Supporting Information

Novel Cambinol Analogs as Sirtuin Inhibitors: Synthesis, Biological Evaluation and Rationalization of Activity

Federico Medda,[1] Rupert J.M. Russell,[2] Maureen Higgins,[3] Anna R. McCarthy,[1,3] Johanna Campbell,[3] Alexandra M.Z. Slawin,[1] David P. Lane,[3] Sonia Lain,[3]* and Nicholas J. Westwood[1]*

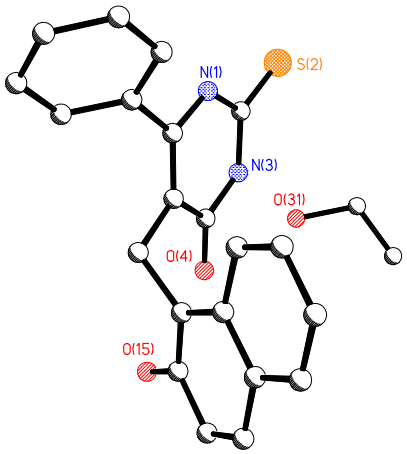


Figure S1: Crystal structure of cambinol (**1**) determined by X-ray crystallography. Crystallization was carried out by slow evaporation from ethanol.

Identification of reaction side products.

The low yields observed in the synthesis of the n1-substituted analogs were rationalized by a competing decomposition pathway of **5a** that resulted in the formation of splitomicin and benzoic acid. On one occasion both of these compounds were purified from the crude reaction mixture by column chromatography and characterized (see Figures S2 and S3).

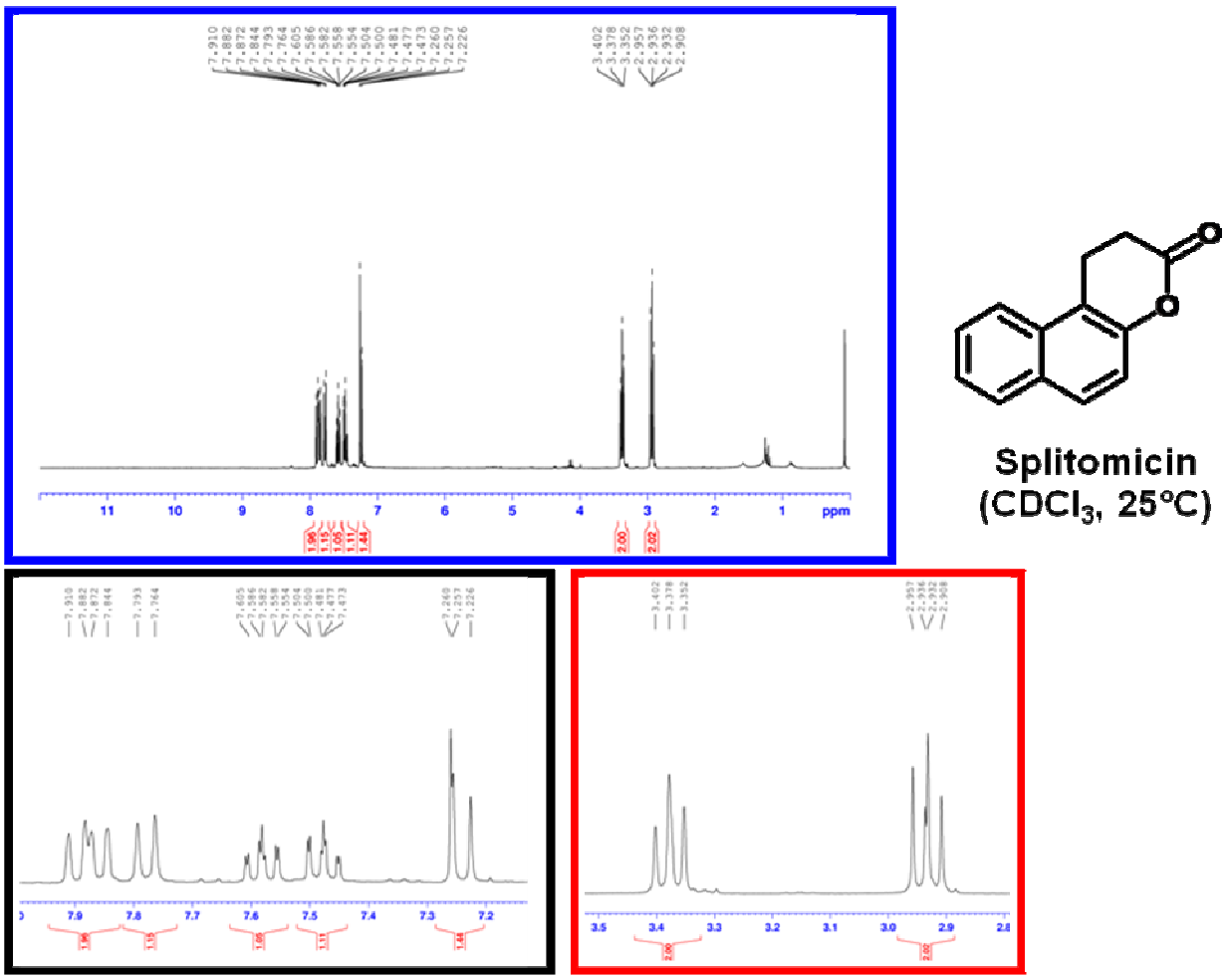


Figure S2: ^{1}H NMR spectrum of Splitomicin (blue) with expansions of the aromatic (black) and aliphatic regions of the same spectrum (red).

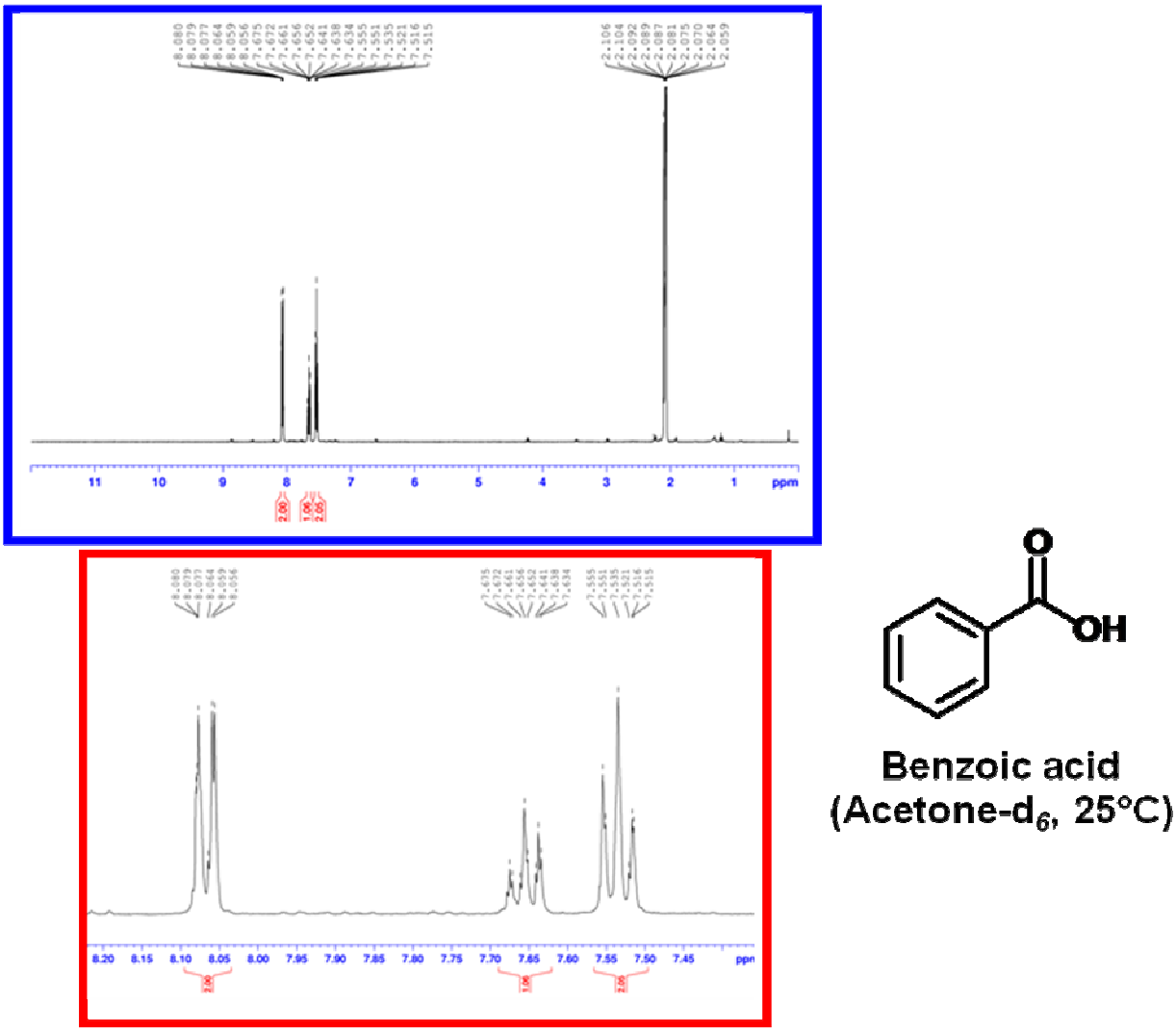


Figure S3: ^{1}H NMR spectrum of benzoic acid (blue) and expansion of the aromatic region of the same spectrum (red).

Proof of structure (selected spectra).

The structures of compounds **6e-j** were assigned using a range of 1D and 2D NMR techniques. For example, a 2D [^{1}H-^{13}C] HMBC experiment (Figure S5a; for ^{1}H NMR spectrum of **6e** see Figure S4) showed that methyl protons of the NMe group in **6e** were coupled to the thiocarbonyl carbon and a second carbon corresponding to the signal observed at 152ppm (Figure S5b). Importantly the carbon atom associated with this signal also coupled to the *ortho*-proton of the phenyl ring in **6e** supporting the assignment of **6e** as the *N*1Me (rather than the *N*3Me) isomer (Figure S5c).

