Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Organocatalytic Regioselective, Diastereoselective, and Enantioselective Annulation of Cyclic 1-Azadiene with γ-Nitro Ketone via 3,4-Cyclization

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Supporting Information

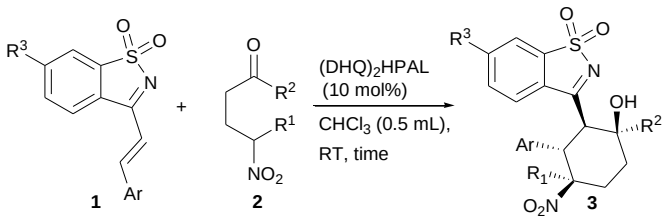
Contents

Experimental section

General

All reactions were carried out with dry, freshly distilled solvents in anhydrous conditions. Toluene and THF were distilled from sodium, while dichloromethane was distilled from CaH_2 immediately prior to use. All chemicals were used without further purification as commercially available unless otherwise noted. Thin-layer chromatography (TLC) was performed on silica gel plates (60F-254) using UV-light (254 and 365 nm). Flash chromatography was conducted on silica gel (300–400 mesh). NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) spectra were recorded in $CDCl_3$ or Acetone with TMS as the internal standard. Chemical shifts are reported in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quarter; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High resolution mass spectral (HRMS) analyses were measured using ESI techniques. Melting points were determined in a hanon auto melting point system (MP 450).

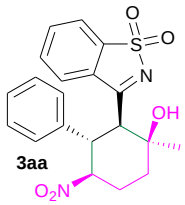
General Procedure for the Reaction



In a sealed tube, cyclic 1-azadiene **1** (0.2 mmol), γ-nitro ketone **2** (0.4 mmol), $(DHQ)_2HPAL$ (10 mol %) were mixed in $CHCl_3$ (0.5 mL) and stirred at room temperature for the time indicated in the tables. After removal of the solvent, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate as eluant) on silica gel to give the corresponding product **3**.

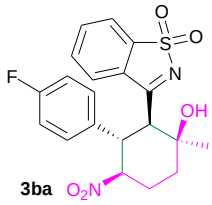
Compounds characterization

3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3aa)



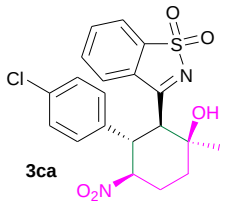
88 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.52-7.48 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.06 (t, *J* = 7.8 Hz, 2H), 6.93 (t, *J* = 7.2 Hz, 1H), 5.12-5.05 (m, 1H), 4.14 (t, *J* = 11.8 Hz, 1H), 3.97 (d, *J* = 2.4 Hz, 1H), 3.40 (d, *J* = 12.0 Hz, 1H), 2.82-2.72 (m, 1H), 2.36-2.31 (m, 1H), 2.20-2.15 (m, 1H), 1.81-1.72 (m, 1H), 1.18 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.8, 138.2, 135.9, 134.2, 133.6, 131.0, 129.1, 128.4, 124.1, 122.6, 88.6, 70.4, 51.3, 47.4, 37.2, 28.8, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{21}N_2SO_5$ $[M+H]^+$ 401.1166, Found 401.1161; HPLC conditions: Daicel Chiralpak AD-3 column, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 16.431 min, t_R (major) = 22.444 min, 93% ee.

3-((*1S,2S,5R,6S*)-6-(4-fluorophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ba)



94 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.78 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.58-7.54 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.19-7.16 (m, 2H), 6.77 (t, *J* = 8.6 Hz, 2H), 5.05-4.98 (m, 1H), 4.15 (t, *J* = 11.6 Hz, 1H), 3.85 (d, *J* = 2.8 Hz, 1H), 3.38 (d, *J* = 12.0 Hz, 1H), 2.81-2.71 (m, 1H), 2.37-2.31 (m, 1H), 2.21-2.16 (m, 1H), 1.81-1.72 (m, 1H), 1.18 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.5, 163.5, 161.0, 138.4, 134.5, 133.8, 131.8, 131.7, 130.9, 124.0, 122.9, 116.2, 116.0, 88.8, 70.4, 51.3, 46.6, 37.2, 28.9, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{20}FN_2SO_5$ $[M+H]^+$ 419.1071, Found 419.1065; HPLC conditions: Daicel Chiralpak AD-3 column, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 22.087 min, t_R (major) = 31.601 min, 86% ee.

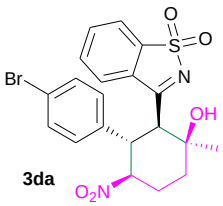
3-((1S,2S,5R,6S)-6-(4-chlorophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ca)



94 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 7.6 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.59-7.55 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 5.04-4.97 (m, 1H), 4.15 (t, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 2.0 Hz, 1H), 3.39 (d, *J* = 11.6 Hz, 1H), 2.81-2.70 (m, 1H), 2.37-2.31 (m, 1H), 2.21-2.16 (m, 1H), 1.81-1.72 (m, 1H), 1.18 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.3, 138.4, 134.5, 134.3, 133.9, 130.9, 129.3, 123.0, 88.6, 70.3, 51.1, 46.7, 37.2, 28.9, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{20}ClN_2SO_5$ $[M+H]^+$ 435.0776, Found 435.0770; HPLC conditions: Daicel Chiralpak AD-3 column, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 15.510 min, t_R (major) = 18.206 min, 85% ee.

3-((*1S,2S,5R,6S*)-6-(4-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3da)

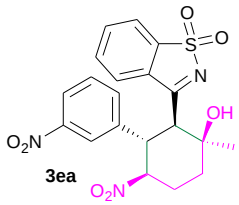
84 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 7.2 Hz, 1H), 7.68 (t, *J* = 7.4 Hz,



3da

1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 5.04-4.97 (m, 1H), 4.13 (t, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 2.4 Hz, 1H), 3.40 (d, *J* = 12.0 Hz, 1H), 2.80-2.70 (m, 1H), 2.36-2.32 (m, 1H), 2.20-2.15 (m, 1H), 1.81-1.72 (m, 1H), 1.18 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.4, 138.3, 135.1, 134.5, 133.9, 132.3, 130.9, 124.0, 123.0, 122.4, 88.6, 70.3, 51.0, 46.7, 37.1, 28.9, 27.0; HRMS (ESI): m/z calcd for $C_{20}H_{20}BrN_2SO_5$ $[M+H]^+$ 481.0250, Found 481.0241; HPLC conditions: Daicel Chiralpak AS-H column, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (major) = 29.534 min, t_R (minor) = 36.298 min, 81% ee.

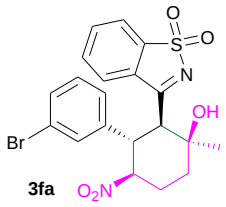
3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-(3-nitrophenyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ea)



3ea

47 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ8.19 (s, 1H), 7.88-7.86 (m, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 11.8 Hz, 1H), 5.07-5.00 (m, 1H), 4.34 (t, *J* = 11.8 Hz, 1H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.51 (d, *J* = 11.6 Hz, 3H), 2.85-2.74 (m, 1H), 2.44-2.38 (m, 1H), 2.27-2.21 (m, 1H), 1.89-1.81 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 176.5, 148.3, 138.6, 138.4, 134.8, 134.1, 130.8, 130.5, 123.8, 123.5, 123.1, 88.7, 70.4, 50.8, 46.8, 37.2, 28.9, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{20}N_3SO_7$ $[M+H]^+$ 446.1016, Found 446.1010; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 16.008 min, t_R (major) = 22.192 min, 95% ee.

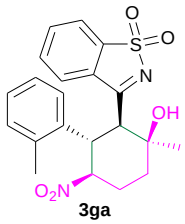
3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3fa)



3fa

43 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.78 (d, *J* = 7.2 Hz, 1H), 7.68-7.64 (m, 1H), 7.61-7.57 (m, 1H), 7.39 (br s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.09-7.07 (m, 2H), 6.93 (t, *J* = 7.8 Hz, 1H), 5.03-4.96 (m, 1H), 4.13 (t, *J* = 11.8 Hz, 1H), 3.91 (d, *J* = 2.8 Hz, 1H), 3.34 (d, *J* = 12.0 Hz, 1H), 2.82-2.71 (m, 1H), 2.40-2.34 (m, 1H), 2.22-2.17 (m, 1H), 1.80-1.71 (m, 1H), 1.20 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.2, 138.3, 134.4, 133.6, 131.5, 130.9, 130.8, 123.9, 122.9, 88.3, 70.3, 51.2, 47.0, 37.3, 28.8, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{20}BrN_2SO_5$ $[M+H]^+$ 481.0250, Found 481.0244; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 23.155 min, t_R (major) = 30.849 min, 97% ee.

3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-(o-tolyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ga)

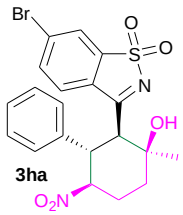


3ga

83 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.56-7.52 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.89-6.82 (m, 2H), 5.02-4.95 (m, 1H), 4.53 (t, *J* = 11.6 Hz, 1H), 3.97 (d, *J* = 2.8 Hz, 1H), 3.40 (d, *J* = 12.0 Hz, 1H), 2.83-2.72 (m, 1H), 2.37-2.32 (m, 4H), 2.21-2.16 (m, 1H), 1.80-1.71 (m, 1H), 1.17 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.4, 138.0, 134.3, 133.6, 131.8, 130.9, 128.2,

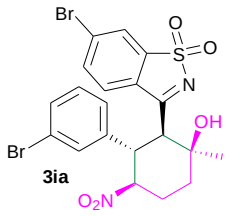
126.2, 125.4, 124.4, 122.6, 89.7, 70.5, 51.9, 41.2, 37.3, 28.7, 27.4, 19.6; HRMS (ESI): m/z calcd for $C_{21}H_{23}N_2SO_5$ $[M+H]^+$ 415.1322, Found 415.1316; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 9.192 min, t_R (major) = 13.991 min, 80% ee.

6-bromo-3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ha)



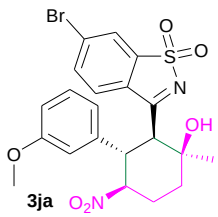
76 % yield; ^{1}H NMR (400 Hz, $CDCl_3$): δ (ppm) 7.86 (d, *J* = 1.2 Hz, 1H), 7.62-7.60 (m, 1H), 7.17-7.07 (m, 5H), 6.99 (t, *J* = 7.2 Hz, 1H), 5.09-5.02 (m, 1H), 4.12 (t, *J* = 11.8 Hz, 1H), 3.88 (d, *J* = 2.8 Hz, 1H), 3.32 (d, *J* = 11.6 Hz, 1H), 2.81-2.71 (m, 1H), 2.37-2.33 (m, 1H), 2.20-2.15 (m, 1H), 1.79-1.70 (m, 1H), 1.17 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.2, 139.9, 136.7, 135.8, 130.2, 129.7, 129.2, 129.1, 128.6, 126.2, 124.9, 88.5, 70.4, 51.5, 47.3, 37.2, 28.8, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{20}BrN_2SO_5$ $[M+H]^+$ 481.0250, Found 481.0245; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, λ = 244 nm, retention time: t_R (minor) = 8.691 min, t_R (major) = 14.456 min, 95% ee.

6-bromo-3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ia)



68 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 1.2 Hz, 1H), 7.72-7.70 (m, 1H), 7.38 (br s, 1H), 7.21-7.06 (m, 3H), 6.96 (t, *J* = 7.8 Hz, 1H), 5.02-4.95 (m, 1H), 4.11 (t, *J* = 11.8 Hz, 1H), 3.77 (d, *J* = 2.4 Hz, 1H), 3.33 (d, *J* = 12.0 Hz, 1H), 2.79-2.69 (m, 1H), 2.39-2.33 (m, 1H), 2.21-2.16 (m, 1H), 1.79-1.71 (m, 1H), 1.18 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 176.6, 140.0, 138.3, 136.8, 131.7, 130.9, 130.5, 129.6, 126.4, 124.8, 123.2, 88.5, 70.4, 51.5, 47.3, 37.2, 28.8, 27.1; HRMS (ESI): m/z calcd for $C_{20}H_{19}Br_2N_2SO_5$ $[M+H]^+$ 556.9376, Found 556.9368; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, λ = 244 nm, retention time: t_R (minor) = 7.145 min, t_R (major) = 9.796 min, 90% ee.

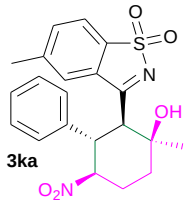
6-bromo-3-((*1S,2S,5R,6S*)-2-hydroxy-6-(3-methoxyphenyl)-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ja)



68 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.87 (d, *J* = 1.6 Hz, 1H), 7.64-7.61 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.64 (br s, 1H), 6.53-6.50 (m, 1H), 5.09-5.02 (m, 1H), 4.09 (t, *J* = 11.6 Hz, 1H), 3.87 (d, *J* = 2.8 Hz, 1H), 3.65 (s, 3H), 3.34 (d, *J* = 12.0 Hz, 1H), 2.79-2.68 (m, 1H), 2.35-2.31 (m, 1H), 2.18-2.13 (m, 1H), 1.78-1.68 (m, 1H), 1.16 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.3, 160.0, 139.8, 137.4, 136.7, 130.2, 129.7, 126.1, 125.0, 88.4, 70.4, 55.3, 51.4, 47.4, 37.2, 28.7, 27.1; HRMS (ESI): m/z calcd for $C_{21}H_{22}BrN_2SO_6$ $[M+H]^+$ 511.0356, Found 511.0349; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 31.243 min, t_R (major) = 38.039 min, 98% ee.

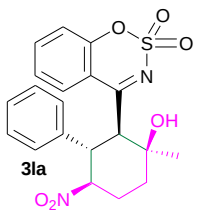
5-methyl-3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo

[d]isothiazole 1,1-dioxide (3ka)



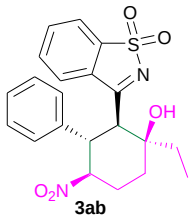
^{1}H NMR (400 Hz, CDCl3): δ (ppm) 7.60 (d, J = 7.6 Hz, 1H), 7.38-7.35 (m, 1H), 7.19-7.13 (m, 2H), 7.09-7.04 (m, 2H), 6.96-6.93 (m, 2H), 5.12-5.05 (m, 1H), 4.16-4.08 (m, 2H), 3.31 (d, J = 11.6 Hz, 1H), 2.83-2.73 (m, 1H), 2.37-2.28 (m, 4H), 2.21-2.16 (m, 1H), 1.80-1.71 (m, 1H), 1.20 (s, 3H). ^{13}C NMR (100 Hz, CDCl3): δ (ppm) 178.0, 144.9, 135.9, 135.4, 134.6, 131.5, 128.9, 128.3, 124.7, 122.3, 88.5, 77.4, 70.3, 51.2, 47.4, 37.2, 28.8, 27.1, 21.7. HRMS (ESI): m/z calcd for $C_{21}H_{23}N_2SO_5$ [M+H] 415.1322, Found 415.1313; HPLC conditions: Daicel Chiralpak AD-3 column, n-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 21.147 min, t_R (major) = 27.136 min, 84% ee.

4-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[e][1,2,3]oxathiazine 2,2-dioxide (3la)



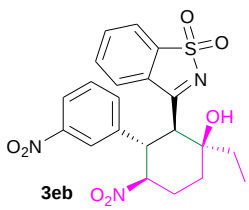
80 % yield; ^{1}H NMR (400 Hz, $CDCl_3$): δ (ppm) 7.62-7.57 (m, 1H), 7.53-7.51 (m, 1H), 7.27-7.23 (m, 1H), 7.15-7.05 (m, 5H), 6.97 (t, *J* = 7.4 Hz, 1H), 5.05-4.98 (m, 1H), 4.15 (t, *J* = 11.6 Hz, 1H), 3.99 (d, *J* = 2.8 Hz, 1H), 3.58 (d, *J* = 12.0 Hz, 1H), 2.82-2.71 (m, 1H), 2.35-2.30 (m, 1H), 2.19-2.14 (m, 1H), 1.79-1.70 (m, 1H), 1.20 (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 182.2, 153.2, 137.9, 135.5, 129.0, 128.3, 128.2, 126.0, 119.5, 117.6, 88.9, 70.7, 53.3, 47.5, 37.6, 29.0, 27.1; HRMS: exact mass calculated for $C_{20}H_{21}N_2SO_6$ $[M+H]^+$ requires m/z 417.1115, found m/z 417.1108; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, *λ* = 224 nm, retention time: t_R (minor) = 9.633 min, t_R (major) = 19.291 min, 80% ee.

3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ab)



95 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.73 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.24-7.17 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 5.12-5.05 (m, 1H), 4.17 (t, *J* = 11.4 Hz, 1H), 3.85 (d, *J* = 2.8 Hz, 1H), 3.41 (d, *J* = 12.0 Hz, 1H), 2.81-2.70 (m, 1H), 2.41-2.35 (m, 1H), 2.23-2.18 (m, 1H), 1.72-1.63 (m, 1H), 1.48-1.37 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 178.1, 138.2, 135.9, 134.1, 133.5, 130.9, 129.1, 128.3, 124.1, 122.6, 88.5, 73.1, 50.3, 47.6, 34.3, 33.1, 26.9, 8.1; HRMS (ESI): m/z calcd for $C_{21}H_{23}N_2SO_5$ $[M+H]^+$ 415.1322, Found 415.1317; HPLC conditions: Daicel Chiralpak OD-H column, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, *λ* = 224 nm, retention time: t_R (minor) = 8.654 min, t_R (major) = 9.782 min, 91% ee.

