

Supporting Information

Diffusion mixing with a volatile tertiary amine as a very efficient technique for 1,3-dipolar cycloaddition reactions proceeding via dehydrohalogenation of stable precursors of reactive dipoles

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Abstract: Spontaneous diffusion of a volatile reagent vapors into a solution, containing a stable precursor of an unstable reactive intermediate, may be the simplest method for carrying out some organic reactions, including 1,3-dipolar cycloaddition. In the present work, this technique was applied to generate nitrile imines and nitrile oxides for the subsequent reactions with dipolarophiles from hydrazonyl halogenides or N-hydroxyimidoyl halogenides by the action of volatile tertiary amines (Et₃N, as well as Me₃N or DIPEA). Generation of highly reactive intermediates as a result of a tertiary amine vapors diffusion into the reaction mixture makes it possible to obtain the products of 1,3-dipolar cycloaddition reactions in high yields and without the side products formation due to the created conditions of "dipole starvation". The proposed method of diffusion reagents mixing allows to carry out 1,3-dipolar cycloaddition reactions with low-stable and easily dimerizing nitrile oxides and nitrile imines in high yields and is incredibly easy experimentally. In fact, 1,3-dipoles are obtained by this method "molecule-by-molecule", which prevents their unwanted dimerization.

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Experimental Procedures

Starting olefins **1-3** are commercially available and were used without further purification. Norbornene derivative **4** and methylidenehydantoin **5** was obtained using the procedures, described in the literature^[1,2]. Experimental details for the preparation of hydroximoyl halides **6a-c** and imidoyl chlorides **6d,e** has been previously described^[3-7].

¹H and ¹³C NMR spectra were recorded on a Bruker Avance instrument with an operating frequency of 400 MHz for ¹H NMR, 101 MHz for ¹³C NMR. Chemical shifts are given in parts per million on a scale of δ relative to hexamethyldisiloxane as an internal standard.

High-resolution mass spectra were recorded on an Orbitrap Elite mass spectrometer (Thermo Scientific) with IREP. To enter solutions with a concentration of 0.1–9 $\mu\text{g/ml}$ (in 1% formic acid in acetonitrile), direct injection into the ion source using a syringe pump (5 $\mu\text{l/min}$) was used. Spray voltage ± 3.5 kV, capillary temperature 275°C.

General reaction procedure using diffusion mixing technique.

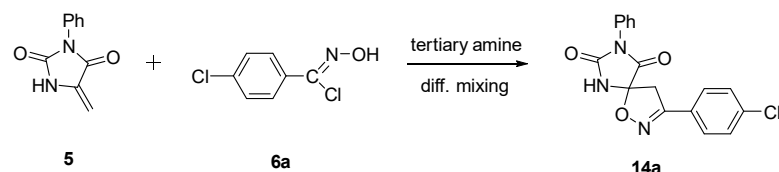
Vial **1** (Figure S1), containing a mixture of dipolarophile and hydroximoyl halide or imidoyl chloride in an organic solvent, was closed with a perforated glass stopper and placed in a larger vial **2** with a tertiary amine or its concentrated solution. If necessary, the reaction apparatus can be placed in a refrigerator or heated in a water bath to maintain the desired reaction temperature. If the mixing of the reaction mixture was used, a magnetic anchor **3** was placed in the inner vial and the device is placed on the switched on magnetic stirrer **4**. The reaction process was monitored by TLC or ¹H NMR of the reaction mixture. After the reaction was completed, the reaction mixture from the inner vial **1** was diluted with chloroform and washed several times with 2% aqueous HCl. The combining organic fractions were dried over anhydrous Na₂SO₄, the solvent was distilled off under reduced pressure, and the product was purified using column chromatography.

Some possibilities of the diffusion mixing technique on example of the interaction of dipolarophyle **5** with hydroximoyl halide **6a** and dipolarophyle **4** with imidoyl chloride **7b** using different solvents, reaction temperatures, and amine in the external vial are presented in Tables S1 and S2.



Figure S1. 1 - inner vial, 2 - external vial, 3 - magnetic anchor, 4 - magnetic stirrer.

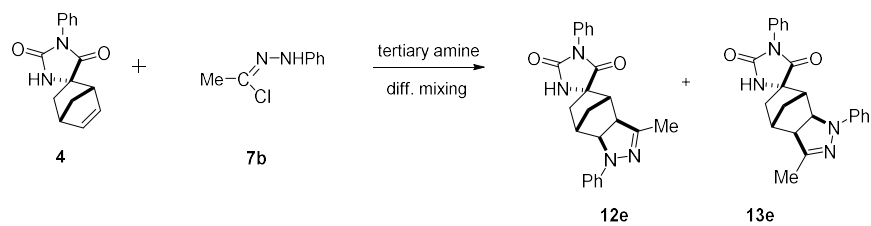
Table S1. The reaction of dipolarophyle **5** with hydroximoyl halide **6a** in different solvents and reaction temperatures^[a].



Contents of the external vial	Solvent in the inner vial	Temperature, °C	Stirring	Reaction time, days	Yield of 14a ^[b] , %
NEt ₃	CHCl ₃	20	yes	1	100
NEt ₃	CHCl ₃	20	no	1	95
NEt ₃	MeOH	20	yes	1	100
NEt ₃	PhH	20	yes	1	91
NEt ₃	Et ₂ O	20	yes	1	83
NEt ₃ /Et ₂ O (1 : 5)	Et ₂ O	20	yes	1	88
NMe ₃ H ⁺ Cl ⁻ , NaOH, H ₂ O ^[c]	CHCl ₃	20	yes	1	91
NEt ₃ H ⁺ Cl ⁻ , NaOH, H ₂ O ^[c]	CHCl ₃	20	yes	1	98
i-Pr ₂ NEt	CHCl ₃	-18	no	3	96
i-Pr ₂ NEt	CHCl ₃	20	no	1	95
i-Pr ₂ NEt	DMSO	20	no	1	97
i-Pr ₂ NEt	o-xylene	80	no	1	94

^[a] Reaction conditions: 20 mg (0.106 mmol) of compound **5** and 20 mg (0.106 mmol) of compound **6a** in inner vial; 35.85 mmol of amine in outer vial. ^[b] Based on ¹H NMR analysis of reaction mixtures. ^[c] Solution in an external vial were prepared immediately before the start of the reaction.

Table S2. The reaction of dipolarophyle **4** with imidoyl chloride **7b** in different solvents and reaction temperatures ^[a].



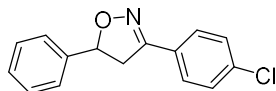
7b/4 , eq.	Reaction conditions	Stirring	Reaction time, days	Yield of 12e + 13e ^[b] , %
1	CHCl ₃ /NEt ₃ , 20°C	yes	1	68
1	CHCl ₃ /NEt ₃ , 20°C	no	1	53
2.1	CHCl ₃ /NEt ₃ , 20°C	yes	2	89
3	CHCl ₃ /NEt ₃ , 20°C	yes	3	100
1	DMSO/ <i>i</i> -Pr ₂ NEt, 20°C	no	1	52
1.4	CHCl ₃ / <i>i</i> -Pr ₂ NEt, 20°C	no	1	100
1.4	CHCl ₃ / <i>i</i> -Pr ₂ NEt, -18°C	no	3	91

^[a] Reaction conditions: 25 mg (0.098 mmol) of compound **7b** and compound **6a** in the amount, indicated in the table, in the inner vial; 35.85 mmol of amine in the outer vial. ^[b] Based on ¹H NMR analysis of reaction mixtures.

Products **12e** and **13e**, regardless of the reaction conditions, were always formed in a ratio of 52:48.

General procedure of 1,3-dipolar cycloaddition to styrene using diffusion mixing technique.

A mixture of styrene **1** (0.263 mmol, 0.027 g) and halogen derivative **6** or **7** (0.263 mmol) in 3 ml of chloroform was placed in a 15 ml vial **1** (diameter 1.3 cm) and closed with a glass stopper with holes. The vial **1** was then placed in a closed 50 ml vial **2** (diameter 3.5 cm) containing triethylamine (35.85 mmol, 5 ml) and the reaction mixture was stirred at room temperature for two days (TLC or NMR control). When the reaction was completed, the mixture from the inner vial was diluted with 10 ml of chloroform, transferred to a separating funnel and washed with 2% aqueous HCl (2 x 10 ml). The organic phase was dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using chloroform as an eluent.



3-(4-chlorophenyl)-5-phenyl-4,5-dihydroisoxazole (**8a**). From 27 mg (0.263 mmol) of styrene **1** and 50 mg (0.263 mmol) of hydroximoyl chloride **6a** compound **8a** (64 mg, 94%) was obtained as a white crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 7.64-7.62 (m, 2H, p-ClC₆H₄), 7.41-7.32 (m, 7H, p-ClC₆H₄ + C₆H₅), 5.76 (dd, J₁=8.3 Hz, J₂=11.1 Hz, 1H, CH), 3.75 (dd, J₁=11.1 Hz, J₂=16.6 Hz, 1H, CH₂), 3.32 (dd, J₁=8.3 Hz, J₂=16.6 Hz, 1H, CH₂). ¹³C NMR (101 MHz, CDCl₃): δ 155.3 (C=N), 140.8 (1C, C₆H₅), 136.2 (1C, p-ClC₆H₄), 129.1 (2C, C₆H₅), 128.9 (2C, p-ClC₆H₄), 128.5 (1C, C₆H₅), 128.1 (1C, p-ClC₆H₄), 128.1 (2C, p-ClC₆H₄), 126.0 (2C, C₆H₅), 83.0 (CH), 43.1 (CH₂). HRMS (ESI+) m/z calcd. for (C₁₅H₁₃ClNO, M+H): 258.0680, found: (M+H): 258.0670.

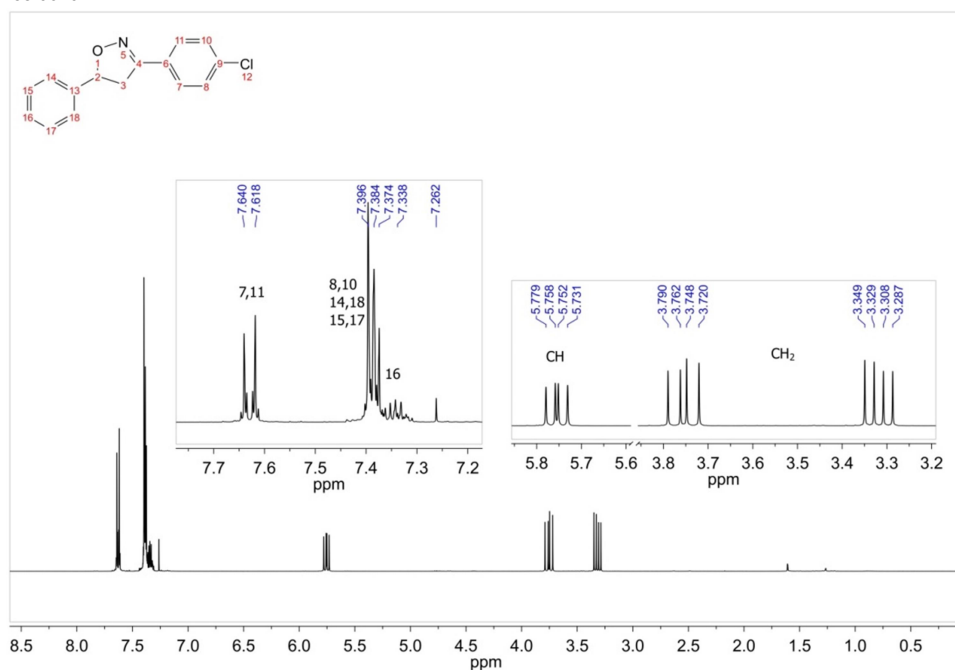


Figure S2. ¹H NMR spectra of compound **8a**.

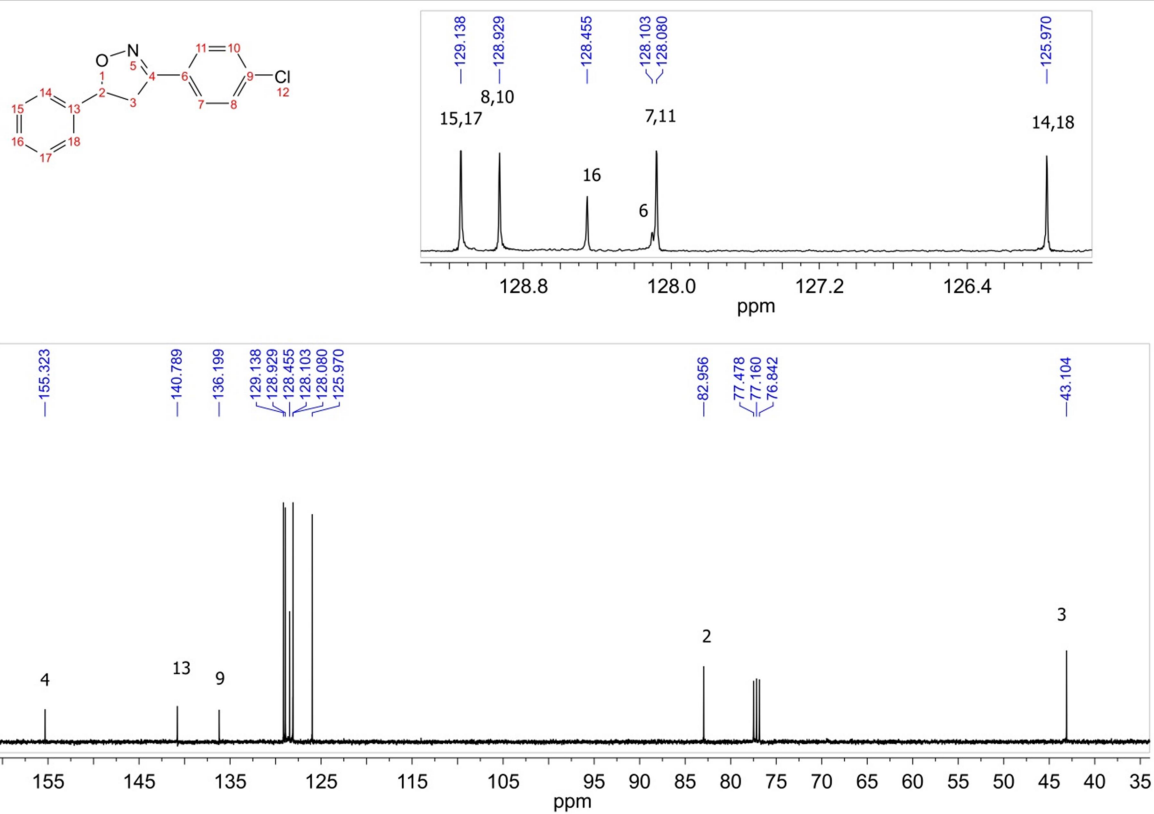
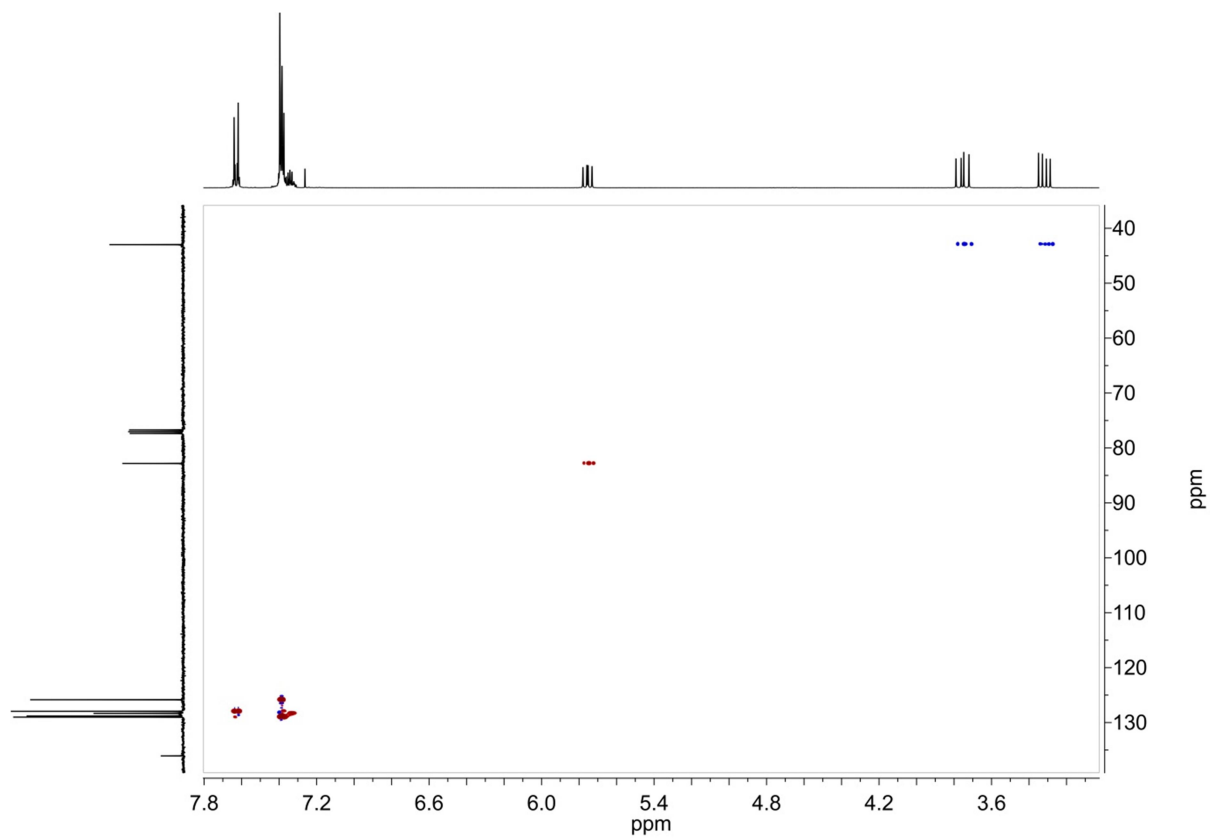
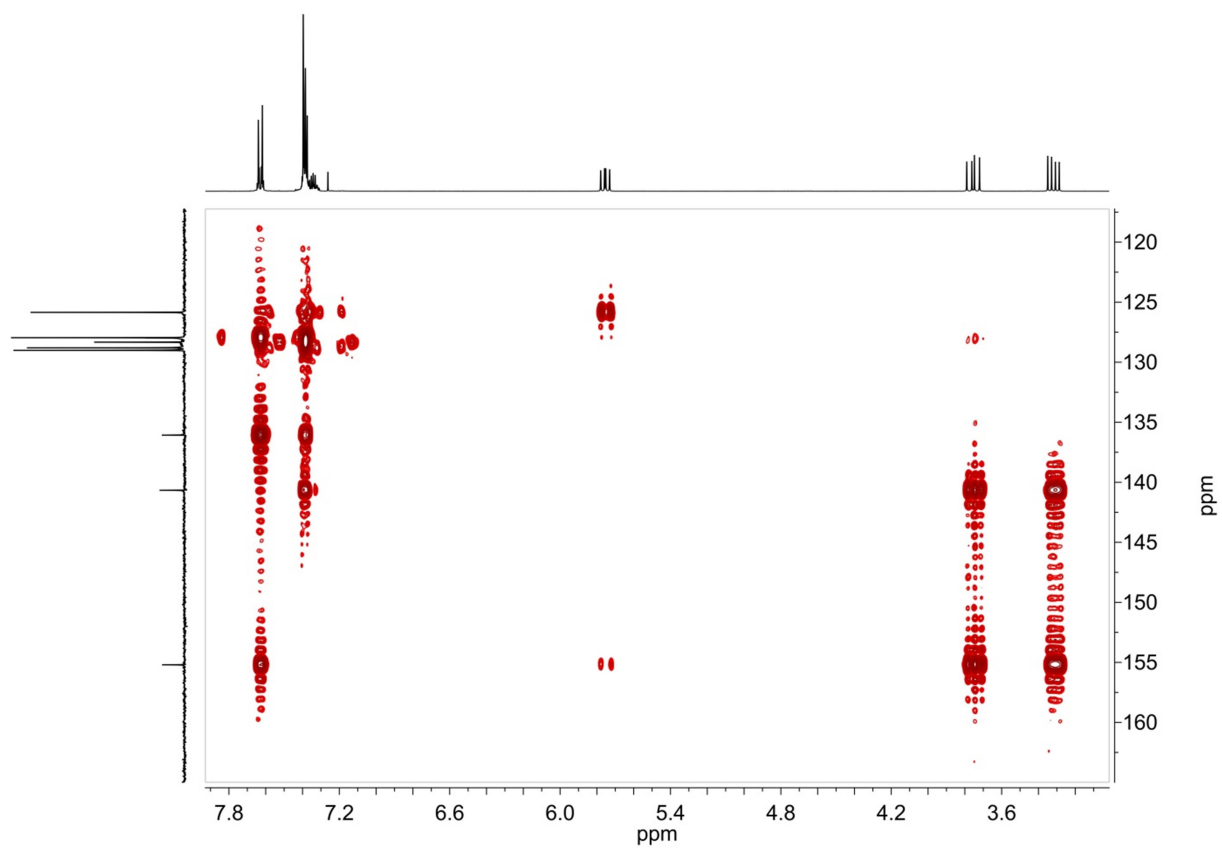
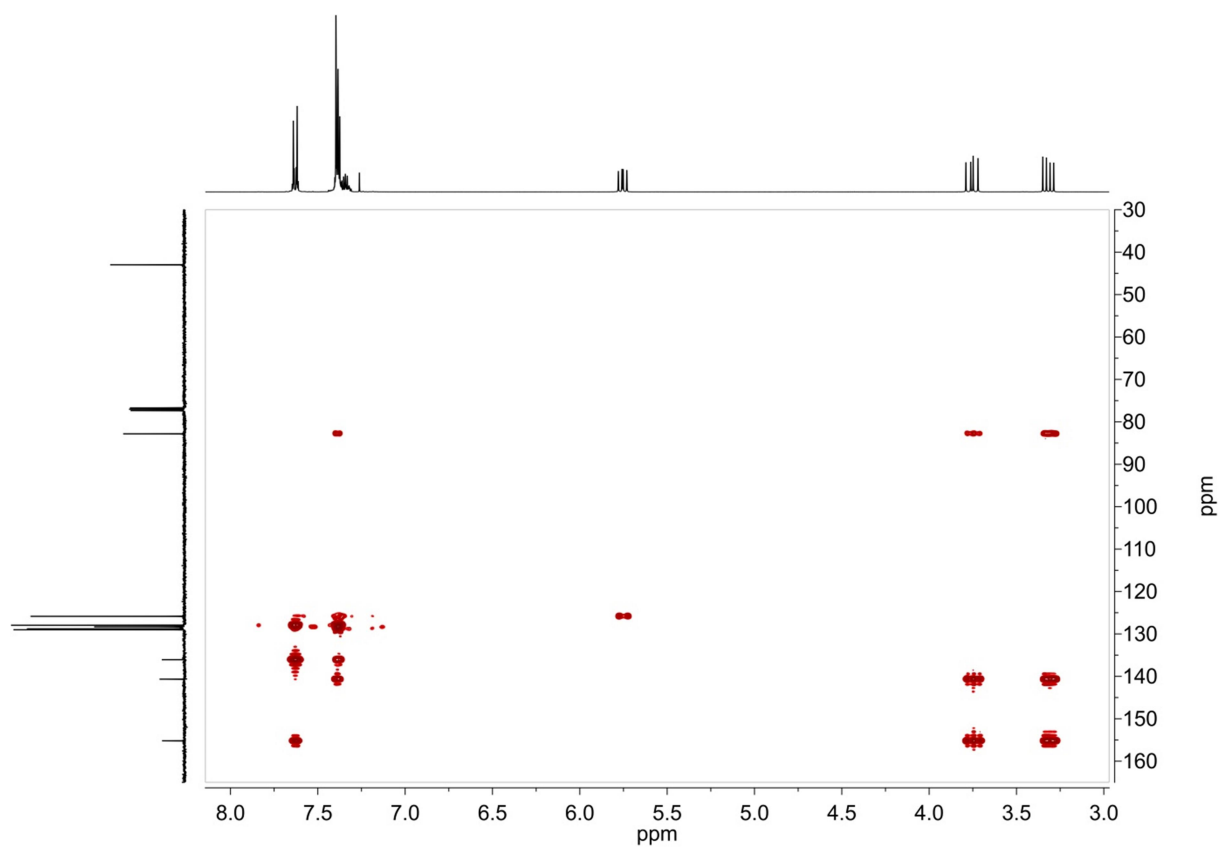


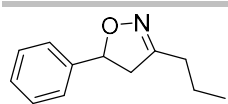
Figure S3. ^{13}C NMR spectra of compound **8a**.



FigureS4. HSQC ^1H - ^{13}C NMR spectra of compound **8a**.



FigureS5. HMBC ^1H - ^{13}C NMR spectra of compound **8a**.



