100 mg, 0.32 mmol) gave crude product that was purified by medium pressure chromatography using DCM-methanol (95:5 v/v) as eluent. The title compound was obtained as a brown solid (24 mg, 22%): R_f = 0.08 (MeOH-DCM 1:19); mp: 259-260 °C (dec.); λ_{max} (EtOH)/nm 251; IR (cm^{-1}) 3409; 2854; 1611; 1578; 1427; 1363; 1229; 1110; 1041; 995; 785; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (4H, m, CH_2N-morpholine); 3.72 (4H, m, CH_2O-morpholine); 4.83 (2H, s, CH_2OH); 5.75 (1H, s, H-3); 7.28-7.56 (6H, m); 8.03 (1H, s, OH); 8.25 (1H, d, *J* = 7.0 Hz, H-5); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 46.7; 66.3; 92.9; 123.5; 124.1; 125.6; 127.3; 127.9; 128.5; 129.5; 132.7; 135.5; 140.2; 140.8; 142.5; 154.4; 179.0; MS (ES+) *m/z* 337.02; Anal. Calcd for 0.93 mol $C_{20}H_{20}N_2O_3$ + 0.07 mol DCM: C, 70.28, H, 5.95, N, 8.13. Found: C, 70.28, H, 5.98, N, 7.83.

9-Substituted 2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-ones 3b-3f

These compounds were prepared using the typical procedure described in the Experimental Section of the paper and exemplified there for **3a**.

2-Morpholin-4-yl-9-thiophen-3-yl-pyrido[1,2-*a*]pyrimidin-4-one (3b)

Thiophen-3-ylboronic acid (51 mg, 0.40 mmol) and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (100 mg, 0.26 mmol) gave crude product that was purified by medium pressure chromatography using ethyl acetate-DCM (70:30 v/v) as eluent. The title compound was obtained as white needles (40 mg, 39%): R_f = 0.16 (MeOH-DCM 1:19); mp: 222-223 °C (dec.); λ_{max} (EtOH)/nm 278; IR (cm^{-1}) 3078, 2991, 2908, 2862, 1689, 1624, 1541, 1492, 1438, 1362, 1229, 1201, 1110, 1002, 763; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.63 (4H, m, 2 x NCH_2-morpholine), 3.79 (4H, m, 2 x OCH_2-morpholine), 5.68 (1H, s, H-3), 6.97 (1H, dd, *J* = 7.0 and 7.1 Hz, H-7), 7.38-7.42 (1H, m), 7.55 (1H, dd, *J* = 7.1 Hz and 1.3 Hz, H-8), 7.80 (2H, m), 8.96 (1H, dd, *J* = 7.0 Hz and 1.3 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 45.1, 67.0, 81.5, 112.8, 125.2, 125.6, 127.1, 129.1, 130.7, 135.8, 137.2, 159.4, 161.0; MS (ES+) *m/z* 314.08; Anal. Calcd for 0.8 mol $C_{16}H_{15}N_3O_3S$ + 0.2 mol H_2O: C, 60.45, H, 4.91, N, 13.22. Found: C, 60.59, H, 4.68, N, 13.11.

9-Benzo[*b*]thiophen-2-yl-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (3c)

Benzo[*b*]thiophen-2-ylboronic acid (70 mg, 0.40 mmol) and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (100 mg, 0.26 mmol) gave crude product that was recrystallised from ethanol. Further purification was achieved by medium pressure chromatography using DCM-methanol (98:2 v/v) as eluent. The title compound was obtained as a yellow solid (24 mg, 20%): R_f = 0.16 (MeOH-DCM 1:19); mp: 252-253 °C (dec.); λ_{max} (EtOH)/nm 289; IR (cm^{-1}) 3057, 2866, 1691, 1619, 1537, 1496, 1422, 1230, 1108, 765; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.84 (8H, m, 4 x CH_2 morpholine), 5.70 (1H, s, H-3), 7.01 (1H, dd, *J* = 7.0 and 7.1 Hz, H-7), 7.28-7.44 (2H, m), 7.84-7.92 (3H, m), 8.08 (1H, dd, *J* = 7.0 Hz and 1.6 Hz, H-8), 9.01 (1H, dd, *J* = 7.1 Hz and 1.6 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 45.7, 67.0, 81.7, 112.7, 112.7, 122.4, 124.1, 124.2, 124.9, 125.3, 127.9, 135.9, 138.1, 139.1,

160.7; MS (ES+) *m/z* 364.07; Anal. Calcd for 0.66 mol $C_{20}H_{17}N_3O_2S$ + 0.33 mol H_2O: C, 64.50, H, 4.87, N, 11.28. Found: C, 64.54, H, 4.53, N, 11.10.