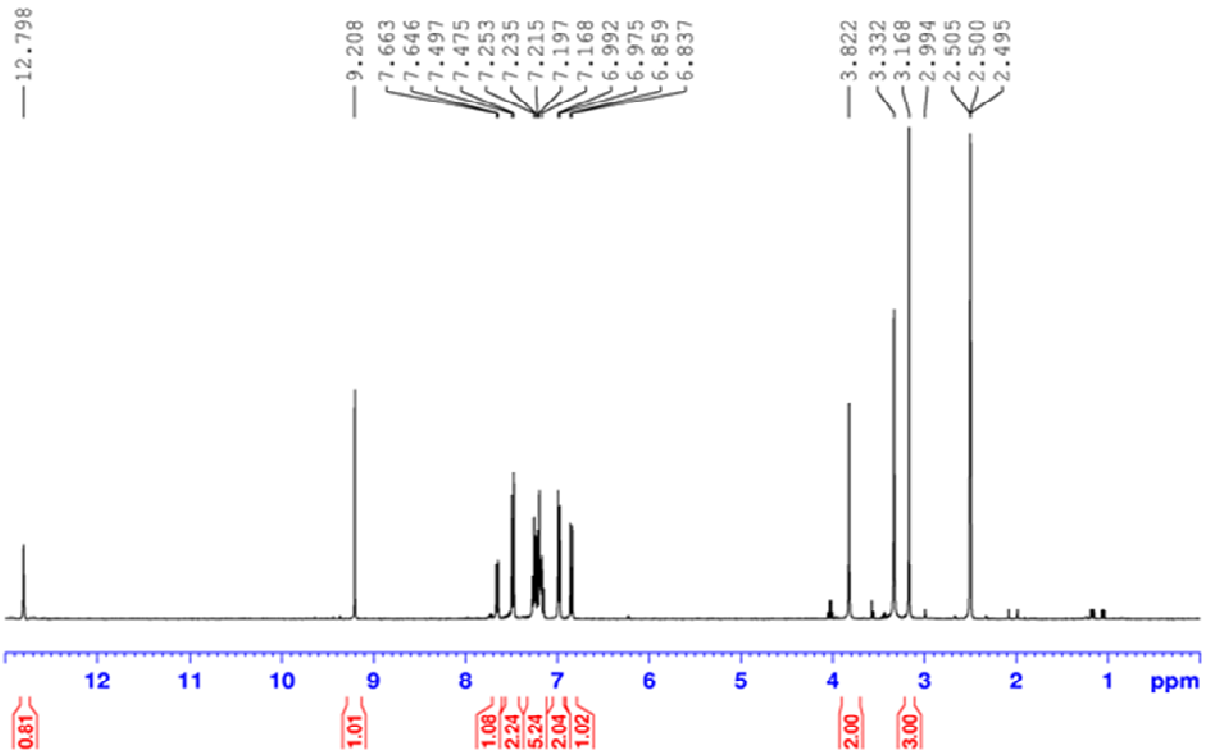


Figure S4: [1]H NMR spectrum of analog **6e** (DMSO-d_6).

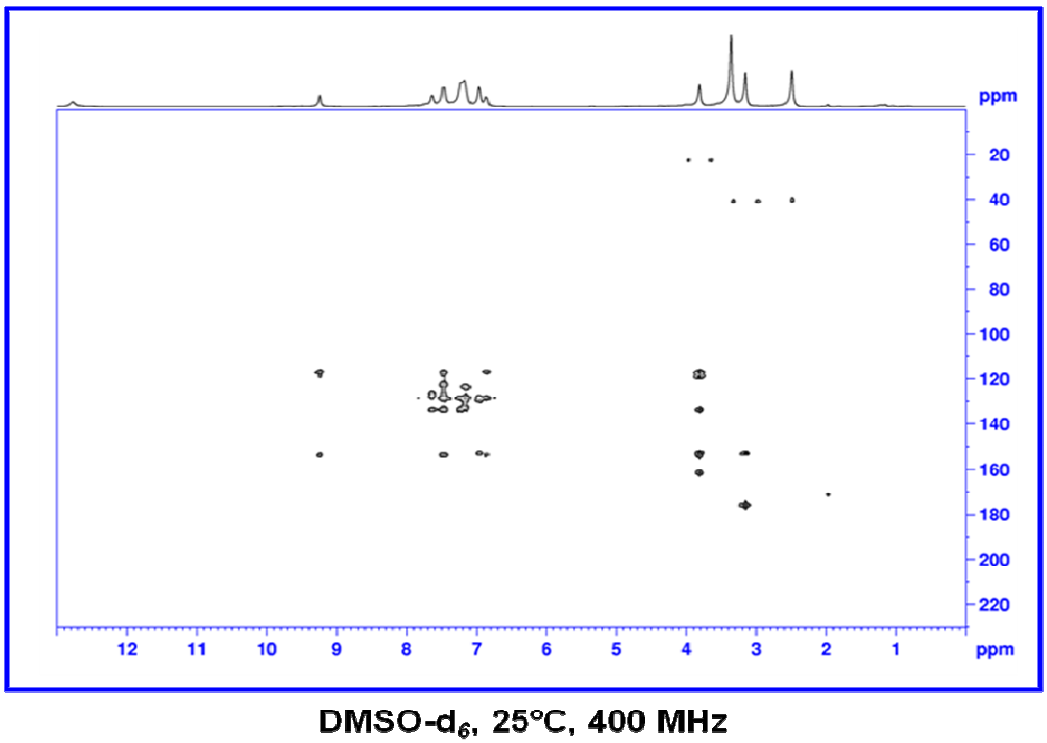


Figure S5a: [^{1}H-^{13}C] HMBC spectrum of analog **6e.**

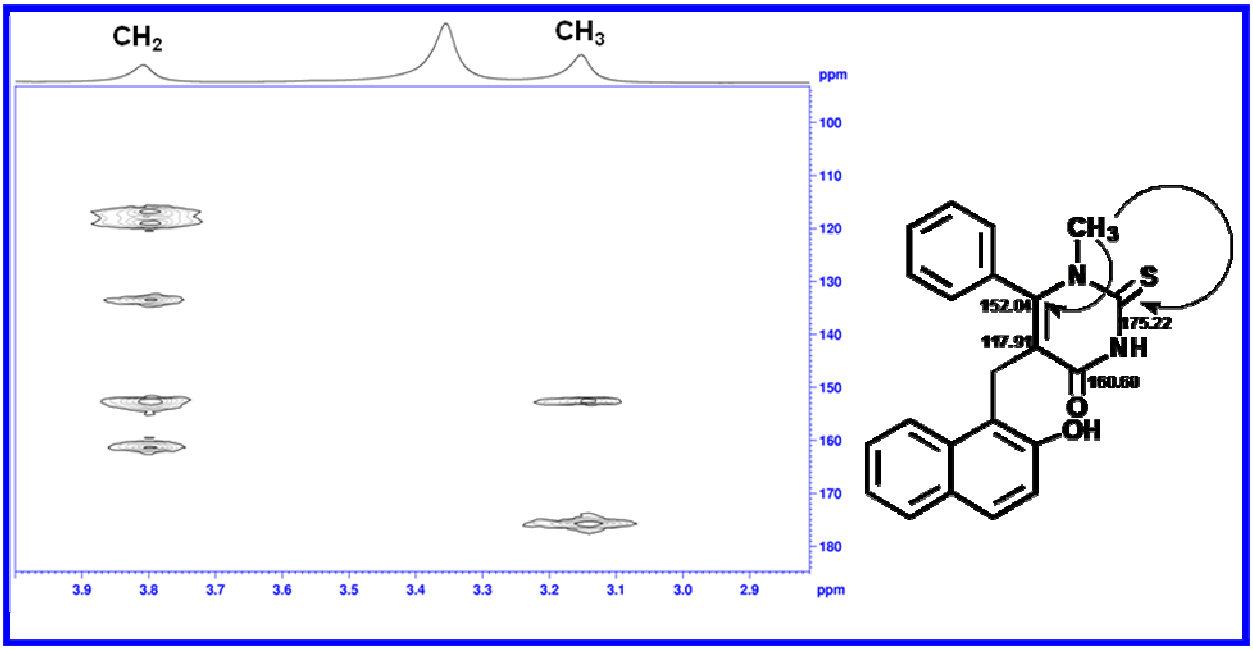


Figure S5b: Expansion of the [^{1}H-^{13}C] HMBC spectrum of compound **6e**. Correlations between the protons of the methyl group (s, 3.14 ppm), the signal derived from the thiocarbonyl functionality (174 ppm) and the quaternary carbon at 152 ppm were observed.

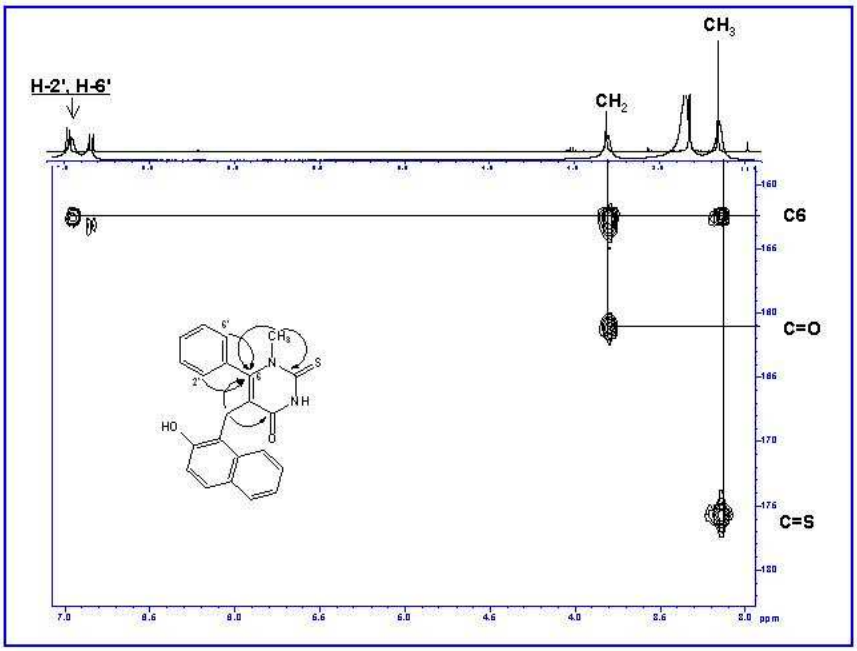


Figure S5c: Expansion of the [^{1}H-^{13}C] HMBC spectrum of compound **6e**. The *ortho*-protons of the phenyl ring correlate with the quaternary carbon at 152 ppm in an analogous manner to the NMe protons, a situation that can only be achieved if **6e** is the *N*1 (not the *N*3) isomer.

For the other analogs in this series, the spectra were further complicated at room temperature by restricted rotation about the *N*1CH_2 bond. Use of elevated temperatures for the NMR analysis alleviated this problem as exemplified below in Figures S6-S9 for **6f** and **6g**.