5-phenyl-3-propyl-4,5-dihydroisoxazole (**8b**). From 27 mg (0.263 mmol) of styrene **1** and 32 mg (0.263 mmol) of hydroximoyl chloride **6b** compound **8b** (45 mg, 91%) was obtained as a colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.39-7.26 (m, 5H), 5.55 (dd, $J_1=8.1$ Hz, $J_2=10.8$ Hz, 1H), 3.36 (dd, $J_1=10.8$ Hz, $J_2=17.0$ Hz, 1H), 2.90 (dd, $J_1=8.1$ Hz, $J_2=17.0$ Hz, 1H), 2.37 (t, $J=7.5$ Hz, 2H), 1.66-1.57 (m, 2H), 0.97 (t, $J=7.4$ Hz, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 158.4, 141.4, 128.7, 128.0, 125.7, 81.2, 45.3, 29.6, 19.8, 13.8. HRMS (ESI+) m/z calcd. for $(\text{C}_{12}\text{H}_{16}\text{NO}, \text{M}+\text{H})$: 190.1226, found:

(M+H): 190.1220.

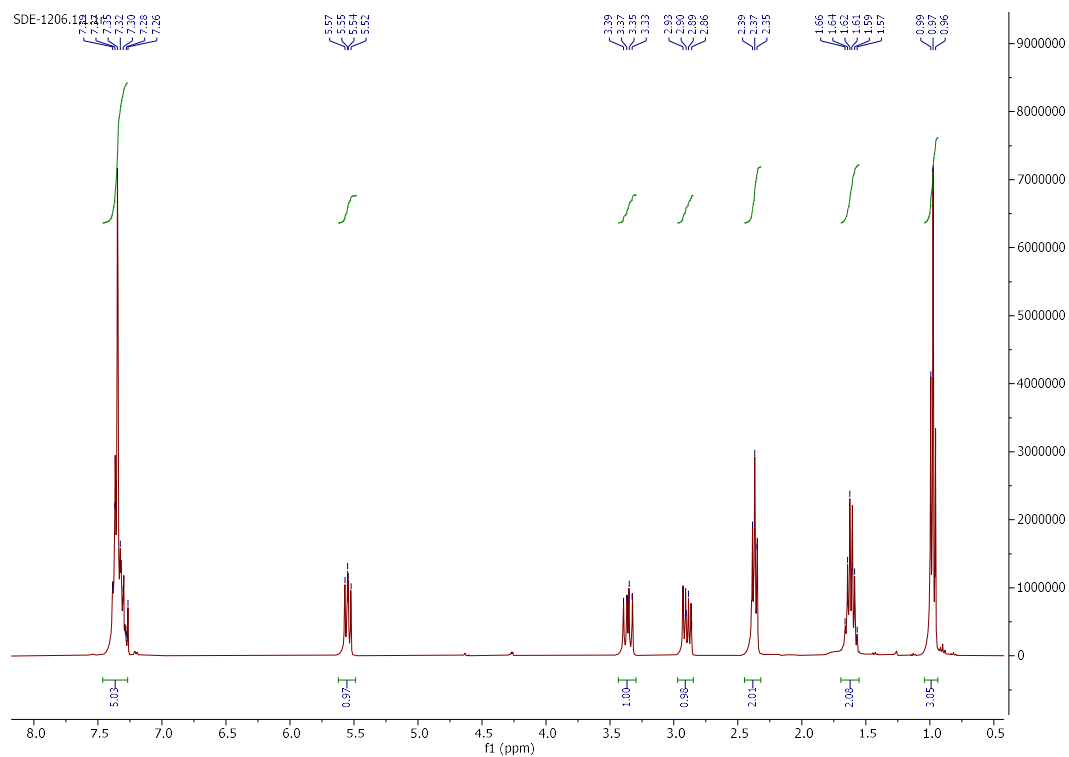


Figure S6. $^1\text{H NMR}$ spectra of compound **8b**.

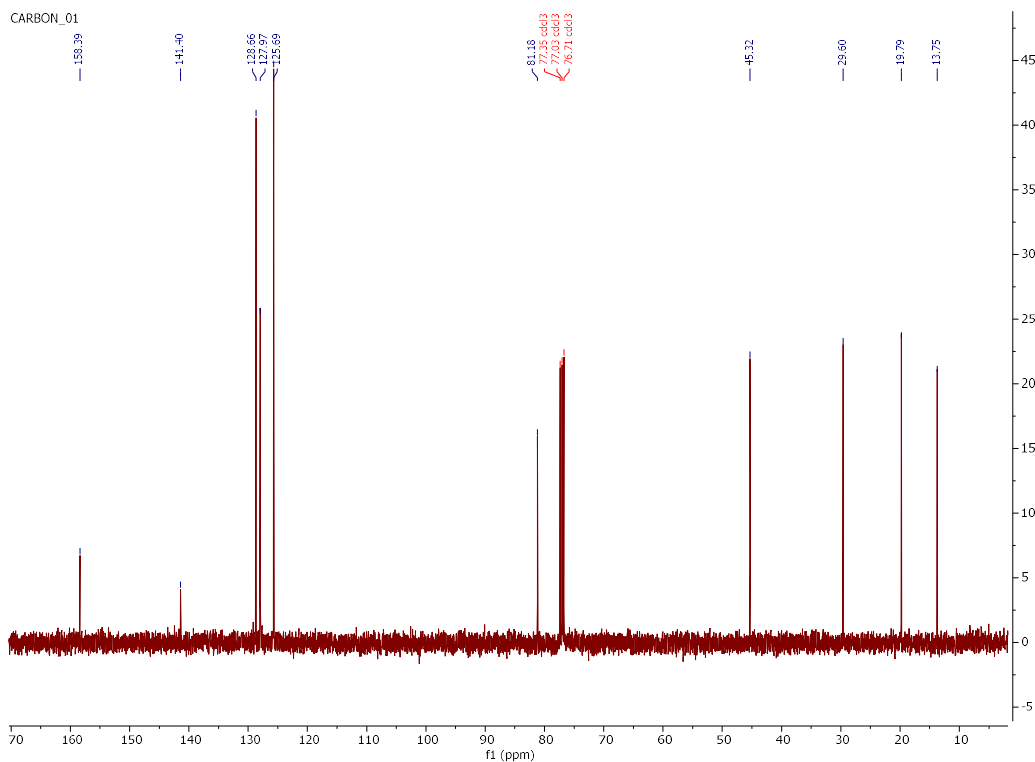
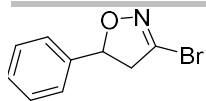


Figure S7. $^{13}\text{C NMR}$ spectra of compound **8b**.



3-bromo-5-phenyl-4,5-dihydroisoxazole (8c). From 27 mg (0.263 mmol) of styrene **1** and 53 mg (0.263 mmol) of hydroximoyl bromide **6c** compound **8c** (53 mg, 89%) was obtained as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.41-7.36 (m, 5H), 5.68 (dd, J₁=9.0 Hz, J₂=10.9 Hz, 1H), 3.63 (dd, J₁=10.9 Hz, J₂=17.2 Hz, 1H), 3.23 (dd, J₁=9.0 Hz, J₂=17.3 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃): δ 138.8, 136.3, 128.5, 128.4, 125.6, 82.8, 48.8. **HRMS** (ESI+) m/z calcd. for (C₉H₉BrNO, M+H): 225.9862, found: (M+H): 225.9864.

SDE-1123-1.1.1.1r

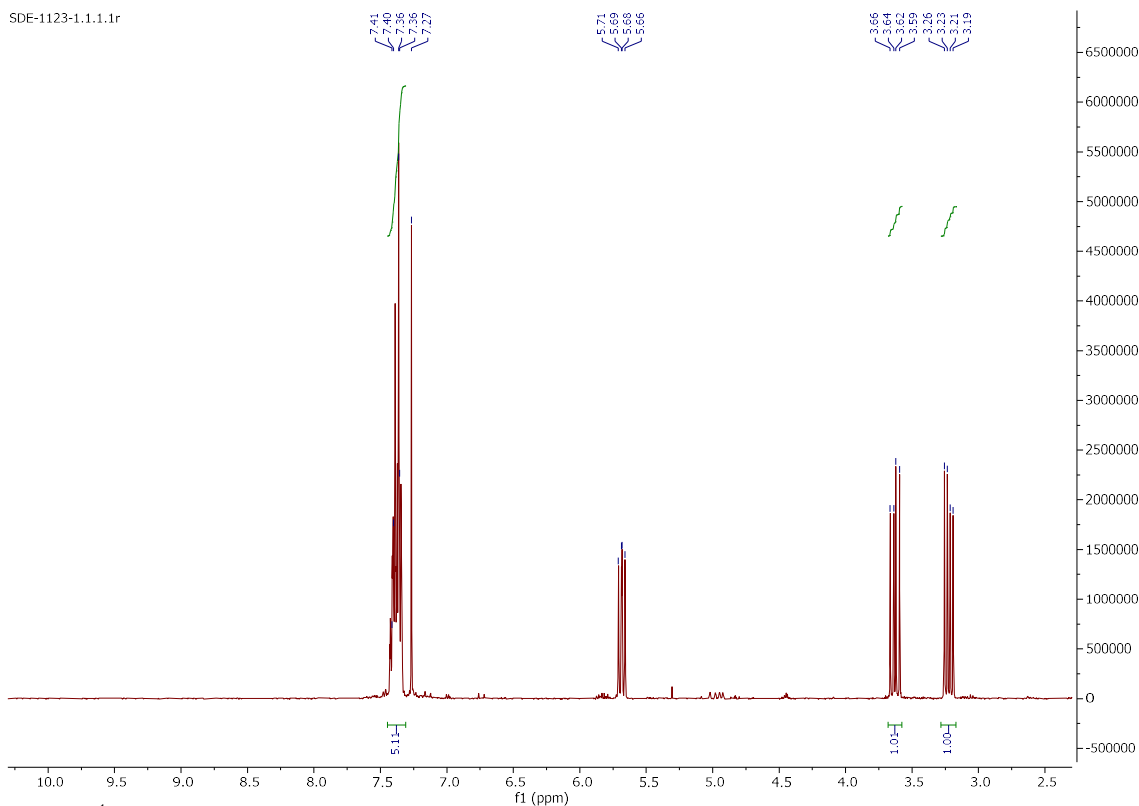


Figure S8. ¹H NMR spectra of compound **8c**.

SDE-1123-1.2.1.1r

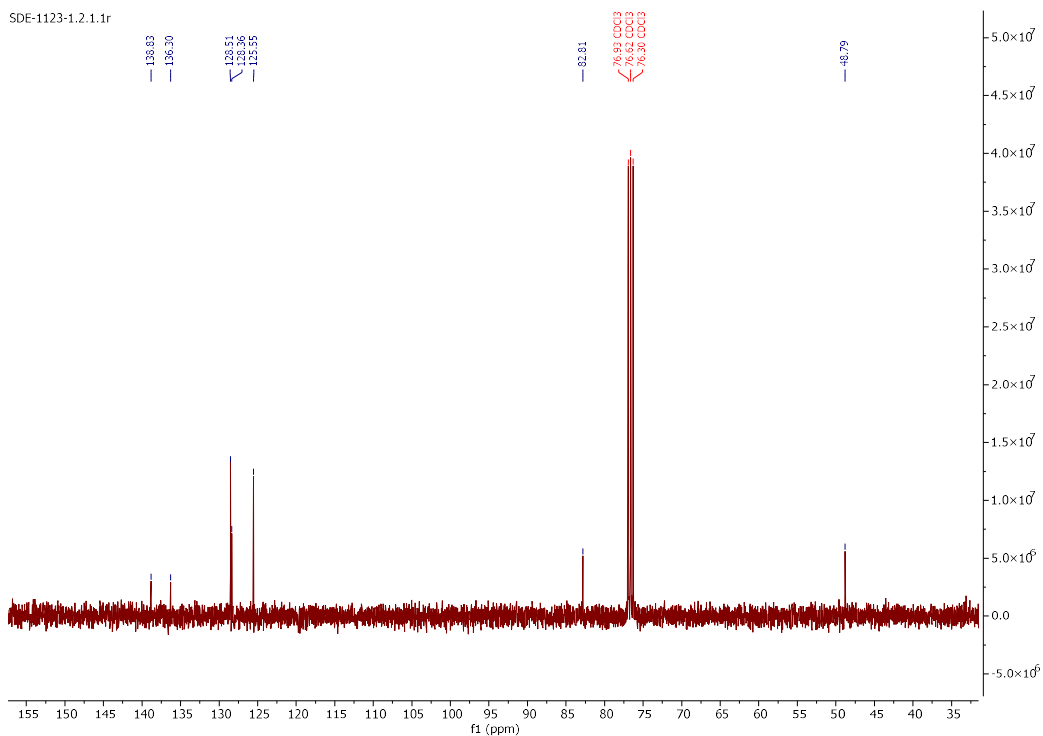
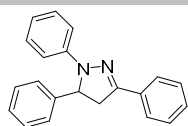


Figure S9. ¹³C NMR spectra of compound **8c**.



1,3,5-triphenyl-4,5-dihydro-1H-pyrazole (**8d**). From 27 mg (0.263 mmol) of styrene **1** and 61 mg (0.263 mmol) of imidoyl chloride **7a** compound **8d** (68 mg, 87%) was obtained as a pale yellow crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 7.78-7.75 (m, 2H), 7.44-7.28 (m, 8H), 7.24-7.20 (m, 2H), 7.14-7.11 (m, 2H), 6.85-6.81 (m, 1H), 5.30 (dd, J₁=7.2 Hz, J₂=12.5 Hz, 1H), 3.86 (dd, J₁=12.5 Hz, J₂=17.1 Hz, 1H), 3.17 (dd, J₁=7.3 Hz, J₂=17.1 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 146.7, 144.9, 142.6, 132.8, 129.2, 129.0, 128.6, 128.6, 127.6, 125.9, 125.8, 119.1, 113.4, 64.5, 43.6. HRMS (ESI+) m/z calcd. for (C₁₈H₁₉N₂, M+H): 299.1542, found: (M+H): 299.1531.

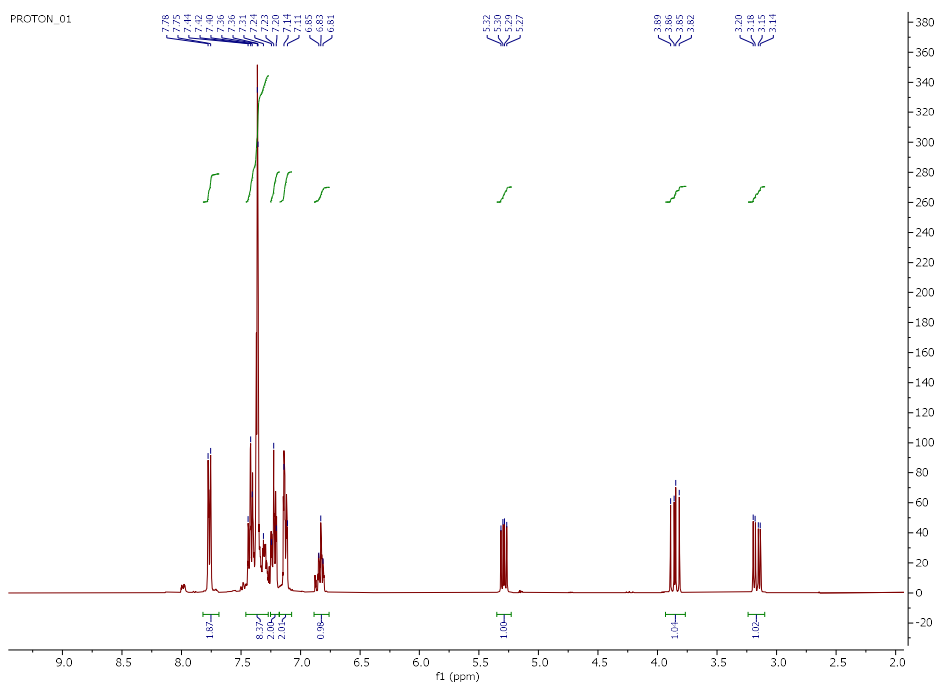


Figure S10. ¹H NMR spectra of compound **8d**.

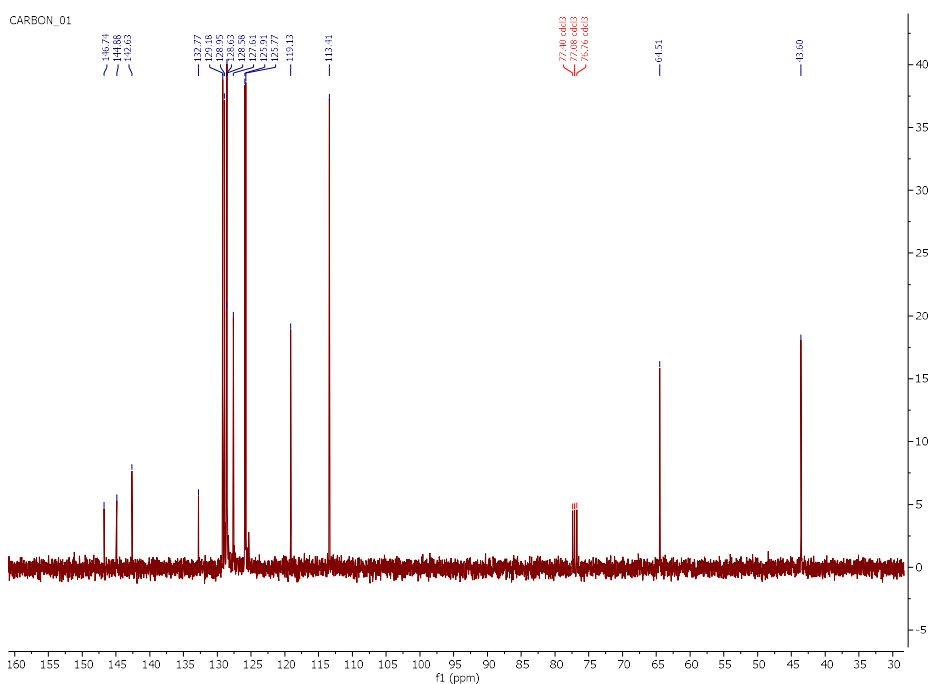
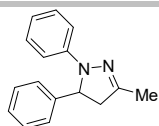


Figure S11. ¹³C NMR spectra of compound **8e**.



3-methyl-1,5-diphenyl-4,5-dihydro-1H-pyrazole (**8e**). From 27 mg (0.263 mmol) of styrene **1** and 32 mg (0.263 mmol) of imidoyl chloride **7b** compound **8e** (58 mg, 94%) was obtained as a yellow crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 7.37-7.24 (m, 5H), 7.17-7.13 (m, 2H), 6.95-6.92 (m, 2H), 6.77-6.73 (m, 1H), 5.03 (dd, J₁=8.1 Hz, J₂=12.0 Hz, 1H), 3.43 (ddd, J₁=1.2 Hz, J₂=12.0 Hz, J₃=17.5 Hz, 1H), 2.74 (ddd, J₁=1.1 Hz, J₂=8.1 Hz, J₃=17.5 Hz, 1H), 2.08 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 148.1, 145.7, 142.6, 128.6, 128.4, 127.0, 125.5, 118.2, 112.7, 64.4, 47.4, 15.5. HRMS (ESI+) m/z calcd. for (C₁₆H₁₇N₂, M+H): 237.1386, found: (M+H): 237.1387.

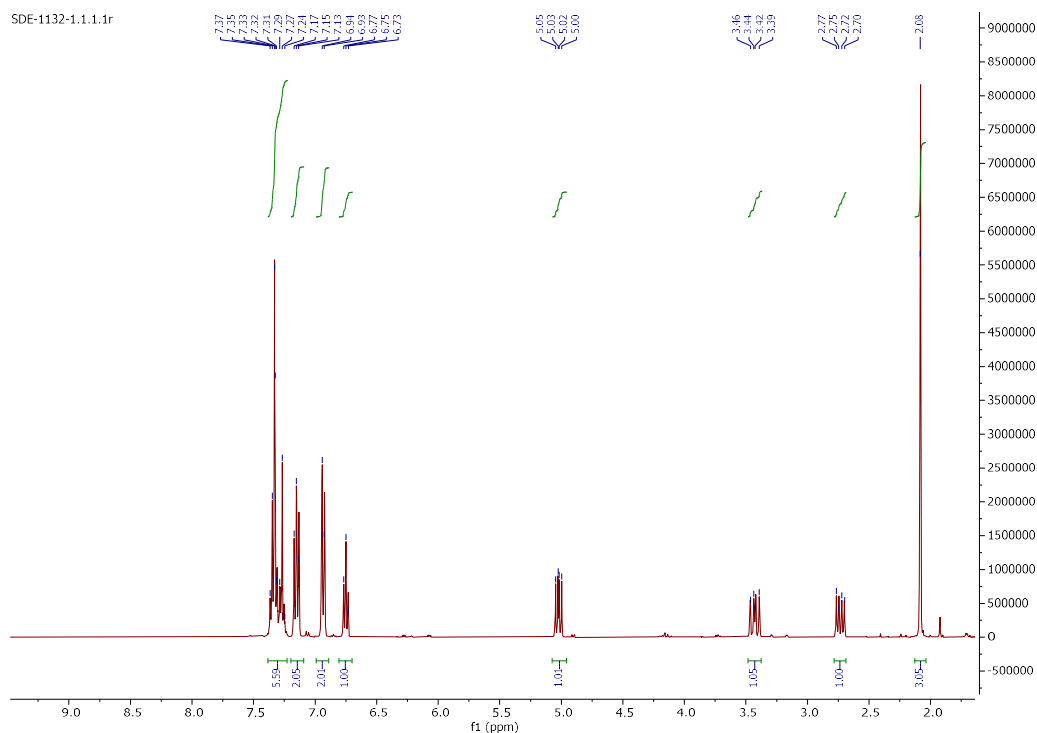


Figure S12. ¹H NMR spectra of compound **8e**.

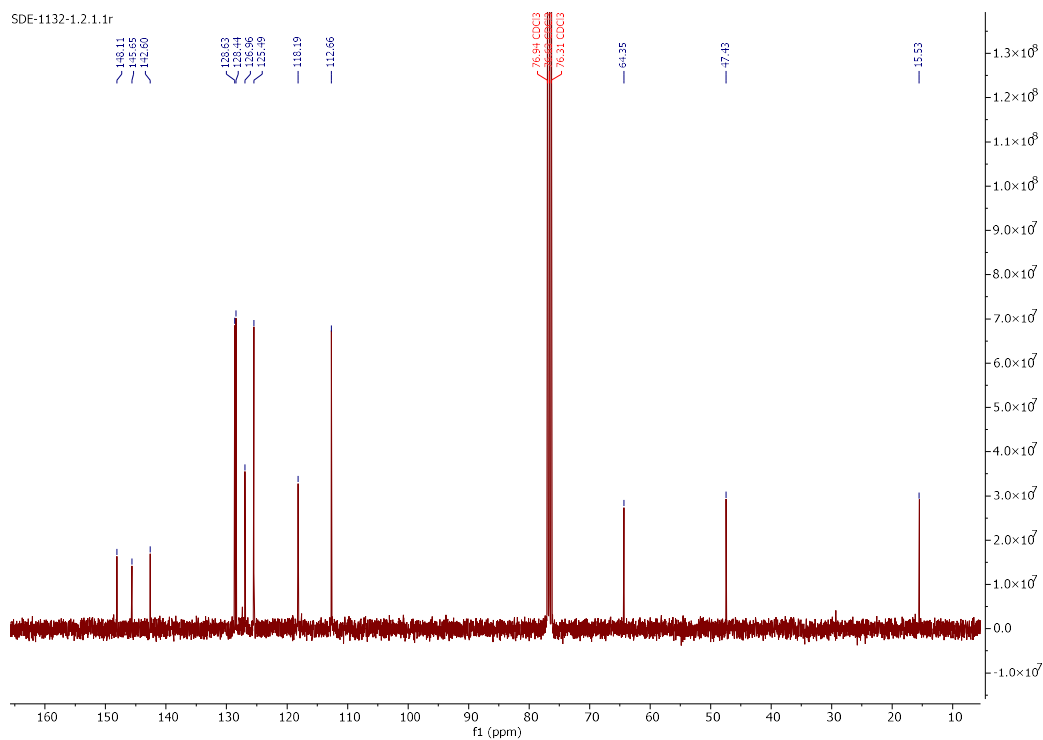
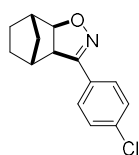


Figure S13. ¹³C NMR spectra of compound **8e**.

General procedure of 1,3-dipolar cycloaddition to norbornene using diffusion mixing technique.

A mixture of norbornene **2** (0.789 mmol, 0.074 g) and halogen derivative **6** or **7** (0.263 mmol) in 3 ml of chloroform was placed in a 15 ml vial **1** (diameter 1.3 cm) and closed with a glass stopper with holes. The vial **1** was then placed in closed 50 ml vial **2** (diameter 3.5 cm) containing triethylamine (35.85 mmol, 5 ml) and the reaction mixture was stirred at room temperature for two days (TLC or NMR control). When the reaction was completed, the mixture from the inner vial was diluted with 10 ml of chloroform, transferred to a separating funnel and washed with 2% aqueous HCl (2 x 10 ml). The organic phase was dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using chloroform as an eluent.



