Electronic Supplementary Material (ESI) for Org. Biomol. Chem.

SUPPORTING INFORMATION

Transition-metal-free synthesis of 3-(1-pyrrolidinyl)quinolines and 3-(1-pyrrolidinyl)quinoline 1-oxides via one-pot reaction of 3-(1-pyrrolidinyl)crotonates with nitrobenzenes

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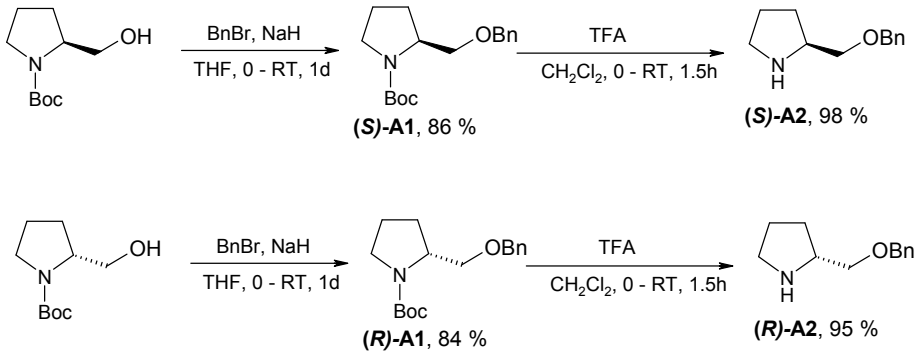
1. General information.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz (500 MHz for ^{1}H and 125 MHz ^{13}C spectra), a Varian-NMR-vnmrs600 (600 MHz for ^{1}H and 150 MHz ^{13}C spectra) instruments. Chemical shifts δ are expressed in ppm referred to TMS (internal standards), and coupling constants in Hertz. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q) and multiplet (m). Electrospray mass spectra (ESI) were obtained on SYNAPT G2-S HDMS. Infrared spectra are recorded on a Perkin-Elmer Model 1600 FT-IR spectrophotometer.

Materials and Methods: THF was dried using sodium/benzophenone under an argon atmosphere and distilled prior to use. Silica gel (Merck 60, 230-400 mesh) was used for column chromatography. Hexane or hexane/ethyl acetate mixtures were used for elution. TLC analyses were performed on Merck Kieselgel 60 F_{254} Alufolien with hexane/ethyl acetate mixtures. Chemicals were obtained from commercial sources and used directly.

2. Synthesis of optically pure pyrrolidines.

2.1. Synthesis of optically pure pyrrolidines (*S*)-A2, (*R*)-A2.



Scheme 1. Synthesis of optically pure 2-benzyloxymethyl pyrrolidines ***(*S*)*-A2**, **(*R*)-A2**.

(*S*)-*tert*-Butyl 2-(benzyloxymethyl)-pyrrolidine-1-carboxylate (*S*)-A1.

The compound was obtained according to modified literature method[1] (NaH was added to mixture of *N*-Boc-L-prolinol and benzyl bromide at 0°C) in 86 % yield. Colourless oil, $[\alpha]_D^{22}$

[1] L. M. Havran, D. C. Chong, W. E. Childers, P. J. Dollings, A. Dietrich, B. L. Harrison, V. Marathias, G. Tawa, A. Aulabaugh, R. Cowling, B. Kapoor, W. Xu, L. Mosyak, F. Moy, W.-T. Hum, A. Wood, A. J. Robichaud, *Bioorg. Med. Chem.*, 2009, **17**, 7755

= –56.4 (*c* 0.80, CH_2Cl_2). ^{1}H NMR spectra is in an agreement with literature data.[1] ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.5, 138.5, 128.3, 127.5, 127.4, 79.1, 73.1, 70.9, 56.5, 46.6, 28.5, 23.3. IR (film): 2974, 2874, 1695, 1454, 1393, 1365, 1254, 1171, 1101, 908, 737, 698 cm^{-1} MS–EI (*m / z*): 291 (0.8, $M^{+\cdot}$), 170 (40), 115 (11), 114 (89), 105 (19), 92 (16), 91 (77), 84 (12), 77 (13), 71 (10), 70 (100), 65 (15), 57 (90), 43 (10), 41 (37). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{17}H_{25}NO_3$ 291.1834; found: 291.1845.

(*R*)-*tert*-Butyl 2-(benzyloxymethyl)-pyrrolidine-1-carboxylate (*R*)-A1.

The compound was obtained according to procedure for **(***S*)- enantiomer from commercial *N*-Boc-D-prolinol in 84 % yield, Colourless oil, $[\alpha]_D^{22}$ = 55.0 (*c* 0.85, CH_2Cl_2). All spectra are identical with data for **(*S*)-A1**

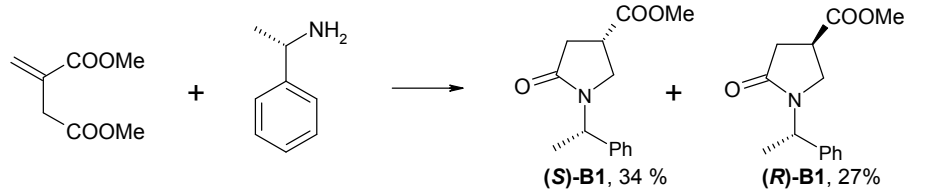
(*S*)-2-(Benzyloxymethyl)-pyrrolidine (*S*)-A2.

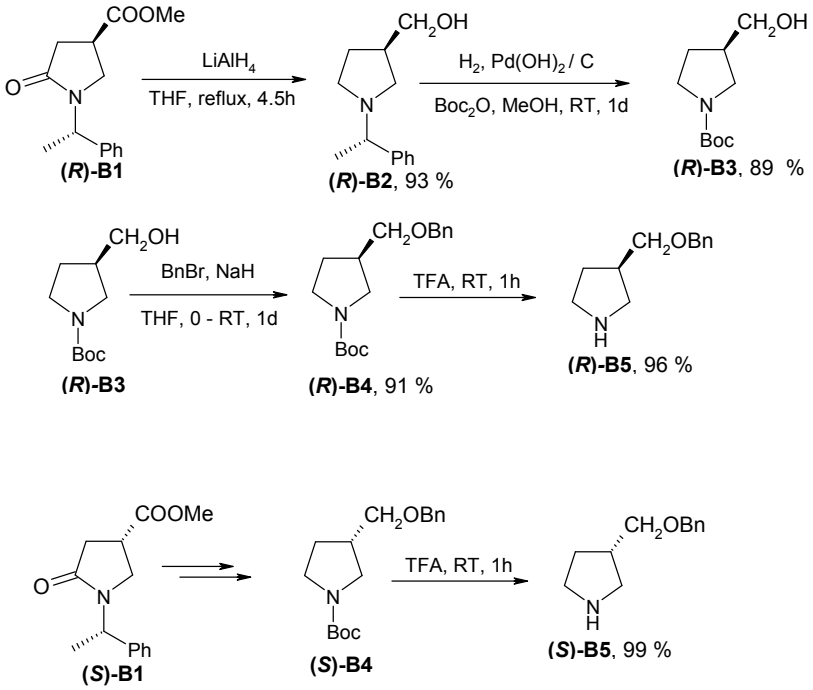
The compound was obtained according to literature method[1] in 98 % yield. Light-yellow oil, $[\alpha]_D^{21}$ = 4.4 (*c* 1.0, CH_2Cl_2). IR (film): 3348, 2959, 2868, 1545, 1402, 1203, 1098, 739, 698 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.31 – 7.36 (m, 4H), 7.26 – 7.29 (m, 1H), 4,47 (s, 2H), 3.15 – 3.32 (m, 3H), 2.76 – 2.80 (m, 1H), 2.68 – 2.73 (m, 1H), 1.70 – 1.76 (m, 1H), 1.54 – 1.65 (m, 2H), 1.29 – 1.35 (m, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 138.6, 128.2, 127.4, 127.3, 73.8, 72.1, 57.2, 45.9, 28.3, 24.9. MS–EI (*m / z*): 192 (3), 191 (1.2, $M^{+\cdot}$), 91 (30), 85 (13), 71 (13), 70 (100), 65 (13).

