Electronic Supporting Information

*N*1-benzyl Substituted Cambinol Analogues as Isozyme Selective Inhibitors of the Sirtuin Family of Protein Deacetylases

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Computational Procedures

Compounds were docked into SIRT2 using a flexible docking approach.[1] SIRT2 (PDBID: 1J8F, chain-A residues 57-356) was used for our molecular docking as well as molecular dynamics simulation. The neighbouring residues around the C pocket were identified from the previously reported work and these residues used to define a sphere (15 Å) in the flexible docking.[2] The selected residues were also allowed to be flexible during docking. The CHARMm force field was used to generate conformers of the protein.[2a]The grid resolution was set to 0.5 Å (default), and the ligand accessible grid was defined such that the minimum distance between a grid point and the protein was 2.0 Å for hydrogen and 2.5 Å for heavy atoms. The docking procedure started with the generation of random ligand conformations. After a new conformation was generated, the fitting was carried out by comparing the shape of the ligand to the shape of the active site and if acceptable, a dock energy was computed between the protein and the ligand trial conformation.[3b] Docking refinement was done using simulated annealing from 300K to 700K. The top ten poses were saved for each ligand after docking and 100 steps of rigid body minimization followed by simulated annealing. Each of the 10 poses saved after docking were rescored with the best score for each molecule retained and subsequently used for further molecular dynamics study. An analogous method was used to study the SIRT2-**4xv** complex.

SIRT1 (uniprot Q96EB6 residues 236-495) was modeled using Modeler keeping 1J8F chain A as template.[4] Molecular docking and dynamics were done using the same protocol as mentioned for SIRT2. The top 2 poses of **3a** bound to both SIRT1 and SIRT2 were selected for the subsequent molecular dynamics study. The *N*- and C-termini of SIRT1 and 2 were capped with acetyl (ACE) and *N*-methyl (NME) respectively to keep them neutral; Molecular dynamics simulations were performed with the SANDER module of the AMBER9 package employing the all-atom Cornell force field.[5,6] Compound parameters were built using antechamber.[7, 8] Each system was solvated with a TIP3P water box whose sides were at least 8 Å from any protein atom.[9] Particle Mesh Ewald method (PME) was used for treating long range electrostatics.[10] All bonds involving hydrogen atoms were constrained by SHAKE.[11] A time step of 2fs was used for the integration. Initially, the whole system was minimized for 4,000 steps, to remove any unfavourable interactions. Subsequently, the systems were heated to 300 K for 75 ps under NPT conditions. After this, each system was simulated for 20 ns at constant temperature (300 K) and pressure (1 atm) and structures were stored every 1 ps. The free energies of binding (ΔG_{bind}) of **3a** to SIRTs 1 and 2 were computed using the MM-GBSA (Molecular Mechanics/Generalized Born surface area) method using the GB module in Amber; the non-polar component was estimated from the solvent accessible surface area using the program MOLSURF with $\Delta G_{solv,np} = 0.00542*SASA + 0.92$.[12-16] Each energy term was averaged over frames taken every 10 ps from the simulations. The vibrational entropy was estimated using normal mode analysis (Nmode module of Amber) and averaged over 100 ps intervals.[17]

Table S1 Components of binding free energy (in kcal/mol) of SIRT2 with **3a**

	Sirtuin2-cambinol		Sirtuin2		Cambinol		Delta	
	Mean	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
ELE	-8025.4	92.9	-7997.3	92.3	-18.8	0.6	-9.3	3.1
VDW	-1329.5	29.3	-1293.0	29.0	20.9	2.8	-57.4	3.1
INT	5163.3	53.9	5086.9	53.3	76.3	5.8	0.0	0.0
GAS	-4191.6	103.7	-4203.3	103.4	78.4	5.4	-66.7	4.3
GBSUR	82.3	1.3	84.0	1.4	4.5	0.1	-6.2	0.1
GB	-3821.1	83.3	-3835.6	82.7	-9.1	0.6	23.6	3.3
GBSOL	-3738.9	82.9	-3751.6	82.3	-4.6	0.6	17.4	3.3
GBELE	-11846.5	30.8	-11832.9	30.8	-27.9	0.4	14.3	1.6
GBTOT	-7930.4	54.6	-7954.9	53.8	73.8	5.4	**-49.3**	2.9
TSTRA	17.1	0.0	17.1	0.0	13.2	0.0	-13.2	0.0
TSROT	17.7	0.0	17.7	0.0	10.9	0.0	-10.9	0.0
TSVIB	3386.2	9.4	3351.8	9.8	28.4	0.2	6.1	7.4
TSTOT	3421.1	9.4	3386.6	9.9	52.4	0.2	**-18.0**	7.4
ΔG_{bind}							**-31.3**	

Table S2 Components of binding free energy (in kcal/mol) of SIRT1 with **3a**

	Sirtuin1-cambinol		Sirtuin1		Cambinol		Delta	
	Mean	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
ELE	-7350.7	83.3	-7330.1	83.3	-18.7	0.5	-2.0	2.8
VDW	-1010.5	27.0	-983.1	26.6	19.8	2.6	-47.2	3.1
INT	4636.4	40.9	4557.1	40.6	79.3	5.1	0.0	0.0
GAS	-3724.9	92.9	-3756.1	93.0	80.5	5.1	-49.2	4.3
GBSUR	83.7	1.4	85.1	1.4	4.5	0.0	-5.9	0.1
GB	-3496.9	73.9	-3504.5	73.9	-8.9	0.4	16.5	2.7
GBSOL	-3413.2	73.1	-3419.3	73.1	-4.4	0.4	10.6	2.7
GBELE	-10847.6	23.6	-10834.5	23.3	-27.6	0.5	14.5	0.9
GBTOT	-7138.0	44.7	-7175.5	44.5	76.1	5.2	**-38.6**	3.0
TSTRA	17.0	0.0	17.0	0.0	13.2	0.0	-13.2	0.0
TSROT	17.6	0.0	17.6	0.0	10.9	0.0	-10.9	0.0
TSVIB	2977.1	12.1	2945.7	9.9	28.5	0.2	2.9	12.5
TSTOT	3011.7	12.1	2980.2	9.9	52.6	0.2	**-21.1**	12.5
ΔG_{bind}							**-17.5**	

Table S3 Energy contributions of SIRT2 residues to the binding of **3a**

Residue	ΔG_{vdw}	ΔG_{ele}	$\Delta G_{ele,sol}$	$\Delta G_{nonpol,sol}$	ΔG_{bind}
Phe96	-1.50	-0.18	0.73	-0.12	-1.08
Arg97	-2.93	-0.55	1.59	-0.23	-2.12
Glu116	-1.75	0.74	0.60	-0.20	-0.60
Phe119	-2.97	-0.07	0.97	-0.25	-2.32
Gln167	-1.83	-0.58	1.62	-0.08	-0.88
Ile169	-1.60	0.06	0.00	-0.11	-1.64
His187	-3.58	-1.70	3.37	-0.28	-2.19
Val266	-0.77	-0.19	0.12	-0.11	-0.94

Table S4 Energy contributions of SIRT1 residues to the binding of **3a**

Residue	ΔG_{vdw}	ΔG_{ele}	$\Delta G_{ele,sol}$	$\Delta G_{nonpol,sol}$	ΔG_{bind}
Ile281	-2.00	-0.02	0.00	-0.14	-2.15
Gln296	-1.56	-0.28	1.38	-0.13	-0.59
Phe299	-3.34	0.21	0.87	-0.24	-2.50
Phe314	-1.41	-0.08	0.54	-0.10	-1.06
Ile318	-1.43	0.07	-0.04	-0.13	-1.53
Ile349	-2.35	-0.21	0.24	-0.28	-2.60

Table S5 Components of binding free energy (in kcal/mol) of SIRT2 with **4xv**

	Sirtuin2-4xv complex		**Sirtuin2**		**4xv**		**Delta**	
	Mean	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
ELE	-7962.8	94.7	-7927.0	94.5	-23.3	0.6	-12.5	2.7
VDW	-1314.9	27.9	-1276.8	27.9	22.8	2.8	-60.9	2.8
INT	5184.4	53.0	5100.3	52.8	84.2	6.6	0.0	0.0
GAS	-4093.3	110.9	-4103.6	110.8	83.7	6.1	-73.4	3.8
GBSUR	83.9	1.2	85.8	1.2	4.9	0.0	-6.9	0.2
GB	-3889.1	88.5	-3906.2	88.8	-12.0	0.5	29.1	2.5
GBSOL	-3805.2	87.8	-3820.4	88.0	-7.1	0.5	22.3	2.5
GBELE	-11851.9	24.1	-11833.2	24.3	-35.3	0.5	16.6	2.1
GBTOT	-7898.5	55.3	-7924.0	54.2	76.6	6.2	-51.1	3.3
TSTRA	17.1	0.0	17.1	0.0	13.3	0.0	-13.3	0.0
TSROT	17.7	0.0	17.7	0.0	11.2	0.0	-11.2	0.0
TSVIB	3402.6	11.7	3360.9	12.4	35.3	0.1	6.4	7.9
TSTOT	3437.4	11.7	3395.7	12.4	59.9	0.1	-18.1	7.9
ΔG_{bind}							**-32.9**	

Table S6 Comparison of the components of the binding free energy (in kcal/mol) of SIRT2 with **3a** and **4xv**

	Delta SIRT2-3a		**Delta SIRT2-4xv**	
	Mean	**Std**	**Mean**	**Std**
ELE	-9.3	3.1	-12.5	2.7
VDW	-57.4	3.1	-60.9	2.8
INT	0.0	0.0	0.0	0.0
GAS	-66.7	4.3	-73.4	3.8
GBSUR	-6.2	0.1	-6.9	0.2
GB	23.6	3.3	29.1	2.5
GBSOL	17.4	3.3	22.3	2.5
GBELE	14.3	1.6	16.6	2.1
GBTOT	**-49.3**	2.9	-51.1	3.3
TSTRA	-13.2	0.0	-13.3	0.0
TSROT	-10.9	0.0	-11.2	0.0
TSVIB	6.1	7.4	6.4	7.9
TSTOT	**-18.0**	7.4	-18.1	7.9
ΔG_{bind}	**-31.3**		**-32.9**	

Table S7 Energy contributions of SIRT2 residues to the binding of **4xv**

Residue	ΔG_{vdw}	ΔG_{ele}	$\Delta G_{ele,sol}$	$\Delta G_{nonpol,sol}$	ΔG_{bind}
Phe96	-1.4	0.0	0.5	-0.2	-1.1
Arg97	-0.9	0.6	-0.2	-0.1	-0.7
Glu116	-1.7	0.1	1.4	-0.2	-0.4
Phe119	-4.1	-0.0	1.2	-0.3	-3.3
Gln167	-1.8	-0.8	1.6	-0.1	-1.2
Ile169	-2.0	-0.4	0.4	-0.1	-2.1
His187	-3.2	-1.3	2.9	-0.2	-1.9
Val266	-0.8	-0.3	0.2	-0.1	-1.0

Table S8. Comparison of theenergy contributions of SIRT2 residues to the binding of **3a** and **4xv**

	3a	**4xv**	**3a**	**4xv**	**3a**	**4xv**
Residue	ΔG_{vdw}	ΔG_{vdw}	ΔG_{ele}	ΔG_{ele}	$\Delta G_{ele,sol}$	$\Delta G_{ele,sol}$
Phe96	-1.5	-1.4	-0.2	0.0	0.7	0.5
Arg97	-2.9	-0.9	-0.6	0.6	1.6	-0.2
Glu116	-1.8	-1.7	0.7	0.1	0.6	1.4
Phe119	-3.0	-4.1	-0.1	-0.0	1.0	1.2
Gln167	-1.8	-1.8	-0.6	-0.8	1.6	1.6
Ile169	-1.6	-2.0	0.1	-0.4	0.0	0.4
His187	-3.6	-3.2	-1.7	-1.3	3.4	2.9
Val266	-0.8	-0.8	-0.2	-0.3	0.1	0.2
	3a	**4xv**	**3a**	**4xv**		
Residue	$\Delta G_{nonpol,sol}$	$\Delta G_{nonpol,sol}$	ΔG_{bind}	ΔG_{bind}		
Phe96	-0.1	-0.2	-1.1	-1.1		
Arg97	-0.2	-0.1	-2.1	-0.7		
Glu116	-0.2	-0.2	-0.6	-0.4		
Phe119	-0.3	-0.3	-2.3	-3.3		
Gln167	-0.1	-0.1	-0.9	-1.2		
Ile169	-0.1	-0.1	-1.6	-2.1		
His187	-0.3	-0.2	-2.2	-1.9		
Val266	-0.1	-0.1	-0.9	-1.0		

Chemistry: Instrumentation and General Techniques

All chemicals and solvents were purchased from Aldrich (UK) or Alfa-Aesar and used without further purification. All reactions were carried out under a positive pressure of nitrogen or argon in flame or oven-dried glassware. Ethanol was dried over Mg/I_2; pyridine was dried over KOH pellets; all the other solvents were dried on a MBRAWN SPS-800 apparatus. *n*$Bu_4I$was recrystalised from hot toluene and dried in a vacuum oven at 40° C.

Thin layer chromatography (TLC) analysis was performed on silica pre-coated SIL G-25 UV_{254} sheets (layer: 0.25 mm silica gel with fluorescent indicator UV_{254}, Alugram, UK). Compounds were visualized by UV light (UV lamp, model UVGL-58, Mineralight LAMP, Multiband UV-254/365 nm) and stained with potassium permanganate. Flash column chromatography was carried out on silica gel (40-63 μm, Fluorochem, UK) or, where indicated, on basic alumina (Brockmann I, Sigma-Aldrich).

Melting points were measured with an Electrothermal 9100 capillary melting point apparatus and are uncorrected.

Fourier Transform infra-red spectra (FT-IR) were acquired on a Perkin Elmer paragon 1000 FT spectrometer. Absorption maxima are reported in wavenumbers (cm^{-1}).