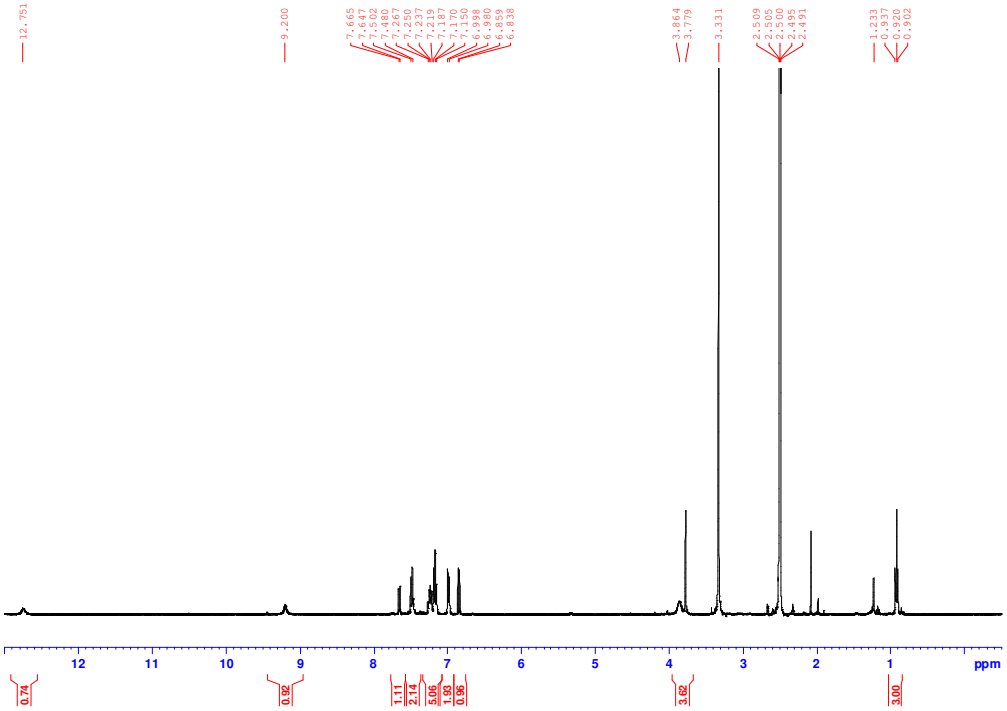


Figure S6: ^{1}H NMR spectrum of compound **6f** (DMSO-d_6).

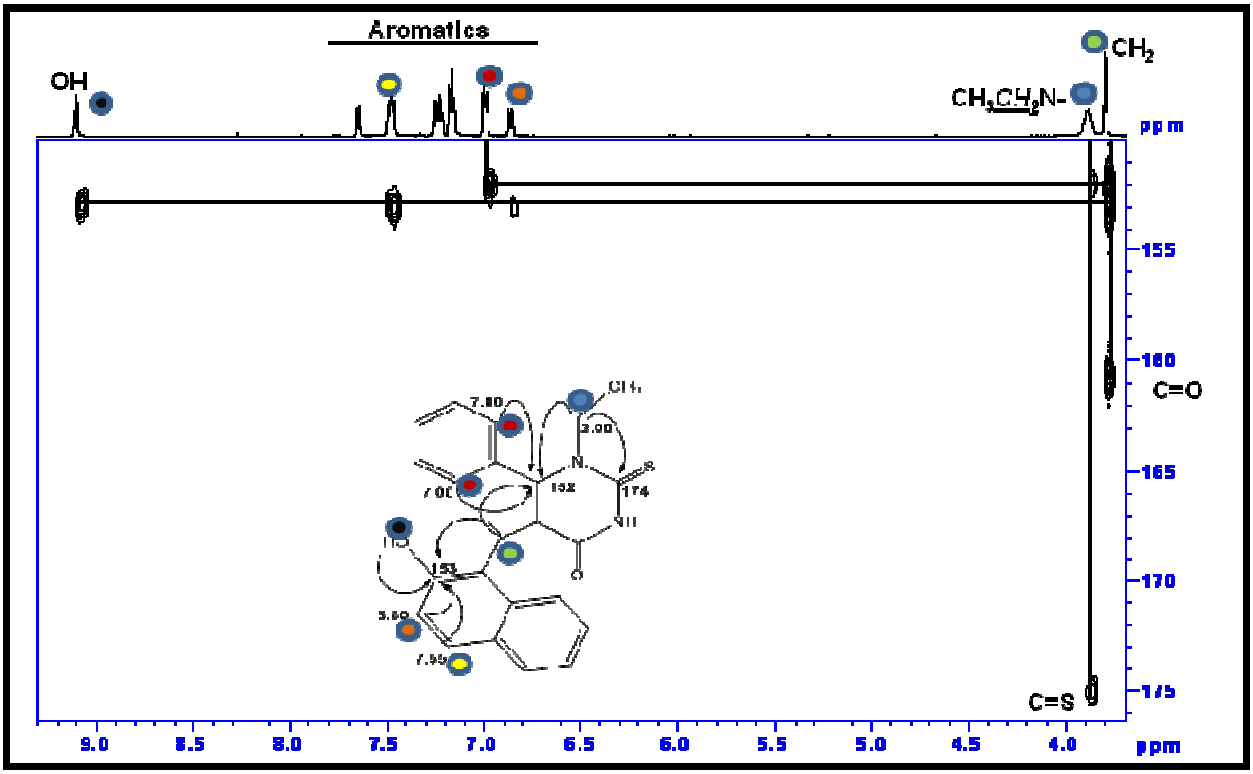


Figure S7: Expansion of the [^{1}H-^{13}C] HMBC spectrum of analog **6f.** Correlations between the protons of the C1''' of the ethyl group (brs, 3.90 ppm), the signal derived from the thiocarbonyl functionality (174 ppm) and the quaternary carbon (152 ppm) were observed.

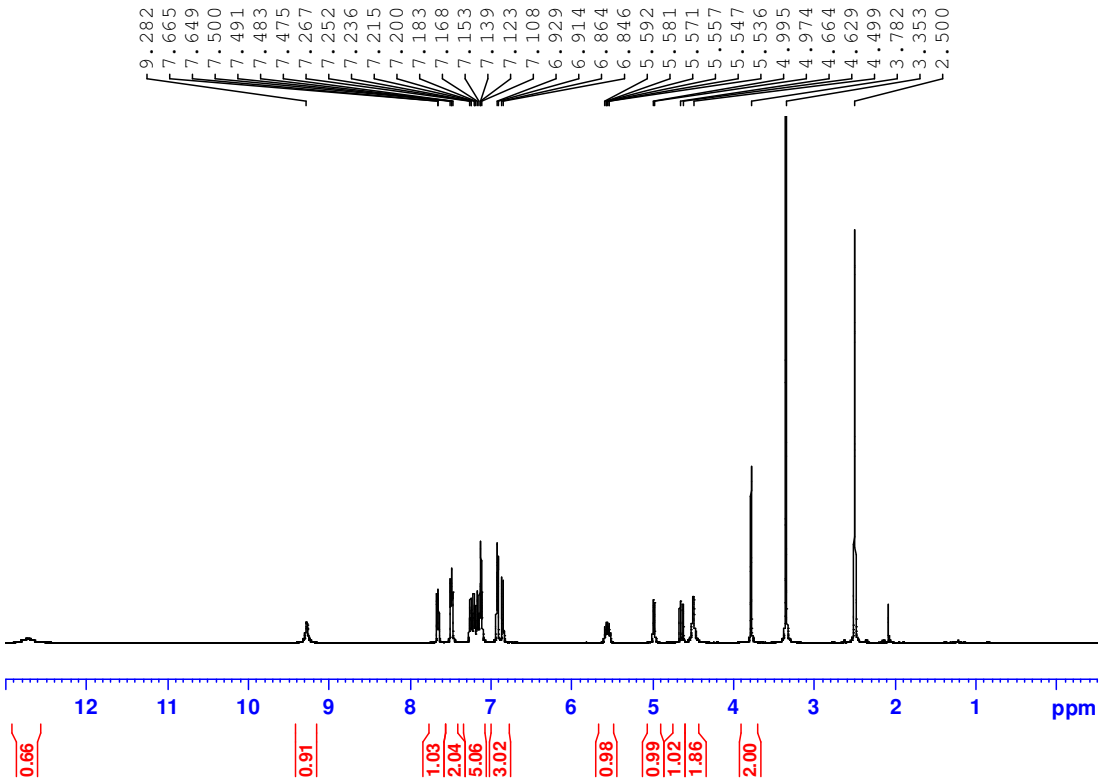


Figure S8: ^{1}H NMR spectrum of analog **6g** (DMSO-d_6).

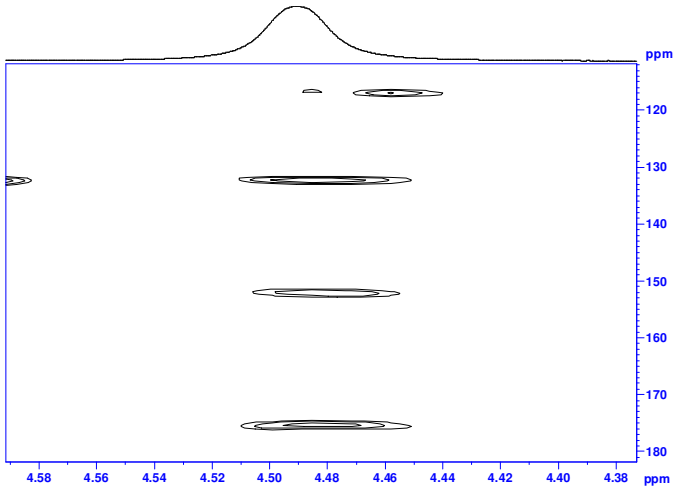


Figure S9: Expansion of the [^{1}H-^{13}C] HMBC spectrum of compound **6g** in DMSO-d_6. Correlations between the protons of the C1''' of the ethyl group (brs, 4.48 ppm), the signal derived from the thiocarbonyl functionality (176 ppm) and the quaternary carbon (152 ppm) were observed.

Parallel Synthesis Approach

Synthesis of 4i-4xviii

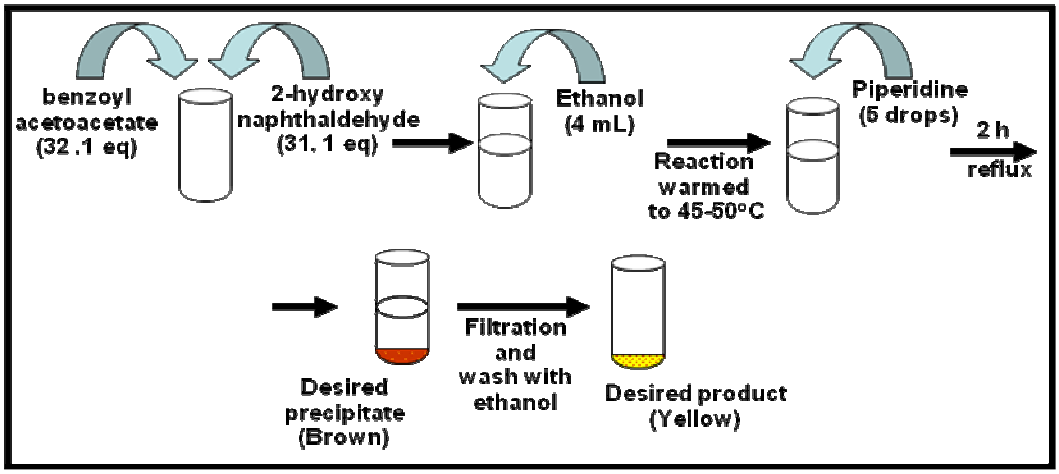


Figure S10: A schematic representation of the procedure followed in the first step of the parallel synthesis of cambinol analogs.