(*R*)-2-(Benzyloxymethyl)-pyrrolidine (*R*)-A2.

The compound was obtained according to procedure for **(***S*)-2-(benzyloxymethyl)-pyrrolidine with 95 % yield. Light-yellow oil, $[\alpha]_D^{23}$ = –3.9 (*c* 1.2, CH_2Cl_2). All spectra are identical with data for **(*S*)-A2.**

2.2. Synthesis of optically pure pyrrolidines (*S*)-B5, (*R*)-B5.





Scheme 2. Synthesis of optically pure 3-benzyloxymethyl pyrrolidines **(*S*)-B5** and **(*R*)-B5**.

Methyl 5-oxo-1-((*S*)-1-phenylethyl)pyrrolidine-3-(*S*)-carboxylate (*S*)-B1 and **Methyl 5-oxo-1-((*S*)-1-phenylethyl)pyrrolidine-3-(*R*)-carboxylate (*R*)-B1.**

The compounds were obtained in the reaction of methyl itaconate with (*S*)-1-phenylethylamine in similar manner to reaction methyl itaconate with (*R*)-1-phenylethylamine[2]. The diastereoisomers were separated by chromatography on silica gel (hexane/AcOEt)

Methyl 5-oxo-1-((*S*)-1-phenylethyl)pyrrolidine-3-(*S*)-carboxylate (*S*)-B1.

Colourless oil, (2.38 g, 34 %), $[\alpha]_D^{22}$ = –78.3 (*c* 1.15, MeOH), lit.: $[\alpha]_D$ = –81.3 (*c* 0.90, MeOH).[3] ^{1}H NMR and IR spectra are in an agreement with literature data.[3] ^{13}C NMR (125

[2] J. Blanchet, M. Pouliquen, M. C. Lasne, J. Rouden, *Tetrahedron Lett.*, 2007, **48**, 5727
[3] D. R. Johnson, D. L. Szotek, J. M. Domagala, T. M. Stickney, *J. Heterocyclic Chem.,* 1992, **29,** 1481

MHz, $CDCl_3$): δ 173.2, 171.7, 139.7, 128.6, 127.6, 127.1, 52.4, 49.1, 44.4, 36.0, 34.5, 15.9

Methyl 5-oxo-1-((*S*)-1-phenylethyl)pyrrolidine-3-(*R*)-carboxylate (*R*)-B1.

White solid (1.90 g, 27 %), mp. 64 – 66°C, lit.: 66.5 – 69.5°C,[3] $[\alpha]_D^{22}$ = –110.7 (*c* 1.2, MeOH), lit.: $[\alpha]_D$ = –117 (*c* 1.1, MeOH).[3] ^{1}H NMR and IR spectra are in an agreement with literature data.[3] ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 171.9, 139.5, 128.6, 127.6, 127.0, 52.3, 49.1, 44.6, 36.1, 34.4, 16.2

(3*S*)-1-[(1*S*)-1-phenylethyl]-3-pyrrolidinemethanol (*S*)-B2.

The compound was obtained according to literature method.[4] The crude product was purified by column chromatography on silica gel (AcOEt then AcOEt / MeOH, 10 / 1)

White solid (0.72 g, 43 %), mp. 85 – 87 °C, lit.: 86 – 88 °C, [5] $[\alpha]_D^{23}$ = –66.1 (*c* 1.1, $CHCl_3$), lit.: $[\alpha]_D$ = –71 (*c* 0.94, $CHCl_3$).[6] ^{1}H NMR spectrum is in an agreement with literature data.[5]

(3*R*)-1-[(1*S*)-1-phenylethyl]-3-pyrrolidinemethanol (*R*)-B2.

The compound was obtained according to procedure for **(*S*)-B2.** The crude product was used for next step without any purification. Yellow oil (1.35 g, ~93%; purity based on ^{1}H NMR, ~95 %) $[\alpha]_D^{21}$ = –43 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21– 7.35 (m, 5H), 3.69 – 3.76 (m, 1H), 3.51 – 3.55 (m, 1H), 3.16 – 3.21 (m, 1H), 2.65 – 2.81 (m, 2H), 2.56 – 2.63 (m, 1H), 2.46 – 2.49 (m, 1H), 2.25 – 2.35 (m, 2H), 1.91 – 2.00 (m, 1H), 1.61 – 1.69 (m, 1H), 1.39 (d, J=6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.8, 128.4, 127.2, 127.0, 67.7, 65.4, 56.7, 52.7, 38.6, 26.7, 23.1

(*S*)-*tert*-butyl 3-(hydroxymethyl)pyrrolidine1-carboxylate (*S*)-B3.

The compound was obtained according to modified literature method[4] (the reaction was carried out under atmospheric pressure of hydrogen at room temperature).

Colourless oil (0.510 g, 82 %), $[\alpha]_D^{23}$ = –17.4 (*c* 0.9, $CHCl_3$). IR (film): 3425, 2975, 2936, 2876, 1696, 1674, 1417, 1366, 1254, 1171, 1132, 881, 773 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.58 – 3.64 (m, 2H), 3.48 – 3.52 (m, 1H), 3.41 – 3.46 (m, 1H), 3.29 – 3.34 (m, 1H), 3.09 – 3.13 (m, 1H), 2.37 – 2.43 (m, 1H), 1.94 – 2.00 (m, 1H), 1.91 (bs, 1H), 1.63 – 1.71 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 79.2, 64.4 48.4, 45.2, 40.9, 28.5, 27.7.

[4] VERTEX PHARMACEUTICALS INCORPORATED; R. L. Makings; B. M. Garcia-Guzman, D. J. Hurley, I. Drutu, G. Raffai, D. M. Bergeron, A. Nakatani, A. P. Termin, A. Silina WO 2007/100670 A1, **2007**

[5] D. P. Walker, B. A. Acker, E. J Jacobsen, D. G. Wishka, *J. Heterocyclic Chem.,* 2008, **45**, 247

[6] D. P. Walker, D. W. Piotrowski, E. J Jacobsen, B. A. Acker, V. E. Groppi JR, US 2003/232853 A1, **2003**

(*R*)-*tert*-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (*R*)-B3.

The compound was obtained according to procedure for **(*S*)**- enantiomer **(*S*)-B3**. Colourless oil (1.02 g, 89 %), $[\alpha]_D^{20}$ = 16.3 (*c* 0.75, $CHCl_3$), lit.: $[\alpha]_D$ = 6,5 (*c* 0.9, $CHCl_3$; ee = 50 %).[7] All spectra are identical with spectra for **(*S*)-B3**.

(*S*)-*tert*-Butyl 3-(benzyloxymethyl)-pyrrolidine-1-carboxylate (*S*)-B4.

The compound was obtained in similar manner to (*S*)-*tert*-Butyl-2-(benzyloxymethyl)-pyrrolidine-1-carboxylate **(*S*)-A1.**

Colourless oil (0.50 g, 69 %), $[\alpha]_D^{22}$ = –5.96 (*c* 1.4, CH_2Cl_2). IR (film): 2975, 2869, 1695, 1404, 1365, 1171, 1103, 884, 738, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.35 (m, 5H), 4.51 (s, 2H), 3.49 – 3.53 (m, 1H), 3.38 – 3.45 (m, 3H), 3.27 – 3.32 (m, 1H), 3.07 – 3.10 (m, 1H), 2.46 – 2.52 (m, 1H), 1.94 – 1.99 (m, 1H), 1.63 – 1.70 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 138.2, 128.4, 127.6, 127.5, 79.0, 73.1, 71.9, 48.9, 45.2, 38.7, 28.5, 28.2. MS–EI (*m / z*): 292 (0.3), 291 (1.5, $M^{+\cdot}$), 236 (10), 235 (41), 232 (11), 218 (16), 190 (28), 144 (25), 129 (36), 100 (33), 92 (15), 91 (82), 85 (36), 84 (22), 82 (21), 68 (13), 65 (15), 57 (100), 56 (15), 55 (18), 43 (28), 41 (36). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{17}H_{25}NO_3$ 291.1834; found: 291.1848.

