Supporting information

Structure activity studies on splitomicin derivatives as sirtuin inhibitors and computational prediction of binding mode

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1. Spectral and experimental data for splitomicin derivatives

8-Bromo-1-phenyl-1,2-dihydro-benzo[*f*]chromen-3-one (5a). See main manuscript.

8-Bromo-1-(4-chlorophenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5b). By Method B. Yield 234 mg (20 %) as white crystals. ^{1}H NMR ($CDCl_3$): 8.03 (d, J = 2.0 Hz, 1H, 7-H), 7.79 (d, J = 9.0 Hz, 1H, 10-H), 7.60 (d, J = 9.0 Hz, 1H, 6-H), 7.54 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.37 (d, J = 9.0 Hz, 1H, 5-H), 7.29-7.20 (m, 2H, Ph-H), 7.04-7.00 (m, 2H, Ph-H), 4.89 (dd, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.7 Hz, J_2 = 7.0 Hz, 1H, 2-H), 3.13 (dd, J_1 = 15.7 Hz, J_2 = 2.0 Hz, 1H, 2-H)

8-Bromo-1-(p-tolyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5c). By Method A. Yield 374 mg (34 %) as a white solid. . ^{1}H NMR ($CDCl_3$): 8.10 (d, J = 2.0 Hz, 1H, 7-H), 7.77 (d, J = 9.0 Hz, 1H, 10-H), 7.66 (d, J = 9.0 Hz, 1H, 6-H), 7.52 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.37 (d, J = 9.0 Hz, 1H, 5-H), 7.10-7.04 (m, 2H, Ph-H), 7.00-6.94 (m, 2H, Ph-H), 4.86 (dd, J_1 = 6.5 Hz, J_2 = 2.5 Hz, 1H, 1-H), 3.20 (dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H, 2-H), 3.10 (dd, J_1 = 15.8 Hz, J_2 = 2.5 Hz, 1H, 2-H), 2.25 (s, 3H, Ph-CH_3)

8-Bromo-1-(4-methoxyphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5d). By Method A. Yield 174 mg (15 %) as a white solid. . ^{1}H NMR ($CDCl_3$): 8.02 (s, 1H, 7-H), 7.80-7.77 (m, 1H, 10-H), 7.70-7.67 (m, 1H, 6-H), 7.55-7.52 (m, 1H, 9-H), 7.38-7.34 (m, 1H, 5-H), 7.05-6.95 (m, 2H, Ph-H), 6.82-6.69 (m, 2H, Ph-H), 4.86 (dd, J_1 = 6.5 Hz, J_2 = 2.5 Hz, 1H, 1-H), 3.75 (s, 3H, PhOCH_3), 3.20 (dd, J_1 = 15.8 Hz, J_2 = 2.5 Hz, 1H, 2-H), 3.10 (dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H, 2-H)

8-Bromo-1-(3,4-dichlorophenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5e). By Method B. Yield 101 mg (8 %) as white crystals. ^{1}H NMR ($CDCl_3$): 8.50 (s, 1H, 7-H), 7.82 (d, J = 9.0 Hz, 1H, 10-H), 7.64 -7.52 (m, 2H, Ar-H), 7.38 (d, J = 9.0 Hz, 1H, 5-H), 7.35 (d, J = 8.2 Hz 1H, 5'-H), 7.20 (d, J = 2.2 Hz, 1H, 6'-H), 4.91 (dd, J_1 = 6.9 Hz, J_2 = 2.0 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.8 Hz, J_2 = 6.9 Hz, 1H, 2-H), 3.13 (dd, J_1 = 15.8 Hz, J_2 = 2.0 Hz, 1H, 2-H)

8-Bromo-1-(4-fluorophenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5f). By Method B. Yield 224 mg (12 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.05 (d, J = 2.0 Hz, 1H, 7-H), 7.81 (d, J = 9.0 Hz, 1H, 6-H), 7.64 (d, J = 9.1 Hz, 1H, 10-H), 7.57 (dd, J = 9.1 Hz, J = 2.0 Hz, 1H, 9-H), 7.39 (d, J = 9.0 Hz, 1H, 5-H), 7.11-7.05 (m, 2H, Ph-H), 7.01-6.95 (m, 2H, Ph-H), 5.95 (dd, J_1 = 2.0 Hz, J_2 = 6.9 Hz, 1H, 1-H), 3.24 (dd, J = 15.8 Hz, J = 6.9 Hz, 1H, 2-H), 3.15 (dd, J_1 = 15.8 Hz, J_2 = 6.9 Hz, 1H, 2-H)

8-Bromo-1-(3,4-difluorophenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5g). By Method B. Yield 107 mg (9 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.07 (d, J = 1.5 Hz, 1H, 7-H), 7.84 (d, J = 9.0 Hz, 1H, 6-H), 7.63-7.57 (m, 2H, 9-H u. 10-H), 7.39 (d, J = 9.0 Hz, 1H, 5-H), 7.09 (dpt, J = 8.3 Hz, 1H, 6`-H), 7.01 (ddd, J = 10.9 Hz, J_{H-F} = 7.35 Hz, J_{H-F} = 2.3 Hz, 1H, 5'-H), 6.84 (m, 1H, 2'-H), 4.91 (dd, J_1 = 1.8 Hz, J_2 = 6.8 Hz, 1H, 1-H), 3.25 (dd, J_1 = 15.9 Hz, J_2 = 6.8 Hz, 1H, 2-H), 3.15 (dd, J_1 = 15.9 Hz, J_2 = 1.8 Hz, 1H, 2-H)

8-Bromo-1-(3-bromophenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5h). By Method B. Yield 227 mg (18 %) as a white solid. . ^{1}H NMR ($CDCl_3$): 8.06 (d, J = 1.9 Hz, 1H, 7-H), 7.83 (d, J = 9.0 Hz, 1H, 6-H), 7.61 (d, J = 9.0, 1H, 10-H), 7.58 (dd, J_1 = 9.0 Hz, J_2 = 1.9 Hz, 1H, 9-H), 7.40, (d, J = 9.0 Hz, 1H, 5-H), 7.39 (pt, J = 1.8 Hz, 1H, 2'-H), 7.24 (m, 1H, Ar-H), 7.16 (pt, J = 7.9 Hz, 5'-H), 6.98 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H, Ar-H), 4.90 (dd, J_1 = 1.9 Hz, J_2 = 7.0 Hz, 1H, 1-H), 3.25 (dd, J_1 = 15.9 Hz, J_2 = 7.0 Hz, 1H, 2-H), 3.16 (dd, J_1 = 15.9 Hz, J_2 = 1.9 Hz, 1H, 2'-H)

8-Bromo-1-(3-fluorophenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5i). By Method A. Yield 156 mg (14 %) as white crystals. ^{1}H NMR ($CDCl_3$): 8.05 (d, J = 1.9 Hz, 1H, 7-H), 7.81 (d, J = 9.0 Hz, 1H, 6-H), 7.63 (d, J = 9.0 Hz, 1H, 10-H), 7.56 (dd, J_1 = 9.0 Hz, J_2 = 1.9 Hz, 1H, 9-H), 7.38 (d, J = 9.0 Hz, 1H, 5-H), 7.30-7.23 (m, 1H, Ph-H), 6.99-6.89 (m, 2H, Ph-H), 6.82-6.77 (m, 1H, Ph-H), 4.93 (dd, J_1 = 1.9 Hz, J_2 = 6.8 Hz, 1H, 1-H), 3.26 (dd, J_1 = 15.9 Hz, J_2 = 6.8 Hz, 1H, 2-H), 3.18 (dd, J_1 = 15.9 Hz, J_2 = 1.9 Hz, 1H, 2-H)

8-Bromo-1-(3-methoxyphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5j). By Method A. Yield 138 mg (12 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.02 (d, J = 2.0 Hz, 1H, 7-H), 7.78 (d, J = 9.0 Hz, 1H, 6-H), 7.68 (d, J = 9.1 Hz, 1H, 10-H), 7.54 (dd, J_1 = 2.0 Hz, J_2 = 9.1 Hz, 1H, 9-H), 7.37 (d, J = 9.0 Hz, 1H, 5-H), 7.21 (pt, J = 8.0 Hz, 1H, 5'-H), 6.78 (ddd, J_1 = 8.2 Hz, J_2 = 2.5 Hz, J_3 = 0.8 Hz, 1H, 6'-H), 6.70 (m, 1H, 4'-H), 6.64 (pt, J = 2.1 Hz, 1H, 2'-H), 4.89 (dd, J_1 = 2.4 Hz, J_2 = 6.6 Hz, 1H, 1-H), 3.73 (s, 3H, -OCH_3), 3.23 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.18 (dd, J_1 = 15.8 Hz, J_2 = 2.4 Hz, 1H, 2'-H)

