Supplementary Information

Dual Responsive Polymeric Nanoparticles Prepared by Direct Functionalization of Polylactic Acid-Based Polymers via Graft-From Ring Opening Metathesis Polymerization

Kate M. Veccharelli, Venus K. Tong, Jennifer L. Young, Jerry Yang and Nathan C. Gianneschi

Department of Chemistry and Biochemistry, University of California, San Diego 9500 Gilman Drive, La Jolla, CA 92093, United States

Correspondence to: Nathan Gianneschi (Email: ngianneschi@ucsd.edu) and Jerry Yang (Email: jerryyang@ucsd.edu)

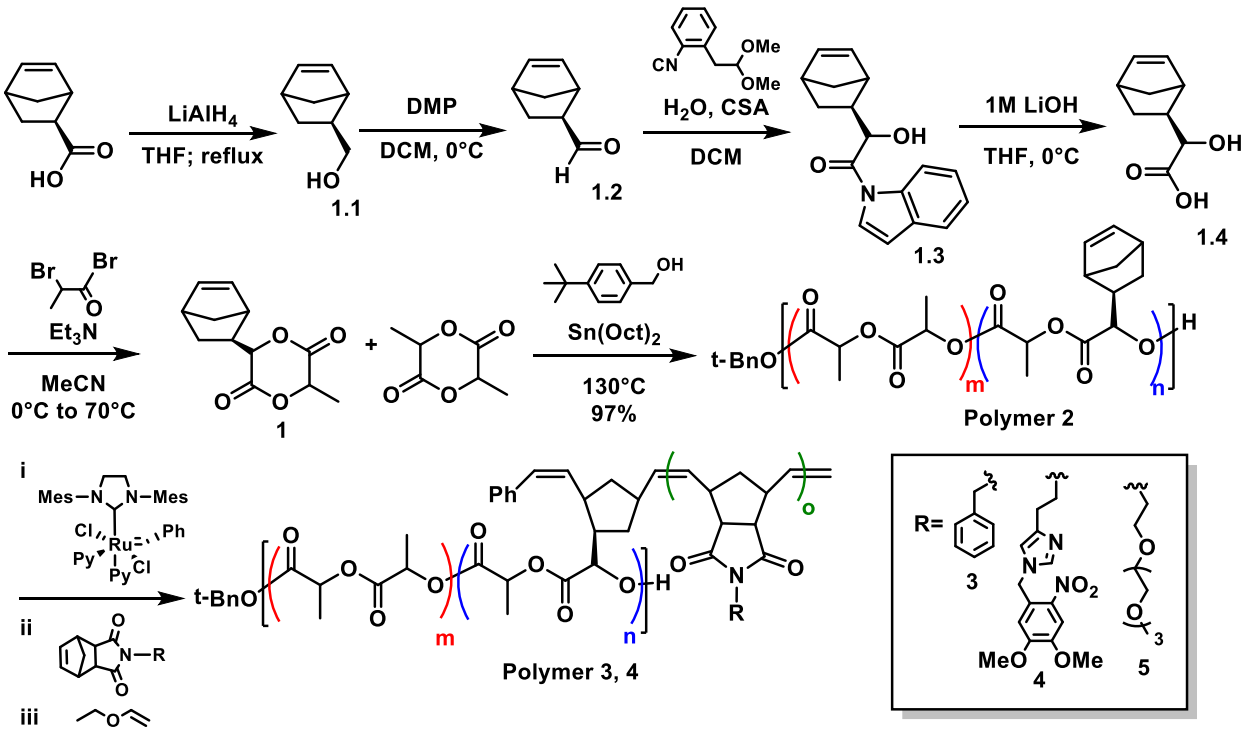
TABLE OF CONTENTS

General Methods

All synthetic reagents were from Aldrich, Fisher Scientific, Alfa Aesar, or Fluka, and were used without further purification unless stated otherwise. All solvents used for reactions were obtained from Fisher scientific and dried on Alumina columns prior to use. Solvents used for chromatography were ACS technical grade and used without further purification. Water (18.2 μΩ/cm) was filtered through a NANOPure DiamondTM (Barnstead) water purification system before use. All ^{1}HNMR spectra of all polymers and small molecule precursors were recorded on a Varian Mercury Plus 400 MHz NMR spectrometer in $CDCl_3$, CD_2Cl_2 or $(CD_3)_2NC(O)D$. ^{13}C NMR spectra of the products were obtained on a Varian VNMRS NMR spectrometer equipped with a 500MHz XSens Cold Probe in $CDCl_3$. Chemical shifts are reported as δ in units of parts per million (ppm) referenced to residue solvent peak. Coupling constants are reported as a J value in Hertz (Hz). Mass spec analysis was performed by the UCSD Chemistry and Biochemistry Molecular Mass Spectrometry Facility on a ThermoFinnigan LCQdeca mass spectrometer with an atmospheric pressure electrospray ionization (APCI) source or an electrospray ionization (ESI) source. Polymer dispersities and molecular weights were determined by size-exclusion chromatography (Phenomenex Phenogel 5u 10, 1K-75K, 300 x 7.80 mm in series with a Phenomex Phenogel 5u 10, 10K-1000K, 300 x 7.80 mm (0.05 M LiBr in DMF, 0.75 mL/min 60oC)) using a Hitachi-Elite LaChrom L-2130 pump equipped with a UV detector (Hitachi- Elite LaChrom L-2420), a multi-angle light scattering detector (DAWN-HELIOS: Wyatt Technology) and a refractive index detector (Optilab T-rEX: Wyatt Technology). Data analysis was performed using the ASTRA software package. TEM images were acquired on a carbon Formvar grid (Ted Pella, Inc.) with 1% uranyl acetate stain on a FEI Tecnai G2 Sphera at 200 kV. The Grubbs' 2nd generation modified catalyst

$(IMesH_2)(C_5H_5N)_2(Cl)_2Ru{=}CHPh$ was prepared according to the published protocols.[1] Irradiation with 350 nm UV light was performed using a Rayonet photoreactor equipped with 8UV-A lamp (8W maximum intensity).

Synthesis Scheme:



Synthesis of PLA with the norbornene molecular handle compound (Polymer 2):

Synthesis of exo-5-Norbornene-2-methanol **(1.1).**

To flame dried 250 mL 3-neck flask, equipped with a stir bar, exo-5-norbornenecarboxylic acid (5.00 g, 36.0 mmol) was added. The flask was purge with N_2 and 125 mL of THF was added via a cannula to dissolve the exo-5-norbornenecarboxylic acid. The flask was cooled in a 0 °C ice bath. While still under N_2, in the ice bath the powdered $LiAlH_4$ (2.75 g, 72.3 mmol) was added slowly. After addition, the reaction was set to reflux for 2 hrs. The reaction was quenched with saturated NH_4Cl solution in an ice bath. The solution was filtered with ether and washed once with water. The organic layer was dried over sodium sulfate and concreted *in vacuo* to give the

alcohol as clear oil (4.49 g, quantitative yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 6.09 (ddd, J = 14.5, 5.7, 3.0 Hz, 2H), 3.78 – 3.64 (m, 1H), 3.55 (d, J = 9.3 Hz, 1H), 2.82 (s, 1H), 2.75 (s, 1H), 1.61 (d, J = 6.3 Hz, 1H), 1.39 (s, 1H), 1.33 (dd, J = 6.1, 4.2 Hz, 1H), 1.31 – 1.27 (m, 1H), 1.27 – 1.22 (m, 1H), 1.15 – 1.06 (m, 1H).

Synthesis of 5-Norbornene-2-carboxaldehyde **(1.2).**

Exo-5-Norbornene-2-methanol **(1.1)** (4.49 g, 36.2 mmol) was dissolved in 150 mL dichloromethane and allowed to stir in a 250 mL round bottom flask at 0 °C in an ice bath. Dess–Martin periodinane (18.42 g, 43.4 mmol) was added and the flask was purged with N_2. The solution was allowed to stir in the ice bath, under N_2, for 4 hrs. The reaction was filtered through a silica plug (100% EtOAc) to purify giving the aldehyde as yellow oil (4.41 g 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ= 9.79 (d, *J* = 2.4 Hz, 1H), 6.16 (ddd, *J* = 25.4, 5.6, 3.1 Hz, 2H), 3.17 – 3.08 (m, 1H), 2.98 (s, 1H), 2.34 – 2.20 (m, 1H), 1.96 (dt, *J* = 11.9, 4.0 Hz, 1H), 1.43 – 1.31 (m, 1H), 1.34 – 1.21 (m, 2H). ESI-MS (*m/z*) calcd for : $C_8H_{10}O$ $[M]^+$ 122.07; found $[M+ Na]^+$ 145.21

Synthesis of 2-(bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxy-1-(1H-indol-1-yl)ethan-1-one **(1.3).**

To a 250 mL round bottom flask 1-(2,2-dimethoxyethyl)-2-isocyanobenzene (7.61g, 39.8 mmol), which was synthesized as previously reported[2], and **1.2** (5.84 g, 47.8 mmol) were dissolved in dichloromethane. While stirring, DI water was added (1.43 g, 79.6 mmol). After 5 min, the camphor sulfonic acid was added to the solution (1.99 g, 8.0 mmol). The solution was allowed to stir for 12 hrs, then the reaction was concentrated *in vacuo* and immediately purified by column chromatography (6:4 DCM: hexanes) giving the desired N-acylindole as a white solid (4.33 g, 41%) . ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.50 (t, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 3.8 Hz, 1H), 7.46 – 7.36 (m, 1H), 7.33 (t, *J* = 7.1 Hz, 1H), 6.70 (t, *J* = 3.7 Hz, 1H), 6.16 –

6.01 (m, 2H), 4.94 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.34 (d, *J* = 8.1 Hz, 1H), 2.81 (d, *J* = 62.0 Hz, 2H), 1.88-1.80 (m, Hz, 1H), 1.68 – 1.50 (m, 2H), 1.42 – 1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 173.43, 137.82, 137.57, 136.82, 130.60, 125.60, 124.48, 121.16, 117.00, 110.33, 74.40, 46.43, 43.93, 43.22, 42.05, 29.13. ESI-MS (*m/z*) calc for $C_{17}H_{17}NO_2$ $[M]^+$ 267.13; found $[M+H]^+$ 268.11.

