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Synthesis of *meta*-vinylated guaiacols from lignin-derived monophenols

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1. General methods

All the reactions were carried out under Ar atmosphere, unless otherwise noted, all of the reagents were purchased from commercial suppliers and used without purification. NMR spectra were detected on a Bruker AVANCE 400 MHz spectrometer for ¹H NMR (400 MHz), ¹³C NMR (100 MHz) using TMS as a reference and CDCl₃ (deuterated chloroform) and DMSO (deuterated dimethyl sulfoxide) as a deuterated reagent. HRMS (ESI) determinations were carried out on a Bruker Daltonics MicrOTOF II spectrometer.

2. The production of guaiacol from lignin

Lignin
$$\xrightarrow{\text{La}(OTf)_3} OH$$

 270° C, 0.1 MPa
N₂, 24h

0.5 g of lignin (alkaline), 0.2 g of La (OTF)₃, and 40.1 mL of a methanol-water mixed solution (methanol: $H_2O = 4:0.01$) were placed in a high-pressure reactor. The reactor was purged with N₂ three times, maintaining a nitrogen pressure of 0.1 MPa at room temperature. The reactor was then heated to 270 °C and allowed to react for 24 hours, resulting in a yield of 12.2 wt% of guaiacol.

3. The production of guaiacol from β -O-4 model compound benzenemethanol



The β -O-4 model compound benzenemethanol (0.1 mmol), NaOH (0.1 mmol), and *tert*-amyl alcohol (1 mL) were placed in a reaction flask and refluxed for 1 hour under an air atmosphere. After the reaction was completed, the solution was cooled to room temperature. Then, EA was added to the mixture for extraction. The aqueous solution was acidified using HCl, yielding guaiacol in a yield of 78%.

4. Installation of template onto monophenols



Step 1: 20 mmol of guaiacol was dissolved in 40 mL of methyl ethyl ketone (MEK). NaOH (100 mmol, 5 equiv.) was then added to this solution, and the mixture

was stirred for 2 hours. Subsequently, bromoisobutyric acid (36 mmol, 1.8 equiv.) was dissolved in 30 mL of MEK and slowly added to the guaiacol/MEK solution. The resulting mixture was stirred at 50°C for 3 hours. After this, 20 mL of water was added, and the stirring was continued overnight. The MEK was removed under reduced pressure. The solution was then washed with EA. The aqueous phase was adjusted to pH 7, and sodium bisulfite (40 mmol, 2 equiv.) was added and stirred for 3 hours. The mixture was filtered, and the pH was adjusted to 1-2. The aqueous phase was then extracted with EA. The EA extract was dried over anhydrous sodium sulfate. The purification was carried out by column chromatography using silica gel with a PE/EA mixture 7/3 as the eluent to afford 2-(2-methoxyphenoxy)-2-methylpropanoic acid.

Step 2 2-(2-methoxyphenoxy)-2-methylpropanoic acid (5 mmol) was reacted with SOCl₂ (15 mmol, 3 equiv.) and stirred at room temperature for 24 hours. Then, the excess SOCl₂ was removed under reduced pressure to obtain 2-(2-methoxyphenoxy)-2-methylpropanoyl chloride.

5-Bromopyrimidine (10 mmol), 2-aminophenylboronic acid (12.5 mmol, 1.25 equiv.), Pd (OAc)₂ (2 mol%), S-Phos (4 mol%), K₃PO₄ (20 mmol, 2 equiv.), and THF (30 mL) were combined in a thick-walled pressure-resistant flask within an inert atmosphere glove box. The mixture was then heated at 80 °C for 24 hours to allow the reaction to proceed. The reaction mixture was extracted and washed with a mixture of EA and water. The organic phase was then dried over anhydrous magnesium sulfate. The purification was carried out by column chromatography using silica gel with a PE/EA mixture 1/1 containing 0.3% triethylamine as the eluent to afford 2-(pyrimidin-5-yl)aniline.



The template (1.06 mmol) was dissolved in 30 mL of DCM, and triethylamine (2.65 mmol, 2.5 equiv.) was added. The acyl chloride reactant (1.06 mmol), dissolved in 20 mL of DCM, was slowly added dropwise to the solution of the guiding group. The mixture was then allowed to react at room temperature for 24 hours. The DCM was removed under reduced pressure. The product was then dissolved in EA and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate. The purification was carried out by column chromatography using silica gel with a PE/EA mixture ranging from 2/1 to 1/1, containing 0.3% triethylamine as the eluent to achieve the desired TM anchored monophenols.