8-Bromo-1-(4-*tert.*-butylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5k). By Method A. Yield 723 mg (59 %) as white crystals. ^{1}H NMR ($CDCl_3$): 8.03 (d, J = 2.0 Hz, 1H, 7-H), 7.78 (d, J = 9.0 Hz, 1H, 6-H), 7.71 (d, J = 9.1 Hz, 1H, 10-H), 7.55 (dd, J_1 = 9.1 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.38 (d, J = 9.0 Hz, 1H, 5-H), 4.90 (dd, J_1 = 2.9 Hz, J_2 = 6.0 Hz, 1H, 1-H), 3.20 (m, 2H, 2-H), 2.55 (s, 9H, (CH_3)$_3$C)

8-Bromo-1-(2-methoxyphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5l). By Method A. Yield 735 mg (64 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.02 (d, J = 1.9 Hz, 1H, 7-H), 7.78 (d, J = 9.0 Hz, 1H, 6-H), 7.61 (d, J = 9.1 Hz, 1H, 10-H), 7.51 (dd, J_1 = 9.1 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.38 (d, J = 9.0 Hz, 1H, 5-H), 7.23 (m, 1H, 5'-H), 6.95 (d, J = 8.2 Hz, 1H, 6'-H), 6.74 (m, 1H, 4'-H), 6.62 (dd, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H, 3'-H), 5.28 (dd, J_1 = 7.4 Hz, J_2 = 1.4 Hz, 1H, 1-H), 3.99 (s, 3H, -OCH_3), 3.21 (dd, J_1 = 16.0 Hz, J_2 = 1.4 Hz, 1H, 2-H), 3.12 (dd, J_1 = 16.0 Hz, J_2 = 7.4 Hz, 1H, 2'-H)

8-Bromo-1-(3-chloro-4-methylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5m). By Method A. Yield 226 mg (19 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.05 (d, J = 1.8 Hz, 1H, 7-H), 7.82 (d, J = 9.0 Hz, 1H, 6-H), 7.63 (d, J = 9.0 Hz, 1H, 10-H), 7.57 (dd, J_1 = 9.0 Hz, J_2 = 1.8 Hz, 1H, 9-H), 7.39 (d, J = 9.0 Hz, 1H, 5-H), 7.13 (d, J = 7.9 Hz, 1H, 5'-H), 7.10 (d, J = 1.6 Hz, 1H, 2'-H), 6.86 (dd, J_1 = 7.9Hz, J_2 = 1.6 Hz, 1H, 6'-H), 4.88 (d, J = 6.9 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.8 Hz, J_2 = 6.9 Hz, 1H, 2-H), 3.15 (dd, J_1 = 15.8 Hz, J_2 = 1.9 Hz, 2-H), 2.31 (s, 3H, Ph-CH_3)

8-Bromo-1-(3-fluoro-4-methylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5n). By Method A. Yield 81 mg (21 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.05 (d, J = 2.0 Hz, 1H, 7-H), 7.81 (d, J = 8.9 Hz, 1H, 6-H), 7.64 (d, J = 9.0 Hz, 1H, 10-H), 7.57 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.39 (d, J = 8.9 Hz, 1H, 5-H), 7.10 (t, J = 7.9 Hz, 1H, 5'-H), 6.79 (dd, J_1 = 1.8 Hz, J_2 = 7.8 Hz, 1H, 6'-H), 6.73 (dd, J_1 = 10.4 Hz, J_2 = 1.8 Hz, 1H, 2'-H), 4.89 (dd, J_1 = 2.2 Hz, J_2 = 6.7 Hz, 1H, 1-H), 3.23 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H, 2-H), 3.18 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H, 2-H), 2.20 (s, 3H, Ph-CH_3)

8-Bromo-1-(3-methoxy-4-methylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5o). By Method A. Yield 236 mg (20 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.04 (d, J = 2.0 Hz, 1H, 7-H), 7.79 (d, J = 8.9 Hz, 1H, 6-H), 7.72 (d, J = 9.0 Hz, 1H, 10-H), 7.55 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.38 (d, J = 8.9 Hz, 1H, 5-H), 7.01 (d, J = 7.6 Hz, 1H, Ar-H), 6.60-6.54 (m, 2H, Ar-H), 4.89 (dd, J_1 = 2.3 Hz, J_2 = 6.4 Hz, 1H, 1-H), 3.72 (s, 3H, Ar-OCH_3), 3.22 (dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, 1H, 2-H), 3.18 (dd, J_1 = 15.8 Hz, J_2 = 2.3 Hz, 1H, 2-H), 2.15 (s, 3H, Ph-CH_3)

8-Bromo-1,2-dihydro-benzo[*f*]chromen-3-one (5p). By Method A. Yield 549 mg (66 %) as colourless crystals. ^{1}H NMR ($CDCl_3$): 7.99 (d, J = 2.2 Hz, 1H, 7-H), 7.75 (d, J = 9.0 Hz, 1H, 10-H), 7.67 (d, J = 9.0 Hz, 1H, 6-H), 7.62 (dd, J_1 = 9.0 Hz, J_2 = 2.2 Hz, 1H, 9-H), 7.25 (d, J = 9.0 Hz, 5-H), 3.34 (t, J = 7.4 Hz, 2H, 2-H), 2.92 (t, J = 7.4 Hz, 2H, 1-H)

1-Benzyl-8-bromo-1,2-dihydrobenzo[*f*]chromen-3-one (5q). **10a** (0.50 mmol) was dissolved in 8 ml dry THF, set under nitrogen and cooled down to 0°C. Benzyl magnesium chloride (1.55 mmol, purchased from Aldrich) was added dropwise and the mixture was stirred for 1 hour at room temperature. Then the reaction mixture was diluted with water and the product was extracted with diethyl ether. The solvents were removed under reduced pressure. Purification by column chromatography yielded 103 mg (56 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.02 (d, J = 2.0 Hz, 1H, 7-H), 7.74 (d, J = 9.1 Hz, 1H, 6-H), 7.70 (d, J =

9.0 Hz, 1H, 10-H), 7.60 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.33-7.26 (m, 4H, Ph-H and 5-H), 7.15-7.12 (m, 2H, Ph-H), 3.82 (m, 1H, 1-H), 3.05 (dd, J_1 = 13.8 Hz, J_2 = 5.1 Hz, 1H, -CH_2-Ph), 2.98 (dd, J_1 = 16.1 Hz, J_2 = 1.8 Hz, 1H, 2-H), 2.78-2.71 (m, 2H, -CH_2-Ph and 2-H)

6,8-Dibromo-1-(phenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5r). By Method A whith 4,6-dibromo-β-naphthol. Yield 377 mg (29 %) as colourless crystals. ^{1}H NMR ($CDCl_3$): 8.44 (d, J = 2.0 Hz, 1H, 7-H), 7.71 (s, 1H, 5-H), 7.65 (d, J = 9.0 Hz, 1H, 10-H), 7.57 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H, 9-H), 7.30-7.23 (m, 3H, Ph-H), 7.09-7.06 (m, 2H, Ph-H), 4.88 (dd, J_1 = 2.4 Hz, J_2 = 6.7 Hz, 1H, 1-H), 3.22 (dd, J_1 = 16.0 Hz, J_2 = 2.4 Hz, 1H, 2-H), 3.16 (dd, J_1 = 16.0 Hz, J_2 = 6.7 Hz, 1H, 2-H)

8-Methyl-1-phenyl-1,2-dihydro-benzo[*f*]chromen-3-one (8a). By method E using **5a** as bromo-substituted splitomicin derivative. Yield 104 mg (72 %) as colourless crystals. ^{1}H NMR ($CDCl_3$): 7.78 (d, J = 9.0 Hz, 1H, 10-H), 7.69 (d, J = 8.6 Hz, 1H, 6-H), 7.63 (s, 1H, 7-H), 7.32-7.20 (m, 5H, Ar-H), 7.13-7.11 (m, 2H, Ph-H), 4.93 (dd, J_1 = 2.2 Hz, J_2 = 6.7 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.7 Hz, J_2 = 2.2 Hz, 1H, 2-H), 3.15 (dd, J_1 = 15.7 Hz, J_2 = 6.7 Hz, 1H, 2-H), 2.47 (s, 3H, CH_3-Np[a])

(*R*)-8-Methyl-1-phenyl-1,2-dihydro-benzo[*f*]chromen-3-one ((*R*)-8a). By method D using **10b** as α,β-unsaturated splitomicin derivative, (*R*)-binap as chiral ligand and phenyl boronic acid. Yield 13 mg (15 %) as a white solid. ee = 97.7 % as determinded by chiral HPLC. $[\alpha]_{589}$ = 8.1 ° (c = 1.0 mg/mL, CH_2Cl_2, T = 20° C); ^{1}H NMR data cf. **8a**.

