

Supporting Information

LpxC Inhibitors: Design, Synthesis, and Biological Evaluation of Oxazolidinones as Gram-negative Antibacterial Agents

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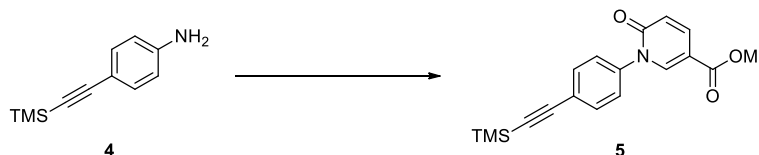
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General Information

All commercial reagents and anhydrous solvents were obtained from commercial sources and were used without further purification, unless otherwise specified. Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded with PerkinElmer spectrum 100. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JEOL JNM-AL300 spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane ($\delta = 0$) as an internal standard (CDCl_3 solution). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Measurements of mass spectra (MS) and high resolution MS (HRMS) were performed with a JEOL JMS SX-102A or a JEOL JMS-T100LP mass spectrometer. Optical rotation ($[\alpha]_D$) was measured with a JASCO P-1020 polarimeter. HPLC analyses were conducted using a JASCO 880-PU with HITACHI 655A UV detection. Column chromatography was carried out on silica gel [silica gel 40-50 μm neutral, Kanto Chemical Co., Inc. or Chromatorex[®] NH DM2035 (200-350 mesh Fuji Silysia Chemical, Ltd.)]. Merck precoated thin layer chromatography (TLC) plates (silica gel 60 F₂₅₄, 0.25 mm, Art 5715) were used for the TLC analysis. After extractive workup, organic layers were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

Synthesis of Compounds

Methyl 1-(4-((trimethylsilyl)ethynyl)phenyl)pyridine-2(1*H*)-one-5-carboxylate (**5**)



4-((Trimethylsilyl)ethynyl)aniline (**4**) (4.91 g, 26.0 mmol) and 5-methoxycarbonyl-2-pyrone (2.00 g, 13.0 mmol) were diluted with pyridine (40 mL) and the solution was purged with argon. The mixture was stirred at 100 °C for 1 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (35% EtOAc in hexanes) to give 1.57 g of the desired product as yellow solid (37%).

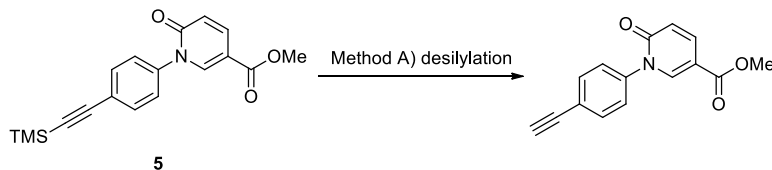
IR (ATR): 2954, 2899, 2156, 1725, 1663 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz) : δ 8.19 (1H, d, $J = 2.4$ Hz, Ar H), 7.90 (1H, dd, $J = 9.8, 3.0$ Hz, Ar H), 7.59 (2H, d, $J = 8.6$ Hz, Ar H), 7.33 (2H, d, $J = 8.6$ Hz, Ar H), 6.62 (1H, d, $J = 9.8$ Hz, Ar H), 3.87 (3H, s, OCH_3), 0.26 (9H, s, CH_3).

HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{Si}$, 325.1134; found, 325.1129.

Method A) Representative procedure of desilylation;

Methyl 1-(4-ethynylphenyl)pyridine-2(1H)-one-5-carboxylate



To a solution of **5** (1.55 g, 4.76 mmol) in methanol (48 mL) was added solid K_2CO_3 (724 mg, 5.24 mmol). The mixture was stirred at room temperature for 30 min. The reaction mixture was filtered through celite and washed with methanol. The filtrate was concentrated *in vacuo* to give a solid which was purified by silica gel chromatography (50% ethyl acetate in hexanes) to give 1.04 g of the desired product as pale yellow solid (86%).

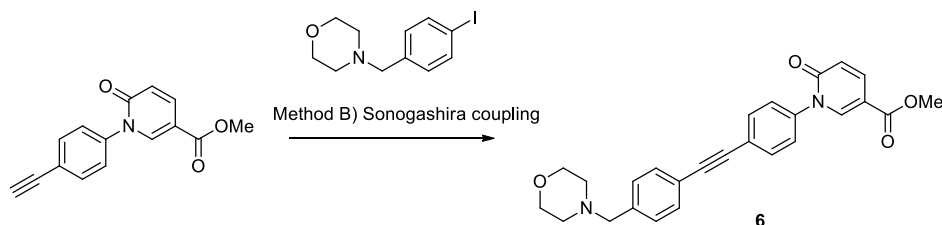
IR (ATR): 3271, 3064, 1718, 1673, 1542, 1504 cm^{-1} .

1H NMR ($CDCl_3$, 400 MHz): δ 8.20 (1H, d, $J = 2.4$ Hz, Ar H), 7.91 (1H, dd, $J = 9.8, 2.4$ Hz, Ar H), 7.63 (2H, d, $J = 8.6$ Hz, Ar H), 7.36 (2H, d, $J = 8.6$ Hz, Ar H), 6.63 (1H, d, $J = 9.8$ Hz, Ar H), 3.87 (3H, s, OCH_3), 3.16 (1H, s, $C\equiv CH$).

HRMS-EI (m/z): $[M]^+$ calcd for $C_{15}H_{11}NO_3$, 253.0739; found, 253.0732.

Method B) Representative procedure of Sonogashira coupling;

Methyl 1-(4-((4-(Morpholinomethyl)phenyl)ethynyl)phenyl)pyridine-2(1H)-one-5-carboxylate (**6**)



Methyl 1-(4-ethynylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (500 mg, 1.97 mmol) and 4-(4-iodobenzyl)morpholine¹⁾ (641 mg, 2.76 mmol) were dissolved in THF (33 mL) and the solution was purged with argon. To this solution was added $Pd(PPh_3)_2Cl_2$ (41.6 mg, 59.1 μ mol), Et_3N (630 μ L, 4.53 mmol) and CuI (25.6 mg, 0.118 mmol) and stirred at room temperature for 21 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (5% methanol in EtOAc) to afford 563 mg of the desired product as pale yellow solid (67%).

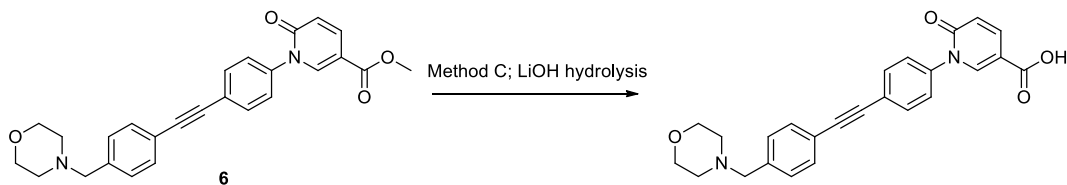
IR (ATR): 2943, 2864, 2813, 2769, 1719, 1674, 1540, 1515 cm^{-1} .

1H NMR ($CDCl_3$, 400 MHz): δ 8.23 (1H, d, $J = 2.4$ Hz, Ar H), 7.92 (1H, dd, $J = 9.8, 2.4$ Hz, Ar H), 7.65 (2H, d, $J = 8.6$ Hz, Ar H), 7.50 (2H, d, $J = 8.0$ Hz, Ar H), 7.38 (2H, d, $J = 8.0$ Hz, Ar H), 7.34 (2H, d, $J = 8.0$ Hz, Ar H), 6.64 (1H, d, $J = 9.8$ Hz, Ar H), 3.75-3.69 (4H, m, CH_2), 3.52 (2H, s, CH_2), 3.38 (3H, s, OCH_3), 2.49-2.42 (4H, m, CH_2).

HRMS-EI (m/z): $[M]^+$ calcd for $C_{26}H_{24}N_2O_4$, 428.1736; found, 428.1735.

Method C) Representative procedure of LiOH hydrolysis;

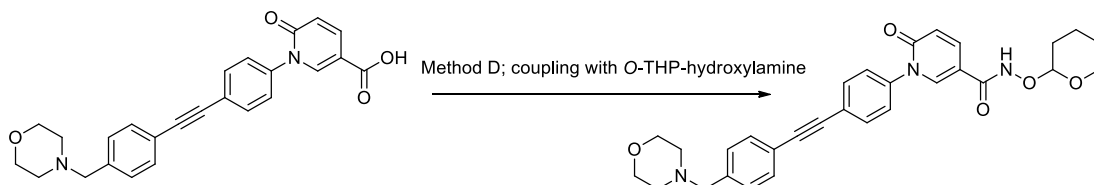
1-[4-(4-Morpholin-4-ylmethyl-phenylethynyl)-phenyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid



To a solution of **6** (400 mg, 934 μmol) in methanol/THF/water (1:1:1, 9 mL) was added LiOH \cdot H₂O (26.8 mg, 1.12 mmol) and stirred at room temperature for 5 h. The solvents were removed under vacuum and the resulting aqueous solution was acidified with 1 mol/L HCl *aq.* to pH 6 at 0 °C. The precipitate that formed was filtered and dried under vacuum to give the product (321 mg, 83%) as white solid, which was used in the next reaction without further purification.

Method D) Representative procedure of coupling with *O*-THP-hydroxylamine;

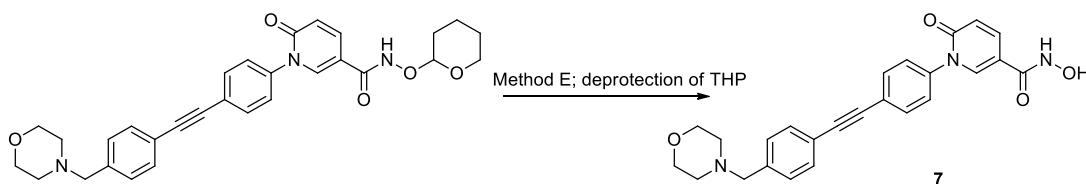
1-[4-(4-Morpholin-4-ylmethyl-phenylethynyl)-phenyl]-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid (tetrahydro-pyran-2-yloxy)-amide



To the solution of the above carboxylic acid (150 mg, 362 μmol) in DMF (3.6 mL) was added NH₂OTHP (46.6 mg, 398 μmol), EDCI \cdot HCl (76.3 mg, 398 μmol) and HOBT \cdot H₂O (61.0 mg, 398 μmol). The reaction mixture was stirred at room temperature for 18 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (70% acetone in hexane) to afford 200 mg of the crude product as colorless foam. The residue was taken to the next step without further purification.

Method E) Representative procedure of deprotection of THP;

N-Hydroxy-1-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)pyridine-2(1*H*)-one-5-carboxylate (**7**)



To the solution of the above compound in dioxane (2 mL) was added 4 mol/L HCl *aq.* (2 mL) and stirred at 0 °C and the reaction was allowed to stir at room temperature for 1 h. The solvents from

the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (CHCl₃:methanol:25% NH₃ aq. = 100:10:1) to give 34.6 mg of the desired product as white solid (18% over three steps from **6**).

IR (ATR): 3197, 2854, 2813, 2220, 1661, 1515 cm⁻¹.

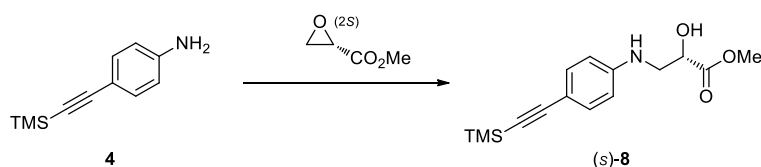
¹H NMR (DMSO-*d*₆, 400 MHz) : δ 11.03 (1H, brs, NH or OH), 9.04 (1H, brs, NH or OH), 8.11 (1H, d, *J* = 2.4 Hz, Ar H), 7.83 (1H, d, *J* = 9.2, 2.4 Hz, Ar H), 7.69 (2H, d, *J* = 8.6 Hz, Ar H), 7.55 (4H, dd, *J* = 8.6, 1.8 Hz, Ar H), 7.37 (2H, d, *J* = 7.9 Hz, Ar H), 6.54 (1H, d, *J* = 9.8 Hz, Ar H), 3.60-3.55 (4H, m, CH₂), 3.49 (2H, s, CH₂), 2.38-2.32 (4H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₂₅H₂₄N₃O₄, 430.1767; found, 430.1777.

LC/MS analysis (Waters MicroMass ZQ system) showed purity 96.1% and retention time 3.36 min for the title compound.

Anal. calcd for C₂₅H₂₃N₃O₄·0.3H₂O: C, 68.20; H, 5.54; N, 9.54. found: C, 68.22; H, 5.41; N, 9.40.

(*S*)-Methyl 2-hydroxy-3-((4-((trimethylsilyl)ethynyl)phenyl)amino)propanoate ((*S*)-**8**)



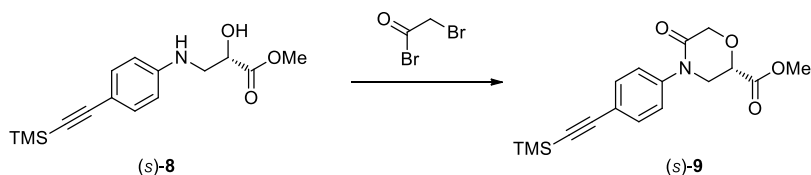
4-((Trimethylsilyl)ethynyl)aniline (**4**) (3.00 g, 15.8 mmol), methyl (2*S*)-glycidate (2.42 g, 23.7 mmol) and TfOLi (3.70 g, 23.7 mmol) were diluted with CH₃CN (54 mL) and the solution was purged with argon. The mixture was stirred at 65 °C for 12 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (35% EtOAc in hexanes) to give 1.59 g of the desired product as white solid (34%).

IR (ATR): 3400, 3307, 2959, 2147, 1738, 1607, 1522 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz) : δ 7.29 (2H, d, *J* = 8.6 Hz, Ar H), 6.55 (2H, d, *J* = 9.2 Hz, Ar H), 4.38-4.42 (1H, m, CH), 4.20 (1H, t, *J* = 6.7 Hz, NH), 3.79 (3H, s, OCH₃), 3.52-3.58 (1H, m, CH₂), 3.41-3.48 (1H, m, CH₂), 3.01 (1H, d, *J* = 4.9 Hz, OH), 0.22 (9H, s, CH₃),.