(3aR,4R,7S,7aR)-3-(4-chlorophenyl)-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isoxazole (**9a**). From 74 mg (0.789 mmol) norbornene **2** and 50 mg (0.263 mmol) hydroximoyl chloride **6a** compound **9a** (64 mg, 99%) was obtained as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃): δ 7.65-7.61 (m, 2H), 7.37-7.33 (m, 2H), 4.63 (d, J=8.3 Hz, 1H), 3.45 (d, J=8.3 Hz, 1H), 2.62 (s, 1H), 2.48 (s, 1H), 1.62-1.48 (m, 3H), 1.37-1.34 (m, 1H), 1.21-1.14 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 155.6, 135.2, 128.5, 127.6, 127.5, 87.8, 56.4, 42.6, 38.8, 31.9, 27.0, 22.2. HRMS (ESI+) m/z calcd. for (C₁₄H₁₅ClNO, M+H): 248.0837, found: (M+H): 248.0837.

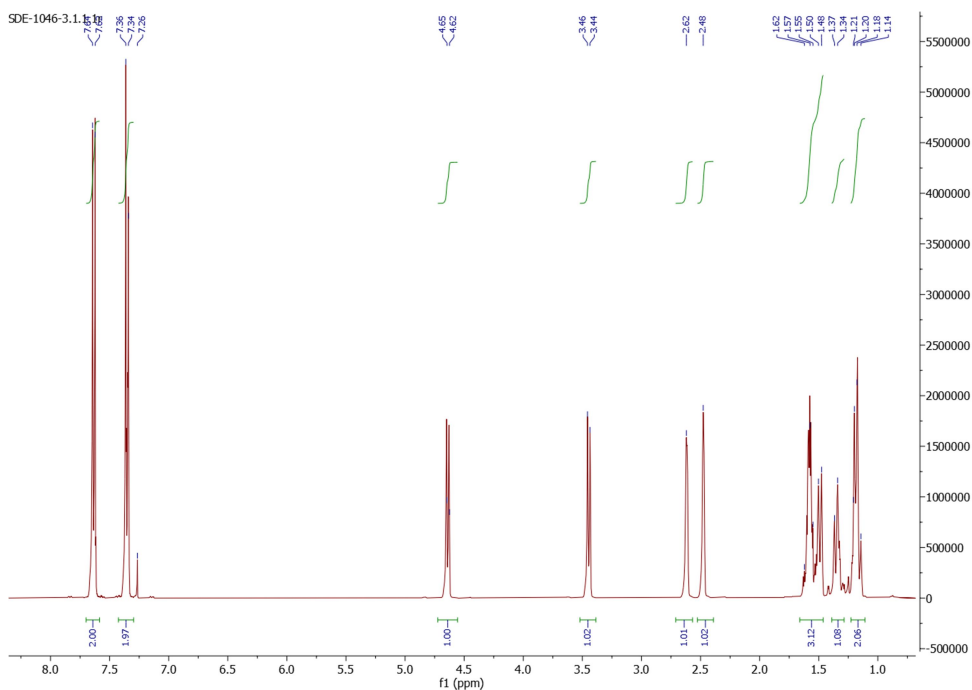


Figure S14. ¹H NMR spectra of compound **9a**.

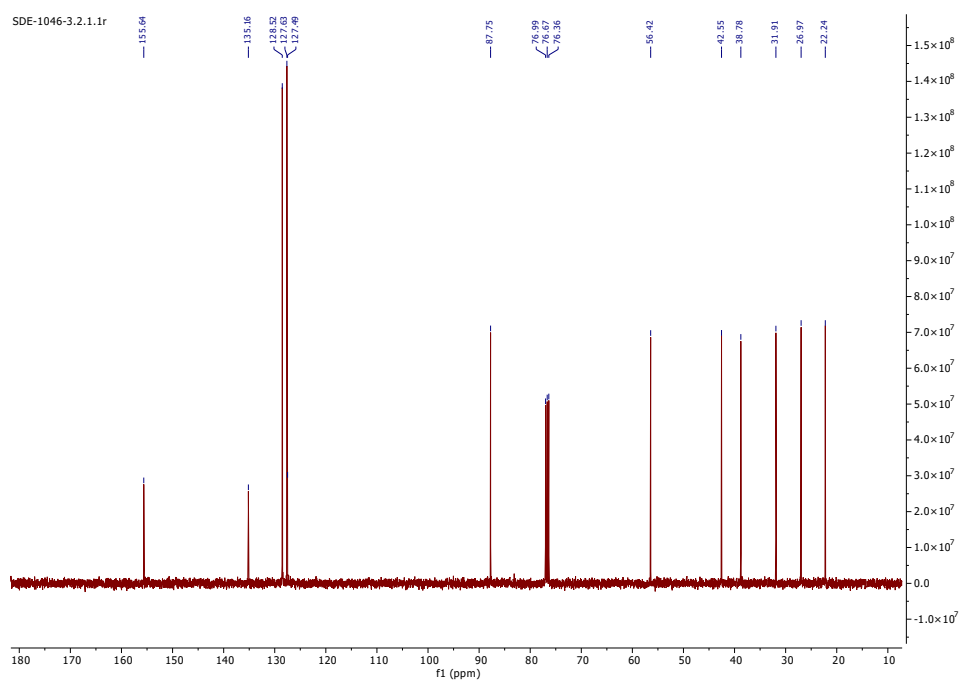
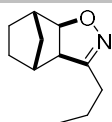


Figure S15. ¹³C NMR spectra of compound **9a**.



(3aR,4R,7S,7aR)-3-propyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isoxazole (**9b**). From 74 mg (0.789 mmol) of norbornene **2** and 32 mg (0.263 mmol) of hydroximoyl chloride **6b** compound **9b** (42 mg, 90%) was obtained as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 4.39 (d, J=8.3 Hz, 1H), 2.98 (d, J=8.2 Hz, 1H), 2.50 (d, J=3.7 Hz, 1H), 2.33-2.25 (m, 2H), 2.19-2.12 (m, 1H), 1.68-1.50 (m, 4H), 1.45-1.39 (m, 1H), 1.26-1.04 (m, 3H), 0.95 (t, J=7.4 Hz, 3H). **¹³C NMR** (101 MHz, CDCl₃): δ 158.3, 85.5, 58.9, 42.4, 37.8, 31.7, 28.2, 26.8, 22.3, 19.2, 13.5. **HRMS** (ESI⁺) m/z calcd. for (C₁₁H₁₈NO, M+H): 180.1383, found: (M+H): 180.1380.

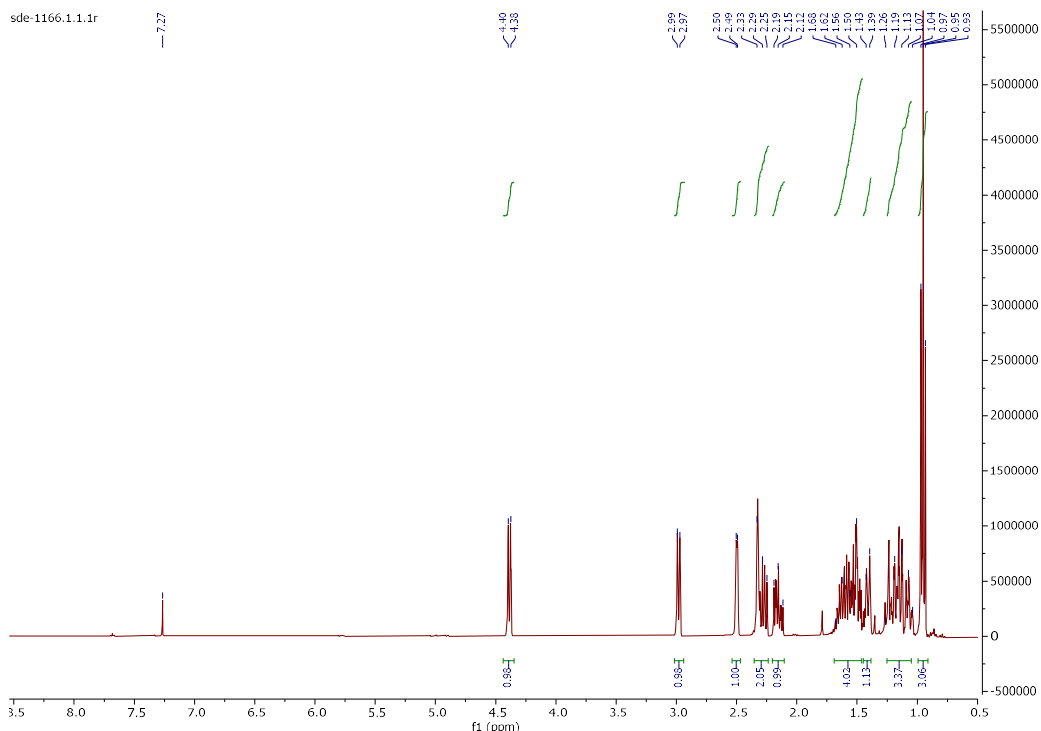


Figure S16. ¹H NMR spectra of compound **9b**.

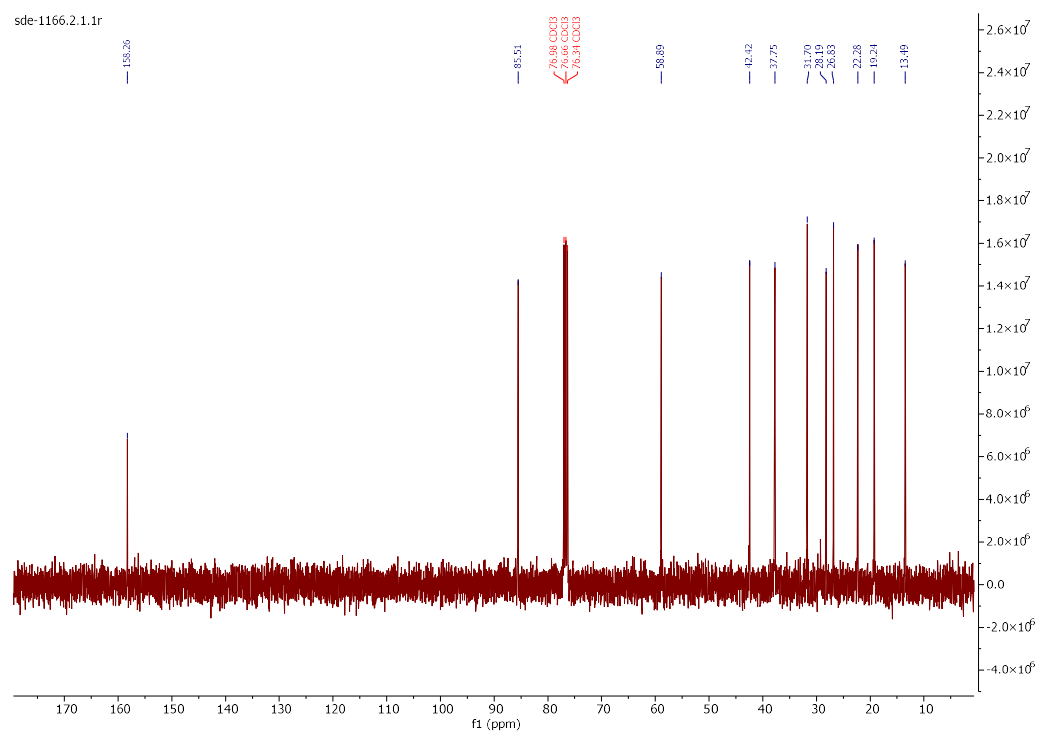
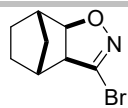


Figure S17. ¹³C NMR spectra of compound **9b**.



(3a*S*,4*R*,7*S*,7a*R*)-3-bromo-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]isoxazole (**9c**). From 74 mg (0.789 mmol) of norbornene **2** and 53 mg (0.263 mmol) of hydroximoyl bromide **6c** compound **9c** (50 mg, 88%) was obtained as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 4.58 (d, J=8.3 Hz, 1H), 3.18 (d, J=8.3 Hz, 1H), 2.61 (s, 1H), 2.52 (d, J=3.2 Hz, 1H), 1.61-1.51 (m, 3H), 1.28-1.22 (m, 1H), 1.13-1.08 (m, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 139.2, 87.5, 61.7, 42.6, 38.2, 31.8, 26.3, 22.2. **HRMS** (ESI+) m/z calcd. for (C₈H₁₁BrNO, M+H): 216.0019, found: (M+H): 216.0017.

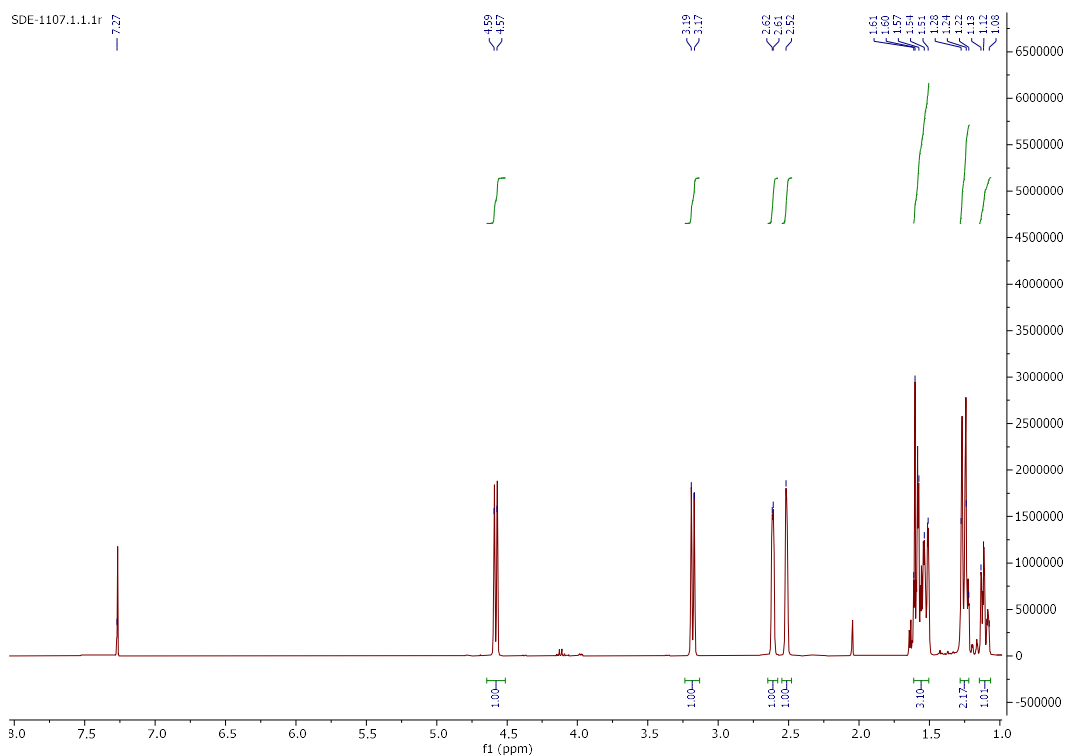


Figure S18. ¹H NMR spectra of compound **9c**.

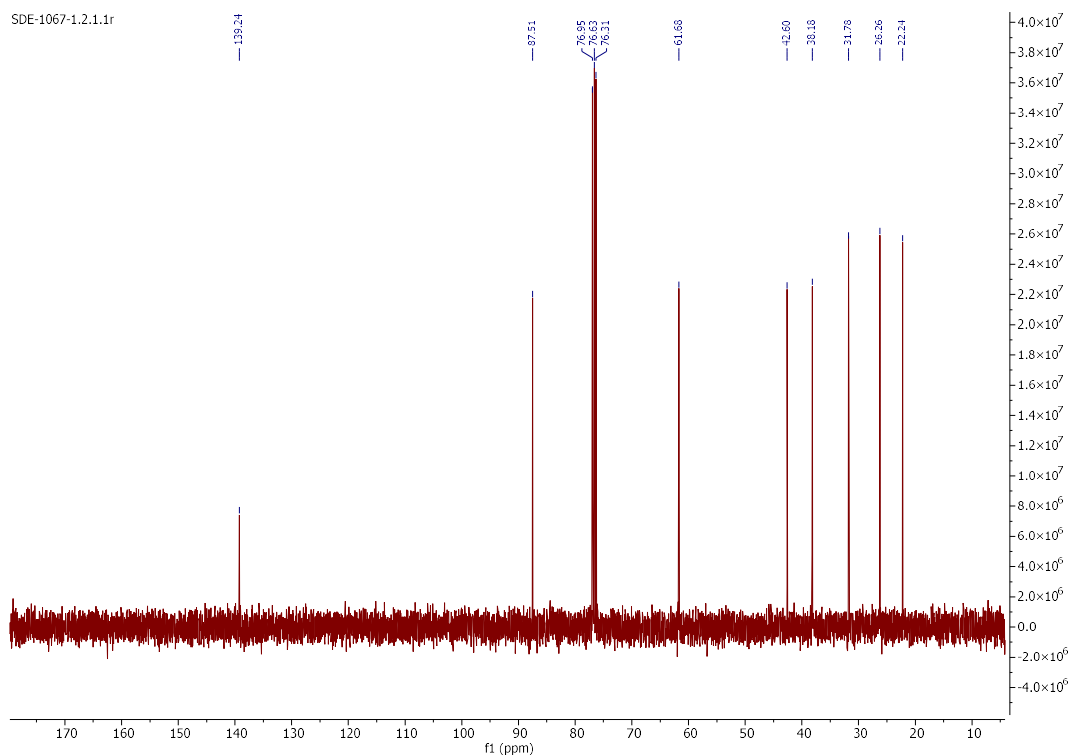
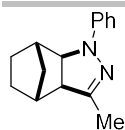


Figure S19. ¹³C NMR spectra of compound **9c**.



(3aS,4R,7S,7aR)-3-methyl-1-phenyl-3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoindazole (**9e**). From 74 mg (0.789 mmol) of norbornene **2** and 44 mg (0.263 mmol) of imidoyl chloride **7b** compound **9e** (52 mg, 87%) was obtained as a yellow crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 7.26-7.22 (m, 2H), 7.01-6.99 (m, 2H), 6.78-6.73 (m, 1H), 3.87 (d, J=9.2 Hz, 1H), 3.01 (d, J=9.2 Hz, 1H), 2.68-2.67 (m, 1H), 2.46-2.45 (m, 1H), 1.99 (s, 3H), 1.67-1.54 (m, 2H), 1.43-1.41 (m, 1H), 1.35-1.27 (m, 2H), 1.20-1.18 (m, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 150.2, 145.1, 128.7, 117.1, 111.3, 67.2, 58.6, 41.0, 38.5, 32.5, 27.6, 23.8, 14.2. HRMS (ESI+) m/z calcd. for (C₁₅H₁₉N₂, M+H): 227.1543, found: (M+H): 227.1543.

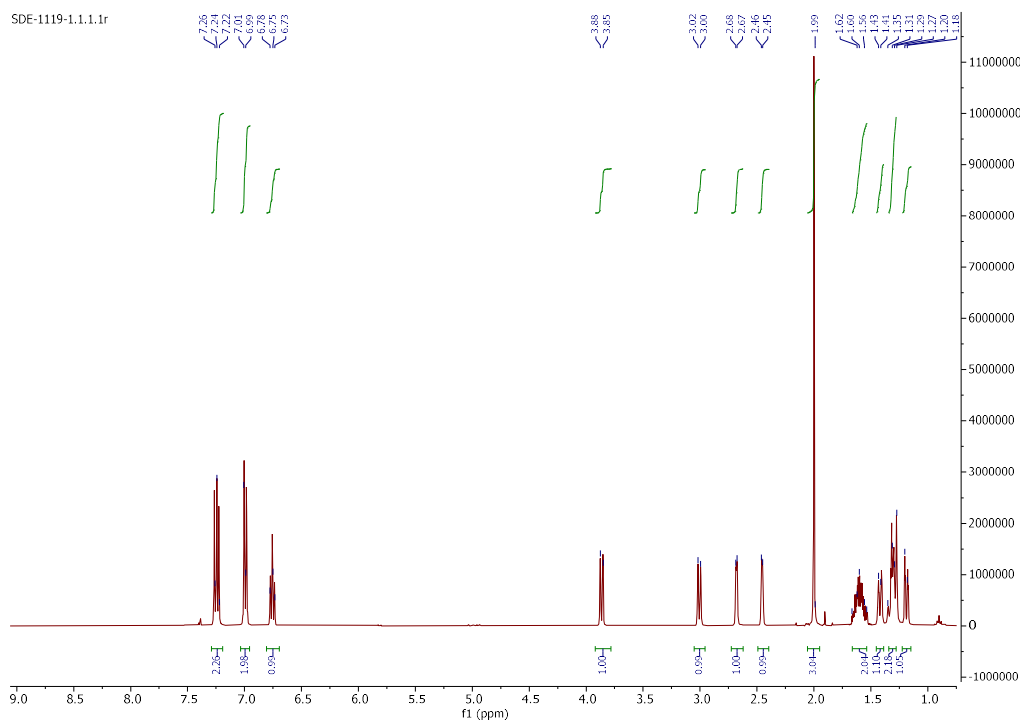


Figure S22. ¹H NMR spectra of compound **9e**.

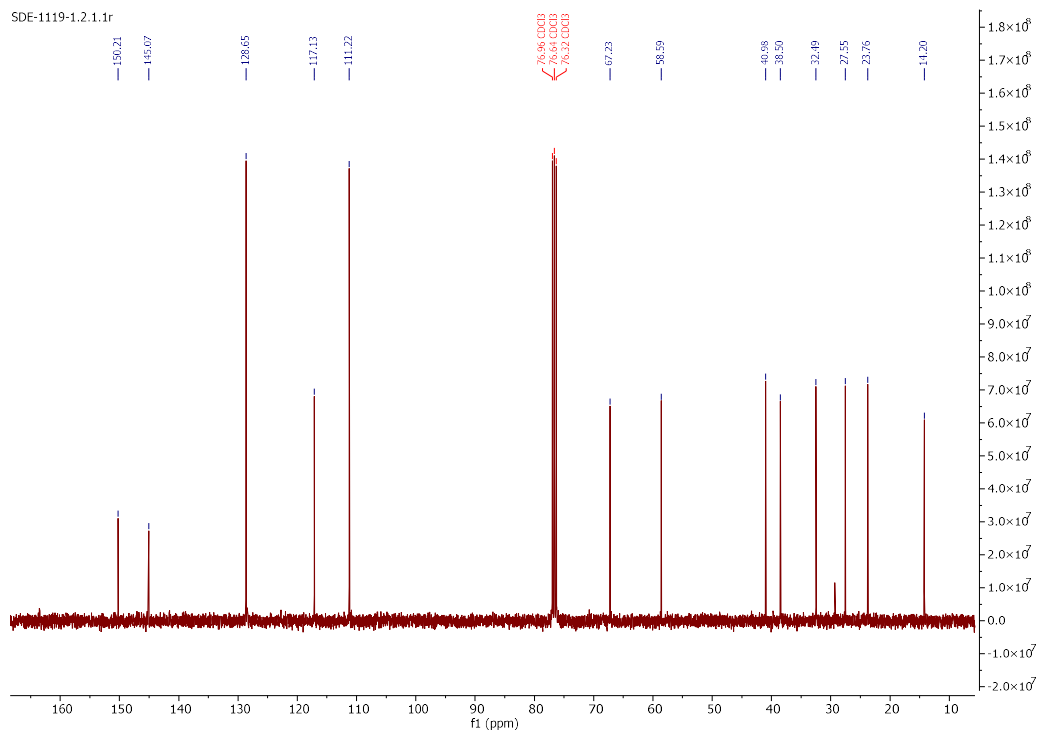
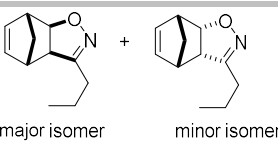


Figure S23. ¹³C NMR spectra of compound **9e**.





 major isomer minor isomer

(3*aR*,4*S*,7*R*,7*aR*)-3-propyl-3*a*,4,7,7*a*-tetrahydro-4,7-methanobenzo[d]isoxazole (**10b**) and (3*aS*,4*S*,7*R*,7*aS*)-3-propyl-3*a*,4,7,7*a*-tetrahydro-4,7-methanobenzo[d]isoxazole (**11b**). From 97 mg (1.053 mmol) of norbornadiene **3** and 32 mg (0.263 mmol) of hydroximoyl chloride **6b** the mixture of compounds **10b** and **11b** in 91/9 ratio (39 mg, 84%) was obtained as a pale yellow oil.