Synthesis of 2-(bicyclo[2.2.1]hept-5-en-2-yl)-2-hydroxyacetic acid **(1.4).**

To a 250 mL round bottom flask a solution of **(1.3)** (4.33 g, 16. 2 mmol) in 150 mL of THF at 0 °C was added 1.0 M LiOH(aq) (32.1 mL, 32.1 mmol). After 2 hrs, 1.0M NaOH (10 mL) was added to the reaction to ensure a basic pH. The aqueous phase was washed with EtOAc (3 x 100 mL) to remove the indole byproduct. The combined organic layers were back-extracted with 1.0M NaOH (2 x 25 mL). The combined aqueous layers were acidified to pH 2 using 6M HCl and then extracted with ether (6 x 100 mL) The combined organic layers were dried with sodium sulfate and concentrated *in vacuo* to give the α-hydroxy acid as a tan solid (2.31 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 – 6.01 (m, 2H), 4.14 (dd, *J* = 73.4, 7.5 Hz, 1H), 3.02 – 2.77 (m, 2H), 1.84 – 1.70 (m, 1H), 1.58 (tdd, *J* = 16.1, 12.9, 4.1 Hz, 2H), 1.39 (dd, *J* = 37.0, 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 179.89, 137.47, 136.26, 74.06, 45.93,43.62, 43.44, 41.74, 28.79 ESI-MS (*m/z*) calc $[M]^+$ for $C_9H_{12}O_3$ 168.08; found $[M-H]^-$ 167.14

Synthesis of 3-(bicyclo[2.2.1]hept-5-en-2-yl)-6-methyl-1,4-dioxane-2,5-dione **(1)**.

Compound **(1.4)** (1.00 g, 5.94 mmol) and triethylamine (0.63 g, 0.87 mL, 0.062 mmol) were added to a 100 mL flask and dissolved in 50 mL dry acetonitrile and allowed to stir at 0 °C under nitrogen. After 5 min, 2-bromopropionyl bromide (1.4 g, 0.65 mL, 6.24 mmol) was added and the solution was allowed to stir at 0 °C for 30 min. Another equivalent of triethylamine (0.63 g,

0.87 mL, 0.062 mmol) was added and the reaction was allowed to stir at 70 °C for 3 hrs. The product was filtered through a silica plug in EtOAc and concentrated *in vacuo*. The product was recrystallized in toluene, giving the product as a white solid (760 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=6.31 – 5.99 (m, 2H), 5.03 (q, *J* = 6.7 Hz, 1H), 4.75 (dd, *J* = 24.3, 8.7 Hz, 1H), 3.11 – 2.80 (m, 2H), 2.03 (d, *J* = 4.7 Hz, 1H), 1.66 (dt, *J* = 6.7, 3.4 Hz, 3H), 1.57 (dd, *J* = 12.1, 8.6 Hz, 1H), 1.50 – 1.43 (m, 1H), 1.37 (dd, *J* = 20.4, 9.0 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ=167.66, 166.55, 137.56, 135.84, 79.22, 72.14, 45.08, 42.25, 39.88, 30.31, 28.31, 15.81 ESI-MS (*m/z*) calc $[M]^+$ for $C_{12}H_{14}O_4$ $[M]^+$ 222.09; found $[M-H]^-$ 221.17 and $[M+H_2O-H]$ 239.22.

Synthesis of ROMP monomers:

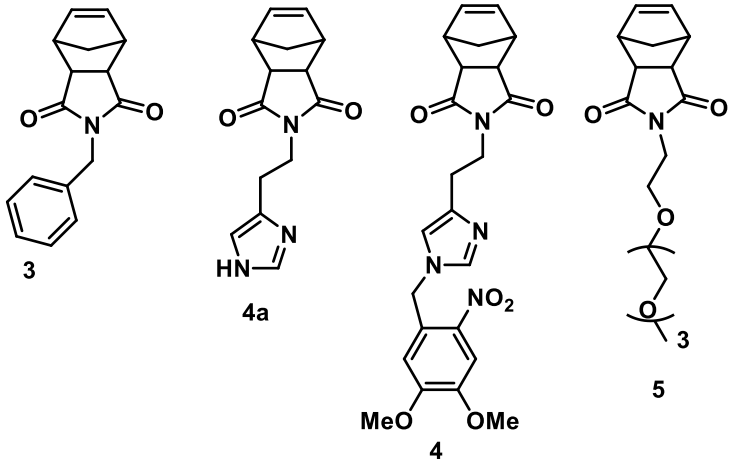


Figure S1. Structure of ROMP monomers.

Synthesis of (N-Benzyl)-5-norborene-exo-2,3-dicarboximide (phenyl monomer **3**).

To a stirred solution of N-benzylamine (2.85 g, 26.6 mmol) in dry toluene (125 mL) were added 5-norbornene-*exo*-2,3-dicarboxylic anhydride (4.10 g, 25.0 mmol) and triethylamine (3.83 mL,

27.5 mmol). The reaction was heated to reflux overnight under an atmosphere of N_2. The reaction was cooled to room temperature and washed with 10% HCl (3 x 50 mL) and brine (2 x 50 mL). The aqueous layers were combined and extracted with ethyl acetate (60 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to dryness, yielding a pale yellow solid that was then recrystallized from ethyl acetate/hexanes to give the product (4.98 g,79%) as white crystals. ^{1}H NMR ($CDCl_3$): δ= 7.25-7.40 (m, 5H), 6.28 (s, 2H), 4.61 (s, 2H), 3.26 (s, 2H), 2.69 (s, 2H), 1.42 (d,1H, *J*=9.6 Hz), 1.07 (d, 1H, *J*=9.6 Hz).). ^{13}C NMR (100 MHz, $CDCl_3$) δ=177.94, 137.71, 135.02, 133.68, 117.20, 47.73, 45.01, 42.56, 38.18, 25.06.

Synthesis of 2-(2-(1H-imidazol-4-yl)ethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (imidazole monomer **4a**).

To a flame dried 100 mL round bottom flask, cis-5-Norbornene-exo-2,3-dicarboxylic anhydride (200 mg, 1.21 mmol) and histamine dihydrochloride (336 mg, 1.82 mmol) were added. The flask was purged with nitrogen and dry DMF was added via a syringe. Triethylamine (1.19 mL, 8.52 mmol) was then added drop wise to the flask while stirring. A condenser was added to the flask and the flask was placed in a 130°C oil bath for 12 hrs. The reaction was concentrated *in vacuo* and purified by column chromatography (9:1:90 MeOH:Et_3N:DCM) giving the product as a brown solid (180 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=11.54 (s, 1H), 7.63 (s, 1H), 6.83 (s, 1H), 6.20 (s, 2H), 3.73 (t, *J* = 7.4 Hz, 2H), 3.15 (s, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.59 (s, 2H), 1.38 (d, *J* = 9.8 Hz, 1H), 1.05 (d, *J* = 9.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ= 177.94, 137.71, 135.02, 133.68, 117.20, 47.73, 45.01, 42.56, 38.18, 25.06. ESI-MS (*m/z*) calc $[M]^+$ for $C_{15}H_{17}N_3O_2$ $[M]^+$ 257.12; found $[M+H]^+$ 258.17 and $[M+Na]^+$ 280.16.

Synthesis of 2-(2-(1-(4,5-dimethoxy-2-nitrobenzyl)-1H-imidazol-4-yl)ethyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (photo-protected imidazole monomer **4**).

Imidazole monomer **(4a)** (100 mg, 0.38 mmol) and 4,5-Dimethoxy-2-nitrobenzyl bromide (128.8 mg, 0.47 mmol) were added to a flame dried 100 mL round bottom flask. The flask was then purged with N_2 and DMF was added via syringe. Potassium carbonate (64.5 mg, 0.47 mmol) was then added to the reaction. The reaction was allowed to stir for 24 hrs at room temperature under a nitrogen atmosphere. The reaction was then diluted with 200 mL DCM and washed with saturated sodium bicarbonate solution (3 x 100 mL), brine (100 mL) and dried over sodium sulfate. The reaction was then filtered, concentrated *in vacuo* and purified by column chromatography (100:0 → 100:3 DCM: MeOH) to yield the product as a pale yellow solid (45 mg, 25%). ^{1}H NMR (400 MHz, CD_3CN) δ =7.73 (d, J = 26.1 Hz, 1H), 7.50 (s, 1H), 6.82 (s, 1H), 6.60 (s, 1H), 6.28 (s, 2H), 5.42 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.63 (t, J = 7.3 Hz, 2H), 3.05 (s, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.58 (s, 2H), 1.29 (d, J = 9.6 Hz, 1H), 1.14 (d, J = 9.7 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ=177.63, 153.81, 148.17, 139.80, 137.57, 137.34, 127.43, 116.19, 109.57, 108.03, 56.20, 47.97, 47.53, 44.81, 42.43, 38.18. 26.19 ESI-MS (*m/z*) calc $[M]^+$ for $C_{24}H_{26}N_4O_6$ 452.17; found $[M+H]^+$ 453.14 and $[M+Na]^+$ 475.07

Synthesis of 2-(2,5,8,11-tetraoxatridecan-13-yl)-3a,4,7,7atetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (tetra(ethylene glycol) norbornene monomer **5**).

A solution of *cis*-5-Norbornene-*exo*-2,3-dicarboxylic anhydride (1.5 g, 9.1 mmol) and 2,5,8,11-tetraoxatridecan-13-amine[3] (2.27 g, 11.0 mmol) in toluene (50 mL) was heated at reflux overnight under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, concentrated to dryness and purified by flash chromatography (2% MeOH in CH_2Cl_2) to give the

product as a light yellow oil, 3.12g (97%). ^{1}H NMR, 400MHz, $CDCl_3$, δ=6.26 (m, 2H), 3.5-3.7 (m, 16H), 3.36 (s, 3H), , 3.24 (m, 2H) , 2.66 (s, 2H) , 1.47, (m, 1H), 1.35 (m, 1H). ^{13}C NMR, 100MHz, $CDCl^3$, δ= 177.91, 137.73, 71.83, 70.50, 69.77, 66.78,58.95, 47.73, 45.19, 42.63, 37.64 HRMS Calc $[M+Na]^+$ = 376.1736, Obs. = 376.1730.