General protocol for the synthesis of 2-benzoyl-benzo[*f*]coumarins: Different phenyl substituted ethyl benzoylacetate **3i-xix** (0.48 mL, 1 eq) and 2-hydroxy-1-naphthaldehyde **2** (430 mg, 1 eq) were mixed together into different vessels of the parallel synthesis apparatus and ethanol (4 mL) added. The reaction was warmed to 50 °C and piperidine (5 drops) added to each vessel. The reaction was heated under reflux for 2 h and the solid products were collected by parallel filtration and washed with ethanol.

Compound	R_1	Yield (%)
4b	*p*-Br-Ph	93
4i	*o*-CH_3-Ph	79
4ii	*m*-CH_3-Ph	66
4iii	*p*-CH_3-Ph	62
4iv	*p*-Cl-Ph	74
4v	*p*-I-Ph	98
4vi	*p*-CF_3-Ph	77
4vii	*o*-Br-Ph	76
4viii	*m*-Br-Ph	83
4ix	*m*-Cl-Ph	87
4x	*o*-F-Ph	86
4xi	*m*-F-Ph	79
4xii	*p*-F-Ph	84
4xiii	*m*-I-Ph	80
4xiv	*m*-NO_2-Ph	80
4xv	furyl-	45
4xvi	*o*-Cl-Ph	83
4xvii	*o*-I-Ph	80
4xviii	*o*-NO_2-Ph	98
4xix	pyridyl-	Failed

Table S1: Yields observed for the products of the first step of the parallel synthesis.

2-(5'-Bromobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4b): Yielded 600 mg (1.58 mmol, 93%) as a yellow powder. Analytical data was consistent to that previously found for **4b** (see page S3).

2-(3'-Methylbenzoyl)-3*H*-benzo[*f*]chromen-3-one (4i): Yielded 624 mg (1.98 mmol, 79%) as a yellow powder. Mp 208-210 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.02 (s, 1H, H-1), 8.27 (d, 1H, *J* = 8.2 Hz, H-10), 8.12 (d, 1H, *J* = 9.0 Hz, H-6), 7.95 (d, 1H, *J* = 7.6 Hz, H-7), 7.77-7.71 (m, 1H, H-9), 7.66-7.60 (m, 1H, H-8), 7.54-7.46 (m, 2H, H-5, ArH), 7.47-7.40 (m, 1H, ArH), 7.36-7.31 (m, 1H, ArH), 7.26 (m, 1H, overlapped with solvent signal, ArH), 2.55 (s, 3H, CH_3). LRMS [ES]$^+$: *m/z* 337.11 [M+Na]$^+$ (100%).

2-(4'-Methylbenzoyl)-3*H*-benzo[*f*]chromen-3-one (4ii): Yielded 280 mg (0.89 mmol, 36%) as a yellow powder. Mp 194-196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.91 (s, 1H, H-1), 8.27 (d, 1H, *J* = 8.4 Hz, H-10), 8.11 (d, 1H, *J* = 9.1 Hz, H-6), 7.96 (d, 1H, *J* = 7.6 Hz, H-7), 7.78-7.66 (m, 3H, H-9 + 2×ArH), 7.66-7.62 (m, 1H, H-8), 7.53 (d, 1H, *J* = 9.1 Hz, H-5), 7.47-7.34 (m, 2H, ArH), 2.42 (s, 3H, CH_3). LRMS [ES]$^+$: *m/z* 337.11 [M+Na]$^+$ (100%).

2-(5'-Methylbenzoyl)-3*H*-benzo[*f*]chromen-3-one (4iii) [S1, S2]: Yielded 490 mg (1.56 mmol, 62%) as a yellow powder. Mp 190-192 °C (*lit* [S2, S7] 190-191 °C). IR (KBr) ν_{max}/cm^{-1}: 1745 (CO), 1224, 1147, 1139 (C-O), 1678 (C-Cl). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.89 (s, 1H, H-1), 8.26 (d, 1H, *J* = 8.2 Hz, H-10), 8.10 (d, 1H, *J* = 9.0 Hz, H-6), 7.95 (d, 1H, *J* = 8.1 Hz, H-7), 7.83 (d, 2H, AA'BB' system, *J* = 8.0 Hz, H-3', H-7'), 7.76-7.71 (m, 1H, H-9), 7.66-7.60 (m, 1H, H-8), 7.52 (d, 1H, *J* = 9.0 Hz, H-5), 7.30 (d, 2H, AA'BB' system, *J* = 8.0 Hz, H-4', H-6'), 2.44 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 191.7 (C1'), 158.7 (C3), 155.3 (C4a), 144.8 (C5'), 141.5 (C1), 135.3 (C6), 133.8 (C2'), 130.3 (C6a), 129.9 (C3', C7'), 129.4 (C2', C6'), 129.3 (C10a), 129.1 (C7), 128.7 (C9), 126.6 (C2), 126.4 (C8), 121.5 (C10), 116.6 (C5), 112.9 (C10b). HRMS [ES]$^+$: *m/z* calc'd for $C_{21}H_{14}ONa$ 337.0935 [M+Na]$^+$, found 337.0928 (-2.0 ppm).

2-(5'-Chlorobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4iv) [S1, S2]: Yielded 614 mg (1.83 mmol, 74%) as a yellow powder. Mp 230-233 °C (*lit.* [S2, S7] 232-233 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.97 (s, 1H, H-1), 8.28 (d, 1H, *J* = 8.3 Hz, H-10), 8.12 (d, 1H, *J* = 9.0 Hz, H-6), 7.96 (d, 1H, *J* = 7.8 Hz, H-7), 7.86 (d, 2H, AA'BB' system, *J* = 8.9 Hz, H-3', H-7'), 7.78-7.70 (m, 1H, H-9), 7.66-7.60 (m, 1H, H-8), 7.52 (d, 1H, *J* = 9.0 Hz, H-5), 7.47 (d, 2H, AA'BB' system, *J* = 8.9 Hz, H-4', H-6'). LRMS [ES]$^+$: *m/z* 357.03 [M+Na]$^+$ (100%).

2-(5'-Iodobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4v): Yielded 874 mg (2.05 mmol, 82%) as a yellow powder. Mp 249-252 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.97 (s, 1H, H-1), 8.28 (d, 1H, *J* = 8.3 Hz, H-10), 8.13 (d, 1H, *J* = 9.0 Hz, H-6), 7.96 (d, 1H, *J* = 8.0 Hz, H-7), 7.86 (d, 2H, AA'BB' system, *J* = 8.5 Hz, H-3', H-7'), 7.78-7.70 (m, 1H, H-9), 7.67-7.61 (m, 3H, H-8, AA'BB' system, *J* = 8.5 Hz, H-4', H-6'), 7.52 (d, 1H, *J* = 9.0 Hz, H-5). LRMS [ES]$^+$: *m/z* 449.04 [M+Na]$^+$ (100%).

2-(5'-Trifluoromethylbenzoyl)-3*H*-benzo[*f*]chromen-3-one (4vi): Yielded 707 mg (1.92 mmol, 77%) as a yellow powder. Mp 192-195 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.00 (s, 1H, H-1), 8.30 (d, 1H, *J* = 8.3 Hz, H-10), 8.14 (d, 1H, *J* = 9.0 Hz, H-6), 7.99 (d, 2H, AA'BB' system, *J* = 8.0 Hz, H-3', H-7'), 7.96 (d, 1H, *J* = 8.7 Hz, H-7), 7.79-7.72 (m, 3H, H-9, AA'BB' system, *J* = 8.0 Hz, H-4', H-6'), 7.68-7.64 (m, 1H, H-8), 7.53 (d, 1H, *J* = 9.0 Hz, H-5). LRMS [ES]$^+$: *m/z* 391.09 [M+Na]$^+$ (100%).

2-(3'-Bromobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4vii): Yielded 761 mg (2.01 mmol, 76%) as a yellow powder. Mp 238-240 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.27 (s, 1H, H-1), 8.36 (d, 1H, *J* = 8.3 Hz, H-10), 8.13 (d, 1H, *J* = 8.8 Hz, H-6), 7.95 (d, 1H, *J* = 7.8 Hz, H-7), 7.80-7.71 (m, 1H, H-9), 7.63 (m, 2H, H-8, ArH), 7.55-7.43 (m, 3H, H-5 + 2×ArH), 7.41-7.36 (m, 1H, ArH). LRMS [ES]$^+$: *m/z* 401.05 [M+Na]$^+$ (100%).

2-(4'-Bromobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4viii): Yielded 785 mg (2.07 mmol, 83%) as a yellow powder. Mp 213-215 °C. IR (KBr) ν_{max}/cm^{-1}: 1708 (CO), 1275, 1210 (C-O), 750, 666 (C-Br). ^{1}H NMR ($CDCl_3$, 400 MHz): 8.98 (s, 1H, H-1). 8.29 (d, 1H, *J* = 8.3 Hz, H-10), 8.13 (d, 1H, *J* =

9.0 Hz, H-6), 8.04 (t, 1H, *J* = 1.8 Hz, H-3'), 7.96 (d, 1H, *J* = 8.1 Hz, H-7), 7.84-7.79 (m, 1H, ArH), 7.78-7.72 (m, 2H, H-9, ArH), 7.66-7.50 (m, 1H, H-8), 7.53 (d, 1H, *J* = 9.0 Hz, H-5), 7.37 (t, 1H, *J* = 7.8 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 192.3 (C1'), 158.3 (C3), 156.5 (C4a), 143.7 (C1), 140.8 (C4'), 136.5 (C6), 133.1 (Ar), 132.1 (Ar), 130.4 (C6a), 129.7 (Ar), 129.4 (C9), 129.3 (C7) , 129.2 (C10a), 127.8 (Ar), 126.8 (C8), 123.7 (C2), 122.8 (C10), 119.6 (C2'), 116.9 (C5), 113.2 (C10b). HRMS [ES]$^+$: *m/z* calc'd for $C_{20}H_{11}O_3Na^{79}Br$ 400.9789 [M+Na]$^+$, found 400.9786 (-0.8 ppm); *m/z* calc'd for $C_{20}H_{11}O_3Na^{81}Br$ 402.9769 [M+Na]$^+$, found 402.9785 (-1.9 ppm).

