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SUPPORTING INFORMATION

Synthesis and cytotoxicity of novel simplified eleutherobin analogs as potential antitumour agents

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1. Materials and instrumentations

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All solvents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on Merck TLC silica gel plates (60 F^{254}), using UV light for visualization and basic aqueous potassium permanganate or iodine fumes as a developing agent. Flash column chromatography purifications were carried out using silica gel 60 (particle size 0.040-0.060 mm). Melting points were measured in open capillaries and are presented without correction.

^{1}H and ^{13}C NMR spectra were recorded at 298 K on Bruker Avance 400 spectrometer with operating frequency of 400 and 100 MHz, respectively, and calibrated using residual $CHCl_3$ (δH =7.26 ppm) and $CDCl_3$ (δC = 77.16 ppm) or DMSO-*d5* (δH = 2.50 ppm) and DMSO-d_6 (δC = 39.52 ppm) as internal references. NMR data are presented as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*) in Hertz (Hz), integration.

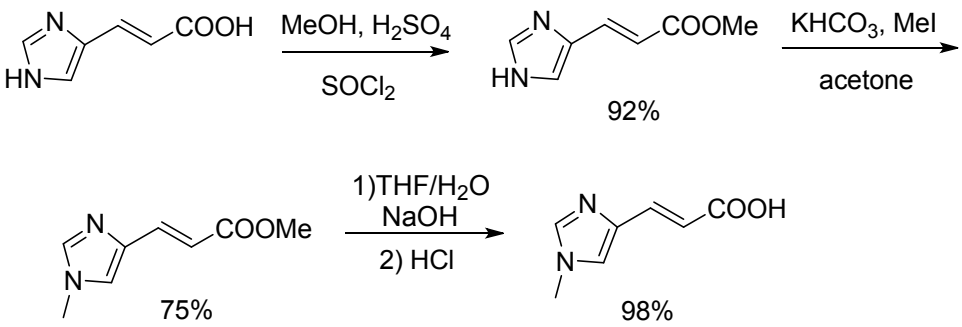
IR spectra were recorded on Thermo Nicolet IR-200 in KBr, or neat. High resolution mass spectra (HRMS) were measured on a Thermo Scientific LTQ Orbitrap instrument using nanoelectrospray ionization (nano-ESI).

Molecular docking into the taxol binding site of tubulin was performed using SYBYL (Silicon Graphic Group) program based on the crystal structure of the tubulin-paclitaxel complex. The paclitaxel binding site of tubulin (PDB ID 1JFF, chain B) was used for docking of eluetherobin and other virtual compounds. The 3D structures were drawn in SybylX 2.1[1] and energy minimized to the nearest local minimum by Powell method in MMFF94s force field[2]. Conformational search was performed in OMEGA[3] with MMFF94s force field, RMSD threshold 0.5 Å and flipper off. MMFF94 charges[4] were assigned in QUACPAC[5]. Docking was performed in FRED 2.2.5[6] using Chemgauss3[7] scoring (eleutherobin and the first series of virtual molecules (Fig. 3B-D)) or in FRED 3.0.1[6] using Chemgauss4[8] scoring (the second series of virtual molecules, Fig. 3E,F). Fourty-five top scored poses for each compound were analyzed visually in VIDA[9].

2. Preparation

8-Oxabicyclo[3.2.1]oct-6-ene-2,4-diols **2a,b** (di-*endo*- and *exo,endo*) was synthesized according to our modified method[9] for multigram quantity, *N*-methylurocanic acid [(*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylic acid] was synthesized according to procedure.[10] Compounds **9a,b**[11,12], **14**[13] were obtained according to the reported protocols.

Synthesis of N-methylurocanic acid ((E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoic acid)[15-18]



1. Synthesis of methyl urocanate

To the suspension of urocanic acid (1.0 g, 7.2 mmol) in 10 ml of anhydrous MeOH, 1 ml of H_2SO_4(conc.) was added followed by a dropwise addition of 1 ml $SOCl_2$ (warning: spontaneous heating). The reaction mixture was heated with reflux for 48 h, concentrated under reduced pressure to a volume 2-3 ml, cooling with ice bath and saturated aq. solution of $NaHCO_3$ was carefully added with temperature control (< 5°C) up to pH 7. After extraction with EtOAc (4x10 ml) the organic layer were dried with Na_2SO_4. Methyl urocanate was obtained as white solid and used without additional purification (0.94 g, 92%). Mp. = 233-234ºC (Mp. lit[18]. = 233-235ºC). δ_H (400 MHz, $CDCl_3$): 7.70 (1H, s), 7.60 (1H, CH=CH, d, *J* 15.7), 7.28 (1H, s), 6.46 (1H, CH=CH, d, *J* 15.9), 3.77 (3H, OCH_3, s); δ_c (100 MHz, $CDCl_3$): 168.03 (C=O), 137.11, 135.00, 122.56, 125.56, 51.68 (OCH_3).

2. Synthesis of methyl *N*-methylurocanate

To the solution of methyl urocanate (0.9 g, 6 mmol) in 15 ml of dry acetone, 0.7 g (7.0 mmol) of $KHCO_3$ and 0.45 ml (1g, 7.0 mmol) of methyl iodide were added. The reaction mixture was stirred at room temperature for 7 days. Ten ml of methylene chloride were added, the formed precipitate was filtered off and the solution was evaporated. Methyl *N*-methylurocanate was obtained after column chromatography (eluent MeOH in Et_2O, gradient 5-30% of MeOH) as a colorless solid (745 mg, 75%). Mp. 113-114ºC (Mp. lit[17]. 114-115ºC). δ_H (400 MHz, $CDCl_3$): 7.52 (1H, CH=CH, d, *J* 15.7), 7.43 (1H, s), 7.06 (1H, s), 6.51 (1H, CH=CH, d, *J* 15.7), 3.74 (3H, OCH_3, s), 3.68 (3H, NCH_3, s); δ_c (100 MHz, $CDCl_3$): 168.16 (C=O), 139.18, 138.33, 136.16, 122.64, 115.57, 51.50 (OCH_3), 33.59 (NCH_3).

3. Synthesis of *N*-methylurocanic acid ((*E*)-3-(1-methyl-*1H*-imidazol-4-yl)prop-2-enoic acid)

To the solution of methyl *N*-methylurocanate (745 mg, 4.5 mmol) in 10 ml of THF/water (1:1) mixture, NaOH (184 mg, 4.6 mmol) was added followed by stirring at room temperature for 24 h. After acidification with 3 ml 2N HCl the reaction mixture was evaporated, the dry residue was filtered through silica gel pad (2 cm, eluent EtOAc/MeOH (2:1), 100 ml). After evaporation of the filtrate *N*-methylurocanic acid (660 mg, 96%) was obtained as a white solid. Mp. 234-235ºC (Mp. lit[18]. 235-237ºC).

δ_H (400 MHz, DMSO-d_6): 12.09 (1H, OH, s), 7.64 (1H, s), 7.47 (1H, s), 7.33 (1H, CH=CH, d, *J* 15.5), 6.27 (1H, CH=CH, d, *J* 15.5), 3.65 (3H, OCH_3, s); δ_c (100 MHz, DMSO-d_6): 169.68 (C=O), 142.88, 136.48, 135.24, 129.12, 111.15, 32.04 (OCH_3).

General procedure for benzoylation of dihydroxyoxabicyclic compounds 2a,b.

The substituted benzoic acid (~1.0 g) was dissolved in 5 ml of dry chloroform, and then thionyl chloride (5 ml) and DMF (0.05 ml) were added to the mixture, the mixture was stirred for 48 h at a temperature of 30-40°C. The volatile components were removed on a rotary evaporator (strong heating should be avoided), the residue was introduced into the acylation reaction.

Diols **2a,2b** (1.06 mmol) were dissolved in 5 ml of dry pyridine and added the resulting benzoyl chloride (~1.2 mmol). The reaction mixture was stirred at room temperature for 48 hours, monitoring by TLC or NMR, then evaporated under vacuum (1 mm Hg). The mixture was

separated by column chromatography (Et_2O eluent in CH_2Cl_2 gradient from 10 to 50%). The following compounds were synthesized using this procedure:

(1S*,2R*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (3a) and (1S*,2R*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (4a)

From 150 mg (1.06 mmol) of **2a** and benzoyl chloride (1.2 mmol) the light yellow solid **3a** (195 mg, 76 %) and colorless solid **4a** (56 mg, 15%), were obtained;

(1S,2R*,4S*,5R*)*-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (**3a**): Mp 93-95 °C;. R_f 0.50 (CH_2Cl_2/Et_2O = 1:1). [Found $C_{14}H_{14}O_4$: C 68.20 H 5.56, requires C 68.28, H 5.73%]; δ_H (400 MHz, $CDCl_3$): 7.98 (2H, Ph, d, *J* 7.2), 7.56 (1H, Ph, t, *J* 7.3), 7.43 (2H, Ph, t, *J* 7.5), 6.41(1H, CH=CH, dd, *J* 1.5, 6.2), 6.35 (CH=CH, d, *J* 1.5, 6.2), 5.08 (1H, (CHOBz, ddd, *J* 4.1, 6.2, 10.1), 4.84 (1H, $H^{1(5)}$, d, *J* 3.9), 4.70 (1H, $H^{1(5)}$, d, *J* 3.9), 3.97 (1H, CHOH, ddd, *J* 4.2, 6.0, 10.0), 2.45 (1H, CH_2, dt, *J* 6.1, 12.2), 1.69 (1H, CH_2, dt, *J* 10.0, 12.3); δ_C (100.6 MHz, $CDCl_3$): 165.59 (C=O), 133.18 (Ph) 131.16 (C=C), 130.46 (C=C), 129.56 (Ph), 128.38(Ph), 81.30($C^{1(5)}$), 78.36($C^{1(5)}$), 65.49 (CHOBz), 63.68 (CHOH), 31.81 (CH_2).

(1*S**,2*R**,4*S**,5*R**)-8-Oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (**4a)**: Mp 125–126 °C;. R_f 0.6 (CH_2Cl_2/Et_2O = 1:1). [Found $C_{21}H_{18}O_5$: C 72.17 H 5.26, requires C 71.99 H 5.18%]; δ_H(400 MHz, $CDCl_3$): 8.03 (4H, Ph, d, *J* 8.1), 7.59 (2H, Ph, t, *J* 7.6), 7.46 (4H, Ph, t, *J* 7.8), 6.45 (2H, CH=CH, s), 5.24 (2H, CHOBz, ddd, *J* 4.4, 6.2, 10.0), 4.97 (2H, (2H, $H^{1(5)}$, d, *J* 4.2), 2.67 (1H, CH_2, dt, *J* 6.1, 12.4), 1.99 (1H, CH_2, dt, *J* 10.1, 12.3); δ_C (100.6 MHz, $CDCl_3$): 165.71 (C=O), 133.62(Ph), 130.91 (C=C), 129.43(Ph), 128.31(Ph), 78.63 ($C^{1(5)}$), 65.01 (CHOBz), 31.24 (CH_2).

(1S*,2S*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (3b) and (1S*,2S*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (4b).

From 150 mg (1.06 mmol) of **2b** and benzoyl chloride (1.2 mmol) the light yellow oil 3**b** (130 mg, 52 %), the light yellow oil **3c** (62 mg, 23 %), and colorless solid **4b** (47 mg, 13%) were obtained.

(1S,2S*,4S*,5R*)*-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (**3b**): R_f 0.55 (CH_2Cl_2/Et_2O = 1:1). [Found $C_{14}H_{14}O_4$: C 68.17 H 5.56, requires C 68.28, H 5.73%]; δ_H (400 MHz, $CDCl_3$): 8.09 (2H, Ph, d, *J* 7.2), 7.56 (1H, Ph, t, *J* 7.4), 7.44 (2H, Ph, t, *J* 7.7), 6.41 (1H, CH=CH, dd, *J* 1.5, 6.2), 6.38 (1H, CH=CH, dd, *J* 1.3, 6.2), 4.97 (1H, d, *J* 5.2), 4.77–4.82 (2H, m), 4.24 (1H, H^4, ddd, *J* 4.3, 6.2, 9.9), 2.74 (1H, OH, bs), 2.13–2.18 (1H, m), 2.01–2.08 (1H, m); δ_C (100.6 MHz, DMSO-d_6): 166.42 (C=O), 133.21, 132.23, 132.14, 129.82, 129.65, 128.42, 81.73 (C^5), 80.64 (C^1), 68.01 (C^4), 62.83 (C^2), 31.92.

(1S*,2R*,4R*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate **(3c)**. R_f 0.45 (CH_2Cl_2/Et_2O = 1:1). [Found $C_{14}H_{14}O_4$: C 68.15 H 5.69, requires C 68.28, H 5.73%]; δ_H (400 MHz, $CDCl_3$): 7.98 (2H, Ph, d, *J* 7.2), 7.58 (1H, Ph, t, *J* 7.4), 7.45 (2H, Ph, t, *J* 7.7), 6.45 (1H, CH=CH, dd, *J* 1.4, 6.1), 6.38 (1H, CH=CH, dd, *J* 1.3, 6.1), 5.23 (1H, H^2, ddd, *J* 4.6, 6.8, 9.8), 4.96 (1H, d, *J* 4.2), 4.63–4.67 (2H, m), 1.94–2.05 (2H, m); δ_C (100.6 MHz, DMSO-d_6): 166.91 (C=O), 133.02, 132.33, 132.21, 129.74, 129.62, 128.43, 82.50, 80.12, 68.33, 64.01, 31.52.

(1*S**,2*S**,4*S**,5*R**)-8-Oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (**4b**). Mp 102–103 C; R_f 0.5 (CH_2Cl_2/Et_2O = 3:1). [Found $C_{21}H_{18}O_5$: C 72.05 H 5.13, C 71.99 H 5.18%]; δ_H (400 MHz, $CDCl_3$): 8.15 (2H, Ph, dd, *J* 1.2, 8.5), 8.01 (2H, Ph, dd, *J* 1.2, 8.5), 7.57–7.62 (2H, Ph, m),

7.48 (4H, Ph, t, *J* 8.1), 6.51 (1H, $H^{6(7)}$, dd, *J* 1.7, 6.1), 6.43 (1H, $H^{6(7)}$, dd, *J* = 1.3, 6.1), 5.50–5.55 (1H, $H^{2(4)}$, m), 5.07 (1H, $H^{2(4)}$, dt, *J* 1.4, 5.1), 5.04 (1H, $H^{1(5)}$, d, *J* 3.7), 4.91 (1H, $H^{1(5)}$, d, *J* 1.4), 2.27–2.42 (2H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 166.33, 165.62, 133.30, 133.21, 132.73, 131.95, 129.92, 129.61, 128.53, 128.42, 80.91, 79.12, 67.53, 65.21, 28.82.

4.2.3.4(1S*,2R*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl 3,4-dimethoxybenzoate (3d) and (1S*,2R*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl bis(3,4-dimethoxybenzoate) (4d).

From 150 mg (1.06 mmol) of **2a** and 3,4-dimethoxybenzoyl chloride (1.2 mmol) the light yellow oil **3d** (225 mg, 70 %) and colorless solid **4d** (68 mg, 14%), were obtained;

(1S,2R*,4S*,5R*)*-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl 3,4-dimethoxybenzoate *(***3d***)* R_f 0.65 (CH_2Cl_2/Et_2O = 1:1), [Found $C_{16}H_{18}O_6$: C 62.57 H 6.03., requires C 62.74 H 5.92%]; δ_H (400 MHz, $CDCl_3$): 7.62 (1H, Ph, d, *J* 8.5), 7.50 (1H, Ph, d, *J* 1.6), 6.87 (2H, Ph, d, *J* 8.5), 6.43 (1H, CH=CH, d, *J* 6.2), 6.35 (1H, CH=CH, d, *J* 6.2), 5.05–5.10 (1H, CHOBz, ddd, *J* 4.3, 6.1, 10.1), 4.85 (1H, $CH^{1(5)}$, d, *J* 2.9), 4.72 (1H, $CH^{1(5)}$, d, *J* 2.7), 3.96–4.01 (1H, CHOH, m), 3.94 (3H, OCH_3, s), 3.93 (3H, OCH_3 , s), 3.07 (1H, OH, bs), 2.42–2.48 (1H, CH_2, m), 1.67–1.75 (1H, CH_2, m). δ_C(100.6 MHz, $CDCl_3$): 165.41 (C=O), 153.53, 148.72, 131.21, 130.50, 124.53, 123.62, 112.00, 110.21, 81.32 (C^5), 78.53 (C^1), 65.41, 63.62, 56.10 (OMe), 56.01 (OMe), 32.02 (CH_2).

(*1S*,2R*,4S*,5R*)*-8-Oxabicyclo[3.2.1]oct-6-en-2,4-diyl bis(3,4-dimethoxybenzoate) (**4d**). Mp 117-118 C; R_f 0.65 (CH_2Cl_2/Et_2O =4:1). [Found $C_{25}H_{26}O_9$: C 63.87 H 5.63, requires C 63.82 H 5.57%]; δ_H (400 MHz, $CDCl_3$): 7.64 (1H, Ph, d, *J* 8.5), 7.51 (1H, Ph, d, *J* 1.6), 6.95 (2H, Ph, d, *J* 8.5), 6.42 (2H, CH=CH, s), 5.17–5.22 (2H, CHOBz, m), 4.94 (2H, $H^{1(5)}$, d, *J* 3.8), 2.60–2.67 (1H, CH_2, m), 1.91–1.96 (1H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 165.61 (C=O), 153.92, 148.73, 131.01, 124.70, 123.32, 112.00, 110.41, 78.22 ($C^{1(5)}$), 66.21 (CHOBz), 31.33 (CH_2).

(1S*,2R*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl 4-acetoxybenzoate (3e) and (1S*,2R*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl bis(4-acetoxybenzoate) (4e)

From 150 mg (1.06 mmol) of **2a** and 4-acetoxybenzoyl chloride (1.2 mmol) the white solid **3e** (200 mg, 62 %) and colorless solid **4e** (60 mg, 12%), were obtained;

(1S,2R*,4S*,5R*)*-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl 4-acetoxybenzoate (**3e**). Mp. 94–95 °C; R_f 0.45 (CH_2Cl_2/Et_2O = 1:1). [Found $C_{16}H_{16}O_6$: C 62.97, H 5.34, requires C 63.15, H 5.30%]; δ_H (400 MHz, $CDCl_3$): 8.02 (2H, Ph, d, *J* 8.7), 7.18 (2H, Ph, d, *J* 8.7), 6.41 (1H, CH=CH, d, *J* 6.1), 6.34 (1H, CH=CH, d, *J* 6.1), 5.06–5.11 (1H, CHOBz, ddd, *J* 4.1, 6.1, 10.0), 4.84 (1H, $H^{1(5)}$, d, *J* 2.7), 4.71 (1H, H1(5), d, *J* 2.7), 3.90–4.00 (1H, CHOH, m), 2.42–2.48 (1H, CH_2, m), 2.33 (3H, OAc, s), 1.66–1.74 (1H, CH_2, m). δ_C (100.6 MHz, $CDCl_3$): 170.32, 169.01, 154.52, 131.93, 131.20, 131.01, 127.42, 121.74, 81.32 (C^5), 78.40 (C^1), 65.71, 63.52, 31.73 (CH_2), 21.10 (CH_3).

(*1S*,2R*,4S*,5R**)-8-Oxabicyclo[3.2.1]oct-6-en-2,4-diyl bis(4-acetoxybenzoate) (**4e**). Mp 131-132°C; R_f 0.40 (CH_2Cl_2/Et_2O =4:1). [Found $C_{25}H_{22}O_9$: C 64.18, H 4.73, requires C 64.37, H 4.75%]. δ_H (400 MHz, $CDCl_3$): 8.11 (2H, Ph, d, *J* 8.7), 7.13 (2H, Ph, d, *J* 8.7), 6.40 (1H, CH=CH, s), 5.12–5.17 (2H, CHOBz, ddd, *J* 4.1, 6.1, 10.0), 4.83 (2H, $H^{1(5)}$, d, *J* 3.4), 2.40–

2.46 (1H, CH_2, m), 2.35 (3H, OAc, s), 1.69–1.75 (1H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 172.02, 169.21, 154.53, 131.42, 130.60, 127.42, 122.11, 79.73 ($C^{1(5)}$), 64.50, 31.22 (CH_2), 21.01 (CH_3).

General procedure for esterification of hydroxyoxabicyclic compounds

N-Methylurocanic acid or phenylisoserine derivative **6** (0.45 mmol were added to the solution of hydroxyoxabicyclic compound **3a-e** (0.30 mol) in 5 ml dry $CHCl_3$ and 20 mg (0.15 mol) *p*-(dimethylamino)pyridine (DMAP). The mixture was stirred for 48 h at 55-60°C, every 12 h adding 60 mg dicyclohexylcarbodiimide (DCC), total 240 mg (2 mmol) DCC. At the end of the reaction, 0.5 ml water was added, mixed for 2 h, then evaporated on a rotary evaporator, and 15 ml EtOAc was added. The resulting suspension was stirred thoroughly and kept frozen (-20°C) for one day, then filtered, the precipitate on the filter was washed with 30 ml EtOAc. The filtrate was evaporated and the esterification product was isolated by column chromatography (MeOH/EtOAc gradient from 1:9 to 1:3). The following compounds were synthesized according to this method:

(1R*,2S*,4R*,5S*)-4-((E)-3-(1-Methyl-1H-(imidazol-4-yl))acryloyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (5a)

White solid (76 mg, 67%), Mp 113–115 °C; R_f 0.4 (Et_2O/MeOH = 4:1). [Found $C_{21}H_{20}N_2O_5$: C 60.45, H 5.36, N 7.42, requires C 66.31, H 5.30, N 7.36%]. δ_H (400 MHz, $CDCl_3$): 7.99 (2H, Ph, d, *J* 8.3), 7.57 (1H, Ph, t, *J* 7.5), 7.56 (1H, $=CH^{uroc}$, d, *J* 15.6), 7.46 (1H, $CH^{imidazole}$, s), 7.44 (2H, Ph, t, *J* 7.6), 7.09 (1H, $CH^{imidazole}$, s), 6.50 (1H, $=CH^{uroc}$, d, *J* 15.6), 6.36-6.40 (2H, $C^6H=C^7H$, m), 5.15–5.20 (1H, CHOBz, m, *J* 4.2, 6.2, 10.2), 5.05–5.10 (1H, CHOR, m, *J* 4.2, 6.2, 10.1), 4.91 (1H, $H^{1(5)}$, d, *J* 4.2), 4.86 (1H, $H^{1(5)}$, d, *J* 4.2), 3.71 (3H, CH_3, s), 2.53–2.59 (1H, CH_2, m), 1.82–1.90 (1H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 166.50 (C=O), 165.52 (C=O), 139.31 (Imz), 138.43 (Imz), 137.82 (Ph), 136.81 (Imz), 133.20 (C=C), 131.22 ($C^6=C^7$), 130.61($C^6=C^7$), 129.80 (Ph), 129.62 (Ph), 128.41 (Ph), 122.83 (C=C), 78.82 ($C^{1(5)}$), 78.71 ($C^{1(5)}$), 65.40 (CHOBz), 64.62 (CHOR), 33.61 (CH_3), 28.50 (CH).

(1R*,2R*,4R*,5S*)-4-((E)-3-(1-Methyl-1H-(imidazol-4-yl))acryloyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (5b)

Yellow oil (78 mg, 68%), R_f 0.35 (Et_2O/MeOH = 4:1), [Found $C_{21}H_{20}N_2O_5$: C 60.45, H 5.36, N 7.42, requires C 66.31, H 5.30, N 7.36%]. δ_H (400 MHz, $CDCl_3$): 8.11 (2H, Ph, d, *J* 8.3), 7.56 (1H, Ph, t, *J* 7.4), 7.56 (1H, $=CH^{uroc}$, d, *J* 15.6), 7.50 (1H, $CH^{imidazole}$, s), 7.46 (2H, Ph, t, *J* 7.4), 7.10 (1H, $CH^{imidazole}$, s), 6.52 (1H, =CH, d, *J* 15.6), 6.45 (1H, $C^6H=C^7H$, d, *J* 6.1), 6.36 (1H, $C^6H=C^7H$, d, *J* 6.1), 5.35 (1H, C^4, ddd, *J* 4.3, 6.4, 9.5), 5.02 (1H, C^2, d, *J* 5.0), 4.94 (1H, $H^{1(5)}$, d, *J* 3.7), 4.85 (1H, $H^{1(5)}$, s), 3.72 (3H, Me, s), 2.19–2.30 (2H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 166.50 (C=O), 166.32 (C=O), 139.21 (Imz), 137.93 (Imz), 136.31, 135.60, 133.12, 132.30, 132.11, 130.12, 129.83 (Ph), 129.64 (Ph), 128.40 (Ph), 122.82 (C=C), 80.90 ($C^{1(5)}$), 79.11 ($C^{1(5)}$), 67.62 (CHOBz), 64.43 (CHOR), 33.81 (CH_3), 28.82 (CH_2).

(1R*, 2S*,4R*, 5S*)-4-((E)-3-(1-Methyl-1H-(imidazol-4-yl))acryloyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl 3,4-dimethoxybenzoate (5c)

White solid (84 mg, 64%), Mp. 104-105 °C; R_f 0.4 (Et_2O/MeOH = 4:1), [Found $C_{23}H_{24}N_2O_7$: C 62.49, H 5.42, N 6.40, requires C 62.72, H 5.49, N 6.36%]. δ_H (400 MHz, $CDCl_3$): 7.62 (1H, Ph,

d, *J* 8.4), 7.56 (1H, =CH^{uroc}, d, *J* 15.6), 7.50 (1H, Ph, d, *J* 1.6), 7.49 (1H, CH^{imidazole}, s), 7.09 (1H, CH^{imidazole}, s), 6.87 (2H, Ph, d, *J* 8.5), 6.53 (1H, =CH, d, *J* 15.6), 6.37 (2H, C^{6}H=C^{7}H, s), 5.12–5.17 (1H, C$^{2(4)}$, ddd, *J* 4.1, 6.2, 10.2), 5.04–5.09 (1H, C$^{2(4)}$, ddd, *J* 4.1, 6.1, 10.1), 4.91 (1H, H$^{1(5)}$, d, *J* 4.1), 4.86 (1H, H$^{1(5)}$, d, *J* 4.1), 3.77 (3H, NMe, s), 3.71 (3H, OMe, s), 3.70 (3H, OMe, s), 2.51–2.58 (1H, CH_2, m), 1.82–1.90 (1H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 166.52 (C=O), 165.31 (C=O), 153.22 (Ph), 148.73 (Ph), 139.31 (Imz), 138.22 (Imz), 136.13 (Imz), 131.21, 130.12, 130.60, 123.61, 122.92, 122.21, 115.44, 112.02 (Ph), 110.23 (Ph), 78.81 (C1(5)), 78.72 (C$^{1(5)}$), 65.34 (CHOR), 64.72 (CHOR), 56.03 (OCH_3), 33.71 (NCH_3), 28.50 (CH).

(1R*, 2S*,4R*,5S*)-4-((E)-3-(1- Methyl-1H-(imidazol-4-yl))acryloyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl 4-acetoxybenzoate (5d)

White solid (78 mg, 60%), Mp. 138–140 °C; R_f 0.4 (Et_2O/MeOH = 4:1), [Found $C_{23}H_{22}N_2O_7$: C 62.92, H 5.15, N 6.41, requires C 63.01, H 5.06, N 6.39%]. δ_H (400 MHz, $CDCl_3$): 8.02 (2H, Ph, d, *J* 8.7), 7.57 (1H, =CH, d, *J* 15.6), 7.49 (1H, CH^{imidazole}, s), 7.18 (2H, Ph, d, *J* 8.7), 7.10 (1H, CH, s), 6.52 (1H, =CH, d, *J* 15.6), 6.36-6.39 (2H, C^{6}H=C^{7}H, m), 5.13-5.18 (1H, C2(4), ddd, *J* 4.2, 6.2, 10.1), 5.05-5.10 (1H, C$^{2(4)}$, ddd, *J* 4.2, 6.2, 10.1), 4.90 (1H, H$^{1(5)}$, d, *J* 4.2), 4.85 (1H, H$^{1(5)}$, d, *J* 4.2), 3.75 (3H, CH_3, s), 2.52–2.58 (1H, CH_2, m), 2.35 (3H, OAc, s), 1.82-1.90 (1H, CH_2, m). δ_C (100.6 MHz, $CDCl_3$): 170.11, 166.53 (C=O), 165.52 (C=O), 154.51, 139.50 (Imz), 138.52 (Imz), 136.83 (Imz), 133.21 (C=C), 131.90, 131.22 (C^6=C^7), 130.63(C^6=C^7), 130.01, 127.43, 122.82 (C=C), 78.71 (C$^{1(5)}$), 78.64 (C$^{1(5)}$), 65.42 (CHOBz), 64.51 (CHOR), 33.62 (NCH_3), 28.73 (CH_2), 21.11 (CH_3).

Synthesis of (1R*,2S*,4R*, 5S*)-4-((E)-3-(1-Methyl-1H-(imidazol-4-yl))acryloyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl 4-hydroxybenzoate (5e)

To the solution of acetate **5d** (70 mg, 0.16 mmol) in 5 ml acetonitrile, 10 µl of hydrazine monohydrate $N_2H_4 \cdot H_2O$ (10 mg, 0.25 mmol) was added drop by drop and stirred for 15 min at room temperature. Then acetic acid (0.5 ml), Et_2O (10 ml) and water (5 ml) were added to the reaction mixture. The aqueous layer was separated and extracted with ethyl acetate (2×10 ml). The organic layers were dried with anhydrous Na_2SO_4 and evaporated. The resulting residue was filtered through a small silica gel pad layer (eluent MeOH in EtOAc gradient 5-30%), isolating the product **5e** as a white crystalline solid (36 mg, 58%). Mp. 145−147°C. R_f 0.5 (EtOAc/MeOH = 3:1), [Found $C_{21}H_{20}N_2O_6$: C 63.50, H 5.17, N 6.98, requires C 63.63, H 5.09, N 7.07%]. δ_H (400 MHz, $CDCl_3$): 7.93 (2H, Ph, d, *J* 8.7), 7.56 (1H, =CH^{uroc}, d, *J* 15.6), 7.50 (1H, CH^{imidazole}, s), 7.10 (1H, CH^{imidazole}, s), 6.98 (2H, Ph, d, *J* 8.7), 6.53 (1H, =CH^{uroc}, d, *J* 15.6), 6.36-6.39 (2H, C^{6}H=C^{7}H, m), 5.16-5.20 (1H, C$^{2(4)}$, ddd, *J* 4.2, 6.2, 10.1), 5.09-5.14 (1H, C$^{2(4)}$, ddd, *J* 4.2, 6.2, 10.1), 4.90 (1H, H$^{1(5)}$, d, *J* 4.2), 4.86 (1H, H$^{1(5)}$,d, *J* 4.2), 3.71 (3H, Me, s), 2.52-2.58 (1H, CH_2, m), 1.82-1.90 (1H, CH_2, m); δ_C (100.6 MHz, $CDCl_3$): 166.52 (C=O), 165.91 (C=O), 154.64, 139.42 (Imz), 138.41 (Imz), 136.82 (Imz), 133.10 (C=C), 131.91, 131.21 (C^6=C^7), 130.52 (C^6=C^7), 129.80, 127.4, 122.82 (C=C), 78.71 (C$^{1(5)}$), 78.54 (C$^{1(5)}$), 65.53 (CHOBz), 64.61 (CHOR), 33.63 (NCH_3), 28.42 (CH_2).

(4R,5R)-5-((1R*,2R*,4S*,5S*)-4-(Benzoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl) 3-tert-butyl 2-(4-methoxyphenyl)-4-phenyloxazolidine-3,5-dicarboxylate (7)

From **3a** and enantiomerically pure phenylisoserine derivative **6** compound **7** was obtained as inseparatable mixture of two diastereomers, white solid (142 mg, 75%). Mp 144–145°C; R_f 0.6 (Et_2O/petroleum ether = 3:1); [Found $C_{36}H_{37}NO_9$: C 68.67, H 5.90, N 2.30, requires C 68.89, H

5.94, N 2.23%]. δ_H (400 MHz, $CDCl_3$): 7.99 (2H, Ph, t, *J* 8.3), 7.33-7.60 (10H, Ph, m), 6.94 (2H, Ph, d, *J* 8.6), 6.90 (2H, Ph, d, *J* 8.6), 6.28-6.49 (2H, m), 6.08 (1H, d, *J* 5.7), 5.85 (1H, br s), 5.36-5.44 (1H, m), 5.04-5.13 (1H, CHOR, m), 4.83-4.87 (2H, m), 4.52-4.54 (1H, m), 3.82 (3H, OMe, s), 2.44-2.50 (1H, CH_2, m), 1.69-1.77 (1H, CH_2, m), 1.09 (9H, Boc, s); δ_C (100.6 MHz, $CDCl_3$): 169.02, 165.43, 160.31, 160.42, 133.33, 130.80, 130.71, 129.62, 128.83, 128.61, 128.50, 128.32, 128.11, 126.63, 126.44, 113.72, 91.90, 91.82, 83.13, 81.42, 80.91, 78.72, 78.63, 78.43, 78.32, 66.01, 65.90, 65.14, 65.02, 63.21, 63.03, 55.42, 55.24, 30.71, 27.92

Synthesis of (1S,2S,4R,5R)-4-((2R,3R)-3-(tert-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (8a) and (1R,2R,4S,5S)-4-((2R,3R)-3-(tert-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (8b)

To the solution of 120 mg oxazolidine **7** (0.20 mmol) in 10 ml MeOH, p-TSA monohydrate (100 mg, 0.50 mmol) was added; the mixture was stirred at room temperature for 12 h. 10 ml of saturated $NaHCO_3$ was added, methanol was evaporated under vacuum. After extraction of water suspension with Et_2O (2x10 ml) and methylene chloride (2x10 ml) the combined organic layers were dried over Na_2SO_4. The mixture of **8a,b** was obtained as a clear oil (60 mg, 62%). Pure isomers were obtained after two separations with column chromatography (eluent Et_2O/petrol ether 4:1).