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₅H₂₂NO₃Si, 292.1369; found, 292.1367.

(*S*)-Methyl 4-(4-((trimethylsilyl)ethynyl)phenyl)morpholin-5-one-2-carboxylate ((*S*)-**9**)



Amino alcohol (*S*)-**8** (250 mg, 858 μmol) was dissolved in THF (4 mL) and the solution was purged with argon. To this solution was added Et₃N (131 mg, 944 μmol) and bromoacetyl bromide (81.7 μL,

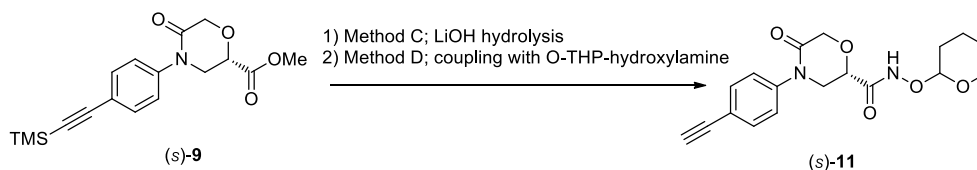
944 μmol). The mixture was stirred at room temperature for 2 h. To the solution was added NaH (75.4 mg, 1.89 mmol, 55% in mineral oil) and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into aqueous solution of saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (50% EtOAc in hexanes) to give 61.3 mg of the desired product as colorless oil (22%).

IR (ATR): 2957, 2157, 1743, 1670, 1671, 1504 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.50 (2H, d, $J = 8.6$ Hz, Ar H), 7.27 (2H, d, $J = 8.6$ Hz, Ar H), 4.62 (1H, dd, $J = 8.0, 3.7$ Hz, CH), 4.58 (1H, d, $J = 17.1$ Hz, CH_2), 4.40 (1H, d, $J = 17.1$ Hz, CH_2), 4.02 (1H, dd, $J = 12.2, 8.0$ Hz, CH_2), 3.95 (1H, dd, $J = 12.2, 3.7$ Hz, CH_2), 3.85 (3H, s, OCH_3), 0.25 (9H, s, CH_3).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_4\text{Si}$, 332.1318; found, 332.1325.

(2*S*)-4-(4-Ethynylphenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)morpholin-5-one-2-carboxamide (*S*)-**11**



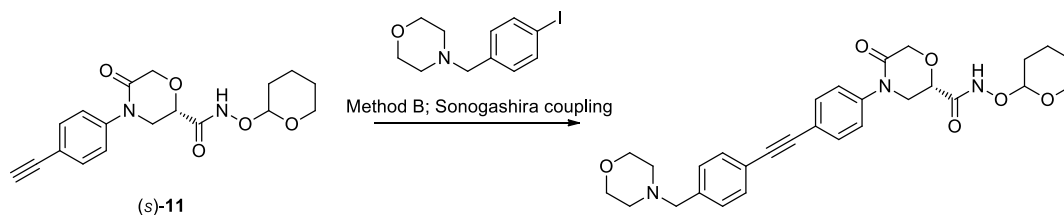
The title compound was prepared according the general procedure of LiOH hydrolysis (Method C) and coupling with *O*-THP-hydroxylamine (Method D) (Colorless foam, 57% over two steps).

IR (ATR): 3280, 2946, 1656, 1601, 1505 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 9.09 (1H, brs, NH), 7.53 (2H, d, $J = 8.0$ Hz, Ar H), 7.30 (2H, dd, $J = 9.2, 3.1$ Hz, Ar H), 5.00 (1H, d, $J = 16.0$ Hz, CH), 4.63-4.57 (1H, m, CH_2), 4.51 (1H, dd, $J = 17.1, 3.7$ Hz, CH_2), 4.39 (1H, d, $J = 16.5$ Hz, CH), 4.06-3.92 (3H, m, CH_2), 3.70-3.66 (1H, m, CH_2), 3.09 (1H, s, $\text{C}\equiv\text{CH}$), 1.93-1.60 (6H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5$, 345.14505; found, 345.14517.

(2*S*)-4-(4-((4-(Morpholinomethyl)phenyl)ethynyl)phenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)morpholin-5-one-2-carboxamide



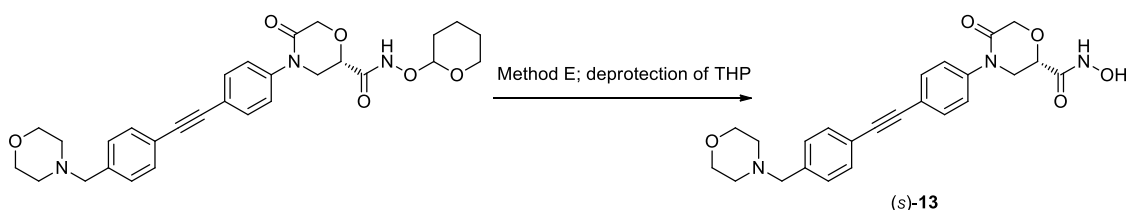
The title compound was prepared according the general procedure of Sonogashira coupling (Method B) (Brown oil, 60%).

IR (ATR): 3220, 2946, 2854, 2810, 1665, 1516 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 9.10 (1H, brs, NH), 7.56 (2H, d, $J = 9.2$ Hz, Ar H), 7.48 (2H, d, $J = 9.2$ Hz, Ar H), 7.33 (4H, apparent d, $J = 7.4$ Hz, Ar H), 5.00 (1H, d, $J = 17.1$ Hz, CH), 4.64-4.57 (1H, m, CH), 4.52 (1H, dd, $J = 16.5, 4.3$ Hz, CH_2), 4.40 (1H, d, $J = 16.5$ Hz, CH_2), 4.07-3.94 (3H, m, CH_2), 3.74-3.67 (5H, m, CH_2), 3.51 (2H, s, CH_2), 2.48-2.43 (4H, s, CH_2), 1.93-1.57 (6H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{34}\text{N}_3\text{O}_6$, 520.2448; found, 520.2454.

(*S*)-*N*-hydroxy-4-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)morpholin-5-one-2-carboxamide ((*S*)-**13**)



The title compound was prepared according to the general procedure of deprotection of THP (Method E) (White solid, 61%).

IR (ATR): 3221, 3047, 2845, 1649, 1516 cm^{-1} .

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 10.89 (1H, brs, NH or OH), 9.00 (1H, brs, NH or OH), 7.57 (2H, d, $J = 9.2$ Hz, Ar H), 7.50 (2H, d, $J = 8.0$ Hz, Ar H), 7.46 (2H, d, $J = 9.2$ Hz, Ar H), 7.35 (2H, d, $J = 8.0$ Hz, Ar H), 4.57 (1H, dd, $J = 8.6, 3.7$ Hz, CH), 4.32 (2H, s, CH_2), 3.96 (1H, dd, $J = 12.2, 8.6$ Hz, CH_2), 3.84 (1H, dd, $J = 12.9, 4.3$ Hz, CH_2), 3.60-3.54 (4H, m, CH_2), 3.48 (2H, s, CH_2), 2.38-2.32 (4H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_5$, 436.1873; found, 436.1869.

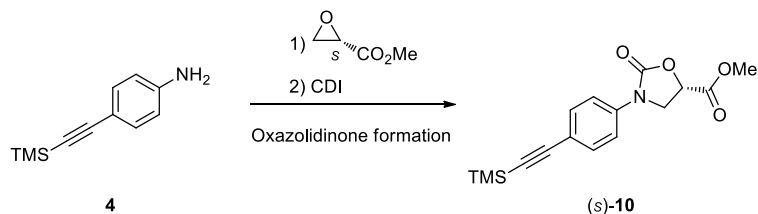
$[\alpha]_D^{26} = +10.3$ ($c = 0.10$, MeOH).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 94.2% and retention time 3.24 min for the title compound.

Anal. calcd for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5 \cdot 0.3\text{H}_2\text{O}$: C, 65.38; H, 5.85; N, 9.53. found: C, 65.49; H, 5.73; N, 9.44.

Method F) Representative procedure of oxazolidinone formation;

(*S*)-Methyl 3-(4-((trimethylsilyl)ethynyl)phenyl)oxazolidin-2-one-5-carboxylate ((*S*)-**10**)



4-((Trimethylsilyl)ethynyl)-aniline (**4**) (1.50 g, 7.92 mmol), methyl (*S*)-glycidate (1.21 g, 11.9

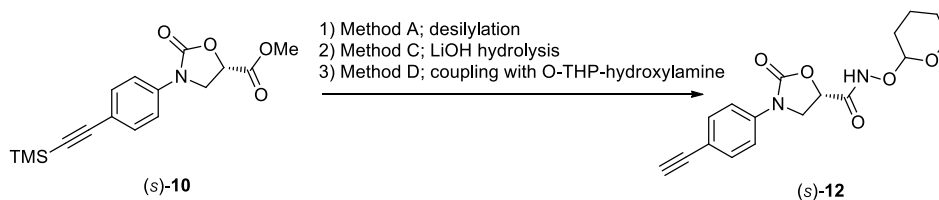
mmol) and TfOLi (1.85 g, 11.9 mmol) were diluted with CH₃CN (27 mL) and the solution was purged with argon. The mixture was stirred at 60 °C for 21 h. To the solution was added CDI (2.57 mg, 15.8 mmol) and the mixture was stirred at 65 °C for 3 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (35% EtOAc in hexanes) to give 1.15 g of the desired product as white solid (46% over two steps).

IR (ATR): 2957, 2899, 2157, 1746, 1606, 1511 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.48 (4H, s, Ar H), 5.07 (1H, dd, *J* = 9.8, 5.5 Hz, CH), 4.29 (1H, t, *J* = 9.2 Hz, CH₂), 4.15 (1H, dd, *J* = 9.2, 5.5 Hz, CH₂), 3.88 (s, 3H, OCH₃), 0.25 (9H, s, CH₃).

HRMS-FI (*m/z*): [M]⁺ calcd for C₁₆H₁₉NO₄Si, 317.1083; found, 317.1085.

(5*S*)-3-(4-Ethynylphenyl)-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)oxazolidin-2-one-5-carboxamide
(*S*)-**12**



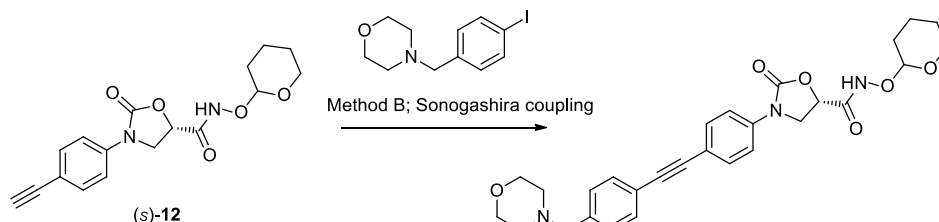
The title compound was prepared according the general procedure of desilylation (MethodA), LiOH hydrolysis (Method C) and coupling with *O*-THP-hydroxylamine (Method D) (Colorless foam, 54% over three steps).

IR (ATR): 3256, 2948, 1757, 1691, 1606, 1510 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 9.18 (1H, d, *J* = 8.0 Hz, NH), 7.54-7.48 (m, 4H, Ar H), 5.00-5.11 (2H, m), 4.34-4.25 (2H, m, CH₂), 4.02-3.92 (1H, m, CH₂), 3.72-3.63 (1H, m, CH₂), 3.08 (1H, s, C≡CH), 1.92-1.76 (3H, m, CH₂), 1.71-1.54 (3H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₇H₁₉N₂O₅, 331.1294; found, 331.1297.

(*S*)-*N*-(Cyclohexyloxy)-3-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-oxazolidin-2-one-5-carboxamide



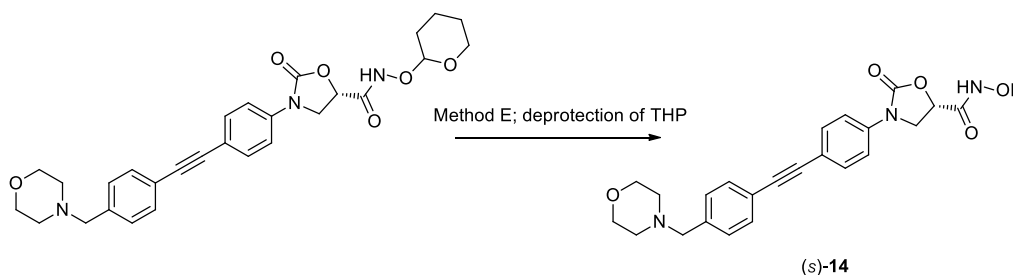
The title compound was prepared according the general procedure of Sonogashira coupling (Method B) (Colorless foam, 30%).

IR (ATR): 3205, 2944, 2854, 2808, 1759, 1693, 1603, 1519 cm⁻¹.

^1H NMR (CDCl_3 , 400 MHz) : δ 9.17 (1H, brs, NH), 7.58-7.50 (4H, m, Ar H), 7.48 (2H, d, $J = 8.6$ Hz, Ar H), 7.32 (2H, d, $J = 8.6$ Hz, Ar H), 5.14-4.98 (2H, m, CH), 4.37-4.25 (2H, m, CH_2), 4.02-3.92 (1H, m, CH_2), 3.75-3.64 (5H, m, CH_2), 3.51 (2H, s, CH_2), 2.48-2.41 (4H, m, CH_2), 1.94-1.76 (3H, m, CH_2), 1.71-1.52 (3H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{32}\text{N}_3\text{O}_6$, 506.2291; found, 506.2295.

(*S*)-*N*-Hydroxy-3-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-oxazolidin-2-one-5-carboxamide ((*S*)-**14**)



The title compound was prepared according to the general procedure of deprotection of THP (Method E) (White solid, 46%).

IR (ATR): 3197, 2819, 1757, 1671, 1602, 1519 cm^{-1} .

