Electronic Supplementary Information

Ynamides enabled 6-, 7-, and 8-endo-dig iodocyclization of ethoxyethyl ethers: rapid construction of medium-sized oxacycles at room temperature

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Scheme S1: Comparison of Reactivity between Ynamides and Other Alkynes

Our rapid and regioselective iodocyclization of ynamide 1 was characterized by comparing with other substrates (Scheme S1). Iodocyclization of ynamide 1a’, having TBS ether as O-nucleophile, also afforded 2a in high yield, albeit trace amount of unreacted 1a’ was observed when reaction was quenched 3 seconds later. Thus, ethoxyethyl group was better leaving group than TBS group in iodocyclization (optimization of protecting group for hydroxyl group, also see: T. Okitsu, D. Nakazawa, R. Taniguchi, A. Wada, Org. Lett. 2008, 10, 4967). Iodocyclization of phenyl-substituted alkyne 1aa was slower than that of 1a, and 6-endo-dig product 2aa was obtained in low yield. Larock and co-workers reported the iodocyclization of phenyl-substituted alkynylbenzylalcohol 1aa’ leading to 6-endo-dig product 2aa with a small amount of 5-exo-dig product 2aa’.
Table S1: Optimization of 8-endo-dig Iodocyclization of 5d

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>I(coll)<em>{2}PF</em>{6}</th>
<th>Time</th>
<th>Yield of 6d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1.1 equiv</td>
<td>1 h</td>
<td>30%</td>
</tr>
<tr>
<td>2a</td>
<td>1.1 equiv</td>
<td>3 h</td>
<td>39%</td>
</tr>
<tr>
<td>3</td>
<td>2.0 equiv</td>
<td>3 h</td>
<td>49%</td>
</tr>
</tbody>
</table>

*a Some of 5d remained.

Reaction conditions of 8-endo-dig iodocyclization were optimized using 5d as substrate (Table S1). 1.1 equiv of I(coll)_{2}PF_{6} was inefficient for the complete consumption of 5d (entries 1-2). Therefore, the use of I(coll)_{2}PF_{6} was increased to 2.0 equiv, and as a result, 5d was almost consumed and 8-endo-dig product 6d was obtained in moderate yield (entry 3).

Scheme S2: Formation of Collidinium Salt C

![Chemical structures](image)

According to GP-3 (see page S36), 4p (27.8 mg, 34%) and C (54.9 mg, 37% as PF_{6} salt, 2,4,6-collidine was contaminated as a molar ratio of C/2,4,6-collidine = 3:2) were obtained from 3p (70.7 mg, 0.200 mmol) and I(coll)_{2}PF_{6} (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 5:1 to CH_{2}Cl_{2}/MeOH = 20:1.

C: brown oil; \textsuperscript{1}H NMR (300 MHz, CDCl_{3}) \delta 7.61 (s, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.55 (q, J = 5.1 Hz, 1H), 3.68-3.26 (m, 7H), 2.72 (br s, 6H), 2.49 (s, 3H), 2.46 (s, 3H), 2.16 (br t, J = 6.9 Hz, 2H), 1.62-1.38 (m, 4H), 1.22 (d, J = 5.1 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl_{3}) \delta 161.4, 154.9, 145.9, 135.1, 133.5, 130.2, 128.8, 127.4, 109.9, 99.8, 64.8, 61.5, 43.1, 39.7, 28.6, 27.8, 22.4, 22.2, 21.9, 21.1, 15.5.
Compound C (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound C (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
General. Melting point was measured by Yanagimoto micro melting point apparatus. Optical rotations were measured on a JASCO P-2200 polarimeter ([α]D values are in units of 104 deg cm2 g−1). IR spectra were measured on a Perkin Elmer Spectrum 100 FT-IR spectrometer using CHCl3. 1H NMR and 13C NMR spectra were determined on a Varian Mercury-300 or a Varian VXR-500 or a Bruker-600 superconducting FT-NMR spectrometer, respectively. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane as internal reference (CDCl3: δ = 0 ppm for 1H) and residual solvent signal (CDCl3: δ = 77.0 ppm for 13C). J-Values are given in Hz. MS was performed on an Exactive Orbitrap mass spectrometer. Column chromatography was performed using Kanto Silica Gel 60 N (spherical, neutral). All reaction was carried out under argon atmosphere. All reagents were directly used as obtained commercially.

General Procedure for the Preparation of Ynamides (GP-1)

According to literature,1 in a 1 L three-neck round-bottom flask equipped with a stir-bar, CuCl2 (0.2 equiv), amide (5 equiv) and Na2CO3 (2 equiv) were combined. The reaction flask was purged with oxygen gas. A solution of pyridine (2 equiv) in 0.1 M dry toluene was added to the reaction flask via a syringe. A balloon filled with oxygen gas was connected to the reaction flask via a needle. The flask was placed in an oil-bath and heated to 70 °C. A solution of terminal alkyne (1 equiv) in 0.1 M dry toluene was added to the flask over 4 h by using a syringe pump. After the addition of terminal alkyne/toluene solution, the reaction mixture was allowed to stir at 70 °C for another 4 h and then cooled to rt. After the crude mixture was filtered through Celite, the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel with hexane/EtOAc to yield the ynamide.

Preparation of Ynamides 1a-g

(2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)trimethylsiline (S1)
To a mixture of 2-iodobenzyl alcohol (10.0 g, 42.7 mmol) and PPTS (1.07 g, 4.27 mmol) in dry CH2Cl2 (200 mL) was added ethyl vinyl ether (7.37 mL, 76.9 mmol) and stirred at rt for 2 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO3 extracted with CH2Cl2, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 1-((1-ethoxyethoxy)methyl)-2-iodobenzene (13.0 g, 99%) as colorless oil. 1H NMR (300 MHz, CDCl3) δ 7.82 (dd, J = 8.1, 1.2 Hz, 1H),
7.47 (dd, J = 7.5, 1.2 Hz, 1H), 7.35 (td, J = 7.2, 1.2 Hz, 1H), 6.98 (td, J = 7.5, 1.5 Hz, 1H), 4.89 (q, J = 5.4 Hz, 1H), 4.63 (d, J = 12.6 Hz, 1H), 4.50 (d, J = 12.6 Hz, 1H), 3.76-3.66 (m, 1H), 3.61-3.50 (m, 1H), 1.42 (d, J = 5.4 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H).

A mixture of 1-((1-ethoxyethoxy)methyl)-2-iodobenzene (13.0 g, 42.4 mmol), PdCl₂ (188 mg, 1.06 mmol), Ph₃P (555 mg, 2.12 mmol), CuI (290 mg, 1.53 mmol), Et₃N (17.7 mL, 127 mmol), and ethynyltrimethylsilane (8.98 mL, 1.53 mmol) in dry MeCN (84.0 mL) was stirred at rt for 24 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH₃. The mixture was extracted with Et₂O, washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S1 (11.4 g, 98%) as brown oil.

IR νmax: 3010, 2155, 1601 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.45 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.29 (td, J = 7.5, 1.5 Hz, 1H), 7.17 (td, J = 7.5, 1.2 Hz, 1H), 4.84 (q, J = 5.4 Hz, 1H), 4.79 (d, J = 12.9 Hz, 1H), 4.68 (d, J = 12.9 Hz, 1H), 3.75-3.64 (m, 1H), 3.58-3.47 (m, 1H), 1.39 (d, J = 5.4 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 0.26 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 140.5, 132.1, 128.5, 127.2, 126.8, 121.4, 102.6, 99.6, 98.8, 65.2, 61.0, 19.9, 15.4, 0.0; HR-ESIMS calcd for C₁₆H₂₄NaO₂Si [M+Na]⁺ 299.1438. Found 299.1435.

1-((1-Ethoxyethoxy)methyl)-2-ethynylbenzene (S2)
To a solution of S1 (5.02 g, 23.2 mmol) in MeOH (11 mL) at rt was added K₂CO₃ (1.60 g, 11.6 mmol), and was stirred for 23 h. After reaction completed, the mixture was quenched with water, extracted with Et₂O, washed with brine, dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S2 (3.60 g, 76%) as colorless oil.

IR νmax: 3305, 3012, 2106, 1602, 1134 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.47 (d, J = 8.1 Hz, 2H), 7.34 (td, J = 7.5, 1.2 Hz, 1H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 4.85 (q, J = 5.7 Hz, 1H), 4.80 (d, J = 12.6 Hz, 1H), 4.70 (d, J = 12.6 Hz, 1H), 3.76-3.64 (m, 1H), 3.58-3.47 (m, 1H), 3.28 (s, 1H), 1.40 (d, J = 5.7 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 140.8, 132.5, 128.9, 127.5, 127.0, 120.4, 99.5, 81.6, 81.3, 65.0, 60.9, 19.9, 15.4; HR-ESIMS calcd for C₁₃H₁₆NaO₂ [M+Na]⁺ 227.1043. Found 227.1040.

N-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)-N,N-dimethylbenzenesulfonamide (1a)
According to GP-1, 1a (496 mg, 85%) was obtained from S2 (306 mg, 1.50 mmol), N-methyl-p-toluenesulfonamide (1.39 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 6:1. Colorless oil; IR νmax: 3010, 2234, 1598, 1368, 1133 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.37-7.24 (m, 4H), 7.18 (td, J = 7.5, 1.5 Hz, 1H), 4.83 (q, J = 5.1 Hz, 1H), 4.74 (d, J = 12.9 Hz, 1H), 4.64 (d, J = 12.9 Hz, 1H), 3.74-3.63 (m, 1H), 3.57-3.46 (m, 1H), 3.15 (s, 3H), 2.44 (s, 3H), 1.37 (d, J = 5.1 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.5, 139.6, 133.0, 131.2, 129.6, 127.7, 127.6, 127.1, 126.8, 120.8, 99.5, 88.2, 66.9, 65.3, 61.1, 39.4, 21.8, 20.1, 15.5; HR-ESIMS calcd for C₂₁H₂₅NNaO₄S [M+Na]⁺ 410.1397. Found 410.1395.
1-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)azetidin-2-one (1b)

According to GP-1, 3b (332 mg, 81%) was obtained from S2 (306 mg, 1.50 mmol), azetidin-2-one (533 mg, 7.50 mmol), CuCl\(_2\) (40.3 mg, 0.300 mmol), Na\(_2\)CO\(_3\) (318 mg, 3.00 mmol), and pyridine (243 \(\mu\)L, 3.00 mmol). Eluent: hexane/EtOAc = 2:1.

Colorless oil; IR \(\nu_{\text{max}}\): 3012, 2239, 1771, 1601 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.45 (d, \(J = 7.5\) Hz, 1H), 7.38 (d, \(J = 7.5\) Hz, 1H), 7.29 (t, \(J = 7.8\) Hz, 1H), 7.19 (t, \(J = 7.5\) Hz, 1H), 4.85 (q, \(J = 5.4\) Hz, 1H), 4.75 (d, \(J = 12.6\) Hz, 1H), 4.64 (d, \(J = 12.6\) Hz, 1H), 3.78-3.65 (m, 3H), 3.59-3.48 (m, 1H), 3.10 (t, \(J = 4.8\) Hz, 2H), 1.40 (d, \(J = 5.4\) Hz, 3H), 1.21 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 166.2, 139.8, 131.8, 128.2, 127.5, 127.0, 120.6, 99.6, 82.8, 67.6, 65.4, 61.0, 43.2, 38.1, 20.0, 15.4; HR-ESIMS calcd for C\(_{16}\)H\(_{19}\)NNaO\(_3\) [M+Na\(^+\)]\(^{2}\) 296.1257. Found 296.1257.

1-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)pyrrolidin-2-one (1c)

According to GP-1, 1c (108 mg, 25%) was obtained from S2 (306 mg, 1.50 mmol), 2-pyrrolidone (0.575 mL, 7.50 mmol), CuCl\(_2\) (40.3 mg, 0.300 mmol), Na\(_2\)CO\(_3\) (318 mg, 3.00 mmol), and pyridine (242 \(\mu\)L, 3.00 mmol). Eluent: hexane/EtOAc = 1:1.

Colorless oil; IR \(\nu_{\text{max}}\): 3012, 2246, 1717, 1602 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.46 (dd, \(J = 7.8, 1.2\) Hz, 1H), 7.41 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.27 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.19 (td, \(J = 7.5, 1.5\) Hz, 1H), 4.86 (q, \(J = 5.1\) Hz, 1H), 4.79 (d, \(J = 12.9\) Hz, 1H), 4.70 (d, \(J = 12.9\) Hz, 1H), 3.77 (t, \(J = 6.9\) Hz, 2H), 3.77-3.65 (m, 1H), 3.58-3.47 (m, 1H), 2.48 (t, \(J = 8.1\) Hz, 2H), 2.17 (quint, \(J = 7.5\) Hz, 2H), 1.39 (d, \(J = 5.1\) Hz, 3H), 1.21 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.3, 139.6, 131.5, 127.9, 127.3, 126.9, 120.9, 99.6, 84.7, 70.3, 65.5, 61.0, 50.0, 29.7, 20.0, 18.9, 15.4; HR-ESIMS calcd for C\(_{17}\)H\(_{21}\)NNaO\(_3\) [M+Na\(^+\)]\(^{2}\) 310.1414. Found 310.1409.

1-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)-3-methyl-1,3-dihydro-2\(H\)-benzo[d]imidazol-2-one (1d)

According to GP-1, 1d (193 mg, 36%) was obtained from S2 (306 mg, 1.50 mmol), 1-methyl-2-benzimidazolinone (1.11 g, 7.50 mmol), CuCl\(_2\) (40.3 mg, 0.300 mmol), Na\(_2\)CO\(_3\) (318 mg, 3.00 mmol), and pyridine (242 \(\mu\)L, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless crystals; mp 67-69 °C (hexane/EtOAc); IR \(\nu_{\text{max}}\): 3011, 2255, 1734, 1621 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.56 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.51 (dd, \(J = 7.5, 1.5\) Hz, 1H), 7.38-7.23 (m, 3H), 7.22-7.12 (m, 2H), 6.98 (dd, \(J = 6.9, 1.5\) Hz, 1H), 4.89 (d, \(J = 12.9\) Hz, 1H), 4.88 (q, \(J = 5.4\) Hz, 1H), 4.80 (d, \(J = 12.9\) Hz, 1H), 3.76-3.65 (m, 1H), 3.58-3.47 (m, 1H), 3.44 (s, 3H), 1.40 (d, \(J = 5.1\) Hz, 3H), 1.18 (t, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 152.9, 140.1, 132.1, 129.7, 128.5, 128.1, 127.5, 127.1, 123.5, 122.2, 120.5, 109.8, 107.9, 99.7, 79.7, 73.0, 65.5, 61.1, 27.7, 20.1, 15.4; HR-ESIMS calcd for C\(_{21}\)H\(_{22}\)N\(_2\)NaO\(_3\) [M+Na\(^+\)]\(^{2}\) 373.1523. Found 373.1524.
**tert-Butyl benzyl((2-((1-ethoxyethoxy)methyl)phenyl)ethynyl)carbamate (1e)**

![Chemical Structure Image]

To a solution of S2 (2.04 g, 10.0 mmol) in dry acetone (60 mL) at rt was added AgNO3 (170 mg, 1.00 mmol) and NBS (1.96 g, 11.0 mmol) were added successively, each in a single portion. After the mixture was stirred at rt under dark for 3.5 h, the reaction mixture was diluted with hexane and vigorously stirred for 5 min. The mixture was filtered and concentrated in vacuo. The residue was purified by short silica gel pad (3 cm) eluting with hexane to give S2' (2.41 g) that was directly used in the next reaction.

According to literature, to a mixture of S2' (2.41 g, 8.51 mmol), tert-butyl benzylcarbamate (1.04 g, 5.00 mmol), CuI (290 mg, 1.50 mmol), 1,10-phenanthroline (320 mg, 1.80 mmol) in dry toluene (8.5 mL) at 90 °C was added KHMDS (0.5 M in toluene, 15.0 mL, 7.50 mmol) over 1 h by using a syringe pump. After the addition of KHMDS solution, the reaction mixture was stirred at 90 °C for another 2.5 h. The reaction mixture was cooled to rt and quenched with water, extracted with EtOAc. The organic layer was washed with brine, and filtered through Celite, and the filtrate was concentrated in vacuo. The crude products were purified by silica gel column chromatography eluting with hexane/EtOAc = 7:1 to afford 1e (143 mg, 4%, 2 steps) as yellow oil.

IR ν max: 2983, 2243, 1715, 1601 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.46-7.29 (m, 7H), 7.24 (td, J = 7.5, 1.5 Hz, 1H), 4.77 (q, J = 5.5 Hz, 1H), 4.68 (s, 2H), 4.67 (d, J = 13.0 Hz, 1H), 4.58 (d, J = 13.0 Hz, 1H), 4.58 (d, J = 13.0 Hz, 1H), 3.69-3.61 (m, 1H), 3.51-3.44 (m, 1H), 1.54 (s, 9H), 1.34 (d, J = 5.5 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 153.8, 139.2, 136.4, 131.0, 128.6, 128.3, 127.0, 126.9, 121.7, 99.5, 88.4, 82.8, 68.8, 65.4, 60.8, 53.1, 28.1, 20.0, 15.3; HR-ESIMS calcd for C₂₅H₃₁NNaO₄ [M+Na⁺] 432.2145. Found 432.2146.

**(4R)-3-((2-((1-Ethoxyethoxy)methyl)phenyl)ethynyl)-4-phenyloxazolidin-2-one (1f)**

According to GP-1, 1f (198 mg, 36%) was obtained as 1:1 diastereomer mixture from S2 (306 mg, 1.50 mmol), (R)-(-)-4-phenyl-2-oxazolidinone (1.22 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless oil; [α]D²⁶ -163 (c 1.01, CHCl₃); IR ν max: 3011, 2254, 1777, 1603 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.35 (m, 6H), 7.22 (t, J = 7.8, 2H), 7.10 (td, J = 7.2, 1.5 Hz, 1H), 5.12 (dd, J = 8.7, 7.2 Hz, 1H), 4.76 (t, J = 8.7 Hz, 1H), 4.69 (q, J = 5.4 Hz, 0.5H), 4.66 (q, J = 5.4 Hz, 0.5H), 4.48 (dd, J = 12.9, 3.0 Hz, 0.5H), 4.38 (dd, J = 12.9, 4.8 Hz, 0.5H), 4.28 (dd, J = 9.3, 7.2 Hz, 1H), 3.68-3.57 (m, 1H), 3.49-3.39 (m, 1H), 1.30 (d, J = 5.4 Hz, 1.5H), 1.29 (d, J = 5.4 Hz, 1.5H), 1.18 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.1, 139.79, 139.75, 135.9, 131.5, 129.4, 129.2, 128.0, 126.90, 126.87, 126.69, 126.68, 120.13, 120.09, 99.66, 99.61, 82.4, 70.7, 70.4, 65.3, 65.2, 62.1, 61.0, 60.9, 20.0, 15.4; HR-ESIMS calcd for C₂₂H₂₃NNaO₄ [M+Na⁺] 388.1519. Found 388.1528.
Methyl 1-((2-(2-(1-ethoxyethoxy)ethyl)phenyl)ethynyl)-1H-indole-3-carboxylate (1g)

According to GP-1, 1g (490 mg, 83%) was obtained from S2 (306 mg, 1.50 mmol), methyl 1H-indole-3-carboxylate (1.31 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (242 µL, 3.00 mmol). Eluent: hexane/EtOAc = 7:1.

Red oil; IR νmax: 3011, 2152, 1596 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.17 (dd, J = 6.9, 2.4 Hz, 1H), 7.96 (s, 1H), 7.57-7.51 (m, 2H), 7.42-7.26 (m, 4H), 4.89 (d, J = 12.6 Hz, 1H), 4.88 (q, J = 5.1 Hz, 1H), 4.78 (d, J = 12.6 Hz, 1H), 3.93 (s, 1H), 3.74-3.63 (m, 1H), 3.58-3.47 (m, 1H), 1.40 (d, J = 5.1 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 164.1, 140.1, 138.3, 134.6, 132.1, 128.8, 127.9, 127.3, 125.3, 124.5, 123.7, 121.9, 120.1, 111.5, 111.1, 99.4, 83.3, 69.7, 65.3, 60.8, 51.4, 20.0, 15.4; HR-ESIMS calcd for C₂₃H₂₅N₃O₄ [M+Na]⁺ 400.1519. Found 400.1520.

Preparation of Ynamide 1h

((1-(1-Ethoxyethoxy)methyl)naphthalen-2-yl)ethynyl)trimethylsilane (S3)

To a mixture of (2-iodonaphthalene-1-yl)methanol³ (306 mg, 3.00 mmol), and pyridine (242 µL, 3.00 mmol), in dry CH₂Cl₂ (11 mL) was added ethyl vinyl ether (373 µL, 3.90 mmol) and stirred at rt for 5.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give 1h (318 mg, 3.00 mmol), and NEWS -indole-3-carboxylate (1g)

IR νmax: 3011, 2254, 1709, 1641 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 11.1 Hz, 1H), 7.77 (d, J = 5.1 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.56-7.43 (m, 1H), 5.29 (d, J = 11.1 Hz, 1H), 5.15 (d, J = 10.8 Hz, 1H), 4.94 (q, J = 5.4 Hz, 1H), 3.83-3.71 (m, 1H), 3.63-3.51 (m, 1H), 1.44 (d, J = 5.4 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H).

A mixture of 1-((2-(2-(1-ethoxyethoxy)ethyl)naphthalen-2-yl)ethynyl)trimethylsilane (750 mg, 2.11 mmol), PdCl₂ (9.4 mg, 0.0530 mmol), Ph₃P (28.9 mg, 0.110 mmol), CuI (14.5 mg, 0.0761 mmol), Et₃N (0.882 mL, 6.33 mmol), and ethynyltrimethylsilane (0.880 mL, 6.23 mmol) in dry MeCN (5.0 mL) was stirred at rt for 16 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH₃. The mixture was extracted with Et₂O, washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give S3 (655 mg, 95%) as brown oil.

IR νmax: 3010, 2152, 1596 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 5.1 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.56-7.43 (m, 1H), 5.29 (d, J = 11.1 Hz, 1H), 5.21 (d, J = 11.4 Hz, 1H), 4.87 (q, J = 5.1 Hz, 1H), 3.78-3.66 (m, 1H), 3.53-3.41 (m, 1H), 1.40 (d, J = 5.1 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 0.29 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 136.4, 133.4, 132.2, 128.7, 128.3, 128.2, 126.3, 126.4, 125.1, 121.3, 104.1, 99.7, 98.9, 63.3, 61.5, 20.2, 15.5, 0.1; HR-ESIMS calcd for C₂₀H₂₆NaO₃Si [M+Na]⁺ 349.1594. Found 349.1593.
**1-((1-Ethoxyethoxy)methyl)-2-ethynylnaphthalene (S4)**

To a solution of S3 (656 mg, 2.01 mmol) in MeOH (1 mL) at rt was added K$_2$CO$_3$ (139 mg, 1.01 mmol), and was stirred for 15 h. After reaction completed, the mixture was quenched with water, extracted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S4 (468 mg, 92%) as colorless oil.