(*R*)-*tert*-Butyl 3-(benzyloxymethyl)-pyrrolidine-1-carboxylate (*R*)-B4.

The compound was obtained in similar manner to (S)-*tert*-Butyl-2-(benzyloxymethyl)-pyrrolidine-1-carboxylate **(*S*)-A1.** Colourless oil (1.084 g, 91 %), $[\alpha]_D^{22}$ = 5.90 (*c* 1.55, CH_2Cl_2). All spectra are identical with data for **(*S*)-B4**.

(*S*)-3-(Benzyloxymethyl)-pyrrolidine (*S*)-B5.

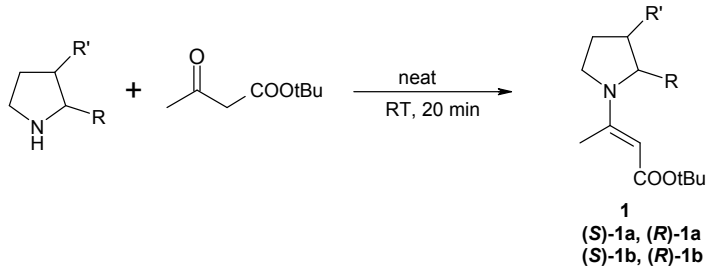
The compound was obtained in similar manner to (S)-2-(benzyloxymethyl)-pyrrolidine **(A2-s).** Light-yellow oil (0.26 5g, 99 %), $[\alpha]_D^{20}$ = – 16.0 (*c* 1.0, CH_2Cl_2). IR (film): 3388, 2936, 2861, 1534, 1421, 1203, 1098, 739, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.36 (m, 4H), 7.26 – 7.29 (m, 1H), 4,51 (s, 2H), 3.40 – 3.43 (m, 1H), 3.34 – 3.37 (m, 1H), 3.02 – 3.06 (m, 1H), 2.92 – 2.97 (m, 1H), 2.84 – 2.89 (m, 1H), 2.69 – 2.72 (m, 1H), 2.36 – 2.44 (m, 1H), 1.86 – 1.93 (m, 1H), 1.41 – 1.47 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 128.3, 127.6, 127.5, 73.4, 73.1, 50.5, 46.9, 39.2, 29.4. HRMS–ESI (*m / z*, MeOH): $[M+H]^+$ calcd for $C_{12}H_{18}NO$ 192.1388; found: 192.1391.

[7] R. N. Loy, E. N. Jacobsen, J. Amer. Chem. Soc., **2009**, 131, 2786

(*R*)-3-(Benzyloxymethyl)-pyrrolidine (*R*)-B5.

The compound was obtained in similar manner to (S)-enantiomer **(*S*)-B5.** Light-yellow oil (0.583 g, 96 %), $[\alpha]_D^{23}$ = 13.0 (*c* 0.9, CH_2Cl_2). All spectra are identical with data for **(*S*)-B5.**

3. General procedure for synthesis of the enamines.



Scheme 3. Synthesis of the enamines.

(E)-3-Pyrrolidin-1-yl-but-2-enoic acid *tert*–butyl ester 1.

Pyrrolidine (4.9 mL**,** 4.26 g, 30 mmol) was treated with *tert*-butyl acetoacetate (2.6 mL, 2.26 g, 32 mmol). After 1 min reaction mixture warmed up to ~ 60°C. The reaction mixture was kept at RT for 20 min, then dried under high vacuum for 2h at RT and 30 min at 60°C. The product was pure according to ^{1}H NMR spectra and it was used to synthesis of quinolines without purification. Light-yellow solid (6.04 g, 95%), mp. 112 – 114 °C. IR (film): 3053, 2976, 2929, 2873, 2851, 1675, 1571, 1429, 1361, 1266, 1129, 1074, 1042, 1028, 906, 863, 787, 738 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (s, 1H), 3.27 (bs, 4H), 2.42 (s, 3H), 1.87 – 1.93 (m, 4H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 158.8, 85.2, 77.2, 47.5, 28.7, 25.2, 16.5. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{12}H_{21}NO_2Na$ $[M+Na]^+$, 234.1462; found: 234.1470.

(E)-3-[(2)-(*S*)-Benzyloxy-pyrrolidin-1-yl]-but-2-enoic acid *tert*–butyl ester (*S*)-1a.

The compound was obtained in similar manner to **(1)**. Yellow oil (1.96 g, 99%), $[\alpha]_D^{22}$ = –37.3 (*c* 0.95, CH_2Cl_2). IR (film): 2973, 2927, 2863, 1680, 1573, 1417, 1362, 1249, 1128, 1065, 795, 738, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.36 (m, 5H), 4,46 – 4.52 (m, 3H), 3.96 – 4.02 (m, 1H), 3.43 – 3.50 (m, 1H), 3.25 – 3.32 (m, 2H), 3.15 – 3.22 (m, 1H), 2.43 (s, 3H), 2.00 – 2.06 (m, 1H), 1.85 – 1.98 (m, 3H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 158.4, 138.1, 128.4, 127.7, 127.5, 86.5, 77.4, 73.3, 57.8, 48.2, 28.7,

28.3, 22.6, 16.4. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{20}H_{29}NO_3Na$ $[M+Na]^+$, 354.2045; found: 354.2043

(E)-3-[(2)-(*R*)-Benzyloxy-pyrrolidin-1-yl]-but-2-enoic acid *tert*–butyl ester (*R*)-1a.
The compound was obtained in similar manner to **(1)**. Yellow oil (0.852 g, 99%), $[\alpha]_D^{21}$ = 36.7 (*c* 1.2, CH_2Cl_2). All spectra are identical with data for **(*S*)-1a.**

(E)-3-[(3)-(*S*)-Benzyloxy-pyrrolidin-1-yl]-but-2-enoic acid *tert*–butyl ester (*S*)-1b
The compound was obtained in similar manner to **(1)**. Yellow oil (0.329 g, 89%; purity ~ 85 % based on ^{1}H NMR), $[\alpha]_D^{20}$ = 13.0 (*c* 0.50, CH_2Cl_2). IR (film): 2972, 2927, 2858, 1678, 1574, 1427, 1362, 1124, 1067, 792, 738, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.37 (m, 5H), 4.53 (s, 2H), 4.40 (s, 1H), 3.44 –3.47 (m, 2H), 3.35 – 3.40 (m, 2H), 3.21 – 3.30 (m, 1H), 3.06 – 3.12 (m, 1H), 2.51 – 2.57 (m, 1H), 2.40 (s, 3H), 2.00 – 2.06 (m, 1H), 1.69– 1.76 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 158.7, 138.1, 128.4, 127.7, 127.6, 85.6, 77.3, 73.3, 71.8, 50.9, 47.2, 38.4, 28.7, 28.0, 16.4. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{20}H_{29}NO_3Na$ $[M+Na]^+$, 354.2045; found: 354.2046

(E)-3-[(3)-(*R*)-Benzyloxy-pyrrolidin-1-yl]-but-2-enoic acid *tert*–butyl ester (*R*)-1b.
The compound was obtained in similar manner to **(1)**. Yellow oil (0.83 g, 99%), $[\alpha]_D^{22}$ = –15.0 (*c* 0.50, CH_2Cl_2). All spectra are identical with data for **(*S*)-1b**

4. General procedure for synthesis of quinolines and quinoline 1-oxides.

To a solution of the enamine **1** (0.317 g, 1.5 mmol) and HMPA[8] (0.35 mL, 0.357 g, 2.0 mmol) in dry THF (10 mL) at – 70 °C under argon, 2.5 M BuLi in hexane (0.67 mL, 1.67 mmol) was added in portions in 4 min. After the addition was completed, the solution was stirred at – 70 °C for 30 min. A solution of the nitroarene (3.0 mmol) in THF (1.7 mL) was added and the resultant mixture was stirred for 10 min at – 70 °C. Et_3N (1.0 mL, 0.727 g, 7.2 mmol) was added and then pivaloyl chloride (0.85 mL, 0.833 g, 6.9 mmol) was added in portions (7 min). After the addition was completed, the solution was stirred at – 70 °C for 2h (colour changed to yellow; the yellow colour indicates that desire reaction occurred). The cooling bath was

[8] HMPA is toxic and should be used carefully.

removed, water (10 mL) was added immediately and the mixture was stirred for 5 min. The resultant mixture was extracted with AcOEt (30 mL), dried and evaporated. The products were purified by column chromatography (SiO_2, hexane/AcOEt).