^1H NMR ($\text{DMSO}-d_6$, 400 MHz) : δ 11.20 (1H, brs, NH or OH), 9.25 (1H, brs, NH or OH), 7.64 (2H, d, $J = 9.2$ Hz, Ar H), 7.56 (2H, d, $J = 9.2$ Hz, Ar H), 7.50 (2H, d, $J = 7.9$ Hz, Ar H), 7.35 (2H, d, $J = 7.9$ Hz, Ar H), 4.98 (1H, dd, $J = 9.2, 5.5$ Hz, CH), 4.29 (1H, t, $J = 9.2$ Hz, CH_2), 4.04 (1H, dd, $J = 9.2, 5.5$ Hz, CH_2), 3.61-3.55 (4H, m, CH_2), 3.54-3.47 (2H, m, CH_2), 2.40-2.31 (4H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_5$, 422.1716; found, 422.1709.

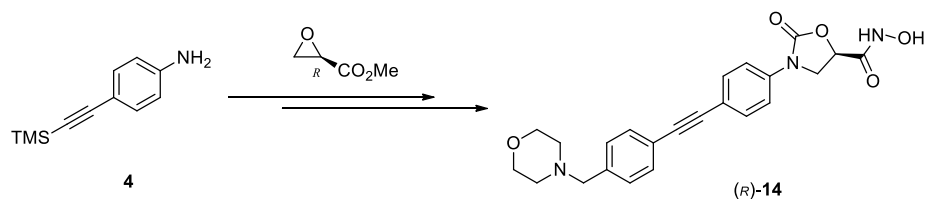
$[\alpha]_D^{25} = +59.9$ ($c = 0.13$, DMSO).

The optical purity of (*S*)-**14** was measured to be >99% ee by chiral HPLC analysis (DAICEL CHIRALPAK IC, 4.6 x 250 mm, measurement of UV254nm absorbance, MTBE-EtOH-TFA 80:20:0.5, 0.5 mL min^{-1} , (*R*)-**14**: 16.6 min, (*S*)-**14**: 23.6 min)

LC/MS analysis (Waters MicroMass ZQ system) showed purity 99.1% and retention time 3.71 min for the title compound.

Anal. calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_5 \cdot 0.04\text{Et}_2\text{O} \cdot 0.6\text{H}_2\text{O}$: C, 63.91; H, 5.70; N, 9.65. found: C, 64.06; H, 5.50; N, 9.33.

(*R*)-*N*-Hydroxy-3-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-oxazolidin-2-one-5-carboxamide ((*R*)-**14**)



The title compound was synthesized as described for (*S*)-**14** from methyl (*2R*)-glycidate.

IR (ATR): 3196, 2855, 2809, 1759, 1671, 1602, 1519 cm^{-1} .

^1H NMR (DMSO-*d*₆, 400 MHz): δ 11.20 (1H, brs, NH or OH), 9.25 (1H, brs, NH or OH), 7.64 (2H, d, $J = 9.2$ Hz, Ar H), 7.56 (2H, d, $J = 9.2$ Hz, Ar H), 7.50 (2H, d, $J = 7.9$ Hz, Ar H), 7.35 (2H, d, $J = 7.9$ Hz, Ar H), 4.98 (1H, dd, $J = 9.2, 5.5$ Hz, CH), 4.29 (1H, t, $J = 9.2$ Hz, CH₂), 4.04 (1H, dd, $J = 9.2, 5.5$ Hz, CH₂), 3.61-3.55 (4H, m, CH₂), 3.54-3.47 (2H, m, CH₂), 2.42-2.33 (4H, m, CH₂).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for C₂₃H₂₄N₃O₅, 422.1716; found, 422.1716.

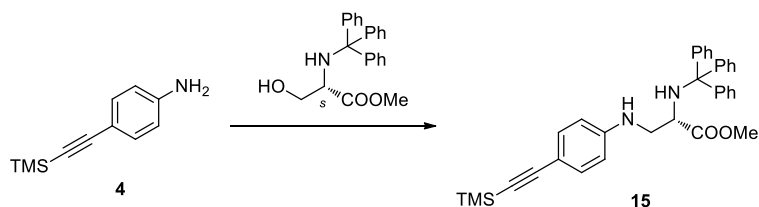
$[\alpha]_D^{25} = -55.6$ ($c = 0.12$, DMSO).

The optical purity of (*R*)-**14** was measured to be >99% ee by chiral HPLC analysis (DAICEL CHIRALPAK IC, 4.6 x 250 mm, measurement of UV254nm absorbance, MTBE-EtOH-TFA 80:20:0.5, 0.5 mL min⁻¹, (*R*)-**14**: 16.6 min, (*S*)-**14**: 23.6 min)

LC/MS analysis (Waters MicroMass ZQ system) showed purity 98.5% and retention time 3.64 min for the title compound.

Anal. calcd for C₂₃H₂₃N₃O₅·0.5H₂O: C, 64.18; H, 5.62; N, 9.76. found: C, 64.12; H, 5.54; N, 9.37.

(*S*)-Methyl 3-((4-((trimethylsilyl)ethynyl)phenyl)amino)-2-(tritylamino)propanoate (**15**)



To the solution of (*S*)-methyl 3-hydroxy-2-(tritylamino)propanoate (10.0 g, 27.6 mmol) in DMSO/CH₂Cl₂ (1:1, 140 mL) was added Et₃N (15.4 mL, 110 mmol) and SO₃Py (8.64 g, 55.4 mmol) at room temperature. The mixture was stirred for 2 h. The solvents from the reaction mixture were removed under vacuum. The reaction mixture was poured into aqueous solution of saturated NH₄Cl (400 mL), extracted with EtOAc (200 mL x 3), washed with brine (400 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (20% EtOAc in hexane) to afford 3.78 g of the corresponding aldehyde as a yellow oil (38%). To a solution of the aldehyde (1.20 g, 3.34 mmol) in CH₂Cl₂ (33 mL) was added 4-((trimethylsilyl)ethynyl) aniline (**4**) (856 mg, 4.34 mmol) and NaBH(OAc)₃ (1.42 g, 6.68 mmol). The mixture was stirred at room temperature for 19 h. The reaction mixture was poured into aqueous

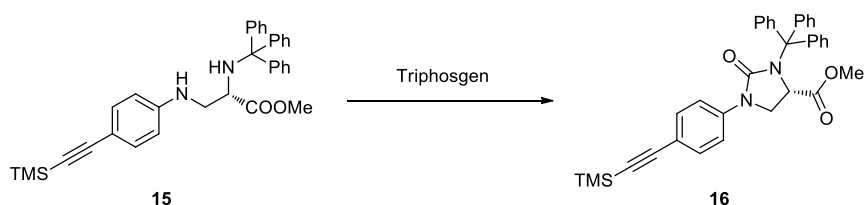
solution of saturated NaHCO₃ (50 mL), extracted with CH₂Cl₂ (20 mL x 2), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (20% EtOAc in hexane) to afford 430 mg of the desired product as yellow foam (24%).

IR (ATR): 3406, 3056, 3031, 2953, 2148, 1732, 1607, 1517 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz) : δ 7.48-7.46 (5H, m, Ar H), 7.30-7.15 (12H, m, Ar H), 6.48 (2H, d, *J* = 9.2 Hz, Ar H), 4.18 (t, 1H, *J* = 6.8 Hz, NH), 3.63-3.55 (1H, m, CH), 3.48-3.40 (1H, m, CH₂), 3.35-3.26 (1H, m, CH₂), 3.17 (3H, s, OCH₃), 2.84 (1H, d, *J* = 10.4, NH), 0.23 (9H, s, CH₃).

HRMS-FD (*m/z*): [M]⁺ calcd for C₃₄H₃₆N₂O₂Si, 532.2546; found, 532.2547.

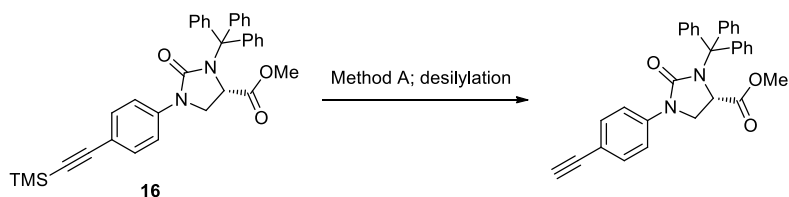
(*S*)-Methyl 1-(4-((trimethylsilyl)ethynyl)phenyl)-3-tritylimidazolidin-2-one-4-carboxylate (**16**)



Diamine **15** (400 mg, 751 μmol) was dissolved in CH₂Cl₂ (7.5 mL) and the solution was purged with argon. To this solution was added Et₃N (521 μL, 3.75 mmol) and triphosgene (334 mg, 1.13 mmol) at 0 °C. The reaction was allowed to stir at room temperature for 30 min. The reaction mixture was poured into aqueous solution of saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (10 mL x 2), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was triturated with Et₂O to give 345 mg of the desired product as white solid (82%).

¹H NMR (CDCl₃, 400 MHz) : δ 7.39-7.25 (19H, m, Ar H), 4.44 (1H, dd, *J* = 11.0, 3.7 Hz, CH), 4.18 (1H, t, *J* = 9.8 Hz, CH₂), 3.70 (1H, dd, *J* = 9.8, 3.6 Hz, CH₂), 3.46 (3H, s, OCH₃), 0.22 (9H, s, CH₃).

(*S*)-Methyl 1-(4-ethynylphenyl)-3-tritylimidazolidin-2-one-4-carboxylate

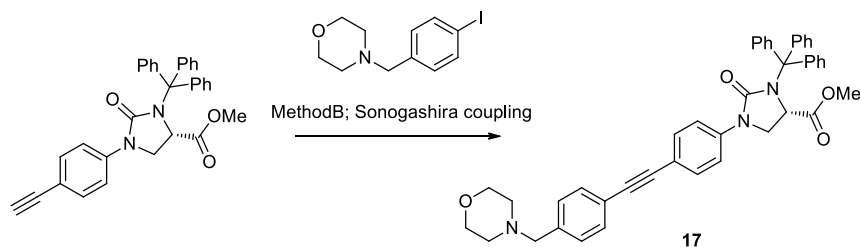


The title compound was prepared according the general procedure of desilylation (Method A) (White solid, 96% yield).

¹H NMR (CDCl₃, 400 MHz) : δ 7.43-7.24 (19H, m, Ar H), 4.45 (1H, dd, *J* = 10.4, 3.6 Hz, CH), 4.19 (1H, t, *J* = 9.8 Hz, CH₂), 3.71 (1H, dd, *J* = 9.2, 3.6 Hz, CH₂), 3.47 (3H, s, OCH₃), 3.00 (1H, s, C≡CH).

(S)-Methyl

1-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-3-tritylimidazolidin-2-one-4-carboxylate (**17**)



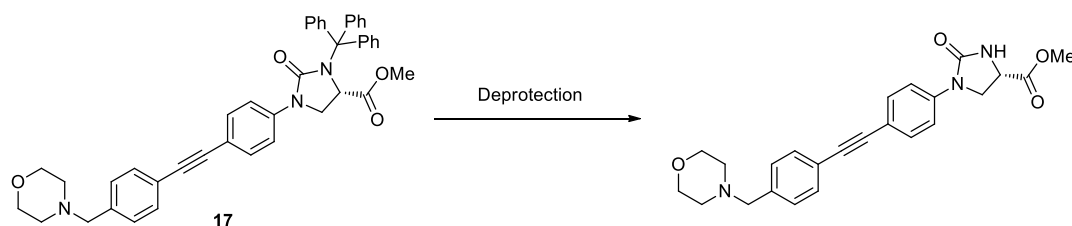
The title compound was prepared according the general procedure of Sonogashira coupling (Method B) (Pale brown foam, 62%).

IR (ATR): 2951, 2852, 2806, 1719, 1601, 1519 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz) : δ 7.47-7.26 (23H, m, Ar H), 4.45 (1H, dd, $J = 10.4, 3.6$ Hz, CH), 4.21 (1H, t, $J = 9.8$ Hz, CH_2), 3.75-3.68 (5H, m, CH_2), 3.49 (2H, s, CH_2), 3.47 (3H, s, OCH_3), 2.46-2.41 (4H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{43}\text{H}_{40}\text{N}_3\text{O}_4$, 662.3019; found, 662.3020.

(S)-Methyl 1-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-imidazolidin-2-one-4-carboxylate



To solution of **17** (200 mg, 30.2 μmol) in THF/water (2:1, 3 mL) was added HCOOH (2 mL) and stirred at 65 $^\circ\text{C}$ for 2 h. The reaction mixture poured into aqueous solution of saturated NaHCO_3 (30 mL) and extracted with CH_2Cl_2 (20 mL x 3), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (EtOAc) to afford 77.7 mg of the desired product as white solid (61%).

IR (ATR): 3231, 3110, 2923, 2857, 2816, 2211, 1745, 1710, 1601, 1520 cm^{-1} .

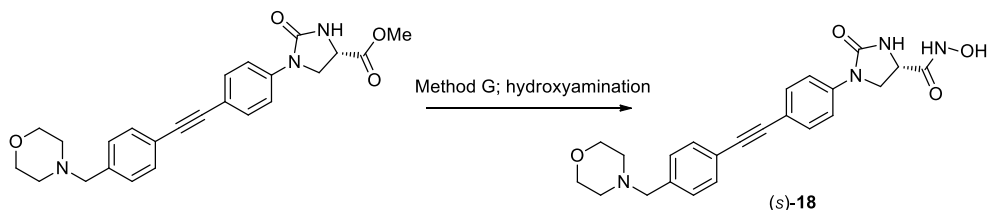
^1H NMR ($\text{DMSO}-d_6$, 400 MHz) : δ 7.75 (1H, s, NH), 7.60 (2H, d, $J = 8.6$ Hz, Ar H), 7.47 (4H, d, $J = 8.6$ Hz, Ar H), 7.33 (2H, d, $J = 8.6$ Hz, Ar H), 4.43 (1H, dd, $J = 10.4, 4.3$ Hz, CH), 4.16 (1H, t, $J = 9.8$ Hz, CH_2), 3.94 (1H, dd, $J = 9.8, 4.3$ Hz, CH_2), 3.71 (3H, s, OCH_3), 3.60-3.54 (4H, m, CH_2), 3.48 (2H, s, CH_2), 2.36-2.32 (4H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_4$, 420.1923; found, 420.1917.

Method G) Representative procedure of hydroxyamination;

(S)-N-Hydroxy-1-(4-((4-(morpholinomethyl)phenyl)ethynyl)phenyl)-imidazolidin-2-one-4-carboxylate

mide ((*S*)-**18**)



To solution of the above compound (20.0 mg) in *i*PrOH/THF (1:1, 1 mL) was added 50% NH₂OH *aq.* (1 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with ethanol to afford 16.0 mg of the desired product as white solid (80%).