3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-(3-nitrophenyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3eb)

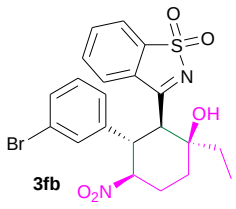


43 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ8.18 (s, 1H), 7.86-7.83 (m, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.66-7.63 (m, 1H), 7.58-7.54 (m, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 5.07-5.00 (m, 1H), 4.36 (t, *J* = 11.6 Hz, 1H), 3.56-3.50 (m, 2H), 2.82-2.72 (m, 1H), 2.47-2.41 (m, 1H), 2.30-2.25 (m, 1H), 1.77-1.69 (m, 1H), 1.43 (q,

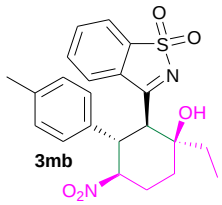
J = 11.6 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 176.9, 138.6, 138.3, 134.7, 133.9, 130.7, 130.5, 123.7, 123.5, 123.1, 88.6, 73.1, 49.9, 47.2, 34.4, 33.0, 26.9, 7.97; HRMS (ESI): m/z calcd for $C_{21}H_{22}N_3SO_7$ $[M+H]^+$ 460.1173, Found 460.1164; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 25.293 min, t_R (major) = 38.645 min, 93% ee.

3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-ethyl-2-hydroxy-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3fb)

65 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.77 (d, *J* = 7.2 HZ, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.39 (br s, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.8 Hz, 1H), 5.04-4.97 (m, 1H), 4.15 (t, *J* = 11.6 Hz, 1H), 3.76 (d, *J* = 2.4 Hz, 1H), 3.38 (d, *J* = 12.0 Hz, 1H), 2.80-2.69 (m, 1H), 2.42-2.36 (m, 1H), 2.24-2.19 (m, 1H), 1.71-1.62 (m, 1H), 1.52-1.36 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 177.5, 138.4, 138.3, 134.4, 133.5, 131.5, 130.8, 124.0, 122.8, 88.3, 73.0, 50.1, 47.3, 34.3, 33.1, 26.9, 8.07; HRMS (ESI): m/z calcd for $C_{21}H_{22}BrN_2SO_5$ $[M+H]^+$ 495.0407, Found 495.0400; HPLC conditions: Daicel Chiralpak ID-3 column, *n*-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 21.364 min, t_R (major) = 30.498 min, 98% ee.



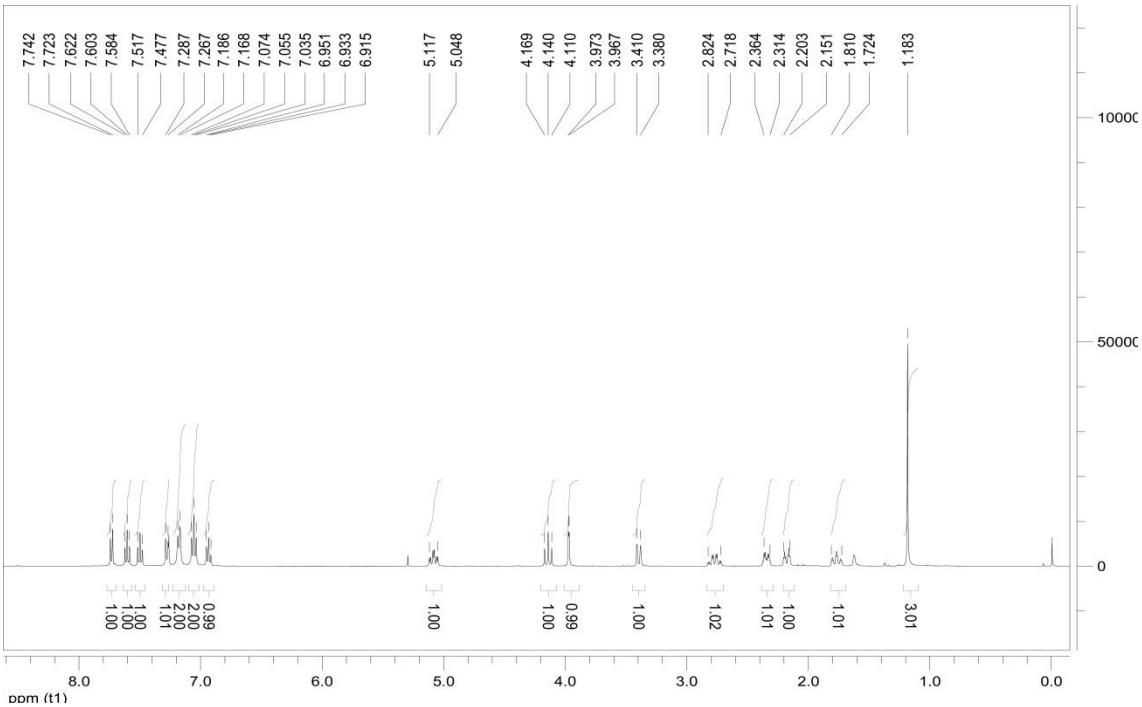
3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-(p-tolyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3mb)

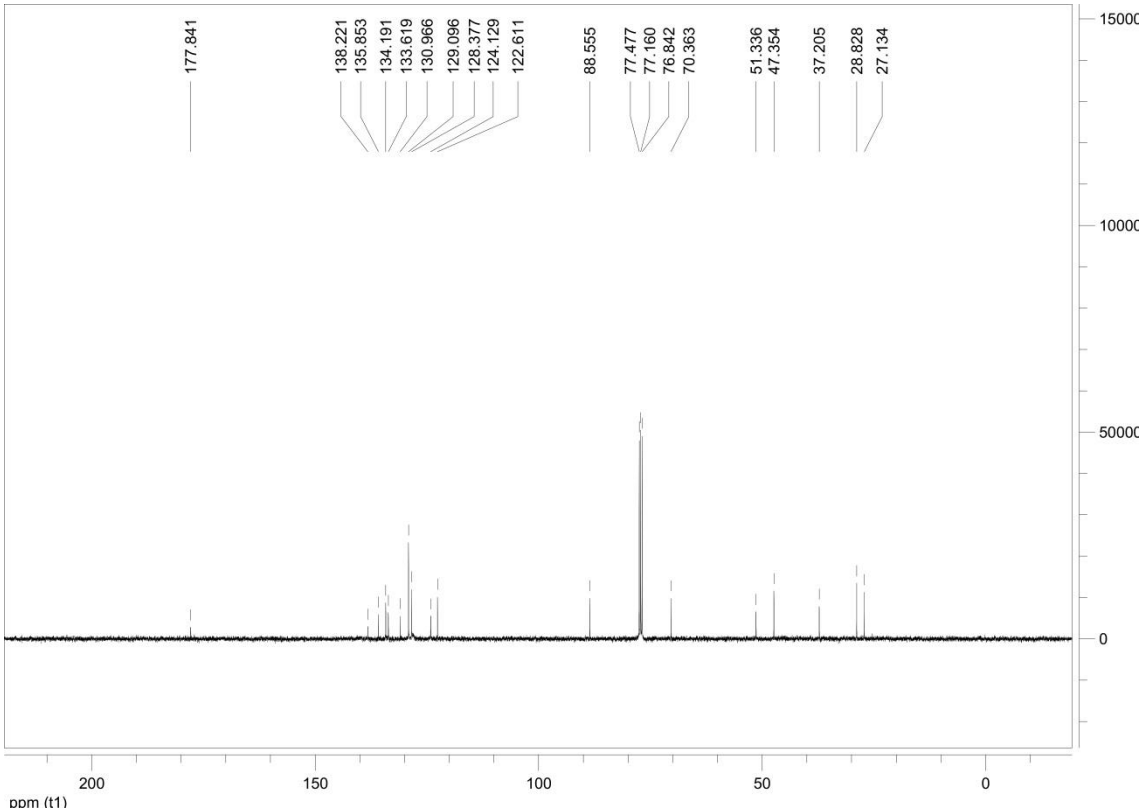


88 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.74 (d, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.85 (t, *J* = 8.0 Hz, 1H), 5.07-5.00 (m, 1H), 4.13 (t, *J* = 11.6 Hz, 1H), 3.84 (d, *J* = 2.8 Hz, 1H), 3.39 (d, *J* = 12.0 Hz, 1H), 2.80-2.69 (m, 1H), 2.38-2.33 (m, 1H), 2.22-2.17 (m, 1H), 2.03 (s, 3H), 1.69-1.61 (m, 1H), 1.47-1.35 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ (ppm) 178.2, 138.2, 138.1, 134.0, 133.5, 132.7, 130.9, 129.7, 124.2, 122.6, 88.8, 73.1, 50.4, 47.2, 34.3, 33.1, 26.9, 20.9, 8.1; HRMS (ESI): m/z calcd for $C_{22}H_{25}N_2SO_5$ $[M+H]^+$ 429.1479, Found 429.1475; HPLC conditions: Daicel Chiralpak OD-H column, *n*-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 224 nm, retention time: t_R (minor) = 12.924 min, t_R (major) = 14.562 min, 83% ee.

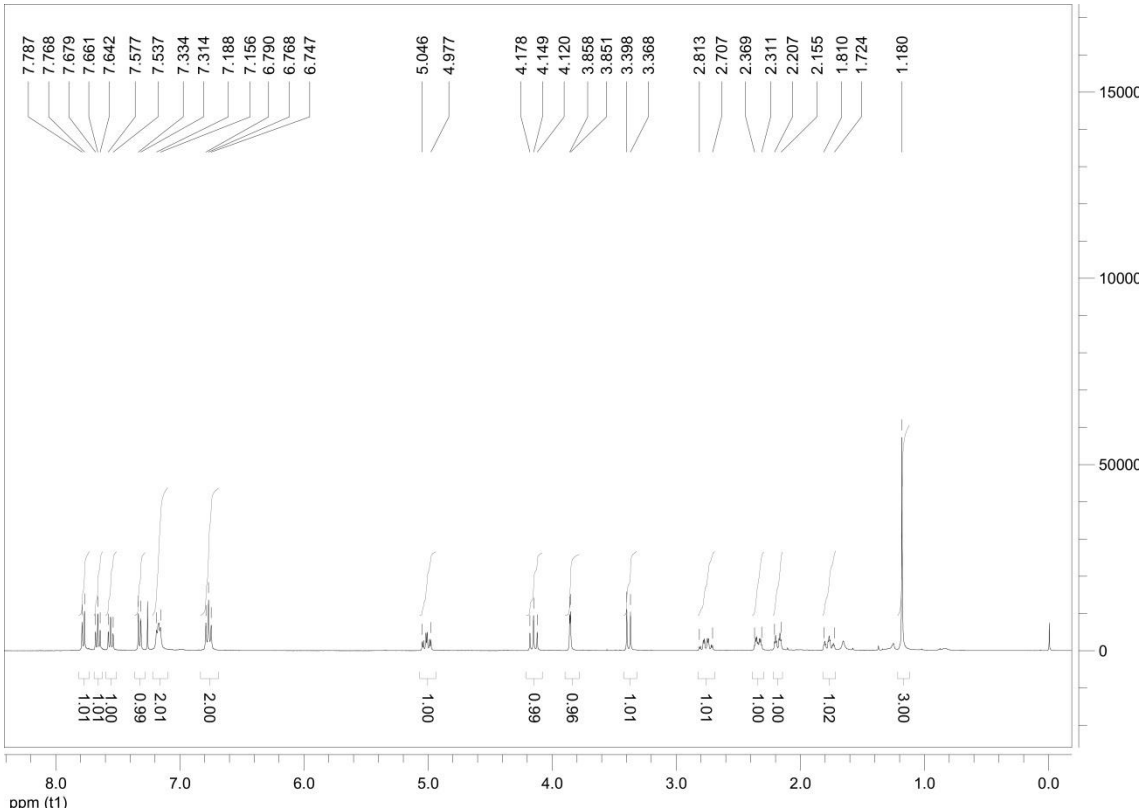
NMR Spectra of compounds

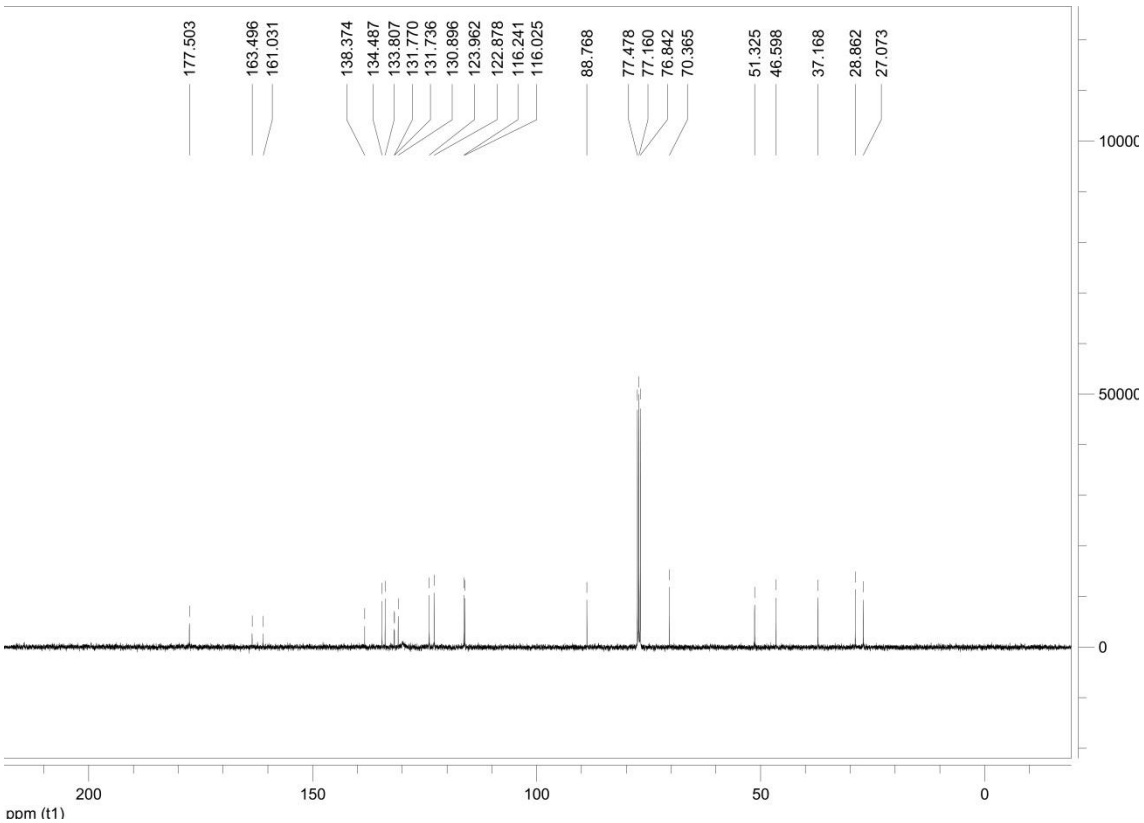
3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3aa)



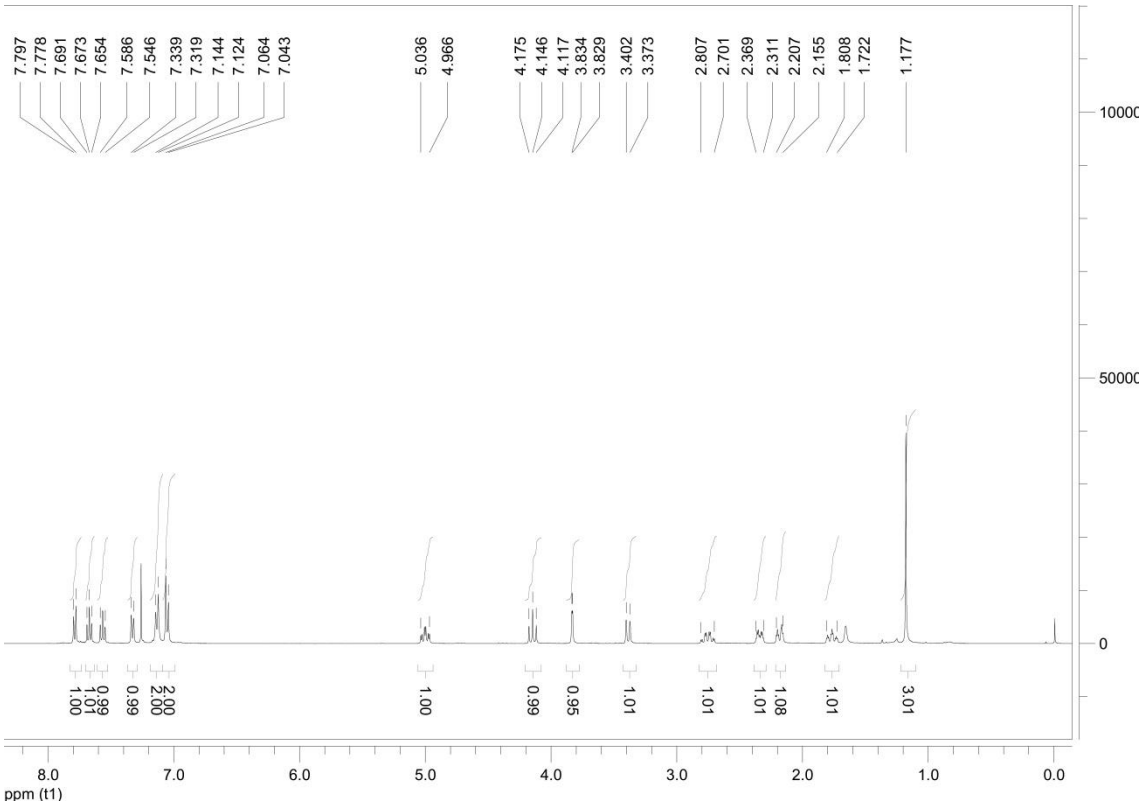


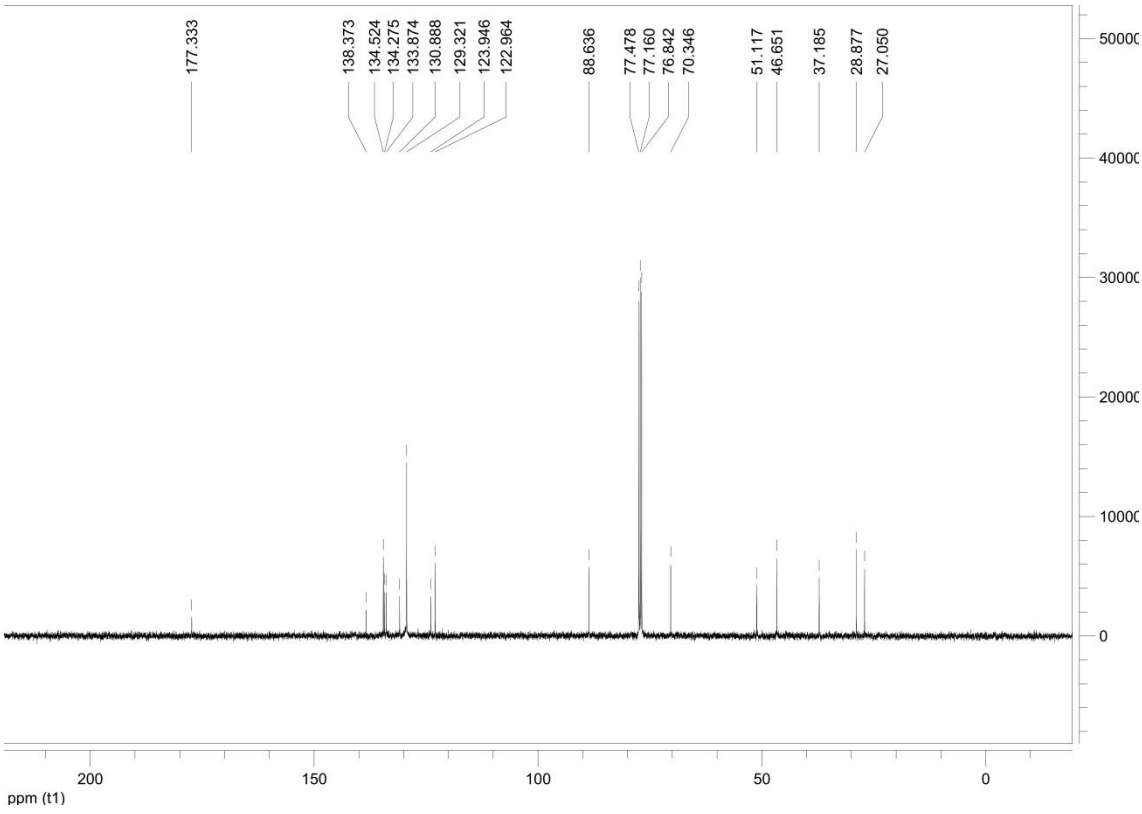
3-((*1S,2S,5R,6S*)-6-(4-fluorophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo [d]isothiazole 1,1-dioxide (3ba)