Unless otherwise stated, ^1H NMR spectra were measured at room temperature (298 K) on a Bruker DPX 400 (^1H = 400 MHz) and Bruker Avance 300 (^1H = 300.1 MHz) instruments. Deuterated solvents were used and ^1H NMR chemical shifts were internally referenced to $CHCl_3$ (7.26 ppm) in chloroform-d_1 solution. Chemical shifts are expressed as δ in unit of ppm.

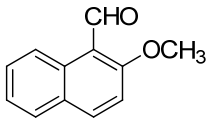
^{13}C NMR spectra were recorded in the same conditions and in the same solvents using the PENDANT sequence mode on a Bruker DPX 400 (^{13}C = 100 MHz). Data processing was carried out using TOPSPIN 2 NMR version (Bruker UK, Ltd). In ^1H NMR assignment the multiplicity used is indicated by the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, brs = broad singlet. Signals of protons and carbons were assigned, as far as possible, by using the following two-dimensional NMR spectroscopy techniques: [^1H-^1H] COSY, [^1H-^{13}C] COSY (HSQC: Heteronuclear Single Quantum Coherence) and long range [^1H-^{13}C] COSY (HMBC: Heteronuclear Multiple Bond Connectivity).

Mass spectrometry (electrospray mode, ES; chemical ionization mode, CI) were recorded on a high performance orthogonal acceleration reflecting TOF mass spectrometer operating in positive and negative mode, coupled to a Waters 2975 HPLC.

Chemistry: Experimental Procedures and Analytical Data

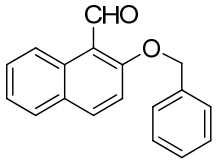
Synthesis of Known Compounds 6i, 6ii and 12i

2-Methoxy-naphthalene-1-carbaldehyde (6i)[18]



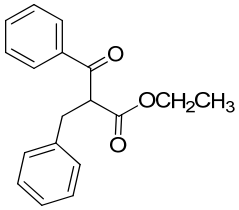
To a stirring solution of 2-hydroxy-1-naphthaldehyde **5** (1 g, 5.8 mmol, 1 eq.) in dry DMF (40 mL), K_2CO_3 (1.60 g, 11.6 mmol, 2 eq.) was added and the resulting suspension stirred at rt for 15 min. MeI (300 µl, 5.8 mmol, 1 eq.) was added and the reaction stirred at rt for 18 h. A solution of NaOH (aqueous, 5%, 20 mL) was added and the resulting mixture extracted with DCM (3 × 30 mL). The organic layers were collected and washed with water (3 × 50 mL), dried ($MgSO_4$) and concentrated at reduced pressure to afford the crude product as colourless crystals (900 mg, 4.8 mmol, 83%) which was used without further purification. Mp 84-86 °C (*lit.* [18] 84 °C); δ_H (300 MHz, $CDCl_3$) 10.86 (s, 1H, CHO), 9.24 (dd, 1H, J = 8.8 Hz, J = 1.0 Hz, ArH), 8.03 (d, 1H, J = 9.1 Hz, ArH), 7.59 (dt, 1H, ^2J = 7.7 Hz, ^3J = 1.5 Hz, ArH), 7.38 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.1 Hz, ArH), 7.23 (d, 1H, J = 6.7 Hz, ArH) and 4.02 (s, 3H, O-CH_3); *m/z* (ES^+) 208.91 [$(M+Na)^+$, 100%].

2-Benzyloxy-naphthalene-1-carbaldehyde (6ii)[19]



To a stirring solution of 2-hydroxy-1-naphthaldehyde **5** (2 g, 11.6 mmol, 1 eq.) in acetone (30 mL) was added K_2CO_3 (2.40 g, 17.4 mmol, 1.5 eq.) and the reaction mixture stirred at room temperature for 15 min. Benzyl bromide (2.57 mL, 12.7 mmol, 1.1 eq.) was added and the reaction stirred at reflux for 18 h. After filtering through a celite pad, the resulting acetone solution was concentrated at reduced pressure, the residue partitioned between EtOAc-H_2O (1:1, 100 mL), the organic layer washed with water (3 × 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated at reduced pressure. The product was obtained as brown solid (2.45 g, 81%) and used without further purification. Mp 119-121 °C (*lit.* [19]118-119 °C); δ_H (300 MHz, $CDCl_3$) 10.98 (s, 1H, CHO), 9.23 (d, 1H, J = 8.8 Hz, ArH), 8.03 (d, 1H, J = 8.9 Hz, ArH), 7.77 (d, 1H, J = 7.5 Hz, ArH), 7.66-7.54 (m, 1H, ArH), 7.50-7.33 (m, 7H, ArH) and 5.33 (s, 2H, C$\underline{H_2}$-Ph); *m/z* (ES^+) 284.86 [$(M+Na)^+$, 100%].

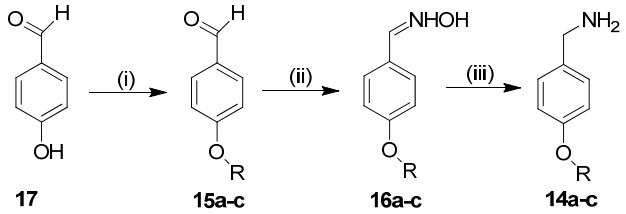
Ethyl 2-benzyl-3-oxo-3-phenyloxopropanoate (12ii)[20]



A solution of NaOEt was prepared by addition of Na metal (0.25 g, 10.8 mmol) to dry ethanol (10 mL). Ethyl benzoylacetate (4.6 mL, 40 mmol, 1 eq.) was added and the resulting solution stirred at room temperature for 10 min. Benzyl bromide (1.18 mL, 10 mmol, 0.25 eq.) was added and the reaction heated at reflux for 15 h. After removing the solvent at reduced pressure, the resulting residue was dissolved in ether (10 mL) and washed with water (3 × 10 mL). The organic layers were collected, dried ($MgSO_4$) and concentrated at reduced pressure. Purification by Kugelrohr distillation afforded the product as an orange oil (3 g, 10.6 mmol, 27%). δ_H (300 MHz, $CDCl_3$) 7.92-7.85 (m, 2H, ArH), 7.49 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.2 Hz, ArH), 7.37 (dt, 2H, ^2J = 8.0 Hz, ^3J = 1.4 Hz, ArH), 7.22-7.07 (m, 5H, ArH), 4.55 (t, 1H, J = 7.3 Hz, H-2), 4.02 (q, 2H, J = 7.1 Hz, O-C$\underline{H_2}$CH$_3$), 3.25 (dd, 2H, ^2J = 7.6 Hz, ^3J = 2.5 Hz, H-1') and 1.04 (t, 3H, J = 7.1 Hz, O-CH$_2$C$\underline{H_3}$); *m/z* (ES$^+$) 304.82 [(M+Na)$^+$, 100%].

Preparation of Benzylamines 14a-c

Prepared according to the 3 steps synthetic methods described by Coxon, **Scheme S1**. [21] All the other benzylamines used were purchased by Aldrich UK and used without further purification.

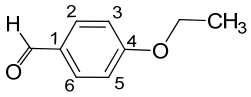


Scheme S1 - Outline of the three step syntheses of benzyl amines **14a-c**. *Reagents and Conditions*: (i) Alkyl bromide (1.2 eq.), K_2CO_3 (2 eq.), H_2O-MeOH (1:1), 18 h, reflux; (ii) NH_2OHHCl (1.2 eq.), K_2CO_3 (2 eq.), H_2O-EtOH (1:1), 4 h, rt; (iii) Nickel-alluminium alloy, NaOH (10%, aq.), 4 h, rt. (a, R = Et; b, R = Pro; c, R = But).

Synthesis of 4-alkyloxybenzaldehydes15a-c

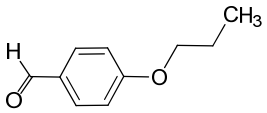
To a stirring solution of 4-hydroxybenzylaldehyde**17** (9.05 g, 74 mmol, 1 eq.) in water/methanol (1:1, 200 mL) were added the required alkyl bromide (2 eq.), K_2CO_3 (1.2 eq) and the reaction mixture stirred at reflux for 18 h. After cooling to room temperature, the solvent was removed at reduced pressure. The resulting residue was dissolved in diethyl ether (100 mL) and washed with 10% aqueous NaOH (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated at reduced pressure to afford the crude product **15a-c** as a colourless oil which was used without further purification.

4-Ethoxybenzaldehyde (15a)[21]



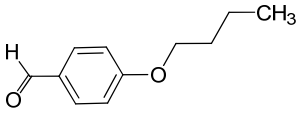
From 4-hydroxybenzaldehyde **17** (9.05 g, 74.1 mmol), yielded **15a** (8.43 g, 0.56 mmol, 76%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 9.85 (s, 1H, CHO), 7.80 (d, 2H, J = 8.8 Hz, AA'BB', H-2, H-6), 6.96 (d, 2H, J = 8.8 Hz, AA'BB', H-3, H-5), 4.09 (q, 2H, J = 7.0 Hz, O-C$\underline{H_2}$$CH_3$) and 1.43 (t, 2H, J = 7.0 Hz, O-CH_2C$\underline{H_3}$). Data is in agreement with the literature.[21]

4-Propyloxybenzaldehyde (15b)[22]



From 4-hydroxybenzaldehyde **17** (9.05 g, 74.1 mmol), yielded **15b** (12.14 g, 74.9 mmol, quant.) as an orange oil. δ_H (400 MHz, $CDCl_3$) 9.87 (s, 1H, CHO), 7.81 (d, 2H, J = 8.8 Hz, AA'BB', H-2, H-6), 6.98 (d, 2H, J = 8.8 Hz, AA'BB', H-3, H-5), 3.99 (t, 2H, J = 6.5 Hz, O-C$\underline{H_2}$$CH_2CH_3$), 1.85-1.80 (m, 2H, O-$CH_2C\underline{H_2}$$CH_3$) and 1.05 (t, 3H, J = 7.4 Hz, O-CH_2CH_2C$\underline{H_3}$). Data is in agreement with the literature.[22]

4-Butoxybenzaldehyde (15c)[22]

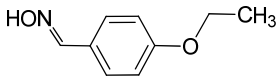


From 4-hydroxybenzaldehyde **17** (4.50 g, 74.1 mmol), yielded **15c** (6.50 g, 36.4 mmol, quant.) as an orange oil. δ_H (400 MHz, $CDCl_3$) 9.86 (s, 1H, CHO), 7.81 (d, 2H, J = 9.0 Hz, AA'BB', H-2, H-6), 6.98 (d, 2H, J = 9.0 Hz, AA'BB', H-3, H-5), 4.03 (t, 2H, J = 6.5 Hz, O-C$\underline{H_2}$$CH_2CH_2CH_3$), 1.86-1.72 (m, 2H, O-$CH_2C\underline{H_2}$$CH_2CH_3$), 1.58-1.42 (m, 2H, O-$CH_2CH_2C\underline{H_2}$$CH_3$) and 0.95 (t, 3H, J = 6.5 Hz, O-$CH_2CH_2CH_2$C$\underline{H_3}$). Data is in agreement with the literature.[22]

Synthesis of 4-alkyloxybenzaldoxymes16a-c

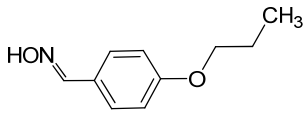
To a stirring solution of 4-alkoxybenzaldehyde **15a-c** (1 eq.) and K_2CO_3 (2 eq) in water/ethanol (1:1, 200 mL, 0.2 M) was added a solution of hydroxylammonium chloride (1.2 eq.) in water (20 mL). The reaction mixture was stirred at room temperature for 4 h. After removing the suspension of K_2CO_3 by filtration, the reaction was cooled to 0 °C and the aldoxime products **16a-c**obtained as colourless crystals which were filtered, dried and used without further purification.

4-Ethoxybenzaldoxime (16a)[21]



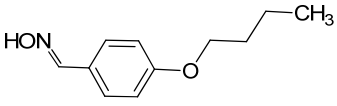
From 4-ethoxybenzaldehyde **15a** (8.43 g, 56.1 mmol), yielded **16a** (5.70 g, 34.5 mmol, 62%) as a white microcrystalline solid. Mp 83-85 °C (*lit.*[21]81-86 °C); δ_H (400 MHz, $CDCl_3$) 8.33 (brs, 1H, OH), 8.09 (s, 1H, C*H*=NOH), 7.50 (d, 2H, J = 8.8 Hz, AA'BB', H-2, H-6), 6.89 (d, 2H, J = 8.8 Hz, AA'BB', H-3, H-5), 4.05 (q, 2H, J = 7.0 Hz, O-CH_2CH$_3$) and 1.42 (t, 3H, J = 7.0 Hz, O-CH$_2$CH_3). Data is in agreement with the literature.[21]

4-Propyloxybenzaldoxyme (16b) [23]



From 4-propyloxybenzaldehyde **15b**(6.92 g, 42.1 mmol), yielded **16b** (6.00 g, 33.5 mmol, 81%) as a white microcrystalline solid. Mp 80-83 °C (*lit.* [23] 82-83 °C); δ_H (400 MHz, $CDCl_3$) 8.08 (s, 1H, C*H*=NOH), 7.49 (d, 2H, J = 8.8 Hz, AA'BB', H-2, H-6), 6.89 (d, 2H, J = 8.8 Hz, AA'BB', H-3, H-5), 3.94 (t, 2H, J = 6.6 Hz, O-CH_2CH$_2$CH$_3$), 1.85-1.75 (m, 2H, O-CH$_2$CH_2CH$_3$) and 1.04 (t, 3H, J = 7.5 Hz, O-CH$_2$CH$_2$CH_3). Data is in agreement with the literature.[23]

4-Butoxybenzaldoxyme (16c)[24]

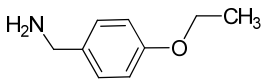


From 4-butoxybenzaldehyde **15c** (6.90 g, 38.7 mmol), yielded **16c** (5.80 g, 30.0 mmol, 78%) as a white microcrystalline solid. Mp 55-57 °C (*lit.* [24]54-56 °C); δ_H (400 MHz, $CDCl_3$) 8.08 (s, 1H, C*H*=NOH), 7.53-7.46 (m, 3H, AA'BB', H-2, H-6, NO*H*), 6.89 (d, 2H, J = 9.0 Hz, AA'BB', H-3, H-5), 3.98 (t, 2H, J = 6.5 Hz, O-CH_2CH$_2$CH$_2$CH$_3$), 1.82-1.71 (m, 2H, O-CH$_2$CH_2CH$_2$CH$_3$) 1.56-1.43 (m, 2H, O-CH$_2$CH$_2$CH_2CH$_3$) and 0.97 (t, 3H, J = 7.4 Hz, O-CH$_2$CH$_2$CH$_2$CH_3). Data is in agreement with the literature.[24]

Synthesis of 4-alkyloxybenzalamines14a-c.

