A metal-catalyzed enyne-cyclization step for the synthesis of bi- and tricyclic scaffolds amenable to molecular library production

Peng Wu,†a Michael Åxman Petersen,†a A. Emil Cohrt,†a Rico Petersen,a Rémy Morgentin,b Hugues Lemoine,b Carine Roche,b Anthony Willaume,b Mads H. Clausen*a,c and Thomas E. Nielsen*a,d

† Authors contributed equally

mhc@kemi.dtu.dk; ten@kemi.dtu.dk
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General Methods

Unless otherwise noticed, all reactions were run under an argon atmosphere. All solvents were of HPLC quality, and were typically dried over molecular sieves.

All reactions were monitored by thin layer chromatography (TLC), reversed-phase high performance liquid chromatography (RP-HPLC), and reversed-phase ultra-performance liquid chromatography mass spectrometry (RP-HPLC/MS). All yields are unoptimized and generally represent the result of a single experiment.

TLC was conducted using Merck aluminum sheets covered with silica gel C-60 F<sub>254</sub>. The plates were either visualized under UV-light (254 nm) or stained by dipping in a developing agent followed by heating. KMnO<sub>4</sub> dipping solution were used as the developing agents: KMnO<sub>4</sub> (1.5 g), K<sub>2</sub>CO<sub>3</sub> (10 g), 5% NaOH aqueous solution (2.5 mL), H<sub>2</sub>O (150 mL).

Column chromatography was performed using a glass column packed with Geduran® Si 60 silica gel (40-63 µm particles). A mixture of heptane and ethyl acetate was used as the liquid phase.

LC/MS analysis was performed on a Waters AQUITY UPLC system equipped with a C-18 column (d 1.7 µm, 2.1 × 50 mm, column temp: 65 °C), a PDA and SQD MS detector. A linear reversed phase gradient (5% to 100% organic in 2.4 min, hold for 0.1 min, total run-time 2.6 min) combining water and acetonitrile (buffered with 0.1% formic acid) was used.

RP-HPLC was conducted on a Waters Alliance 2695 RP-HPLC system using a Symmetry C-18 column (d 2.5 µm, 4.6 × 75 mm, column temp: 25 °C), with detection at 215 nm and 254 nm. 0.1% TFA in H<sub>2</sub>O (A) and 0.1% TFA in acetonitrile (B) were used (100% A to 100% B, total run-time 13 min) as the elusion phase.

<sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded using a Bruker Ascend-400 MHz instrument in DMSO-<em>d</em><sub>6</sub> or CDCl<sub>3</sub> using the residual solvent peak as the internal standard. All 13C NMR spectra were proton decoupled. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) in Hz. Multiplicities of peaks in <sup>1</sup>H NMR are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (double doublet), ddd (double double doublet) and m (multiplet).

Melting points were measured using a Stuart® SMP 30 capillary melting point apparatus.
Experimental Procedures and Characterization Data

(Z)-3-Bromocyclooctene (3)

Cyclooctene (5.90 ml, 45.4 mmol), NBS (8.08 g, 45.37 mmol), and AIBN (75 mg, 0.45 mmol) were added to CCl₄ (45 mL) under argon atmosphere and heated to 80°C for 4 h. The solution was cooled to 25°C and the solvent was removed under reduced pressure. The product was distilled at 80°C (3 Torr) to give the title product (3) as colorless oil (5.33 g, 62%).

1H NMR (400 MHz, DMSO-d₆) δ 5.75 (ddd, 1H, J = 10.5, 8.3, 1.3 Hz, CH=CH), 5.67 – 5.52 (m, 1H, CH=CH), 5.20 – 5.10 (m, 1H, CHBr), 2.33 – 1.98 (m, 3H; CH₂CHBrCH₂), 1.97 – 1.87 (m, 1H, CH₂CH=CHCH₂), 1.68 – 1.38 (m, 5H, cyclooctene CH₂), 1.31 – 1.20 ppm (m, 1H, cyclooctene CH₂);

13C NMR (100 MHz, DMSO-d₆) δ 132.9, 130.0, 50.3, 40.5, 28.6, 26.1, 25.3, 24.9.


(Z)-N-(Cyclooct-1-en-3-yl)-2-nitrobenzenesulfonamide (4)

(Z)-3-Bromocyclooctene (3) (5.33 g, 28.2 mmol) was dissolved in dry DMF (110 mL). K₂CO₃ (4.80 g, 39.5 mmol) and 2-nitrobenzenesulfonamide (6.84 g, 33.8 mmol) were added to the solution and stirred for 1h at 60°C. The reaction mixture was cooled to 21°C and diluted with EtOAc (200 mL). The product was washed with sat. aq. NH₄Cl (2×200 mL) and 1M HCl (aq.) (2×150 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuo. The product was purified by flash chromatography (1:4, EtOAc/heptane) to give the product as a pale yellow powder (4.23 g, 49%), mp 82°C – 83°C. 

1H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 1H, NH), 8.00 (dd, 1H, J = 5.9, 3.4 Hz, phenyl H), 7.92 (dd, 1H, J = 5.7, 3.2 Hz, phenyl H), 7.88 – 7.80 (m, 2H, phenyl H), 5.52 – 5.43 (m, 1H, CH=CH), 5.31 – 5.18 (m, 1H, CH=CH), 4.21 – 4.11 (m, 1H, NHCH), 2.08 – 1.87 (m, 2H, cyclooctene CH₂), 1.69 – 1.36 (m, 5H, cyclooctene CH₂), 1.36 – 1.11 (m, 3H, cyclooctene CH₂); 

13C NMR (100 MHz, DMSO-d₆) δ 147.6, 134.0, 133.3, 132.3, 130.9, 129.8, 129.2, 124.0, 51.0, 36.5, 28.7, 26.0, 25.9, 23.8. HRMS (ESI) m/z: [M+H]⁺ calcd. for C₁₄H₁₉N₂O₄S 311.1066, found 311.1063.

(Z)-N-(Cyclooct-1-en-3-yl)-N-(prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (1)
(Z)-N-(Cyclooct-1-en-3-yl)-2-nitrobenzenesulfonamide (4) (3.62 g, 11.67 mmol), and propargyl bromide (1.56 mL, 14.00 mmol), were dissolved in dry DMF (100 mL) and added K$_2$CO$_3$ (1.95 g, 14.00 mmol) under argon atmosphere. The temperature was raised to 60 °C and the reaction mixture was stirred for 1 h before sat. aq. NH$_4$Cl (100 mL) was added. The resulting mixture was extracted with EtOAc (3×100 mL) and the combined organic phases were washed with water (100 mL), then brine (100 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo, yielding desired sulfonamide (1) (4.4 g, quant.) as a yellow powder, mp 89°C – 92°C. 

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.09 (dd, 1H, $J = 7.8$, 1.5 Hz, phenyl H), 7.96 (dd, 1H, $J = 7.8$ and 1.4 Hz, phenyl H), 7.88 (td, 1H, $J = 7.6$ and 1.6 Hz, phenyl H), 7.83 (td, 1H, $J = 7.6$ and 1.5 Hz, phenyl H), 5.74 – 5.54 (m, 2H, CH=CH), 4.71 (ddd, 1H, $J = 11.9$, 7.4, 4.2 Hz, NCH), 4.28 (dd, 1H, $J = 18.5$ and 2.0 Hz, propargyl CH$_2$) and 4.23 (dd, 1H, $J = 18.5$ and 2.0 Hz, propargyl CH$_2$), 3.25 (t, 1H, J = 2.4 Hz, propargyl CH), 2.12 -1.97 (m, 2H, cyclooctene CH$_2$), 1.87 – 1.76 (m, 1H, cyclooctene CH$_2$), 1.69 – 1.51 (m, 4H, cyclooctene CH$_2$), 1.41 – 1.32 (m, 2H, cyclooctene CH$_2$), 1.30 – 1.20 (m, 1H, cyclooctene CH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 147.6, 134.7, 132.3, 132.0, 130.3, 130.0, 127.6, 124.2, 80.6, 75.1, 55.6, 33.8, 33.1, 28.5, 25.6, 25.5, 23.9. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{17}$H$_{21}$N$_2$O$_4$S 349.1222, found 349.1219.