9-Biphenyl-3-yl-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (3d)

3-Biphenylboronic acid (78 mg, 0.39 mmol) and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (100 mg, 0.26 mmol) gave crude product that was purified by medium pressure chromatography using DCM-methanol (98:2 v/v) as eluent, followed by a recrystallisation from methanol. The title compound was obtained as a white solid (60 mg, 59%): R_f = 0.29 (MeOH-DCM 1:19); mp: 191-192 °C; λ_{max} (EtOH)/nm 275; IR (cm^{-1}) 2870, 1692, 1627, 1541, 1496, 1431, 1371, 1334, 1304, 1263, 1233, 1157, 1113, 1072, 997, 899, 854, 749, 688; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.56 (4H, m, 2 x N-CH_2-morpholine), 3.67 (4H, m, 2 x O-CH_2-morpholine), 5.68 (1H, s, H-3), 7.01 (1H, dd, *J* = 7.0 and 7.1 Hz, H-7), 7.28-7.75 (9H, m), 7.95 (1H, s), 9.00 (1H, d, *J* = 7.1 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 44.9, 66.9, 81.3, 113.0, 127.3, 127.4, 127.6, 127.9, 128.9, 129.0, 129.3, 129.4, 135.8, 136.8, 137.6, 141.2, 149.5, 159.5; MS (ES+) *m/z* 384.17; HRMS calcd for $C_{24}H_{21}N_3O_2$ $[M+H]^+$ 384.1707, found 384.1704.

9-Dibenzofuran-4-yl-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (3e)

Dibenzofuran-4-ylboronic acid (84 mg, 0.40 mmol) and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (100 mg, 0.26 mmol) gave crude product that was purified by HPLC (aqueous acetonitrile as eluent). The title compound was obtained as a white solid (36 mg, 28%): R_f = 0.18 (ethyl acetate); mp: 258-260 °C (dec.); λ_{max} (EtOH)/nm 279; IR (cm^{-1}) 2859, 2362, 1699, 1625, 1544, 1496, 1435, 1366, 1236, 1118; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.35 (4H, m, 2 x NCH_2-morpholine), 3.54 (4H, m, 2 x OCH_2-morpholine), 5.66 (1H, s, H-3), 7.08 (1H, dd, *J* = 7.0 and 7.0 Hz, H-7), 7.38-7.51 (4H, m), 7.67 (1H, dd, *J* =

7.0 Hz and 1.3 Hz, H-8), 7.94 (1H, dd, *J* = 7.0 Hz and 1.6 Hz), 8.01-8.05 (2H, m), 9.06 (1H, dd, *J* = 7.0 Hz and 1.3 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 44.8, 66.8, 81.4, 112.0, 112.7, 121.1, 121.8, 122.8, 123.3, 124.4, 124.9, 127.8, 128.0, 129.3, 131.4, 138.1, 156.3, 159.5, 160.7; MS (ES+) *m/z* 398.15; Anal. Calcd for 0.83 mol $C_{24}H_{19}N_3O_3$ + 0.17 mol H_2O: C, 71.88, H, 4.88, N, 10.48. Found: C, 71.93, H, 4.73, N, 10.34.

9-Dibenzothiophene-4-yl-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one (3f).

Dibenzothiophen-4-ylboronic acid (107 mg, 0.46 mmol) and 9-hydroxy-2-morpholin-4-yl-pyrido[1,2-*a*]pyrimidin-4-one 9-*O*-triflate (160 mg, 0.42 mmol) gave crude product that was purified by medium pressure chromatography using DCM-methanol (95:5 v/v) as eluent to remove the phosphines. This was followed by a recrystallisation from ethyl acetate to afford the title compound as a white solid (66 mg, 38%): R_f = 0.30 (MeOH-DCM 1:19); mp: 203-204 °C; λ_{max} (EtOH)/nm 277; IR (cm^{-1}) 2851, 1690, 1620, 1542, 1431, 1219, 1113, 742; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.36 (4H, m, 2 x N-CH_2-morpholine), 3.56 (4H, m, 2 x O-CH_2-morpholine), 5.64 (1H, s, H-3), 7.01 (1H, dd, *J* = 7.0 and 7.1 Hz, H-7), 7.45-7.49 (2H, m), 7.56-7.57 (2H, m), 7.79-7.82 (1H, m), 7.87 (1H, dd, *J* = 7.1 and 1.5 Hz, H-8), 8.19-8.23 (2H, m), 9.04 (1H, dd, *J* = 7.0 and 1.5 Hz, H-6); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 44.8, 66.8, 81.4, 112.5, 121.7, 122.1, 122.9, 124.6, 124.9, 127.4, 128.3, 128.9, 132.4, 134.8, 135.9, 136.4, 137.5, 139.6, 140.1, 148.8, 159.4, 160.5; MS (ES+) *m/z* 414.04 M^+; Anal. Calcd for 0.83 mol $C_{19}H_{18}N_2O_2S$ + 0.17 mol DCM: C, 67.64, H, 4.61, N, 9.70. Found: C, 67.73, H, 4.37, N, 9.72.