Synthesis of polymers

Procedure for ring opening polymerization (ROP) **(Polymer 2).**

The polymerization was carried out with tin(II) 2-ethylhexanoate (stannous octoate, $Sn(Oct)_2$) (purchased from Alfa Aesar) and 4-tert-butylbenzyl alcohol (purchased from Acros) without further purification. The polymerization method is similar to that described by Baker and coworkers.[3] $Sn(Oct)_2$ (0.01M in anhydrous toluene, 7.76 mL) and 4-*tert*-butylbenzyl alcohol (0.01M in anhydrous toluene, 7.76 mL) were added to a small 20 mL pear shaped flask and the solution was concentrated *in vacuo*.

To the flask was then added D,L-lactide (1.0 g, 9.7 mmol) (freshly recrystallized from toluene) and compound **(1)** (333.6 mg, 1.5 mmol). The flask was then equipped with a small stir bar and placed under vacuum. After 1 hour, the flask was flushed with nitrogen, tightly sealed and heated at 130 °C in a silicone oil bath for 2 hrs. After the reaction was complete, the flask was cooled in an ice bath, dissolved in CD_2Cl_2 and the crude was analyzed by ^{1}H NMR. A small aliquot of the CD_2Cl_2 solution was concentrated *in vacuo*, redissolved in DMF, filtered through a Whatman Anontop 10 0.2 μm filter and analyzed by SEC-MALS to determine the molecular weight of the polymer. To purify, the polymer was dissolved in dichloromethane and precipitated with cold methanol. The degree of polymerization (conversion of monomer to polymer) calculated from ^{1}H NMR was 98%. The polymer was obtained as a light brown solid (1.55 g, 90%).

Procedure for graft-from ring opening metathesis polymerization of phenyl monomer **(Polymer 3).**

Graft-from PLA polymers were polymerized using Grubbs' modified second generation catalyst [$(H_2IMES)(pyr)_2(Cl)_2Ru$=CHPh]. Polymer **2** (10 mg, 0.0026 mmol) was dissolved in in dry, degassed CH_2Cl_2 (8 mL) in a 10 mL vial under a nitrogen atmosphere. The catalyst (2.13 mg, 0.0029 mmol) 1.1 equivalents with respect to norbornene units, was also dissolved in dry, degassed CH_2Cl_2 in a separate vial (0.2 mL). The polymer solution was added to the Grubb's catalyst and the solution was allowed to stir for 10 min. Degassed cold MeOH was added to the vial via a syringe to precipitate out the catalyst loaded PLA polymer. The vial was centrifuged at 4000 rpm for 5 min. The supernatant was removed via syringe, to ensure that there was no free Grubbs' catalyst in solution. The polymer was resuspended in degassed dichloromethane and monomer **3** was added (3.36 mg, 0.013 mmol), 5 equivalents with respect to norbornene units. The reaction was left to stir for 1 hr before quenching with ethyl vinyl ether. The polymer was purified by precipitation into cold ether. ^{1}H-NMR, in CD_2Cl_2, was used to determine the degree of polymerization of the PLA-ROMP polymer. A small aliquot of the polymer was dissolved in DMF, filtered through a Whatman Anontop 10 0.2 μm filter and analyzed by SEC-MALS to determine the molecular weight and dispersity of the polymer.

Procedure for the negative control reaction: verification of precipitation step.

Unfunctionalized PLA (10 mg, 0.0030 mmol) is dissolved in 8 mL of degassed, dry CD_2Cl_2 and added to a solution of Grubb's catalyst (2.40 mg, 0.033 mmol), 1.1 equivalents with respect to

the number of norbornene units on polymer **2** and was stirred for 10 min under a nitrogen atmophere. Degassed cold MeOH was added to the vial via a syringe to precipitate out the unfunctionalized PLA polymer. The vial was centrifuged at 4000 rpm for 5 min. The supernatant was removed via syringe, to ensure that there was no free Grubbs' catalyst in solution. The polymer was then resuspended in degassed CD_2Cl_2 and monomer 3 was added (3.80 mg, 0.150 mmol), 5 equivalents with respect to norbornene units on polymer **2**. The reaction was left to stir for 30 min before taking an ^1H NMR spectrum. None of the phenyl peaks in the NMR are broadened and olefin peak $\delta = 6.26$ ppm is still present which indicates no polymerization. After the reaction: the polymer was precipitated with cold MeOH, which yielded unfunctionalized PLA.

Procedure for graft-from ring opening metathesis polymerization of nitro benzyl protected imidazole monomer **(Polymer 4).**

Graft-from PLA polymers were polymerized using Grubbs' modified second generation catalyst [$(H_2IMES)(pyr)_2(Cl)_2Ru$=CHPh]. Polymer **2** (10 mg, 0.0026 mmol) was dissolved in in dry, degassed CH_2Cl_2 (8 mL) in a 10 mL vial under a nitrogen atmosphere. The catalyst (2.13 mg, 0.0029 mmol), 1.1 equivalents with respect to norbornene units was also dissolved in dry, degassed CH_2Cl_2 in a separate vial (0.2 mL). The polymer solution was added to the Grubb's catalyst and the solution was allowed to stir for 10 min. Degassed cold MeOH was added to the vial via a syringe to precipitate out the catalyst loaded PLA polymer.. The vial was centrifuged at 4000 rpm for 5 min. The supernatant was removed via syringe, to ensure that there was no free Grubbs' catalyst in solution. The polymer was resuspended in degassed dichloromethane and the imidazole ROMP monomer **4**, was added (6.03 mg, 0.013 mmol), 5 equivalents with respect to

norbornene units on PLA polymer **2**. The reaction was left to stir for 6 hrs before quenching with ethyl vinyl ether. The polymer was purified by precipitation into cold ether. ^{1}H-NMR, in $CDCl_3$ was used to determine the degree of polymerization of the PLA-ROMP polymer and molecular weight (M_n). Dispersity (Đ) was not able to be determined since the polymer aggregates in the conditions used for SEC-MALS.

Procedure for graft-from ring opening metathesis polymerization of nitro benzyl protected imidazole monomer **4** with tetra(ethylene glycol) norbornene monomer **5 (Polymer 4b).**

Graft-from PLA polymers were polymerized using Grubbs' modified second generation catalyst [$(H_2IMES)(pyr)_2(Cl)_2Ru$=CHPh]. The PLA polymer (10 mg, 0.0026 mmol) was dissolved in in dry, degassed CH_2Cl_2 in a 10 mL vial under a nitrogen atmosphere. The catalyst (2.13 mg, 0.0029 mmol), 1 equivalent with respect to norbornene units on the PLA backbone, was also dissolved in dry, degassed CH_2Cl_2. Polymer **2** was added to the Grubb's catalyst solution and the solution was allowed to stir for 10 min. Degassed cold MeOH was added to the vial via a syringe to precipitate out the catalyst loaded PLA polymer. The vial was centrifuged at 4000 rpm for 5 min. The supernatant was removed via syringe, to ensure that there was no free Grubbs' catalyst in solution. The polymer was resuspended in degassed dichloromethane and the imidazole ROMP monomer **4**, was added (6.03 mg, 0.013 mmol), 5 equivalents with respect to the norbornene units. The reaction was left to stir for 6 hrs before the tetra(ethylene glycol) norbornene monomer **5**, (4.17 mg, 0013 mmol), 5 equivalents with respect to norbornene units, was added. The reaction was left to stir for another 3 hrs before quenching with ethyl vinyl ether. The polymer was purified by precipitation into cold ether. ^{1}H-NMR, in $CDCl_3$ was used to determine the degree of polymerization of the PLA-ROMP polymer and molecular weight (M_n).

Dispersity (Đ) was not able to be determined since the polymer aggregates in the conditions used for SEC-MALS.

Procedure for nanoparticle synthesis

Procedure for nanoparticle formation via the solvent evaporation: 2 mg of **polymer 2** or unfunctionalized PLA was dissolved into 2 mL of THF. This solution was added to 2 mL of DI H_2O via syringe pump at a rate of 8 mL/hr. The solution was allowed to stir for 30 min and was subsequently concentrated *in vacuo* to remove the THF. Nanoparticles were analyzed by DLS and TEM.

Procedure for nanoparticle formation via the dialysis method: Unsuccessful attempts with polymer 4: Many solvents were screened to attempt to formulate nanoparticles of **polymer 4** via the solvent evaporation method. The polymer was only soluble in methylene chloride, THF, DMF and DMSO. Methylene chloride is not soluble in water thus 2 mg of the polymer was added to 2 mL of DI H_2O and 2 mL of methylene chloride and sonicated attempting formulation of nanoparticles via the nanoprecipitation method, but the only result was large aggregated polymers, not well defined nanostructures. **Polymer 4** was only sparingly soluble in THF, even with heating. When nanoparticle formation was attempted at the same concentrations as above, the polymer crashed out of solution. Luckily the polymers were very soluble in DMF and DMSO, however both solvents have a higher boiling point than water so the solvent evaporation method was not possible. Therefore the dialysis method was used to formulate nanostructures of **polymer 4**. 1 mg of **polymer 4** was dissolved in 900 μL of DMSO. 100 μL of DI H_2O was added to the solution over 10 min while stirring. The solution was allowed to stir for 12 hrs. The solution was transferred to a MWCO 3,500 Slide-A-Lyzer™ MINI Dialysis Device, 2 mL and

placed in 1 L of 0.02M pH 7.4 MOPS buffer or 0.02M pH 5.5 MES buffer. The dialysis water was changed 3 times over 24 hrs. This procedure yielded only large aggregates and not well-dispersed spherical particles. Thus in an attempt to create spherical nanoparticles **polymer 2** was polymerized with monomer **4** and the tetra(ethylene glycol) norbornene monomer **5** to increase water solubility(yielding **polymer 4b**.) Dialysis conditions (DMSO into water or buffer) was utilized to create well-defined nanostructures. Dialyzing from DMSO gave more uniform nanostructures than dialyzing from DMF into water or buffer.

Procedure for nanoparticle formation via the dialysis method: Successful attempts with polymer 4b: 1 mg of **polymer 4b** was dissolved in 900 µL of DMSO. 100 µL of DI H_2O was added to the solution over 10 min while stirring. The solution was allowed to stir for 12 hrs. The solution was transferred to a MWCO 3,500 Slide-A-Lyzer™ MINI Dialysis Device, 2 mL and placed in 1 L of 0.02M pH 7.4 MOPS buffer or 0.02M pH 5.5 MES buffer. The dialysis water was changed 3 times over 24 hrs. Nanoparticles were transferred to a small Eppendorf tube for TEM and DLS analysis.