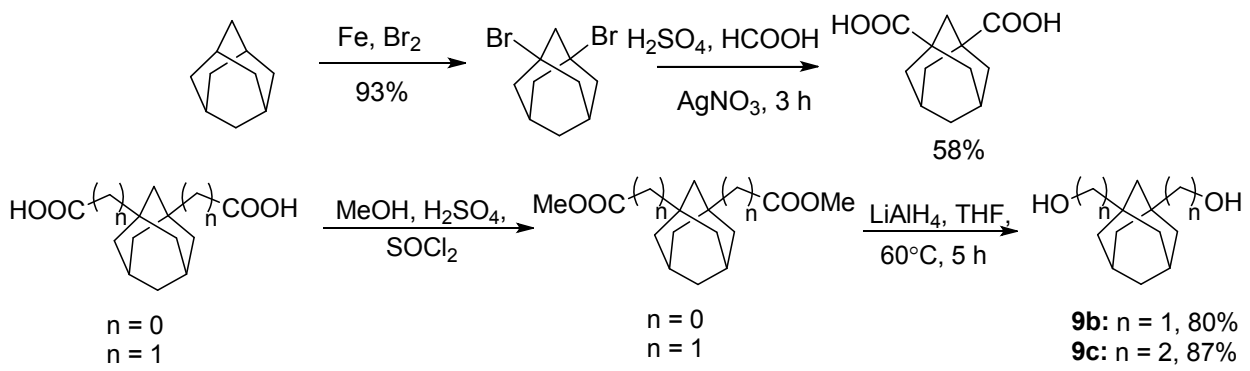
*(1S,2S,4R,5R)- **(8a)***

White crystalline (16 mg, 17%). Mp. 156–157°C; R_f 0.6 (Et_2O/petroleum ether = 4:1). $[\alpha]^{25}_D$ = 15.2 (c = 1.0, $CHCl_3$); [Found $C_{28}H_{31}NO_8$: C 68.67, H 5.90, N 2.30, requires C 66.00, H 6.13, N 2.75%]. δ_H (400 MHz, $CDCl_3$): 8.01 (2H, Bz, d, *J* 7.3), 7.61 (1H, Bz, t, *J* 7.3), 7.47 (2H, Bz, t, *J* 7.8), 7.36-7.41 (4H, Ph, m), 7.30-7.34 (1H, Ph, m), 6.56 (1H, CH=CH, d, *J* 5.8), 6.40 (1H, CH=CH, dd, *J* 6.2, 1.4), 5.40 (1H, d, *J* 9.3), 5.19 (2H, CHOR, ddd, 4.3, 6.1, 10.2), 5.12 (1H, CHOR, ddd, *J* 4.1, 6.1, 10.1), 4.90 (1H, d, *J* 3.8), 4.84 (1H, d, *J* 2.7), 4.47 (1H, br s), 3.16 (1H, d, *J* 3.0), 2.52 (1H, CH_2, dt, *J* 6.4, 12.3), 1.96 (1H, CH_2, dt, *J* 10.2, 11.8), 1.45 (9H, Boc, s); δ_C (100.6 MHz, $CDCl_3$): 172.21, 165.42, 155.23, 139.12, 133.31, 131.43, 130.70, 129.62, 128.73, 128.51, 127.82, 126.73, 79.12, 78.73, 78.32, 73.41, 66.72, 65.31, 55.92, 30.73, 28.30.

*(1R,2R,4S,5S)- **(8b)***

White crystalline (14 mg, 15%). Mp 156–157°C; R_f 0.5 (Et_2O/ petroleum ether = 4:1). $[\alpha]^{25}_D$ = -25.8 (c = 1.0, $CHCl_3$); [Found $C_{28}H_{31}NO_8$: C 65.87 H 5.98 N 2.70, requires C 66.00 H 6.13 N 2.75%]. δ_H (400 MHz, $CDCl_3$): 8.0 (2H, Bz, d, *J* 7.3), 7.59 (1H, Bz, t, *J* 7.6), 7.46 (2H, Bz, t, *J* 7.6), 7.37–7.39 (4H, Ph, m), 7.30–7.33 (1H, Ph, m), 6.44 (1H, CH=CH, dd, *J* 6.1, 1.3), 6.40 (1H, CH=CH, d, *J* 6.1), 5.36 (1H, d, *J* 10.4), 5.19 (2H, CHOR, ddd, *J* 10.1, 6.1, 4.3), 5.07 (1H, CHOR, ddd, *J* 10.2, 6.2, 4.3), 4.92 (1H, d, *J* 4.0), 4.82 (1H, d, *J* 3.5), 4.49 (1H, br s), 3.13 (1H, br s), 2.60 (1H, CH_2, dt, *J* 12.4, 6.0), 1.89 (1H, CH_2, dt, *J* 12.6, 11.2), 1.34 (9H, Boc, s); δ_C (100.6 MHz, $CDCl_3$): 172.01, 165.42, 155.03, 139.15, 133.32, 131.32, 130.62, 129.71, 128.70, 128.42, 127.82, 126.81, 78.92, 78.81, 78.53, 73.41, 67.02, 65.11, 55.83, 30.70, 28.21.

Synthesis of adamantanediols[19-20] (9a,b)



Synthesis of 1,3-di(hydroxymethyl)adamantane[21] (9a)

1. Synthesis of 1,3-dibromoadamantane[19]

Bromine (20 ml, 60 g, 0.38 mol) was added to adamantane (10.4 g, 0.076 mol) dropwise, the reaction mixture was stirred with ice-cooling (0 °C), 0.3 g of iron powder and 1-2 drops of water were added carefully. A vigorous reaction occurred, with evolution of HBr. The reaction mixture was stirred at 40-50 °C for 3 h until solidification. Methylene chloride (40-50 ml) was added to the ice-cooled mixture, the solution of sodium sulfite (50-60 g in 50–100 ml of water) was added dropwise until the reaction mixture became colorless. Methylene chloride (20-30 ml) was added, and the organic layer was separated. After an additional extraction of aqueous layer with methylene chloride (3x30 ml) the combined organic layers were washed with sodium sulfite solution and aq. K_2CO_3 and dryed with $CaCl_2$. After solvent evaporation the dry residue was recrystallized from the mixture MeOH/Et_2O (8:1) to obtain 1,3-dibromoadamantane (20.7 g, 93%) as a white powder. Mp. 105-107°C (Mp. lit[19]. 110-115°C, Mp. lit[20]. 112-113°C). δ_H (400 MHz, $CDCl_3$): 2.87-2.90 (1H, m), 2.77-2.82 (2H, m), 2.29-2.34 (6H, m), 2.23-2.28 (4H, m), 1.69-1.74 (1H, m).

1-Bromoadamantane was obtained as a by-product after recrystallization. For 1-bromoadamantane: δ_H (400 MHz, $CDCl_3$): 2.37-2.40 (6H, m), 2.12 (3H, br. s), 1.72-1.77 (6H, m).

2. Synthesis of adamantane-1,3-dicarboxylic acid[20]

The concentrated sulfuric acid (175 ml) was added to 1,3-dibromoadamantane (3 g, 0.01 mol) followed by a dropwise addition of 12.5 ml freshly distilled HCOOH simultaneously with a portionwise addition of solid $AgNO_3$ (2.7 g, 0.016 mol) for 2 h. The reaction mixture was stirred overnight, the precipitate was filtered off and the solution was added to 500 g of ice. The precipitate was collected, dissolved in saturated NaOH and filtered. The clear solution was acidified with aq. HCl until precipitate formation. Adamantane-1,3-dicarboxylic acid was obtained as a white solid (1.3 g, 58%). Mp. 276-277ºC (Mp.lit[20]. 276-278ºC).

δ_H (400 MHz, DMSO-d_6): 12.12 (2H, OH), 2.05 (2H, br s), 1.83 (2H, br s), 1.73 (8H, dd, *J* 11.7, 26.0), 1.60 (2H, br s); δ_C (100 MHz, DMSO-d_6): 178.41 (C=O), 46.91, 44.68, 38.09, 35.43, 27.80.

3. Synthesis of dimethyl adamantane-1,3-dicarboxylate[22]

To the solution of 1,3-adamantanedicarboxylic acid (500 mg, 2.23 mol) in 15 ml MeOH, 0.6 ml $SOCl_2$ was added. The reaction mixture was stirred with reflux for 24 h and evaporated. Ice water (30 ml) was added to the dry residue, and the mixture was neutralized by solid $NaHCO_3$ (pH 7). Water solution was extracted with EtOAc (3x20 ml), the combined organic

layers were dried with Na_2SO_4 and evaporated. Dimethyl adamantane-1,3-dicarboxylate (438 mg, 78%) was obtained as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 3.65 (6H, s, OCH_3), 2.12-2.18 (2H, m), 2.02 (2H, br s), 1.85 (8H, dd, *J* 12.8, 20.2), 1.67 (2H, br s); δ_C (100 MHz, $CDCl_3$): 177.52 (C=O), 52.13 (OCH_3), 42.34 (C-COOMe), 39.06, 37.55, 37.22, 25.38

4. Synthesis of 1,3-di(hydroxymethyl)adamantane[21] (9a)

To the solution of dimethyl adamantane-1,3-dicarboxylate (350 mg, 1.39 mmol) in 15 ml THF lithium alumohydride (211 mg, 5.56 mmol) was added. The reaction mixture was stirred with reflux for 8 h, 3 ml water and 1.5 ml of 15% aq. NaOH solution were added. The precipitate was filtered off and washed with THF. The filtrate was evaporated to dry; 1,3-di(hydroxymethyl)adamantane (270 mg, 98%) was obtained as a white solid. Mp. 182ºC (Mp.lit[21]. 181-182ºC). δ_H (400 MHz, $CDCl_3$/DMSO-d_6): 2.95-3.0 (4H, m, CH_2OH), 1.98 (2H, br s), 1.54 (2H, br s), 1.35 (8H, dd, *J* 11.7, 32.3), 1.13 (2H, br s); δ_C (100 MHz, DMSO-d_6): 72.18 (CH_2OH), 41.38, 39.25, 37.04, 31.13, 28.33.

Synthesis of 1,3-di(hydroxyethyl)adamantane[23,24] (9b)

1. Synthesis of dimethyl adamantane-1,3-diyldiacetate

To the solution of 1,3-adamantanediacetic acid (1.5 g, (Mp.lit[23]. 232-234ºC)) in 30 ml MeOH, 1.2 ml $SOCl_2$ was added. The reaction mixture was stirred with reflux for 24 h and evaporated. Ice water (30 ml) was added to the dry residue, the mixture was neutralized by solid $NaHCO_3$ (pH 7). Water solution was extracted with EtOAc (3x20 ml), the combined organic layers were dried with Na_2SO_4 and evaporated. Dimethyl adamantane-1,3-dicarboxylate (1.55, 93%) was obtained as a yellow oil[23]. δ_H (400 MHz, $CDCl_3$): 3.63 (6H, CH_3, s), 2.09 (4H, C$\underline{H}_2$-C=O, s), 2.04 (2H, C$\underline{H}$, s), 1.45-1.60 (10H, ad, m), 1.55 (2H, C$\underline{H}$, s); δ_C (100 MHz, $CDCl_3$): 170.23 (C=O), 51.14 (OCH_3), 46.78, 42.36, 40.56 (C$\underline{H}_2$-COOMe), 35.81, 34.30, 24.83.

2. Synthesis of 1,3-di(hydroxyethyl)adamantane

To the solution of dimethyl adamantane-1,3-diyldiacetate (1.55 g) in 45 ml THF lithium alumohydride was added. The reaction mixture was stirred with reflux for 8 h, 10 ml of water and 4.5 ml of 15% aq. NaOH solution were added. The precipitate was filtered off and washed with THF. The filtrate was evaporated to dry and 1,3-di(hydroxyethyl)adamantane (1.21 g, 98%) was obtained as white solid. Mp. 118-119ºC (Mp.lit[24]. 117-118ºC). δ_H (400 MHz, DMSO-d_6): 3.40-3.46 (4H, C$\underline{H}_2$-OH, m), 1.92 (2H, CH_2-C$\underline{H}$-CH_2, s), 1.52 (2H, C-C$\underline{H}_2$-CH_2, s), 1.38 (8H, dd, *J* 11.0, 27.7), 1.19-1.25 (6H, m). d_H (400 MHz, $CDCl_3$): 3.71 (4H, C$\underline{H}_2$-OH, t, *J* 7.5), 2.01 (2H, CH_2-C$\underline{H}$-CH_2, s), 1.60 (2H, C-C$\underline{H}_2$-CH_2, s), 1.38-1.54 (12H, ad., m), 1.34 (2H, br s, OH), 1.30 (2H, s); δ_C (100 MHz, DMSO-d_6): 56.73 (CH_2-OH), 48.15 (C-C$\underline{H}_2$-CH_2), 47.08, 42.21, 36.60, 32.47, 28.89.

Synthesis of 1,4-dihydroxyadamantanes (10a,b)

To the ice-cooled solution of 150 mg (0.9mmol) of kemantane (**11**) in mixture of 8 ml MeOH and 4 ml of Et_2O the 68 mg (1.8 mmol) of sodium borohydride was added portionwise. The cooling bath was removed and reaction mixture allowed to stir for 5 h. The organic solvent was removed followed by addition of 30 ml of water with a few drop of acetic acid. After extraction with Et_2O (3x20 ml) the combined organic layers were dried with Na_2SO_4. The mixture of *cis*-

and *trans*-1,4-adamantandiols was obtained as white crystalline with 88% yield. The separated isomers were obtained after column chromatography (eluent Et_2O/MeOH 4:1).

Cis-1,4-adamantanediol (**10a**)

White crystalline, 20 mg (15%); R_f 0.80 (eluent Et_2O/MeOH 4:1); Mp. 327-328 °C; δ_H (400 MHz, $CDCl_3$): 3.63 (1H, CH-OH, c), 1.95 (1H, CH_2-CH-CH_2, s), 1.92-1.18 (14H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 72.17 (C-OH), 66.17 (CH-OH), 45.97, 43.99, 36.28, 30.10, 29.93

Trans-1,4-adamantanediol (**10b**)

White crystalline, 26 mg (19%); R_f 0.70 (eluent Et_2O/MeOH 4:1); Mp. 315-317 °C; δ_H (400 MHz, $CDCl_3$): 3.47 (1H, CH-OH, c), 1.94 (1H, CH_2-CH-CH_2, s), 1.91-1.22 (14H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 71.40 (C-OH), 66.28 (CH-OH), 45.75, 39.42, 37.15, 35.22, 29.48

General procedure for benzoylation of dihydroxyadamantane compounds 9a,b

Benzoyl chloride or acetic anhydride was added dropwise to the mixture of **9a,b** and pyridine (10 mL), then 4-(dimethylamino)pyridine (DMAP) (1.19 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and concentrated under reduced pressure, and then CH_2Cl_2 was added to the dry residue, and the mixture was washed with aq. $NaHCO_3$ solution. The organic layer was separated, concentrated, and purified by silica gel column chromatography from dibenzoylated byproducts. The following compounds were obtained using this procedure:

2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl 3,4-dimethoxybenzoate (12a)
From 200 mg (0.89 mmol) of diol **9b** and 230 mg (1.16 mmol) of 3,4-dimethoxybenzoyl chloride the compound **10a** was obtained as yellow oil (234 mg, 68%). R_f 0.30 (CH_2Cl_2:EtOAc = 2:1). [Found $C_{23}H_{32}O_5$: C 70.88, H 8.51, requires C 71.11, H 8.30%]. δ_H (400 MHz, $CDCl_3$): 7.67 (1H, dd, *J* 1.8, 6.6), 7.54 (1H, d, *J* 1.8), 6.89 (1H, d, *J* 8.6), 4.36 (2H, CH_2-CH_2-OBz, t, *J* 7.5), 3.93 (3H, CH_3, s), 3.92 (3H, CH_3, s), 3.72 (2H, CH_2-CH_2-OH, t, *J* 7.2), 2.02 (2H, CH, s), 1.28-1.59 (17H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 166.49 (C=O), 152.87, 148.57, 123.46, 123.02, 111.95, 110.23, 61.25 (CH_2-OBz), 58.68 (CH_2-OH), 55.98 (CH_3), 55.97 (CH_3), 49.29, 47.95, 46.80, 42.25, 42.05, 36.35, 32.55, 32.46, 28.90 $\nu_{max(neat),}$ cm^{-1}: 3417, 2937, 1709, 1269.

(3-(Hydroxymethyl)-1-adamantyl)methyl benzoate (12b)
From 200 mg (1.02 mmol) of diol **9a** and 0.14 ml (1.22 mmol) BzCl compound **12b** was obtained as yellow oil (186 mg, 62%). R_f 0.50 (CH_2Cl_2/EtOAc = 2:1). [Found $C_{19}H_{24}O_3$: C 75.89, H 8.10, requires C 75.97, H 8.05%]. δ_H (400 MHz, $CDCl_3$): 8.07 (2H, Ph, d, *J* 7.2), 7.57 (1H, Ph, t, *J* 7.4), 7.45 (2H, Ph, t, *J* 7.7), 3.98 (2H, CH_2-OBz, s), 3.27 (2H, CH_2-OH, s), 2.14 (2H, CH, s), 1.68-1.25 (13H, (OH, ad.), m.); δ_C (100.6 MHz, $CDCl_3$): 165.37 (C=O), 132.86, 129.56, 129.25, 128.37, 74.09 (CH_2-OBz), 73.33 (CH_2-OH), 40.91, 39.06, 38.51, 36.50, 35.01, 34.05, 28.05. ν_{max} (KBr), cm^{-1}: 3312, 2922, 1714, 1264, 1175.

2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl benzoate (12c).

From 200 mg (0.89 mmol) of diol **9b** and 0.13 ml (1.07 mmol) of BzCl compound **12c** was obtained as yellow oil (207 mg, 71%). Dibenzoate **13c** was obtained as byproduct with yield 15%.

*2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl benzoate (**12c**).*

R_f 0.5 (CH_2Cl_2/Et_2O = 2:1). [Found $C_{21}H_{28}O_3$: C 76.56 H 8.63, requires C 76.56, H 8.63%]. δ_H (400 MHz, $CDCl_3$): 8.04 (2H, Ph, dd, *J* 7.1, 1.4), 7.54 (1H, Ph, t, *J* 7.4), 7.42 (2H, Ph, t, *J* 7.7), 4.37 (2H, CH_2-OBz, t, *J* 7.5), 3.69 (2H, CH_2-OH, t, *J* 7.2), 2.02 (2H, CH, s), 1.60-1.23 (17H, (OH, ad), m). δ_C (100.6 MHz, $CDCl_3$): 166.75 (C=O), 132.83, 130.47, 129.51, 128.34, 61.42 (CH_2-OBz), 58.60 (CH_2-OH), 47.92 (CH_2-CH_2-OH), 46.75 (CH_2-CH_2-OBz), 42.20, 42.05, 41.93, 41.82, 36.35, 32.53, 28.89; ν_{max} (neat), cm^{-1}: 3315, 2919, 1715, 1267, 1171.

*2-(1,3-adamantanediyl)diethyl dibenzoate (**13c**)*

δ_H (400 MHz, $CDCl_3$): 8.05 (4H, Ph, dd, *J* 7.1, 1.4), 7.54 (2H, Ph, t, *J* 7.4), 7.44 (4H, Ph, t, *J* 7.7), 4.39 (2H, CH_2-OBz, t, *J* 7.5), 2.07 (2H, CH, s), 1.4-1.65 (17H, CH, ad, m); δ_C (100.6 MHz, $CDCl_3$): 166.69 (C=O), 132.81, 129.52, 128.35, 65.36 (CH_2-OBz), 61.35, 47.86 (CH_2-CH_2-OBz), 42.20, 41.36, 36.28, 32.58, 29.71, 28.87, 15.29.

2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl 4-hydroxybenzoate (12d)

To the solution of 170 mg (0.76 mmol) of diol **9b** and 126 mg (0.91 mmol) of 4-hydroxybenzoic acid in methylene chloride 313 mg (1.52 mmol) of DCC and 93 mg (0.76 mmol) DMAP were added and reaction mixture was stirred for 24 h. Compound **12d** was obtained as transparent oil (51 mg, 20%).

R_f 0.45 (CH_2Cl_2:EtOAc = 1:1). [Found $C_{21}H_{28}O_4$: C 73.05, H 8.34, requires C 73.23, H 8.19 %]. δ_H (400 MHz, $CDCl_3$): 7.97 (2H, CH-C(COOAd)), d, *J* 8.8), 6.89 (2H, CH-C(OH), d, *J* 8.8), 5.75 (1H, OH, s), 4.37 (2H, CH_2-OPh, t, *J* 7.0), 3.76 (2H, CH_2-OH, t, *J* 5.9), 2.06 (2H, CH, s), 1.63-1.23 (17H, (OH, ad), m) δ_C (100.6 MHz, $CDCl_3$): 167.65 (O=C-Ph), 162.53 (C-OH), 131.65, 119.78, 115.54, 61.34, 58.97 (CH_2-OH), 46.98, 46.74, 42.12, 42.05, 37.33, 34.45, 34.16, 26.87.

2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl 4-(acetoxy)benzoate (12e).

From 200 mg (0.89 mmol) of diol **9b** and 265 mg (1.34 mmol) of 4-acetoxybenzoyl chloride without DMAP addition the compound **12e** was obtained as yellow oil (192 mg, 56%). 2-(1,3-adamantanediyl)diethyl diacetate **13a** and 2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl acetate **12f** were obtained as byproducts with yields 12 and 20%, respectively. Spectral data for compound 2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl acetate **12f** see below.

*2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl 4-(acetoxy)benzoate (**12e**)* R_f 0.40 (CH_2Cl_2:EtOAc = 2:1). [Found $C_{23}H_{30}O_5$: C 71.25, H 7.88, requires C 71.48, H 7.82%]. δ_H (400 MHz, $CDCl_3$): 8.08 (2H, Ar-C(COOAd), d, *J* 8.6); 7.18 (2H, Ar-C(OAc), d, *J* 8.6); 4.38 (2H, CH_2-OBz, t, *J* 7.0); 3.71 (2H, CH-OH, t, *J* 6.6); 2.32 (3H, CH_3, s); 2.04 (2H, CH, s); 1.60-1.19 (17H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 169.66 (O=C-Ph), 168.93 (CH_3-C=O), 154.38, 131.60, 128.23, 121.54, 61.56, 58.62 (CH_2-OH), 47.88, 46.64, 42.16, 42.03, 36.33, 32.65, 32.55, 28.87, 21.15 (CH_3). ν_{max} (neat), cm^{-1}: 3315, 2923, 1725, 1274.

2-(1,3-adamantanediyl)diethyl diacetate (***13b***) δ_H (400 MHz, $CDCl_3$): 4.2 (4H, CH_2-OH, t, *J* 6.6), 2.19 (3H, CH, s); 2.08 (6H, CH_3, br.s); 1.57(2H, CH, br.s, ad,); 1.42-1.5 (10H, ad, m), 1.2-1.3 (2H, ad, m).

2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl acetate (12f)
From 200 mg (0.89 mmol) of diol **9b** and 0.1 ml (0.98 mmol) of Ac_2O the compound **12f** was obtained as yellow oil (210 mg, 89%).

R_f 0.35 (CH_2Cl_2:EtOAc = 2:1). [Found $C_{16}H_{26}O_3$: C 71.93, H 9.97, requires C 71.48, H 7.82%]. δ_H (400 MHz, $CDCl_3$): 4.12 (2H, CH_2-OAc, t, *J* 7.5), 3.71 (2H, CH_2-OH, t, *J* 7.2), 2.03 (3H, CH_3,s), 2.01 (2H, CH, s), 1.58-1.20 (17H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 171.27 (C=O), 60.90 (CH_2-OAc), 58.65 (CH_2-OH), 47.81, 46.82, 42.04, 41.84, 41.76, 36.34, 32.51, 32.42, 28.86, 21.11 (CH_3); ν_{max} (neat), cm^{-1}: 3423, 2900, 2846, 1741, 1240.

Reduction of ketobenzoate 14

Ketone **14**[36] (300 mg, 1.12 mmol) was added to a mixture of MeOH (8 mL) and Et_2O (4 mL). The solution was cooled on ice to 0°C, then sodium borohydride was added portionwise (vigorous bubbling was observed). The reaction mixture was warmed to room temperature, stirred for 8 h, and concentrated under reduced pressure. Water (30 mL) and 1-2 drops of acetic acid were added. The mixture was extracted with CH_2Cl_2 (3x20 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to obtain 280 mg (93%) of a yellow oil. The mixture of isomers was separated by silica gel column chromatography (CH_2Cl_2:EtOAc = 2:1).

*cis-4-Hydroxy-1-adamantyl benzoate (**12g**)*
Monoester **12g** was obtained as a white crystalline compound, R_f 0.30. Yield 185 mg (61%). Mp. 65-66 °C. δ_H (400 MHz, $CDCl_3$): 8.00 (2H, Ph, d, *J* 7.2), 7.55 (1H, Ph, t, *J* 7.4), 7.44 (2H, Ph, t, *J* 7.7), 3.81 (1H, C<u>H</u>-OH, s), 2.55 (1H, C<u>H</u>, d, *J* 8.4), 1.52-2.31 (13H, OH, ad, m); δ_C (100.6 MHz, $CDCl_3$): 165.50 (C=O), 132.54, 131.81, 129.47, 128.20, 79.82 (CH_2-<u>C</u>(OBz)), 72.56 (<u>C</u>H-OH), 41.42, 39.66, 36.24, 30.09, 29.75

*trans-4-Hydroxy-1-adamantyl benzoate (**12h**)*
Monoester **12h** was obtained as a white crystalline compound, *Rf* 0.35. Yield 95 mg (32%). Mp. 58-60°C. δ_H (400 MHz, $CDCl_3$): 8.00 (2H, Ph, d, *J* 7.2), 7.55 (1H, Ph, t, *J* 7.4), 7.44 (2H, Ph, t, *J* 7.7), 4.02 (1H, CH-OH, s), 2.30 (1H, CH, d, *J* 7.5), 2.13-1.51 (13H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 165.52 (C=O), 132.54, 131.81, 129.43, 128.20, 79.82 (CH_2-C(OBz)), 73.12 (CH-OH), 41.42, 39.69, 36.38, 30.07, 29.75

General procedure for esterification of adamantane derivatives 9, 12

To the solution of 0.367 mmol of compound ***9 or 12*** and 0.55 mmol of methylurocanic acid in 10 ml CH_2Cl_2 151 mg (0.735 mmol) of DCC and 45 mg (0.367 mmol) of DMAP were added. After stirring for 48 h at room temperature the reaction mixture was evaporated to dry, 15 ml of EtOAc were added and left overnight at -18 °C. The precipitate was filtered, washed with cold EtOAc and the filtered solution was evaporated. The product was purified by column chromatography (eluent acetone:Et_2O 1:1). The following compounds were obtained according to this procedure:

(3-(((2E)-3-(1-Methyl-1H-imidazol-4-yl)prop-2-enoyl)oxymethyl)-1-adamantyl)methyl benzoate (15a)

From 120 mg (0.3 mmol) **12b** compound **15a** was obtained as a white solid (45 mg, 88%). Mp.152-153ºC. R_f 0.35 (Et_2O/MeOH = 5:1). [Found $C_{26}H_{30}N_2O_4$: C 71.87, H 6.96, N 6.45, requires C 71.53, H 7.20, N 6.30%]. δ_H (400 MHz, $CDCl_3$): 8.07 (2H, Ph, d, *J* 7.2), 7.56 (1H, Ph, t, *J* 7.4), 7.52 (1H, CH=CH, d, *J* 15.7), 7.47 (2H, Ph, t, *J* 7.7), 7.44 (1H, s), 7.07 (1H, s), 6.61 (1H, CH=CH, d, *J* 15.7), 3.97 (2H, C-CH_2-OUr, c), 3.86 (2H, C-CH_2-OBz, s), 3.71 (3H, CH_3, s), 2.14 (2H, CH, s), 1.27-1.68 (12H, ad, m); δ_C (100.6 MHz, $CDCl_3$): 167.76 (O=C-Ph), 166.64 (O=C-CH), 139.11, 135.98, 132.81, 130.50, 129.55, 129.53, 128.38, 122.40, 116.11, 74.02 (C-CH_2-OUr), 73.24 (C-CH_2-OBz), 41.20, 38.91, 38.78, 36.31, 33.97 (CH_2-C-CH_2OUr), 33.88 (CH_2-C-CH_2OBz), 33.57 (CH_3), 27.96; ν_{max} (KBr), cm^{-1}: 2908, 1714, 1693, 1633, 1279, 1169.

2-(3-(2-((2E)-3-(1-Methyl-1H-imidazol-4-yl)prop-2-enoyloxy)ethyl)-1-adamantyl)ethyl benzoate (15b)

From 100 mg (0.37 mmol) **12c** compound **15b** was obtained as a white solid (83 mg, 60%). Mp. 137-138ºC. R_f 0.35 (Et_2O/MeOH = 5:1). [Found $C_{28}H_{34}N_2O_4$: 72.42, H 7.40, N 6.20, requires C 72.70, H 7.41, N 6.06%]. δ_H (400 MHz, $CDCl_3$): 8.05 (2H, Ph, d, *J* 7.2), 7.55 (1H, CH=CH, d, *J* 15.7), 7.53 (1H, Ph, t, *J* 7.4), 7.46 (2H, Ph, t, *J* 7.7), 7.44 (1H, s), 7.08 (1H, s), 6.55 (1H, CH=CH, d, *J* 15.7), 4.38 (2H, CH_2-OBz, t, *J* 7.2), 4.24 (2H, CH_2-OUr, t, *J* 7.2), 3.69 (3H, CH_3, s), 2.05 (2H, CH, s), 1.26-1.62 (16H, ad, m); δ_C (100.6 MHz, $CDCl_3$): 167.67 (O=C-Ph), 166.68 (O=C-CH), 147.12, 139.14, 138.43, 135.77, 132.78, 129.50, 128.32, 122.44, 116.29, 61.37 (CH_2-CH_2-OBz), 60.59 (CH_2-CH_2-OUr), 47.83, 42.20, 41.85, 41.82, 40.86, 36.29, 33.57 (CH_2-C-$(CH_2)_2$OUr), 32.55 (CH_2-C-$(CH_2)_2$OBz), 29.68 (CH_3), 28.87; ν_{max} (KBr), cm^{-1}: 2902, 1722, 1699, 1630, 1275, 1174.

2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl (2E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoate(15c)

From 110 mg (0.49 mmol) **9b** compound **15c** was obtained as a white solid (92 mg, 52%). Mp. 185-186ºC, R_f 0.35 (Et_2O/MeOH = 4:1). [Found $C_{21}H_{30}N_2O_3$: 70.09, H 8.56, N 7.71, requires 70.36, H 8.44, N 7.81%]. δ_H (400 MHz, $CDCl_3$): 7.54 (1H, CH=CH, d, *J* 15.7), 7.45 (1H, s), 7.09 (1H, s), 6.51 (1H, CH=CH, d, *J* 15.7), 4.24 (2H, CH_2-OUr, t, *J* 7.1), 3.71 (2H, CH_2-OH, t, *J* 7.2), 3.70 (3H, CH_3, s), 2.01 (2H, CH_2-CH-CH_2, s), 1.25-1.72 (17H, (OH, ad), m); δ_C (100.6 MHz, $CDCl_3$): 167.63 (O=C-Ph), 148.25, 139.07, 135.62, 122.32, 116.59, 60.72 (CH_2-CH_2-OUr), 58.50 (CH_2-CH_2-OH), 47.76, 46.80, 42.13, 41.95, 37.78, 36.42, 35.65, 30.38 (CH_3), 28.91; ν_{max} (KBr), cm^{-1}: 3350, 2904, 1705, 1639, 1167.

2-(3-(2-((2E)-3-(1-Methyl-1H-imidazol-4-yl)prop-2-enoyloxy)ethyl)-1-adamantyl)ethyl 4-acetoxybenzoate (15d)

From 95 mg (0.25 mmol) **12e** compound **15d** was obtained as a white solid (70 mg, 55%). Mp. 184-185ºC, R_f 0.35 (Et_2O/MeOH = 5:1). [Found $C_{30}H_{36}N_2O_6$: C 69.02, H 7.12, N 5.24, requires C 69.21, H 6.97, N 5.38%]. δ_H (400 MHz, $CDCl_3$): 8.07 (2H, Ph, d, *J* 8.6), 7.73 (1H, CH=CH, d, *J* 15.7), 7.44 (1H, s), 7.23 (2H, CH-C(OAc), d, *J* 8.6), 7.05 (1H, s), 6.73 (1H, CH=CH, d, *J* 15.7), 4.38 (2H, CH_2-OBz, t, *J* 7.1), 4.04 (2H, CH2-OUr, t, *J* 7.2), 3.69 (3H, N-CH_3,s), 2.16 (3H, CH_3, s), 1.95 (2H, CH, s), 1.18-1.83 (16H, ad, m); δ_C (100.6 MHz, $CDCl_3$): 168.67 (O=C-Ph), 168.61 (O=C-CH), 166.00, 154.23, 148.44, 139.16, 135.40, 131.42, 130.99, 123.52, 122.80, 121.70, 117.22, 58.49 (CH_2-CH_2-OBz), 57.10 (CH_2-CH_2-OUr), 46.75, 42.17 (CH_2-CH_2-OBz),

42.06, 42.04, 41.94 (CH_2-CH_2-OUr), 36.35, 33.57, 32.77, 30.89 (N-CH_3), 26.36, 24.69 (CH_3); ; ν_{max} (KBr), cm^{-1}: 2918, 1737, 1702, 1638, 1275, 1162.