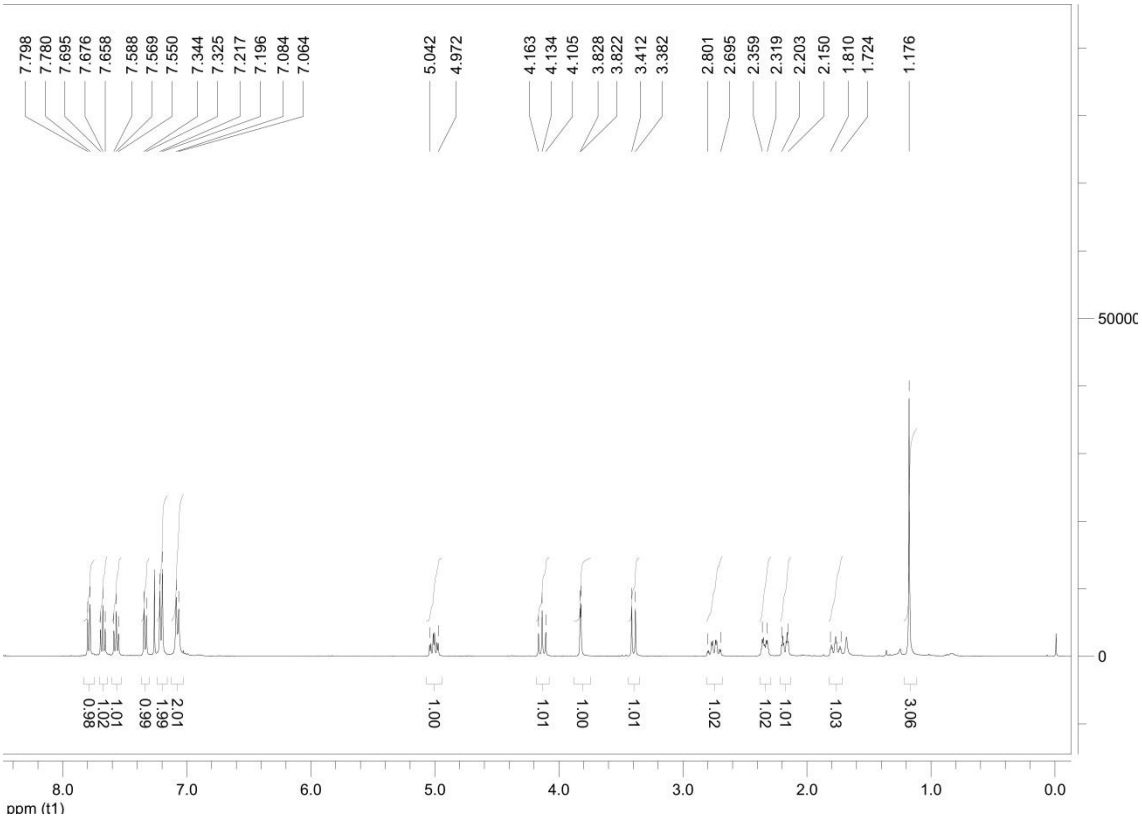


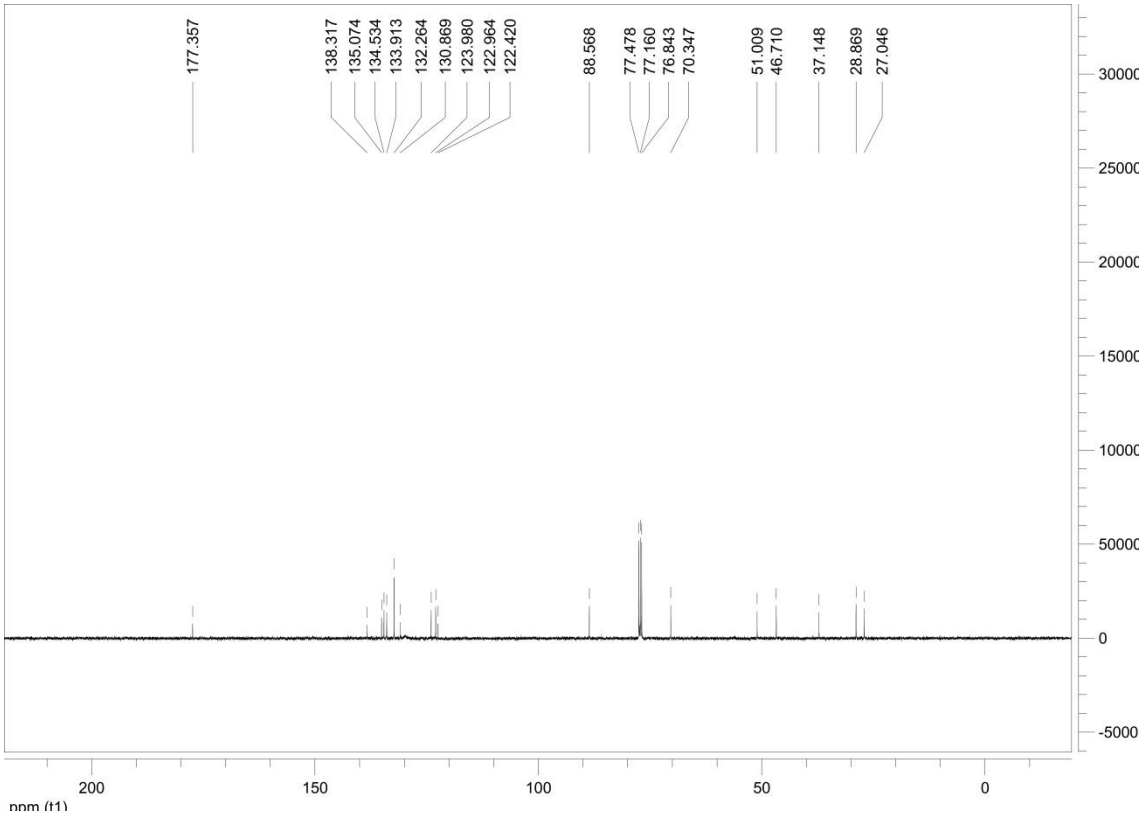
3-((*1S,2S,5R,6S*)-6-(4-chlorophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo [d]isothiazole 1,1-dioxide (3ca)



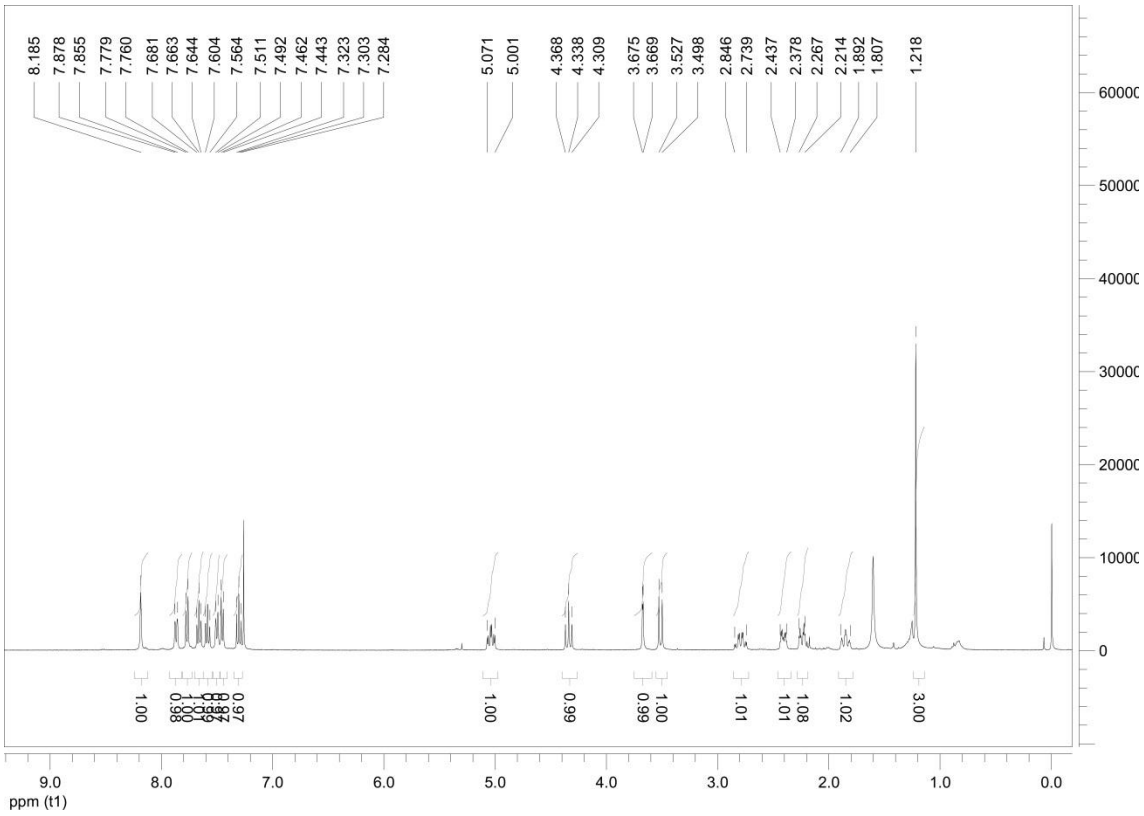


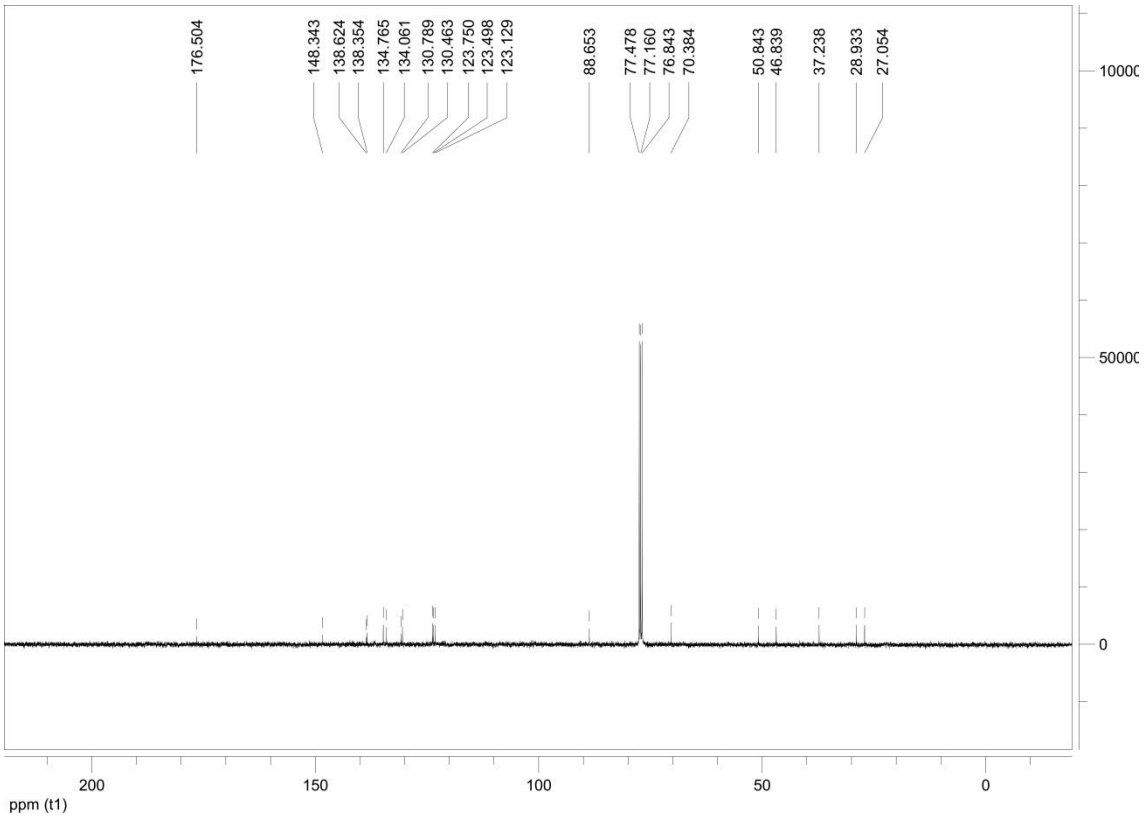
3-((*1S,2S,5R,6S*)-6-(4-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3da)



