Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Electronic Supporting Information

Design, synthesis and antiproliferative activity of urocanic-chalcone hybrid derivatives

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Experimental

General Experimental

Chemicals, solvents and reagents used are commercially available and were used without further purification. PE refers to petroleum ether, bp 40-60 °C. TLCs were carried out on Merck Aluminium backed TLC plates Silica Gel 60 F254 and viewed using UV light of wavelength 254 nm and then stained with potassium permanganate. Merck Silica Gel (0.040-0.063 mm) was used for column chromatography. Compounds were loaded as an oil, CH_2Cl_2 solution or dry loaded by adsorption onto silica.

Melting points were obtained using a Reichert-Jung heated-stage microscope. Infrared spectra were recorded on a Perkin-Elmer Spectrum RXI FT-IR system and all values are recorded in cm^{-1}.

NMR spectra were obtained on Varian Mercury VX (400 MHz) or Bruker Avance III (400 MHz) spectrometers. The chemical shifts are recorded in parts per million (ppm) with reference to tetramethylsilane. The coupling constants *J* are quoted to the nearest 0.5 Hz and are not corrected. The multiplicities are assigned as a singlet (s), doublet (d), triplet (t), doublet of doublets (dd) and multiplet (m). Mass spectra and high resolution mass spectra were obtained on a micrOTOF™ from Bruker Daltonics (Bremen, Germany) coupled with an electrospray source (ESI-TOF) using an autosampler in an Agilent 1100 LC system. Data was processed using external calibration with the Bruker Daltonics software, DataAnalysis™ as part of the overall hardware control software, Compass 1.1™.

HPLC

Analytical RP-HPLC was performed on a Dionex HPLC system equipped with a Dionex Acclaim 3 µm C-18 (150 × 4.6 mm) column with a flow rate of 1 mL/min. with detection at 214 nm and 254 nm shown (pages S30-S41). Mobile phase A was 0.1% TFA in H_2O and mobile phase B was 0.1% TFA in MeCN. The gradient was T = 0 min., B = 5%; T = 10 min., B = 95%; T = 15 min., B = 95%; T = 15.1 min., B = 5%; T = 18.1 min., B = 5%.

MTS cell proliferation assay[1]

1: Human cancer cell lines HT29, MDA-MB-231 and LNCaP were supplied by Cancer Research UK. They were maintained in DMEM with high glucose (4.5 g/L) and L-glutamine, supplemented with penicillin 100 U/mL, streptomycin 100 µg/mL and foetal bovine serum at 10% for HT29 and MDA-MB-231, and 20% for LNCaP. FEK-4 primary human skin fibroblasts were a gift from Prof. Rex M. Tyrrell (University of Bath) and were maintained in MEM supplemented with L-glutamine, supplemented with penicillin 100 U/mL, streptomycin 100 µg/mL and 15% foetal bovine serum. All reagents supplied by Invitrogen.
Cells were maintained in 75 cm^2 tissue culture flasks (Nunc) with a weekly 1:10 split.

2: For the MTS assay, seed densities of 500, 1000, 1500 and 2000 cells per well in 50 µL were used for HT29, MDA-MB-231, FEK-4 and LNCaP cell lines respectively.
The seed densities had been determined previously to give an acceptable optical density value after 3 days incubation.

3: Plates were incubated at 37 ^oC, in humidified 5% CO_2 in air for 2-4 hours.

4: Test agents were prepared at 100 × final concentration in DMSO (Sigma), diluted 1 in 50 in culture medium and 50 µl added to the appropriate wells, to give a final volume of 100 µl.

5: Quadruplicate samples were run as follows:

Culture medium only (background)
Cells only
Cells + 1% DMSO
Cells + test compound

6: Plates were incubated at 37 ^oC, in humidified 5% CO_2 in air for 3 days.
This exposure time appears to be adequate to demonstrate anti-proliferative activity, and is routinely used by other workers.

7: The MTS reagent was added, 20 µl per well.
This is Promega Cell Titer® Aqueous One Solution Cell Proliferation Assay.

8: Plates were incubated at 37 ^oC, in humidified 5% CO_2 in air, for colour development.

9: Optical density readings at 490nm were taken at 1-4 hours.

10: Because the culture medium gives a high OD_{490nm} this was subtracted from all other OD_{490nm} values prior to calculation of mean and s.d.

11: Means and standard deviations were calculated from background corrected OD_{490nm} values.

12: IC_{50} values were calculated using the pharmacology function in SigmaPlot 8 (SPSS Inc). Each assay was repeated on three separate occasions, except **A3** FEK-4 (twice) and **C3-H_2** FEK-4 and Doxorubicin (once), and average IC_{50} values with standard deviations determined. Doxorubicin was used as a positive control.

Note: This assay is based upon the development of a coloured metabolite from viable cells. Therefore the inhibition of colour development by an active agent does not distinguish between inhibition of cell metabolism *ie* cytostasis and reduction in cell number *ie* cytotoxicity. Nevertheless, this assay provides a very quick and easy first approach for screening test compounds.

General Methods

Method i (A1, B1, C1)

Following the procedure reported,[2] except using 1 equivalent $LiOH.H_2O$, $LiOH.H_2O$ (2.5 mmol) was added to rapidly stirred solution of acetophenone (2.5 mmol) in EtOH (2 mL) at 30 ^oC open to the atmosphere for 10 min. resulting in a rapid colour change from colourless to yellow. The aldehyde (2.5 mmol) was then added and stirring continued for 6 h resulting in a gradual colour change from yellow to orange. After 6 h the solvent was removed under reduced pressure and distilled water (5 mL) added followed by 1.5M HCl(aq) (5 mL) to the remaining residue. The product was extracted with EtOAc (3 × 20 mL), the organic layers were combined and washed with saturated brine solution (20 mL). The organic fraction was dried (Na_2SO_4), filtered and solvent removed under reduced pressure to give a yellow solid. The solid was purified by column chromatography with silica gel using PE:EtOAc 6:4 to afford the desired chalcone.

(*E*)-1-(4-methoxyphenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one (A1)

Following **Method i** on a 5 mmol scale, the product **A1** was obtained as a yellow solid (0.49 g, 43%).

Mp 170-172 ^oC (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 3050, 1649 and 1594;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.87 (3 H, s, OCH_3), 6.31-6.33 (1 H, m, pyrrole CH), 6.65-6.70 (1 H, m, pyrrole CH), 6.95 (2 H, d, *J* 9.0 Hz, Ar CH), 6.94-6.96 (1 H, m, pyrrole CH), 7.16 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.73 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.99 (2 H, d, *J* 8.5 Hz, Ar CH) and 8.95 (1 H, br s, pyrrole NH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 55.46 (OCH_3), 111.4 (pyrrole CH), 113.8 (pyrrole CH), 114.7 (Ar CH), 115.7 (pyrrole CH), 122.3 (Ar CH), 129.5 (Cq), 130.5 (HC=CH), 131.6 (Cq), 133.8 (HC=CH), 163.2 (Cq) and 188.7 (C=O);

MS m/z (ES^+) Found 228.1025 (MH^+) and 250.0846 (MNa^+). $C_{14}H_{14}NO_2$ (MH^+) requires 228.1025 and $C_{14}H_{13}NO_2Na$ (MNa^+) requires 250.0844.

(*E*)-1-(3,4-dimethoxyphenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one (B1)

Following **Method i**, the product **B1** was obtained as a yellow solid (0.34 g, 53%).

Mp 80-81 ^{o}C (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 3458, 1651 and 1584;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.91 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 6.31-6.33 (1 H, m, pyrrole CH), 6.69-6.71 (1 H, m, pyrrole CH), 6.85 (1 H, d, *J* 8.0, Ar CH), 6.95-6.98 (1 H, m, pyrrole CH), 7.21 (1 H, d, *J* 15.5 Hz, COCH=CH), 7.59 (1 H, d, *J* 1.5 Hz, Ar CH), 7.61 (1 H, dd, *J* 1.5 and 8.5 Hz, Ar CH), 7.75 (1 H, d, *J* 15.5 Hz, COCH=CH) and 9.25 (1 H, br s, pyrrole NH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 56.0 (OCH_3), 110.1 (pyrrole CH), 111.0 (pyrrole CH), 111.4 (pyrrole CH), 115.0 (Ar CH), 115.4 (Ar CH), 122.6 (Ar CH), 122.9 (HC=CH), 129.5 (Cq), 131.8 (Cq), 134.0 (HC=CH), 149.2 (Cq), 153.0 (Cq) and 188.7 (C=O);

MS m/z (ES$^+$) Found 258.1135 (MH^+) and 280.0949 (MNa^+). $C_{15}H_{16}NO_3$ (MH^+) requires 258.1130 and $C_{15}H_{15}NO_3Na$ (MNa^+) requires 280.0950.

(*E*)-3-(1*H*-pyrrol-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (C1)

Following **Method i**, the product **C1** was obtained as a yellow solid (0.53 g, 74%).

Mp 104-106 ^{o}C (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 3457, 1654 and 1575;

^{1}H NMR δ_H(400 MHz; DMSO) 3.76 (3 H, s, OCH_3), 3.90 (6 H, s, OCH_3), 6.22-6.24 (1 H, m, pyrrole CH), 6.74-6.75 (1 H, m, pyrrole CH), 7.15-7.16 (1 H, m, pyrrole CH), 7.35 (2 H, s, Ar CH), 7.54 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.62 (1 H, d, *J* 15.0 Hz, COCH=CH) and 11.71 (1 H, br s, pyrrole NH);

^{13}C NMR δ_c(100MHz; DMSO) 56.1 (OCH_3), 60.2 (OCH_3), 105.7 (Ar CH), 110.6 (pyrrole CH), 114.4 (pyrrole CH), 116.4 (pyrrole CH), 124.1 (HC=CH) 129.2 (Cq), 133.7 (Cq), 134.1 (HC=CH), 141.5 (Cq), 152.9 (Cq) and 187.1 (C=O);

MS m/z (ES$^+$) Found 288.1241 (MH^+) and 310.1061 (MNa^+). $C_{16}H_{18}NO_4$ (MH^+) requires 288.1236 and $C_{16}H_{17}NO_4Na$ (MNa^+) requires 310.1055.

Method ii (A2, B2, C2)

Following the procedure reported,[3] acetophenone (5 mmol), the aldehyde (5 mmol) and NaOH (7 mmol) was added to a porcelain mortar and ground using a porcelain pestle at room temperature (20 ^{o}C) for 5 min. resulting in the formation of a viscous yellow paste. The paste was then purified by column chromatography with silica gel using PE:EtOAc 6:4 solvent system to afford the desired chalcone.

(*E*)-1-(4-methoxyphenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)prop-2-en-1-one (A2)

Following **Method ii**, the product **A2** was obtained as a yellow solid (0.76 g, 63%).
Mp 101-103 ^{o}C (EtOAc/heptane);
IR ν_{max}(film)/cm^{-1} 1654 and 1575;
^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.74 (3 H, s, pyrrole CH_3), 3.87 (OCH_3), 6.20-6.22 (1 H, m, pyrrole CH), 6.79-6.80 (1 H, m, pyrrole CH), 6.82-6.83 (1 H, m, pyrrole CH), 6.96 (2 H, d, *J* 9.0 Hz, Ar CH), 7.31 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.79 (1 H, d, *J* 15.0 Hz, COCH=CH) and 8.02 (2 H, d, *J* 9.0 Hz, Ar CH);
^{13}C NMR δ_c(100MHz; $CDCl_3$) 34.3 (pyrrole CH_3), 55.4 (OCH_3), 109.5 (pyrrole CH), 111.9 (pyrrole CH), 113.7 (Ar CH), 116.5 (pyrrole CH), 127.4 (HC=CH), 130.3 (Cq), 130.4 (Ar CH), 131.4 (HC=CH), 131.5 (Cq), 163.0 (Cq) and 188.2 (C=O);
MS m/z (ES$^+$) Found 242.1191 (MH^+) and 264.1007 (MNa^+). $C_{15}H_{16}NO_2$ (MH^+) requires 242.1181 and $C_{15}H_{15}NO_2Na$ (MNa^+) requires 264.1001.

(*E*)-1-(3,4-dimethoxyphenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)prop-2-en-1-one (B2)

Following **Method ii**, the product **B2** was obtained as a yellow solid (1.07 g, 79%).

Mp 126-126 ^{o}C (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 1647, 1597 and 1573;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.75 (3 H, s, pyrrole CH_3), 3.94 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 6.19-6.21 (1 H, m, pyrrole CH), 6.78-6.79 (1 H, m, pyrrole CH), 6.82-6.83 (1 H, m, pyrrole CH), 6.90 (1 H, d, *J* 8.5 Hz, Ar CH), 7.30 (1 H, d, *J* 15.5 Hz, COCH=CH), 7.61 (1 H, d, *J* 2.0 Hz, Ar CH), 7.64 (1 H, dd, *J* 2.0 and 8.0 Hz, Ar CH) and 7.79 (1 H, d, *J* 15.0 Hz, COCH=CH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 34.3 (pyrrole CH_3), 55.9 (OCH_3), 56.0 (OCH_3), 109.6 (pyrrole CH), 109.9 (pyrrole CH), 110.6 (pyrrole CH), 111.9 (Ar CH), 116.3 (Ar CH), 122.4 (HC=CH), 127.5 (Ar CH) 130.3 (HC=CH), 131.4 (Cq), 131.7 (Cq), 149.0 (Cq), 152.8 (Cq) and 188.0 (C=O);

MS m/z (ES$^+$) Found 272.1273 (MH^+) and 294.1094 (MNa^+). $C_{16}H_{18}NO_3$ (MH^+) requires 272.1287 and $C_{16}H_{17}NO_3Na$ (MNa^+) requires 294.1106.

(*E*)-3-(1-methyl-1*H*-pyrrol-2-yl)-(3,4,5-trimethoxyphenyl)prop-2-one (C2)

Following **Method ii**, the product **C2** was obtained as an orange oil (1.25 g, 83%).

IR ν_{max}(film)/cm^{-1} 1647 and 1568;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.77 (3 H, s, pyrrole CH_3), 3.92 (3 H, s, OCH_3), 3.94 (6 H, s, OCH_3), 6.21-6.24 (1 H, m, pyrrole CH), 6.81-6.83 (1 H, m, pyrrole CH), 6.85-6.87 (1 H, m, pyrrole CH), 7.21 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.26 (2 H, s, Ar CH) and 7.80 (1 H, d, *J* 15.0 Hz, COCH=CH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 34.3 (pyrrole CH_3), 56.3 (OCH_3), 56.3 (OCH_3), 105.7 (Ar CH), 109.7 (pyrrole CH), 112.2 (pyrrole CH), 116.4 (pyrrole CH), 127.8 (HC=CH), 130.2 (Cq), 132.1 (HC=CH), 134.1 (Cq), 153.0 (Cq), 153.0 (Cq) and 188.7 (C=O);

MS m/z (ES$^+$) Found 302.1371 (MH^+) and 324.1192 (MNa^+). $C_{17}H_{20}NO_4$ (MH^+) requires 302.1392 and $C_{17}H_{19}NO_4Na$ (MNa^+) requires 324.1212.

Method iii (A3, B3, C3)

Following the procedure reported,[4] except using 2 equivalents of $BF_3 \cdot OEt_2$, $BF_3 \cdot OEt_2$ (5 mmol) was added dropwise under dry conditions to a rapidly stirred solution of acetophenone (2.5 mmol) and aldehyde (2.5 mmol) in dry dioxane (2 mL) under N_2 at 25 ^oC. The solution was heated to 75 ^oC for 6 h and the reaction followed by TLC. The reaction was cooled and quenched by addition of EtOAc (100 mL) and distilled water (100 mL) and the aqueous fractions extracted with EtOAc (3 × 50 mL). 2M NaOH (50 mL) was added to the aqueous layer and gently heated at 50 ^oC with magnetic stirring for 30 min., resulting in a slight colour change and formation of a black precipitate. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the organic layers were combined and washed with saturated brine solution (50 mL) and dried using Na_2SO_4. The solvent was filtered and removed under reduced pressure to produce a yellow/orange solid/oil which was purified by column chromatography with silica gel using CH_2Cl_2:MeOH 9:1 solvent system to afford the desired chalcone.

(*E*)-3-(1*H*-imidazol-5-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (A3)

Following **Method iii**, the product **A3** was obtained as an orange solid (0.30 g, 53%).

Mp 173-175 ^oC (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 3458, 1660 and 1604;

^{1}H NMR δ_H(400 MHz; DMSO) 3.85 (3 H, s, OCH_3), 7.08 (2 H, d, *J* 9.0 Hz, Ar CH), 7.63 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.67 (1 H, d, *J* 15.5 Hz, COCH=CH), 7.64 (1 H, s, Im CH), 7.85 (1 H, s, Im CH), 8.03 (2 H, d, *J* 9.0 Hz, Ar CH) and 12.56 (1 H, br s, Im NH);

^{13}C NMR δ_c(100MHz; DMSO) 55.5 (OCH_3), 114.0, 117.8, 130.4 (Ar CH, Im CH and HC=CH), 130.8 (Cq), 162.8 (Cq), 162.9 (Cq) and 187.2 (C=O);

MS m/z (ES^+) Found 229.0978 (MH^+). $C_{13}H_{13}N_2O_2$ (MH^+) requires 229.0977.

(*E*)-1-(3,4-dimethoxyphenyl)-3-(1*H*-imidazol-5-yl)prop-2-en-1-one (B3)

Following **Method iii**, the product **B3** was obtained as a pale yellow solid (0.48 g, 74%).

Mp 170-171 ^{o}C (THF/heptane);

IR ν_{max}(film)/cm^{-1} 3457, 1659 and 1605;

^{1}H NMR δ_H(400 MHz; DMSO) 3.85 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 7.10 (1 H, d, *J* 8.5 Hz, Ar CH), 7.54 (1 H, d, *J* 2.0 Hz, Ar CH), 7.64 (1 H, d, *J* 15.0 Hz, COCH=CH), 7.64 (1 H, s, Im CH), 7.68 (1 H, d, *J* 15.5 Hz, COCH=CH), 7.73 (1 H, dd, *J* 2.0 and 8.5 Hz, Ar CH), 7.86 (1 H, s, Im CH) and 12.30 (1 H, br s, Im NH);

^{13}C NMR δ_c(100MHz; DMSO) 55.5 (OCH_3), 55.7 (OCH_3), 110.5 (Ar CH), 110.9 (Ar CH), 117.7 (Im CH), 122.6 (Ar CH), 130.9 (Cq), 135.0 (HC=CH) 135.6 (HC=CH). 138.0 (Im CH) 148.8 (Cq), 152.9 (Cq) and 187.2 (C=O);

MS m/z (ES$^+$) Found 259.1082 (MH^+) and 281.0897 (MNa^+). $C_{14}H_{15}N_2O_3$ (MH^+) requires 259.1083 and $C_{14}H_{14}N_2O_3Na$ (MNa^+) requires 281.0902.

(*E*)-3-(1*H*-imidazol-5-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (C3)

Following **Method iii**, the product **C3** was obtained as an orange solid (0.53 g, 74%).

Mp 174-176 ^{o}C (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 3456, 1661 and 1581;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.85 (6 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 7.26 (2 H, Ar CH), 7.38 (1 H, s, Im CH), 7.69 (1 H, d, *J* 15.5 Hz, COCH=CH), 7.77 (1 H, s, Im CH), 7.77 (1 H, d, *J* 15.0 Hz, COCH=CH) and 8.17 (1 H, br s, Im NH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 56.2 (OCH_3), 60.9 (OCH_3), 105.9 (Ar CH), 119.3 (Im CH), 123.4 (Im CH), 133.4 (Cq), 134.6 (HC=CH), 135.9 (Cq), 137.2 (HC=CH), 142.3 (Cq), 153.0 (Cq) and 189.1 (C=O);

MS m/z (ES$^+$) Found 289.1183 (MH^+). $C_{15}H_{17}N_2O_4$ (MH^+) requires 289.1188.

(*E*)-3-(1-methyl-1*H*-imidazol-5-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (C4)

Following **Method iii**, the product **C4** was obtained as an orange oil (0.41 g, 54%).

IR ν_{max}(film)/cm^{-1} 1657, 1591 and 1579;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.78 (3 H, s, Im CH_3), 3.94 (3 H, s, OCH_3), 3.95 (6 H, s, OCH_3), 7.25 (2 H, s, Ar CH), 7.37 (1 H, d, *J* 15.5 Hz, COCH=CH), 7.57 (1 H, s, Im CH), 7.65 (1 H, s, Im CH) and 7.69 (1 H, d, *J* 15.0 Hz, COCH=CH);

^{13}C NMR δ_c(100 MHz; $CDCl_3$) 32.1 (Im CH_3), 56.4 (OCH_3), 61.0 (OCH_3), 105.9 (Ar CH), 119.6 (Im CH), 129.1 (Im CH), 129.6 (Cq), 132.3 (HC=CH), 133.3 (Cq), 141.1 (HC=CH), 142.6 (Cq), 153.1 (Cq) and 188.2 (C=O);

MS m/z (ES$^+$) Found 303.1337 (MH$^+$) and 325.1150 (MNa$^+$). $C_{16}H_{19}N_2O_4$ (MH$^+$) requires 303.1345 and $C_{16}H_{18}N_2O_4Na$ (MNa$^+$) requires 325.1164.

(*E*)-3-(1*H*-imidazol-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (C6)

Following **Method iii** on a 5 mmol scale, the product **C6** was obtained as a yellow solid (0.55 g, 38%).

Mp 198-201 ^{o}C (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 3439, 1661, 1607 and 1582;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.89 (6 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 7.26-7.30 (4 H, m, Ar CH and Im CH), 7.75 (1 H, d, *J* 15.0 Hz, COCH=CH) and 7.86 (1 H, d, *J* 15.0 Hz, COCH=CH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 56.3 (OCH_3), 61.0 (OCH_3), 106.1 (Ar CH and Im CH), 122.4 (HC=CH), 131.0 (HC=CH), 132.8 (Cq), 142.8 (Cq), 143.8 (Cq), 153.2 (Cq) and 188.7 (C=O);

MS m/z (ES$^+$) Found 289.1184 (MH$^+$) and 311.0998 (MNa$^+$). $C_{15}H_{17}N_2O_4$ (MH$^+$) requires 289.1188 and $C_{15}H_{16}N_2O_4Na$ (MNa$^+$) requires 311.1008.

Method iv (C3-H_2)

3-(1*H*-imidazol-5-yl)-(3,4,5-trimethoxyphenyl)propan-1-one (C3-H_2)

The chalcone **C3** (100 mg, 0.347 mmol) was added to a stirred solution of 10wt% Pd/C (20 mg) in MeOH (4 mL) under 1 atm of H_2 and stirring continued at 25 ^oC for 19 h. The reaction was then quenched with EtOAc (50 mL) and washed through celite with distilled water, the organic layer was extracted with EtOAc (3 × 50 mL) and the organic layers were combined and washed with saturated brine solution (50 mL). The organic fraction was dried (Na_2SO_4), filtered and solvent removed under reduced pressure to give the product **C3-H_2** as a pale yellow oil (0.057 g, 57%) without the need for further purification.

IR ν_{max}(film)/cm^{-1} 3454, 1678, 1586 and 1505;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.05 (2 H, t, *J* 7.0 Hz, CH_2), 3.35 (2 H, t, *J* 7.0 Hz, CH_2), 3.89 (6 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 6.85 (1 H, s, Im CH), 7.21 (2 H, s, Ar CH), 7.45 (1 H, br s, Im NH) and 7.65 (1 H, s, Im CH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 20.5 (CH_2), 38.2 (CH_2), 56.3 (OCH_3), 60.9 (OCH_3), 105.5 (Ar CH), 118.2 (Im CH), 131.9 (Cq), 134.2 (Im CH), 135.1 (Cq), 142.7 (Cq), 153.0 (Cq) and 198.7 (C=O);

MS m/z (ES^+) Found 291.1350 (MH^+) and 313.1162 (MNa^+). $C_{15}H_{19}N_2O_4$ (MH^+) requires 291.1345 and (MNa^+) $C_{15}H_{18}N_2O_4Na$ requires 313.1164.

Method v (C5)

(*E*)-3-(1-methyl-1*H*-imidazol-4-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (C5)

Following the procedure reported,[5] except cooled to 0 ^{o}C, NaH (60% dispersion in mineral oil, 1.5 mmol) was added to a stirred solution of the chalcone (1.0 mmol) in DMF (5 mL) at 0 ^{o}C followed by dropwise addition of MeI (1.5 mmol) and the reaction was kept at 0 ^{o}C and followed by TLC until the disappearance of the chalcone starting material. The reaction was quenched with the addition of EtOAc (50 mL) and H_2O (50 mL), the organic layer separated and the aqueous fraction extracted with EtOAc (2 × 50 mL). The organic fractions were combined and washed with saturated brine solution (20 mL). The organic fraction was dried (Na_2SO_4), filtered and solvent removed under reduced pressure. Crude ^{1}H NMR revealed the presence of **C4**, in addition to the product **C5** in a ratio of 25:75 (**C4**:**C5**). The mixture was purified by column chromatography with silica gel using CH_2Cl_2:IPA solvent system increasing from 0% to 12% IPA in 1% increments of 200 mL to afford the desired product **C5** as an orange oil (0.11g, 36%).

R$_f$ (12% IPA in CH_2Cl_2) = 0.63 (**C5**), 0.47 (**C4**);

IR ν_{max}(film)/cm^{-1} 1659, 1603 and 1580;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.71 (3 H, s, Im CH_3), 3.90 (3 H, s, OCH_3), 3.92 (6 H, s, OCH_3), 7.15 (1 H, s, Im CH), 7.33 (2 H, s, Ar CH), 7.49 (1 H, s, Im CH) and 7.70 (2 H, s, COCH=CH); ***NB*** The peak at δ_H 7.70 ppm can vary depending on the concentarion of the sample and can appear as two doublets;

^{1}H NMR – Diluted δ_H(400 MHz; $CDCl_3$) 3.73 (3 H, s, Im CH_3), 3.92 (3 H, s, OCH_3), 3.94 (6 H, s, OCH_3), 7.17 (1 H, s, Im CH), 7.34 (2 H, s, Ar CH), 7.50 (1 H, s, Im CH), 7.69 (1 H, d, *J* 15.0 Hz, COCH=CH) and 7.74 (1 H, d, *J* 15.0 Hz, COCH=CH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 33.8 (Im CH_3), 56.4 (OCH_3), 60.9 (OCH_3), 106.0 (Ar CH), 119.6 (Im CH) 124.1 (Im CH), 133.6 (Cq), 135.1 (HC=CH), 138.0 (Cq), 139.1 (HC=CH), 142.3 (Cq), 153.1 (Cq) and 188.9 (C=O);

MS m/z (ES$^+$) Found 303.1354 (MH^+) and 325.1166 (MNa^+). $C_{16}H_{19}N_2O_4$ (MH^+) requires 303.1345 and $C_{16}H_{18}N_2O_4Na$ (MNa^+) requires 325.1164.

Method vi (C7)

(*E*)-3-(1-methyl-1*H*-imidazol-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (C7)

The chalcone (1.4 mmol) was added to a rapidly stirred solution of 3 equivalents of Cs_2CO_3 (4.2 mmol) in THF (30 mL) at 30 ^oC open to the atmosphere for 15 min. followed by dropwise addition of 3 equivalents of MeI (4.2 mmol) and stirring continued for 6 h. The reaction was then cooled and quenched by addition of CH_2Cl_2 (50 mL) and distilled water (50 mL) and the organic layer extracted with CH_2Cl_2 (3 × 50 mL), the organic layers were combined and washed with saturated brine solution (50 mL). The organic fraction was dried (Na_2SO_4), filtered and solvent removed under reduced pressure to give a pale yellow oil. The oil was purified by column chromatography with silica using CH_2Cl_2:MeOH 9:1 solvent system to afford the product **C7** as a yellow solid (0.23 g, 54%).

Mp 100-102 ^oC (EtOAc/heptane);

IR ν_{max}(film)/cm^{-1} 1658, 1605 and 1580;

^{1}H NMR δ_H(400 MHz; $CDCl_3$) 3.81 (3 H, s, Im CH_3), 3.93 (3 H, s, OCH_3), 3.94 (6 H, s, OCH_3), 7.03 (1 H, s, Im CH), 7.21 (1 H, s, Im CH), 7.36 (2 H, s, Ar CH), 7.68 (1 H, d, *J* 15.0 Hz, COCH=CH) and 8.06 (1 H, d, *J* 15.0 Hz, COCH=CH);

^{13}C NMR δ_c(100MHz; $CDCl_3$) 33.0 (Im CH_3), 56.4 (OCH_3), 60.9 (OCH_3), 106.0 (Ar CH), 123.9 (HC=CH), 127.2 (Im CH), 130.3 (HC=CH), 131.4 (Im CH), 133.0 (Cq), 142.7 (Cq), 143.7 (Cq), 153.2 (Cq) and 188.1 (C=O);

MS m/z (ES^+) Found 303.1360 (MH^+) and 325.1172 (MNa^+). $C_{16}H_{19}N_2O_4$ (MH^+) requires 303.1345 and $C_{16}H_{18}N_2O_4Na$ (MNa^+) requires 325.1164.

References

1. MTS is 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium. A. H. Cory, T. C. Owen, J. A. Barltrop and J. G. Cory, *Cancer Commum.*, 1991, **3**, 207.
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3. N. M. Rateb and H. F. Zohdi, *Synth. Commun.*, 2009, **39**, 2789.
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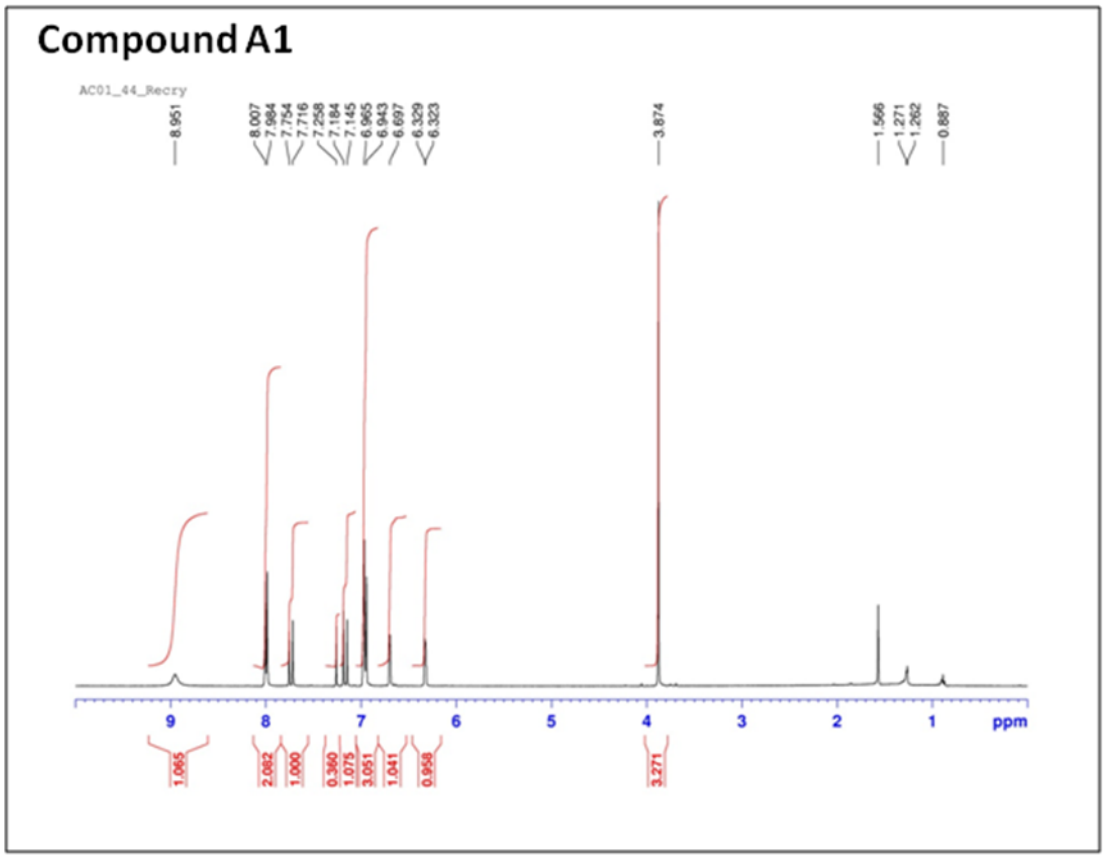
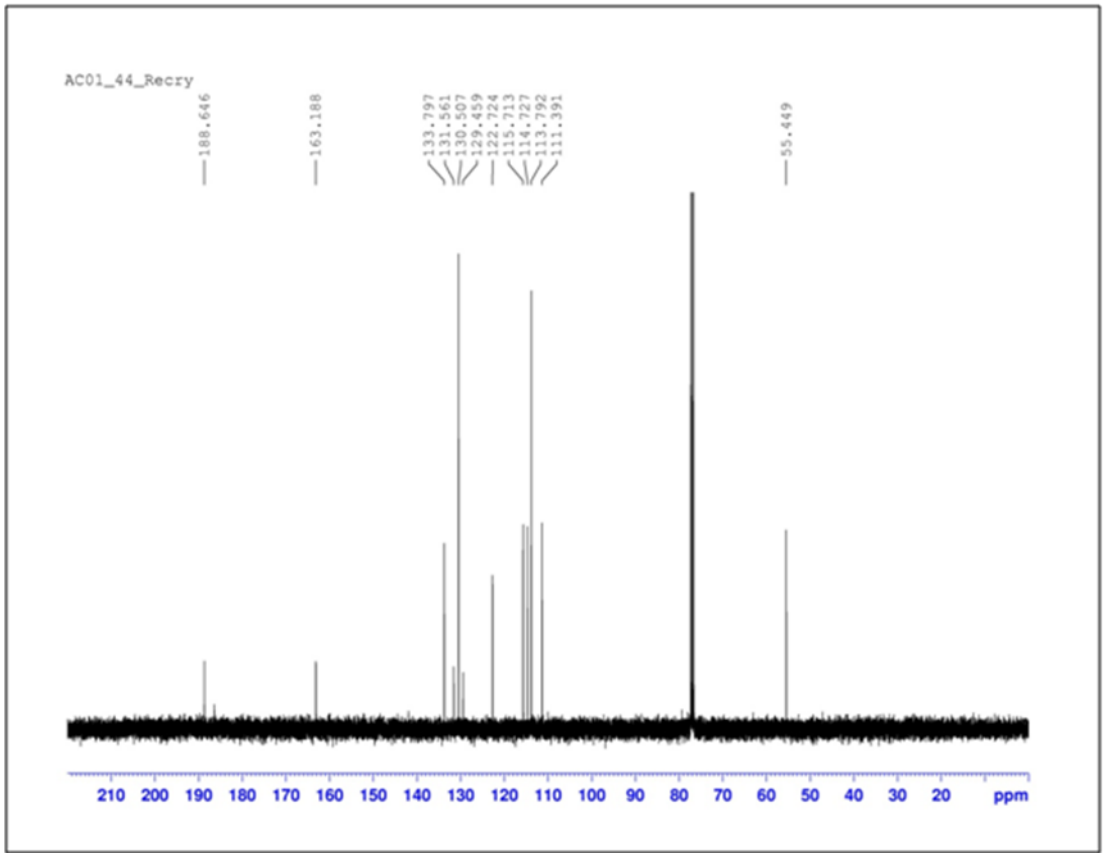
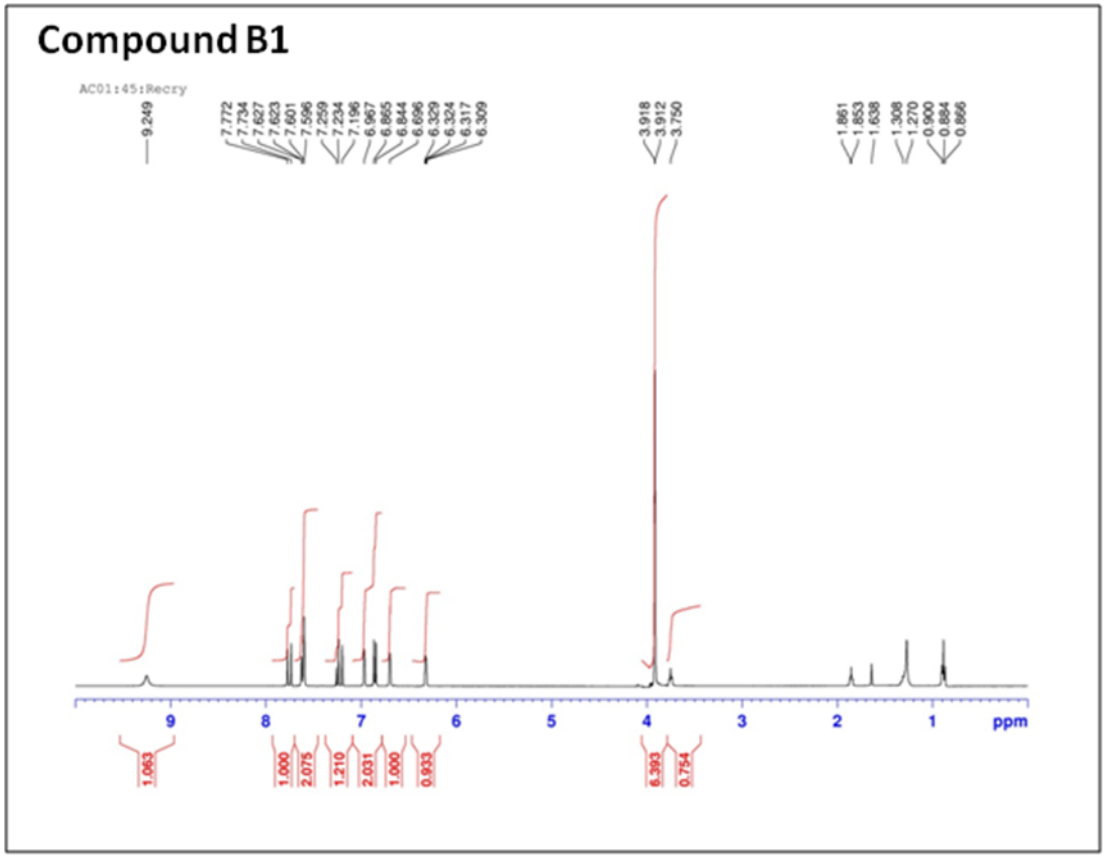
5. N. Lauth-de Viguerie, N. Sergueeva, M. Damiot, H. Mawlawi, M. Riviere and A. Lattes, *Heterocycles*, 1994, **37**, 1561.