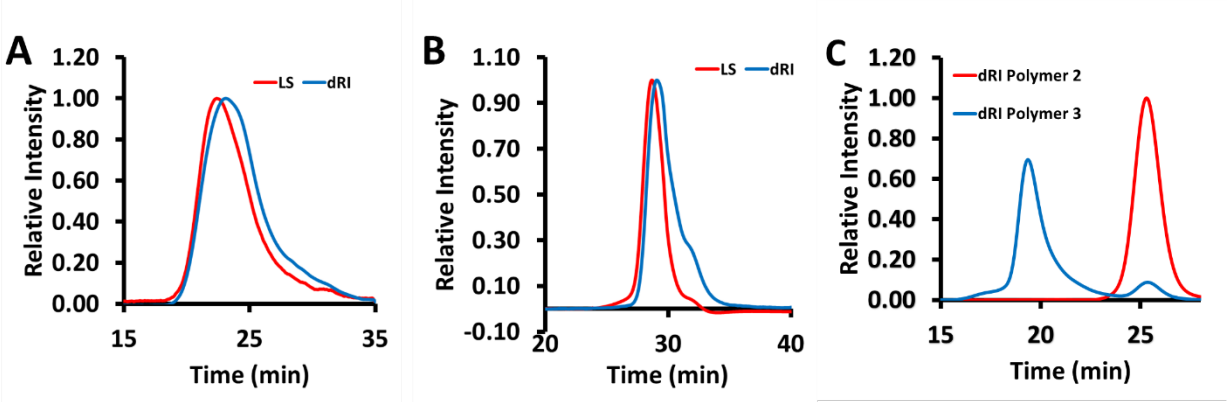


Figure S2: SEC-MALS traces of (A) polymer **2** in DMF as the eluent M_n= 32,260, Đ=1.4 and (B) polymer **3** in chloroform as the eluent M_n= 51,290, Đ=1.8 (C) comparison of dRI of polymer **2** and polymer **3** with DMF as the eluent.

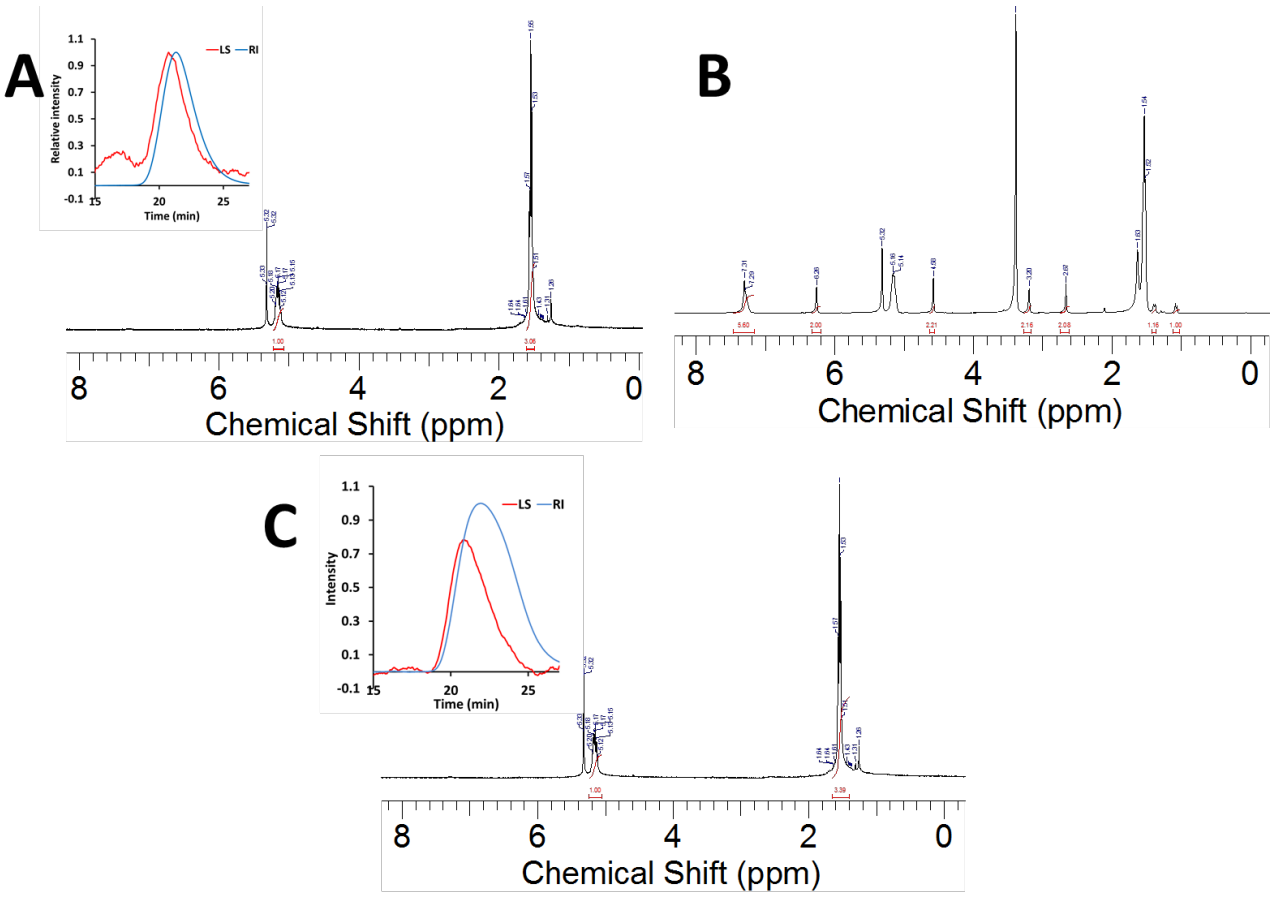


Figure S3: (A) Before reaction SEC-MALS in DMF as the eluent (Mn= 12,000 and Đ 1.2) and ^{1}H NMR. Unfunctionalized PLA polymer was added to a solution of 2nd generation Grubb's catalyst followed by precipitate with cold degassed methanol (B) Add 5 equivalents of phenyl monomer ^{1}H NMR t = 30 min. None of the phenyl peaks in the NMR are broadened and olefin peak δ = 6.26 ppm is still present which indicates no polymerization. (C) After the reaction: SEC-MALS in DMF as the eluent (Mn= 13,000 and Đ 1.3) and ^{1}H NMR. The product was precipitated with cold MeOH which yielded unfunctionalized PLA.

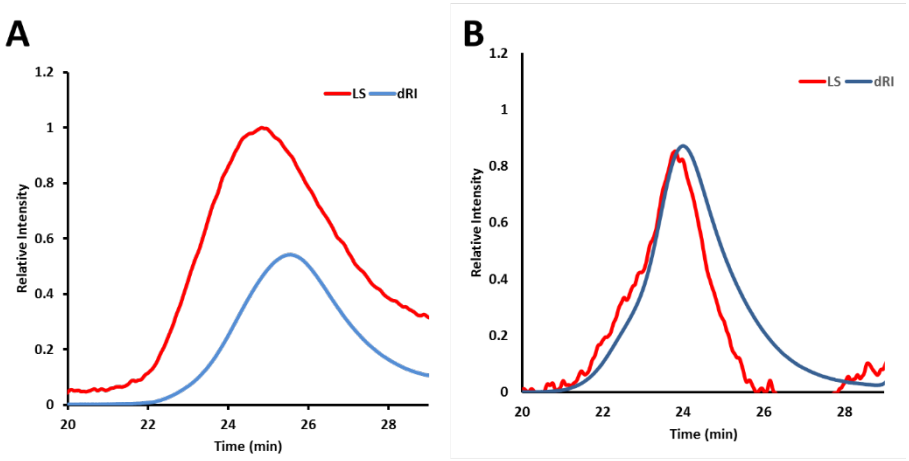


Figure S4: SEC-MALS traces of cross-linking control reaction. (A) SEC-MALS traces of polymer **2** in DMF as the eluent M_n= 44,000 Đ=1.1 and (B) after loading 2nd generation Grubb's and utilizing ethyl vinyl ether as a cross metathesis reactant. DMF as the eluent M_n= 46,000 Đ=1.1 There is no evidence of crosslinked polymers based on SEC-MALS.

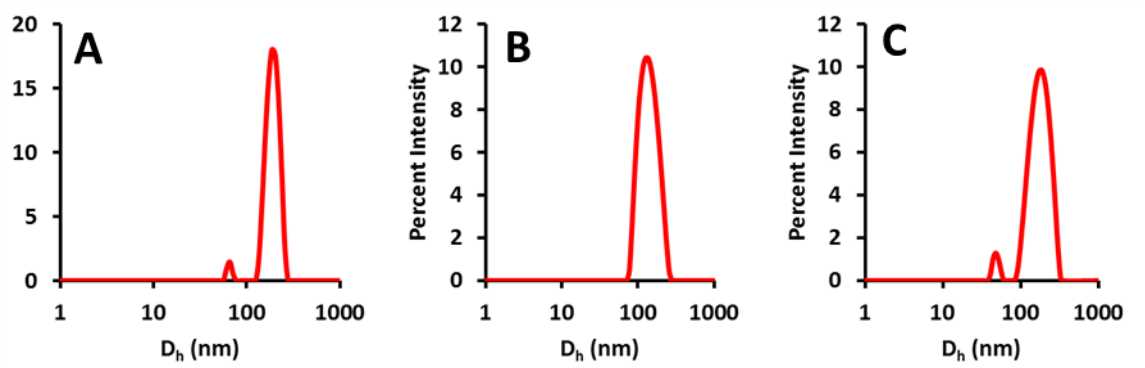


Figure S5: DLS of (A) unfunctionalized PLA (B) polymer **2** and (C) polymer **3**. All DLS traces

are in DI water.