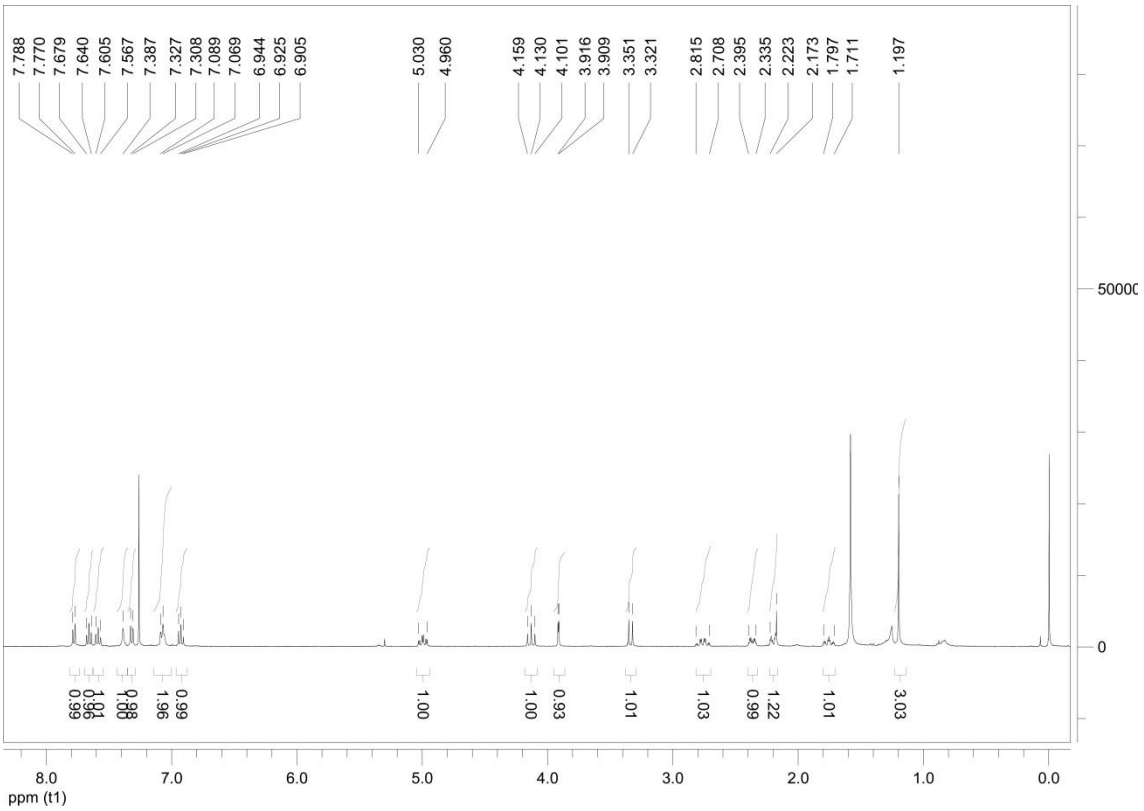


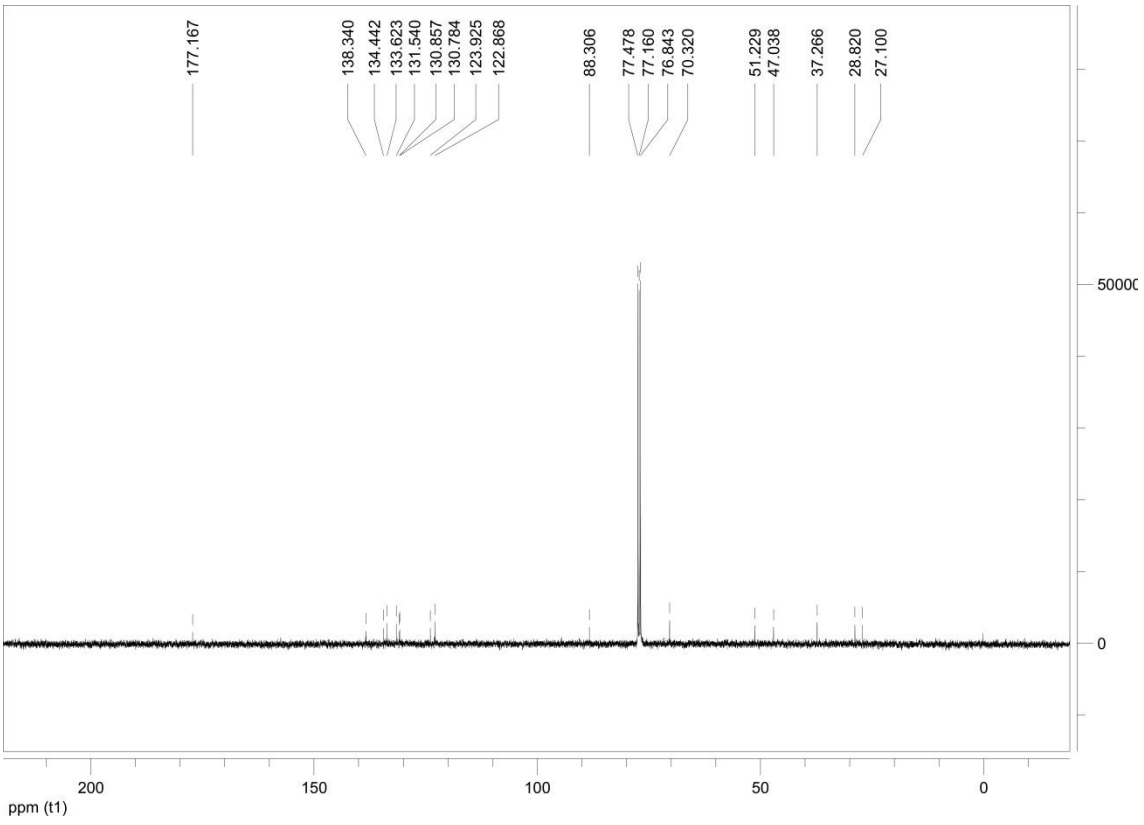
3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-(3-nitrophenyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ea)



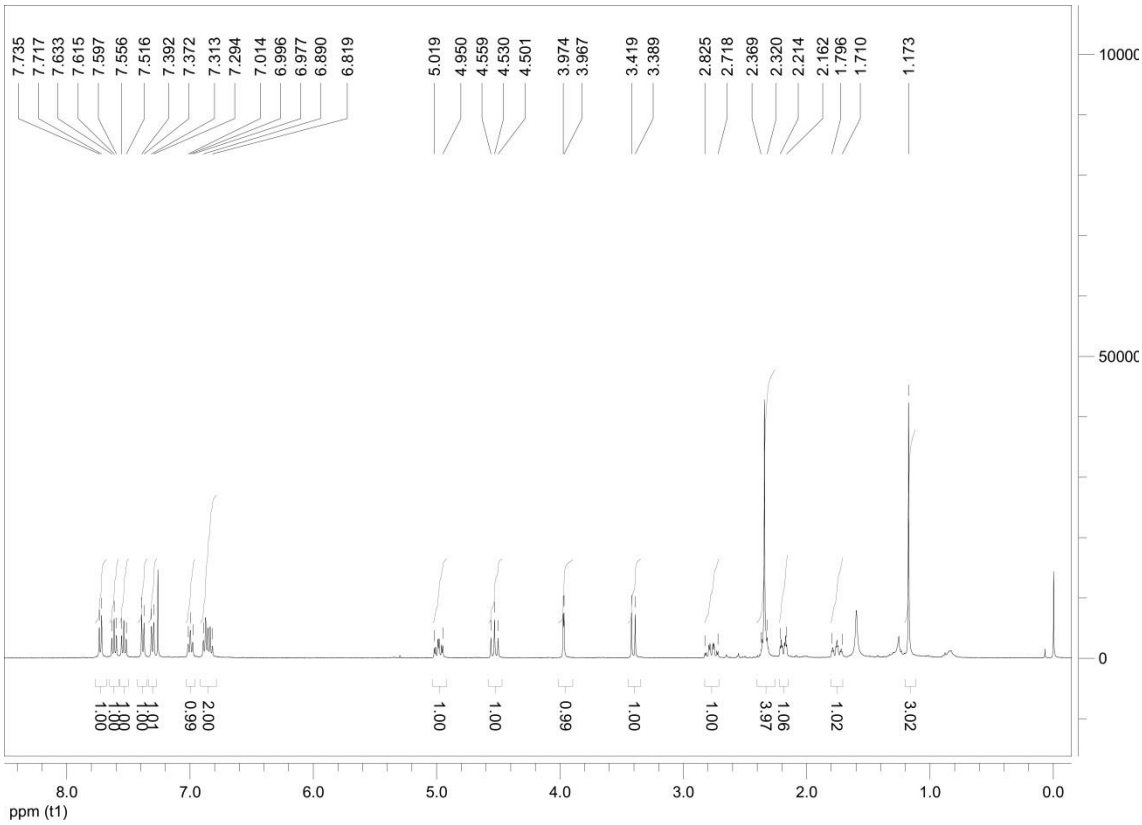


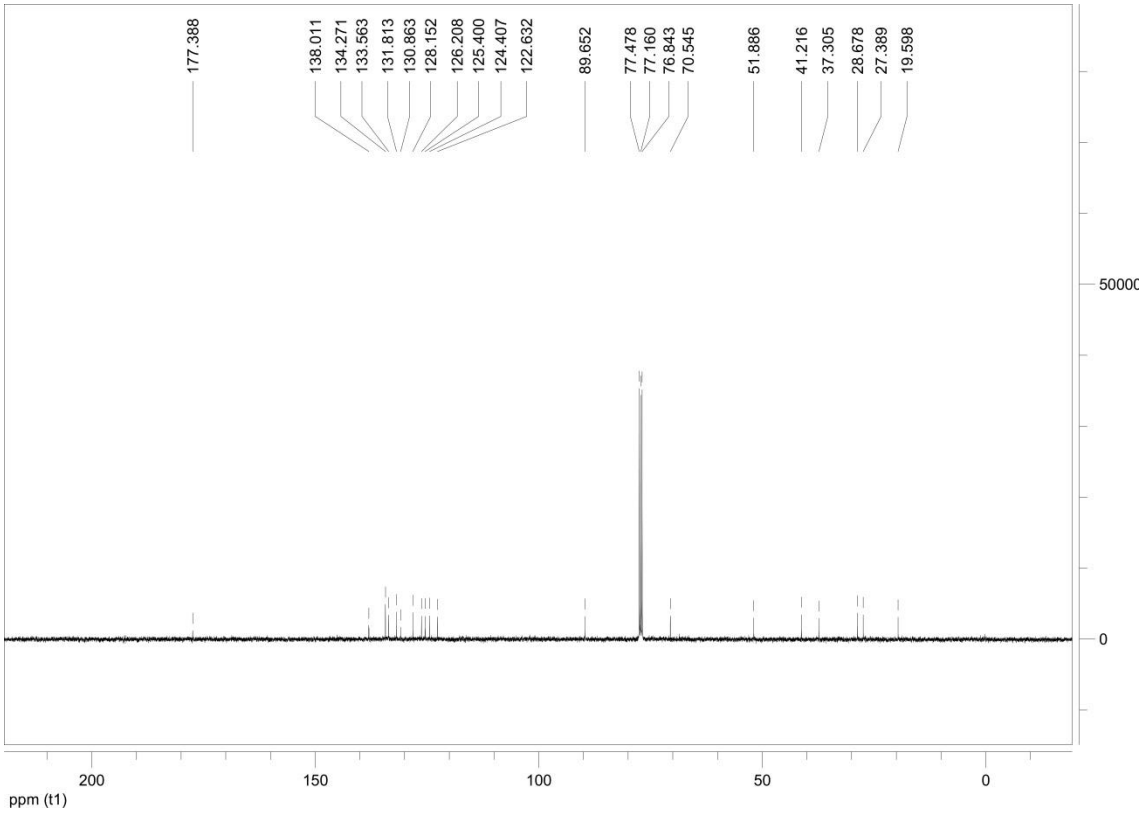
3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3fa)



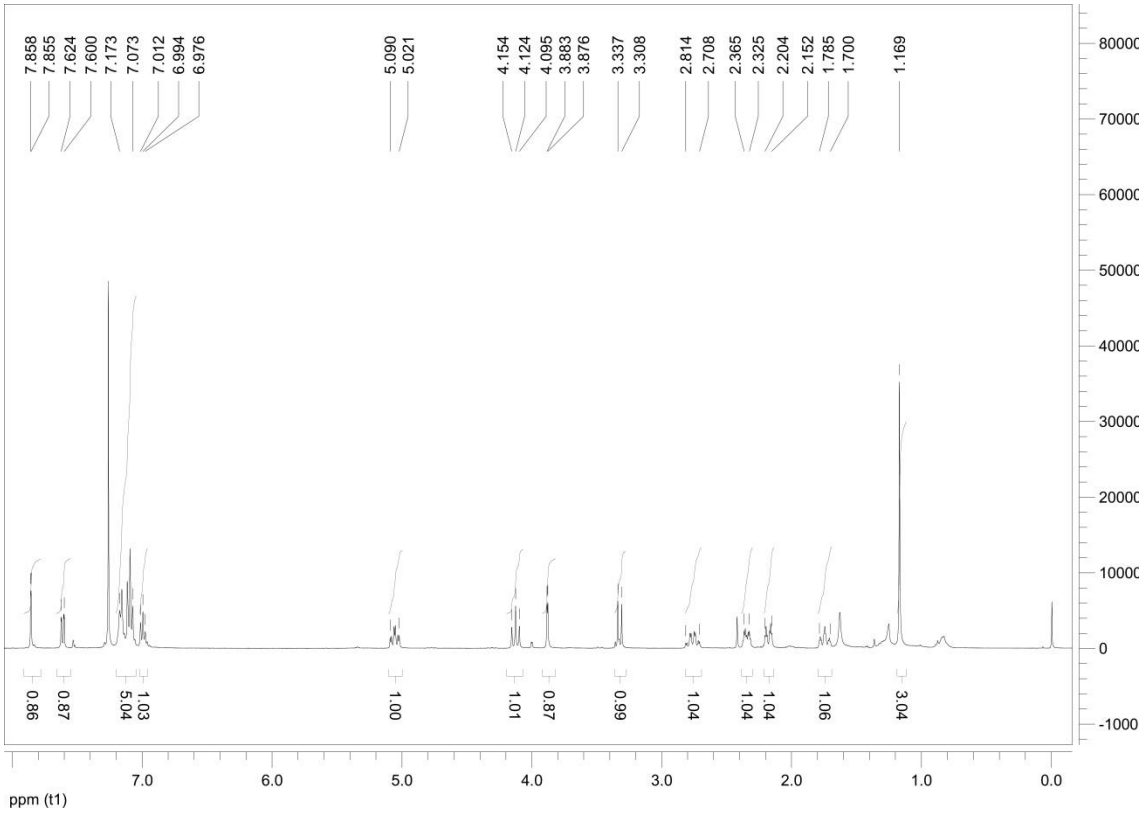


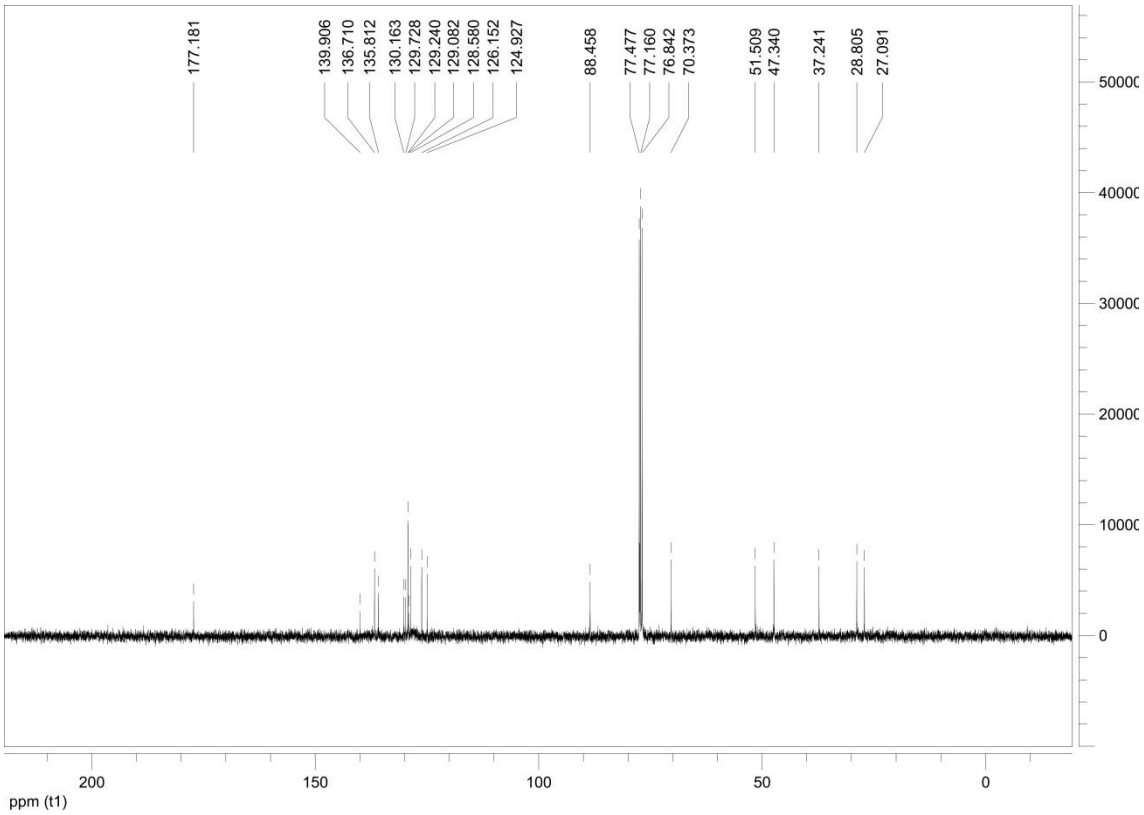
3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-(o-tolyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ga)