(*S*)-8-Methyl-1-phenyl-1,2-dihydro-benzo[*f*]chromen-3-one ((*S*)-8a). By method D using **10b** as α,β-unsaturated splitomicin derivative, (*S*)-binap as chiral ligand and phenyl boronic acid. Yield 10 mg (12 %) as a white solid. ee = 98.2 % as determinded by chiral HPLC. $[\alpha]_{589}$ = −8.1° (c = 1.0 mg/mL, CH_2Cl_2, T = 20° C) ; ^{1}H NMR data cf. **8a**.

1-(4-Chlorophenyl)-8-methyl-1,2-dihydro-benzo[*f*]chromen-3-one (8b). By method E using **5b** as bromo-substituted splitomicin derivative. Yield 68 mg (42 %) as colourless crystals. ^{1}H NMR ($CDCl_3$): 7.79 (d, J = 9.0 Hz, 1H, 10-H), 7.64 (s, 1H, 7-H), 7.63 (d, J = 9.0 Hz, 1H, 6-H), 7.32 (d, J = 9.0 Hz, 1H, 9-H), 7.31 (d, J = 9.0 Hz, 1H, 5-H), 7.24-7.22 (m, 2H, Ph-H), 7.06-7.03 (m, 2H, Ph-H), 4.91 (dd, J_1 = 2.0 Hz, J_2 = 7.0 Hz, 1H, 1-H), 3.21 (dd, J_1 = 15.7 Hz, J_2 = 7.0 Hz, 1H, 2-H), 3.12 (dd, J_1 = 15.7 Hz, J_2 = 2.0 Hz, 1H, 2-H), 2.48 (s, 3H, CH_3-Np)

8-Methyl-1-(4-methylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one (8c). See main manuscript.

(*R*)-8-Methyl-1-(4-methylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one ((*R*)-8c). See main manuscript.

(*S*)-8-Methyl-1-(4-methylphenyl)-1,2-dihydro-benzo[*f*]chromen-3-one ((*S*)-8c). By Method D using **10b** as α,β-unsaturated splitomicin derivative, (*S*)-binap as chiral ligand and *p*-tolyl boronic acid. Yield 13 mg (14 %) as a white solid. ee = 98.6 % as determined by chiral HPLC. $[\alpha]_{589}$ = −11.3° (c = 1.0 mg/mL, CH_2Cl_2, T = 20° C) ; ^{1}H NMR data cf. **8c**.

1-(3-Fluoro-4-methylphenyl)-8-methyl-1,2-dihydro-benzo[*f*]chromen-3-one (8d). By method E using **5n** as bromo-substituted splitomicin derivative. Yield 111 mg (69 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.81 (d, J = 8.9 Hz, 1H, 10-H), 7.67 (pd, J = 9.0 Hz, 2H, Np-H), 7.33 (d, J = 8.9 Hz, 1H, 9-H), 7.36-7.28 (m, 2H, Np-H), 7.08 (t, J = 7.9 Hz, 1H, 5'-H), 6.83 (d, J = 8.0 Hz, 1H, 6'-H), 6.75 (d, $J_{F\text{-}H}$ = 10.6 Hz, 1H, 2'-H), 4.91 (d, J = 6.5 Hz, 1H, 1-H), 3.20 (dd, J = 15.8 Hz, J = 6.5 Hz, 1H, 2-H), 3.14 (dd, J = 15.8 Hz, J = 1.7 Hz, 1H, 2-H), 2.51 (s, 3H, CH_3-Np), 2.23 (s, 3H, CH_3-Ph)

1-(3-Methoxy-4-methylphenyl)-8-methyl-1,2-dihydro-benzo[*f*]chromen-3-one (8d). By method E using **5o** as bromo-substituted splitomicin derivative. Yield 109 mg (68 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.78 (d, J = 8.9 Hz, 1H, 10-H), 7.73 (d, J = 8.6 Hz, 1H, 6-H), 7.65 (s, 1H, 7-H), 7.34 (dd, J = 8.9 Hz, J = 1.8 Hz, 1H, 9-H), 7.33 (d, J = 8.6 Hz, 1H,

[a] Np: Naphthyl-

5-H), 7.01 (d, J = 7.2, 1H, Ph-H), 6.61 (m, 2H, Ph-H), 4.91 (dd, J_1 = 2.3 Hz, J_2 = 6.6 Hz, 1H, 1-H), 3.73 (s, 3H, Ar-OCH_3), 3.21 (dd, J_1 = 15.7 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.7 Hz, J_2 = 2.3 Hz, 1H, 2-H), 2.49 (s, 3H, CH_3-Np)

3-(8-Methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)benzonitrile (8f). By method G using **5l** as bromo-substituted splitomicin derivative. Yield 76 mg (81 %) as a white solid. ^{1}H NMR ($CDCl_3$): 9.38 (d, J = 8.8 Hz, 1H, 10-H), 7.93 (d, J = 9.0 Hz, 1H, 6-H), 7.89 (s, 1H, 7-H), 7.75-7.70 (m, 2H, Ph-H), 7.62-7.58 (m, 2H, Ph-H), 7.53 (dd, J_1 = 8.8 Hz, J_2 = 1.7 Hz, 1H, 8-H), 5.63 (dd, J_1 = 3.2 Hz, J_2 = 13.5 Hz, 1H, 1-H), 3.15 (dd, J_1 = 16.5 Hz, J_2 = 13.5 Hz, 1H, 2-H), 3.01 (dd, J_1 = 16.5 Hz, J_2 = 3.2 Hz, 1H, 2-H), 2.52 (s, 3H, CH_3-Np)

3-(8-Methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)benzamide (8g). By method H using **8f** as cyano-substituted splitomicin derivative. Yield 108 mg (65 %) as a white solid. ^{1}H NMR (DMSO-d^6): 9.28 (d, J = 8.7 Hz, 1H, 10-H), 8.10 (m, 2H, Ar-H), 8.05 (s, 1H, $CONH_2$), 7.92 (d, J = 7.8 Hz, 1H, Ar-H), 7.72 (m, 2H, Ar-H), 7.53 (m, 2H, Ar-H), 7.44 (s, 1H, $CONH_2$), 7.27 (d, J = 9.0 Hz, 1H, Ar-H), 5.84 (dd, J_1 = 3.0 Hz, J_2 = 13.5 Hz, 1H, 1-H), 3.35 (dd, J_1 = 16.5 Hz, J_2 = 13.5 Hz, 1H, 2-H), 2.95 (dd, J_1 = 16.5 Hz, J_1 = 3.0 Hz, 1H, 2-H)

8-Methyl-1-(*m*-tolyl)-1,2-dihydrobenzo[*f*]chromen-3-one (8h). By method G using **5h** as bromo-substituted splitomicin derivative. Yield 62 mg (68 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.80 (d, J = 8.9 Hz, 1H, 10-H), 7.72 (d, J = 8.6 Hz, 1H, 6-H), 7.65 (s, 1H, 7-H), 7.33 (m, 2H, Ar-H), 7.15 (t, J = 7.6 Hz, 1H, 3'-H), 7.02 (m, 1H, Ar-H), 6.93 (m, 2H, Ar-H), 4.85 (dd, J_1 = 1.9 Hz, J_2 = 6.9 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.7 Hz, J_2 = 6.9 Hz, 1H, 2-H), 3.14 (dd, J_1 = 15.7 Hz, J_2 = 1.9 Hz, 1H, 2-H), 2.50 (s, 3H, CH_3-Np), 2.28 (s, 3H, CH_3-Ph)