(Z)-N-(Cyclooct-1-en-3-yl)-N-(3-iodoprop-2-yn-1-yl)-2-nitrobenzenesulfonamide (5) (4.07 g, 11.67 mmol) was dissolved in dry DMF (100 mL) under argon atmosphere and added N-iodosuccinimide (2.85 g, 12.67 mmol) and AgNO$_3$ (0.198 g, 1.17 mmol). The reaction mixture was stirred in the dark at 25°C for 2h, quenched by addition of sat. aq. Na$_2$S$_2$O$_3$ (100 mL), and extracted with EtOAc (4×50 mL). The combined organic phases were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to give desired iodide as yellow oil contaminated with succinimide and DMF. The compound was redissolved in diethyl ether (250 mL), washed with water (3×50 mL), then brine (50 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to give desired iodide (5) as a light yellow solid (3.5 g, 63%), mp 94°C – 96°C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.05 (m, 1H, phenyl H), 7.97 (m, 1H, phenyl H), 7.90-7.82 (m, 2H, phenyl H), 5.64-5.58 (m, 2H, CH=CH), 4.74 (m, 1H, NCH), 4.37 (s, 2H, propargyl CH$_2$), 2.12-1.99 (m, 2H, cyclooctene CH$_2$), 1.81-1.72 (m, 1H, cyclooctene CH$_2$), 1.67-1.50 (m, 4H, cyclooctene CH$_2$), 1.42-1.20 (m, 3H, cyclooctene CH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 147.5, 134.7, 132.2, 132.0, 130.2, 127.6, 124.2, 123.0, 130.3, 130.0, 127.6, 124.2, 80.6, 75.1, 55.6, 33.8, 33.1, 28.5, 25.6, 25.5, 23.9, 11.2. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{17}$H$_{20}$IN$_2$O$_4$S 475.0188, found 475.0185.
1-((2-Nitrophenyl)sulfonyl)-1,2,2a,4,5,6,7,8,9,9a-decahydro-4H-1-azacycloocta[cd]pentalen-4-one (6)

(Z)-N-(Cyclooct-1-en-3-yl)-N-(prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (1) (18 mg, 0.05 mmol) was dissolved in dry toluene (2 mL) at room temperature under nitrogen atmosphere and added powdered 4 Å activated molecular sieves (140 mg). Co\(_2\)(CO)\(_8\) (21 mg, 0.06 mmol) was added to the reaction mixture, which was stirred at room temperature under a 1 atm of CO for 2 d (TLC indicated full consumption of the starting enyne substrate). The mixture was filtrated, and the filtrate was concentrated in vacuo to give brown crude, which was purified by flash chromatography (1:1, EtOAc/heptane) to give the product as a white solid (17 mg, 87%), mp 121°C – 123°C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.05-8.02 (m, 1H, phenyl H), 7.68-7.65 (m, 2H, phenyl H), 7.61-7.59 (m, 1H, phenyl H), 5.95 (s, 1H, COCH=C), 4.61 (dt, 1H, \(J = 16\) Hz and \(1.2\) Hz, \(\text{CH}_2\text{NSO}_2\)), 4.34 (d, 1H, \(J = 16\) Hz, \(\text{CH}_2\text{NSO}_2\)), 3.68 (td, 1H, \(J = 10.8\) Hz and \(4.0\) Hz, cyclooctane CH), 3.05-3.00 (m, 1H, cyclooctane CH), 2.38-2.33 (m, 1H, cyclooctane CH), 2.13-2.07 (m, 1H, cyclooctane CH\(_2\)), 1.96-1.92 (m, 1H, cyclooctane CH\(_2\)), 1.79-1.76 (m, 1H, cyclooctane CH\(_2\)), 1.61-1.55 (m, 2H, cyclooctane CH\(_2\)), 1.31-1.22 (m, 5H, cyclooctane CH\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 210.8 (C=O), 175.2 (COCH=C), 148.1 (phenyl C), 148.0 (phenyl C), 133.9 (phenyl C), 131.9 (phenyl C), 130.6 (phenyl C), 124.3 (phenyl C), 124.3 (COCH=C), 62.2 (cyclooctane CH), 54.2 (cyclooctane CH), 50.4 (cyclooctane CH), 50.2 (CH\(_2\)NSO\(_2\)), 34.4 (cyclooctane CH\(_2\)), 30.6 (cyclooctane CH\(_2\)), 27.3 (cyclooctane CH\(_2\)), 25.3 (cyclooctane CH\(_2\)), 24.2(cyclooctane CH\(_2\)). HRMS (ESI) m/z: [M+H]\(^+\) calcd. for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_5\)S 377.1171, found 377.1168.

\((Z,2Z)-10-((2-Nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (7a)

(Z)-N-(Cyclooct-1-en-3-yl)-N-(prop-2-yn-1-yl)-2-nitrobenzenesulfonamide (1) (1.0 g, 2.87 mmol) and PtCl\(_2\) (38.2 mg, 0.14 mmol) was added to dry toluene (150 ml) and heated to 80°C for 3 h. The solution was concentrated in vacuo to give brown crude, which was purified by flash chromatography (1:4, EtOAc/heptane) to give the product as a white solid (17 mg, 87%), mp 121°C – 123°C.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.01 – 7.96 (m, 2H, phenyl H), 7.94 – 7.81 (m, 2H, phenyl H), 5.99 (d, 1H, \(J = 11.0\) Hz, \(\text{CH}=\text{CH}–\text{C(\text{CH}_2)=CH}\)), 5.79 (ddd, 1H, \(J = 11.1, 8.2, 6.2\) Hz, \(\text{CH}=\text{CH}–\text{C(\text{CH}_2)=CH}\)), 5.64 (s, 1H, \(\text{CH}=\text{CH}–\text{C(\text{CH}_2)=CH}\)), 4.86 (s, 1H, \(\text{SO}_2\text{NCH}\)), 4.34 (d, 1H, \(J = 14.6\) Hz, \(\text{CH}=\text{CH}–\text{C(\text{CH}_2)=CH}\)), 4.26 (dd, 1H, \(J = 14.6\) and \(4.4\) Hz, \(\text{CH}=\text{CH}–\text{C(\text{CH}_2)=CH}\)), 2.27 – 2.15 (m, 1H, cyclodecadiene CH\(_2\)), 2.09 – 1.88 (m, 2H, cyclodecadiene CH\(_2\)), 1.63 – 1.49 (m, 3H, cyclodecadiene CH\(_2\)), 1.47 – 1.34 (m, 1H, cyclodecadiene CH\(_2\)), 1.33 – 1.15 (m, 3H, cyclodecadiene CH\(_2\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 148.5, 136.5, 135.1, 134.7, 133.0, 130.9,
129.6, 129.0, 124.8, 124.2, 67.7, 58.5, 35.5, 28.5, 28.4, 25.6, 20.5; UPLC-MS (ESI) m/z: [M+H]^+ 349.2; HRMS (ESI) m/z: [M+H]^+ calcd. for C_{17}H_{21}N_{2}O_{4}S 349.1222, found 349.1238.

(1E,2E)-2-Iodo-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (7b)

(Z)-N-(Cyclooct-2-en-1-yl)-N-(3-iodoprop-2-yn-1-yl)-2-nitrobenzenesulfonamide (5) (522 mg, 1.10 mmol) was dissolved in dry CH2Cl2 (12 mL) and cooled to 5°C, before PPh3AuCl (27 mg, 5 mol%) was added, followed by AgSbF6 (42 mg, 10 mol%) dissolved in dry toluene (0.2 mL). The reaction mixture was stirred at this temperature for 1 h and then filtered. The filtrate was washed with water (10 mL) and brine (10 mL), dried (Na2SO4), and concentrated in vacuo to give vinyl iodide (7b) as light yellow semisolid (458 mg, 88%) contaminated with trace amount of catalyst. Purification by flash column chromatography (4:5, CH2Cl2/heptane) afforded pure vinyl iodide.