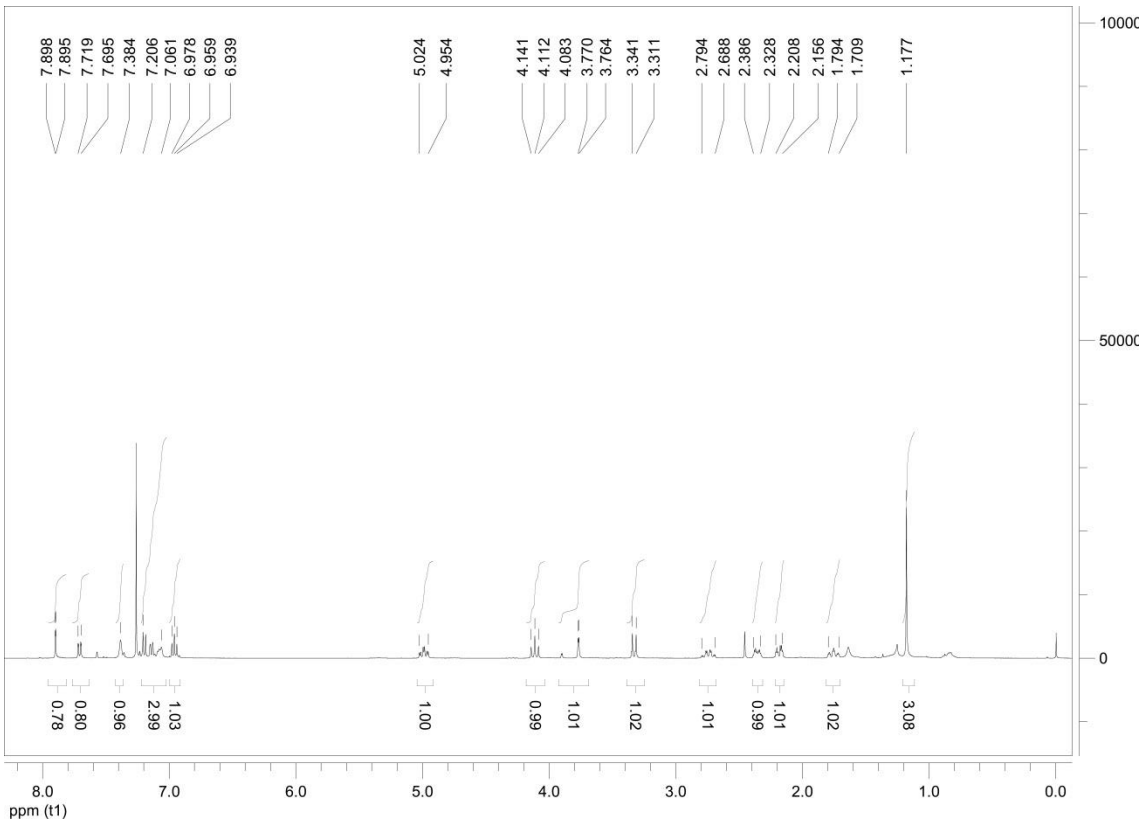


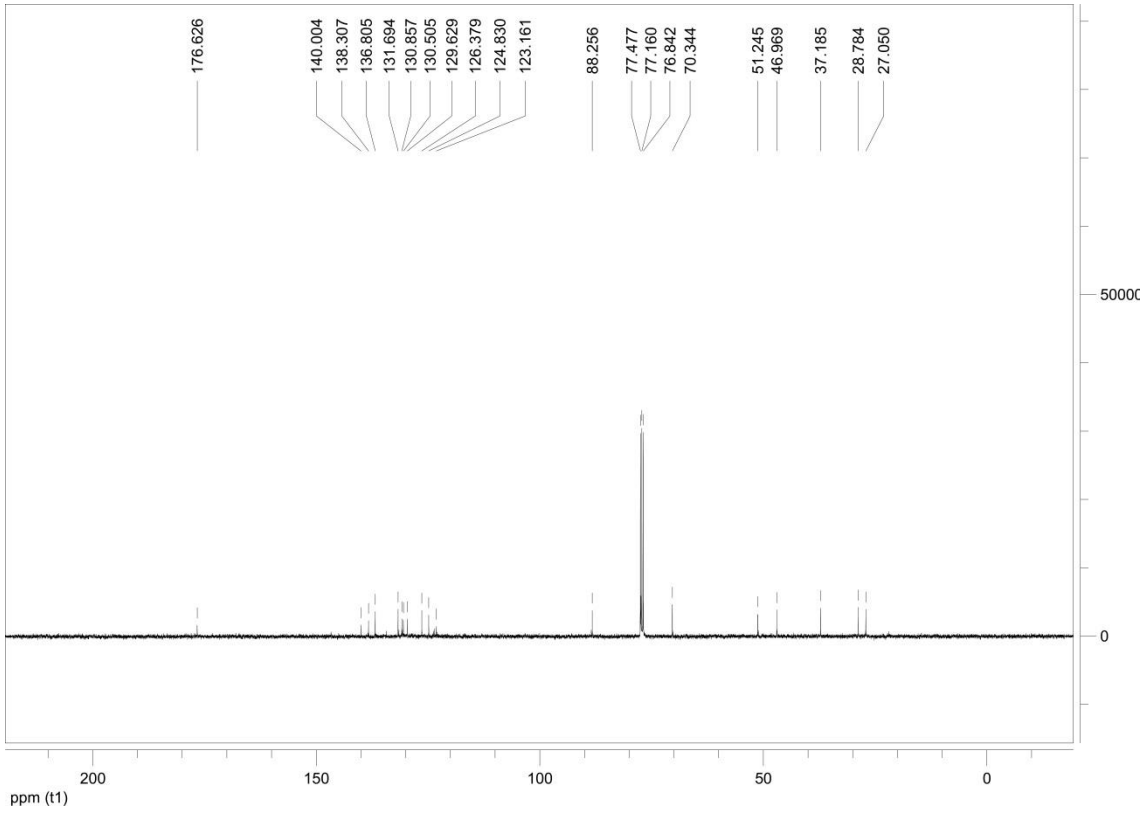
6-bromo-3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo [d]isothiazole 1,1-dioxide (3ha)



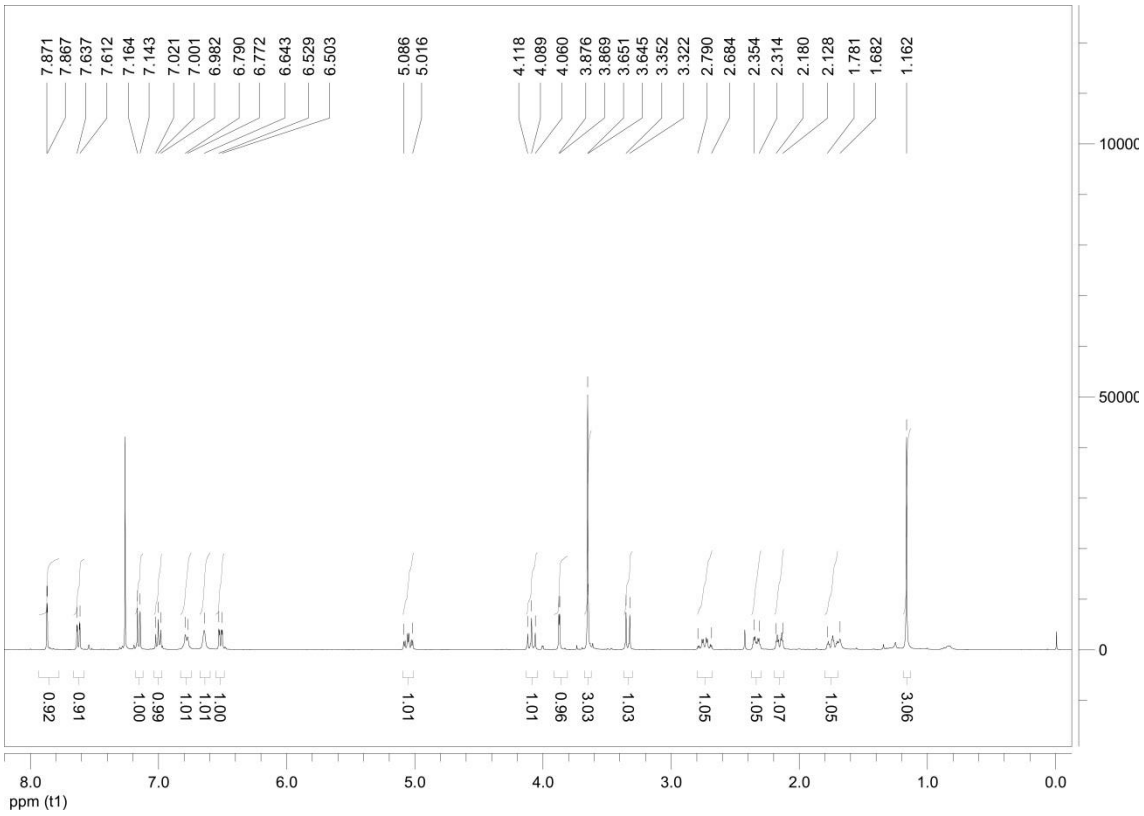


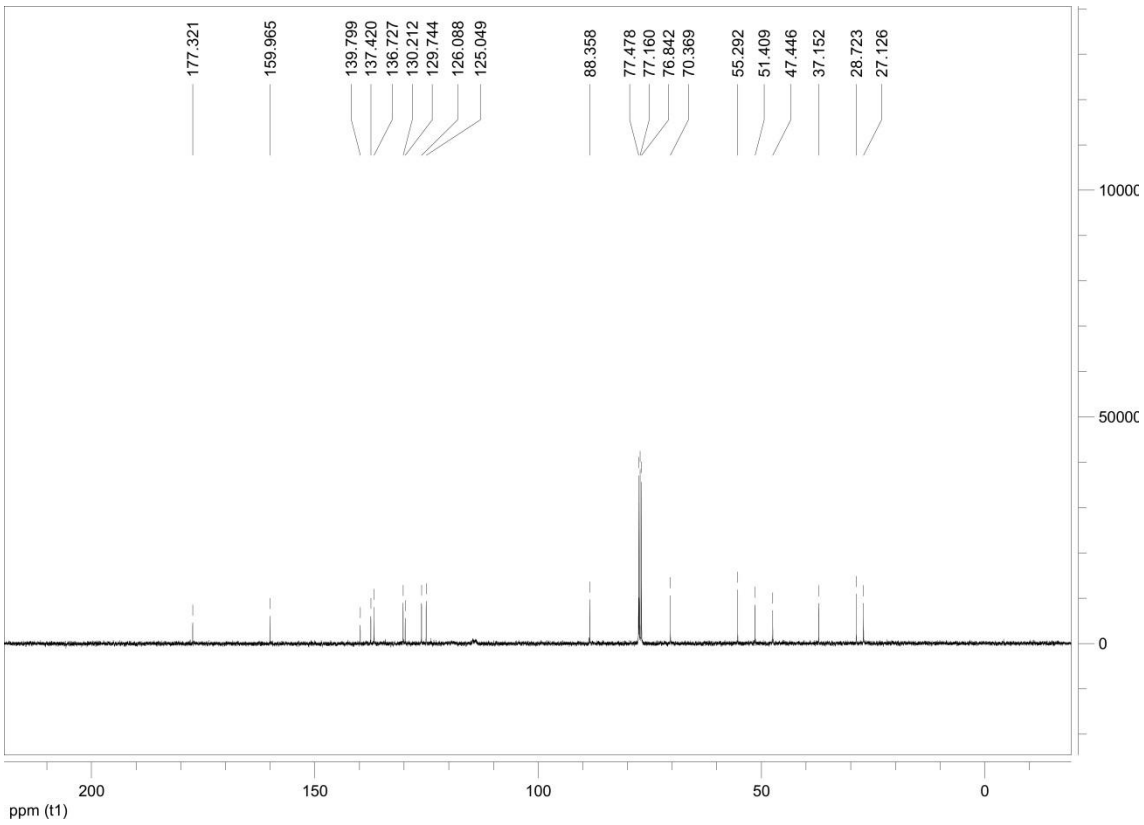
6-bromo-3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ia)



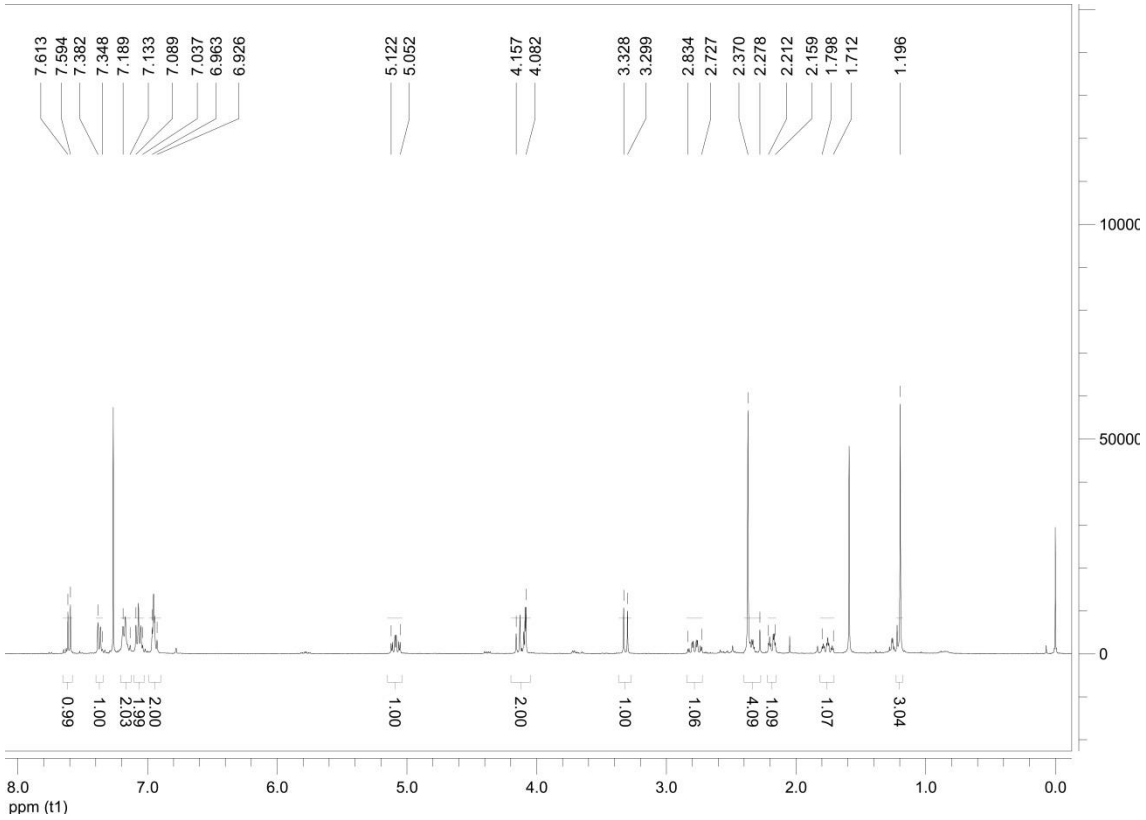


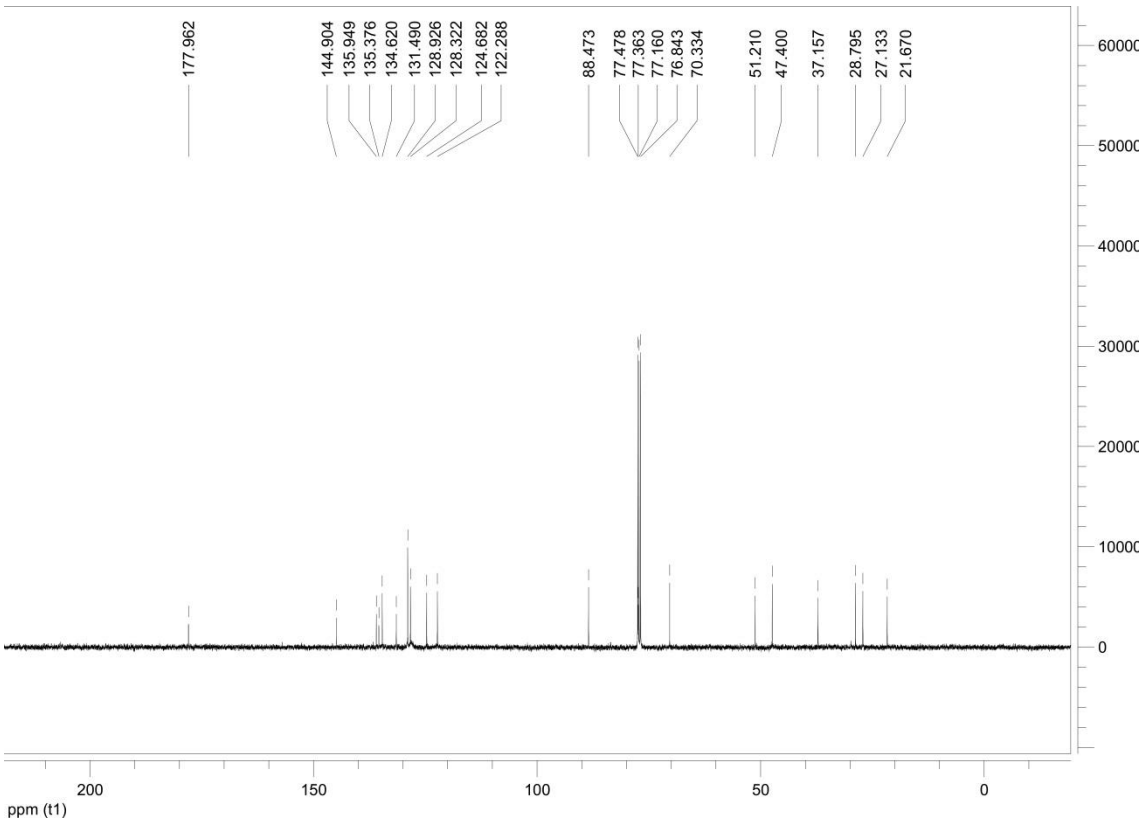
6-bromo-3-((*1S,2S,5R,6S*)-2-hydroxy-6-(3-methoxyphenyl)-2-methyl-5-nitrocyclo hexyl)benzo[d]isothiazole 1,1-dioxide (3ja)