1-(3-Hydroxyphenyl)-8-methyl-1,2-dihydrobenzo[*f*]chromen-3-one (8i). By method C using **10b** as α,β-unsaturated splitomicin derivative and *m*-hydroxyphenyl boronic acid. Yield 91 mg (30 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.79 (d, J = 8.9 Hz, 1H, 10-H), 7.70 (d, J = 8.6 Hz, 1H, 6-H), 7.65 (s, 1H, 7-H), 7.35-7.30 (m, 2H, H-Np), 7.15 (t, J = 7.9 Hz, 1H, 5'-H), 6.74 (dd, J_1 = 7.7 Hz, J_2 = 0.7 Hz, 1H, 6'-H), 6.67 (dd, J_1 = 8.1 Hz, J_2 = 2.5 Hz, 1H, 4'-H), 6.55 (t, J = 2.1 Hz, 1H, 2'-H), 5.07 (s, 1H, Ph-OH), 4.88 (dd, J_1 = 2.4 Hz, J_2 = 6.5 Hz, 1H, 1-H), 3.20 (dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H, 2-H), 3.15 (dd, J_1 = 15.8 Hz, J_2 = 2.4 Hz, 1H, 2-H), 2.50 (s, 3H, CH_3-Np)

1-(Biphenyl-4-yl)-8-methyl-1,2-dihydrobenzo[*f*]chromen-3-one (8j). By method C using **10b** as α,β-unsaturated splitomicin derivative and biphenyl boronic acid. Yield 69 mg (19 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.83 (d, J = 8.9 Hz, 1H, 10-H), 7.76 (d, J = 8.7 Hz, 1H, 6-H), 7.67 (s, 1H, 7-H), 7.54-7.48 (m, 4H, Ar-H), 7.45-7.39 (m, 2H, Ar-H), 7.37-7.32 (m, 3H, Ar-H), 7.23-7.19 (m, 2H, Ar-H), 5.00 (dd, J_1 = 2.3 Hz, J_2 = 6.4 Hz, 1H, 1-H), 3.27 (dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, 1H, 2-H), 3.22 (dd, J_1 = 15.8 Hz, J_2 = 2.3 Hz, 1H, 2-H)

***N*-(3-(8-Methyl-3-oxo-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)phenyl)acetamide (8k)**. By method C using **10b** as α,β-unsaturated splitomicin derivative and 3-acetamidophenyl boronic acid. Yield 90 mg (26 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.80 (d, J = 8.9 Hz, 1H, 6-H), 7.69 (d, J = 8.7 Hz, 1H, 10-H), 7.65 (s, 1H, 7-H), 7.44 (dd, J_1 = 8.0 Hz, J_2 = 0.7 Hz, 1H, 4'-H), 7.33 (dd, J_1 = 8.9 Hz, J_2 = 1.6 Hz, 1H, 9-H), 7.31 (d, J = 8.9 Hz, 1H, 5-H), 7.26 (s, 1H, 2'-H), 7.22 (bs, 1H, NH), 7.21 (t, J = 7.8 Hz, 1H, 5'-H), 6.85 (d, J = 7.7 Hz, 1H, 6'-H), 4.92 (dd, J_1 = 1.8 Hz, J_2 = 6.6 Hz, 1H, 1-H), 3.20 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.8 Hz, J_2 = 1.8 Hz, 1H, 2-H), 2.49 (s, 3H, CH_3-Np), 2.08 (s, 3H, CH_3CONH-Ar)

1-(3-Bromophenyl)-8-methyl-1,2-dihydrobenzo[*f*]chromen-3-one (8l). By method A. Yield 165 mg (15 %) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): 9.38 (d, J = 8.8 Hz, 1H, 10-H), 7.92 (d, J = 9.0 Hz, 1H, H-6), 7.73 (t, J = 1.7 Hz, 1H, H-2'), 7.58 (s, 1H, H-7), 7.57-7.52 (m, 1H, Ph-H), 7.54 (d, J = 8.8 Hz, 1H, H-9), 7.45 (m, 1H, Ph-H), 7.33 (t, J = 7.9 Hz, 1H, H-5'), 7.18 (d, J = 9.0 Hz, 1H, H-5), 5.58 (dd, J_1 = 3.0 Hz, J_2 = 13.8 Hz, 1H, 1-H), 3.19

(dd, J_1 = 16.6 Hz, J_2 = 13.8 Hz, 1H, 2-H), 2.98 (dd, J_1 = 16.6 Hz, 1H, J_2 = 3.0 Hz, 1H, H-2)

8-Ethyl-1-phenyl-1,2-dihydro-benzo[*f*]chromen-3-one (9a). By method E using triethylaluminium solution instead of trimethylaluminium solution and with **5a** as bromo-substituted splitomicin derivative. Yield 98 mg (65 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.83 (d, J = 8.9 Hz, 1H, 10-H), 7.74 (d, J = 8.7 Hz, 1H, 6-H), 7.67 (s, 1H, 7-H), 7.38-7.30 (m, 2H, Ar-H), 7.29-7.20 (m, 3H, Ar-H), 7.15 (m, 2H, Ar-H), 4.96 (dd, J_1 = 1.5 Hz, J_2 = 6.5 Hz, 1H, 1-H), 3.24 (dd, J_1 = 15.7 Hz, J_2 = 6.5 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.7 Hz, J_2 = 1.5 Hz, 1H, 2-H), 2.80 (q, J = 7.6 Hz, 2H, CH_3-CH_2-), 1.32 (t, J = 7.6 Hz, 3H, CH_3-CH_2-)

8-Iodo-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9b). By method A. Yield 384 mg (32 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.23 (d, J = 1.8 Hz, 1H, 7-H), 7.74 (d, J = 9.0 Hz, 1H, 10-H), 7.68 (dd, J_1 = 9.0 Hz, J_2 = 1.8 Hz, 1H, 9-H), 7.51 (d, J_1 = 8.9 Hz, 1H, 6-H), 7.34 (d, J = 8.9 Hz, 1H, 5-H), 7.28-7.20 (m, 3H, Ph-H), 7.09-7.05 (m, 2H, Ph-H), 4.89 (dd, J_1 = 2.3 Hz, J_2 = 6.7 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.7 Hz, J_2 = 6.7 Hz, 1H, 2-H), 3.16 (dd, J_1 = 15.7 Hz, J_2 = 2.3 Hz, 1H, 2-H)

3-Oxo-1-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromene-8-carbonitrile (9c). By method G using **5a** as bromo-substituted splitomicin derivative. Yield 74 mg (82 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.22 (d, J = 1.6 Hz, 1H, 7-H), 7.92 (d, J = 9.0 Hz, 1H, 6-H), 7.86 (d, J = 8.8 Hz, 1H, 10-H), 7.58 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H, 9-H), 7.46 (d, J = 9.0 Hz, 1H, 5-H), 7.29-7.20 (m, 3H, Ph-H), 7.08 (m, 2H, Ph-H), 4.93 (dd, J_1 = 2.5 Hz, J_2 = 6.5 Hz, 1H, 1-H), 3.23 (dd, J_1 = 15.9 Hz, J_2 = 6.5 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.9 Hz, J_2 = 2.5 Hz, 1H, 2-H)

1,8-Diphenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9d). By method F using **5a** as bromo substituted splitomicin derivative and phenyl boronic acid. Yield 181 mg (86 %) as a yellow solid. ^{1}H NMR ($CDCl_3$): 8.06 (d, J = 1.7 Hz, 1H, 7-H), 7.93 (d, J = 8.9 Hz, 1H, 6-H), 7.87 (d, J = 8.8 Hz, 1H, 10-H), 7.74 (dd, J_1 = 8.8 Hz, J_2 = 1.7 Hz, 1H, 9-H), 7.68-7.64 (m, 2H, Ar-H), 7.50-7.44 (m, 2H, Ar-H), 7.40-7.36 (m, 2H, Ar-H), 7.32-7.22 (m, 3H, Ar-H), 7.18-7.14 (m, 2H, Ar-H), 4.99 (dd, J_1 = 6.6 Hz, J_2 = 2.2 Hz, 1H, 1-H), 3.25 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.18 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H, 2-H)

8-Benzyl-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9e). By method A. Yield 339 mg (31 %) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): 7.81 (d, J = 8.9 Hz, 1H, 10-H), 7.73 (d, J = 8.6 Hz, 1H, 6-H), 6.67 (s, 1H, 7-H), 7.35-7.11 (m, 12H, Ar-H), 4.94 (dd, J_1 = 2.2 Hz, J_2 = 6.6 Hz, 1H, 1-H), 4.12 (s, 2H, Ph-CH_2-Np), 3.21 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H, 2-H)

3-Oxo-1-phenyl-2,3-dihydro-1H-benzo[*f*]chromene-8-carboxyamide (9f). By method H using **9c** as cyano-substituted splitomicin derivative. Yield 101 mg (64 %) as a pale yellow solid. ^{1}H NMR (dmso-d^6): 8.54 (s, 1H, 7-H), 8.11 (bs, 1H, NH), 8.10 (d, J = 8.9 Hz, 1H, 9-H), 7.98-7.92 (m, 2H, 7-H, 6-H), 7.50 (d, J = 8.9 Hz, 1H, 5-H), 7.47 (bs, 1H, NH), 7.32-7.22 (m, 5H, Ph-H), 5.21 (d, J = 6.0 Hz, 1H, 1-H), 3.56 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H, 2-H), 3.02 (dd, J_1 = 16.0 Hz, J_2 = 1.5 Hz, 1H, 2-H)