2-(4'-Chlorobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4ix): Yielded 722 mg (2.16 mmol, 87%) as a yellow powder. Mp 228-230 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.98 (s, 1H, H-1), 8.29 (d, 1H, *J* = 8.3 Hz, H-10), 8.14 (d, 1H, *J* = 9.0 Hz, H-6), 7.96 (d, 1H, *J* = 7.9 Hz, H-7), 7.90-7.86 (m, 1H, ArH), 7.78-7.72 (m, 2H, H-9, ArH), 7.67-7.60 (m, 1H, H-8), 7.62-7.58 (m, 1H, ArH), 7.53 (d, 1H, *J* = 9.0 Hz, H-5), 7.46-7.42 (m, 1H, ArH). HRMS [CI]$^+$: *m/z* calc'd for $C_{20}H_{12}O_3Cl$ 335.0475 [M+H]$^+$, found 335.0467 (-2.4 ppm).

2-(3'-Fluorobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4x): Yielded 685 mg (2.15 mmol, 86%) as a yellow powder. Mp 190-192 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.08 (s, 1H, H-1), 8.35 (d, 1H, *J* = 8.4 Hz, H-10), 8.11 (d, 1H, *J* = 8.9 Hz, H-6), 7.89-7.75 (m, 2H, H-9, H-6), 7.67-7.61 (m, 1H, H-8), 7.59-7.54 (m, 2H, ArH), 7.51 (d, 1H, *J* = 8.9 Hz, H-5), 7.34-7.30 (m, 1H, ArH), 7.13-7.09 (m, 1H, ArH). LRMS [ES]$^+$: *m/z* 341.05 [M+Na]$^+$ (100%).

2-(4'-Fluorobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xi): Yielded 630 mg (1.98 mmol, 79%) as a yellow powder. Mp 226-228 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.98 (s, 1H, H-1), 8.29 (d, 1H, *J* = 8.3 Hz, H-10), 8.14 (d, 1H, *J* = 9.0 Hz, H-6), 7.99-7.92 (m, 1H, H-7), 7.77-7.71 (m, 1H, H-9), 7.70-7.62 (m, 1H, H-8), 7.66-7.59 (m, 2H, ArH), 7.53 (d, 1H, *J* = 9.0 Hz, H-5), 7.47-7.41 (m, 1H, ArH), 7.38-7.30 (m, 1H, ArH). LRMS [ES]$^+$: *m/z* 341.07 [M+Na]$^+$ (100%).

2-(5'-Fluorobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xii): Yielded 664 mg (2.08 mmol, 84%) as a yellow powder. Mp 214-215 °C. IR (KBr) ν_{max}/cm^{-1}:1755, 1455 (CO), 1285, 1222 (C-O), 1140, 743 (C-F). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.95 (s, 1H, H-1), 8.29 (d, 1H, *J* = 8.4 Hz, H-10), 8.13 (d, 1H, *J* = 9.0 Hz, H-6), 8.00-7.93 (m, 3H, H-7, AA'BB' system, *J* = 8.8 Hz, H-3', H-7'), 7.78-7.70 (m, 1H, H-9), 7.66-7.60 (m, 1H, H-8), 7.52 (d, 1H, *J* = 9.0 Hz, H-5), 7.16 (d, 2H, AA'BB' system, *J* = 8.8 Hz, H-4', H-6'). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 190.9 (C1'), 164.5 (C5'), 158.2 (C3), 155.6 (C4a), 141.7 (C1), 135.0 (C6), 131.8 (C3', C7'), 130.4 (C6a), 130.6 (C7), 129.7 (C2'), 129.5 (C10a), 128.5 (C9), 126.7 (C8), 125.2 (C2), 121.6 (C10), 116.9 (C5), 113.3 (C4', C6'), 112.1 (C10b). LRMS [ES]$^+$: *m/z* 341.07 [M+Na]$^+$ (100%).

2-(4'-Iodobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xiii): Yielded 861 mg (2.02 mmol, 80%) as a yellow powder. Mp 237-239 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.97 (s, 1H, H-1), 8.29 (d, 1H, *J* = 8.4 Hz, H-10), 8.23 (t, 1H, *J* = 1.7 Hz, H-3'), 8.14 (d, 1H, *J* = 9.0 Hz, H-6), 7.99-7.92 (m, 2H, H-7, ArH), 7.87-7.81 (m, 1H, ArH), 7.79-7.71 (m, 1H, H-9), 7.67-7.61 (m, 1H, H-8), 7.53 (d, 1H, *J* = 9.0 Hz, H-5), 7.24 (d, 1H, *J* = 7.8 Hz, ArH). LRMS [ES]$^+$: *m/z* 449.02 [M+Na]$^+$ (100%).

2-(3'-Nitrobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xiv): Yielded 847 mg (2.45 mmol, 98%) as a yellow powder. Mp 218-221 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.64 (s, 1H, H-1), 8.46 (dd, 1H, *J* = 8.2 Hz, *J* = 0.9 Hz, H-10), 8.28 (d, 1H, *J* = 8.2 Hz, ArH), 8.13 (d, 1H, *J* = 9.0 Hz, H-6), 7.95 (d, 1H, *J* = 8.1 Hz, H-7), 7.84-7.76 (m, 2H, H-9, ArH), 7.70-7.62 (m, 2H, H-8, ArH), 7.48-7.42 (m, 2H, H-5, ArH). LRMS [ES]$^+$: *m/z* 368.11 [M+Na]$^+$ (100%).

2-(Furan-2'-carbonyl)-3*H*-benzo[*f*]chromen-3-one (4xv): Yielded 327 mg (1.12 mmol, 45%) as a yellow powder. Mp 227-230 °C. IR (KBr) ν_{max}/cm^{-1}: 1710, 1459 (CO), 1215 (C-O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.95 (s, 1H, H-1), 8.28 (d, 1H, *J* = 8.3 Hz, H-10), 8.10 (d, 1H, *J* = 9.0 Hz, H-6), 7.94 (d, 1H, *J* = 8.0 Hz, H-7), 7.78-7.73 (m, 1H, H-9), 7.70-7.68 (m, 1H, H-5'), 7.65-7.60 (m, 1H, H-8), 7.51 (d, 1H, *J* = 9.0 Hz, H-5), 7.43 (m, 1H, H-3'), 6.63 (dd, 1H, ^3J = 3.6 Hz, ^4J = 1.6 Hz, H-3'). ^{13}C NMR ($CDCl_3$, 100MHz): δ = 178.3 (C1'), 158.3 (C3), 155.4 (C4a), 151.8 (C2'), 147.7

(C5'), 141.9 (C1), 135.6 (C6), 130.3 (C6a), 129.9 (C7), 129.4 (C10a), 129.2 (C9), 126.6 (C8), 124.6 (C2), 121.5 (C10), 120.8 (C3'), 116.7 (C5), 113.1 (C10b), 112.6 (C4'). HRMS $[ES]^+$: *m/z* calc'd for $C_{18}H_{10}O_4Na$ 313.0477 $[M+Na]^+$, found 313.0482 (+ 1.8 ppm).

2-(3'-Chlorobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xvi): Yielded 690 mg (2.06 mmol, 83%) as a yellow powder. Mp 225-227 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.23 (s, 1H, H-1), 8.36 (d, 1H, *J* = 8.1 Hz, H-10), 8.12 (d, 1H, *J* = 8.8 Hz, H-6), 7.95 (d, 1H, *J* = 8.1 Hz, H-7), 7.80-7.72 (m, 1H, H-9), 7.65-7.57 (m, 2H, H-8, ArH), 7.52-7.39 (m, 4H, H-5 + 3×ArH). LRMS $[ES]^+$: *m/z* 356.99 $[M+Na]^+$ (100%).

2-(3'-Iodobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xvii): Yielded 853 mg (2.00 mmol, 80%) as a yellow powder. Mp 239-240 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.29 (s, 1H, H-1), 8.35 (d, 1H, *J* = 8.4 Hz, H-10), 8.14 (d, 1H, *J* = 8.9 Hz, H-6), 7.98-7.90 (m, 2H, H-7, ArH), 7.80-7.74 (m, 1H, H-9), 7.67-7.61 (m, 1H, H-8), 7.53-7.42 (m, 3H, H-5 + 2×ArH), 7.18-7.24 (m, 1H, ArH). HRMS $[ES]^+$: *m/z* calc'd for $C_{20}H_{11}O_3NaI$ 448.9651 $[M+Na]^+$, found 448.9652 (+ 0.3 ppm).

2-(4'-Nitrobenzoyl)-3*H*-benzo[*f*]chromen-3-one (4xviii): Yielded 694 mg (2.00 mmol, 80%) as a yellow powder. Mp 243-246 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.15 (s, 1H, H-1), 8.69 (t, 1H, *J* = 1.8 Hz, H-3'), 8.47 (m, 1H, H-10), 8.35 (d, 1H, *J* = 8.3 Hz, ArH), 8.23-8.15 (m, 2H, H-6, ArH), 7.99 (d, 1H, *J* = 7.9 Hz, H-7), 7.81-7.76 (m, 1H, H-9), 7.73-7.63 (m, 2H, H-8, ArH), 7.55 (d, 1H, *J* = 9.0 Hz, H-5). LRMS $[ES]^+$: *m/z* 368.14 $[M+Na]^+$ (100%).

b) Synthesis of 5i-xv

General protocol for the parallel synthesis of 5i-xv: To the different solutions of 2-benzoyl-benzo[*f*]benzocoumarins **4i-xviii** (400 mg, 1 eq) in dry pyridine (4 mL) was added $NaBH_4$ (1 eq). The reactions were stirred at room temperature for 2 h. All reaction mixtures were poured into cold aqueous HCl (10 mL, 2M) resulting in the formation of white precipitates. The solids were collected by parallel filtration, washed with aqueous HCl (2M) and recrystallized in parallel from ethanol.