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6.317
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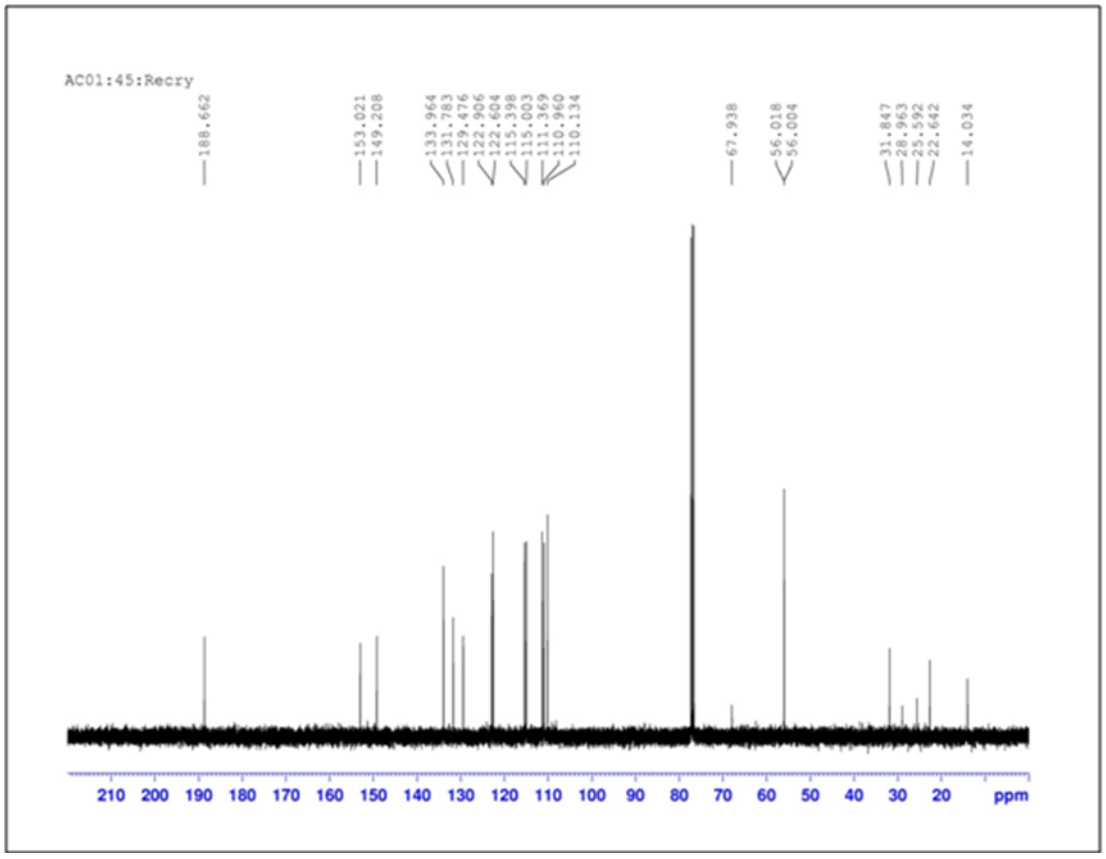
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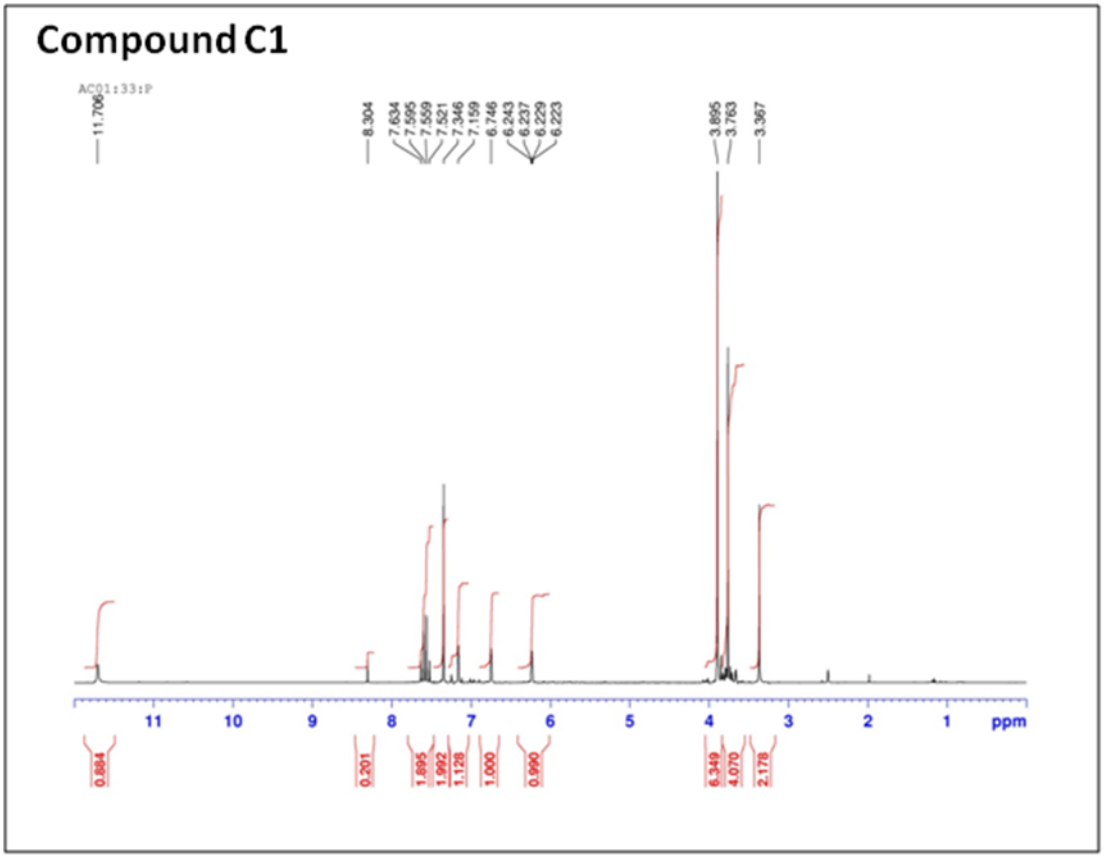
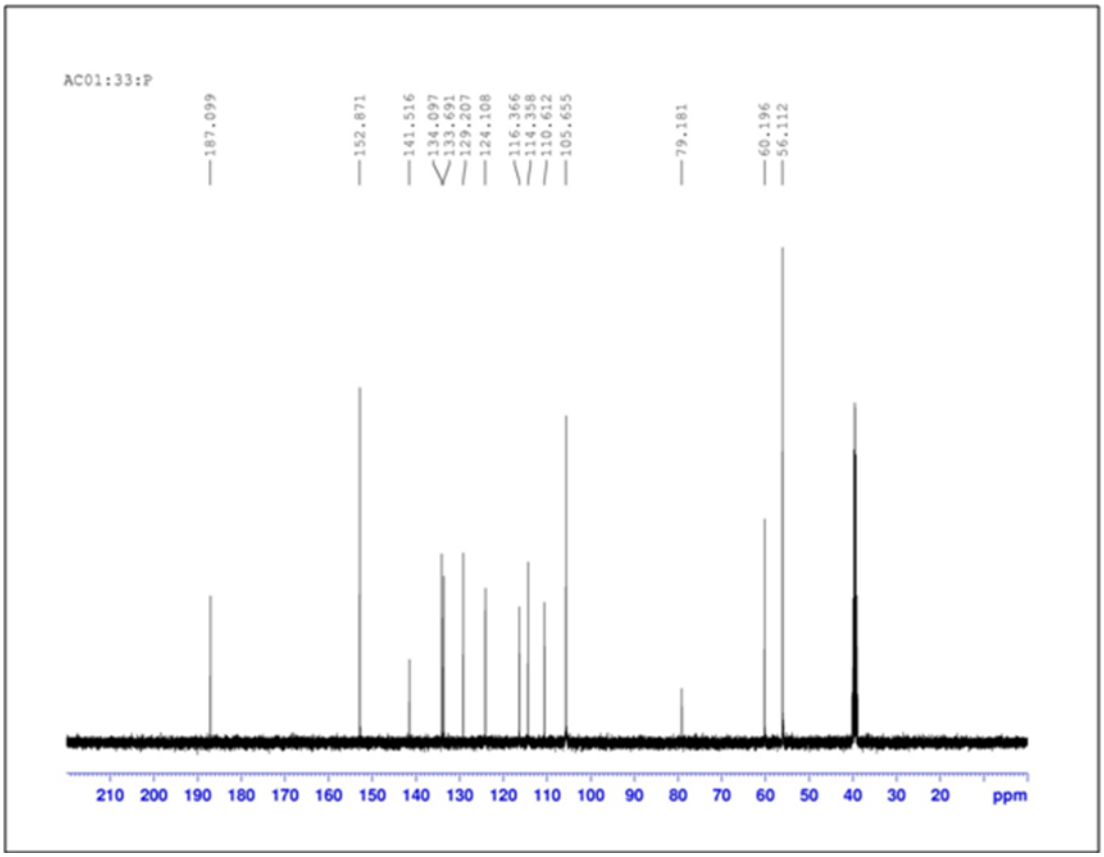
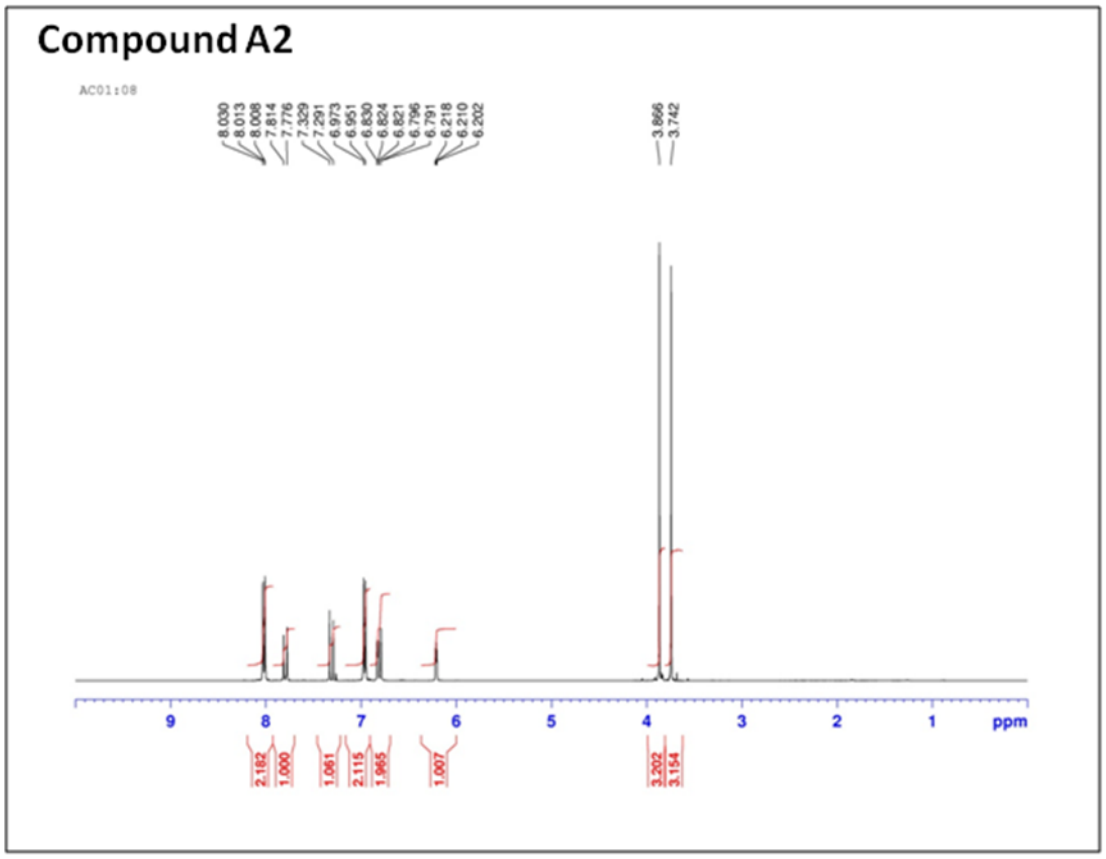
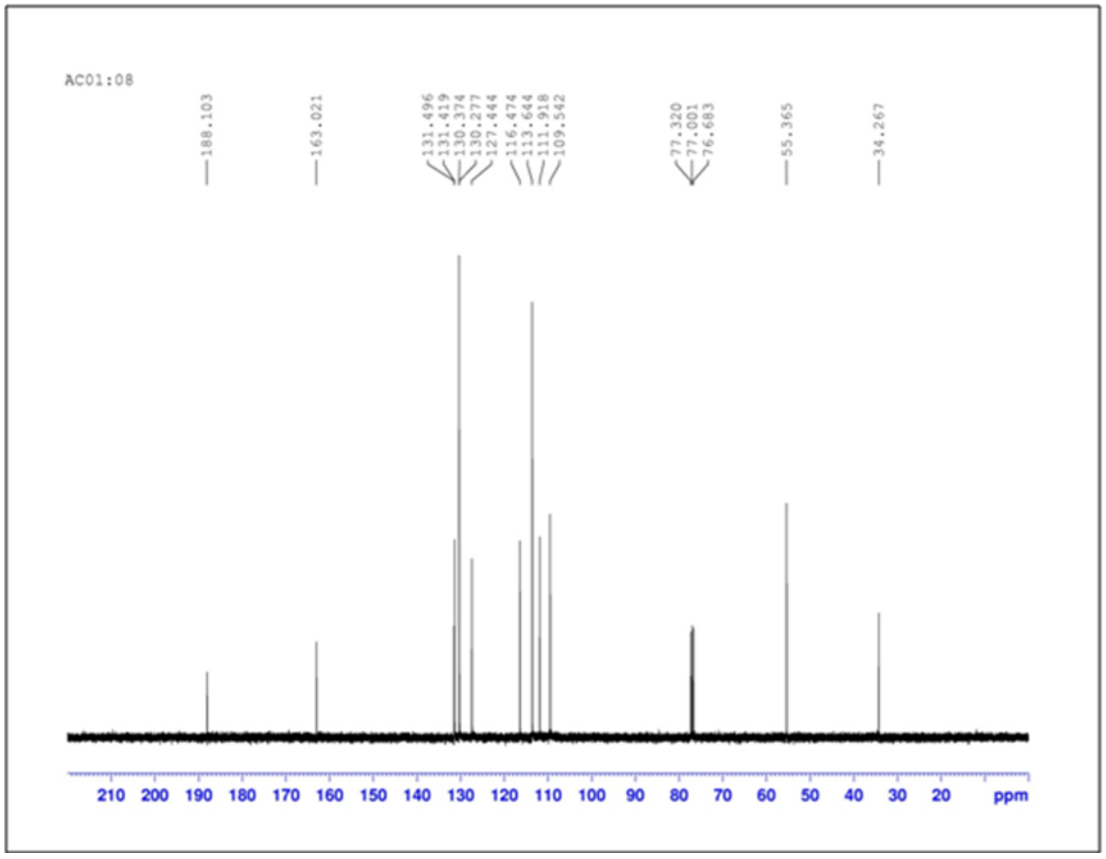
ppm