2-(3-(2-((2E)-3-(1-Methyl-1H-imidazol-4-yl)prop-2-enoyloxy)ethyl)-1-adamantyl)ethyl 3,4-dimethoxybenzoate (15e)

From 100 mg (0.26 mmol) **12a** compound **15e** was obtained as a white solid (67 mg, 50%). Mp. 157-158ºC, R_f 0.35 (Et_2O/MeOH = 5:1). [Found $C_{30}H_{38}N_2O_6$: C 68.53, H 7.70, N 5.64, requires C 68.94, H 7.33, N 5.36%]. δ_H (400 MHz, $CDCl_3$): 7.69 (1H, Ph, dd, *J* 1.8, 6.6), 7.56 (1H, Ph, d, *J* 1.8), 7.55 (1H, CH=CH, d, *J* 15.7), 7.46 (1H, s), 7.08 (1H, s), 6.92 (1H, Ph, d, *J* 8.6), 6.56 (1H, CH=CH, d, *J* 15.7), 4.37 (2H, CH_2-OBz, t, *J* 13.8), 4.25 (2H, CH_2-OUr, t, *J* 13.8), 3.95 (3H, CH_3, s), 3.94 (3H, CH_3, s), 3.70 (3H, CH_3, s), 2.04 (2H, CH_2-CH-CH_2, s), 1.20-1.66 (14H, ad, m), 0.89 (2H, ad, t, *J* 14.0); δ_C (100.6 MHz, $CDCl_3$): 172.35 (O=C-Ph), 172.13 (O=C-CH), 153.91, 148.55, 145.23, 139.13, 135.95, 123.47, 122.45, 122.44, 116.15, 111.91, 110.25, 61.25 (CH_2-O-COPh), 60.60 (CH_2-OUr), 55.98 (CH_3), 55.97 (CH_3), 47.87, 42.27, 42.19, 41.89, 41.84, 36.30, 33.57, 32.59, 29.70 (N-CH_3), 28.88

2-(3-(2-(acetoxy)ethyl)-1-adamantyl)ethyl ((E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoate (15f)

From 100 mg (0.38 mmol) **12f** compound **15f** was obtained as a white solid (80 mg, 53%). Mp. 194-195°C. R_f 0.40 (Et_2O/MeOH = 5:1). [Found $C_{23}H_{32}N_2O_4$: C 68.58, H 8.24, N 7.16, requires C 68.97, H 8.05, N 6.99%]. δ_H (400 MHz, $CDCl_3$): 7.54 (1H, CH=CH, d, *J* 15.7), 7.44 (1H, s), 7.08 (1H, s), 6.54 (1H, CH=CH, d, *J* 15.7), 4.23 (2H, CH_2-OAc, t, *J* 7.1), 4.12 (2H, CH_2-OUr, t, *J* 7.2), 3.70 (3H, N-CH_3,s), 2.03 (3H, CH_3, s), 1.94 (2H, CH, s), 1.20-1.58 (16H, ad, m); δ_C (100.6 MHz, $CDCl_3$): 171.27 (O=C-CH_3), 167.76 (O=C-CH), 139.13, 135.95, 130.63, 122.49, 116.10, 60.89 (CH_2-CH_2-OUr), 60.59 (CH_2-CH_2-OAc), 47.68, 42.13 (CH_2-CH_2-OUr), 42.00 (CH_2-CH_2-OAc), 41.77, 41.75, 36.26, 33.58 (N-CH_3), 32.50, 32.43, 28.82, 21.16 (CH_3); ν_{max} (KBr), cm^{-1}: 2902, 1736, 1705, 1639, 1273, 1163.

Cis-4-((E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enyloxy)-1-adamantyl benzoate (15g)

From 100 mg (0.37 mmol) **12g** compound **15g** was obtained as a white solid (87 mg, 58%). Mp. 163-164ºC. [Found $C_{24}H_{26}N_2O_4$: C 70.67, H 6.63, N 7.05, requires 70.92, H 6.45, N 6.89%].δ_H (400 MHz, $CDCl_3$): 8.01 (2H, Ph, d, *J* 7.2), 7.61 (1H, CH=CH, d, *J* 15.7), 7.55 (1H, Ph, t, *J* 7.4), 7.44 (1H, s), 7.42 (2H, Ph, t, *J* 7.7), 7.10 (1H, s), 6.62 (1H, CH=CH, d, *J* 15.7), 4.96 (1H, CH-OUr, s), 3.70 (3H, CH_3, s), 2.48 (1H, CH, s), 1.75-2.38 (12H, ad, m); δ_C (100.6 MHz, $CDCl_3$): 166.77 (O=C-Ph), 161.88(O=C-CH), 147.77, 138.61, 136.55, 136.10, 132.46, 129.45, 128.18, 122.39, 116.52, 79.81 (CH-OUr), 74.39 (CH_2-C(OBz)), 40.74, 36.03, 34.89, 31.02, 30.55 (CH_3), 29.59; ν_{max} (KBr), cm^{-1}: 2920, 1716, 1693, 1635, 1277, 1174.

Trans-4-((E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enyloxy)-1-adamantyl benzoate (15h)

From 100 mg (0.37 mmol) of **12h** the compound **15h** was obtained as white solid (100 mg, 67%). Mp. 163-164ºC. [Found $C_{24}H_{26}N_2O_4$: C 70.17, H 6.85, N 7.22, requires C 70.92, H 6.45, N 6.89%]. δ_H (400 MHz, $CDCl_3$): 8.00 (2H, Ph, d, *J* 7.2), 7.59 (1H, CH=CH, d, *J* 15.7), 7.55 (1H, Ph, t, *J* 7.4), 7.47 (1H, s), 7.44 (2H, Ph, t, *J* 7.7), 7.10 (1H, s), 6.63 (1H, CH=CH, d, *J* 15.7), 5.10 (1H, CH-OUr, s), 3.72 (3H, CH_3, s), 2.33 (1H, CH, s), 1.57-2.18 (12H, ad, m); δ_C (100.6 MHz, $CDCl_3$): 168.18 (O=C-Ph), 162.68 (O=C-CH), 147.74, 139.13, 136.55, 135.94, 132.52,

129.45, 128.19, 122.36, 116.5, 81.09 (CH-OUr), 74.91 (CH_2-C(OBz)), 41.08, 39.74, 33.84, 30.92, 30.55 (CH_3), 29.82; ν_{max} (KBr), cm^{-1}: 2920, 1716, 1693, 1635, 1277, 1174.

3. Cytotoxicity assay

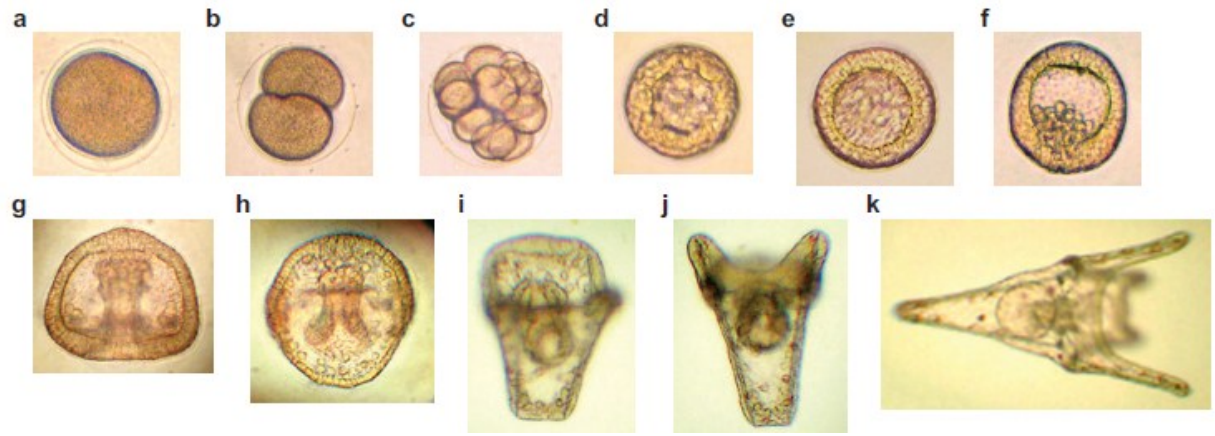
Assays were performed using the breast (MCF7), ovarian (SKOV), and colon (HCT116) carcinoma cell lines obtained from the American Type Culture Collection (Manassas, VA). Cells were cultured in modified Dulbecco's medium with the addition of 5% fetal calf serum, 2 mM *L*-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37°C, 5% CO_2. Cells were plated in 96-well plates (Costar; 10^4 cells in 190 μL of culture medium). Newly synthesized compounds and the reference drug paclitaxel were dissolved in 10% aqueous DMSO as 7 mM stock solutions followed by serial dilutions in the culture medium immediately before experiments to reach final concentrations 0.1-50 μM; DMSO was used as a vehicle control. Each concentration was tested in triplicate. Cells were incubated for 72 h at 37 °C, 5% CO_2 followed by the assessment of cell viability in an MTT test[13]. Optical densities in drug treated wells were averaged, and the percentage of viable (that is, MTT converting) cells at a given drug concentration was calculated. The optical density in the wells incubated with the vehicle was taken as 100%.

5. Sea Urchin Embryo Assay[25,26]

Adult sea urchins, *Paracentrotus lividus* L. (Echinidae), were collected from the Mediterranean Sea on the Cyprus coast and kept in an aerated seawater tank. Gametes were obtained by intracoelomic injection of 0.5 M KCl. Eggs were washed with filtered seawater and fertilized by adding drops of diluted sperm. Embryos were cultured at room temperature (22.5–24.5 °C) under gentle agitation with a motor-driven plastic paddle (60 rpm) in filtered seawater. The embryos were observed with a Biolam light microscope (LOMO, St. Petersburg, Russia). For treatment with the test compounds, 5 mL aliquots of embryo suspension were transferred to six-well plates and incubated as a monolayer at a concentration up to 2000 embryos/mL. Stock solutions of urocanic acid derivatives (I-III, see Supp. Inform.), were prepared in 95% EtOH at 200 mM concentration. Stock solutions of compounds **5a,b** and **8a** were prepared in DMSO at 10 mM concentration followed by a 10-fold dilution with 96% EtOH. This procedure enhanced the solubility of the test compounds in the salt-containing medium (seawater), as evidenced by microscopic examination of the samples. The maximal tolerated concentrations of DMSO and EtOH in the in vivo assay were determined to be 0.2% and 0.5%, respectively. Higher concentrations of either DMSO (>0.5%) or EtOH (≥1%) caused nonspecific alteration and retardation of the sea urchin embryo development independent of the treatment stage. Taxol (paclitaxel from *Taxus brevifoila*, Sigma-Aldrich) served as a reference compound. The antiproliferative activity was assessed by exposing fertilized eggs (8–15 min after fertilization, 45–55 min before the first mitotic cycle completion) to 2-fold decreasing concentrations of the compound. Cleavage alteration and arrest were clearly detected at 2.5 h and 5.5 h after fertilization, when control embryos reached 8-cell and early blastula stages, respectively. The effects were estimated quantitatively as an effective threshold concentration, resulting in cleavage alteration and embryo death before hatching or full mitotic arrest. At these concentrations all tested tubulin/microtubule modulators caused 100% cleavage alteration and embryo death before hatching, whereas at 2-fold lower concentrations the compounds failed to produce any effect. For microtubule-destabilizing activity, the compounds were tested on free-swimming blastulae just after hatching (8–10 h after fertilization), which originated from the

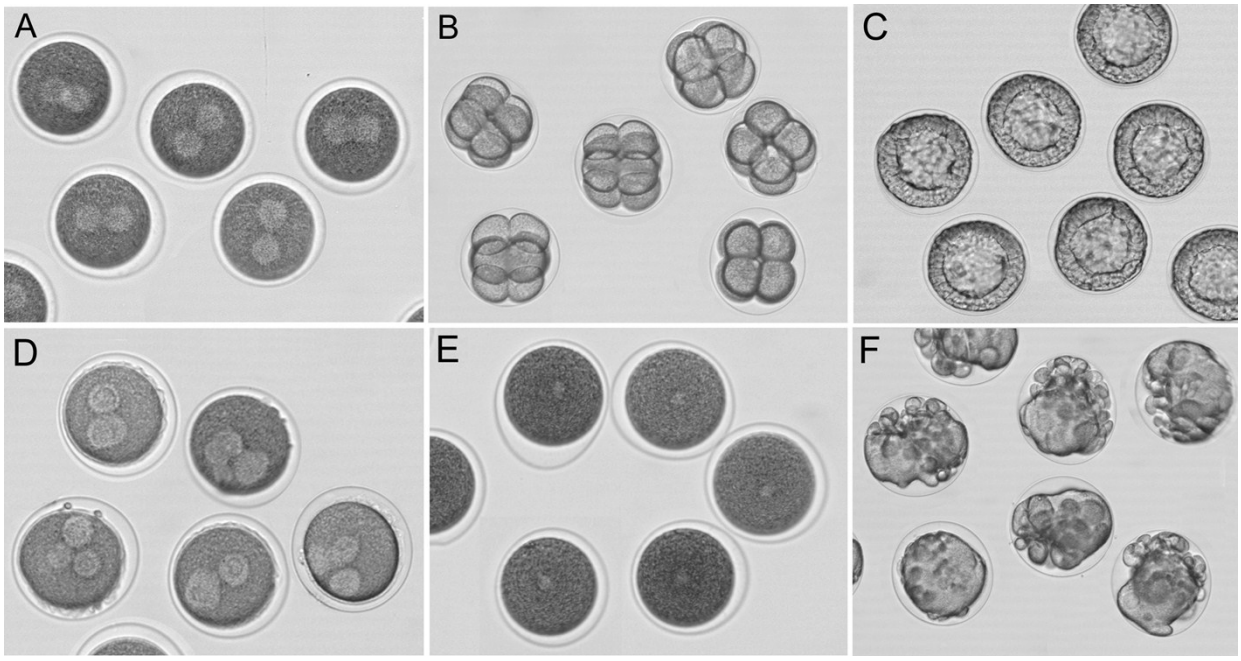
same embryo culture. Embryo spinning was observed after 15 min to 20 h of treatment, depending on the structure and concentration of the compound. Both spinning and lack of forward movement were interpreted to be the result of the microtubule-destabilizing activity of a molecule. Video illustrations are available at http://www.chemblock.com. Sea urchin embryo assay data are available at http://www.zelinsky.ru. Experiments with the sea urchin embryos fulfill the requirements of biological ethics. The artificial spawning does not cause animal death, embryos develop outside the female organism, and both post spawned adult sea urchins and the excess of intact embryos are returned to the sea, their natural habitat.

Figure 1. Normal development of the sea urchin embryo (Paracentrotus lividus) at 20 °C



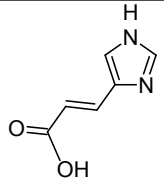
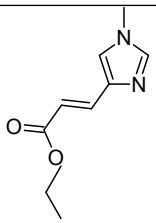
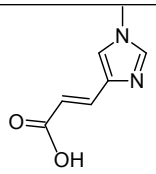
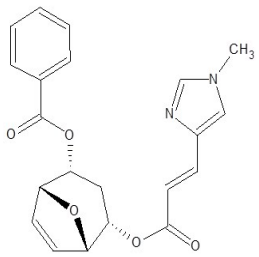
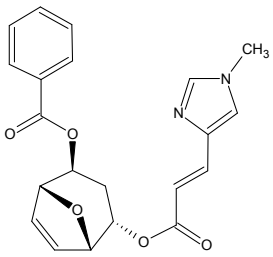
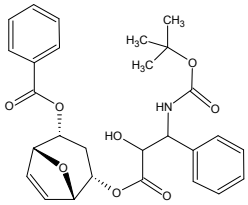
Time after fertilization is shown in parentheses. a) Fertilized egg. b) 2-cell stage (1 h 20 min). c) 16-cell stage (3 h). d) Early blastula (6 h). e) Hatched midblastula (10 h). f) Late mesenchyme blastula (13 h). g) Late gastrula (17 h). h) Prism (22 h). i) Early pluteus (26 h). j) Early pluteus (30 h). k) Four-arm midpluteus (40 h). Beginning of the active feeding. (published in M. N. Semenova, D. V. Tsyganov, A. P. Yakubov, A. S. Kiselyov, V. V. Semenov A Synthetic Derivative of Plant Allylpolyalkoxybenzenes Induces Selective Loss of Motile Cilia in Sea Urchin Embryos, *ACS CHEMICAL BIOLOGY*, VOL.3 NO.2, pp 95-100, 2008)

Figure 2. Typical effects of tubulin/microtubule targeting compounds on the sea urchin eggs and embryos.



(A) Intact egg with normal bipolar mitotic spindle (light spots), the first cleavage anaphase. (B) Eight-cell embryo. (C) Early blastula. (D) Effect of the microtubule stabilizer paclitaxel (5 μM). Arrested eggs with aberrant multipolar mitotic apparatus. (E) Eggs devoid of mitotic apparatus in the presence of the microtubule destabilizer combretastatin A-4 at 5 nM. (F) Tuberculate arrested eggs caused by combretastatin A-4 at 20 nM. Compounds were added to zygotes at 8–15 min postfertilization. Samples were incubated at 21 °C. Eggs/embryos were observed at 1 h (A), 2.5 h (B, D, E), and 6 h (C, F) postfertilization. The average egg/embryo diameter is 115 μm. Photographs A, B, D, E were from I. Yu. Strobykina, M. G. Belenok, M. N. Semenova, V. V. Semenov, V. M. Babaev, I. Kh. Rizvanov, V. F. Mironov, V. E. Kataev, Triphenylphosphonium cations of diterpenoid isosteviol: Synthesis and antimitotic activity in the sea urchin embryo model. J. Nat. Prod., 2015, v. 78, pp. 1300–1308. DOI: 10.1021/acs.jnatprod.5b00124.

Effects of compounds I-III, 5a,b and 8a on the sea urchin embryos.[a]

Compd ID	Compound structure	Effective concentrations, μM				
		Fertilized egg treatment			Hatched blastulae treatment	
		Cleavage alteration	Cleavage arrest	Blastula malformation	Developmental alteration	Toxicity, embryo death (duration of exposure)
I		800	>800	800	200	800 (18 h)
II		4	10	2	1	5.2 (12 h)
III		40	200	20	20	40 (18 h)
5a		0.5	2 (TE)[b]	0.5	2[c]	>5 (24 h)
5b		>4	>4	>4	>4	>4 (24 h)
8a		>4	>4	>4	>4	>4 (24 h)
Taxol		2	5	0.5	NA[d]	2 (8–10 h)

[a] The sea urchin embryo assay was conducted as described (M.N. Semenova, A.S. Kiselyov, V.V. Semenov, BioTechniques 40 (2006) 765–774. https://doi.org/10.2144/000112193). Fertilized eggs and hatched blastulae were exposed to 2-fold decreasing concentrations of compounds. Duplicate measurements showed no differences in effective threshold concentration (EC) values.

[b] TE: tuberculate eggs typical of microtubule destabilizing agents.

[c] Embryo spinning typical of microtubule destabilizing agents was not observed up to 5 μM concentration.

[d] NA: not available.

6.Thiol oxidation-based protein binding assay[27]

5,5'-dithio-bis-2-nitrobenzoic acid (DTNB), known as Ellman's reagent, reacts with protein thiols to produce 5-thio-2-nitrobenzoic acid (TNB), a yellow product with maximum absorbance at 412 nm[27]. Tested compounds as 10 mM stock solutions in DMSO were serially diluted in 0.1 M phosphate buffer (pH 8) immediately before experiments to final concentrations 0.1-100 μM; DMSO was used as a vehicle control, paclitaxel were used as a positive control. Bovine brain tubulin samples (20 μl total) were treated with tested compound followed by the addition of DTNB (300 μM). The optical density was continuously monitored by spectrophotometry for 30 min at 37 °C. The optical density of the vehicle treated well was taken as 100%. The kinetic curves were analyzed and total (specific and non-specific) binding to tubulin was expressed as IC_{50}.

Thiol oxidation-based protein binding assay for compound ***5a***

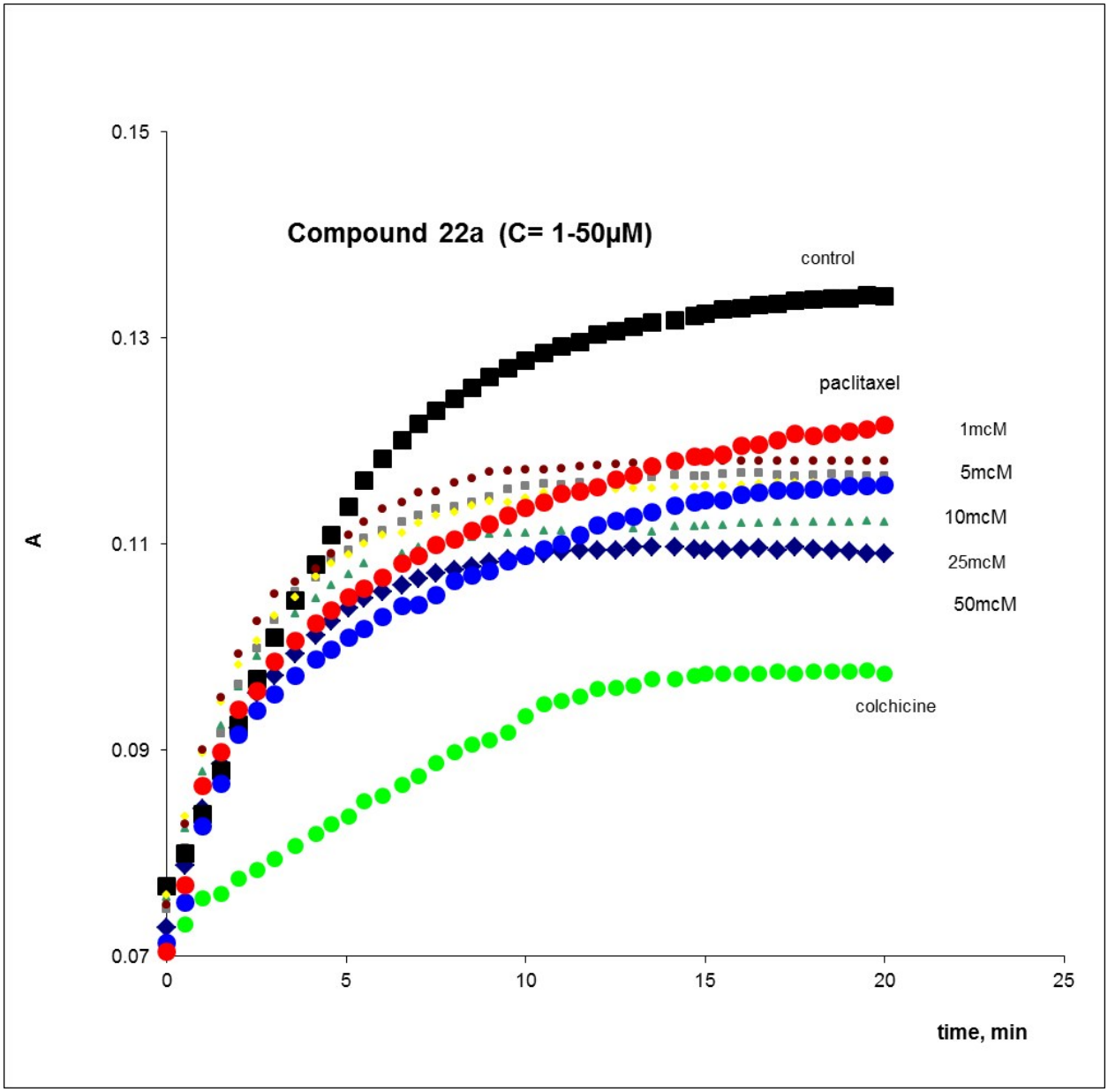


Figure 3 Kinetic curves for tubulin binding with compound **5a** at concentration 1 – 50 μM in Ellman's test. DMSO was used as vehicle control, colchicine and paclitaxel were used as positive controls.

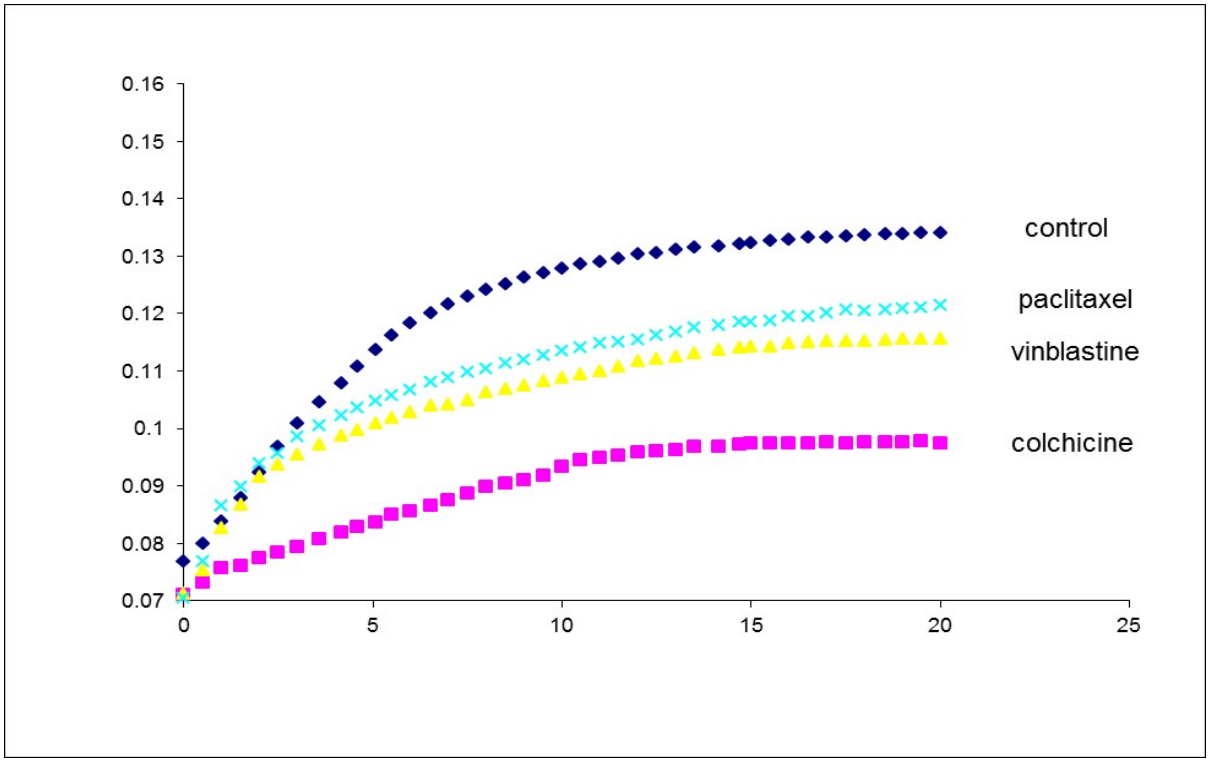


Figure 4 Kinetic curves for tubulin binding with positive control compounds at concentration 50 μM in Ellman's test. DMSO was used as vehicle control.

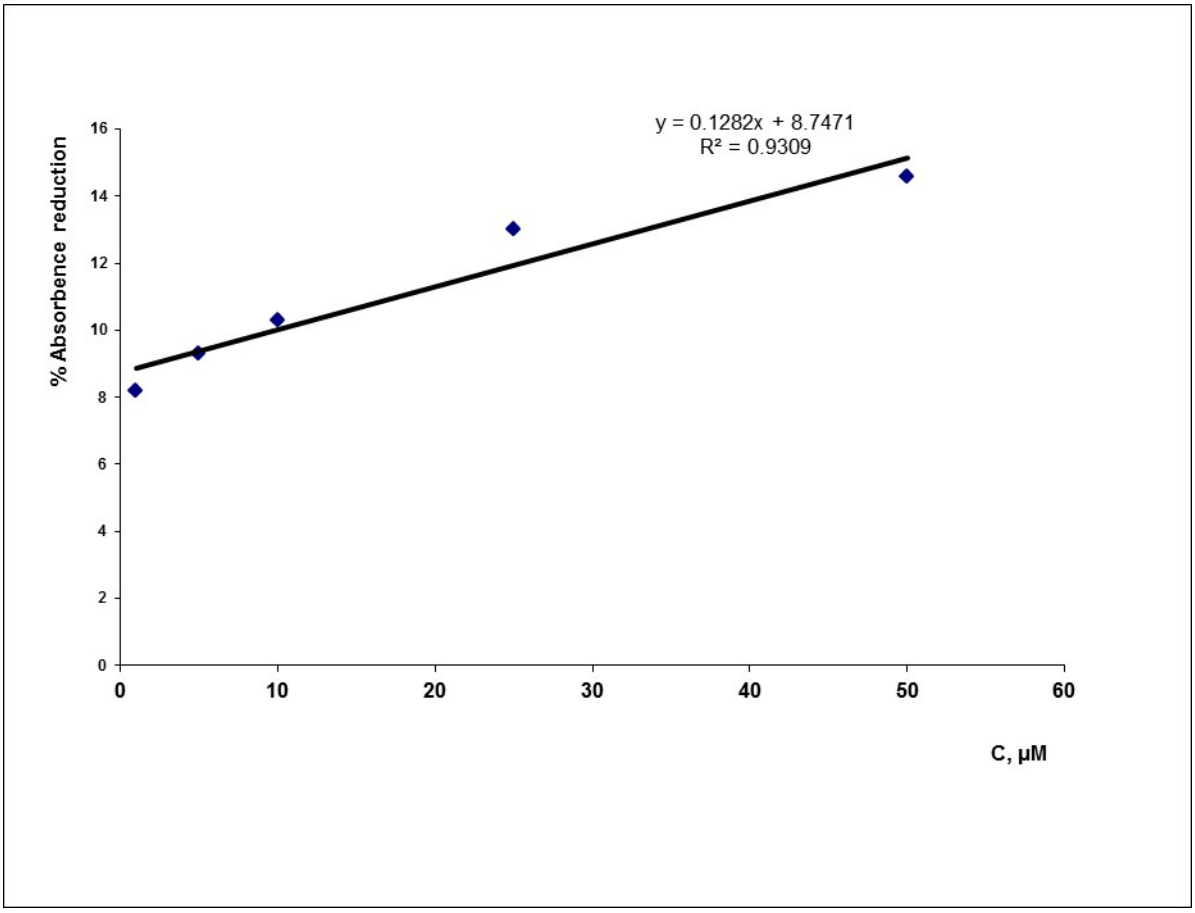


Figure 5 Concentration-dependent tubulin binding affinity for compound **5a**.