IR (ATR): 3195, 2856, 2806, 2215, 1709, 1654, 1519 cm⁻¹.

¹H NMR (DMSO-*d*₆, 400 MHz) : δ 10.8 (1H, s, NH or OH), 9.06 (1H, s, NH or OH), 7.61 (2H, d, *J* = 8.6 Hz, Ar H), 7.51 (1H, s, NH), 7.47 (4H, d, *J* = 8.6 Hz, Ar H), 7.33 (2H, d, *J* = 8.0 Hz, Ar H), 4.11-4.05 (2H, m, CH₂ and CH), 3.74 (1H, dd, *J* = 14.7, 10.4 Hz, CH₂), 3.60-3.54 (4H, m, CH₂), 3.47 (2H, s, CH₂), 2.38-2.30 (4H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₂₃H₂₅N₄O₄ 421.1876; found, 421.1869.

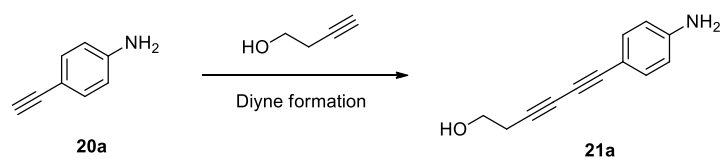
[α]_D²⁵ = +4.13 (*c* = 0.10, MeOH).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 95.7% and retention time 3.31 min for the title compound.

Anal. calcd for C₂₃H₂₄N₄O₄·0.2H₂O: C, 65.14; H, 5.80; N, 13.21. found: C, 65.23; H, 5.67; N, 13.20.

Method H) Representative procedure of diyne formation;

6-(4-Aminophenyl)hexa-3,5-diyne-1-ol (**21a**)



CuI (239 mg, 1.26 mmol) and NiCl₂·6H₂O (298 mg, 1.26 mmol) were dissolved in THF (50 mL) and stirred for 5 min. TMEDA (773 uL, 5.02 mmol) was added and the solution was stirred at room temperature for 5 min. (2-Hydroxyethyl)acetylene (8.80 g, 125 mmol) and 4-ethynylaniline (**20a**) (2.94 g, 25.1 mmol) in THF (50 mL) were added subsequently and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography (40% EtOAc in hexane) to afford 2.55 g (55%) of the desired product as yellow solid.

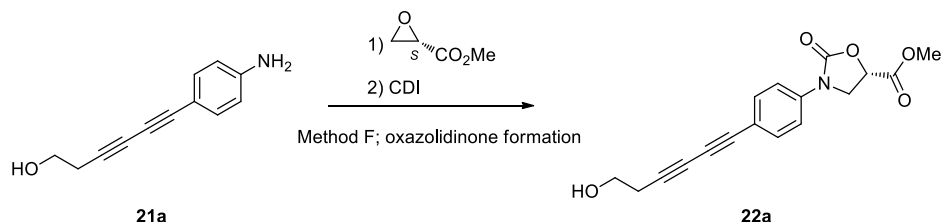
IR (ATR): 3364, 3216, 2870, 2154, 1604, 1509 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz) : δ 7.28 (2H, d, *J* = 8.6 Hz, Ar H), 6.57 (2H, d, *J* = 8.6 Hz, Ar H), 3.87

(1H, brs, OH), 3.77 (2H, t, $J = 5.5$ Hz, CH₂), 2.63 (2H, t, $J = 6.1$ Hz, CH₂).

MS-FD (m/z): [M]⁺ 185.

(*S*)-Methyl 3-(4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-oxazolidin-2-one-5-carboxylate (**22a**)



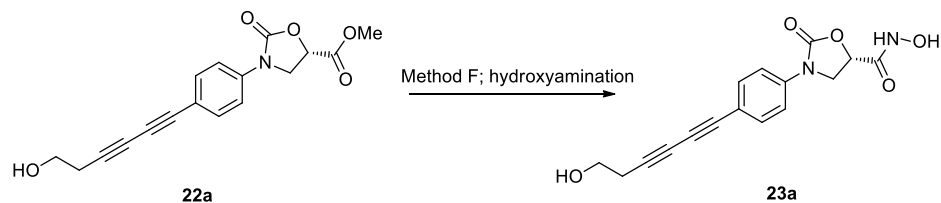
The title compound was prepared according the general procedure of oxazolidinone formation (Method F) (Pale pink solid, 20% over two steps).

IR (ATR): 3363, 2954, 2241, 2160, 1736, 1604, 1515 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz) : δ 7.50 (4H, apparent s, Ar H), 5.08 (1H, dd, $J = 9.2, 4.9$ Hz, CH), 4.30 (1H, t, $J = 9.2$ Hz, CH₂), 4.15 (1H, dd, $J = 9.2, 5.5$ Hz, CH₂), 3.88 (3H, s, OCH₃), 3.80 (2H, q, $J = 6.1$ Hz, CH₂), 2.65 (2H, t, $J = 6.1$ Hz, CH₂), 1.77 (1H, t, $J = 6.1$ Hz, OH).

HRMS-ESI (m/z): [M + H]⁺ calcd for C₁₇H₁₆NO₅ 314.1029; found, 314.1039.

(*S*)-*N*-Hydroxy-3-(4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-oxazolidin-2-one-5-carboxamide (**23a**)



The title compound was prepared according the general procedure of hydroxyamination (Method F) (Pale blue solid, 41%).

IR (ATR): 3204, 2888, 2244, 1749, 1652, 1601, 1512 cm⁻¹.

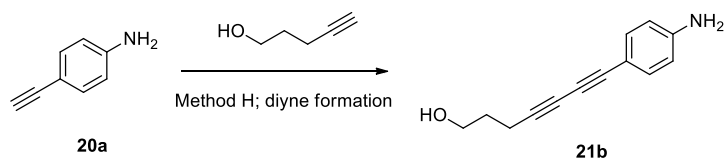
¹H NMR (DMSO-*d*₆, 400 MHz) : δ 11.16 (1H, brs, NH or OH), 9.26 (1H, brs, NH or OH), 7.61 (2H, d, $J = 9.2$ Hz, Ar H), 7.56 (2H, d, $J = 9.2$ Hz, Ar H), 5.00-4.95 (2H, m, CH and OH), 4.28 (1H, t, $J = 9.2$ Hz, CH₂), 4.03 (1H, dd, $J = 9.2, 5.5$ Hz, CH₂), 3.55 (2H, q, $J = 6.7$ Hz, CH₂), 2.54 (2H, t, $J = 6.1$ Hz, CH₂).

HRMS-ESI (m/z): [M - H]⁻ calcd for C₁₆H₁₃N₂O₅ 313.0825; found, 313.0830.

$[\alpha]_D^{26} = +64.2$ ($c = 0.10$, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 95.6% and retention time 3.35 min for the title compound.

7-(4-Aminophenyl)hepta-4,6-diyn-1-ol (**21b**)



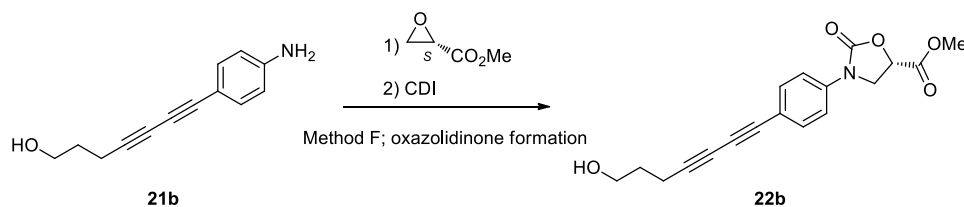
The title compound was prepared according the general procedure of diyne formation (Method H) (Pale orange solid, 55%).

IR (ATR): 3381, 3181, 2956, 2934, 2874, 2142, 1892, 1603, 1508 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz) : δ 7.28 (2H, d, $J = 8.6$ Hz, Ar H), 6.57 (2H, d, $J = 8.6$ Hz, Ar H), 3.85 (1H, brs, OH), 3.78 (2H, t, $J = 6.1$ Hz, CH_2), 2.49 (2H, t, $J = 7.3$ Hz, CH_2), 1.82 (2H, apparent quintet, $J = 6.7$ Hz, CH_2).

HRMS-FD (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{NO}$ 199.0997; found, 199.0991.

(*S*)-Methyl 3-(4-(7-hydroxyhepta-1,3-diyne-1-yl)phenyl)-oxazolidin-2-one-5-carboxylate (**22b**)



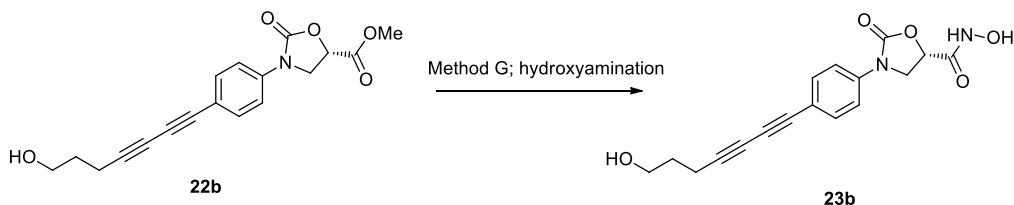
The title compound was prepared according the general procedure of oxazolidinone formation (Method F) (White solid, 16% over two steps).

IR (ATR): 3358, 2955, 2248, 2140, 1737, 1604, 1514 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz) : δ 7.49 (4H, apparent s, Ar H), 5.08 (1H, dd, $J = 9.8, 5.5$ Hz, CH), 4.30 (1H, t, $J = 9.2$ Hz, CH_2), 4.14 (1H, dd, $J = 9.2, 5.5$ Hz, CH_2), 3.88 (3H, s, OCH_3), 3.82-3.75 (2H, m, CH_2), 2.51 (2H, t, $J = 6.8$ Hz, CH_2), 1.84 (2H, apparent quintet, $J = 6.7$ Hz, CH_2), 1.41 (1H, t, $J = 4.9$ Hz, OH).

HRMS-FD (m/z): $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_5$ 327.1107; found, 327.1103.

(*S*)-*N*-Hydroxy-3-(4-(7-hydroxyhepta-1,3-diyne-1-yl)phenyl)-oxazolidin-2-one-5-carboxamide (**23b**)



The title compound was prepared according the general procedure of hydroxyamination (Method G) (Pale pink solid, 72%).

IR (ATR): 3449, 3201, 2884, 2241, 1729, 1692, 1602, 1512 cm^{-1} .

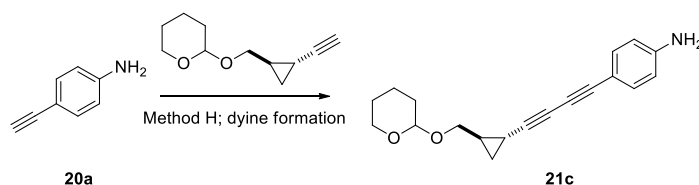
^1H NMR (DMSO- d_6 , 400 MHz): δ 11.16 (1H, brs, NH or OH), 9.26 (1H, brs, NH or OH), 7.61 (2H, d, $J = 8.6$ Hz, Ar H), 7.56 (2H, d, $J = 9.2$ Hz, Ar H), 4.98 (1H, dd, $J = 9.2, 5.5$ Hz, CH), 4.57 (1H, t, $J = 4.9$ Hz, OH), 4.28 (1H, t, $J = 9.2$ Hz, CH₂), 4.03 (1H, dd, $J = 9.2, 5.5$ Hz, CH₂), 3.49-3.45 (2H, m, CH₂), 2.46 (2H, t, $J = 6.7$ Hz, CH₂), 1.63 (2H, apparent quintet, $J = 6.7$ Hz, CH₂).

HRMS-ESI (m/z): [M - H]⁻ calcd for C₁₇H₁₅N₂O₅ 327.0981; found, 327.0985.

$[\alpha]_D^{26} = +118$ ($c = 0.10$, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 95.9% and retention time 3.57 min for the title compound.

4-[[*trans*-2-[[*(Tetrahydro-2H-pyran-2-yl)oxy*]methyl]cyclopropyl]buta-1,3-diyn-1-yl]aniline (**21c**)



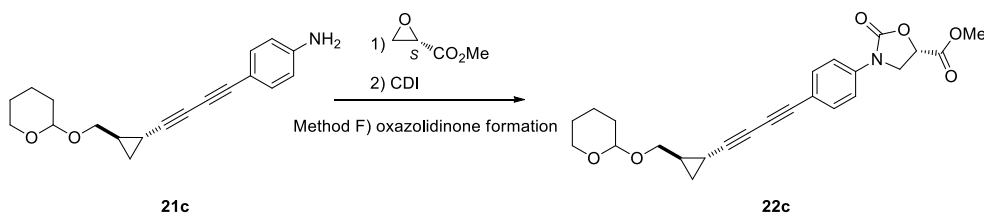
The title compound was prepared according the general procedure of dyne formation (Method H) using 2-((*trans*-2-ethynylcyclopropyl)methoxy)tetrahydro-2H-pyran²) (Brown oil, 24%).

^1H NMR (CDCl₃, 400 MHz): δ 7.29-7.24 (2H, m, Ar H), 6.59-6.53 (2H, m, Ar H), 4.67-4.58 (1H, m, CH), 3.92-3.75 (3H, m, CH₂), 3.56 (1H, ddd, $J = 17.0, 10.9, 6.1$ Hz, CH₂), 3.54-3.45 (1H, m, CH₂), 3.39 (1H, ddd, $J = 14.5, 10.9, 6.1$ Hz, CH₂), 1.90-1.77 (1H, m, CH₂), 1.77-1.65 (1H, m, CH₂), 1.63-1.46 (3H, m, CH₂), 1.41-1.32 (1H, m, CH₂), 1.32-1.21 (1H, m, CH), 1.07-0.98 (1H, m, CH), 0.92-0.79 (2H, m, CH₂).

ESIMS (m/z): [M + H]⁺ 296.