X-ray Crystallography

Crystal data for **10a**: $C_{17}H_{22}BrN_3O_3$, *M* = 396.3, monoclinic, space group $P2_1/c$, *a* = 7.8129(4), *b* = 28.2692(13), *c* = 7.6955(3) Å, β = 99.413(1)°, *V* = 1676.78(13) Å^3, *Z* = 4, *T* = 150 K; 14873 reflections measured, 4117 unique (R_{int} = 0.028), 218 parameters, *R* (*F*, F^2 >

2σ) = 0.033, R_w (F^2, all data) = 0.083, difference map features within ±0.61 e Å^{-3}. *Crystal data for* **16**: $C_{13}H_{12}F_3N_3O_5S$, M = 379.3, monoclinic, space group $P2_1/c$, a = 20.220(9), b = 16.889(7), c = 23.103(10) Å, β = 110.821(7)°, V = 7374(6) Å^3, Z = 20, T = 120 K; 60275 reflections measured, 15066 unique (R_{int} = 0.065), 1127 parameters, R (F, $F^2 > 2\sigma$) = 0.047, R_w (F^2, all data) = 0.128, difference map features within ±0.52 e Å^{-3}. Data were collected on Bruker SMART CCD diffractometers with Mo $K\alpha$ radiation (λ = 0.71073 Å) for **10a**, and with synchrotron radiation (λ = 0.6898 Å) at the CCLRC Daresbury Laboratory SRS Station 9.8 for **16**. Standard programs (Bruker SMART, SAINT, SADABS and SHELXTL) were used for data collection and processing, absorption corrections, structure solution and refinement.

CCDC reference numbers 647931 and 647932.

See http://www.rsc.org/suppdata/ob/b7/b705095j/ for crystallographic data in .cif or other electronic format.

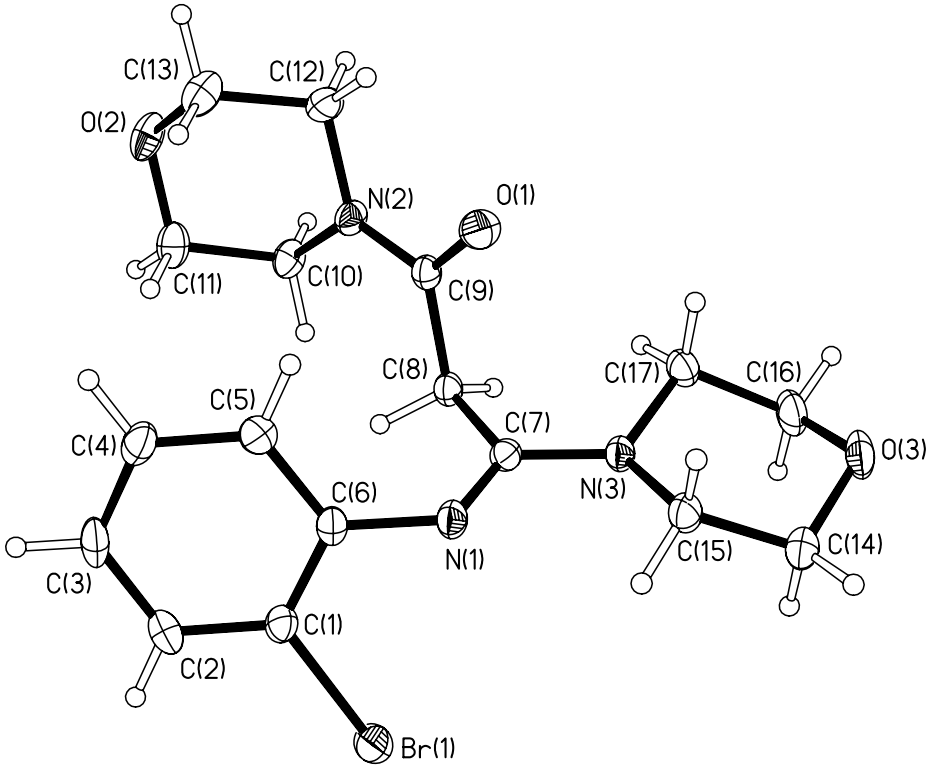

Fig. 1. The molecular structure of **10a** with 50% probability displacement ellipsoids.