- IR $\nu_{\text{max}}$: 3303, 3011, 2104, 1597 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J$ = 8.7 Hz, 1H), 7.78 (d, $J$ = 7.5 Hz, 1H), 7.73 (d, $J$ = 8.4 Hz, 1H), 7.57-7.44 (m, 3H), 5.28 (d, $J$ = 11.1 Hz, 1H), 5.23 (d, $J$ = 10.8 Hz, 1H), 4.89 (q, $J$ = 5.1 Hz, 1H), 3.79-3.66 (m, 1H), 3.56-3.54 (m, 1H), 3.36 (s, 1H), 1.41 (d, $J$ = 5.1 Hz, 3H), 1.22 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 136.9, 133.5, 132.2, 128.7, 128.5, 128.2, 126.8, 126.6, 125.0, 120.2, 99.4, 82.7, 81.5, 62.7, 61.1, 20.0, 15.3; HR-ESIMS calcd for C$_{17}$H$_{18}$NaO$_2$ [M+Na]$^+$ 227.1199. Found 277.1203.

**N-((1-((1-Ethoxyethoxy)methyl)naphthalen-2-yl)ethynyl)-N,N,4-dimethylbenzenesulfonamide (1h)**

According to GP-1, 1h (484 mg, 77%) was obtained from S4 (366 mg, 1.44 mmol), N-methyl-p-toluenesulfonamide (1.34 g, 7.20 mmol), CuCl$_2$ (39.0 mg, 0.288 mmol), Na$_2$CO$_3$ (305 mg, 2.88 mmol), and pyridine (233 $\mu$L, 2.88 mmol). Eluent: hexane/EtOAc = 5:1.

Yellow oil; IR $\nu_{\text{max}}$: 3010, 2234, 1598, 1369, 1170 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.18 (d, $J$ = 8.4 Hz, 1H), 7.85 (d, $J$ = 8.4 Hz, 2H), 7.78 (dd, $J$ = 7.8, 1.5 Hz, 1H), 7.70 (d, $J$ = 8.4 Hz, 1H), 7.56-7.49 (m, 1H), 7.48-7.42 (m, 1H), 7.39-7.30 (m, 3H), 5.23 (d, $J$ = 10.8 Hz, 1H), 5.15 (d, $J$ = 10.8 Hz, 1H), 4.87 (q, $J$ = 5.4 Hz, 1H), 3.74-3.63 (m, 1H), 3.53-3.42 (m, 1H), 3.20 (s, 3H), 2.44 (s, 3H), 1.35 (d, $J$ = 5.4 Hz, 3H), 1.17 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 144.7, 134.9, 132.9, 129.8, 129.6, 128.4, 128.2, 127.9, 127.7, 126.7, 126.1, 124.8, 121.0, 99.8, 88.2, 68.6, 63.5, 61.4, 39.3, 21.7, 20.3, 15.4; HR-ESIMS calcd for C$_{25}$H$_{27}$NNaO$_4$S [M+Na]$^+$ 424.1553. Found 460.1549.

**Preparation of Ynamide 1i**

2-((1-Ethoxyethoxy)methyl)-1-ethynyl-4-methylbenzene (S5)

To a mixture of (2-ethynyl-5-methylphenyl)methanol $^4$ (770 mg, 5.27 mmol) and PPTS (132 mg, 0.527 mmol) in dry CH$_2$Cl$_2$ (26.3 mL) was added ethyl vinyl ether (0.757 mL, 7.90 mmol) and stirred at rt for 3.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give S5 (1.13 g, 99%) as pale yellow oil.

- IR $\nu_{\text{max}}$: 3300, 3011, 1611 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J$ = 7.8 Hz, 1H), 7.28 (br s, 1H), 7.02 (br d, $J$ = 7.8 Hz, 1H), 4.85 (q, $J$ = 5.4 Hz, 1H), 4.76 (d, $J$ = 12.6 Hz, 1H), 4.66 (d, $J$ = 12.6 Hz,
1H), 3.76-3.65 (m, 1H), 3.59-3.48 (m, 1H), 3.23 (s, 1H), 2.35 (s, 1H), 1.40 (d, J = 5.4 Hz, 3H), 1.22 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.3, 138.9, 132.4, 128.2, 127.7, 117.4, 99.5, 81.4, 80.8, 65.1, 60.9, 21.7, 20.0, 15.5; HR-ESIMS calcd for C$_{14}$H$_{18}$NaO$_2$ [M+Na]$^+$ 241.1199. Found 241.1198.

N-((2-((1-Ethoxyethoxy)methyl)-4-methylphenyl)ethynyl)-N,4-dimethylbenzenesulfonylamide (1i)

According to GP-1, 1i (456 mg, 76%) was obtained from S5 (327 mg, 1.50 mmol), N-methyl-p-toluenesulfonylamide (1.39 g, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/acetone = 8:1.

Colorless oil; IR ν$_{max}$: 3010, 2235, 1598, 1368, 1169 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.82 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.26 (br s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 6.99 (br d, J = 7.8 Hz, 1H), 4.83 (q, J = 5.4 Hz, 1H), 4.70 (d, J = 12.6 Hz, 1H), 4.59 (d, J = 12.6 Hz, 1H), 3.75-3.63 (m, 1H), 3.57-3.46 (m, 1H), 3.14 (s, 3H), 2.44 (s, 3H), 2.34 (s, 3H), 1.37 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 144.5, 139.5, 137.9, 133.0, 131.4, 129.6, 127.9, 127.62, 127.57, 117.8, 99.6, 87.3, 66.8, 65.3, 61.1, 39.5, 21.8, 21.7, 20.1, 15.5; HR-ESIMS calcd for C$_{22}$H$_{27}$NNaO$_4$S [M+Na]$^+$ 424.1553. Found 420.1555.

Preparation of Ynamide 1j

![Chemical structure](image)

2-((1-Ethoxyethoxy)methyl)-1-ethynyl-4-fluorobenzene (S6)

To a mixture of (2-ethynyl-5-fluorophenyl)methanol$^6$ (368 mg, 2.45 mmol) and PPTS (61.6 mg, 0.245 mmol) in dry CH$_2$Cl$_2$ (12.3 mL) was added ethyl vinyl ether (352 µL, 3.68 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give S6 (530 mg, 97%) as pale yellow oil.

IR ν$_{max}$: 3306, 2981, 2107, 1609 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.43 (dd, J = 8.4, 5.7 Hz, 1H), 7.22 (dd, J = 9.6, 3.0 Hz, 1H), 6.90 (td, J = 8.4, 3.0 Hz, 1H), 4.86 (q, J = 5.4 Hz, 1H), 4.78 (d, J = 13.5 Hz, 1H), 4.67 (d, J = 13.5 Hz, 1H), 3.74-3.63 (m, 1H), 3.58-3.47 (m, 1H), 3.27 (s, 1H), 1.40 (d, J = 5.4 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 162.6 (d, J = 247.6 Hz), 143.9 (d, J = 8.0 Hz), 134.1 (d, J = 8.6 Hz), 115.7 (d, J = 3.4 Hz), 114.1 (d, J = 23.4 Hz), 114.0 (d, J = 22.2 Hz), 99.5, 81.5, 80.1, 64.3 (d, J = 1.1 Hz), 61.0, 19.9, 15.5; HR-ESIMS calcd for C$_{13}$H$_{15}$FNaO$_2$ [M+Na]$^+$ 245.0948. Found 245.0949.

N-((2-((1-Ethoxyethoxy)methyl)-4-fluorophenyl)ethynyl)-N,4-dimethylbenzenesulfonylamide (1j)

According to GP-1, 1j (403 mg, 66%) was obtained from S6 (333 mg, 1.50 mmol), N-methyl-p-toluenesulfonylamide (1.39 g, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/acetone = 8:1.
Colorless oil; IR $\nu_{\text{max}}$: 2983, 2237, 1607, 1369, 1168 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J$ = 8.1 Hz, 2H), 7.36 (d, $J$ = 8.1 Hz, 2H), 7.27 (dd, $J$ = 8.4, 5.7 Hz, 1H), 7.20 (dd, $J$ = 9.6, 2.7 Hz, 1H), 6.87 (td, $J$ = 8.4, 2.7 Hz, 1H), 4.84 (q, $J$ = 5.4 Hz, 1H), 4.71 (d, $J$ = 13.5 Hz, 1H), 4.60 (d, $J$ = 13.5 Hz, 1H), 3.73-3.62 (m, 1H), 3.57-3.46 (m, 1H), 3.15 (s, 3H), 2.45 (s, 3H), 1.38 (d, $J$ = 7.2 Hz, 0.5H), 1.27-1.10 (m, 0.5H), 1.30 (d, $J$ = 5.4 Hz, 0.5H), 4.58 (q, $J$ = 5.4 Hz, 1H), 4.60 (q, $J$ = 5.4 Hz, 1H), 3.64-3.46 (m, 1H), 3.41-3.30 (m, 0.5H), 1.31 (d, $J$ = 5.4 Hz, 1.5H), 1.30 (d, $J$ = 5.4 Hz, 1.5H), 1.21 (t, $J$ = 7.2 Hz, 0.5H), 1.11 (t, $J$ = 7.2 Hz, 0.5H).

A mixture of 1-(1-ethoxyethoxy)allyl-2-iodobenzene (6.38 g, 99%) as 1:1 diastereomer mixture.

Preparation of Ynamide 1k

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\begin{align*}
\text{I} & \quad \text{(2-iodophenyl)prop-2-en-1-ol} \\
\text{OH} & \quad \text{PPTS, CH}_2\text{Cl}_2 \\
& \quad \text{rt, 23 h, 99%} \\
\rightarrow & \quad \text{TMS} \\
\text{TMS} & \quad \text{PdCl}_2, \text{Ph}_3\text{P, Cul} \\
& \quad \text{EtN, MeCN} \\
& \quad \text{rt, 24 h, 98%} \\
\rightarrow & \quad \text{K}_2\text{CO}_3 \\
\text{MeOH} & \quad \text{rt} \\
& \quad 20 h, 96% \\
\rightarrow & \quad \text{CuSO}_4 \cdot 5\text{H}_2\text{O} \\
& \quad 1,10\text{-phenanthroline} \\
& \quad \text{K}_3\text{PO}_4 \\
\rightarrow & \quad \text{toluene, 80°C} \\
& \quad 17 h \\
& \quad (83\%, 2\text{ steps}) \\
\rightarrow & \quad \text{1k} \\
\end{align*}
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\((2\text{-}(1\text{-}(1\text{-ethoxyethoxy)allyl})\text{phenyl})\text{ethynyl})\text{trimethylsilane (S7)}\)

To a mixture of 1-(2-iodophenyl)prop-2-en-1-ol (5.20 g, 20.0 mmol) and PPTS (503 mg, 2.00 mmol) in dry CH$_2$Cl$_2$ (100 mL) was added ethyl vinyl ether (3.45 mL, 36.0 mmol) and stirred at rt for 23 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 1-(1-ethoxyethoxy)allyl-2-iodobenzene (6.38 g, 99%) as 1:1 diastereomer mixture.

A mixture of 1-(1-ethoxyethoxy)allyl)-2-iodobenzene (6.38 g, 9.2 mmol), PdCl$_2$ (85.5 mg, 0.482 mmol), Ph$_3$P (253 mg, 0.964 mmol), Cul (132 mg, 0.694 mmol), Et$_3$N (8.07 mL, 57.9 mmol), and ethynyltrimethylsilane (4.09 mL, 28.9 mmol) in dry MeCN (5.0 mL) was stirred at rt for 24 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH$_3$. The mixture was extracted with Et$_2$O, washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S7 (5.68 g, 98%).
Brown oil; IR $\nu_{\text{max}}$: 3010, 2156, 1640, 1599 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.52-7.48 (m, 0.5H), 7.45-7.38 (m, 1.5H), 7.31 (t, $J$ = 7.5 Hz, 1H), 7.21-7.13 (m, 1H), 6.01-5.77 (m, 1H), 5.71 (d, $J$ = 6.3 Hz, 0.5H), 5.61 (d, $J$ = 6.6 Hz, 0.5H), 5.34 (ddd, $J$ = 16.2, 1.8, 1.2 Hz, 0.5H), 5.28 (dt, $J$ = 16.5, 1.5 Hz, 0.5H), 5.13 (ddd, $J$ = 9.0, 1.5, 1.2 Hz, 0.5H), 5.10 (dt, $J$ = 9.0, 1.5 Hz, 0.5H), 4.84 (q, $J$ = 5.4 Hz, 0.5H), 4.60 (q, $J$ = 5.4 Hz, 0.5H), 3.66-3.45 (m, 1.5H), 3.41-3.30 (m, 0.5H), 1.32 (d, $J$ = 5.4 Hz, 1.5H), 1.29 (d, $J$ = 5.4 Hz, 1.5H), 1.20 (t, $J$ = 7.2 Hz, 1.5H), 0.27 (s, 4.5H), 0.26 (s, 4.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.8, 143.3, 138.03, 137.95, 132.1, 131.9, 128.75, 128.74, 126.9, 126.7, 126.2, 121.6, 120.7, 115.4, 114.9, 102.9, 102.7, 99.2, 99.1, 98.2, 98.1, 75.8, 75.3, 61.0, 60.8, 20.9, 20.7, 15.6, 15.4, 0.21, 0.19; HR-ESIMS calcd for C$_{18}$H$_{26}$NaO$_2$Si $[\text{M}+\text{Na}]^+$ 325.1594. Found 325.1602.

1-(1-(1-Ethoxyethoxy)allyl)-2-ethynylbenzene (S8)

To a solution of S5 (5.53 g, 18.9 mmol) in MeOH (9.2 mL) at rt was added K$_2$CO$_3$ (1.26 g, 9.15 mmol), and was stirred for 20 h. After reaction completed, the mixture was quenched with water, extracted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S8 (4.03 g, 96%) as 1:1 diastereomer mixture.

Colorless oil; IR $\nu_{\text{max}}$: 3304, 3011, 2105, 1640, 1601 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54-7.50 (m, 0.5H), 7.48-7.42 (m, 1.5H), 7.34 (t, $J$ = 7.5 Hz, 1H), 7.24-7.15 (m, 1H), 6.03-5.81 (m, 1H), 5.69 (d, $J$ = 6.0 Hz, 0.5H), 5.61 (d, $J$ = 6.6 Hz, 0.5H), 5.32 (dt, $J$ = 17.1, 1.5 Hz, 0.5H), 5.26 (dt, $J$ = 17.1, 1.5 Hz, 0.5H), 5.13 (dt, $J$ = 10.5, 1.5 Hz, 0.5H), 5.11 (dt, $J$ = 10.5, 1.5 Hz, 0.5H), 4.86 (q, $J$ = 5.1 Hz, 0.5H), 4.62 (q, $J$ = 5.4 Hz, 0.5H), 3.64-3.43 (m, 1.5H), 3.41-3.32 (m, 0.5H), 3.31 (s, 1H), 1.32 (d, $J$ = 5.1 Hz, 1.5H), 1.29 (d, $J$ = 5.1 Hz, 1.5H), 1.19 (t, $J$ = 7.2 Hz, 1.5H), 1.10 (t, $J$ = 7.2 Hz, 1.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.8, 143.3, 138.03, 137.95, 132.1, 131.9, 128.75, 128.74, 126.9, 126.7, 126.2, 121.6, 120.7, 115.4, 114.9, 102.9, 102.7, 99.2, 99.1, 98.2, 98.1, 75.8, 75.3, 61.0, 60.8, 20.9, 20.7, 15.6, 15.4, 0.21, 0.19; HR-ESIMS calcd for C$_{15}$H$_{18}$NaO$_2$Si $[\text{M}+\text{Na}]^+$ 253.1199. Found 253.1200.

N-((2-(1-(1-Ethoxyethoxy)allyl)phenyl)ethynyl)-N',4-dimethylbenzenesulphonamide (1k)

To a solution of S8 (461 mg, 2.00 mmol) in dry THF (10 mL) at -78 °C was added n-BuLi (1.57 M in hexane, 1.53 mL, 2.40 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br$_2$ (133 $\mu$L, 2.60 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of Na$_2$S$_2$O$_3$, extracted with Et$_2$O, washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S8' (520 mg) that was directly used in the next reaction.

According to literature, a solution of S8' (520 mg, 1.68 mmol), N-methyl-p-toluenesulphonamide (374 mg, 2.02 mmol), CuSO$_4$•5H$_2$O (83.9 mg, 0.336 mmol), 1,10-phenanthroline (121 mg, 0.672 mmol), and K$_3$PO$_4$ (856 mg, 4.03 mmol) in dry toluene (5.1 mL) was stirred at 80 °C for 17 h. The mixture was cooled to rt, diluted with Et$_2$O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give 1k (689 mg, 83% in 2 steps) as 1:1 diastereomer mixture.

Pale yellow oil; IR $\nu_{\text{max}}$: 3010, 2234, 1598, 1370, 1168 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J$ = 8.5
Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.52 (dd, J = 8.0, 1.5 Hz, 0.5H), 7.44 (dd, J = 8.0, 1.5 Hz, 0.5H), 7.36 (d, J = 8.5 Hz, 2H), 7.34-7.27 (m, 2H), 7.21-7.15 (m, 1H), 5.97 (ddd, J = 17.5, 10.0, 6.0 Hz, 0.5H), 5.60 (dt, J = 6.0, 1.5 Hz, 0.5H), 5.53 (d, J = 6.5 Hz, 0.5H), 5.33 (dt, J = 17.0, 1.5 Hz, 0.5H), 5.27 (dt, J = 17.0, 1.5 Hz, 0.5H), 5.14-5.09 (m, 1H), 4.84 (q, J = 5.0 Hz, 0.5H), 4.64 (q, J = 5.0 Hz, 0.5H), 3.64-3.55 (m, 1H), 3.52-3.45 (m, 0.5H), 3.38-3.30 (m, 0.5H), 3.173 (s, 1.5H), 3.166 (s, 1.5H), 2.45 (s, 3H), 1.30 (d, J = 5.5 Hz, 1.5H), 1.28 (d, J = 5.5 Hz, 1.5H), 1.13 (t, J = 7.0 Hz, 1.5H), 1.06 (t, J = 7.0 Hz, 1.5H); 13C NMR (125 MHz, CDCl3) δ 144.8, 143.1, 142.5, 138.4, 138.3, 133.39, 133.38, 131.5, 131.4, 129.87, 129.86, 128.2, 128.1, 127.8, 127.1, 126.9, 126.7, 126.6, 121.3, 120.5, 115.6, 115.3, 98.5, 98.3, 88.33, 88.25, 75.8, 75.4, 67.1, 67.0, 61.0, 60.7, 39.27, 39.25, 21.6, 20.6, 15.3, 15.2; HR-ESIMS calcd for C23H27NNaO4S [M+Na]+ 436.1558. Found 436.1553.

Preparation of Ynamide 1l

5-(1-Ethoxyethoxy)pent-1-yn (S9)

To a mixture of 4-pentyn-1-ol (1.68 g, 20.0 mmol) and PPTS (503 mg, 2.00 mmol) in dry CH2Cl2 (100 mL) was added ethyl vinyl ether (2.87 mL, 30.0 mmol) and stirred at rt for 1 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO3, extracted with CH2Cl2, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S9 (2.89 g, 93%) as colorless oil.

IR νmax: 3308, 3011, 2118 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 4.68 (q, J = 5.4 Hz, 1H), 3.71-3.59 (m, 2H), 3.55-3.42 (m, 2H), 2.30 (td, J = 7.2, 2.7 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.78 (quint, J = 7.2 Hz, 2H), 1.30 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 99.4, 83.8, 68.5, 63.2, 60.8, 28.8, 19.9, 15.45, 15.43; HR-ESIMS calcd for C9H16NaO2 [M+Na]+ 179.1048. Found 179.1044.

N-(5-(1-Ethoxyethoxy)pent-1-yn-1-yl)-N,4-dimethylbenzenesulfonamide (II)

To a solution of S9 (1.25 g, 8.00 mmol) in dry THF (40 mL) at -78 °C was added n-BuLi (1.57 M in hexane, 6.11 mL, 9.60 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br2 (0.533 mL, 10.4 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of Na2S2O3, extracted with Et2O, washed with brine, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S9' (913 mg) that was directly used in the next reaction.

According to literature, a solution of S9 (913 mg, 3.88 mmol), N-methyl-p-toluenesulfonamide (862 mg, 4.66 mmol), CuSO4·5H2O (194 mg, 0.777 mmol), 1,10-phenanthroline (280 mg, 1.55 mmol), and K3PO4 (1.98 g, 9.31 mmol) in dry toluene (11.8 mL) was stirred at 80 °C for 15 h. The mixture was cooled to rt,
diluted with Et₂O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 5:1 to give 11 (468 mg, 17% in 2 steps) as pale yellow oil.

IR ν\textsubscript{max}: 3009, 2254, 1598, 1365, 1172 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.75 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.66 (q, J = 5.4 Hz, 1H), 3.69-3.57 (m, 2H), 3.52-3.40 (m, 2H), 3.00 (s, 3H), 2.45 (s, 3H), 2.35 (t, J = 6.9 Hz, 2H), 1.74 (quint, J = 6.9 Hz, 2H), 1.29 (d, J = 5.4 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 144.2, 132.9, 129.4, 127.5, 99.6, 75.1, 67.9, 63.6, 60.9, 39.4, 29.3, 21.8, 20.1, 15.51, 15.47; HR-ESIMS caleld for C\textsubscript{17}H\textsubscript{25}NNaO\textsubscript{3} [M+Na]\textsuperscript{+} 362.1402. Found 362.1398.

Preparation of Ynamides 3a-g

\((2\text{-}(2\text{-}(1\text{-Ethoxyethoxy})\text{ethyl})\text{phenyl})\text{ethynyl})\text{trimethylsilane} (S10)

To a mixture of 2-(2-iodophenyl)ethan-1-ol\textsuperscript{7} (4.84 g, 19.5 mmol) and PPTS (490 mg, 1.95 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (100 mL) was added ethyl vinyl ether (3.47 mL, 35.1 mmol) and stirred at rt for 16 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO\textsubscript{3}, extracted with CH\textsubscript{2}Cl\textsubscript{2}, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give 1-(2-(1-ethoxyethoxy)ethyl)-2-iodobenzene (5.63 g, 90%) as colorless oil. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.79 (d, J = 7.8 Hz, 1H), 7.27-7.20 (m, 2H), 6.92-6.83 (m, 1H), 4.68 (q, J = 5.1 Hz, 1H), 3.80-3.51 (m, 3H), 3.46-3.35 (m, 1H), 3.00 (t, J = 6.9 Hz, 2H), 1.29 (d, J = 5.1 Hz, 3H), 1.16 (t, J = 6.9 Hz, 3H).

A mixture of 1-(2-(1-ethoxyethoxy)ethyl)-2-iodobenzene (5.63 g, 17.6 mmol), PdCl\textsubscript{2} (78.0 mg, 0.440 mmol), Ph\textsubscript{3}P (231 mg, 0.880 mmol), CuI (121 mg, 0.634 mmol), Et\textsubscript{3}N (7.36 mL, 52.8 mmol), and ethynyltrimethylsilane (3.73 mL, 26.4 mmol) in dry MeCN (35 mL) was stirred at rt for 17 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH\textsubscript{3}. The mixture was extracted with Et\textsubscript{2}O, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S10 (4.97 g, 97%) as brown oil.

IR ν\textsubscript{max}: 3010, 2155, 1600 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.42 (d, J = 7.8 Hz, 1H), 7.24-7.17 (m, 2H), 7.16-7.08 (m, 1H), 4.66 (q, J = 5.1 Hz, 1H), 3.84-3.75 (m, 1H), 3.72-3.50 (m, 2H), 3.45-3.34 (m, 1H), 3.06 (t, J = 7.2 Hz, 2H), 1.28 (d, J = 5.1 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 0.25 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 141.1, 132.4, 129.5, 128.4, 126.0, 122.7, 103.6, 99.6, 97.9, 64.9, 60.9, 35.3, 20.0, 15.4, 0.1; HR-ESIMS calcd for C\textsubscript{17}H\textsubscript{26}NaO\textsubscript{2}S [M+Na]\textsuperscript{+} 313.1594. Found 313.1590.