Methyl

(5*S*)-3-[4-[[*trans*-2-[[*(Tetrahydro-2H-pyran-2-yl)oxy*]methyl]cyclopropyl]buta-1,3-diyn-1-yl]phenyl]-1,3-oxazolidin-2-one-5-carboxylate (**22c**)



The title compound was prepared according the general procedure of oxazolidinone formation (Method F) (Brown oil, 21% over two steps).

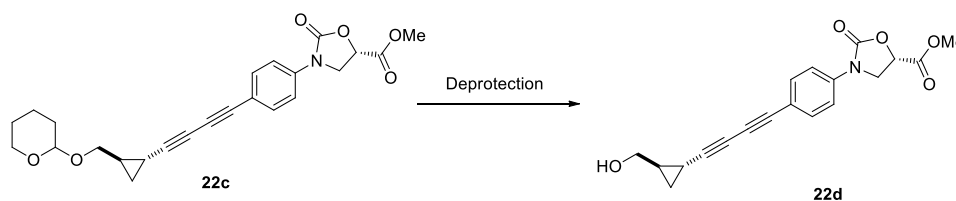
^1H NMR (CDCl₃, 400 MHz): δ 7.48 (4H, s, Ar H), 5.11 (1H, dd, $J = 9.7, 5.4$ Hz, CH), 4.68-4.59 (1H, m, CH), 4.32 (1H, t, $J = 9.4$ Hz, CH₂), 4.19-4.09 (1H, m, CH₂), 3.88 (3H, s, OCH₃), 3.57-3.48 (2H, m, CH₂), 3.38 (2H, s, CH₂), 1.90-1.78 (1H, m, CH₂), 1.78-1.66 (1H, m, CH₂), 1.65-1.48 (4H, m,

CH₂), 1.44-1.34 (1H, m, CH), 1.10-1.00 (1H, m, CH), 0.96-0.80 (2H, m, CH₂).

ESIMS (*m/z*): [M + H]⁺ 424.

Methyl

(*S*)-3-[4-[[*trans*-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl]-1,3-oxazolidin-2-one-5-carboxylate (**22d**)

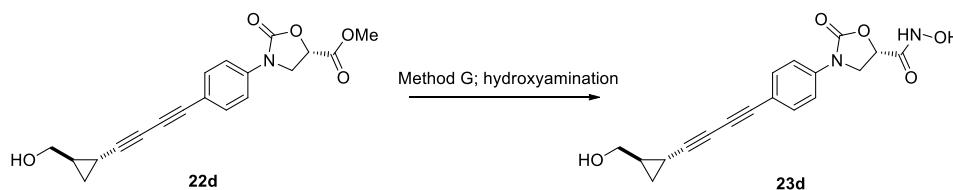


To the solution of **22c** (22.3 mg, 52.7 μ mol) in methanol (0.7 mL) was added PPTS (1.32 mg, 5.27 μ mol) and stirred at 50 °C for 2 h. The reaction mixture were concentrated *in vacuo* and the residue was purified by silica gel chromatography (30% EtOAc in hexane) to afford 13.7 mg of the desired product as colorless oil in 77% yield.

¹H NMR (CDCl₃, 400 MHz): δ 7.48 (4H, s, Ar H), 5.08 (1H, dd, *J* = 9.7, 5.4 Hz, CH), 4.29 (1H, t, *J* = 9.7 Hz, CH₂), 4.17-4.08 (1H, m, CH₂), 3.88 (3H, s, OCH₃), 3.64-3.55 (1H, m, CH₂OH), 3.55-3.46 (1H, m, CH₂OH), 1.44-1.34 (1H, m, CH), 1.10-1.01 (1H, m, CH), 0.93-0.82 (2H, m, CH₂).

ESIMS (*m/z*): [M + H]⁺ 340.

(*S*)-*N*-Hydroxy-3-[4-[[*trans*-2-(hydroxymethyl)cyclopropyl]buta-1,3-diyn-1-yl]phenyl]-1,3-oxazolidin-2-one-5-carboxamide (**23d**)



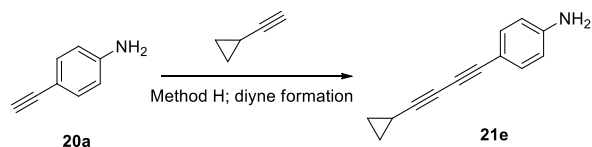
The title compound was prepared according the general procedure of hydroxyamination (Method G) (White solid, 56%).

IR (ATR): 3209, 2879, 2230, 2149, 1740, 1685, 1601, 1512 cm⁻¹.

¹H NMR (DMSO-d₆, 400 MHz): δ 9.23 (1H, brs, NH or OH), 7.62-7.57 (2H, m, Ar H), 7.57-7.50 (2H, m, Ar H), 4.97 (1H, dd, *J* = 9.1, 5.4 Hz, CH), 4.69 (1H, t, *J* = 5.4 Hz, OH), 4.26 (1H, t, *J* = 9.1 Hz, CH₂), 4.01 (1H, dd, *J* = 9.1, 5.4 Hz, CH₂), 3.45-3.17 (2H, m, CH₂), 1.48-1.34 (2H, m, CH), 0.96-0.80 (2H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₈H₁₇N₂O₅ 341.1138; found, 341.1139.

4-(Cyclopropylbuta-1,3-diyn-1-yl)aniline (**21e**)



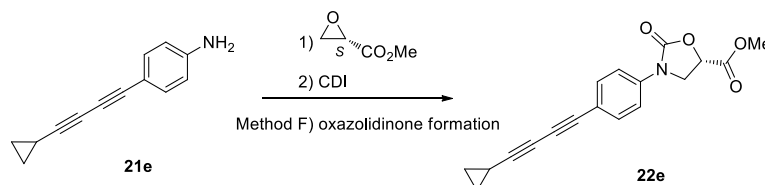
The title compound was prepared according to the general procedure of diyne formation (Method H) (Yellow oil, 73%).

IR (ATR): 3472, 3382, 3210, 3009, 2227, 2144, 1725, 1618, 1601, 1512 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 7.26 (2H, d, $J = 8.6$ Hz, Ar H), 6.56 (2H, d, $J = 8.6$ Hz, Ar H), 3.84 (2H, brs, NH_2), 1.43-1.35 (1H, m, CH), 0.88-0.78 (4H, m, CH_2).

HRMS-FI (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{13}\text{H}_{11}\text{N}$ 181.0892; found, 181.0894.

Methyl (*S*)-3-[4-(cyclopropylbuta-1,3-diyne-1-yl)phenyl]oxazolidin-2-one-5-carboxylate (**22e**)

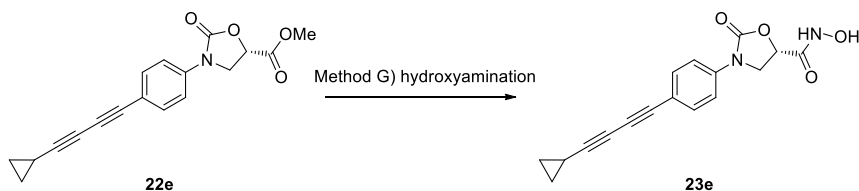


The title compound was prepared according to the general procedure of oxazolidinone formation (Method F) (Yellow solid, 81% over two steps).

^1H NMR (CDCl_3 , 400 MHz): δ 7.48 (4H, s, Ar H), 5.07 (1H, dd, $J = 9.8, 5.5$ Hz, CH), 4.29 (1H, t, $J = 9.5$ Hz, CH_2), 4.14 (1H, dd, $J = 9.2, 5.5$ Hz, CH_2), 3.87 (3H, s, OCH_3), 1.45-1.36 (1H, m, CH), 0.92-0.79 (4H, m, CH_2).

ESIMS (m/z): $[\text{M} + \text{H}]^+$ 310.

(*S*)-3-[4-(Cyclopropylbuta-1,3-diyne-1-yl)phenyl]-*N*-hydroxyoxazolidin-2-one-5-carboxamide (**23e**)



The title compound was prepared according to the general procedure of hydroxyamination (Method G) (Blue solid, 57%).

IR (ATR): 3200, 3062, 2921, 2231, 2151, 1755, 1724, 1683, 1648, 1603, 1514 cm^{-1} .

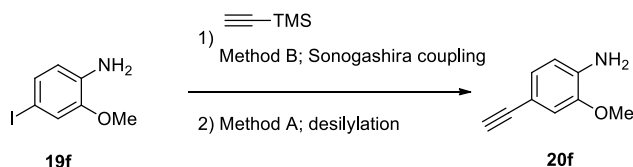
^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 11.20 (1H, brs, NH or OH), 9.26 (1H, brs, NH or OH), 7.62-7.54 (2H, m, Ar H), 7.62-7.54 (2H, m, Ar H), 4.98 (1H, dd, $J = 9.2, 5.5$ Hz, CH), 4.27 (1H, dd, $J = 9.8, 9.2$ Hz, CH_2), 4.03 (1H, dd, $J = 9.8, 5.5$ Hz, CH_2), 1.60-1.51 (1H, m, CH), 0.95-0.88 (2H, m, CH_2), 0.81-0.75 (2H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_4$ 309.0875; found, 309.0868.

$[\alpha]_D^{26} = +11.4$ ($c = 0.10$, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 99.9% and retention time 4.32 min for the title compound.

4-Ethynyl-2-methoxyaniline (**20f**)



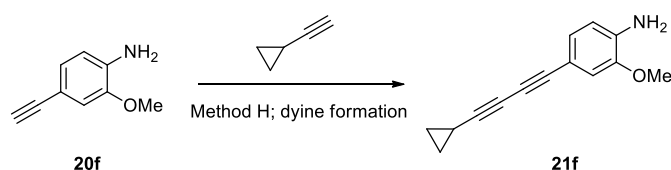
The title compound was prepared according the general procedure of Sonogashira coupling (Method B) and desilylation (Method A) (Black oil, 81% over two steps).

IR (ATR): 3472, 3376, 3281, 3004, 2960, 2937, 2833, 2632, 2098, 1860, 1614, 1576, 1512 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 6.81-6.83 (2H, m, Ar H), 6.56 (1H, d, $J = 7.3$ Hz, Ar H), 5.14 (2H, brs, NH_2), 3.80 (1H, s, $\text{C}\equiv\text{CH}$), 3.76 (3H, s, OCH_3).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{10}\text{NO}$ 148.0762; found, 148.0762.

4-(Cyclopropylbuta-1,3-diyn-1-yl)-2-methoxyaniline (**21f**)



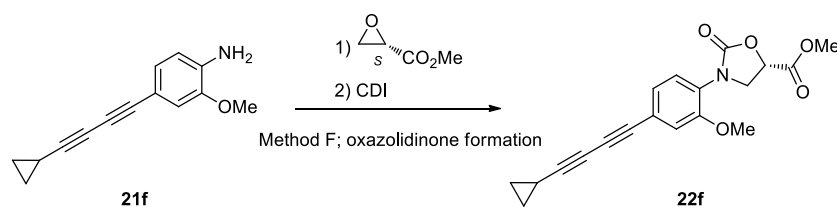
The title compound was prepared according the general procedure of diyne formation (Method H) (Black oil, 65%)

IR (ATR): 3479, 3382, 3192, 3008, 2961, 2937, 2833, 2639, 2300, 2223, 2141, 1939, 1860, 1611, 1515 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 6.88-6.86 (2H, m, Ar H), 6.55 (1H, d, $J = 8.6$ Hz, Ar H), 5.32 (2H, brs, NH_2), 3.75 (3H, s, OCH_3), 1.55-1.48 (1H, m, CH), 0.90-0.86 (2H, m, CH_2), 0.75-0.71 (2H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ 212.1075; found, 212.1076.

(*S*)-Methyl 3-(4-(cyclopropylbuta-1,3-diyn-1-yl)-2-methoxyphenyl)-oxazolidin-2-one-5-carboxylate (**22f**)



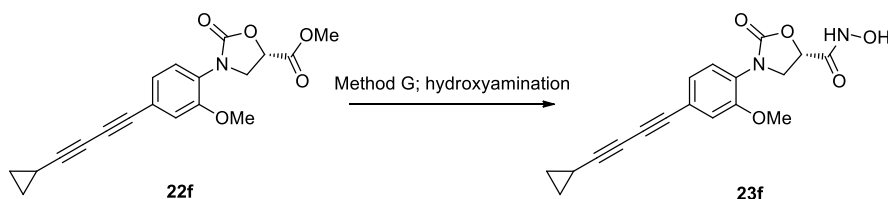
The title compound was prepared according the general procedure of oxazolidinone formation (Method F) (Brown solid, 46% over two steps).

IR (ATR): 3512, 3009, 2955, 2230, 2148, 1759, 1599, 1567, 1513, 1402 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.33 (1H, d, 7.9 Hz, Ar H), 7.27 (1H, d, J = 1.8 Hz, Ar H), 7.15 (1H, dd, J = 7.9, 1.8 Hz, Ar H), 5.32 (1H, dd, J = 9.8, 4.9 Hz, CH), 4.20 (1H, t, J = 9.8 Hz, CH_2), 3.97 (1H, dd, J = 9.8, 4.9 Hz, CH_2), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 1.61-1.54 (1H, m, CH), 0.95-0.90 (2H, m, CH_2), 0.81-0.77 (2H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_5$ 340.11850; found, 340.11935.

(*S*)-3-(4-(Cyclopropylbuta-1,3-dien-1-yl)-2-methoxyphenyl)-*N*-hydroxy-oxazolidin-2-one-5-carboxamide (**23f**)



The title compound was prepared according the general procedure of hydroxyamination (Method G) (White solid, 69%).

IR (ATR): 3191, 2939, 2230, 2149, 1762, 1747, 1686, 1567, 1515 cm^{-1} .

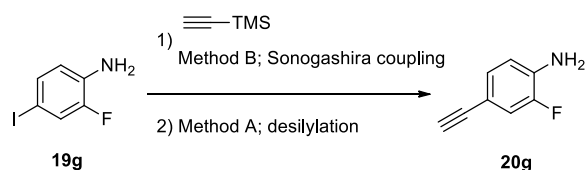
^1H NMR (DMSO- d_6 , 400 MHz) : δ 11.12 (1H, brs, NH or OH), 9.19 (1H, brs, NH or OH), 7.33 (1H, d, J = 8.3 Hz, Ar H), 7.27 (1H, d, J = 1.5 Hz, Ar H), 7.15 (1H, dd, J = 8.3, 1.5 Hz, Ar H), 4.98 (1H, dd, J = 8.9, 6.1 Hz, CH), 4.08 (1H, t, J = 8.9 Hz, CH_2), 3.91 (1H, dd, J = 8.9, 6.1 Hz, CH_2), 3.83 (3H, s, $-\text{OCH}_3$), 1.61-1.54 (1H, m, CH), 0.95-0.90 (2H, m, CH_2), 0.81-0.77 (2H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_5$ 341.11375; found, 341.11324.