***tert*-Butyl 6,8-dichloro-3-(1-pyrrolidinyl)quinoline-2-carboxylate (2a).**

Yellow solid (0.294 g, 57%), mp. 142 – 144 °C. IR (KBr): 3081, 2982, 2884, 1718, 1595, 1539, 1459, 1433, 1390, 1359, 1316, 1285, 1250, 1167, 1148, 1102, 1082, 1001, 917, 872, 840, 777, 689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 2.1 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.09 (s, 1H), 3.38 – 3.42 (m, 4H), 2.01 – 2.05 (m, 4H), 1.66 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 143.3, 140.3, 134.9, 134.8, 132.6, 131.1, 125.7, 123.3, 114.1, 82.9, 50.3 28.1, 25.8. MS–EI (*m / z*): 368 (9), 366 (13, $M^{+\cdot}$), 312 (10), 310 (16), 293 (13), 269 (12), 268 (18), 267 (66), 266 (40), 265 (100), 264 (25), 240 (14), 239 (28), 238 (25), 237 (39), 199 (12), 198 (12), 197 (19), 196 (15), 70 (19), 57 (17), 41 (21). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{18}H_{20}N_2O_2\,^{35}Cl_2$, 366.0902; found: 366.0913.

***tert*-Butyl 6,8-difluoro-3-(1-pyrrolidinyl)quinoline-2-carboxylate (2b).**

Light-yellow solid (0.296 g, 61%), mp. 145 – 147 °C. IR (KBr): 3092, 2979, 2876, 2843, 1717, 1635, 1594, 1566, 1485, 1438, 1398, 1324, 1293, 1224, 1170, 1106, 880, 835, 766, 663, 534 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.42 (bs, 1H), 7.37 – 7.39 (m, 1H), 7.26 – 7.31 (m, 1H), 3.25 – 3.31 (m, 4H), 1.95 – 1.99 (m, 4H), 1.59 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.4, 159.8 (dd, *J* = 226 Hz, 12 Hz), 157.8 (dd, *J* = 242 Hz, 12 Hz), 142.4, 140.0, 131.0 – 131.2 (m), 125.9 (d, *J* = 13 Hz), 113.6 – 113.7 (m), 104.7 (dd, *J* = 22 Hz, 5 Hz), 100.7 (dd, *J* = 30 Hz, 22 Hz),, 82.7, 49.6, 27.5, 25.2. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{18}H_{20}N_2O_2F_2Na$ $[M+Na]^+$, 357.1391; found: 357.1395.

***tert*-Butyl 8-chloro-6-methoxy-3-(1-pyrrolidinyl)quinoline-2-carboxylate (2c).**

Yellow solid (0.362 g, 67%), mp. 171 – 173 °C. IR (KBr): 2976, 2871, 1710, 1600, 1555, 1479, 1441, 1390, 1363, 1287, 1227, 1150, 1099, 1087, 997, 849, 815 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, *J* = 2.0 Hz, 1H), 7.05 (s, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 4.00 (s, 3H), 3.35 – 3.38 (m, 4H), 1.99 – 2.02 (m, 4H), 1.68 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 158.9, 144.3, 143.4, 136.1, 134.0, 133.0, 119.1, 116.5, 108.1, 85.3, 58.8, 52.8, 30.8, 28.4. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{19}H_{23}N_2O_3\,^{35}ClNa$ $[M+Na]^+$, 385.1295; found: 385.1295.

***tert*-Butyl 6-chloro-8-methyl-3-(1-pyrrolidinyl)quinoline-2-carboxylate (2d).**

Yellow solid (0.280 g, 54%), mp. 112 – 115 °C. IR (KBr): 2979, 2879, 1716, 1591, 1470, 1436, 1366, 1316, 1292, 1217, 1160, 1100, 880, 861, 785, 650 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.49 (bs, 1H), 7.43 (d, J = 1.4 Hz, 1H), 7.34 (s, 1H), 3.31 – 3.34 (m, 4H), 2.42 (s, 3H), 1.95 – 1.98 (m, 4H), 1.60 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.8, 142.4, 139.5, 137.5, 133.4, 131.4, 130.7, 127.1, 124.1, 114.3, 82.3, 49.5, 27.6, 25.2, 21.0. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{19}H_{23}N_2O_2{}^{35}ClNa$ $[M+Na]^+$, 369.1346; found: 369.1338.

***tert*-Butyl 6-fluoro-8-methyl-3-(1-pyrrolidinyl)quinoline-2-carboxylate (2e).**

Light-yellow solid (0.262 g, 55%), mp. 108 – 109 °C. IR (KBr): 2981, 2875, 2822, 1715, 1633, 1590, 1557, 1485, 1442, 1397, 1372, 1294, 1230, 1103, 855, 784, 693, 664, 585, 520 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.33 – 7.36 (m, 2H), 7.07 (dd, J = 11.9 Hz, 1.3 Hz, 1H), 3.30 – 3.33 (m, 4H), 2.42 (s, 3H), 1.96 – 1.97 (m, 4H), 1.59 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.7, 156.9 (d, J = 253Hz), 142.2, 139.6, 137.7 (d, J = 7 Hz), 131.1 (d, J = 2 Hz), 127.3 (d, J = 13 Hz), 120.5 (d, J = 3 Hz), 113.6 (d, J = 2 Hz), 111.1 (d, J = 18 Hz), 82.4, 49.6, 27.6, 25.2, 21.4. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{19}H_{23}N_2O_2FNa$ $[M+Na]^+$, 353.1641; found: 353.1635.

***tert*-Butyl 3-(1-pyrrolidinyl)-6-trifluoromethylquinoline-2-carboxylate 1-oxide (3a).**

Yellow solid (0.214 g, 38%), mp. 191 – 194 °C (decomp.). IR (KBr): 3096, 2976, 2884, 1736, 1575, 1489, 1454, 1369, 1346, 1316, 1259, 1153, 1126, 1058, 934, 890, 829, 718 cm^{-1}. ^{1}H NMR (600 MHz, DMSO–d_6): δ 8.42 (d, J = 9.0 Hz, 1H), 8.32 (bs, 1H), 7.65 (dd, J = 9.0 Hz, 1.7 Hz, 1H), 7.29 (s, 1H), 3.38 – 3.42 (m, 4H), 1.99 – 2.00 (m, 4H), 1.60 (s, 9H). ^{13}C NMR (150 MHz, DMSO–d_6): δ 161.6, 139.8, 134.2, 132.6, 129.4, 129.2, 124.8 (q, J = 4 Hz), 123.8 (q, J = 271 Hz), 120.5, 120.4, 106.0, 84.3, 49.0 27.4, 25.1. MS–EI (*m / z*): 382 (20, $M^{+\cdot}$), 281 (10), 266 (31), 265 (100), 264 (11), 263 (12), 237 (12), 196 (20). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{19}H_{21}N_2O_3F_3$ 382.1504; found: 382.1512.

***tert*-Butyl 6-chloro-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3b).**

Yellow solid (0.258 g, 50%), mp. 166 – 170 °C (decomp.). IR (KBr): 3089, 3086, 2979, 2873, 1730, 1605, 1575, 1561, 1481, 1446, 1366, 1343, 1286, 1254, 1197, 1175, 1147, 1127, 1069, 929, 864, 813, 790, 604 cm^{-1}. ^{1}H NMR (500 MHz, DMSO–d_6): δ 8.24 (d, J = 9.5 Hz, 1H), 7.92 (d, J = 2.5 Hz, 1H), 7.41 (dd, J = 9.5 Hz, 2.5 Hz, 1H), 7.04 (s, 1H), 3.36 – 3.39 (m, 4H), 1.96 – 1.98 (m, 4H), 1.59 (s, 9H). ^{13}C NMR (125 MHz, DMSO–d_6): δ 161.8, 139.7,

133.9, 131.9, 131.5, 130.9, 125.8, 124.9, 120.8, 104.4, 84.1, 49.0 27.4, 25.1. MS–EI (*m / z*): 350 (6), 348 (16, $M^{+\cdot}$), 248 (18), 247 (14), 233 (47), 232 (37), 231 (100), 230 (10), 162 (17), 57 (12), 42 (19). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{18}H_{21}N_2O_3\ ^{35}Cl$, 348.1241; found: 348.1253.