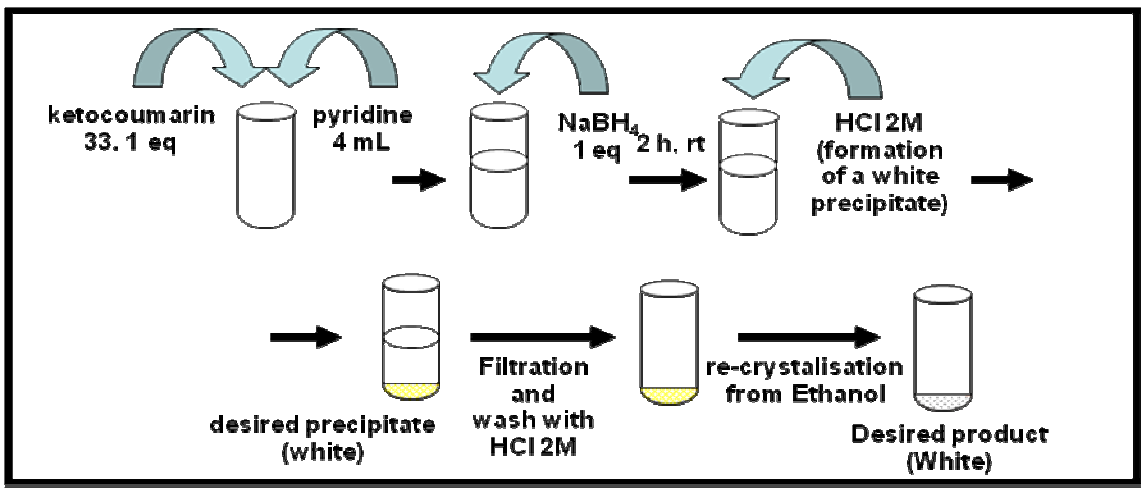


Figure S11: A schematic representation of the practical procedures adopted in the second step of the parallel synthesis.

Compound	R_1	Yield (%)
5b	***p*-Br-Ph**	**93**
5i	***o*-CH_3-Ph**	**78**
5ii	***m*-CH_3-Ph**	**35**
5iii	***p*-CH_3-Ph**	**60**
5iv	***p*-Cl-Ph**	**90**
5v	***p*-I-Ph**	**85**
5vi	***p*-CF_3-Ph**	**89**
5vii	***o*-Br-Ph**	**80****
5viii	***m*-Br-Ph**	**90**
5ix	***m*-Cl-Ph**	**85**
5x	***o*-F-Ph**	**40**
5xi	***m*-F-Ph**	**62**
5xii	***p*-F-Ph**	**71**
5xiii	***m*-I-Ph**	**90**
5xiv	***m*-NO_2-Ph**	**92**
5xv	**Furyl-**	**60****
5xvi	***o*-Cl-Ph**	*
5xvii	***o*-I-Ph**	*
5xviii	***o*-NO_2-Ph**	*

Table S2: Yields observed for the products of the second step of the parallel synthesis. *: product not recovered when the reaction was run in parallel. **: yields refer to reaction run in normal glassware.

2-(3'-Methylbenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5i): Yielded 310 mg (0.98 mmol, 78%) as a white powder. Mp 123-126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92-7.76 (m, 3H, H-7, H-10, ArH), 7.63 (d, 1H, *J* = 7.8 Hz, H-6), 7.59-7.37 (m, 3H, H-9, H-8, ArH), 7.34-7.19 (m, 3H, H-5 + 2×ArH), 4.69 (dd, 1H, ^3J = 8.8 Hz, $^{3'}J$ = 6.6 Hz, H-2), 3.79 (dd, 1H, ^2J = 16.5 Hz, ^3J = 8.8 Hz, H-1), 3.56 (dd, 1H, ^2J = 16.5 Hz, ^3J = 6.6 Hz, H-1), 2.24 (s, 3H, CH_3). LRMS [ES]$^+$: *m/z* 337.11 [M+Na]$^+$ (100%).

2-(4'-Methylbenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5ii): Yielded 65 mg (0.20 mmol, 35%) as a white powder. Mp 180-183 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.91-7.76 (m, 5H, H-10, H-7, H-6 + 2×ArH), 7.60-7.52 (m, 1H, H-9), 7.52-7.46 (m, 1H, H-8), 7.45-7.36 (m, 2H, ArH), 7.29 (d, 1H, *J* = 9.0 Hz, H-5), 4.81 (dd, 1H, ^3J = 10.3 Hz, $^{3'}J$ = 6.9 Hz, H-2), 3.83 (dd, 1H, ^2J = 16.7 Hz, ^3J = 10.3 Hz, H-1), 3.61 (dd, 1H, ^2J = 16.7 Hz, ^3J = 6.9 Hz, H-1), 2.42 (s, 3H, CH_3). LRMS [ES]$^+$: *m/z* 337.11 [M+Na]$^+$ (100%).

2-(5'-Methylbenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5iii): Yielded 230 mg (0.72 mmol, 60%) as a white powder. Mp 173-175 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.93-7.78 (m, 5H, H-10, H-7, H-6, AA'BB' system, H-7', H-3'), 7.60-7.52 (m, 1H, H-9), 7.51-7.44 (m, 1H, H-8), 7.34-7.24 (m, 3H, overlapped with solvent signal, H-5, AA'BB' system, H-4', H-6'), 4.80 (dd, 1H, ^3J = 10.1 Hz, $^{3'}J$ = 6.9 Hz, H-2), 3.84 (dd, 1H, ^2J =16.6 Hz, ^3J = 10.2 Hz, H-1), 3.60 (dd, 1H, ^2J = 16.6 Hz, ^3J = 6.9 Hz, H-1), 2.43 (s, 3H, CH_3). LRMS [ES]$^+$: *m/z* 337.14 [M+Na]$^+$ (100%).

2-(5'-Chlorobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5iv): Yielded 360 mg (1.07 mmol, 90%) as a white powder. Mp 206-208 °C. IR (KBr) ν_{max}/cm^{-1}: 1755 (CO), 1223, 1148 (C-O), 1678 (C-Cl). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.95 (d, 2H, AA'BB' system, *J* = 8.8 Hz, H-3', H-7'), 7.91-7.85 (m, 2H, H-7, H-10), 7.82 (d, 1H, *J* = 8.8 Hz, H-6), 7.61-7.53 (m, 1H, H-9), 7.42-7.54 (m, 3H,

H-8, AA'BB' system, *J* = 8.8 Hz, H-4', H-6'), 7.28 (d, 1H, *J* = 8.8 Hz, H-5), 4.75 (dd, 1H, ^{3}J = 10.5 Hz, $^{3'}J$ = 6.8 Hz, H-2), 3.83 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.5 Hz, H-1), 3.61 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 6.8 Hz, H-1). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 192.9 (C1'), 165.9 (C3), 148.0 (C4a), 139.6 (C5'), 134.4 (C2'), 131.9 (C6a) , 131.3 (C10a), 130.6 (C3', C7'), 129.6 (C6), 129.6 (C4', C6'), 129.5 (C7), 127.7 (C8), 125.7 (C9), 123.1 (C10), 117.3 (C5), 114.8 (C10b), 46.8 (C2), 23.3 (C1). HRMS [CI]$^+$: *m/z* calc'd for $C_{20}H_{14}O_3Cl$ 337.0631 $[M+H]^+$, found 337.0630 (- 0.4 ppm).

2-(5'-Iodobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5v): Yielded 340 mg (0.79 mmol, 85%) as a white powder. Mp 229-233 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92-7.85 (m, 4H, H-7, H-10, AA'BB' system, *J* = 8.7 Hz, H-3', H-7'). 7.81 (d, 1H, *J* = 8.8 Hz, H-6), 7.70 (d, 2H, AA'BB' system, *J* = 8.7 Hz, H-4', H-6'), 7.61-7.54 (m, 1H, H-9), 7.52-7.45 (m, 1H, H-8), 7.28 (d, 1H, *J* = 8.8 Hz, H-5), 4.73 (dd, 1H, ^{3}J = 10.5 Hz, $^{3'}J$ = 6.8 Hz, H-2), 3.82 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.5 Hz, H-1), 3.61 (dd, 1H, ^{2}J= 16.6 Hz, ^{3}J = 6.8 Hz, H-1). LRMS [CI]$^+$: *m/z* 428.99 $[M+H]^+$ (30%).

2-(5'-Trifluoromethylbenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5vi): Yielded 360 mg (0.97 mmol, 89%) as a white powder. Mp 192-193 °C. IR (KBr) ν_{max}/cm^{-1}: 1710 (CO), 1251 (C-O), 747, 691 (C-F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.12 (d, 2H, AA'BB' system, *J* = 8.2 Hz, H-3', H-7'), 7.93-7.86 (m, 3H, H-10, H-7, 6-H), 7.78 (d, 2H, AA'BB' system, *J* = 8.2 Hz, H-4', H-6'), 7.62-7.54 (m, 1H, H-9), 7.54-7.45 (m, 1H, H-8), 7.28 (d, 1H, *J* = 8.8 Hz, H-5), 4.79 (dd, 1H, ^{3}J = 10.7 Hz, $^{3'}J$ = 6.7 Hz, H-2), 3.85 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.7 Hz, H-1), 3.64 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 6.7 Hz, H-1). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 193.0 (C1'), 164.4 (C3), 147.9 (C4a), 137.4 (C2'), 134.9 (C5'), 131.7 (C10a), 131.1 (C6a), 129.5 (C3', C7'), 129.1 (C7), 128.7 (C6), 127.6 (C8), 126.1 (C4', C6'), 125.6 (C9), 122.9 (C10), 121.9 (CF_3), 117.0 (C5), 114.5 (C10b), 45.7 (C2), 21.8 (C1). HRMS [ES]$^-$: *m/z* calc'd for $C_{21}H_{12}O_3F_3$ 369.0739 $[M-H]^-$, found 369.0737(-0.5 ppm).

2-(5'-bromobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5vii): yielded 41 mg, (0.1 mmol, 80%) as a yellow powder. For spectroscopic details concerning **5vii** see below.

2-(4'-Bromobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5viii): Yielded 340 mg (0.89 mmol, 90%) as a white powder. Mp 219-221 °C. IR (KBr) ν_{max}/cm^{-1}: 1745 (CO), 1283, 1222, 1150 and 1071 (C-O), 743 (C-Br). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.97 (t, 1H, *J* = 1.9 Hz, H-3'), 7.91-7.71 (m, 5H, H-10, H-7, H-6 + 2×ArH), 7.63-7.54 (m, 1H, H-9), 7.53-7.43 (m, 1H, H-8), 7.38 (t, 1H, *J* = 7.9 Hz, ArH), 7.29 (d, 1H, *J* = 8.9 Hz, H-5), 4.74 (dd, 1H, ^{3}J = 10.7 Hz, $^{3'}J$ = 6.8 Hz, 2-H), 3.83 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.7 Hz, H-1), 3.62 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 6.8 Hz, H-1). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 192.8 (C1'), 164.5 (C3), 149.0 (C4a), 137.6 (C2'), 136.9 (C6'), 131.9 (Ar), 131.3 (C6a) 131.1 (C10a), 130.6 (Ar), 129.5 (C6), 129.0 (C7), 127.5 (C8), 127.4 (Ar), 125.6 (C9), 123.4 (C4'), 122.9 (C10), 117.0 (C5), 114.5 (C10b), 46.6 (C1), 23.1 (C2). LRMS [ES]$^-$: *m/z* 379.09 $[M-H]^-$ (100%).