1-Phenyl-8-(pyridin-3-yl)-1,2-dihydrobenzo[*f*]chromen-3-one (9g). By method F using **5b** as bromo-substituted splitomicin derivative and pyridin-3-yl boronic acid. Yield 112 mg (52 %) as a off white solid. ^{1}H NMR ($CDCl_3$): 8.95 (d, J = 2.3 Hz, 1H, Py-H), 8.64 (dd, J_1 = 1.3 Hz, J_2 = 4.8 Hz, 1H, Py-H), 8.08 (d, J = 1.7 Hz, 1H, 7-H), 7.97 (overlapping d, J = 9.0 Hz, 2H, H-6, Ar-H), 7.92 (d, J = 8.7 Hz, 1H, 10-H), 7.73 (dd, J = 8.7 Hz, J = 1.7 Hz, 1H, 9-H), 7.43 (overlapping d, J = 9.0 Hz, 2H, H-5, Ar-H), 7.35-7.22 (m, 3H, Ar-H), 7.18 (m, 2H, Ar-H), 5.02 (dd, J_1 = 1.8 Hz, J_2 = 7.0 Hz, 1H, 1-H), 3.29 (dd, J_1 = 15.6 Hz, J_2 = 7.0 Hz, 1H, 2-H), 3.22 (dd, J_1 = 15.6 Hz, J_2 = 1.8 Hz, 1H, 2-H)

8-(3-Hydroxyphenyl)-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9h). By method F using **5b** as bromo-substituted splitomicin derivative and 3-hydroxyphenyl boronic acid. Yield 136 mg (62 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.06 (d, J = 1.8 Hz, 1H, 7-H),

7.92 (d, J = 8.9 Hz, 1H, 6-H), 7.86 (d, J = 8.8 Hz, 1H, 10-H), 7.72 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1H, 9-H), 7.42-7.36 (m, 2H, Ar-H), 7.34-7.23 (m, 4H, Ar-H), 7.19-7.13 (m, 3H, Ar-H), 6.88 (ddd, J_1 = 7.9 Hz, J_2 = 0.6 Hz, J_3 = 2.5 Hz, 1H, 4''-H), 5.08 (s, 1H, Ph-OH), 5.00 (dd, J_1 = 2.0 Hz, J_2 = 6.6 Hz, 1H, 1-H), 3.27 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.20 (dd, J_1 = 15.8 Hz, J_2 = 2.0 Hz, 1H, 2-H)

***N*-(3-(3-Oxo-1-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-8-yl)phenyl)acetamide (9i).** By method F using 3-acetamido phenyl boronic acid. Yield 120 mg (49 %) as a white solid. ^{1}H NMR ($CDCl_3$) : 8.02 (d, J = 1.7 Hz, 1H, 7-H), 7.94 (s, 1H, Ar-NH-CO-), 7.85 (d, J = 9.0 Hz, 1H, 6-H), 7.81 (m, 2H, Ar-H), 7.68 (dd, J_1 = 8.8 Hz, J_2 = 1.7 Hz, 1H, 9-H), 7.47 (m, 1H, Ar-H), 7.37 (m, 2H, Ar-H), 7.33 (d, J = 9.0 Hz, 1H, 5-H), 7.30-7.20 (m, 3H, Ar-H), 7.14 (m, 2H, Ar-H), 4.95 (dd, J_1 = 2.0 Hz, J_2 = 6.6 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H, 2-H), 3.16 (dd, J_1 = 15.8 Hz, J_2 = 2.0 Hz, 1H, 2'-H), 2.18 (s, 3H, *CH*$_3$CONH-Ar)

8-(Biphenyl-4-yl)-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9j). By method F using 4-biphenyl boronic acid. Yield 151 mg (59 %) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): 8.04 (d, J = 1.8 Hz, 1H, 7-H), 7.93 (d, J = 8.9 Hz, 1H, 6-H), 7.91 (d, J = 9.0 Hz, 1H, 10-H), 7.82-7.72 (m, 6H, Ar-H), 7.69-7.66 (m, 2H, Ar-H), 7.53-7.48 (m, 2H, Ar-H), 7.35-7.24 (m, 4H, Ar-H), 7.21-7.18 (m, 2H, Ar-H), 5.02 (dd, J_1 = 2.2 Hz, J_2 = 6.6 Hz, 1H, 1-H), 3.23 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H 2-H), 3.20 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H, 2-H)

8-(Naphthalene-2-yl)-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9k). By method F using naphthalene-2-yl boronic acid. Yield 132 mg (55 %) as a off white solid. ^{1}H NMR ($CDCl_3$): 8.20 (d, J = 1.8 Hz, 1H, 7-H), 8.14 (s, 1H, 2'-H), 7.98 (d, J = 9.0, 1H, 4'-H) 7.95-7.87 (m, 5H, Ar-H), 7.84 (dd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, 1H, 9-H), 7.55 (2 × dt, overlapping, J_1 = 8.6 Hz, J_2 = 1.8 Hz, J_3 = 2.8 Hz, 2H, 6'-H, 7'-H), 7.43 (d, J = 9.0, 1H, 3'-H), 7.34-7.26 (m, 3H, Ar-H), 7.21-7.17 (m, 2H, Ar-H), 5.02 (dd, J_1 = 2.4 Hz, J_2 = 6.5 Hz, 1H, 1-H), 3.27 (dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H, 2-H), 3.21 (dd, J_1 = 15.8 Hz, J_2 = 2.4 Hz, 1H, 2-H)

9-Methoxy-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9l). By method A using 7-methoxy-β-naphthol. Yield 10 % (91 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 7.80 (d, J = 9.0 Hz, 1H, 7-H), 7.77 (d, J = 9.1 Hz, 1H, 6-H), 7.32-7.16 (m, 6H, Ar-H), 7.12 (dd, J_1 = 9.0, J_2 = 2.4 Hz, 1H, 8-H), 7.06 (d, J = 2.4 Hz, 1H, 10-H), 4.86 (dd, J_1 = 1.9 Hz, J_2 = 7.0 Hz, 1H, 1-H), 3.81 (s, 3H, OCH_3), 3.24 (dd, J_1 = 15.8 Hz, J_2 = 7.0 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.8 Hz, J_2 = 1.9 Hz, 1H, 2-H)

8-Hydroxy-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9m). By method A using 2,6-dihydroxynaphthalene as β-naphthol. Yield 148 mg (17 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.71 (d, J = 8.9 Hz, 2H, 10-H, 6-H), 7.32 (d, J = 8.9 Hz, 1H, 5-H), 7.29-7.23 (m, 3H, Ph-H), 7.21 (d, J = 2.5 Hz, 1H, 7-H), 7.15-7.11 (m, 2H, Ph-H), 7.11 (dd, J_1 = 8.9 Hz, J_2 = 2.56 Hz, 1H, 9-H), 5.37 (s, 1H, Np-OH), 4.92 (dd, J_1 = 1.6 Hz, J_2 = 6.4 Hz, 1H, 1-H), 3.23 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H, 2-H), 3.17 (dd, J_1 = 15.8 Hz, J_2 = 1.6 Hz, 1H, 1-H)

8-Acetyl-1-phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9n). By method A using 6-acetyl-β-naphthol. Yield 171 mg (17 %) as a white solid. ^{1}H NMR ($CDCl_3$): 8.49 (d, J = 1.9 Hz, 1H, H-7), 8.05 (dd, J_1 = 8.9 Hz, J_2 = 1.9 Hz, 1H, 9-H), 8.02 (d, J = 8.9 Hz, 1H, H-6), 7.87 (d, J = 8.9 Hz, 1H, 10-H), 7.45 (d, J = 8.9 Hz, 1H, 5-H), 7.35-7.24 (m, 3H, Ph-H), 7.15-7.10 (m, 2H, Ph-H), 5.00 (dd, J_1 = 2.2 Hz, J_2 = 6.8 Hz, 1H, 1-H), 3.25 (dd, J_1 = 15.8 Hz, J_2 = 6.8 Hz, 1H, 2-H), 3.21 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H, 2-H), 2.72 (s, 3H, *CH*$_3$-CO)