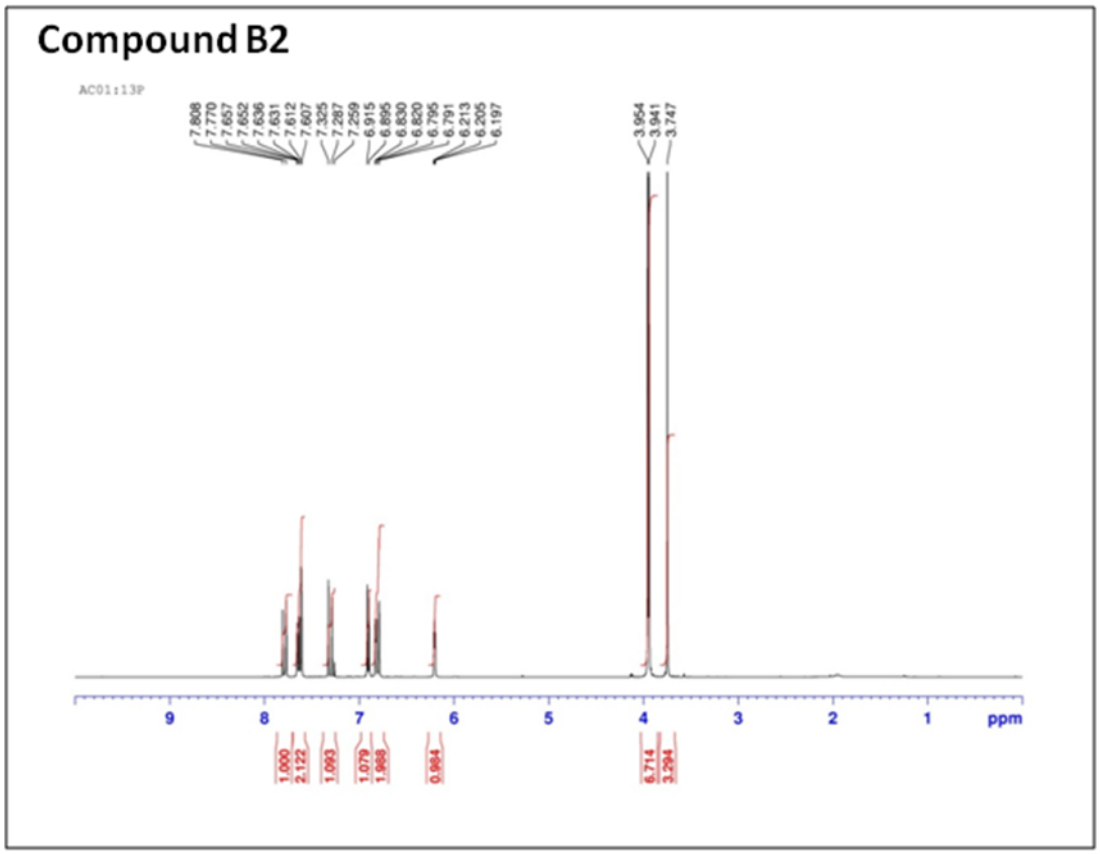
Compound C1

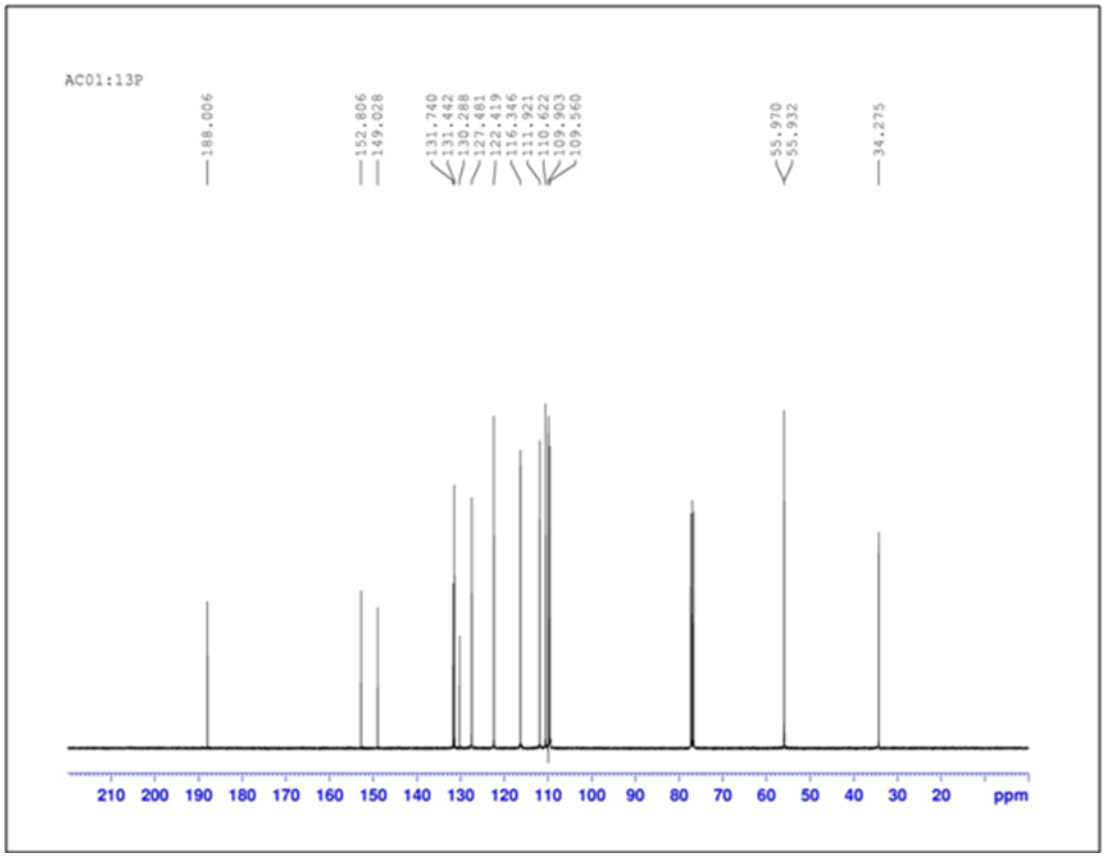


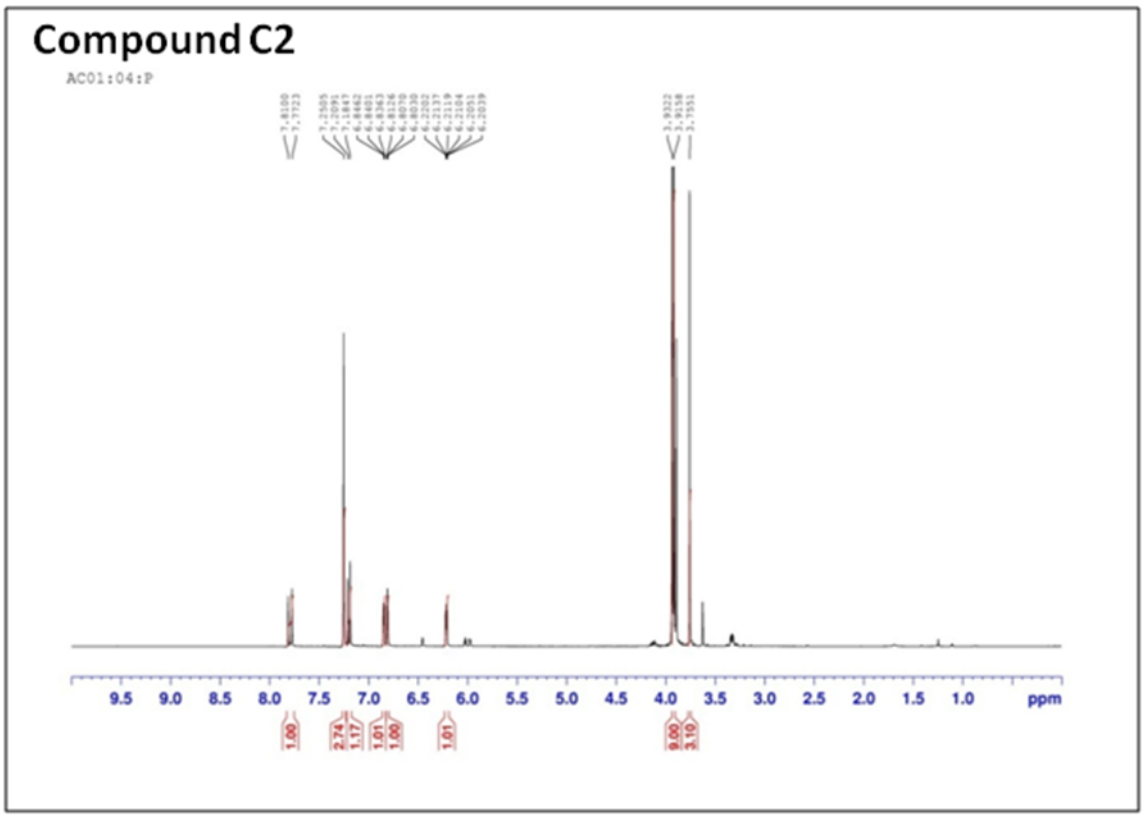


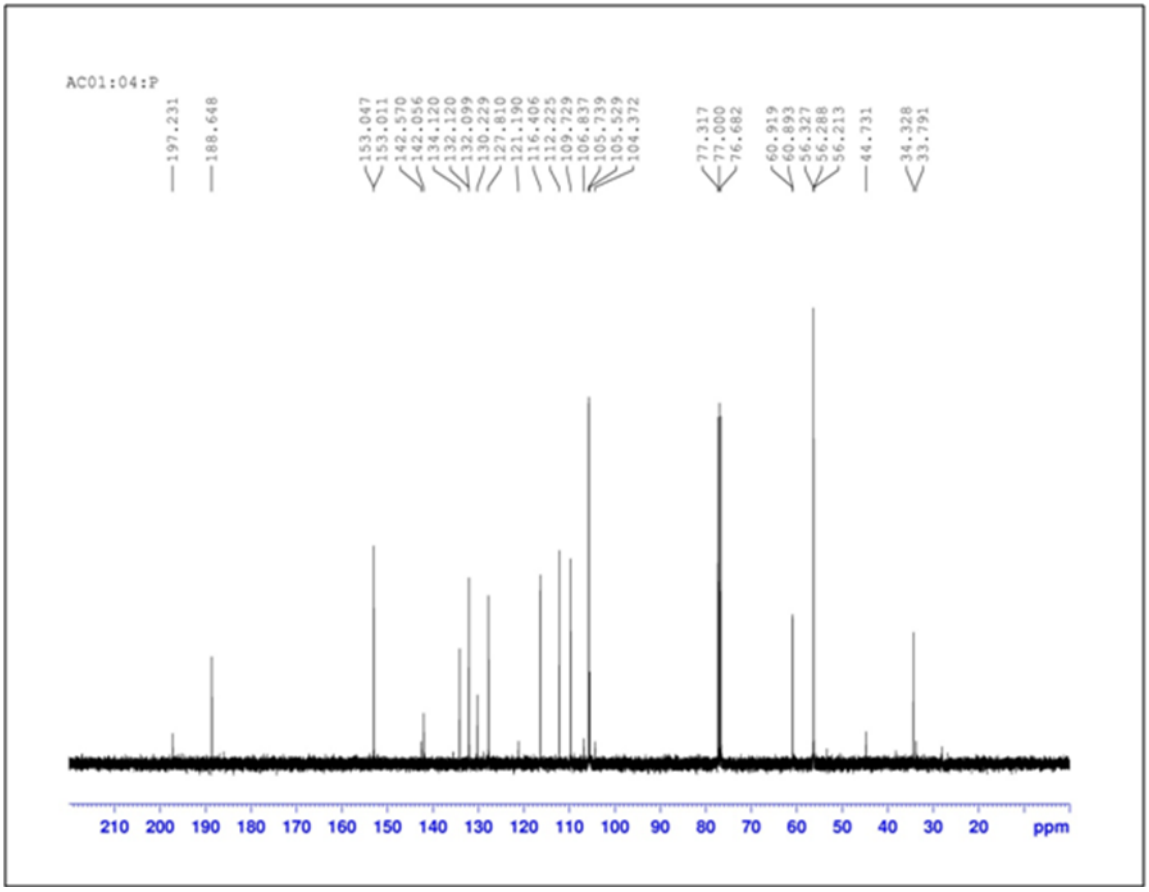


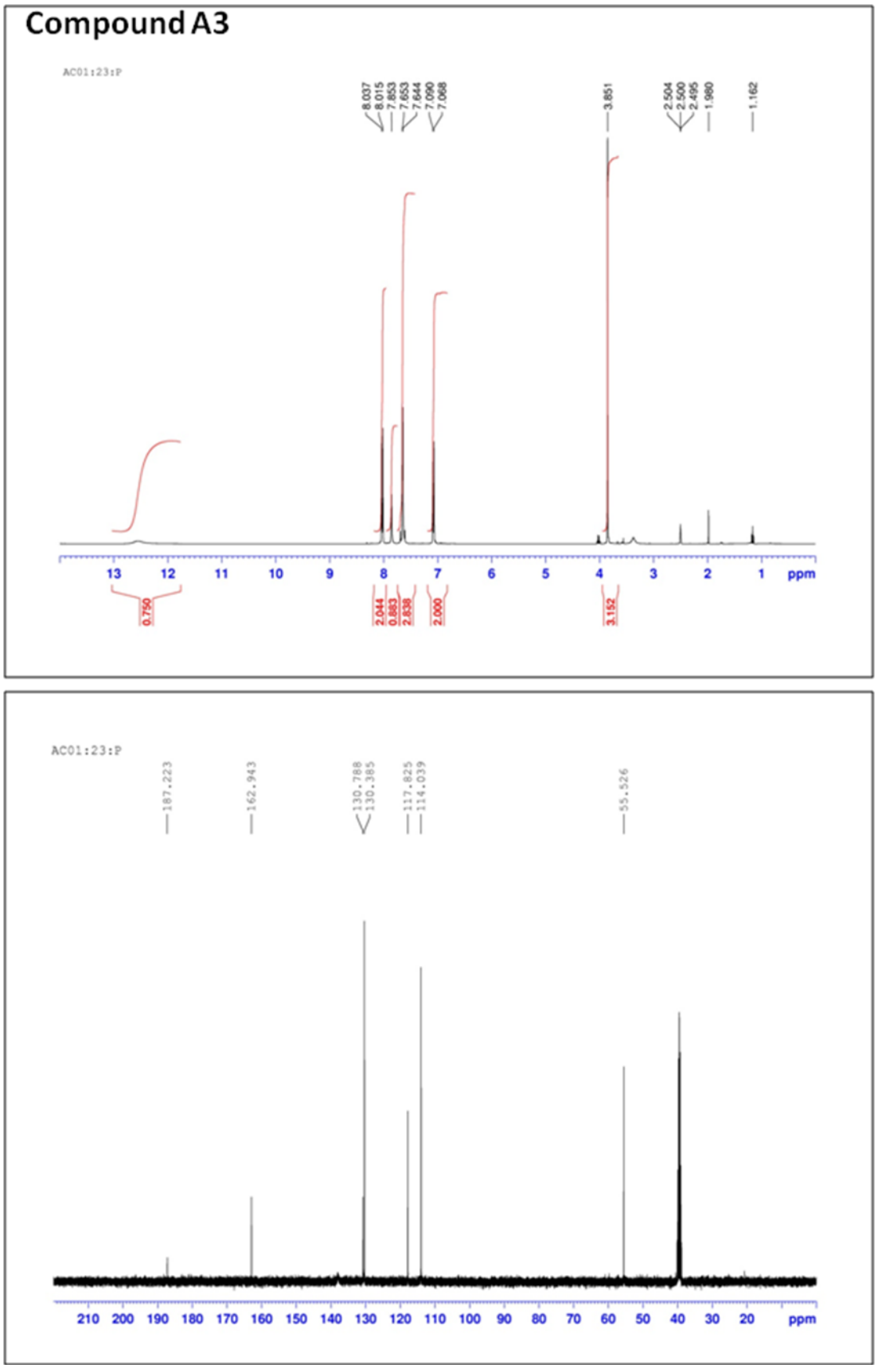


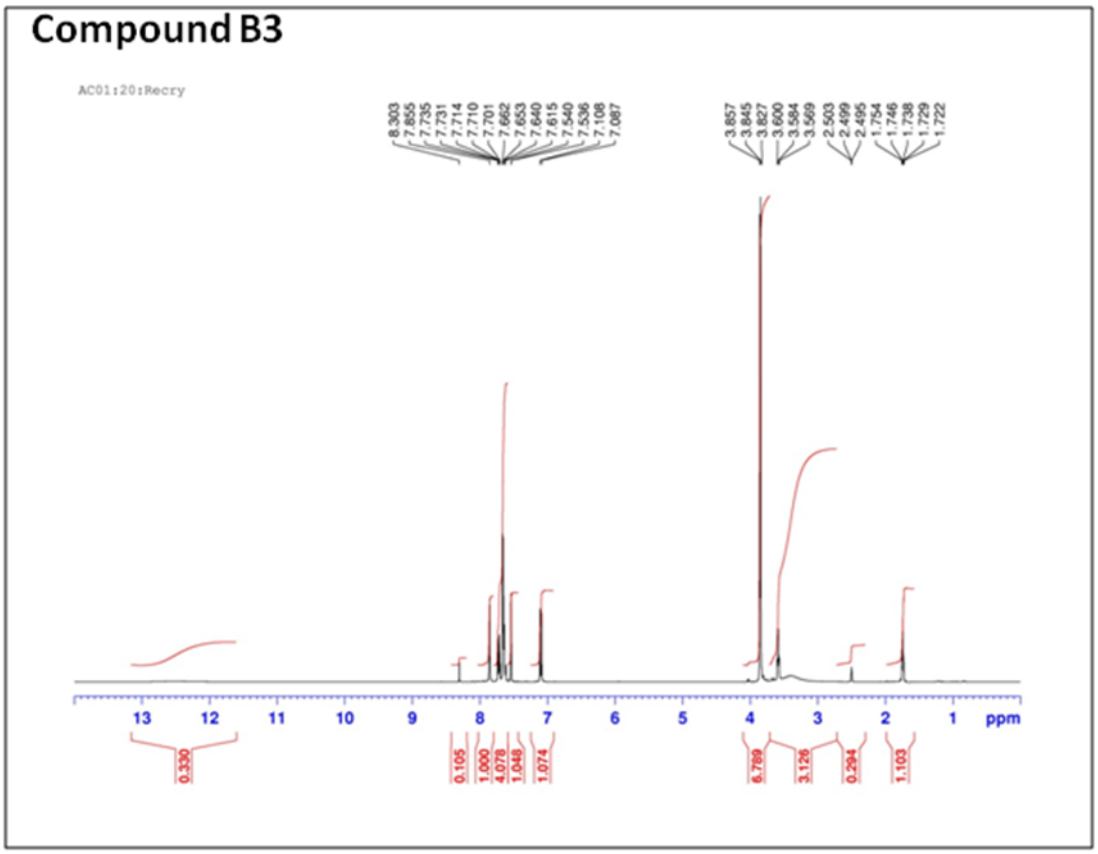


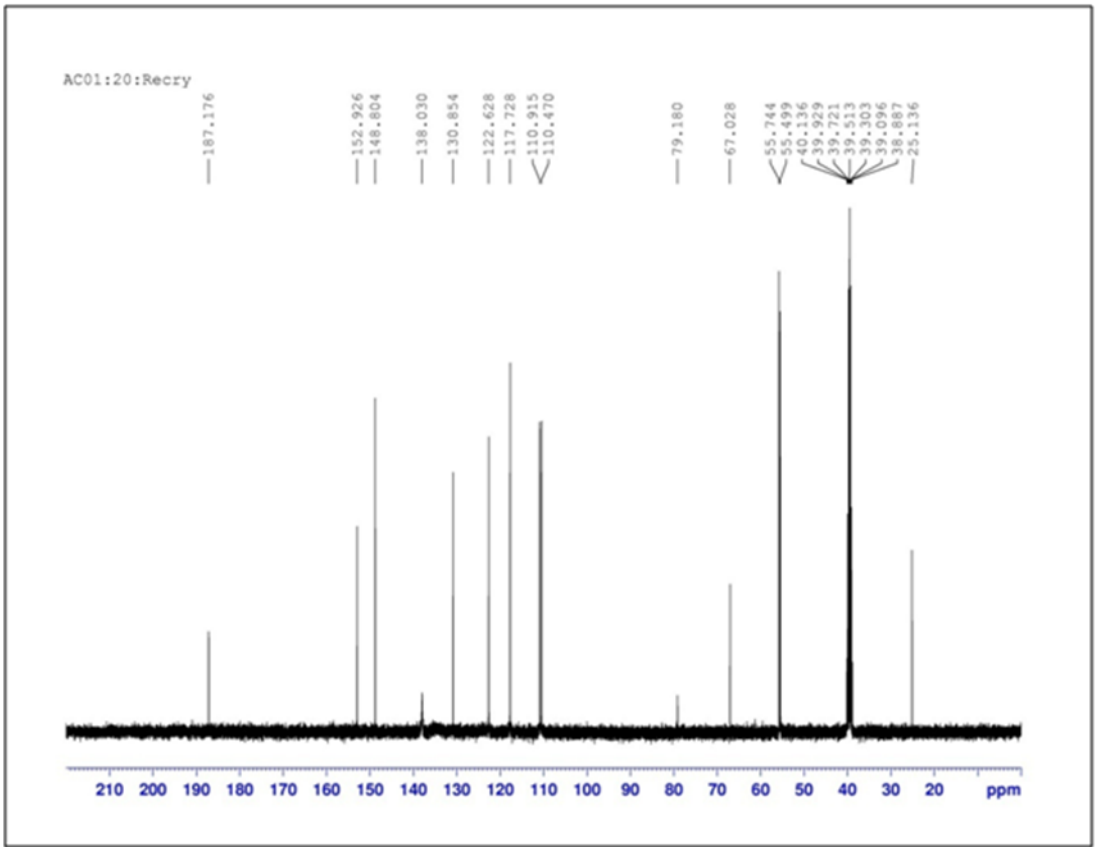


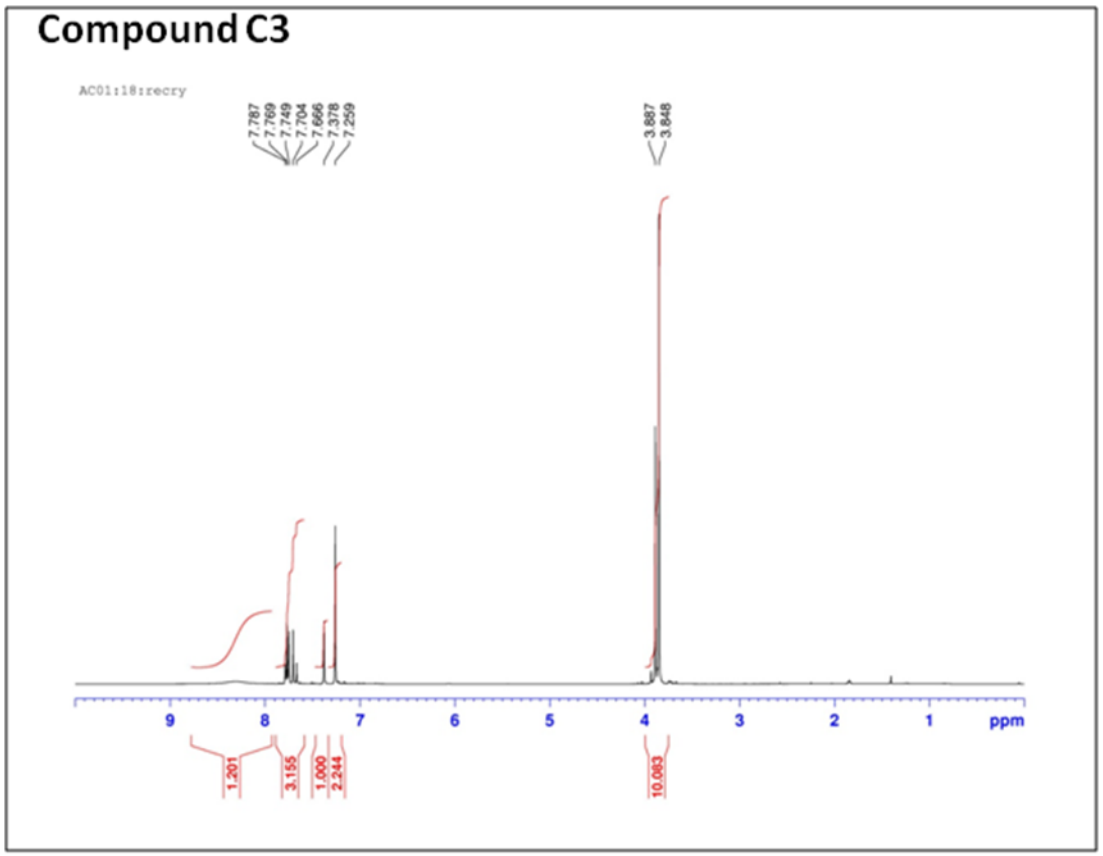


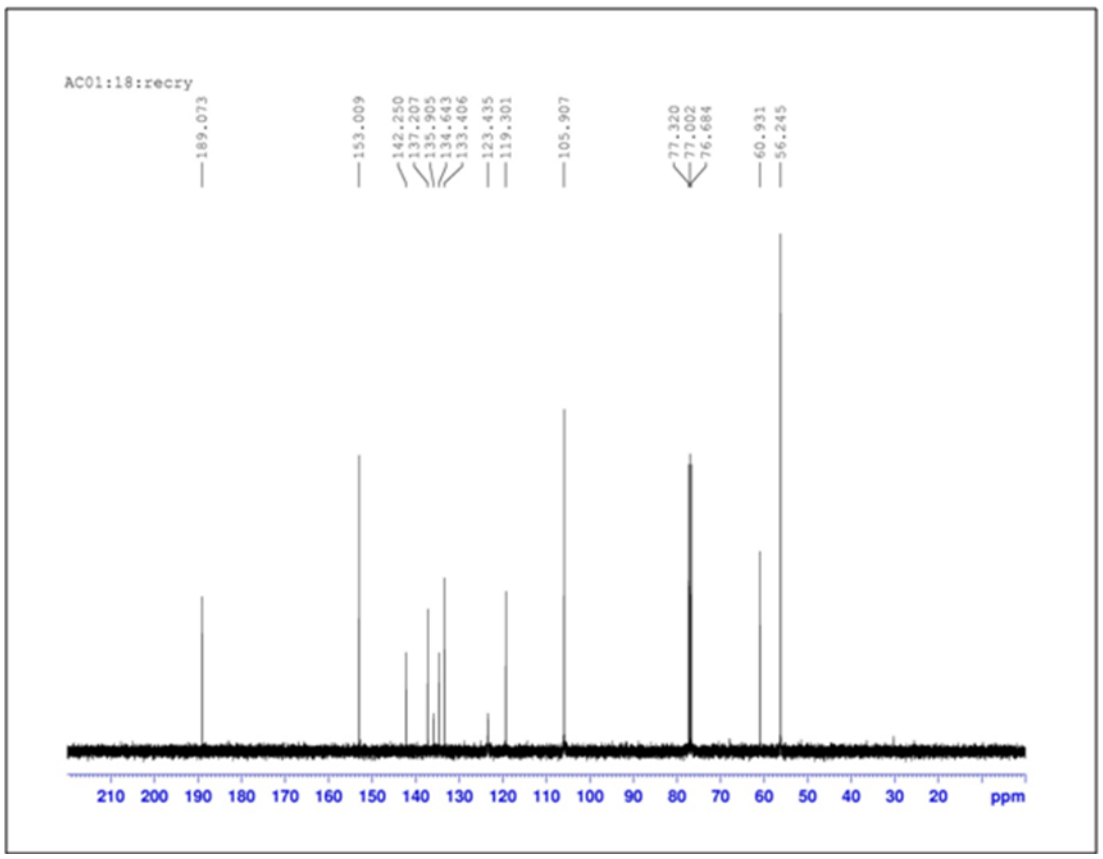


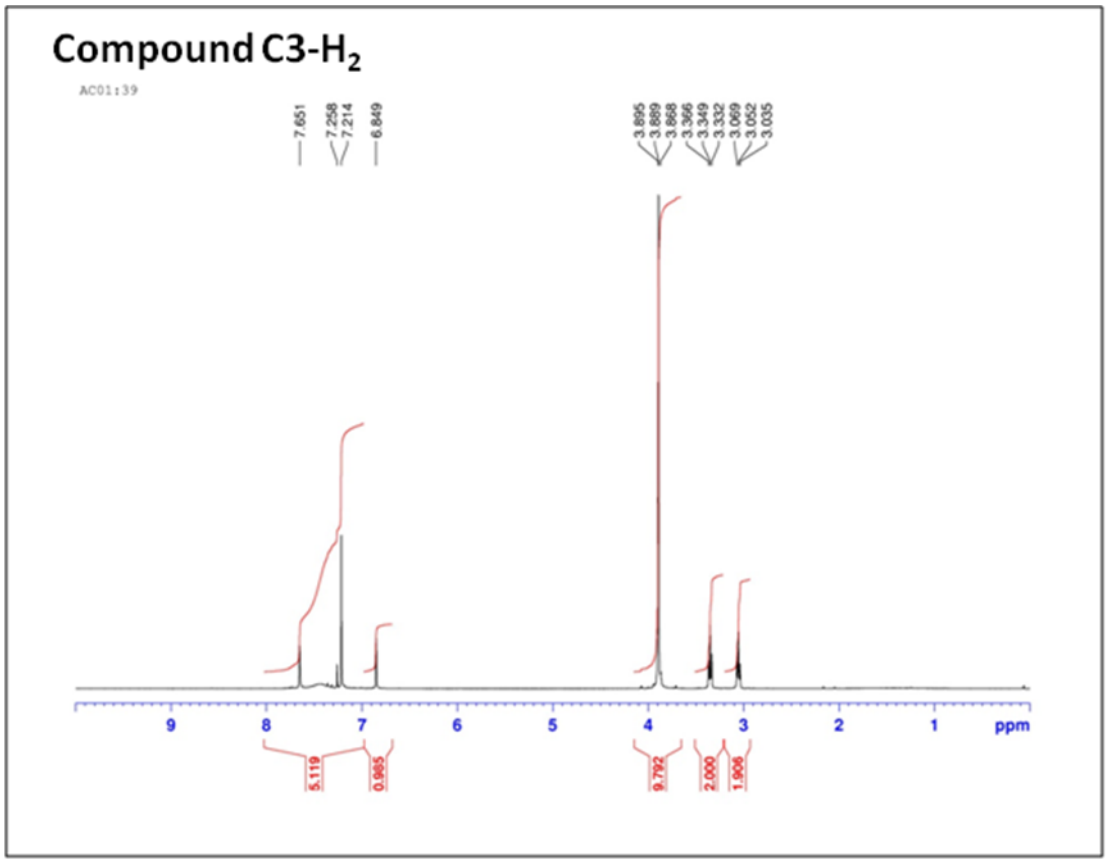


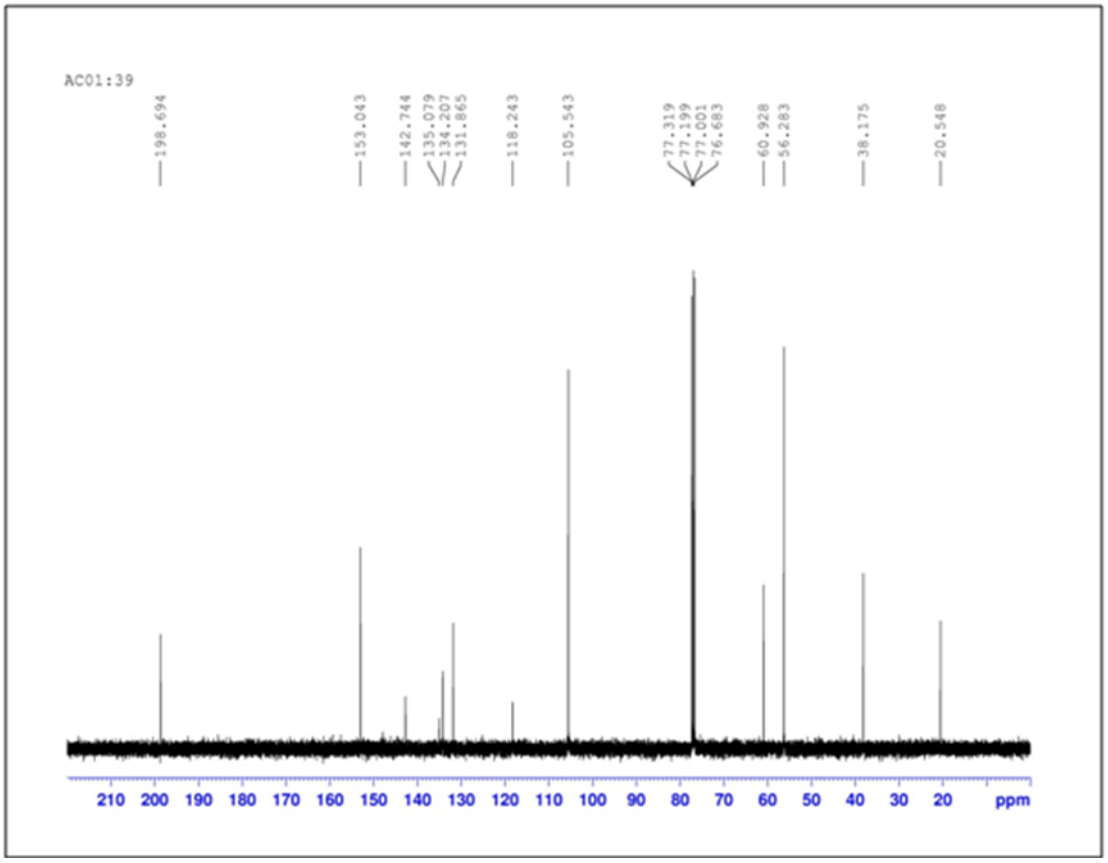


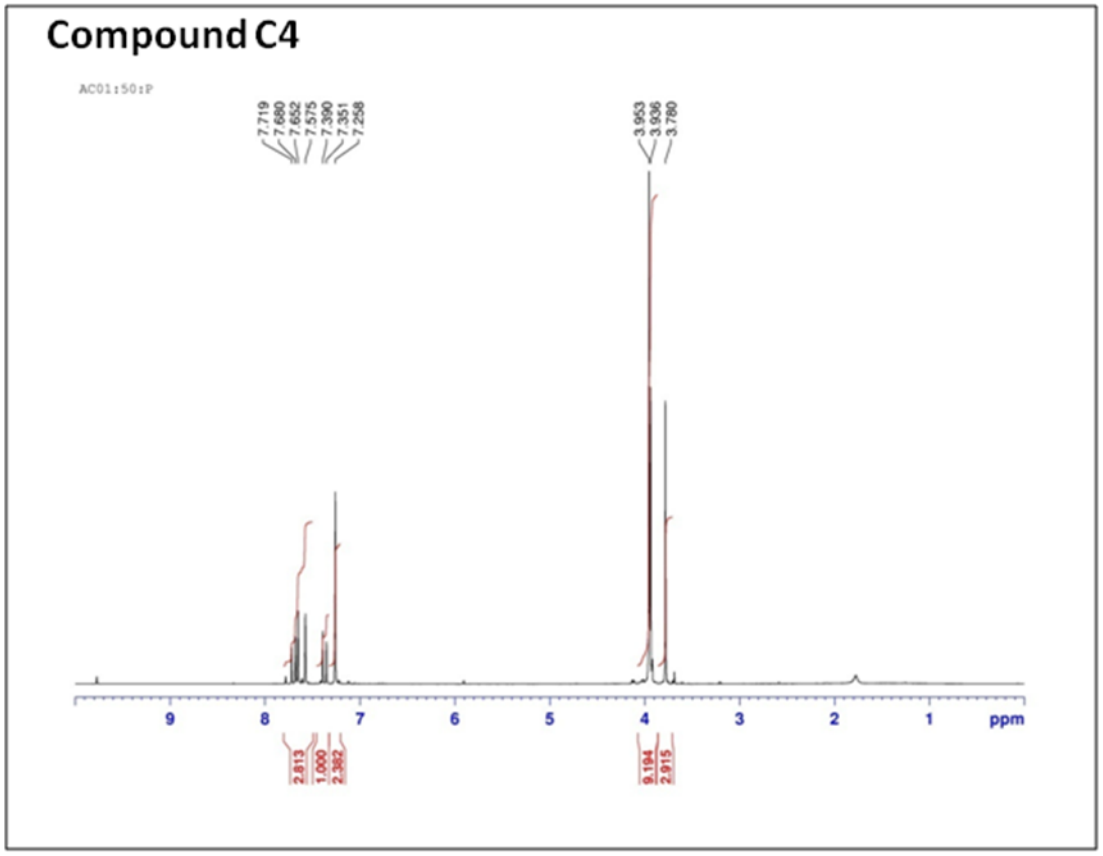


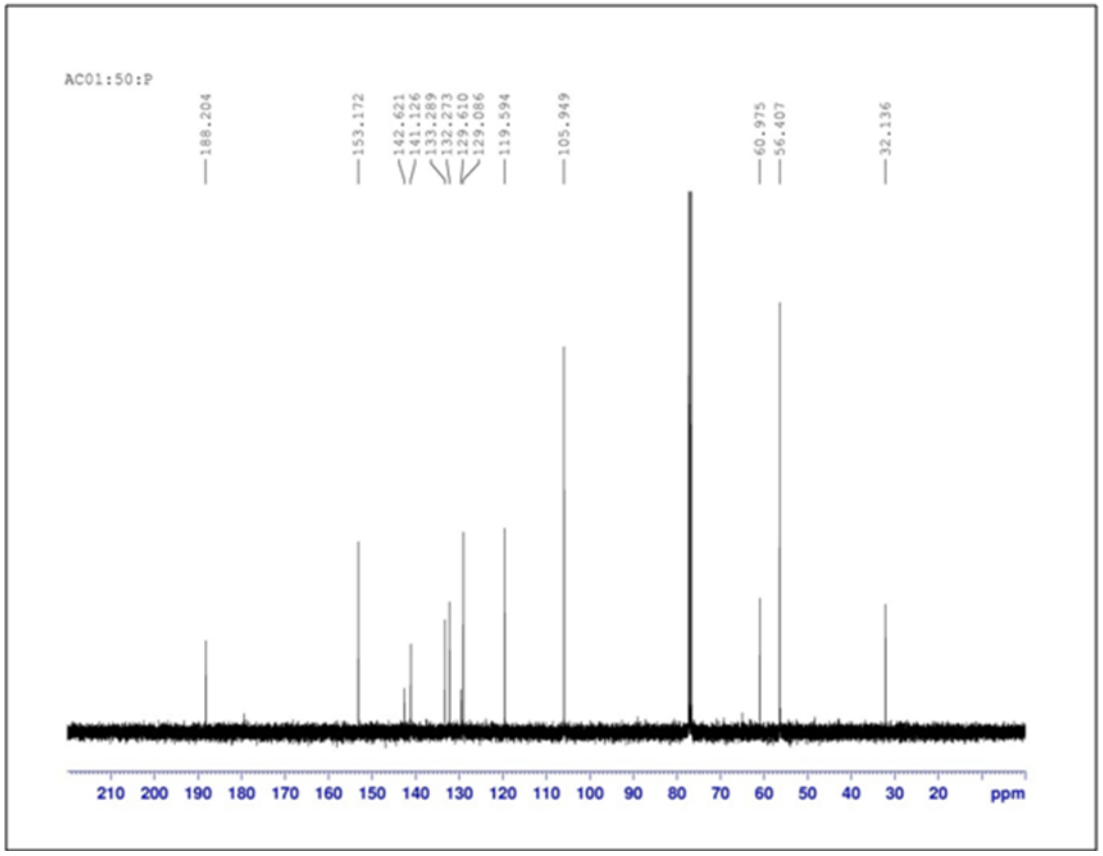












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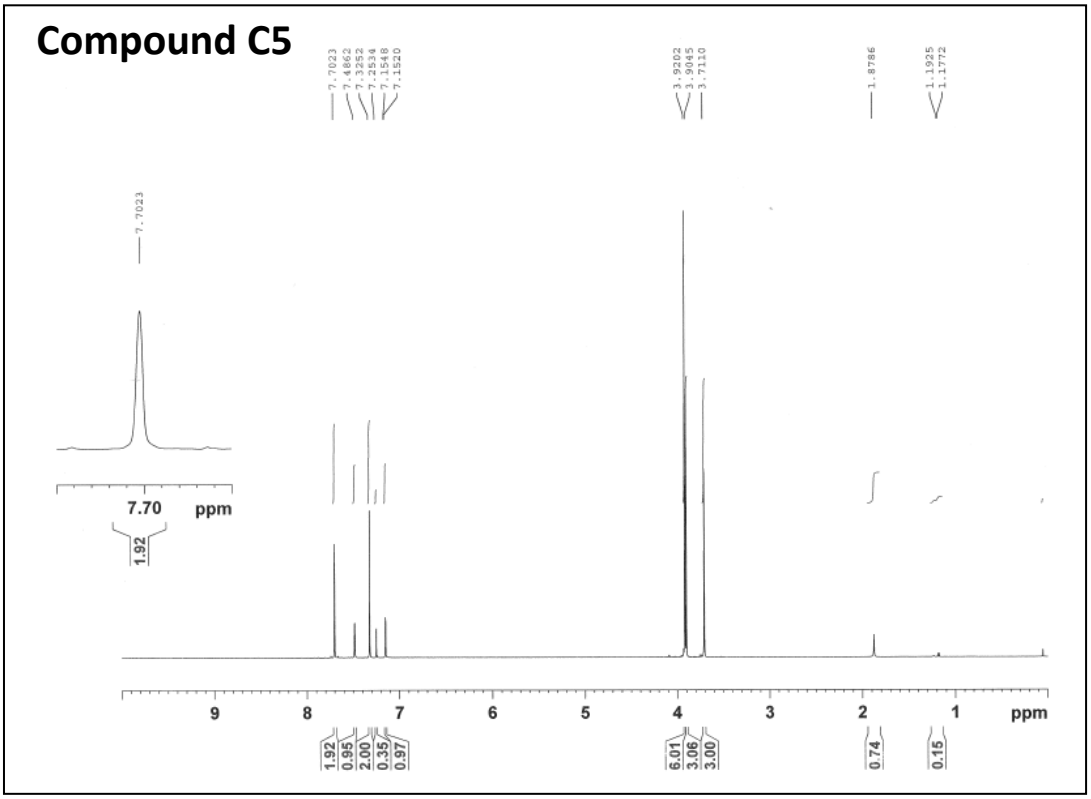
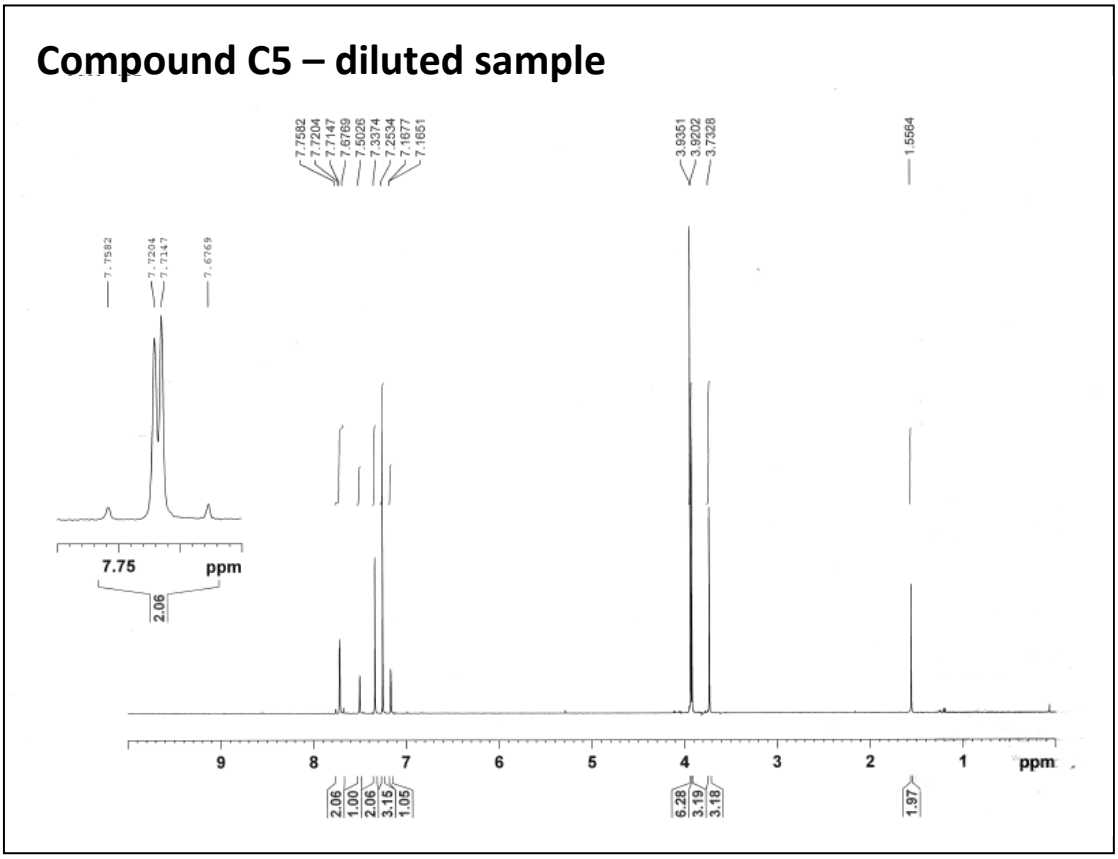
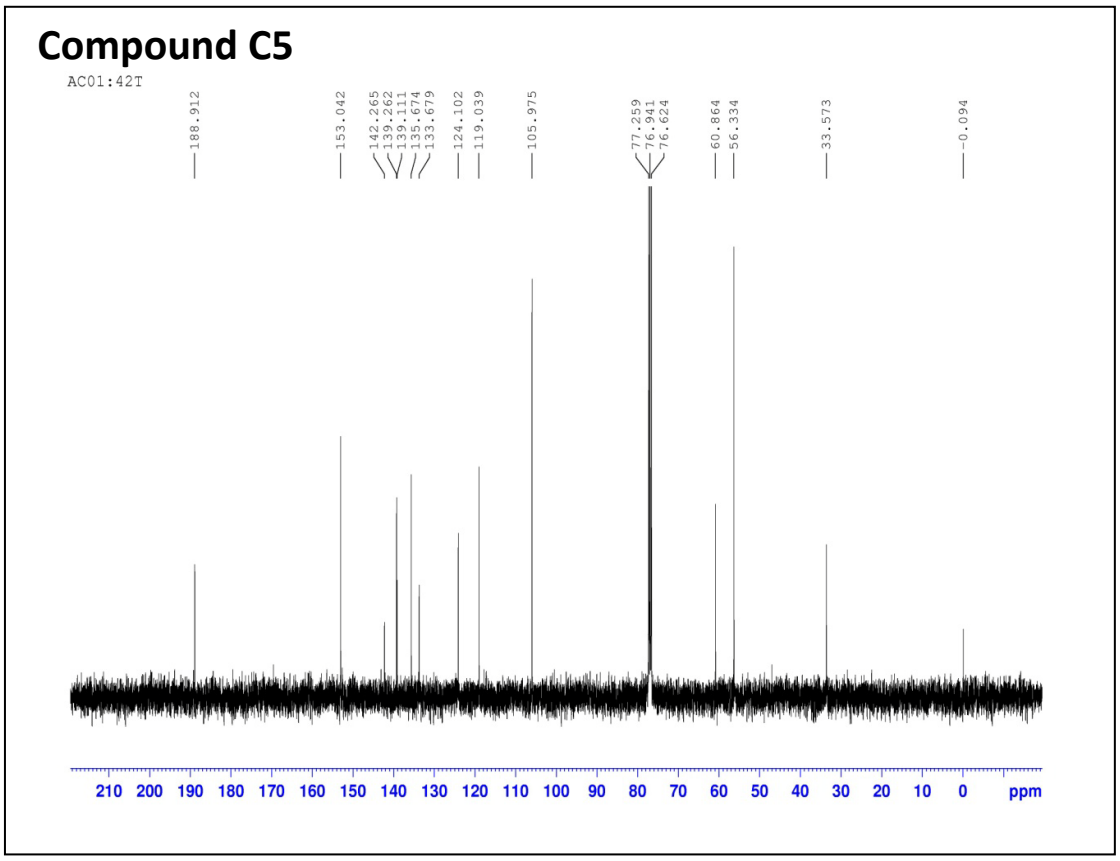
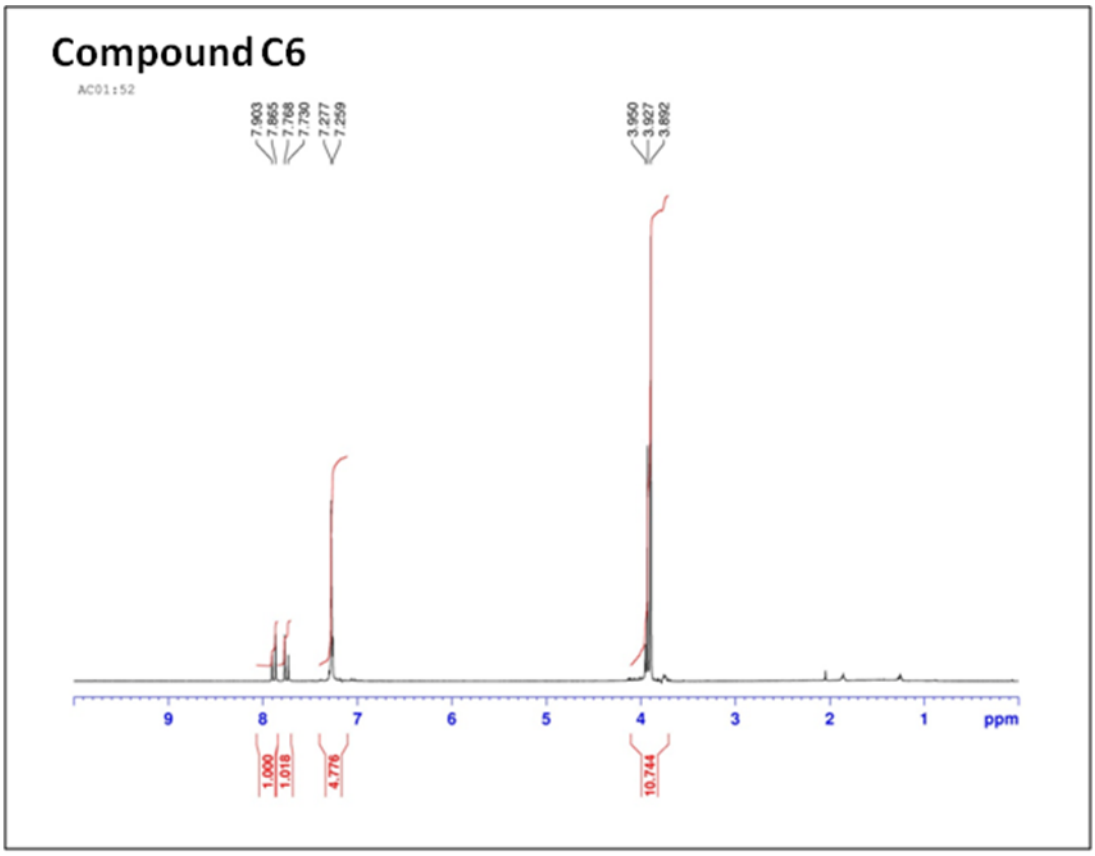
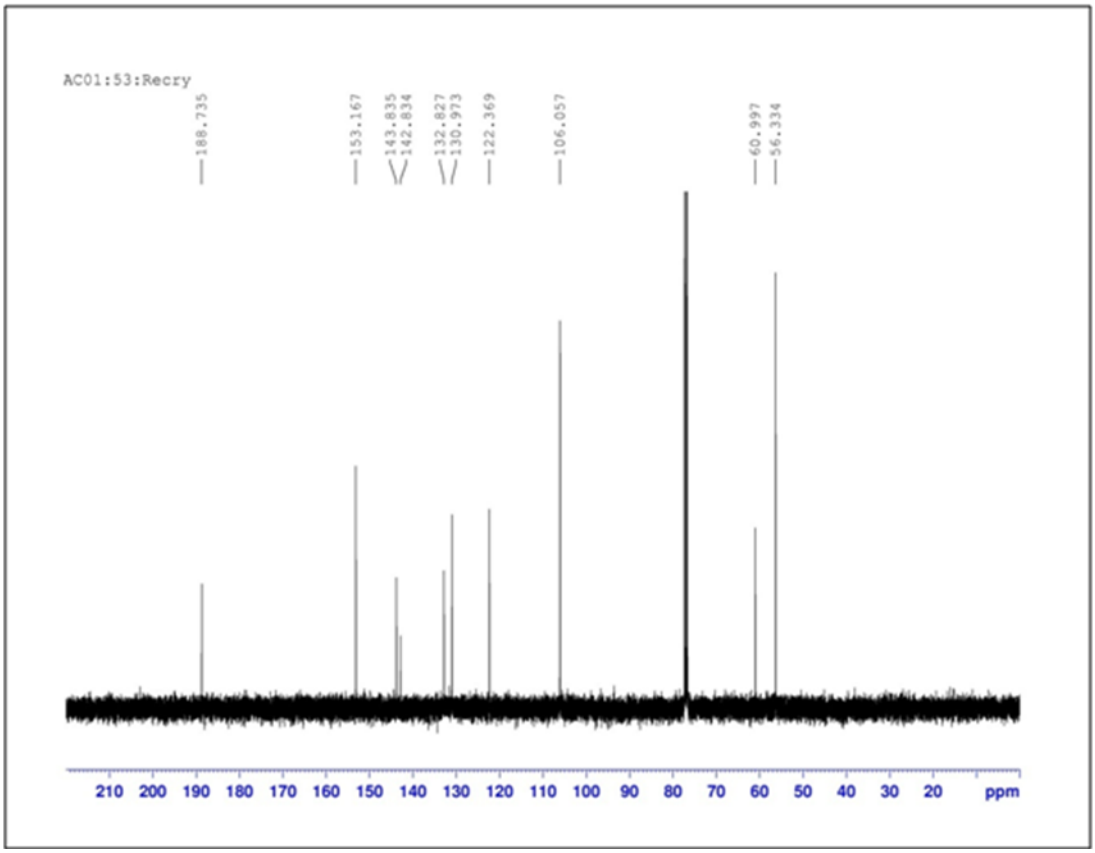