1-((1-Ethoxyethoxy)methyl)-2-ethynylbenzene (S11)

To a solution of S10 (4.98 g, 17.2 mmol) in MeOH (8.5 mL) at rt was added K\textsubscript{2}CO\textsubscript{3} (1.19 g, 8.58 mmol), and was stirred for 23 h. After reaction completed, the mixture was quenched with water, extracted with Et\textsubscript{2}O, washed with brine, dried over MgSO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by
flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S11 (3.42 g, 91%) as colorless oil.

IR $\nu_{\text{max}}$: 3304, 3011, 2105, 1600 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.45 (d, $J = 7.5$ Hz, 1H), 7.28-7.22 (m, 2H), 7.19-7.10 (m, 1H), 4.67 (q, $J = 5.1$ Hz, 1H), 3.85-3.65 (m, 2H), 3.59-3.48 (m, 1H), 3.44-3.33 (m, 1H), 3.24 (s, 1H), 3.07 (t, $J = 7.2$ Hz, 2H), 1.28 (d, $J = 5.1$ Hz, 3H), 1.15 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 141.3, 132.7, 129.5, 128.6, 126.1, 121.7, 99.4, 82.1, 80.7, 64.7, 60.8, 35.2, 19.9, 15.3; HR-ESIMS calcd for C$_{14}$H$_{18}$NaO$_2$ [M+Na]$^+$ 241.1199. Found 241.1200.

$N$-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)-$N$,4-dimethylbenzenesulfonamide (3a)

According to GP-1, 3a (516 mg, 86%) was obtained from S11 (327 mg, 1.50 mmol), N-methyl-p-toluenesulfonamide (1.39 g, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/EtOAc = 4:1. Colorless oil; IR $\nu_{\text{max}}$: 3009, 2235, 1598, 1369, 1168 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.82 (d, $J = 8.4$ Hz, 2H), 7.37-7.29 (m, 3H), 7.24-7.09 (m, 3H), 4.65 (q, $J = 5.4$ Hz, 1H), 3.83-3.74 (m, 1H), 3.71-3.63 (m, 1H), 3.57-3.46 (m, 1H), 3.42-3.31 (m, 1H), 3.16 (s, 3H), 2.99 (t, $J = 7.2$ Hz, 2H), 2.44 (s, 3H), 1.26 (d, $J = 5.4$ Hz, 3H), 1.12 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.6, 140.3, 133.3, 131.7, 129.7, 129.5, 127.7, 127.6, 126.0, 122.3, 99.5, 87.3, 67.6, 65.0, 60.9, 39.4, 35.3, 21.7, 20.0, 15.4; HR-ESIMS calcd for C$_{22}$H$_{27}$NNaO$_4$ [M+Na]$^+$ 424.1553. Found 424.1548.

1-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)azetidin-2-one (3b)

According to GP-1, 3b (170 mg, 39%) was obtained from S11 (327 mg, 1.50 mmol), azetidin-2-one (533 mg, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/EtOAc = 2:1. Colorless oil; IR $\nu_{\text{max}}$: 3011, 2241, 1770, 1600 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40-7.35 (m, 1H), 7.25-7.10 (m, 3H), 4.68 (q, $J = 5.4$ Hz, 1H), 3.85-3.75 (m, 1H), 3.73-3.64 (m, 3H), 3.60-3.49 (m, 1H), 3.45-3.34 (m, 1H), 3.09 (t, $J = 4.8$ Hz, 2H), 3.03 (t, $J = 7.2$ Hz, 2H), 1.28 (d, $J = 5.4$ Hz, 3H), 1.15 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 166.2, 140.3, 133.3, 131.7, 129.7, 127.7, 127.6, 126.0, 122.3, 99.5, 87.3, 67.6, 65.0, 60.9, 39.4, 35.3, 21.7, 20.0, 15.4; HR-ESIMS calcd for C$_{17}$H$_{21}$NNaO$_3$ [M+Na]$^+$ 310.1414. Found 310.1412.

1-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)pyrrolidin-2-one (3c)

According to GP-1, 3c (206 mg, 38%) was obtained from S11 (327 mg, 1.50 mmol), 2-pyrrolidone (0.575 mL, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (242 µL, 3.00 mmol). Eluent: hexane/EtOAc = 4:3. Colorless oil; IR $\nu_{\text{max}}$: 3011, 2246, 1716, 1602 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.40 (d, $J = 6.6$ Hz, 1H), 7.30-7.10 (m, 3H), 4.68 (q, $J = 5.4$ Hz, 1H), 3.87-3.66 (m, 4H), 3.60-3.48 (m, 1H), 3.45-3.33 (m, 1H), 3.06 (t, $J = 7.2$ Hz, 2H), 2.48 (t, $J = 7.8$ Hz, 2H), 2.18 (quint, $J = 7.8$ Hz, 2H), 1.28 (d, $J = 5.4$ Hz, 3H), 1.14 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 175.3, 140.3, 131.8, 129.4, 127.7, 126.0, 122.2, 99.5, 83.9, 71.1, 65.0, 64.8, 60.8, 43.2, 38.1, 35.2, 19.9, 15.3; HR-ESIMS calcd for C$_{18}$H$_{23}$NNaO$_3$ [M+Na]$^+$ 324.1570. Found 324.1561.
1-((2-(2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)-3-methyl-1H-benzo[d]imidazol-2(3H)-one (3d)

According to GP-1, 3d (174 mg, 32%) was obtained from S11 (327 mg, 1.50 mmol), 1-methyl-2-benzimidazolinone (1.11 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 3:1.

Colorless oil; IR ν max: 3011, 2258, 1733, 1621 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, J = 7.2 Hz, 1H), 7.33-7.12 (m, 6H), 6.97 (dd, J = 6.6, 2.1 Hz, 1H), 4.67 (q, J = 5.1 Hz, 1H), 3.94-3.73 (m, 2H), 3.58-3.44 (m, 1H), 3.44 (s, 3H), 3.43-3.29 (m, 1H), 3.17 (s, J = 7.2 Hz, 2H), 1.27 (d, J = 5.1 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 152.9, 140.6, 132.2, 129.6, 129.5, 128.3, 128.0, 126.1, 123.4, 122.1, 121.7, 109.7, 107.9, 99.6, 78.9, 73.7, 65.0, 60.9, 35.4, 27.6, 20.0, 15.3; HR-ESIMS calcd for C₂₂H₂₄N₂NaO₃ [M+Na]+ 387.1679. Found 387.1689.

tert-Butyl benzyl((2-(2-(1-ethoxyethoxy)ethyl)phenyl)ethynyl)carbamate (3e)

To a solution of S11 (202 mg, 0.925 mmol) in dry acetone (6 mL) at rt was added AgNO₃ (15.7 mg, 0.0925 mmol) and NBS (191 mg, 1.07 mmol) were added successively, each in a single portion. After the mixture was stirred at rt under dark for 3.5 h, the reaction mixture was diluted with hexane and vigorously stirred for 5 min. The mixture was filtered and concentrated in vacuo. The residue was purified by short silica gel pad (3 cm) eluting with hexane to give S11' (252 mg) that was directly used in the next reaction. According to literature,⁸ a solution of S11' (252 mg, 0.847 mmol), tert-butyl benzylcarbamate (211 mg, 1.02 mmol), CuSO₄·5H₂O (42.3 mg, 0.169 mmol), 1,10-phenanthroline (61.1 mg, 0.339 mmol), and K₃PO₄ (432 mg, 2.03 mmol) in dry toluene (2.6 mL) was stirred at 80 °C for 43.5 h. The mixture was cooled to rt, diluted with EtOAc and filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/acetone = 20:1 to give 3e (156 mg, 40% in 2 steps) as colorless oil.

IR ν max: 2983, 2243, 1714, 1600 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.05 (m, 9H), 4.67 (s, 2H), 4.60 (q, J = 5.4 Hz, 1H), 3.76-3.67 (m, 1H), 3.64-3.42 (m, 2H), 3.39-3.28 (m, 1H), 2.92 (t, J = 6.9 Hz, 2H), 1.53 (s, 9H), 1.24 (d, J = 5.4 Hz, 3H), 1.11 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.5, 139.3, 136.2, 130.9, 129.2, 128.3, 128.1, 127.7, 126.8, 125.8, 123.1, 99.4, 87.5, 82.7, 69.7, 64.8, 60.7, 53.2, 35.1, 28.3, 20.1, 15.5; HR-ESIMS calcd for C₂₆H₃₅NNaO₄ [M+Na]+ 446.2302. Found 446.2299.
(4R)-3-((2-(1-Ethoxyethoxy)ethyl)phenyl)ethynyl)-4-phenyloxazolidin-2-one (3f)

According to GP-1, 3f (141 mg, 25%) was obtained as 1:1 diastereomer mixture from S11 (328 mg, 1.50 mmol), (R)-(-)-4-phenyl-2-oxazolidinone (1.22 g, 7.50 mmol), CuCl (40.3 mg, 0.300 mmol), Na2CO3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 1:3.

Colorless oil; [α]D 26 -153 (c 1.09, CHCl3); IR νmax: 3008, 2255, 1776, 1602 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.48-7.36 (m, 5H), 7.25 (dd, J = 6.9, 1.5 Hz, 1H), 7.17-7.12 (m, 2H), 7.11-7.01 (m, 1H), 5.18-5.10 (m, 1H), 4.77 (t, J = 8.7 Hz, 1H), 4.55 (q, J = 5.4 Hz, 0.5H), 4.54 (q, J = 5.4 Hz, 0.5H), 4.30 (dd, J = 8.7, 7.2 Hz, 1H), 3.60-3.25 (m, 4H), 2.72 (t, J = 7.2 Hz, 2H), 1.221 (d, J = 5.4 Hz, 1.5H), 1.219 (d, J = 5.4 Hz, 1.5H), 1.12 (t, J = 7.2 Hz, 1.5H), 1.11 (t, J = 7.2 Hz, 1.5H); 13C NMR (75 MHz, CDCl3) δ 155.2, 140.64, 140.57, 136.0, 131.83, 131.79, 129.5, 129.4, 129.2, 127.84, 127.83, 126.8, 125.9, 121.6, 99.5, 99.4, 81.5, 71.4, 70.8, 64.6, 62.3, 60.8, 60.7, 35.0, 19.99, 19.97, 15.4; HR-ESIMS calcd for C25H23NNaO4 [M+Na]+ 402.1676. Found 402.1673.

Methyl 1-((2-(2-(1-ethoxyethoxy)ethyl)phenyl)ethynyl)-1H-indole-3-carboxylate (3g)

According to GP-1, 3g (449 mg, 77%) was obtained from S11 (327 mg, 1.50 mmol), methyl 1H-indole-3-carboxylate (1.31 g, 7.50 mmol), CuCl2 (40.3 mg, 0.300 mmol), Na2CO3 (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 7:1.

Red oil; IR νmax: 3011, 2255, 1776, 1602 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.48-7.36 (m, 5H), 7.25 (dd, J = 6.9, 1.5 Hz, 1H), 7.17-7.12 (m, 2H), 7.11-7.01 (m, 1H), 5.18-5.10 (m, 1H), 4.77 (t, J = 8.7 Hz, 1H), 4.55 (q, J = 5.4 Hz, 0.5H), 4.54 (q, J = 5.4 Hz, 0.5H), 4.30 (dd, J = 8.7, 7.2 Hz, 1H), 3.60-3.25 (m, 4H), 2.72 (t, J = 7.2 Hz, 2H), 1.221 (d, J = 5.4 Hz, 1.5H), 1.219 (d, J = 5.4 Hz, 1.5H), 1.12 (t, J = 7.2 Hz, 1.5H), 1.11 (t, J = 7.2 Hz, 1.5H); 13C NMR (75 MHz, CDCl3) δ 155.2, 140.64, 140.57, 136.0, 131.83, 131.79, 129.5, 129.4, 129.2, 127.84, 127.83, 126.8, 125.9, 121.6, 99.5, 99.4, 81.5, 71.4, 70.8, 64.6, 62.3, 60.8, 60.7, 35.0, 19.99, 19.97, 15.4; HR-ESIMS calcd for C23H22NNaO4 [M+Na]+ 414.1676. Found 414.1679.

Preparation of Ynamide 3h

To a mixture of 2-(2-(1-Iodonaphthalen-1-yl)acetic acid (4.24 g, 13.6 mmol) in dry THF (35 mL) at 0 °C was added NaBH4 (1.03 g, 27.2 mmol). Then, BF3·OEt2 (3.41 mL, 27.2 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 80 min, followed by rt for 75 min. After reaction completed, the mixture was cooled to 0 °C, and was quenched with MeOH (23 mL) and 1 M HCl (23 mL), extracted with Et2O, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 2-(2-Iodonaphthalen-1-yl)ethan-1-
ol (2.43 g, 60%) as colorless solid.

To a mixture of 2-(2-iodonaphthalen-1-yl)ethan-1-ol (2.43 g, 8.17 mmol) and PPTS (205 mg, 0.817 mmol) in dry CH$_2$Cl$_2$ (42 mL) was added ethyl vinyl ether (1.41 mL, 14.7 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 25:1 to give 1-(2-(1-ethoxyethoxy)ethyl)-2-iodonaphthalene (2.98 g, 99%) as colorless oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.11 (d, $J$ = 7.5 Hz, 1H), 7.83 (d, $J$ = 8.7 Hz, 1H), 7.81-7.74 (m, 1H), 7.56-7.44 (m, 2H), 7.39 (d, $J$ = 8.7 Hz, 1H), 4.73 (q, $J$ = 5.1 Hz, 1H), 3.85-3.54 (m, 5H), 3.52-3.39 (m, 1H), 1.32 (d, $J$ = 5.1 Hz, 3H), 1.17 (t, $J$ = 6.9 Hz, 3H).

A mixture of 1-(2-(1-ethoxyethoxy)ethyl)-2-iodonaphthalene (2.98 g, 9.32 mmol), PdCl$_2$ (41.3 mg, 0.233 mmol), Ph$_3$P (122 mg, 0.466 mmol), CuI (64.0 mg, 0.336 mmol), Et$_3$N (3.90 mL, 28.0 mmol), and ethynyltrimethylsilane (1.98 mL, 14.0 mmol) in dry MeCN (19 mL) was stirred at rt for 16 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH$_3$. The mixture was extracted with Et$_2$O, washed with brine, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S12 (2.65 g, 84%) as brown oil. IR $\nu$ max: 3009, 2154, 1596 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.09 (d, $J$ = 8.4 Hz, 1H), 7.76 (dd, $J$ = 7.8, 1.8 Hz, 1H), 7.62 (d, $J$ = 8.4 Hz, 1H), 7.54-7.38 (m, 3H), 4.70 (q, $J$ = 5.4 Hz, 1H), 3.90-3.78 (m, 1H), 3.77-3.54 (m, 4H), 3.48-3.37 (m, 1H), 1.30 (d, $J$ = 5.4 Hz, 3H), 1.15 (t, $J$ = 6.9 Hz, 3H), 0.29 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.3, 133.3, 131.9, 128.7, 128.5, 126.6, 126.4, 126.2, 124.3, 120.6, 104.6, 99.7, 98.7, 64.9, 60.9, 31.6, 20.1, 15.4, 0.2; HR-ESIMS calcd for C$_{21}$H$_{28}$NaO$_2$Si [M+Na]$^+$ 363.1751. Found 363.1751.

1-((1-Ethoxyethoxy)methyl)-2-ethynylnaphthalene (S13) To a solution of S12 (1.35 g, 3.96 mmol) in MeOH (2 mL) at rt was added K$_2$CO$_3$ (274 mg, 1.98 mmol), and was stirred for 19 h. After reaction completed, the mixture was quenched with water, extracted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S13 (954 mg, 90%) as colorless oil. IR $\nu$ max: 3303, 3011, 2102, 1597 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.10 (d, $J$ = 8.1 Hz, 1H), 7.77 (d, $J$ = 8.4 Hz, 1H), 7.62 (d, $J$ = 8.4 Hz, 1H), 7.54-7.38 (m, 3H), 4.70 (q, $J$ = 5.4 Hz, 1H), 3.90-3.78 (m, 1H), 3.77-3.54 (m, 4H), 3.48-3.37 (m, 1H), 1.30 (d, $J$ = 5.4 Hz, 3H), 1.15 (t, $J$ = 6.9 Hz, 3H), 0.29 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 138.6, 133.4, 131.9, 128.7, 128.5, 126.4, 126.6, 126.2, 124.3, 120.6, 104.6, 99.7, 98.7, 64.9, 60.9, 31.6, 20.1, 15.4, 0.2; HR-ESIMS calcd for C$_{18}$H$_{20}$NaO$_2$ [M+Na]$^+$ 291.1356. Found 291.1353.

$^{N}$-((1-(2-(1-Ethoxyethoxy)ethyl)naphthalen-2-yl)ethynyl)-N,N-dimethylbenzenesulfonamide (3h) According to GP-1, 3h (597 mg, 88%) was obtained from S13 (403 mg, 1.00 mmol), $N$-methyl-p-toluenesulfonamide (1.39 g, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (243 $\mu$L, 3.00 mmol). Eluent: hexane/EtOAc = 5:1. Colorless crystals; mp 99-101 ºC (hexane/EtOAc); IR $\nu$ max: 3010, 2234, 1598, 1368, 1169 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.07 (d, $J$ = 8.7 Hz, 1H), 7.90-7.82 (m, 2H), 7.76 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.62 (d, $J$ = 8.4 Hz, 1H), 7.54-7.28 (m, 5H), 4.68 (q, $J$ = 5.4 Hz, 1H), 3.90-3.66 (m, 2H), 3.60-3.46 (m, 3H), 3.46-3.32 (m, 1H), 3.20 (s, 3H), 2.44 (s, 3H), 1.27 (d, $J$ = 5.4 Hz, 3H), 1.10 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (75
MHz, CDCl\textsubscript{3} δ 144.6, 136.7, 133.4, 132.9, 132.0, 129.8, 128.4, 128.3, 127.7, 126.6, 126.4, 125.8, 124.1, 120.2, 99.7, 88.0, 68.8, 65.0, 60.9, 39.4, 31.7, 21.7, 20.1, 15.4; HR-ESIMS calcld for C\textsubscript{26}H\textsubscript{29}NNaO\textsubscript{4}S [M+Na]\textsuperscript{+} 474.1710. Found 474.1710.

**Preparation of Ynamide 3i**

2-(2-(1-Ethoxyethoxy)ethyl)-1-ethynyl-4-methylbenzene (S14)

To a mixture of 2-(2-ethynyl-5-methylphenyl)ethan-1-ol\textsuperscript{10} (234 mg, 1.46 mmol) and PPTS (36.7 mg, 0.146 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (7.3 mL) was added ethyl vinyl ether (210 μL, 2.19 mmol) and stirred at rt for 16.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO\textsubscript{3}, extracted with CH\textsubscript{2}Cl\textsubscript{2}, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S14 (305 mg, 90%) as yellow oil.

IR ν\textsubscript{max}: 3301, 3010, 2103, 1611 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.36 (d, \textit{J} = 7.8 Hz, 1H), 7.07 (d, \textit{J} = 1.2 Hz, 1H), 6.98 (dd, \textit{J} = 7.8, 1.2 Hz, 1H), 4.69 (q, \textit{J} = 5.4 Hz, 1H), 5.35-3.51 (m, 1H), 3.46-3.36 (m, 1H), 3.20 (s, 1H), 3.04 (t, \textit{J} = 7.2 Hz, 2H), 2.32 (s, 3H), 1.30 (d, \textit{J} = 5.4 Hz, 3H), 1.16 (t, \textit{J} = 7.2 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 141.1, 138.9, 132.7, 130.4, 127.0, 118.8, 99.4, 82.2, 80.0, 64.7, 60.8, 35.0, 21.4, 19.8, 15.2; HR-ESIMS calcld for C\textsubscript{15}H\textsubscript{20}NaO\textsubscript{2} [M+Na]\textsuperscript{+} 255.1356. Found 255.1358.

N-((2-(2-(1-Ethoxyethoxy)ethyl)-4-methylphenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (3i)

According to GP-1, 3i (96.4 mg, 27%) was obtained from S14 (204 mg, 0.877 mmol), N-methyl-\textit{p}-toluenesulfonamide (813 mg, 4.39 mmol), CuCl\textsubscript{2} (23.5 mg, 0.175 mmol), Na\textsubscript{2}CO\textsubscript{3} (185 mg, 1.75 mmol), and pyridine (142 μL, 1.75 mmol). Eluent: hexane/CH\textsubscript{2}Cl\textsubscript{2}/EtOAc = 15:15:1.

Colorless oil; IR ν\textsubscript{max}: 3009, 2236, 1599, 1368, 1169 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.82 (d, \textit{J} = 8.4 Hz, 2H), 7.34 (d, \textit{J} = 7.8 Hz, 2H), 7.21 (d, \textit{J} = 7.8 Hz, 1H), 7.03 (d, \textit{J} = 1.2 Hz, 1H), 6.94 (dd, \textit{J} = 7.8, 1.2 Hz, 1H), 4.65 (q, \textit{J} = 5.4 Hz, 1H), 3.81-3.48 (m, 3H), 3.44-3.32 (m, 1H), 3.14 (s, 3H), 2.95 (t, \textit{J} = 7.2 Hz, 2H), 2.45 (s, 3H), 2.31 (s, 3H), 1.27 (d, \textit{J} = 5.4 Hz, 3H), 1.13 (t, \textit{J} = 7.2 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 144.4, 140.1, 137.7, 133.1, 131.7, 130.2, 129.6, 127.6, 126.8, 119.1, 99.5, 86.5, 67.5, 65.1, 61.0, 39.5, 35.3, 21.8, 21.6, 20.1, 15.5; HR-ESIMS calcld for C\textsubscript{23}H\textsubscript{29}NNaO\textsubscript{4}S [M+Na]\textsuperscript{+} 438.1715. Found 438.1710.
Preparation of Ynamide 3j

2-(2-(1-Ethoxyethoxy)ethyl)-1-ethynyl-4-fluorobenzene (S15)

To a mixture of 2-(2-ethynyl-5-fluorophenyl)ethan-1-ol (550 mg, 3.35 mmol) and PPTS (84.2 mg, 0.335 mmol) in dry CH$_2$Cl$_2$ (16.8 mL) was added ethyl vinyl ether (481 µL, 5.02 mmol) and stirred at rt for 15.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S15 (655 mg, 83%) as orange oil.

IR ν$_{max}$: 3305, 3011, 1608 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.43 (dd, J = 8.4, 5.7 Hz, 1H), 6.98 (dd, J = 8.4, 2.7 Hz, 1H), 6.86 (td, J = 8.4, 2.7 Hz, 1H), 4.67 (q, J = 5.1 Hz, 1H), 3.85-3.76 (m, 1H), 3.73-3.64 (m, 1H), 3.59-3.48 (m, 1H), 3.44-3.33 (m, 1H), 3.59-3.33 (m, 2H), 3.21 (s, 1H), 3.05 (t, J = 7.2 Hz, 1H), 1.29 (d, J = 5.1 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 162.2 (d, J = 247.6 Hz), 144.1 (d, J = 8.0 Hz), 134.1 (d, J = 8.6 Hz), 117.7 (d, J = 3.5 Hz), 116.5 (d, J = 21.8 Hz), 113.3 (d, J = 21.7 Hz), 99.3, 81.1, 80.5 (d, J = 1.7 Hz), 64.1, 60.8, 35.1 (d, J = 1.1 Hz), 19.9, 15.4; HR-ESIMS calcd for C$_{14}$H$_{17}$FNaO$_2$ [M+Na]$^+$ 259.1110. Found 259.1105.