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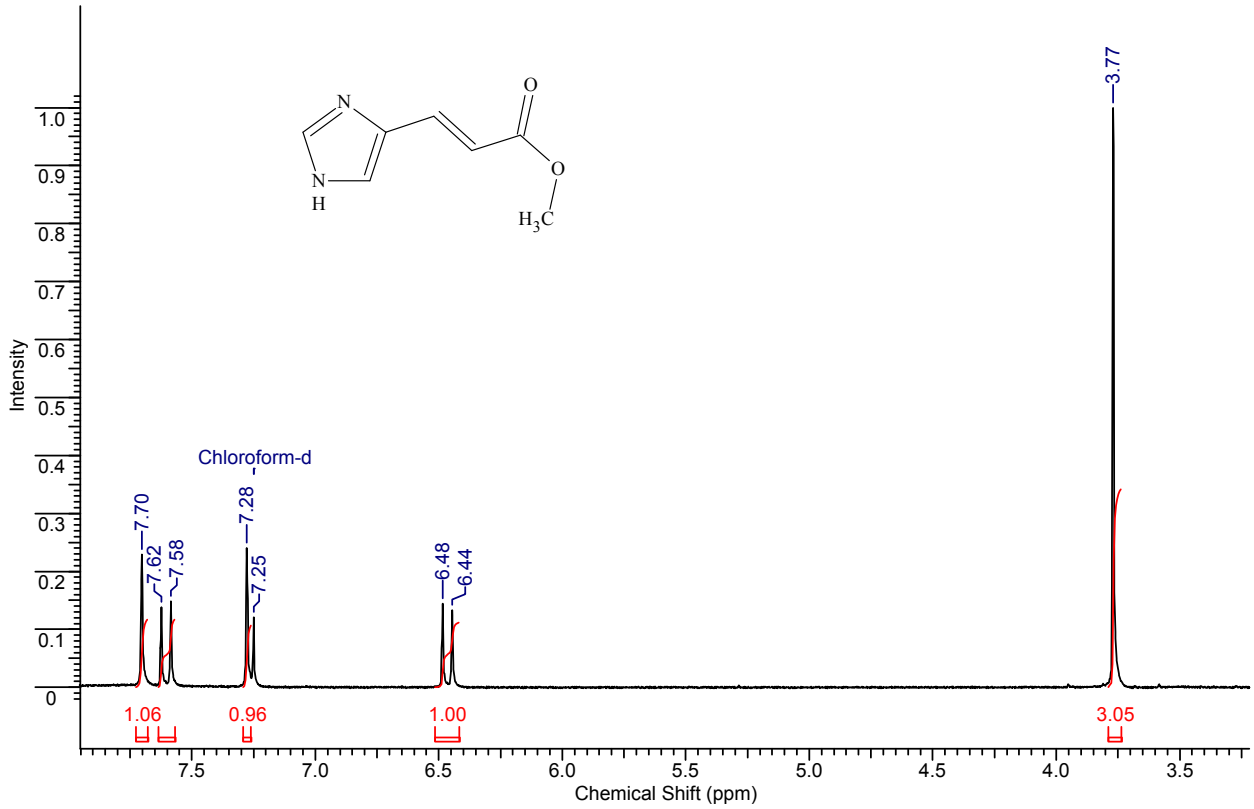
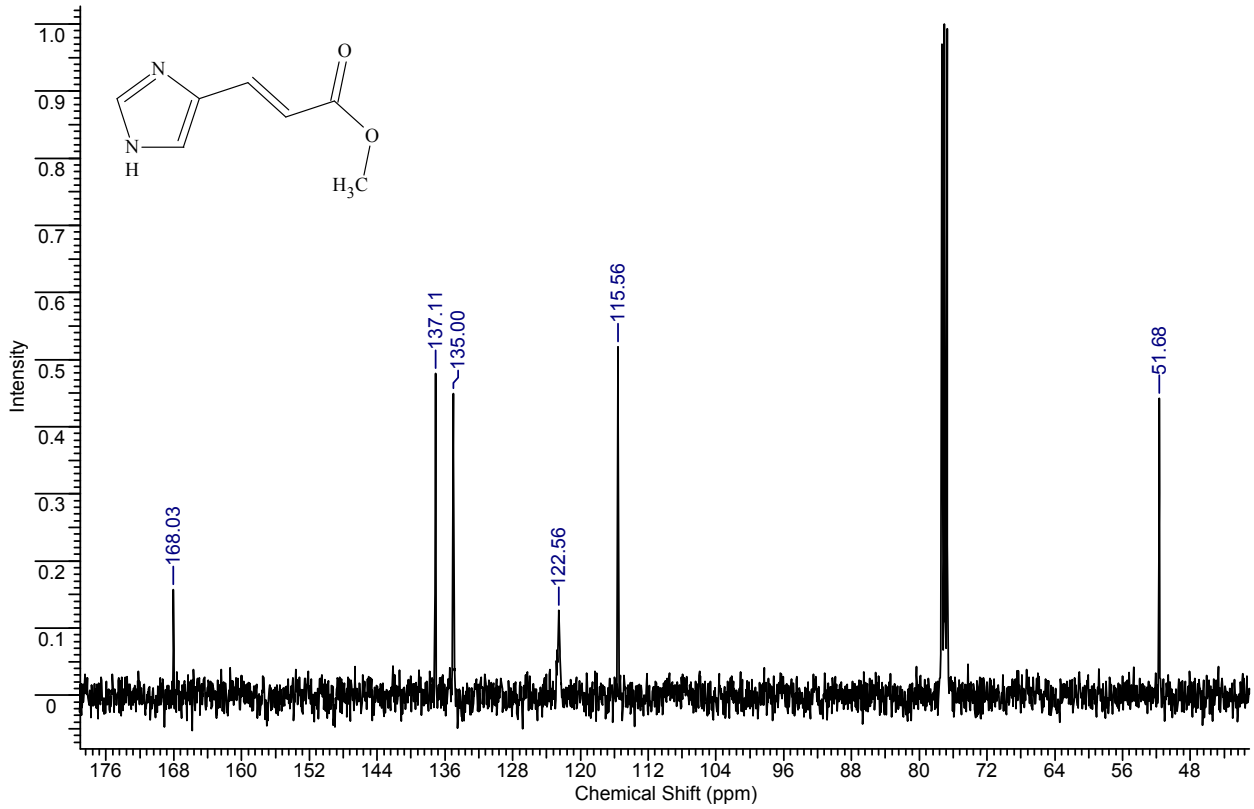
7. Copies of ^{1}H NMR and ^{13}C NMR spectra

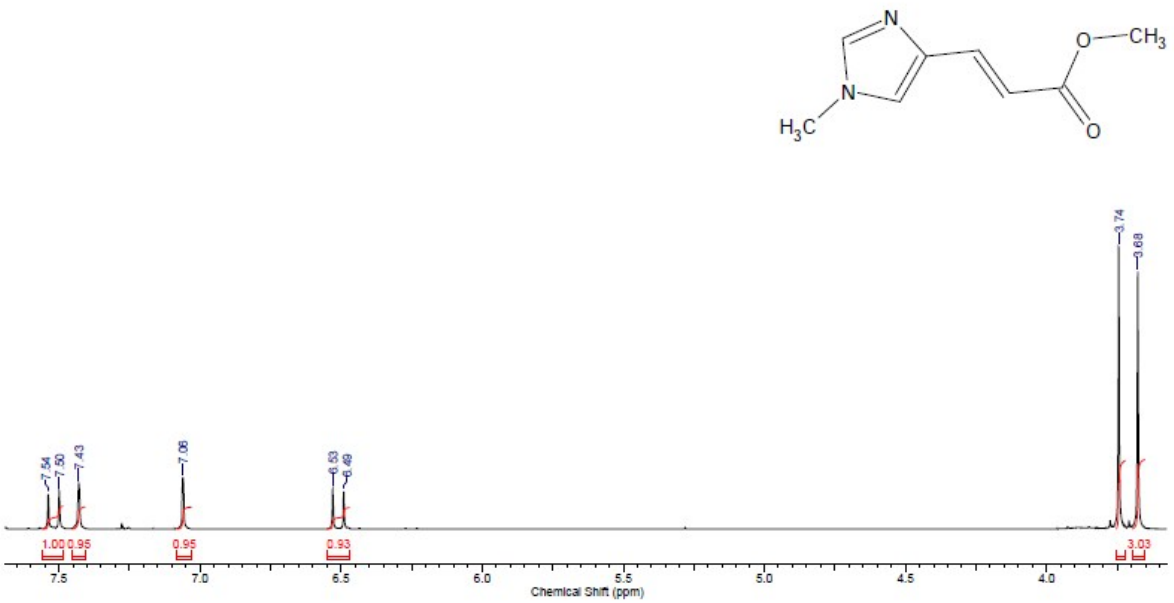
Methyl urocanate ^{1}H NMR



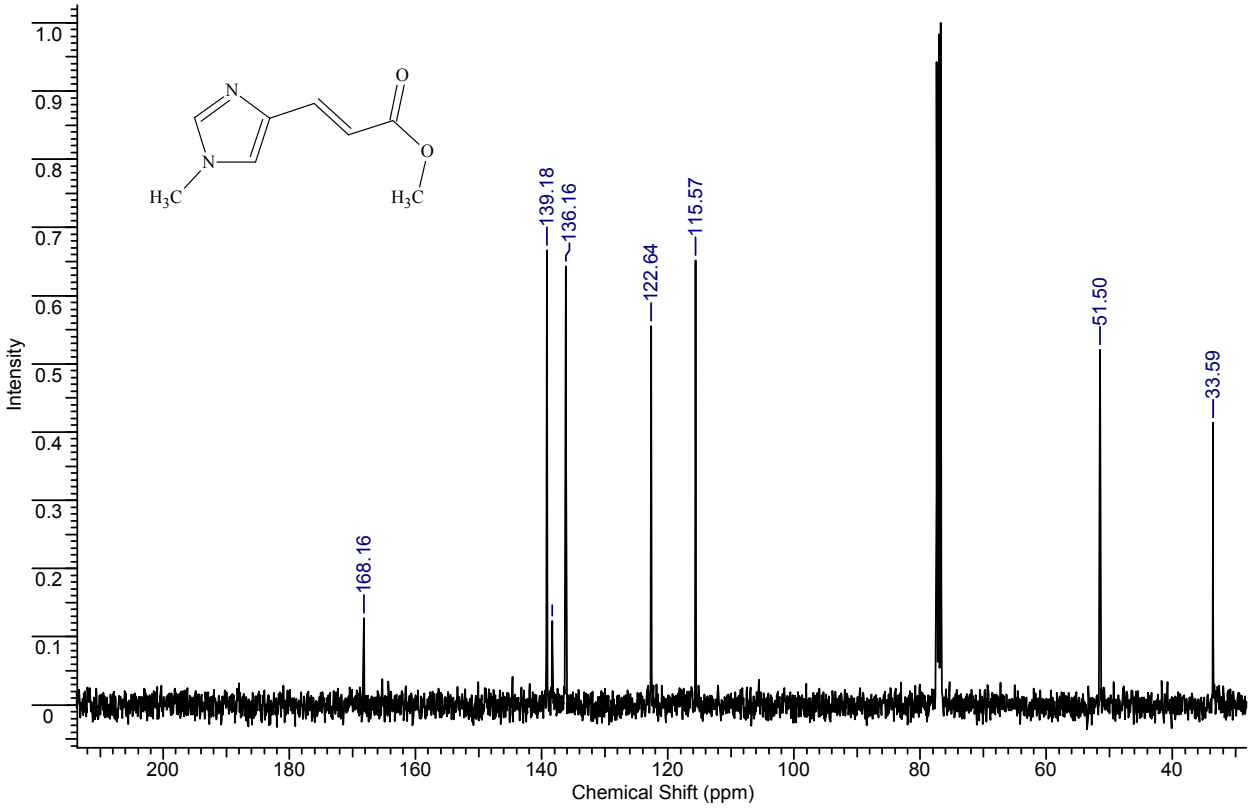
Methyl urocanate ^{13}C NMR



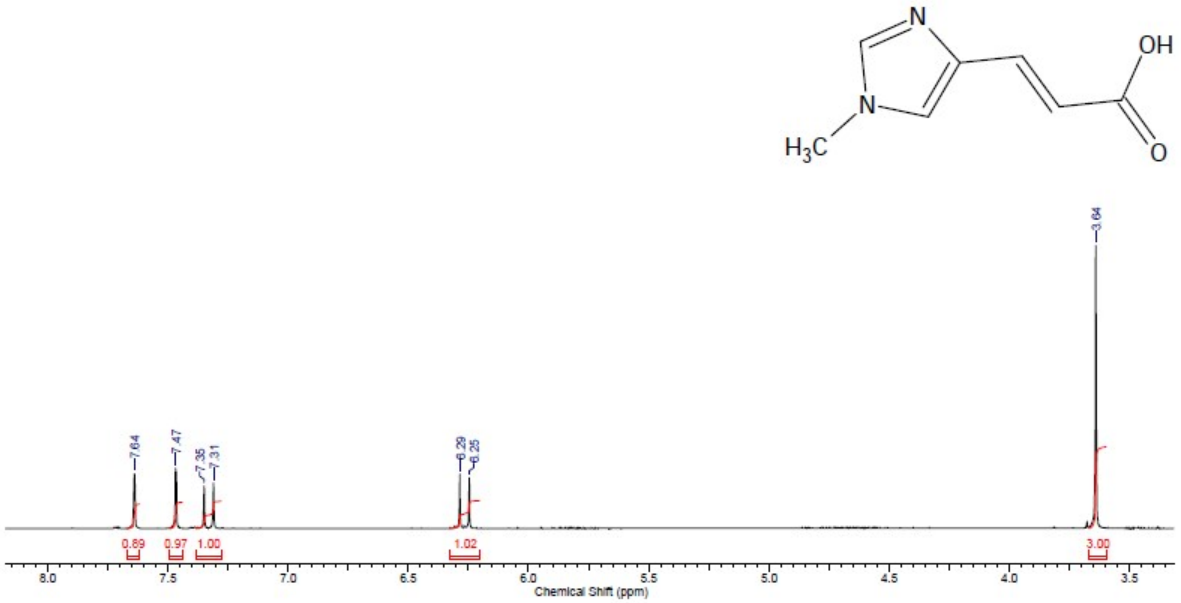
Methyl N-methylurocanate ^{1}H NMR



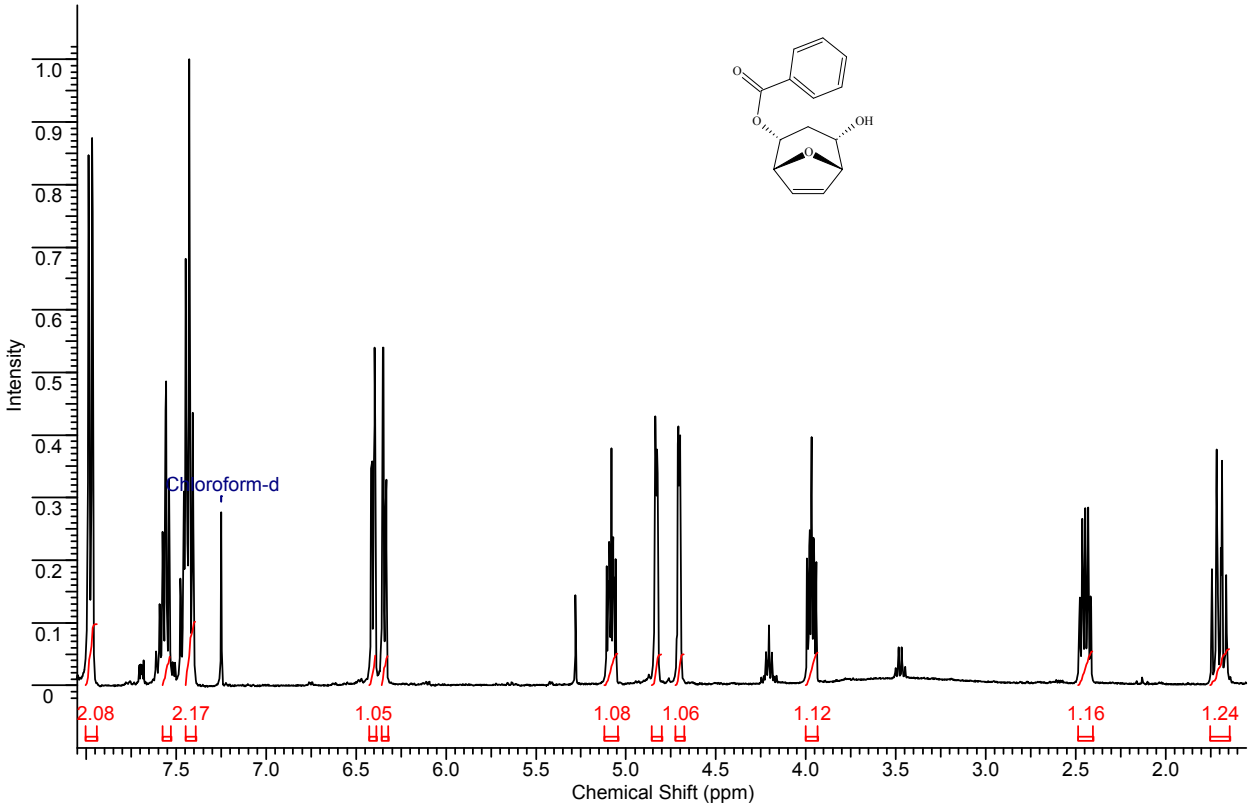
Methyl N-methylurocanate ^{13}C NMR



N-methylurocanic acid ^{1}H NMR



(1S*,2R*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (3a) ^{1}H NMR



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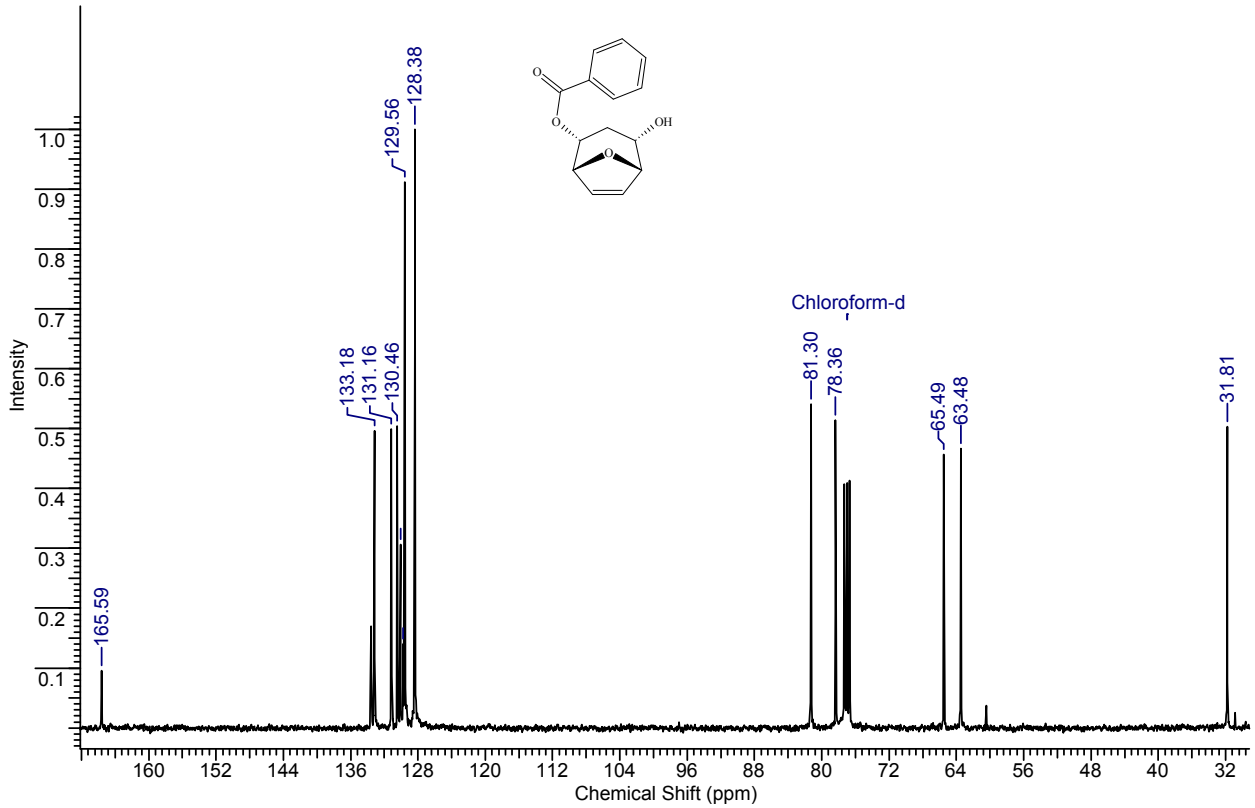
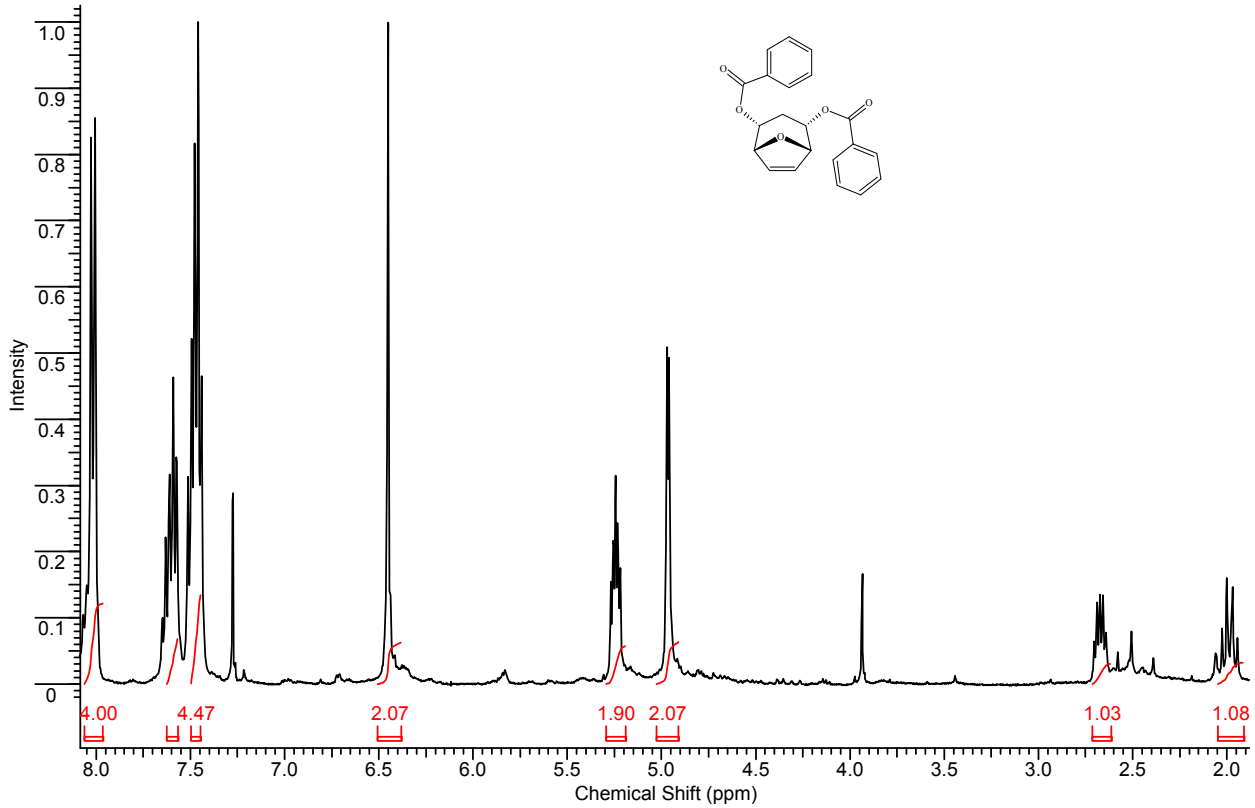
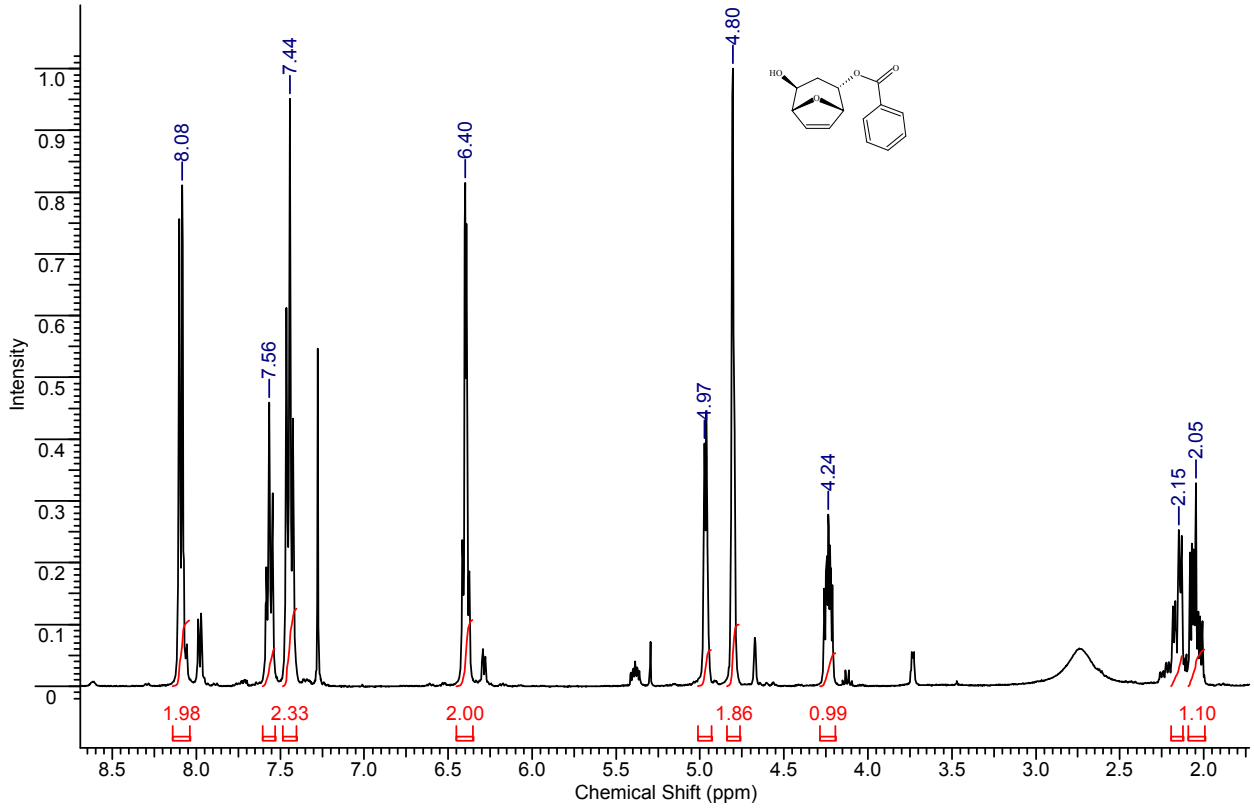


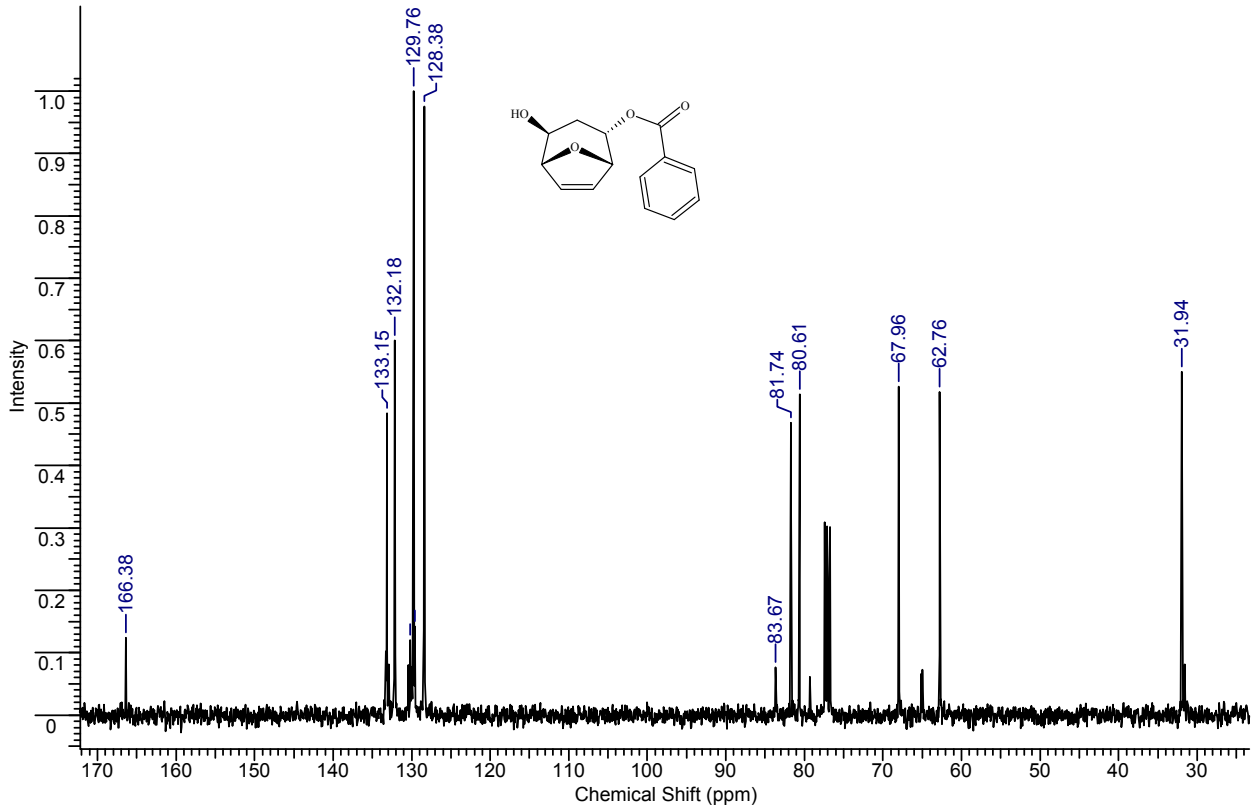
(1S,2R*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (4a) ^{1}H NMR*



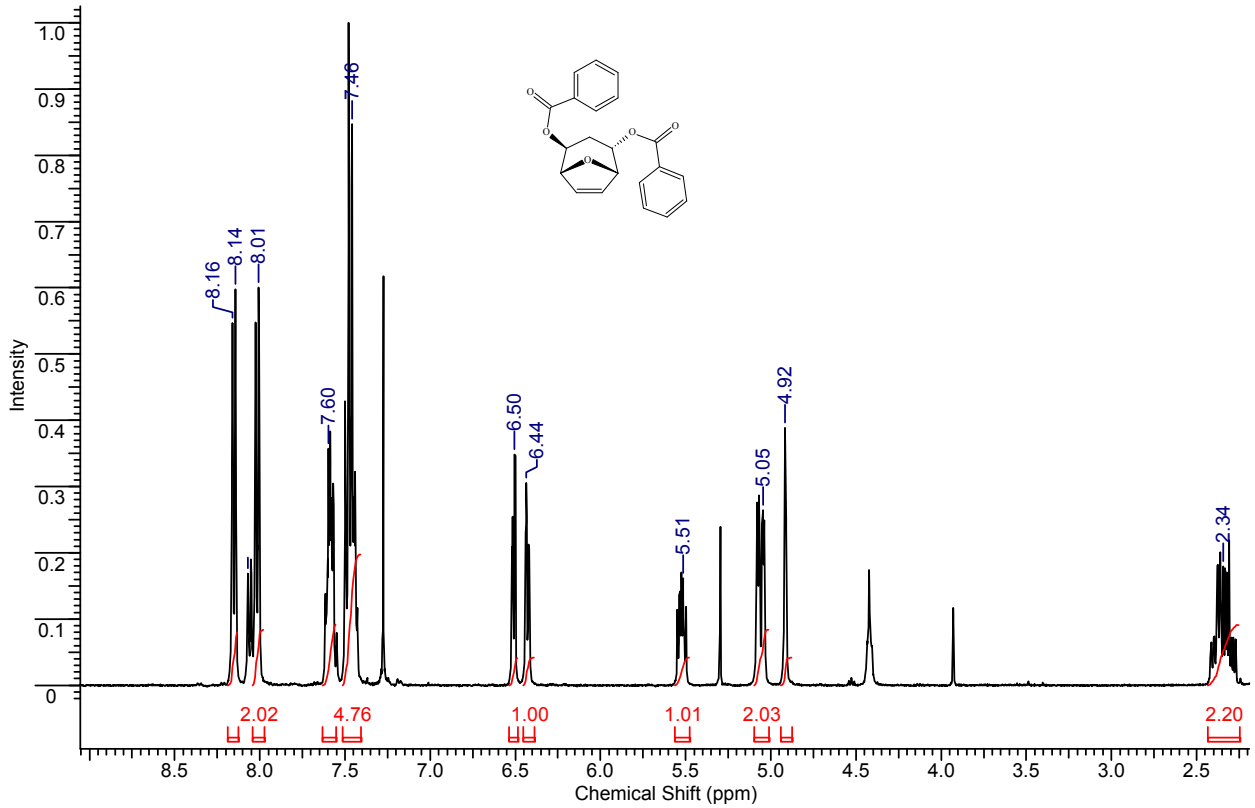
(1S,2S*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (3b) ^{1}H NMR*



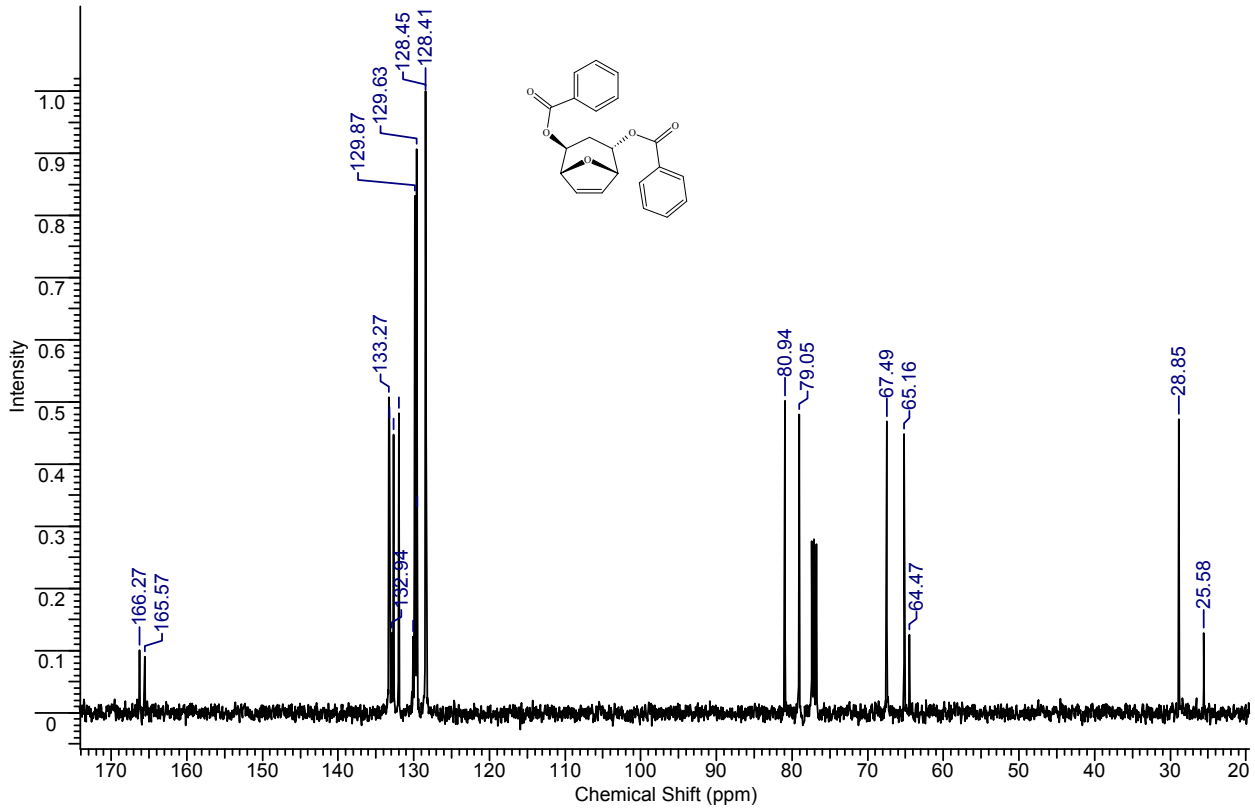
(1S,2S*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (3b) ^{13}C NMR*



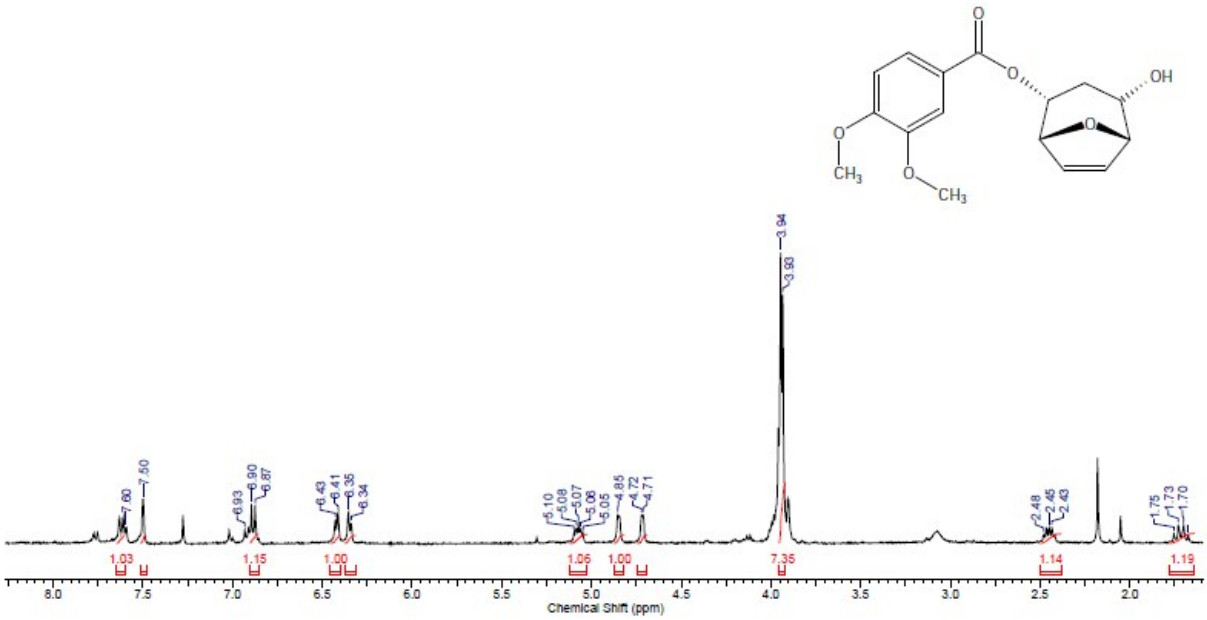
(1S,2S*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (4b) ^{1}H NMR*