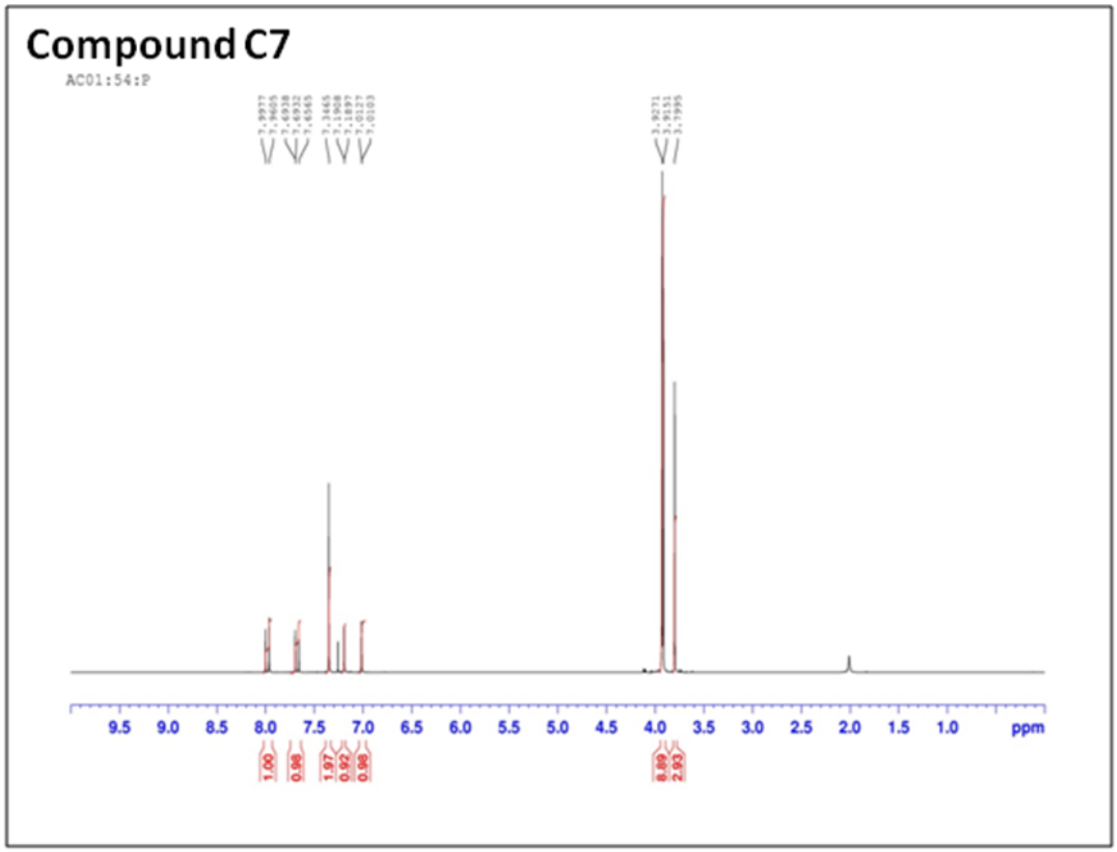
Compound C5 – diluted sample

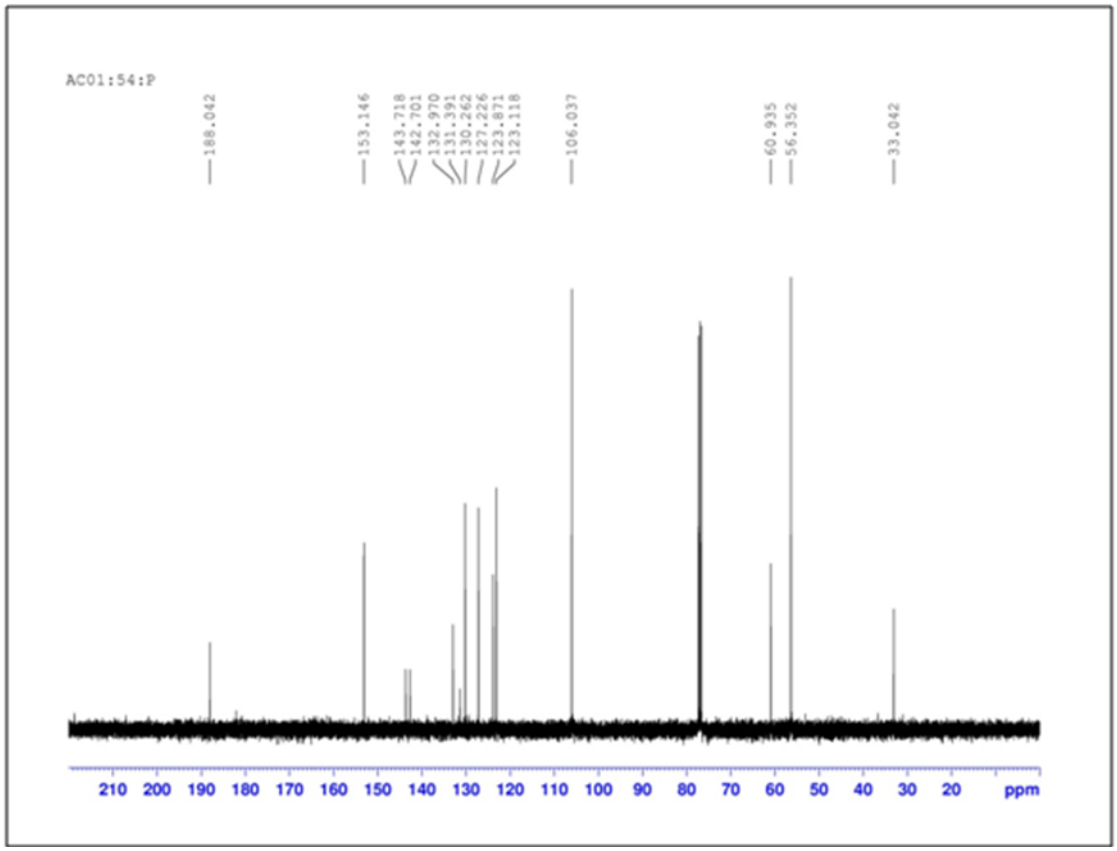






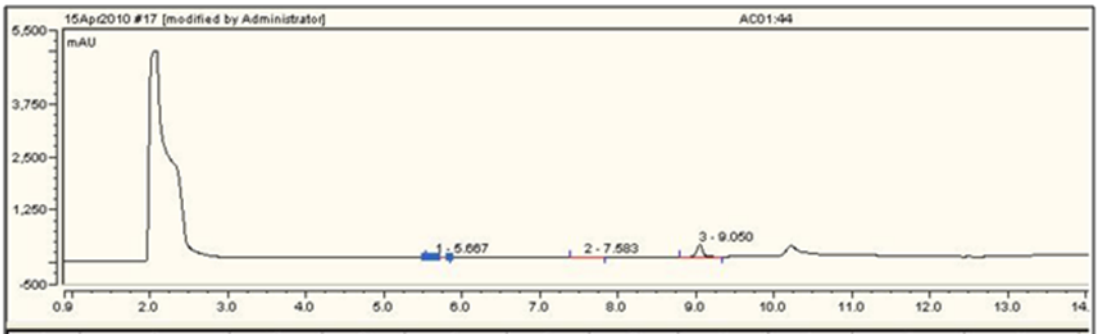






HPLC traces at 214 nm

Compound A1



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1	n.a.	5.667	0.4513	n.a.	BMB*	10.325	1.78	11.06
2	n.a.	7.583	0.2672	n.a.	BMB*	1.482	1.05	7.49
3	n.a.	9.050	24.6394	n.a.	BMB*	288.319	97.17	n.a.
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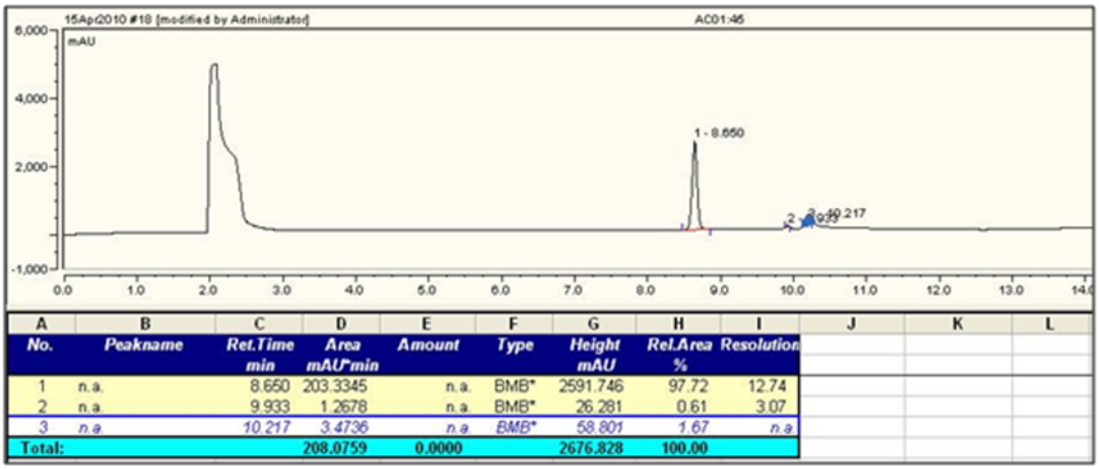
Compound B1



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2	n.a.	9.933	1.2678	n.a.	BMB*	26.281	0.61	3.07
3	n.a.	10.217	3.4736	n.a.	BMB*	58.801	1.67	n.a.
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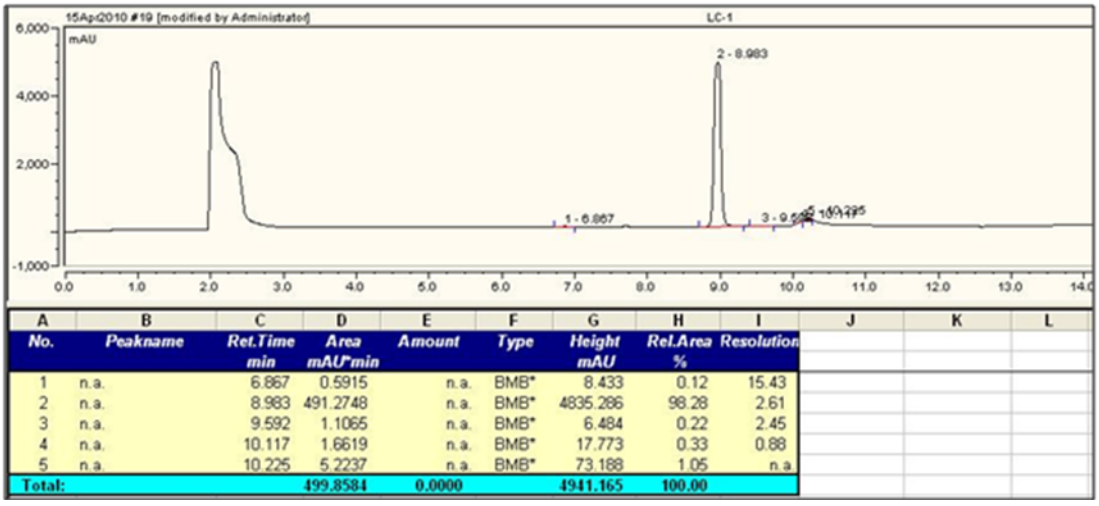
Compound C1



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1	n.a.	6.867	0.5915	n.a.	BMB*	8.433	0.12	15.43
2	n.a.	8.983	491.2748	n.a.	BMB*	4835.286	98.28	2.61
3	n.a.	9.592	1.1065	n.a.	BMB*	6.484	0.22	2.45
4	n.a.	10.117	1.6619	n.a.	BMB*	17.773	0.33	0.88
5	n.a.	10.225	5.2237	n.a.	BMB*	73.188	1.05	n.a.
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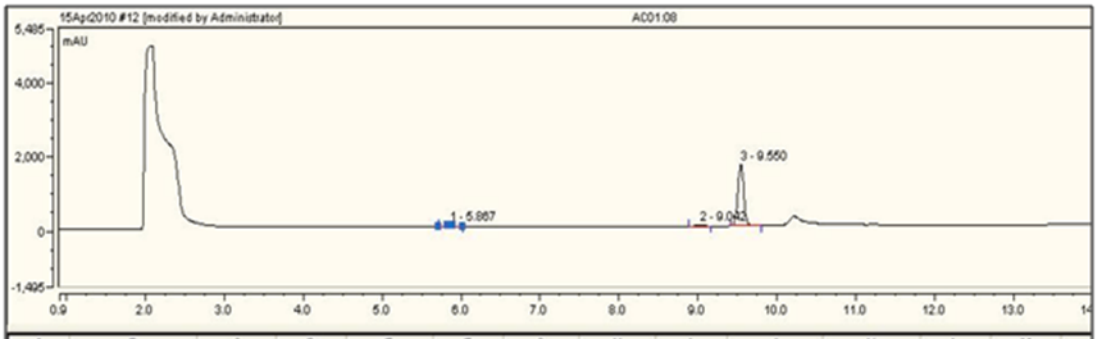
Compound A2



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1	n.a.	5.867	3.2133	n.a.	BMB*	32.603	2.14	25.49
2	n.a.	9.042	2.1066	n.a.	BMB*	25.083	1.40	3.81
3	n.a.	9.550	144.8830	n.a.	BMB*	1668.767	96.46	n.a.
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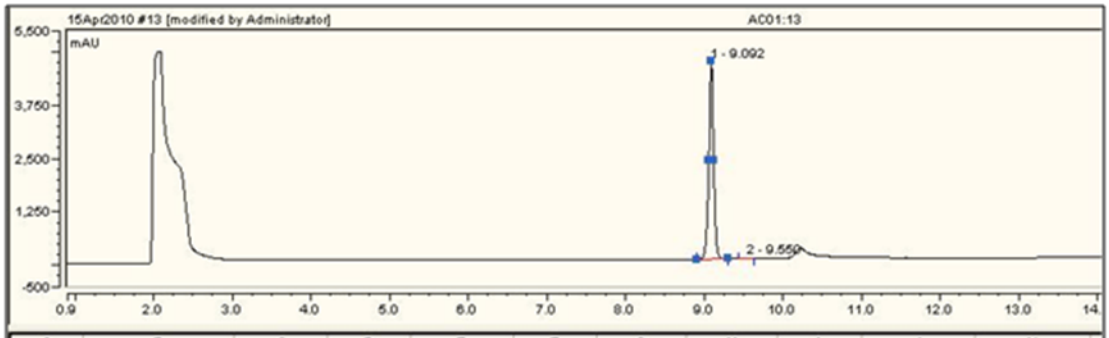
Compound B2



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1	n.a.	9.092	329.2724	n.a.	BMB*	4626.317	99.66	3.49
2	n.a.	9.550	1.1371	n.a.	BMB*	11.596	0.34	n.a.
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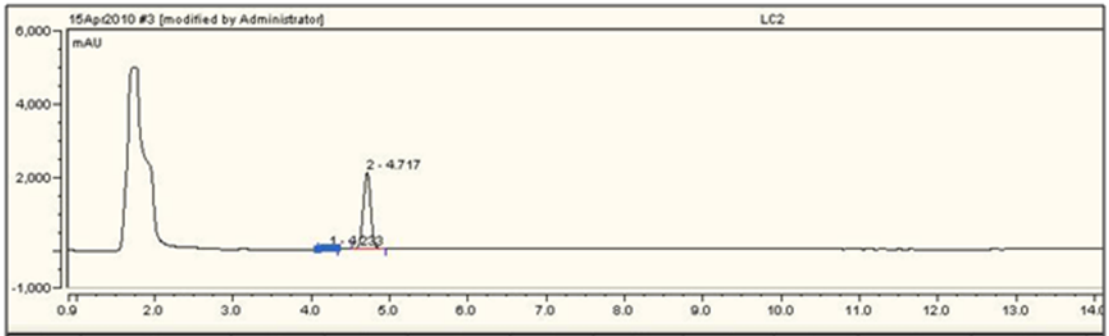
Compound C2



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
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2	n.a.	4.717	228.9224	n.a.	BMB	2069.192	99.42	n.a.
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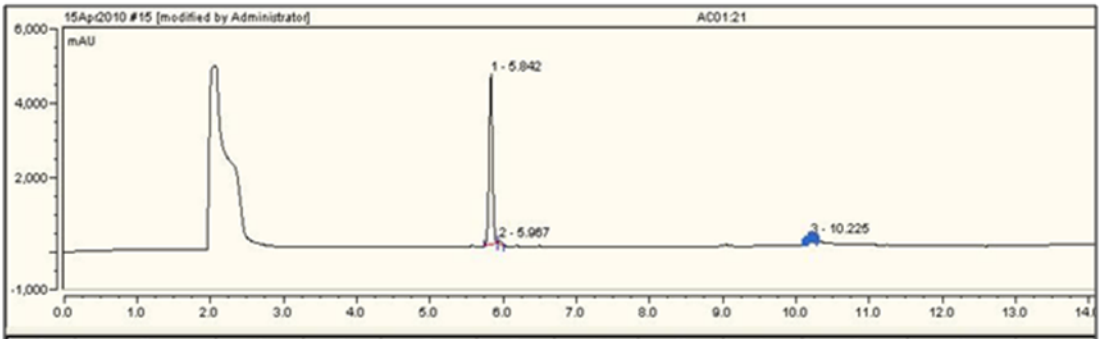
Compound A3



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
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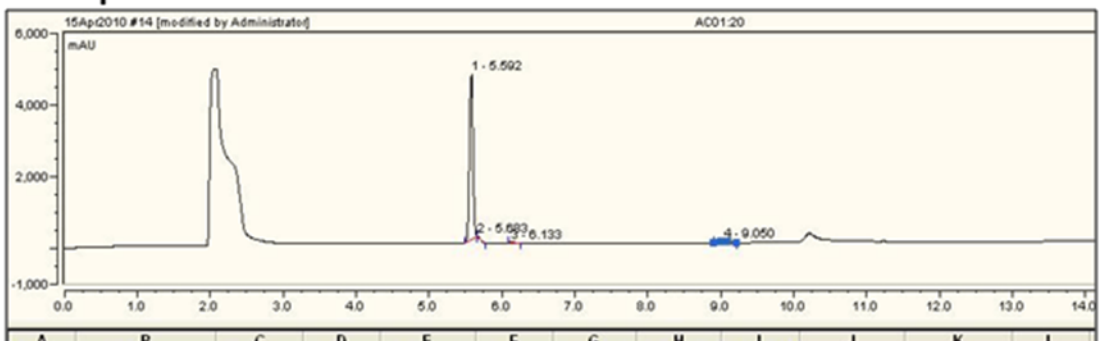
2	n.a.	5.967	3.7106	n.a.	BMB*	89.013	1.40	37.13
3	*n.a.*	*10.225*	*10.7105*	*n.a.*	*BMB**	*116.815*	*4.05*	*n.a.*
Total:			264.6820	0.0000		4785.913	100.00	

Compound B3



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
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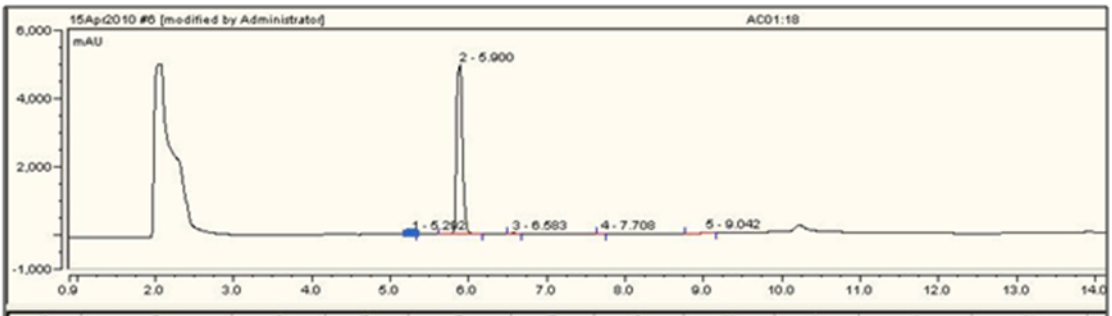
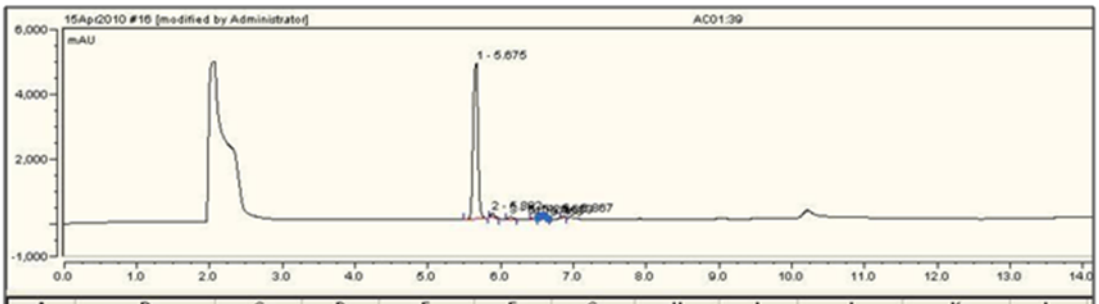
2	n.a.	5.683	0.5653	n.a.	bMB*	33.291	0.21	n.a.
3	n.a.	6.133	1.3155	n.a.	BMB*	23.315	0.49	22.54
4	*n.a.*	*9.050*	*3.6120*	*n.a.*	*BMB**	*34.654*	*1.35*	*n.a.*
Total:			267.8601	0.0000		4707.901	100.00	

Compound C3



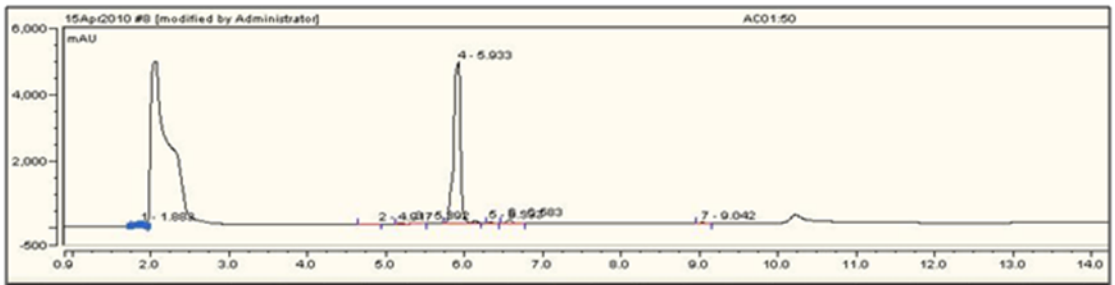
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	*n.a.*	*5.292*	*1.9355*	*n.a.*	*BMB**	*35.368*	*0.43*	*5.31*
2	n.a.	5.900	440.1924	n.a.	BMB*	4958.699	98.41	5.73
3	n.a.	6.583	2.3953	n.a.	BMB*	37.602	0.54	10.68
4	n.a.	7.708	0.4409	n.a.	BMB*	6.687	0.10	11.21
5	n.a.	9.042	2.3615	n.a.	BMB*	31.463	0.53	n.a.
Total:			447.3255	0.0000		5069.818	100.00	

Compound C3-H_2



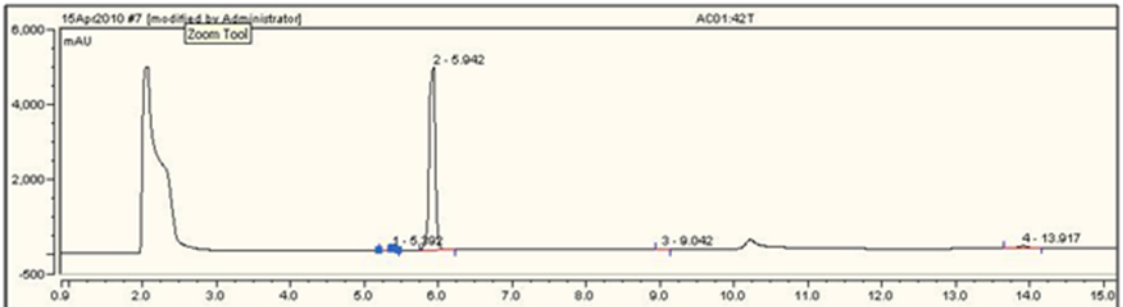
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.675	367.9384	n.a.	BMB*	4800.382	94.70	2.06
2	n.a.	5.892	7.6641	n.a.	BMB*	133.713	1.97	2.81
3	n.a.	6.142	4.6159	n.a.	BMB*	80.722	1.19	3.51
4	n.a.	6.458	0.6464	n.a.	BMB*	11.934	0.17	1.29
5	*n.a.*	*6.583*	*4.9572*	*n.a.*	*BMB**	*76.324*	*1.28*	*2.98*
6	n.a.	6.867	2.7265	n.a.	BMB*	54.991	0.70	n.a.
Total:			388.5485	0.0000		5158.066	100.00	

Compound C4



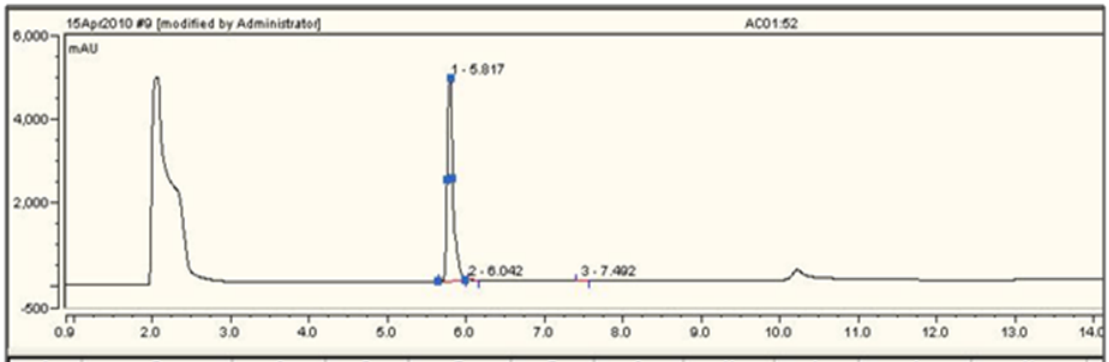
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	*n.a.*	*1.883*	*5.3431*	*n.a.*	*BMB**	*59.912*	*1.11*	*10.46*
2	n.a.	4.917	0.0052	n.a.	BMB*	0.544	0.00	1.08
3	n.a.	5.392	3.7916	n.a.	BMB*	25.610	0.78	1.84
4	n.a.	5.933	460.6892	n.a.	BM *	4832.323	95.35	3.26
5	n.a.	6.333	2.0148	n.a.	BMB*	31.379	0.42	2.17
6	n.a.	6.583	9.2173	n.a.	BMB*	113.470	1.91	20.21
7	n.a.	9.042	2.0747	n.a.	BMB*	27.293	0.43	n.a.
Total:			483.1359	0.0000		5090.530	100.00	

Compound C5



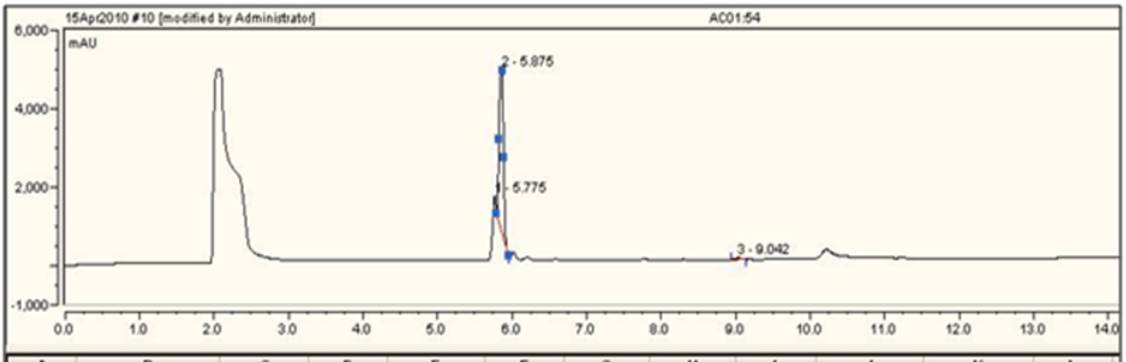
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	*n.a.*	*5.392*	*2.0870*	*n.a.*	*BMB**	*37.141*	*0.47*	*4.78*
2	n.a.	5.942	434.0589	n.a.	BMB*	4840.438	97.88	23.42
3	n.a.	9.042	1.7820	n.a.	BMB*	22.015	0.40	31.78
4	n.a.	13.917	5.5295	n.a.	BMB*	46.658	1.25	n.a.
Total:			443.4574	0.0000		4946.252	100.00	

Compound C6



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	*n.a.*	*5.817*	*421.9690*	*n.a.*	*BMB**	*4813.616*	*99.77*	*2.54*
2	n.a.	6.042	0.2849	n.a.	BMB*	12.210	0.07	19.12
3	n.a.	7.492	0.6799	n.a.	BMB*	11.153	0.16	n.a.
Total:			**422.9338**	**0.0000**		**4836.979**	**100.00**	

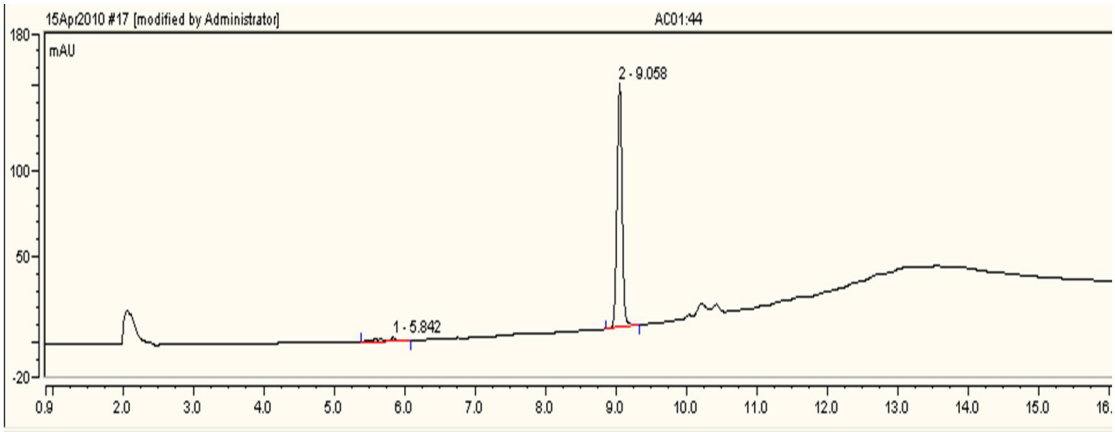
Compound C7



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.775	11.3521	n.a.	BMB*	424.979	3.88	1.25
2	*n.a.*	*5.875*	*277.8768*	*n.a.*	*BMB**	*4169.528*	*95.01*	*26.28*
3	n.a.	9.042	3.2385	n.a.	BMB*	40.846	1.11	n.a.
Total:			**292.4674**	**0.0000**		**4635.353**	**100.00**	

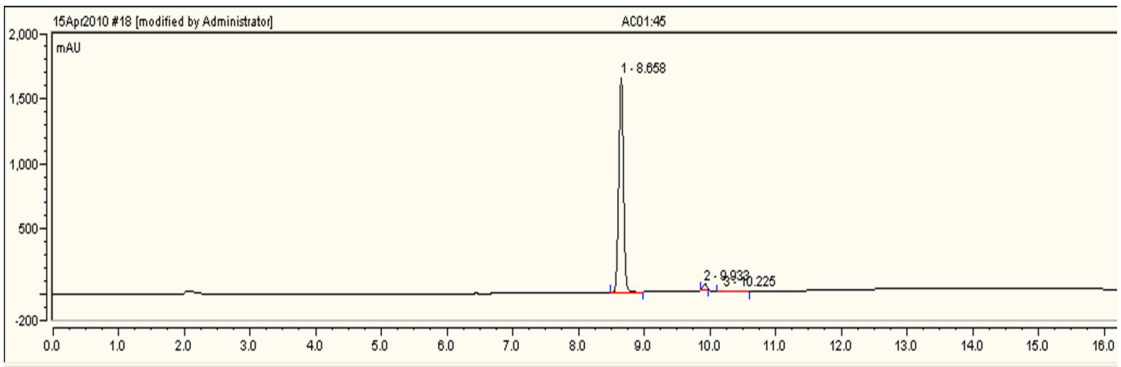
HPLC traces at 254 nm

Compound A1



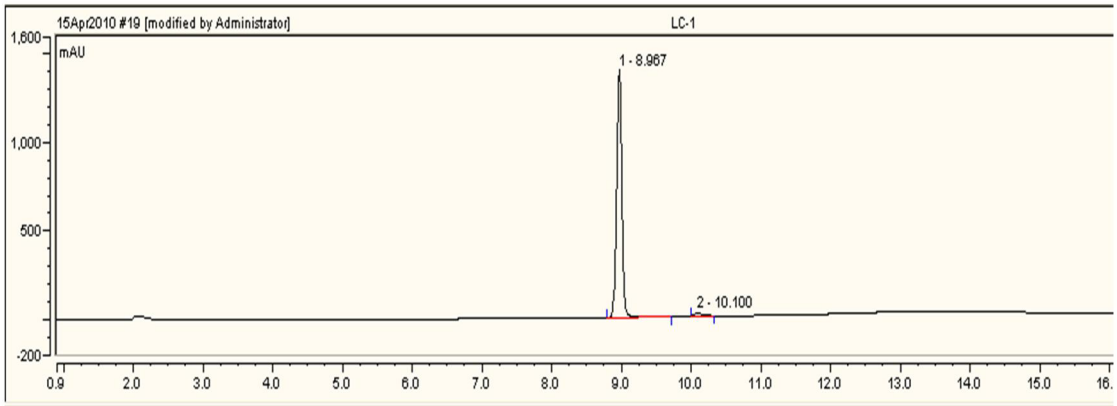
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.842	0.2842	n.a.	BMB*	1.871	2.30	9.91
2	n.a.	9.058	12.0754	n.a.	BMB*	142.019	97.70	n.a.
Total:			12.3596	0.0000		143.890	100.00	