Major isomer **10b**: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.24 (dd, $J_1=3.0$ Hz, $J_2=5.7$ Hz, 1H), 6.03 (dd, $J_1=3.2$ Hz, $J_2=5.7$ Hz, 1H), 4.75 (dd, $J_1=1.0$ Hz, $J_2=8.1$ Hz, 1H), 3.29 (d, $J=7.9$ Hz, 1H), 3.18 (s, 1H), 2.97 (s, 1H), 2.33-2.25 (m, 1H), 2.20-2.13 (m, 1H), 1.68-1.55 (m, 4H), 0.99-0.94 (m, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 157.5, 139.4, 135.1, 87.1, 59.3, 49.3, 43.6, 42.6, 28.3, 19.2, 13.5.

Minor isomer **11b**: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.17 (dd, $J_1=3.0$ Hz, $J_2=5.7$ Hz, 1H), 6.06-6.04 (m, 1H), 5.20 (dd, $J_1=4.2$ Hz, $J_2=9.5$ Hz, 1H), 3.70 (dd, $J_1=4.2$ Hz, $J_2=9.5$ Hz, 1H), 3.30-3.28 (m, 1H), 3.12 (s, 1H), 2.33-2.25 (m, 1H), 2.20-2.13 (m, 1H), 1.68-1.55 (m, 4H), 0.99-0.94 (m, 3H).

HRMS (ESI+) m/z calcd. for ($\text{C}_{11}\text{H}_{16}\text{NO}$, M+H): 178.1226, found: (M+H): 178.1228.

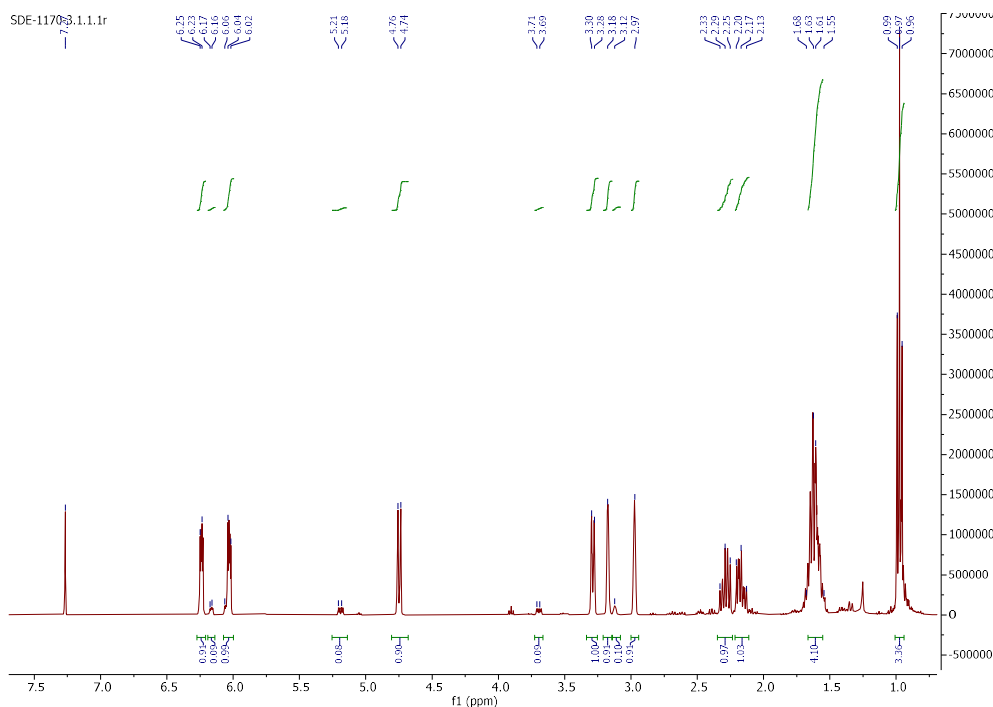


Figure S26. $^1\text{H NMR}$ spectra of mixture of compounds **10b** and **11b**.

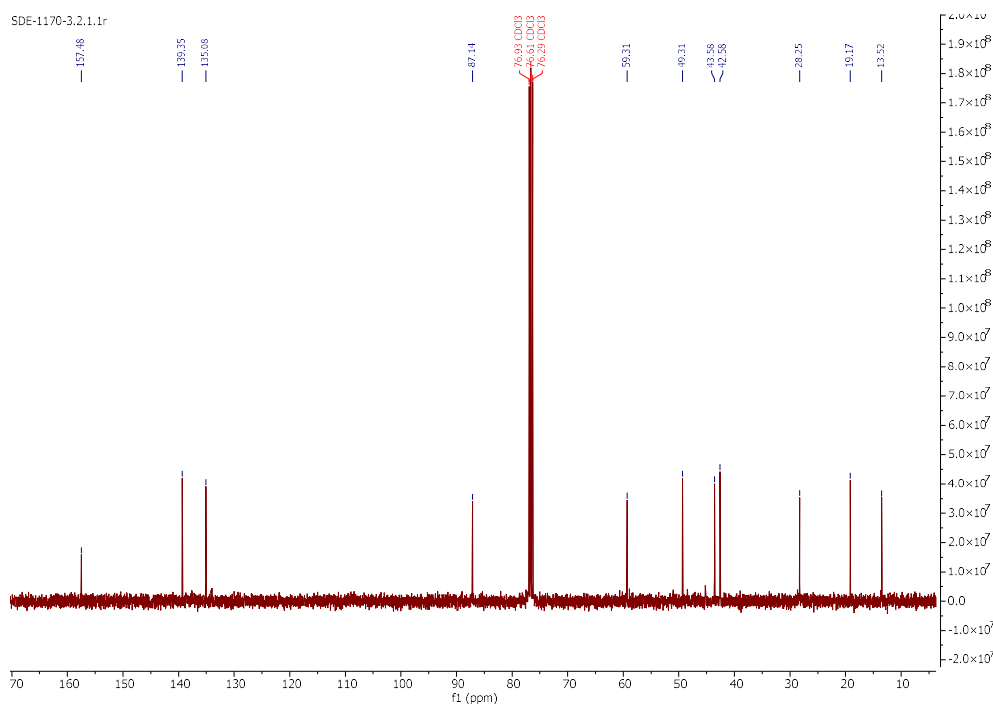
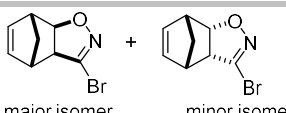


Figure S27. $^{13}\text{C NMR}$ spectra of compound **10b**.



 major isomer minor isomer

(3a*S*,4*S*,7*R*,7a*R*)-3-bromo-3a,4,7,7a-tetrahydro-4,7-methanobenzo[d]isoxazole (10c) and **(3a*R*,4*S*,7*R*,7a*S*)-3-bromo-3a,4,7,7a-tetrahydro-4,7-methanobenzo[d]isoxazole (11c)**. From 97 mg (1.053 mmol) of norbornadiene **3** and 53 mg (0.263 mmol) of hydroximoyl bromide **6c** the mixture of compounds **10c** and **11c** in 85/15 ratio (43 mg, 77%) was obtained as a colorless oil.

Major isomer 10c: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.26 (dd, $J_1=3.0$ Hz, $J_2=5.6$ Hz, 1H), 6.06 (dd, $J_1=3.2$ Hz, $J_2=5.6$ Hz, 1H), 4.88 (dd, $J_1=0.9$ Hz, $J_2=8.1$ Hz, 1H), 3.43 (d, $J=8.1$ Hz, 1H), 3.26 (s, 1H), 3.14 (s, 1H), 1.71-1.65 (m, 2H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 139.5, 138.5, 135.5, 89.4, 62.1, 49.9, 44.4, 42.9.

Minor isomer 11c: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.21-6.17 (m, 2H), 5.33 (dd, $J_1=4.2$ Hz, $J_2=9.5$ Hz, 1H), 3.85 (dd, $J_1=4.2$ Hz, $J_2=9.5$ Hz, 1H), 3.38 (s, 1H), 3.26 (s, 1H), 1.71-1.65 (m, 1H), 1.59 (dd, $J_1=1.4$ Hz, $J_2=9.2$ Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 138.7, 134.8, 134.5, 87.9, 61.7, 48.1, 45.7, 45.9.

HRMS (ESI+) m/z calcd. for $(\text{C}_8\text{H}_9\text{BrNO}, \text{M}+\text{H})$: 213.9862, found: $(\text{M}+\text{H})$: 213.9850.

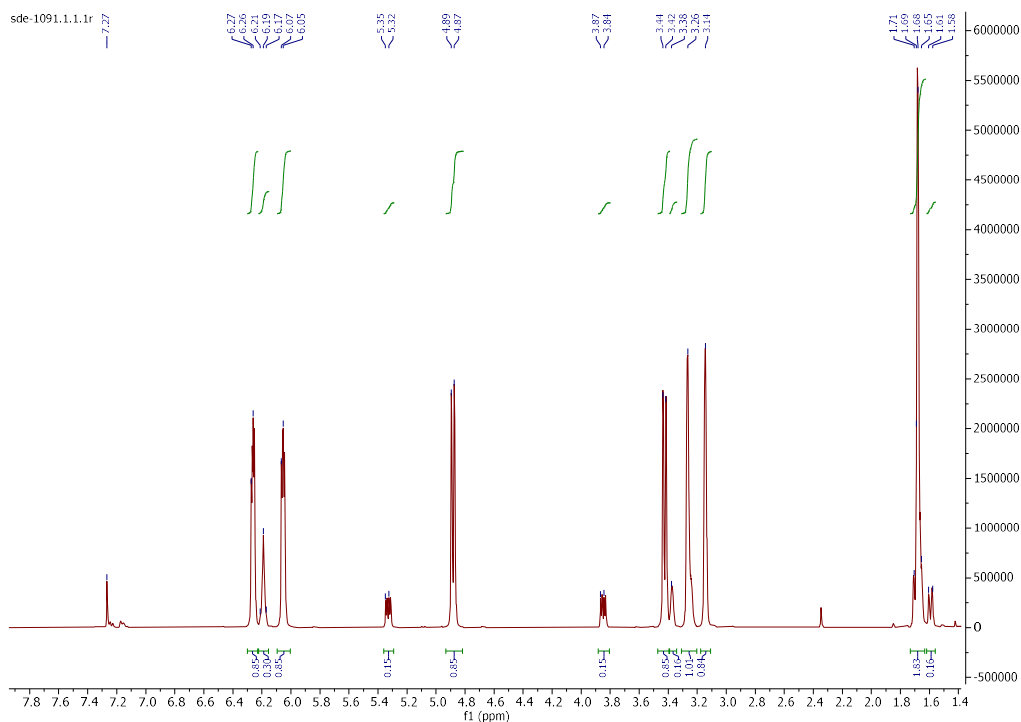


Figure S28. $^1\text{H NMR}$ spectra of the mixture of compounds **10c** and **11c**.

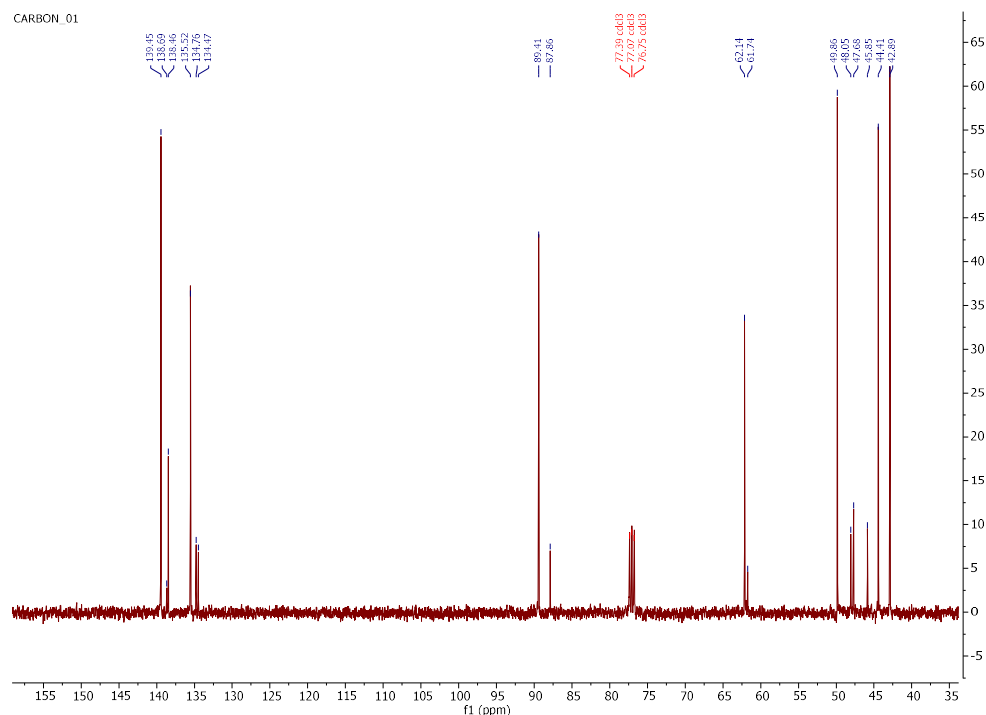
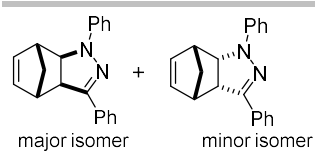


Figure S29. $^{13}\text{C NMR}$ spectra of the mixture of compounds **10c** and **11c**.



(3a*S*,4*S*,7*R*,7a*R*)-1,3-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindazole (**10d**) and (3a*R*,4*S*,7*R*,7a*S*)-1,3-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoindazole (**11d**). From 97 mg (1.053 mmol) of norbornadiene **3** and 61 mg (0.263 mmol) of imidoyl chloride **7a** the mixture of compounds **10d** and **11d** in 92/8 ratio (65 mg, 86%) was obtained as a emerald crystalline solid.

Major isomer **10d**: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.84-7.79 (m, 2H), 7.44-7.41 (m, 2H), 7.37-7.34 (m, 3H), 7.27-7.22 (m, 2H), 6.90-6.85 (m, 1H), 6.44 (dd, $J_1=3.0$ Hz, $J_2=5.7$ Hz, 1H), 6.24 (dd, $J_1=3.1$ Hz, $J_2=5.7$ Hz, 1H), 4.46 (dd, $J=9.3$ Hz, 1H), 3.86 (d, $J=9.3$ Hz, 1H), 3.52 (s, 1H), 3.33 (s, 1H), 1.67 (d, $J=9.3$ Hz, 1H), 1.56-1.53 (m, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 147.1, 144.1, 140.0, 135.8, 132.5, 129.2, 128.5, 128.2, 125.7, 118.6, 112.3, 69.0, 55.4, 48.1, 46.3, 43.4.

Minor isomer **11d**: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.84-7.79 (m, 2H), 7.44-7.41 (m, 2H), 7.37-7.34 (m, 3H), 7.27-7.22 (m, 2H), 6.90-6.85 (m, 1H), 6.01-5.94 (m, 2H), 4.86 (dd, $J_1=3.5$ Hz, $J_2=10.3$ Hz, 1H), 4.21 (dd, $J_1=3.8$ Hz, $J_2=10.4$ Hz, 1H), 3.66 (s, 1H), 3.50 (s, 1H), 1.68-1.66 (m, 1H), 1.56-1.53 (m, 1H).

HRMS (ESI+) m/z calcd. for ($\text{C}_{20}\text{H}_{19}\text{N}_2$, M+H): 287.1543, found: (M+H): 287.1540.

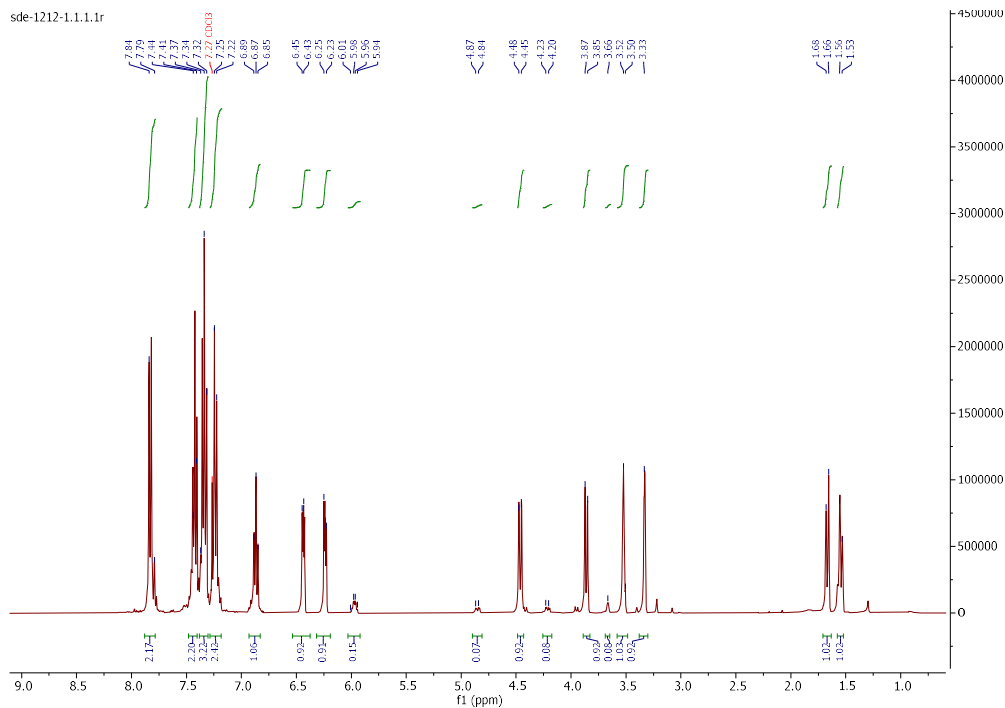


Figure S30. $^1\text{H NMR}$ spectra of the mixture of the compounds **10d** and **11d**.

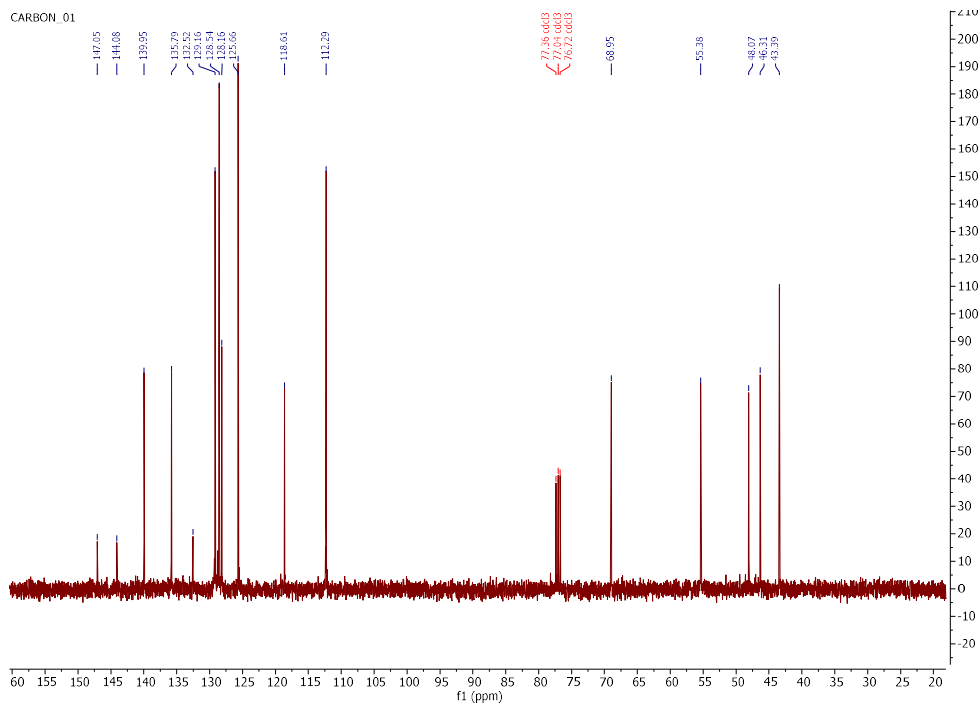
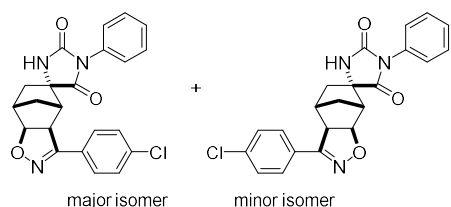


Figure S31. $^{13}\text{C NMR}$ spectra of compound **10d**.

General procedure of 1,3-dipolar cycloaddition of nitrile oxides to hydantion 4 using diffusion mixing technique.

A mixture of hydantoin **4** (0.219 mmol, 0.056 g) and halogen derivative **6** (0.263 mmol) in 3 ml of chloroform was placed in a 15 ml vial **1** (diameter 1.3 cm) and closed with a glass stopper with holes. The vial **1** was then placed in a closed 50 ml vial **2** (diameter 3.5 cm) containing triethylamine (35.85 mmol, 5 ml) and the reaction mixture was stirred at room temperature for two days (TLC or NMR control). When the reaction was completed, the mixture from the inner vial was diluted with 10 ml of chloroform, transferred to a separating funnel and washed with 2% aqueous HCl (2 x 10 ml). The organic phase was dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using methanol/chloroform (1:100) as an eluent.



(3a'S, 4S, 4'S, 7'S, 7a'S)-3'-(4-chlorophenyl)-1-phenyl-3a', 6', 7', 7a'-tetrahydro-4'H-spiro[imidazolidine-4,5'-[4,7]methanobenzo[d]isoxazole]-2,5-dione (**12a**) and (3a'R, 4S, 4'S, 7'R, 7a'R)-3'-(4-chlorophenyl)-1-phenyl-3a', 4', 7', 7a'-tetrahydro-5'H-spiro[imidazolidine-4,6'-[4,7]methanobenzo[d]isoxazole]-2,5-dione (**13a**). From 56 mg (0.219 mmol) of hydantoin **4** and 50 mg (0.263 mmol) of hydroximoyl chloride **6a** the mixture of compounds **12a** and **13a** in 57/43 ratio (81 mg, 91%) was obtained as a white crystalline solid.

Major isomer **12a**: ¹H NMR (400 MHz, DMSO-d₆): δ 8.84 (bs, 1H), 7.69-7.67 (m, 2H), 7.53-7.51 (m, 2H), 7.44-7.37 (m, 5H), 4.81 (d, J=8.3 Hz, 1H), 4.21 (d, J=8.3 Hz, 1H), 2.77 (s, 1H), 2.63 (d, J=4.3 Hz, 1H), 2.26-2.12 (m, 2H), 1.42 (dd, J₁=2.6 Hz, J₂=13.5 Hz, 1H), 1.34 (d, J=10.8 Hz, 1H).

Minor isomer **13a**: ¹H NMR (400 MHz, DMSO-d₆): δ 8.85 (bs, 1H), 7.80-7.79 (m, 2H), 7.53-7.51 (m, 2H), 7.44-7.37 (m, 5H), 5.10 (d, J=8.3 Hz, 1H), 3.90 (d, J=8.3 Hz, 1H), 2.89 (s, 1H), 2.56 (d, J=3.5 Hz, 1H), 2.26-2.12 (m, 2H), 1.70 (dd, J₁=2.9 Hz, J₂=13.2 Hz, 1H), 1.34 (d, J=10.8 Hz, 1H).

Mixture of isomers **12a** and **13a**: ¹³C NMR (101 MHz, DMSO-d₆): δ 176.3, 176.2, 156.4, 155.4, 135.2, 135.1, 132.5, 129.6, 129.5, 129.1, 129.0, 128.9, 128.3, 128.2, 127.8, 127.7, 127.4, 127.2, 87.1, 84.4, 79.6, 64.6, 62.8, 56.0, 52.1, 51.9, 48.2, 43.4, 40.3, 36.5, 31.2, 30.9.

HRMS (ESI⁺) m/z calcd. for (C₂₂H₁₉ClN₃O₃, M+H): 408.1109, found: (M+H): 408.1116.

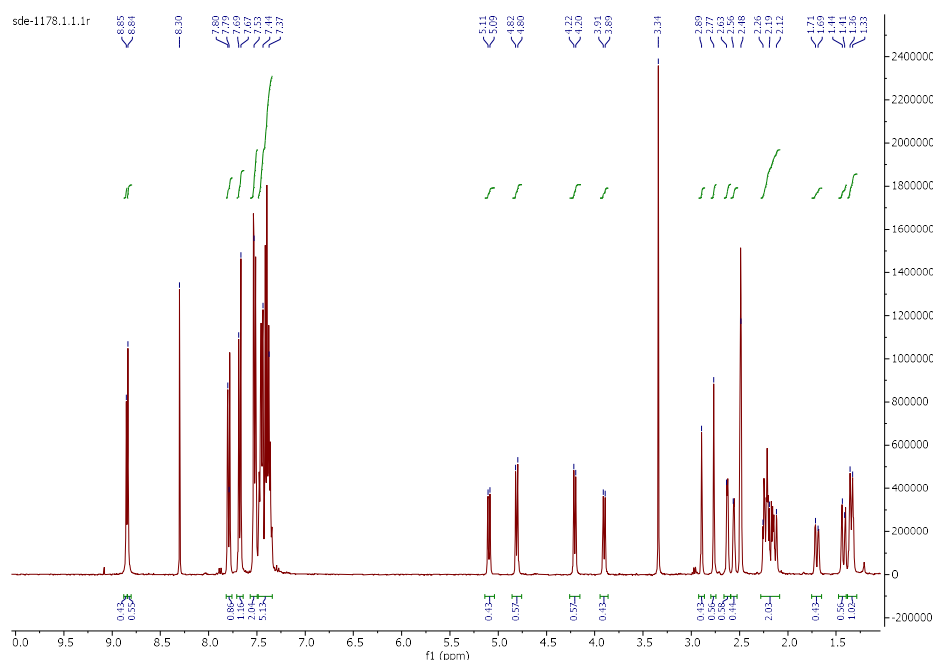


Figure S34. ¹H NMR spectra of the mixture of compounds **12a** and **13a**.