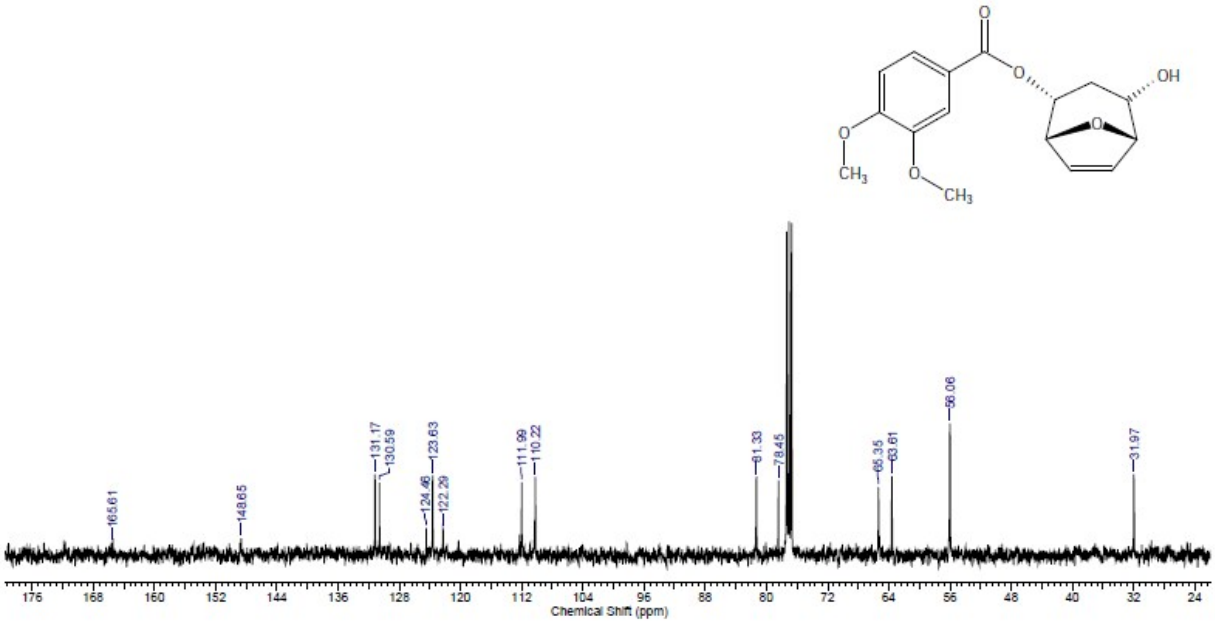
(1S,2S*,4S*,5R*)-8-oxabicyclo[3.2.1]oct-6-en-2,4-diyl dibenzoate (4b) ^{13}C NMR*



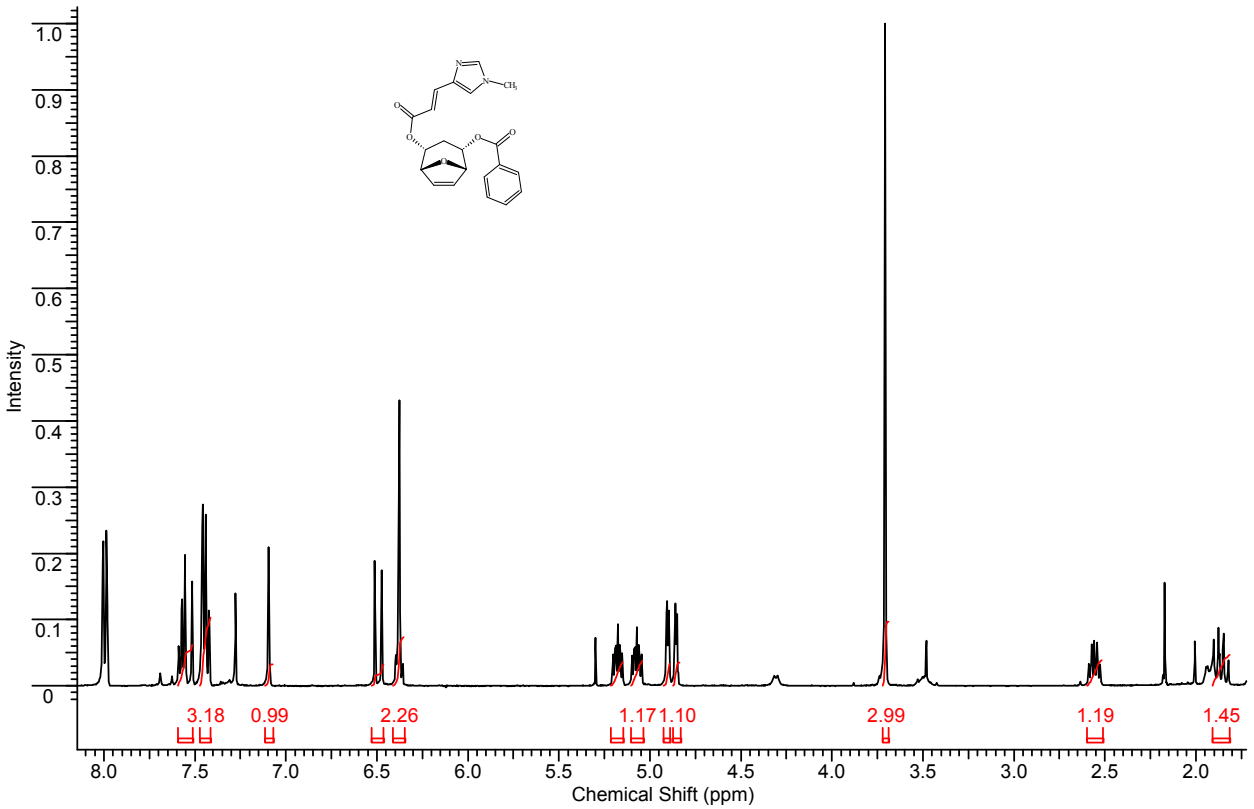
(1S,2R*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl 3,4-dimethoxybenzoate (3d) ^{1}H NMR*



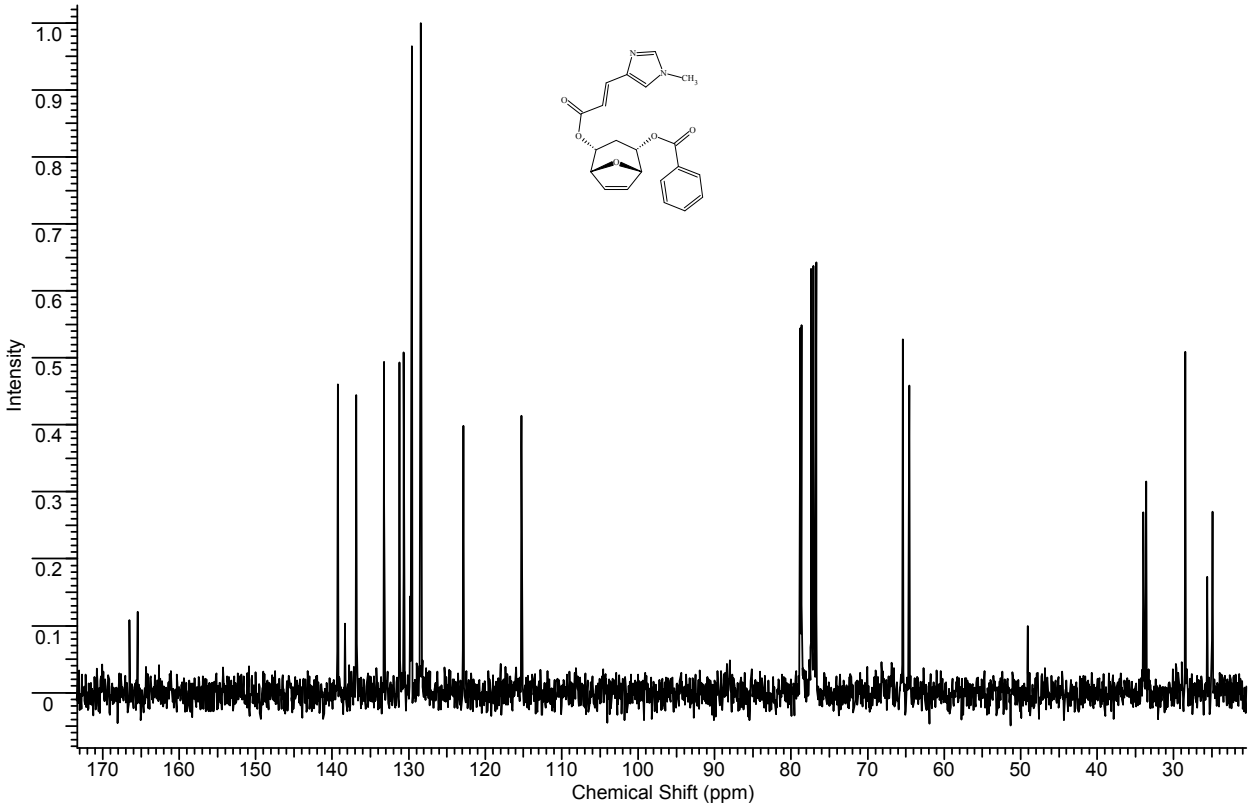
(1S,2R*,4S*,5R*)-4-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-2-yl 3,4-dimethoxybenzoate (3d) ^{13}C NMR*



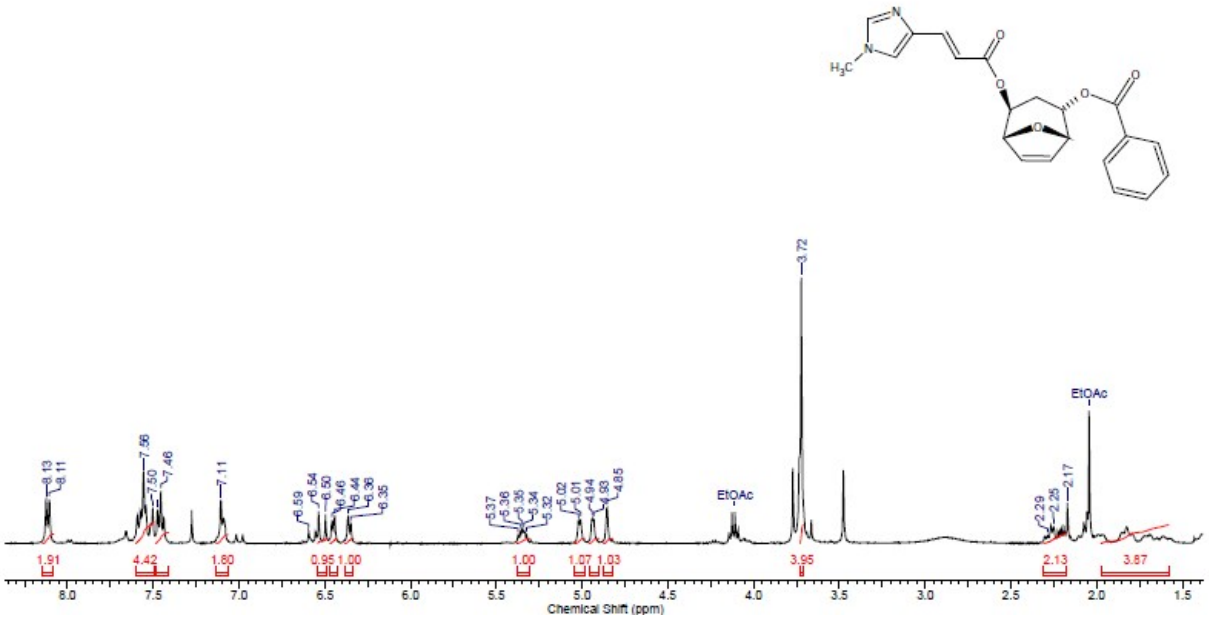
(1R*,2S*,4R*,5S*)-4-((E)-3-(1-Methyl-1H-[imidazol-4-yl)acryloyloxy) 8- oxabicyclo[3.2.1]oct-6-en-2,4-diyl benzoate (5a) ^{1}H NMR



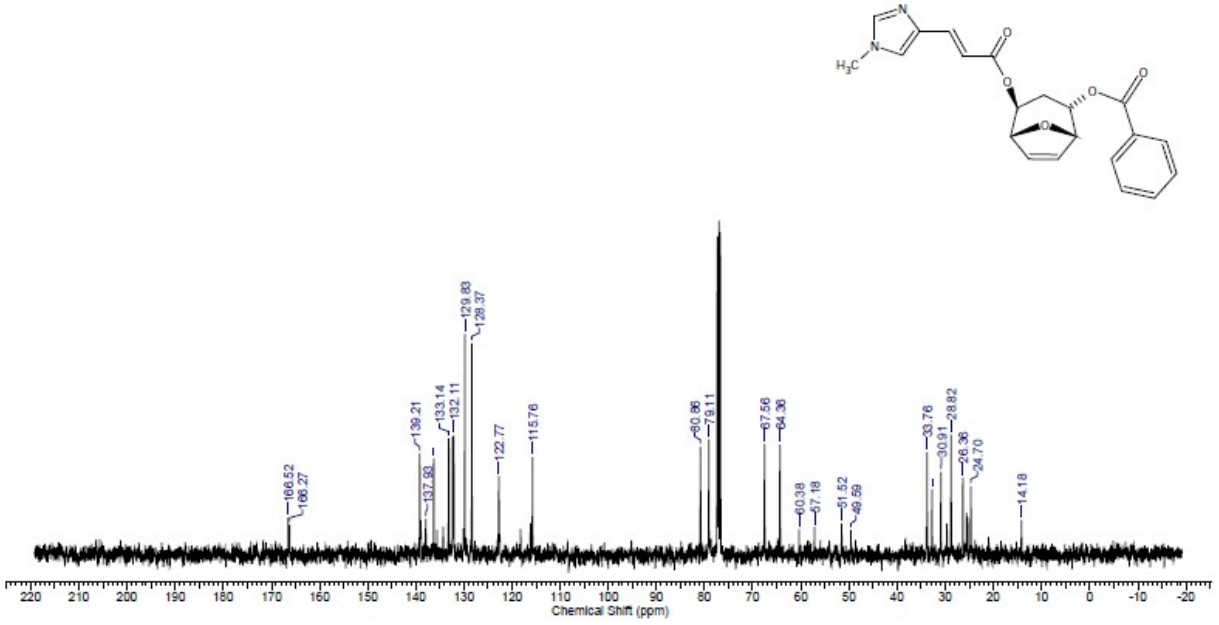
(1R*,2S*,4R*,5S*)-4-((E)-3-(1-Methyl-1H-[imidazol-4-yl)acryloyloxy) 8- oxabicyclo[3.2.1]oct-6-en-2,4-diyl benzoate (5a) ^{13}C NMR



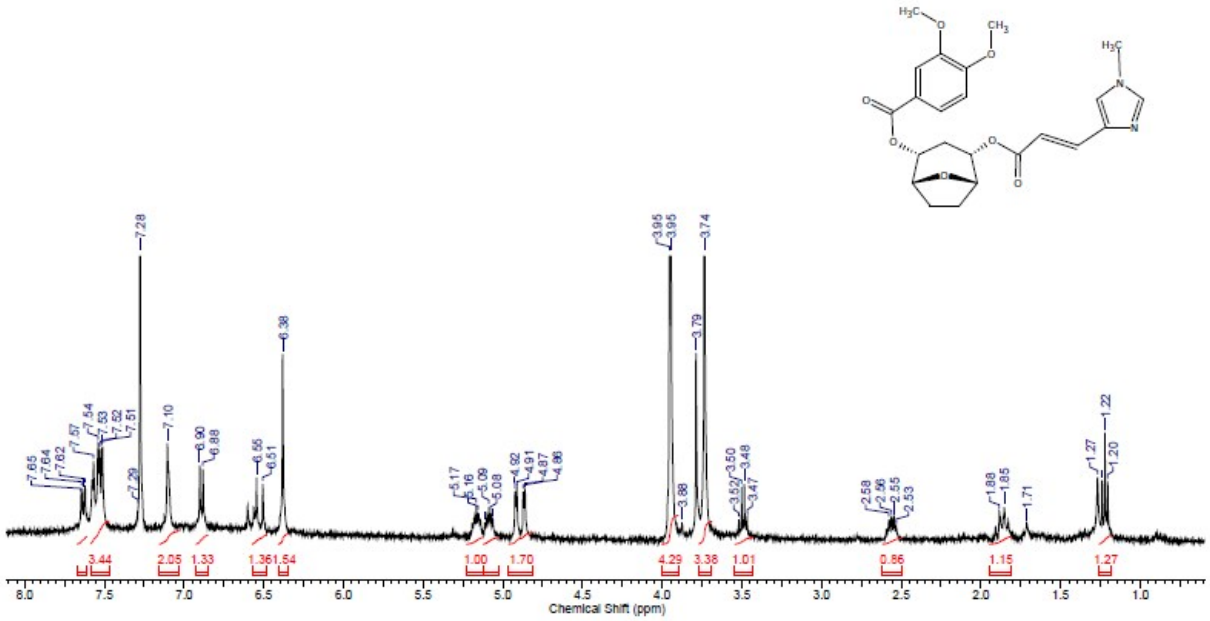
(1R*,2R*,4R*,5S*)-4-((E)-3-(1-1-Methyl-1H-[imidazol-4-yl)acryloyloxy-8- oxabicyclo[3.2.1]oct-6-en-2,4-diyl benzoate (5b) ^{1}H NMR



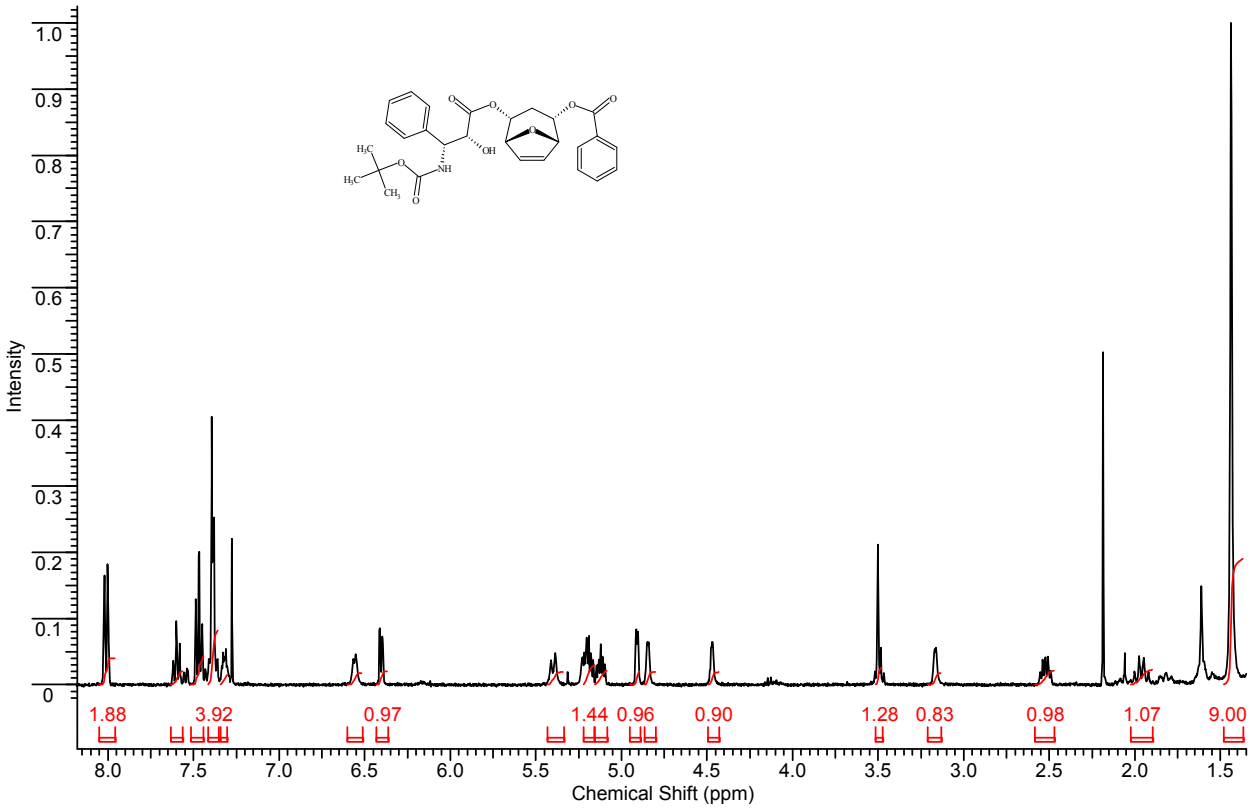
(1R*,2R*,4R*,5S*)-4-((E)-3-(1-1-Methyl-1H-[imidazol-4-yl)acryloyloxy-8- oxabicyclo[3.2.1]oct-6-en-2,4-diyl benzoate (5b) ^{13}C NMR



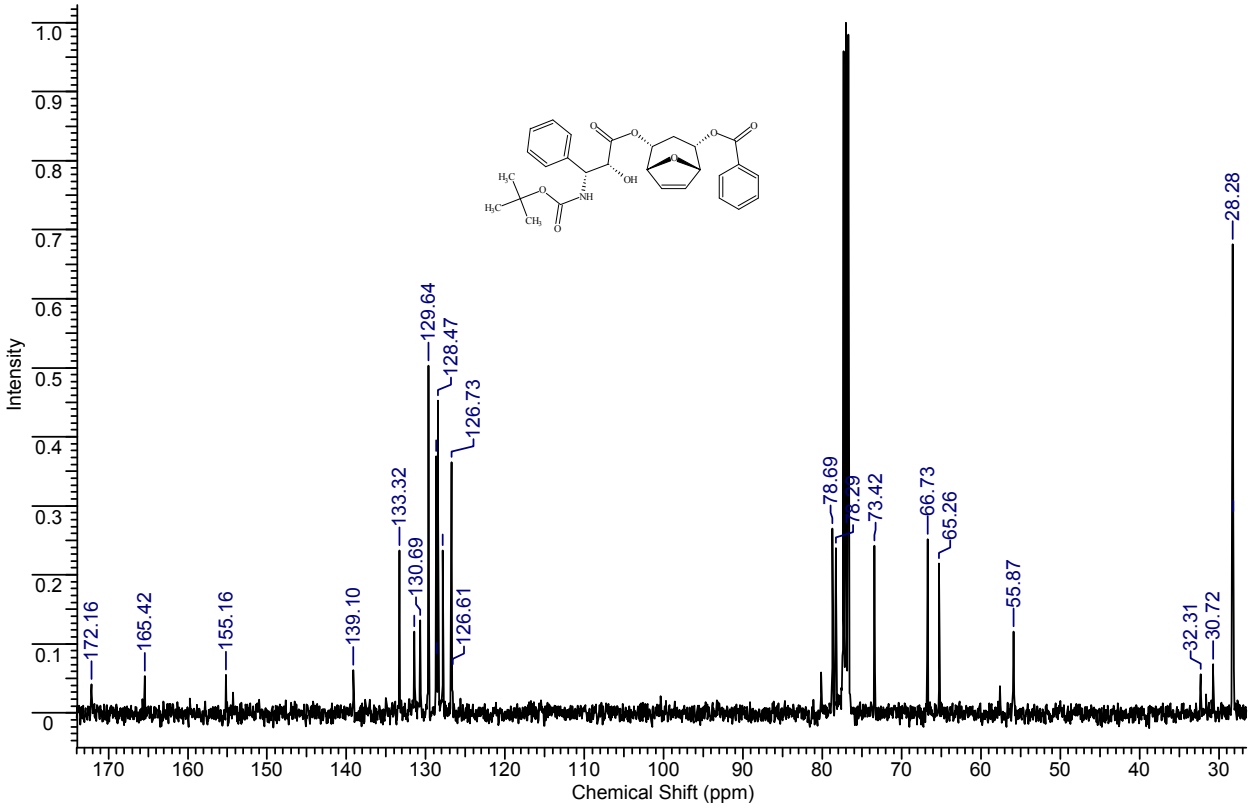
(1R*,2S*,4R*,5S*)-4-((E)-3-(1-Methyl-1H-[(imidazol-4-yl)acryloyloxy)-8- oxabicyclo[3.2.1]oct-6-en-2,4-diyl] 3,4-dimethoxybenzoate (5c) ^{1}H NMR



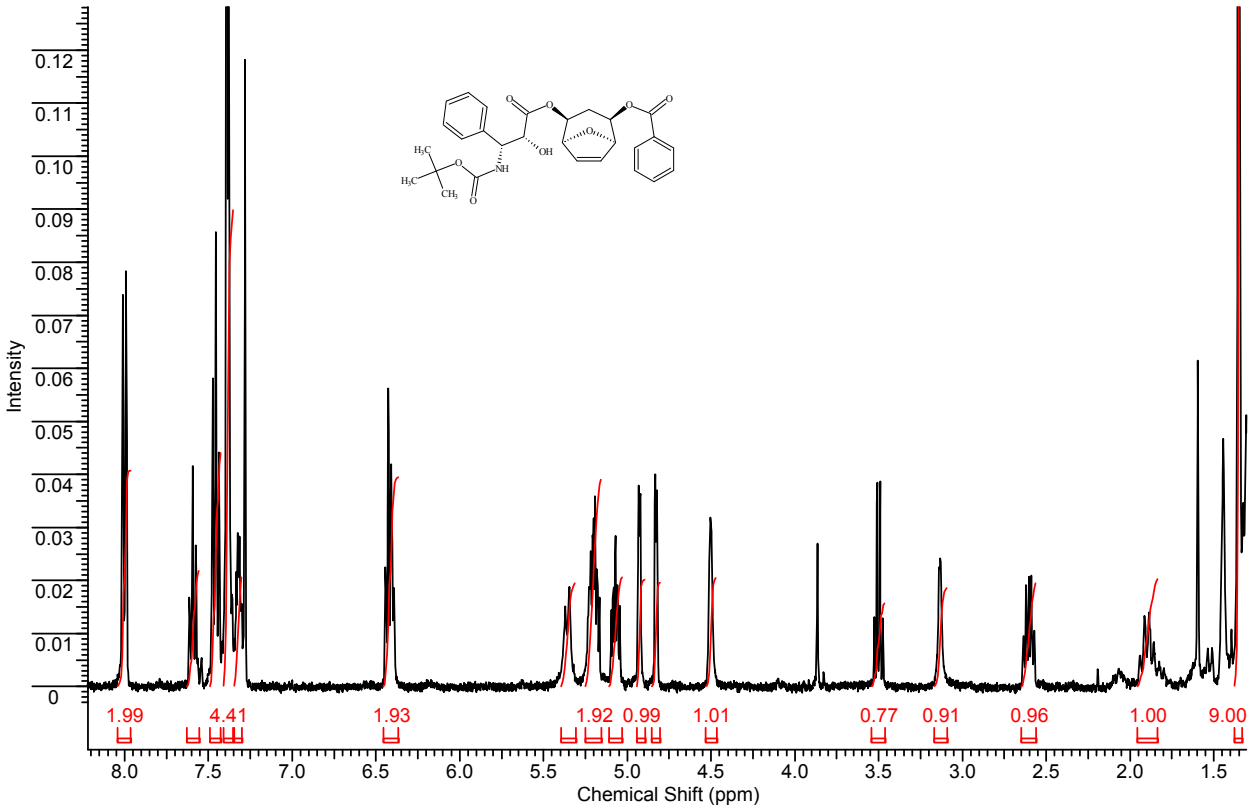
(1S,2S,4R,5R)-4-((2R,3R)-3-(tert-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (8a) ^{1}H NMR



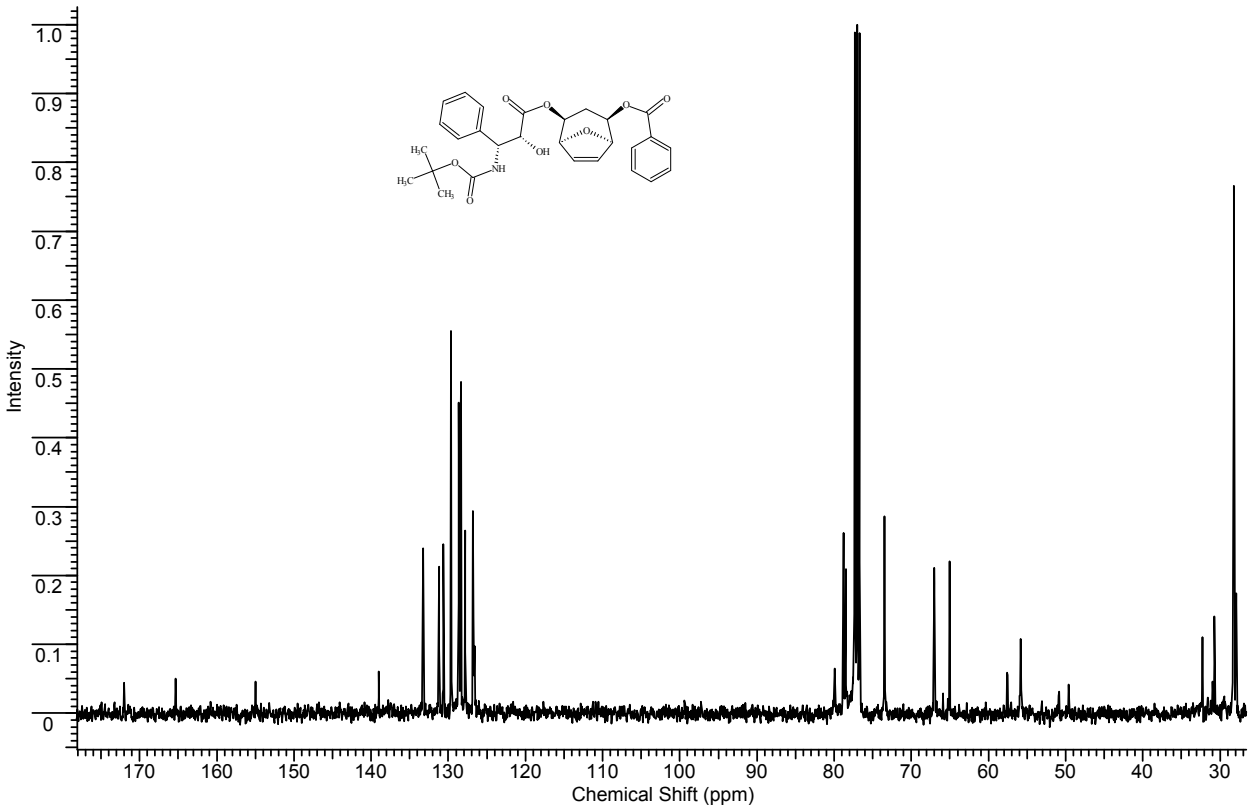
(1S,2S,4R,5R)-4-((2R,3R)-3-(tert-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (8a) ^{13}C NMR



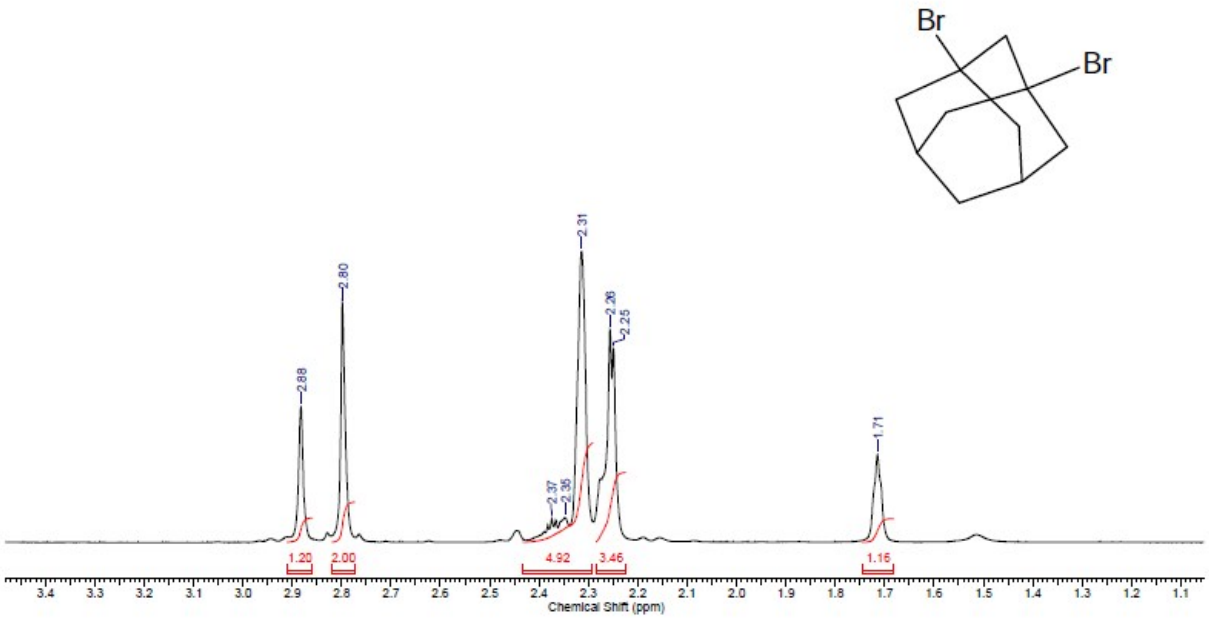
(1R,2R,4S,5S)-4-((2R,3R)-3-(tert-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (8b) ^{1}H NMR