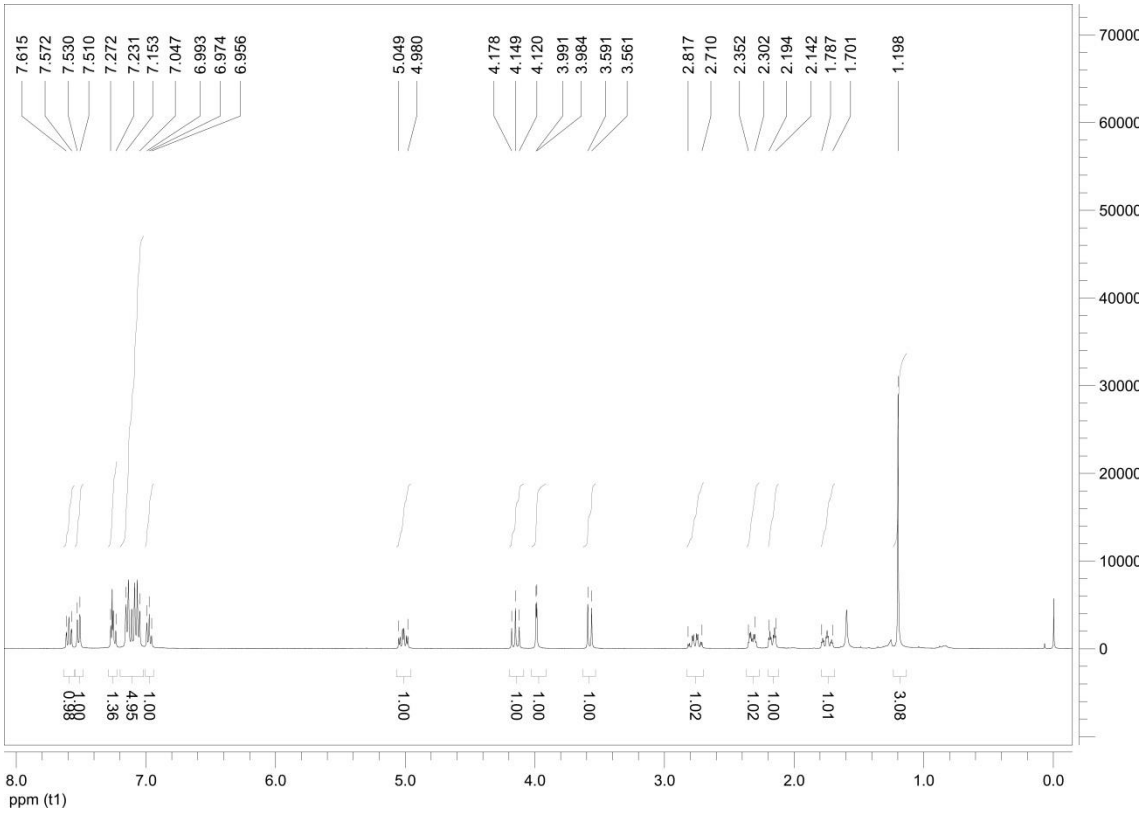


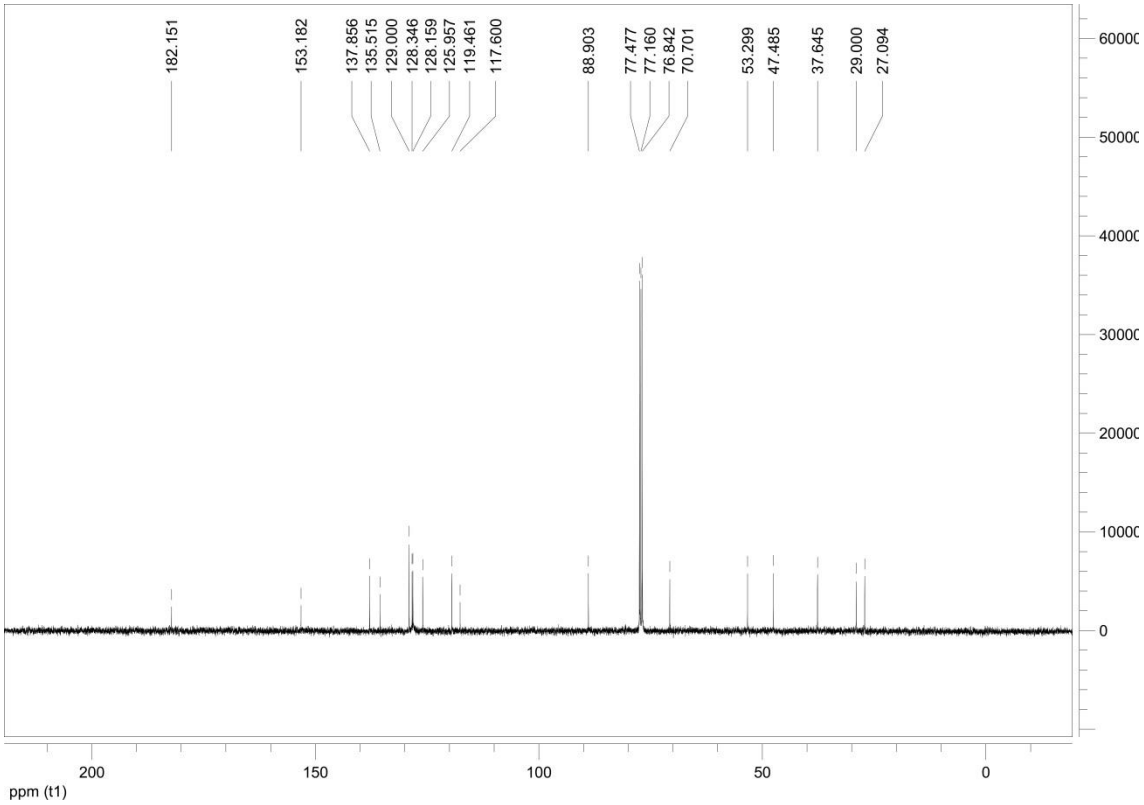
5-methyl-3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo [d]isothiazole 1,1-dioxide (3ka)



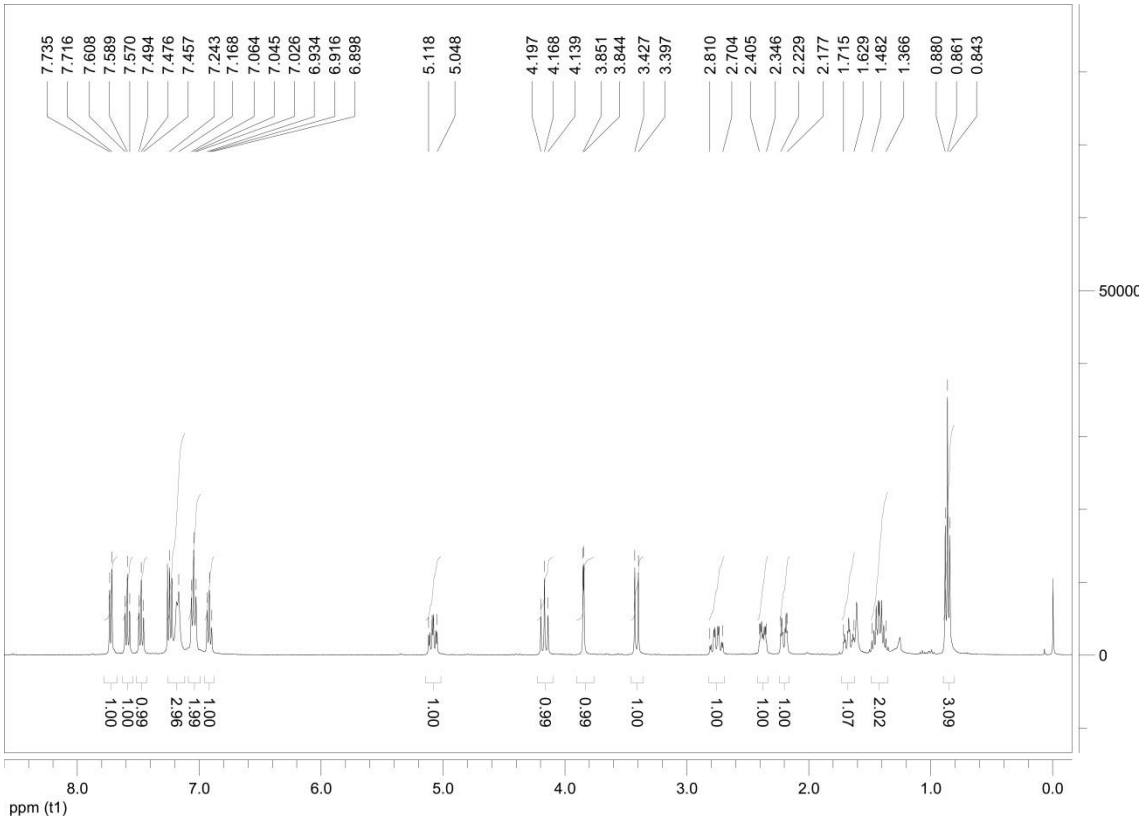


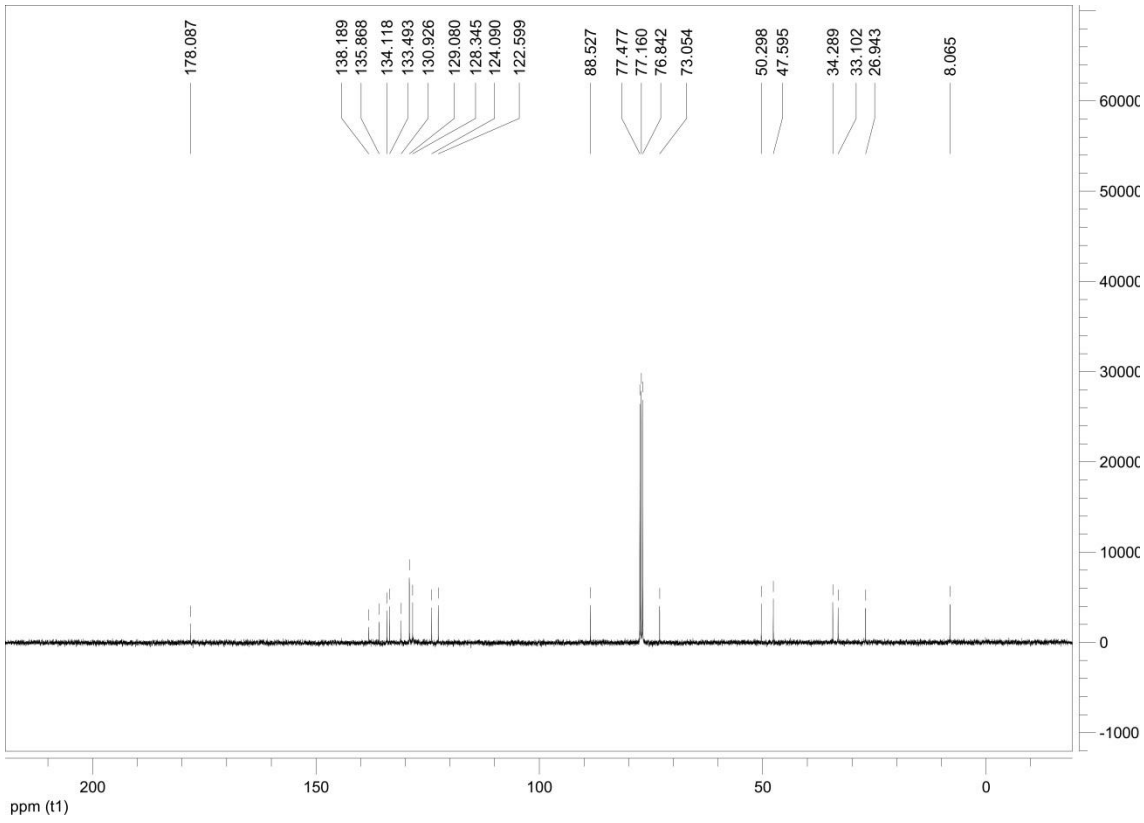
4-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[e][1,2,3]oxathiazine 2,2-dioxide (3la)



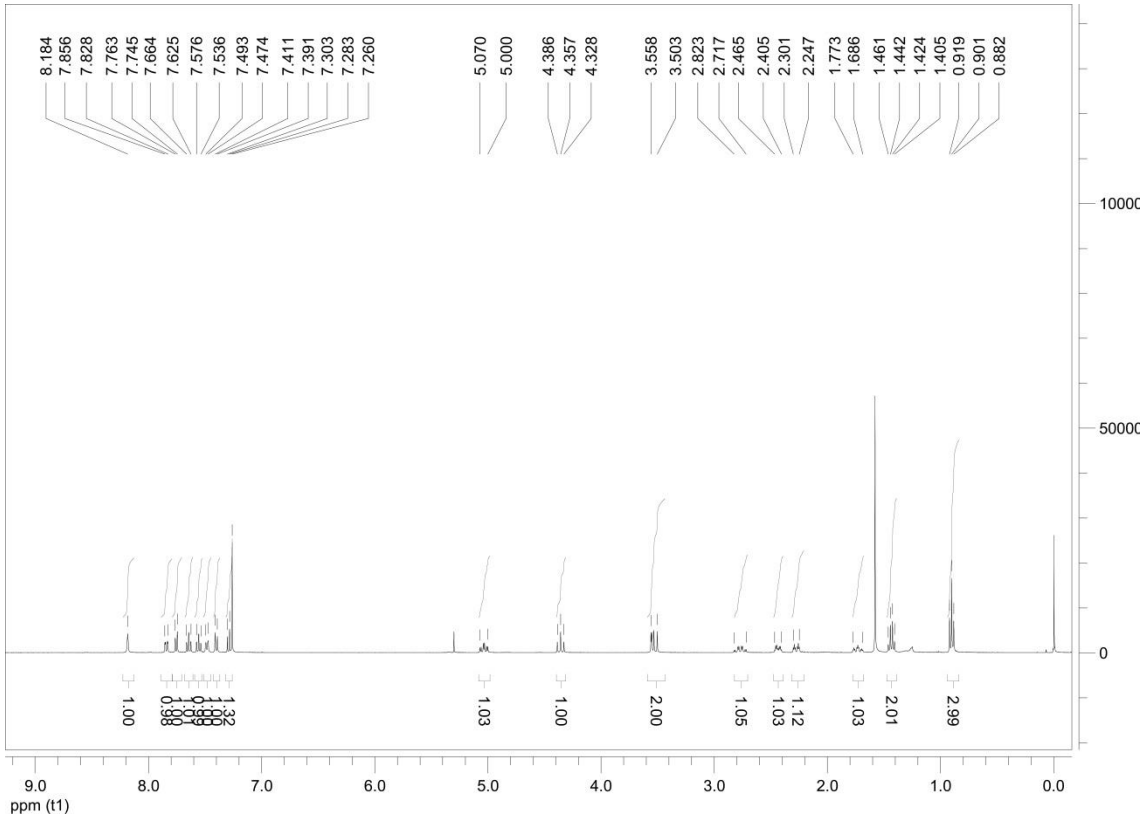


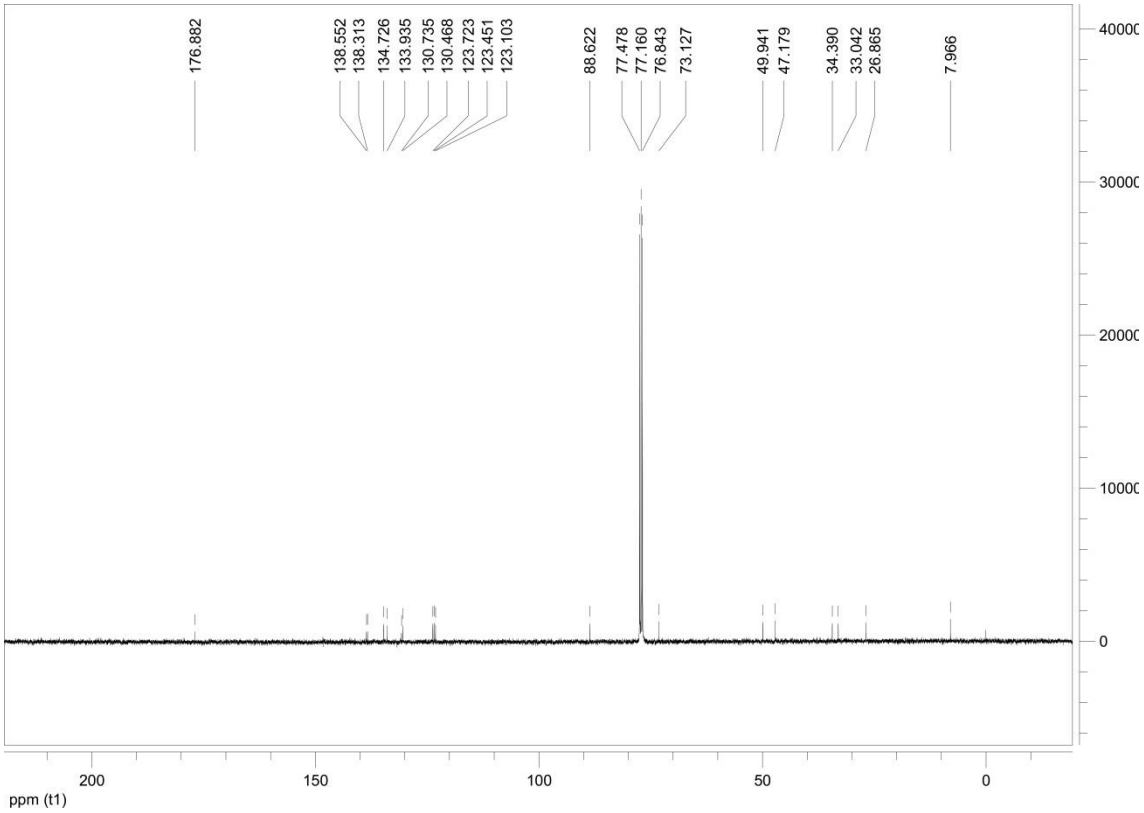
3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ab)