1H NMR (400 MHz, CDCl3): δ = 7.95 (m, 1H, phenyl H), 7.74-7.64 (m, 3H, phenyl H), 6.43 (dd, 1H, J = 6.3 and 8.1 Hz, CH=CI–C(CH2)=CH), 5.75 (m, 1H, CH=CI–C(CH2)=CH), 4.99 (m, 1H, SO2NCH), 4.54 (td, 1H, J = 14.0 and 2.1 Hz, CH=Cl–C(CH2)=CH), 4.40 (ddd, 1H, J = 14.0, 4.7, 1.6 Hz, CH=Cl–C(CH2)=CH), 2.28 -2.16 (m, 2H, cyclodecadiene CH2), 1.99-1.91 (m, 1H, cyclodecadiene CH2), 1.68-1.59 (m, 2H, cyclodecadiene CH2), 1.56-1.44 (m, 2H, cyclodecadiene CH2), 1.41-1.25 (m, 2H, cyclodecadiene CH2) 1.22-1.12 (m, 1H, cyclodecadiene CH2); 13C NMR (100 MHz, CDCl3): δ = 145.7, 138.3, 133.6, 132.4, 131.7, 130.8, 129.8, 126.7, 124.3, 85.2, 67.5, 56.7, 34.9, 29.5, 28.4, 27.6, 20.1. UPLC-MS (ESI) m/z: [M+H]^+ 475.0; HRMS (ESI) m/z: [M+H]^+ calcd. for C_{17}H_{21}N_{2}O_{4}S 475.0188, found 475.0185.

(3Z,4Z)-3-(Iodomethylene)-1-((2-nitrophenyl)sulfonyl)-2,3,3a,6,7,8,9a-octahydro-1H-cycloocta[b]pyrrole (8)

(Z)-N-(Cyclooct-2-en-1-yl)-N-(3-iodoprop-2-yn-1-yl)-2-nitrobenzenesulfonamide (5) (20 mg, 0.04 mmol) was dissolved in dry THF (1 mL), followed by the adding of Cp*RuCl(COD) (2.29 mg, 10 mol%). The reaction mixture was stirred at room temperature for 2 h and filtered through a pad of celite. The filtrate was concentrated in vacuo. Purification by flash column chromatography (1:4, EtOAc/heptane) afforded the product as a light yellow solid (12 mg, 60%), mp 136°C -139°C. 1H NMR (400 MHz, CDCl3) δ 8.02-8.00 (m, 1H, phenyl H), 7.67-7.65 (m, 2H, phenyl H), 7.60-7.57 (m, 1H, phenyl H), 5.95 (dd, 1H, J = 5.2 and 2.4 Hz, JCH=CH), 5.71-5.64 (m, 1H, CH=CH), 5.48-
5.44 (m, 1H, CH=CH), 4.19 (dt, 1H, $J = 15.6$ and 2.0 Hz, CH$_2$NSO$_2$), 4.02 (dq, 1H, $J = 15.6$ and 1.2 Hz, CH$_2$NSO$_2$), 3.38-3.34 (m, 1H, $CH=CHCHCHNSO_2$), 2.23-2.13 (m, 2H, cyclooctene CH$_2$), 2.08-2.01 (m, 1H, cyclooctene CH$_2$), 1.52-1.41 (m, 2H, cyclooctene CH$_2$), 1.21-1.14 (m, 3H, cyclooctene CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.5 ($ICH=C$), 148.2 (phenyl C), 133.8 (phenyl C), 133.4 (phenyl C), 133.3 ($CH=CH$), 131.8 (phenyl C), 130.4 (phenyl C), 126.7 ($CH=CH$), 124.2 (phenyl C), 70.2 ($ICH=C$), 58.7 (CH$_2$N), 50.4 (cyclooctene CH), 30.9 (cyclooctene CH$_2$), 27.3 (cyclooctene CH$_2$), 25.0 (cyclooctene CH$_2$), 20.9 (cyclooctene CH$_2$). HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{17}$H$_{20}$IN$_2$O$_4$S 475.0188, found 475.0185.

**1Z,2Z**-10-((2-Nitrophenyl)sulfonyl)-2-phenyl-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (9a)

![Chemical Structure](image)

**1E,2E**-2-Iodo-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 7b (507 mg, 0.9 mmol), potassium carbonate (251 mg, 1.8 mmol), Pd(II)OAc$_2$ (20 mg, 0.09 mmol), phenylboronic acid (222 mg, 1.82 mmol), S-phos (75 mg, 0.18 mmol) were dissolved in DMF (2 mL) under argon atmosphere. The reaction mixture was heated to 50°C and stirred for 2 d, before saturated NH$_4$Cl aqueous solution (25 mL) was added, followed by extraction with EtOAc (3 × 50 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried (MgSO$_4$), and concentrated in vacuo. Purification by flash column chromatography (7:13, EtOAc/heptane) afforded the desired compound as a foam (145 mg, 38%) with minor impurities. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (dd, 1H, $J = 7.3$ and 1.8 Hz, phenyl H), 7.33-7.20 (m, 5H, phenyl H), 6.31 (dd, 1H, $J = 8.3$ and 7.5 Hz, CH=CH=CHCHN), 5.56 (m, 1H), 5.10 (m, 1H), 4.51 (dd, 1H, $J = 14.4$, 4.6, 1.6 Hz, CH$_2$NSO$_2$), 4.43 (td, 1H, $J = 14.4$ and 2.1 Hz, CH$_2$NSO$_2$), 4.03-2.23 (m, 2H, cyclooctadiene CH$_2$), 2.09 (m, 1H, cyclooctadiene CH$_2$), 1.60-1.46 (m, 6H, cyclooctadiene CH$_2$), 1.30 (m, 1H, cyclooctadiene CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.4, 136.6, 134.9, 133.6, 132.9, 131.7, 131.1, 130.8, 130.3, 128.7 (2), 127.6, 127.0, 125.5 (2), 124.4, 68.1, 58.4, 34.8, 28.5, 28.4, 25.0, 18.5. UPLC-MS (ESI) m/z: [M+H]$^+$ found 425.3; HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{23}$H$_{25}$N$_2$O$_4$S 425.1535, found 425.1536.

**1Z,2Z**-2-(4-Methoxyphenyl)-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (9b)

![Chemical Structure](image)
(1E,2E)-2-Iodo-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 7b (207 mg, 0.37 mmol), potassium carbonate (103 mg, 0.74 mmol), Pd(II)OAc₂ (8 mg, 0.04 mmol), (4-methoxyphenyl)boronic acid (113 mg, 0.74 mmol), S-phos (31 mg, 0.07 mmol) was dissolved in DMF (4 mL) under argon atmosphere and heated to 50°C stirred overnight. 5% additional catalyst was added and the reaction was stirred for additional 6 h before saturated NH₄Cl aqueous solution (25 mL) was added, followed by extraction with EtOAc (3 × 50 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried (MgSO₄), and concentrated in vacuo. Purification by flash column chromatography (EtOAc/heptane, 4/6, v/v) afforded the desired compound as a foam (98 mg, 58%).

1H NMR (400 MHz, CDCl₃) δ 8.00 (dd, 1H, J = 7.5 and 1.7 Hz, phenyl H), 7.68 (m, 3H; phenyl H), 7.25 (d, 2H, J = 9.0 Hz, phenyl H), 6.81 (d, 2H, J = 9.0 Hz, phenyl H), 6.18 (dd, 1H, J = 8.2 and 7.6 Hz, CH=CC=CHCH₂NSO₂), 5.53 (m, 1H, CH=CC=CHCH₂NSO₂), 4.49 (ddd, 1H, J = 14.3, 4.6, 1.5 Hz, CH₂NSO₂), 4.41 (td, 1H, J = 14.4 and 2.1 Hz, CH₂NSO₂), 3.79 (s, 3H, OCH₃), 2.29 (m, 2H, cyclodecadiene CH₂), 2.05 (m, 1H, cyclodecadiene CH₂), 1.62-1.25 (m, 7H, cyclodecadiene CH₂); 13C NMR (100 MHz, CDCl₃) δ 159.2, 148.6, 136.0, 135.1, 133.6, 132.8, 131.7, 131.0, 130.8, 130.2, 128.6, 126.6, 124.4, 114.0, 68.1, 58.4, 55.4, 34.8, 28.4, 28.4, 24.8, 18.4; UPLC-MS (ESI) m/z: [M+H]+ found 455.3; HRMS (ESI) m/z: [M+H]+ calcd. for C₂₄H₂₇N₂O₅S 455.1640, found 455.1643.