$[\alpha]_D^{26} = +199$ (c = 0.10, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 99.3% and retention time 4.27 min for the title compound.

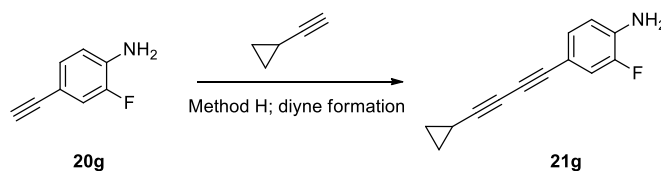
4-Ethynyl-2-fluoroaniline (**20g**)



The title compound was prepared according the general procedure of Sonogashira coupling (Method B) and desilylation (Method A) (Brown oil, quant. over two steps).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.14-7.07 (2H, m, Ar H), 6.68 (1H, t, $J = 8.0$ Hz, Ar H), 3.89 (2H, brs, NH_2), 2.96 (1H, s, $\text{C}\equiv\text{CH}$).

4-(Cyclopropylbuta-1,3-diyne-1-yl)-2-fluoroaniline (**21g**)



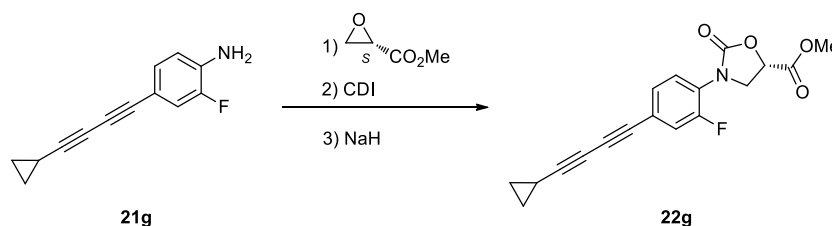
The title compound was prepared according the general procedure of diyne formation (Method H) (Yellow oil, 45%).

IR (ATR): 3482, 3388, 3220, 3012, 2224, 2144, 1624, 1571, 1513 cm^{-1} .

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.11-7.05 (2H, m, Ar H), 6.65 (1H, t, $J = 8.6$ Hz, Ar H), 3.91 (2H, brs, $-\text{NH}_2$), 1.43-1.35 (1H, m, CH), 0.89-0.79 (4H, m, CH_2).

HRMS-FI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{10}\text{FN}$ 199.0797; found, 199.0799.

(*S*)-Methyl 3-(4-(cyclopropylbuta-1,3-diyne-1-yl)-2-fluorophenyl)-oxazolidin-2-one-5-carboxylate (**22g**)



Aniline **21g** (800 mg, 4.02 mmol), methyl (*S*)-glycidate (527 μL , 6.02 mmol) and TfOLi (940 mg, 6.02 mmol) were diluted with CH_3CN (14 mL) and the solution was purged with argon. The mixture was stirred at 95 $^\circ\text{C}$ for 21 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (35% EtOAc in hexanes) to give 900 mg of the intermediate as white solid. The intermediate (200 mg, 0.664 mmol) in CH_3CN (6 mL) and to the solution was added CDI (161 mg, 0.993 mmol) and the mixture was stirred at 60 $^\circ\text{C}$ for 1 h. The solvents from the reaction mixture were removed under vacuum. The crude material was purified by silica gel chromatography (50% EtOAc in hexanes) to give 230 mg of corresponding

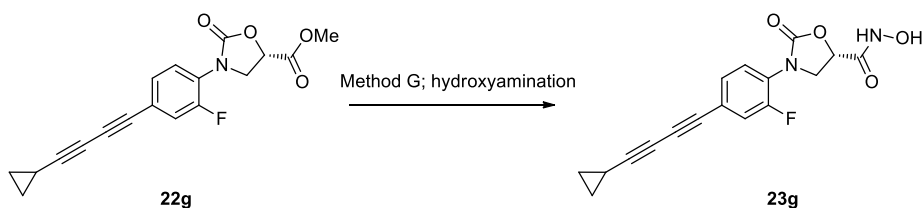
intermediate (*O*-carbonyl imidazole) as white solid. To the solution of the *O*-carbonyl imidazole (200 mg, 0.582 mmol) in THF (6 mL) and to the solution was added NaH (27.9 mg, 0.640 mmol, 55% in mineral oil) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into aqueous solution of saturated NH₄Cl (30 mL) and extracted with CH₂Cl₂/methanol (10:1, 10 mL x 3), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (25% CH₃CN in toluene) to give 71.4 mg of the desired product as colorless oil (27% over three steps).

IR (ATR): 3010, 2957, 2227, 2154, 1762, 1563, 1513 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.55 (1H, t, *J* = 8.6 Hz, Ar H), 7.27 (1H, d, *J* = 8.6 Hz, Ar H), 7.21 (1H, dd, *J* = 11.6, 1.8 Hz, Ar H), 5.08 (1H, dd, *J* = 9.2, 4.9 Hz, CH), 4.35 (1H, t, *J* = 9.8 Hz, CH₂), 4.13 (1H, dd, *J* = 10.4, 5.5 Hz, CH₂), 3.88 (3H, s, OCH₃), 1.45-1.37 (1H, m, CH), 0.94-0.82 (4H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₈H₁₅FNO₄ 328.0985; found, 328.0983.

(*S*)-3-(4-(Cyclopropylbuta-1,3-diyne-1-yl)-2-fluorophenyl)-*N*-hydroxy-oxazolidin-2-one-5-carboxamide (**23g**)



The title compound was prepared according the general procedure of hydroxyamination (Method G) (White solid, 40%).

IR (ATR): 3299, 3145, 2891, 2225, 1773, 1744, 1670, 1513 cm⁻¹.

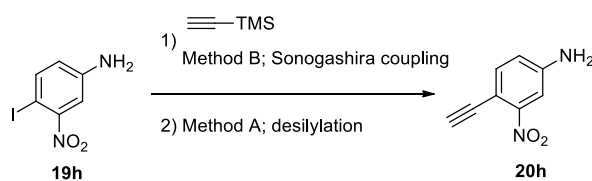
¹H NMR (DMSO-*d*₆, 400 MHz): δ 11.15 (1H, brs, NH or OH), 9.24 (1H, brs, NH or OH), 7.58 (1H, apparent t, *J* = 8.0 Hz, Ar H), 7.56 (1H, dd, *J* = 14.0, 2.4 Hz, Ar H), 7.42 (1H, dd, *J* = 8.0, 1.8 Hz, Ar H), 5.02 (1H, dd, *J* = 9.2, 6.1 Hz, CH), 4.24 (1H, t, *J* = 8.6 Hz, CH₂), 4.01 (1H, dd, *J* = 8.6, 6.1 Hz, CH₂), 1.62-1.54 (1H, m, CH), 0.96-0.90 (2H, m, CH₂), 0.83-0.78 (2H, m, CH₂).

HRMS-ESI (*m/z*): [M - H]⁻ calcd for C₁₇H₁₂FN₂O₄ 327.0781; found, 327.0782.

[α]_D²⁶ = +12.1 (*c* = 0.10, MeOH).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 97.1% and retention time 4.32 min for the title compound.

4-Ethynyl-3-nitroaniline (**20h**)



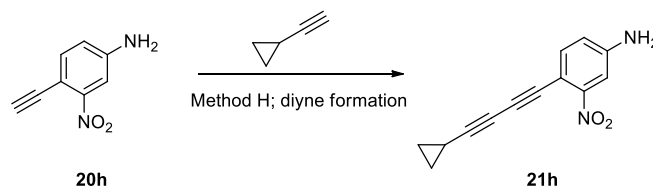
The title compound was prepared according the general procedure of Sonogashira coupling (Method B) and desilylation (Method A) (Orange solid, quant. over two steps).

IR (ATR): 3469, 3376, 3278, 1723, 1643, 1618, 1555, 1515 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.36 (1H, d, J = 8.6 Hz, Ar H), 7.15 (1H, d, J = 2.4 Hz, Ar H), 6.82 (1H, dd, J = 8.6, 2.4 Hz, Ar H), 6.22 (2H, brs, NH_2), 4.24 (1H, s, $\text{C}\equiv\text{CH}$).

HRMS-ESI (m/z): $[\text{M} - \text{H}]^-$ calcd for $\text{C}_8\text{H}_5\text{N}_2\text{O}_2$ 161.0351; found, 161.0354.

4-(Cyclopropylbuta-1,3-diyne-1-yl)-3-nitroaniline (**21h**)



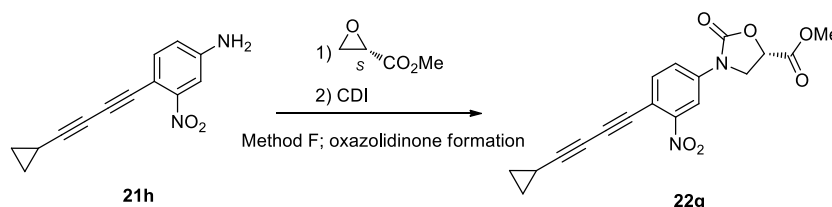
The title compound was prepared according the general procedure of diyne formation (Method H) (Orange solid, 56%).

IR (ATR): 3441, 3325, 3214, 3076, 3003, 2844, 2224, 2147, 1742, 1627, 1553, 1519 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.41 (1H, d, J = 8.6 Hz, Ar H), 7.22 (1H, d, J = 1.8 Hz, Ar H), 6.82 (1H, dd, J = 8.6, 1.8 Hz, Ar H), 6.37 (2H, brs, NH_2), 1.59-1.53 (1H, m, CH), 0.93-0.88 (2H, m, CH_2), 0.80-0.76 (2H, m, CH_2).

HRMS-EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$ 226.0742; found, 226.0741.

(S)-Methyl 3-(4-(cyclopropylbuta-1,3-diyne-1-yl)-3-nitrophenyl)-oxazolidine-2-one-5-carboxylate (**22g**)



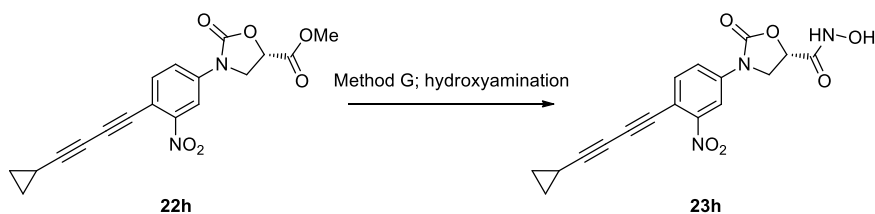
The title compound was prepared according the general procedure of oxazolidinone formation (Method F) (Brown solid, 46% over two steps).

IR (ATR): 3508, 3115, 3013, 2958, 2225, 2152, 1932, 1759, 1618, 1556 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 8.41 (1H, t, J = 1.2 Hz, Ar H), 7.86 (2H, d, J = 1.2 Hz, Ar H), 5.40 (1H, dd, J = 9.8, 4.9 Hz, CH), 4.44 (1H, t, J = 9.8 Hz, CH_2), 4.29 (1H, dd, J = 9.8, 4.9 Hz,

CH₂), 3.76 (3H, s, OCH₃), 1.65-1.59 (1H, m, CH), 0.98-0.93 (2H, m, CH₂), 0.86-0.82 (2H, m, CH₂).
HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₈H₁₅N₂O₆ 355.0930; found, 355.0931.

(*S*)-3-(4-(Cyclopropylbuta-1,3-diyne-1-yl)-3-nitrophenyl)-*N*-hydroxy-oxazolidin-2-one-5-carboxamide (**23h**)



The title compound was prepared according the general procedure of hydroxyamination (Method G) (Yellow solid, 86%).

IR (ATR): 3130, 2903, 2224, 1743, 1677, 1620, 1556, 1524 cm⁻¹.

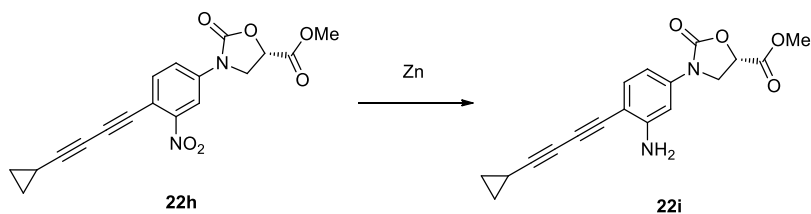
¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.45 (1H, s, Ar H), 7.86 (2H, s, Ar H), 5.03 (1H, dd, *J* = 9.2, 5.5 Hz, CH), 4.34 (1H, t, *J* = 9.2 Hz, CH₂), 4.13 (1H, dd, *J* = 9.2, 5.5 Hz, CH₂), 1.65-1.59 (1H, m, CH), 0.98-0.93 (2H, m, CH₂), 0.86-0.82 (2H, m, CH₂).

HRMS-ESI (*m/z*): [M - H]⁻ calcd for C₁₇H₁₂N₃O₆ 354.0726; found, 354.0729.

[α]_D²⁶ = +78.9 (*c* = 0.10, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 97.3% and retention time 4.42 min for the title compound.

(*S*)-Methyl 3-(3-amino-4-(cyclopropylbuta-1,3-diyne-1-yl)phenyl)-oxazolidin-2-one-5-carboxylate (**22i**)



Ester **22h** (167 mg, 471 μmol) and zinc dust (308 mg, 4.71 g atm) were dissolved in acetic acid (471 μL) under air. The mixture was stirred at room temperature for 1 h. The crude material was filtered through celite, concentrated *in vacuo*, and purified by silica gel chromatography (50% EtOAc in hexanes) to give 134 mg of the desired product as pale yellow oil (88%).