2-(4'-Chlorobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5ix): Yielded 340 mg (1.01 mmol, 85%) as a white powder. Mp 172-174 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.97 (t, 1H, *J* = 1.8 Hz, H-3'), 7.92-7.85 (m, 3H, H-10, H-7, ArH), 7.82 (d, 1H, *J* = 9.0 Hz, H-6), 7.63-7.54 (m, 2H, H-9, ArH), 7.52-7.42 (m, 2H, H-8, ArH), 7.29 (d, 1H, *J* = 9.0 Hz, H-5), 4.74 (dd, 1H, ^{3}J = 10.7 Hz, $^{3'}J$ = 6.8 Hz, H-2), 3.83 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.8 Hz, H-1), 3.62 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 6.8 Hz, H-1). LRMS [CI]$^+$: *m/z* 337.06 $[M+H]^+$ (100%).

2-(3'-Fluorobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5x): Yielded 50 mg (0.15 mmol, 40%) as a white powder. Mp 122-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02-7.81 (m, 4H, H-10, H-7 , H-6, ArH), 7.65-7.44 (m, 3H, H-9, H-8, ArH), 7.29 (d, 2H, *J* = 8.6 Hz, H-5, ArH), 7.22-7.15 (m, 1H, ArH), 4.74 (dd, 1H, ^{3}J = 10.5 Hz, $^{3'}J$ = 7.4 Hz, H-2), 3.76-3.64 (m, 2H, H-1). LRMS [ES]$^+$: *m/z* 343.09 $[M+Na]^+$ (100%).

2-(4'-Fluorobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5xi): Yielded 77 mg (0.24 mmol, 62%) as a white powder. Mp 143-145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92-7.76 (m, 4H, H-10, H-7, H-6, ArH), 7.72-7.66 (m, 1H, ArH), 7.61-7.55 (m, 1H, H-9), 7.53-7.46 (m, 2H, H-8, ArH),

7.37-7.23 (m, 2H, H-5, ArH), 4.75 (dd, 1H, ^{3}J = 10.5 Hz, $^{3'}J$ = 6.7 Hz, H-2), 3.84 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.5 Hz, H-1), 3.62 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 6.7 Hz, H-1). LRMS $[ES]^{+}$: *m/z* 343.11 $[M+Na]^{+}$ (100%); LRMS $[ES]^{-}$: *m/z* 319.10 $[M-H]^{-}$; HRMS $[ES^{+}]$: *m/z* calc'd for $C_{20}H_{13}O_3NaF$ 343.0746 $[M+Na]^{+}$, found 343.0750 (+ 1.0 ppm).

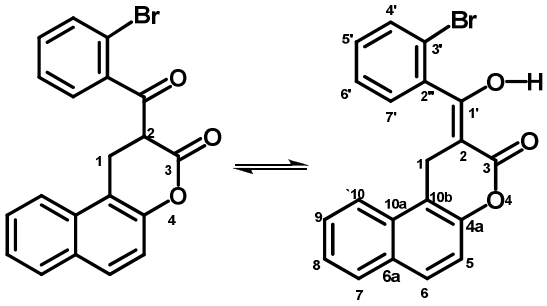
2-(5'-Fluorobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5xii): Yielded 100 mg (0.31 mmol, 71%) as a white powder. Mp 139-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87-7.79 (m, 2H, H-7, H-10), 7.76 (d, 2H, AA'BB' system, *J* = 8.7 Hz, H-3', H-7'), 7.56 (d, 1H, *J* = 9.0 Hz, H-6), 7.56-7.48 (m, 1H, H-9), 7.48-7.40 (m, 1H, H-8), 7.32 (d, 1H, *J* = 9.0 Hz, H-5), 7.22 (d, 2H, AA'BB' system, *J* = 8.7 Hz, H-4', H-6'), 4.80 (dd, 1H, ^{3}J = 10.2 Hz, $^{3'}J$ = 6.8 Hz, H-2), 3.78 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.2 Hz, H-1), 3.59 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 6.8 Hz, H-1). LRMS $[ES]^{+}$: *m/z* 343.08 $[M+Na]^{+}$ (100%).

2-(4'-Iodobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5xiii): Yielded 360 mg (0.84 mmol, 90%) as a white powder. Mp 199-202 °C. IR (KBr) ν_{max}/cm^{-1}: 1705 (CO), 1262, 1217, 1066 and 1057 (C-O), 750 (C-I). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31 (t, 1H, *J* = 1.7 Hz, H-3'), 7.98-7.72 (m, 5H, H-10, H-7, H-6 + 2×ArH), 7.62-7.53 (m, 1H, H-9), 7.53-7.44 (m, 1H, H-8), 7.31-7.20 (m, 2H, overlapped with solvent signal, H-6'), 4.73 (dd, 1H, ^{3}J = 10.8 Hz, $^{3'}J$ = 6.8 Hz, H-2), 3.82 (dd, 1H, ^{2}J = 16.6 Hz, ^{3}J = 10.8 Hz, H-1), 3.61 (dd, 1H, ^{3}J = 16.6 Hz, ^{2}J = 6.8 Hz, 1-H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 192.8 (C1'), 165.7 (C3), 149.1 (C4a), 142.9 (C6'), 136.9 (C3'), 136.4 (C2'), 131.1 (C6a), 131.0 (C10a), 130.6 (Ar), 129.5 (Ar), 129.0 (C6), 128.2 (C7), 127.6 (C8), 125.6 (C9), 122.9 (C10), 117.2 (C5), 114.6 (C10b), 93.6 (C4'), 46.5 (C2), 23.1 (C1). HRMS $[CI]^{+}$: *m/z* calc'd for $C_{20}H_{14}O_3I$ 428.9988 $[M+H]^{+}$, found 428.9985 (- 0.6 ppm).

2-(4'-Nitrobenzoyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5xiv): Yielded 279 mg (0.80 mmol, 92%) as a white powder. Mp 203-206 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 8.86 (t, 1H, *J* = 1.8 Hz, H-3'), 8.59-8.48 (m, 2H, H-10, H-7), 8.06-7.93 (m, 3H, H-6 + 2×ArH), 7.86 (t, 1H, *J* = 8.0 Hz, ArH), 7.65-7.57 (m, 1H, H-9), 7.56-7.48 (m, 1H, H-8), 7.38 (d, 1H, *J* = 8.8 Hz, H-5), 5.51 (dd, 1H, ^{3}J = 11.8 Hz, $^{3'}J$ = 6.8 Hz, H-2), 3.80 (dd, 1H, ^{2}J = 16.5 Hz, ^{3}J = 6.8 Hz, H-1), 3.64 (dd, 1H, ^{2}J = 16.5 Hz, ^{3}J = 11.8 Hz, H-1). HRMS $[ES]^{-}$: *m/z* calc'd for $C_{20}H_{12}NO_5$ 346.0715 $[M-H]^{-}$, found 346.0711 (- 1.3 ppm).

2-(furan-2'-carbonyl)-1,2-dihydro-benzo[*f*]chromen-3-one (5xv): Yielded 30 mg (0.1 mmol, 60 %), as a yellow powder. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.93-7.77 (m, 3H, H-10, H-7, H-6), 7.66-7.45 (m, 3H, H-9, H-8, ArH), 7.38 (dd, 1H, ^{3}J = 3.6 Hz, ^{4}J = 0.7 Hz, ArH), 7.28 (d, 1H, *J* = 9.0 Hz, H-5), 6.62 (dd, 1H, ^{3}J = 3.6 Hz, ^{4}J = 1.7 Hz, ArH), 4.63 (dd, 1H, ^{3}J = 6.9 Hz, $^{3'}J$ = 11.5 Hz, 2-H), 3.81 (dd, 1H , ^{2}J = 16.5 Hz, ^{3}J = 11.5 Hz, H-1), 3.62 (dd, 1H, ^{2}J = 16.5 Hz, ^{3}J = 6.9 Hz, H-1). LRMS $[ES]^{+}$: *m/z* 314.92 $[M+Na]^{+}$ (100%).

NMR spectra associated 5vii



Keto-5vii Enol-5vii

The ^{1}H NMR spectrum of **5vii** showed that **keto-5vii** exists as an equilibrium with **enol-5vii** (ratio of **keto-5vii**: **enol-5vii** = 1:14). The signal derived from the proton at C2 of **keto-5vii** was observed at δ = 4.77 (dd, ^{3}J = 10.2 Hz, $^{3'}J$ = 7.0 Hz). ^{1}H NMR (**enol-5vii**) ($CDCl_3$, 400MHz): δ = 7.88-7.71 (m, 3H, H-10, H-7, H-6), 7.54-7.36 (m, 6H, H-9, H-8, + 4×ArH), 7.28-7.21 (m, overlapping with solvent signal, 1H, H-5), 3.71 (br, 2H, H-1). ^{13}C NMR (**enol-5vii**) ($CDCl_3$, 75.5 MHz): δ = 169.2 (C3), 164.2 (C1'), 147.5 (C4a), 135.3 (C2'), 133.6 (C4'), 131.6 (C6), 131.1 (C6a), 131.0 (C10a), 129.2 (Ar), 129.1 (Ar), 128.8 (C7), 128.2 (Ar), 127.2 (C8), 125.4 (C9), 122.6 (C10), 120.9 (C3'), 117.4 (C5), 112.8 (C10b), 93.4 (C2), 23.7 (C1). HRMS [CI]$^{+}$: *m/z* calc'd for $C_{20}H_{11}O_3Na^{79}Br$ $[M+Na]^{+}$ 402.9769, found 402.9762 (-1.9 ppm).