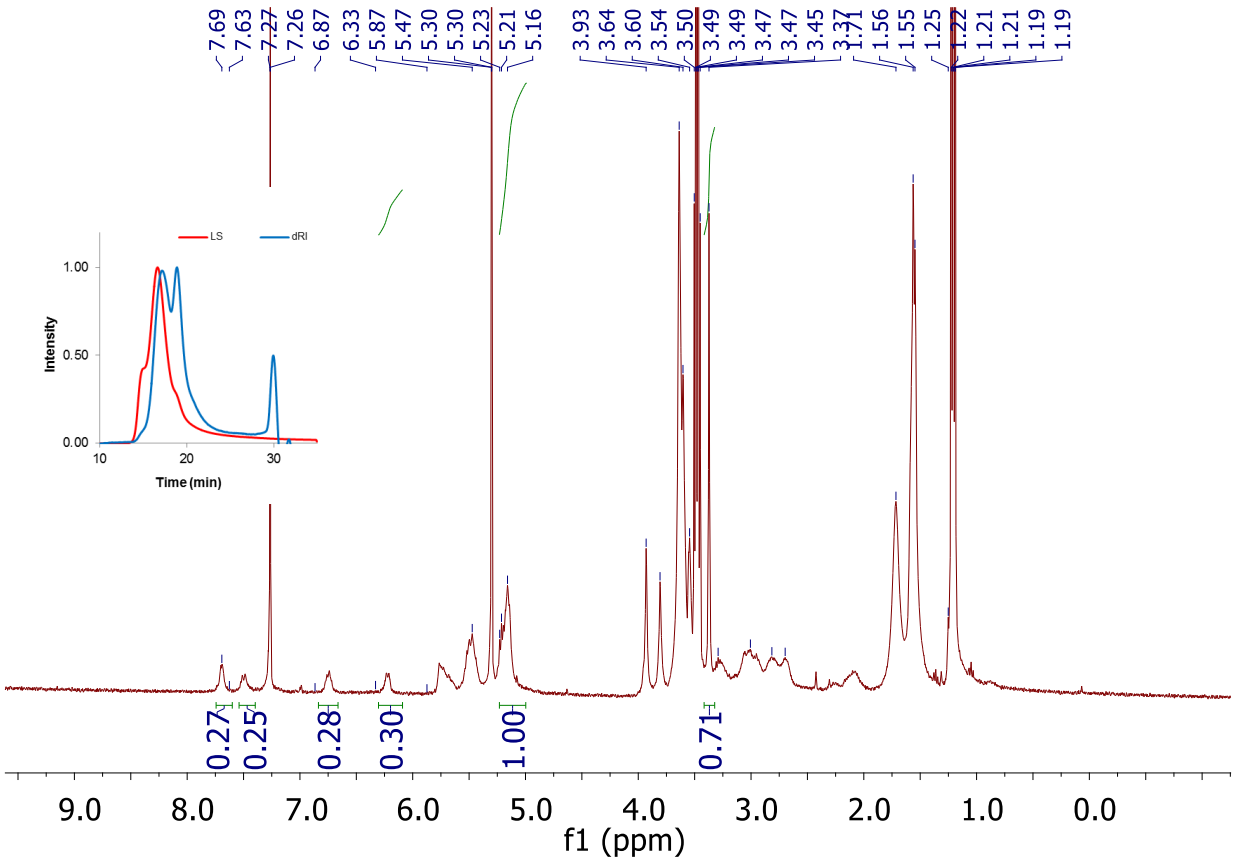


Figure S6: ^{1}H NMR and SEC-MALS in DMF as the eluent of polymer **4b**. Dispersity was not able to be determined since the polymer aggregates in the conditions used for SEC-MALS.

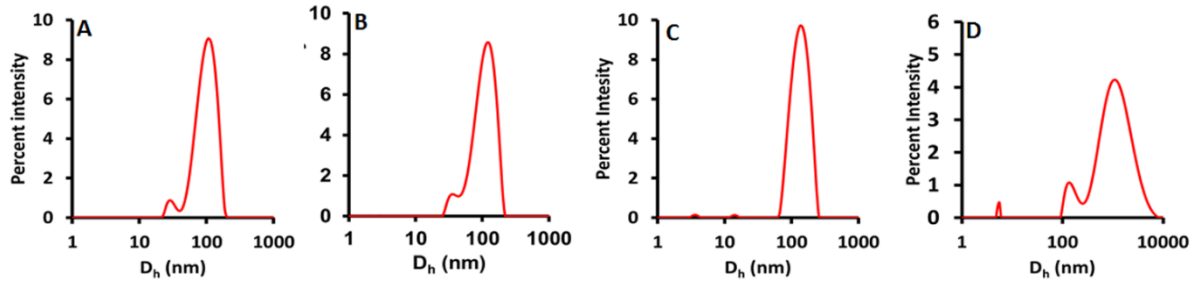


Figure S7: DLS of polymer **4b** (A) Before UV irradiation pH 7.4 in 0.02M MOPS buffer (B) After UV irradiation 3 min pH 7.4 in 0.02M MOPS buffer (C) Before UV irradiation pH 5.5 in 0.02M MES buffer and (D) After UV irradiation 3 min pH 5.5 in 0.02M MES buffer

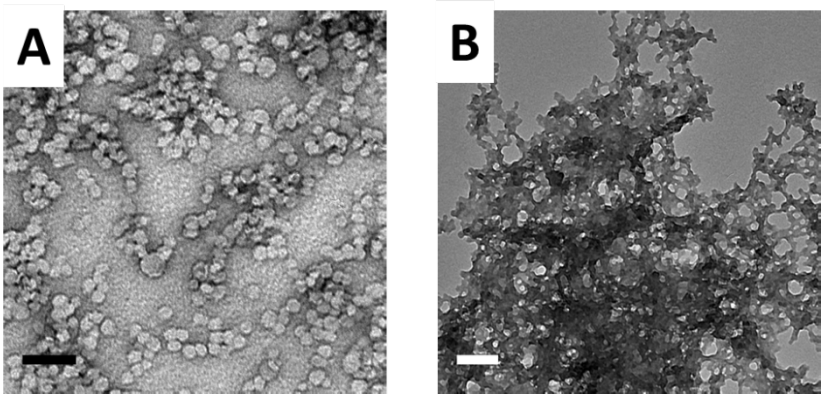


Figure S8: (A) Nanoparticles of polymer **4b** after UV exposure for3 min in 0.02M pH 7.4 MOPS buffer. (B) Reduction of the pH from pH 7.4 to pH 5.5 with 0.1M HCl resulted in a morphology change to micron scale aggregates. Scale bar = 200 nm.

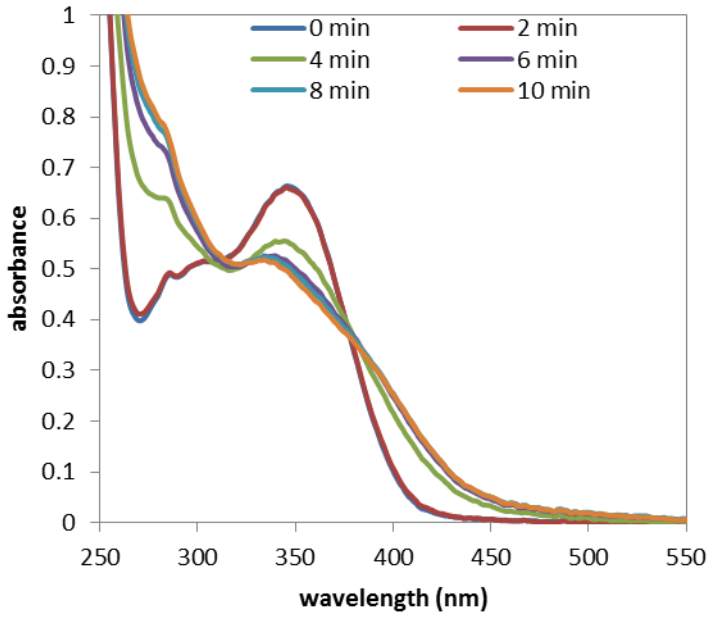
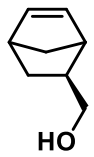
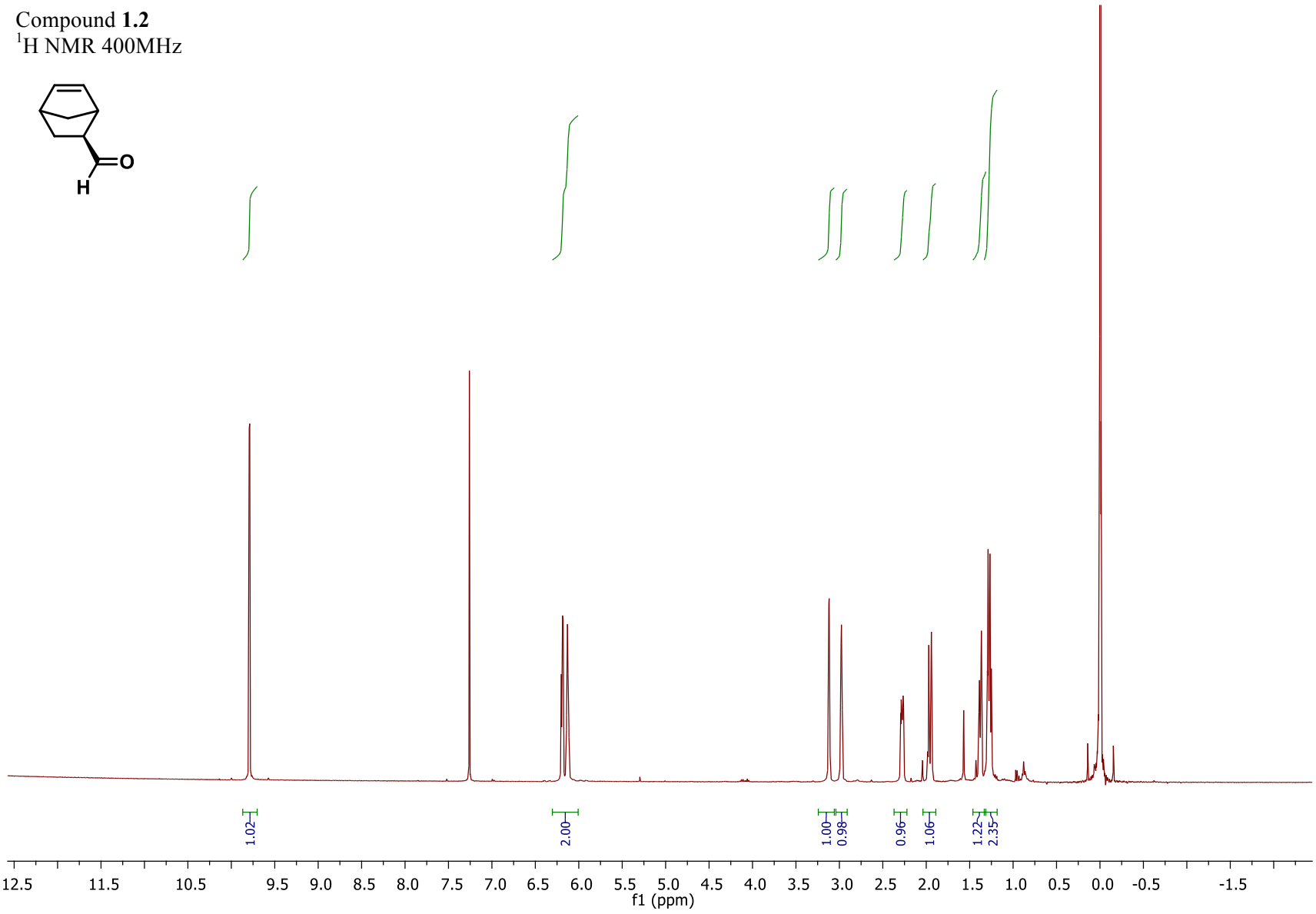


Figure S9: Absorbance spectra of polymer **4b** upon photolysis at 350 nm after 3 minutes the nitrobenzyl group is fully cleaved from polymer **4b**.