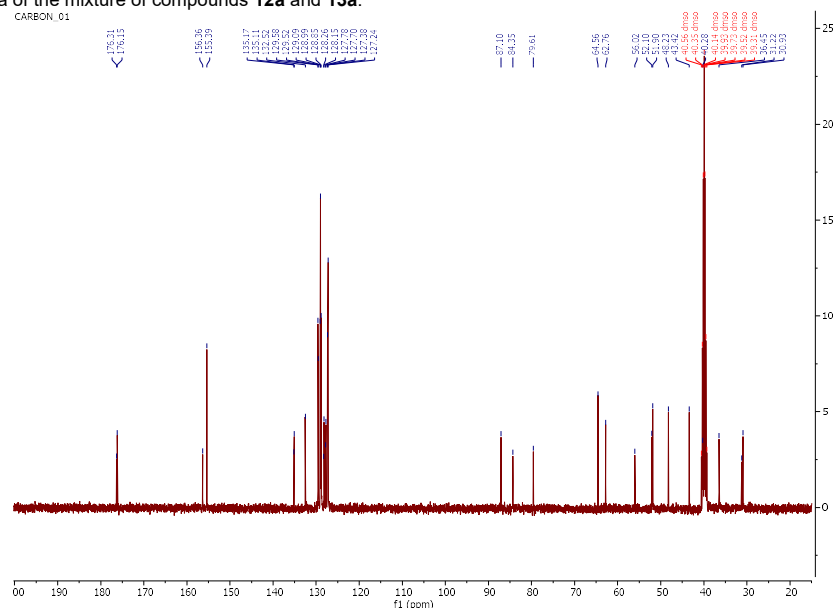


Figure S35. ¹³C NMR spectra of the mixture of compounds **12a** and **13a**.

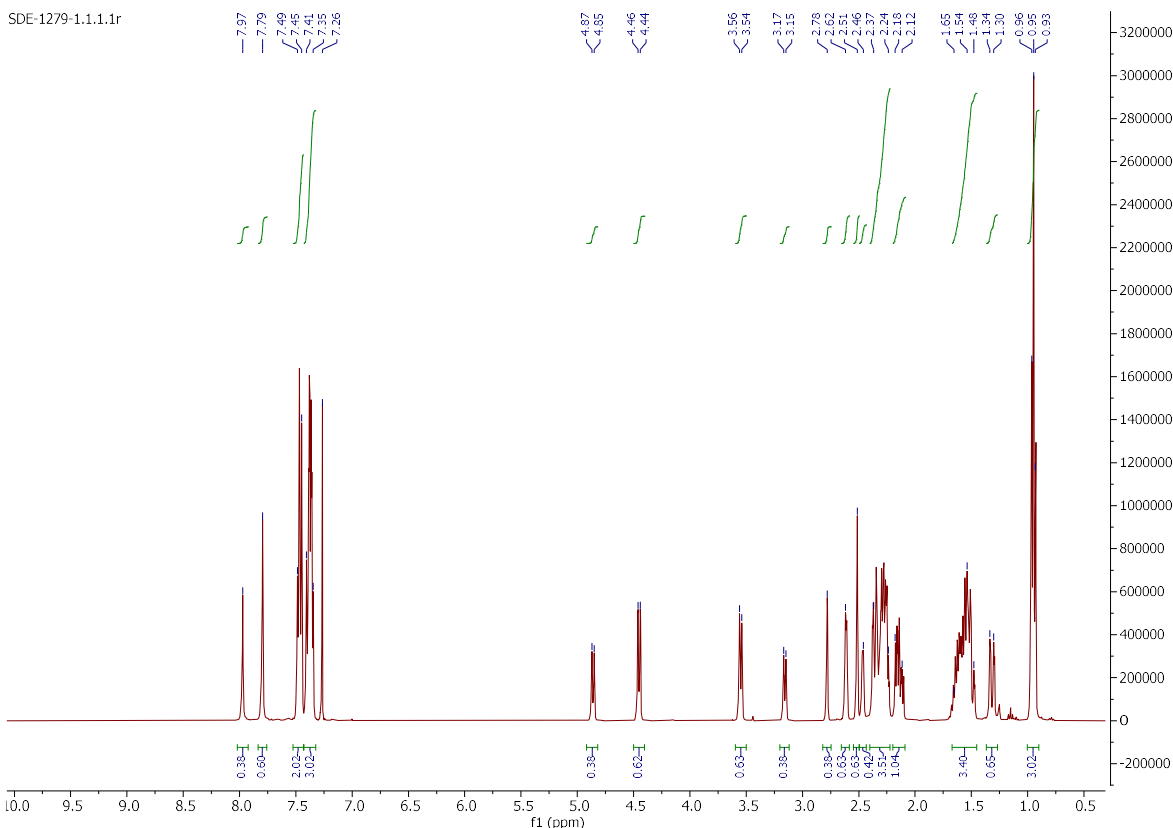
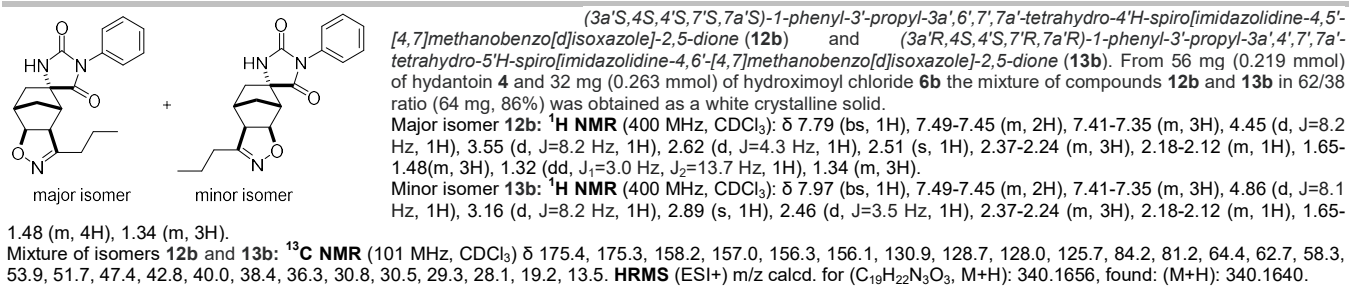


Figure S36. ¹H NMR spectra of the mixture of compound **12b** and **13b**.

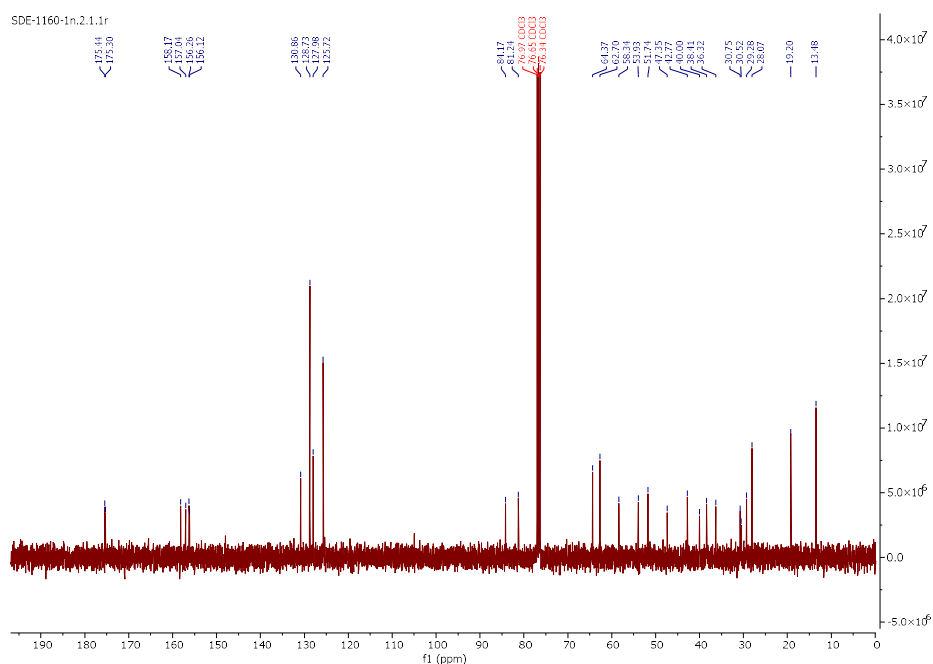
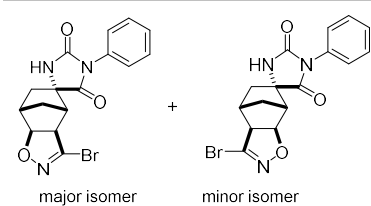


Figure S37. ¹³C NMR spectra of the mixture of compounds **12b** and **13b**.



(3a'R,4S,4'S,7'S,7a'S)-3-bromo-1-phenyl-3a',6',7',7a'-tetrahydro-4'H-spiro[imidazolidine-4,5'-[4,7]methanobenzo[d]isoxazole]-2,5-dione (**12c**) and (3a'S,4S,4'S,7'R,7a'R)-3-bromo-1-phenyl-3a',4',7',7a'-tetrahydro-5'H-spiro[imidazolidine-4,6'-[4,7]methanobenzo[d]isoxazole]-2,5-dione (**13c**). From 56 mg (0.219 mmol) of hydantoin **4** and 53 mg (0.263 mmol) of hydroximoyl bromide **6c** the mixture of compounds **12c** and **13c** in 58/42 ratio (70 mg, 85%) was obtained as a white crystalline solid.

Major isomer **12c**: ¹H NMR (400 MHz, DMSO-d₆): δ 8.75 (bs, 1H, NH), 7.49-7.45 (m, 2H, Ph), 7.42-7.36 (m, 3H, Ph), 4.77 (d, J=8.3 Hz, 1H, HC-O), 3.89 (d, J=8.3 Hz, 1H, CH-C=N), 2.78 (s, 1H, CH), 2.63 (d, J=4.6 Hz, 1H, CH), 2.27-2.16 (m, 2H), 1.40-1.34 (m, 2H). ¹³C NMR (101 MHz, DMSO-d₆): δ 175.5 (C=O), 154.9 (C=O), 138.9 (BrC=N), 132.0 (C, Ph), 128.6 (2C, Ph), 127.8 (C, Ph), 127.0 (2C, Ph), 86.4 (HC-O), 63.6 (C_{quat}), 57.1 (CH-C=N), 47.3 (CH), 43.0 (CH), 35.9 (CH₂), 30.3 (CH₂).

Minor isomer **13c**: ¹H NMR (400 MHz, DMSO-d₆): δ 8.75 (bs, 1H, NH), 7.49-7.45 (m, 2H, Ph), 7.42-7.36 (m, 3H, Ph), 5.05 (d, J=8.3 Hz, 1H, HC-O), 3.61 (d, J=8.3 Hz, 1H, CH-C=N), 2.92 (s, 1H, CH), 2.58 (d, J=4.1 Hz, 1H, CH), 2.27-2.16 (m, 2H), 1.56 (dd, J₁=3.2 Hz, J₂=13.4 Hz, 1H), 1.40-1.34 (m, 1H). ¹³C NMR (101 MHz, DMSO-d₆): δ 175.6 (C=O), 154.9 (C=O), 139.7 (BrC=N), 132.0 (C, Ph), 128.6 (2C, Ph), 127.8 (C, Ph), 127.0 (2C, Ph), 83.8 (HC-O), 62.1 (C_{quat}), 60.8 (CH-C=N), 51.5 (CH), 39.1 (CH), 38.9 (CH₂), 30.7 (CH₂).

HRMS (ESI+) m/z calcd. for (C₁₆H₁₅BrN₃O₃, M+H): 376.0291, found: (M+H): 376.0292.

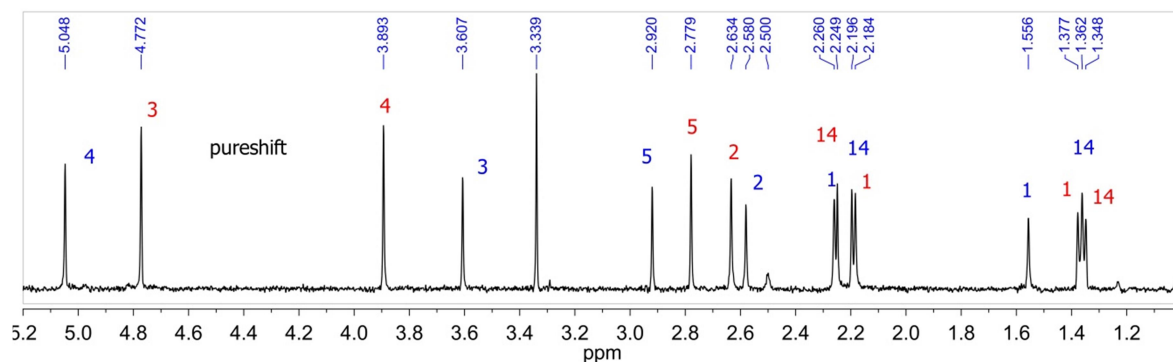


Figure S38. ¹H NMR spectra (pure shifts) of the mixture of compounds **12c** and **13c**.

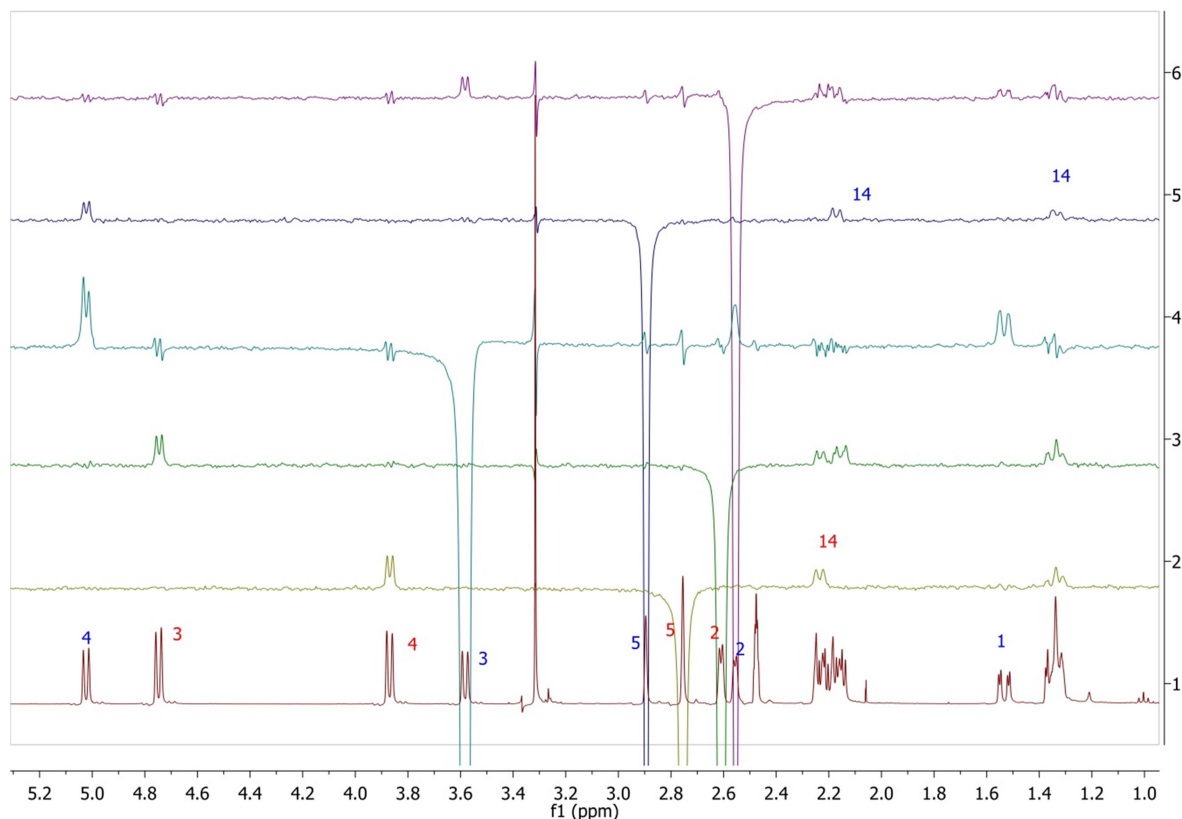


Figure S39. NOESY ¹H NMR spectra of the mixture of compounds **12c** and **13c**.

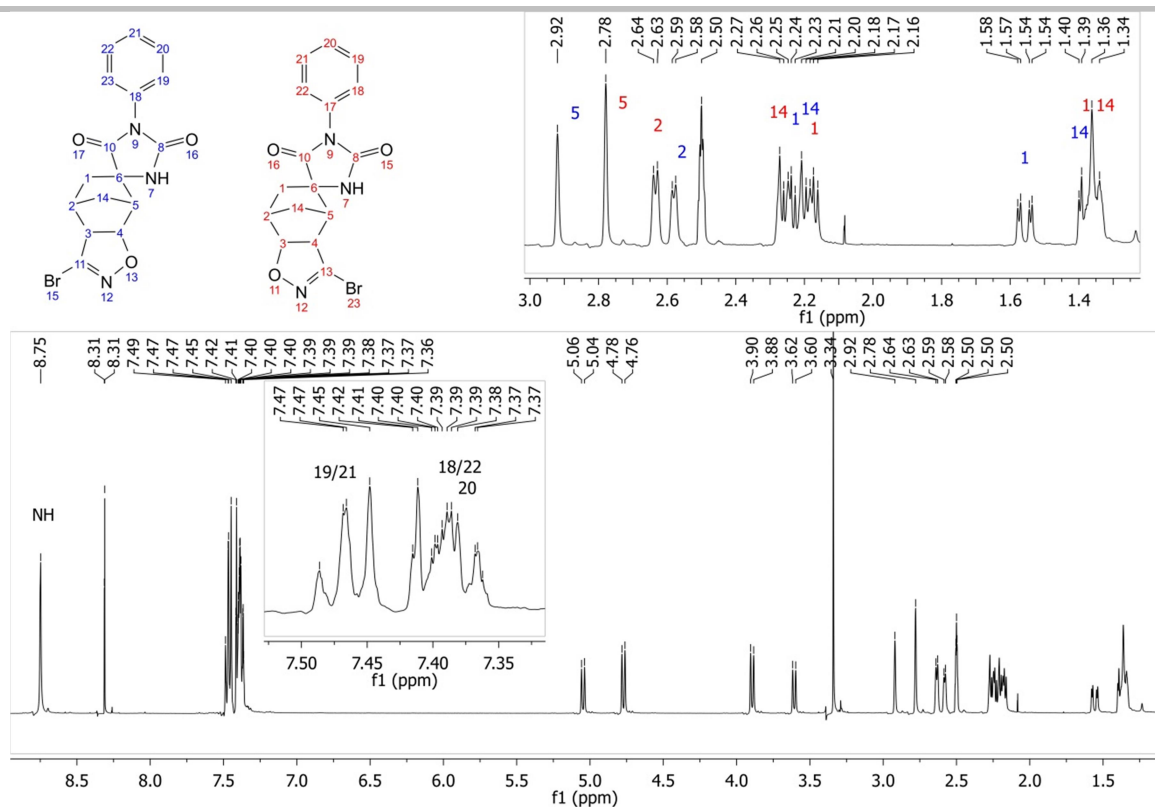


Figure S40. ^1H NMR spectra of the mixture of compounds 12c and 13c.

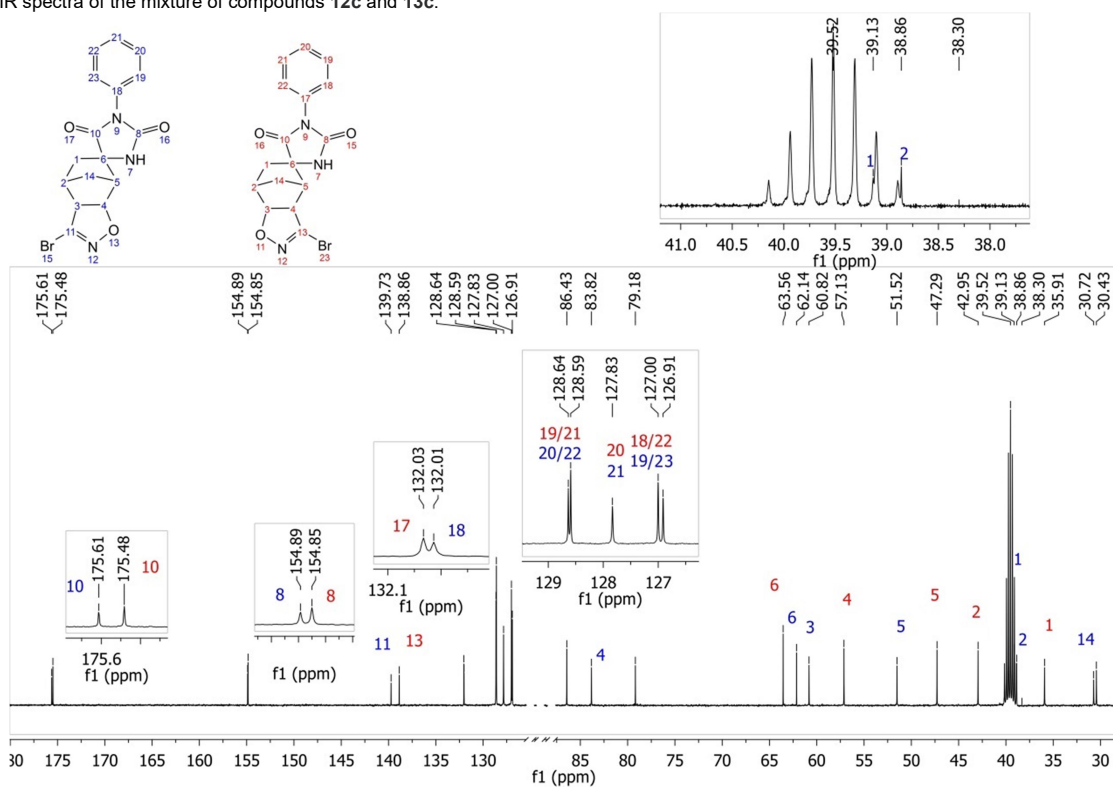


Figure S41. ^{13}C NMR spectra of the mixture of compounds 12c and 13c.

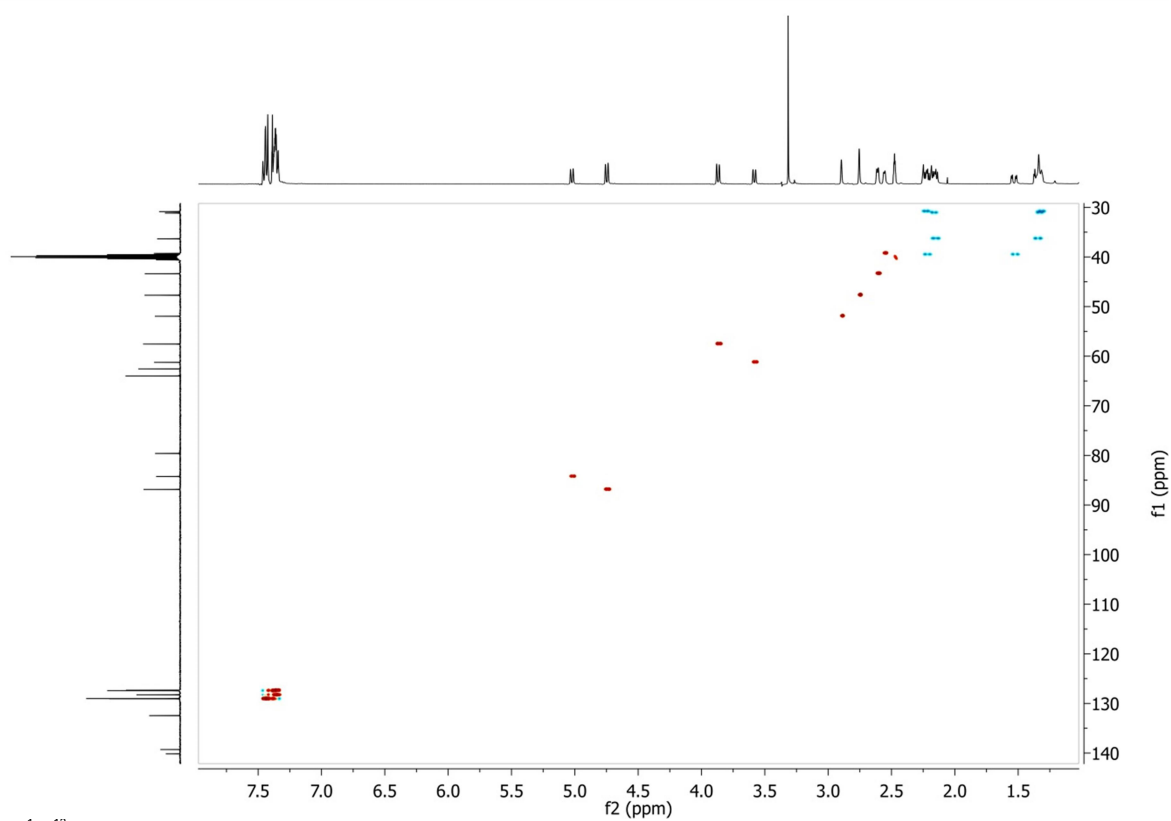


Figure S42. HSQC ^1H - ^{13}C NMR spectra of the mixture of compounds **12c** and **13c**.