Compound B1



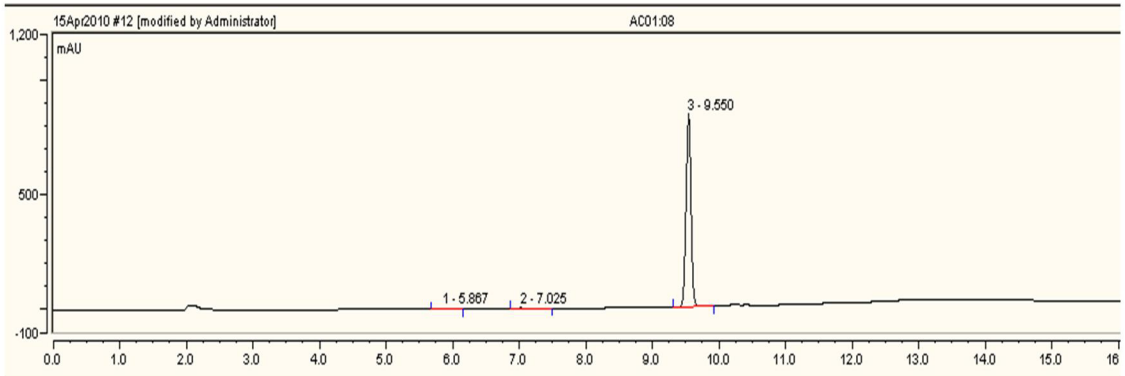
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8.658	138.7999	n.a.	BMB	1652.064	95.75	10.32
2	n.a.	9.933	2.7237	n.a.	BMB*	40.686	1.88	1.69
3	n.a.	10.225	1.0293	n.a.	BMB	6.316	0.71	46.07
4	n.a.	17.500	2.4068	n.a.	BMB*	5.234	1.66	n.a.
Total:			144.9597	0.0000		1704.300	100.00	

Compound C1



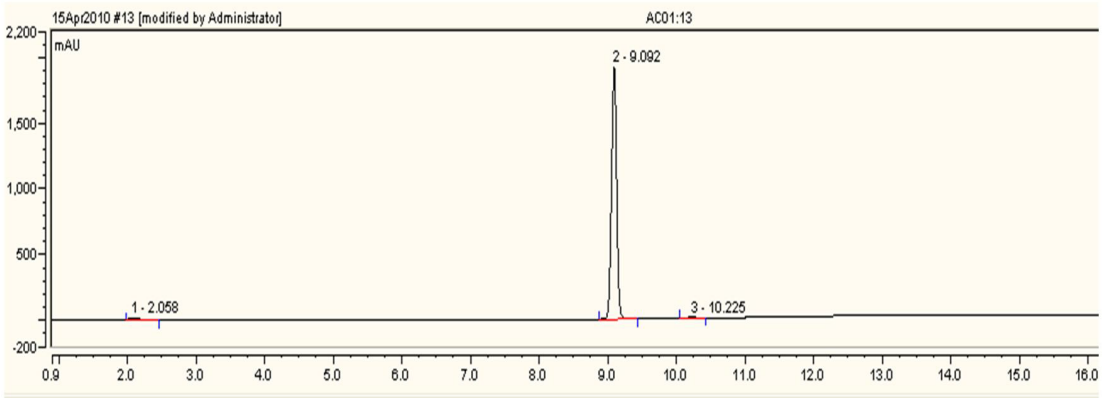
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8.967	120.7461	n.a.	BMB	1401.517	98.38	8.00
2	n.a.	10.100	1.9920	n.a.	BMB*	18.484	1.62	n.a.
Total:			122.7381	0.0000		1420.002	100.00	

Compound A2



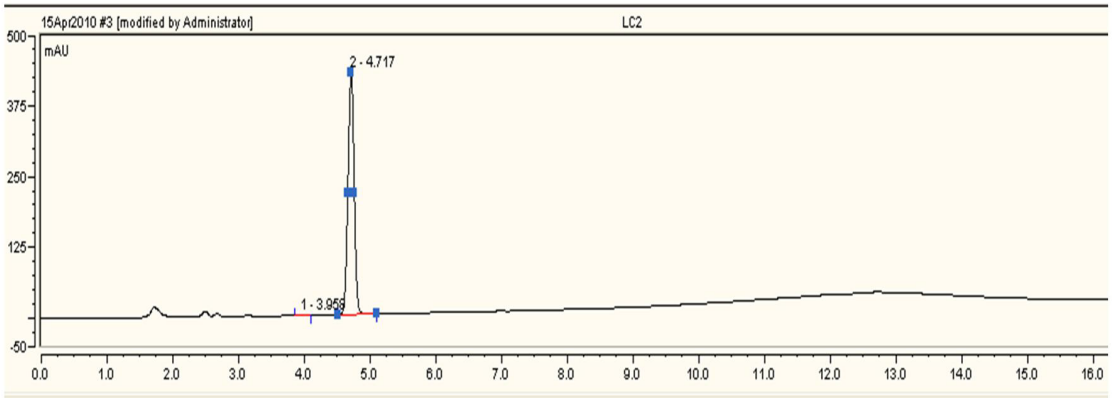
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.867	0.4265	n.a.	BMB*	4.279	0.57	9.81
2	n.a.	7.025	0.3386	n.a.	BMB*	3.911	0.46	19.73
3	n.a.	9.550	73.5954	n.a.	BMB	838.764	98.97	n.a.
Total:			74.3605	0.0000		846.955	100.00	

Compound B2



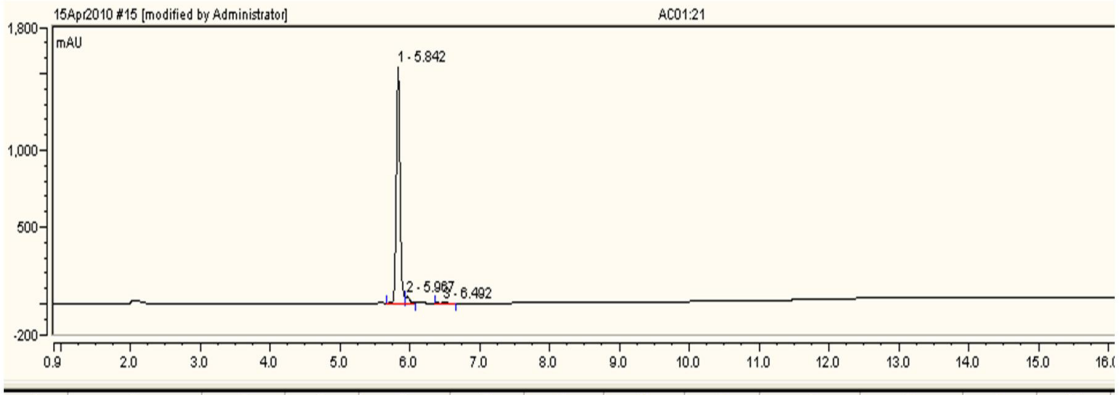
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	2.058	3.8919	n.a.	BMB	19.661	2.27	32.09
2	n.a.	9.092	166.7938	n.a.	BMB	1919.342	97.32	6.53
3	n.a.	10.225	0.6929	n.a.	BMB*	5.448	0.40	n.a.
Total:			171.3787	0.0000		1944.451	100.00	

Compound C2



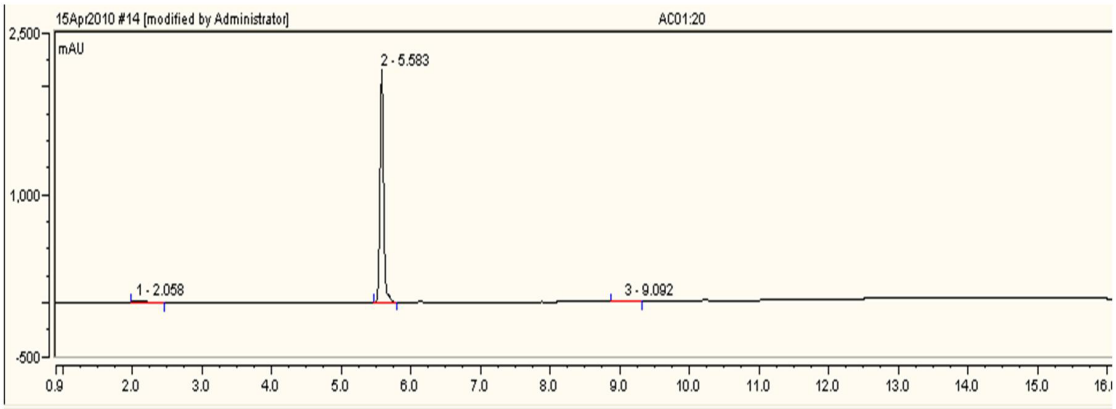
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	3.958	0.1656	n.a.	BMB*	1.695	0.34	4.49
2	*n.a.*	*4.717*	*47.5166*	*n.a.*	*BMB*	*428.387*	*98.74*	*83.65*
3	n.a.	17.583	0.4420	n.a.	BMB*	18.685	0.92	n.a.
Total:			48.1242	0.0000		448.768	100.00	

Compound A3



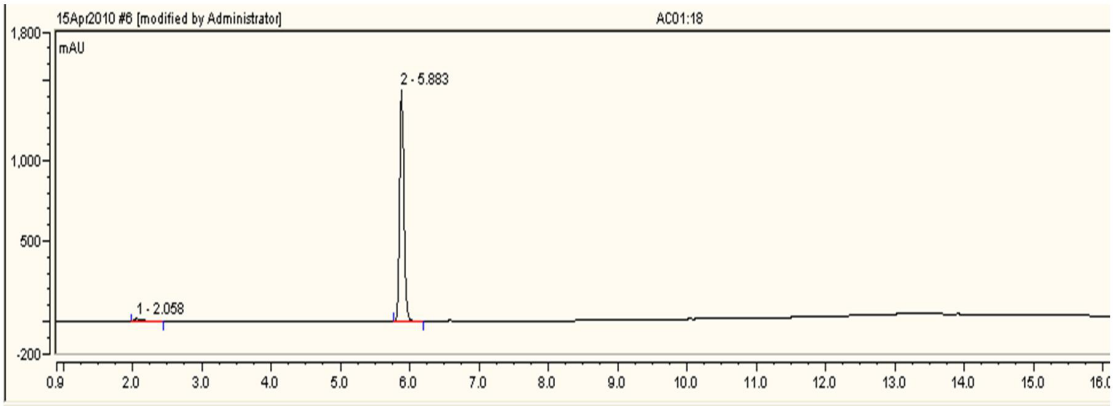
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.842	94.3217	n.a.	BM	1537.105	97.02	n.a.
2	n.a.	5.967	2.6473	n.a.	MB	42.983	2.72	n.a.
3	n.a.	6.492	0.2496	n.a.	BMB*	3.584	0.26	n.a.
Total:			97.2187	0.0000		1583.672	100.00	

Compound B3



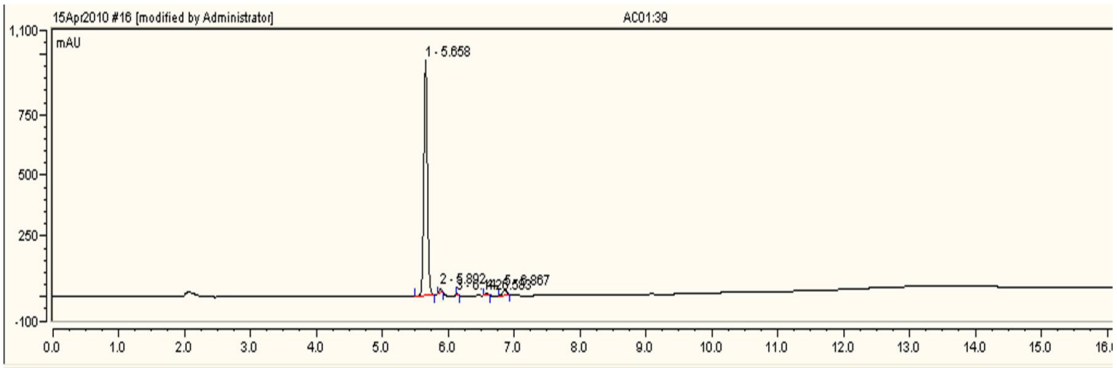
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	2.058	3.9898	n.a.	BMB	20.017	2.93	17.75
2	n.a.	5.583	130.9587	n.a.	BMB	2147.899	96.24	29.15
3	n.a.	9.092	1.1213	n.a.	BMB	10.635	0.82	n.a.
Total:			136.0698	0.0000		2178.550	100.00	

Compound C3



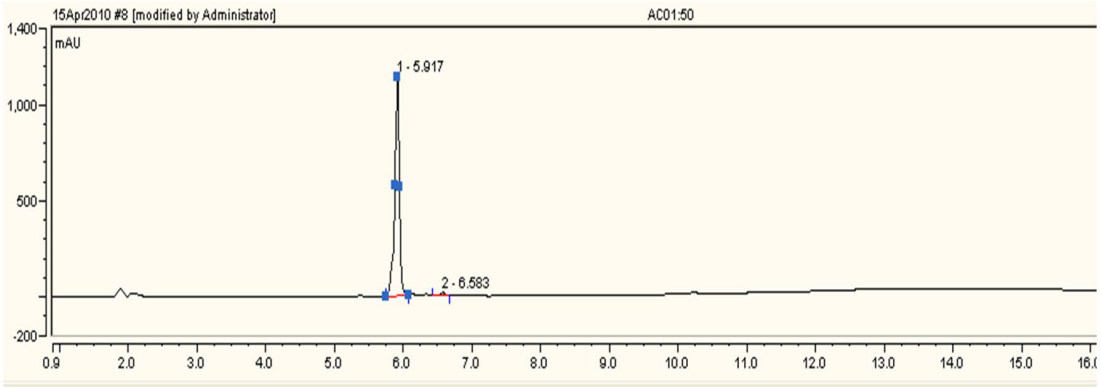
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	2.058	3.6580	n.a.	BMB	19.179	3.74	19.44
2	n.a.	5.883	94.1320	n.a.	BMB	1441.401	96.26	n.a.
Total:			97.7901	0.0000		1460.580	100.00	

Compound C3-H_2



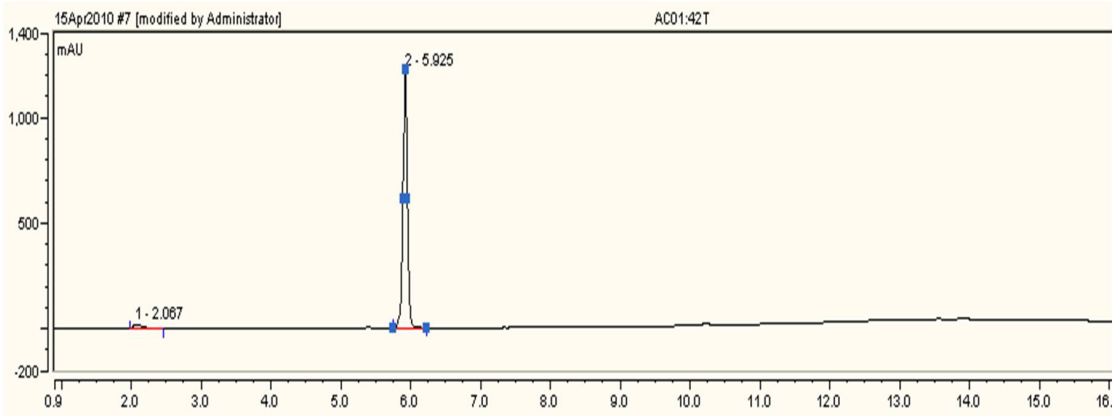
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.658	60.8107	n.a.	BMB*	970.814	95.64	2.74
2	n.a.	5.892	0.7964	n.a.	BMB*	18.200	1.25	3.73
3	n.a.	6.142	0.1519	n.a.	BMB*	4.422	0.24	5.84
4	n.a.	6.583	0.3856	n.a.	BMB*	7.136	0.61	2.80
5	n.a.	6.867	1.4400	n.a.	BMB	21.168	2.26	n.a.
Total:			63.5847	0.0000		1021.740	100.00	

Compound C4



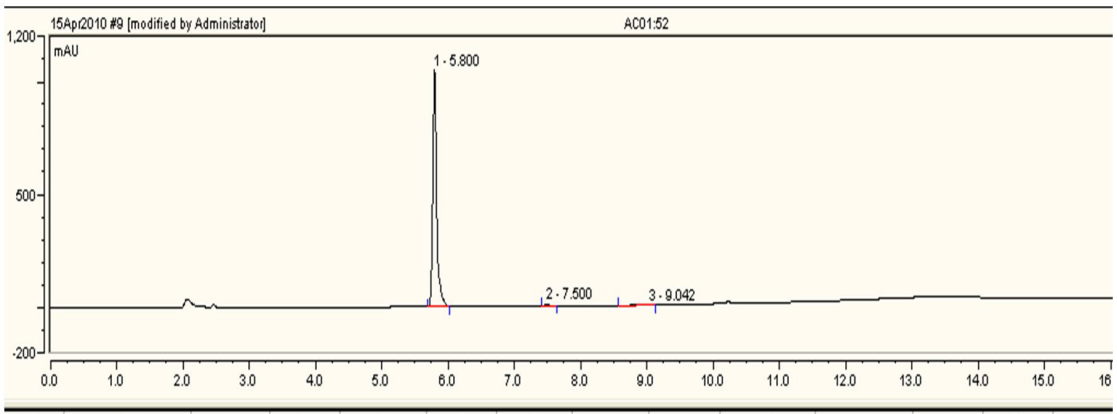
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.917	81.5733	n.a.	BMB	1141.063	95.40	5.86
2	n.a.	6.583	1.3916	n.a.	BMB	16.506	1.63	106.02
3	n.a.	17.500	2.5373	n.a.	BMB*	4.470	2.97	n.a.
Total:			85.5022	0.0000		1162.040	100.00	

Compound C5



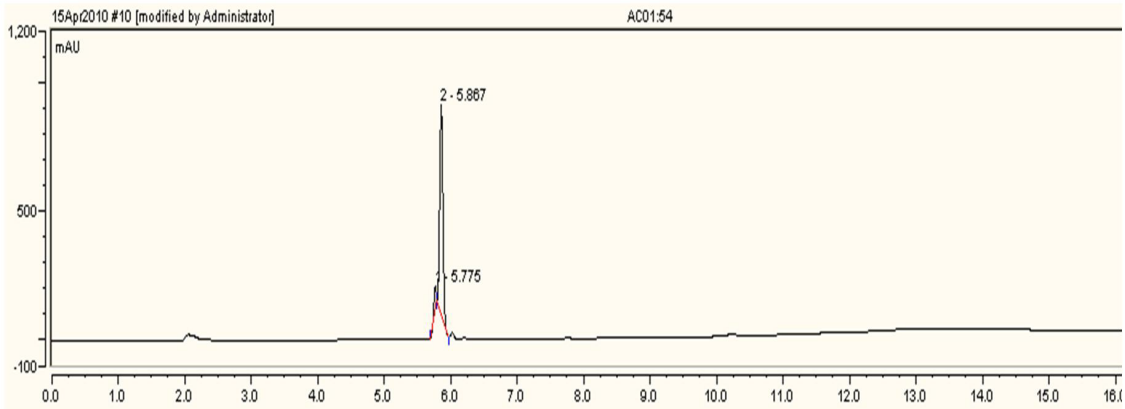
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	2.067	3.3479	n.a.	BMB	18.037	3.84	20.37
2	n.a.	5.925	83.8075	n.a.	BMB	1220.600	96.16	n.a.
Total:			87.1555	0.0000		1238.637	100.00	

Compound C6



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.800	71.7100	n.a.	BMB	1050.466	99.38	16.88
2	n.a.	7.500	0.4280	n.a.	BMB*	6.300	0.59	13.76
3	n.a.	9.042	0.0163	n.a.	BMB*	0.432	0.02	n.a.
Total:			72.1543	0.0000		1057.198	100.00	

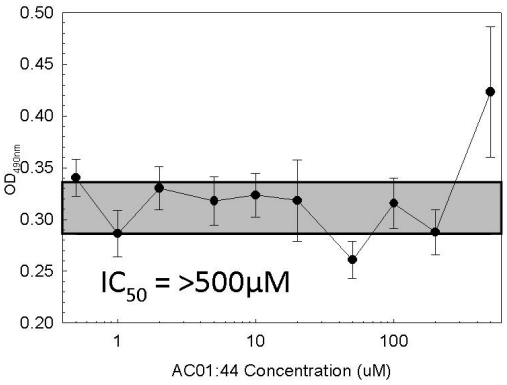
Compound C7



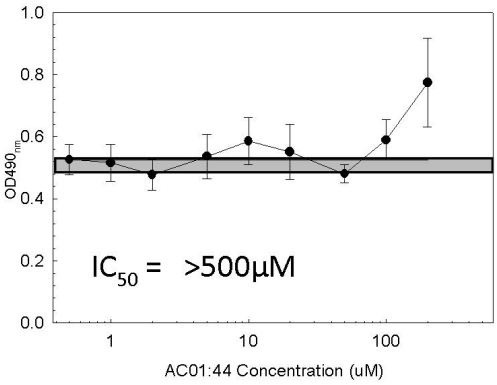
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	5.775	2.6857	n.a.	BMb*	88.759	5.66	1.20
2	n.a.	5.867	44.7922	n.a.	bMB*	809.994	94.34	n.a.
Total:			47.4779	0.0000		898.753	100.00	

Compound A1

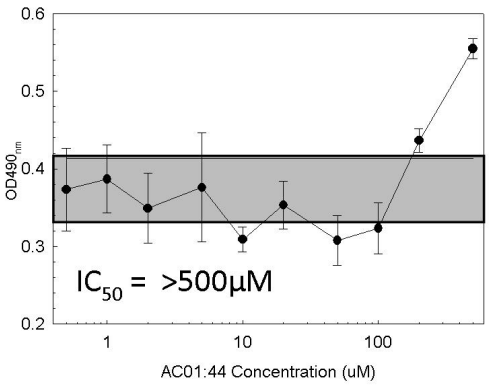
HT29 Human Colon Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



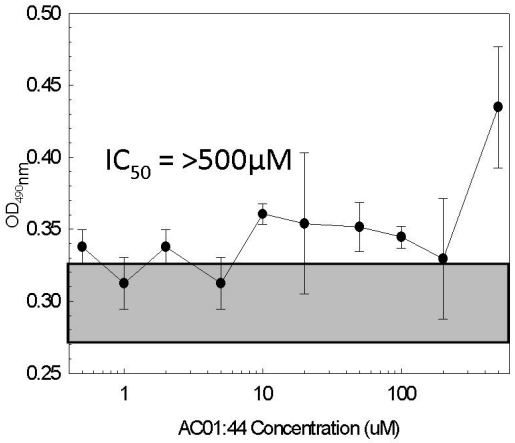
HT29 Human Colon Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



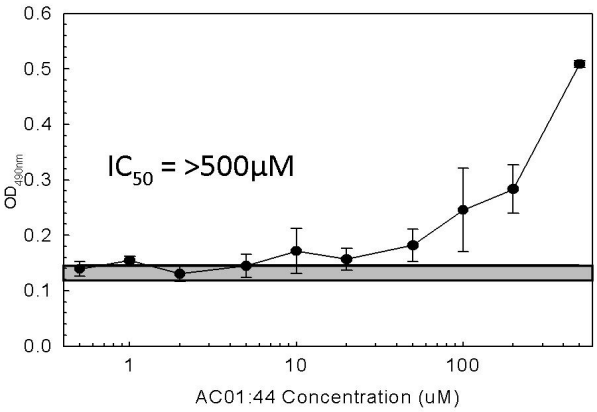
1% DMSO only
Points are means ± s.d
n = 4

Compound A1

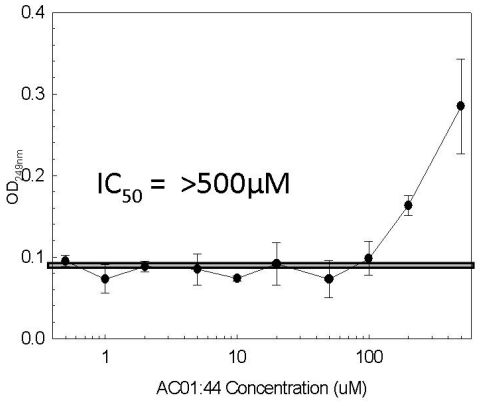
MDA231 Human Breast Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



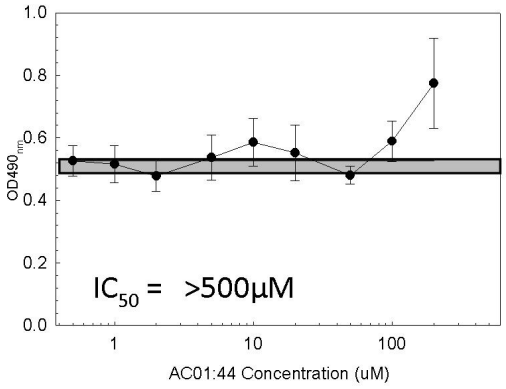
MDA231 Breast Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



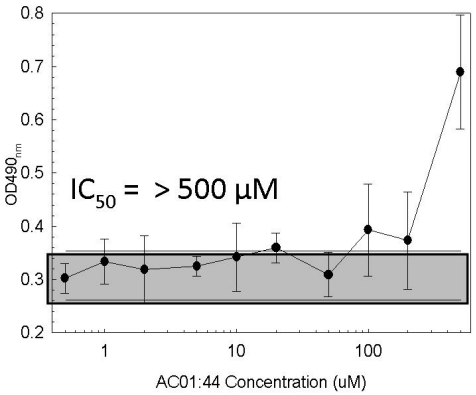
1% DMSO only
Points are means ± s.d
n = 4

Compound A1

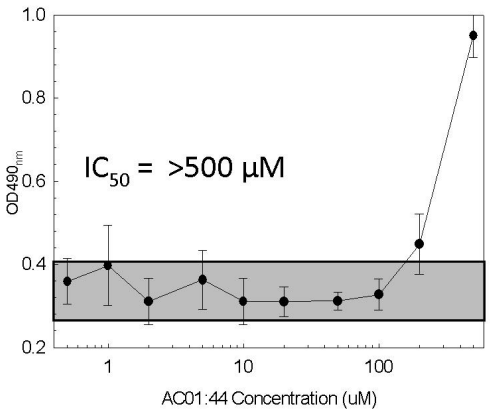
LNCAP Prostate Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



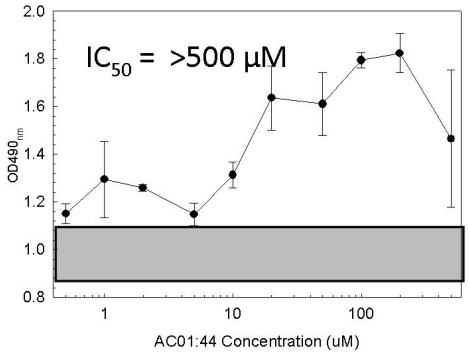
LNCAP Prostate Carcinoma
Test Compound AC01:44
3 Day Exposure MTS



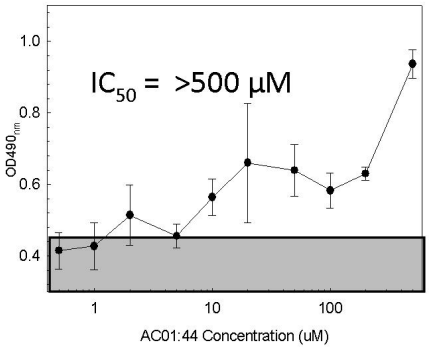
1% DMSO only
Points are means ± s.d
n = 4

Compound A1

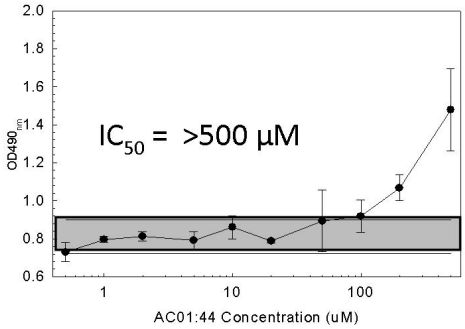
FEK-4 Human Skin Fibroblast
Test Compound AC01:44
3 Day Exposure MTS



FEK-4 Human Skin Cells
Test Compound AC01:44
3 Day Exposure MTS



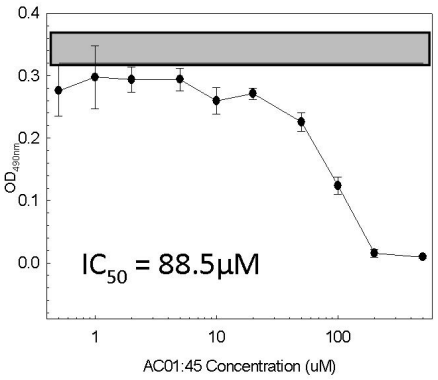
FEK-4 Human Skin Fibroblast
Test Compound AC01:44
3 Day Exposure MTS



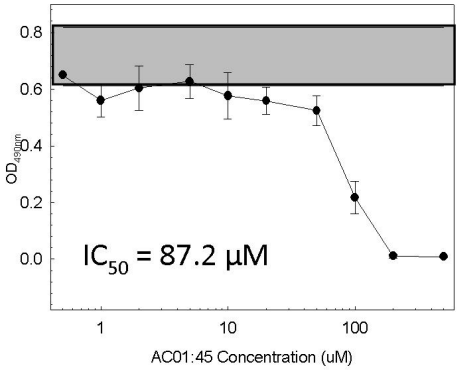
1% DMSO only
Points are means ± s.d
n = 4

Compound B1

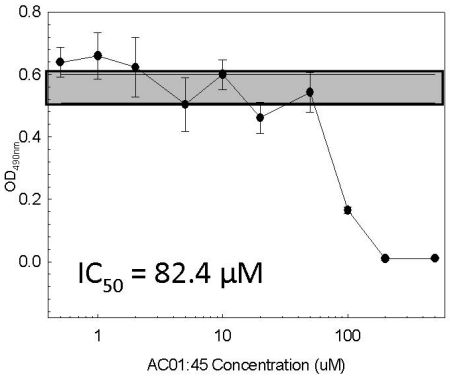
HT29 Human Colon Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



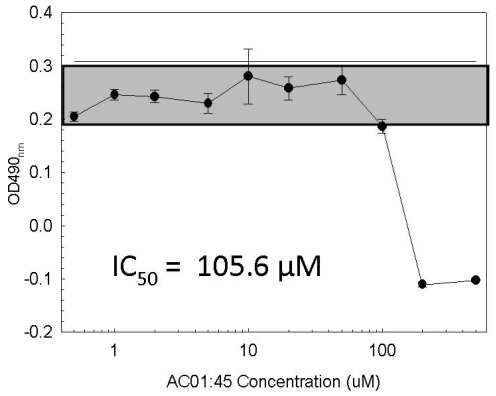
HT29 Human Colon Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



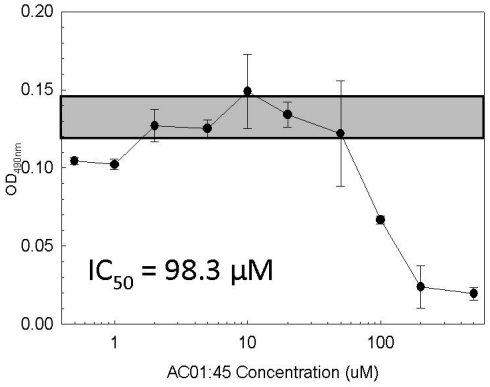
1% DMSO only
Points are means ± s.d
n = 4

Compound B1

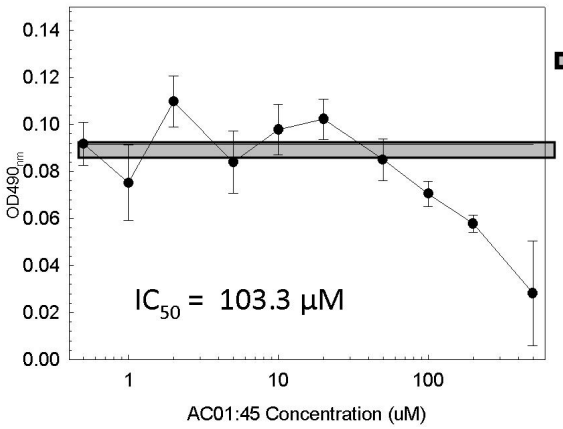
MDA231 Human Breast Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



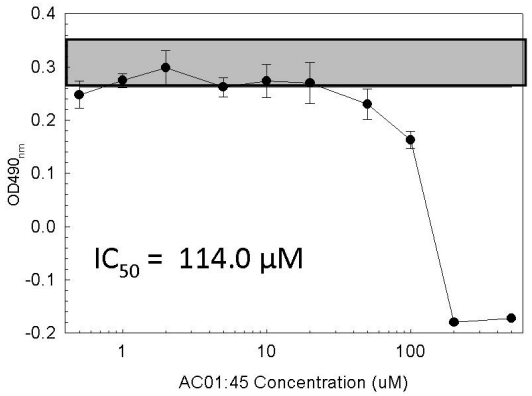
MDA231 Breast Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



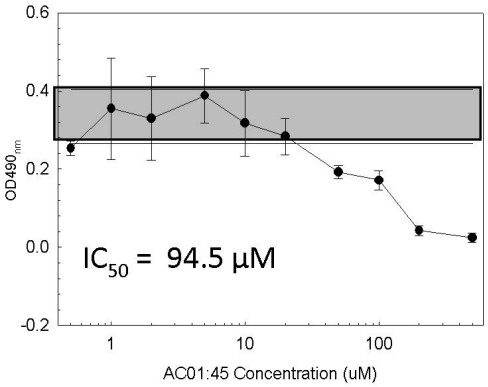
1% DMSO only
Points are means ± s.d
n = 4

Compound B1

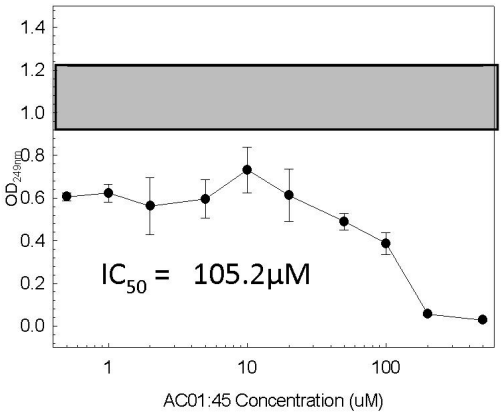
LNCAP Prostate Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



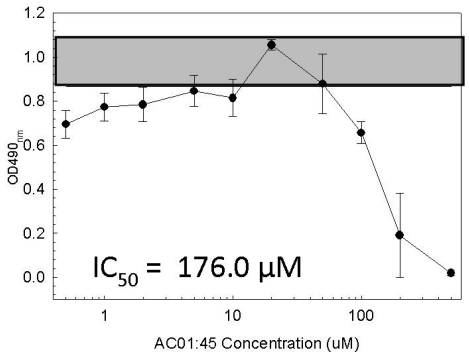
LNCAP Prostate Carcinoma
Test Compound AC01:45
3 Day Exposure MTS



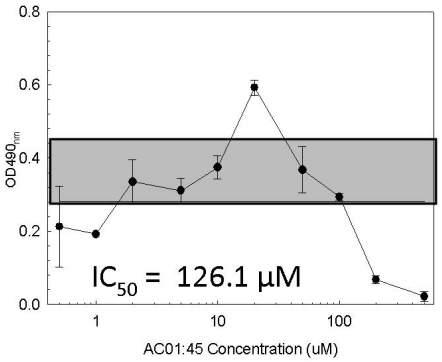
1% DMSO only
Points are means ± s.d
n = 4

Compound B1

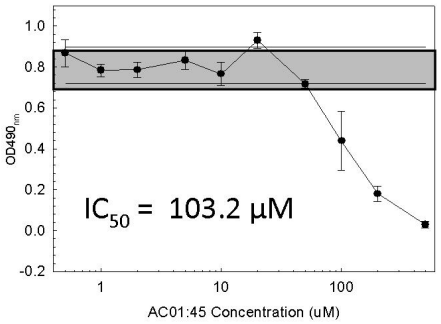
FEK-4 Human Skin Fibroblast
Test Compound AC01:45
3 Day Exposure MTS