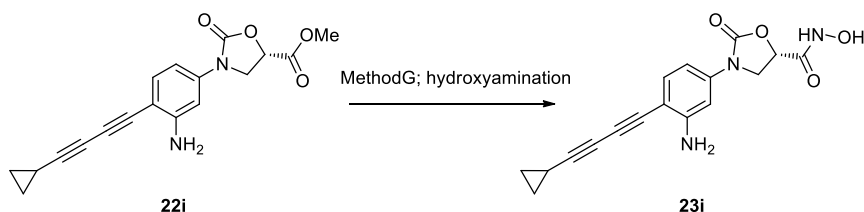
IR (ATR): 3473, 3372, 3216, 3009, 2955, 2615, 2225, 2144, 1747, 1616, 1561, 1510 cm⁻¹.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.25 (1H, d, *J* = 8.6 Hz, Ar H), 6.94 (1H, d, *J* = 2.4 Hz, Ar H), 6.71 (1H, dd, *J* = 8.6, 2.4 Hz, Ar H), 5.64 (2H, brs, NH₂), 5.28 (1H, dd, *J* = 9.8, 4.9 Hz, CH), 4.29 (1H, t, *J* = 9.8 Hz, CH₂), 4.07 (1H, dd, *J* = 9.8, 4.9 Hz, CH₂), 3.75 (3H, s, OCH₃), 1.59-1.52 (1H, m,

CH), 0.93-0.88 (2H, m, CH₂), 0.78-0.74 (2H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₈H₁₇N₂O₄ 325.1188; found, 325.1195.

(*S*)-3-(3-Amino-4-(cyclopropylbuta-1,3-diyn-1-yl)phenyl)-*N*-hydroxy-oxazolidin-2-one-5-carboxamide (**23i**)



The title compound was prepared according the general procedure of hydroxyamination (Method G) (White solid, 81%).

IR (ATR): 3199, 2223, 2144, 1742, 1667, 1613, 1563, 1509 cm⁻¹.

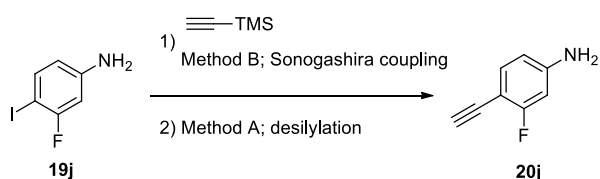
¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.19 (1H, d, *J* = 8.6 Hz, Ar H), 6.96 (1H, d, *J* = 2.4 Hz, Ar H), 6.72 (1H, dd, *J* = 8.6, 2.4 Hz, Ar H), 5.63 (2H, brs, NH₂), 4.93 (1H, dd, *J* = 9.2, 5.5 Hz, CH), 4.18 (1H, t, *J* = 9.2 Hz, CH₂), 3.91 (1H, dd, *J* = 9.2, 5.5 Hz, CH₂), 1.59-1.52 (1H, m, CH), 0.93-0.88 (2H, m, CH₂), 0.78-0.74 (2H, m, CH₂).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₁₇H₁₆N₃O₄ 326.1141; found, 326.1143.

[α]_D²⁶ = +57.8 (*c* = 0.04, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 99.2% and retention time 4.07 min for the title compound.

4-Ethynyl-3-fluoroaniline (**20j**)



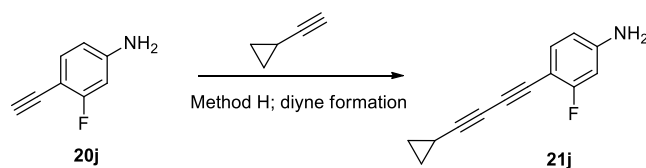
The title compound was prepared according the general procedure of Sonogashira coupling (Method B) and desilylation (Method A) (Black oil, 83% over two steps).

IR (ATR): 3481, 3388, 3286, 2104, 1892, 1619, 1508 cm⁻¹.

¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.12 (1H, d, *J* = 8.6 Hz, Ar H), 6.35 (1H, d, *J* = 2.4 Hz, Ar H), 6.32 (1H, dd, *J* = 8.6, 2.4 Hz, Ar H), 5.85 (2H, brs, NH₂), 4.05 (1H, s, C≡CH).

HRMS-ESI (*m/z*): [M + H]⁺ calcd for C₈H₇FN₂ 136.0563; found, 136.0560.

4-(Cyclopropylbuta-1,3-diyn-1-yl)-3-fluoroaniline (**21j**)



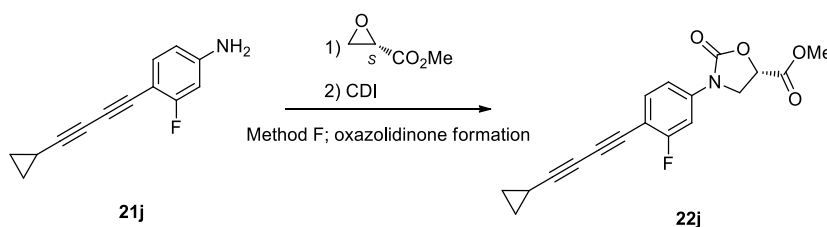
The title compound was prepared according to the general procedure of diyne formation (Method H) (Brown solid, 60%).

IR (ATR): 3456, 3346, 3230, 3014, 2147, 1897, 1633, 1616, 1563, 1510 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.16 (1H, t, $J = 8.6$ Hz, Ar H), 6.35-6.32 (2H, m, Ar H), 6.04 (2H, brs, NH_2), 1.56-1.50 (1H, m, CH), 0.91-0.86 (2H, m, CH_2), 0.77-0.74 (2H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{FN}$ 200.0876; found, 200.0874.

(*S*)-Methyl 3-(4-(cyclopropylbuta-1,3-diyne-1-yl)-3-fluorophenyl)-oxazolidin-2-one-5-carboxylate (**22j**)



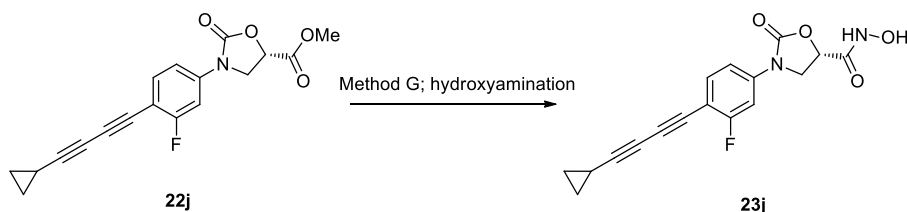
The title compound was prepared according to the general procedure of oxazolidinone formation (Method F) (White solid, 56% over two steps).

IR (ATR): 3093, 3014, 2961, 2233, 2156, 1752, 1619, 1561, 1514 cm^{-1} .

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.64-7.56 (2H, m, Ar H), 7.42 (1H, dd, $J = 8.6, 2.4$ Hz, Ar H), 5.36 (1H, dd, $J = 9.8, 4.9$ Hz, CH), 4.37 (1H, t, $J = 9.8$ Hz, CH_2), 4.20 (1H, dd, $J = 9.8, 4.9$ Hz, CH_2), 3.76 (3H, s, OCH_3), 1.62-1.55 (1H, m, CH), 0.95-0.91 (2H, m, CH_2), 0.83-0.79 (2H, m, CH_2).

HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{15}\text{FNO}_4$ 328.0985; found, 328.0988.

(*S*)-3-(4-(Cyclopropylbuta-1,3-diyne-1-yl)-3-fluorophenyl)-*N*-hydroxy-oxazolidin-2-one-5-carboxamide (**23j**)



The title compound was prepared according to the general procedure of hydroxyamination (Method G) (Blue solid, 83%).

IR (ATR): 3220, 2900, 2231, 2153, 1749, 1681, 1618, 1560, 1511 cm^{-1} .

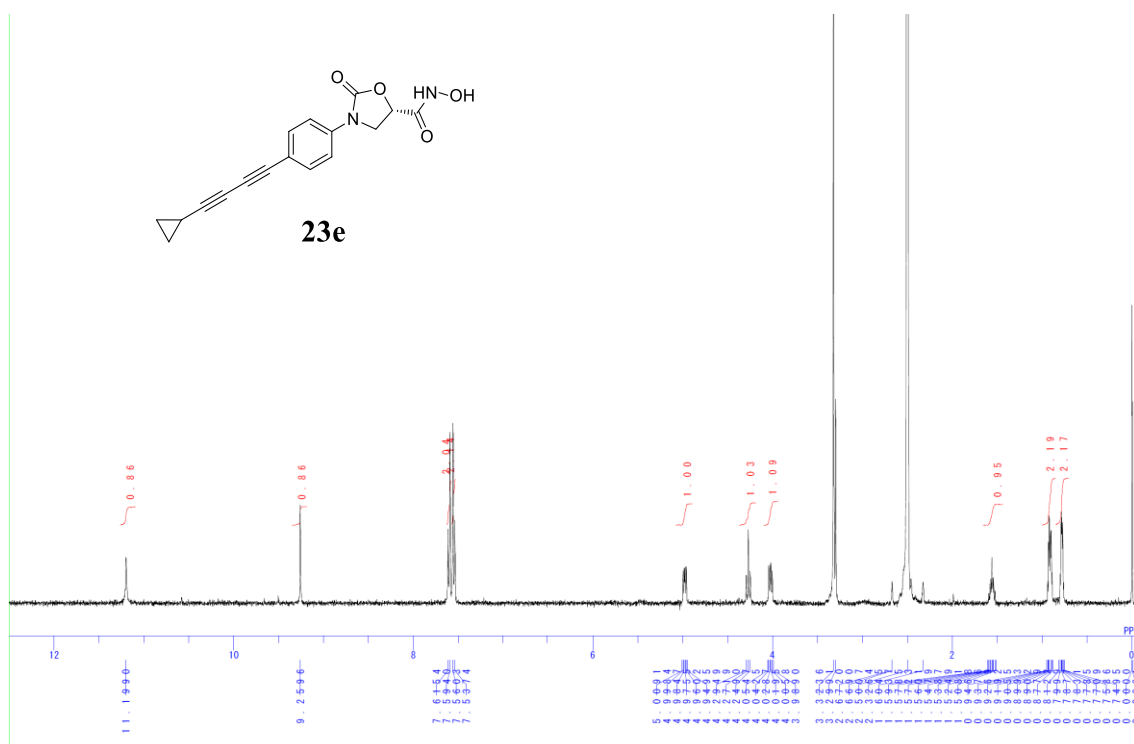
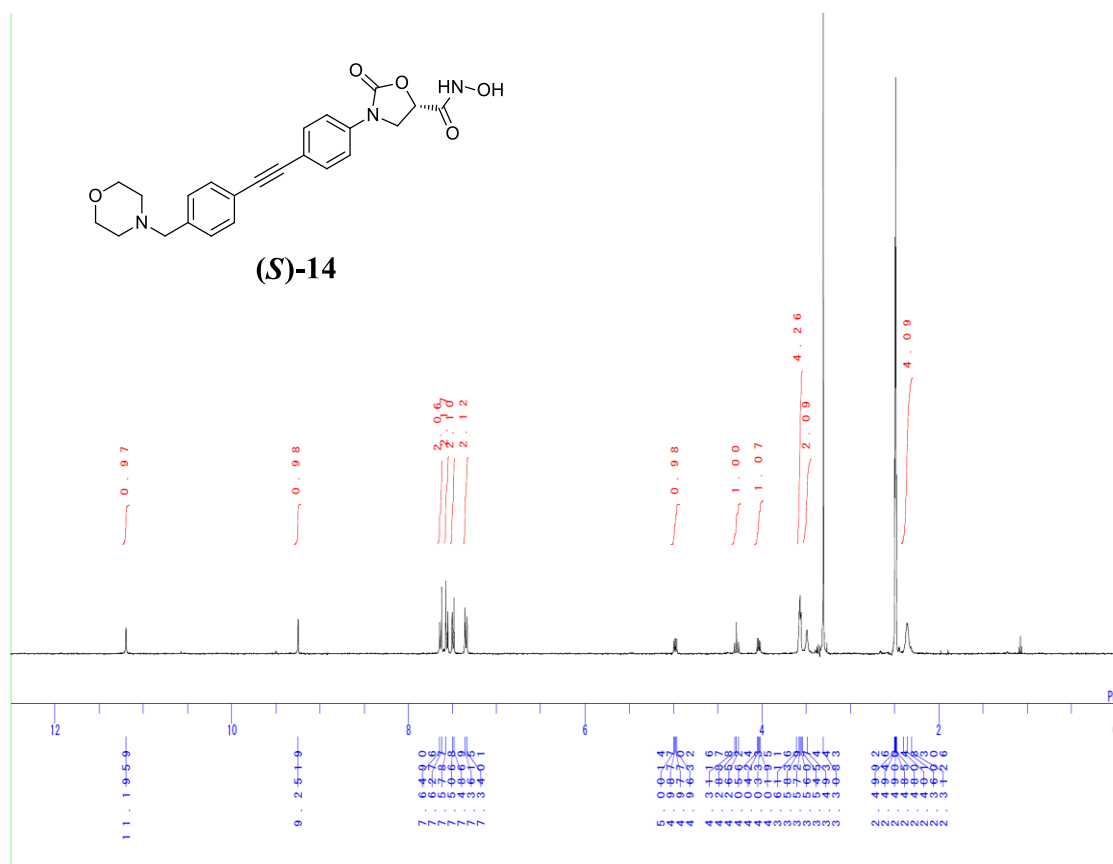
^1H NMR (DMSO- d_6 , 400 MHz) : δ 11.21 (1H, brs, NH or OH), 9.28 (1H, brs, NH or OH), 7.64-7.58 (2H, m, Ar H), 7.43 (1H, dd, $J = 8.6, 2.4$ Hz, Ar H), 4.99 (1H, dd, $J = 9.2, 5.5$ Hz, CH), 4.27 (1H, t, $J = 9.2$ Hz, CH₂), 4.04 (1H, dd, $J = 9.2, 5.5$ Hz, CH₂), 1.62-1.55 (1H, m, CH), 0.95-0.91 (2H, m, CH₂), 0.83-0.79 (2H, m, CH₂).