5. General procedure for Pd(II)-catalyzed meta-alkenylation of mononphenols



TM anchored mononphenols (0.2 mmol), Pd (OAc)₂ (0.02 mmol, 10 mol%), Nacetyl glycine (Ac-Gly-OH, 0.04 mmol, 20 mol%), AgOAc (0.4 mmol, 2 equiv.), and alkene (0.4 mmol, 2 equiv.) were mixed in a thick-walled pressure-resistant flask. Then, 1.0 mL of HFIP was added to the flask via a pipette, with all materials being handled within a glove box. The reaction was carried out with vigorous stirring at 80 °C for 24 hours. After the reaction, the mixture was cooled to room temperature and filtered through filter paper with the aid of ethyl acetate (10 mL). The filtrate was then concentrated under reduced pressure and purified by column chromatography using silica gel with petroleum ether/ethyl acetate as the eluent 15/1 to afford *meta*-vinylated mononphenols.

6. Characteristic data

2-(2-methoxyphenoxy)-2-methyl-N-(2-(pyrimidin-5-yl)phenyl)propenamide (1a)



Yield: 272 mg, 75%, yellow solid, mp: 115-116 °C.

¹**H NMR (400 MHz, CDCl₃)** δ 9.38 (s, 1H), 9.13 (s, 1H), 8.84 (s, 2H), 8.07 (d, *J* = 8.0, 1H), 7.54-7.48 (m, 1H), 7.36-7.30 (m, 2H), 7.11-7.03 (m, 1H), 6.97-6.93 (m, 1H), 6.89-6.81 (m, 2H), 3.60 (s, 3H), 1.43 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.6, 157.5, 156.6 (2C), 152.8, 142.6, 134.9, 132.7, 130.3, 129.9, 127.9, 125.8, 125.0, 124.0, 123.7, 120.7, 111.6, 83.4, 55.3, 24.5 (2C) ppm.
HRMS (ESI): [M+H]⁺ calcd for C₂₁H₂₂N₃O₃ 364.1656, found 364.1649.

2-(2-methoxy-4-methylphenoxy)-2-methyl-N-(2-(pyrimidin-5-

yl)phenyl)propenamide (11)



Yield: 264 mg, 70%, yellow solid, mp: 106-108°C.

¹**H NMR (400 MHz, CDCl₃)** δ 9.40 (s, 1H), 9.13 (s, 1H), 8.84 (s, 2H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.54-7.47 (m, 1H), 7.35-7.29 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.69-6.61 (m, 2H), 3.58 (s, 3H), 2.31 (s, 3H), 1.41 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.7, 157.5, 156.6 (2C), 152.4, 140.1, 135.0, 134.8, 132.7, 130.3, 129.9, 127.9, 125.7, 124.0, 123.4, 121.0, 112.5, 83.2, 55.3, 24.5 (2C), 21.2 ppm.

HRMS (ESI): [M+H]⁺ calcd for C₂₂H₂₄N₃O₃ 378.1812, found 378.1805.

2-(4-ethyl-2-methoxyphenoxy)-2-methyl-N-(2-(pyrimidin-5-

yl)phenyl)propenamide (1m)



Yield: 258 mg, 66%, yellow solid, mp: 91-92°C.

¹H NMR (400 MHz, CDCl₃) δ 9.40 (s, 1H), 9.13 (s, 1H), 8.84 (s, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.54-7.47 (m, 1H), 7.38-7.29 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.72-6.63 (m, 2H), 3.59 (s, 3H), 2.60 (q, *J* = 8.0 Hz, 2H), 1.41 (s, 6H), 1.22 (t, *J* = 8.0 Hz, 3H) ppm.
¹³C NMR (100 MHz, CDCl₃) δ 173.8, 157.5, 156.6 (2C), 152.5, 141.2, 140.3, 135.0, 132.7, 130.0, 129.9, 127.9, 125.8, 124.0, 123.4, 119.6, 111.3, 83.2, 55.3, 28.6, 24.5 (2C), 15.5 ppm.

HRMS (ESI): [M+H]⁺ calcd for C₂₃H₂₆N₃O₃ 392.1969, found 392.1963.

2-(2-methoxy-4-propylphenoxy)-2-methyl-N-(2-(pyrimidin-5-

yl)phenyl)propenamide (1n)



Yield: 308 mg, 76%, yellow solid, mp: 70-72°C.

¹**H NMR (400 MHz, CDCl₃)** δ 9.39 (s, 1H), 9.13 (s, 1H), 8.84 (s, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.54-7.47 (m, 1H), 7.37-7.29 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.69-6.61 (m, 2H), 3.58 (s, 3H), 2.54-2.50 (m, 2H), 1.64-1.59 (m, 2H), 1.41 (s, 6H), 0.93 (t, *J* = 8.0 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.8, 157.5, 156.6 (2C), 152.5, 140.3, 139.8, 135.0, 132.8, 130.3, 129.9, 128.0, 125.8, 124.1, 123.3, 120.3, 111.8, 83.2, 55.3, 37.8, 24.5 (3C), 13.8 ppm.