N-((2-(2-(1-Ethoxyethoxy)ethyl)-4-fluorophenyl)ethynyl)-N,N-dimethylbenzenesulfonamide (3j)

According to GP-1, 3j (422 mg, 47%) was obtained from S15 (503 mg, 2.13 mmol), N-methyl-p-toluenesulfonamide (1.97 g, 10.6 mmol), CuCl$_2$ (57.3 mg, 0.426 mmol), Na$_2$CO$_3$ (452 mg, 4.26 mmol), and pyridine (345 µL, 4.26 mmol). Eluent: hexane/EtOAc = 5:1. Colorless oil; IR ν$_{max}$: 2987, 2238, 1599, 1369, 1168 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.28 (dd, J = 8.7, 5.7 Hz, 1H), 6.96 (dd, J = 9.6, 2.4 Hz, 1H), 6.83 (td, J = 8.4, 2.7 Hz, 1H), 4.65 (q, J = 5.4 Hz, 1H), 3.83-3.74 (m, 1H), 3.70-3.62 (m, 1H), 3.57-3.46 (m, 1H), 3.43-3.32 (m, 1H), 3.15 (s, 3H), 2.97 (t, J = 6.9 Hz, 2H), 2.45 (s, 3H), 1.27 (d, J = 5.4 Hz, 3H), 1.13 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 161.7 (d, J = 246.5 Hz), 144.6, 143.3 (d, J = 8.0 Hz), 133.4 (d, J = 8.6 Hz), 133.1, 129.7, 127.6, 118.1 (d, J = 3.5 Hz), 116.4 (d, J = 21.7 Hz), 113.2 (d, J = 21.7 Hz), 99.5, 86.9, 86.6, 64.4, 60.9, 39.4, 35.2 (d, J = 1.5 Hz), 21.8, 20.0, 15.5; HR-ESIMS calcd for C$_{12}$H$_{26}$FNNaO$_4$S [M+Na]$^+$ 442.1464. Found 442.1462.
Preparation of Ynamide 3k

![Ynamide 3k Preparation](image)

1-(2-(1-Ethoxyethoxy)-2-methylpropyl)-2-ethynylbenzene (S16)

To a mixture of 1-(2-ethynylphenyl)-2-methylpropan-2-ol\(^{10}\) (1.64 g, 9.43 mmol) and PPTS (237 mg, 0.943 mmol) in dry CH\(_2\)Cl\(_2\) (47.2 mL) was added ethyl vinyl ether (1.35 mL, 14.1 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 40:1 to give S16 (1.94 g, 83%) as pale yellow oil.

IR \(\nu_{\text{max}}\): 3305, 2981, 1600 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.45 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.37 (dd, \(J = 7.8, 1.5\) Hz, 2H), 7.24 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.14 (td, \(J = 7.5, 1.5\) Hz, 1H), 4.94 (q, \(J = 5.4\) Hz, 1H), 3.57-3.38 (m, 2H), 3.21 (s, 1H), 3.10 (d, \(J = 16.2\) Hz, 1H), 3.05 (d, \(J = 16.2\) Hz, 1H), 1.29 (d, \(J = 5.4\) Hz, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.15 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 140.7, 132.5, 131.1, 127.9, 125.8, 122.7, 93.7, 83.4, 80.3, 76.9, 58.5, 46.0, 26.7, 25.7, 21.9, 15.6; HR-ESIMS calcd for C\(_{16}\)H\(_{22}\)NaO\(_2\) \([\text{M+Na}]^+\) 269.1512. Found 269.1511.

**N-((2-(1-Ethoxyethoxy)-2-methylpropyl)phenyl)ethynyl-N,4-dimethylbenzenesulfonamide (3k)**

According to GP-1, 3k (845 mg, 68%) was obtained from S16 (713 mg, 2.89 mmol), N-methyl-p-toluenesulfonamide (2.68 g, 14.5 mmol), CuCl\(_2\) (77.8 mg, 0.579 mmol), Na\(_2\)CO\(_3\) (614 mg, 5.79 mmol), and pyridine (468 \(\mu\)L, 5.79 mmol). Eluent: hexane/EtOAc = 6:1. Pale yellow oil; IR \(\nu_{\text{max}}\): 2981, 2234, 1598, 1368, 1167 cm\(^{-1}\);

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.83 (d, \(J = 8.5\) Hz, 2H), 7.38-7.34 (m, 3H), 7.31 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.19 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.13 (td, \(J = 7.5, 1.5\) Hz, 1H), 4.94 (q, \(J = 5.0\) Hz, 1H), 3.54-3.40 (m, 2H), 3.17 (s, 3H), 3.02 (d, \(J = 15.5\) Hz, 1H), 2.99 (d, \(J = 15.5\) Hz, 1H), 2.45 (s, 3H), 1.28 (d, \(J = 5.0\) Hz, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.13 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.7, 140.0, 133.4, 131.6, 131.4, 129.8, 127.7, 127.2, 125.9, 123.5, 93.8, 86.6, 76.9, 68.9, 58.6, 46.1, 39.3, 26.5, 25.3, 21.8, 21.6, 15.4; HR-ESIMS calcd for C\(_{24}\)H\(_{31}\)NNaO\(_2\)S \([\text{M+Na}]^+\) 452.1866. Found 452.1862.
Preparation of Ynamide 3l

To a mixture of \((1^R*, 2^S*)-2-(2-ethynylphenyl)cyclopentan-1-ol\)\(^{10}\) (1.44 g, 7.71 mmol) and PPTS (194 mg, 0.771 mmol) in dry CH\(_2\)Cl\(_2\) (39 mL) was added ethyl vinyl ether (1.11 mL, 11.6 mmol) and stirred at rt for 22.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 40:1 to give \(\text{S17}\) (1.37 g, 69%) as yellow oil as 1:1 diastereomer mixture.

**IR** \(\nu_{\max}^\text{max}\): 3305, 2976, 2104, 1598 cm\(^{-1}\); **\(^1\)H NMR** (300 MHz, CDCl\(_3\)) \(\delta\) 7.45 (d, \(J = 7.8\) Hz, 1H), 7.32-7.24 (m, 1H), 7.21 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.15-7.08 (m, 1H), 4.65 (q, \(J = 5.1\) Hz, 0.5H), 4.55 (q, \(J = 5.1\) Hz, 0.5H), 4.36-4.26 (m, 1H), 3.66-3.55 (m, 1H), 3.54-3.43 (m, 0.5H), 3.35-3.13 (m, 2.5H), 2.18-2.15 (m, 1H), 2.12-1.97 (m, 1H), 1.94-1.58 (m, 4H), 1.21 (d, \(J = 5.1\) Hz, 1.5H), 1.18 (d, \(J = 5.1\) Hz, 1.5H), 1.00 (t, \(J = 6.9\) Hz, 1.5H), 0.99 (t, \(J = 6.9\) Hz, 1.5H); **\(^{13}\)C NMR** (75 MHz, CDCl\(_3\)) \(\delta\) 146.7, 146.5, 132.95, 132.90, 128.9, 128.7, 126.42, 126.39, 125.58, 125.57, 121.5, 121.4, 99.0, 98.3, 83.1, 82.55, 82.49, 82.0, 81.13, 81.09, 60.6, 59.8, 50.6, 50.3, 33.7, 33.0, 32.7, 32.5, 23.6, 23.2, 21.0, 20.6, 15.3, 15.2; HR-ESIMS calcd for C\(_{17}\)H\(_{22}\)NaO\(_2\)\([\text{M+Na}]^+\) 281.1512. Found 281.1509.

**N-((2-((1^R*, 2^S*)-2-(1-Ethoxyethoxy)cyclopentyl)phenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (3l)**

According to GP-1, \(3l\) (940 mg, 84%) was obtained as 1:1 diastereomer mixture from S17 (644 mg, 2.49 mmol), N-methyl-p-toluensulfonamide (2.31 g, 12.5 mmol), CuCl\(_2\) (67.0 mg, 0.499 mmol), Na\(_2\)CO\(_3\) (523 mg, 4.99 mmol), and pyridine (403 \(\mu\)L, 4.99 mmol). Eluent: hexane/EtOAc = 9:1. Pale yellow oil; **IR** \(\nu_{\max}^\text{max}\): 2977, 2234, 1598, 1369, 1168 cm\(^{-1}\); **\(^1\)H NMR** (300 MHz, CDCl\(_3\)) \(\delta\) 7.88-7.82 (m, 2H), 7.38-7.29 (m, 3H), 7.26-7.17 (m, 2H), 7.13-7.06 (m, 1H), 4.63 (q, \(J = 5.4\) Hz, 0.5H), 4.50 (q, \(J = 5.4\) Hz, 0.5H), 4.35-4.27 (m, 1H), 3.52-3.36 (m, 1.5H), 3.34-3.08 (m, 4.5H), 2.45 (s, 3H), 2.22-1.98 (m, 2H), 1.89-1.51 (m, 4H), 1.77 (d, \(J = 5.4\) Hz, 1.5H), 1.15 (d, \(J = 5.4\) Hz, 1.5H), 1.00 (t, \(J = 6.9\) Hz, 1.5H), 0.95 (t, \(J = 6.9\) Hz, 1.5H); **\(^{13}\)C NMR** (75 MHz, CDCl\(_3\)) \(\delta\) 145.7, 145.5, 144.41, 144.38, 133.1, 132.1, 129.6, 129.5, 127.94, 127.85, 127.8, 127.7, 127.6, 126.4, 126.3, 125.6, 125.5, 122.1, 122.0, 99.1, 98.4, 87.4, 87.3, 82.7, 81.6, 68.0, 67.9, 60.7, 59.7, 50.8, 50.5, 39.5, 33.7, 33.2, 32.7, 32.6, 23.4, 23.1, 21.8, 21.0, 20.7, 15.3, 15.2; HR-ESIMS calcd for C\(_{25}\)H\(_{31}\)NNaO\(_4\)S [M+Na]^+ 464.1866. Found 464.1864.
1-((1R*,2S*)-2-(1-Ethoxyethoxy)cyclohexyl)-2-ethynylbenzene (S18)
To a mixture of (1R*,2S*)-2-(2-ethynylphenyl)cyclohexan-1-ol (10.179 g, 8.91 mmol) and PPTS (224 mg, 0.891 mmol) in dry CH2Cl2 (44.6 mL) was added ethyl vinyl ether (1.28 mL, 13.4 mmol) and stirred at rt overnight. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO3, extracted with CH2Cl2, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S18 (1.15 g, 48%) as colorless oil as 4:3 diastereomer mixture.

IR νmax: 3305, 2936, 2104, 1599 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.47-7.42 (m, 1H), 7.31-7.23 (m, 2H), 7.15-7.07 (m, 1H), 4.57 (q, J = 5.1 Hz, 3/7H), 4.11 (q, J = 5.1 Hz, 4/7H), 3.76 (br s, 1H), 3.38 (q, J = 7.2 Hz, 1H), 3.25 (s, 4/7H), 3.2 (s, 3/7H), 3.24-3.05 (m, 10/7), 2.61-2.50 (m, 4/7H), 2.20-2.12 (m, 1H), 1.92-1.68 (m, 3H), 1.64-1.25 (m, 4H), 1.12 (d, J = 5.4 Hz, 0.5H), 1.11 (t, J = 5.1 Hz, 0.5H), 0.89 (t, J = 7.2 Hz, 1.5H), 0.84 (d, J = 5.4 Hz, 1.5H); 13C NMR (75 MHz, CDCl3) δ 146.9, 146.6, 145.8, 144.3, 133.1, 133.0, 131.2, 129.6, 127.9, 127.71, 127.67, 127.27, 127.25, 126.4, 125.5, 125.3, 122.7, 100.7, 97.5, 87.2, 80.9, 68.3, 59.3, 59.1, 48.2, 39.34, 39.32, 34.5, 33.4, 26.1, 26.0, 25.4, 25.2, 21.8, 21.1, 20.5, 16.5, 15.3; HR-ESIMS calcd for C18H20NaO2 [M+Na]+ 295.1669. Found 295.1667.

N-((2-((1R*,2S*)-2-(1-Ethoxyethoxy)cyclohexyl)phenyl)ethynyl)-N4-dimethylbenzenesulfonamide (3m)
According to GP-1, 3m (639 mg, 70%) was obtained as 1:1 diastereomer mixture from S18 (545 mg, 2.00 mmol), N-methyl-p-toluenesulfonamide (1.85 g, 10.0 mmol), CuCl2 (53.8 mg, 0.400 mmol), Na2CO3 (434 mg, 4.00 mmol), and pyridine (324 µL, 4.00 mmol). Eluent: hexane/EtOAc = 9:1. Colorless oil; IR νmax: 2936, 2234, 1598, 1367, 1168 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.92-7.84 (m, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.29-7.17 (m, 3H), 7.12-7.03 (m, 1H), 4.56 (q, J = 5.4 Hz, 0.5H), 4.15 (q, J = 5.1 Hz, 0.5H), 3.71 (br s, 1H), 3.50-3.33 (m, 1H), 3.27-3.01 (m, 4.5H), 2.61-2.49 (m, 0.5H), 2.43 (s, 3H), 2.23-2.11 (m, 1H), 1.88-1.66 (m, 3H), 1.56-1.25 (m, 4H), 1.15 (d, J = 5.1 Hz, 1.5H), 1.12 (t, J = 5.1 Hz, 1.5H), 0.87 (t, J = 7.2 Hz, 1.5H), 0.79 (d, J = 5.4 Hz, 1.5H); 13C NMR (75 MHz, CDCl3) δ 145.8, 145.6, 144.3, 133.1, 133.0, 131.2, 129.6, 127.71, 127.67, 127.27, 127.25, 126.4, 125.5, 125.3, 122.7, 100.7, 97.5, 87.2, 80.9, 68.3, 59.3, 59.1, 48.2, 39.34, 39.32, 34.5, 33.4, 26.1, 26.0, 25.4, 25.2, 21.8, 21.1, 20.5, 16.5, 15.3; HR-ESIMS calcd for C26H33NNaO4S [M+Na]+ 478.2023. Found 478.2027.
Preparation of Ynamide 3n

1) NaBH₄, BF₃·OEt₂, THF, 0 °C, 80 min; rt, 40 min, 71%

2) PPTS, CH₂Cl₂, rt, 1.5 h, 97%

3) TMS, PdCl₂, Ph₃P, CuI, Et₃N, MeCN, rt, 18 h, 74%

(2-(1-(1-Ethoxyethoxy)propan-2-yl)-5-isobutylphenyl)ethynyl)trimethylsilane (S19)

To a mixture of 2-(2-iodo-4-isobutylphenyl)propanoic acid⁹ (5.36 g, 16.1 mmol) in dry THF (40 mL) at 0 °C was added NaBH₄ (1.22 g, 32.3 mmol). Then, BF₃·OEt₂ (4.05 mL, 32.3 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 80 min, followed by rt for 40 min. After reaction completed, the mixture was cooled to 0 °C, and was quenched with MeOH (18 mL) and 1 M HCl (18 mL), extracted with Et₂O, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 7:1 to give 2-(2-iodo-4-isobutylphenyl)propan-1-ol (3.63 g, 71%) as colorless oil.¹ H NMR (300 MHz, CDCl₃) δ 7.64 (s, 1H), 7.11-7.05 (m, 2H), 3.80-3.59 (m, 2H), 3.28 (sext, J = 6.6 Hz, 1H), 2.37 (d, J = 7.2 Hz, 2H), 1.92-1.73 (m, 1H), 1.50 (br s, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.6 Hz, 6H).

To a mixture of 2-(2-iodo-4-isobutylphenyl)propan-1-ol (3.62 g, 11.4 mmol) and PPTS (286 mg, 1.14 mmol) in dry CH₂Cl₂ (57 mL) was added ethyl vinyl ether (1.63 mL, 17.1 mmol) and stirred at rt for 1.5 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 40:1 to give 1-(1-(1-ethoxyethoxy)propan-2-yl)-2-iodo-4-isobutylbenzene (4.30 g, 97%) as colorless oil.¹ H NMR (300 MHz, CDCl₃) δ 7.61 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.05 (dd, J = 8.1, 1.5 Hz, 1H), 4.72-4.64 (m, 1H), 3.72-3.24 (m, 5H), 2.37 (d, J = 7.2 Hz, 2H), 1.90-1.74 (m, 1H), 1.30-1.25 (m, 6H), 1.16 (t, J = 6.9 Hz, 1.5H), 1.15 (t, J = 6.9 Hz, 1.5H), 0.89 (d, J = 6.6 Hz, 6H).

A mixture of 1-(1-(1-ethoxyethoxy)propan-2-yl)-2-iodo-4-isobutylbenzene (4.30 g, 11.0 mmol), PdCl₂ (48.8 mg, 0.275 mmol), Ph₃P (144 mg, 0.551 mmol), CuI (75.5 mg, 0.397 mmol), Et₃N (4.61 mL, 33.1 mmol), and ethynyltrimethylsilane (2.33 mL, 16.5 mmol) in dry MeCN (22 mL) was stirred at rt for 18 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH₃. The mixture was extracted with Et₂O, washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 60:1 to give S19 (2.94 g, 74%) as yellow oil as 1:1 diastereomer mixture. IR νmax: 2961, 2149, 1606 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.05 (dd, J = 8.1, 1.5 Hz, 1H), 4.72-4.64 (m, 1H), 3.72-3.24 (m, 5H), 2.37 (d, J = 7.2 Hz, 2H), 1.90-1.74 (m, 1H), 1.30-1.25 (m, 6H), 1.16 (t, J = 6.9 Hz, 1.5H), 1.15 (t, J = 6.9 Hz, 1.5H), 0.89 (d, J = 6.6 Hz, 6H).

S25
MHz, CDCl$_3$ δ 7.23 (d, $J = 1.8$ Hz, 1H), 7.12 (d, $J = 8.1$ Hz, 1H), 7.03 (dd, $J = 8.1$, 1.8 Hz, 1H), 4.70-4.64 (m, 1H), 3.74 (dd, $J = 8.4$, 4.8 Hz, 0.5H), 3.69-3.33 (m, 4.5H), 2.39 (d, $J = 7.2$ Hz, 2H), 1.92-1.74 (m, 1H), 1.32 (d, $J = 6.6$ Hz, 1.5H), 1.31 (d, $J = 6.6$ Hz, 1.5H), 1.29 (d, $J = 5.4$ Hz, 1.5H), 1.28 (d, $J = 5.4$ Hz, 1.5H), 1.16 (t, $J = 7.2$ Hz, 1.5H), 1.15 (t, $J = 7.2$ Hz, 1.5H), 0.88 (d, $J = 6.6$ Hz, 6H), 0.25 (s, 9H); 13C NMR (75 MHz, CDCl$_3$) δ 143.4, 143.3, 139.1, 139.0, 133.09, 133.08, 129.4, 125.7, 122.0, 104.1, 104.0, 99.6, 99.4, 97.55, 97.45, 70.3, 69.5, 61.0, 60.9, 44.8, 37.4, 37.2, 30.2, 22.5, 20.3, 20.0, 17.8, 17.7, 15.5, 0.3; HR-ESIMS calcd for C$_{22}$H$_{36}$NaO$_2$Si [M+Na]$^+$ 383.2377. Found 383.2372.

1-(1-(1-Ethoxyethoxy)propan-2-yl)-2-ethynyl-4-isobutylbenzene (S20)

To a solution of S19 (2.93 g, 8.13 mmol) in MeOH (4.1 mL) at rt was added K$_2$CO$_3$ (561 mg, 4.06 mmol), and was stirred for 4.5 h. After reaction completed, the mixture was quenched with water, extracted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 30:1 to give S20 (2.23 g, 95%) as colorless oil as 1:1 diastereomer mixture.

IR $\nu_{\text{max}}$: 3305, 2961, 2102, 1607 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 7.25 (d, $J = 1.8$ Hz, 1H), 7.15 (d, $J = 8.1$ Hz, 1H), 7.06 (dd, $J = 8.1$, 1.8 Hz, 1H), 4.71 (q, $J = 5.4$ Hz, 1H), 3.75 (dd, $J = 9.0$, 5.4 Hz, 0.5H), 3.70-3.31 (m, 4.5H), 3.220 (s, 0.5H), 3.216 (s, 0.5H), 2.40 (d, $J = 7.2$ Hz, 2H), 1.90-1.73 (m, 1H), 1.33-1.26 (m, 6H), 1.15 (t, $J = 7.2$ Hz, 1.5H), 1.14 (t, $J = 7.2$ Hz, 1.5H), 0.88 (d, $J = 6.3$ Hz, 6H); 13C NMR (75 MHz, CDCl$_3$) δ 143.63, 143.60, 139.11, 139.09, 133.3, 129.7, 125.7, 121.0, 99.5, 99.3, 82.5, 80.5, 69.8, 69.6, 60.9, 60.7, 44.7, 37.1, 37.0, 30.2, 22.5, 20.0, 19.9, 18.0, 17.9, 15.4; HR-ESIMS calcd for C$_{19}$H$_{28}$NaO$_2$ [M+Na]$^+$ 311.1982. Found 311.1974.

N-((2-(1-(1-Ethoxyethoxy)propan-2-yl)-5-isobutylphenyl)ethynyl)-N-,4-dimethylbenzenesulfonamide (3n)

According to GP-1, 3n (476 mg, 67%) was obtained as 1.1 diastereomer mixture from S20 (433 mg, 1.50 mmol), N-methyl-p-toluenesulfonamide (1.39 g, 7.50 mmol), CuCl$_2$ (40.3 mg, 0.300 mmol), Na$_2$CO$_3$ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/EtOAc = 30:1 to give S20 (2.23 g, 95%) as colorless oil as 1:1 diastereomer mixture.

IR $\nu_{\text{max}}$: 2960, 2236, 1598, 1368, 1168 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$) δ 7.83 (d, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.14-7.10 (m, 2H), 7.00 (dd, $J = 8.1$, 2.1 Hz, 1H), 4.64 (q, $J = 5.1$ Hz, 1H), 3.74-3.67 (m, 0.5H), 3.63-3.29 (m, 4.5H), 3.16 (s, 3H), 2.45 (s, 3H), 2.39 (d, $J = 7.2$ Hz, 2H), 1.92-1.73 (m, 1H), 1.30-1.24 (m, 6H), 1.13 (t, $J = 7.2$ Hz, 1.5H), 1.12 (t, $J = 7.2$ Hz, 1.5H), 0.89 (d, $J = 6.6$ Hz, 6H), 1.30 (t, $J = 7.2$ Hz, 1.5H); 13C NMR (75 MHz, CDCl$_3$) δ 144.4, 142.6, 142.5, 139.1, 139.0, 133.1, 132.4, 129.6, 128.7, 127.64, 127.63, 125.63, 125.61, 121.54, 121.51, 99.54, 99.47, 86.9, 70.1, 69.7, 67.9, 67.8, 60.9, 60.8, 44.8, 39.5, 37.20, 37.15, 30.2, 22.52, 22.51, 21.8, 20.1, 19.9, 18.13, 18.05, 15.48, 15.46; HR-ESIMS calcd for C$_{27}$H$_{37}$NNaO$_4$S [M+Na]$^+$ 494.2336. Found 494.2324.
Preparation of Ynamide 3o

\[
\text{Br} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\begin{array}{c}
\text{THF} \\
\text{r-BuLi} \\
\text{-78 °C, 1 h} \\
\text{BF}_3\cdot\text{OEt}_2 \\
\text{-78 °C, 3 h} \\
\text{K}_2\text{CO}_3 \\
\text{MeOH} \\
\text{rt, 21 h} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{TMS} \\
\text{OH} \\
\text{TMS} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

(\text{2R,4S}-4,8-Dimethyl-1-(2-((trimethylsilyl)ethynyl)phenyl)non-7-en-2-ol (S21))

According to literature\textsuperscript{11} to a solution of ((2-bromophenyl)ethynyl)trimethylsilane (1.53 g, 6.05 mmol) in dry THF (18 mL) at -78 °C was added \textit{n}-BuLi (8.36 mL, 1.57 M in hexane, 6.05 mmol). After stirring for 1 h at -78 °C, \((R)-2-((S)-2,6-dimethylhept-5-en-1-yl)oxirane\textsuperscript{12} (764 mg, 4.54 mmol) in THF (3 mL) was added via cannula followed by adding BF\textsubscript{3}\cdot\text{OEt}_2 (0.684 mL, 5.45 mmol). After stirring for 3 h at -78 °C, the reaction mixture was quenched with saturated aqueous solution of NaHCO\textsubscript{3}, extracted with EtOAc, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 15:1 to give S21 (1.07 g, 69%) as colorless oil.