FEK-4 Human Skin Cells
Test Compound AC01:45
3 Day Exposure MTS



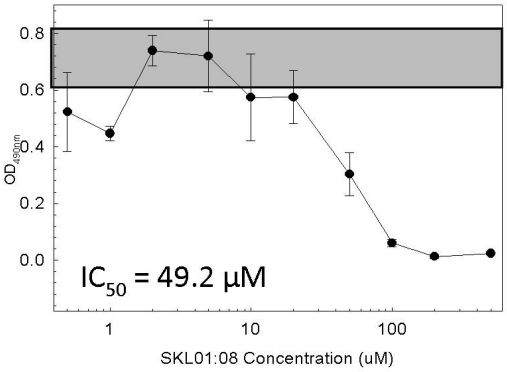
FEK-4 Human Skin Fibroblast
Test Compound AC01:45
3 Day Exposure MTS



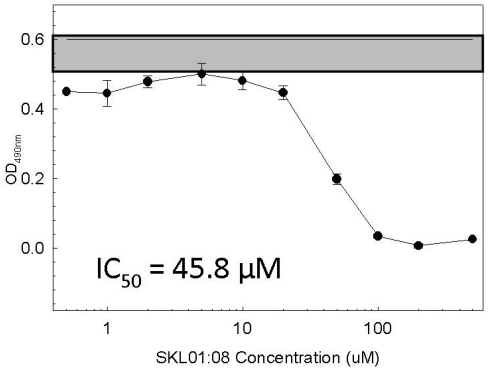
1% DMSO only
Points are means ± s.d
n = 4

Compound C1

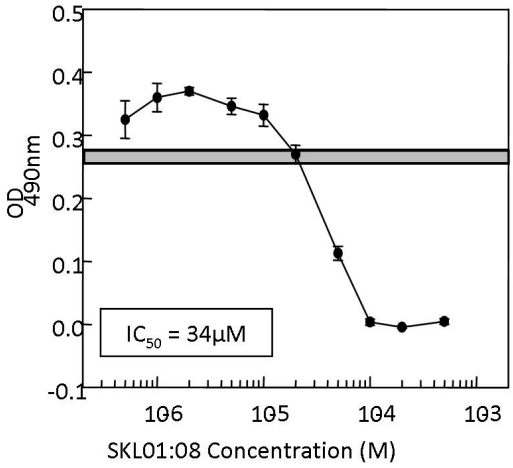
HT29 Human Colon Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



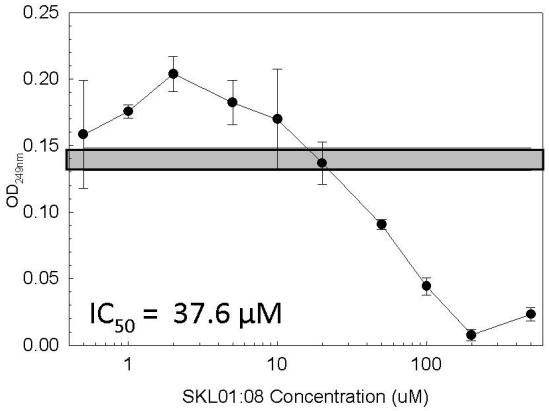
HT29 Human Colon Carcinoma
Test Compound SKL01:08
3 Day Exposure



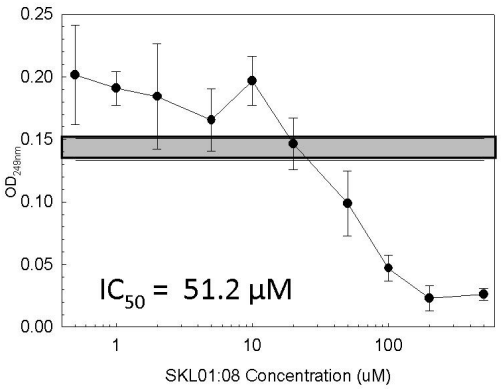
1% DMSO only
Points are means ± s.d
n = 4

Compound C1

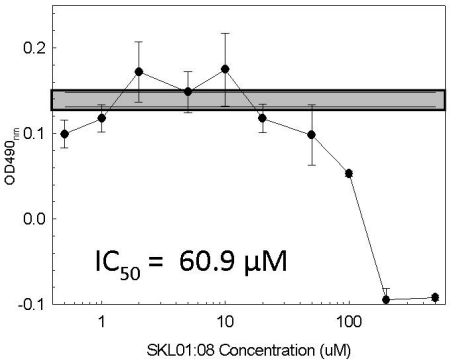
MDA231 Breast Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



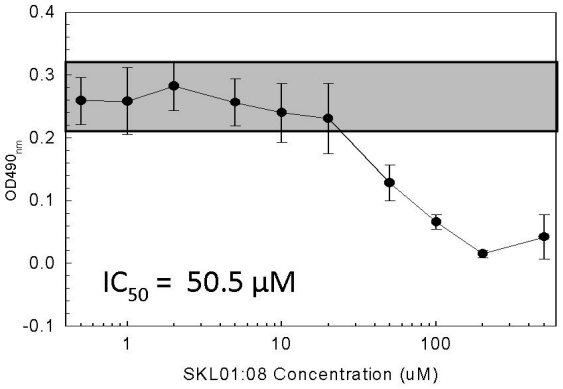
MDA231 Breast Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



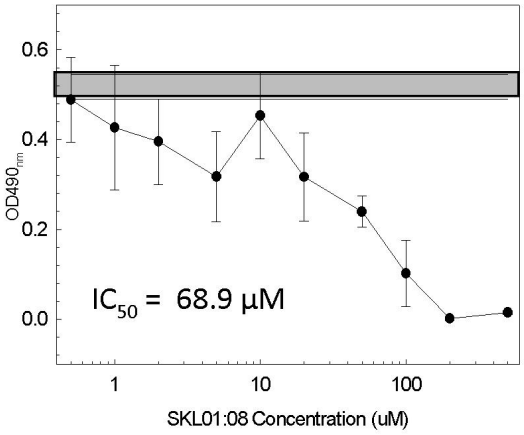
1% DMSO only
Points are means ± s.d
n = 4

Compound C1

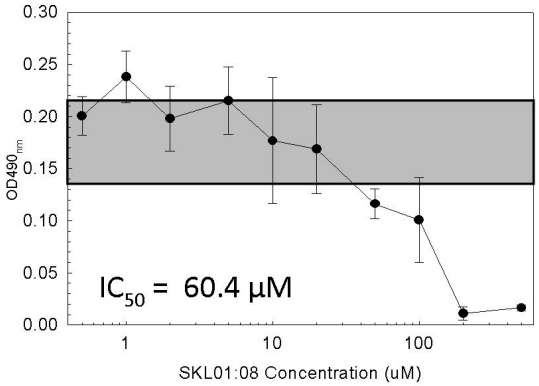
LNCAP Prostate Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



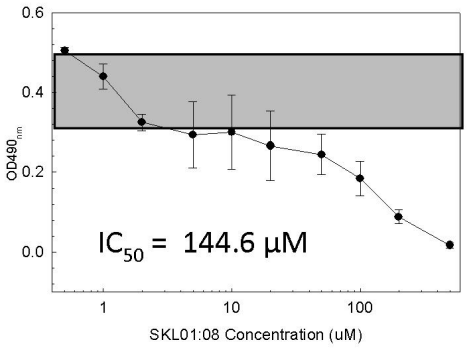
LNCAP Prostate Carcinoma
Test Compound SKL01:08
3 Day Exposure MTS



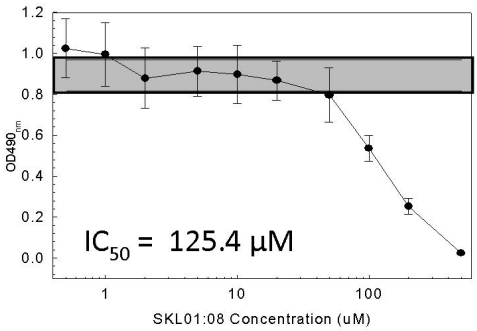
1% DMSO only
Points are means ± s.d
n = 4

Compound C1

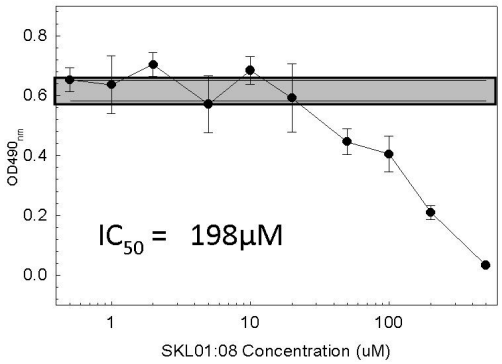
FEK-4 Human Skin Cells
Test Compound SKL01:08
3 Day Exposure MTS



FEK-4 Human Skin Fibroblast
Test Compound SKL01:08
3 Day Exposure MTS



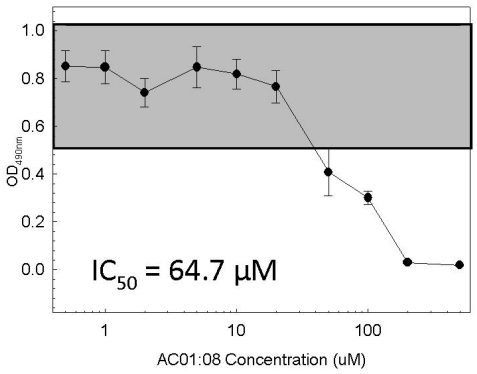
FEK-4
Test Compound SKL01:08
3 Day Exposure MTS



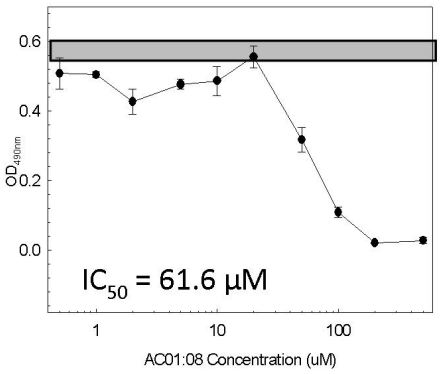
1% DMSO only
Points are means ± s.d
n = 4

Compound A2

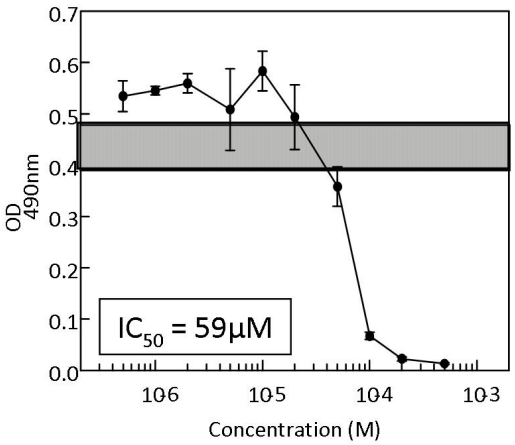
HT29 Human Colon Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



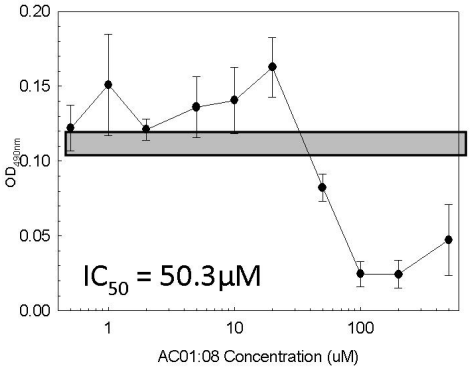
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound: AC01:08
72h Exposure



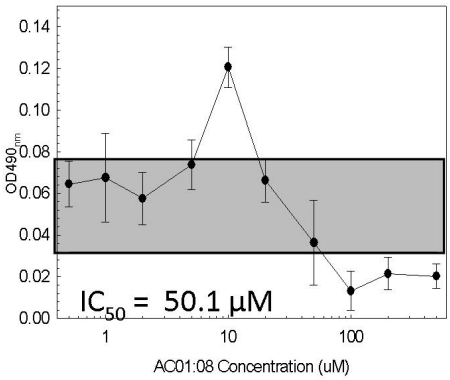
1% DMSO only
Points are means ± s.d
n = 4

Compound A2

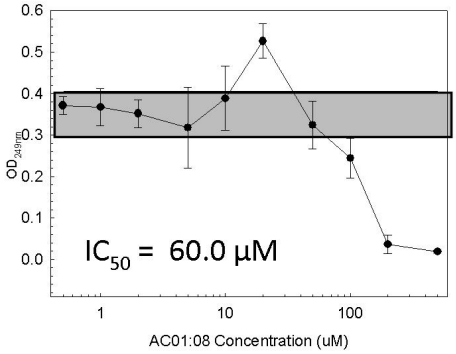
MDA231 Breast Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



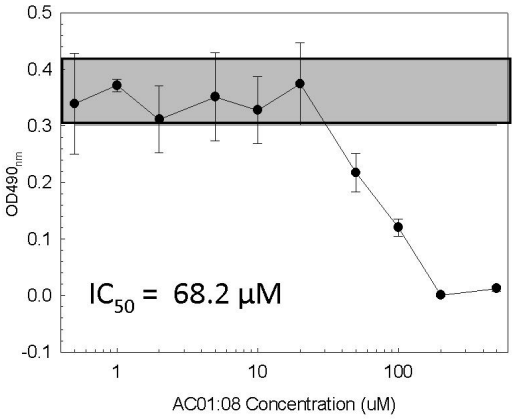
MDA231 Human Breast Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



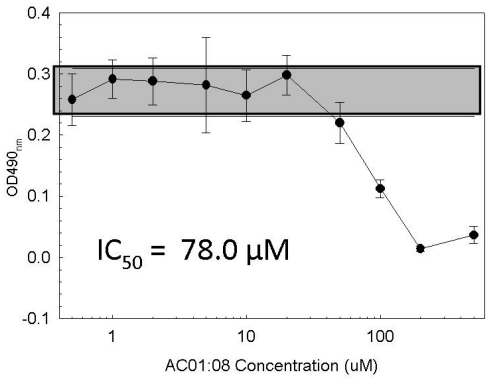
1% DMSO only
Points are means ± s.d
n = 4

Compound A2

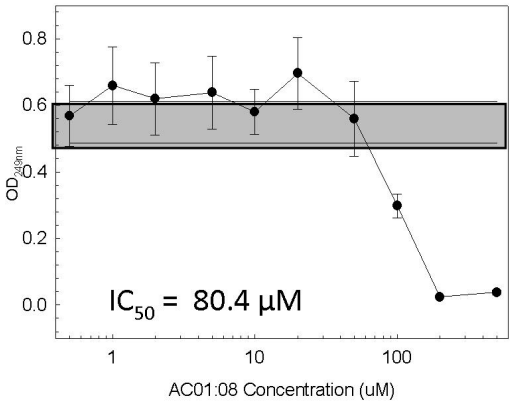
LNCAP Prostate Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



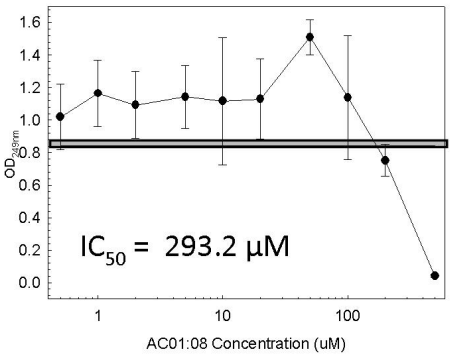
LNCAP Prostate Carcinoma
Test Compound AC01:08
3 Day Exposure MTS



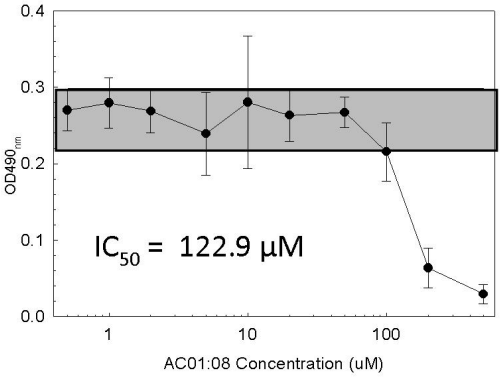
1% DMSO only
Points are means ± s.d
n = 4

Compound A2

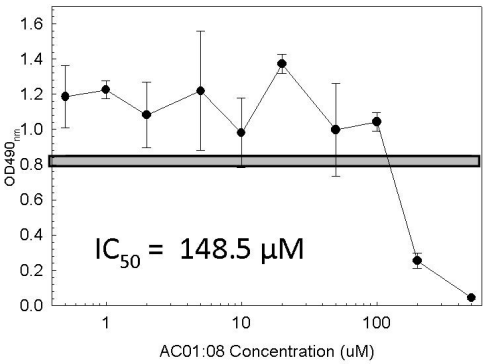
FEK-4 Human Skin Fibroblast
Test Compound AC01:08
3 Day Exposure MTS



FEK-4 Human Skin Cells
Test Compound AC01:08
3 Day Exposure MTS



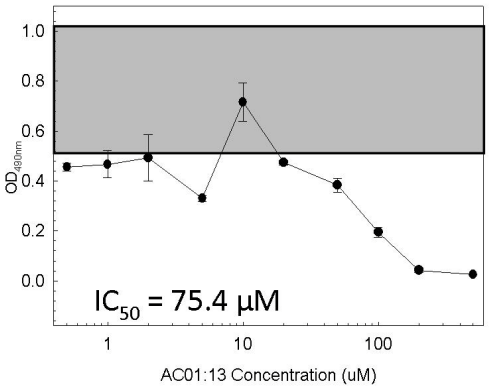
FEK-4 Human Skin Fibroblast
Test Compound AC01:08
3 Day Exposure MTS



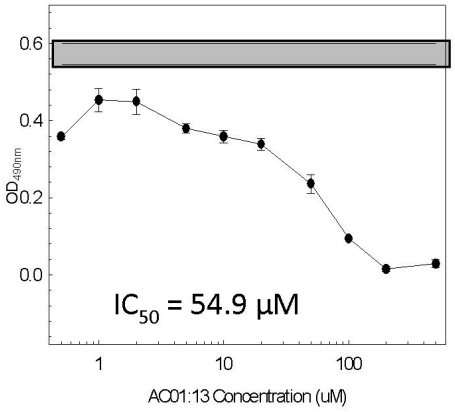
1% DMSO only
Points are means ± s.d
n = 4

Compound B2

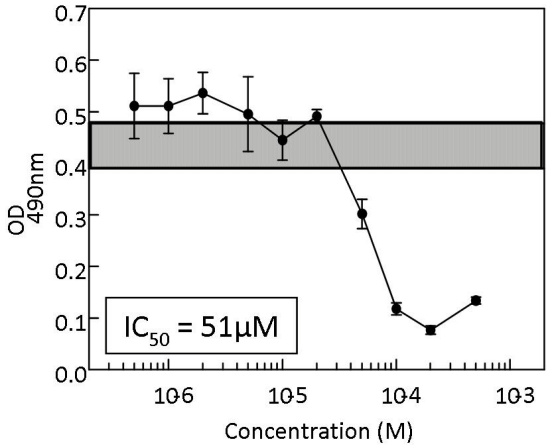
HT29 Human Colon Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



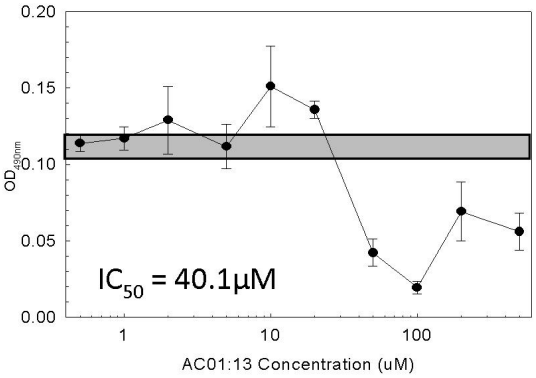
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound: AC01:13
72h Exposure



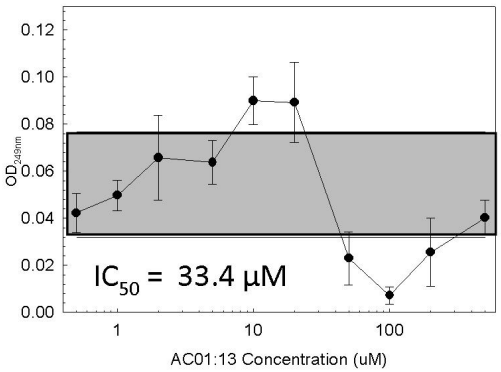
1% DMSO only
Points are means ± s.d
n = 4

Compound B2

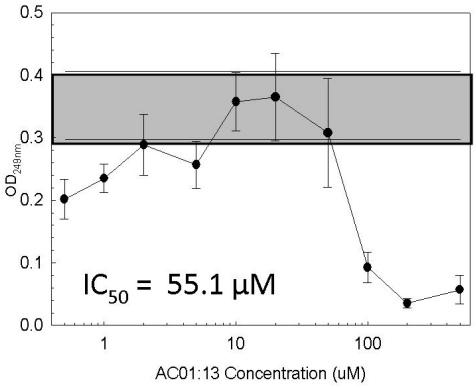
MDA231 Breast Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



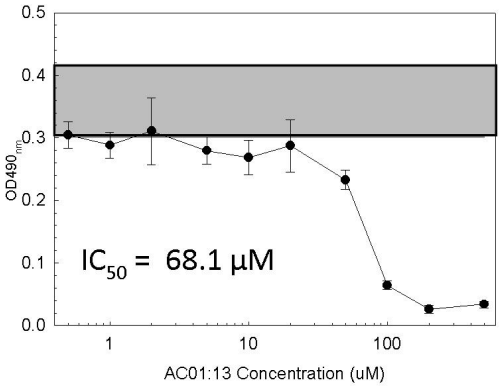
MDA231 Human Breast Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



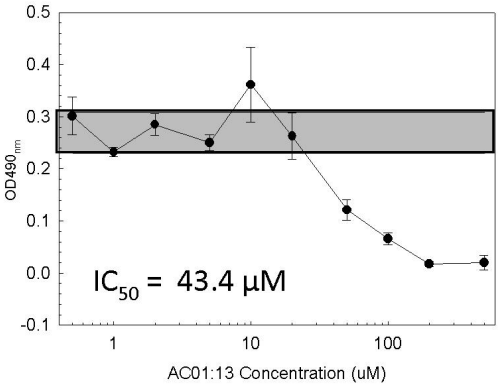
1% DMSO only
Points are means ± s.d
n = 4

Compound B2

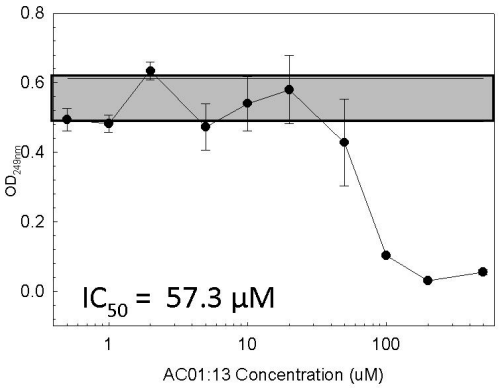
LNCAP Prostate Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



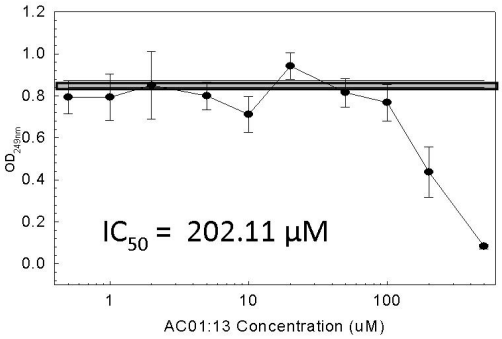
LNCAP Prostate Carcinoma
Test Compound AC01:13
3 Day Exposure MTS



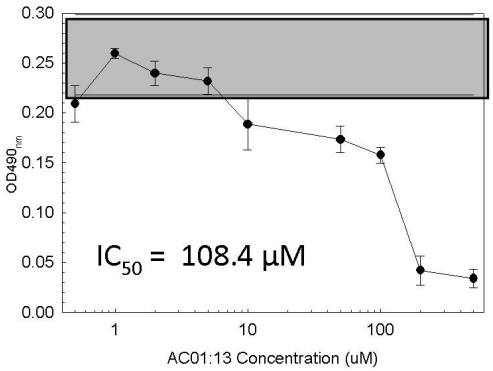
1% DMSO only
Points are means ± s.d
n = 4

Compound B2

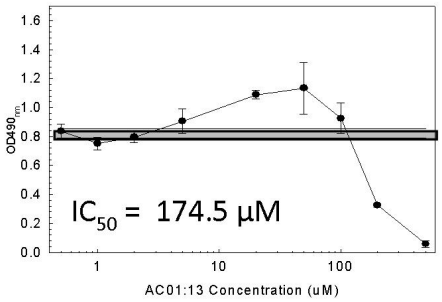
FEK-4 Human Skin Fibroblast
Test Compound AC01:13
3 Day Exposure MTS



FEK-4 Human Skin Cells
Test Compound AC01:13
3 Day Exposure MTS

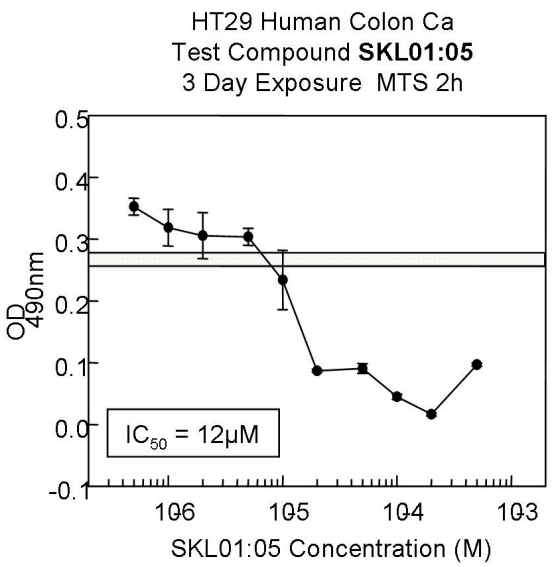


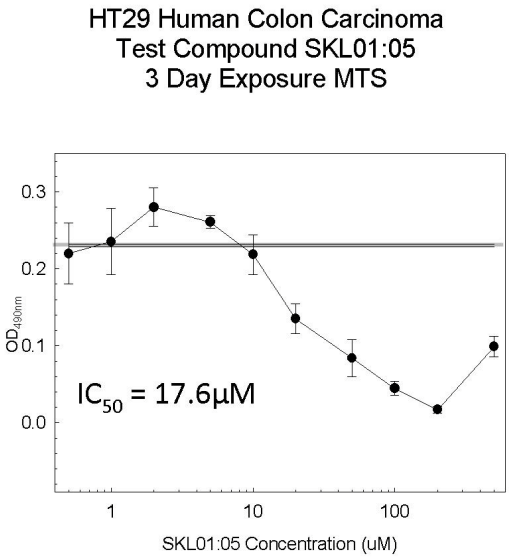
FEK-4 Human Skin Fibroblast
Test Compound AC01:13
3 Day Exposure MTS

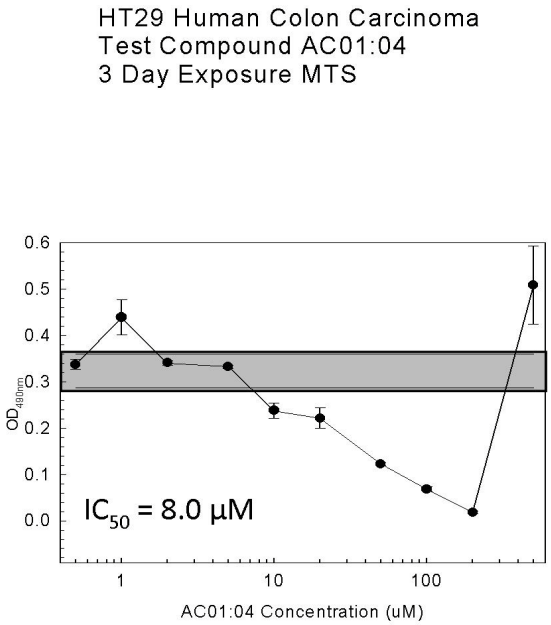


1% DMSO only
Points are means ± s.d
n = 4

Compound C2



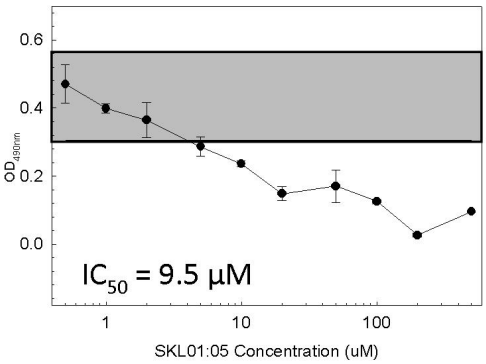




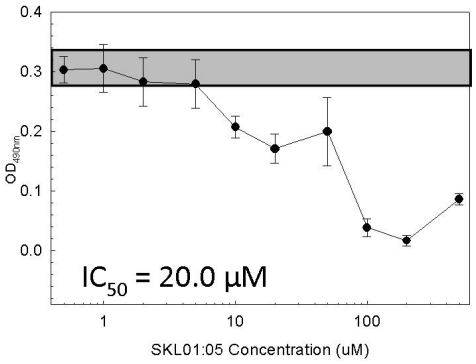
1% DMSO only
Points are means ± s.d
n = 4

Compound C2

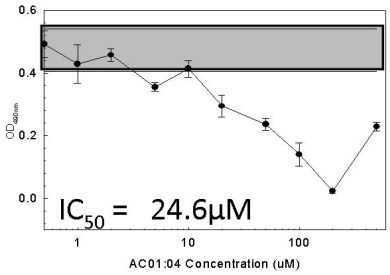
MDA231 Breast Carcinoma
Test Compound SKL01:05
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound SK01:05
3 Day Exposure MTS



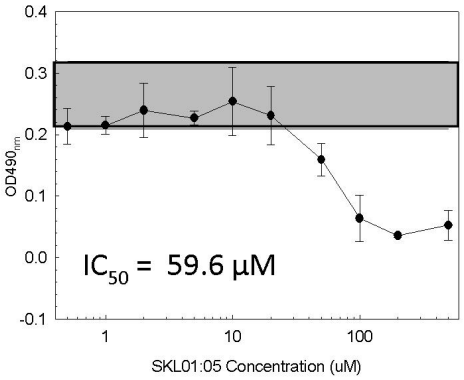
MDA231 Human Breast Carcinoma
Test Compound AC01:04
3 Day Exposure MTS



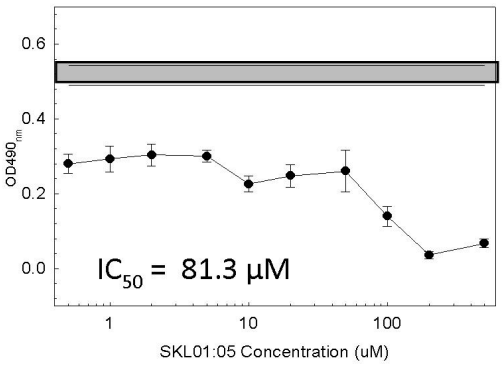
1% DMSO only
Points are means ± s.d
n = 4

Compound C2

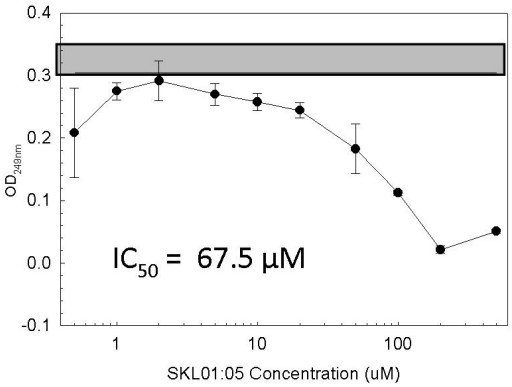
LNCAP Prostate Carcinoma
Test Compound SKL01:05
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound SKL01:05
3 Day Exposure MTS



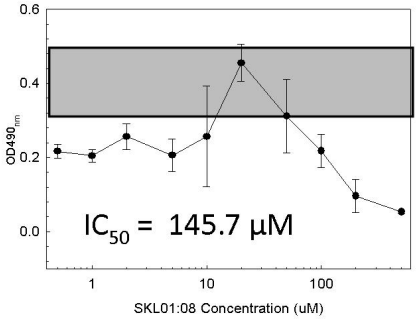
LNCAP Prostate Carcinoma
Test Compound SKL01:05
3 Day Exposure MTS



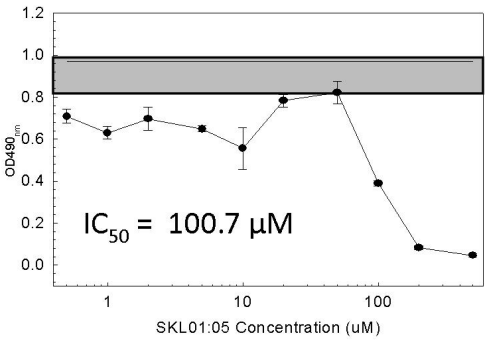
1% DMSO only
Points are means ± s.d
n = 4

Compound C2

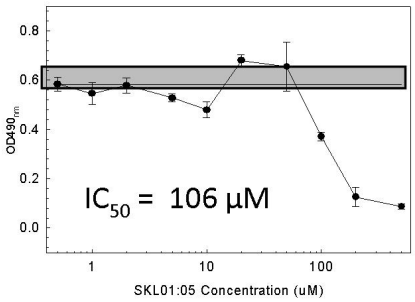
FEK-4 Human Skin Cells
Test Compound SKL01:05
3 Day Exposure MTS



FEK-4 Human Skin Fibroblast
Test Compound SKL01:05
3 Day Exposure MTS



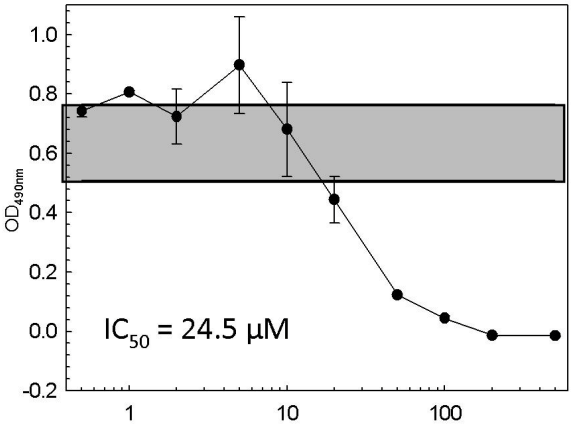
FEK-4
Test Compound SKL01:05
3 Day Exposure MTS



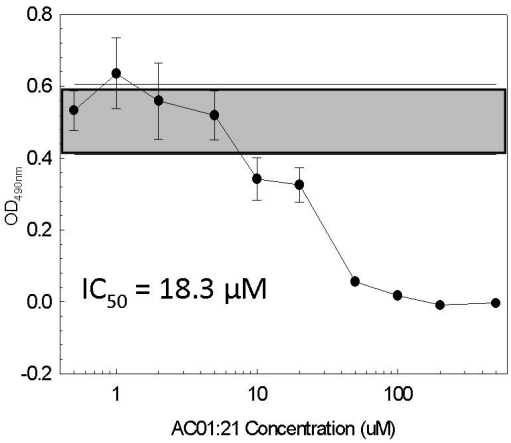
1% DMSO only
Points are means ± s.d
n = 4