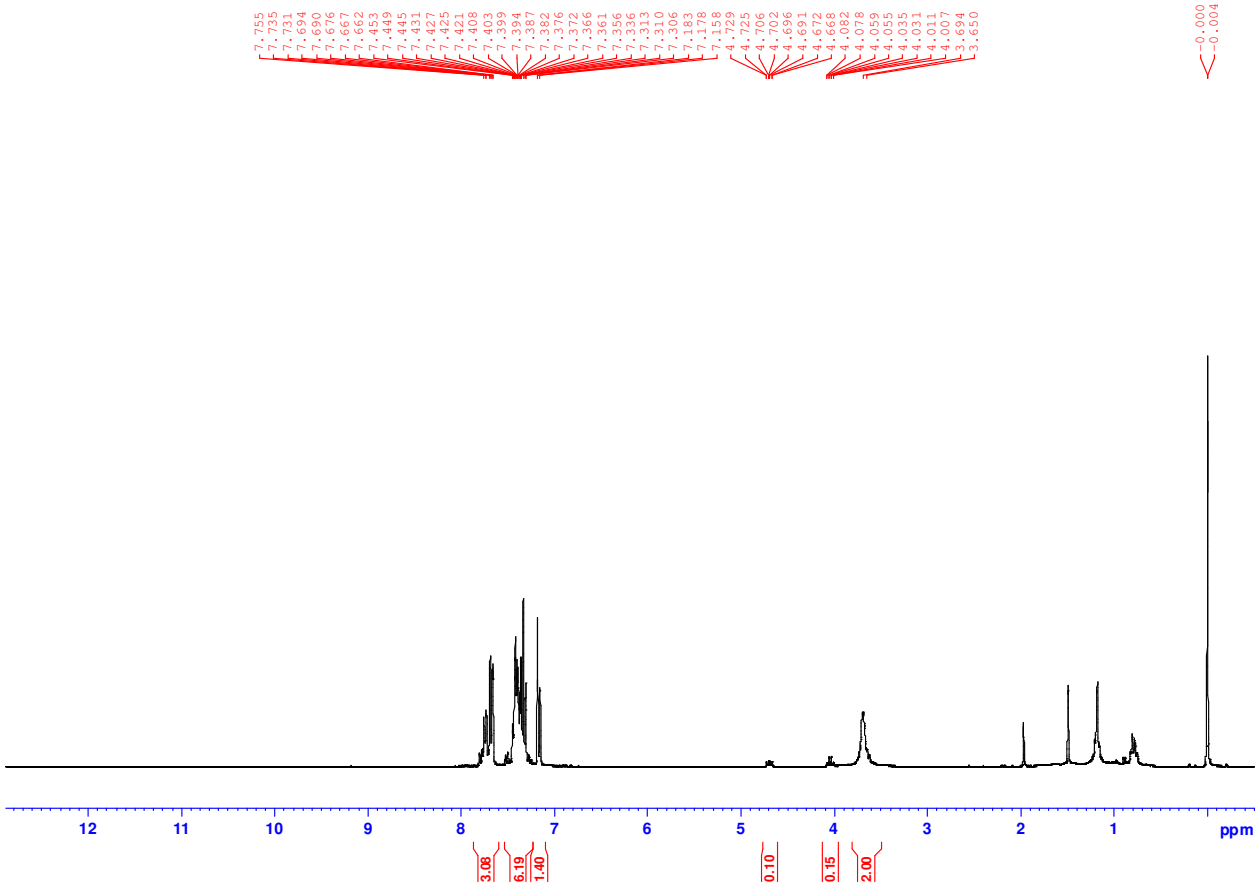


Figure S12: ^{1}H NMR spectrum of compound **5vii** in $CDCl_3$.

HPLC Analysis of Purity

HPLC analyses were performed on a GILSON UV-VIS 155 HPLC system under gradient conditions. Method A (RP, reverse phase) Gemini 5µ C18 110A column (250 mm × 4.6 mm, 5 micron, Phenomenex). Method B (NP, normal phase) Luna 5µ Silica 100A column (250 mm × 4.6 mm, 5 micron, Phenomenex). The concentration of the compounds were ca. 4 mmol, injection volumes were 20µL, flow rate was 1 mL/min and detection was acquired with UV (254 nm).

Method A (RP)			Method B (NP)		
time (min)	% H_2O[a]	% CH_3CN[a]	time (min)	% Hexane	% EtOAc
0	80	20	0	90	10
20	20	80	27	10	90
24	20	80	30	10	90
27	80	20	32	90	10
30	80	20			

[a] With 0.1% TFA

Table S3. HPLC Elution Methods.

Compound	**HPLC Method A (RP)**		**HPLC Method B (NP)**	
	Rt	**purity (%)**	**Rt**	**purity (%)**
1	**12.74**	**98.7**	**13.35**	**99.0**
6a	**15.59**	**95.0**	**14.83**	**95.0**
6b	**22.80**	**98.4**	**13.54**	**98.0**
6c	**19.72**	**96.1**	**16.26**	**96.4**
6d	**19.87**	**99.0**	**14.49**	**99.0**
6i	**20.85**	**96.5**	**19.01**	**96.8**
6ii	**20.82**	**97.3**	**11.94**	**97.6**
6iii	**21.08**	**98.1**	**12.05**	**98.3**
6iv	**20.51**	**98.2**	**13.71**	**97.8**
6v	**21.61**	**95.2**	**13.99**	**95.0**
6vi	**20.85**	**96.5**	**19.01**	**96.8**
6vii	**19.03**	**95.8**	**16.21**	**96.1**
6viii	**20.45**	**96.0**	**19.48**	**95.8**
6ix	**20.09**	**96.2**	**14.43**	**96.4**
6x	**18.26**	**98.2**	**16.45**	**98.0**
6xi	**18.93**	**95.0**	**19.51**	**95.5**
6e	**21.54**	**98.2**	**13.80**	**98.3**

6f	**22.75**	**98.8**	**11.68**	**99.0**
6g	**22.99**	**97.4**	**11.68**	**98.0**
6h	**24.43**	**98.1**	**11.27**	**98.0**
6j	**26.30**	**98.2**	**12.19**	**98.5**

Table S4. retention times and purities of cambinol analogs

In vitro SIRT1 activity of intermediates 4 and 5.

R_1	Compound	SirT1	Compound	SirT1
***p*-Br-Ph**	**4b**	**20.1 ± 2**	**5b**	**22.2 ± 3**
o-CH_3	**4i**	**N. T.**	**5i**	**N. T.**
m-CH_3	**4ii**	**N. T.**	**5ii**	**N. T.**
p-CH_3	**4iii**	**N. T.**	**5iii**	**N. T.**
***p*-Cl-Ph**	**4iv**	**6 ± 18**	**5iv**	**27 ± 4**
***p*-I-Ph**	**4v**	**32 ± 5**	**5v**	**13.7 ± 9**
***p*-CF_3**	**4vi**	**20 ± 0**	**5vi**	**9.2 ± 2**
***o*-Br-Ph**	**4vii**	**38 ± 31**	**5vii**	**N. T.**
***m*-Br-Ph**	**4viii**	**3.7 ± 0**	**5viii**	**47.3 ± 2**
***m*-Cl-Ph**	**4ix**	**3.7 ± 18**	**5ix**	**26.2 ± 2**
***o*-F-Ph**	**4x**	**3.3 ± 3**	**5x**	**N. T.**
***m*-F-Ph**	**4xi**	**No inhibition**	**5xi**	**N. T.**
***p*-F-Ph**	**4xii**	**N. T.**	**5xii**	**12.3 ± 33**
***o*-Cl-Ph**	**4xiii**	**3 ± 1**	**5xiii**	**N. T.**
***o*-I-Ph**	**4xiv**	**No inhibition**	**5xiv**	**N. T.**
***m*-I-Ph**	**4xv**	**17 ± 2**	**5xv**	**7.3 ± 0**
***o*-CF_3-Ph**	**4xvi**	**21 ± 0**		
***m*-CF_3Ph**	**4xvii**	**32 ± 21**		
***o*-NO_2**	**4xviii**	**26 ± 8**		
***m*-NO_2**	**4xix**	**No inhibition**		
***p*-NO_2**	**4xx**	**N. T.**		
Furyl-	**4xxi**	**26 ± 7**		

Table S5: Inhibitory activities of compounds of general structures **4** and **5**. Data are reported as percent of inhibition at a concentration of 60 μM. The inhibition assays were performed in duplicate for each compound N. T.: not tested.

Western blot analysis

Acetylated α-tubulin levels with cambinol (1) and the SIRT1 selective analog 6b

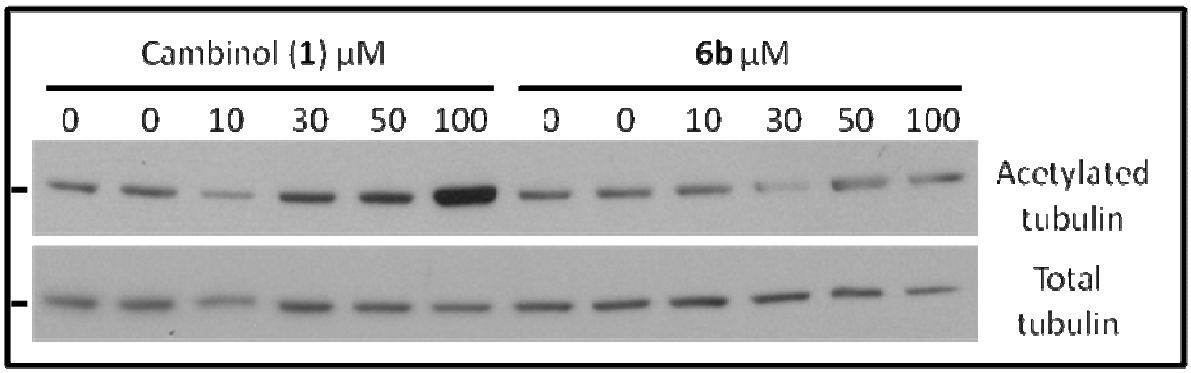


Figure S13: Detection of the levels of α-tubulin acetylated at K40 and total α-tubulin in H1299 cells treated with different concentrations of cambinol (**1**) and analog **6b**. All samples were also treated with trichostatin A, an inhibitor of class I and II HDACs, to reduce the background effect of these deacetylases. Black line represents the position of the 51KDa molecular weight marker. Samples were first analysed with the K40-acetylated α-tubulin antibody and subsequently reloaded and analysed with the antibody against total α-tubulin.

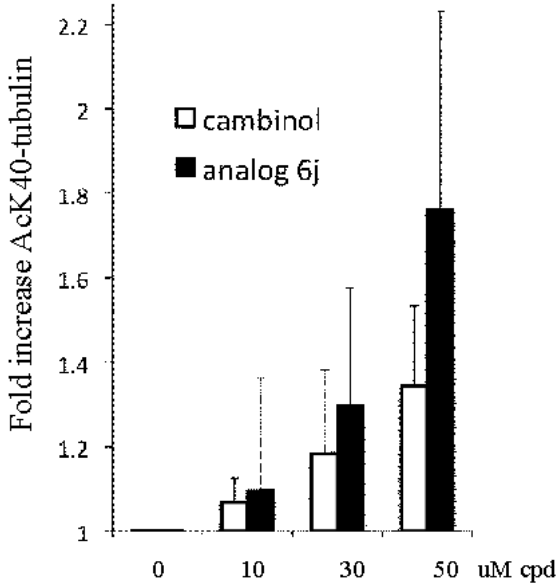


Figure S14. H1299 cells were treated with different concentrations of cambinol (**1**) and analog **6j** (in the presence of 40 nM trichostatin A) as in Figure 3 of the main text. Samples were first analysed with the K40-acetylated α-tubulin antibody and subsequently reloaded and analysed with the antibody against total α-tubulin. The ratio between the intensity of the acetylated α-tubulin band

and the total α-tubulin band for each sample was calculated. The histogram shows the average of the values obtained in three independent experiments. Error bars indicate standard deviation.

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S2) Surya Prakash Rao, H.; Sivakumar, S. *J. Org. Chem.* **2006**, *71*, 8715-8723.