\([\alpha]_D^{24}\textsuperscript{29} -40.0 (c 1.44, \text{CHCl}_3)\); IR \(\nu_{\text{max}}\): 3598, 2963, 2154, 1599 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.45 (dd, \(J = 7.5, 0.6\) Hz, 1H), 7.27-7.11 (m, 3H), 5.09 (tt, \(J = 6.9, 1.5\) Hz, 1H), 4.10-3.98 (m, 1H), 3.05 (dd, \(J = 13.2, 3.9\) Hz, 1H), 2.74 (dd, \(J = 13.2, 8.7\) Hz, 1H), 2.07-1.92 (m, 2H), 1.81-1.53 (m, 8H), 1.46 (d, \(J = 3.6\) Hz, 1H), 1.39-1.15 (m, 3H), 0.90 (d, \(J = 6.6\) Hz, 3H), 0.25 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 141.0, 132.5, 130.9, 129.9, 128.4, 126.1, 124.6, 122.9, 103.9, 98.2, 69.7, 44.8, 43.8, 38.3, 29.1, 25.9, 25.7, 19.3, 17.9, 0.3; HR-ESIMS calcd for C\textsubscript{22}H\textsubscript{34}NaOSi [M+Na\textsuperscript{+}] 365.2271. Found 365.2276.

(\text{2R,4S})-1-(2-Ethynylphenyl)-4,8-dimethyl-7-en-2-ol (S22)

To a solution of S21 (1.07 g, 3.12 mmol) in MeOH (9.4 mL) at rt was added K\textsubscript{2}CO\textsubscript{3} (431 mg, 3.12 mmol), and was stirred for 21 h. After reaction completed, the mixture was quenched with water, extracted with Et\textsubscript{2}O, washed with brine, dried over MgSO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 8:1 to give S22 (798 mg, 95%) as colorless oil.

\([\alpha]_D^{24}\textsuperscript{29} -21.6 (c 1.40, \text{CHCl}_3)\); IR \(\nu_{\text{max}}\): 3599, 3304, 2926, 2104, 1600 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.48 (dd, \(J = 7.5, 1.2\) Hz, 1H), 7.31-7.14 (m, 3H), 5.09 (tt, \(J = 7.2, 1.5\) Hz, 1H), 4.10-3.98 (m, 1H), 3.25 (s, 1H), 3.05 (dd, \(J = 13.2, 3.9\) Hz, 1H), 2.79 (dd, \(J = 13.2, 8.7\) Hz, 1H), 2.09-1.87 (m, 2H), 1.77-1.53 (m, 8H), 1.47 (d, \(J = 3.3\) Hz, 1H), 1.42-1.11 (m, 3H), 0.90 (d, \(J = 6.6\) Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 141.2,
132.9, 130.9, 129.9, 128.7, 126.2, 124.6, 121.9, 82.4, 81.0, 69.8, 44.7, 43.4, 37.9, 29.2, 25.9, 25.7, 19.3, 17.8; HR-ESIMS calcd for C_{19}H_{26}NaO [M+Na]^+ 293.1876. Found 293.1872.

**1-((2R,4S)-2-(1-Ethoxyethoxy)-4,8-dimethylnon-7-en-1-yl)-2-ethynylbenzene (S23)**

To a mixture of S22 (707 mg, 2.61 mmol) and PPTS (65.7 mg, 0.261 mmol) in dry CH_2Cl_2 (13 mL) was added ethyl vinyl ether (376 μL, 3.92 mmol) and stirred at rt for 3 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO_3, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 50:1 to give S23 (810 mg, 90%) as colorless oil as 1:1 diastereomer mixture.

IR ν_max: 3304, 2930, 2104, 1600 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 7.45 (br d, J = 6.9 Hz, 1H), 7.28-7.09 (m, 3H), 5.12-5.03 (m, 1H), 4.72 (q, J = 5.4 Hz, 0.5H), 4.41 (q, J = 5.4 Hz, 0.5H), 4.07-3.90 (m, 1H), 3.56-3.36 (m, 1.5H), 3.25 (s, 0.5H), 3.23 (s, 0.5H), 3.20-2.92 (m, 2.5H), 2.08-1.83 (m, 2H), 1.76-1.49 (m, 8H), 1.42-1.29 (m, 1H), 1.27-1.00 (m, 8H), 0.85 (d, J = 6.6 Hz, 1.5H), 0.82 (d, J = 6.6 Hz, 1.5H); ^13C NMR (75 MHz, CDCl_3) δ 141.5, 141.4, 132.69, 132.66, 130.8, 130.7, 130.5, 130.1, 128.4, 125.9, 125.8, 124.8, 124.6, 121.7, 99.0, 98.9, 82.65, 82.58, 80.9, 80.8, 74.7, 74.6, 60.1, 59.8, 43.4, 42.7, 41.1, 37.7, 37.6, 29.0, 28.9, 25.9, 25.7, 20.8, 20.6, 19.8, 19.5, 17.8, 15.5, 15.4; HR-ESIMS calcd for C_{23}H_{34}NaO_2 [M+Na]^+ 365.2451. Found 365.2448.

**N-((2-((2R,4S)-2-(1-Ethoxyethoxy)-4,8-dimethylnon-7-en-1-yl)phenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (3o)**

According to GP-1, 3o (637 mg, 81%) was obtained as 1:1 diastereomer mixture from S23 (514 mg, 1.50 mmol), N-methyl-p-toluenesulfonamide (1.39 g, 7.50 mmol), CuCl_2 (40.3 mg, 0.300 mmol), Na_2CO_3 (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 9:1. Colorless oil; IR ν_max: 2930, 2234, 1598, 1369, 1168 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 7.82 (d, J = 7.8 Hz, 2H), 7.38-7.29 (m, 3H), 7.24-7.08 (m, 3H), 5.10-5.00 (m, 1H), 4.71 (q, J = 5.1 Hz, 0.5H), 4.40 (q, J = 5.1 Hz, 0.5H), 4.01-3.83 (m, 1H), 3.54-3.38 (m, 1.5H), 3.27-3.18 (m, 0.5H), 3.154 (s, 1.5H), 3.149 (s, 1.5H), 3.09 (dd, J = 13.2, 6.0 Hz, 0.5H), 2.97-2.77 (m, 1.5H), 2.45 (s, 3H), 2.02-1.80 (m, 2H), 1.72-1.43 (m, 8H), 1.32-1.18 (m, 2.5H), 1.17-1.02 (m, 6.5H), 0.80 (d, J = 6.6 Hz, 1.5H), 0.78 (d, J = 6.6 Hz, 1.5H); ^13C NMR (75 MHz, CDCl_3) δ 144.4, 140.6, 140.5, 133.1, 132.2, 132.1, 130.8, 130.7, 130.1, 129.6, 127.63, 127.62, 125.9, 125.8, 124.7, 124.6, 122.4, 99.3, 98.7, 87.2, 87.1, 75.2, 74.5, 67.94, 67.87, 59.7, 43.1, 42.4, 41.08, 41.05, 39.42, 39.40, 38.1, 38.0, 28.8, 28.7, 25.9, 25.64, 25.60, 21.8, 20.7, 20.5, 19.6, 19.3, 17.8, 15.6, 15.5; HR-ESIMS calcd for C_{31}H_{43}NNaO_4S [M+Na]^+ 548.2805. Found 548.2809.
Preparation of Ynamide 3p

6-(1-Ethoxyethoxy)hex-1-yne (S24)

To a mixture of 5-hexyn-1-ol (2.21 mL, 20.0 mmol) and PPTS (503 mg, 2.00 mmol) in dry CH₂Cl₂ (100 mL) was added ethyl vinyl ether (2.87 mL, 30.0 mmol) and stirred at rt for 1 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO₃, extracted with CH₂Cl₂, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S24 (3.17 g, 93%) as colorless oil.

IR νmax: 3308, 3011, 2117 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.67 (q, J = 5.4 Hz, 1H), 3.70–3.54 (m, 2H), 3.53–3.39 (m, 2H), 2.22 (td, J = 6.9, 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.78–1.55 (m, 4H), 1.30 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 99.4, 84.2, 68.4, 64.5, 60.7, 29.0, 25.4, 20.0, 18.4, 15.5; HR-ESIMS calcd for C₁₀H₁₈NaO₂ [M+Na]⁺ 193.1199. Found 193.1200.

N-(6-(1-Ethoxyethoxy)hex-1-yn-1-yl)-N',4-dimethylbenzenesulfonamide (3p)

To a solution of S24 (1.36 g, 8.00 mmol) in dry THF (40 mL) at -78 °C was added n-BuLi (1.57 M in hexane, 6.11 mL, 9.60 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br₂ (0.533 mL, 10.4 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of Na₂S₂O₃, extracted with Et₂O, washed with brine, dried over MgSO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S24' (1.85 g) that was directly used in the next reaction.

According to literature,⁶ a solution of S24' (1.85 g, 7.43 mmol), N-methyl- p-toluenesulfonamide (1.65 g, 8.91 mmol), CuSO₄ • 5H₂O (371 mg, 1.49 mmol), 1,10-phenanthroline (535 mg, 2.97 mmol), and K₃PO₄ (3.78 g, 17.8 mmol) in dry toluene (22.3 mL) was stirred at 80 °C for 24 h. The mixture was cooled to rt, diluted with Et₂O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to 5:1 to give 3p (2.43 g, 86% in 2 steps) as colorless oil.

IR νmax: 2939, 2254, 1598, 1364, 1172 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.66 (q, J = 5.4 Hz, 1H), 3.69–3.36 (m, 4H), 3.00 (s, 3H), 2.45 (s, 3H), 2.27 (t, J = 6.6 Hz, 2H), 1.69–1.50 (m, 4H), 1.30 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.2, 132.9, 129.4, 127.6, 99.5, 75.1, 68.3, 64.7, 60.8, 39.5, 29.1, 25.9, 21.8, 20.1, 18.4, 15.6; HR-ESIMS calcd for C₁₈H₂₇NNaO₄S [M+Na]⁺ 376.1553. Found 376.1556.
Preparation of Ynamide 3q

(1-(1-Ethoxyethoxy)hex-5-yn-1-yl)benzene (S25)
To a mixture of 1-phenylhex-5-yn-1-ol 13 (605 mg, 3.47 mmol) and PPTS (87.3 mg, 0.347 mmol) in dry CH$_2$Cl$_2$ (17.6 mL) was added ethyl vinyl ether (499 μL, 5.21 mmol) and stirred at rt for 70 min. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO$_3$, extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S25 (825 mg, 96%) as colorless oil as 1:1 diastereomer mixture.

IR $\nu_{\text{max}}$: 3308, 3010, 2117, 1603 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37-7.22 (m, 5H), 4.68 (q, $J$ = 5.4 Hz, 0.5H), 4.62 (dd, $J$ = 7.8, 6.0 Hz, 0.5H), 4.51 (q, $J$ = 5.4 Hz, 0.5H), 4.42 (dd, $J$ = 7.2, 5.7 Hz, 0.5H), 3.61-3.44 (m, 1.5H), 3.22-3.10 (m, 0.5H), 2.30-2.09 (m, 2H), 1.99-1.39 (m, 5H), 1.28 (d, $J$ = 5.4 Hz, 1.5H), 1.24 (d, $J$ = 5.4 Hz, 1.5H), 1.19 (t, $J$ = 6.9 Hz, 1.5H), 0.97 (t, $J$ = 6.9 Hz, 1.5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 143.2, 142.5, 128.3, 128.2, 127.5, 127.3, 126.8, 126.6, 99.0, 97.3, 84.2, 84.1, 77.6, 77.3, 68.5, 68.4, 61.2, 59.6, 37.3, 37.1, 24.8, 24.6, 20.33, 20.29, 18.3, 18.2, 15.4, 14.9; HR-ESIMS calcd for C$_{16}$H$_{22}$NaO$_2$ [M+Na]$^+$ 269.1512. Found 269.1509.

N-(6-(1-Ethoxyethoxy)-6-phenylhex-1-yn-1-yl)-N,N-dimethylbenzenesulfonamide (3q)
To a solution of S25 (818 mg, 3.32 mmol) in dry THF (16.6 mL) at -78 °C was added n-BuLi (1.59 M in hexane, 2.51 mL, 3.98 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br$_2$ (221 μL, 4.32 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of Na$_2$S$_2$O$_3$, extracted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S25' (840 mg) that was directly used in the next reaction.

According to literature, a solution of S25' (840 mg, 2.58 mmol), N-methyl-p-toluenesulfonamide (574 mg, 3.10 mmol), CuSO$_4$·5H$_2$O (129 mg, 0.517 mmol), 1,10-phenanthroline (186 mg, 1.03 mmol), and K$_3$PO$_4$ (1.32 g, 6.20 mmol) in dry toluene (7.7 mL) was stirred at 80 °C for 19 h. The mixture was cooled to rt, diluted with Et$_2$O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to give 3q (1.07 g, 75% in 2 steps) as colorless oil as 1:1 diastereomer mixture.

IR $\nu_{\text{max}}$: 3009, 2254, 1598, 1365, 1172 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J$ = 8.5 Hz, 2H), 7.36-7.31 (m, 3H), 7.30-7.24 (m, 4H), 4.66 (q, $J$ = 5.0 Hz, 0.5H), 4.60 (dd, $J$ = 7.5, 5.5 Hz, 0.5H), 4.50 (q, $J$ = 5.0 Hz, 0.5H), 4.39 (dd, $J$ = 7.5, 5.5 Hz, 0.5H), 3.57-3.46 (m, 1.5H), 3.18-3.12 (m, 0.5H), 2.984 (s, 1.5H), 1.19 (t, $J$ = 6.9 Hz, 1.5H), 0.97 (t, $J$ = 6.9 Hz, 1.5H).
Preparation of Ynamide 3

(1-(1-Ethoxyethoxy)hex-5-yn-1-yl)benzene (S26)

To a mixture of 2-(prop-2-yn-1-xyloxy)ethan-1-ol\textsuperscript{14} (1.03 g, 10.3 mmol) and PPTS (259 mg, 1.03 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (51 mL) was added ethyl vinyl ether (1.48 mL, 15.4 mmol) and stirred at rt for 75 min. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO\textsubscript{3}, extracted with CH\textsubscript{2}Cl\textsubscript{2}, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 8:1 to give S26 (1.62 g, 91%) as yellow oil. IR \textit{\nu}\textsubscript{max}: 3308, 3012, 2120 cm\textsuperscript{-1}; \textit{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3})} \textit{\delta} 4.75 (q, \textit{J} = 5.4 Hz, 1H), 4.20 (dd, \textit{J} = 2.4, 1.2 Hz, 2H), 3.78-3.59 (m, 5H), 3.54-3.43 (m, 1H), 2.44 (t, \textit{J} = 1.2 Hz, 1H), 1.95 (t, \textit{J} = 2.7 Hz, 1H), 1.78-1.55 (m, 4H), 1.33 (d, \textit{J} = 5.4 Hz, 3H), 1.20 (t, \textit{J} = 6.9 Hz, 3H); \textit{\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3})} \textit{\delta} 144.37, 144.35, 143.3, 142.6, 133.1, 129.6, 128.4, 128.2, 127.8, 127.5, 127.3, 126.8, 126.6, 99.0, 97.4, 77.7, 77.4, 75.12, 75.08, 68.2, 68.1, 61.3, 59.8, 39.3, 37.3, 37.1, 25.2, 25.1, 21.6, 20.4, 18.3, 18.2, 15.5, 14.9; HR-ESIMS calcd for C\textsubscript{28}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2}S \textit{[M+Na]\textsuperscript{+}} 452.1866. Found 452.1862.

N-(6-(1-Ethoxyethoxy)-6-phenylhex-1-yn-1-yl)-N,4-dimethylbenzenesulfonamide (3r)

To a solution of S26 (689 mg, 4.00 mmol) in dry THF (20 mL) at -78 °C was added n-BuLi (1.55 M in hexane, 3.10 mL, 4.80 mmol) dropwise, and the reaction mixture was stirred at -78 °C for 30 min. Then, Br\textsubscript{2} (266 \textmu L, 5.20 mmol) was added dropwise, and the reaction mixture was stirred at -78 °C for 15 min. After reaction completed, the mixture was quenched with a saturated aqueous solution of NaHCO\textsubscript{3}, extracted with Et\textsubscript{2}O, washed with brine, dried over MgSO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 10:1 to give S26’ (852 mg) that was directly used in the next reaction.

According to literature,\textsuperscript{6} a solution of S26’ (852 mg, 3.39 mmol), N-methyl-p-toluenesulfonamide (754 mg, 4.07 mmol), CuSO\textsubscript{4}•5H\textsubscript{2}O (169 mg, 0.679 mmol), 1,10-phenanthroline (245 mg, 1.36 mmol), and K\textsubscript{3}PO\textsubscript{4} (1.73 g, 8.14 mmol) in dry toluene (10.2 mL) was stirred at 80 °C for 23 h. The mixture was cooled to rt, diluted with Et\textsubscript{2}O, and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/acetone = 5:1 to give 3r (545 mg, 51% in 2 steps) as colorless oil.

IR \textit{\nu}\textsubscript{max}: 3011, 2244, 1598, 1369, 1173 cm\textsuperscript{-1}; \textit{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3})} \textit{\delta} 7.78 (d, \textit{J} = 8.1 Hz, 2H), 7.36
(d, J = 8.1 Hz, 2H), 4.76 (q, J = 5.4 Hz, 1H), 4.31 (s, 2H), 3.78-3.56 (m, 5H), 3.55-3.43 (m, 1H), 3.07 (s, 3H), 2.46 (s, 3H), 1.33 (d, J = 5.4 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 144.8, 133.2, 129.7, 127.7, 99.5, 81.1, 68.7, 65.5, 63.5, 60.8, 58.6, 39.0, 21.6, 19.6, 15.2; HR-ESIMS calcd for C17H25NNaO5S [M+Na]+ 378.1346. Found 378.1349.

Preparation of Ynamide 3s

\[ \text{N-(2-(1-Ethoxyethoxy)ethyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (S27)} \]

To a mixture of N-(2-hydroxyethyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (1.46 mg, 5.76 mmol) and PPTS (145 mg, 0.576 mmol) in dry CH2Cl2 (29 mL) was added ethyl vinyl ether (0.827 mL, 8.63 mmol) and stirred at rt for 70 min. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO3, extracted with CH2Cl2, dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S27 (1.87 g, quant.) as pale yellow oil.

IR νmax: 3308, 2982, 1599, 1349, 1161 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) δ 7.72 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.68 (q, J = 5.4 Hz, 1H), 4.24 (d, J = 2.4 Hz, 2H), 3.80-3.71 (m, 1H), 3.68-3.56 (m, 2H), 3.51-3.42 (m, 1H), 3.38 (t, J = 5.7 Hz, 2H), 2.41 (s, 3H), 2.04 (t, J = 2.4 Hz, 1H), 1.28 (d, J = 5.4 Hz, 3H), 1.19 (t, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 143.2, 135.9, 129.2, 127.5, 99.6, 77.2, 73.5, 63.9, 61.1, 46.3, 38.2, 21.7, 19.9, 15.5; HR-ESIMS calcd for C16H23NNaO4S [M+Na]+ 348.1240. Found 348.1232.

N-(3-((N,4-Dimethylphenyl)sulfonamido)prop-2-yn-1-yl)-N-(2-(1-ethoxyethoxy)ethyl)-4-methylbenzenesulfonamide (3s)

According to GP-1, 3s (841 mg, 65%) was obtained as from S27 (824 mg, 2.53 mmol), N-methyl-p-toluenesulfonamide (2.35 g, 12.7 mmol), CuCl2 (68.1 mg, 0.506 mmol), Na2CO3 (537 mg, 5.06 mmol), and pyridine (410 µL, 5.06 mmol). Eluent: hexane/EtOAc = 3:1 to 7:3. Colorless oil; IR νmax: 3031, 2248, 1598, 1369, 1161 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) δ 7.70 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.38-7.29 (m, 3H), 4.69 (q, J = 5.1 Hz, 1H), 4.35 (s, 2H), 3.79-3.71 (m, 1H), 3.69-3.58 (m, 2H), 3.43-3.41 (m, 1H), 3.32 (t, J = 5.7 Hz, 2H), 2.82 (s, 3H), 2.46 (s, 3H), 2.38 (s, 3H), 1.29 (d, J = 5.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 144.8, 143.3, 136.2, 133.1, 129.8, 129.5, 127.6, 127.5, 99.7, 79.9, 64.0, 62.8, 61.2, 45.9, 38.7, 38.4, 21.6, 21.4, 19.8, 15.3; HR-ESIMS calcd for C24H32N2NaO6S2 [M+Na]+ 531.1594. Found 531.1594.
Preparation of Ynamides 5a-f

(2-(3-(1-Ethoxyethoxy)propyl)phenyl)aryltrimethylsilane (S25)

To a mixture of 3-(2-iodophenyl)propan-1-ol \(^{16}\) (2.22 g, 8.48 mmol) and PPTS (213 mg, 0.848 mmol) in dry CH\(_2\)Cl\(_2\) (43 mL) was added ethyl vinyl ether (1.46 mL, 15.3 mmol) and stirred at rt for 17 h. After reaction completed, the mixture was quenched with saturated aqueous solution of NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 1-(3-(1-ethoxyethoxy)propyl)-2-iodobenzene (2.42 g, 85%) as colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.78 (dd, \(J = 8.1\), 0.9 Hz, 1H), 7.27-7.19 (m, 2H), 6.88-6.83 (m, 1H), 4.70 (q, \(J = 5.4\) Hz, 1H), 3.72-3.58 (m, 2H), 3.55-3.42 (m, 2H), 2.79 (t, \(J = 7.5\) Hz, 2H), 1.92-1.82 (m, 2H), 1.33 (d, \(J = 5.4\) Hz, 3H), 1.21 (t, \(J = 7.2\) Hz, 3H).