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (9c)

The reaction mixture was heated to 50°C and stirred overnight. The resulting mixture added saturated NH₄Cl aqueous solution (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried (Na₂SO₄), and concentrated in vacuo. Purification by flash column chromatography (7:3, CH₂Cl₂/heptane) gave the desired compound as a white foam (56 mg, 55%).

1H NMR (400 MHz, CDCl₃) δ 7.64-7.59 (m, 3H, phenyl H), 7.34 (d, 1H, J = 2.1 Hz, phenyl H), 7.33 (d, 1H, J = 8.4 Hz, phenyl H), 7.16 (dd, 1H, J = 8.4 and 2.1 Hz, phenyl H), 6.32 (dd, 1H, J = 8.3 and 7.5 Hz, CH=C=CC=CHCH₂NSO₂), 5.10 (m, 1H, CH=CC=CHCH₂NSO₂), 4.39 (ddd, 1H, J = 14.5, 4.7, 1.5 Hz, CH₂NSO₂), 3.81 (s, 3H, OCH₃), 2.39-2.21 (m, 2H, cyclodecadiene CH₂), 2.08 (m, 1H, cyclodecadiene CH₂), 1.65-1.42 (m, 6H, cyclodecadiene CH₂), 1.31-1.24 (m, 1H, cyclodecadiene CH₂); 13C NMR (100 MHz, CDCl₃, 25°C, 77.0 ppm): δ = 148.6, 138.5, 134.6, 134.0, 133.8, 132.7, 132.7, 132.6, 132.0, 131.8, 131.3, 130.5, 130.2, 127.4, 124.7, 124.4, 68.1, 58.2, 34.8, 28.5, 28.2, 25.1, 18.5 ppm. UPLC-MS (ESI) m/z: [M+H]+ found 455.3; HRMS (ESI) m/z: [M+H]+ calcd. for C₂₃H₂₅N₂O₄S 453.1640, found 453.1643.
(1Z,2E)-2-(1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (9d)

The crude iodo-functionalized bicycle (9d) (106 mg, 0.223 mmol), potassium carbonate (62 mg, 0.45 mmol), Pd(II)OAc$_2$ (5 mg, 0.021 mmol), (1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)boronic acid (87 mg, 0.45 mmol), S-phos (18 mg, 0.045 mmol) dissolved in DMF (2 mL) under argon atmosphere. The reaction mixture was heated to 50°C and stirred overnight. The resulting mixture added saturated aqueous solution NH$_4$Cl (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried (MgSO$_4$) and concentrated in vacuo. Purification by flash column chromatography (9:11, EtOAc/heptane) gave desired compound as a yellow foam (64 mg, 58%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (dd, 1H, $J = 7.7$ and 1.6 Hz, phenyl H), 7.75-7.61 (m, 3H, phenyl H), 6.30 (s, 1H, pyrazolyl H), 6.14 (dd, 1H, $J = 8.7$ and 6.8 Hz, CH=C=CHCHN), 5.66 (m, 1H, CH=C=CH), 5.02 (m, 1H, CH=C=CHCHN), 4.51 (ddd, 1H, $J = 14.5$, 4.7, 1.4 Hz, CH$_2$NSO$_2$), 4.39 (td, 1H, $J = 14.5$ and 2.0 Hz, CH$_2$NSO$_2$), 3.79 (s, 3H, CH$_3$), 2.41 (m, 1H, cyclodecadiene CH$_2$), 2.18 (m, 2H, cyclodecadiene CH$_2$), 1.69-1.34 (m, 6H, cyclodecadiene CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.5, 143.2, 141.7 and 141.3 and 140.9 (2$J_{C-F} = 38$ Hz), 138.4, 134.0, 133.7, 132.3, 132.2, 131.8, 130.4, 125.6, 124.3, 122.6 and 119.9 ($^3J_{C-F} = 267$ Hz), 104.2 and 104.2 ($^3J_{C-F} = 3$ Hz), 67.8, 57.9, 38.8, 35.0, 28.5, 28.2, 25.5, 19.3. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{22}$H$_{24}$F$_3$N$_4$O$_4$S 497.1470, found 497.1475.

(1Z,2Z)-2-Phenyl-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (10a)

(1Z,2Z)-10-((2-Nitrophenyl)sulfonyl)-2-phenyl-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 9a (110 mg, 0.26 mmol) was dissolved in DMF (2 mL) and added 2-mercaptopropanoic acid (72 µl, 1.04 mmol) followed by LiOH (50 mg, 2.07 mmol). The reaction mixture was stirred at rt for 1 h, before saturated NaHCO$_3$ aqueous solution (25 mL) was added and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo to give desired amine 10a. The crude was used in the next step without further purification. UPLC-MS (ESI) m/z: [M+H]$^+$ calcd. for C$_{17}$H$_{22}$N 240.2, found 240.2.

(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (10b)
(1Z,2Z)-2-(4-Methoxyphenyl)-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 9b (510 mg, 1.12 mmol) was dissolved in DMF (5.5 ml) and added 2-mercaptoacetic acid (312 µl, 4.5 mmol) and LiOH (215 mg, 9 mmol). The reaction mixture was stirred at rt for 20 min, before saturated NaHCO₃ aqueous solution (75 mL) was added followed by extraction with EtOAc (3 × 75 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (50 mL), dried (Na₂SO₄), and concentrated in vacuo to give desired amine 10b. The crude was used in the next step without further purification. UPLC-MS (ESI) m/z: [M+H]⁺ calcd. for C₁₈H₂₄NO 270.2, found 270.2.

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (10c)

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 9c (89 mg, 0.18 mmol) was dissolved in in DMF (0.9 ml) added 2-mercaptoacetic acid (25 µl, 0.36 mmol) and LiOH (17 mg, 0.72 mmol). The reaction mixture was stirred at rt and monitored by UPLC-MS. After 1 h and 45 min the reaction was almost complete, but formation of side-product was observed. Saturated NaHCO₃ aqueous solution (25 mL) was added and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (3 × 25 mL) and brine (25 mL), dried (Na₂SO₄), and concentrated in vacuo to give desired amine 10c with some impurities. The crude was used in the next step without further purification. UPLC-MS (ESI) m/z: [M+H]⁺ calcd. for C₁₇H₂₀Cl₂N 308.1, found 308.1.

(1Z,2E)-2-(1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (10d)

(1Z,2E)-2-(1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-10-((2-nitrophenyl)sulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 9d (55 mg, 0.11 mmol) was dissolved in DMF (1 ml) and added 2-mercaptoacetic acid (31 µl, 0.44 mmol) and LiOH (21 mg, 0.89 mmol). The reaction mixture was stirred for 1 h at 25 °C, before saturated NaHCO₃ aqueous solution (25 mL) was added followed by extraction with EtOAc (3 × 25 mL). The combined organic phases were washed with water (25 mL) and brine (25 mL), dried (Na₂SO₄). Concentration in vacuo afforded the desired amine 10d, which was used in the next step without further purification. UPLC-MS (ESI) m/z: [M+H]⁺ calcd. for C₁₆H₂₁F₃N₃ 312.2, found 312.2.
(1Z,2Z)-2-(4-Methoxyphenyl)-N-phenyl-10-azabicyclo[7.2.1]dodeca-1(12),2-diene-10-carboxamide (11a)

(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10b (30 mg, 0.11 mmol) was dissolved in DMF (1 mL) and phenyl isocyanate (19 mg, 0.18 mmol) was added followed by triethylamine (16 µl, 0.11 mmol). After stirring the reaction mixture at rt for 1 h, additional 4 mg of phenyl isocyanate was added, and the reaction mixture was stirred for another 1 h, after which full conversion of the starting amine was observed as monitored by UPLC-MS. Purification by preparative HPLC (acetonitrile/water, 0.1% HCOOH) afforded the desired urea 11a (32 mg, 74%).