1-Phenyl-1,2-dihydrobenzo[*f*]chromen-3-one (9o). By Method A . Yield 280 mg (34 %) as a white solid. ^{1}H NMR ($CDCl_3$): 7.89-7.86 (m, 2H, Ar-H), 7.80 (d, J = 8.2 Hz, 1H, Ar-H), 7.50-7.42 (m, 2H, Ar-H), 7.36 (d, J = 9.0 Hz, 1H, Ar-H), 7.29-7.19 (m, 3H, Ar-H), 7.14-7.11 (m, 2H, Ar-H), 4.88 (dd, J_1 = 2.4 Hz, J_2 = 6.7 Hz, 1H, 1-H), 3.22 (dd, J_1 = 15.6 Hz, J_2 = 6.7 Hz, 1H, 2-H), 3.16 (dd, J_1 = 15.6 Hz, J_2 = 2.4 Hz, 1H, 2-H)

8-Bromo-1-phenyl-1,2-4*H*-dihydrobenzo[*f*]quinolin-3-one (12). 8-Bromo-β-naphthylamine (1.7 mmol), which was prepared according to a literature procedure[a] starting from 8-bromo-2-naphthoic acid, was treated with cinnamoyl chloride (2.6 mmol) and triethyl amine (3.0 mmol) in refluxing toluene for 3 h. Evaporation and subsequent flash chromatography yielded 8-bromo-β-naphthylcinnamide. Cyclization of the cinnamide was carried out in polyphosphoric acid (1:20 ratio) at 140 °C for 2h. After cooling, the reaction mixture was diluted with saturated sodium bicarbonate solution and *tert*-butylmethylether. The aqueos phase was extracted thrice with dichloromethane and the combined organic layers were washed with sodium bicarbonate solution, dried, and concentrated. Flash chromatography of the residue furnished the desired product as an off-white solid. Yield 50 mg (8 %, over two steps). ^{1}H-NMR (DMSO-d^6): 10.41 (s, 1H, NH), 8.18 (d, J = 1.6 Hz, 1H, 7-H), 7.83 (d, J = 8.8 Hz, 1H, 6-H), 7.77 (d, J = 9.0 Hz, 1H, 10-H), 7.52 (dd, J_1= 9.0 Hz, J_2= 1.6 Hz, 1H, 9-H), 7.40-7.16 (m, 4H, Ar-H), 7.11 (overlapping d, 2H, Ar-H and 5-H), 5.01 (d, J = 7.1 Hz, 1H, 1-H), 3.19 (dd, J_1 = 16.2 Hz, J_2 = 7.1 Hz, 1H, 2-H), 2-62 (d, J_1 = 16.2, 1H, 2-H)

[a] Pfister, J.R., Wymann, W.E. A Useful Variant of the Curtius Reaction. *Synthesis* **1983**, 38-40

2. HPLC analysis of purity

All HPLC runs were performed on a JASCO HPLC system under isocratic conditions. HPLC A refers to a Luna 5µ Phenylhexyl column (25 cm × 4.6 mm, 5 µm; Phenomenex) and acetonitrile/water mixtures (eluent A, in v/v). HPLC B refers to a Synergi Max-RP column (15 cm × 4.6 mm, 4 µm; Phenomenex) and methanol/water mixtures (eluent B, in v/v). The concentrations of the compounds were about 100 µM, injection volumes were 30 µL, flow was 1 mL/min and detection was performed with UV (254 nm).

Compound	R_t HPLC A (% purity)	Eluent A	R_t HPLC B (% purity)	Eluent B
5f	6.76 (>97)	80/20	19.43 (>97)	70/30
5g	6.73 (98)	80/20	22.73 (>98)	70/30
5h	10.19 (>97)	80/20	23.55 (98)	70/30
5j	6.88 (>97)	80/20	24.58 (98)	70/30
5q	7.85 (>98)	80/20	29.83 (>98)	70/30
5r	10.40 (>95)	60/40	12.83 (>95)	70/30
8a	5.64 (>98)	80/20	5.90 (>98)	85/15
(*R*)-**8a**	21.58 (>99)	60/40	27.18 (>99)	70/30
(*S*)-**8a**	22.00 (>99)	60/40	27.43 (>99)	70/30
8c	6.93 (>96)	80/20	21.43 (>96)	70/30
(*R*)-**8c**	7.183 (>99)	80/20	22.43 (>98)	70/30
(*S*)-**8c**	7.28 (98)	80/20	22.46 (>99)	70/30
8d	6.98 (>95)	80/20	5.59 (>96)	85/15
8e	7.12 (>97)	80/20	5.83 (>98)	85/15
8f	6.28 (>99)	80/20	16.87 (>99)	70/30
8g	6.14 (98)	65/35	5.43 (>98)	85/15
8h	7.68 (>97)	80/20	23.68 (>97)	70/30
8i	4.21 (98)	80/20	6.40 (>98)	70/30
8j	8.63 (>98)	80/20	7.46 (98)	85/15
8k	4.00 (>98)	80/20	8.30 (>98)	70/30
8l	27.54 (>96)	65/35	28.38 (>97)	70/30
9a	9.73 (>97)	80/20	19.88 (99)	70/30
9b	7.48 (>96)	80/20	20.42 (>95)	70/30
9c	4.81 (>98)	80/20	4.59 (97)	70/30
9d	7.56 (>99)	80/20	23.06 (>98)	70/30
9e	7.92 (>97)	80/20	6.50 (>96)	85/15
9f	4.80 (>98)	80/20	8.21 (>99)	70/30
9g	5.16 (>99)	80/20	11.83 (>99)	70/30
9h	4.63 (99)	80/20	4.25 (>97)	70/30
9i	4.39 (>97)	80/20	17.44 (>99)	70/30
9j	11.23 (>98)	80/20	11.87 (>98)	85/15
9k	10.13 (>98)	80/20	9.32 (>98)	85/15
9m	7.96 (>99)	50/50	5.26 (>99)	70/30
9n	4.07 (>99)	63/35	11.04 (>99)	70/30
12	21.36 (>96)	50/50	14.72 (>96)	70/30

3. HPLC analysis of enantiomeric excess

Chiral HPLC. For the determination of the enantiomeric excess (ee), chiral HPLC was carried out using a YMC CHIRAL NEA (R) column (25 cm × 4.6 mm, 5 μm), flow rate 0.7 mL/min, temperature 5° C, sample concentration 1 mg/mL, injection volume 5 μL, detection UV (254 nm) and acetonitrile/water 50/50 (v/v), isocratic, as eluent.

Compound	**R_t**	**ee (%)**
(*R*)-**8a**	30.84	97.7
(*S*)-**8a**	32.32	98.2
(*R*)-**8c**	42.86	98.9
(*S*)-**8c**	44.83	98.6

4. Competition analysis

Figure 1

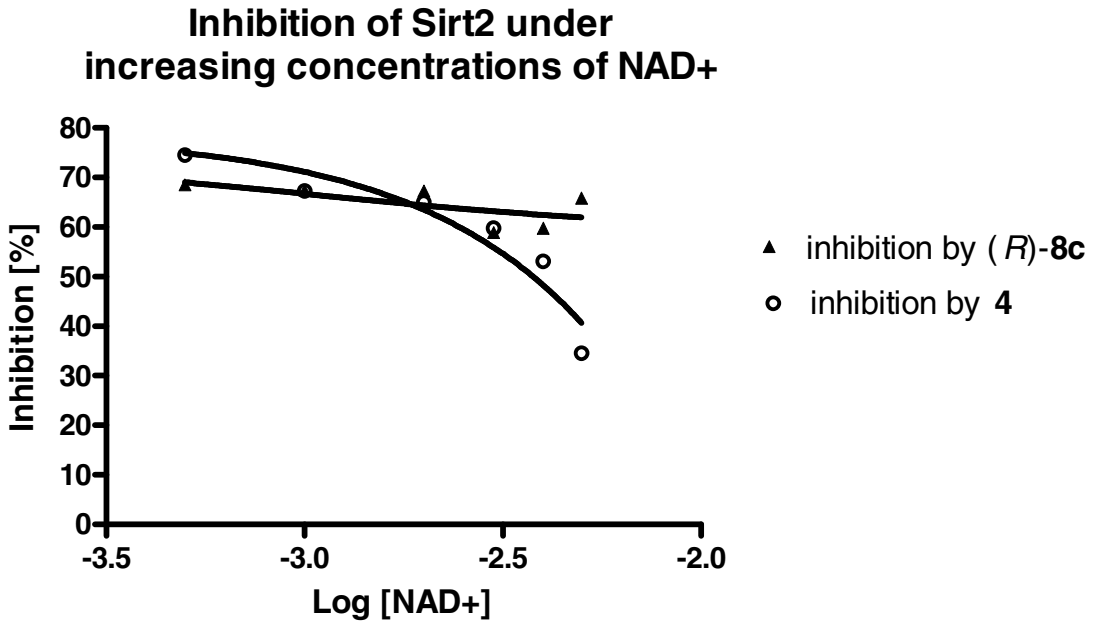


Figure 1: The inhibition of (*R*)-**8c** was determined using increasing concentrations of NAD^+ (500, 1000, 2000, 3000, 4000 and 5000 µM) whereas the concentration of the acetylated substrate (10.5 µM), the inhibitor (3 µM) and the amount of enzyme was kept constant in all samples. Figure 1 also shows the same experiment carried out for the bisindolylmaleinimide **4**[a] which, in contrast, was shown to be competitive in respect to NAD^+.