A mixture of 1-(3-(1-ethoxyethoxy)propyl)-2-iodobenzene (2.37 g, 7.09 mmol), PdCl\(_2\) (31.4 mg, 0.177 mmol), Ph\(_3\)P (93.0 mg, 0.355 mmol), CuI (48.6 mg, 0.255 mmol), Et\(_3\)N (2.97 mL, 21.3 mmol), and ethynyltrimethylsilane (1.50 mL, 10.6 mmol) in dry MeCN (14 mL) was stirred at rt for 40 h. After reaction completed, the mixture was quenched with 5% aqueous solution of NH\(_2\)OH, washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give S25 (2.13 g, 99%) as brown oil. IR \(\nu_{\text{max}}\): 3009, 2154, 1599 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.43 (dd, \(J = 7.5\), 0.9 Hz, 1H), 7.24-7.17 (m, 2H), 7.13 (td, \(J = 7.5\), 1.8 Hz, 1H), 4.70 (q, \(J = 5.4\) Hz, 1H), 3.72-3.57 (m, 2H), 3.54-3.40 (m, 2H), 2.86 (t, \(J = 7.8\) Hz, 2H), 1.98-1.88 (m, 2H), 1.32 (d, \(J = 5.4\) Hz, 3H), 1.20 (t, \(J = 7.2\) Hz, 3H), 0.25 (s, 9H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.4, 132.3, 128.4, 128.7, 128.4, 125.6, 121.6, 132.4, 130.3, 99.5, 80.7, 93.8, 99.5, 97.8, 64.7, 60.7, 31.5, 30.5, 20.0, 15.4, 0.1; HR-ESIMS calcd for C\(_{16}\)H\(_{33}\)NaO\(_2\)Si [M+Na\(^+\)] \(327.1753\). Found 327.1753.

1-(3-(1-Ethoxyethoxy)propyl)-2-ethynylbenzene (S26)

To a solution of S25 (2.13 g, 6.98 mmol) in MeOH (3.5 mL) at rt was added K\(_2\)CO\(_3\) (482 mg, 3.49 mmol), and was stirred for 27 h. After reaction completed, the mixture was quenched with water, extracted with Et\(_2\)O, washed with brine, dried over MgSO\(_4\), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 10:1 to give S26 (1.43 g, 88%) as colorless oil. IR \(\nu_{\text{max}}\): 3305, 3011, 2104, 1599 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.45 (dd, \(J = 7.5\), 1.8 Hz, 1H), 7.26 (td, \(J = 7.5\), 1.8 Hz, 1H), 7.20 (dd, \(J = 7.5\), 1.8 Hz, 1H), 7.13 (td, \(J = 7.5\), 1.8 Hz, 1H), 4.68 (q, \(J = 5.4\) Hz, 1H), 3.71-3.57 (m, 2H), 3.54-3.23 (m, 2H), 2.72 (s, 1H), 2.87 (t, \(J = 7.5\) Hz, 2H), 1.93 (quint, \(J = 7.5\) Hz, 2H), 1.32 (d, \(J = 5.4\) Hz, 3H), 1.20 (t, \(J = 7.2\) Hz, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 144.5, 132.8, 128.69, 128.66, 125.6, 121.5, 99.5, 82.2, 80.7, 84.6, 60.8, 31.2, 30.6, 20.0, 15.4; HR-ESIMS calcd for C\(_{15}\)H\(_{29}\)NaO\(_2\) [M+Na\(^+\)] \(255.1356\). Found 255.1355.
N-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)-N,4-dimethylbenzenesulfonamide (5a)

According to GP-1, 5a (470 mg, 75%) was obtained from S26 (327 mg, 1.50 mmol), N-methyl-p-toluene sulfonamide (1.39 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (242 µL, 3.00 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless oil; IR ν max: 3010, 2235, 1598, 1369, 1168 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, J = 8.1 Hz, 2H), 7.38-7.27 (m, 3H), 7.21-7.15 (m, 2H), 7.14-7.06 (m, 1H), 4.66 (q, J = 5.4 Hz, 1H), 3.69-3.55 (m, 2H), 3.52-3.38 (m, 2H), 3.16 (s, 3H), 2.79 (t, J = 7.8 Hz, 2H), 2.44 (s, 3H), 1.88 (quint, J = 7.8 Hz, 2H), 1.29 (d, J = 5.4 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.4, 143.2, 133.2, 131.5, 129.6, 128.6, 127.6 (2C), 125.5, 121.9, 99.6, 87.3, 67.8, 64.8, 60.9, 39.4, 31.5, 30.7, 21.8, 20.2, 15.5; HR-ESIMS calcd for C₂₃H₂₉NNaO₄S [M+Na]⁺ 438.1710. Found 438.1711.

N-Benzyl-N-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)-4-methylbenzenesulfonamide (5b)

According to GP-1, 5b (422 mg, 57%) was obtained from S26 (327 mg, 1.50 mmol), N-benzyl-p-toluene sulfonamide (1.96 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/EtOAc = 6:1.

Colorless oil; IR ν max: 3008, 2235, 1599, 1367, 1169 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 8.4 Hz, 2H), 7.34-7.25 (m, 7H), 7.19-7.09 (m, 3H), 7.08-7.02 (m, 1H), 4.62 (q, J = 5.4 Hz, 1H), 4.58 (s, 2H), 3.68-3.56 (m, 1H), 3.52-3.39 (m, 2H), 3.35-3.25 (m, 1H), 2.62 (t, J = 7.5 Hz, 2H), 2.43 (s, 3H), 1.80-1.70 (m, 2H), 1.28 (d, J = 5.4 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.3, 143.0, 134.5, 134.2, 131.5, 129.5, 128.6, 128.51, 128.49, 128.3, 128.1, 127.4 (2C), 125.4, 121.9, 99.6, 85.8, 70.0, 64.7, 60.9, 55.7, 31.2, 30.5, 21.8, 20.2, 15.5; HR-ESIMS calcd for C₂₉H₃₃NNaO₄S [M+Na]⁺ 514.2023. Found 514.2027.

N-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethynyl)-N-methylmethanesulfonamide (5c)

According to GP-1, 5c (383 mg, 75%) was obtained from S26 (327 mg, 1.50 mmol), N-methylmethanesulfonamide (0.640 mL, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (243 µL, 3.00 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless oil; IR ν max: 3008, 2235, 1599, 1367, 1169 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, J = 7.2 Hz, 1H), 7.21-7.15 (m, 2H), 7.15-7.07 (m, 1H), 4.66 (q, J = 5.4 Hz, 1H), 3.70-3.55 (m, 2H), 3.51-3.39 (m, 2H), 3.30 (s, 3H), 3.11 (s, 3H), 2.82 (t, J = 7.8 Hz, 2H), 1.90 (quint, J = 7.8 Hz, 2H), 1.30 (d, J = 5.4 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.3, 131.5, 128.6, 127.8, 125.6, 121.5, 99.6, 86.3, 68.2, 64.8, 60.9, 39.3, 36.8, 31.6, 30.8, 20.2, 15.5; HR-ESIMS calcd for C₁₇H₂₅NNaO₄S [M+Na]⁺ 362.1397. Found 362.1398.
N-Benzyl-N-((2-(3-(1-ethoxyethoxy)propyl)phenyl)ethyl)methanesulfonamide (5d)
According to GP-1, 5d (418 mg, 67%) was obtained from S26 (327 mg, 1.50 mmol), N-benzylmethanesulfonamide (1.39 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (243 μL, 3.00 mmol). Eluent: hexane/EtOAc = 4:1. Colorless oil; IR ν_max: 3010, 2235, 1600, 1362, 1163 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.52-7.46 (m, 2H), 7.44-7.34 (m, 3H), 7.32 (d, J = 7.2 Hz, 1H), 7.21 (td, J = 6.0, 1.5 Hz, 2H), 7.16-7.08 (m, 1H), 4.73 (s, 2H), 4.65 (q, J = 5.4 Hz, 1H), 3.69-3.33 (m, 4H), 2.95 (s, 3H), 2.74 (t, J = 7.5 Hz, 2H), 1.89-1.78 (m, 2H), 1.28 (d, J = 5.4 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.5, 134.6, 131.8, 128.9, 128.82, 128.80, 128.7, 128.0, 125.7, 121.8, 99.6, 85.3, 70.2, 64.6, 60.9, 55.8, 38.9, 31.3, 30.5, 19.9, 15.3; HR-ESIMS calcd for C₂₃H₂₉NNaO₄S [M+Na]⁺ 438.1710. Found 438.1706.

1-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethyl)azetidin-2-one (5e)
According to GP-1, 5e (809 mg, 80%) was obtained from S26 (778 mg, 3.36 mmol), azetidin-2-one (1.19 g, 16.8 mmol), CuCl₂ (90.2 mg, 0.671 mmol), Na₂CO₃ (711 mg, 6.71 mmol), and pyridine (0.543 mL, 6.71 mmol). Eluent: hexane/EtOAc = 7:3. Pale yellow oil; IR ν_max: 3009, 2241, 1769, 1601 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36 (d, J = 7.5 Hz, 1H), 7.21-7.15 (m, 2H), 7.14-7.08 (m, 1H), 4.68 (q, J = 5.4 Hz, 1H), 3.70 (t, J = 4.8 Hz, 2H), 3.67-3.58 (m, 2H), 3.53-3.41 (m, 2H), 3.09 (t, J = 4.8 Hz, 2H), 2.82 (t, J = 7.8 Hz, 2H), 1.92 (quint, J = 7.5 Hz, 2H), 1.31 (d, J = 5.4 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 143.4, 131.8, 128.5, 127.9, 125.6, 121.4, 99.6, 82.1, 68.5, 64.8, 60.9, 43.2, 38.1, 31.4, 30.6, 20.1, 15.5; HR-ESIMS calcd for C₁₈H₂₃NNaO₃ [M+Na]⁺ 324.1570. Found 324.1567.

1-((2-(3-(1-Ethoxyethoxy)propyl)phenyl)ethyl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (5f)
According to GP-1, 5f (178 mg, 31%) was obtained from S26 (327 mg, 1.50 mmol), 1-methyl-2-benzimidazolinone (1.11 g, 7.50 mmol), CuCl₂ (40.3 mg, 0.300 mmol), Na₂CO₃ (318 mg, 3.00 mmol), and pyridine (242 μL, 3.00 mmol). Eluent: hexane/EtOAc = 7:3. Colorless oil; IR ν_max: 3011, 2257, 1733, 1621, 1601 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.53 (d, J = 7.5 Hz, 1H), 7.29-7.22 (m, 3H), 7.21-7.14 (m, 3H), 6.97 (dd, J = 6.9, 2.1 Hz, 1H), 4.67 (q, J = 5.4 Hz, 1H), 3.68-3.57 (m, 2H), 3.52-3.40 (m, 5H), 2.97 (t, J = 7.8 Hz, 2H), 2.06-1.96 (m, 2H), 1.29 (d, J = 5.4 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 152.8, 143.4, 131.8, 128.5, 127.9, 125.6, 121.4, 99.6, 82.1, 68.5, 64.8, 60.9, 43.2, 38.1, 31.4, 30.6, 20.1, 15.5; HR-ESIMS calcd for C₂₃H₂₆N₂NaO₃ [M+Na]⁺ 401.1836. Found 401.1828.
General Procedure for 6-endo-dig Iodocyclization of 1 (Table 1, GP-2)

Three seconds were precisely counted by stopwatch just after I(coll)2PF6 (1.1 equiv) added in one portion to a stirred solution of 1 (1 equiv) in CH2Cl2 (0.1 M) at rt, and after 3 seconds the reaction mixture was immediately quenched with a saturated aqueous solution of Na2S2O3, and was extracted with CH2Cl2. The organic layer was dried over Na2SO4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give 2.

N-(4-Iodo-1H-isochromen-3-yl)-N,4-dimethylbenzenesulfonamide (2a)

According to GP-2, 2a (88.0 mg, quant.) was obtained from 1a (77.5 mg, 0.200 mmol) and I(coll)2PF6 (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 6:1. Colorless crystals; mp 162-164 °C (hexane/EtOAc); IR νmax: 3030, 1611, 1355, 1157 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.87 (d, J = 8.4 Hz, 2H), 7.38-7.29 (m, 4H), 7.24 (td, J = 7.2, 1.8 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 5.16 (s, 2H), 3.05 (s, 3H), 2.45 (s, 3H); ¹³C NMR (75 MHz, CDCl3) δ 151.1, 144.0, 135.6, 133.2, 129.5, 128.9, 128.6, 128.4, 128.3, 128.1, 123.4, 73.9, 70.1, 36.5, 21.6; HR-ESIMS calcd for C17H16INaO3 [M+Na]+ 463.9788. Found 463.9791.

1-(4-Iodo-1H-isochromen-3-yl)azetidin-2-one (2b)

According to GP-2, 2b (65.1 mg, 98%) was obtained from 1b (55.0 mg, 0.200 mmol) and I(coll)2PF6 (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 2:1. Yellow oil; IR νmax: 3013, 1769, 1607 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.34-7.25 (m, 2H), 7.19 (td, J = 6.9, 2.1 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 5.10 (s, 2H), 3.80 (t, J = 4.8 Hz, 2H), 3.06 (t, J = 4.8 Hz, 2H); ¹³C NMR (75 MHz, CDCl3) δ 164.3, 133.4, 128.6, 128.3, 127.9, 127.3 (2C), 123.4, 69.8, 62.0, 41.3, 37.1; HR-ESIMS calcd for C12H10INaO2 [M+Na]+ 349.9648. Found 349.9646.

1-(4-Iodo-1H-isochromen-3-yl)pyrrolidin-2-one (2c)

According to GP-2, 2c (47.8 mg, 87%) was obtained from 1c (46.0 mg, 0.200 mmol) and I(coll)2PF6 (90.3 mg, 0.220 mmol). Eluent: hexane/EtOAc = 3:2. Colorless oil; IR νmax: 3011, 1714, 1616, 1571 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.34-7.25 (m, 2H), 7.19 (td, J = 6.9, 2.1 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 5.17 (s, 2H), 3.76 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 8.1 Hz, 2H), 2.17 (quint, J = 7.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl3) δ 173.8, 132.9, 128.5 (2C), 128.4, 128.3, 127.8, 123.3, 71.4, 70.0, 47.9, 31.2, 19.2; HR-ESIMS calcd for C13H12INaO2 [M+Na]+ 363.9805. Found 363.9801.
1-(4-Iodo-1H-isochromen-3-yl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (2d)

According to GP-2, 2d (79.8 mg, 98%) was obtained from 1d (70.1 mg, 0.200 mmol) and I(coll)_2PF_6 (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 3:1. Colorless crystals; mp 180-183 °C (hexane/EtOAc); IR ν_{max}: 3011, 1724, 1618 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.22 (m, 3H), 7.18-6.96 (m, 5H), 5.40 (d, J = 12.6 Hz, 1H), 5.28 (d, J = 12.6 Hz, 1H), 3.44 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 151.9, 144.6, 132.7, 130.1, 128.8, 128.62, 128.57, 128.5, 127.2, 123.6, 122.5, 121.5, 109.9, 107.8, 74.1, 70.4, 27.4; HR-ESIMS calcd for C_{17}H_{13}IN_2NaO_2 [M+Na]^+ 426.9914. Found 426.9906.

tert-Butyl benzyl(4-iodo-1H-isochromen-3-yl)carbamate (2e)

According to GP-2, 2e (170 mg, 80%) was obtained from 1e (188 mg, 0.458 mmol) and I(coll)_2PF_6 (259 mg, 0.504 mmol). Eluent: hexane/EtOAc = 9:1. Pale yellow oil; IR ν_{max}: 3027, 1708, 1615, 1572 cm^{-1}; ^1H NMR (600 MHz, CDCl_3) δ 7.39 (d, J = 7.2 Hz, 2H), 7.31-7.21 (m, 5H), 7.19-7.15 (m, 1H), 6.93 (d, J = 7.2 Hz, 1H), 5.03 (br d, J = 8.4 Hz, 1H), 4.85-4.70 (br m, 2H), 4.63 (br d, J = 14.4 Hz, 1H), 1.47 (s, 9H); ^13C NMR (150 MHz, CDCl_3) δ 153.1, 151.4, 136.8, 133.7, 128.8, 128.7, 128.4, 128.24, 128.19, 127.6, 127.4, 123.3, 81.6, 72.9, 69.7, 53.4, 51.8, 28.2; HR-ESIMS calcd for C_{21}H_{22}INNaO_3 [M+Na]^+ 486.0537. Found 486.0532.

(R)-3-(4-Iodo-1H-isochromen-3-yl)-4-phenyloxazolidin-2-one (2f)

According to GP-2 except for reaction time (1 min), 2f (50.0 mg, 85%) was obtained from 1f (51.0 mg, 0.140 mmol) and I(coll)_2PF_6 (79.0 mg, 0.154 mmol). Eluent: hexane/EtOAc = 3:1. Colorless amorphous solid; [α]_D^{26} -84.6 (c 1.03, CHCl_3); IR ν_{max}: 3027, 1774, 1621, 1572 cm^{-1}; ^1H NMR (600 MHz, CDCl_3) δ 7.50 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.25 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 5.41 (t, J = 9.0 Hz, 1H), 4.89 (d, J = 12.6 Hz, 1H), 4.72 (t, J = 8.4 Hz, 1H), 4.39 (br s, 1H), 4.28 (t, J = 9.6 Hz, 1H); ^13C NMR (150 MHz, CDCl_3) δ 152.7, 145.7, 135.5, 133.0, 129.3, 129.0, 128.7, 128.60, 128.56, 127.81, 127.76, 123.3, 71.7, 70.4, 69.5, 61.2; HR-ESIMS calcd for C_{18}H_{14}INNaO_3 [M+Na]^+ 441.9911. Found 441.9904.

Methyl 1-(4-iodo-1H-isochromen-3-yl)-1H-indole-3-carboxylate (2g)

According to GP-2 except for reaction time (1 min), 2g (80.8 mg, 94%) was obtained from 1g (75.0 mg, 0.200 mmol) and I(coll)_2PF_6 (79.0 mg, 0.154 mmol). Eluent: hexane/EtOAc = 9:1. Colorless amorphous solid; IR ν_{max}: 3012, 1708, 1618 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 8.23-8.16 (m, 1H), 8.01 (s, 1H), 7.46-7.26 (m, 6H), 7.06 (d, J = 7.5 Hz, 1H), 5.36 (s, 2H), 3.92 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 164.5, 147.0, 136.0, 134.6, 132.8, 128.9, 128.8, 128.3, 128.1, 126.1, 123.7, 123.6, 122.9, 121.7, 112.0, 110.1, 70.4, 68.6, 51.4; HR-ESIMS calcd for C_{19}H_{14}INNaO_3 [M+Na]^+ 453.9911. Found 453.9909.
N-(4-Iodo-1H-benzo[h]isochromen-3-yl)-N,4-dimethylbenzenesulfonamide (2h)
According to GP-2, 2h (98.0 mg, quant.) was obtained from 1h (88.0 mg, 0.200 mmol) and I(coll)PF₆ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 5:1.
Colorless amorphous solid; IR νₘₐₓ: 3031, 1610, 1355, 1157 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.90-7.75 (m, 5H), 7.57-7.42 (m, 3H), 7.32 (d, J = 7.8 Hz, 2H), 5.64 (s, 2H), 3.09 (s, 3H), 2.45 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 151.1, 143.9, 135.7, 133.3, 130.6, 129.4, 128.7, 128.4, 128.3, 127.9, 127.1, 127.0, 125.8, 122.9, 122.2, 73.7, 66.8, 36.7, 21.7; HR-ESIMS calcd for C₂₁H₁₈INaO₃S [M+Na]⁺ 513.9944. Found 513.9947.

N-(4-Iodo-7-methyl-1H-isochromen-3-yl)-N,4-dimethylbenzenesulfonamide (2i)
According to GP-2, 2i (82.2 mg, 90%) was obtained from 1i (80.3 mg, 0.200 mmol) and I(coll)PF₆ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 5:1.
Colorless crystals; mp 157-159 ºC (hexane/EtOAc); IR νₘₐₓ: 3030, 1613, 1354, 1159 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 7.8 Hz, 1H), 7.08 (br d, J = 7.8 Hz, 1H), 6.78 (br s, 1H), 5.10 (s, 2H), 3.02 (s, 3H), 2.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 150.0, 143.7, 138.1, 135.4, 130.4, 129.3, 128.9, 128.7, 128.2, 128.1, 123.9, 74.2, 70.1, 36.6, 21.8, 21.3; HR-ESIMS calcd for C₁₈H₁₈INaO₃S [M+Na]⁺ 477.9944. Found 477.9948.

N-(7-Fluoro-4-iodo-1H-isochromen-3-yl)-N,4-dimethylbenzenesulfonamide (2j)
According to GP-2, 2j (88.0 mg, 96%) was obtained from 1j (81.1 mg, 0.200 mmol) and I(coll)PF₆ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 6:1.
Colorless amorphous solid; IR νₘₐₓ: 3031, 1615, 1355, 1158 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83 (d, J = 8.4 Hz, 2H), 7.35-7.29 (m, 3H), 6.97 (td, J = 8.7, 2.7 Hz, 1H), 6.73 (dd, J = 8.1, 2.7 Hz, 1H), 5.11 (s, 2H), 3.03 (s, 3H), 2.44 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 162.2 (d, J = 246.5 Hz), 150.4, 143.8, 135.3, 130.6 (d, J = 8.6 Hz), 130.0 (d, J = 7.4 Hz), 129.3, 128.1, 115.0 (d, J = 21.7 Hz), 110.6 (d, J = 22.8 Hz), 72.8, 69.52, 69.53, 36.6, 21.8; HR-ESIMS calcd for C₁₇H₁₅FINaO₃S [M+Na]⁺ 481.9694. Found 481.9698.

N-(4-Iodo-1-vinyl-1H-isochromen-3-yl)-N,4-dimethylbenzenesulfonamide (2k)
According to GP-2, 2k (88.4 mg, 75%) was obtained from 1k (104 mg, 0.251 mmol) and I(coll)PF₆ (141 mg, 0.276 mmol). Eluent: hexane/EtOAc = 6:1.
Colorless crystals; mp 63-65 ºC (hexane/EtOAc); IR νₘₐₓ: 3031, 1616, 1600, 1356, 1157 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.34-7.19 (m, 4H), 6.94 (d, J = 7.5 Hz, 1H), 6.28-6.12 (m, 1H), 5.61 (d, J = 7.2 Hz, 1H), 5.43 (d, J = 10.2 Hz, 1H), 5.30 (d, J = 17.1 Hz, 1H), 3.02 (s, 3H), 2.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 149.3, 143.6, 135.4, 133.7, 132.5, 130.0, 129.2, 128.5, 128.2, 128.1, 123.7, 120.2, 80.9, 73.9, 70.6, 36.4, 21.8; HR-ESIMS calcd for C₁₉H₁₈INaO₃S [M+Na]⁺ 489.9945. Found 489.9945.
N-(5-Iodo-3,4-dihydro-2H-pyran-6-yl)-N,4-dimethylbenzenesulfonamide (2l) (Scheme 2a)

According to GP-2, 2l (80.8 mg, 95%) was obtained from 1l (73.2 mg, 0.216 mmol) and I(coll)PF6 (122 mg, 0.237 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless amorphous solid; IR νmax: 3029, 1654, 1599, 1352, 1157 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.80 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 4.13 (t, J = 5.1 Hz, 2H), 2.90 (s, 3H), 2.61 (t, J = 6.3 Hz, 2H), 2.42 (s, 3H), 1.88 (quint, J = 5.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl3) δ 148.3, 143.6, 135.9, 129.3, 128.3, 70.3, 67.4, 35.4, 34.7, 24.8, 21.6; HR-ESIMS calcd for C_{13}H_{16}INaO_3S [M+Na]⁺ 415.9788. Found 415.9787.