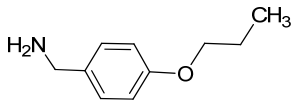
To a stirring solution of 4-alkoxybenzaldoxime **16a-c** (1 eq.) in ethanol (200 mL, 0.12 M) and 10% aqueous NaOH (200 mL) was added *with caution* portionwise nickel aluminium alloy (240 mg per mmol of aldoxyme). The reaction mixture was stirred at room temperature for 4 h, filtered through a pad of celite and the solvent removed at reduced pressure. DCM (200 mL) was added to the residue and the resulting solution washed with brine (3 × 100 mL). The organic layers were dried ($MgSO_4$) and concentrated at reduced pressure to afford 4-alkoxybenzylamines **14a-c** as pale yellow oils which were used without further purification.

4-Ethoxybenzylamine (14a)[21]



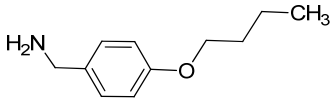
From 4-ethoxybenzaldoxime **16a** (5.60 g, 33.9 mmol), yielded **14a** (3.20 g, 21.1 mmol, 62%) as a white solid. Mp 224-228 °C (*lit.* [18]226-227 °C); δ_H (400 MHz, $CDCl_3$) 7.20 (d, 2H, J = 8.6 Hz, AA'BB', H-2, H-6), 6.85 (d, 2H, J = 8.6 Hz, AA'BB', H-3, H-5), 4.01 (q, 2H, J = 6.8 Hz, O-C$\underline{H_2}$$CH_3$), 3.79 (s, 2H, CH_2), 1.49 (br, 2H, NH_2) and 1.40 (t, 3H, J = 6.8 Hz, O-CH_2C$\underline{H_3}$). Data is in agreement with the literature.[21]

4-Propiloxybenzylamine (14b)[25]



From 4-propyloxybenzaldoxime **16b**(6.00 g, 33.5 mmol), yielded **14b** (3.80 g, 23.0 mmol, 69%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.20 (d, 2H, J = 8.6 Hz, AA'BB', H-2, H-6), 6.86 (d, 2H, J = 8.6 Hz, AA'BB', H-3, H-5), 3.94 (t, 2H, J = 6.2 Hz, O-C$\underline{H_2}$$CH_2CH_3$), 3.78 (s, 2H, CH_2), 1.79-1-71 (m, 2H, O-CH_2C$\underline{H_2}$$CH_3$), 1.44-1.32 (m, 2H, NH_2) and 0.96 (t, 3H, J = 7.4 Hz, O-CH_2CH_2C$\underline{H_3}$). Data is in agreement with the literature.[25]

4-Butoxybenzylamine (14c)[26]

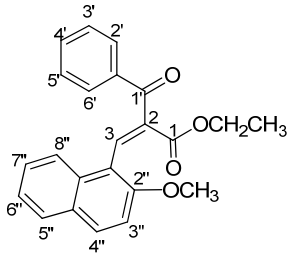


From 4-butoxybenzaldoxime **16c**(5.80 g, 30.0 mmol), yielded **14c** (3.50 g, 19.5 mmol, 65%) as a white solid. Mp96-98 °C (*lit.*[26]95-100 °C); δ_H (400 MHz, $CDCl_3$) 7.20 (d, 2H, J = 8.8 Hz, AA'BB', H-2, H-6), 6.86 (d, 2H, J = 8.8 Hz, AA'BB', H-3, H-5), 3.94 (t, 2H, J = 6.6 Hz, O-C$\underline{H_2}$$CH_2CH_2CH_3$), 3.78 (s, 2H, CH_2), 1.82-1-67 (m, 2H, O-CH_2C$\underline{H_2}$$CH_2CH_3$), 1.60-1.41 (m, 4H, O-$CH_2CH_2C\underline{H_2}$$CH_3$ + NH_2) and 0.96 (t, 3H, J = 7.4 Hz, O-$CH_2CH_2CH_2$C$\underline{H_3}$). Data is in agreement with the literature.[26]

Synthesis of 7i-iv

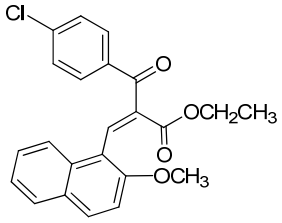
To a stirring solution of **6i**or **6ii**(1 eq.) in dry ethanol (10 mL), were added ethyl benzoylacetate (2 eq.) and piperidine (10 drops) and the reaction stirred at reflux for 18 h. After cooling to 0 °C, each product was precipitated as a yellow microcrystalline powder which was isolated by filtration and washed with cold ethanol.

Ethyl 2-benzoyl-3-(2''-methoxynaphthalen-1''-yl)acrylate (7i)



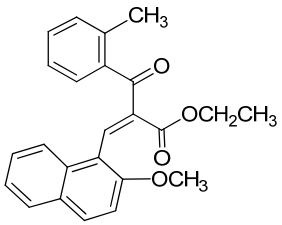
Yielded **7i** (250 mg, 0.69 mmol, 32%) from **6i** (0.404 g, 2.1 mmol) as a yellow microcrystalline powder. Mp 128-130 °C; ν_{max} cm^{-1} (KBr) 2940, 2836(C-O-CH_2), 1720 (C=O), 1590, 1510 (C-HAr) ; δ_H (300 MHz, $CDCl_3$) 8.44 (s, 1H, H-3), 7.96 (dd, 1H, ^2J = 8.5 Hz, ^3J = 0.6 Hz, H-8''), 7.90-7.84 (m, 2H, ArH), 7.74 (t, 2H, J = 7.7 Hz, ArH), 7.57-7.28 (m, 5H, ArH), 7.02 (d, 1H, J = 9.0 Hz, H-3''), 4.25 (q, 2H, J = 7.0 Hz, O-C$\underline{H_2}$$CH_3$), 3.35 (s, 3H, CH_3O) and 1.16 (t, 3H, J = 7.0 Hz, O-CH_2C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 193.2 (C=O), 166.3 (C=O), 154.4 (C2''), 141.5 (C2), 139.0 (C3), 137.5 (C1'a), 133.0 (C8''a), 132.8 (C4'), 132.3 (CH, Ar), 129.0 (C7''), 128.8 (C4''a), 128.7 (C4''), 128.3 (C5''), 127.7 (CH, Ar), 124.3 (C6''), 123.9 (C8''), 116.0 (C1''), 112.6 (C3''), 61.8 (O-$\underline{C}$$H_2CH_3$), 54.9 (O-$CH_3$) and 14.4 (O-$CH_2$$\underline{C}$$H_3$); *m/z* ($ES^+$) 382.85 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 383.1271, $C_{23}H_{20}O_4Na$ requires 383.1259] (+3.0 ppm).

Ethyl 2-(4'-chlorobenzoyl)-3-(2''-methoxynaphthalen-1''-yl)acrylate (7ii)



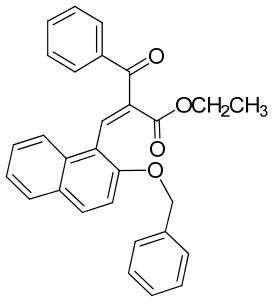
Yielded **7ii** (706 mg, 1.79 mmol, 46%) from **6i** (723 mg, 3.88 mmol) as a yellow microcrystalline solid. Mp 126-128 °C; ν_{max} cm^{-1} (KBr): 2983 (C-O-CH$_2$), 1715 (C=O), 1679 (C=O), 1613 (C-HAr), 1508 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.45 (s, 1H, H-3), 7.94 (d, 1H, J = 8.5 Hz, H-8''), 7.86-7.79 (m, 4H, H-2', H-6', H-5'', H-7''), 7.57-7.49 (m, 1H, H-4''), 7.42-7.20 (m, 3H, H-3', H-5', H-6''), 7.04 (d, 1H, J = 9.4 Hz, H-3''), 4.26 (q, 2H, J = 7.1 Hz, O-C$\underline{H_2}$CH$_3$), 3.40 (s, 3H, O-CH$_3$) and 1.19 (t, 3H, J = 7.1 Hz, O-CH$_2$C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 192.0 (C=O), 165.7 (C=O), 154.2 (C2''), 139.1 (C3), 138.9 (C4'), 135.7 (C2), 133.8 (C1'a), 132.6 (C8''a), 132.3 (C3', C5'), 130.3 (C2', C6'), 128.7 (C4''a), 128.6 (C4''), 128.5 (C5''), 127.6 (C7''), 124.2 (C6''), 123.6 (C8''), 115.5 (C1''), 112.3 (C3''), 61.6 (O-C$\underline{H_2}$CH$_3$), 54.7 (O-CH$_3$) and 14.2 (O-CH$_2$C$\underline{H_3}$); *m/z* (ES$^+$) 416.81 [(M+Na)$^+$, 100%]; HRMS (ES$^+$) [Found: (M+Na)$^+$, 417.0874, $C_{23}H_{19}O_4NaCl$ requires 417.0870] (+1.0 ppm).

Ethyl 3-(2''-methoxynaphthalen-1''-yl)-2-(2'-methylbenzoyl)acrylate (7iii)



Yielded **7iii** (386 mg, 1.03 mmol, 43%) from **6i** (447 mg, 2.40 mmol) as a yellow microcrystalline solid. Mp 146-148 °C; ν_{max} cm^{-1} (KBr): 2937, 2841(C-O-CH$_2$), 1726, 1670 (C=O), 1621 (C-HAr), 1508 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.31 (s, 1H, H-3), 7.87 (d, 1H, J = 8.7 Hz, H-8''), 7.76-7.65 (m, 3H, ArH), 7.49 (dt, 1H, ^2J = 7.6 Hz, ^3J = 1.3 Hz, ArH), 7.34 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.0 Hz, ArH), 7.23-7.18 (m, 1H, ArH), 7.11-6.99 (m, 3H, H-3'' + 2 × ArH), 4.21 (q, 2H, J = 7.0 Hz, O-C$\underline{H_2}$CH$_3$), 3.55 (s, 3H, O-CH$_3$), 2.29 (s, 3H, CH$_3$) and 1.16 (t, 3H, J = 7.0 Hz, O-CH$_2$C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 195.2 (C=O), 165.8 (C=O), 153.9 (C2''), 139.4 (C3), 139.2 (C2'), 136.8 (C1'a), 136.3 (C2), 132.4 (C8''a), 131.5 (C4'), 131.3 (C3'), 130.6 (C6'), 128.6 (C4''), 128.4 (C5''), 127.4 (C7''), 124.9 (C5'), 124.0 (C6''), 123.9 (C8''), 116.2 (C1''), 112.3 (C3''), 61.3 (O-C$\underline{H_2}$CH$_3$), 55.2 (O-CH$_3$), 20.8 (CH$_3$) and 14.0 (O-CH$_2$C$\underline{H_3}$); *m/z* (ES$^+$) 396.86 [(M+Na)$^+$, 100%]; HRMS (ES$^+$) [Found: (M+Na)$^+$, 397.1414, $C_{24}H_{20}O_4Na$ requires 397.1416] (-0.3 ppm).

Ethyl 2-benzoyl-3-(2''-benzyloxynaphthalen-1''-yl)acrylate (7iv)

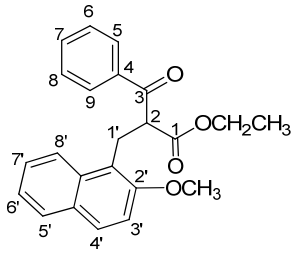


Yielded **7iv** (358 mg, 0.82 mmol, 42%) from **6ii** (513 mg, 1.95 mmol) as a yellow microcrystalline solid. Mp 122-124 °C; ν_{max} cm^{-1} (KBr): 3065 (CO-CH), 2982 (C-O-C), 1706 (C=O), 1670 (C=O), 1591 (C-HAr), 1509 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.33 (s, 1H, H-3), 7.94 (dd, 1H, J = 8.6 Hz, J = 0.5 Hz, H-8"), 7.81 (dd, 2H, ^2J = 8.4 Hz, ^3J = 1.0 Hz, ArH), 7.66 (d, 1H, J = 8.1 Hz, ArH), 7.61 (d, 1H, J = 9.1 Hz, ArH), 7.50 (dt, 1H, ^2J = 7.7 Hz, ^3J = 1.5 Hz, ArH), 7.39-7.17 (m, 9H, ArH), 6.94 (d, 1H, J = 9.1 Hz, ArH), 4.82 (s, 2H, OC$\underline{H_2}$-Ph), 4.27 (q, 2H, J = 7.2 Hz, O-C$\underline{H_2}$$CH_3$) and 1.18 (t, 3H, J = 7.2 Hz, O-CH_2C$\underline{H_3}$); δ_C (75.5 MHz, $CDCl_3$) 193.2 (C=O), 165.7 (C=O), 153.3 (C2"), 139.2 (C3), 137.1 (C1'a), 137.0 (C2"'a), 135.0 (C2), 132.7 (C8"a), 132.5 (CH, Ar), 131.5 (CH, Ar), 128.8 (CH, Ar), 128.7 (C4"a), 128.6 (CH, Ar), 128.3 (CH, Ar), 128.0 (CH, Ar), 127.8 (CH, Ar), 127.4 (CH, Ar), 126.5 (CH, Ar), 124.2 (C8"), 124.0 (C6"), 116.6 (C1"), 114.0 (C3"), 70.0 ($\underline{C}H_2$-Ph), 61.6 (O-$\underline{C}H_2CH_3$) and 14.1 (O-$CH_2\underline{C}H_3$); *m/z* (ES^+) 458.95 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 459.1574, $C_{29}H_{24}O_4Na$ requires 459.1572] (+0.4 ppm).