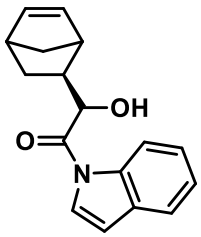
Compound **1.1**
^{1}H NMR 400MHz



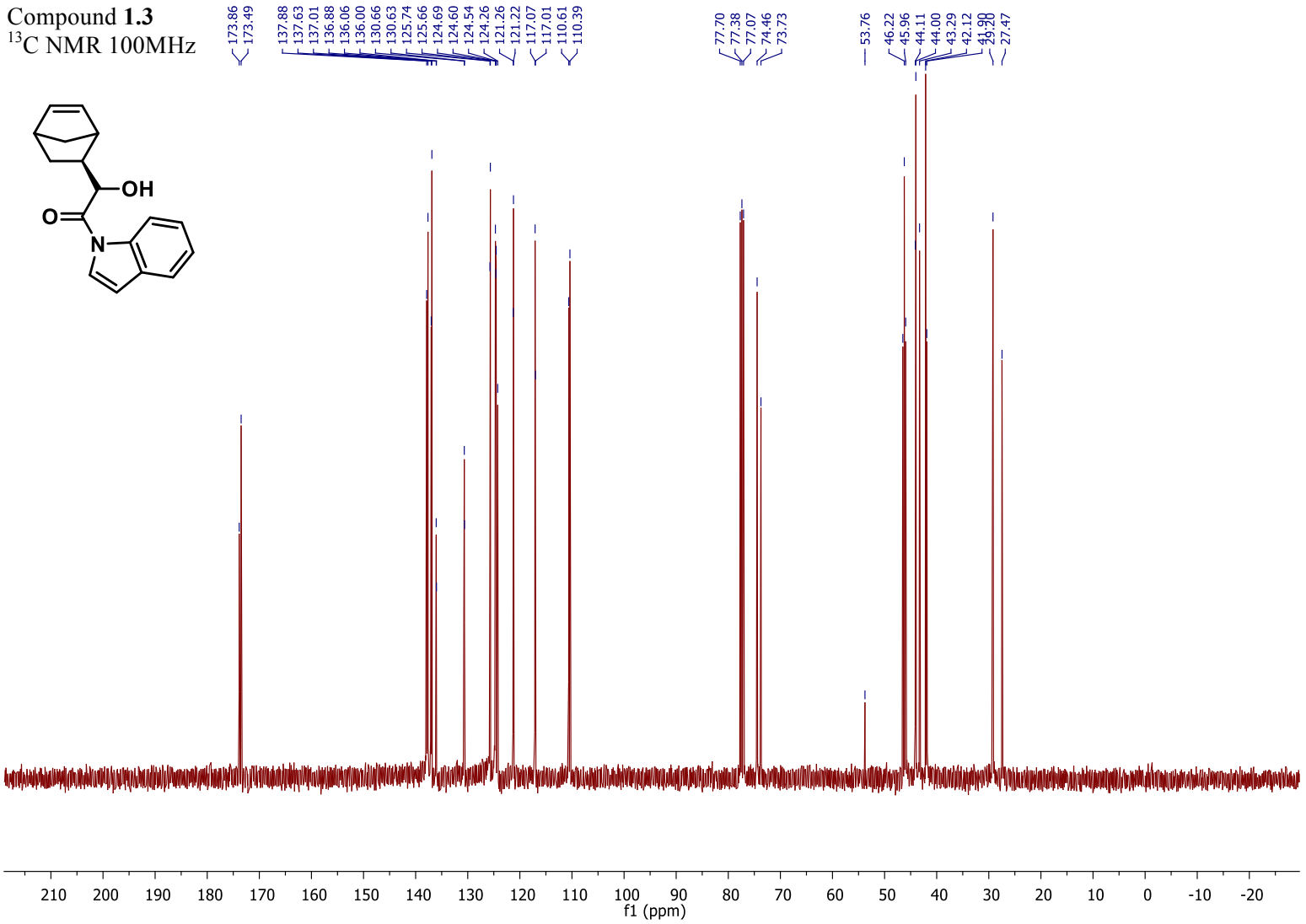
Compound **1.2**
^{1}H NMR 400MHz



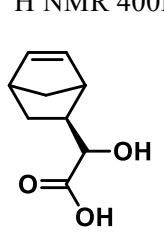
Compound **1.3**
^{1}H NMR 400MHz



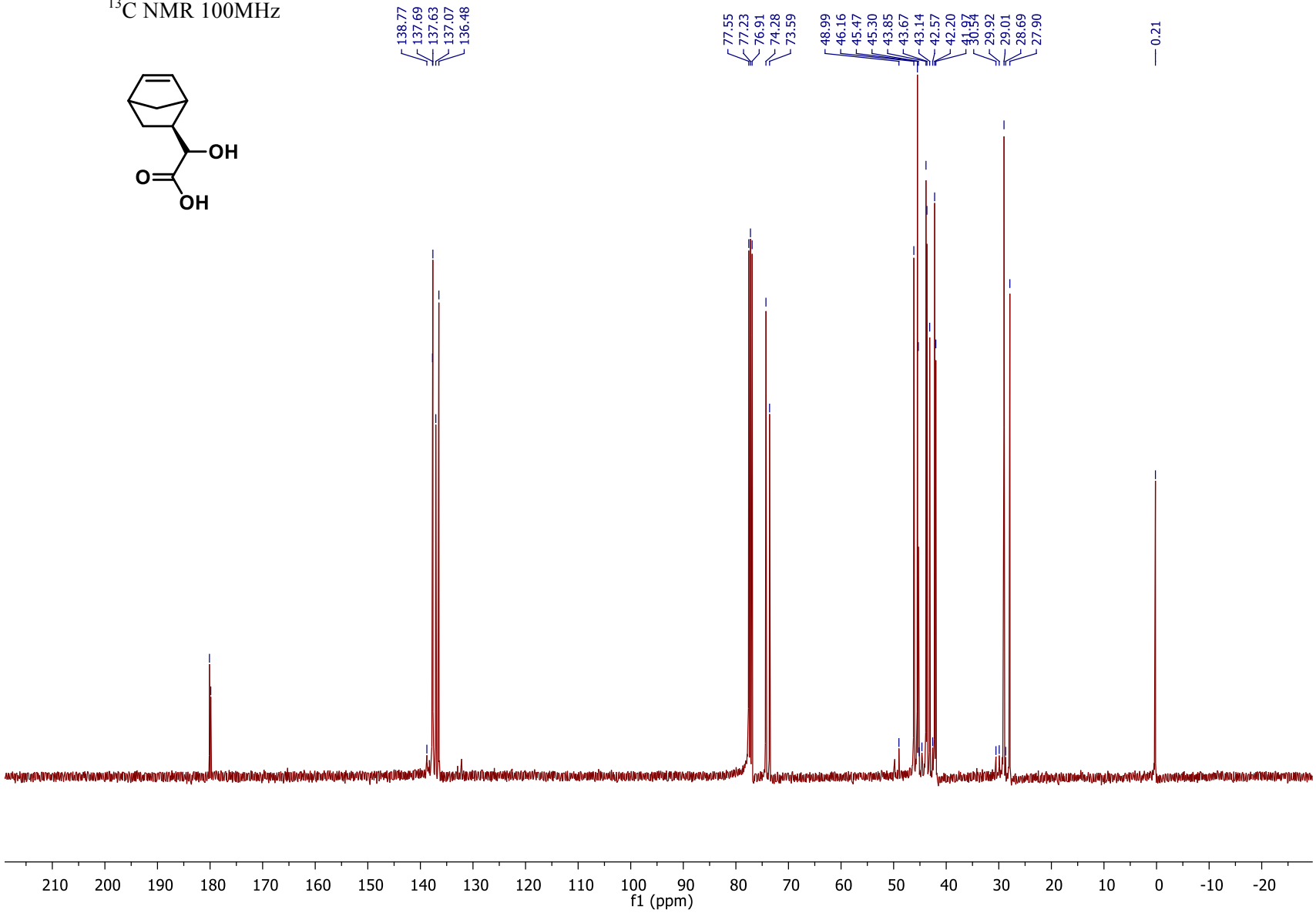
Compound **1.3**
^{13}C NMR 100MHz



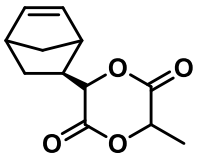
Compound **1.4**
^{1}H NMR 400MHz



Compound **1.4**
^{13}C NMR 100MHz

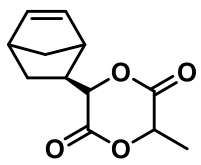


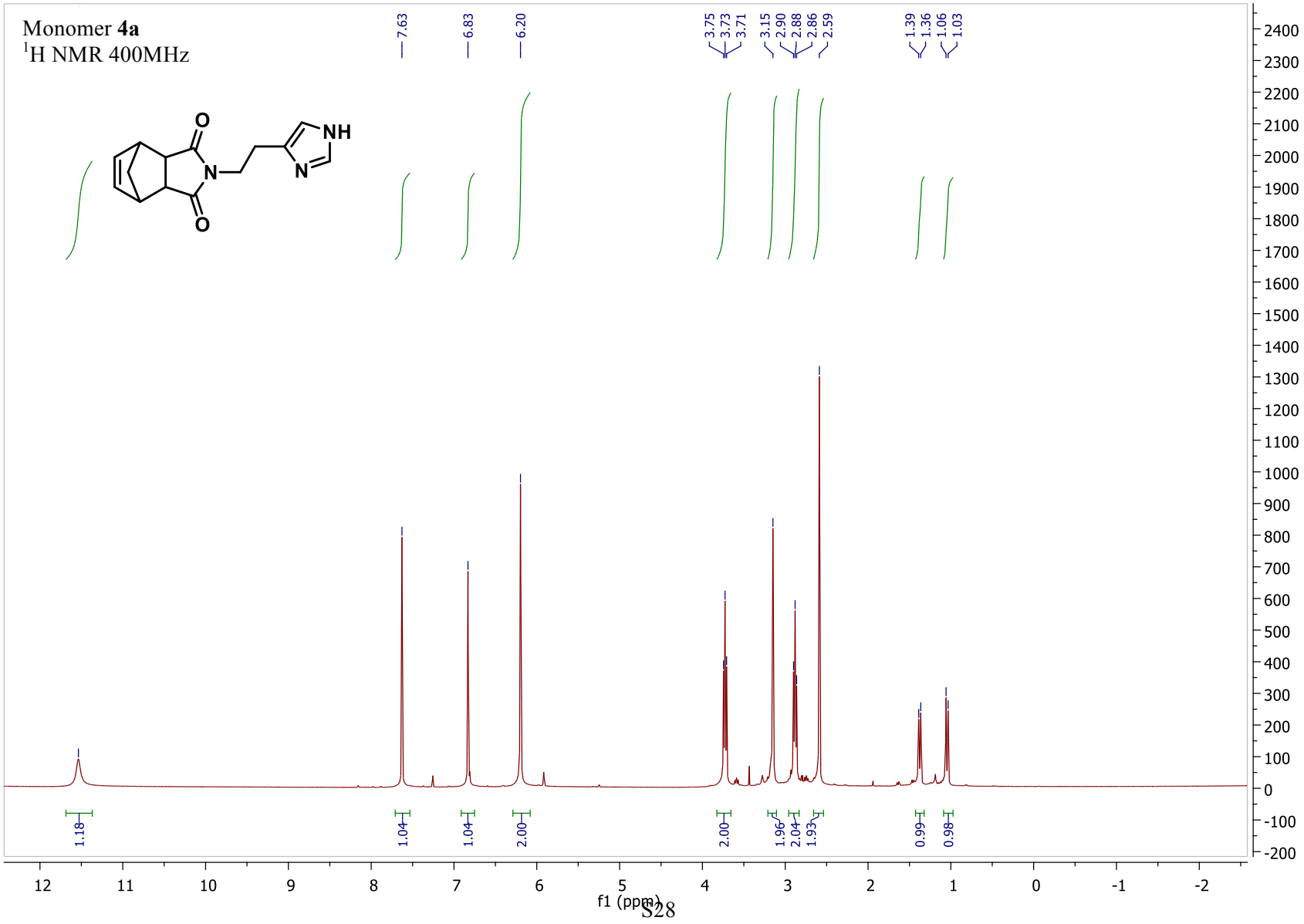
Compound **1**
^{1}H NMR 400MHz

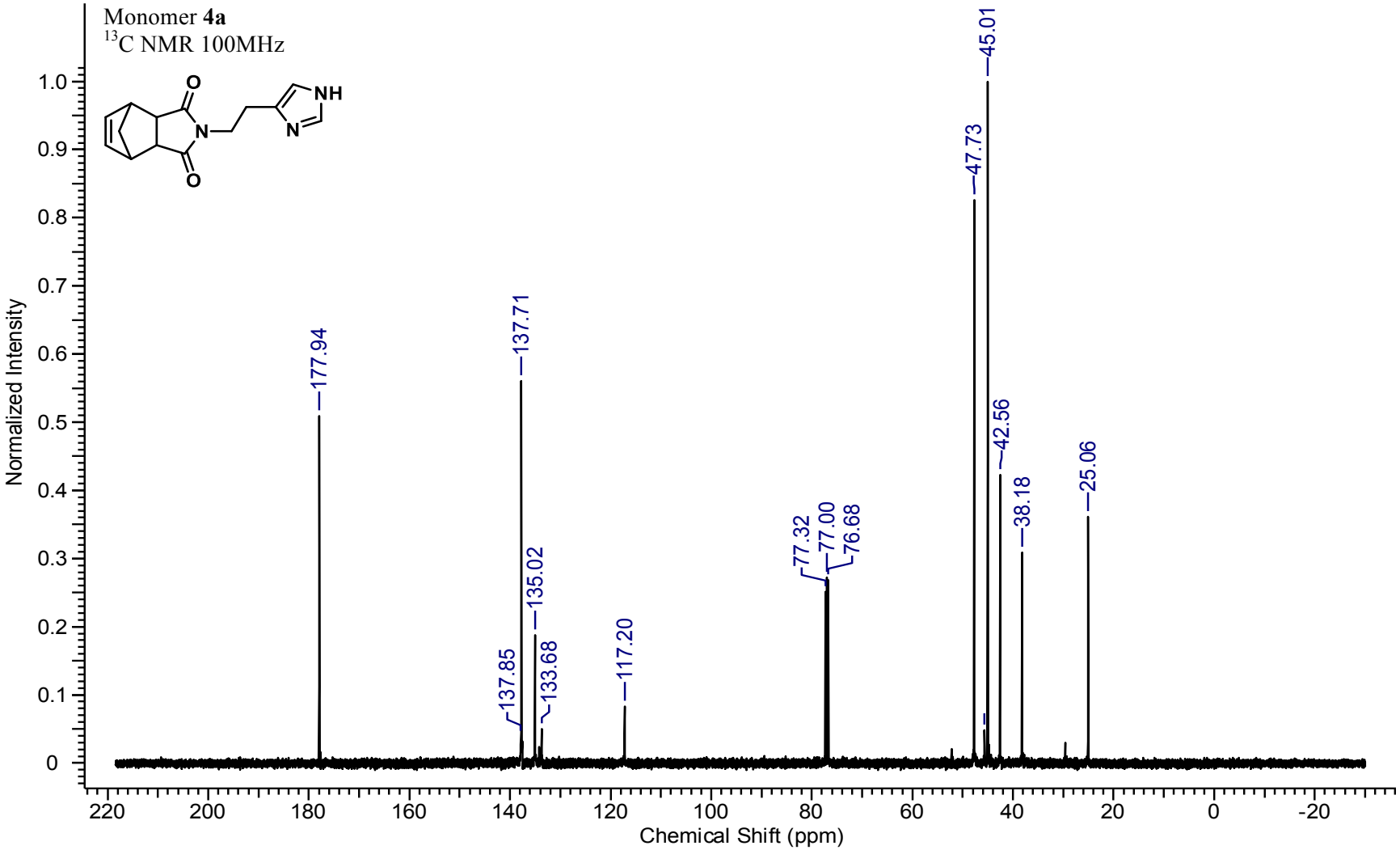