[a] data taken from Trapp, J., Jochum, A., Meier, R., Saunders, L., Marshall, B., Kunick, C., Verdin, E., Goekjian, P., Sippl, W., Jung, M.; Adenosine mimetics as inhibitors of NAD^+-dependent histone deacetylases, from kinase to sirtuin inhibition. *J Med Chem* **2006**, *49*, 7307-7316. In this paper **4** is called **12j**.

5. Tubulin hyperacetylation

Figure 2

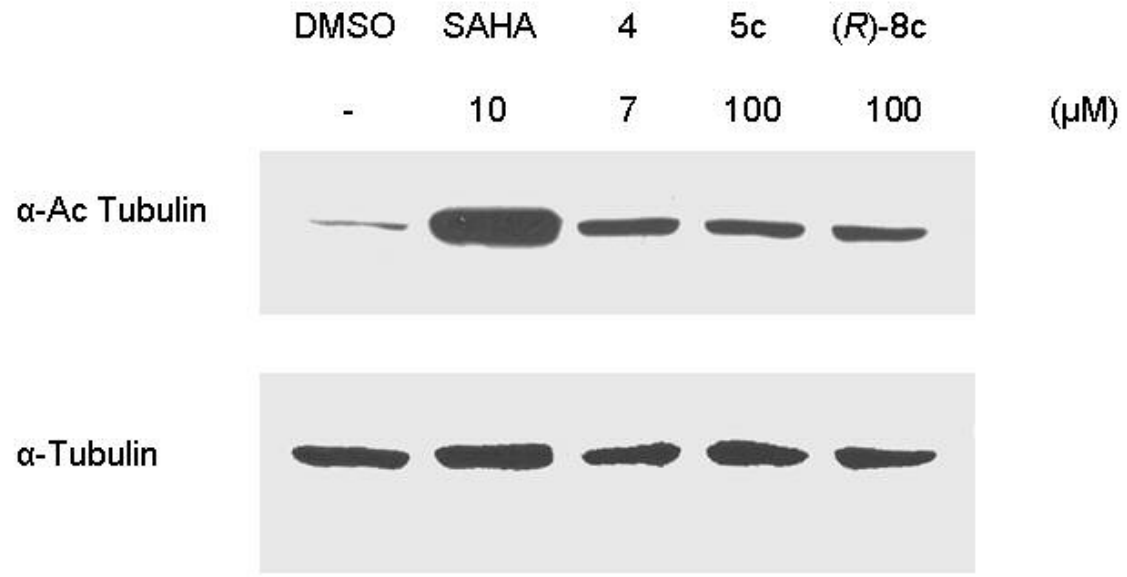
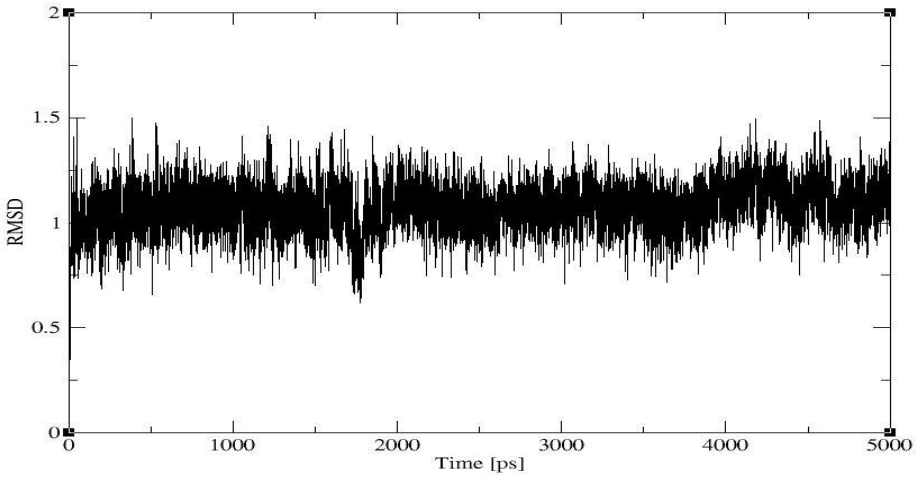


Figure 2. The experiments were performed as outlined in the experimental section of the main paper. Class I/II-HDAC inhibitor SAHA and sirtuin inhibitor **4** served as positive controls. Upper panel: tubulin acetylation. Lower panel: total tubulin levels (protein loading controls).

6. Modelling Results

Figure 3

(A)



(B)

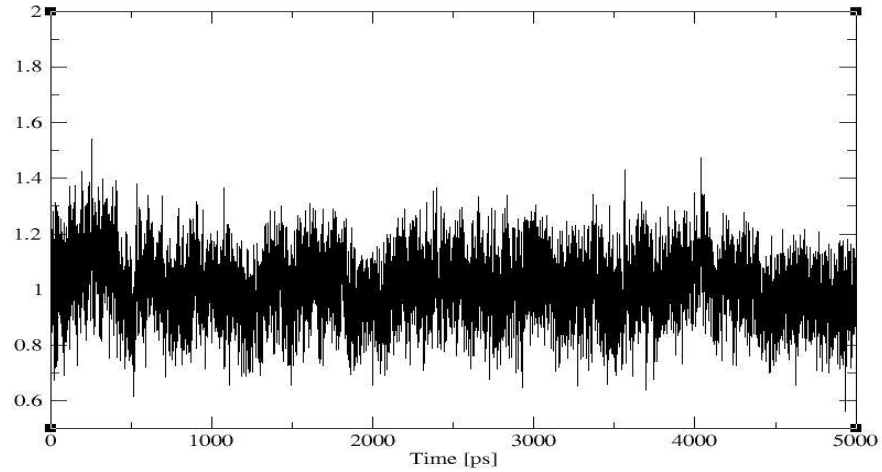
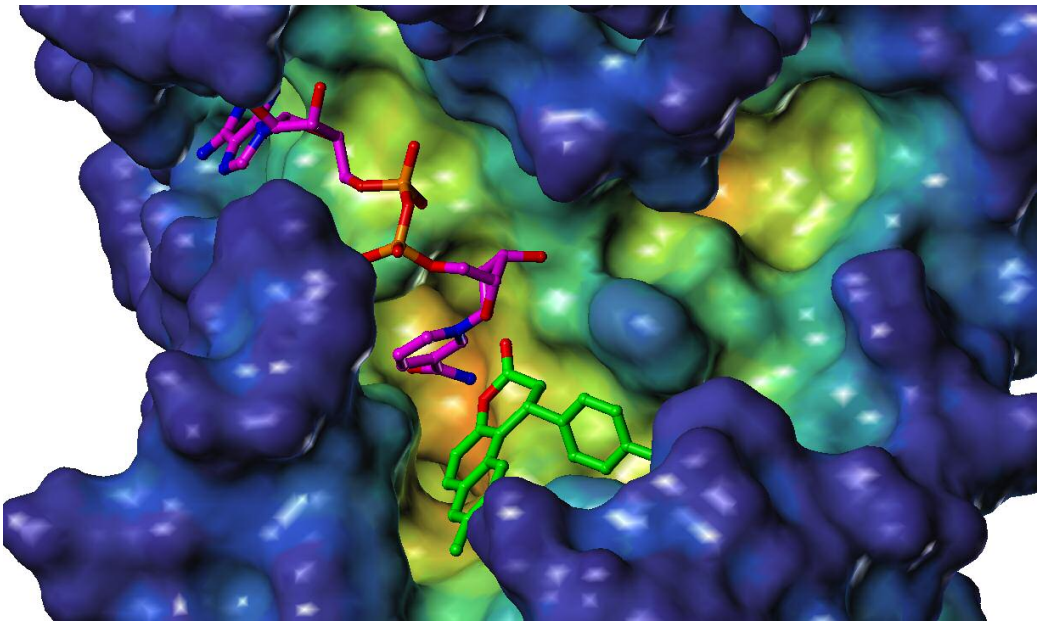