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{) } & \delta 7.42 (d, 2H, J = 7.6 Hz, phenyl H), 7.35 (d, 2H, J = 8.8 Hz, phenyl H), 7.28 (m, 2H, phenyl H), 7.02 (t, J = 7.4 Hz, 1H, phenyl H), 6.85 (d, 2H, J = 8.8 Hz, phenyl H), 6.21 (m, 2H, NH and CH=C–C=CHCHN), 5.67 (m, 1H, CH=C–C=CHCHN), 5.08 (m, 1H, CH=C–C=CHCHN), 4.42 (m, 2H, CH$_2$NCONH), 3.81 (s, 3H, OCH$_3$), 2.36 (m, 2H, cyclodecadiene CH$_2$), 2.09 (m, 1H, cyclodecadiene CH$_2$), 1.63-1.31 (m, 7H, cyclodecadiene CH$_2$). \\
\text{C NMR (100 MHz, CDCl}_3\text{) } & \delta 159.2, 153.4, 139.1, 136.7, 131.3, 129.0 (2), 129.0, 128.3, 126.8 (2), 123.1, 120.0, 119.7 (2), 114.0 (2), 64.7, 56.5, 55.5, 32.8, 28.6, 28.6, 25.0, 18.9. \\
\text{HRMS (ESI) m/z: } [M+H]^+ \text{ calcd. for C}_{25}\text{H}_{29}\text{N}_2\text{O}_2 \text{ 389.2229, found 389.2225.}
\end{align*}
\]

(1Z,2Z)-N-(4-Chlorophenyl)-2-(4-methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene-10-carboxamide (11b)

(1Z,2Z)-N-(4-Chlorophenyl)-2-(4-methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 11b (30 mg, 64%).

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{) } & \delta 7.38 (d, J = 8.9 Hz, 2H, phenyl H), 7.34 (d, 2H, J = 8.8 Hz, phenyl H), 7.23 (d, 2H, J = 8.8 Hz, phenyl H), 6.85 (d, 2H, J = 8.8 Hz, phenyl H), 6.21 (m, 2H, NH and CH=C–C=CHCHN), 5.68 (m, 1H, CH=C–C=CHCHN), 5.07 (m, 1H, CH=C–C=CHCHN), 4.42 (m, 2H, CH$_2$NCONH), 3.80 (s, 3H, OCH$_3$), 2.34 (m, 2H, cyclodecadiene CH$_2$),
\end{align*}
\]
2.09 (m, 1H, cyclodecadiene CH$_2$), 1.63-1.33 (m, 7H, cyclodecadiene CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.3, 153.1, 137.8, 136.6, 131.3, 129.0 (2), 128.4, 127.9, 126.8 (2), 121.2, 120.8 (2), 114.0 (2), 64.8, 56.5, 55.5, 32.8, 28.6, 28.6, 25.0, 19.0. HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{25}$H$_{28}$ClN$_2$O$_2$ 423.1839, found 423.1837.

(1Z,2Z)-10-(4-Methoxybenzyl)-2-phenyl-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (12a)

(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10a (27 mg, 0.11 mmol) was dissolved in CH$_2$Cl$_2$ (1 mL) and added AcOH (1.3 µl, 0.022 mmol), sodium triacetoxyhydroborate (71 mg, 0.33 mmol), and anisaldehyde (26 mg, 0.19 mmol). The reaction mixture was stirred overnight at rt, before water was added followed by extraction with CH$_2$Cl$_2$ (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification by flash column chromatography (5:25:75, triethylamine/EtOAc/heptane) afforded desired amine 12a (16 mg, 36%) with trace impurities. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, $J$ = 7.6 Hz, 2H, phenyl H), 7.30 (m, 4H, phenyl H), 7.20 (m, 1H, phenyl H), 6.85 (d, 2H, $J$ = 8.6 Hz, phenyl H), 6.19 (dd, 1H, $J$ = 8.4 and 6.8 Hz, CH=C–C=CHCHN), 5.61 (m, 1H, CH=C–C=CHCHN), 4.11 (m, 1H, CH=C–C=CHCHN), 3.93 (d, 1H, $J$ = 13.5 Hz, benzyl CH$_2$), 3.91 (d, 1H, $J$ = 13.5 Hz, benzyl CH$_2$), 3.82 (m, 1H, CH$_2$), 3.80 (s, 3H, OCH$_3$), 3.60 (td, 1H, $J$ = 14.2 and 2.5 Hz, CH=CCH$_3$N), 2.43 (m, 1H, cyclodecadiene CH$_2$), 2.04 (m, 1H, cyclodecadiene CH$_2$), 1.72 (m, 2H, cyclodecadiene CH$_2$), 1.64-1.30 (m, 6H, cyclodecadiene CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.6, 139.6, 138.5, 136.9, 133.4, 129.7, 129.5, 128.4, 128.4, 127.0, 125.8, 113.7, 70.4, 64.0, 58.7, 55.4, 34.8, 28.9, 28.5, 25.7, 20.0; HRMS (ESI) m/z: [M+H]$^+$ calcd. for C$_{25}$H$_{30}$NO 360.2327, found 360.2342.

(1Z,2Z)-10-Benzyl-2-(4-methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (12b)

(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10b (30 mg, 0.11 mmol), AcOH (1.3 µl, 0.022 mmol), sodium triacetoxyhydroborate (71 mg, 0.33 mmol), and benzaldehyde (18 mg, 0.17 mmol) were dissolved in DMA (1 mL). The reaction mixture was stirred at rt overnight. Purification by preparative HPLC (acetonitrile/H$_2$O, 0.1% HCOOH) afforded amine 12b (23 mg, 57%) with traces of HCOOH. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.53 (m, 2H, phenyl H), 7.43
(m, 3H, phenyl H), 7.08 (d, 2H, \(J = 8.8\) Hz, phenyl H), 6.81 (d, 2H, \(J = 8.8\) Hz, phenyl H), 6.21 (t, 1H, \(J = 8.0\) Hz, CH=\(-\)C=CHCHN), 5.67 (m, 1H, CH=\(-\)C=CHCHN), 4.71 (d, 1H, \(J = 16.4\) Hz, CH=CH=\(-\)CHCHN), 4.62 (m, 1H, CH=\(-\)C=CHCHN), 4.54 (d, 1H, \(J = 13.0\) Hz, benzyl CH\(_2\)), 4.26 (d, 1H, \(J = 13.0\) Hz, benzyl CH\(_2\)), 4.13 (d, 1H, \(J = 13.0\) Hz, benzyl CH\(_2\)), 3.89 (dd, 1H, \(J = 16.4\) and \(2.0\) Hz, CH=C\(-\)CH\(_2\)), 3.81 (s, 3H, OCH\(_3\)), 2.30-2.11 (m, 3H, cyclodecadiene CH\(_2\)), 1.71-1.25 (m, 7H, cyclodecadiene CH\(_2\)).

\[\text{13}^C\text{ NMR (100 MHz, CDCl}_3\text{)} \delta 166.2, 159.4, 135.3, 134.8, 130.8, 130.7, 130.3, 129.9, 129.7, 129.4, 129.1, 126.7, 114.1, 72.3, 60.8, 59.4, 55.5, 30.7, 28.2, 27.8, 24.6, 19.6; \text{HRMS (ESI)} \text{ m/z: [M+H]+ calcd. for C}_{25}\text{H}_{30}\text{NO}} 360.2327, \text{ found 360.2342.}

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-(pyridin-2-ylmethyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (12c)