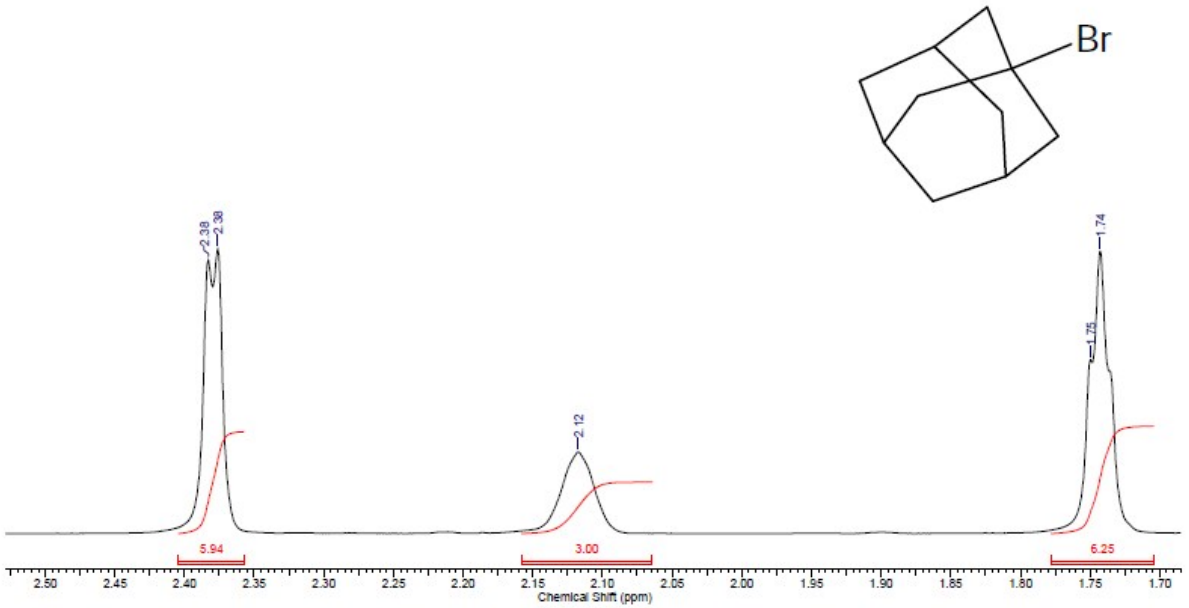
(1R,2R,4S,5S)-4-((2R,3R)-3-(tert-Butoxycarbonylamino)-2-hydroxy-3-phenylpropanoyloxy)-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (8b) ^{13}C NMR



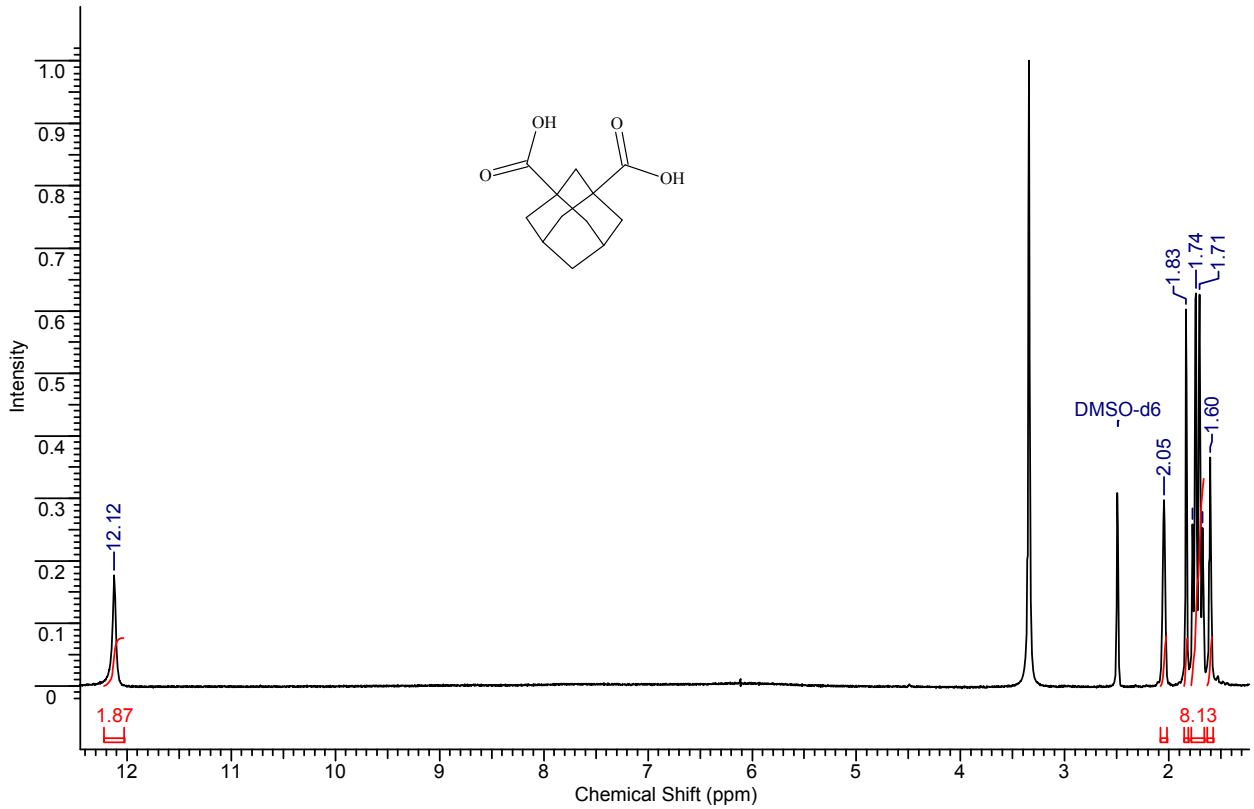
1,3-dibromoadamantane ^{1}H NMR



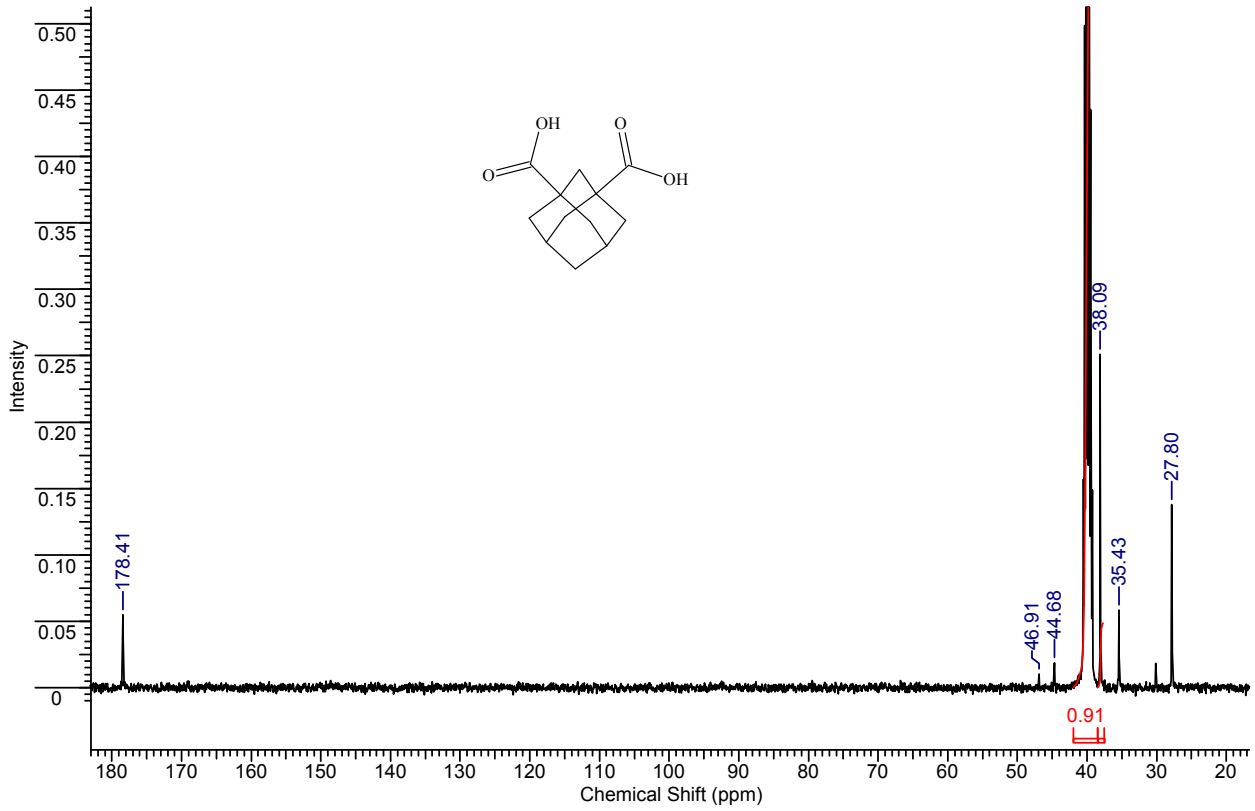
1-bromoadamantane ^{1}H NMR



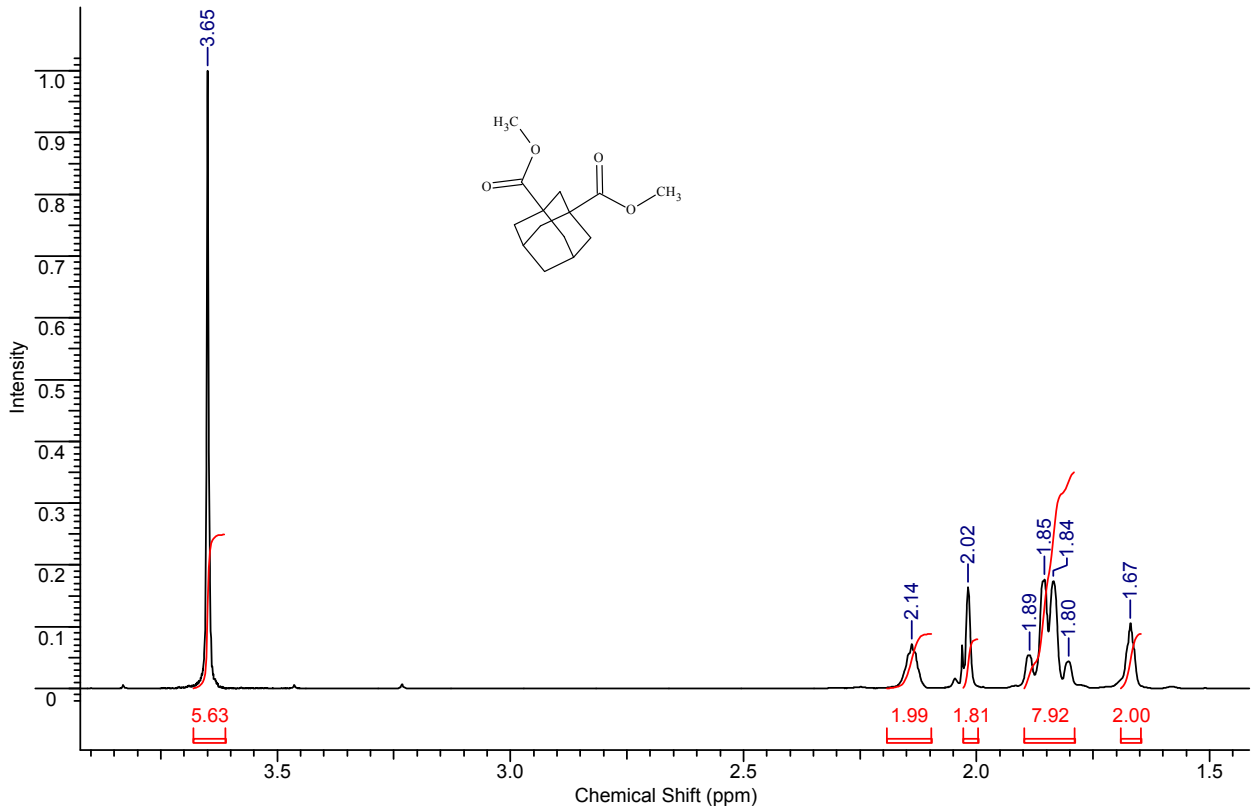
Adamantane-1,3-dicarboxylic acid ^{1}H NMR



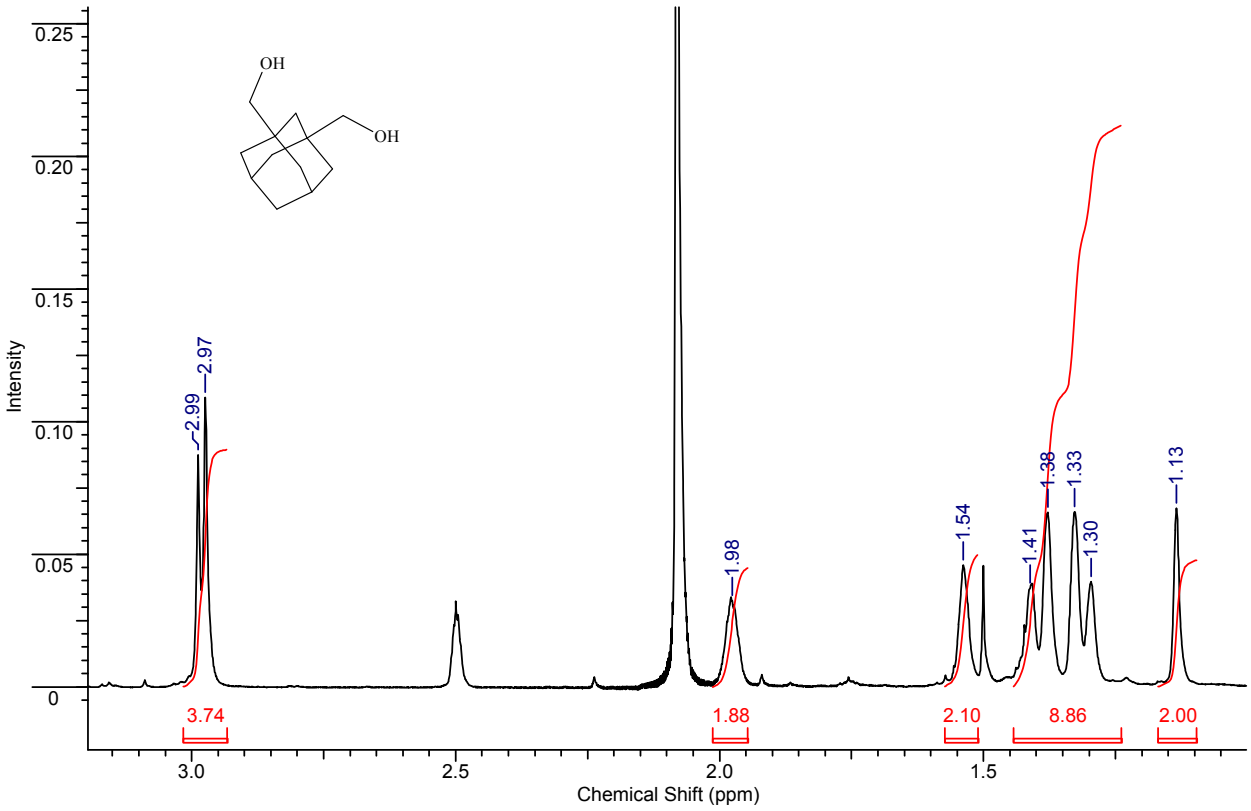
Adamantane-1,3-dicarboxylic acid ^{13}C NMR



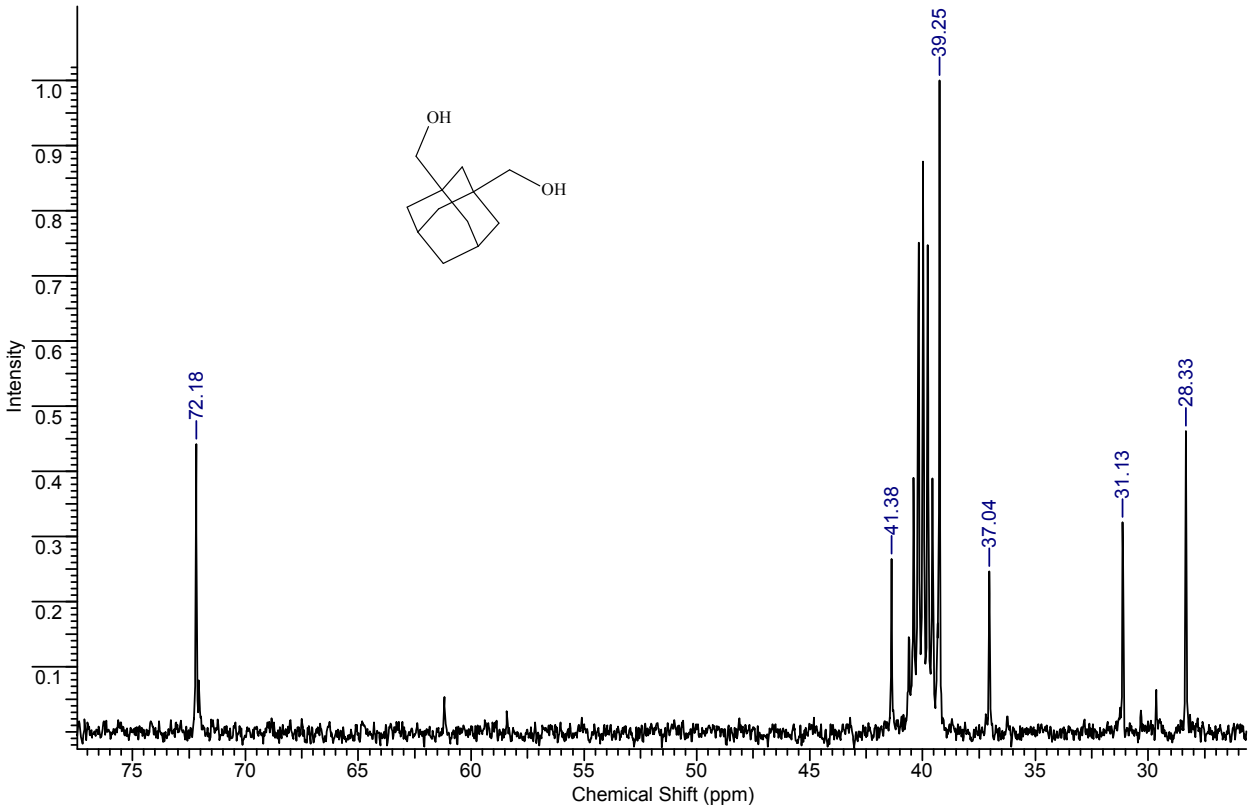
Dimethyl adamantane-1,3-dicarboxylate ^{1}H NMR



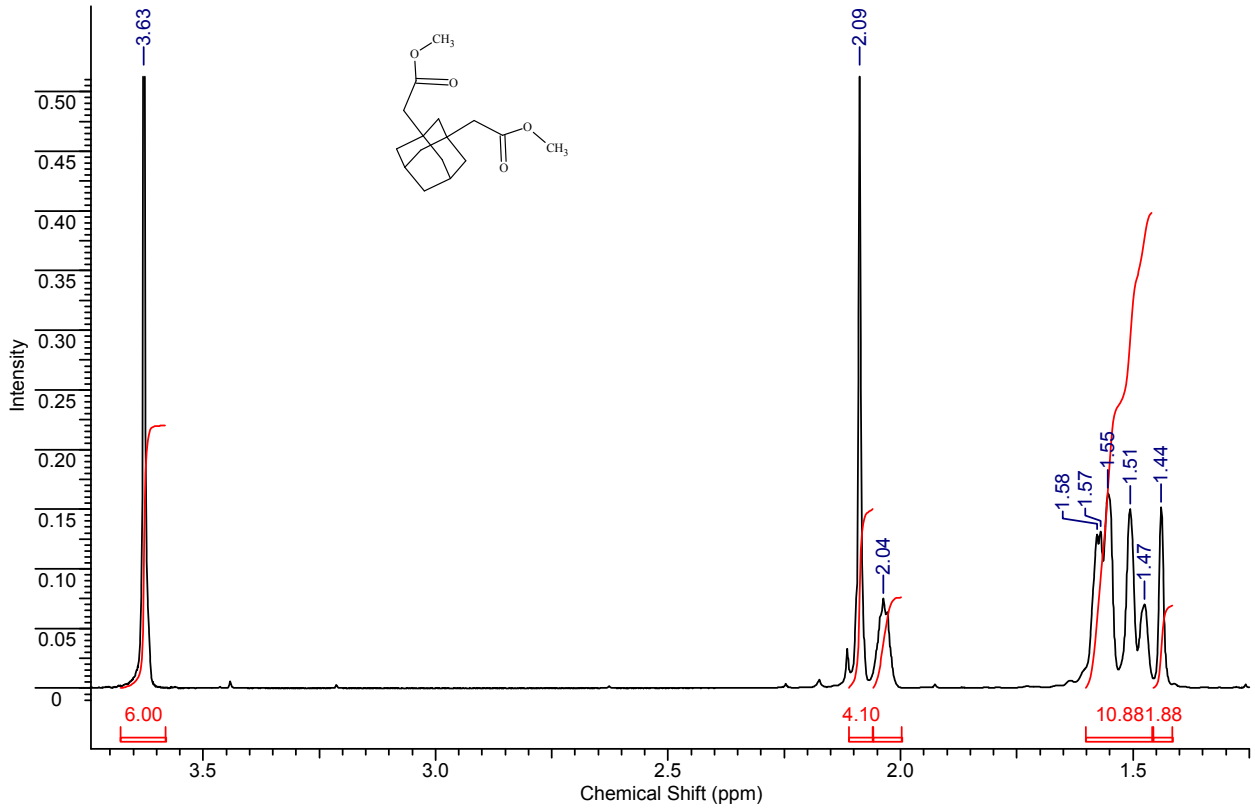
1,3-(dihydroxymethyl)adamantane (9a) ^{1}H NMR



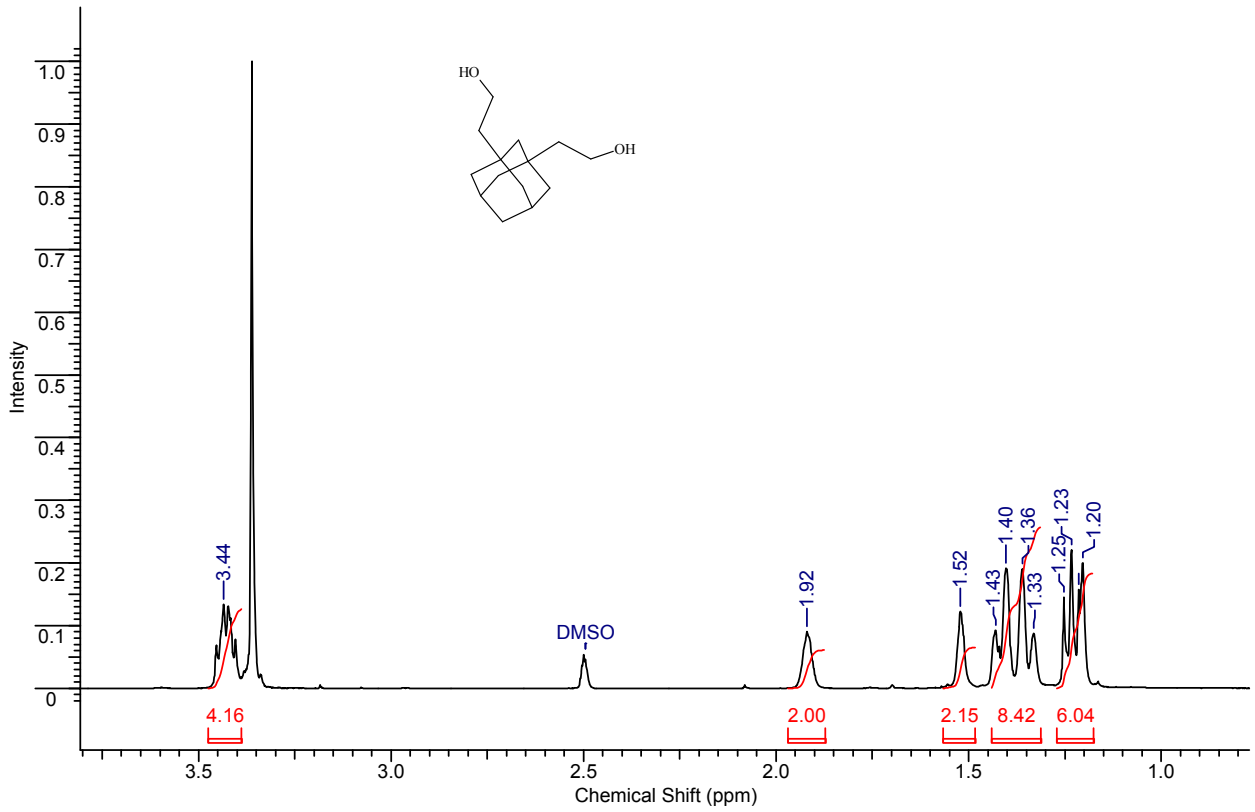
1,3-(dihydroxymethyl)adamantane (9a) ^{13}C NMR



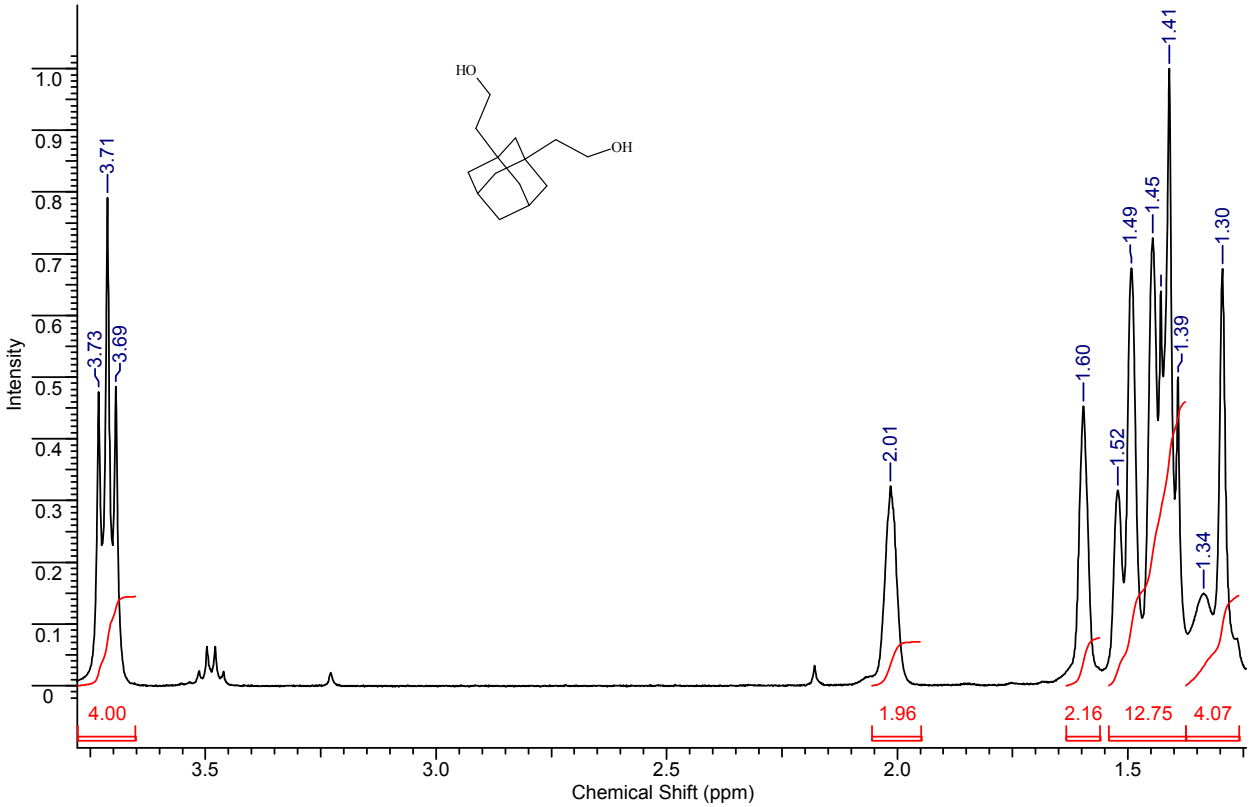
Dimethyl adamantane-1,3-diyldiacetate ^1H NMR



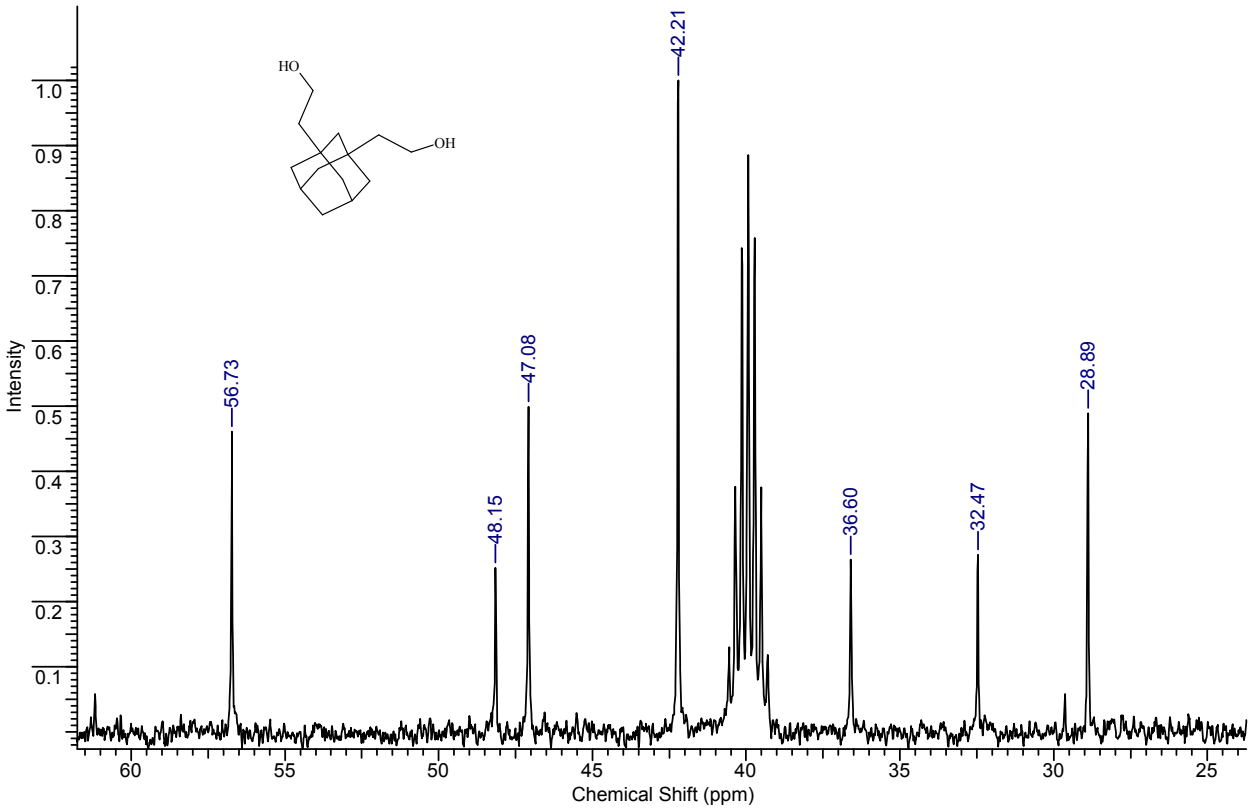
1,3-(dihydroxyethyl)adamantane (9b) ^1H NMR (DMSO-d_6)



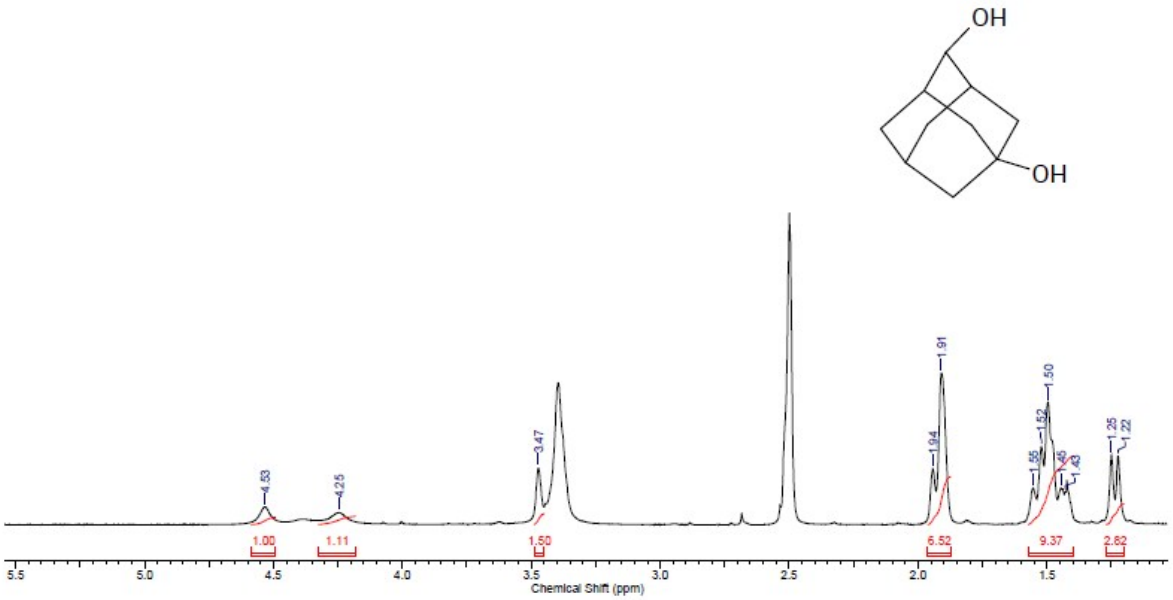
1,3-(dihydroxyethyl)adamantane (9b) ^{1}H NMR ($CDCl_3$)