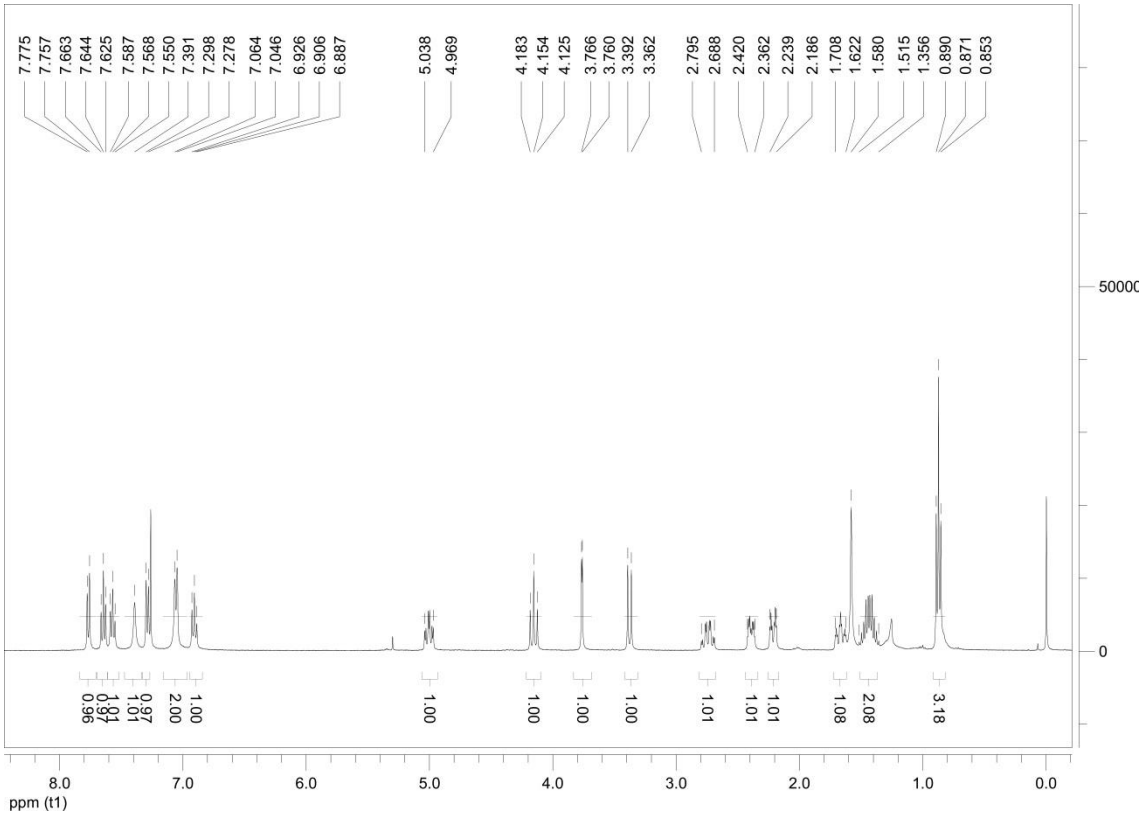


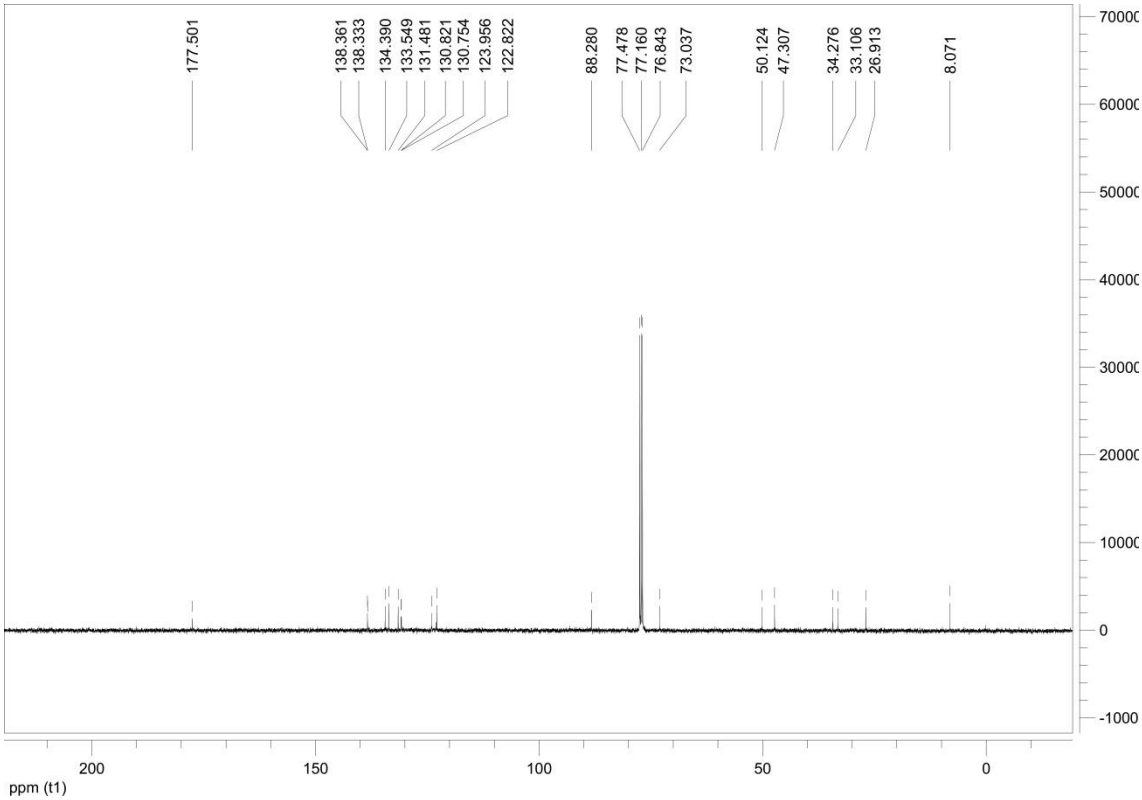
3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-(3-nitrophenyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3eb)



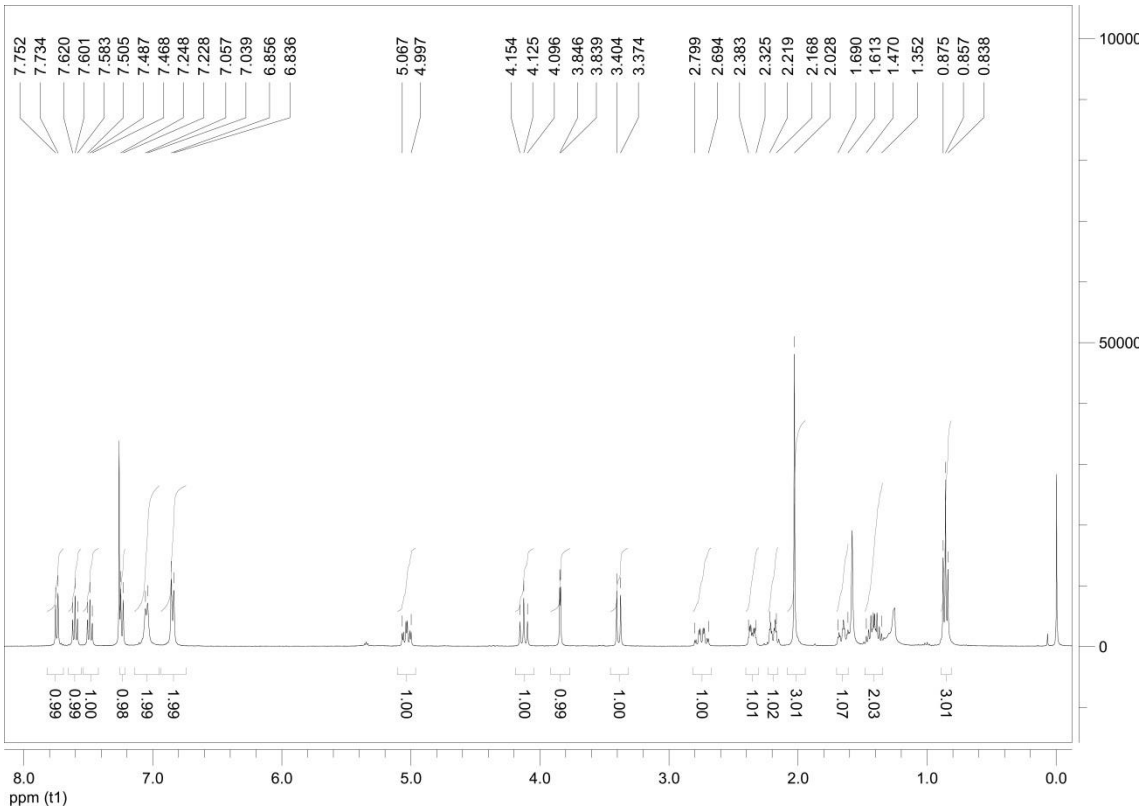


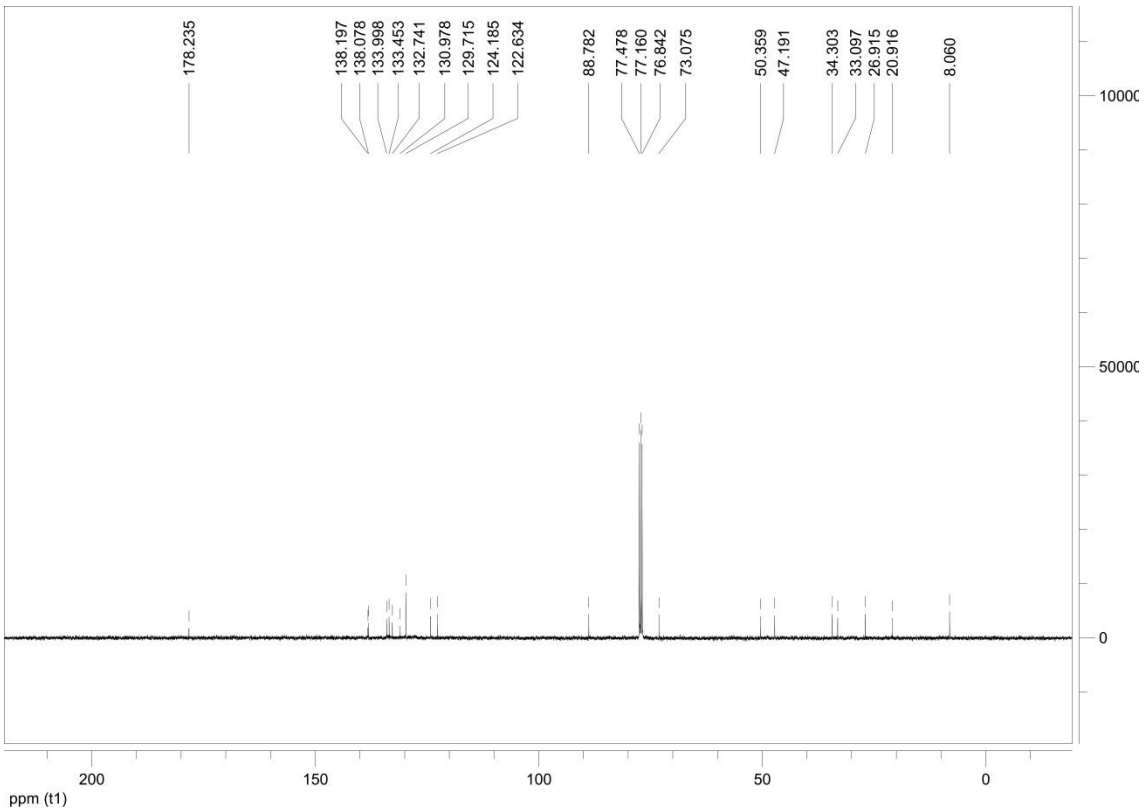
3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-ethyl-2-hydroxy-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3fb)





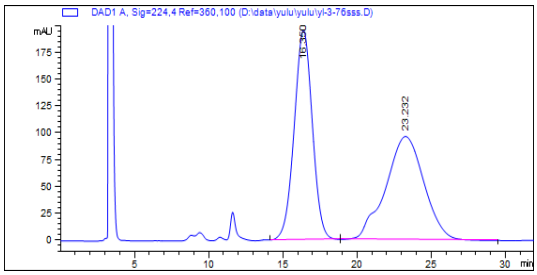
3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-(p-tolyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3lb)

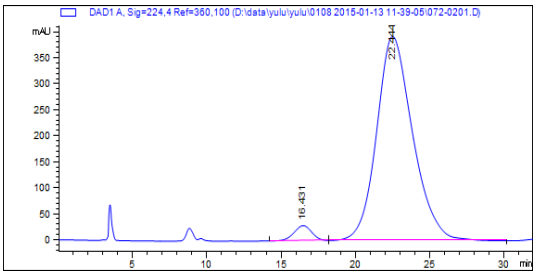




Chiral HPLC chromatograms

3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3aa)





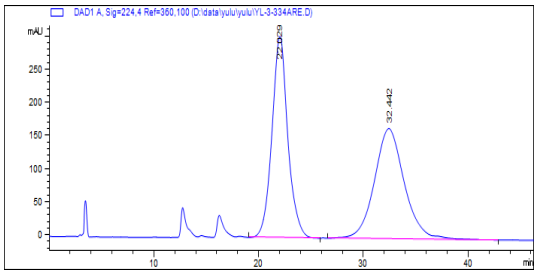
Racemic

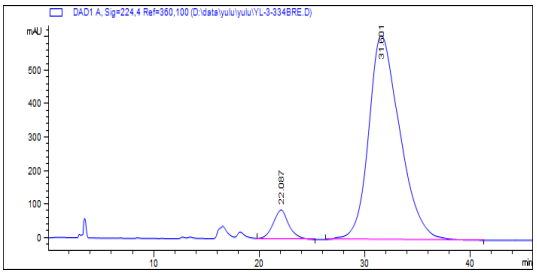
#	Time	Area	Height	Width	Area%	Symmetry
1	16.35	16599.5	195.2	1.3159	48.925	1.001
2	23.232	17328.7	96.4	2.626	51.075	1.062

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	16.431	2410.5	28.9	1.2781	3.511	1.082
2	22.444	66251.8	393.2	2.4658	96.489	0.77

3-((*1S,2S,5R,6S*)-6-(4-fluorophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ba)





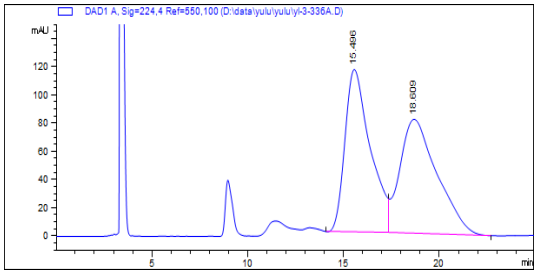
Racemic

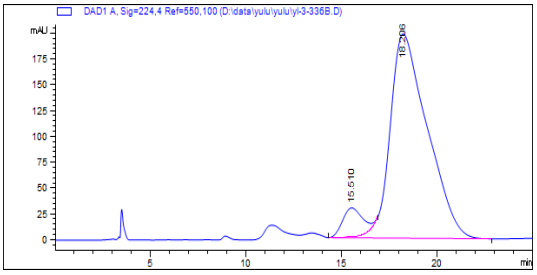
#	Time	Area	Height	Width	Area%	Symmetry
1	22.029	32146.2	304.6	1.5714	49.261	0.97
2	32.442	33110.5	166.7	2.9971	50.739	0.898

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	22.087	9139.3	87.1	1.5523	6.784	0.992
2	31.601	125581	609.3	3.0207	93.216	0.66

3-((*1S,2S,5R,6S*)-6-(4-chlorophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ca)





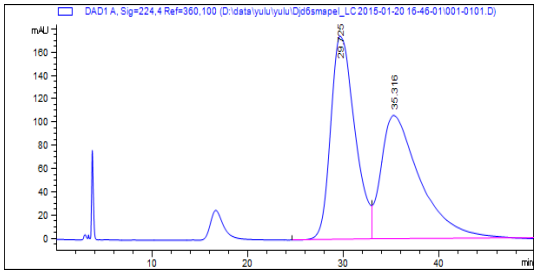
Racemic

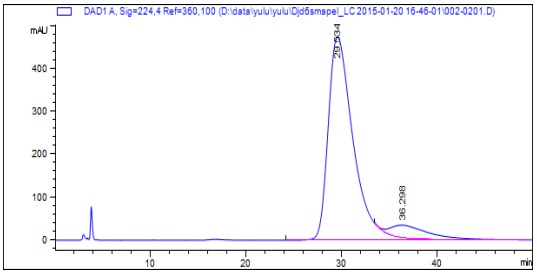
#	Time	Area	Height	Width	Area%	Symmetry
1	15.496	10683.8	115.3	1.3535	49.593	0.546
2	18.609	10859	81	1.9276	50.407	0.577

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	15.51	2095	28.3	1.116	7.296	0.789
2	18.206	26620.6	196.8	1.942	92.704	0.774

3-((*1S,2S,5R,6S*)-6-(4-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3da)





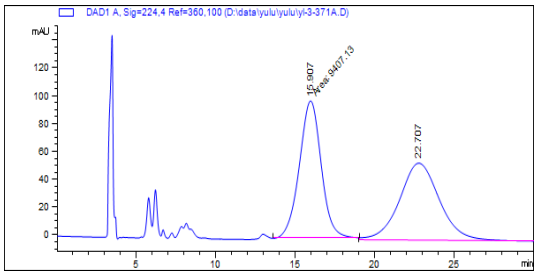
Racemic

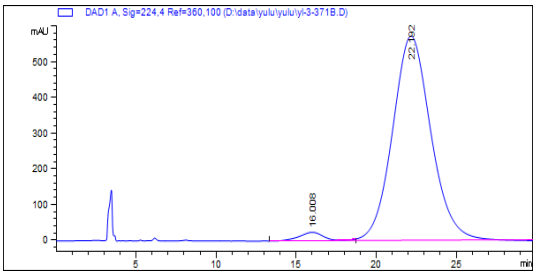
Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	29.725	31041.9	176	2.6662	49.972	0.651
2	35.316	31076.5	107.1	4.0891	50.028	0.438

#	Time	Area	Height	Width	Area%	Symmetry
1	29.534	86287.2	479.5	2.7076	90.378	0.547
2	36.298	9186.7	30.8	4.0902	9.622	0.378

3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-(3-nitrophenyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ea)





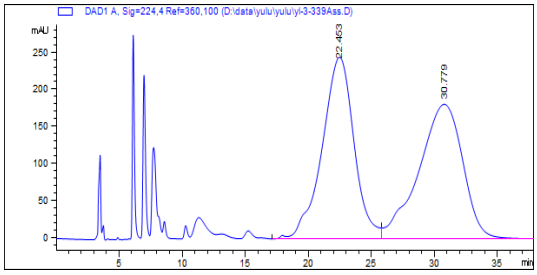
Racemic

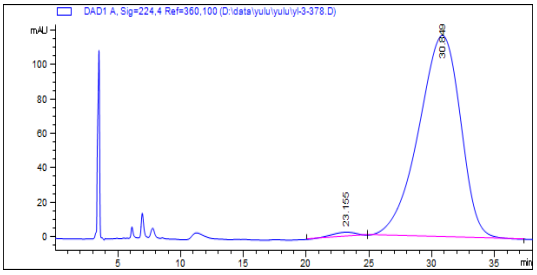
Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	15.907	9407.1	98.3	1.5951	49.061	1.03
2	22.707	9767.1	55.4	2.6502	50.939	0.907

#	Time	Area	Height	Width	Area%	Symmetry
1	16.008	2549.2	24.2	1.5751	2.585	1.169
2	22.192	96053.7	572.8	2.5503	97.415	1.01

3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3fa)





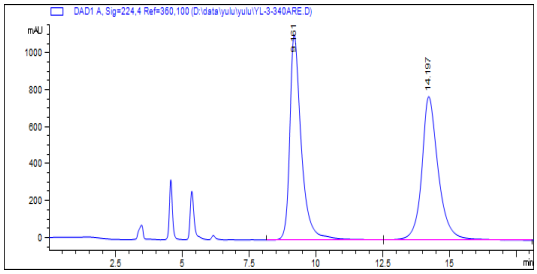
Racemic

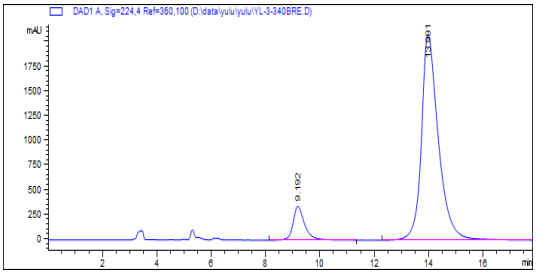
Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	22.453	43213.7	245.2	2.6552	49.412	1.175
2	30.779	44242.3	181.8	3.715	50.588	1.362