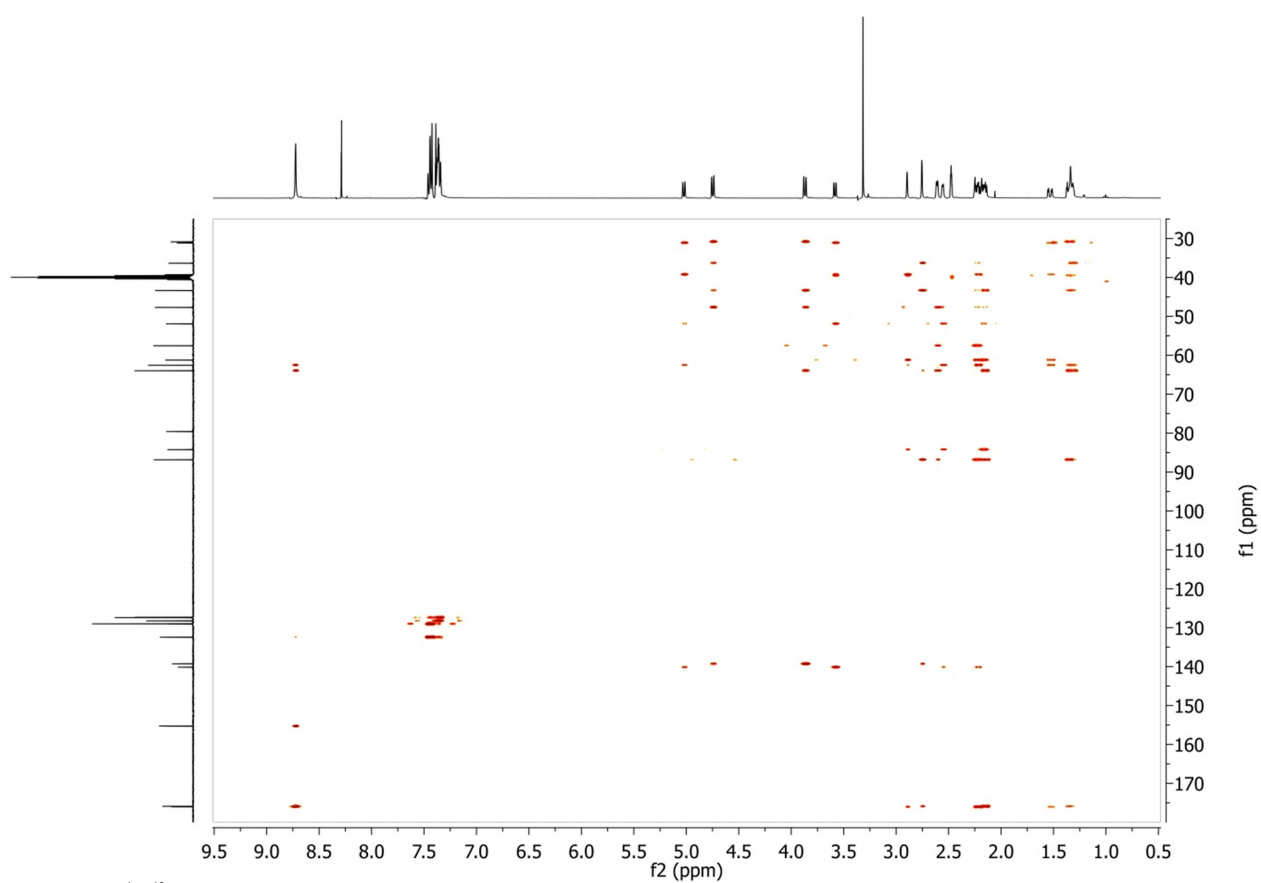
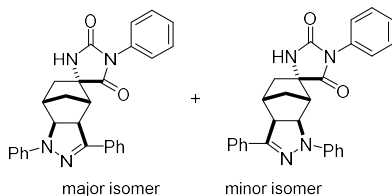


Figure S43. gHSQC ^1H - ^{13}C NMR spectra of mixture of compounds **12c** and **13c**.

General procedure of 1,3-dipolar cycloaddition of nitrile imines to hydantion 4 using diffusion mixing technique.

A mixture of hydantoin **4** (0.118 mmol, 0.030 g) and halogen derivative **7** (0.354 mmol) in 3 ml of chloroform was placed in a 15 ml vial **1** (diameter 1.3 cm) and closed with a glass stopper with holes. The vial **1** was then placed in closed 50 ml vial **2** (diameter 3.5 cm) containing triethylamine (35.85 mmol, 5 ml) and the reaction mixture was stirred at room temperature for two days (TLC or NMR control). After the reaction was complete, the mixture from the inner vial was diluted with 10 ml of chloroform, transferred to a separating funnel and washed with 2% aqueous HCl (2 x 10 ml). The organic phase was dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using methanol/chloroform (1:100) as an eluent.



(3a'R,4S,4'S,7'S,7a'S)-1,1',3'-triphenyl-1',3a',4',6',7',7a'-hexahydrospiro[imidazolidine-4,5'-[4,7]methanoindazole]-2,5-dione (**12d**) and (3a'S,4S,4'S,7'S,7a'R)-1,1',3'-triphenyl-1',3a',4',5',7',7a'-hexahydrospiro[imidazolidine-4,6'-[4,7]methanoindazole]-2,5-dione (**13d**). From 30 mg (0.118 mmol) of hydantoin **4** and 82 mg (0.354 mmol) of imidoyl chloride **7a** the mixture of compounds **12d** and **13d** in 54/46 ratio (49 mg, 93%) was obtained as a light yellow crystalline solid.

Major isomer **12d**: ¹H NMR (400 MHz, CDCl₃): δ 7.92 (bs, 1H), 7.72-7.70 (m, 2H), 7.44-7.30 (m, 9H), 7.21-7.10 (m, 3H), 6.92-6.85 (m, 1H), 4.11-4.03 (m, 2H), 2.98 (s, 1H), 2.78 (s, 1H), 2.45-2.32 (m, 2H), 1.68-1.52 (m, 2H).

Minor isomer **13d**: ¹H NMR (400 MHz, CDCl₃): δ 7.77 (bs, 1H), 7.72-7.70 (m, 2H), 7.44-7.30 (m, 9H), 7.21-7.10 (m, 3H), 6.92-6.85 (m, 1H), 4.57 (d, J=8.9 Hz, 1H), 3.59 (d, J=8.9 Hz, 1H), 2.87 (s, 1H), 2.73 (s, 1H), 2.45-2.32 (m, 2H), 1.68-1.52 (m, 2H).

Mixture of isomers **12d** and **13d**: ¹³C NMR (101 MHz, CDCl₃): δ 176.0, 175.8, 156.9, 156.9, 148.9, 147.2, 144.4, 143.9, 131.9, 131.1, 129.4, 129.3, 129.1, 128.7, 128.6, 128.6, 128.5, 128.4, 126.1, 125.9, 125.7, 119.4, 119.1, 112.5, 66.9, 65.4, 64.1, 63.7, 54.4, 50.9, 49.7, 49.6, 41.7, 41.0, 40.5, 37.6, 32.1, 31.7. HRMS (ESI+) m/z calcd. for (C₂₈H₂₅N₄O₂, M+H): 449.1972, found: (M+H): 449.1968.

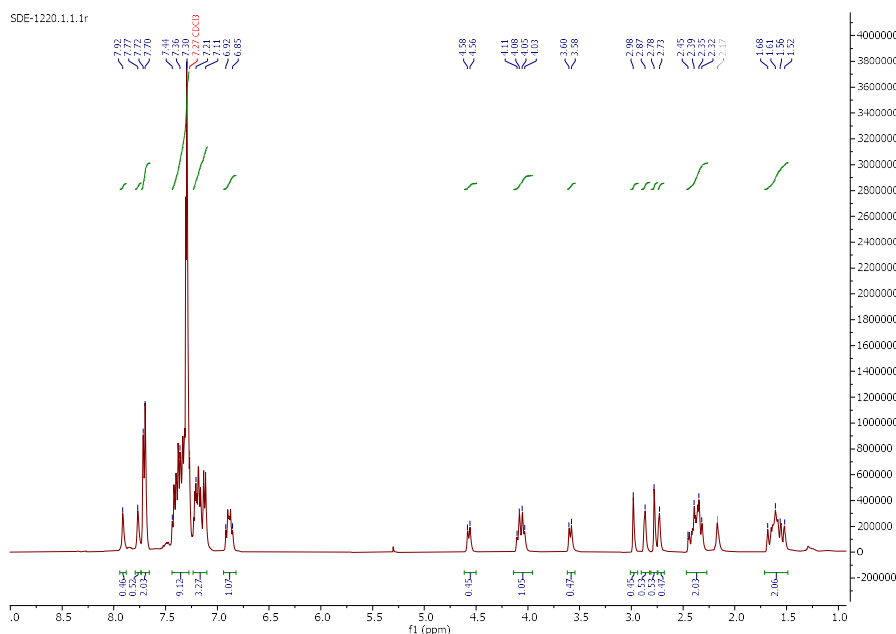


Figure S44. ¹H NMR spectra of the mixture of compounds **12d** and **13d**.

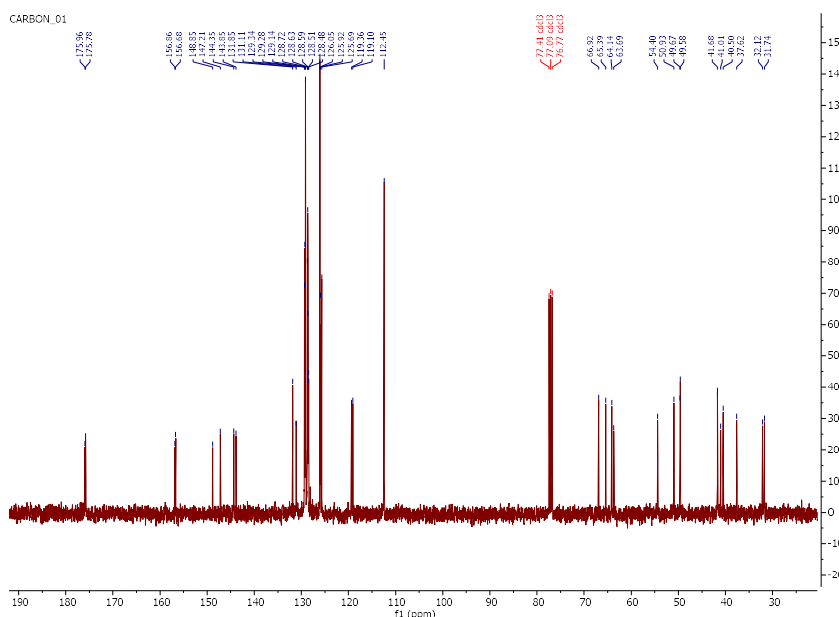
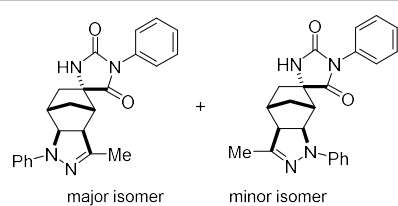


Figure S45. ¹³C NMR spectra of the mixture of compounds **12d** and **13d**.



(3a'R,4S,4'S,7'S,7a'S)-3'-methyl-1,1'-diphenyl-1',3a',4',6',7',7a'-hexahydrospiro[imidazolidine-4,5'-[4,7]methanoindazole]-2,5-dione (**12e**) and (3a'S,4S,4'S,7'S,7a'R)-1'-methyl-1,3'-diphenyl-1',3a',4',5',7',7a'-hexahydrospiro[imidazolidine-4,6'-[4,7]methanoindazole]-2,5-dione (**13e**). From 30 mg (0.118 mmol) of hydantoin **4** and 60 mg (0.354 mmol) of imidoyl chloride **7b** the mixture of compounds **12e** and **13e** in 53/47 ratio (37 mg, 81%) was obtained as a yellow crystalline solid.

Major isomer **12e**: ¹H NMR (400 MHz, CDCl₃): δ 7.55 (bs, 1H, NH), 7.42-7.26 (m, 7H, 2Ph), 6.95-6.93 (m, 2H, Ph), 6.82-6.80 (m, 1H, Ph), 3.85 (d, J=9.3 Hz, 1H, HC-N), 3.42 (d, J=9.3 Hz, 1H, CH-C=N), 2.75 (d, J=4.4 Hz, 1H, CH), 2.60 (s, 1H, CH), 2.41-2.29 (m, 2H), 1.96 (s, 3H, CH₃), 1.53-1.46 (m, 2H). ¹³C NMR (101 MHz, CDCl₃): δ 176.0 (C=O), 156.5 (C=O), 148.3 (C=N), 144.8 (C, Ph), 131.2 (C, Ph), 129.3 (2C, Ph), 129.2 (2C, Ph), 128.5 (C, Ph), 126.2 (2C, Ph), 118.4 (C, Ph), 111.9 (2C, Ph), 66.3 (HC-N), 65.3 (C_{quat}), 53.6 (CH-C=N),

48.5 (CH), 41.6 (CH), 37.7 (CH₂), 31.7 (CH₂), 14.5 (CH₃).

Minor isomer **13e**: ¹H NMR (400 MHz, CDCl₃): δ 7.79 (bs, 1H, NH), 7.42-7.26 (m, 7H, 2Ph), 7.00-6.99 (m, 2H, Ph), 6.82-6.80 (m, 1H, Ph), 4.30 (d, J=9.3 Hz, 1H, HC-N), 2.97 (d, J=9.3 Hz, 1H, CH-C=N), 2.84 (s, 1H, CH), 2.51 (d, J=4.4 Hz, 1H, CH), 2.41-2.29 (m, 2H), 1.95 (s, 3H, CH₃), 1.53-1.46 (m, 1H), 1.43 (dd, J₁=3.2 Hz, J₂=13.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 176.0 (C=O), 156.9 (C=O), 150.1 (C=N), 145.6 (C, Ph), 131.3 (C, Ph), 129.3 (2C, Ph), 129.2 (2C, Ph), 128.5 (C, Ph), 126.2 (2C, Ph), 118.7 (C, Ph), 112.0 (2C, Ph), 64.1 (C_{quat}), 63.3 (HC-N), 58.2 (CH-C=N), 51.1 (CH), 41.1 (CH₂), 39.4 (CH), 32.0 (CH₂), 14.5 (CH₃).

HRMS (ESI+) m/z calcd. for (C₂₃H₂₃N₄O₂, M+H): 387.1816, found: (M+H): 387.1813.

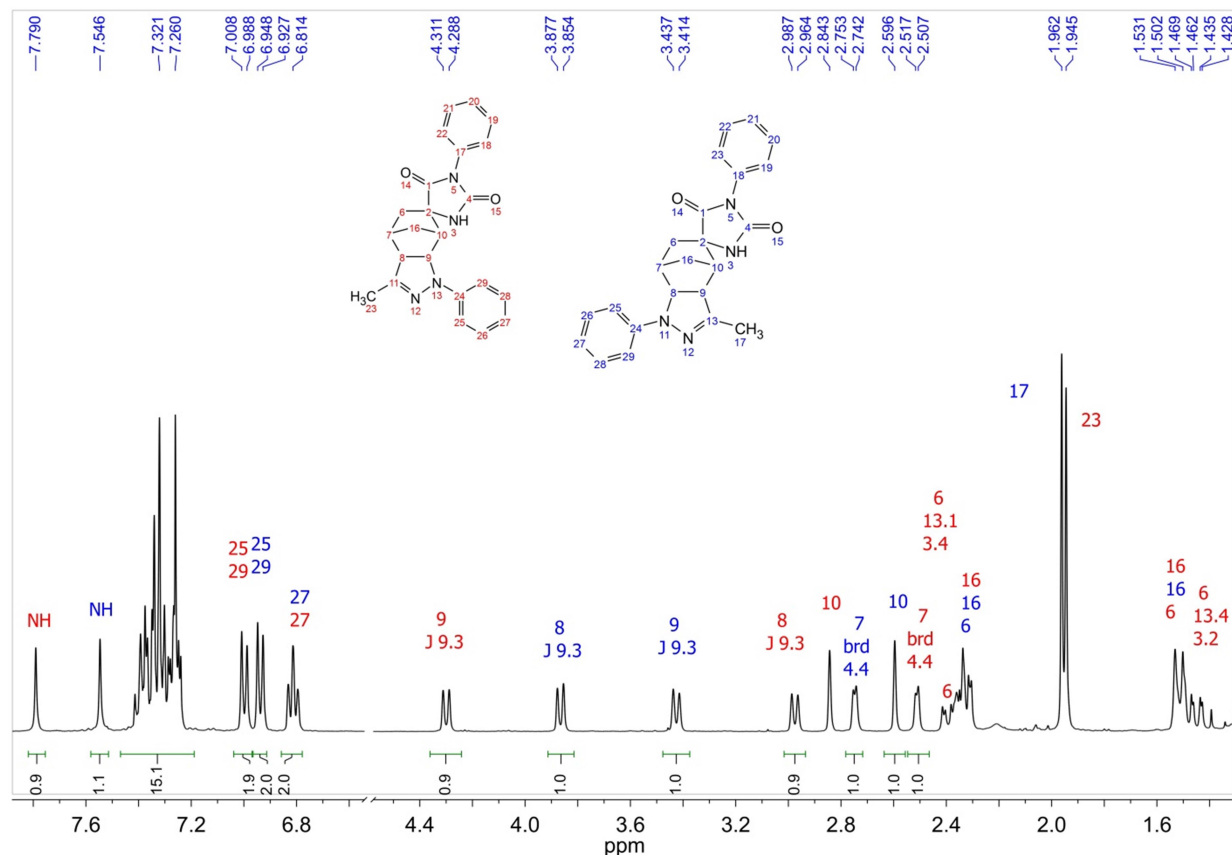


Figure S46. ¹H NMR spectra of the mixture of compounds **12e** and **13e**.

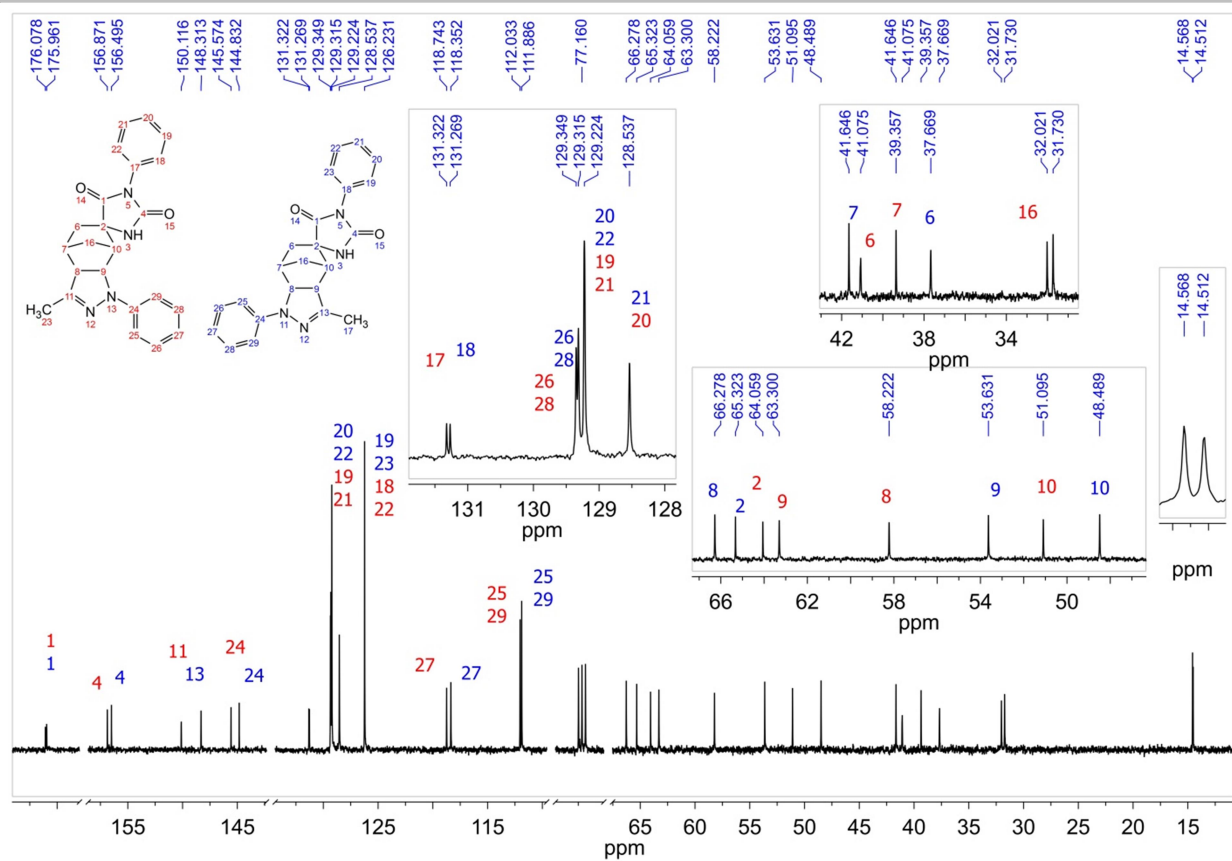


Figure S47. ^{13}C NMR spectra of the mixture of compounds **12e** and **13e**.