***tert*-Butyl 6-iodo-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3c).**

Yellow solid (0.332 g, 50%), mp. 173 – 176 °C (decomp.). IR (KBr): 3097, 2974, 2870, 1730, 1599, 1556, 1477, 1439, 1365, 1343, 1319, 1235, 1194, 1176, 1147, 1126, 910, 867, 812 cm^{-1}. ^1H NMR (600 MHz, DMSO–d_6): δ 8.27 (d, *J* = 1.8 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.66 (dd, *J* = 9.0 Hz, 1.8 Hz, 1H), 7.01 (s, 1H), 3.35 – 3.38 (m, 4H), 1.95 – 1.98 (m, 4H), 1.59 (s, 9H). ^{13}C NMR (150 MHz, DMSO–d_6): δ 161.8, 139.4, 134.6, 133.7, 132.5, 131.6, 131.5, 120.4, 104.1, 96.5, 84.0, 49.0, 27.4, 25.1. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{18}H_{21}N_2O_3INa$ $[M+Na]^+$, 463.0495; found: 463.0486.

***tert*-Butyl 6-fluoro-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3d).**

Yellow solid (0.427 g, 48%), mp. 144 – 146 °C (decomp.). IR (KBr): 2977, 2880, 1732, 1628, 1597, 1569, 1460, 1365, 1344, 1266, 1209, 1154, 1113, 1078, 962, 939, 855, 812 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.47 – 8.50 (m, 1H), 7.17 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 7.09 – 7.13 (m, 1H), 6.69 (s, 1H), 3.43 – 3.46 (m, 4H), 2.00 – 2.03 (m, 4H), 1.68 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5 (d, *J* = 248 Hz), 162.4, 140.1, 131.9, 131.4, 131.3, 122.4 (d, *J* = 10 Hz), 115.6 (d, *J* = 26 Hz), 109.1 (d, *J* = 23 Hz), 105.2, 84.7, 49.2 27.9, 25.6. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{18}H_{21}N_2O_3FNa$ $[M+Na]^+$, 355.1434; found: 355.1433.

***tert*-Butyl 6-phenylsulfanyl-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3e).**

Orange solid (0.305 g, 50%), mp. 158 – 162 °C (decomp.). IR (KBr): 2973, 2870, 2840, 1723, 1602, 1574, 1562, 1479, 1439, 1360, 1344, 1322, 1146, 930, 876, 845, 756, 692 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, *J* = 9.1 Hz, 1H), 7.46 – 7.47 (m, 2H), 7.33 – 7.40 (m, 4H), 7.20 – 7.22 (m, 1H), 6.61 (s, 1H), 3.39 – 3.44 (m, 4H), 1.97 – 2.04 (m, 4H), 1.68 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5 139.9, 139.1, 133.3, 132.9, 130.7, 129.5, 128.2, 126.7 124.6, 120.2, 105.3, 84.6, 49.3 27.9, 25.6. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{24}H_{26}N_2O_3SNa$ $[M+Na]^+$, 445.1562; found: 445.1558.

***tert*-Butyl 6-phenyl-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3f).**

Yellow-orange solid (0.427 g, 48%), mp. 145 – 148 °C (decomp.). IR (KBr): 2972, 1735, 1614, 1577, 1566, 1482, 1454, 1428, 1360, 1346, 1235, 1149, 1127, 1094, 939, 862, 840, 795,

698, 603 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 1.5 Hz, 1H), 7.64 – 7.68 (m, 3H), 7.46 – 7.49 (m, 2H), 738 – 7.41 (m, 1H), 6.87 (s, 1H), 3.46 – 3.49 (m, 4H), 2.02 – 2.04 (m, 4H), 1.71 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 141.8, 139.9, 139.6, 133.7, 132.4, 130.5, 128.9, 128.0, 127.3, 125.6, 123.7, 119.9, 106.5, 84.6, 49.3 27.9, 25.6. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{24}H_{26}N_2O_3Na$ $[M+Na]^+$, 413.1841; found: 413.1832.

***tert*-Butyl 6-methyl-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3g).**

Yellow-orange solid (0.195 g, 40%), mp. 137 – 140 °C (decomp.). IR (KBr): 2981, 2871, 1730, 1619, 1574, 1487, 1446, 1365, 1343, 1240, 1206, 1150, 1126, 1091, 936, 868, 844, 813 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.8 Hz, 1H), 7.34 (bs, 1H), 7.22 (dd, *J* = 8.8 Hz, 1.7 Hz, 1H), 6.74 (s, 1H), 3.42 – 3.45 (m, 4H), 1.99 – 2.03 (m, 4H), 1.69 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 139.4, 139.1, 132.9, 132.0, 130.3, 128.2, 124.9, 119.1, 106.1, 84.4, 49.3 27.9, 25.6, 21.5. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{19}H_{25}N_2O_3$ $[M+H]^+$, 329.1865; found: 329.1862.

***tert*-Butyl 6-*tert*-butyl-3-(1-pyrrolidinyl)quinoline-2-carboxylate 1-oxide (3h).**

Orange solid (0.185 g, 33%), mp. 179 – 182 °C (decomp.). IR (KBr): 2995, 2839, 1734, 1619, 1573, 1485, 1442, 1367, 1347, 1250, 1182, 1151, 941, 878, 846, 822, 797, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 9.1 Hz, 1H), 7.46 – 7.51 (m, 2H), 6.81 (s, 1H), 3.42 – 3.47 (m, 4H), 1.99 – 2.04 (m, 4H), 1.69 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.8, 152.1, 139.5, 132.9, 132.1, 130.1, 125.0, 121.1, 119.0, 106.7, 84.3, 49.3, 34.9, 31.0, 27.9, 25.6. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{22}H_{30}N_2O_3Na$ $[M+Na]^+$, 393.2154; found: 393.2156.

(*S*)-*tert*-Butyl 3-[(2-benzyloxymethyl)-6, 8-dichloro-1-pyrrolidinyl]quinoline-2-carboxylate (4a).

Yellow oil (0.139 g, 37%), $[\alpha]_D^{22}$ = –264 (c 0.95, CH_2Cl_2). IR (film): 2977, 2872, 1721, 1595, 1455, 1426, 1367, 1285, 1205, 1165, 1105, 1085, 843, 737, 697 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.86 (d, *J* = 2.1 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.65 (s, 1H), 7.20 – 7.26 (m, 5H), 4.45 (d, *J* = 12.5 Hz, 1H), 4.43 (d, *J* = 12.5 Hz, 1H), 4.14 – 4.17 (m, 1H), 3.50 – 3.54 (m, 2H), 3.40 – 3.43 (m, 1H), 3.22 – 3.27 (m, 1H), 2.11 – 2.17 (m, 1H), 1.91 – 2.02 (m, 2H), 1.83 – 1.88 (m, 1H), 1.57 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.2, 145.2, 139.7, 138.3, 133.9, 133.3, 131.2, 130.8, 128.0, 127.2, 127.1, 125.5, 124.2, 116.5, 82.7, 72.2,

69.8, 58.3, 51.3, 28.3, 27.5, 23.8. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{26}H_{28}N_2O_3{}^{35}Cl_2Na$ $[M+Na]^+$, 509.1375; found: 509.1362.

(*S*)-*tert*-Butyl 3-[(2-benzyloxymethyl)-1-pyrrolidinyl]-6-chloro-8-methoxy-quinoline-2-carboxylate (4b).