Synthesis of 8i-iv

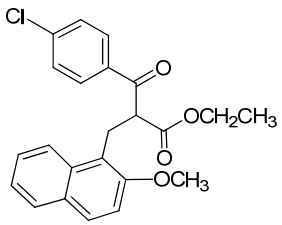
To a stirring solution of acrylates **7i-iv** (1 eq.) in pyridine (10 mL), was added $NaBH_4$ (1.1 eq.) and the reaction mixture stirred at rt for 2 h. After pouring into cold 2M HCl (40 mL) the mixture was extracted with DCM (3 × 50 mL), the organic layers dried ($MgSO_4$) and concentrated at reduced pressure. Purification by column chromatography (Hexane/EtOAc 95:5) afforded the pure products as colourless oils.

Ethyl 2-[2"-methoxynaphthyl-(1")-methyl]-3-oxo-3-phenylpropanoate (8i)



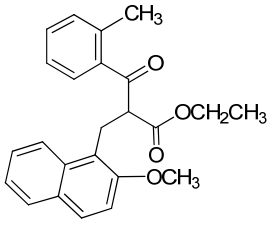
Yielded **8i** (706 mg, 1.94 mmol, 75%) from **7i** (936 mg, 2.58 mmol) as a colourless oil after purification by column chromatography (Hexane/EtOAc, 95:5). ν_{max} cm^{-1} (KBr): 3065, 2982 (C-O-CH_2), 1706 (C=O), 1670 (C=O), 1591 (C-HAr), 1509 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.04 (dd, 1H, ^2J = 8.7 Hz, ^3J = 0.6 Hz, H-8'), 7.88-7.82 (m, 2H, ArH), 7.78-7.69 (m, 2H, H-4' + 1 × ArH), 7.54-7.42 (m, 2H, ArH), 7.40-7.26 (m, 3H, ArH), 7.18 (d, 1H, J = 9.0 Hz, H-3'), 4.75 (m, 1H, H-2), 4.04-3.80 (m, 6H, H-1', O-C$\underline{H_2}$$CH_3$, O-C$\underline{H_3}$), 3.72 (d, 1H, J = 6.5 Hz, H-1') and 0.99 (t, 3H, J = 7.2 Hz, O-CH_2C$\underline{H_3}$); δ_C (75.5 MHz, $CDCl_3$) 195.9 (C=O), 170.4 (C=O), 155.2 (C2'), 136.7 (C4), 133.5 (C7), 133.3 (C8'a), 129.4 (C4'a), 128.9 (CH, Ar), 128.8 (CH, Ar), 128.7 (C5'), 128.6 (C4'), 126.8 (C7'), 123.5 (C6'), 123.4 (C8'), 119.7 (C1'a), 112.7 (C3'), 61.6 (O-CH_3), 56.3 (O-$\underline{C}H_2CH_3$), 54.0 (C2), 25.0 (C1') and 14.0 (O-$CH_2\underline{C}H_3$); *m/z* (ES^+) 484.87 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 385.1428, $C_{23}H_{22}O_4Na$ requires 385.1416] (+3.1 ppm).

Ethyl 3-(4-chlorophenyl)-2-[2''-methoxynaphthyl-(1'')-methyl]-3-oxopropanoate (8ii)



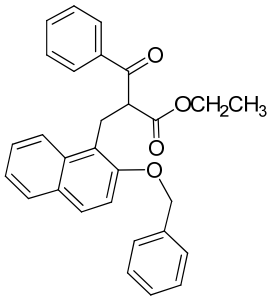
Yielded **8ii** (400 mg, 1.00 mmol, 76%) from **7ii** (523 mg, 1.38 mmol) as a colourless oil after purification by column chromatography (Hexane/EtOAc, 95:5). ν_{max} cm^{-1} (KBr): 2800 (C-O-CH_2), 1750 (C=O), 1680 (C=O), 1550 (C-HAr), 1510 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.00 (d, 1H, J = 8.0 Hz, H-8'), 7.82-7.67 (m, 4H, H-5, H-9, H-4', H-5'), 7.53-7.45 (m, 1H, H-7'), 7.37-7.22 (m, 3H, H-6, H-8, H-6'), 7.17 (d, 1H, J = 9.0 Hz, H-3'), 4.68 (t, 1H, J = 7.1 Hz, H-2), 3.85 (q, 2H, J = 7.1 Hz, O-C$\underline{H_2}$$CH_3$), 3.90-3.80 (m, 4H, O-C$\underline{H_3}$, H-1'), 3.70 (m, 1H, H-1') and 1.01 (t, 3H, J = 7.1 Hz, O-CH_2C$\underline{H_3}$); δ_C (75.5 MHz, $CDCl_3$) 194.7 (C=O), 169.9 (C=O), 154.9 (C2'), 139.7 (C7), 134.8 (C4), 133.0 (C8'a), 129.9 (C5, C9), 129.2 (C4'a), 128.9 (C8, C6), 128.8 (C4'), 128.6 (C5'), 126.7 (C7'), 123.4 (C8'), 123.2 (C6'), 119.2 (C1'a), 112.5 (C3'), 61.5 (O-$\underline{C}H_2CH_3$), 56.1 (C2), 53.7 (O-CH_3), 24.8 (C1') and 13.8 (O-$CH_2\underline{C}H_3$); *m/z* (ES^+) 418.81 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 419.1034, $C_{23}H_{21}O_4NaCl$ requires 419.1026] (+1.8 ppm).

Ethyl 2-[2''-methoxynaphtyl-(1'')-methyl]-3-oxo-3-(*o*-tolyl)-propanoate (8iii)



Yielded **8iii** (338 mg, 0.89 mmol, 75%) from **7iii** (448 mg, 1.19 mmol) as a colourless oil after purification by column chromatography (Hexane/EtOAc, 95:5). ν_{max} cm^{-1} (KBr): 2900 (C-O-CH_2), 1739 (C=O), 1514 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.05 (d, 1H, J = 8.7 Hz, H-8'), 7.79-7.67 (m, 2H, H-4', H-5'), 7.51-7.40 (m, 2H, H-6', H-7'), 7.36-7.04 (m, 5H, H-3', H-6, H-7, H-8, H-9), 4.70 (t, 1H, J = 7.3 Hz, H-2), 4.06-3.84 (m, 6H, OCH_3, O-C$\underline{H_2}$$CH_3$, H-1'), 3.76 (d, 2H, J = 7.3 Hz, H-1'), 2.40 (s, 3H, CH_3) and 0.97 (t, 3H, J = 7.0 Hz, O-CH_2C$\underline{H_3}$); δ_C (75.5 MHz, $CDCl_3$) 199.1 (C=O), 170.1 (C=O), 155.0 (C2'), 138.8 (C5), 137.5 (C4), 133.1 (C8'a), 131.8 (CH, Ar), 131.4 (CH, Ar), 129.2 (C4'a), 128.7 (C4'), 128.5 (C5'), 126.6 (C7'), 125.4 (C8), 123.4 (C8'), 123.3 (C6'), 119.6 (C1'a), 112.6 (C3'), 61.2 (O-$\underline{C}$$H_2CH_3$), 56.1 (O-$CH_3$), 24.5 (C1'), 20.9 ($CH_3$) and 13.8 (O-$CH_2$$\underline{C}$$H_3$); *m/z* ($ES^+$) 398.85 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 399.1567, $C_{24}H_{24}O_4Na$ requires 399.1572] (-1.4 ppm).

Ethyl 2-[2''-benzyloxynaphthyl-(1'')-methyl]-3-oxo-3-phenylpropanoate (8iv)



Yielded **8iv** (378 mg, 0.86 mmol, 71%) from **7iv** (537 mg, 1.23 mmol) as a colourless oil after purification by column chromatography (Hexane/EtOAc, 95:5). ν_{max} cm^{-1} (KBr): 3065, 2982 (C-O-CH_2), 1706 (C=O), 1670 (C=O), 1591 (C-HAr), 1509 (C-HAr); δ_H (300 MHz, $CDCl_3$) 8.06 (d, 1H, J = 8.5 Hz, H-8'), 7.82-7.66 (m, 4H, ArH), 7.54-7.18 (m, 11H, ArH), 5.18 (s, 2H, OC$\underline{H_2}$-Ph), 4.85 (dd, 1H, J = 6.4 Hz, H-2), 4.00-3.80 (m, 3H, O-C$\underline{H_2}$$CH_3$, H-1'), 3.76 (d, 1H, J = 6.6 Hz, H-1') and 0.91 (t, 3H, J = 7.2 Hz, O-CH_2C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 195.7 (C=O), 170.0 (C=O), 154.3 (C2'), 137.2 (C2''a), 136.5 (C4), 133.3 (CH, Ar), 133.2 (C8'a), 129.4 (C4'a), 128.7 (CH, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 128.5 (CH, Ar), 128.0 (CH, Ar), 127.3 (CH, Ar), 126.6 (CH, Ar), 126.4 (CH, Ar), 124.0 (C8'), 123.5 (C6'), 120.1 (C1'a), 113.9 (C3'), 70.9 ($\underline{C}$$H_2$-Ph), 61.3 (O-$\underline{C}$$H_2CH_3$), 53.9 (C2), 25.0 (C1') and 13.8 (O-$CH_2$$\underline{C}$$H_3$); *m/z* ($ES^+$) 460.90 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 461.1728, $C_{29}H_{26}O_4Na$ requires 461.1729] (-0.2 ppm).

Synthesis of Enamines 13i-v.

To a stirring solution of **12i-ii(**1 eq.) in dry ethanol (10 mL), were added the required amine (5 eq.) and acetic acid (5 eq.) and the reaction mixture stirred at reflux for 24 h. After the reaction had gone to completion, the solvent was removed at reduced pressure, the residue dissolved in DCM and washed with 1M HCl (2 × 20 mL). The organic layers were dried ($MgSO_4$) and concentrated at reduced pressure to afford the crude enamine which was used in the next step without further purification.

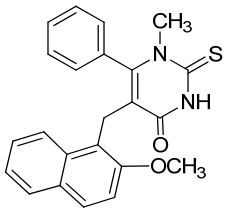
Synthesis of Enamines 9i-xii

Analogous to **13i-v**, starting from **8i-iv,** using 10 equivalents of amine and acetic acid. After removal of the solvent at reduced pressure, purification by basic alumina column chromatography (Hexane/EtOAc, 97.5:2.5 to 95:5) afforded the crude products **9i-xii** which were used in the next step without further purification.

Synthesis of 4i-xii, 10 and 11i-v

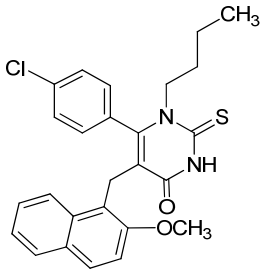
Crude enamines **9i-xii** and **13i-v** were dissolved in TMSNCS (2-3 mL) and the reaction mixture stirred at reflux for 3 h. After cooling to room temperature, saturated $NaHCO_3$ solution (10 mL) was added dropwise. The resulting mixture was extracted with DCM (3 × 10 mL), the organic layers dried ($MgSO_4$) and the solvent removed at reduced pressure. The pure products were obtained after purification by silica column chromatography (Hexane/EtOAc).

1-Methyl -5-[2''-methoxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4i)



Yielded **4i**(100 mg, 0.25 mmol, 24%) over 2 steps from **8i** (400 mg, 1.34 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 235-237 °C; ν_{max} cm^{-1} (KBr): 1650 (C=O), 1267 (C=S), 1140 (C=S); δ_H (400 MHz, DMSO-d_6) 12.78 (brs, 1H, NH), 7.74 (d, 1H, J = 7.7 Hz, H-5"), 7.66 (d, 1H, J = 9.0 Hz, H-4"), 7.62 (d, 1H, J = 8.5 Hz, H-6"), 7.33 (dt, 1H, ^2J = 7.6 Hz, ^3J = 1.6 Hz, H-7"), 7.29-7.17 (m, 2H, H-8", H-4'), 7.13 (t, 2H, J = 7.8 Hz, H-3', H-5'), 7.01 (d, 1H, J = 9.0 Hz, H-3"), 6.80 (d, 2H, J = 6.9 Hz, H-2', H-6'), 3.92 (s, 2H, H-1"), 3.54 (s, 3H, O-CH_3) and 3.10 (s, 3H, N-CH_3); δ_C (100 MHz, DMSO-d_6) 175.3 (C=S), 160.5 (C=O), 154.1 (C2"), 152.3 (C6), 132.4 (C8"a), 132.1 (C1'), 128.7 (C5"), 128.3 (C4"a), 128.2 (C4"), 128.1 (CH, Ar), 127.8 (CH, Ar), 127.5 (CH, Ar), 125.9 (C7"), 123.1 (C6"), 122.7 (C8"), 119.5 (C1"a), 118.5 (C5), 112.7 (C3"), 55.6 (O-CH_3), 40.1 (N-CH_3) and 20.9 (C1"); *m/z* (ES^+) 410.78 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 411.1140, $C_{23}H_{20}N_2O_2NaS$ requires 411.1143] (-0.7 ppm).