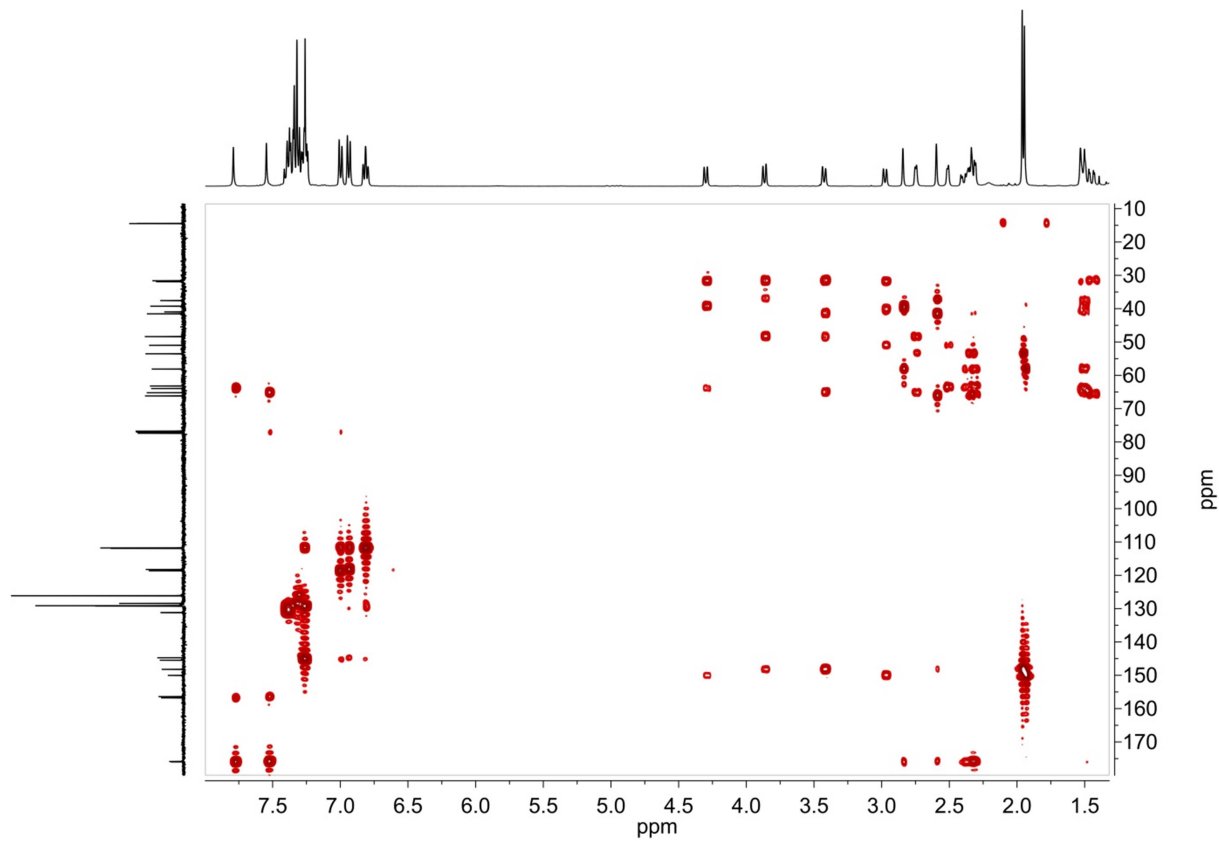
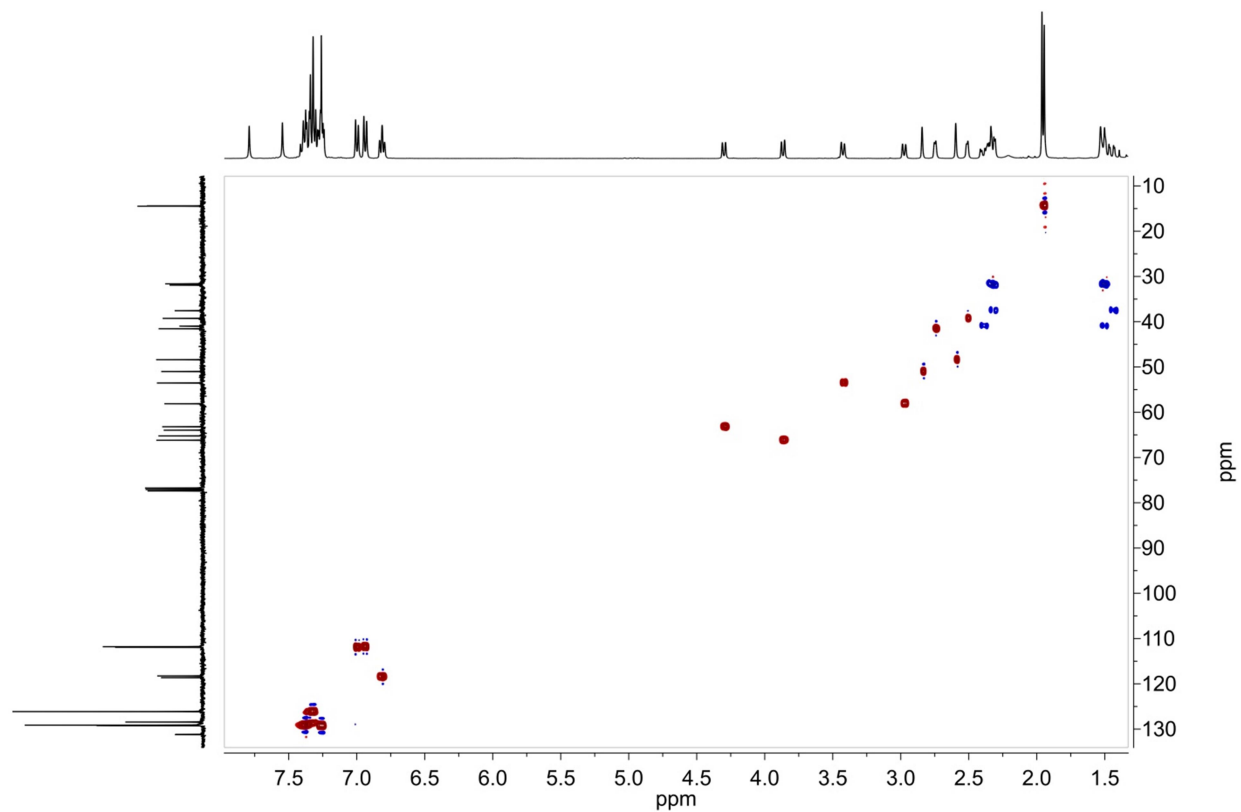


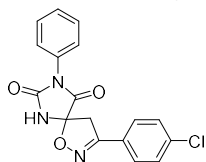
Figure S48. $\text{HMBC}^1\text{H}-^{13}\text{C}$ NMR spectra of the mixture of compounds **12e** and **13e**.



FigureS49. HSQC ^1H - ^{13}C NMR spectra of the mixture of compounds 12e and 13e.

General procedure of 1,3-dipolar cycloaddition to methyldenehydantoin **5** using diffusion mixing technique.

A mixture of methyldenehydantoin **5** (0.263 mmol, 0.049 g) and halogen derivative **6** or **7** (0.263 mmol) in 3 ml of chloroform was placed in a 15 ml vial **1** (diameter 1.3 cm) and closed with a glass stopper with holes. The vial **1** was then placed in a closed 50 ml vial **2** (diameter 3.5 cm) containing triethylamine (35.85 mmol, 5 ml) and the reaction mixture was stirred at room temperature for two days (TLC or NMR control). When the reaction was completed, the mixture from the inner vial was diluted with 10 ml of chloroform, transferred to a separating funnel and washed with 2% aqueous HCl (2 x 10 ml). The organic phase was dried over anhydrous Na₂SO₄, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using methanol/chloroform (1:100) as an eluent.



3-(4-chlorophenyl)-8-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (14a). From 49 mg (0.263 mmol) of methyldenehydantoin **5** and 50 mg (0.263 mmol) of hydroximoyl chloride **6a** compound **14a** (86 mg, 96%) was obtained as a white crystalline solid.

¹H NMR (400 MHz, DMSO-d₆): δ 9.80 (bs, 1H), 7.78-7.76 (m, 1H), 7.72-7.70 (m, 1H), 7.61-7.57 (m, 1H), 7.53-7.47 (m, 3H), 7.44-7.40 (m, 3H), 4.01 (d, J=18.5 Hz, 1H), 3.72 (d, J=18.5 Hz, 1H). **¹³C NMR** (101 MHz, DMSO-d₆): δ 169.2, 155.9, 153.8, 133.8, 131.4, 131.0, 130.7, 130.2, 129.0, 128.3, 126.7, 126.5, 125.6, 93.2, 40.9. **HRMS** (ESI+) m/z calcd. for (C₁₇H₁₃ClN₃O₃, M+H): 342.0640, found: (M+H): 342.0640.

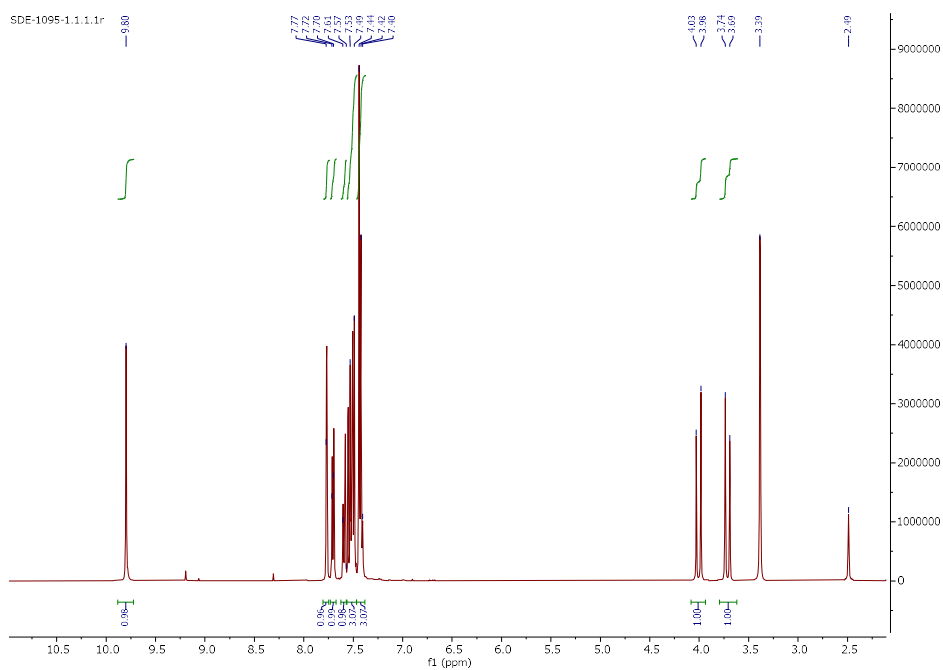


Figure S50. ¹H NMR spectra of compound **14a**.

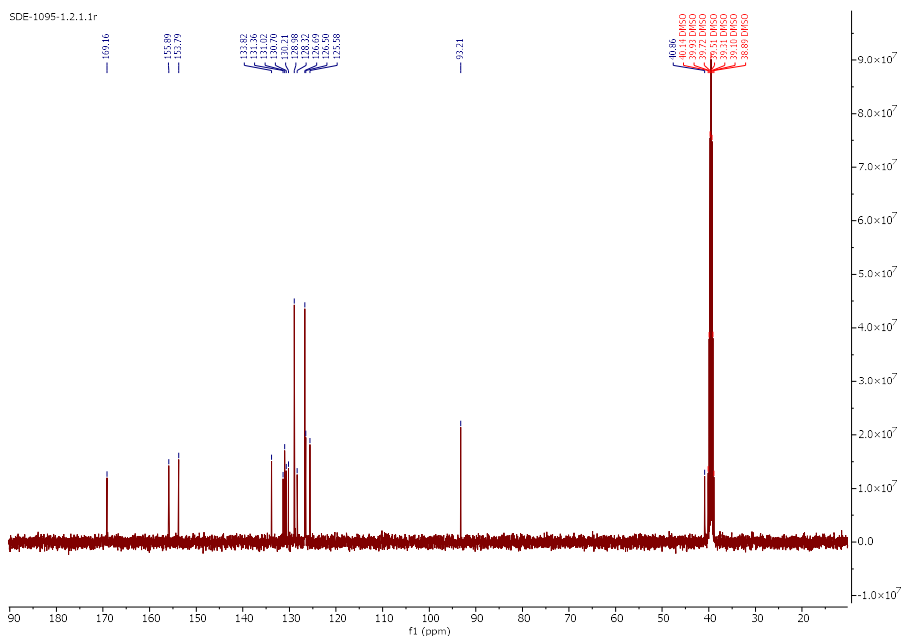
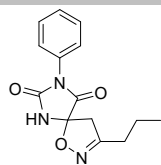


Figure S51. ¹³C NMR spectra of compound **14a**.



8-phenyl-3-propyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (14b). From 49 mg (0.263 mmol) of methylidenehydantion **5** and 32 mg (0.263 mmol) of hydroximoyl chloride **6b** compound **14b** (63 mg, 88%) was obtained as a white crystalline solid.

¹H NMR (400 MHz, DMSO-d₆): δ 9.63 (bs, 1H), 7.50-7.47 (m, 2H), 7.43-7.36 (m, 3H), 3.51 (d, J=18.6 Hz, 1H), 2.34 (t, J=7.4 Hz, 2H), 1.61-1.51 (m, 2H), 0.93 (t, J=7.4 Hz, 3H). **¹³C NMR** (101 MHz, DMSO-d₆): δ 170.2, 159.5, 154.3, 131.9, 129.3, 128.6, 127.1, 92.1, 43.9, 29.1, 19.5, 14.0. **HRMS** (ESI+) m/z calcd. for (C₁₄H₁₆N₃O₃, M+H): 274.1186, found: (M+H): 274.1175.

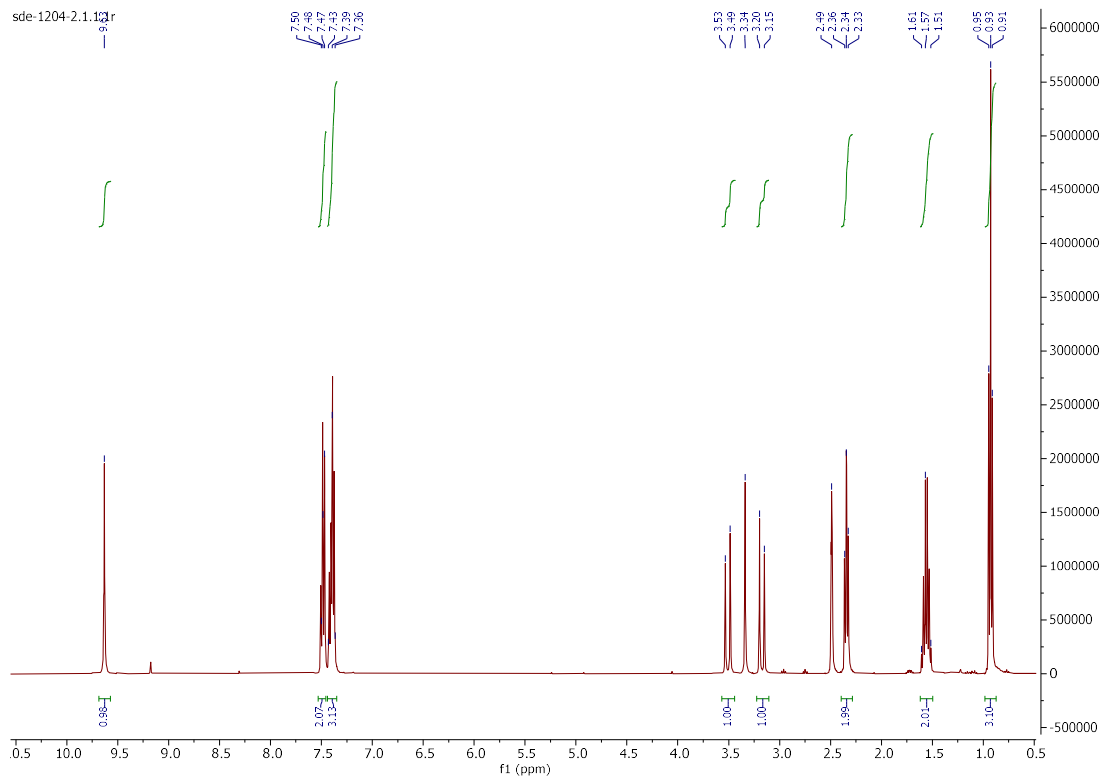


Figure S52. ¹H NMR spectra of compound **14b**.

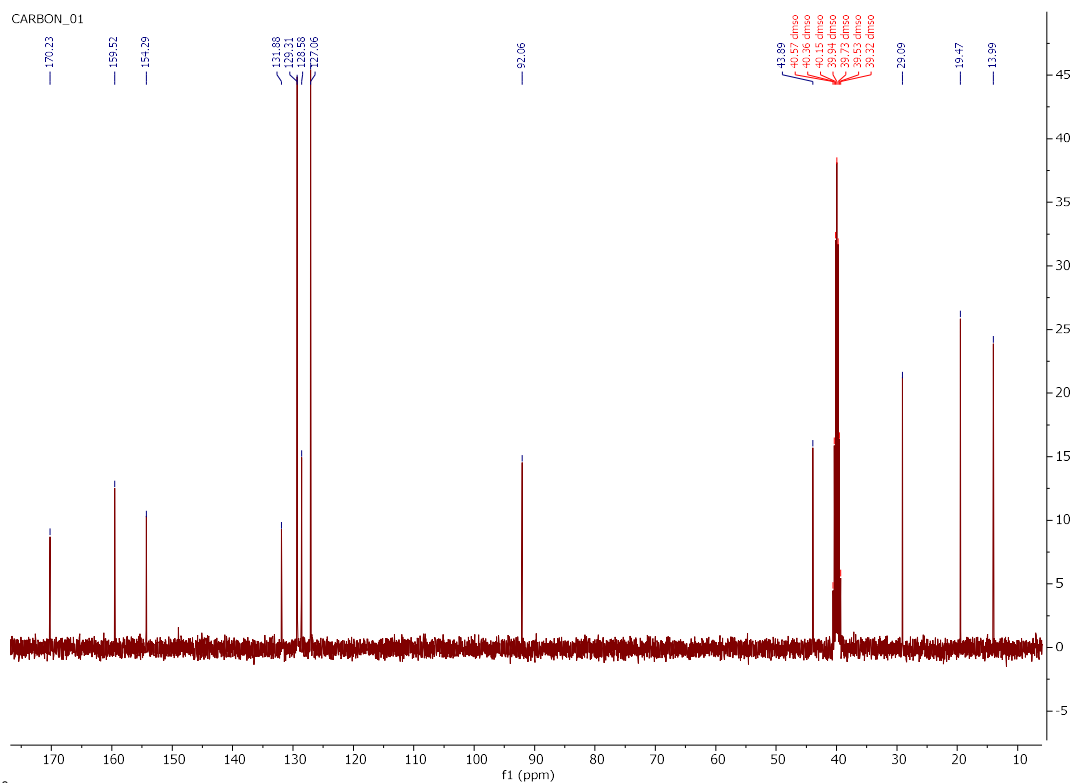
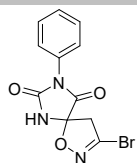


Figure S53. ¹³C NMR spectra of compound **14b**.



3-bromo-8-phenyl-1-oxa-2,6,8-triazaspiro[4.4]non-2-ene-7,9-dione (8c). From 49 mg (0.263 mmol) of methylidenehydantion **5** and 53 mg (0.263 mmol) of hydroximoyl bromide **6c** compound **14c** (68 mg, 84%) was obtained as a pale yellow crystalline solid. $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 9.76 (bs, 1H), 7.51-7.48 (m, 2H), 7.43-7.37 (m, 3H), 3.86 (d, $J=19.0$ Hz, 1H), 3.49 (d, $J=19.0$ Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, DMSO- d_6): δ 168.4, 153.7, 137.8, 131.2, 129.0, 128.4, 126.7, 93.0, 46.5. HRMS (ESI+) m/z calcd. for $(\text{C}_{11}\text{H}_9\text{BrN}_3\text{O}_3, \text{M}+\text{H})$: 309.9822, found: (M+H): 309.9820.

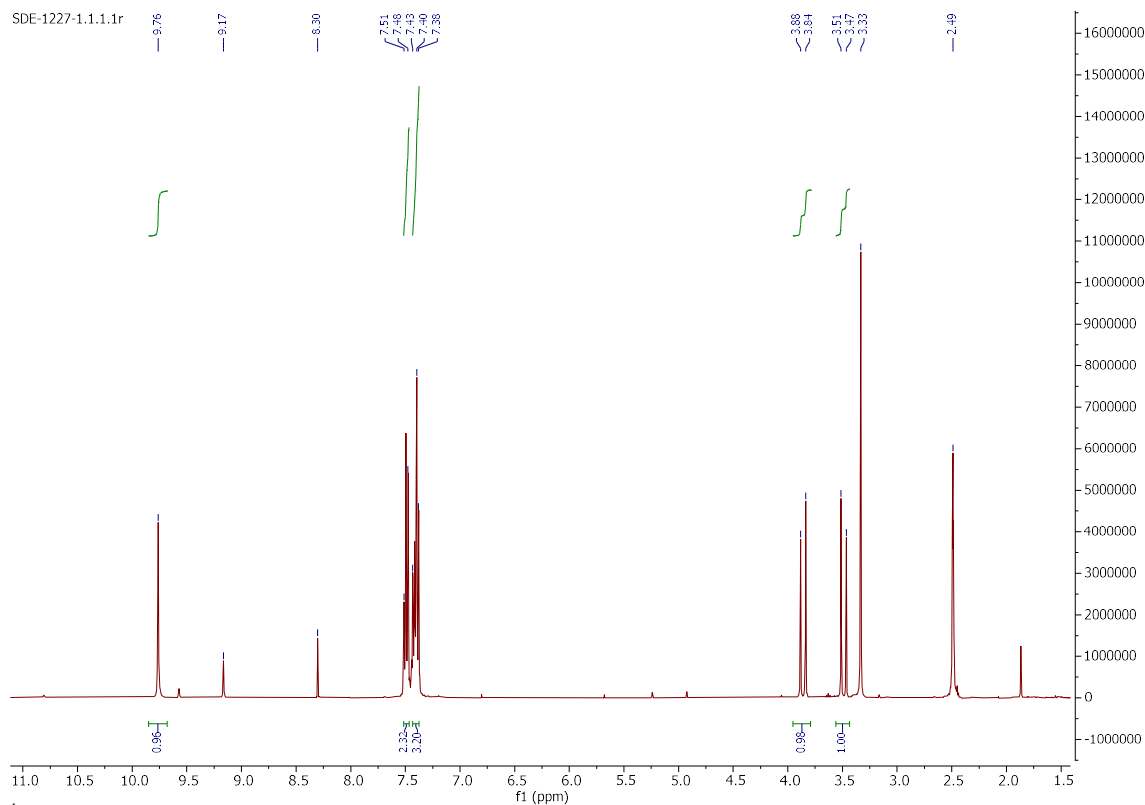


Figure S54. $^1\text{H NMR}$ spectra of compound **14c**.

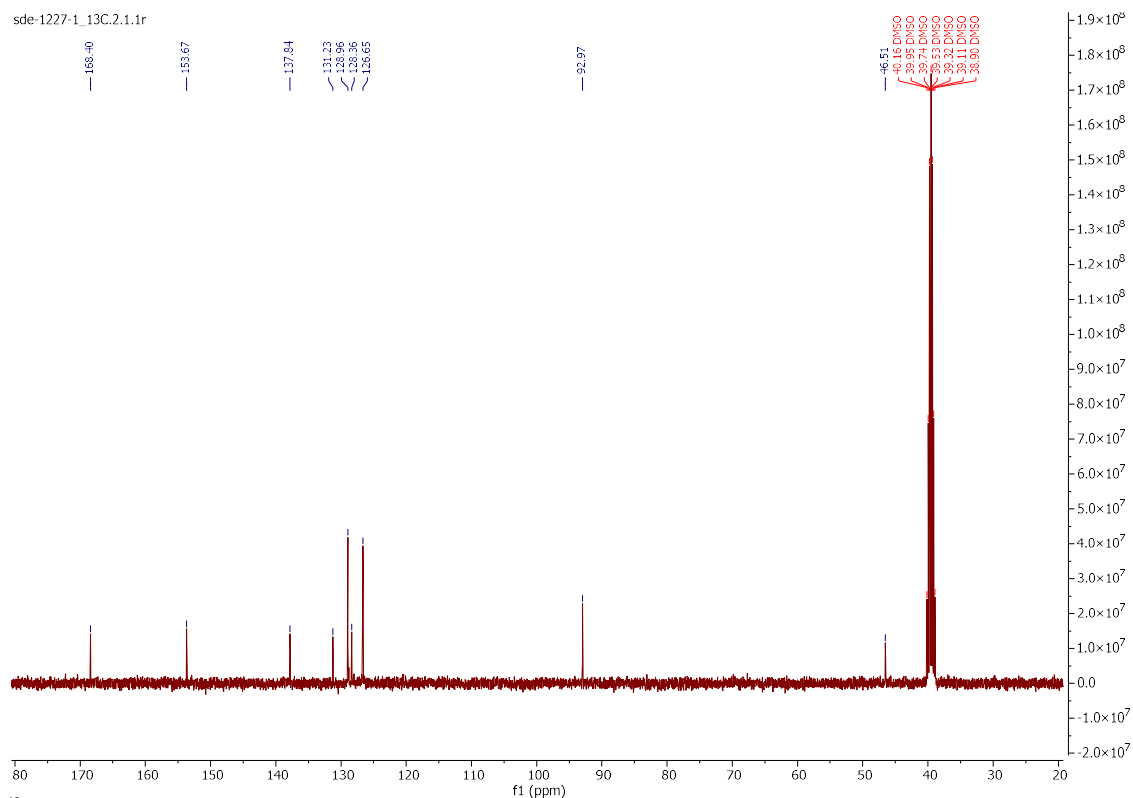
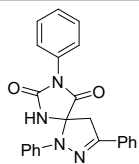


Figure S55. $^{13}\text{C NMR}$ spectra of compound **14c**.



1,3,8-triphenyl-1,2,6,8-tetraazaspiro[4.4]non-2-ene-7,9-dione (**14d**). From 49 mg (0.263 mmol) of methylidenehydantion **5** and 61 mg (0.263 mmol) of imidoyl chloride **7a** compound **14d** (95 mg, 94%) was obtained as a yellow crystalline solid.

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.68-7.65 (m, 2H), 7.46-7.38 (m, 6H), 7.29-7.24 (m, 4H), 7.18-7.16 (m, 2H), 7.08-7.04 (m, 1H), 6.76 (bs, 1H), 4.01 (d, $J=17.6$ Hz, 1H), 3.72 (d, $J=17.6$ Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 170.8, 153.9, 147.5, 142.4, 131.2, 130.9, 129.7, 129.4, 129.3, 128.8, 128.7, 126.0, 125.9, 123.8, 117.9, 81.7, 45.2. HRMS (ESI+) m/z calcd. for $(\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_2, \text{M}+\text{H})$: 383.1503, found: (M+H): 383.1507.