Yellow oil (0.251 g, 43%), $[\alpha]_D^{23}$ = –258 (c 0.50, CH_2Cl_2). IR (film): 2975, 2926, 2855, 1720, 1602, 1557, 1426, 1364, 1293, 1229, 1147, 1091, 1000, 893, 846, 737, 699 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.54 (s, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.20 – 7.27 (m, 5H), 6.90 (d, *J* = 2.0 Hz, 1H), 4.43 (bs, 2H), 4.09 – 4.14 (m, 1H), 3.95 (s, 3H), 3.47 – 3.54 (m, 2H), 3.36 – 3.39 (m, 1H), 3.17 – 3.21 (m, 1H), 2.11 – 2.17 (m, 1H), 1.81 – 2.01 (m, 3H), 1.55 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 166.5, 156.0, 143.7, 139.6, 138.3, 132.3, 130.6, 130.0, 128.0, 127.2, 127.1, 116.6, 116.4, 106.0, 82.3, 72.2, 70.0, 58.1, 56.0, 51.4, 28.4, 27.6, 23.8. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{27}H_{32}N_2O_4{}^{35}Cl$ $[M+H]^+$, 483.2051; found: 483.2043.

(*S*)-*tert*-Butyl 3-[(3-benzyloxymethyl)-1-pyrrolidinyl]-6-chloro-8-methoxy-quinoline-2-carboxylate (4c).

Yellow oil (0.175 g, 57%), $[\alpha]_D^{22}$ = –57.0 (c 0.75, CH_2Cl_2). IR (film): 2976, 2935, 2867, 1719, 1602, 1556, 1477, 1439, 1364, 1293, 1233, 1153, 1091, 999, 893, 857, 737, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.35 (m, 5H), 7.16 (d, *J* = 1.9 Hz, 1H), 7.03 (s, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.00 (s, 3H), 3.39 – 3.56 (m, 5H), 3.24 – 3.27 (m, 1H), 2.61 – 2.70 (m, 1H), 2.10 – 2.17 (m, 1H), 1.75 – 1.85 (m, 1H), 1.66 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 156.3, 141.8, 140.6, 138.1, 133.5, 131.2, 130.5, 128.4, 127.7, 127.6, 116.5, 114.1, 105.6, 82.8, 73.3, 72.1, 56.2, 53.5, 49.5, 39.1, 28.5, 28.1. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{27}H_{32}N_2O_4{}^{35}Cl$ $[M+H]^+$, 483.2051; found: 483.2048.

(*R*)-*tert*-Butyl 3-[(3-benzyloxymethyl)-1-pyrrolidinyl]-6,8-difluoro-quinoline-2-carboxylate (4d).

Yellow solid (0.134 g, 40 %), mp. 96 – 99 °C, $[\alpha]_D^{22}$ = 65.2 (*c* 0.55, CH_2Cl_2). IR (film): 2978, 2934, 2870, 1719, 1633, 1595, 1568, 1485, 1444, 1399, 1369, 1293, 1234, 1155, 1108, 987, 868, 844, 738, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.36 (m, 5H), 7.11 (s, 1H), 7.01 (d, *J* = 9.4 Hz, 1H), 6.86 – 6.91 (m, 1H), 4.53 (s, 2H), 3.53 – 3.57 (m, 2H), 3.43 – 3.48 (m, 2H), 3.27 – 3.31 (m, 1H), 2.61 – 2.70 (m, 1H), 2.10 – 2.17 (m, 1H), 1.75 – 1.85 (m,

1H), 1.66 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 160.8 (dd, *J* = 219 Hz, 12 Hz), 158.8 (dd, *J* = 232 Hz, 14 Hz), 142.6, 140.4, 138.1, 131.2 (dd, *J* = 12 Hz, 3 Hz), 128.4, 127.7, 127.6, 127.5 (d, *J* = 6 Hz), 113.8 (d, *J* = 5 Hz), 104.3 (dd, *J* = 22 Hz, 5 Hz), 101.1 (dd, *J* = 30 Hz, 22 Hz),, 83.1, 73.3, 71.9, 53.5, 49.5, 39.2, 27.5, 25.2. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{26}H_{28}N_2O_3F_2Na$ $[M+Na]^+$, 477.1966; found: 477.1955.

(*S*)-*tert*-Butyl 3-[(2-benzyloxymethyl)-1-pyrrolidinyl]-6-iodo-quinoline-2-carboxylate 1-oxide (5a).

Yellow solid (0.235 g, 35%), mp. 51 – 55 °C , $[\alpha]_D^{22}$ = -36.1 (c 0.70, CH_2Cl_2). IR (KBr): 2974, 2868, 1729, 1599, 1555, 1475, 1430, 1366, 1317, 1293, 1237, 1147, 1119, 1090, 912, 839, 813, 736, 697, 601 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 9.1 Hz, 1H), 7.90 (d, *J* = 1.1 Hz, 1H), 7.65 (dd, *J* = 9.1 Hz, 1.1 Hz, 1H), 7.24 – 7.32 (m, 5H), 6.80 (s, 1H), 4.47 (bs, 2H), 4.03 – 4.05 (m, 1H), 3.55 – 3.61 (m, 2H), 3.36 – 3.41 (m, 2H), 2.15 – 2.19 (m, 1H), 1.92 – 2.04 (m, 3H), 1.66(s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.9, 139.9, 138.0, 135.0, 134.8, 134.4, 134.1, 131.4, 128.4, 127.8, 127.7, 121.0, 107.7, 95.6, 84.9, 73.3, 70.4, 59.5, 50.8, 29.1, 27.9, 24.1. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{26}H_{29}N_2O_4INa$ $[M+Na]^+$, 583.1070; found: 583.1072.

(*S*)-*tert*-Butyl 3-[(2-benzyloxymethyl)-1-pyrrolidinyl]-6-fluoro-quinoline-2-carboxylate 1-oxide (5b).

Yellow oil (0.178 g, 41%), $[\alpha]_D^{20}$ = –29.8 (c 1.2, CH_2Cl_2). IR (film): 2977, 2872, 1731, 1627, 1586, 1570, 1451, 1367, 1346, 1215, 1153, 1119, 1087, 966, 842, 737, 699 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.31 – 8.33 (m, 1H), 7.61 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 7.37 – 7.41 (m, 1H), 7.27 (s, 1H), 7.18 – 7.24 (m, 5H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.09 – 4.13 (m, 1H), 3.47 – 3.51 (m, 2H), 3.40 – 3.43 (m, 1H), 3.15 – 3.31 (m, 1H), 2.07 – 2.13 (m, 1H), 1.89 – 2.02 (m, 3H), 1.56 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 161.7 (d, *J* = 246 Hz), 161.5, 139.9, 138.3, 133.0, 131.5, 131.0 (d, *J* = 11 Hz), 128.0, 127.3, 127.2, 121.8 (d, *J* = 10 Hz),, 116.2 (d, *J* = 26 Hz),, 110.0 (d, *J* = 23 Hz),, 108.0, 83.8, 72.2, 69.4, 58.6, 50.6, 28.0, 27.4, 23.4. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{26}H_{29}N_2O_4FNa$ $[M+Na]^+$, 475.2009; found: 475.2002.

(*R*)-*tert*-Butyl 3-[(2-benzyloxymethyl)-1-pyrrolidinyl]-6-fluoro-quinoline-2-carboxylate 1-oxide (5c). Yellow oil (0.210 g, 40%), $[\alpha]_D^{23}$ = 26.7 (c 0.6, CH_2Cl_2). All spectra are identical with data for **(5b)**

5. General procedure for hydrolysis / decarboxylation domino reaction of compounds 2–5

A suspension of compounds **2–5** (0.2 – 0.4 mmol) in 20 % H_2SO_4 (2–4 mL) was heated to reflux for 3h. The mixture was cooled to RT, diluted with water (15 mL) and solid K_2CO_3 was added to pH=10 in portions. The mixture was extracted with AcOEt (2 x 25 mL), the combined extracts were dried and evaporated. The crude products were washed with pentane or Et_2O. Obtained products were pure according to ^{1}H NMR.

6,8-Dichloro-3-(1-pyrrolidinyl)quinoline (6a).