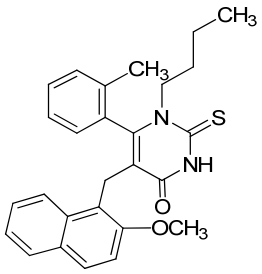
1-Butyl-6-(4'-chlorophenyl)-5-[2-methoxynaphthyl-(1")-methyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4ii)



Yielded **4ii**(84 mg, 0.18 mmol, 33%) over 2 steps from **8ii** (215 mg, 0.64 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 172-174 °C; ν_{max} cm^{-1} (KBr): 3399 (CONH), 3069 (CONH), 2958 (CH_2), 1656 (C=O), 1594 (NH), 1488 (CSNH), 1252 (C=S); δ_H (400 MHz, $CDCl_3$) 9.71 (brs, 1H, NH), 7.69 (d, 1H, J = 7.7 Hz, H-5"), 7.62 (d, 1H, J = 8.9 Hz, H-4"), 7.46 (d, 1H, J = 8.5 Hz, H-8"), 7.34-7.22 (m, 2H, H-6", H-7"), 6.95-6.84 (m, 3H, H-3", H-3', H-5'), 6.42 (d, 2H, J = 8.4 Hz, AA'BB', H-2', H-6'), 4.10 (s, 2H, H-1"), 3.70 (brs, 2H, N-C$\underline{H_2}$$CH_2CH_2CH_3$), 3.64 (s, 3H, O-$CH_3$), 1.60 (brs, 2H, N-$CH_2C\underline{H_2}$$CH_2CH_3$), 1.40 (brs, 2H, br, 2H, N-CH_2CH_2C$\underline{H_2}$$CH_3$) and 0.60 (t, 3H, J = 7.3 Hz, N-$CH_2CH_2CH_2$C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 174.9 (C=S), 160.1 (C=O), 154.2 (C2"), 151.8 (C6), 135.3 (C4'), 132.8 (C8"a), 129.7 (C1'), 129.1 (CH, Ar), 128.8 (C4"a), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.1 (CH, Ar), 126.7 (C7"), 123.3 (C8"), 123.1 (C6"),

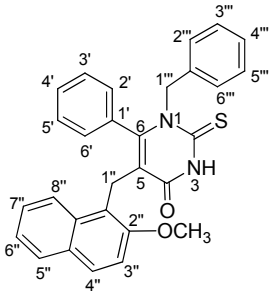
120.7 (C5), 120.0 (C1"a), 112.1 (C3"), 55.7 (O-CH_3), 51.6 (N-$\underline{C}H_2CH_2CH_2CH_3$), 29.3 (N-$CH_2\underline{C}H_2CH_2CH_3$), 20.7 (N-$CH_2CH_2\underline{C}H_2CH_3$), 19.6 (C1") and 13.2 (N-$CH_2CH_2CH_2\underline{C}H_3$); *m/z* ($ES^+$) 486.74 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 487.1223, $C_{26}H_{25}N_2O_2NaSCl$ requires 487.1231] (+1.7 ppm).

1-Butyl-5-[2''-methoxynaphthyl-(1'')-methyl]-2-thioxo-6-(*o*-tolyl)-2,3-dihydro-1*H*-pyrimidin-4-one (4iii)



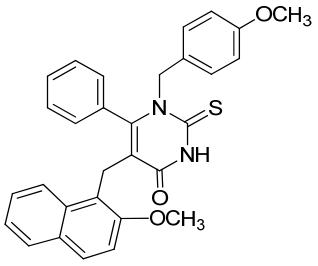
Yielded **4iii**(117 mg, 0.26 mmol, 31%) over 2 steps from **8iii** (320 mg, 1.0 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 176-178 °C; ν_{max} cm^{-1} (KBr): 2954 (CH_2), 1659 (C=O), 1493 (CSNH), 1252 (C=S); δ_H (400 MHz, $CDCl_3$) 9.78 (brs, 1H, NH), 7.66 (dd, 1H, ^2J = 7.7 Hz, ^3J = 1.7 Hz, H-5''), 7.56 (d, 1H, J = 9.0 Hz, H-4''), 7.51 (d, 1H, J = 8.4 Hz, H-6''), 7.34-7.18 (m, 2H, H-7'', H-8''), 7.04 (dt, 1H, ^2J = 7.6 Hz, ^3J = 1.2 Hz, ArH), 6.87-6.74 (m, 3H, H-3'', ArH), 6.50 (d, 1H, J = 7.3 Hz, ArH), 4.28-4.02 (m, 3H, H1'', N-C$\underline{H_2}CH_2CH_2CH_3$), 3.56 (s, 3H, O-$CH_3$), 3.10 (m, 1H, N-C$\underline{H_2}CH_2CH_2CH_3$), 1.58 (m, 1H, N-$CH_2C\underline{H_2}CH_2CH_3$), 1.07 (m, 1H, N-$CH_2C\underline{H_2}CH_2CH_3$), 0.87-0.69 (m, 2H, N-$CH_2CH_2C\underline{H_2}CH_3$) and 0.54 (t, 3H, J = 7.4 Hz, N-$CH_2CH_2CH_2C\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 175.1 (C=S), 160.4 (C=O), 153.0 (C2''), 152 (C6), 135.8 (C2'), 133.1 (C8''a), 130.9 (C1'), 129.7 (CH, ArH), 129.5 (CH, ArH), 128.8 (C4''a), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.0 (CH, Ar), 126.5 (C7''), 125.4 (CH, Ar), 123.2 (C6''), 123.0 (C8''), 120.0 (C1''a), 119.7 (C5), 112.1 (C3''), 55.6 (O-CH_3), 51.2 (N-$\underline{C}H_2CH_2CH_2CH_3$), 28.9 (N-$CH_2\underline{C}H_2CH_2CH_3$), 19.6 (N-$CH_2CH_2\underline{C}H_2CH_3$), 18.7 ($CH_3$) and 13.1 (N-$CH_2CH_2CH_2\underline{C}H_3$); *m/z* ($ES^+$) 466.84 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 467.1755, $C_{27}H_{28}N_2O_2NaS$ requires 467.1769] (-3.0 ppm).

1-Benzyl-5-[2''-methoxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4iv)



Yielded**4iv**(30 mg, 0.66 mmol, 23%) over 2 steps from **8i** (100 mg, 0.33mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 211-214 °C; ν_{max} cm^{-1} (KBr): 3172, 3071 (CONH), 2952 (CH_2), 2831 (C-O-CH_2), 1655 (C=O), 1592 (NH), 1493 (CSNH), 1251 (C=S), 1172 (C=S); δ_H (400 MHz, $CDCl_3$) 9.77 (brs, 1H, NH), 7.64 (dd, 1H, ^2J = 8.4 Hz, ^3J = 1.1 Hz, H-5"), 7.55 (d, 1H, J = 8.9 Hz, H-4"), 7.49 (d, 1H, J = 8.3 Hz, H-6"), 7.35-7.20 (m, 2H, H-7" + 1 × ArH), 7.18-7.08 (m, 3 H-8" + 2 × ArH), 6.98 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.0 Hz, ArH), 6.84 (d, 1H, J = 8.9 Hz, ArH), 6.82-6.71 (m, 2H, H-3" + 1 × ArH), 6.68 (dd, 2H, ^2J = 7.8 Hz, ^3J = 1.8 Hz, ArH), 6.26 (brs, 2H, ArH), 4.07 (s, 2H, H-1") and 3.60 (s, 3H, O-CH_3); δ_C (100 MHz, $CDCl_3$) 176.4 (C=S), 160.1 (C=O), 154.4 (C2"), 153.1 (C6), 135.6 (C1'"a), 132.9 (C8"a), 131.1 (C1'), 128.9 (CH, Ar), 128.8 (C4"a), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.2 (C4"), 127.9 (C5"), 127.6 (CH, Ar), 127.4 (CH, Ar), 126.4 (C4'"), 126.1 (C8"), 123.2 (C6"), 123.0 (C7"), 120.9 (C1"a), 120.1 (C5), 112.4 (C3"), 55.8 (O-CH_3) and 21.5 (C1"); *m/z* (ES^+) 486.79 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 487.1447, $C_{29}H_{24}N_2O_2NaS$ requires 487.1456] (-1.9 ppm).

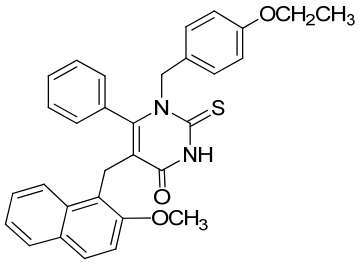
1-(4'''-Methoxybenzyl)-5-[2''-methoxynaphtyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4v)



Yielded**4v**(90 mg, 0.18 mmol, 33%) over 2 steps from **8i** (200 mg, 0.67 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 80:20). Mp 159-161 °C; ν_{max} cm^{-1} (KBr): 3446 (CONH), 3058 (CONH), 2937 (CH_2), 1651 (C=O), 1591 (NH), 1486 (CSNH), 1251 (C=S), 1165 (C=S); δ_H (400 MHz, $CDCl_3$) 9.76 (brs, 1H, NH), 7.64 (dd, 1H, ^2J = 7.7 Hz, ^3J = 1.5 Hz, H-5"), 7.54 (d, 1H, J = 9.0 Hz, H-4"), 7.48 (d, 1H, J = 8.4 Hz, H-6"), 7.35-7.17 (m, 2 H, ArH), 7.00 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.0 Hz, ArH), 6.90-6.70 (m, 3H, H-3' + 2 × ArH), 6.70-6.55 (m, 4H, H-2", H-3", H-5", H-6"), 6.26 (brs, 2H, ArH), 4.06 (s, 2H, H-1"), 3.74 (s, 3H, O-CH_3) and 3.60 (s, 3H, O-CH_3); δ_C (100 MHz, $CDCl_3$) 176.4 (C=S), 160.2 (C=O), 158.9 (C4'"), 154.0 (C2"), 153.0 (C6),

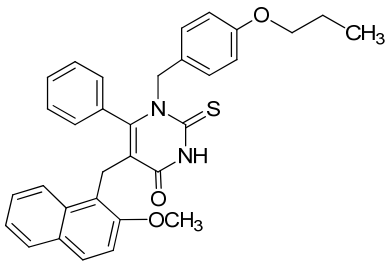
132.9 (C8"a), 131.1 (C1'), 129.0 (C4"a), 128.8 (C1'"a), 128.8 (C4"), 128.3 (C5"), 128.2 (CH, ArH 127.9 (C2'", C6'"), 127.6 (CH, ArH), 127.5 (CH, ArH), 126.3 (C7"), 123.2 (C6"), 123.1 (C8"), 120.8 (C1"a), 120.1 (C5), 113.8 (C3'", C5'"), 112.4 (C3"), 55.8 (O-CH_3), 55.3 (O-CH_3) and 21.4 (C1"); *m/z* (ES^+) 516.81 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 517.1550, $C_{30}H_{26}N_2O_3NaS$ requires 517.1562] (-2.4 ppm).

1-(4'''-Ethoxybenzyl)-5-[2''-methoxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4vi)



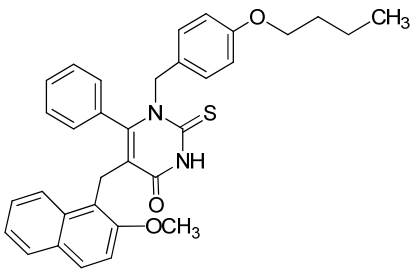
Yielded **4vi**(79 mg, 0.15 mmol, 26%) over 2 steps from **8i** (220 mg, 0.73 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 112-115 °C; ν_{max} cm^{-1} (KBr): 3059 (CONH), 2934 (CH_2), 1659 (C=O), 1593 (NH), 1475 (CSNH), 1250 (C=S), 1165 (C=S); δ_H (400 MHz, $CDCl_3$) 10.01 (brs, 1H, NH), 7.54 (d, 1H, *J* = 7.9 Hz, H-5"), 7.44 (d, 1H, *J* = 9.0 Hz, H-4"), 7.39 (d, 1H, *J* = 8.4 Hz, H-8"), 7.26-7.09 (m, 2H, H-6", H-7"), 6.89 (t, 1H, *J* = 7.6 Hz, H-4'), 6.74 (d, 1H, *J* = 9.0 Hz, H-3"), 6.69 (brs, 2H, H-3', H-5'), 6.55 (d, 2H, *J* = 8.9 Hz, AA'BB', H-3'", H-5'"), 6.48 (d, 2H, *J* = 8.9 Hz, AA'BB', H-2'", H-6'"), 6.16 (brs, 2H, H-2', H-6'), 3.97 (s, 2H, H-1"), 3.84 (q, 2H, *J* = 6.9 Hz, O-C$\underline{H_2}$$CH_3$), 3.49 (s, 3H, O-$CH_3$) and 1.27 (t, 3H, *J* = 6.9 Hz, O-CH_2C$\underline{H_3}$)δ_C (100 MHz, $CDCl_3$) 176.4 (C=S), 160.3 (C=O), 158.2 (C4'"), 154.4 (C2"), 153.1 (C6), 132.8 (C8"a), 131.1 (C1'), 128.9 (C4"a), 128.8 (C4'), 128.3 (C5"), 128.1 (C4"), 127.9 (C2', C6'), 127.6 (C1'"a), 127.5 (C3', C5'), 127.2 (C2'", C6'"), 126.3 (C7"), 123.2 (C6"), 123.0 (C8"), 120.8 (C1"a), 120.0 (C5), 114.3 (C3'", C5'"), 112.4 (C3"), 63.5 (O-$\underline{C}H_2CH_3$), 55.8 (O-CH_3), 21.4 (C1") and 14.9 (O-$CH_2\underline{C}H_3$); *m/z* (ES^+) 530.78 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 531.1728, $C_{31}H_{28}N_2O_3NaS$ requires 531.1718] (+1.8 ppm).