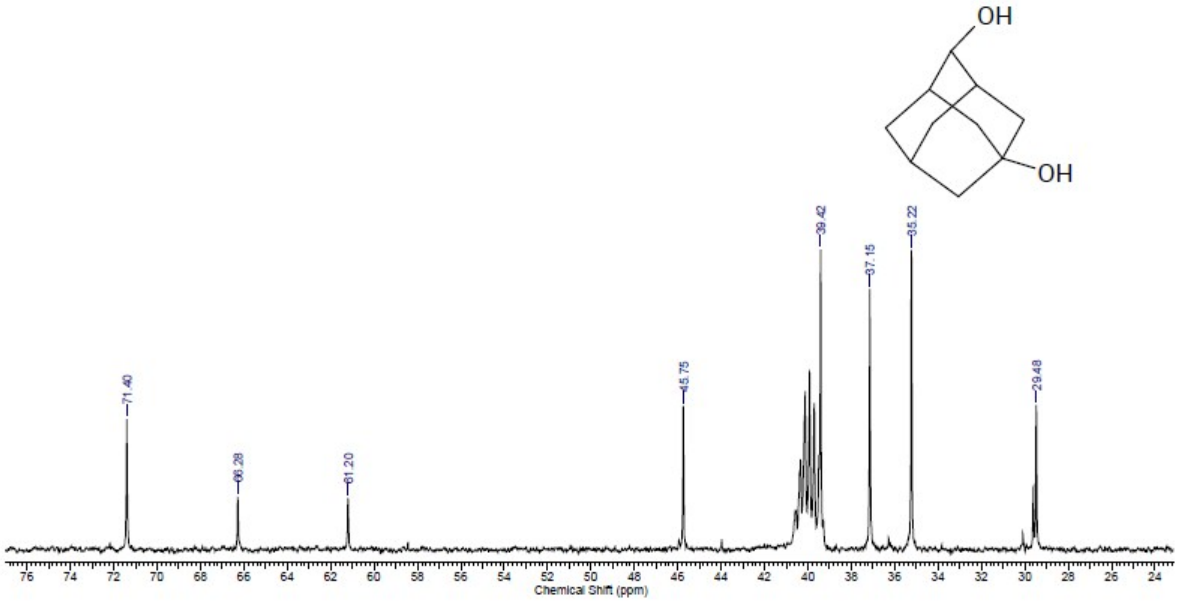
1,3-(dihydroxyethyl)adamantane (9b) ^{13}C NMR (DMSO-d_6)



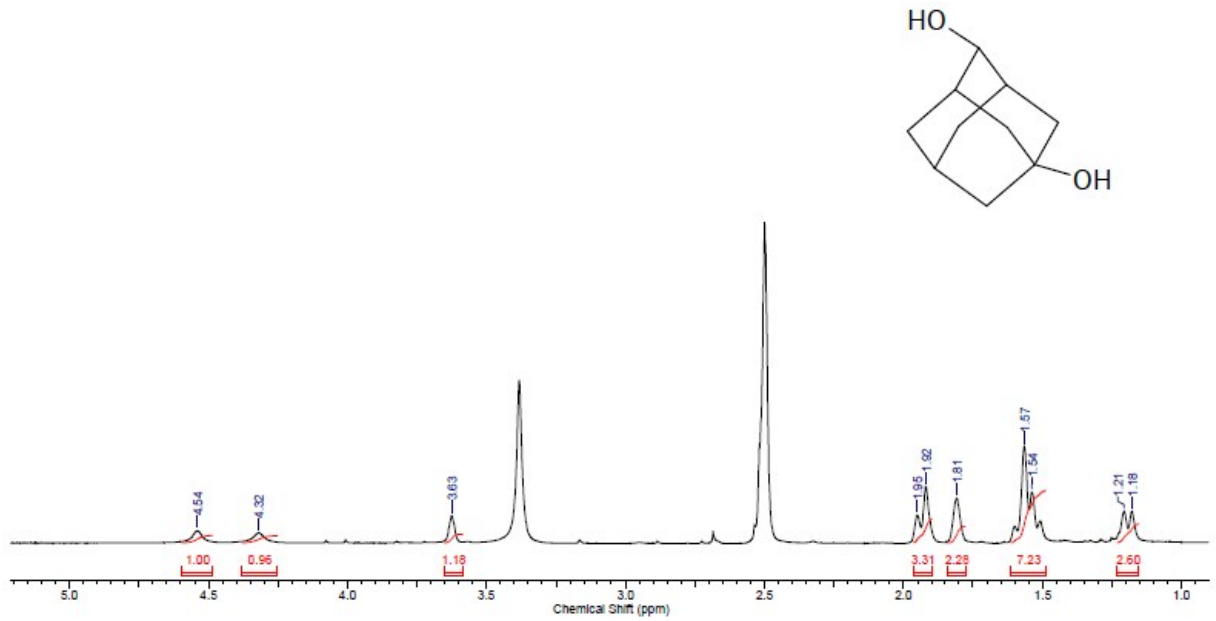
Cis-1,4-adamantanediol (10a) ^{1}H NMR



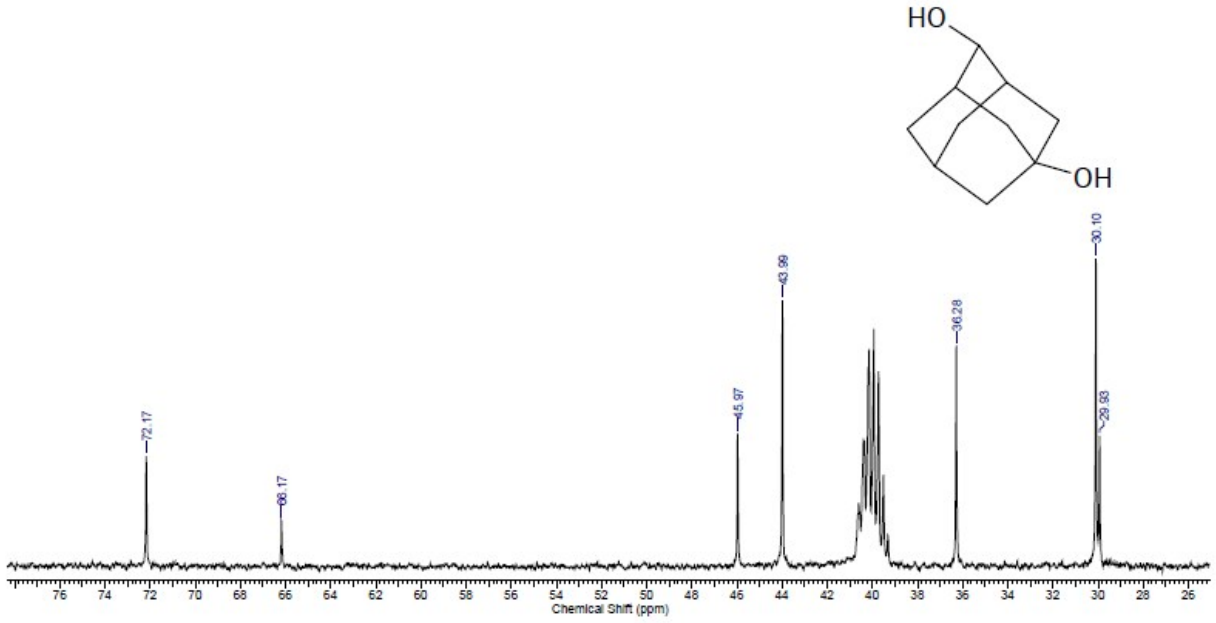
Cis-1,4-adamantanediol (10a) ^{13}C NMR



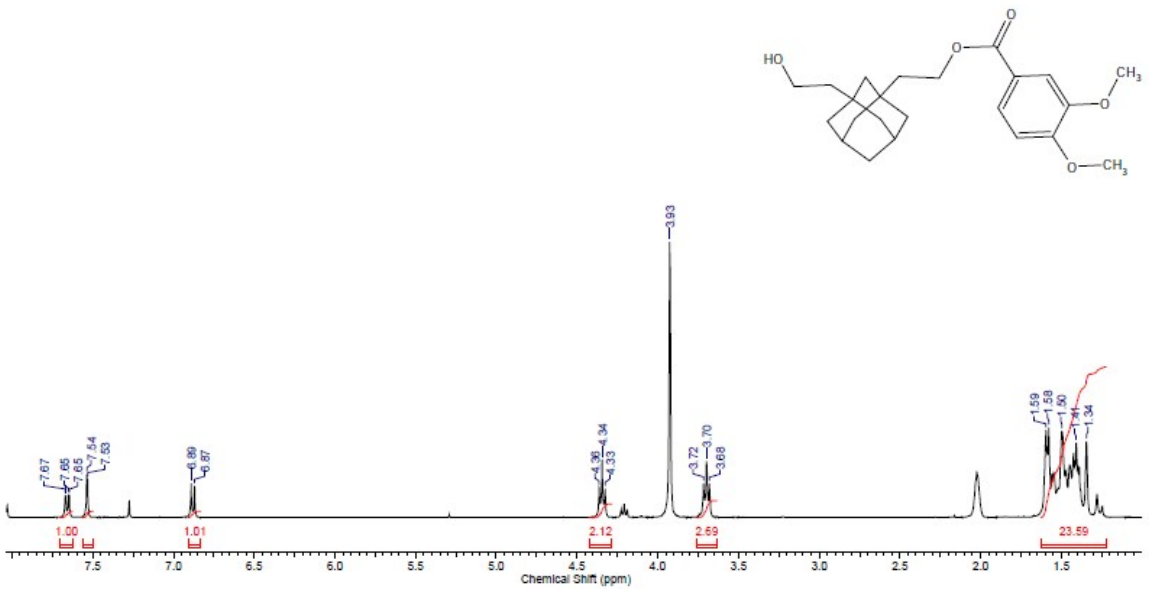
Trans-1,4-adamantanediol (10b) ^{1}H NMR



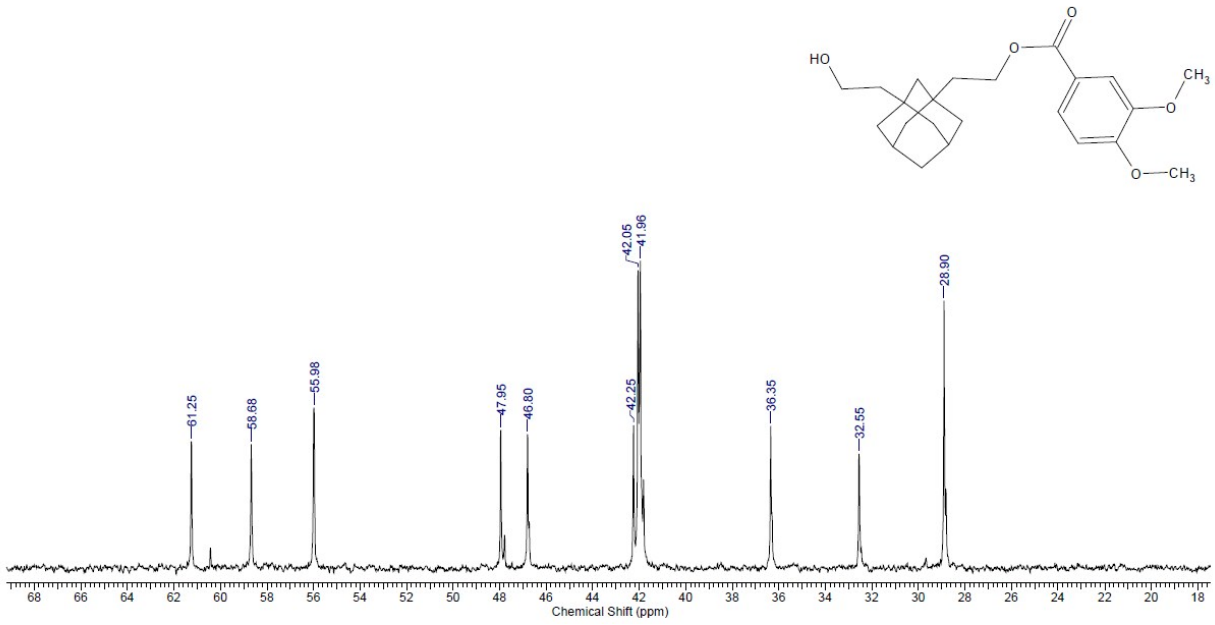
Trans-1,4-adamantanediol (10b) ^{13}C NMR



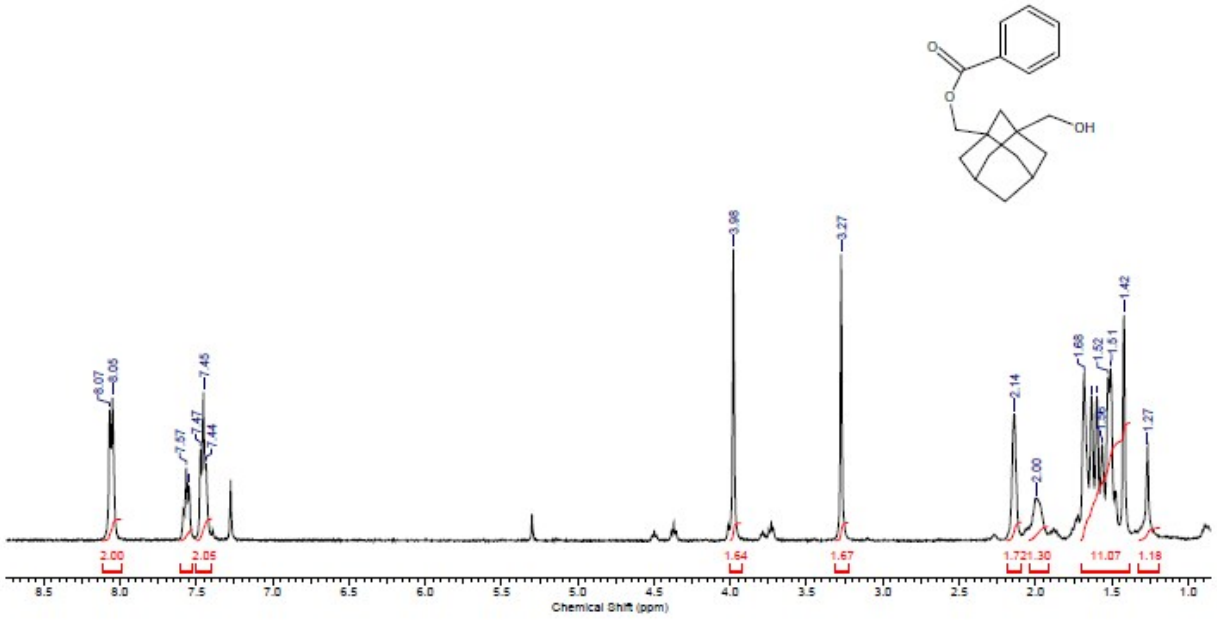
***2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl 3,4-dimethoxybenzoate (12a)* ^{1}H NMR**



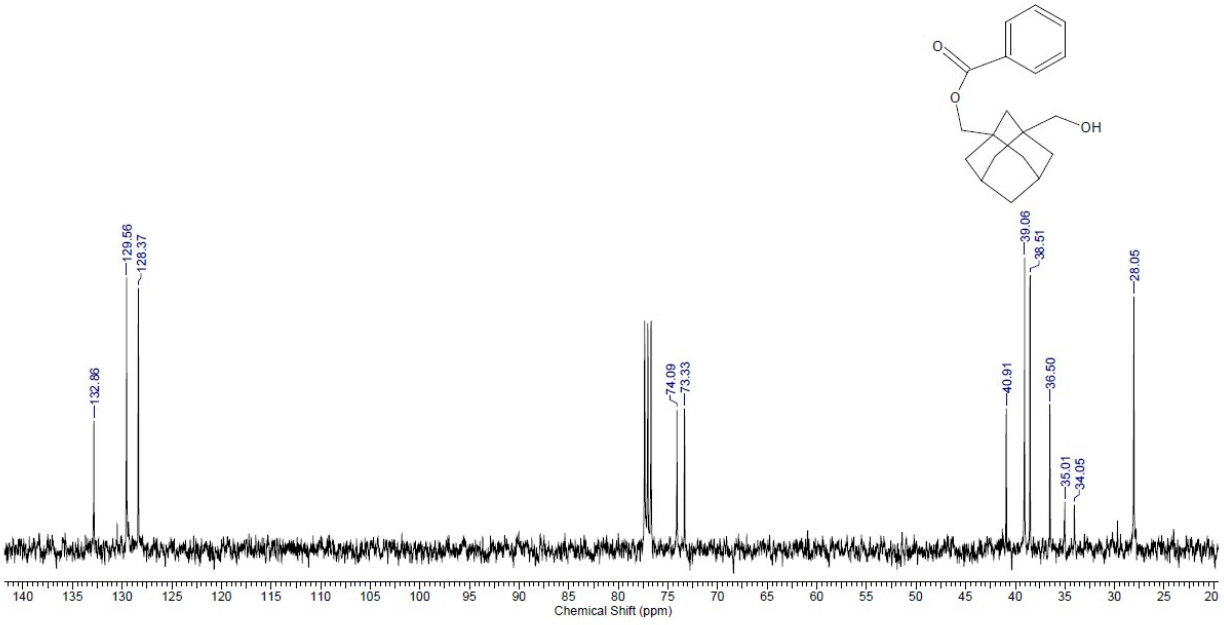
***2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl 3,4-dimethoxybenzoate (12a)* ^{13}C NMR**



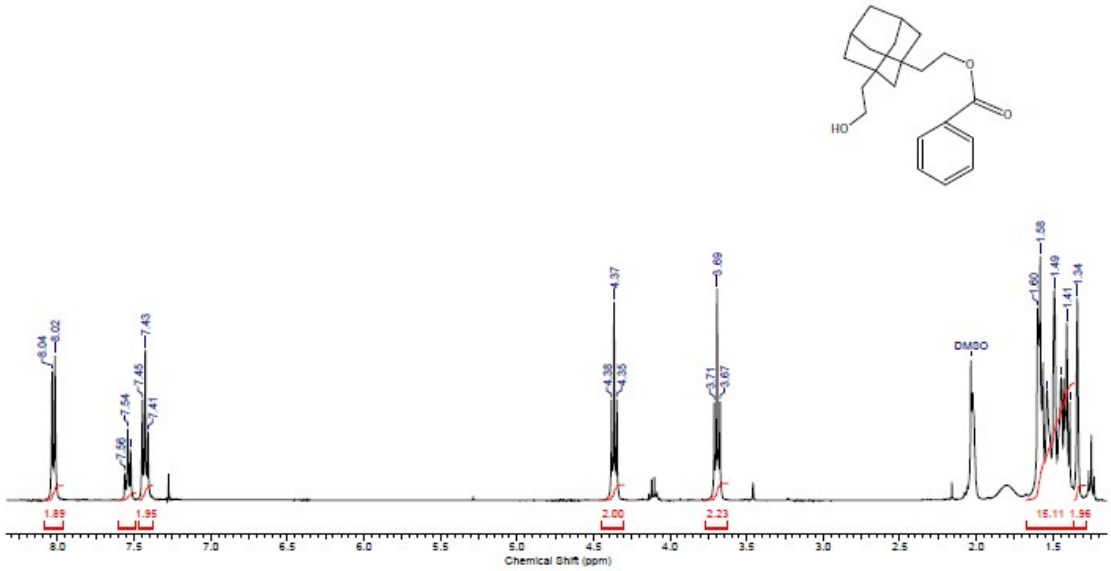
3-(hydroxymethyl)-1-adamantyl)methyl benzoate (12b) ^{1}H NMR



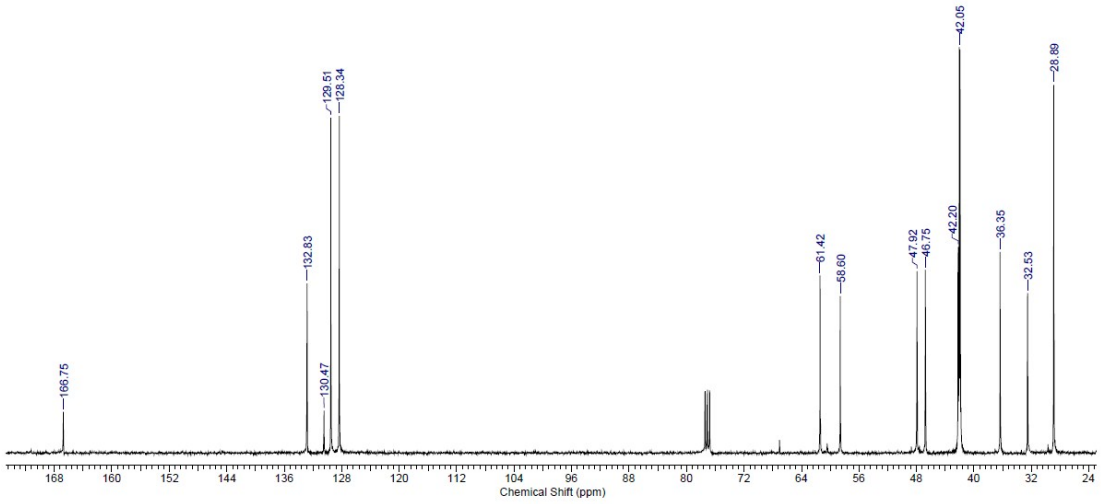
3-(hydroxymethyl)-1-adamantyl)methyl benzoate* (*12b*) ^{13}C *NMR



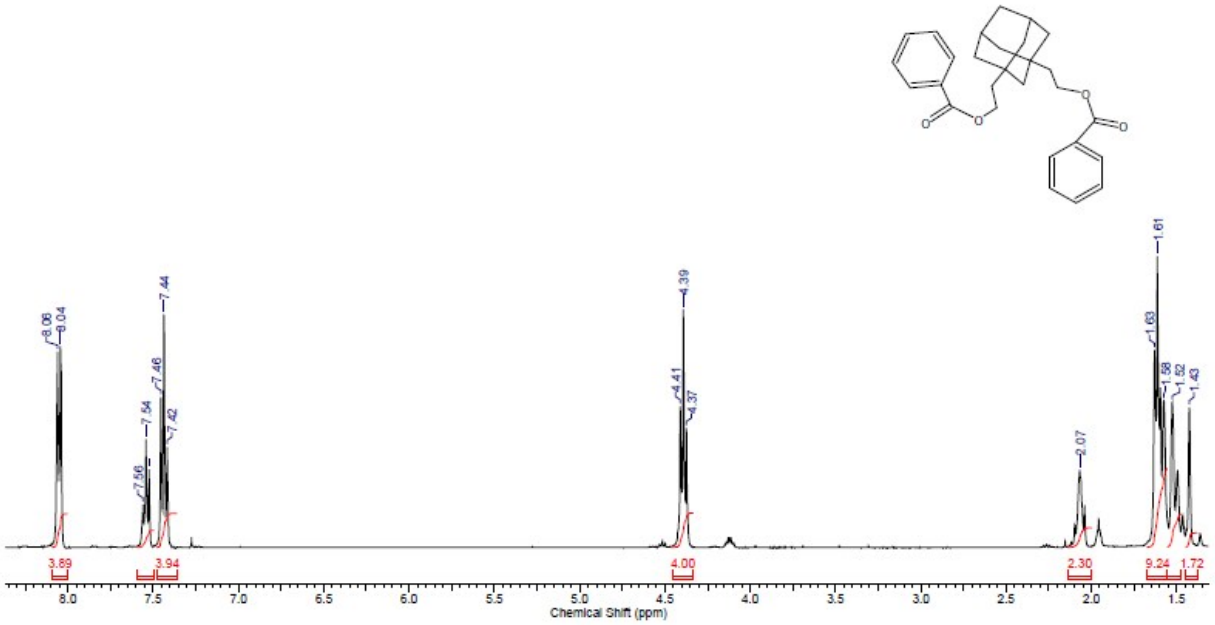
2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl benzoate* (*12c*) *^{1}H NMR



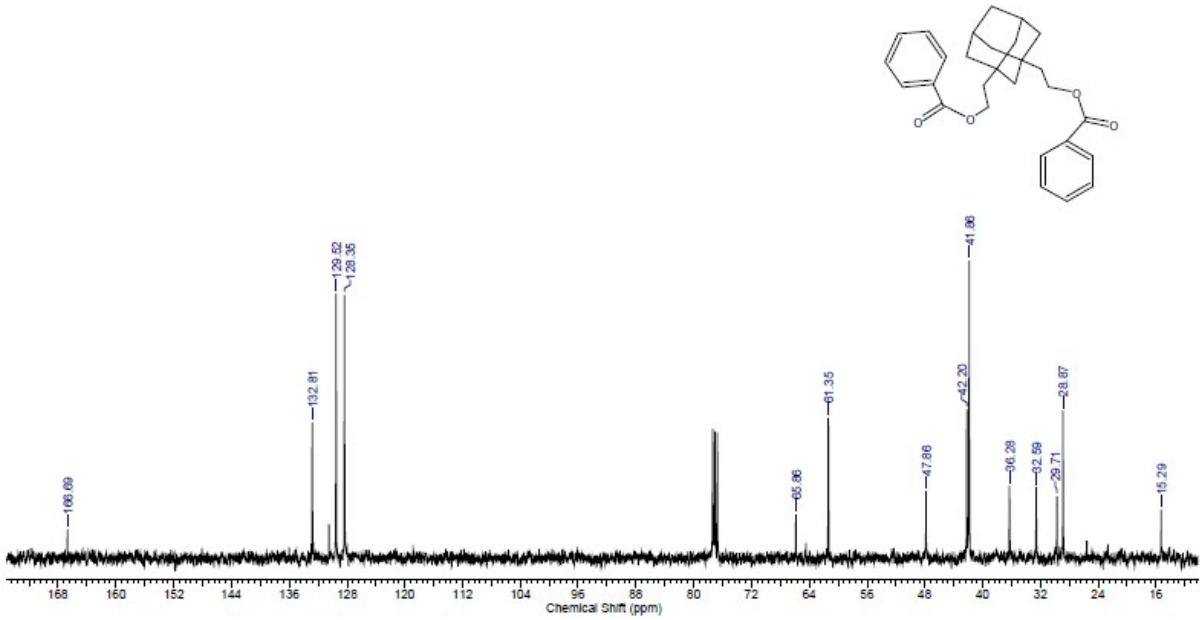
2-(3-(2-hydroxyethyl)-1-adamantyl)ethyl benzoate (12c) ^{13}C NMR



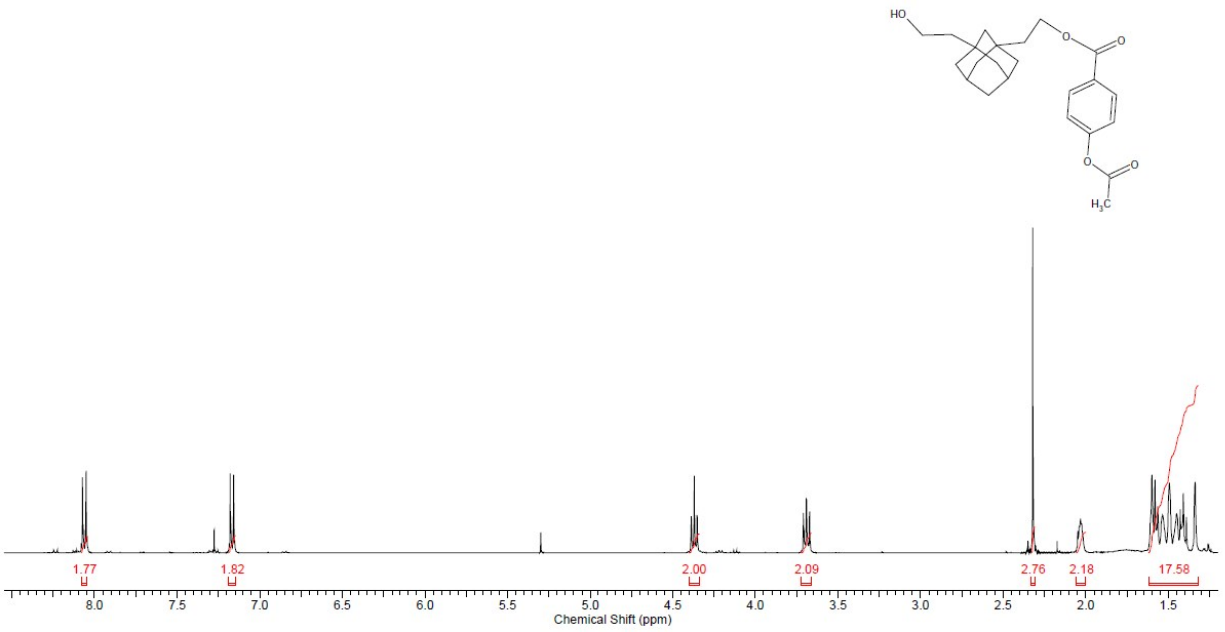
2-(1,3-adamantyl)diethyl dibenzoate (13c) ^{1}H NMR



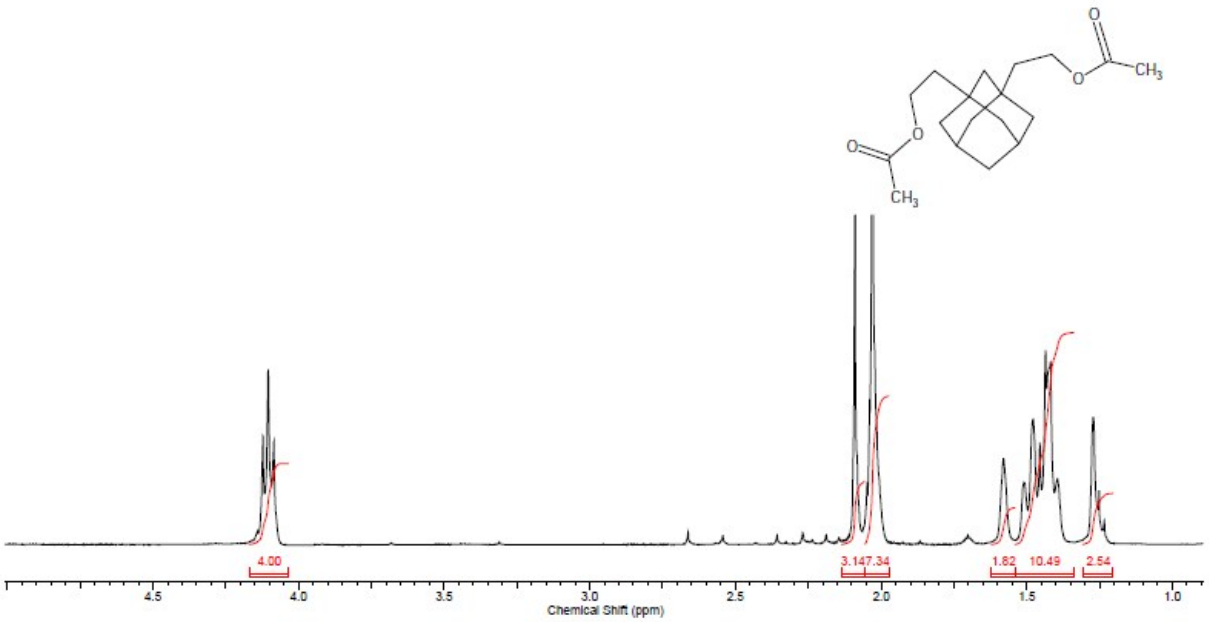
2-(1,3-adamantyl)diethyl dibenzoate (13c) ^{13}C NMR



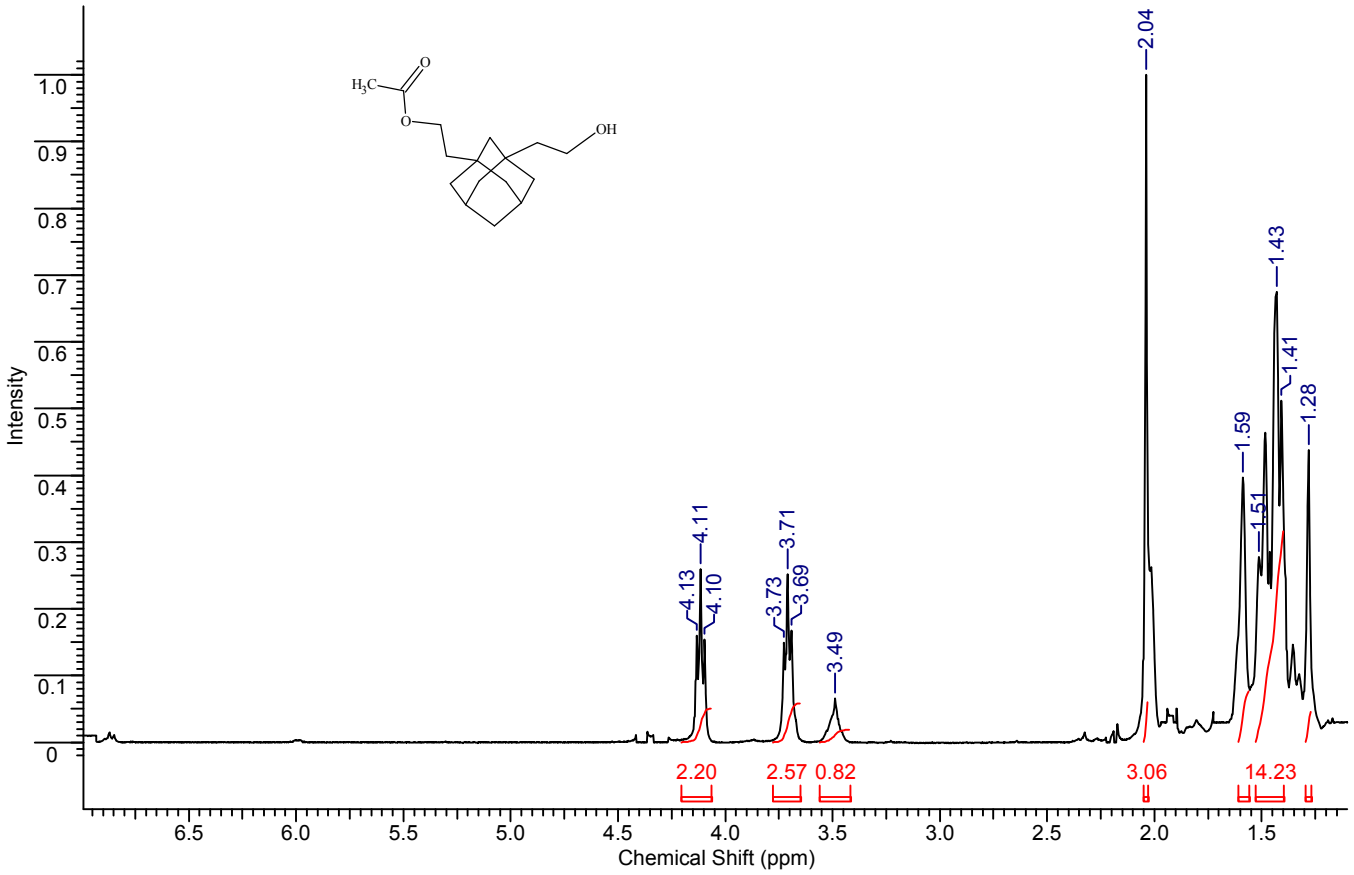
2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl 4-(acetoxy)benzoate (12e) ^{1}H NMR