Yellow-brown solid (0.065 g, 93%), mp. 147 – 149 °C. IR (KBr): 3036, 2973, 2862, 1602, 1478, 1453, 1426, 1389, 1354, 1328, 1290, 1172, 978, 899, 855, 841, 773. 710, 627 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.47 (d, *J* = 2.8 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 3.41 – 3.46 (m, 4H), 2.07 – 2.11 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ 143.9, 142.0, 135.9, 134.7, 133.1, 132.8, 125.4, 125.0, 111.4, 48.5, 26.4. MS–EI (*m / z*): 368 (9), 366 (13, $M^{+\cdot}$), 312 (10), 310 (16), 293 (13), 269 (12), 268 (18), 267 (66), 266 (40), 265 (100), 264 (25), 240 (14), 239 (28), 238 (25), 237 (39), 199 (12), 198 (12), 197 (19), 196 (15), 70 (19), 57 (17), 41 (21). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{18}H_{20}N_2O_2\,^{35}Cl_2$, 366.0902; found: 366.0913.

6,8-Difluoro-3-(1-pyrrolidinyl)quinoline (6b).

Light-brown solid (0.083 g, 92%), mp. 148 – 150 °C. IR (KBr): 3077, 3023, 2963, 1631, 1604, 1573, 1501, 1472, 1439, 1404, 1384, 1351, 1270, 1139, 1085, 1008, 850, 774, 664 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.52 (d, *J* = 2.7 Hz, 1H), 7.28 – 7.31 (m, 1H), 7.14 – 7.18 (m, 1H), 7.08 (s, 1H), 3.38 – 3.41 (m, 4H), 1.99 – 2.02 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 159.5 (dd, *J* = 152 Hz, 13 Hz), 157.9 (dd, *J* = 163 Hz, 13 Hz), 142.2, 140.3, 131.3 (dd, *J* = 13 Hz, 4 Hz), 127.0 (d, *J* = 13 Hz), 109.1 (dd, *J* = 5 Hz, 3 Hz), 104.5 (dd, *J* = 22 Hz, 5 Hz), 99.2 (dd, *J* = 30 Hz, 23 Hz), 47.1, 24.9. MS–EI (*m / z*): 235 (29), 234 (100, $M^{+\cdot}$), 233 (98), 206 (11), 205 (37), 192 (13), 191 (12), 178 (48), 165 (11), 164 (43), 151 (10), 144 (11). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{13}H_{12}N_2F_2$, 234.0969; found: 234.0965.

6-Chloro-8-methoxy-3-(1-pyrrolidinyl)quinoline (6c).

Beige solid (0.092 g, 91%), mp. 201 – 203 °C. IR (KBr): 2970, 2844, 1601, 1562, 1493, 1452, 1427, 1361, 1294, 1258, 1226, 1138, 1090, 1006, 881, 851, 815, 780. 756 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.33 (d, *J* = 2.5 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6,99 (d, *J* = 2.5 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 4.00 (s, 3H), 3.40 – 3.43 (m, 4H), 2.07 – 2.10 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ 157.2, 144.0, 139.4, 133.9, 132.8, 131.4, 117.7, 111.6, 105.7, 56.5, 26.4. MS–EI (*m / z*): 264 (32), 263 (43), 262 (100, $M^{+\cdot}$), 261 (88), 235 (19), 234 (13), 233 (61), 232 (13), 231 (14), 227 (12), 73 (12), 44 (21), 43 (17), 42 (11), 41 (18). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{14}H_{15}N_2O\,^{35}Cl$, 262.0873; found: 262.0872.

8-Chloro-6-methyl-3-(1-pyrrolidinyl)quinoline (6d).

Beige solid (0.066 g, 93%), mp. 131 – 134 °C. IR (KBr): 2962, 2841, 1602, 1483, 1435, 1395, 1293, 1223, 1174, 1150, 982, 863, 776, 646 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.37 (d, *J* = 2.7 Hz, 1H), 7.35 (bs, 1H), 7.30 (d, *J* = 1.7 Hz, 1H), 6,98 (d, *J* = 2.7 Hz, 1H), 3.37 – 3.41 (m, 4H), 2.42 (s, 3H), 2.06 – 2.09 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ 143.5, 140.6, 138.3, 136.0, 132.8, 132.7, 127.5, 125.4, 112.2, 48.5, 26.4, 21.4. MS–EI (*m / z*): 248 (33), 247 (41), 246 (100, $M^{+\cdot}$), 245 (80), 217 (12), 190 (17), 176 (14). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{14}H_{15}N_2{}^{35}Cl$, 246.0924; found: 246.0915.

6-Chloro-3-(1-pyrrolidinyl)quinoline 1-oxide (7b).

Yellow-brown solid (0.052 g, 81%), mp. 207 – 210 °C (decomp.). IR (KBr): 3070, 2971, 2849, 1606, 1582, 1496, 1484, 1455, 1427, 1393, 1358, 1327, 1263, 1195, 887, 812, 615, 542 cm^{-1}. ^{1}H NMR (600 MHz, DMSO–d_6): δ 8.27 – 8.29 (m, 2H), 7.86 (d, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 9.3 Hz, 2.3 Hz, 1H), 6,80 (bs, 1H), 3.33 – 3.35 (m, 4H), 1.97 – 1.99 (m, 4H). ^{13}C NMR (150 MHz, DMSO–d_6): δ 143.0, 133.8, 133.7, 132.5, 126.5, 125.1, 124.9, 121.6, 101.6, 47.9, 25.3. MS–EI (*m / z*): 250 (33), 249 (22), 248 (100, $M^{+\cdot}$), 247 (24), 234 (15), 233 (27), 232 (52), 231 (69), 230 (16), 229 (14), 203 (14), 189 (10), 176 (16), 164 (16), 162 (25), 151 (10), 150 (10), 116 (13), 114 (14). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{13}H_{13}N_2O^{35}Cl$, 248.0716; found: 248.0710.

6-Iodo-3-(1-pyrrolidinyl)quinoline 1-oxide (7c).

Brown solid (0.077 g, 87%), mp. 205 – 209 °C (decomp.). IR (KBr): 2944, 2853, 1602, 1579, 1496, 1451, 1401, 1357, 1323, 1191, 1084, 878, 819, 789 cm^{-1}. ^{1}H NMR (500 MHz, DMSO–d_6): δ 8.27 (d, *J* = 1.8 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.58 (dd, *J* = 9.2 Hz, 1.8 Hz, 1H), 6,77 (d, *J* = 1.8 Hz, 1H), 3.31 – 3.34 (m, 4H), 1.97 – 1.99 (m,

4H). ^{13}C NMR (125 MHz, DMSO–d_6): δ 142.3, 134.4, 132.9, 132.8 132.4, 126.0, 120.8, 100.8, 95.7, 47.4, 24.8. HRMS–ESI$^+$ (*m / z*, MeOH): calcd for $C_{13}H_{14}N_2OI$ $[M+H]^+$, 341.0151; found: 341.0138.

6-Fluoro-3-(1-pyrrolidinyl)quinoline 1-oxide (7d).

Yellow-brown solid (0.068 g, 97%), mp. 193 – 194 °C (decomp.). IR (KBr): 3074, 2967, 2850, 1627, 1592, 1505, 1461, 1435, 1398, 1358, 1331, 1264, 1200, 1148, 957, 895, 868, 806, 613, 542 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ 8.38 – 8.42 (m, 1H), 8.21 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.41 (m, 1H), 7.20 – 7.24 (m, 1H), 6,91 (d, *J* = 2.1 Hz, 1H), 3.35 – 3.38 (m, 4H), 2.07 – 2.10 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ 163.7 (d, *J* = 247 Hz), 143.8, 134.1 (d, J = 11 Hz), 131.6, 127.8, 122.7 (d, J = 12 Hz), 116.5 (d, J = 27 Hz), 110.5 (d, J = 24 Hz), 106.7 (d, J = 5 Hz), 48.8, 26.4. MS–EI (*m / z*): 233 (15), 232 (100, $M^{+\cdot}$), 231 (25), 216 (22), 215 (39), 214 (11), 213 (12), 187 (12) 160 (10), 146 (19), 134 (10), 107 (12) 41 (12). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{13}H_{13}N_2OF$, 232.1012; found: 232.1023.