1-(4'''-Propoxybenzyl)-5-[2''-methoxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4vii)



Yielded **4vii**(181 mg, 0.34 mmol, 39%) over 2 steps from**8i**(325mg, 1.0 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). ν_{max} cm^{-1} (KBr): 3420 (CONH), 2963 (CH_2), 1656 (C=O), 1512 (NH), 1474 (CSNH), 1251 (C=S), 1175 (C=S); δ_H (400 MHz, $CDCl_3$) 10.04 (brs, 1H, NH), 7.64 (d, 1H, J = 8.0 Hz, H-5"), 7.54 (d, 1H, J = 9.1 Hz, H-4"), 7.48 (d, 1H, J = 8.4 Hz, H-8"), 7.32-7.19 (m, 2H, H-6", H-7"), 7.14 (d, 1H, J = 8.5 Hz, ArH), 6.99 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.1 Hz, ArH), 6.88-6.74 (m, 2H, H-3" + 1 × ArH), 6.67-6.55 (m, 4H, H-2"', H-3"', H-5"', H-6"'), 6.27 (brs, 2H, ArH), 4.05 (s, 2H, H-1"), 3.85 (t, 2H, J = 6.6 Hz, O-C$\underline{H_2}$$CH_2CH_3$), 3.60 (s, 3H, O-$CH_3$), 1.85-1.69 (m, 2H, O-$CH_2C\underline{H_2}$$CH_3$) and 1.01 (t, 3H, J = 5.3 Hz, O-CH_2CH_2C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 176.4 (C=S), 160.3 (C=O), 158.4 (C4"'a), 154.4 (C2"), 153.1 (C6), 132.9 (C8"a), 131.1 (C1'), 129.0 (CH, Ar), 128.8 (CH, ArH), 128.7 (C1"'a), 128.3 (CH, Ar), 128.1 (CH, Ar), 128.0 (CH, Ar), 127.5 (C2"', C6"'), 126.3 (C7"), 123.2 (C6"), 123.0 (C8"), 120.8 (C1"a), 120.0 (C5), 114.9 (C3"', C5"'), 112.4 (C3"), 69.6 (O-$\underline{C}$$H_2CH_2CH_3$), 55.8 (O-$CH_3$), 22.6 (O-$CH_2$$\underline{C}$$H_2CH_3$), 21.4 (C1") and 10.6 (O-$CH_2CH_2$$\underline{C}$$H_3$); *m/z* ($ES^+$) 544.78 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 545.1879, $C_{32}H_{30}N_2O_3NaS$ requires 545.1875] (+ 0.7 ppm).

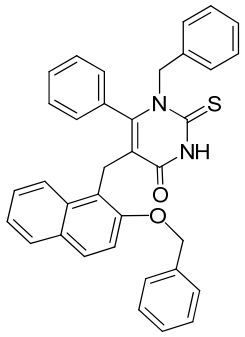
1-(4"'-Butoxybenzyl)-5-[2"-methoxynaphthyl-(1")-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4viii)



Yielded **4viii**(94 mg, 0.17 mmol, 20%) over 2 steps from **8i** (325 mg, 1.08 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 95 °C (decomposes); ν_{max} cm^{-1} (KBr): 3426 (CONH), 2958 (CH_2), 1679 (C=O), 1613 (NH), 1512, 1473 (CSNH), 1176 (C=S); δ_H (400 MHz, $CDCl_3$) 9.82 (brs,1H, NH), 7.64 (d, 1H, J = 7.9 Hz, H-5"), 7.55 (d, 1H, J = 9.0 Hz, H-4"), 7.47 (d, 1H, J = 8.5 Hz, H-6"), 7.33-7.17 (m, 2H, H-7", H-8"), 6.99 (m, 1H, ArH), 6.90-6.73 (m, 3H, H-3" + 2 × ArH), 6.66-6.54 (m, 4H, H-2", H-3", H-5", H-6"), 6.28 (brs, 2H, ArH), 4.06 (s, 2H, H-1"), 3.87 (t, 2H, J = 6.5 Hz, O-C$\underline{H_2}$$CH_2CH_2CH_3$), 3.60 (s, 3H, O-$CH_3$), 1.79-1.65

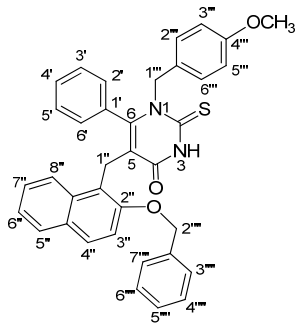
(m, 2H, O-$CH_2C\underline{H_2}CH_2CH_3$), 1.53-1.40 (m, 2H, O-$CH_2CH_2C\underline{H_2}CH_3$) and 0.96 (t, 3H, J = 7.4 Hz, O-$CH_2CH_2CH_2C\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 176.6 (C=S), 160.4 (C=O), 158.7 (C4'''), 154.6 (C2''), 153.3 (C6), 133.1 (C8''a), 131.3 (C1'), 129.1 (C4''a), 129.0 (CH, Ar), 128.5 (CH, Ar), 128.4 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 127.6 (C1'''a), 126.5 (C7''), 123.4 (C6''), 123.2 (C8''), 120.7 (C1''a), 119.9 (C5), 114.6 (CH, ArH), 112.6 (C3''), 68.0 (O-$\underline{C}H_2CH_2CH_2CH_3$), 56.0 (O-$CH_3$), 31.6 (O-$CH_2\underline{C}H_2CH_2CH_3$), 21.7 (C1''), 19.5 (O-$CH_2CH_2\underline{C}H_2CH_3$) and 14.2 (O-$CH_2CH_2CH_2\underline{C}H_3$); *m/z* ($ES^+$) 558.77 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 559.2036, $C_{33}H_{32}N_2O_3NaS$ requires 559.2031] (+0.9 ppm).

1-Benzyl-5-[2''-benzyloxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4ix)



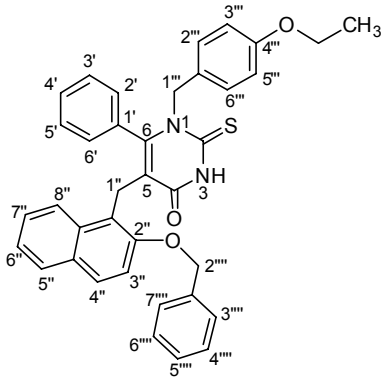
Yielded **4ix**(313 mg, 0.57 mmol, 31%) over 2 steps from **8iv** (820 mg, 2.1 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 189-191 °C; ν_{max} cm^{-1} (KBr): 3062 (CONH), 1593 (NH), 1646 (C=O), 1495 (CSNH), 1249 (C=S), 1171 (C=S); δ_H (400 MHz, $CDCl_3$) 10.43 (brs, 1H, NH), 7.53 (d, 1H, J = 8.1 Hz, H-5''), 7.42 (t, 2H, J = 9.8 Hz, H-6'' + 1 × ArH), 7.35-7.07 (m, 8H, ArH), 7.04-6.96 (m, 3H, ArH), 6.84 (t, 1H, J = 7.6 Hz, ArH), 6.78 (d, 1H, J = 9.0 Hz, H-3''), 6.62-6.49 (m, 3H, ArH), 6.06 (brs, 2H, ArH), 4.73 (s, 2H, H-2''') and 4.03 (s, 2H, H-1'');δ_C (100 MHz, $CDCl_3$) 176.3 (C=S), 160.5 (C=O), 153.5 (C2''), 153.1 (C6), 137.1 (C2''''a), 135.6 (C1'''a), 132.8 (C8''a), 131.1 (C1'), 129.0 (C4''a), 128.6 (CH, Ar), 128.3 (C5''), 128.0 (CH, Ar × 2), 127.7 (C4''), 127.5 (CH, Ar × 2), 127.4 (CH, Ar), 127.2 (CH, Ar), 127.1 (CH, Ar), 126.3 (CH, Ar), 126.1 (C7''), 123.3 (C6''), 123.1 (C8''), 120.6 (C1''a), 120.4 (C5), 113.3 (C3''), 70.3 (C2'''') and 21.6 (C1''); *m/z* (ES^+) 562.77 [$(M+Na)^+$, 100%].

1-(4'''-Methoxybenzyl)-5-[2''-benzyloxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4x)



Yielded **4x**(131 mg, 0.23 mmol, 25%) over 2 steps from **8iv** (400 mg, 1.06 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 100 °C (decomposes); ν_{max} cm^{-1} (KBr): 3420 (CONH), 2933 (CH_2), 1663 (C=O), 1594 (NH), 1513, 1431 (CSNH), 1248 (C=S), 1176 (C=S), 1084; δ_H (300 MHz, $CDCl_3$) 9.74 (brs, 1H, NH), 7.64 (dd, 1H, J^2 = 8.0 Hz, J^3 = 1.0 Hz, H-5"), 7.56-7.44 (m, 2H, H-4" + 1 × ArH), 7.46-7.21 (m, 7H, H-6", H-7" + 5 × ArH), 7.00-6.87 (m, 2H, H-3" + 1 × ArH), 6.76-6.66 (m, 2H, H-2' + 1 × ArH), 6.65-6.52 (m, 4H, H-2"', H-3"', H-5"', H-6"'), 6.30-6.09 (m, 2, ArH), 4.85 (s, 2H, H-2""), 4.12 (s, 2H, H-1") and 3.75 (s, 3H, O-CH_3)δ_C (100 MHz, $CDCl_3$) 176.3 (C=S), 160.1 (C=O), 158.8 (C4"'), 153.5 (C2"), 152.9 (C6), 137.1 (C2""a), 132.9 (C8"a), 131.1 (C1'), 129.1 (C4"a), 128.7 (CH, Ar × 2), 128.3 (C5"), 128.2 (CH, Ar), 128.1 (CH, Ar), 127.9 (CH, Ar), 127.6 (CH, Ar), 127.5 (CH, Ar), 126.3 (C7"), 123.3 (C8"), 123.2 (C6"), 120.7 (C1"a), 120.5 (C5), 113.7 (C3"', C5"'), 113.5 (C3"), 70.4 (C2""), 55.3 (O-CH_3) and 21.7 (C1"); *m/z* (ES^+) 592.99 $[(M+Na)^+$, 100%].

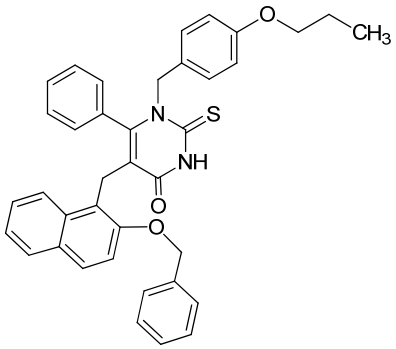
1-(4"'-Ethoxybenzyl)-5-[2"-benzyloxynaphthyl-(1")-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4xi)



Yielded **4xi**(80 mg, 0.13 mmol, 39%) over 2 steps from **8iv** (442 mg, 1.18 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 85-90 °C (decomposes); ν_{max} cm^{-1} (KBr): 3446 (CONH), 1655 (C=O), 1513 (CSNH), 1177 (C=S); δ_H (400 MHz, $CDCl_3$) 9.58 (brs, 1H, NH), 7.64 (d, 1H, J = 7.8 Hz, ArH), 7.58-7.46 (m, 2H, ArH), 7.46-7-19 (m, 7H, ArH), 6.99-6.87 (m, 2H, ArH), 6.71 (brs, 2H, ArH), 6.61 (d, 2H, J = 8.7 Hz, ArH), 6.55 (d, 2H, J = 8.7 Hz, ArH), 6.19 (brs, 2H, ArH), 4.85 (s, 2H, H-2""), 4.11 (s, 2H, H-1"), 3.94 (q, 2H,

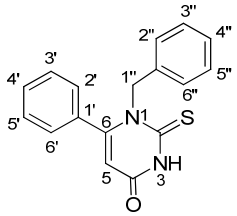
J = 7.0 Hz, O-C*H*$_2$CH$_3$) and 1.37 (t, 3H, *J* = 7.0 Hz, O-CH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 176.3 (C=S), 160.0 (C=O), 158.2 (C4'''), 153.5 (C2''), 152.9 (C6), 137.1 (C2''''a), 132.9 (C8''a), 131.1 (C1'), 130.1 (C4''a), 128.7 (CH, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 128.0 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, ArH), 127.6 (CH, Ar), 127.5 (CH, Ar), 127.5 (C1'''a), 126.3 (CH, Ar), 123.3 (CH, Ar), 123.2 (CH, Ar), 120.8 (C1''a), 120.5 (C5), 114.3 (CH, Ar), 113.4 (CH, Ar), 70.5 (*C*H$_2$-Ph), 63.5 (O-*C*H$_2$CH$_3$), 21.7 (C1'') and 14.9 (O-CH$_2$*C*H$_3$); *m/z* (ES^+) 607.10 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 607.2032, $C_{37}H_{32}N_2O_3NaS$ requires 607.2031] (0.1 ppm).

1-(4'''-Propoxybenzyl)-5-[2''-benzyloxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4xii)



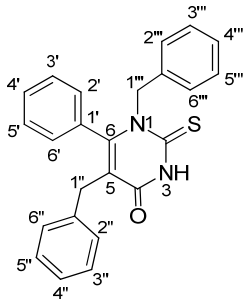
Yielded **4xii**(90 mg, 0.15 mmol, 21%) over 2 steps from **8iv** (246 mg, 0.65 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 85-90 °C (decomposes); ν_{max} cm^{-1} (KBr): 3420, 2963 (CH_2), 1678 (C=O), 1594 (CONH), 1512 (NH), 1474 (CSNH), 1274 (C=S), 1176 (C=S); δ_H (400 MHz, $CDCl_3$) 9.75 (brs, 1H, NH), 7.64 (d, 1H, *J* = 7.6 Hz, ArH), 7.52 (t, 2H, *J* = 9.3 Hz, ArH), 7.47-7.20 (m, 7H, ArH), 7.00-6.88 (m, 2H, ArH), 6.71 (brs, 2H, ArH), 6.62 (d, 2H, *J* = 8.7 Hz, ArH), 6.55 (d, 2H, *J* = 8.7 Hz, ArH), 6.20 (brs, 2H, ArH), 4.86 (s, 2H, H-2''''), 4.12 (s, 2H, H-1''), 3.82 (t, 2H, *J* = 6.6 Hz, O-C*H*$_2$CH$_2$CH$_3$), 1.80-1.72 (m, 2H, O-CH$_2$C*H*$_2$CH$_3$) and 1.04 (t, 3H, *J* = 7.5 Hz, O-CH$_2$CH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 176.3 (C=S), 160.1 (C=O), 158.5 (C4'''), 153.5 (C2''), 152.9 (C6), 137.1 (C2''''a), 132.9 (C8''a), 131.1 (C1'), 129.0 (CH, Ar), 128.7 (CH, Ar), 128.3 (CH, Ar), 128.1 (CH, Ar), 128.0 (CH, Ar), 127.9 (CH, Ar), 127.6 (CH, Ar), 127.5 (CH, Ar × 2), 127.4 (C1'''a), 126.3 (CH, Ar), 123.3 (CH, Ar), 123.2 (CH, Ar), 120.7 (C1''a), 120.5 (C5), 114.3 (CH, Ar), 113.5 (CH, Ar), 70.4 (*C*H$_2$-Ph), 69.6 (O-*C*H$_2$CH$_2$CH$_3$), 22.6 (O-CH$_2$*C*H$_2$CH$_3$), 21.7 (C1'') and 10.6 (O-CH$_2$CH$_2$*C*H3); *m/z* (ES^+) 620.74 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 621.2180, $C_{38}H_{34}N_2O_3NaS$ requires 621.2188] (-1.2 ppm).