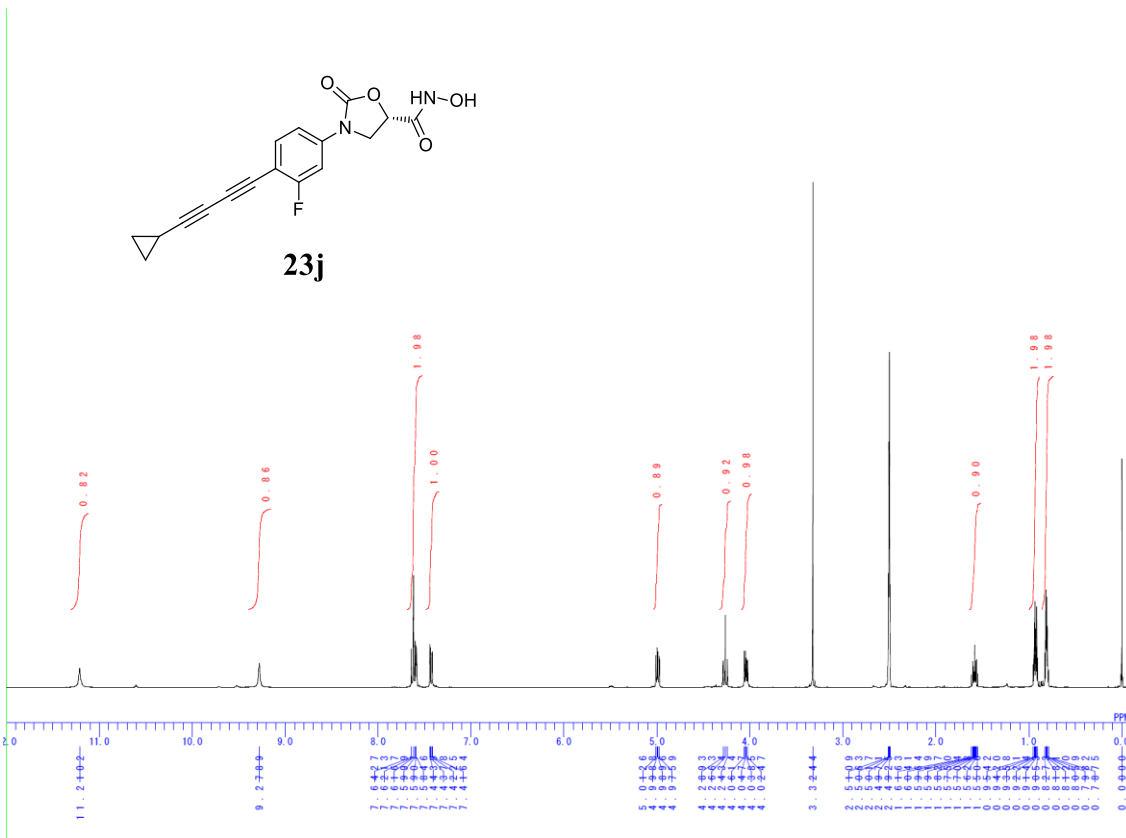
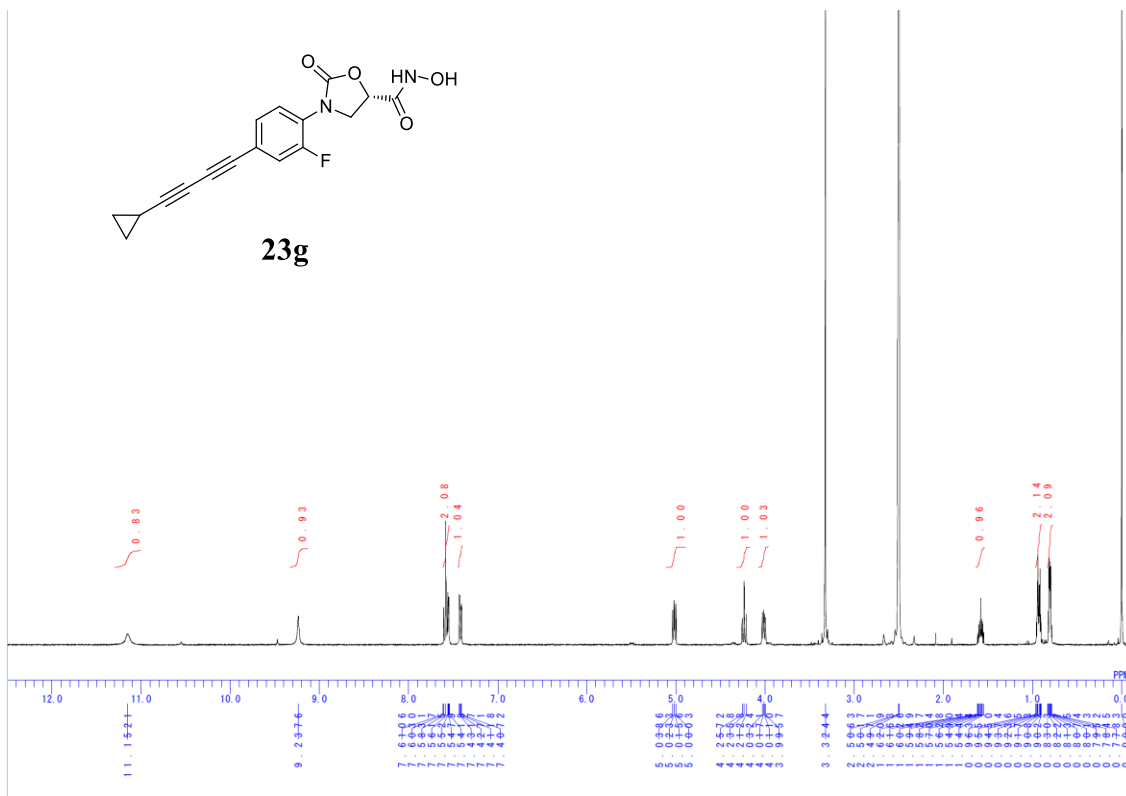
HRMS-ESI (m/z): [M - H]⁻ calcd for C₁₇H₁₂FN₂O₄ 327.0781; found, 327.0791.

$[\alpha]_D^{26} = +174$ ($c = 0.10$, DMSO).

LC/MS analysis (Waters MicroMass ZQ system) showed purity 99.9% and retention time 4.47 min for the title compound.

¹H-NMR-spectra for (S)-14, 23e, 23g and 23j.





Modeling data for dihedral angles of oxazolidinones

According to the docking study of **23e** and **23j**, both of which having strong enzyme activity, these dihedral angles between oxazolidinone and benzen are 22.9° and 41.2° , respectively (Figure S1). Therefore, it is speculated that a biologically active conformer of oxazolidinone is located in the vicinity of these dihedral angles. In order to determine why **23g** was more active than **23f**, a torsional scan of a model of **23g** and one of **23f** was performed (HF/6-31G* level of theory, Figure S2). In the case of the model of **23g**, the relative energy of the global minimum structure is a relatively broad, from 31° to 116° . It seems that this angle range includes the range of the proposed active conformer. On the other hand, the dihedral angle of the global minimum of the model of **23f** is near 106° . The relative energy of the proposed active conformer is a little more unstable than that of the global minimum structure of the model of **23f**. However, the energy difference is quite small (ca. 1-2 kcal/mol).

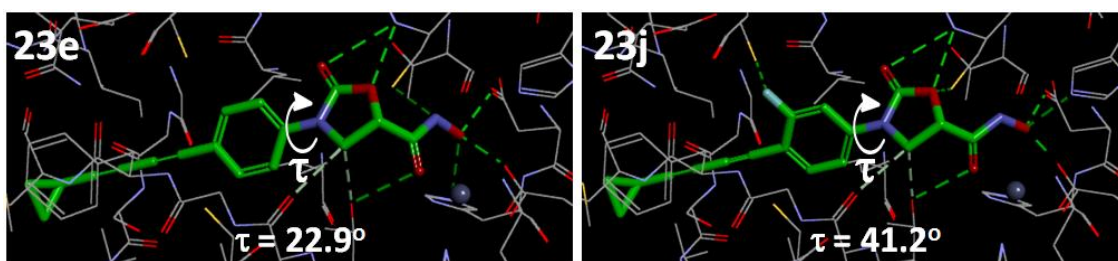


Figure S1. Docking poses of **23e** and **23j** bound to *E. coli* LpxC

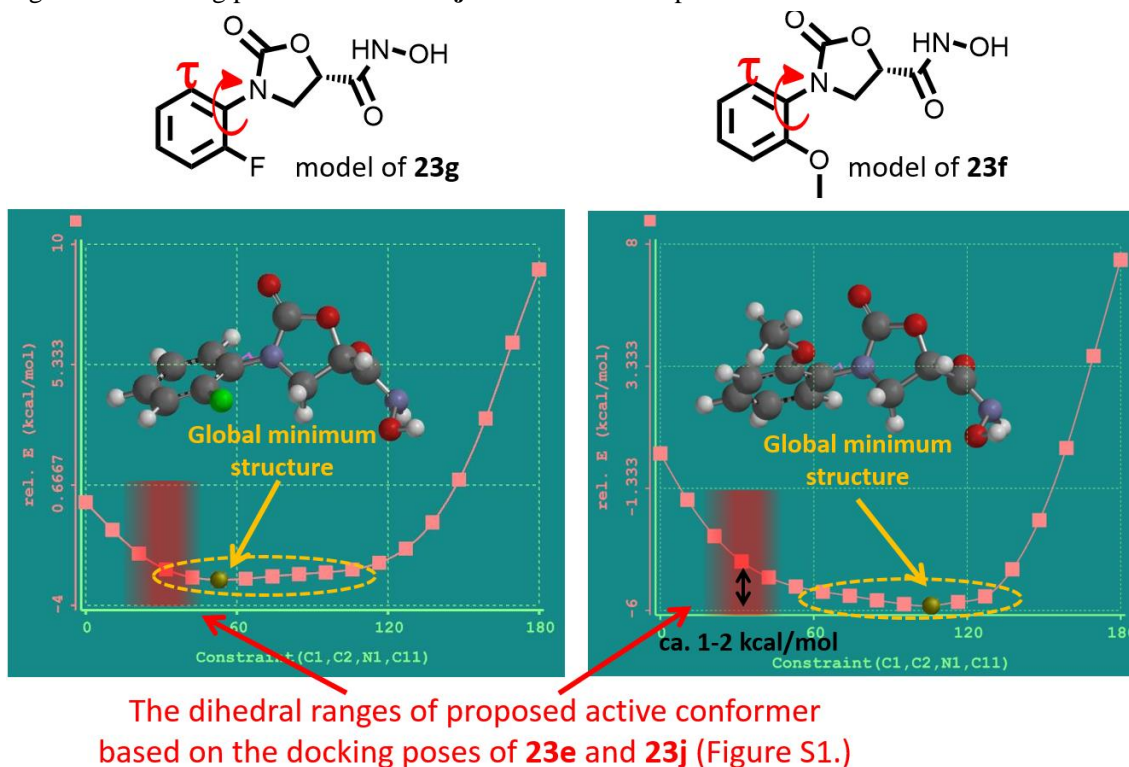


Figure S2. Torsional scan relating the energy of **23g** and **23f** model systems to the dihedral angle τ .

Enzymatic inhibition Assay with *E. coli* LpxC

LpxC enzyme assays were performed as previously described³⁾ with partial modifications. 7.5 μ L of 0.25 mM UDP-3-*O*-(*R*-3-hydroxymyristoyl)GlcNAc (Alberta Innovates-Technology Futures, AB, Canada) was added to 67.5 μ L of reaction mixture containing 15 μ L of 5 x reaction buffer (200 mM sodium morpholinoethanesulfonic acid (MES) buffer (pH 6.0), 0.1% Brij 35, 0.4 mM dithiothreitol) and *E. coli* LpxC enzyme with or without each compound. After incubation for 60 min at 37°C, 30 μ L of 0.625 M NaOH was added to the reaction mixture and was incubated for an additional 10 min at 37°C. After hydrolyzation, 30 μ L of 0.625 M AcOH was added to the mixture. 30 μ L of OPA (*O*-phthaldialdehyde) solution of Phthaldialdehyde Reagent Solution Complete (Sigma Aldrich, St, Louis, Mo, USA) was added to 100 μ L of the reaction mixture, and the mixture was incubated for 30 min at room temperature with shaking. Fluorescence (355 nm excitation/ 460 nm emission) was measured with EnVision (PerkinElmer, Waltham, MA, USA). The % of inhibition was calculated from the average of three wells at each concentration of compounds, and IC₅₀s were determined from single or duplicate assays. CHIR-090 was used as the reference standard for each assay.

Determination of minimum inhibitory concentrations (MICs)

Minimum inhibitory concentrations were determined with agar dilution method according to the protocol of Clinical and Laboratory Standards Institute⁴⁾.

Table S1. MIC values of selected oxazolidinones against Gram-negative pathogens.

Organisms	Strain	(5)-14	23e	23g	23j
<i>E. coli</i>	TG1	0.5	0.063	0.5	0.016
	KAM3	0.063	0.016	0.25	0.004
	ATCC 25922	0.25	0.031	0.5	0.08
	ML4707	0.25	0.031	0.5	0.008
<i>K. pneumoniae</i>	ATCC 13883	2	0.25	4	0.063
	ATCC700603	8	1	8	0.25
<i>P. aeruginosa</i>	K799/61	1	2	0.125	1
	K799/WT	>32	>16	4	>32
	PAO4009	32	>16	4	>32
<i>E. cloacae</i>	IID977	1	0.125	1	0.031
<i>A. baumannii</i>	ATCC 19606	>32	>16	128	>32

Computational Methods

Following calculations were performed using protocols of BIOVIA Discovery Studio version 3.5⁵⁾. The complex structure retrieved from the Protein Data Bank (PDB code 3P3G⁶⁾) was prepared and minimized using CHARMM⁷⁾ version 36.2. Prepare Protein protocol was used for the preparation of the complex structure. First all hydrogen atoms were minimized using implicit solvent model (Generalized Born with a Simple Switching⁸⁾) with a RMS gradient convergence criterion of 0.001 kcal/(mol Å). Then the complex structure was gradually minimized using some sets of fixed atom constraints. Finally all atoms of the complex structure were minimized.

Docking calculation of **23e** and **23j** into the binding site of LpxC with Zn²⁺ was performed using the standard LibDock protocol.

References

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- 8) Im, W.; Lee, M.; Brooks, C.; Generalized born model with a simple smoothing function. *Journal of Computational Chemistry.* **2003**, *24*, 14, 1691-1702.