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (12c) was dissolved in CH\(_2\)Cl\(_2\) (4 ml) and added 4Å molecular sieves, picolinaldehyde (30 mg, 0.28 mmol), and sodium triacetoxyhydroborate (44 mg, 0.21 mmol). The reaction mixture was stirred at rt for 1 h before being diluted with CH\(_2\)Cl\(_2\) (25 mL). The organic phase was washed with water (25 mL) and brine (25 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. Purification by flash column chromatography (1:2:18, triethylamine/EtOAc/heptane) afforded the desired compound 12c with minor impurities (10 mg, 24%). \(\text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 8.54 (d, 1H, \(J = 4.6\) Hz, pyridinyl H), 7.69 (m, 1H, pyridinyl H), 7.59 (m, 1H, pyridinyl H), 7.43 (d, 1H, \(J = 1.2\) Hz, phenyl H), 7.32 (d, 1H, \(J = 8.4\) Hz, phenyl H), 7.19 (m, 2H, phenyl and pyridinyl H), 6.22 (m, 1H, CH=\(-\)C=CHCHN), 5.64 (m, 1H, CH=\(-\)C=CHCHN), 4.35-4.02 (m, 4H, CH=C\(-\)CH\(_2\)), 3.74 (d, 1H, \(J = 13.7\) Hz, CH=C\(-\)CH\(_2\)), 2.42 (m, 1H, cyclodecadiene CH\(_2\)), 2.07 (m, 1H, cyclodecadiene CH\(_2\)), 1.89 (m, 1H, cyclodecadiene CH\(_2\)), 1.69-1.25 (m, 7H, cyclodecadiene CH\(_2\)). \(\text{13C NMR (100 MHz, CDCl}_3\text{)} \delta 149.1, 149.0, 137.2, 136.6, 132.4, 130.8, 130.7, 130.3, 132.9, 129.9, 129.4, 129.1, 126.7, 114.1, 72.3, 60.8, 59.4, 55.5, 30.7, 28.2, 27.8, 24.6, 19.6; \text{HRMS (ESI)} \text{ m/z: [M+H]+ calcd. for C}_{23}\text{H}_{25}\text{Cl}_2\text{N}_2\text{S} 399.1395, \text{ found 399.1401.}

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-(phenylsulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (14a)

(1Z,2Z)-2-(3,4-Dichlorophenyl)-10-(phenylsulfonyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene (14a) was dissolved in CH\(_2\)Cl\(_2\) (4 ml) and added 4Å molecular sieves, picolinaldehyde (30 mg, 0.28 mmol), and sodium triacetoxyhydroborate (44 mg, 0.21 mmol). The reaction mixture was stirred at rt for 1 h before being diluted with CH\(_2\)Cl\(_2\) (25 mL). The organic phase was washed with water (25 mL) and brine (25 mL), dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. Purification by flash column chromatography (1:2:18, triethylamine/EtOAc/heptane) afforded the desired compound 14a with minor impurities (10 mg, 24%). \(\text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 8.54 (d, 1H, \(J = 4.6\) Hz, pyridinyl H), 7.69 (m, 1H, pyridinyl H), 7.59 (m, 1H, pyridinyl H), 7.43 (d, 1H, \(J = 1.2\) Hz, phenyl H), 7.32 (d, 1H, \(J = 8.4\) Hz, phenyl H), 7.19 (m, 2H, phenyl and pyridinyl H), 6.22 (m, 1H, CH=\(-\)C=CHCHN), 5.64 (m, 1H, CH=\(-\)C=CHCHN), 4.35-4.02 (m, 4H, CH=C\(-\)CH)\(_2\)), 3.74 (d, 1H, \(J = 13.7\) Hz, CH=C\(-\)CH\(_2\))NCH\(_2\)), 2.42 (m, 1H, cyclodecadiene CH\(_2\)), 2.07 (m, 1H, cyclodecadiene CH\(_2\)), 1.89 (m, 1H, cyclodecadiene CH\(_2\)), 1.69-1.25 (m, 7H, cyclodecadiene CH\(_2\)). \(\text{13C NMR (100 MHz, CDCl}_3\text{)} \delta 149.1, 149.0, 137.2, 136.6, 132.4, 130.8, 130.7, 130.3, 129.7, 124.9, 122.5, 122.0, 121.7, 121.0, 119.1, 70.8, 63.7, 60.6, 31.6, 28.5, 28.1, 25.4, 19.8; \text{HRMS (ESI)} \text{ m/z: [M+H]+ calcd. for C}_{23}\text{H}_{25}\text{Cl}_2\text{N}_2\text{S} 399.1395, \text{ found 399.1401.}

\[\text{S14}\]
Triethylamine (19 µl, 0.14 mmol) and benzenesulfonyl chloride (15 µl, 0.14 mmol) were dissolved in dry CH₂Cl₂ (0.4 mL) under argon atmosphere and cooled to 0 °C. A solution of amine 10c (0.9 mmol) in CH₂Cl₂ (0.5 mL) was added and the reaction mixture was allowed to warm to rt. After stirring for 1 h the reaction mixture was concentrated in vacuo. Purification by flash column chromatography (3:17, EtOAc/heptane) afforded the desired sulfonamide 14a (12 mg, 30%) with solvent traces.

1H NMR (400 MHz, CDCl₃) δ 7.87 (m, 2H, phenyl H), 7.65 (m, 1H, phenyl H), 7.57 (m, 2H, phenyl H), 7.25 (d, 1H, J = 8.4 Hz, phenyl H), 7.10 (d, 1H, J = 2.2 Hz, phenyl H), 6.89 (dd, 1H, J = 8.4 and 2.2 Hz, phenyl H), 6.28 (dd, 1H, J = 8.2 and 7.3 Hz, CH=C–C=CHCHN), 5.45 (m, 1H, CH=C–C=CHCHN), 4.89 (m, 1H, CH=C–C=CHCHN), 4.34 (ddd, 1H, J = 15.0, 4.6, 1.6 Hz, CH₂NSO₂), 4.22 (td, 1H, J = 15.0 and 2.0 Hz, CH₂NSO₂), 2.28 (m, 2H, cyclodecadiene CH₂), 2.06 (m, 1H, cyclodecadiene CH₂), 1.54 (m, 6H, cyclodecadiene CH₂), 1.23 (m, 1H, cyclodecadiene CH₂).

13C NMR (100 MHz, CDCl₃) δ 138.4, 138.0, 134.5, 134.3, 133.0, 132.7, 132.4, 132.2, 131.3, 130.4, 129.4, 127.3, 127.2, 124.5, 67.9, 58.2, 35.7, 28.6, 28.3, 25.2, 19.0; HRMS (ESI) m/z: [M+H]+ calcd. for C₂₃H₂₄Cl₂NO₂S 448.0905, found 448.0900.

1-(4-(((1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-10-yl)sulfonyl)phenyl)ethan-1-one (14b)

Triethylamine (23 µl, 0.16 mmol) and 4-acetylbenzenesulfonyl chloride (35 mg, 0.16 mmol) were dissolved in dry CH₂Cl₂ (0.5 mL) and the reaction mixture was cooled to 0 °C. (1Z,2Z)-2-(4-methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10b (29 mg, 0.11 mmol) dissolved in dry CH₂Cl₂ (0.5 mL) was added to the reaction mixture, which was stirred and allowed to warm to rt over 1 h. Concentration in vacuo and purification by preparative HPLC (acetonitrile/H₂O, 0.1% HCCOH) afforded pure sulfonamide 14b (20 mg, 41%). 1H NMR (400 MHz, CDCl₃) δ 8.11 (d, 2H, J = 8.5 Hz, phenyl H), 7.96 (d, 2H, J = 8.5 Hz, phenyl H), 6.97 (d, 2H, J = 8.8 Hz, phenyl H), 6.13 (dd, 1H, J = 8.1 and 7.5 Hz, CH=C–C=CHCHN), 5.43 (m, 1H, CH=C–C=CHCHN), 4.90 (m, 1H, CH=C–C=CHCHN), 4.35 (ddd, 1H, J = 14.8, 4.5, 1.5 Hz, CH₂NSO₂), 4.24 (td, 1H, J = 14.8 and 1.9 Hz, CH₂NSO₂), 3.78 (s, 3H, OCH₃), 2.68 (s, 3H, COCH₃), 2.25 (m, 2H, cyclodecadiene CH₂), 2.02 (m, 1H, cyclodecadiene CH₂), 1.63-1.36 (m, 6H, cyclodecadiene CH₂), 1.26 (m, 1H, cyclodecadiene CH₂). 13C NMR (100 MHz, CDCl₃) δ 197.0, 159.2, 142.3, 140.1, 135.7, 135.4, 130.9, 130.7, 129.1, 128.4, 127.7, 126.4, 113.9, 68.0, 58.3, 55.4, 35.6, 28.6, 28.5, 27.0, 25.0, 19.0; HRMS (ESI) m/z: [M+H]+ calcd. for C₂₃H₂₄Cl₂NO₄S 452.1895, found 452.1897.