1-Benzyl-6-phenyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (10)



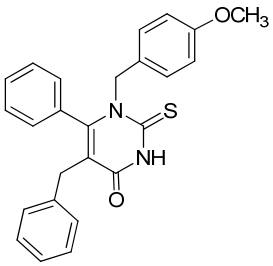
Yielded**10**(175 mg, 0.59 mmol, 80%) from enamine **13i** (210 mg, 0. 74 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 80:20). Mp 184-186 °C; ν_{max} cm^{-1} (KBr): 3180 (CONH), 3060 (CONH), 2928 (CH_2), 1670 (C=O), 1594 (NH), 1489 (CSNH), 1411 (CSNH), 1246 (C=S); δ_H (300 MHz, $CDCl_3$) 10.77 (brs, 1H, NH), 7.48-7.37 (m, 1H, ArH), 7.36-7.14 (m, 5H, ArH), 7.11-7.00 (m, 2H, ArH), 6.92-6.81 (m, 2H, ArH), 5.90 (s, 1H, H-5) and 5.52 (brs, 2H, H-1''); δ_C (100 MHz, $CDCl_3$) 178.5 (C=S), 159.6 (C=O), 157.7 (C6), 135.5 (C1''a), 133.2 (C1'), 130.3 (CH, Ar), 128.7 (CH, Ar), 128.6 (CH, Ar), 127.9 (CH, Ar), 127.7 (CH, Ar), 126.5 (CH, C4'), 109.1 (C5) and 54.6 (C1''); *m/z* (ES^+) 316.89 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 317.0722, $C_{17}H_{14}N_2ONaS$ requires 317.0725] (-0.9 ppm).

1,5-Dibenzyl-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (11i)



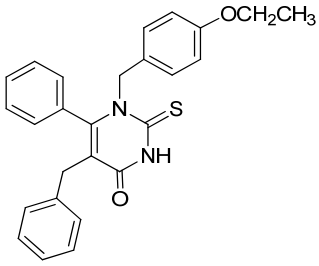
Yielded**11i**(117 mg, 0.30 mmol, 76%) from enamine **13ii** (150 mg, 0.40 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 80:20). Mp135-137 °C; ν_{max} cm^{-1} (KBr): 3060 (CONH), 2930 (CH_2), 1662 (C=O), 1494 (CSNH), 1259 (C=S); δ_H (300 MHz, $CDCl_3$) 9.66 (brs, 1H, NH), 7.39 (dt, 1H, ^2J = 5.5 Hz, ^3J = 1.2 Hz, ArH), 7.31-7.07 (m, 9H, ArH), 6.89-6.70 (m, 5H, ArH) and 3.41 (s, 2H, H-1''); δ_C (100 MHz, $CDCl_3$) 176.9 (C=S), 159.9 (C=O), 154.1 (C6), 138.8 (C1''a), 135.5 (C1'''a), 131.5 (C1'), 130.0 (CH, Ar), 128.7 (CH, Ar), 128.5 (CH, Ar), 128.6 (CH, Ar × 2), 128.5 (CH, Ar), 128.4 (CH, Ar), 127.6 (CH, Ar), 126.4 (CH, Ar), 119.6 (C5) and 32.1 (C1''); *m/z* (ES^+) 406.92 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 407.1194, $C_{24}H_{20}N_2ONaS$ requires 407.1194] (-0.1 ppm).

1-(4'''-Methoxybenzyl)-5-benzyl-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (11ii)



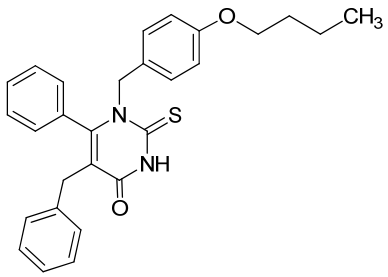
Yielded **11ii**(298 mg, 0.71 mmol, 60%) over 2 steps from**12ii** (510 mg, 1.27 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 192-195 °C; ν_{max} cm^{-1} (KBr): 3108 (CONH), 2953 (CH_2), 2832 (C-O-CH_2), 1697 (C=O), 1595 (NH), 1489 (CSNH), 1244 (C=S);δ_H (500 MHz, $CDCl_3$) 9.90 (brs, 1H, NH), 7.41 (dt, 1H, ^2J = 5.7 Hz, ^3J = 1.1 Hz, ArH), 7.32-7.23 (m, 2H, ArH), 7.15-7.10 (m, 3H, ArH), 6.89-6.67 (m, 8H, H-2''', H-3''', H-5''', H-6''' + 4 × ArH), 3.76 (s, 3H, O-CH_3) and 3.40 (s, 2H, H-1''); δ_C (100 MHz, $CDCl_3$) 176.8 (C=S), 160.0 (C=O), 159.1 (C4'''), 154.1 (C6), 138.8 (C1''a), 131.5 (C1'), 130.0 (CH, Ar), 128.7 (CH, Ar), 128.5 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 127.9 (CH, Ar), 127.5 (C1'''a), 126.4 (CH, Ar), 119.5 (C5), 113.9 (CH, Ar), 55.4 (O-CH_3) and 32.1 (C1''); *m/z* (ES^+) 436.76 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 437.1308, $C_{25}H_{22}N_2O_2NaS$ requires 437.1300] (+1.9 ppm).

1-(4'''-Ethoxybenzyl)-5-benzyl-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (11iii)



Yielded **11iii**(359 mg, 0.83 mmol, 68%) over 2 steps from **12ii** (512 mg, 1.23 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 203-206 °C; ν_{max} cm^{-1} (KBr): 3450 (NH), 3092 (CH_2), 2976 (C-O-CH_2), 1696 (C=O), 1594 (NH), 1491 (CSNH), 1247 (C=S); δ_H (400 MHz, $CDCl_3$) 9.70 (brs, 1H, NH), 7.40 (dt, 1H, ^2J = 7.5 Hz, ^3J = 1.2 Hz, ArH), 7.33-7.22 (m, 2H, ArH), 7.17-7.07 (m, 3H, ArH), 6.91-6.64 (m, 8H, H-2''', H-3''', H-5''', H-6''' + 4 × ArH), 3.97 (q, 2H, J = 7.0 Hz, O-C$\underline{H_2}$$CH_3$), 3.40 (s, 2H, H-1'') and 1.39 (t, 3H, J = 7.0 Hz, O-CH_2C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 177.1 (C=S), 160.0 (C=O), 158.5 (C4'''), 154.1 (C6), 138.8 (C1''a), 131.6 (C1'), 130.0 (CH, Ar), 128.7 (CH, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 128.3 (CH, Ar), 127.9 (CH, Ar), 127.4 (C1'''a), 126.4 (CH, Ar), 119.6 (C5), 114.5 (CH, Ar), 63.6 (O-$\underline{C}H_2CH_3$), 32.1 (C1'') and 14.9 (O-$CH_2\underline{C}H_3$); *m/z* (ES^+) 450.80 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 451.1440, $C_{26}H_{24}N_2O_2NaS$ requires 451.1452] (-0.1 ppm).

1-(4'''-Butoxybenzyl)-5-benzyl-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (11iv)

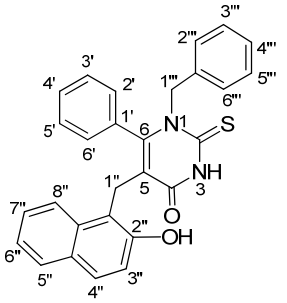


Yielded **11iv**(263 mg, 0.57 mmol, 57%) over 2 steps from **12ii** (450 mg, 1.0 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 90:10 to 80:20). Mp 140-142 °C; ν_{max} cm^{-1} (KBr): 2944 (CH_2), 1673 (C=O), 1508 (NH), 1228 (C=S); δ_H (300 MHz, $CDCl_3$) 9.69 (brs, 1H, NH), 7.40 (t, 1H, J = 7.6 Hz, ArH), 7.35-7.20 (m, 2H, ArH), 7.18-7.06 (m, 3H, ArH), 6.91-6.64 (m, 8H, H-2''', H-3''', H-5''', H-6''' + 4 × ArH), 3.90 (t, 2H, J = 6.6 Hz, O-C$\underline{H_2}$$CH_2CH_2CH_3$), 3.40 (s, 2H, H-1''), 1.81-1.66 (m, 2H, O-CH_2C$\underline{H_2}$$CH_2CH_3$), 1.53-1.38 (m, 2H, O-$CH_2CH_2C\underline{H_2}$$CH_3$) and 0.96 (t, 3H, J = 7.5 Hz, O-$CH_2CH_2CH_2$C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 176.9 (C=S), 160.0 (C=O), 158.7 (C4'''), 154.1 (C6), 138.8 (C1''a), 131.5 (C1'), 129.9 (CH, Ar), 128.7 (CH, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 127.8 (CH, Ar), 127.4 (C1'''a), 126.4 (CH, Ar), 119.6 (C5), 114.5 (CH, Ar), 67.8 (O-$\underline{C}H_2CH_2CH_2CH_3$), 32.1 (C1''), 31.4 (O-$CH_2\underline{C}H_2CH_2CH_3$), 19.3 (O-$CH_2CH_2\underline{C}H_2CH_3$) and 13.9 (O-$CH_2CH_2CH_2\underline{C}H_3$); *m/z* ($ES^+$) 478.80 [$(M+Na)^+$, 100%]; HRMS ($ES^+$) [Found: $(M+Na)^+$, 479.1760, $C_{28}H_{28}N_2O_2NaS$ requires 479.1769] (-1.9 ppm).

Synthesis of 4xiii-xvi

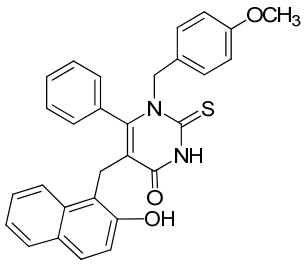
To a stirring solution of **4ix-xii** (1 eq) in DCM (4 mL) at -78 °C was added $n$$Bu_4NI$ (1.1 eq.) and the resulting solution stirred for 5 min at -78 °C. BCl_3 (1.0 M in heptane, 2.5 eq.) was added dropwise and the reaction stirred for 5 min at the same temperature. After warming to 0 °C, the reaction mixture was stirred for further 2 h. After this time, an ice-water mixture was added, DCM removed at reduced pressure and the aqueous layer extracted with diethyl ether (3 × 5 mL). The organic layers were collected, washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The product was obtained as a white microcrystalline powder after purification by column chromatography (Hexane/EtOAc, 85:15).

1-Benzyl-5-[2''-hydroxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4xiii)



Yielded **4xiii**(15 mg, 0.03 mmol, 53%) from **4ix** (41 mg, 0.07 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 85:15 to 80:20). Mp 94 °C (decomposes); ν_{max} cm^{-1} (KBr): 3420 (CONH or OH), 1655 (C=O), 1482 (CSNH), 1166 (C=S); δ_H (400 MHz, $CDCl_3$) 8.69 (brs, 1H, OH), 7.64 (d, 1H, J = 7.8 Hz, H-5"), 7.59 (d, 1H, J = 8.7 Hz, H-4"), 7.44-7.36 (m, 1H, H-4'), 7.31-7.09 (m, 8H, H-3", H-6" + 6 × ArH), 6.98 (dt, 2H, ^2J = 7.7 Hz, ^3J = 1.1 Hz, ArH), 6.91 (brs, 1H, ArH), 6.76 (dd, 1H, ^2J = 7.8 Hz, ^3J = 1.8 Hz, ArH), 6.71 (d, 1H, J = 8.8 Hz, ArH) and 3.90 (s, 2H, H-1"); δ_C (100 MHz, $CDCl_3$) 176.2 (C=S), 162.7 (C=O), 155.5 (C2"), 153.8 (C6), 135.2 (C1'"a), 133.2 (C1'), 131.2 (C8"a), 130.6 (CH, Ar), 129.3 (C4"a), 129.2 (CH, Ar), 129.0 (CH, Ar), 128.9 (CH, Ar), 128.6 (C4"), 128.5 (C5"), 127.7 (CH, Ar), 126.2 (CH, Ar), 125.7 (C7"), 122.5 (C6"), 122.4 (C8"), 120.5 (C3"), 118.2 (C1"a), 116.3 (C5) and 23.1 (C1"); *m/z* (ES^+) 472.81 [$(M+Na)^+$, 100%]; *m/z* (ES^-) 448.78 [$(M-H)^-$, 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 449.1323, $C_{28}H_{21}N_2O_2S$ requires 449.1324] (-0.2 ppm).