Compound A3

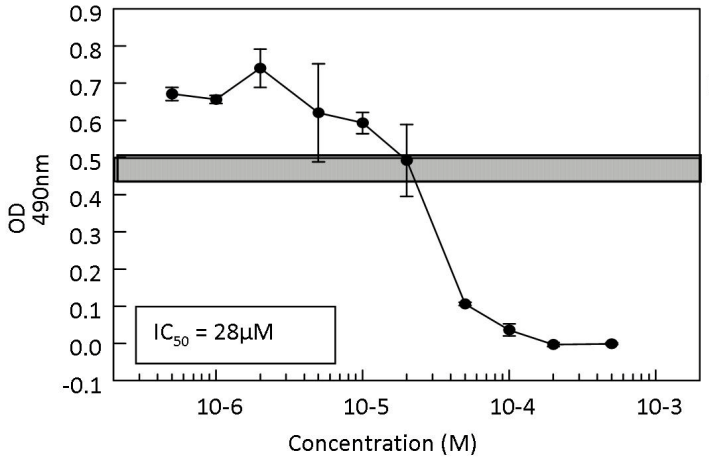
HT29 Human Colon Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



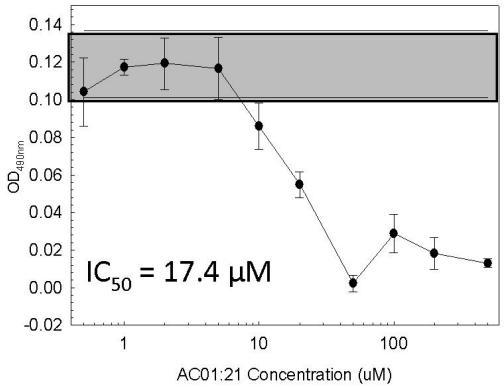
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound: AC01:21
72h Exposure



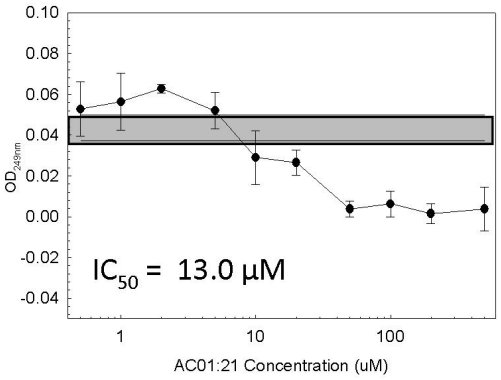
1% DMSO only
Points are means ± s.d
n = 4

Compound A3

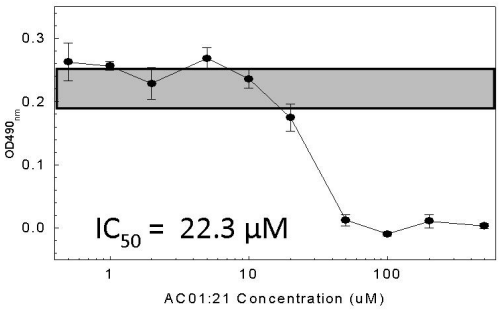
MDA231 Breast Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



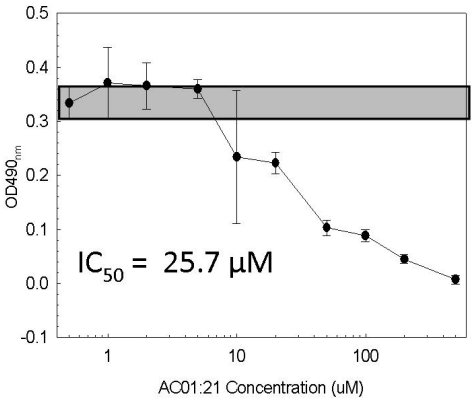
MDA231 Human Breast Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



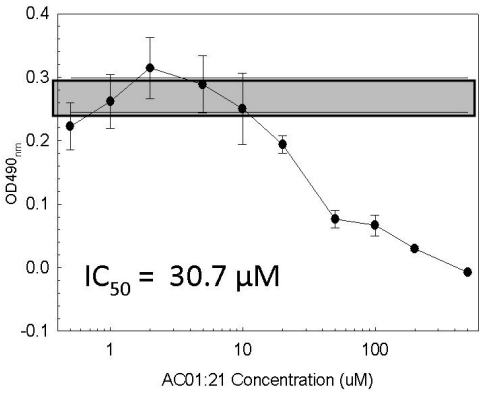
1% DMSO only
Points are means ± s.d
n = 4

Compound A3

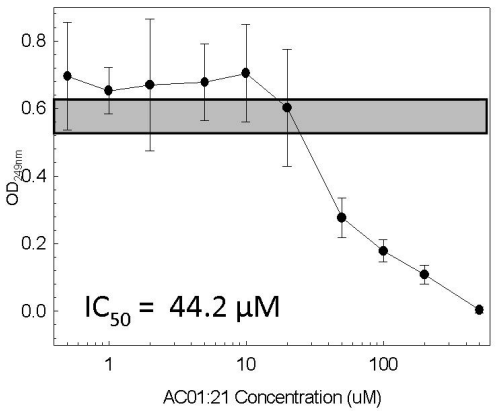
LNCAP Prostate Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



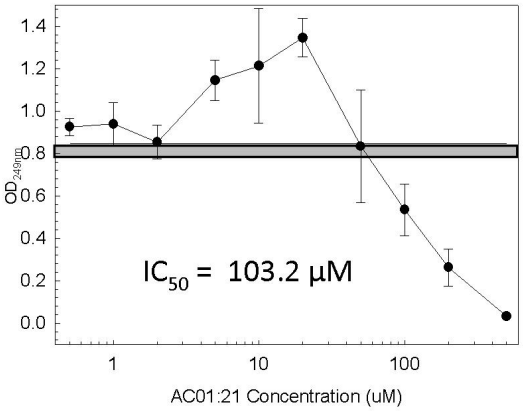
LNCAP Prostate Carcinoma
Test Compound AC01:21
3 Day Exposure MTS



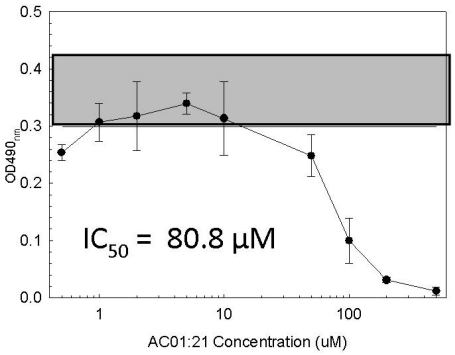
1% DMSO only
Points are means ± s.d
n = 4

Compound A3

FEK-4 Human Skin Fibroblast
Test Compound AC01:21
3 Day Exposure MTS



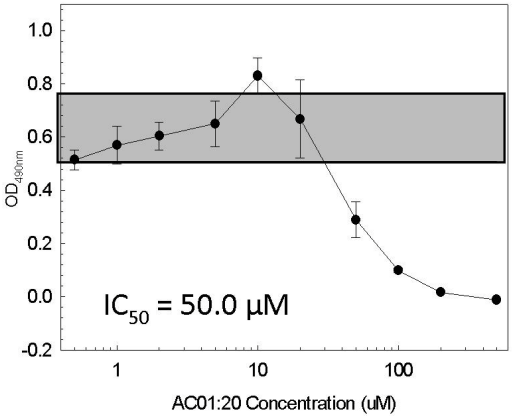
FEK-4 Human Skin Cells
Test Compound AC01:21
3 Day Exposure MTS



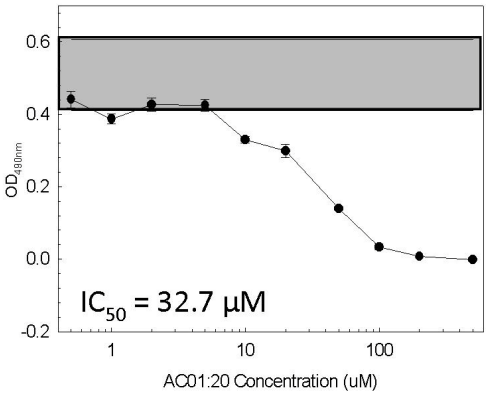
1% DMSO only
Points are means ± s.d
n = 4

Compound B3

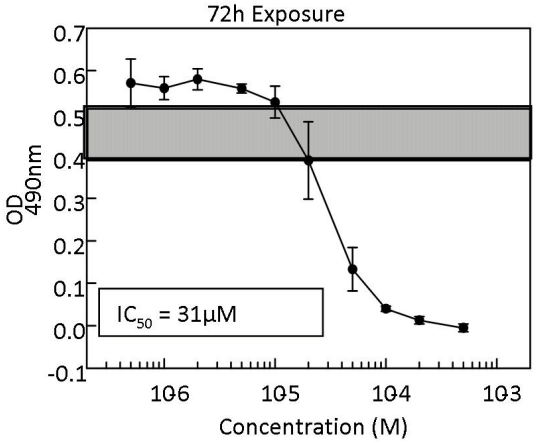
HT29 Human Colon Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



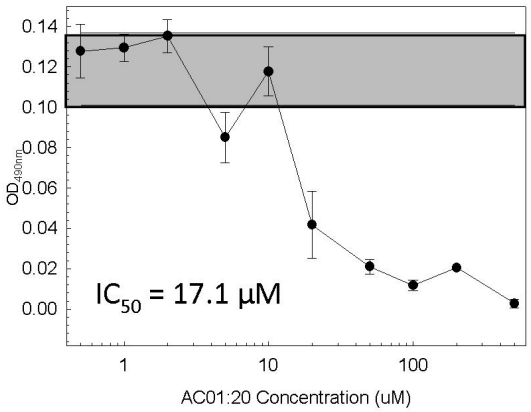
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound:AC01:20
72h Exposure



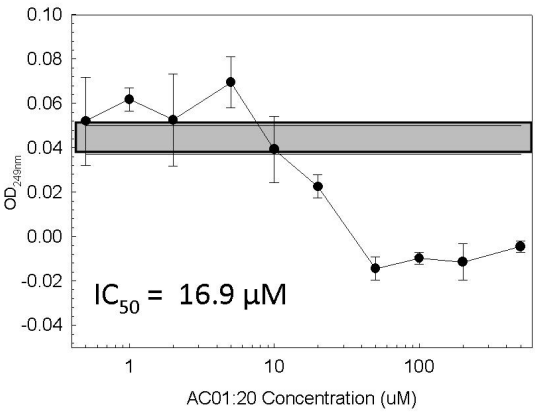
1% DMSO only
Points are means ± s.d
n = 4

Compound B3

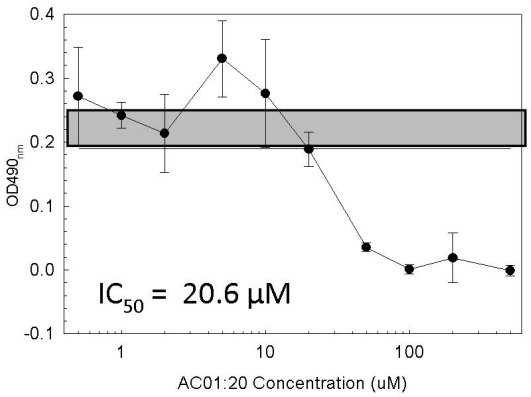
MDA231 Breast Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



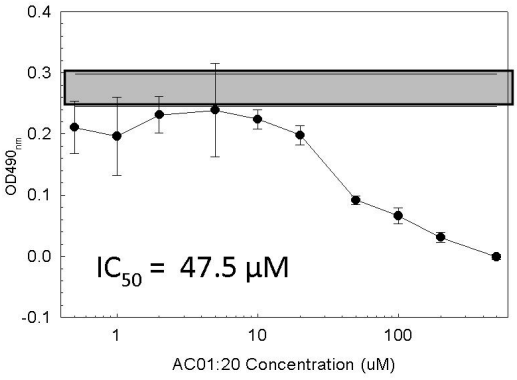
MDA231 Human Breast Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



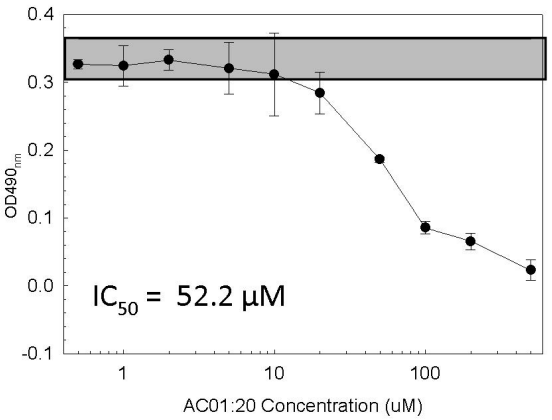
1% DMSO only
Points are means ± s.d
n = 4

Compound B3

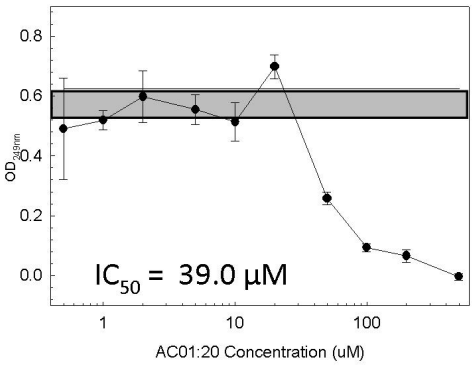
LNCAP Prostate Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



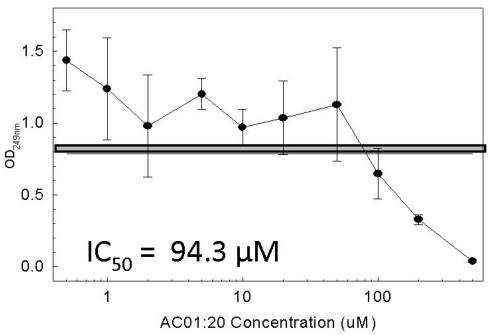
LNCAP Prostate Carcinoma
Test Compound AC01:20
3 Day Exposure MTS



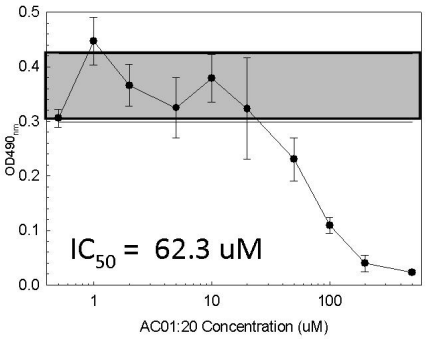
1% DMSO only
Points are means ± s.d
n = 4

Compound B3

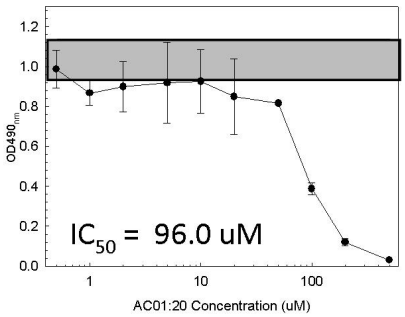
FEK-4 Human Skin Fibroblast
Test Compound AC01:20
3 Day Exposure MTS



FEK-4 Human Skin Cells
Test Compound AC01:20
3 Day Exposure MTS



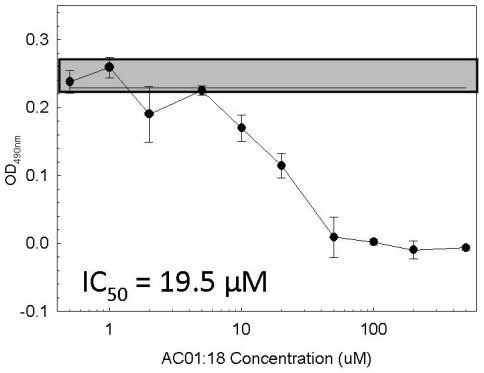
FEK-4 Human Skin Fibroblast
Test Compound AC01:20
3 Day Exposure MTS



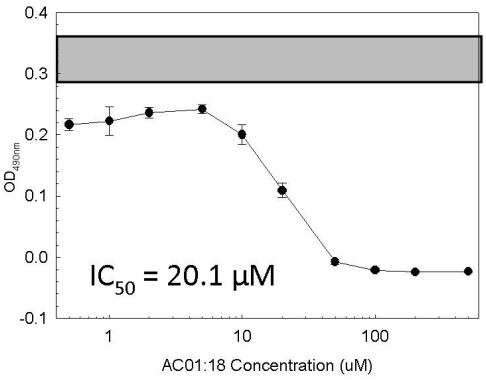
1% DMSO only
Points are means ± s.d
n = 4

Compound C3

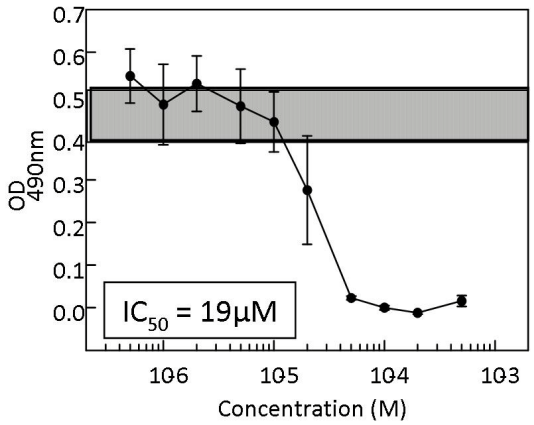
HT29 Human Colon Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



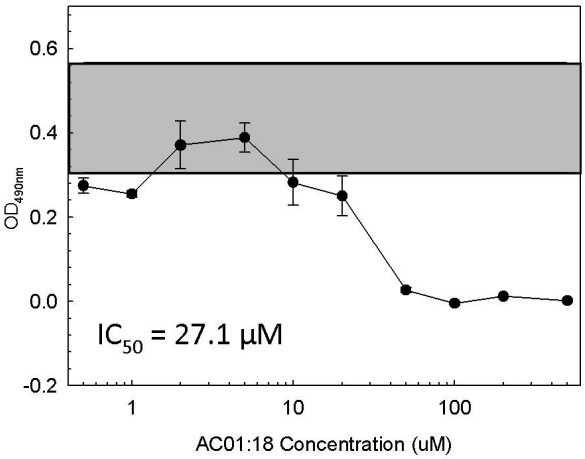
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound:AC01:18
72h Exposure



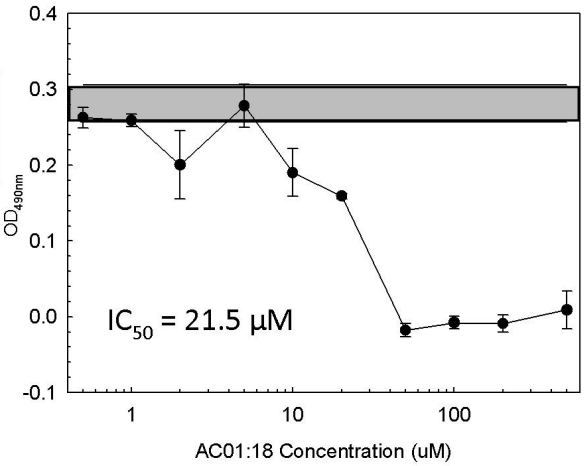
1% DMSO only
Points are means ± s.d
n = 4

Compound C3

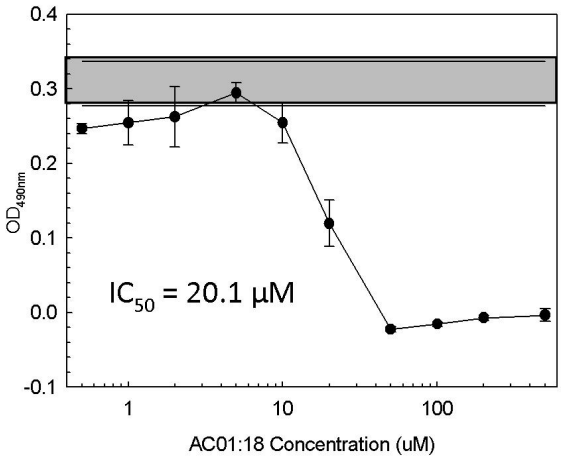
MDA231 Breast Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



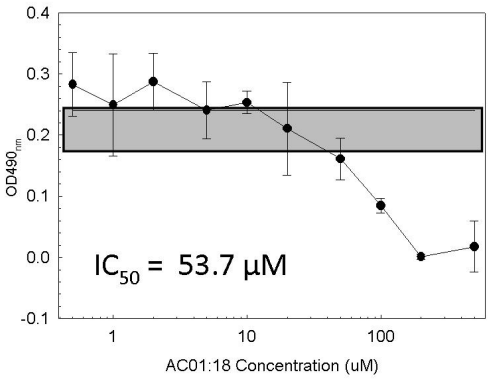
MDA231 Breast Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



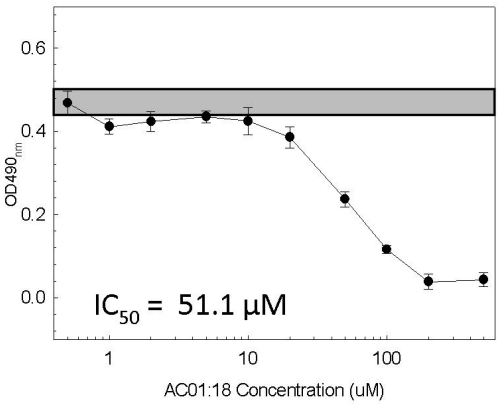
1% DMSO only
Points are means ± s.d
n = 4

Compound C3

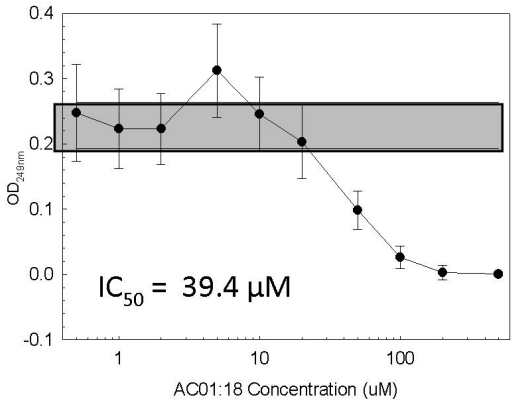
LNCAP Prostate Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



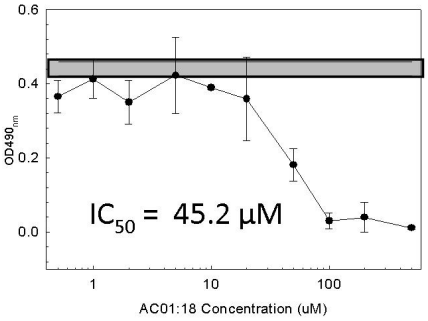
LNCAP Prostate Carcinoma
Test Compound AC01:18
3 Day Exposure MTS



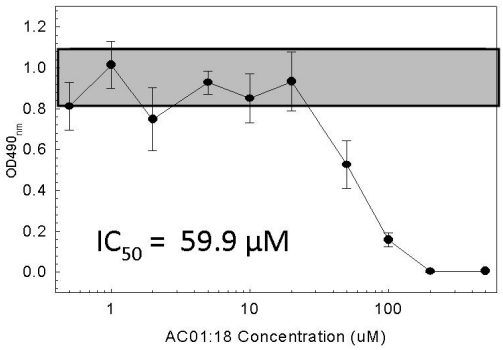
1% DMSO only
Points are means ± s.d
n = 4

Compound C3

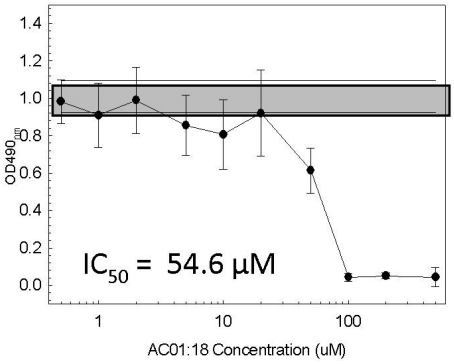
FEK-4 Human Skin Cells
Test Compound AC01:18
3 Day Exposure MTS



FEK-4 Human Skin Fibroblast
Test Compound AC01:18
3 Day Exposure MTS



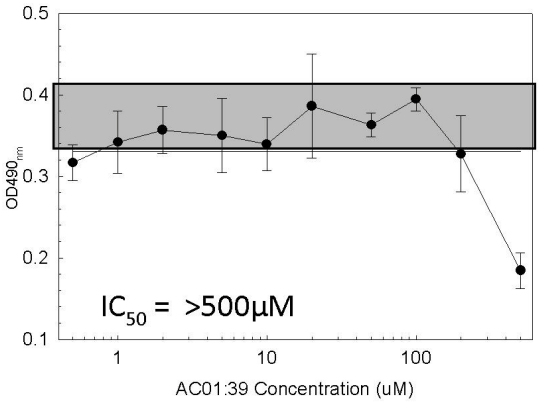
FEK-4 Human Skin Fibroblast
Test Compound AC01:18
3 Day Exposure MTS



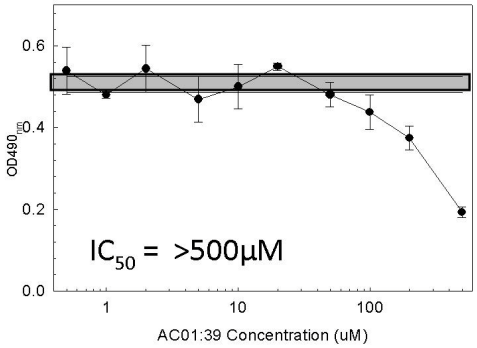
1% DMSO only
Points are means ± s.d
n = 4

Compound C3-H_2

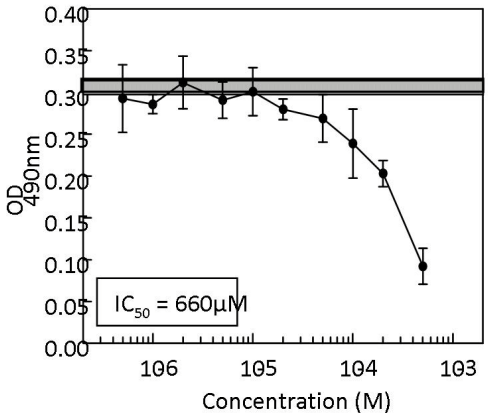
HT29 Colon Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



HT29 Colon Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



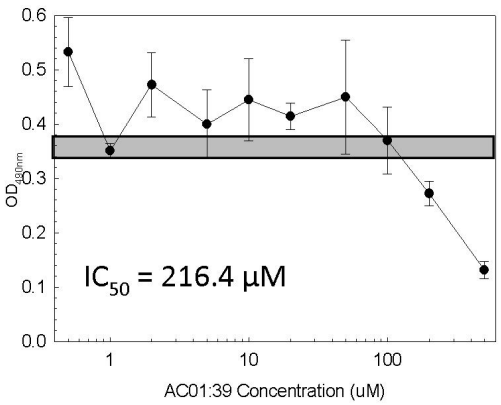
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound AC01:39
72h Exposure



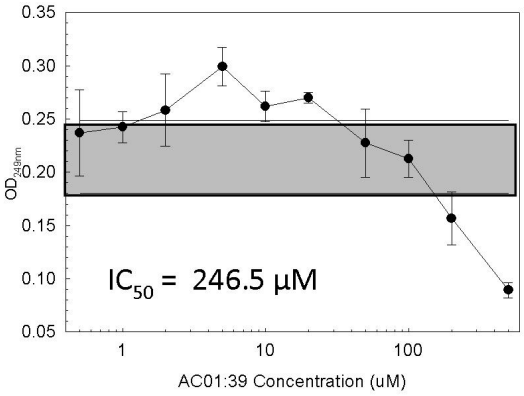
1% DMSO only
Points are means ± s.d
n = 4

Compound C3-H_2

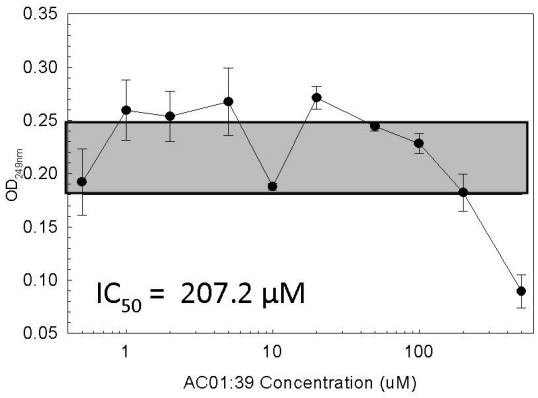
MDA231 Breast Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



MDA231 Human Breast Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



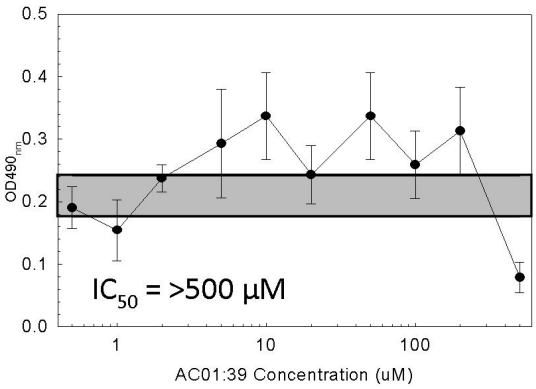
MDA231 Human Breast Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



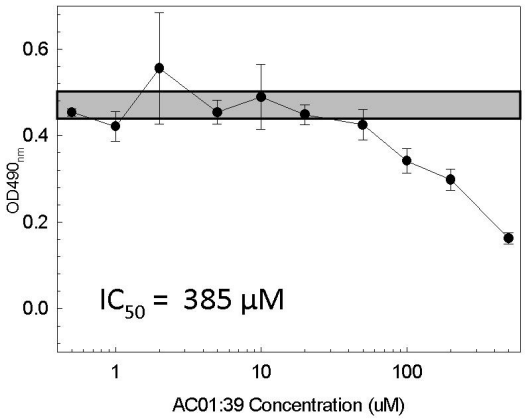
1% DMSO only
Points are means ± s.d
n = 4

Compound C3-H_2

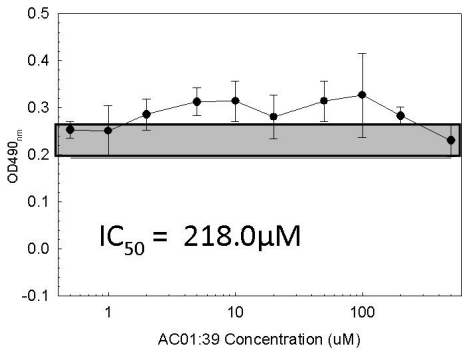
LNCAP Prostate Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



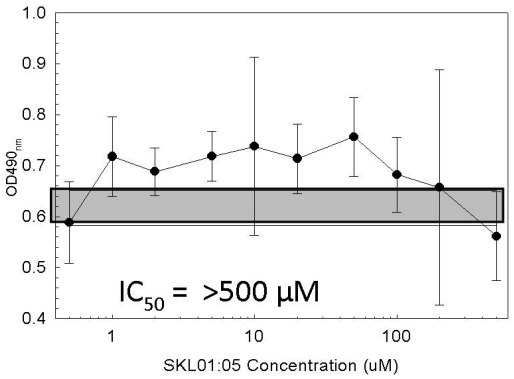
LNCAP Prostate Carcinoma
Test Compound AC01:39
3 Day Exposure MTS



1% DMSO only
Points are means ± s.d
n = 4

Compound C3-H_2

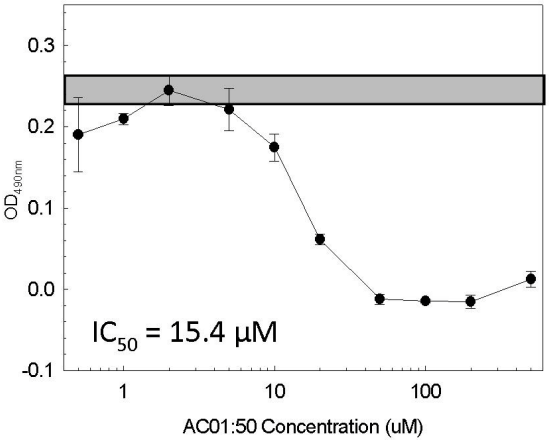
FEK-4
Test Compound AC01:39
3 Day Exposure MTS



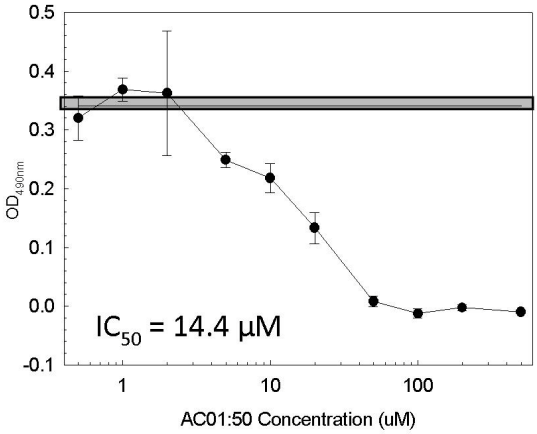
1% DMSO only
Points are means ± s.d
n = 4

Compound C4

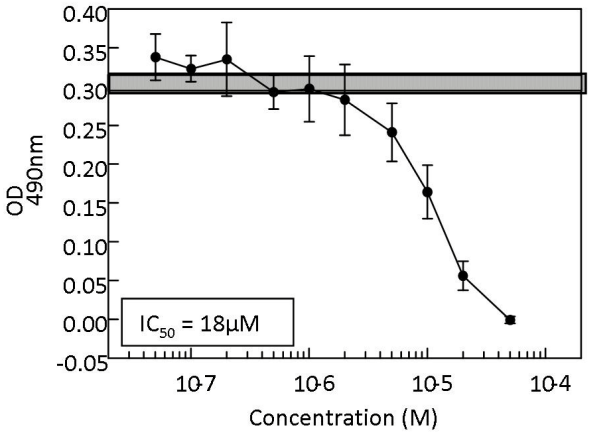
HT29 Human Colon Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



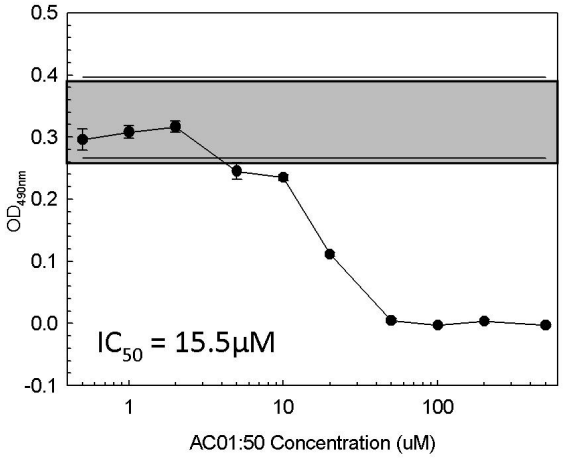
HT29 Human Colon Carcinoma
MTS Cell Proliferation Assay
Test Compound AC01:50
72h Exposure



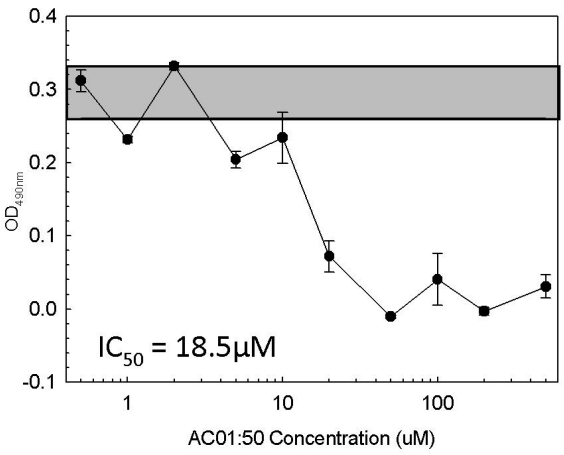
1% DMSO only
Points are means ± s.d
n = 4