Compound **1**

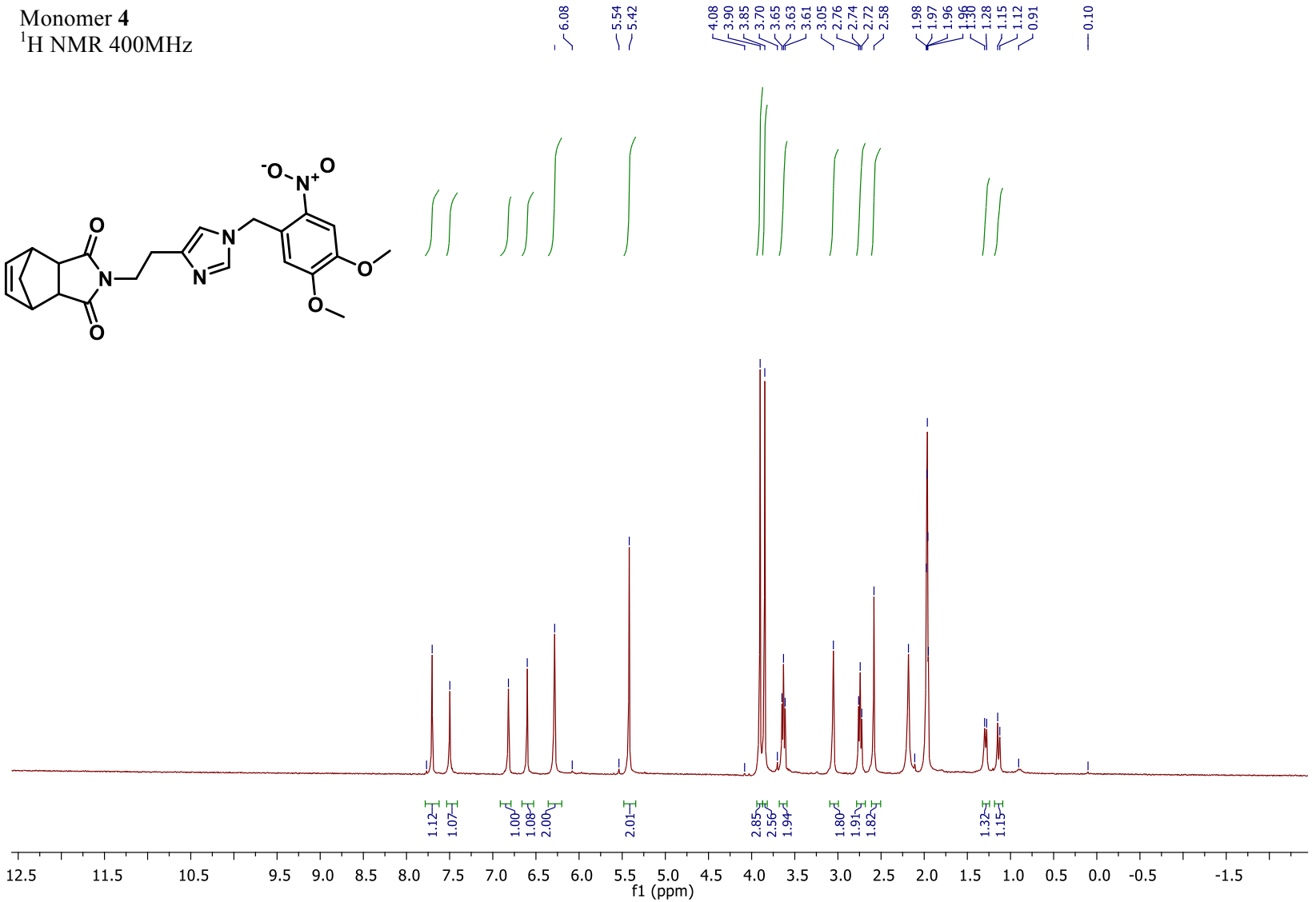
^{13}C NMR 100MHz

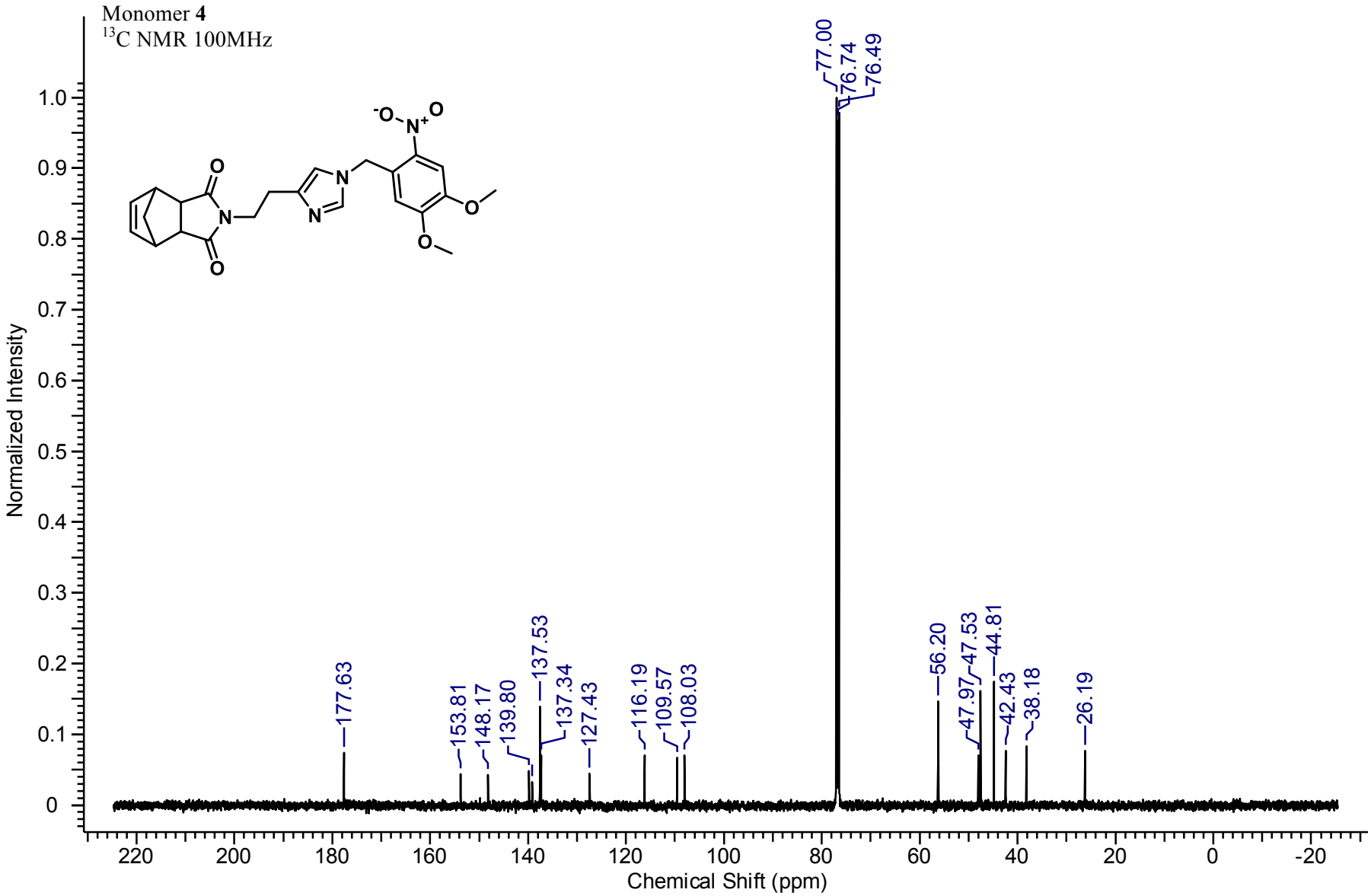



Monomer **4a**
^{1}H NMR 400MHz
7.63
6.83
6.20
3.75
3.73
3.71
3.15
2.90
2.88
2.86
2.59
1.39
1.36
1.06
1.03
O
N
O
N
NH
1.18
1.04
1.04
2.00
2.00
1.96
2.04
1.93
0.99
0.98
f1 (ppm)

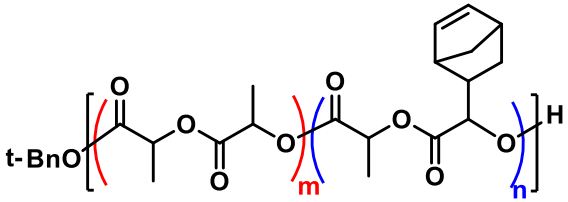

Monomer 4a
13C NMR 100MHz
O
N
O
NH
N
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
177.94
137.71
135.02
137.85
133.68
117.20
77.32
77.00
76.68
47.73
45.01
42.56
38.18
25.06
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

Monomer **4**
^{1}H NMR 400MHz