6-Phenyl-3-(1-pyrrolidinyl)quinoline 1-oxide (7f).

Yellow–brown solid (0.073 g, 84%), mp. 217 – 220 °C (decomp.). IR (KBr): 2968, 2866, 2839, 1612, 1597, 1511, 1481, 1458, 1429, 1398, 1356, 1267, 1218, 1194, 1152, 889, 825, 800, 772, 704 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (d, *J* = 9.0 Hz, 1H), 8.30 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 1.3 Hz, 1H), 7.66 – 7.70 (m, 2H), 7.64 (dd, *J* = 9.0 Hz, 1.6 Hz, 1H), 7.46 – 7.50 (m, 2H), 7.39 – 7.42 (m, 1H), 6,76 (bs, 1H), 3.36 – 3.42 (m, 4H), 2.07 – 2.12 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.9, 141,6, 140.0, 133.6, 131.6, 128.9, 128.0, 127.4, 126.6, 125.1 123.7, 119.9, 104.6, 47.8, 25.4. MS–EI (*m / z*): 291 (22), 290 (100, $M^{+\cdot}$), 275 (15), 274 (71), 273 (57), 272 (16), 271 (13), 245 (10), 218 (12), 204 (19). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{19}H_{18}N_2O$, 290.1419; found: 290.1418.

6-*tert*-Butyl-3-(1-pyrrolidinyl)quinoline 1-oxide (7h).

Yellow–brown solid (0.053 g, 91%), mp. 175 – 180 °C (decomp.). IR (KBr): 2963, 2865, 1602, 1592, 1506, 1454, 1398, 1356, 1223, 1187, 1170, 897, 870, 789 cm^{-1}. ^{1}H NMR (600 MHz, DMSO–d_6): δ 8.22 (d, *J* = 9.1 Hz, 1H), 8.20 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.48 (dd, *J* = 9.1 Hz, 2.1 Hz, 1H), 6,85 (d, *J* = 1.8 Hz, 1H), 3.31 – 3.33 (m, 4H), 1.97 – 1.99 (m, 4H), 1.35 (s 9H). ^{13}C NMR (150 MHz, DMSO–d_6): δ 150.9, 141.9, 132.3, 130.9, 125.1 123.4, 121.3, 118.4, 102.8, 47.4, 34.6, 30.8, 24.8. MS–EI (*m / z*): 271 (19), 270 (100, $M^{+\cdot}$), 269 (11), 255 (17), 254 (71), 253 (43), 252 (17), 239 (33), 237 (19), 169 (11), 168 (12),

115 (10), 57 (12), 43 (11), 41 (23). HRMS–EI (*m / z*): $[M]^{+\cdot}$ calcd for $C_{17}H_{22}N_2O$, 270.1732; found: 270.1732.

(*S*)-3-[2-(Benzyloxymethyl)-1-pyrrolidinyl]-6-iodo-quinoline 1-oxide 8a.

The compound was purified by column chromatography on silica gel (AcOEt, then AcOEt/MeOH, 10 /1). Yellow oil (058 g, 79%), $[\alpha]_D^{22} = -125$ (*c* 0.50, CH_2Cl_2). IR (film): 3370, 3086, 3060, 2855, 1601, 1574, 1495, 1448, 1395, 1358, 1322, 1257, 1223, 1195, 1086, 809, 737, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.49 (bs, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.97 (bs, 1H), 7.58 – 7.62 (m, 1H), 7.27 – 7.36 (m, 5H), 6.58 (s, 1H), 4.47 (bs, 2H), 4.03 – 4.05 (m, 1H), 3.55 – 3.61 (m, 2H), 3.36 – 3.41 (m, 2H), 2.15 – 2.19 (m, 1H), 1.92 – 2.04 (m, 3H), 1.66(s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0, 137.9, 134.7, 133.8, 133.7, 132.7, 128.5, 127.8, 127.7, 127.1, 121.1, 102.9, 95.3, 73.4, 70.3, 58.8, 48.7, 29.0, 23.3. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{21}H_{22}N_2O_2I$ $[M+H]^+$, 461.0726; found: 461.0718.

6. Transformation of *tert*-butyl ester into acid.

To solution of compound **2a** (0.358 mmol) in CH_2Cl_2 (3.8 mL) trifluroacetic acid (1.0 mL) was added and the solution was stirred at RT for 1h. The solvent was evaporated and the crude product was washed with Et_2O. Obtained product was pure according to ^1H NMR.

6,8-Dichloro-3-pyrrolidin-1-yl-quinoline-2-carboxylic acid (9a).

Yellow solid (0.094 g, 80%), mp. 135 – 138 °C (decomp.). IR (KBr): 3217, 2994, 2954, 2884, 2839, 1733, 1594, 1560, 1459, 1422, 1324, 1284, 1133, 1080, 868, 808, 749 cm^{-1}. ^1H NMR (500 MHz, DMSO–d_6): δ 13.85 (bs, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.43 (bs, 1H), 3.35 – 3.37 (m, 4H), 1.96 – 1.98 (m, 4H). ^{13}C NMR (125 MHz, DMSO–d_6): δ 168.9, 144.0, 140.0, 133.3, 133.2, 131.2, 31.1, 124.7, 123.9, 113.7, 49.4, 25.3. HRMS–ESI^+ (*m / z*, MeOH): calcd for $C_{14}H_{12}N_2O_2Cl_2Na$ $[M+Na]^+$, 333.0174; found: 333.0174. Elemental analysis indicated no fluorine presence. Anal. Calcd for: $C_{14}H_{12}N_2O_2Cl_2$: C, 54.04; H, 3.88; N, 9.00; found: C, 53.65; H, 4.02; N, 9.01.

8-Fluoro-6-methyl-3-pyrrolidin-1-yl-quinoline-2-carboxylic acid (9e).

Light–brown solid (0.078 g, 76%), mp. 116 – 119 °C (decomp.). IR (KBr): 3044, 2963, 2885, 1779, 1702, 1635, 1477, 1366, 1193, 1155, 1122, 862, 782, 672, 521, 453 cm^{-1}. ^1H NMR (500 MHz, DMSO–d_6): δ 7.36 (bs, 2H), 7.05 – 7.08 (m, 1H), 3.33 (bs, 4H), 2.42 (s, 3H), 1.95 (bs,

4H). ^{13}C NMR (125 MHz, DMSO–d_6): δ 169.1, 157.0 (d, J = 253 Hz), 142.5, 140.0, 137.7 (d, J = 8.0 Hz), 131.2, 127.3 (d, J = 12 Hz), 120.5, 113.4, 111.1 (d, J = 18 Hz), 49.5, 25.3, 21.4. ^{19}F NMR (470 MHz, DMSO–d_6): δ -75.2 ("1.6 F"; CF_3), -127.1 (1F, C_{arom}–F). HRMS–ESI$^+$ (m / z, MeOH): calcd for $C_{15}H_{15}N_2O_2FNa$ $[M+Na]^+$, 297.1015; found 297.1011. Anal. Calcd for: $C_{15}H_{15}N_2O_2F$ * $0.5CF_3COOH$: F, 14.33; found F, 14.35.

7. Synthesis of 4-(5-chloro-2-nitro-phenyl)-3-pyrrolidin-1-yl-but-2-enoic acid tert-butyl ester (III).

The compound was obtained by ONSH reaction of enamine **1** with *p*-chloronitrobenzene with using DDQ as oxidant in 32 % yield. Yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 – 7.93 (m, 1H), 7.31 – 7.33 (m, 2H), 4.73 (s, 1H), 4.71 (s, 2H), 3.19 (bs, 4H), 1.86 (bs, 4H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3, 156.1, 147.5, 139.9, 135.2, 129.5, 127.3, 126.2, 88.9, 78.1, 47.8, 31.9, 26.5, 25.1. HRMS–EI (m / z): calcd for $C_{181}H_{23}N_2O_4Cl$ $[M]^{+\cdot}$, 366.1346; found: 366.1328.