General Procedure for 7-endo-dig Iodocyclization of 3 (Table 2, GP-3)

One minute was precisely counted by stopwatch just after I(coll)PF6 (1.1 equiv) added in one portion to a stirred solution of 3 (1 equiv) in CH_2Cl_2 (0.1 M) at rt, and after 1 min the reaction mixture was quenched with a saturated aqueous solution of Na_2S_2O_3, and was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give 4.

N-(1-Iodo-4,5-dihydrobenzo[d]oxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4a)

According to GP-3, 4a (85.8 mg, 94%) was obtained from 3a (80.2 mg, 0.200 mmol) and I(coll)PF6 (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless crystals; mp 162-164 ºC (hexane/EtOAc); IR νmax: 3030, 1599, 1348, 1153 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.87 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 7.8, 1.2 Hz, 1H), 7.35-7.22 (m, 3H), 7.18 (td, J = 7.2, 1.2 Hz, 1H), 7.10 (dd, J = 7.5, 1.5 Hz, 1H), 4.62 (t, J = 5.7 Hz, 2H), 3.07 (s, 3H), 2.43 (s, 3H); ¹³C NMR (75 MHz, CDCl3) δ 148.5, 143.7, 139.1, 137.0, 135.7, 132.3, 129.3, 128.2, 128.1, 127.7, 126.7, 83.9, 81.1, 36.1, 33.9, 21.6; HR-ESIMS calcd for C_{18}H_{18}INaO_3S [M+Na]⁺ 477.9944. Found 477.9934.

1-(1-Iodo-4,5-dihydrobenzo[d]oxepin-2-yl)azetidin-2-one (4b)

According to GP-3, 4b (61.6 mg, 90%) was obtained from 3b (57.5 mg, 0.200 mmol) and I(coll)PF6 (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 2:1.

Colorless oil; IR νmax: 3013, 1760, 1614 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 7.54 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 4.62 (t, J = 6.0 Hz, 2H), 3.80-3.77 (m, 2H), 3.06-3.02 (m, 2H), 2.96 (t, J = 6.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl3) δ 164.8, 144.0, 139.7, 136.7, 131.9, 128.0, 127.9, 127.0, 80.1, 72.8, 41.3, 36.8, 33.9; HR-ESIMS calcd for C_{13}H_{12}INaO_2 [M+Na]⁺ 363.9805. Found 363.9803.
1-(1-Iodo-4,5-dihydrobenzo[d]oxepin-2-yl)pyrrolidin-2-one (4c)
According to GP-3, 4c (53.6 mg, 76%) was obtained from 3c (72.9 mg, 0.200 mmol) and I(coll)₂PF₆ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 3:1.
Pale yellow crystals; mp 110-112 ºC (hexane/EtOAc); IR νmax: 3011, 1701, 1610 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.55 (dd, J = 7.5, 1.2 Hz, 1H), 7.28 (td, J = 7.5, 1.5 Hz, 1H), 7.21-7.09 (m, 2H), 4.58 (t, J = 6.0 Hz, 2H), 3.72 (t, J = 6.9 Hz, 2H), 3.07 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 8.1 Hz, 2H), 2.16 (quint, J = 7.5 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 174.2, 145.5, 139.1, 137.1, 131.9, 128.1, 127.9, 126.8, 82.7, 81.3, 47.1, 34.4, 31.0, 19.1; HR-ESIMS calcd for C₁₄H₁₄INaO₂ [M+Na]⁺ 377.9961. Found 377.9959.

1-(1-Iodo-4,5-dihydrobenzo[d]oxepin-2-yl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (4d)
According to GP-3, 4d (62.3 mg, 75%) was obtained from 3d (72.9 mg, 0.200 mmol) and I(coll)₂PF₆ (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 4:1.
Colorless crystals; mp 203-204 ºC (hexane/EtOAc); IR νmax: 3011, 1708, 1618 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.64 (d, J = 7.5 Hz, 1H), 7.34 (td, J = 7.2, 1.5 Hz, 1H), 7.29-6.94 (m, 6H), 4.95-4.83 (m, 1H), 4.62-4.48 (m, 1H), 3.60-3.40 (m, 1H), 3.45 (s, 3H), 2.95-2.80 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 152.4, 142.3, 139.1, 137.1, 132.1, 130.1, 128.6, 128.1, 127.3, 127.0, 122.2, 121.6, 109.7, 107.8, 85.7, 82.0, 34.4, 27.4; HR-ESIMS calcd for C₁₈H₁₄IN₂NaO₂ [M+Na]⁺ 441.0070. Found 441.0062.

tert-Butyl benzyl(1-iodo-4,5-dihydrobenzo[d]oxepin-2-yl)carbamate (4e)
According to GP-3, 4e (1.28 g, 97%) was obtained from 3e (1.17 g, 2.75 mmol) and I(coll)₂PF₆ (1.56 g, 3.03 mmol). Eluent: hexane/EtOAc = 15:1.
Colorless amorphous solid; IR νmax: 3011, 1702, 1618 cm⁻¹; The ¹H and ¹³C NMR spectra of 4e showed the presence of two rotamers (3:1); ¹H NMR (600 MHz, CDCl₃) δ 7.49 (br s, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.29-7.23 (m, 2H), 7.16 (td, J = 7.2, 1.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 4.74 (d, J = 14.4 Hz, 1H), 4.65-4.43 (br m, 2H), 4.31 (br s, 1H), 3.34 (br s, 0.25H), 3.18 (br s, 0.75H), 2.62 (br d, J = 13.2 Hz, 1H), 1.56 (br s, 6.75H), 1.45 (br s, 2.25H); ¹³C NMR (150 MHz, CDCl₃) δ 153.3, 148.8, 139.9, 137.2, 136.6, 131.9, 129.0, 128.1, 128.0, 127.8, 127.3, 126.8, 83.4, 81.4, 80.5, 51.3, 33.7, 28.5; HR-ESIMS calcd for C₂₂H₂₄N₂NaO₃ [M+Na]⁺ 500.0693. Found 500.0692.

(R)-3-(1-Iodo-4,5-dihydrobenzo[d]oxepin-2-yl)-4-phenyloxazolidin-2-one (4f)
According to GP-3 except for the equivalents of I(coll)₂PF₆ (1.5 equiv), 4f (40.6 mg, 63%) was obtained from 3f (56.9 mg, 0.150 mmol) and I(coll)₂PF₆ (115 mg, 0.225 mmol). Eluent: hexane/EtOAc = 3:1.
Colorless amorphous solid; [α]D²⁷⁻⁴₉.₉ (c 0.700, CHCl₃); IR νmax: 3029, 1765, 1602 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, J = 7.0 Hz, 2H), 7.49 (dd, J = 7.5, 1.0 Hz, 1H), 7.44-7.36 (m, 3H), 7.25 (td, J = 8.0, 1.5 Hz, 1H), 7.13 (td, J = 7.5, 1.0 Hz, 1H), 7.02 (dd, J = 7.5, 1.0 Hz, 1H), 5.36 (t, J = 9.0 Hz, 1H), 4.72 (t, J = 8.5 Hz, 1H), 4.43-4.30 (m, 2H), 4.27 (t, J = 8.5 Hz, 1H), 2.74-2.58 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 143.5, 139.3, 136.5, 136.3, 132.2, 129.3, 129.1, 128.2, 127.8, 127.7, 126.9, 82.6, 81.2, 70.4, 60.6, 33.6; HR-ESIMS calcd for C₁₉H₁₆INaO₃ [M+Na]⁺ 456.0067. Found 456.0054.
Methyl 1-(1-iodo-4,5-dihydrobenzo[d]oxepin-2-yl)-1H-indole-3-carboxylate (4g)

According to GP-3 except for the equivalents of I(coll)2PF6 (1.5 equiv) and reaction time (10 min), 4g (78.2 mg, 88%) was obtained from 3g (78.2 mg, 0.200 mmol) and I(coll)2PF6 (154 mg, 0.300 mmol). Eluent: hexane/EtOAc = 7:1.

Colorless crystals; mp 147-149 °C (hexane/EtOAc); IR νmax: 3012, 1705, 1620 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.24-8.16 (m, 1H), 8.03 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.50-7.16 (m, 6H), 4.62 (t, J = 6.0 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.05 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 164.9, 145.1, 138.6, 136.5, 134.2, 132.7, 128.6, 128.2, 127.3, 126.1, 123.7, 122.7, 121.8, 111.9, 109.8, 81.4, 80.8, 51.3, 34.5; HR-ESIMS calcd for C₂₅H₁₆INaO₃ [M+Na]+ 468.0067. Found 468.0060.

N-(5-Iodo-1,2-dihydrophtal[1,2-d]oxepin-4-yl)-N,4-dimethylbenzenesulfonamide (4h)

According to GP-3, 4h (100 mg, 99%) was obtained from 3h (90.3 mg, 0.200 mmol) and I(coll)2PF6 (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless amorphous solid; IR νmax: 2929, 1599, 1349, 1154 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.76-7.44 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.81 (t, J = 5.7 Hz, 2H), 3.56 (t, J = 5.7 Hz, 2H), 3.04 (s, 3H), 2.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 149.1, 143.8, 136.7, 135.8, 133.5, 133.1, 130.1, 129.4, 128.9, 128.8, 128.2, 126.8, 126.7, 126.3, 123.1 84.1, 82.9, 36.3, 27.6, 21.7; HR-ESIMS calcd for C₂₅H₂₀INaO₃S [M+Na]+ 528.0101. Found 528.0103.

N-(1-Iodo-7-methyl-4,5-dihydrobenzo[d]oxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4i)

According to GP-3, 4i (90.3 mg, 86%) was obtained from 3i (93.5 mg, 0.225 mmol) and I(coll)2PF6 (127 mg, 0.248 mmol). Eluent: hexane/EtOAc = 8:1.

Colorless crystals; mp 191-192 °C (hexane/EtOAc); IR νmax: 3030, 1705, 1349, 1154 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.01 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.86-7.78 (m, 1H), 7.76-7.70 (m, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.56-7.44 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.81 (t, J = 5.7 Hz, 2H), 3.56 (t, J = 5.7 Hz, 2H), 3.04 (s, 3H), 2.43 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.2, 143.8, 138.4, 137.0, 136.3, 135.8, 132.4, 129.5, 128.4, 128.2, 127.6, 84.3, 81.1, 36.0, 33.8, 21.6, 21.1; HR-ESIMS calcd for C₁₉H₂₀INaO₃S [M+Na]+ 492.0104. Found 492.0104.

N-(7-Fluoro-1-iodo-4,5-dihydrobenzo[d]oxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4j)

According to GP-3, 4j (124 mg, quant.) was obtained from 3j (110 mg, 0.263 mmol) and I(coll)2PF6 (148 mg, 0.289 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless crystals; mp 143-145 °C (hexane/EtOAc); IR νmax: 3030, 1610, 1349, 1152 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, J = 8.1 Hz, 2H), 7.54 (dd, J = 8.7, 5.4 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 6.97 (td, J = 8.7, 2.4 Hz, 1H), 6.84 (dd, J = 8.7, 2.4 Hz, 1H), 4.62 (t, J = 5.7 Hz, 2H), 3.05 (t, J = 5.7 Hz, 2H), 3.00 (s, 3H), 2.44 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 161.6 (d, J = 247.0 Hz), 148.3, 143.8, 139.1 (d, J = 8.0 Hz), 135.5, 135.2 (d, J = 2.9 Hz), 134.2 (d, J = 8.6 Hz), 129.3, 128.1, 114.3 (d, J = 21.7 Hz), 113.7 (d, J = 21.7 Hz), 83.0, 80.8, 36.2, 34.0, 21.8; HR-ESIMS calcd for C₁₈H₁₇FINaO₃S [M+Na]+ 495.9850. Found 495.9851.
**N-(1-Iodo-4,4-dimethyl-4,5-dihydrobenzo[d]oxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4k)**

According to **GP-3** except for reaction time (5 h), **4k** (110 mg, 87%) was obtained from **3k** (112 mg, 0.261 mmol) and I(coll)PF₆ (147 mg, 0.287 mmol). Eluent: hexane/acetone = 9:1.

Colorless needle crystals; mp 154-156 ºC (hexane/EtOAc); IR νmax: 2981, 1599, 1353, 1153 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, J = 8.0 Hz, 2H), 7.68 (dd, J = 8.0, 1.0 Hz, 1H), 7.32-7.27 (m, 3H), 7.17 (td, J = 7.5, 1.5 Hz, 1H), 7.02 (dd, J = 7.5, 1.0 Hz, 1H), 3.08 (s, 3H), 2.78 (s, 2H), 2.43 (s, 3H), 1.12 (br s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 143.5, 138.7, 136.1, 135.1, 133.1, 129.1, 129.0, 128.6, 127.7, 126.9, 94.8, 84.1, 45.1, 36.4, 28.1, 21.6; HR-ESIMS calcd for C₂₀H₂₂INaO₃S [M+Na]⁺ 506.0257. Found 506.0260.

**N-((3aR*,10bS*)-6-Iodo-2,3,3a,10b-tetrahydro-1H-benzo[6]cyclopenta[b]oxepin-5-yl)-N,4-dimethylbenzenesulfonamide (4l)**

According to **GP-3, 4l** (101 mg, 82%) was obtained from **3l** (113 mg, 0.248 mmol) and I(coll)PF₆ (140 mg, 0.272 mmol). Eluent: hexane/EtOAc = 4:1.

Pale yellow crystals; mp 172-173 ºC (hexane/EtOAc); IR νmax: 2966, 1598, 1350, 1158 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.65 (br m, 3H), 7.34-7.06 (m, 4H), 6.97 (d, J = 7.2 Hz, 1H), 4.20-4.18 (br m, 1H), 3.04 (s, 3H), 2.71 (br s, 1H), 1.95-1.76 (m, 1H), 1.37 (d, J = 6.9 Hz, 3H), 0.92 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.3, 143.3, 140.1, 137.0, 136.4, 135.9, 128.9, 128.1, 127.0, 126.0, 122.4, 90.4, 79.4, 50.1, 36.2, 32.7, 28.4, 24.4, 21.7; HR-ESIMS calcd for C₂₁H₂₂INaO₃S [M+Na]⁺ 518.0260. Found 518.0260.

**N-((4aR*,11bS*)-7-Iodo-1,2,3,4,4a,11b-hexahydrodibenzo[6]oxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4m)**

According to **GP-3, 4m** (86.7 mg, 88%) was obtained from **3m** (88.4 mg, 0.194 mmol) and I(coll)PF₆ (110 mg, 0.213 mmol). Eluent: hexane/EtOAc = 5:1.

Colorless crystals; mp 164-165 ºC (hexane/EtOAc); IR νmax: 2941, 1599, 1353, 1153 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, J = 8.4 Hz, 2H), 7.01 (dd, J = 8.0, 1.0 Hz, 1H), 3.58-3.45 (m, 1H), 3.01 (s, 3H), 2.76 (br s, 1H), 2.44 (s, 3H), 1.87-1.54 (m, 5H), 1.05 (s, 3H), 0.92 (br s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 149.3, 143.5, 138.7, 136.1, 135.1, 129.1, 129.0, 128.6, 127.7, 126.9, 94.8, 84.1, 45.1, 36.4, 28.1, 21.6; HR-ESIMS calcd for C₂₂H₂₃INaO₃S [M+Na]⁺ 532.0423. Found 532.0423.
(d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H); \(^{13}\text{C} NMR (75 MHz, CDCl\textsubscript{3}) \delta 148.5, 143.6, 139.7, 138.6, 137.2, 135.6, 132.7, 129.3, 129.0, 128.0, 123.5, 86.3, 84.2, 45.0, 36.3, 34.6, 30.2, 22.7 (CH\textsubscript{3} of iBu), 22.4 (CH\textsubscript{3} of iBu), 21.8, 13.2; HR-ESIMS calcd for C\textsubscript{23}H\textsubscript{28}INaO\textsubscript{3} \[M+Na\]\(^+\) 548.0727. Found 548.0711.

\textit{N-((R)-4-((S)-2,6-Dimethylhept-5-en-1-yl)-1-iodo-4,5-dihydrobenzo[d]oxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4o)}

According to \textit{GP-3}, 4o (107 mg, 93%) was obtained from 3o (105 mg, 0.200 mmol) and I(coll)\textsubscript{2}PF\textsubscript{6} (113 mg, 0.220 mmol). Eluent: hexane/EtOAc = 10:1. Colorless oil; [\(\alpha\)]\textsubscript{D}\textsubscript{25} = -32.0 (c 1.80, CHCl\textsubscript{3}); IR \(\nu_{\max}\): 2931, 1599, 1351, 1153 cm\textsuperscript{-1}; \(^{1}H\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 7.85 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 7.8, 1.2 Hz, 1H), 7.31-7.23 (m, 3H), 7.16 (td, J = 7.5, 1.2 Hz, 1H), 7.04 (dd, J = 7.5, 1.2 Hz, 1H), 4.99 (tt, J = 14.1, 3.3 Hz, 1H), 2.42 (s, 3H), 1.96-1.71 (m, 2H), 1.65 (s, 3H), 1.59 (dt, J = 17.4, 4.2 Hz, 1H), 1.53 (s, 3H), 1.40-0.97 (m, 4H), 0.75 (d, J = 6.6 Hz, 3H); \(^{13}\text{C} NMR (75 MHz, CDCl\textsubscript{3}) \delta 148.4, 143.4, 138.9, 135.6, 135.4, 132.4, 130.9, 129.2, 128.7, 128.1, 127.7, 126.6, 124.4, 89.5, 85.1, 42.0, 38.7, 37.7, 35.9, 28.5, 25.9, 25.5, 21.7, 18.8, 17.8; HR-ESIMS calcd for C\textsubscript{27}H\textsubscript{34}INaO\textsubscript{3} \[M+Na\]\(^+\) 602.1196. Found 602.1195.

\textit{General Procedure for 7-\textit{endo}-dig Iodocyclization of 3p-s (Scheme 2b-c, GP-4)}

To a yellow solution of I(coll)\textsubscript{2}PF\textsubscript{6} (113 mg, 0.220 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (0.8 mL) was added BF\textsubscript{3}∙OEt\textsubscript{2} (27.6 \(\mu\)L, 0.220 mmol) at rt. The color of solution was immediately changed to purple, and the solution was stirred at rt for 5 min. The resulting solution was added to a stirred solution of 3 (0.200 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2.0 mL) at rt via cannula, rinsed with dry CH\textsubscript{2}Cl\textsubscript{2} (0.2 mL), and after 1 min the reaction mixture was quenched with a saturated aqueous solution of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}/NaHCO\textsubscript{3} = 1:1, and was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give \(4\). \textit{N-((3-Iodo-4,5,6,7-tetrahydrooxepin-2-yl)-N,4-dimethylbenzenesulfonamide (4p)}

According to \textit{GP-4}, 4p (54.0 mg, 66%) was obtained from 3p (70.7 mg, 0.200 mmol). Eluent: hexane/EtOAc = 5:1. Colorless oil; IR \(\nu_{\max}\): 2938, 1636, 1599, 1351, 1155 cm\textsuperscript{-1}; \(^{1}H\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta 7.78 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 2.93 (s, 3H), 2.82-2.76 (m, 2H), 2.42 (s, 3H), 1.83 (quint, J = 5.7 Hz, 2H), 1.66 (quint, J = 5.7 Hz, 2H); \(^{13}\text{C} NMR (75 MHz, CDCl\textsubscript{3}) \delta 154.0, 143.3, 135.9, 129.2, 127.8, 79.9, 73.3, 41.2, 36.1, 29.9, 24.3, 21.8; HR-ESIMS calcd for C\textsubscript{14}H\textsubscript{18}INaO\textsubscript{3} \[M+Na\]\(^+\) 429.9944. Found 429.9943.
**N-(3-Iodo-7-phenyl-4,5,6,7-tetrahydrooxepin-2-yl)-N\(^\text{,}\)4-dimethylbenzenesulfonamide (4q)**

According to GP-4, 4q (22.5 mg, 23%) was obtained from 3q (85.9 mg, 0.200 mmol). Eluent: hexane/EtOAc = 6:1.

Colorless amorphous solid; IR \(\nu_{\text{max}}\): 2937, 1635, 1599, 1350, 1154 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.80-6.80 (br m, 9H), 5.00 (br s, 1H), 2.91 (s, 2H), 2.88 (s, 3H), 2.33 (s, 3H), 2.08-1.91 (m, 3H), 1.74-1.66 (m, 1H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 153.2, 143.2, 141.4, 135.7, 129.1, 128.3, 128.0, 127.7, 126.0, 85.6, 81.4, 40.9, 37.7, 35.8, 24.6, 21.5; HR-ESIMS calcd for C\(_{20}\)H\(_{22}\)INaO\(_3\)S \([\text{M+Na}]^+\) 506.0257. Found 506.0260.

**N-(6-Iodo-2,3-dihydro-5\(^H\)-1,4-dioxepin-7-yl)-N\(^\text{,}\)4-dimethylbenzenesulfonamide (4r)**

According to GP-4, 4r (29.7 mg, 36%) was obtained from 3r (71.1 mg, 0.200 mmol). Eluent: hexane/EtOAc = 4:1.

Colorless oil; IR \(\nu_{\text{max}}\): 3029, 1629, 1599, 1359, 1157 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.81 (d, \(J=8.1\) Hz, 2H), 7.32 (d, \(J=8.1\) Hz, 2H), 4.48 (s, 2H), 4.23-4.17 (m, 2H), 3.87-3.81 (m, 2H), 2.98 (s, 3H), 2.44 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.7, 143.9, 135.8, 129.5, 128.0, 74.5, 72.8, 70.8, 36.2, 21.6; HR-ESIMS calcd for C\(_{13}\)H\(_{16}\)INaO\(_4\)S \([\text{M+Na}]^+\) 431.9737. Found 431.9740.

**N-(6-Iodo-4-tosyl-2,3,4,5-tetrahydro-1,4-oxazepin-7-yl)-N\(^\text{,}\)4-dimethylbenzenesulfonamide (4s)**

According to GP-4, 4s (93.1 mg, 83%) was obtained from 3s (102 mg, 0.200 mmol). Eluent: hexane/acetone = 3:1.

Colorless amorphous solid; IR \(\nu_{\text{max}}\): 3031, 1642, 1599, 1356, 1160 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.71 (d, \(J=8.4\) Hz, 4H), 7.34-7.27 (m, 4H), 4.28 (s, 2H), 4.16 (t, \(J=5.1\) Hz, 2H), 3.59 (t, \(J=5.1\) Hz, 2H), 2.74 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.2, 144.0, 143.7, 136.0, 135.6, 129.8, 129.4, 127.9, 127.3, 72.3, 70.4, 55.3, 48.9, 35.8, 21.54, 21.45; HR-ESIMS calcd for C\(_{20}\)H\(_{23}\)IN\(_2\)NaO\(_5\)S\(_2\) \([\text{M+Na}]^+\) 584.9985. Found 584.9976.