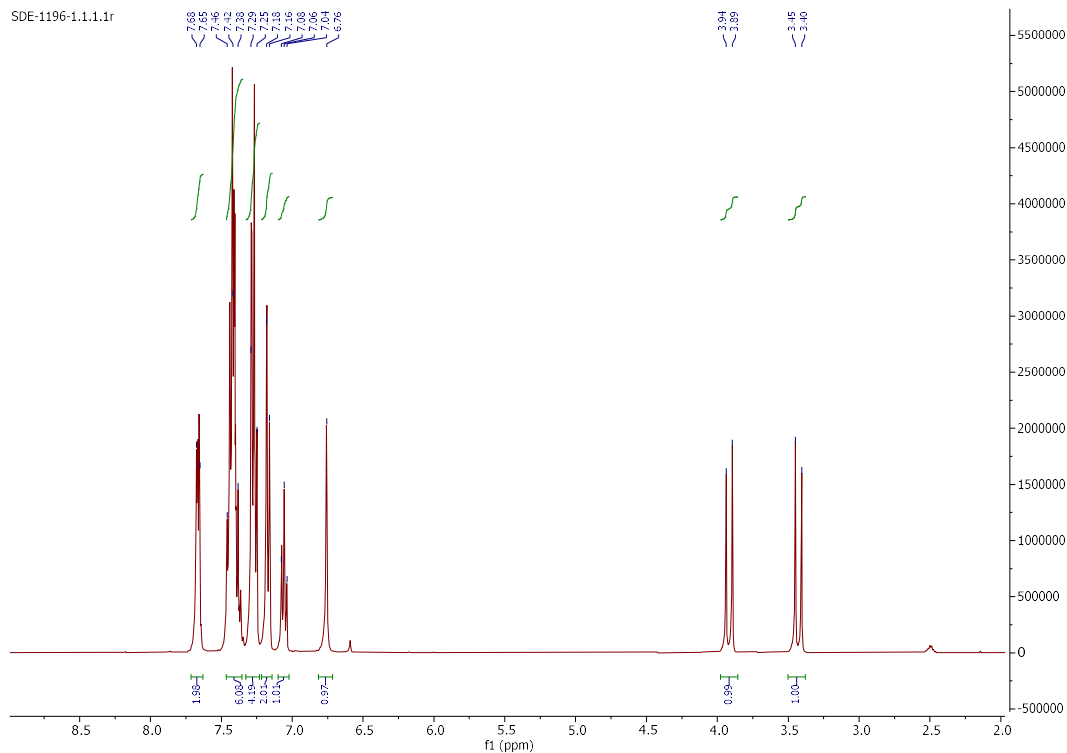


Figure S56. $^1\text{H NMR}$ spectra of compound **14d**.

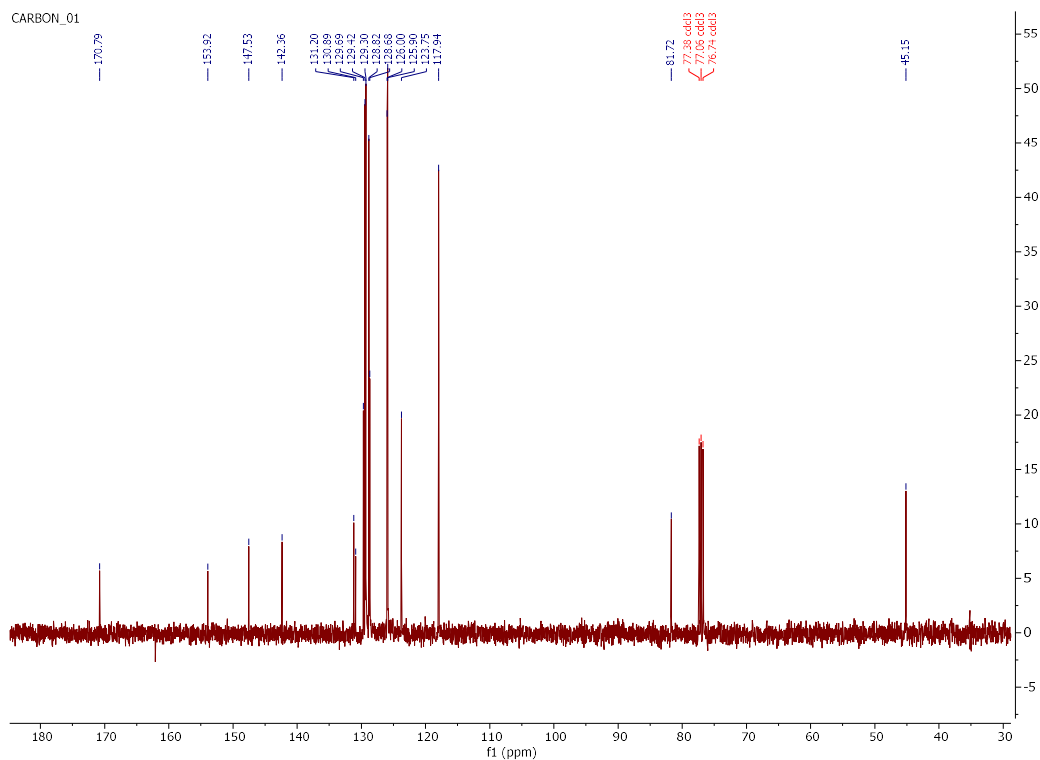
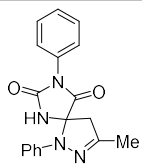


Figure S57. $^{13}\text{C NMR}$ spectra of compound **14d**.



3-methyl-1,8-diphenyl-1,2,6,8-tetraazaspiro[4.4]non-2-ene-7,9-dione (14e). From 49 mg (0.263 mmol) of methyldenehydantion **5** and 44 mg (0.263 mmol) of imidoyl chloride **7b** compound **14e** (73 mg, 87%) was obtained as a yellow crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 7.48-7.43 (m, 2H), 7.41-7.37 (m, 1H), 7.30-7.25 (m, 4H), 7.12-7.09 (m, 2H), 7.07-7.03 (m, 1H), 6.84 (bs, 1H), 3.55 (d, J=17.9 Hz, 1H), 3.01 (d, J=17.9 Hz, 1H), 2.02 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃): δ 171.1, 154.2, 148.9, 142.9, 130.9, 129.3, 129.3, 128.6, 125.9, 123.6, 118.1, 81.9, 48.6, 15.5. **HRMS** (ESI+) m/z calcd. for (C₁₈H₁₇N₄O₂, M+H): 321.1346, found: (M+H): 321.1344.

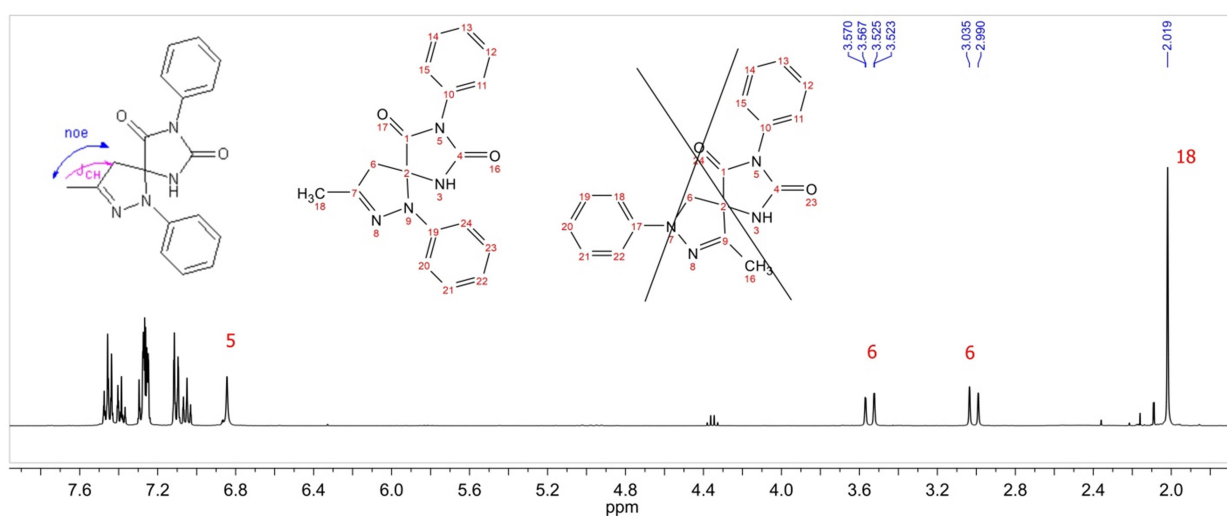
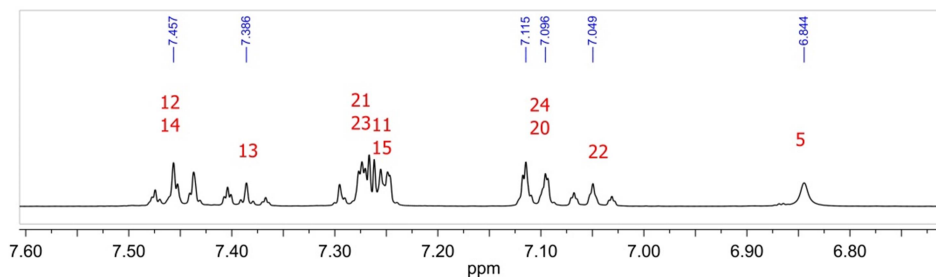


Figure S58. ¹H NMR spectra of compound **14e**.

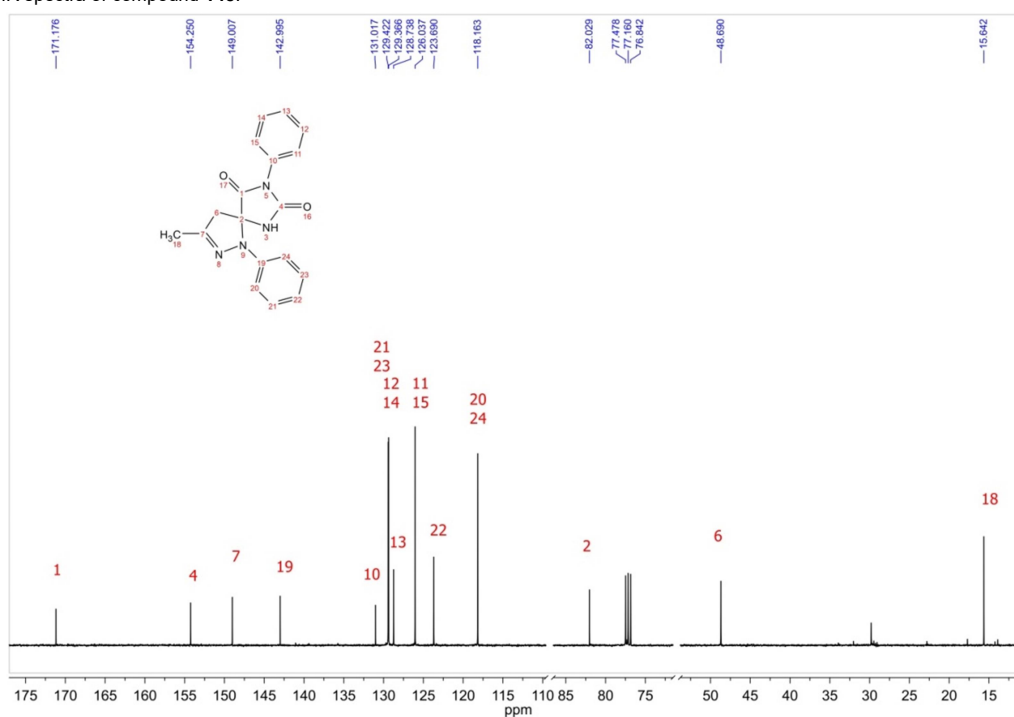


Figure S59. ¹³C NMR spectra of compound **14e**.

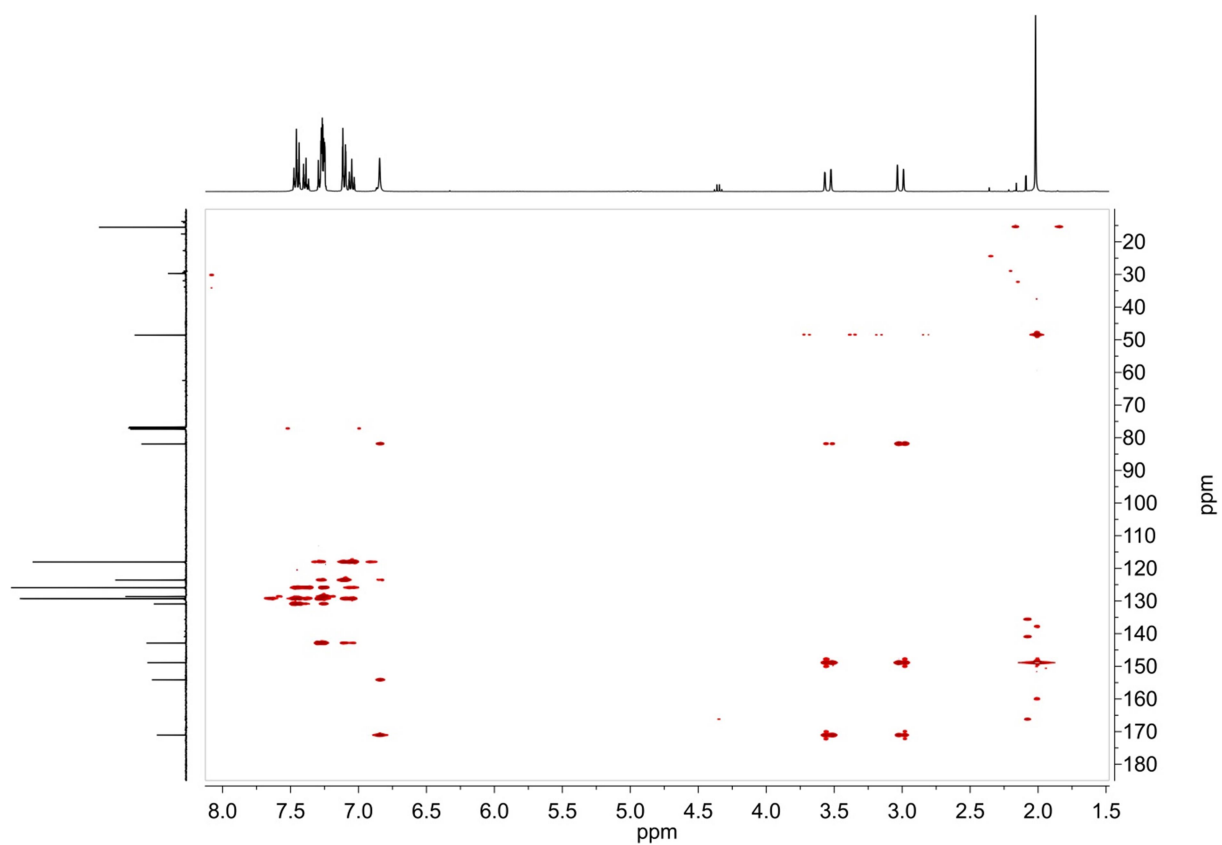


Figure S60. HMBC ^1H - ^{13}C NMR spectra of compound **14e**.

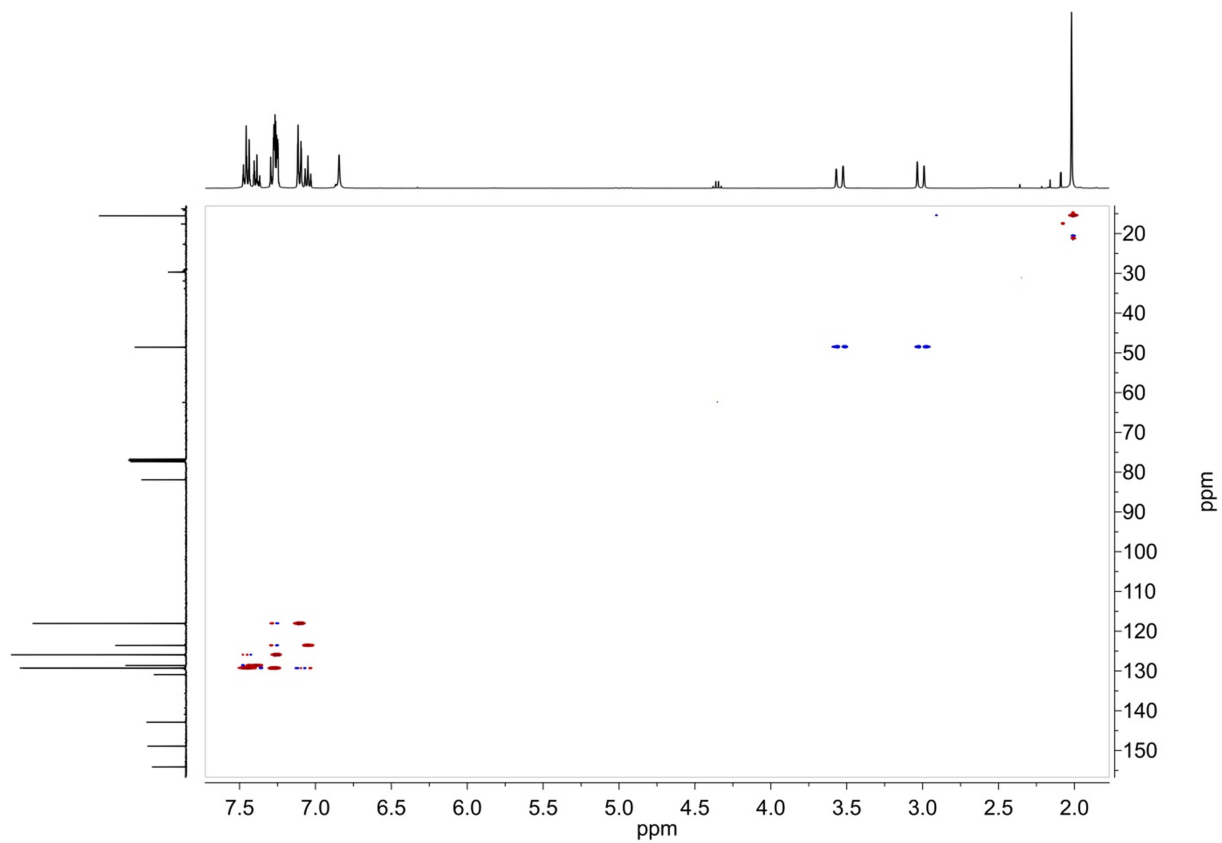


Figure S61. HSQC ^1H - ^{13}C NMR spectra of compound **14e**.

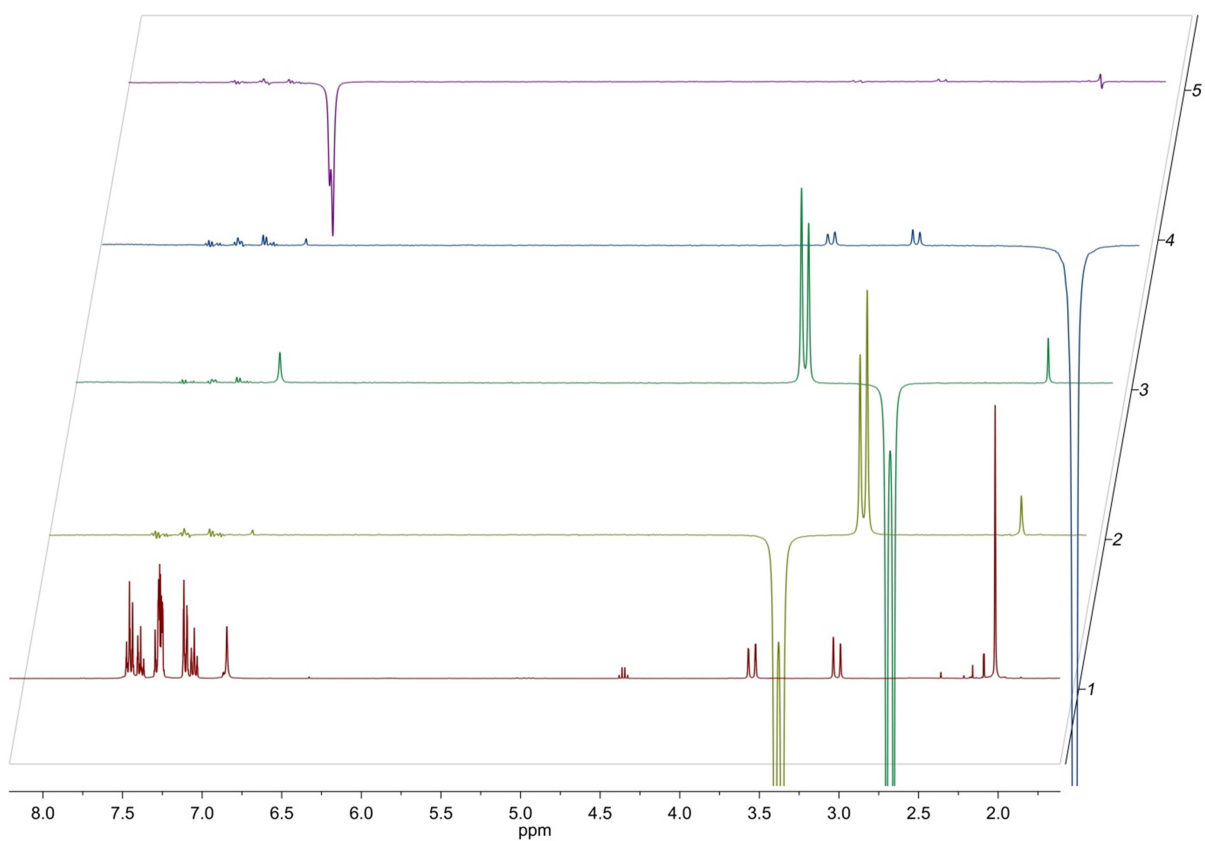


Figure S62. NOESY ^1H NMR spectra of compound **14e**.

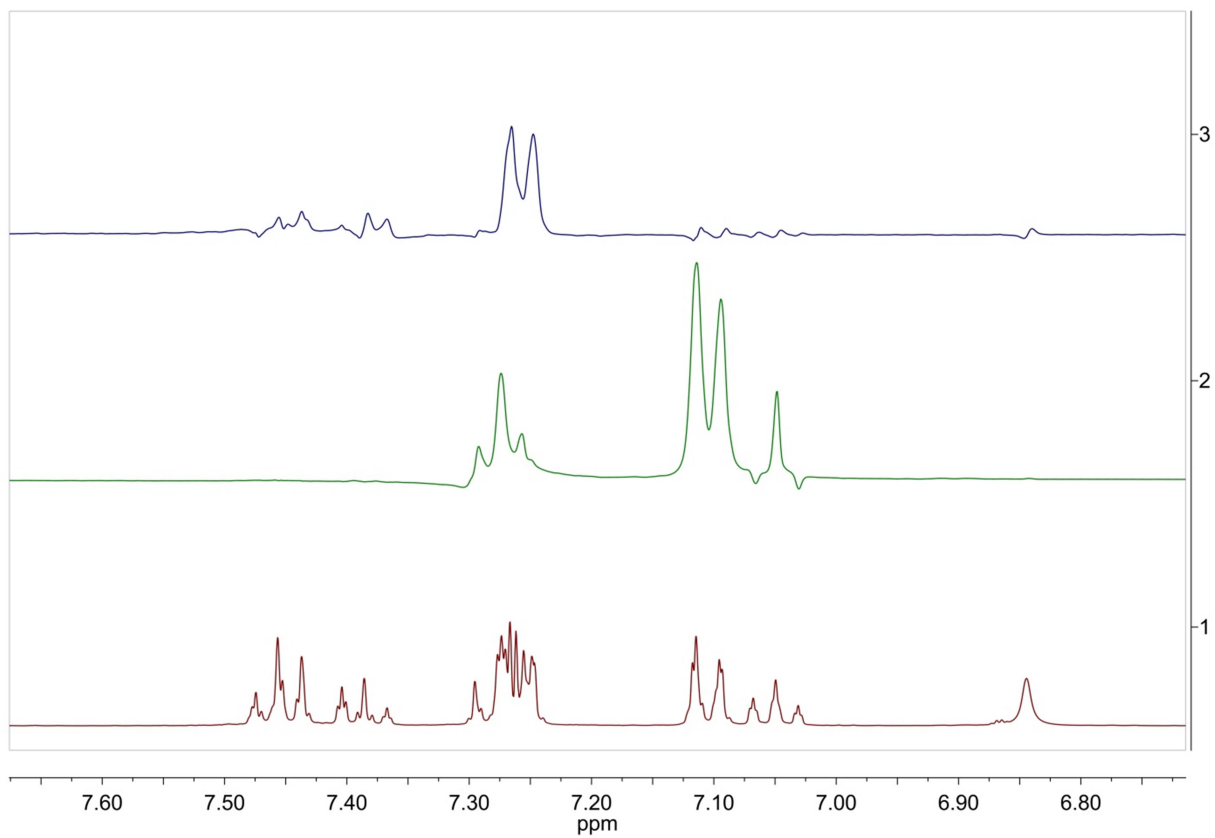


Figure S63. TOCSY ^1H NMR spectra of compound **14e**.

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