(3-Fluorophenyl)((1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-10-yl)methanone (15a)
(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10b (30 mg, 0.11 mmol), 3-fluorobenzoic acid (20 mg, 0.14 mmol), N-ethyl-N-diisopropylamine (24 µL, 0.14 mmol) were dissolved in dry DMF (1 ml) under argon atmosphere. TBTU (45 mg, 0.14 mmol) was added to the reaction mixture which was stirred for 10 min. Purification by preparative HPLC (acetonitrile/H\textsubscript{2}O, 0.1% HCOOH) afforded the desired amide 15a (28 mg, 64%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) Rotamers 2/1. Rotamer I: \(\delta 7.45-7.25\) (m, 5H, phenyl H), 7.12 (m, 1H, phenyl H), 6.87 (d, 2H, \(J = 8.8\) Hz, phenyl H). 6.20 (m, 1H, CH=CH=CHCHN), 5.39 (m, 1H, \(CH=CH=CHCHN\)), 4.47 (ddd, 1H, \(J = 14.8, 4.0, 1.4\) Hz, CH\textsubscript{2}NCO), 4.17 (d, 1H, \(J = 14.9\) Hz, CH\textsubscript{2}NCO), 3.78 (s, 3H, OCH\textsubscript{3}), 2.58 (m, 1H, cyclodecadiene CH\textsubscript{2}), 2.31 (m, 1H, cyclodecadiene CH\textsubscript{2}), 2.09 (m, 1H, cyclodecadiene CH\textsubscript{2}), 1.69-1.14 (m, 7H, cyclodecadiene CH\textsubscript{2}).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}), major rotamer: 168.5 and 168.5 (\(4J_{C,F} = 2\) Hz), 163.8 and 161.3 (\(1J_{C,F} = 246\) Hz), 159.2, 139.2 and 139.1 (\(3J_{C,F} = 8\) Hz), 136.6, 134.4, 131.8, 131.1 and 130.7 (\(2J_{C,F} = 22\) Hz), 116.9, 114.4 and 114.2 (\(2J_{C,F} = 22\) Hz), 114.0 (2), 65.0, 59.4, 55.4, 32.2, 28.9, 28.6, 25.0, 19.3. HRMS (ESI) m/z: [M+H]\textsuperscript{+} calcd. for C\textsubscript{25}H\textsubscript{27}FNO\textsubscript{2} 392.2026, found 392.2029.

Cyclopropyl((1Z,2Z)-2-(4-methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-10-yl) methanone (15b)

(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10b (30 mg, 0.11 mmol), cyclopropanecarboxylic acid (12 mg, 0.14 mmol), and N-ethyl-N-diisopropylamine (24 µL, 0.14 mmol) were dissolved in dry DMF (1 ml) under argon atmosphere. TBTU (45 mg, 0.14 mmol) was added to the reaction mixture, which was stirred for another 10 min. Purification by preparative HPLC (acetonitrile/H\textsubscript{2}O, 0.1% HCOOH) afforded amide 15b (28 mg, 75%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}), rotamers 1:1, \(\delta 7.37\) (d, 2H, \(J = 8.8\) Hz, aromatic H), 6.84 (d, 2H, \(J = 8.8\) Hz, aromatic H), 6.19 (m, 1H, CH=CH=CHCHN), 5.65 and 5.57 (m, 1H, \(CH=CH=CHCHN\)), 5.11 (m, 1H, \(CH=CH=CHCHN\)), 4.63-4.33 (m, 2H, CH\textsubscript{2}NCO), 3.80/3.79 (s, 3H, OCH\textsubscript{3}), 2.50-2.28 (m, 2H, cyclodecadiene CH\textsubscript{2}), 2.10-2.04 (m, 1H, cyclopropyl CH), 1.73-1.24 (m, 8H, cyclodecadiene CH\textsubscript{2}), 1.13-0.74 (m, 4H, cyclopropyl CH\textsubscript{2}). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}), rotamer one: \(\delta 172.3, 159.1, 198.4, 159.2, 159.1, 139.2, 139.1, 136.6, 134.4, 131.8, 131.1, 130.7, 116.9, 114.4, 114.2, 72, 65.0, 59.4, 55.4, 32.2, 28.9, 28.6, 25.0, 19.3. HRMS (ESI) m/z: [M+H]\textsuperscript{+} calcd. for C\textsubscript{25}H\textsubscript{27}F2NO\textsubscript{3} 394.1935, found 394.1936.
137.1, 135.9, 131.6, 130.6, 127.5, 126.7 (2), 113.9 (2), 64.3, 57.0, 55.4, 34.2, 28.7, 28.4, 25.0, 18.9, 12.7, 8.2, 7.7; rotamer two: 171.9, 159.2, 136.8, 134.1, 132.3, 131.4, 128.3, 126.8 (2), 114.0 (2), 64.8, 57.2, 55.4, 31.8, 28.6, 28.3, 24.5, 18.3, 12.7, 7.8, 7.4. HRMS (ESI) m/z: [M+H]+ calcd. for C_{22}H_{28}N_{2}O_{3} 338.2120, found 338.2128.

\[ \text{t-Butyl (2-((1Z,2Z)-2-(4-methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-10-yl)-2-oxoethyl)carbamate (15c)} \]

(1Z,2Z)-2-(4-Methoxyphenyl)-10-azabicyclo[7.2.1]dodeca-1(12),2-diene 10b (30 mg, 0.11 mmol), (tert-butoxycarbonyl)glycine (24 mg, 0.14 mmol), and N-ethyl-N-diisopropylamine (24 µL, 0.14 mmol) were dissolved in dry DMF (1 ml) under argon atmosphere. TBTU (45 mg, 0.14 mmol) was added to the reaction mixture, which was stirred for another 10 min. Purification by preparative HPLC (acetonitrile/H_{2}O, 0.1% HCOOH) afforded pure amide 15c (30 mg, 63%). \(^1\)H NMR (400 MHz, CDCl\(_3\)), rotamers 2:1, major rotamer: \(\delta\) 7.32 (d, 2H, \(J = 8.8\) Hz, phenyl H), 6.85 (d, 2H, \(J = 8.8\) Hz, phenyl H), 6.21-6.19 (m, 1H, CH=C–C–CHCHN), 5.66 (d, 1H, \(J = 1.6\) Hz CH=C–C=CHCHN), 5.48 (br s, 1H, NH), 5.14 (m, 1H, CH=C–C=CHCHN), 4.40-4.30 (m, 2H, CH\(_2\)NCO), 3.92-3.88 (m, 2H, NCOCH\(_2\)), 3.81 (s, 3H, OCH\(_3\)), 2.52-2.46 (m, 1H, cyclodecadiene CH\(_2\)), 2.30-2.07 (m, 2H, cyclodecadiene CH\(_2\)), 1.60-1.53 (m, 3H, cyclodecadiene CH\(_2\)), 1.44 (s, 9H, t-butyl CH\(_3\)), 1.42-1.28 (m, 4H, cyclodecadiene CH\(_2\)). Minor rotamer: \(\delta\) 7.31 (d, 2H, \(J = 8.8\) Hz, phenyl H), 6.84 (d, 2H, \(J = 8.8\) Hz, phenyl H), 6.20-6.18 (m, 1H, CH=C–C=CHCHN), 5.56 (d, 1H, \(J = 1.6\) Hz, CH=C–C=CHCHN), 5.24 (br s, 1H, NH), 4.89 (m, 1H, CH=C–C=CHCHN), 4.55-4.34 (m, 2H, CH\(_2\)NCO), 4.10-3.92 (m, 2H, NCOCH\(_2\)), 3.80 (s, 3H, OCH\(_3\)), 2.31-2.07 (m, 3H, cyclodecadiene CH\(_2\)), 1.60-1.53 (m, 3H, cyclodecadiene CH\(_2\)), 1.44 (s, 9H, t-butyl CH\(_3\)), 1.42-1.28 (m, 4H, cyclodecadiene CH\(_2\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)), major rotamer: \(\delta\) 166.7, 159.3, 156.0, 136.4, 134.0, 131.9, 128.5, 126.7 (2), 114.0 (2), 79.7, 65.2, 55.8, 55.4, 43.1, 31.5, 28.5 (3), 28.3-28.2, 24.9, 19.0. Minor rotamer: \(\delta\) 167.4, 159.2, 156.0, 136.7, 135.6, 131.3, 130.3, 127.7, 126.7 (2), 113.9 (2), 79.8, 64.0, 56.9, 55.4, 42.8, 33.3, 28.5 (3), 28.3, 28.2, 24.5, 18.3. HRMS (ESI) m/z: [M+H]+ calcd. for C\(_{25}\)H\(_{35}\)N\(_2\)O\(_4\) 427.2597, found 427.2598 and 327.2067.