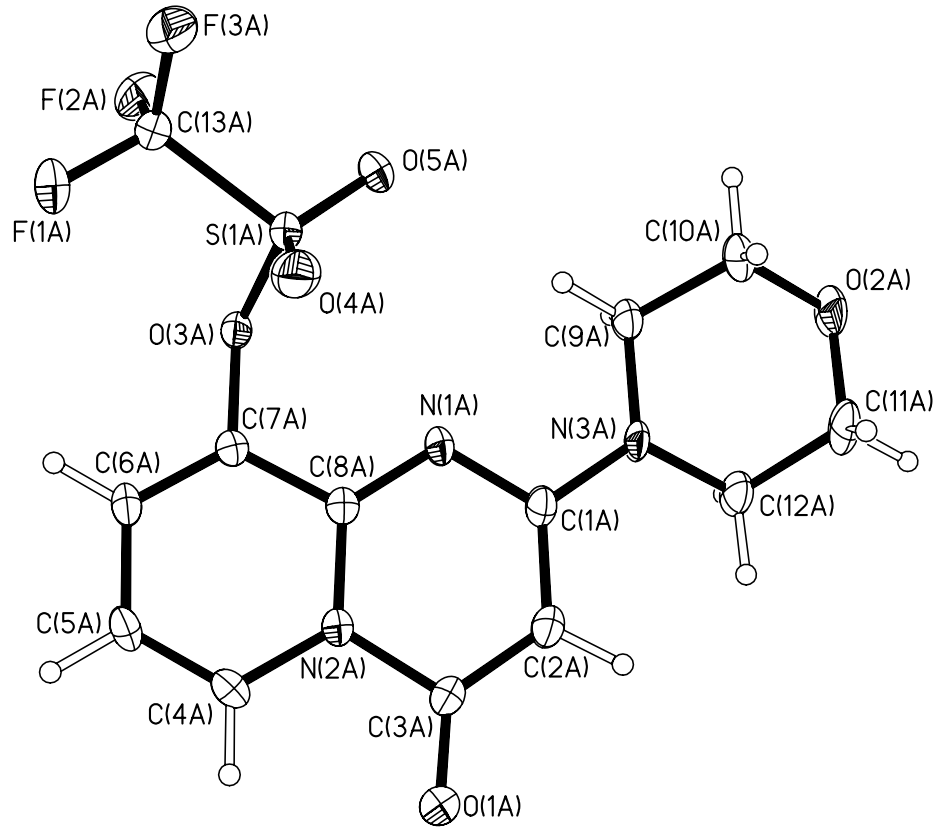

Fig. 2. The molecular structure of **16** with 50% probability displacement ellipsoids.

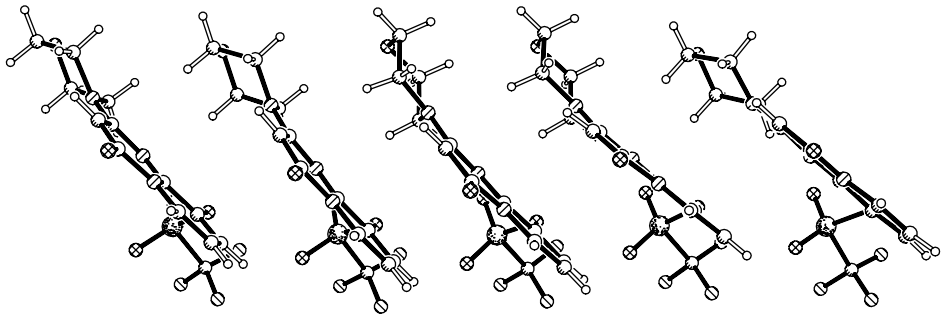

Fig. 3. The five independent molecules in the asymmetric unit of **16**, showing their very similar conformations and orientations and their stacking.