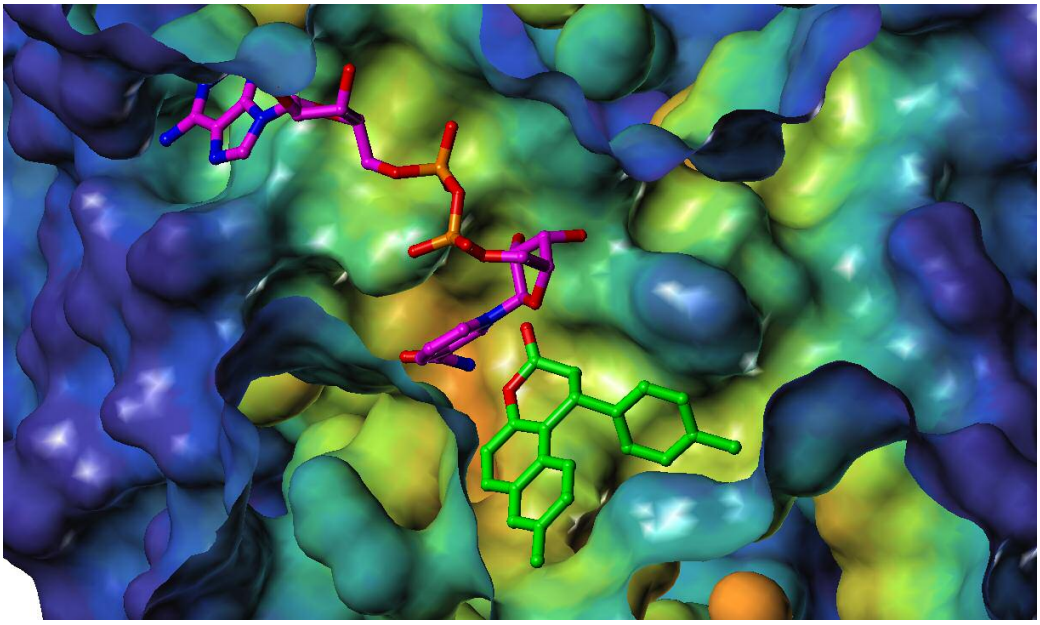
Figure 3. Analysis of the MD simulations of Sirt2 complexed with *(R)*-**8a** (A) and *(S)*-**8a** (B). RMSD between the heavy atoms of the starting X-ray structures and the complexes are given for the free 5ns MD.

Figure 4

(A)



(B)



Figures 4a and 4b. Comparison of the interaction of *(R)*-**8c** (green) and NAD^+ (magenta) at the Sirt2 binding pocket. The NAD^+ conformation was taken from the X-ray structure of the bacterial sirtuin homolog Sir2-Af2 (1YC2.pdb). a) The molecular surface is colored according the cavity depth (blue = surface, orange = buried). b) The molecular surface of the pocket is displayed in sliced mode.

Figure 5.

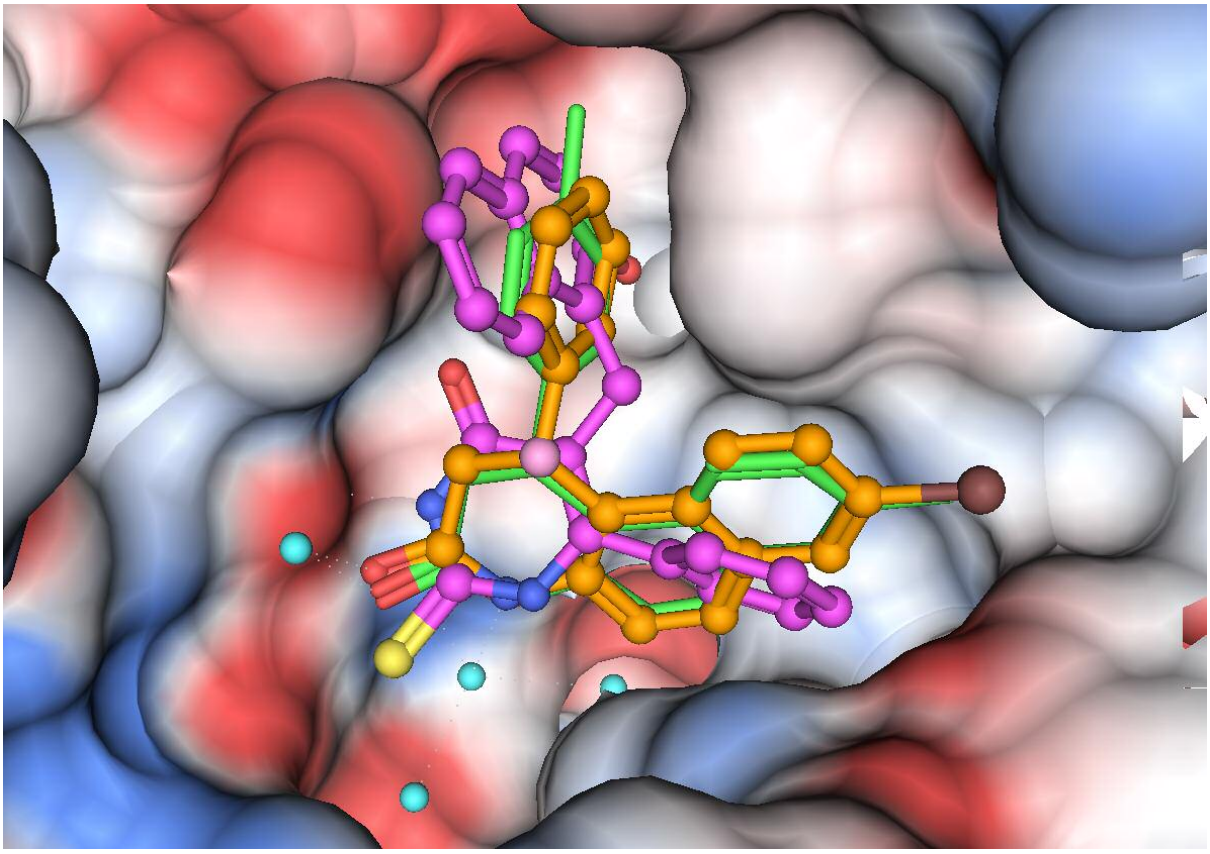


Figure 5. Comparison of the docking results obtained for the lactone *(R)*-**8c** (green), the lactam **12** (orange) and cambinol (magenta). Both inhibitors are interacting by hydrogen bonding to water molecules and Gln167 at Sirt2.

6. Elemental analysis data

Compound	Formula	Calculated	Found
5a	$C_{19}H_{13}BrO_2$	C, 64.61; H, 3.71	C, 64.70; H, 3.76
5b	$C_{19}H_{12}BrClO_2$	C, 58.87; H, 3.12	C, 58.89; H, 2.92
5c	$C_{20}H_{15}BrO_2$	C, 65.41; H, 4.12	C, 64.66; H, 4.15
5d	$C_{20}H_{15}BrO_3$	C, 62.68; H, 3.94	C, 61.33; H, 3.92
5e	$C_{19}H_{11}Cl_2O_2$	C, 54.06; H, 2.63	C, 54.06; H, 2.71
5i	$C_{19}H_{12}BrFO_2$	C, 61.48; H, 3.26	C, 61.37; H, 3.37
5k	$C_{23}H_{21}BrO_2$	C, 67.49; H, 5.17	C, 67.54; H, 5.34
5l	$C_{20}H_{15}BrO_3$	C, 62.68; H, 3.95	C, 62.38; H, 3.97
5m	$C_{20}H_{14}BrClO_2$	C, 59.80; H, 3.51	C, 59.51; H, 3.51
5n	$C_{20}H_{14}BrFO_2$	C, 62.36; H, 3.66	C, 62.54; H, 3.66
5o	$C_{21}H_{17}BrO_3$	C, 63.49; H, 4.31	C, 63.57; H, 4.37
5p	$C_{13}H_9BrO_2$	C, 56.35; H, 3.27	C, 56.30; H, 3.12
9l	$C_{20}H_{16}O_3$	C, 78.93; H, 5.30	C, 78.94; H, 5.39
9o	$C_{19}H_{14}O_3$	C, 83.19; H, 5.14	C, 83.23; H, 5.11