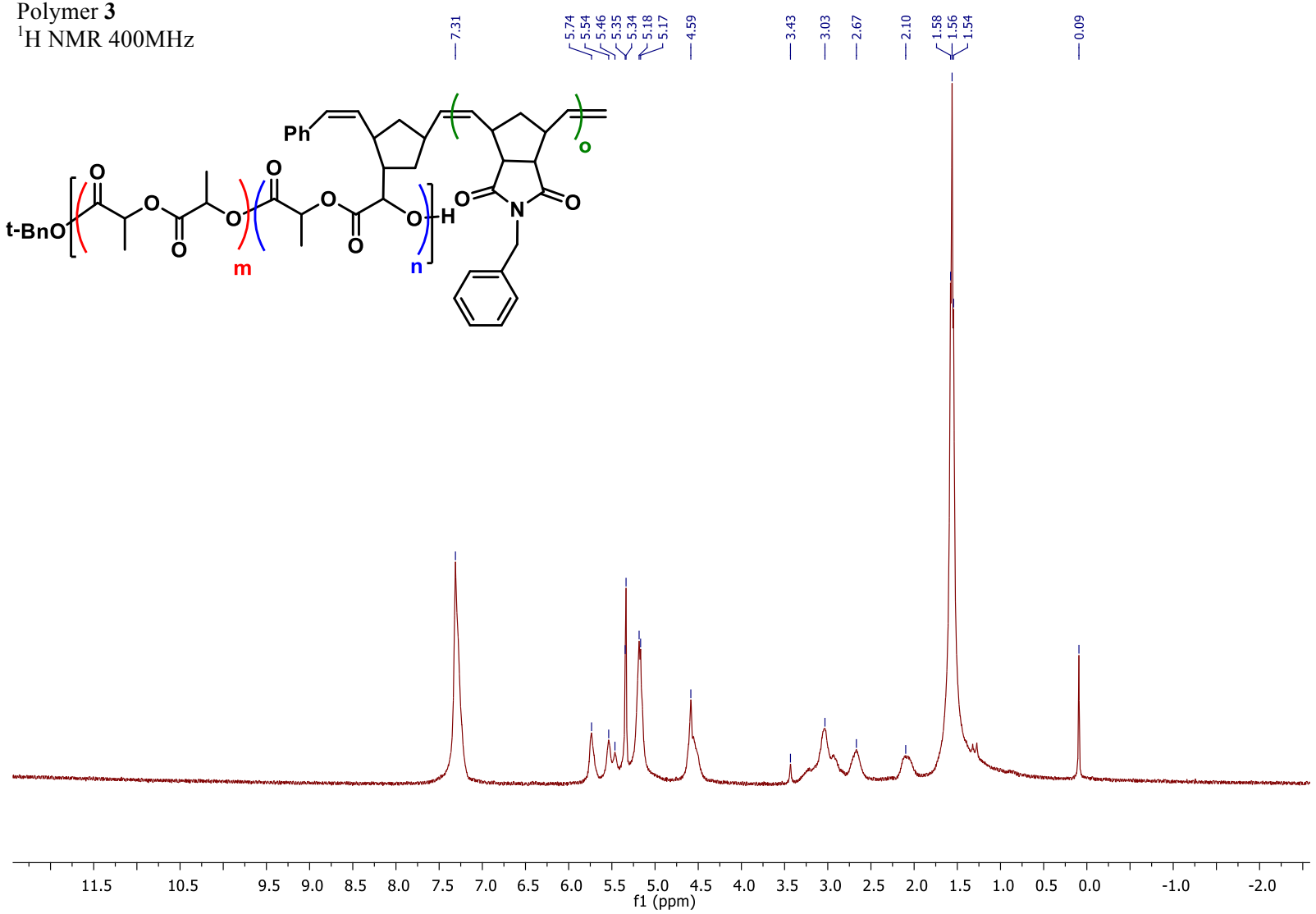



Monomer 4
13C NMR 100MHz
Normalized Intensity
Chemical Shift (ppm)
177.63
153.81
148.17
139.80
137.53
137.34
127.43
116.19
109.57
108.03
77.00
76.74
76.49
56.20
47.97
47.53
44.81
42.43
38.18
26.19

Polymer **2**
^{1}H NMR 400MHz



Polymer **3**
^{1}H NMR 400MHz



REFERENCES

(1) Conrad, R. M.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **2009**, *48* (44), 8328.

(2) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9* (18), 3631.

(3) Jiang, X.; Vogel, E. B.; Smith, M. R.; Baker, G. L. *Macromolecules* **2008**, *41* (6), 1937.