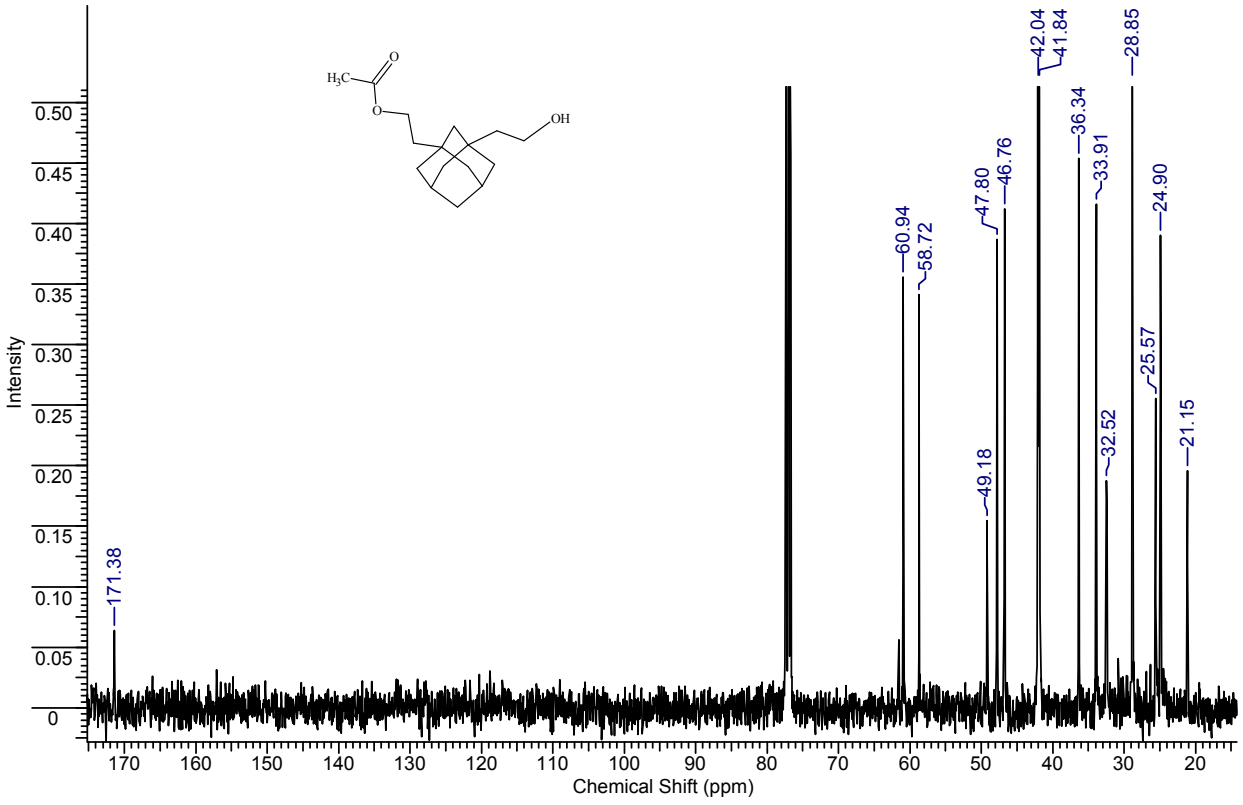
2-(1,3-adamantyl)diethyl diacetate (13a) ^{1}H NMR



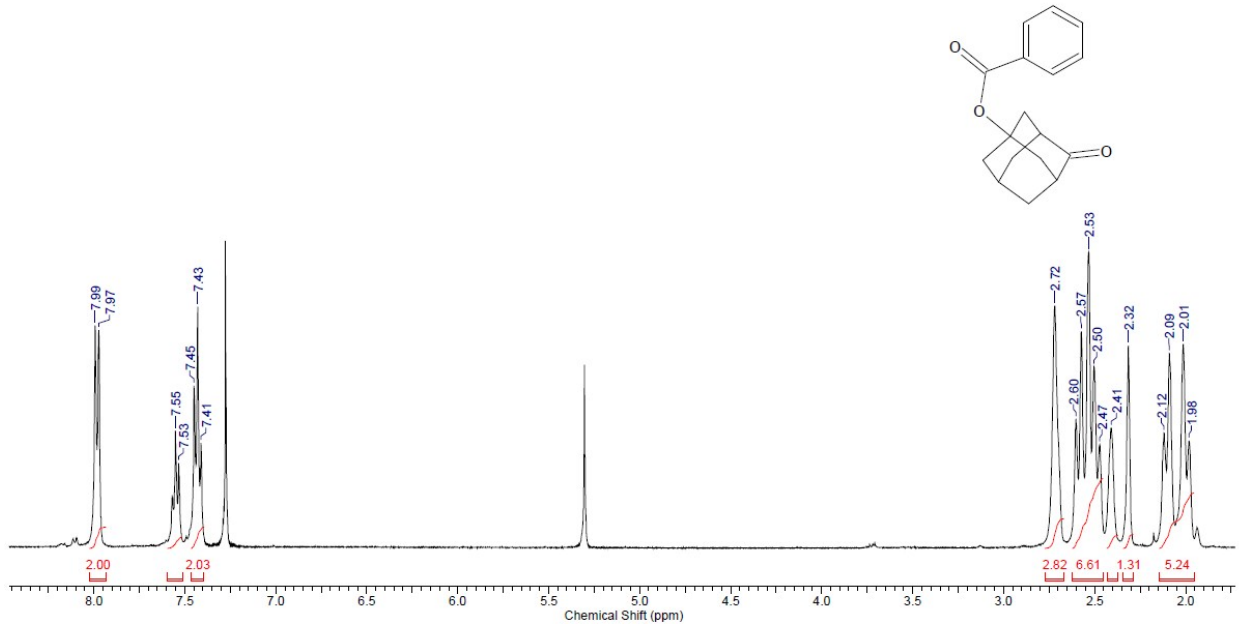
2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl acetate (12f) ^{1}H NMR



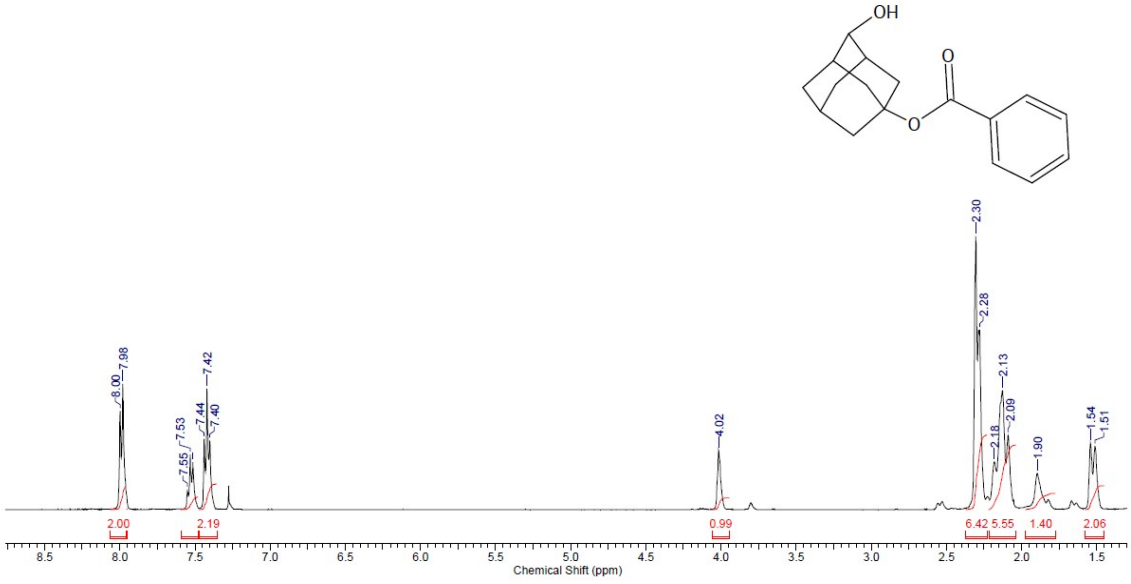
2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl acetate (12f) ^{13}C NMR



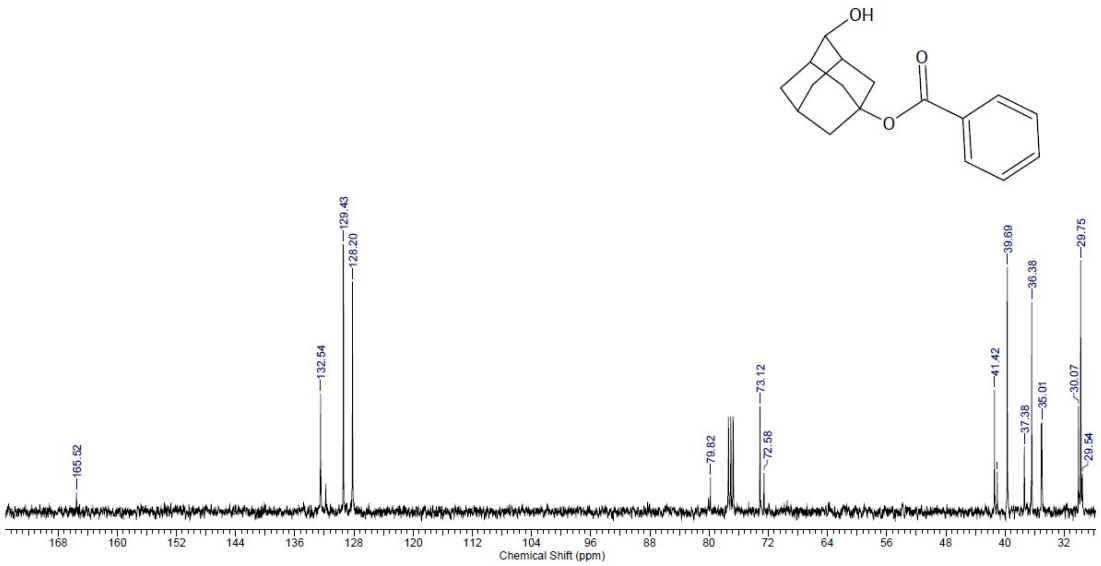
4-oxo-1-adamantyl benzoate (14) ^{1}H NMR



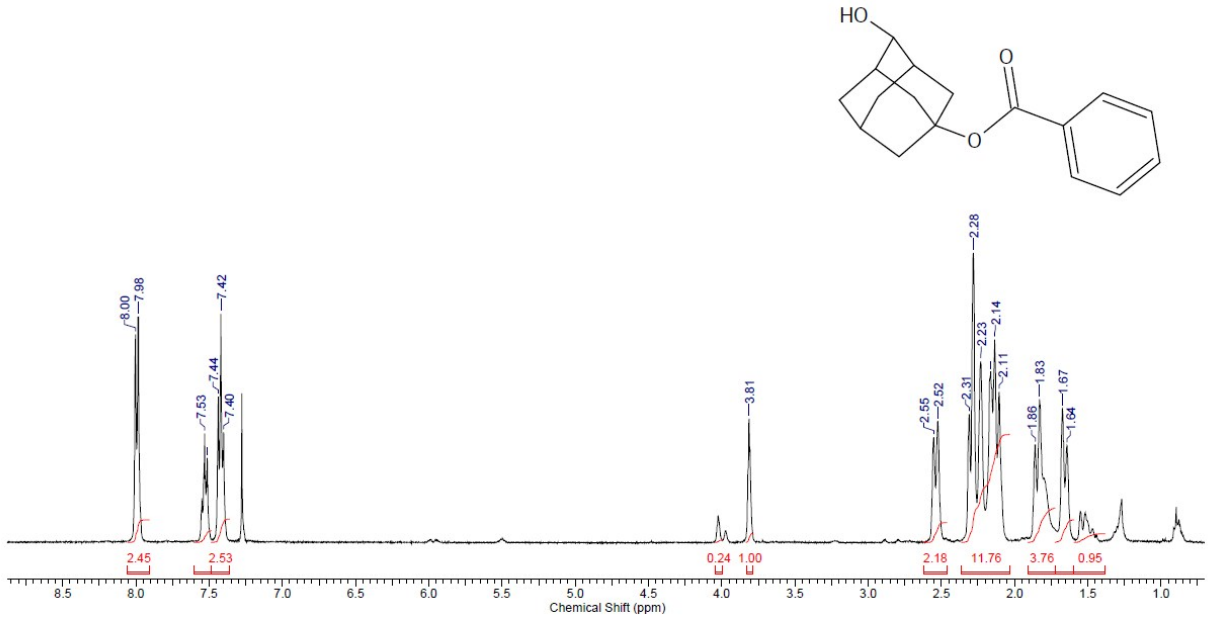
cis-4-Hydroxy-1-adamantyl benzoate (12g) ^{1}H NMR



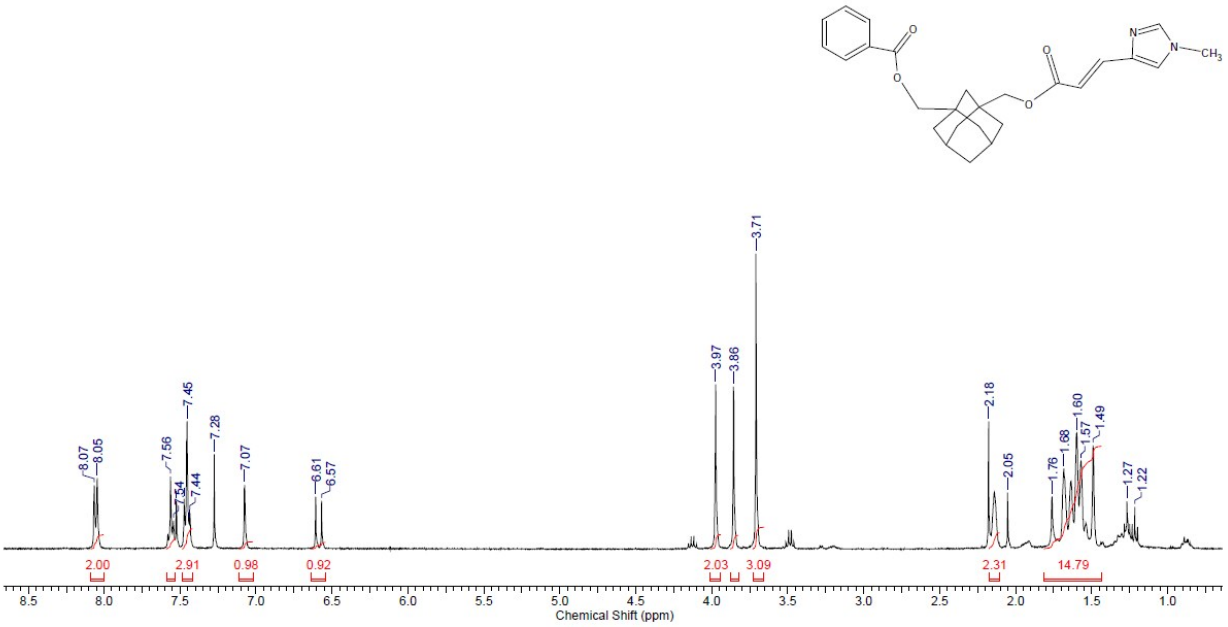
cis-4-Hydroxy-1-adamantyl benzoate (12g) ^{13}C NMR



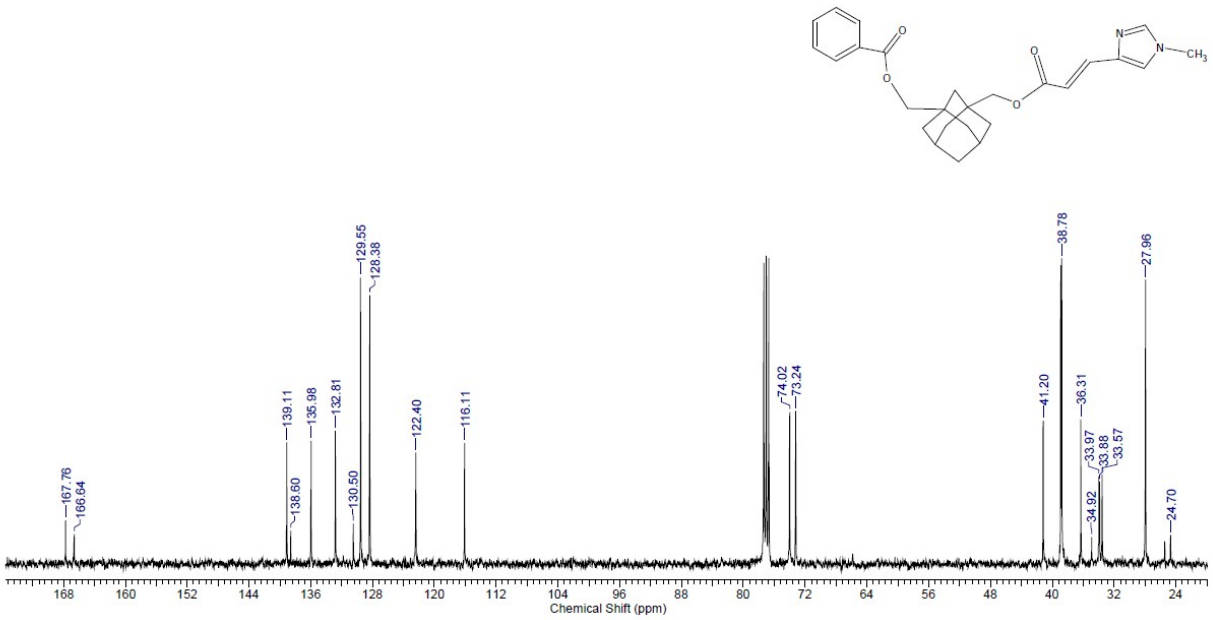
trans-4-Hydroxy-1-adamantyl benzoate (12h) ^{1}H NMR



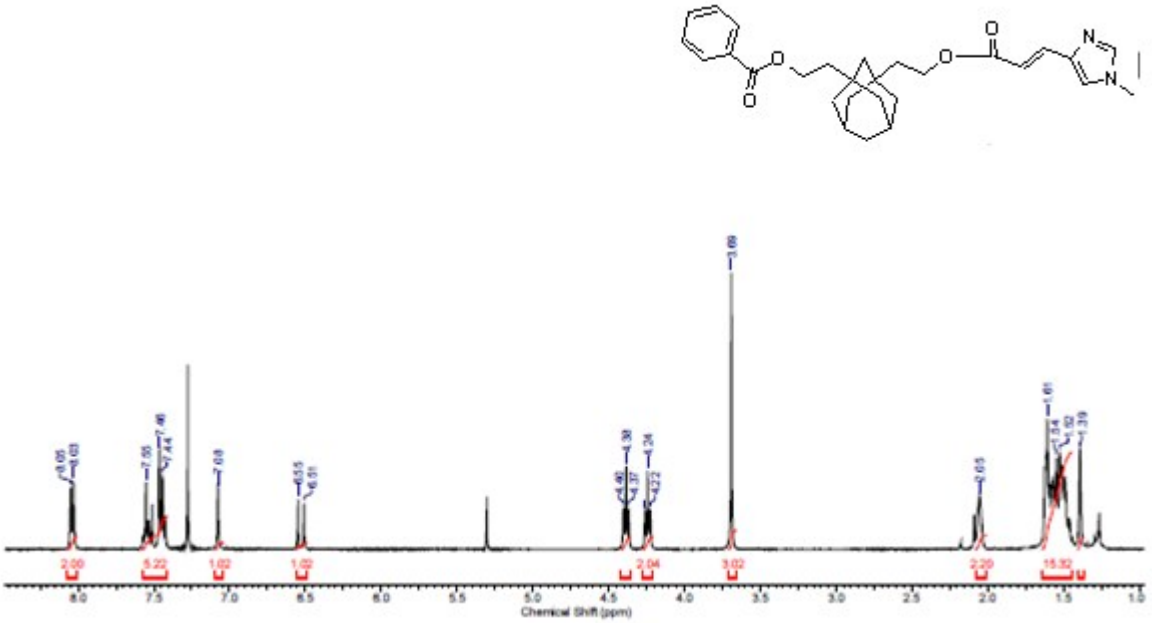
2-(3-((2-(E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoyl)oxy)methyl)-1-adamantyl)methyl benzoate (15a) ^{1}H NMR



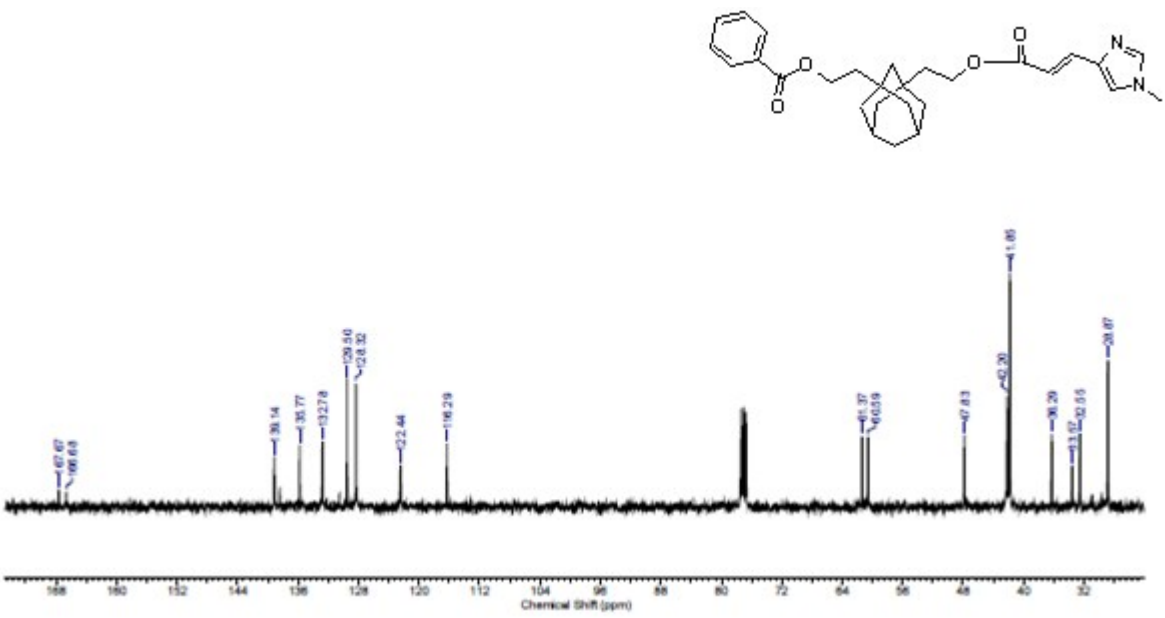
2-(3-((2-(E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoyl)oxy)methyl)-1-adamantyl)methyl benzoate (15a) ^{13}C NMR



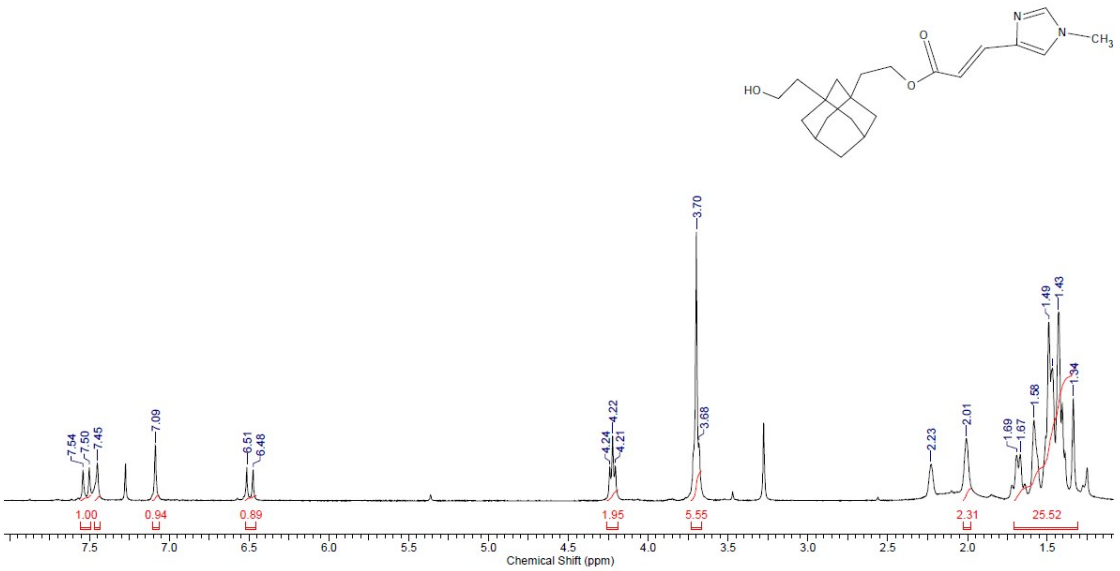
3-((2-(E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoyl)oxy)ethyl)-1-adamantyl)ethyl benzoate (15b) ^{1}H NMR



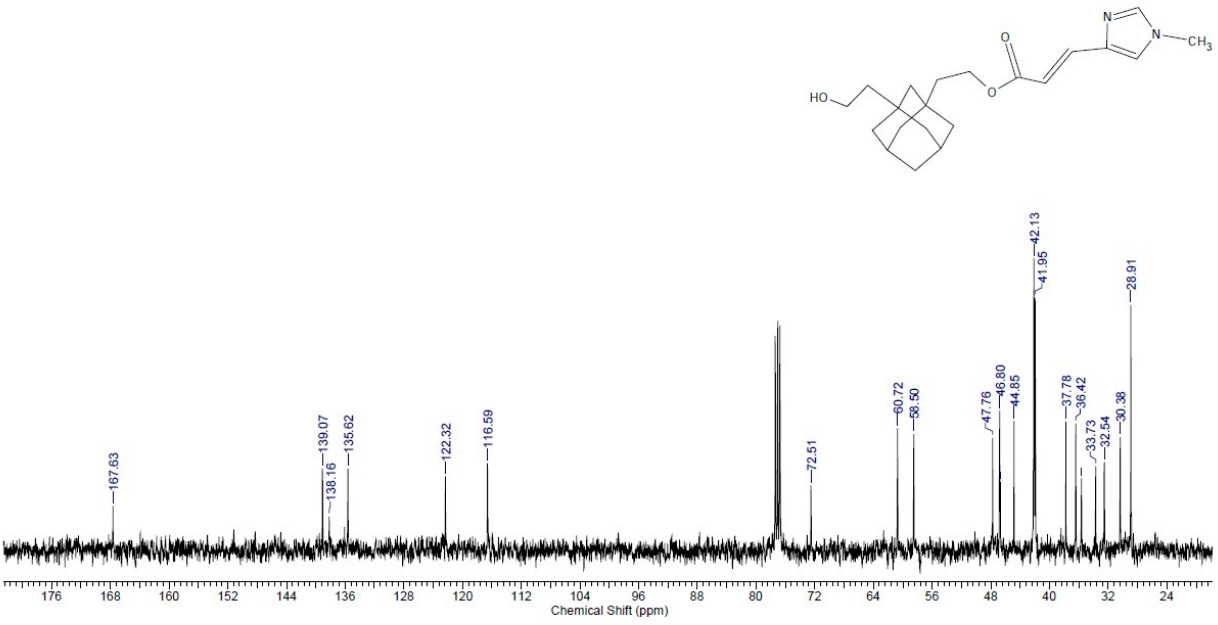
3-((2-(E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoyl)oxy)ethyl)-1-adamantyl)ethyl benzoate (15b) ^{13}C NMR



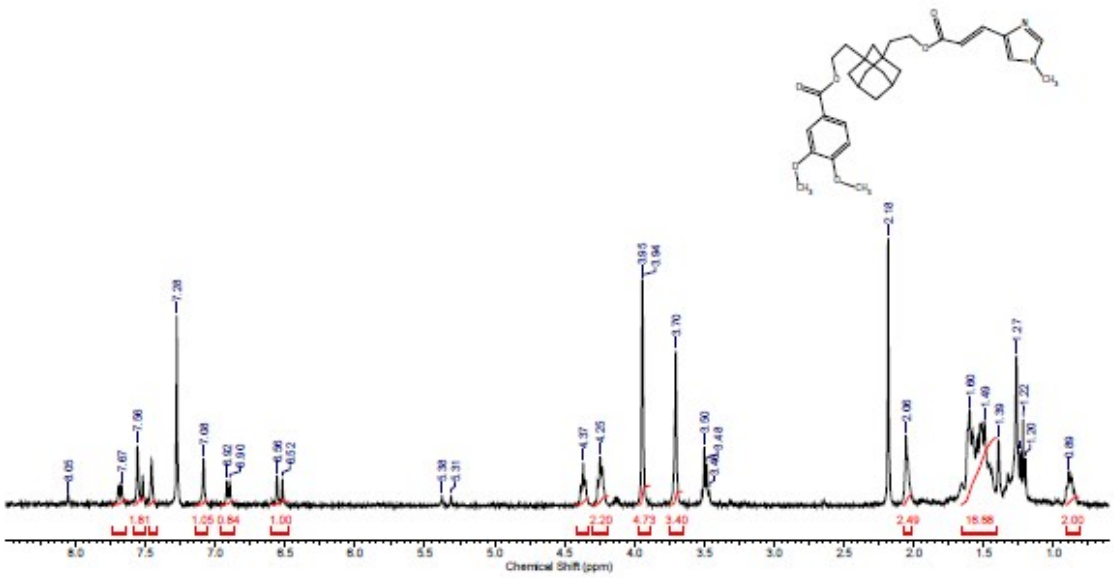
2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl (E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoate (15c) ^{1}H NMR



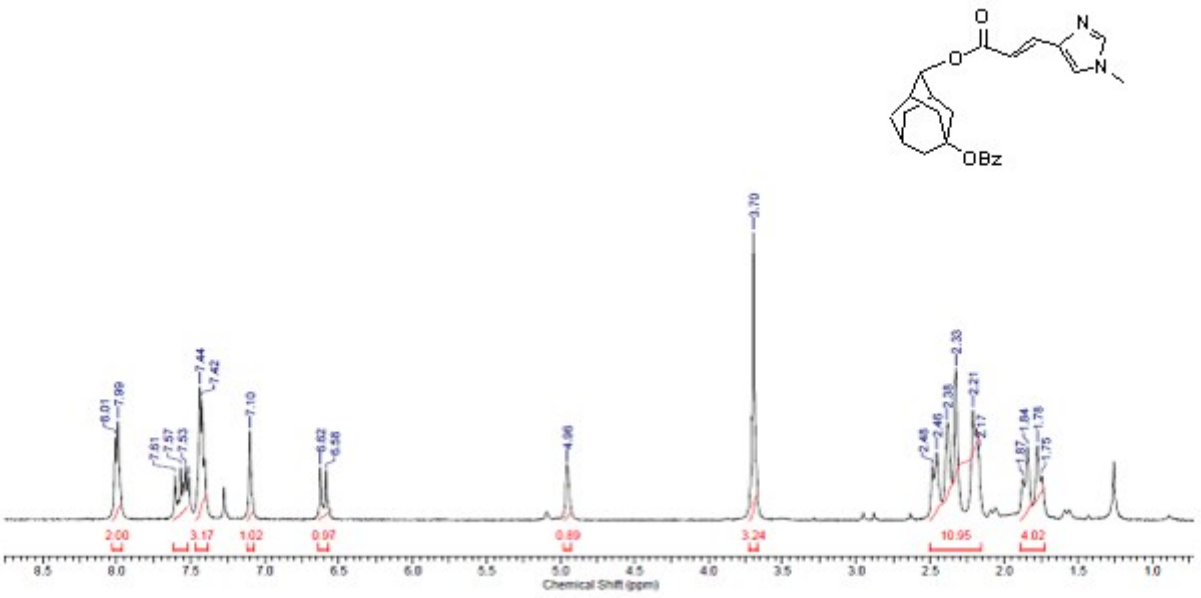
2-(3-(2-Hydroxyethyl)-1-adamantyl)ethyl (E)-3-(1-methyl-1H-imidazol-4-yl)prop-2-enoate (15c) ^{13}C NMR



2-(3-(2-(((E)-3-(1-methyl-1H-imidazol-4-yl)prop-2enoyl)oxy)ethyl)-1-adamantyl)ethyl 3,4-dimethoxybenzoate (15e) ^{1}H NMR



cis-4-(((E)-3-(1-Methyl-1H-imidazol-4-yl)prop-2-enoyl)oxy)-1-adamantyl benzoate (15g) ^{1}H NMR



cis-4-(((E)-3-(1-Methyl-1H-imidazol-4-yl)prop-2-enoyl)oxy)-1-adamantyl benzoate (15g) ^{13}C NMR