Compound C4

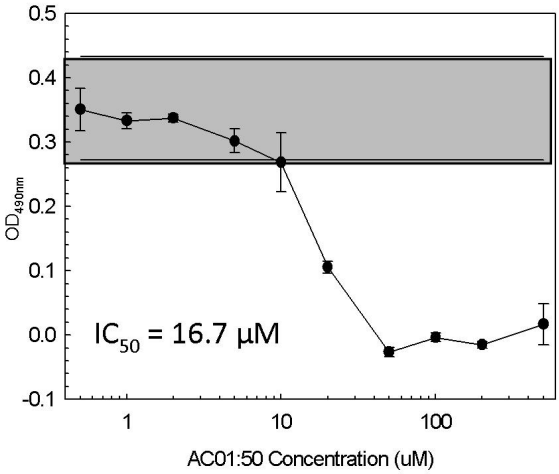
MDA231 Breast Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



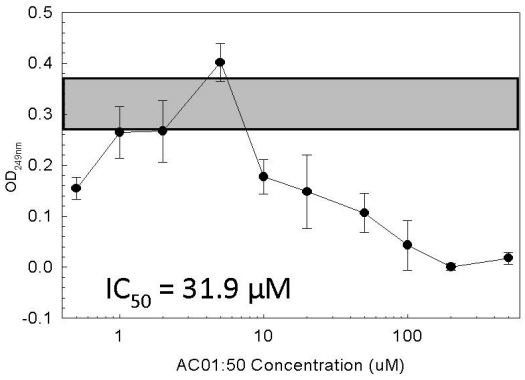
MDA231 Breast Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



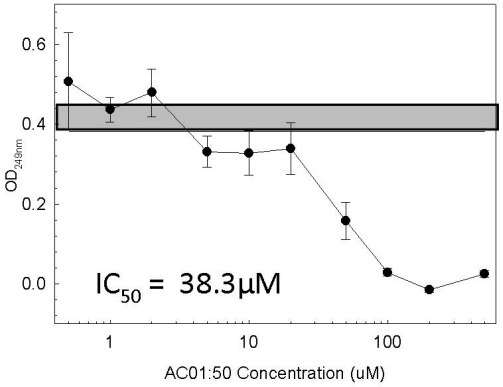
1% DMSO only
Points are means ± s.d
n = 4

Compound C4

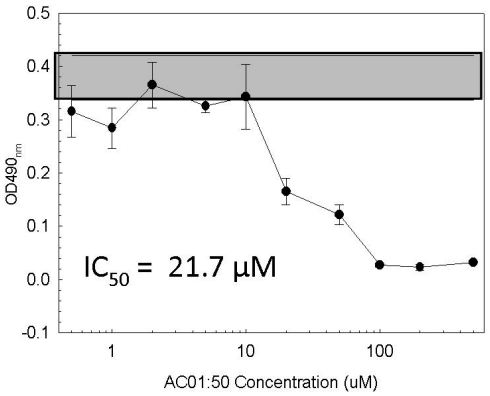
LNCAP Prostate Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



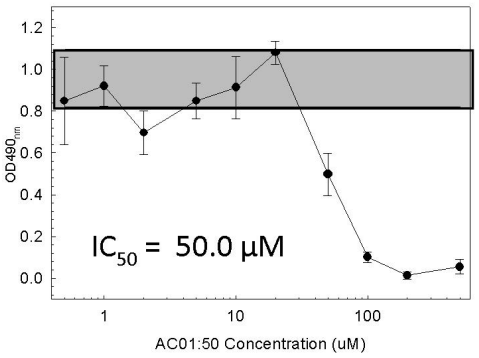
LNCAP Prostate Carcinoma
Test Compound AC01:50
3 Day Exposure MTS



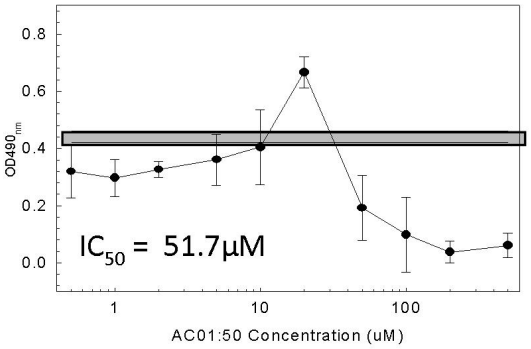
1% DMSO only
Points are means ± s.d
n = 4

Compound C4

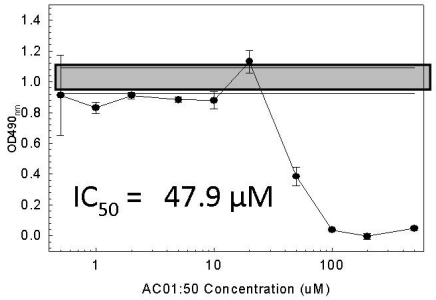
FEK-4 Human Skin Fibroblast
Test Compound AC01:50
3 Day Exposure MTS



FEK-4 Human Skin Cells
Test Compound AC01:50
3 Day Exposure MTS

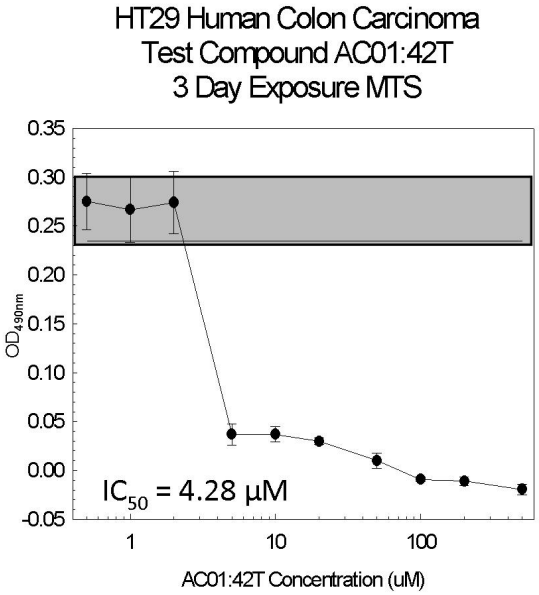


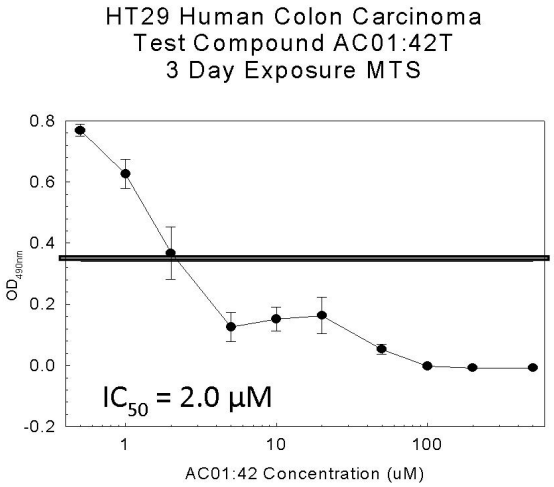
FEK-4 Human Skin Fibroblast
Test Compound AC01:50
3 Day Exposure MTS

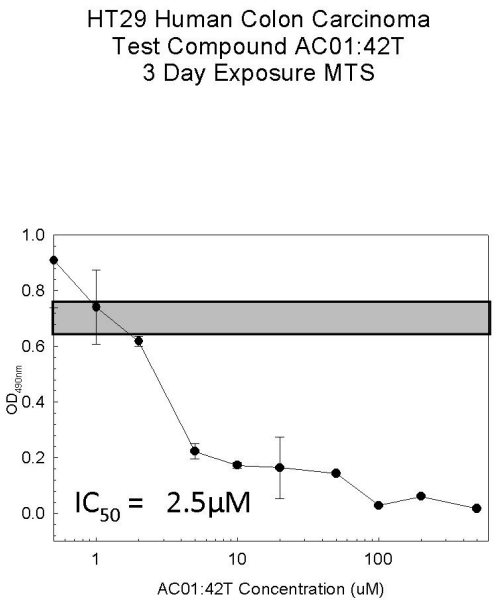


1% DMSO only
Points are means ± s.d
n = 4

Compound C5



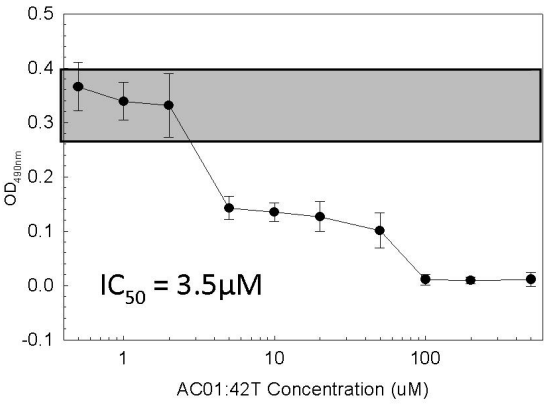




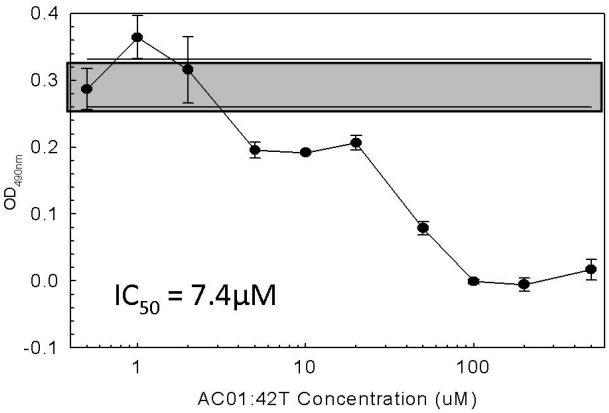
1% DMSO only
Points are means ± s.d
n = 4

Compound C5

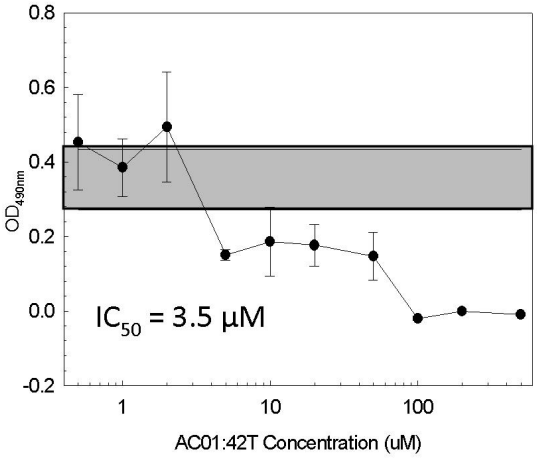
MDA231 Breast Carcinoma
Test Compound AC01:42T
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:42T
3 Day Exposure MTS



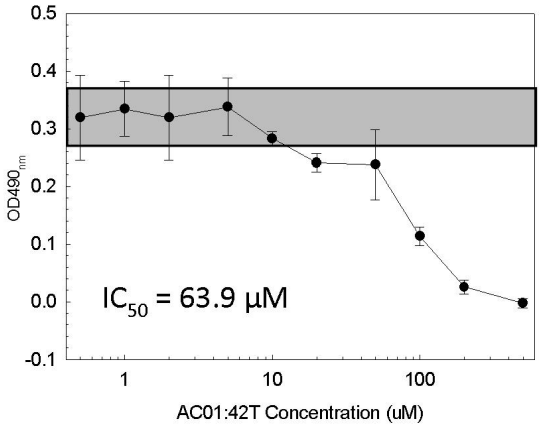
MDA231 Breast Carcinoma
Test Compound AC01:42T
3 Day Exposure MTS



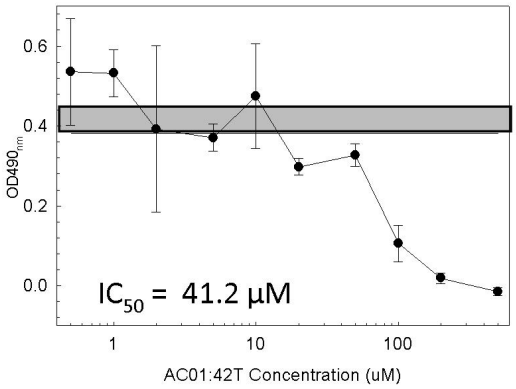
1% DMSO only
Points are means ± s.d
n = 4

Compound C5

LNCAP Prostate Carcinoma
Test Compound AC01:42T
3 Day Exposure MTS

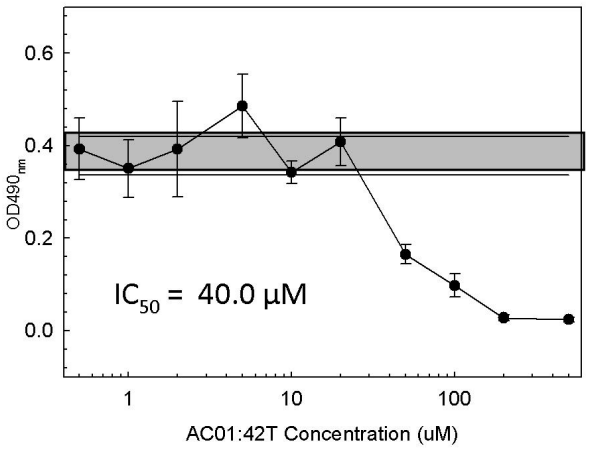


LNCAP Prostate Carcinoma
Test Compound AC01:42T
3 Day Exposure MTS



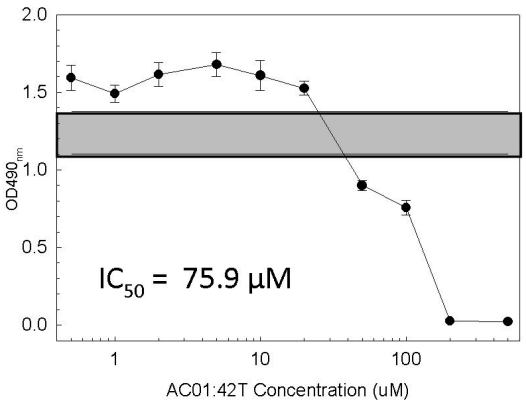
LNCAP Prostate Carcinoma
Test Compound AC01:42T
3 Day Exposure MTS

1% DMSO only
Points are means ± s.d
n = 4

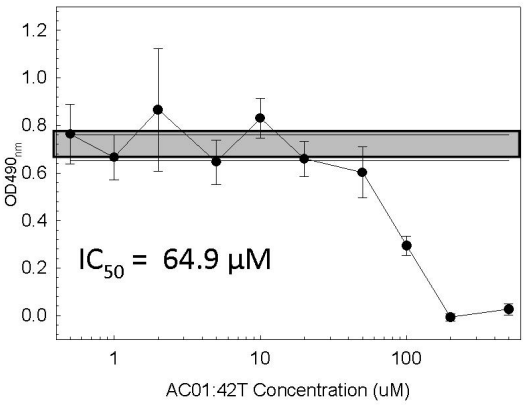


Compound C5

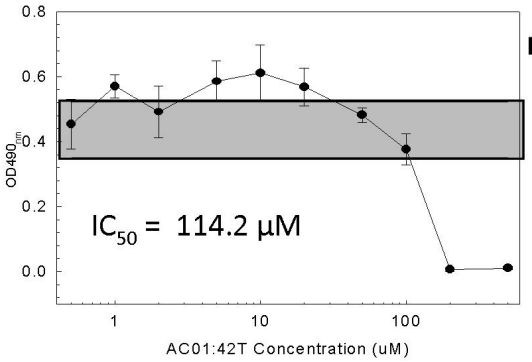
FEK-4 Human Skin Fibroblast Cells
Test Compound AC01:42T
3 Day Exposure MTS



FEK-4 Human Skin Fibroblast
Test Compound AC01:42T
3 Day Exposure MTS



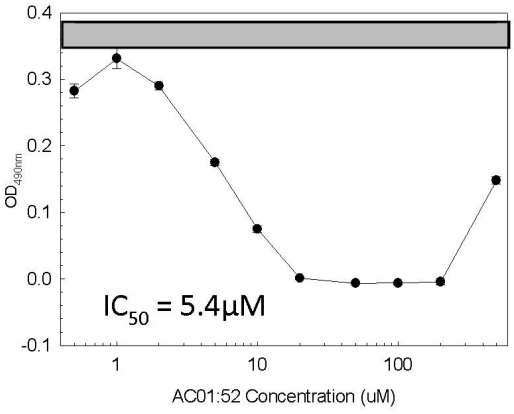
FEK4 Human Skin Fibroblast
Test Compound AC01:42T
3 Day Exposure MTS



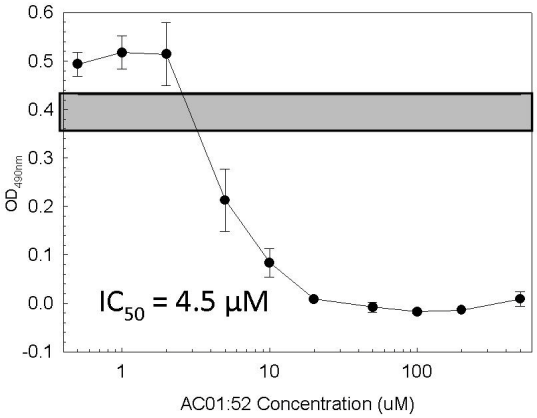
1% DMSO only
Points are means ± s.d
n = 4

Compound C6

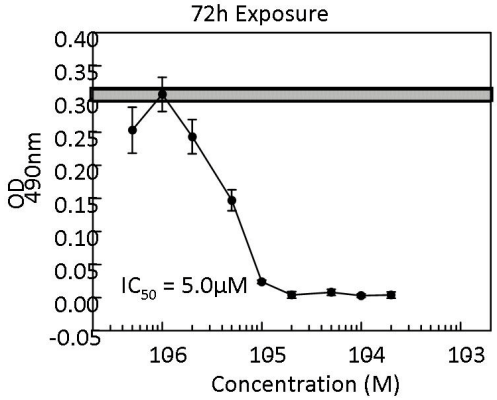
HT29 Human Colon Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



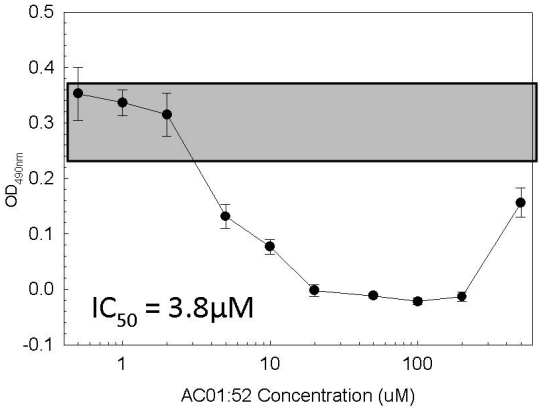
MTS Cell Proliferation Assay
HT29 Human Colon Carcinoma
Test Compound AC01:52
72h Exposure



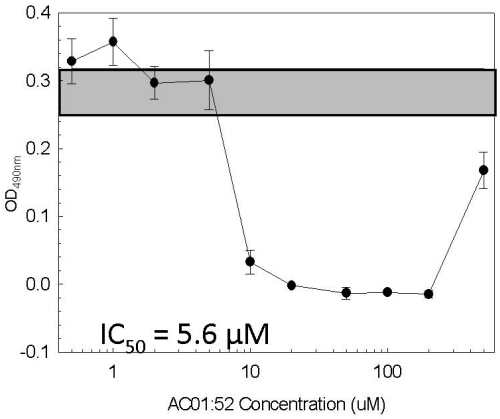
1% DMSO only
Points are means ± s.d
n = 4

Compound C6

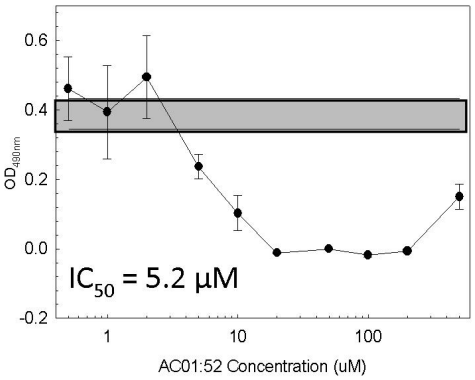
MDA231 Breast Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



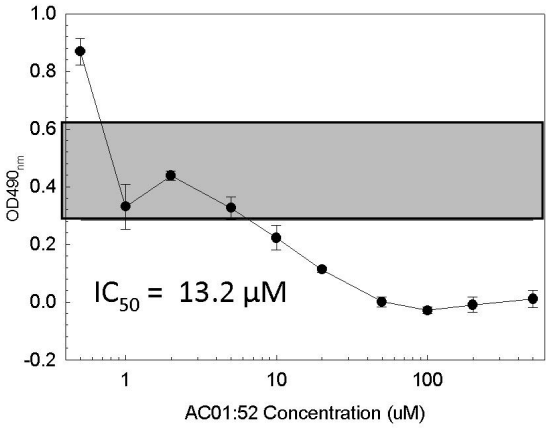
MDA231 Breast Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



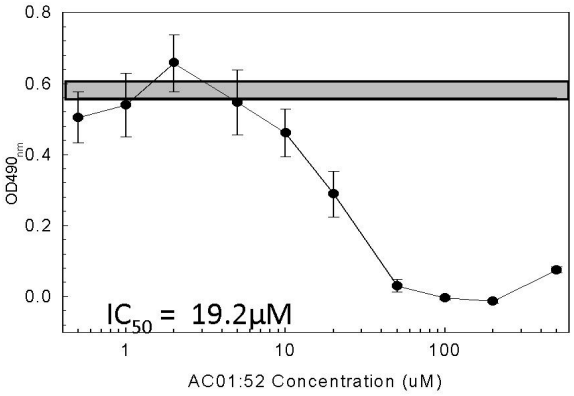
1% DMSO only
Points are means ± s.d
n = 4

Compound C6

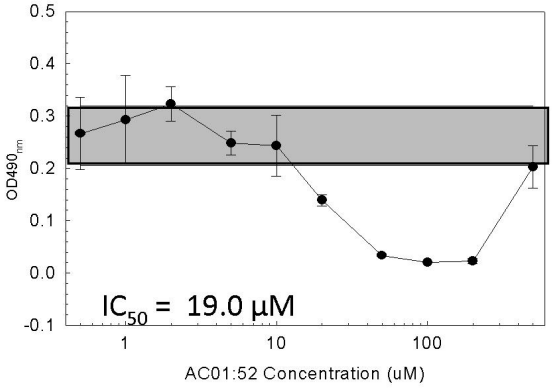
LNCAP Prostate Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



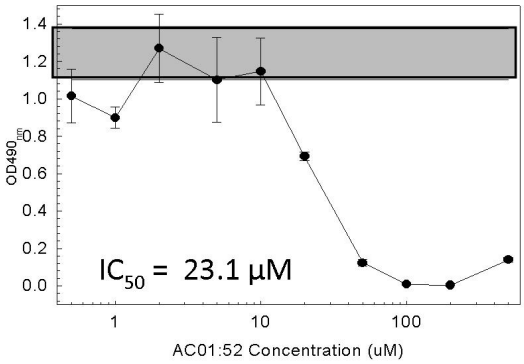
LNCAP Prostate Carcinoma
Test Compound AC01:52
3 Day Exposure MTS



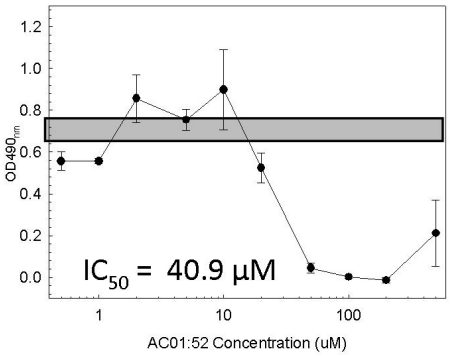
1% DMSO only
Points are means ± s.d
n = 4

Compound C6

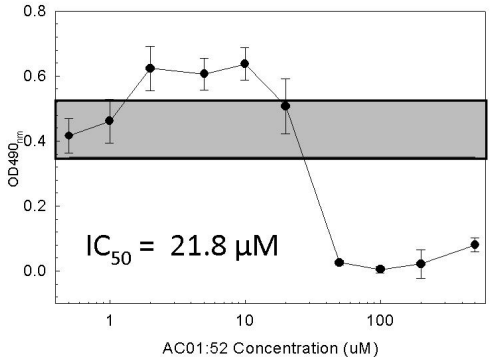
FEK-4 Human Skin Fibroblast Cells
Test Compound AC01:52
3 Day Exposure MTS



FEK-4 Human Skin Fibroblast
Test Compound AC01:52
3 Day Exposure MTS



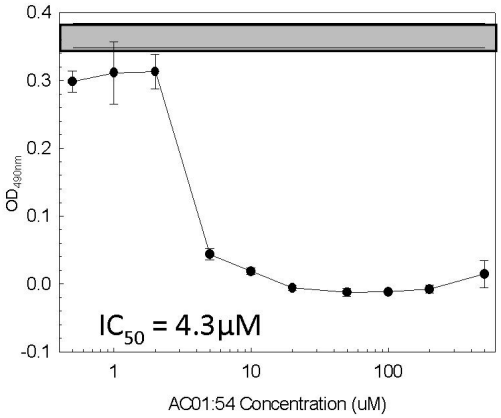
FEK4 Human Skin Fibroblast
Test Compound AC01:52
3 Day Exposure MTS



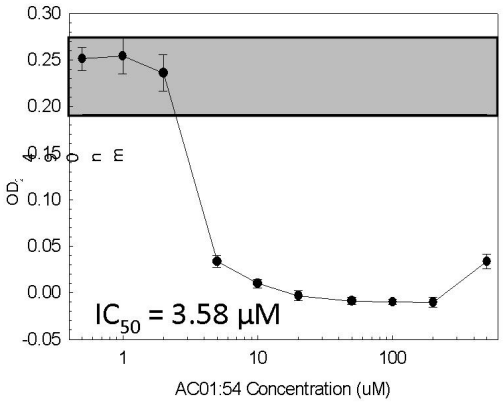
1% DMSO only
Points are means ± s.d
n = 4

Compound C7

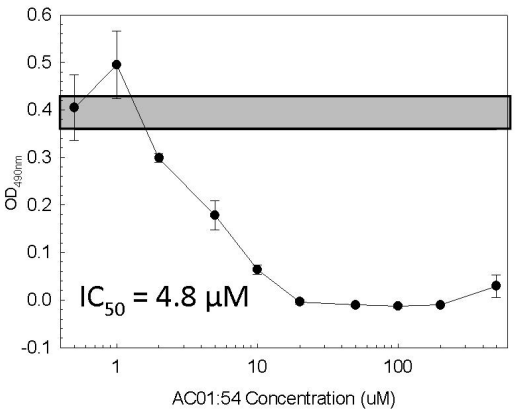
HT29 Human Colon Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



HT29 Human Colon Carcinoma
Test Compound AC01:54
3 Day Exposure MTS

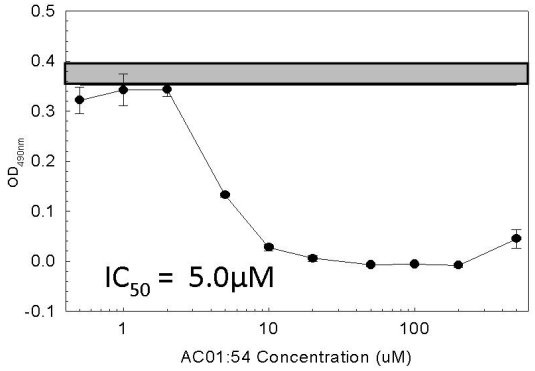


HT29 Human Colon Carcinoma
Test Compound AC01:54
3 Day Exposure MTS

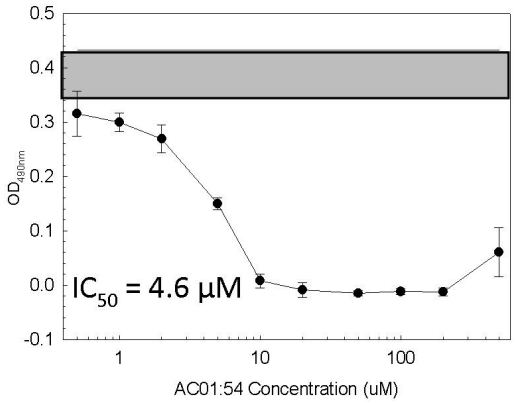


Compound C7

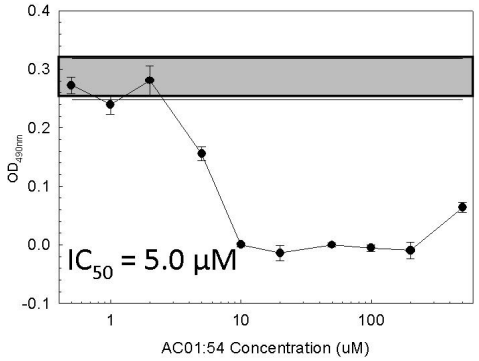
MDA231 Human Breast Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



MDA231 Breast Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



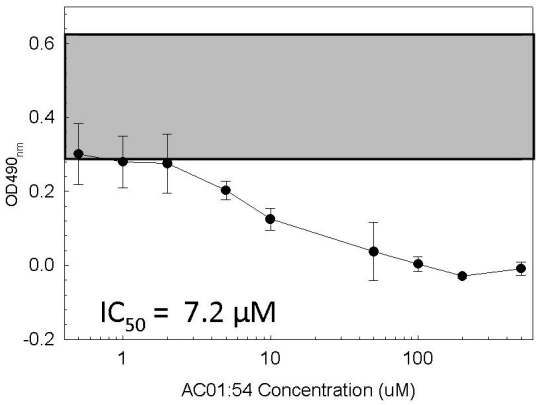
MDA231 Breast Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



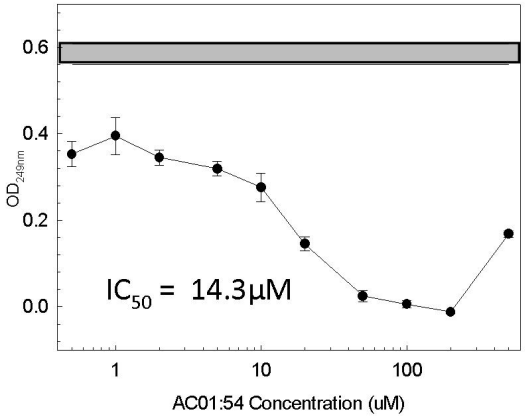
1% DMSO only
Points are means ± s.d
n = 4

Compound C7

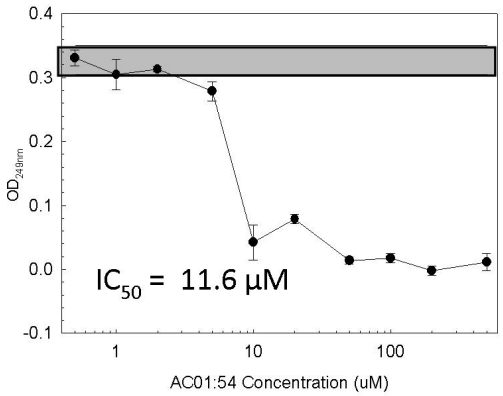
LNCAP Prostate Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



LNCAP Prostate Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



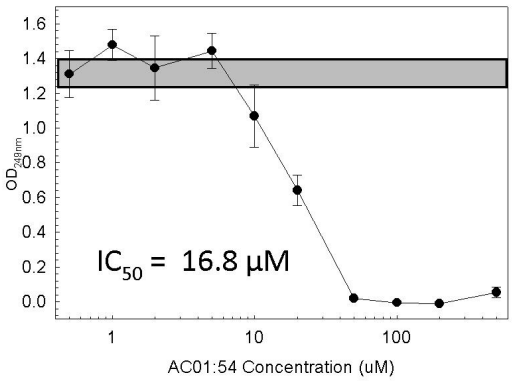
LNCAP Prostate Carcinoma
Test Compound AC01:54
3 Day Exposure MTS



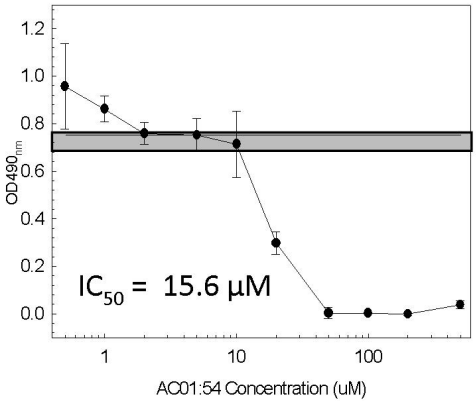
1% DMSO only
Points are means ± s.d
n = 4

Compound C7

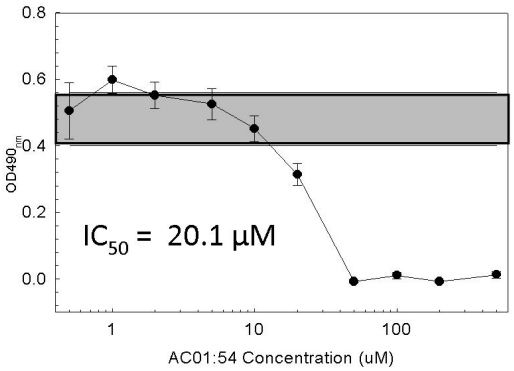
FEK-4 Human Skin Fibroblast Cells
Test Compound AC01:54
3 Day Exposure MTS



FEK-4 Human Skin Fibroblast
Test Compound AC01:54
3 Day Exposure MTS



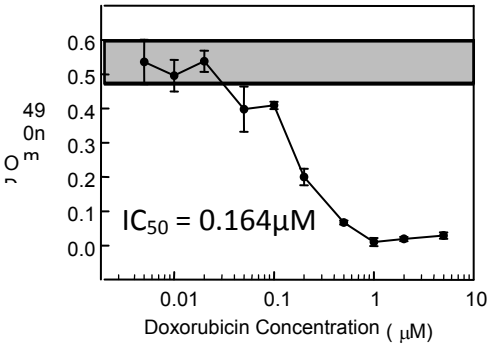
FEK4 Human Skin Fibroblast
Test Compound AC01:54
3 Day Exposure MTS



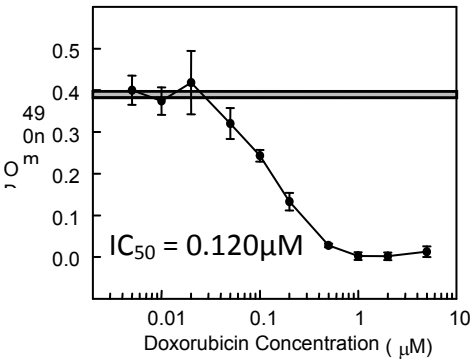
1% DMSO only
Points are means ± s.d
n = 4

Doxorubicin

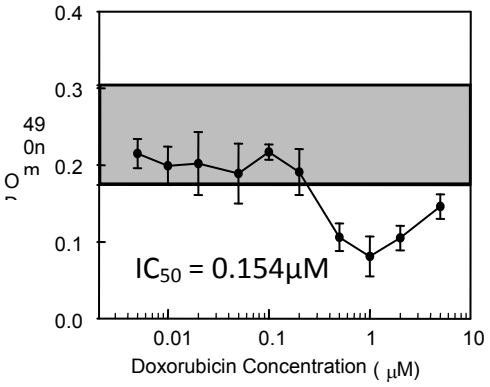
HT29 Human Colon Carcinoma
Doxorubicin



MDA-MB-231 Human Breast Carcinoma
Doxorubicin



LNCaP Prostate Carcinoma
Doxorubicin



1% DMSO only
Points are means ± s.d
n = 4