**General Procedure for 8-endo-dig Iodocyclization of 5 (Table 3, GP-5)**

To a solution of 5 (1 equiv) in dry CH\(_2\)Cl\(_2\) (0.1 M) was added I\((\text{coll})_2PF_6\) (2 equiv) at rt and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\), and was extracted with CH\(_2\)Cl\(_2\). The organic layer was dried over Na\(_2\)SO\(_4\), filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel to give 6.
(E)-N-(1-Iodo-5,6-dihydro-4H-benzo[d]oxocin-2-yl)-N,4-dimethylbenzenesulfonamide (6a)
According to GP-5, 6a (52.8 mg, 56%) was obtained from 5a (83.1 mg, 0.200 mmol) and I(coll)2PF6 (205 mg, 0.400 mmol). Eluent: hexane/EtOAc/acetone = 8:1:1.
Yellow amorphous solid; IR νmax: 2930, 1618, 1599, 1353, 1156 cm⁻¹; ¹H NMR (600 MHz, CDCl3) δ 7.86 (d, J = 7.8 Hz, 2H), 7.62 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.2 Hz, 1H), 3.84-3.62 (br m, 2H), 3.25-2.92 (br m, 2H), 2.83 (br d, J = 12.6 Hz, 1H), 2.44 (s, 3H), 2.04 (br s, 1H), 1.43 (br s, 1H); ¹³C NMR (150 MHz, CDCl3) δ 149.1, 143.7, 139.3, 137.3, 136.1, 132.7, 129.3, 128.8, 128.6, 128.4, 126.3, 99.8, 66.0, 36.3, 30.5, 27.5, 21.6; HR-ESIMS calcd for C19H20INaO3S [M+Na]⁺ 492.0101. Found 492.0102.

(E)-N-Benzyl-N-(1-iodo-5,6-dihydro-4H-benzo[d]oxocin-2-yl)-4-methylbenzenesulfonamide (6b)
According to GP-5, 6b (75.5 mg, 69%) was obtained from 5b (98.3 mg, 0.200 mmol) and I(coll)2PF6 (205 mg, 0.400 mmol). Eluent: hexane/EtOAc = 7:1.
Pale yellow amorphous solid; IR νmax: 3018, 1610, 1599, 1352, 1163 cm⁻¹; The ¹H and ¹³C NMR spectra of 6b showed the presence of some rotamers; ¹H NMR (600 MHz, CDCl3) δ 8.06-7.77 (br m, 1.6H), 7.73-7.58 (br m, 0.4H), 7.48-7.17 (br m, 8H), 7.11 (br s, 2H), 7.06-6.95 (br m, 0.6H), 6.90-6.76 (br m, 0.4H), 4.80 (br s, 0.3H), 4.59 (br s, 0.7H), 4.40 (br s, 0.5H), 4.25 (br s, 0.5H), 3.93 (br s, 0.5H), 3.74 (br s, 1H), 3.52 (br s, 0.5H), 3.32 (br s, 0.6H), 2.83 (br s, 0.6H), 2.46 (s, 3H), 2.28 (br s, 0.4H), 2.11 (br s, 0.6H), 1.80 (br s, 0.4H), 1.57 (br s, 0.4H), 1.43 (br s, 0.6H), 1.07 (br s, 0.4H); ¹³C NMR (150 MHz, CDCl3) δ 146.4, 145.6, 143.9, 139.9, 137.6, 136.3, 134.2, 133.7, 132.0, 130.2, 129.3, 128.8, 128.6, 128.4, 128.0 (2C), 126.1, 81.8, 65.7, 65.3, 52.6, 52.0, 30.3, 29.7, 27.6, 27.2, 21.6; HR-ESIMS calcd for C25H24INaO3S [M+Na]⁺ 568.0414. Found 568.0416.

(E)-N-(1-Iodo-5,6-dihydro-4H-benzo[d]oxocin-2-yl)-N-methylmethanesulfonamide (6c)
According to GP-5, 6c (46.4 mg, 59%) was obtained from 5c (67.9 mg, 0.200 mmol) and I(coll)2PF6 (205 mg, 0.400 mmol). Eluent: hexane/EtOAc = 6:1.
Colorless amorphous solid; IR νmax: 3030, 1624, 1601, 1346, 1147 cm⁻¹; ¹H NMR (600 MHz, CDCl3) δ 7.60 (d, J = 7.8 Hz, 1H), 7.22 (td, J = 7.2, 1.8 Hz, 1H), 7.19 (td, J = 7.2, 1.2 Hz, 1H), 7.05 (dd, J = 7.2, 1.2 Hz, 1H), 3.92 (t, J = 5.4 Hz, 2H), 3.13 (br s, 4H), 3.12 (s, 3H), 2.84-2.79 (m, 1H), 2.16-2.05 (br m, 1H), 1.53-1.43 (br m, 1H); ¹³C NMR (150 MHz, CDCl3) δ 188.1, 139.1, 137.7, 132.4, 128.9, 128.8, 126.3, 123.8, 66.0, 39.4, 30.3 (2C), 27.5; HR-ESIMS calcd for C13H18INaO3S [M+Na]⁺ 415.9788. Found 415.9788.

(E)-N-Benzyl-N-(1-ioco-5,6-dihydro-4H-benzo[d]oxocin-2-yl)methanesulfonamide (6d)
According to GP-5, 6d (45.9 mg, 49%) was obtained from 5d (83.1 mg, 0.200 mmol) and I(coll)2PF6 (205 mg, 0.400 mmol). Eluent: hexane/EtOAc = 5:1.
Colorless amorphous solid; IR νmax: 3032, 1621, 1600, 1341, 1152 cm⁻¹; ¹H NMR (600 MHz, CDCl3) δ 7.50 (br s, 2H), 7.40-7.34 (m, 4H), 7.18-7.13 (m, 2H), 7.06 (br s, 1H), 4.75-4.48 (br m, 2H), 4.07-3.86 (br m, 2H), 3.19 (br s, 1H), 3.03 (s, 3H), 2.77 (br s, 1H), 2.03 (br s, 1H), 1.65-1.50 (br m, 1H); ¹³C NMR (150 MHz, CDCl3) δ 146.6, 139.2, 138.8, 134.5, 131.4, 129.9, 129.0, 128.8, 128.5, 128.4, 126.1, 82.5, 65.8, 52.6, 41.6, 30.2, 27.5; HR-ESIMS calcd for
$C_{19}H_{20}INaO_3S$ [M+Na]$^+$ 492.0101. Found 492.0103.

(E)-1-(1-Iodo-5,6-dihydro-4H-benzo[d]oxocin-2-yl)azetidin-2-one (6e)

According to GP-5, 6e (9.5 mg, 13%) was obtained from 5e (60.3 mg, 0.200 mmol) and I(coll)PF$_6$ (205 mg, 0.400 mmol). Eluent: hexane/acetone = 6:1.

Pale yellow amorphous solid; IR $\nu_{\text{max}}$: 3012, 1761, 1628, 1601 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.54 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.22 (td, $J = 7.8$, 1.8 Hz, 1H), 7.19 (td, $J = 7.8$, 1.8 Hz, 1H), 7.14 (dd, $J = 7.8$, 1.8 Hz, 1H), 3.95 (dd, $J = 11.4$, 3.6 Hz, 1H), 3.75-3.69 (br m, 2H), 3.59-3.54 (m, 1H), 3.18-3.11 (m, 1H), 3.07-3.00 (m, 1H), 2.91 (dd, $J = 13.2$, 7.2 Hz, 1H), 2.80 (t, $J = 13.2$, 1H), 1.96-1.90 (br m, 1H), 1.80-1.70 (br m, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 164.8, 144.1, 139.7, 137.9, 131.3, 129.3, 128.6, 126.2, 76.4, 68.1, 39.9, 36.8, 31.9, 27.8; HR-ESIMS calcd for $C_{14}H_{14}INaO_2$ [M+Na]$^+$ 377.9961. Found 377.9964.

**tert-Butyl benzyl(1-cyano-4,5-dihydrobenzo[d]oxepin-2-yl)carbamate (7) (Scheme 4)**

A mixture of 4e (71.6 mg, 0.150 mmol), CuCN (26.9 mg, 0.300 mmol), L-proline (17.3 mg, 0.150 mmol) in dry DMF (0.45 mL) was heated at 120 °C for 63 h. After the reaction completed, the reaction mixture was cooled to rt, filtered through Celite, and the filtrate was diluted with water and brine. After the mixture was extracted with EtOAc, the organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 8:1 to 6:1 to give 7 (26.0 mg, 46%).

Colorless oil; IR $\nu_{\text{max}}$: 3014, 2221, 1714, 1602 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 7.2$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 1H), 7.25 (t, $J = 7.2$ Hz, 1H), 7.15 (td, $J = 7.2$, 1.2 Hz, 1H), 7.03 (d, $J = 7.8$ Hz, 1H), 4.77 (s, 2H), 4.30 (br s, 2H), 2.97 (br s, 2H), 1.50 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.4, 152.8, 137.7, 136.2, 129.2, 129.1, 128.8, 128.6, 126.2, 76.4, 68.1, 39.9, 36.8, 31.9, 27.8; HR-ESIMS calcd for $C_{23}H_{24}N_2O_3$ [M+Na]$^+$ 399.1679. Found 399.1682.

**tert-Butyl benzyl(1-phenyl-4,5-dihydrobenzo[d]oxepin-2-yl)carbamate (8) (Scheme 4)**

A solution of 4e (71.6 mg, 0.150 mmol), phenylboronic acid (54.9 mg, 0.450 mmol), PdCl$_2$(PPh$_3$)$_2$ (10.5 mg, 0.0150 mmol) and Cs$_2$CO$_3$ (147 mg, 0.450 mmol) in dry 1,4-dioxane (3 mL) was heated under reflux...
for 30 h. After the reaction completed, the reaction mixture was cooled to rt, and was quenched with water, extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 8 (61.8 mg, 96%).

Colorless needle crystals; mp 136-137 °C (hexane); IR νₘₐₓ: 3012, 1697, 1633 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36 (br s, 2H), 7.33-7.18 (m, 7H), 7.15 (t, J = 7.0 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.95 (br s, 2H), 6.83 (d, J = 7.5 Hz, 1H), 4.72 (br s, 1H), 4.47 (br s, 1H), 4.31 (br s, 2H), 3.23 (br s, 1H), 2.68 (br s, 1H), 1.22 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 153.7, 144.0, 140.0, 139.0 (2C), 138.1, 129.8, 129.6, 128.9, 128.24, 128.18, 128.0, 127.2, 126.9, 126.6, 126.4, 123.1, 80.6, 78.6, 50.8, 34.2, 28.0; HR-ESIMS calcd for C₂₈H₂₉NNaO₃ [M+Na]⁺ 450.2040. Found 450.2026.

tert-Butyl (E)-benzyl(1-(3-oxobut-1-en-1-yl)-4,5-dihydrobenzo[d]oxepin-2-yl)carbamate (9) (Scheme 4)

A mixture of 4e (57.2 mg, 0.120 mmol), methyl vinyl ketone (48.6 µL, 0.599 mmol), PdCl₂(PPh₃)₂ (5.0 mg, 7.19 µmol), and Et₃N (50.0 µL, 0.359 mmol) in dry MeCN (2.4 mL) was heated under reflux for 20 h. After the reaction completed, the reaction mixture was cooled to rt, and was quenched with water, extracted with EtOAc. The organic layer was washed with saturated aqueous solution of NH₄Cl, dried over Na₂SO₄, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 6:1 to 4:1 to give 9 (33.2 mg, 66%).

Colorless amorphous solid; IR νₘₐₓ: 3012, 1701, 1655, 1613, 1597 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, J = 7.2 Hz, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.30-7.23 (m, 4H), 7.14 (br d, J = 7.2 Hz, 1H), 6.99 (br d, J = 16.2 Hz, 2H), 5.96 (d, J = 16.2 Hz, 1H), 4.95 (br s, 1H), 4.63 (br s, 1H), 4.49 (br s, 1H), 4.41 (br s, 1H), 3.13 (br s, 1H), 2.66 (br s, 1H), 2.04 (s, 3H), 1.47 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 198.5, 154.0, 149.0, 141.0, 138.2, 137.1, 134.5, 129.2, 128.9, 128.7, 128.5, 128.3, 127.9, 127.8, 126.6, 126.0, 81.7, 81.1, 50.8, 33.0, 28.3, 26.5; HR-ESIMS calcd for C₂₆H₂₉NNaO₄ [M+Na]⁺ 442.1989. Found 442.1987.

tert-Butyl 8,9-dihydrobenzo[4,5]oxepino[2,3-c]isoquinoline-6(5H)-carboxylate (10) (Scheme 4)

A mixture of 4e (50.0 mg, 0.105 mmol), PdCl₂(PPh₃)₂ (3.7 mg, 5.24 µmol), and AcONa (17.2 mg, 0.210 mmol) in dry DMA (2 mL) was stirred at 120 °C for 24 h. After the reaction completed, the reaction mixture
was cooled to rt, and was quenched with water, extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with hexane/EtOAc = 20:1 to give 10 (22.7 mg, 62%).

Colorless amorphous solid; IR $\nu_{\max}$: 2928, 1702, 1617, 1601 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.33-7.22 (m, 4H), 7.21-7.12 (m, 3H), 7.06-6.99 (m, 1H), 4.77 (br s, 4H), 3.00 (br s, 2H), 1.52 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.4, 145.4, 139.5, 135.6, 134.5, 132.3, 129.5, 128.1, 127.0, 126.9, 126.4, 125.8, 124.9, 124.8, 109.7, 81.6, 81.4, 48.6, 33.9, 28.5; HR-ESIMS calcd for C$_{22}$H$_{23}$NNaO$_3$ [M+Na]$^+$ 372.1570. Found 372.1576.

References
Compound 1a ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 1a ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 1b ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 1b ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 1c (\(^1\)H NMR, 300 MHz, CDCl\(_3\) )

Compound 1c (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\) )
Compound 1d (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

\[\text{Diagram of \(^1\)H NMR spectrum}\]

Compound 1d (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))

\[\text{Diagram of \(^{13}\)C NMR spectrum}\]
Compound 1e (\(^1\)H NMR, 500 MHz, CDCl\(_3\))

N-1386
H-1

Compound 1e (\(^{13}\)C NMR, 125 MHz, CDCl\(_3\))

N-1386
C-13
Compound 1f ($^1$H NMR, 300 MHz, CDCl$_3$)

49-H

Compound 1f ($^{13}$C NMR, 75 MHz, CDCl$_3$)

13C OBSERVE
Compound 1g ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 1g ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 1h (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

STANDARD 1H OBSERVABLE

Compound 1h (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))

61-C
Compound 1i ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 1i ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 1j (1H NMR, 300 MHz, CDCl₃)

1223

Compound 1j (13C NMR, 75 MHz, CDCl₃)

1223-C
Compound 1k (\(^1\)H NMR, 500 MHz, CDCl\(_3\))

Compound 1k (\(^{13}\)C NMR, 125 MHz, CDCl\(_3\))
Compound 11 ($^1$H NMR, 300 MHz, CDCl$_3$)

38-3

Compound 11 ($^{13}$C NMR, 75 MHz, CDCl$_3$)

38-C
Compound 2a (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 2a (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
Compound 2b ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 2b ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 2c ($^1$H NMR, 300 MHz, CDCl$_3$)

52-H

Compound 2c ($^{13}$C NMR, 75 MHz, CDCl$_3$)

52-C
Compound 2d (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

\begin{align*}
46-\text{H} & \\
\end{align*}

Compound 2d (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))

\begin{align*}
46-\text{C} & \\
\end{align*}
Compound 2e (\(^1\)H NMR, 600 MHz, CDCl\(_3\))

N-1239 H-1

\[
\begin{array}{c}
7.380 \\
7.288 \\
7.171 \\
6.910
\end{array}
\]

\[
7.380 \\
7.288 \\
7.171
\]

\[
5.128 \\
2.751 \\
5.328
\]

Compound 2e (\(^{13}\)C NMR, 150 MHz, CDCl\(_3\))

N-1239 C-13

\[
\begin{array}{c}
123.39 \\
138.64 \\
138.64 \\
128.56 \\
129.58 \\
129.58 \\
127.40 \\
127.40 \\
53.40 \\
51.78 \\
33.24
\end{array}
\]

\[
123.39 \\
128.56 \\
128.56 \\
127.40 \\
127.40 \\
53.40 \\
51.78 \\
33.24
\]

S65
Compound 2f (1H NMR, 600 MHz, CDCl₃)

N-1194 H. S

Compound 2f (13C NMR, 150 MHz, CDCl₃)
Compound 2g ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 2g ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 2h (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 2h (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
Compound 2i ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 2i ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 2j (1H NMR, 300 MHz, CDCl₃)

1224

Compound 2j (13C NMR, 75 MHz, CDCl₃)

1224-C
Compound 2k ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 2k ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 21 (1H NMR, 300 MHz, CDCl$_3$)

37-2

Compound 21 (13C NMR, 75 MHz, CDCl$_3$)

37-C
Compound 3a (¹H NMR, 300 MHz, CDCl₃)

38

Compound 3a (¹³C NMR, 75 MHz, CDCl₃)

38-C

S73
Compound 3b (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 3b (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
Compound 3c ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 3c ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 3d (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 3d (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
Compound 3e (1H NMR, 300 MHz, CDCl₃)

Compound 3e (13C NMR, 75 MHz, CDCl₃)
Compound 3f (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 3f (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
Compound 3g ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 3g ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 3h (1H NMR, 300 MHz, CDCl₃)

Compound 3h (13C NMR, 75 MHz, CDCl₃)

83-C
Compound 3i ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 3i ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 3j ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 3j ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 3k ($^1$H NMR, 500 MHz, CDCl$_3$)

$^1$H NMR Spectra

Compound 3k ($^{13}$C NMR, 125 MHz, CDCl$_3$)

$^{13}$C NMR Spectra
Compound 31 ($^1$H NMR, 300 MHz, CDCl$_3$)

$^1$H NMR spectrum showing chemical shifts for various protons.

Compound 31 ($^{13}$C NMR, 75 MHz, CDCl$_3$)

$^{13}$C NMR spectrum showing chemical shifts for various carbon atoms.
Compound 3m ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 3m ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 3n (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

1267

![H NMR spectrum](image)

Compound 3n (\(^13\)C NMR, 75 MHz, CDCl\(_3\))

1267-C

![C NMR spectrum](image)
Compound 3o (\( ^1 \text{H} \) NMR, 300 MHz, CDCl\(_3\))

Compound 3o (\( ^{13} \text{C} \) NMR, 75 MHz, CDCl\(_3\))
Compound 3p (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

41-4

Compound 3p (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))

41-C
Compound 3q ($^1$H NMR, 300 MHz, CDCl$_3$)

TO-1296

Compound 3q ($^{13}$C NMR, 75 MHz, CDCl$_3$)

TO-1296-C
Compound 3r \((^1H\text{ NMR, 300 MHz, CDCl}_3)\)

1288

Compound 3r \((^{13}C\text{ NMR, 75 MHz, CDCl}_3)\)

1288-C
Compound 3s ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 3s ($^{13}$C NMR, 75 MHz, CDCl$_3$)

S91
Compound 4a ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 4a ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 4b ($^1$H NMR, 500 MHz, CDCl$_3$)

N-1389
H-1

Compound 4b ($^{13}$C NMR, 125 MHz, CDCl$_3$)

N-1389
C-13

S93
Compound 4c (¹H NMR, 300 MHz, CDCl₃)

Compound 4c (¹³C NMR, 75 MHz, CDCl₃)
Compound 4d (\(^1\)H NMR, 300 MHz, CDCl$_3$)

Compound 4d (\(^{13}\)C NMR, 75 MHz, CDCl$_3$)
Compound 4e ($^1$H NMR, 600 MHz, CDCl$_3$)

$^1$H NMR spectrum showing chemical shifts and peak intensities.

Compound 4e ($^{13}$C NMR, 150 MHz, CDCl$_3$)

$^{13}$C NMR spectrum showing chemical shifts and peak intensities.
Compound 4f (1H NMR, 500 MHz, CDCl3)

Compound 4f (13C NMR, 125 MHz, CDCl3)
Compound 4g ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 4g ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 4h ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 4h ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 4i \((^1\text{H} \text{NMR, 300 MHz, CDCl}_3)\)

52

Compound 4i \((^{13}\text{C} \text{NMR, 75 MHz, CDCl}_3)\)

52-C
Compound 4j (1H NMR, 300 MHz, CDCl₃)

57-D

Compound 4j (13C NMR, 75 MHz, CDCl₃)

57-C
Compound 4k ($^1$H NMR, 500 MHz, CDCl$_3$)

Compound 4k ($^{13}$C NMR, 125 MHz, CDCl$_3$)
Compound 41 ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 41 ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 4m (¹H NMR, 300 MHz, CDCl₃)

S104

Compound 4m (¹³C NMR, 75 MHz, CDCl₃)

S104
Compound 4n (¹H NMR, 300 MHz, CDCl₃)

Compound 4n (¹³C NMR, 75 MHz, CDCl₃)
Compound 4o ($^1$H NMR, 300 MHz, CDCl$_3$)

Compound 4o ($^{13}$C NMR, 75 MHz, CDCl$_3$)
Compound 4p (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

1271-1

Compound 4p (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))

1271-1-C
Compound 4q \((^1\text{H} \text{NMR, } 600 \text{ MHz, CDCl}_3)\)

**N-1493 H-1**

Compound 4q \((^{13}\text{C} \text{NMR, } 150 \text{ MHz, CDCl}_3)\)

**N-1493 C-13**
Compound 4r (1H NMR, 300 MHz, CDCl₃)

Compound 4r (13C NMR, 75 MHz, CDCl₃)
Compound 4s ($^1$H NMR, 300 MHz, CDCl$_3$)
Compound 5a ($^1$H NMR, 300 MHz, CDCl$_3$)

20

Compound 5a ($^{13}$C NMR, 75 MHz, CDCl$_3$)

20-C
Compound 5b (1H NMR, 300 MHz, CDCl₃)

Compound 5b (13C NMR, 75 MHz, CDCl₃)
Compound 5c (\( ^1H \) NMR, 300 MHz, CDCl₃)

S113

Compound 5c (\( ^{13}C \) NMR, 75 MHz, CDCl₃)

S113-C
Compound 5d (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 5d (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
Compound 5e (^1^H NMR, 300 MHz, CDCl₃)

Compound 5e (^1^C NMR, 75 MHz, CDCl₃)
Compound 5f (¹H NMR, 600 MHz, CDCl₃)

Compound 5f (¹³C NMR, 150 MHz, CDCl₃)
Compound 6a (¹H NMR, 600 MHz, CDCl₃)

N-1305 H=N

Compound 6a (¹³C NMR, 150 MHz, CDCl₃)

N-1305 C-13
Compound 6b (\( ^1 \)H NMR, 600 MHz, CDCl\(_3\))

N-1334 H-1

Compound 6b (\( ^{13} \)C NMR, 150 MHz, CDCl\(_3\))

N-1334 C-13
Compound 6c \((^1\text{H} \text{ NMR, 600 MHz, CDCl}_3)\)

N-1323 H-1

Compound 6c \((^{13}\text{C} \text{ NMR, 150 MHz, CDCl}_3)\)

N-1323 C-13
Compound 6d \((^1\text{H NMR, 600 MHz, CDCl}_3)\)

N-1309 H-1

Compound 6d \((^{13}\text{C NMR, 150 MHz, CDCl}_3)\)

N-1309 C-13
Compound 6e ($^1$H NMR, 600 MHz, CDCl$_3$)

Compound 6e ($^{13}$C NMR, 150 MHz, CDCl$_3$)
Compound 7 (\(^1\)H NMR, 600 MHz, CDCl\(_3\))

Compound 7 (\(^{13}\)C NMR, 150 MHz, CDCl\(_3\))
Compound 8 ($^1$H NMR, 500 MHz, CDCl$_3$)

N-1483
H-1

Compound 8 ($^{13}$C NMR, 125 MHz, CDCl$_3$)

N-1483
C-13
Compound 9 ($^1$H NMR, 600 MHz, CDCl$_3$)

$^1$H NMR spectrum of Compound 9.

Compound 9 ($^{13}$C NMR, 150 MHz, CDCl$_3$)

$^{13}$C NMR spectrum of Compound 9.
Compound 10 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

Compound 10 (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))