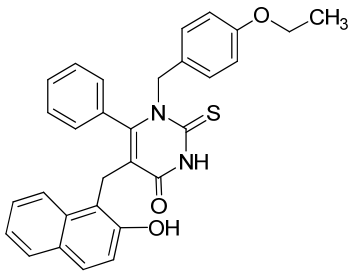
1-(4'''-Methoxybenzyl)-5-[2''-hydroxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4xiv)



Yielded **4xiv**(25 mg, 0.05 mmol, 46%) from **4x** (65 mg, 0.11 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 85:15 to 80:20). Mp90 °C (decomposes); ν_{max} cm^{-1} (KBr): 3201 (CONH or OH), 1655 (C=O), 1513 (NH), 1176 (C=S); δ_H (400 MHz, $CDCl_3$) 10.15 (brs, 1H, NH), 8.70 (s, 1H, OH), 7.64 (d, 1H, J = 8.0 Hz, H-5"), 7.59 (d, 1H, J = 8.8 Hz, H-4"), 7.43 (t, 1H, J = 7.4 Hz, H-4'), 7.28 (brs, 2H, ArH), 7.21-7.07 (m, 2H, H-6" + 1 × ArH), 7.04-6.84 (m, 3H, H-3", H-7" + 1 × ArH), 6.73-6.65 (m, 5H, H-2'", H-3'", H-5'", H-6'", H-8"), 3.89 (s, 2H, H-1") and 3.75 (s, 3H, O-CH_3); δ_C (100 MHz, $CDCl_3$) 176.2 (C=S), 162.7 (C=O), 159.2 (C4'"), 155.6 (C2"), 153.8 (C6), 133.2 (C8"a), 131.2 (C1'), 130.6 (CH, Ar), 129.3 (CH, Ar), 129.3 (C4"a), 129.0 (C4"),

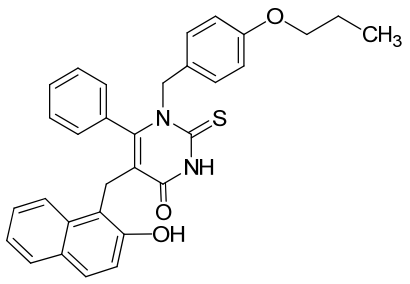
128.9 (C2''', C6'''), 128.5 (C5''), 127.8 (CH, Ar), 127.2 (C1'''a), 125.3 (C7''), 122.6 (C6''), 122.5 (C8''), 120.5 (C3''), 118.3 (C1''a), 116.4 (C5), 113.9 (C3''', C5'''), 55.4 (O-CH_3) and 23.2 (H-1''); *m/z* (ES^-) 478.84 [$(M-H)^-$, 100%]; HRMS (ES^+) [Found: $(M-H)^-$, 479.1439, $C_{29}H_{23}N_2O_3S$ requires 479.1429] (+1.9 ppm).

1-(4'''-Ethoxybenzyl)-5-[2''-hydroxynaphthyl-(1'')-methyl]-6-phenyl-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4xv)



Yielded **4xv**(10 mg, 0.02 mmol, 22%) from **4xi** (54 mg, 0.09 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 85:15). Mp 185 °C (decomposes); δ_H (400 MHz, $CDCl_3$) 9.87 (brs, 1H, NH), 8.72 (brs, 1H, OH), 7.64 (d, 1H, *J* = 7.8 Hz, H-5''), 7.59 (d, 1H, *J* = 8.8 Hz, H-4''), 7.44 (t, 1H, *J* = 7.5 Hz, H-4'), 7.34-7.22 (m, 2H, H-6'', H-7''), 7.19-7.10 (m, 2H, ArH), 7.02-6.83 (m, 3H, ArH), 6.73-6.60 (m, 5H, H-2''', H-3''', H-5''', H-6''', H-8''), 3.89 (s, 2H, H-1''), 3.97 (q, 2H, *J* = 7.0 Hz, O-C$\underline{H_2}$$CH_3$) and 1.39 (t, 3H, *J* = 7.0 Hz, O-CH_2C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 176.0 (C=S), 162.7 (C=O), 158.4 (C4'''), 155.4 (C2''), 153.7 (C6), 133.1 (C8''a), 131.1 (C1'), 130.5 (CH, Ar), 129.3 (CH, Ar), 129.0 (CH, Ar), 128.8 (CH, ArH), 128.4 (CH, Ar), 127.7 (CH, Ar) , 126.9 (C), 125.7 (C7''), 122.4 (C8''), 122.3 (C6''), 120.4 (C3''), 118.2 (C1''a), 116.2 (C5), 114.4 (C3''', C5'''), 67.7 (O-$\underline{C}H_2CH_3$), 23.3 (C1''), 14.8 (O-$CH_2\underline{C}H_3$); *m/z* (ES^-) 493.11 [$(M-H)^-$, 100%]; *m/z* (ES^+) 517.12 [$(M+Na)^+$, 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 493.1581, $C_{30}H_{25}N_2O_3S$ requires 493.1586] (-1.0 ppm).

1-(4'''-Propoxybenzyl)-5-[2''-hydroxynaphthyl-(1'')-methyl]-6-phenyl2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (4xvi)



Yielded **4xvi**(14 mg, 0.02 mmol, 25%) from **4xii** (67 mg, 0. 11 mmol) as a white microcrystalline powder after column chromatography (Hexane/EtOAc, 85:15). Mp 185 °C (decomposes); δ_H (400 MHz, $CDCl_3$) 9.75 (brs, 1H, NH), 8.72 (brs, 1H, OH), 7.64 (d, 1H, J = 7.9 Hz, H-5''), 7.59 (d, 1H, J = 8.9 Hz, H-4''), 7.46-7.39 (m, 1H, H-4'), 7.34-7.22 (m, 2H, H-6'', H-7''), 7.19-7.10 (m, 2H, ArH), 7.02-6.85 (m, 3H, ArH), 6.73-6.59 (m, 5H, H-2''', H-3''', H-5''', H-6''', H-8''), 3.89 (s, 2H, H-1''), 3.85 (t, 2H, J = 6.5 Hz, O-C$\underline{H_2}$$CH_2CH_3$), 1.84-1.71 (m, 2H, O-$CH_2C\underline{H_2}CH_3$) and 1.02 (t, 3H, J = 7.6 Hz, O-$CH_2CH_2C\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 176.0 (C=S), 162.7 (C=O), 158.6 (C4'''), 155.4 (C2''), 153.7 (C6), 133.1 (C8''a), 131.1 (C1'), 130.5 (CH, Ar), 129.2 (CH, Ar), 128.9 (CH, Ar), 128.8 (CH, Ar), 128.4 (CH, Ar), 127.7 (CH, Ar), 126.9 (C), 125.6 (CH, Ar), 122.4 (CH, Ar), 122.3 (CH, Ar), 120.4 (CH, Ar), 118.1 (C), 116.3 (C), 114.4 (C3''', C5'''), 69.5 (O-$\underline{C}H_2CH_2CH_3$), 29.7 (O-$CH_2\underline{C}H_2CH_3$), 22.5 (C1''), 10.5 (O-$CH_2CH_2\underline{C}H_3$).

X-ray Crystal Structure of Analogue 4iv

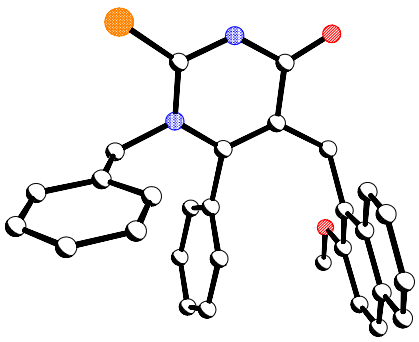


Figure S1 - Crystal structure determination of **4iv**. Crystals were obtained by slow evaporation from ethanol.

HPLC Analysis of Purity

HPLC analyses were performed on a GILSON UV-VIS 155 HPLC system under gradient conditions. Method A (RP, reverse phase), XTerra RP 18 5µM column (3.0 × 50 mm, Waters). The concentration of the compounds were *ca.* 4 mmol, injection volumes were 20 µL, flow rate was 1 mL/min and detection was acquired using UV spectroscopy (254 nm).

Table S9

Method A (RP)		
Time (min)	**% H_2O[a]**	**% CH_3CN**
0	80	20
7	20	80
8	20	80
9	80	20
10	80	20

[a] With 0.1% TFA

Table S10, Retention Times and Purities of Tested Compounds.

Compound	**HPLC Method A (RP)**	
	Rt	**Purity (%)**
4i	1.07	> 95
4ii	1.24	> 95
4iii	1.26	> 95
4iv	1.13	> 95
4v	1.11	> 95
4vi	1.12	> 95
4vii	1.24	> 95
4viii	1.12	> 95
4ix	1.09	> 95
4x	1.17	> 95
4xi	1.15	> 95
4xii	1.20	> 95
4xiii	0.87	> 95
4xiv	1.11	> 95
4xv	1.07	> 95
4xvi	1.17	> 95
10	1.04	> 95
11i	1.06	> 95
11ii	1.09	> 95
11iii	1.11	> 95
11iv	1.08	> 95

In Vitro SIRT1 and SIRT2 Inhibition Assay

Compounds were tested for inhibition of SIRT1 and SIRT2 using the human recombinant SIRT1 and SIRT2 enzymes provided with the Fluor de Lys^{TM} fluorescent-based assay kit (BML AK555, BML AK556, Enzo LifeSciences, UK).[105] All the other required reagents were provided with the kit. All kit components were stored at -78 °C to ensure stability. Positive controls were provided by the known SIRT1/T2 inhibitors cambinol (**2**)and analogues **3a** and **3b**.

Fresh dilutions of cambinol analogues were prepared in DMSO (Aldrich), added to the assay buffer and pipetted (10 μL) into a white 96 well white microplate. Enzyme (15 μL, 0.02 U/μL for SIRT1, 0.1 U/μL for SIRT2) and Fluor de Lys SIRT1 or SIRT2 (15 µM, 12.5 µL) plus NAD^+ (1 mM, 12.5 µL) in assay buffer were added. After incubating for 1 h at 37 °C, a developer solution (250 μL developer and 2 mM, 50 μL of nicotinamide in 950 μL of buffer) was added (50 μL) to each well and the microplate incubated for a further 45 min at room temperature. Plates were read in a microplate Thermo Scientific Multiskan FC fluorimeter with an excitation wavelength of 355 nm and an emission wavelength of 460 nm.

Cell Culture and Western Blotting

Human cancer cell line H1299 cells were cultured in RPMI supplemented with 10% fetal calf serum (FCS, Hyclone, UK) and gentamycin (complete medium). Cells were seeded at a concentration of 6×10^4 in a 6 well collagen pre-coated plates (TPP, Helena Biosciences, UK) and incubated in a humidified atmosphere containing 5% CO_2:95% air at 37 °C for 24 h. A range of concentrations of the target compounds in DMSO were added to H1299 cells with 40 nM trichostatin A (TSA) also being added and the mixture incubated for a further 24 h. After lysing the cells with 1 × LDS sample buffer (200 µL per well, Invitrogen, UK), the protein concentration was assessed with a BCA protein assay kit (Pierce, UK) and the concentration of proteins equalised with 1 × LDS sample buffer. Proteins were separated with 4-12% bis-tris gels (Invitrogen, USA) and electrophoretically transferred to PVDF transfer membranes (Millipore, UK). Membranes were blocked with Marvel non-fat milk (45 min, 5% solution in PBS/0.1% tween) and immunoblotted using anti-K40 acetylated tubulin (SIGMA) and anti α-tubulin (SIGMA). All the primary antibodies were diluted in Marvel non-fat milk (5% solution in PBS/0.1% tween). The secondary antibody used against the remaining primary antibodies was a HRP-tagged polyclonal rabbit anti-mouse IgG (DAKO, UK). After incubation with primary (1 h) and secondary antibodies (45 min), bound antibody was visualized with enhanced chemiluminescence (ECL) western blotting developer (Amersham, UK) in a darkroom.

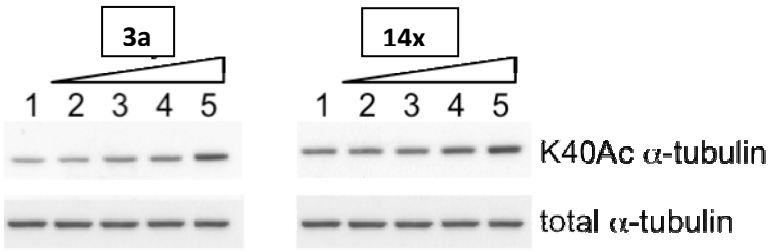


Figure S2.**Comparison of the ability of 3a and 14xv**to increase tubulin acetylation in cells. H1299 cells were treated with trichostatin A (40 nM) to inhibit HDAC6 deacetylase activity together with vehicle (DMS0) (lane 1), 10, 30, 50 or 60 µM **3a** or **14xv** for 16 hours (lanes 2-5). K40Ac α-tubulin and total α-tubulin were detected by Western blot as described.[1]

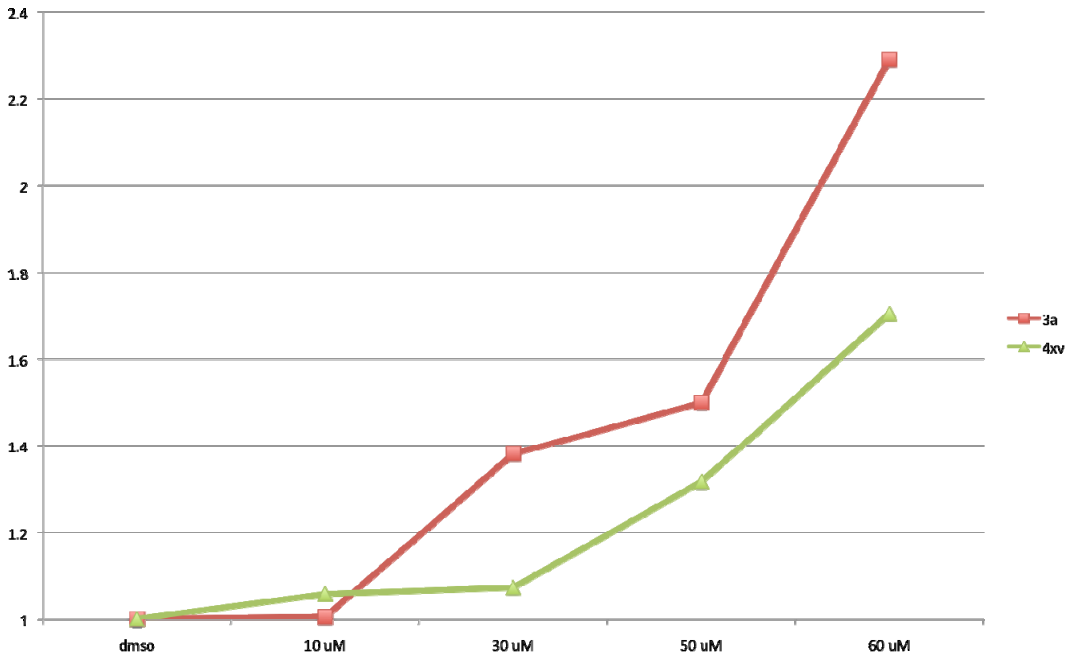


Figure S3. **Comparison of the ability of 3a and 14xv**to increase tubulin acetylation in cells.

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