#	Time	Area	Height	Width	Area%	Symmetry
1	23.155	362.4	2.6	1.6613	1.315	1.678
2	30.849	27190.1	117.4	3.5583	98.685	1.277

3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-(o-tolyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ga)





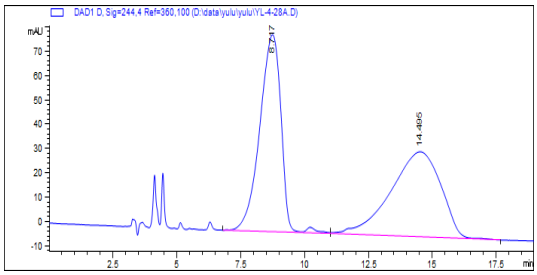
Racemic

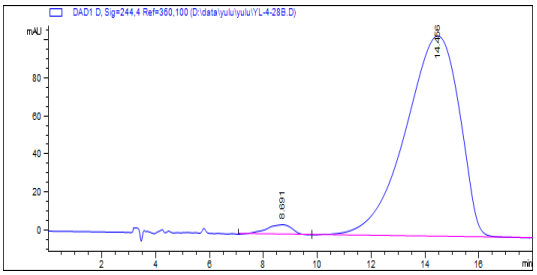
#	Time	Area	Height	Width	Area%	Symmetry
1	9.161	33343.3	1108.9	0.4428	49.971	0.57
2	14.197	33382.4	774.9	0.6306	50.029	0.714

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	9.192	10090.1	339.5	0.4387	10.044	0.667
2	13.991	90368.1	2077.2	0.6435	89.956	0.62

6-bromo-3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ha)





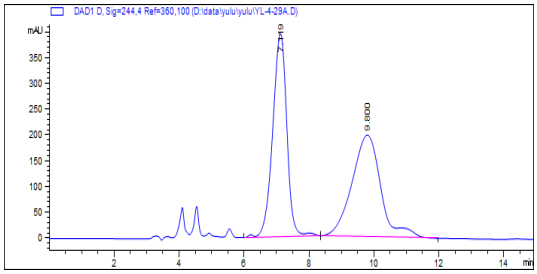
Racemic

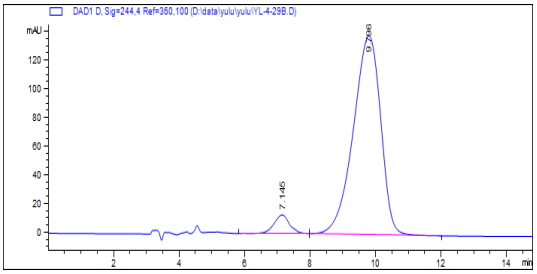
#	Time	Area	Height	Width	Area%	Symmetry
1	8.717	4684.3	80.5	0.926	49.504	1.518
2	14.495	4778	34.9	2.0548	50.496	1.446

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	8.691	352.1	5.2	0.9802	2.350	1.695
2	14.456	14630.7	105.3	2.2089	97.650	1.47

6-bromo-3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-hydroxy-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ia)





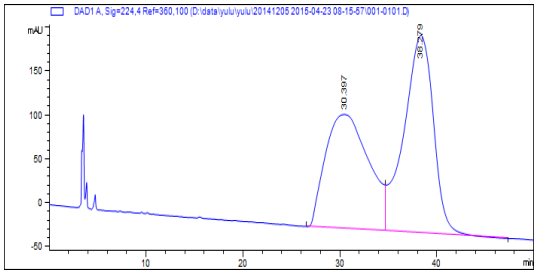
Racemic

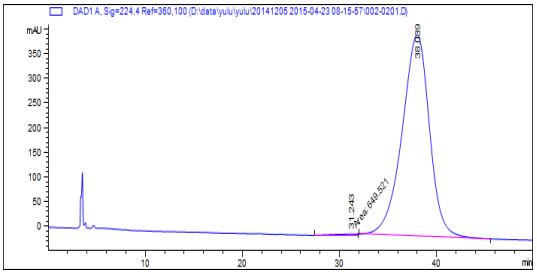
#	Time	Area	Height	Width	Area%	Symmetry
1	7.119	11836.8	391.2	0.4643	49.564	1.207
2	9.8	12044.9	195.7	0.9169	50.436	1.195

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	7.145	435.5	13	0.5061	5.124	1.097
2	9.796	8064.9	139	0.9051	94.876	1.294

6-bromo-3-((*1S,2S,5R,6S*)-2-hydroxy-6-(3-methoxyphenyl)-2-methyl-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ja)





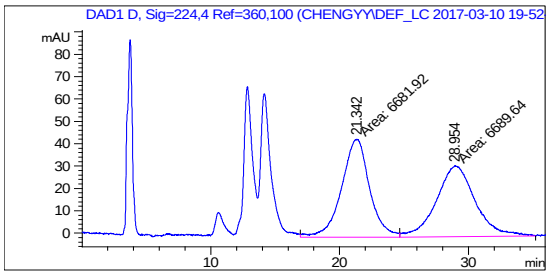
Racemic

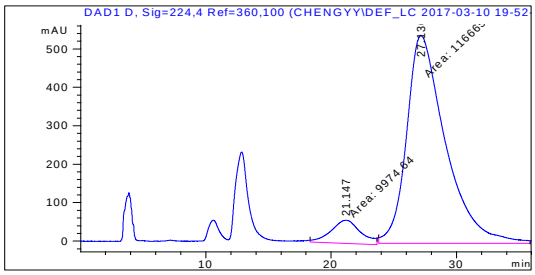
#	Time	Area	Height	Width	Area%	Symmetry
1	30.397	40745	130.3	3.679	46.065	0.75
2	38.279	47706.5	225.8	3.1432	53.935	1.315

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	31.243	649.5	3.7	2.9476	0.804	3.13
2	38.039	80177.8	407.9	3.0053	99.196	1.185

5-methyl-3-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ka)





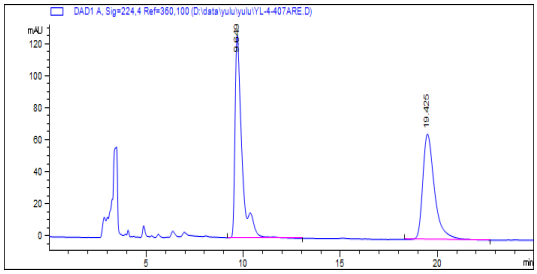
Racemic

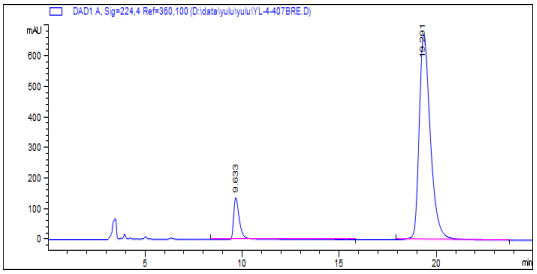
#	Time	Area	Height	Width	Area%	Symmetry
1	21.342	6681.9	43.9	2.5372	49.971	1.171
2	28.954	6689.6	32	3.4856	50.029	0.904

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	21.147	9974.6	60.9	2.7315	7.876	0.922
2	27.136	116664.7	541.9	3.5881	92.124	0.551

4-((*1S,2S,5R,6S*)-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexyl)benzo[e][1,2,3]oxathiazine 2,2-dioxide (3la)





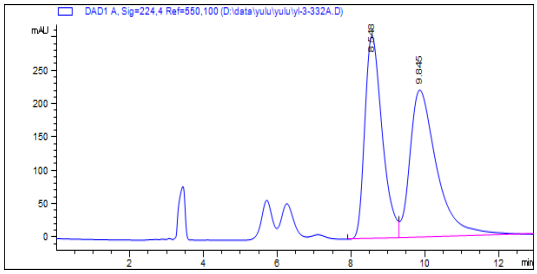
Racemic

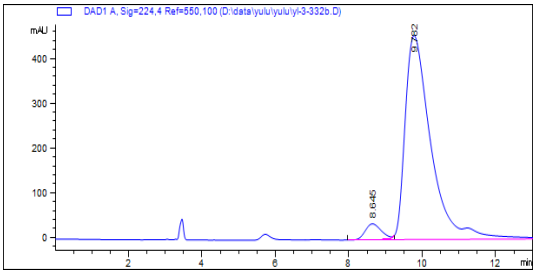
#	Time	Area	Height	Width	Area%	Symmetry
1	9.649	3135	126.6	0.3262	52.987	0.505
2	19.425	2781.5	65.9	0.6364	47.013	0.619

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	9.633	2967.8	136.4	0.314	9.969	0.526
2	19.291	26802.3	670.4	0.6104	90.031	0.659

3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-phenylcyclohexyl)benzo[d]isothiazole 1,1-dioxide (3ab)





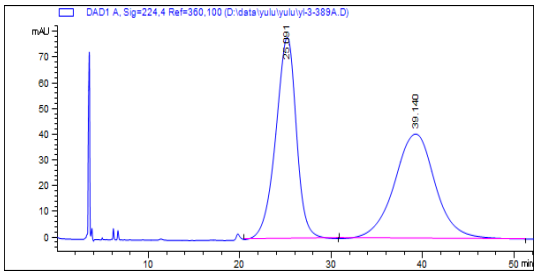
Racemic

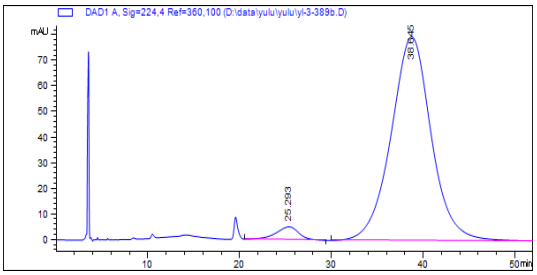
#	Time	Area	Height	Width	Area%	Symmetry
1	8.548	10008.9	305.3	0.5045	47.039	0.651
2	9.845	11268.8	221.8	0.7606	52.961	0.527

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	8.645	1114.8	36	0.479	4.697	0.773
2	9.782	22618.9	456.7	0.7174	95.303	0.669

3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-(3-nitrophenyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3eb)





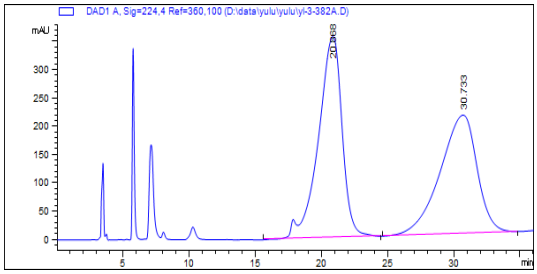
Racemic

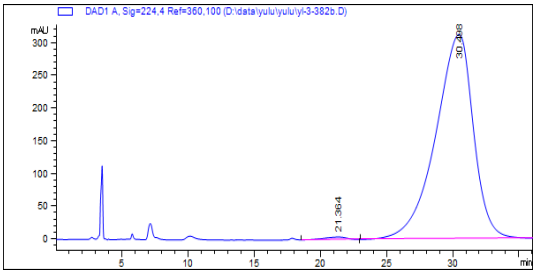
#	Time	Area	Height	Width	Area%	Symmetry
1	25.091	12406.3	79	2.3686	49.170	1.2
2	39.14	12825	41	4.1864	50.830	1.06

Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	25.293	878.7	5.1	2.1155	3.499	1.256
2	38.645	24231.8	79.9	4.3702	96.501	1

3-((*1S,2S,5R,6S*)-6-(3-bromophenyl)-2-ethyl-2-hydroxy-5-nitrocyclohexyl)benzo[d]isothiazole 1,1-dioxide (3fb)





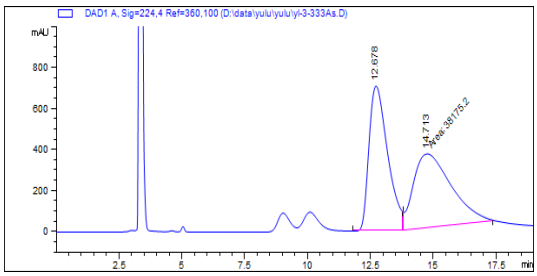
Racemic

#	Time	Area	Height	Width	Area%	Symmetry
1	20.868	44863.4	358	1.8519	52.205	1.592
2	30.733	41072.8	210.4	2.9211	47.795	1.591

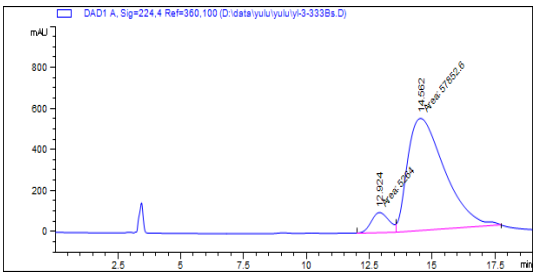
Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	21.364	452.2	3.9	1.6601	0.723	1.77
2	30.498	62074.9	312	2.9055	99.277	1.55

3-((*1S,2S,5R,6S*)-2-ethyl-2-hydroxy-5-nitro-6-(p-tolyl)cyclohexyl)benzo[d]isothiazole 1,1-dioxide (3lb)



Racemic

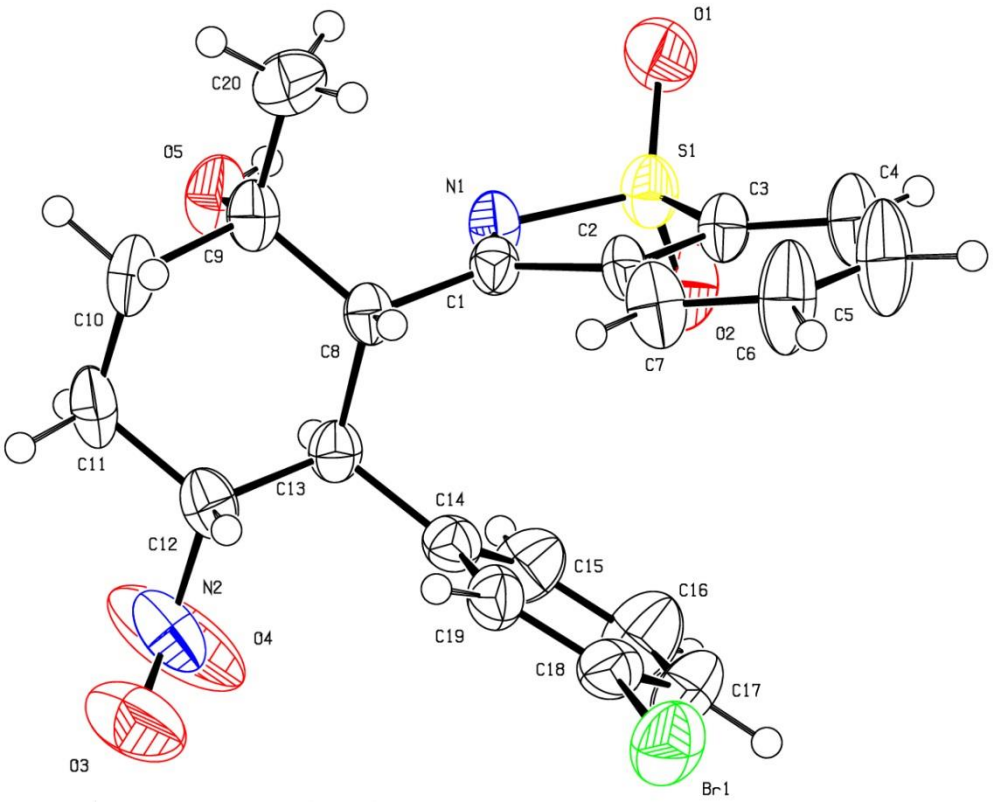


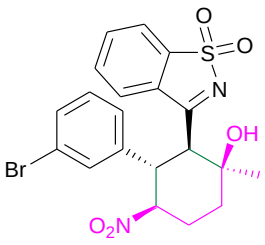
Chiral

#	Time	Area	Height	Width	Area%	Symmetry
1	12.678	36919.2	709.1	0.7974	49.164	0.566
2	14.713	38175.2	363.2	1.7519	50.836	0.552

#	Time	Area	Height	Width	Area%	Symmetry
1	12.924	5264	103.5	0.8478	8.340	0.889
2	14.562	57852.6	553.3	1.7427	91.660	0.525

Crystal Structure and data for compound 3fa





3fa

Table 1. Crystal data and structure refinement for SUSTLPF4 (16 Feb 2015).

Identification code	lpf4	
Empirical formula	C_{20} H_{19} Br N_2 O5 S	
Formula weight	479.34	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.8208(3) Å	α= 90 °.
	b = 12.8570(4) Å	β= 90 °.
	c = 18.1141(5) Å	γ = 90 °.
Volume	2054.30(11) $Å^3$	
Z	4	
Density (calculated)	1.550 Mg/m^3	
Absorption coefficient	2.137 mm^{-1}	
F(000)	976	
Crystal size	0.46 x 0.40 x 0.32 mm^3	
Theta range for data collection	1.94 to 27.39 °.	
Index ranges	-11<=h<=10, -16<=k<=16, -22<=l<=23	
Reflections collected	24921	
Independent reflections	4619 [R(int) = 0.1516]	
Completeness to theta = 27.39 °	99.5 %	
Absorption correction	None	
Max. and min. transmission	0.7456 and 0.5966	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4619 / 0 / 307	
Goodness-of-fit on F^2	0.994	
Final R indices [I>2sigma(I)]	R1 = 0.0514, wR2 = 0.0608	
R indices (all data)	R1 = 0.1259, wR2 = 0.0689	
Absolute structure parameter	0.030(8)	
Largest diff. peak and hole	0.275 and -0.347 e.$Å^{-3}$	