\[((1Z,2E)-2-(1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-10-yl)(phenyl)methanone (15d)\]

\[((1Z,2E)-2-(1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-10-azabicyclo[7.2.1]dodeca-1(12),2-dien-10-yl)(phenyl)methanone (15d)\]

S17
(1Z,2E)-2-(1-Methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-10-azabicyclo[7.2.1]dodeca-1(12),2-
diene 10d (34 mg, 0.11 mmol) was dissolved in dry DMF (1 mL) under argon atmosphere. TBTU
to (44 mg, 0.14 mmol) and DIPEA (18 mg, 0.14 mmol) were added. The reaction mixture was stirred
for 1.5 h, before saturated NH₄Cl aqueous solution (25 mL) was added, followed by extraction with
EtOAc (3 x 25 mL). The combined organic phases were washed with brine (25 mL), dried
(MgSO₄), and concentrated in vacuo. Purification by flash column chromatography (11: 9,
EtOAc/heptane) afforded the desired amide 15d (24 mg, 53%) with trace impurities. ¹H NMR (400
MHz, CDCl₃), rotamers 5:3, major rotamer, δ 7.53-7.40 (m, 5H, phenyl H), 6.34 (s, 1H, pyrazolyl
H), 6.17-6.10 (m, 1H, CH=C–C=CHCHN), 5.87 (m, 1H, CH=C–C=CHCHN), 5.38 (m, 1H, 
CH=C–C=CHCHN), 4.51 (dd, 1H, J = 16.8 and 2.8 Hz, CH₂NCO), 4.14 (d, 1H, J = 16.8 Hz, 
CH₂NCO), 3.82 (s, 3H, NCH₃), 2.57-2.37 (m, 2H, cyclodecadiene CH₂), 2.23-2.18 (m, 1H, 
cyclodecadiene CH₂), 1.71-1.55 (m, 4H, cyclodecadiene CH₂), 1.37-1.21 (m, 3H, cyclodecadiene
CH₂). ¹³C NMR (100 MHz, CDCl₃), major rotamer, δ 170.3, 141.4 and 141.0 (²J_C-F = 35 Hz), 139.9,
138.2, 136.9, 133.3, 133.2, 130.2, 128.7 (2), 127.0 (2), 126.3, 122.6 and 119.9 (²J_C-F = 267 Hz),
104.3 and 104.3 (³J_C-F = 3 Hz), 64.7, 59.1, 38.8, 32.5, 28.9, 28.4, 25.8, 20.2. HRMS (ESI) m/z:
[M+H]⁺ calcd. for C₂₃H₂₅F₃N₃O 416.1949, found 416.1948. HRMS (ESI) m/z: [M+H]⁺ calcd. for
C₂₃H₂₅F₃N₃O 416.1949, found 416.1948.
Characterization Spectra

3, $^1$H NMR (400 MHz, DMSO-$d_6$):
3, $^{13}$C NMR (100 MHz, DMSO-$d_6$):
4. \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): 

![NMR Spectrum]

![Chemical Structure]

\( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)): 

- 9.5, 9.0 ppm
- 8.5, 8.0 ppm
- 7.5, 7.0 ppm
- 6.5, 6.0 ppm
- 5.5, 5.0 ppm
- 4.5, 4.0 ppm
- 3.5, 3.0 ppm
- 2.5, 2.0 ppm
- 1.5, 1.0 ppm

ppm
4. $^{13}$C NMR (100 MHz, DMSO-$d_6$):

![Chemical structure diagram]
1. $^1$H NMR (400 MHz, DMSO-$d_6$): 

![NMR spectrum diagram](attachment:image.png)
1, $^{13}$C NMR (100 MHz, DMSO-$d_6$):
5, $^1$H NMR (400 MHz, DMSO-$d_6$):
5, $^{13}$C NMR (100 MHz, DMSO-$d_6$):

![NMR spectrum diagram]
$^6$H NMR (400 MHz, CDCl$_3$):
$\text{6, }^{13}\text{C NMR (100 MHz, CDCl}_3\text{)}$: 

![Diagram of 13C NMR spectrum]
6. COSY (400 MHz, CDCl₃):
6. HSQC (400 MHz, CDCl$_3$):
6. HMBC (400 MHz, CDCl$_3$):
6, H2BC (400 MHz, CDCl$_3$):
7a. $^1$H NMR (400 MHz, DMSO-$d_6$):
$^{13}$C NMR (100 MHz, DMSO-$d_6$)

7a.
7b, $^1$H NMR (400 MHz, CDCl$_3$):
$7b$, $^{13}$C NMR (100 MHz, CDCl$_3$):
$^1$H NMR (400 MHz, CDCl$_3$):
8. $^{13}$C NMR (100 MHz, CDCl$_3$):
8. COSY (400 MHz, CDCl₃):
8, HSQC (400 MHz, CDCl$_3$):
8, HMBC (400 MHz, CDCl$_3$):
8, H2BC (400 MHz, CDCl$_3$):
9a, $^1$H NMR (400 MHz, CDCl$_3$):
9a, $^{13}$C NMR (100 MHz, CDCl$_3$):
9b, $^1$H NMR (400 MHz, CDCl$_3$):
9b, $^{13}$C NMR (100 MHz, CDCl$_3$):
9c, $^1$H NMR (400 MHz, CDCl$_3$):
9c, $^{13}$C NMR (100 MHz, CDCl$_3$):
9d, $^1$H NMR (400 MHz, CDCl$_3$):
9d, $^{13}$C NMR (100 MHz, CDCl$_3$):
9d. $^{13}$C NMR (100 MHz, CDCl$_3$), partially enlarged showing the C-F splitting peaks (100-150 ppm):
11a, $^1$H NMR (400 MHz, CDCl$_3$):
$^{13}$C NMR (100 MHz, CDCl$_3$):
11b. $^1$H NMR (400 MHz, CDCl$_3$):
11b. $^{13}$C NMR (100 MHz, CDCl$_3$):
12a, $^1$H NMR (400 MHz, CDCl$_3$):
12a, $^{13}$C NMR (100 MHz, CDCl$_3$):
12b. $^1$H NMR (400 MHz, CDCl$_3$):
12b. $^{13}$C NMR (100 MHz, CDCl$_3$):
12c, $^1$H NMR (400 MHz, CDCl$_3$):
$^{13}$C NMR (100 MHz, CDCl$_3$):
14a, $^1$H NMR (400 MHz, CDCl$_3$):
14a. $^{13}$C NMR (100 MHz, CDCl$_3$):
14b. $^1$H NMR (400 MHz, CDCl$_3$):
14b. $^{13}$C NMR (100 MHz, CDCl$_3$):
15a, $^1$H NMR (400 MHz, CDCl$_3$):
15a, $^{13}$C NMR (100 MHz, CDCl$_3$):
15a. $^{13}$C NMR (100 MHz, CDCl$_3$), partially enlarged showing C-F splitting peaks (120-140 ppm):
15b. $^1$H NMR (400 MHz, CDCl$_3$):
15b. $^{13}$C NMR (100 MHz, CDCl$_3$):
$^{15c, 1}H$ NMR (400 MHz, CDCl$_3$):
$^{13}$C NMR (100 MHz, CDCl$_3$):
15d, $^1$H NMR (400 MHz, CDCl$_3$): 

![NMR Spectrum Image]
15d, $^{13}$C NMR (100 MHz, CDCl$_3$):