HRMS (ESI): [M+H]⁺ calcd for C₂₄H₂₈N₃O₃ 406.2125, found 406.2121.

2-(2-methoxy-6-methylphenoxy)-2-methyl-N-(2-(pyrimidin-5-

yl)phenyl)propenamide (10)



Yield: 268 mg, 71%, yellow solid, mp: 105-107°C

¹**H NMR (400 MHz, CDCl₃)** δ 9.11 (s, 1H), 8.99 (s, 1H), 8.82 (s, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.53-7.46 (m, 1H), 7.34-7.29 (m, 2H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.79-6.74 (m,

1H), 6.68-6.64 (m, 1H), 3.60 (s, 3H), 2.21 (s, 3H), 1.37 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 174.1, 157.5, 156.5 (2C), 152.7, 141.8, 135.3, 133.4, 132.9, 130.3, 129.9, 127.8, 125.4, 124.3, 123.2, 123.0, 108.9, 83.1, 55.1, 25.0 (2C), 17.3 ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{22}H_{24}N_3O_3$ 378.1812, found 378.1807.

2-(2,6-dimethoxyphenoxy)-2-methyl-N-(2-(pyrimidin-5-yl)phenyl)propenamide (1p)



Yield: 279 mg, 71%, yellow solid, mp: 86-88°C

¹**H NMR (400 MHz, CDCl₃)** δ 9.73 (s, 1H), 9.11 (s, 1H), 8.85 (s, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.55-7.44 (m, 1H), 7.37-7.30 (m, 2H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 3.70 (s, 6H), 1.43 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 174.3, 157.3, 156.5 (2C), 154.4, 135.3, 133.0, 132.2, 130.3, 129.8, 128.4, 125.8 (2C), 124.5, 124.2, 104.7 (2C), 84.3, 55.7 (2C), 24.3 (2C) ppm.

HRMS (ESI): [M+H]⁺ calcd for C₂₂H₂₄N₃O₄ 394.1761, found 394.1761.

2-(2,6-dimethoxy-4-methylphenoxy)-2-methyl-N-(2-(pyrimidin-5-

yl)phenyl)propenamide (1q)



Yield: 252 mg, 62%, yellow solid, mp: 96-98°C

¹**H NMR (400 MHz, CDCl₃)** δ 9.61 (s, 1H), 9.11 (s, 1H), 8.84 (s, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.53-7.48 (m, 1H), 7.38-7.29 (m, 2H), 6.79 (d, *J* = 12.0 Hz, 1H), 6.55 (d, *J* = 12.0 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 1.46 (s, 6H), 1.27 (s, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.7, 157.4, 156.5 (2C), 154.0, 137.5, 135.0, 133.0, 130.3, 130.0, 128.3, 127.7, 126.0, 124.2, 121.4, 107.6, 85.5, 60.7, 55.8 (2C), 24.5, 24.3

(2C) ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{23}H_{26}N_3O_4$ 408.1918, found 408.1918.

2-methyl-2-phenoxy-N-(2-(pyrimidin-5-yl)phenyl)propenamide (1r)



Yield: 206 mg, 62%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.16 (s, 1H), 8.73 (s, 2H), 8.51 (s, 1H), 8.05 (d, *J* = 8.0, 1H), 7.53-7.46 (m, 1H), 7.35-7.26 (m, 4H), 7.13-7.05 (m, 1H), 6.83-6.77 (m, 2H), 1.48 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.10, 157.7, 156.6 (2C), 153.4, 134.4, 132.4, 130.3,

130.0, 129.3 (2C), 127.6, 125.8, 123.7, 123.6, 121.3 (2C), 81.8, 24.7 (2C) ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{20}H_{20}N_3O_2$ 334.1550, found 334.1552.

2-(4-fluorophenoxy)-2-methyl-N-(2-(pyrimidin-5-yl)phenyl)propenamide (1s)



Yield: 147 mg, 42%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.18 (s, 1H), 8.77 (s, 2H), 8.53 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.57-7.46 (m, 1H), 7.38-7.28 (m, 2H), 6.98-6.92 (m, 2H), 6.84-6.73 (m, 2H), 1.44 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 172.7, 159.1 (d, *J* = 241.0 Hz), 157.6, 156.6 (2C), 149.1 (d, *J* = 3.0 Hz) (2C), 134.3, 132.4, 130.2, 130.0, 127.7, 125.9, 123.7, 123.2 (d, *J* = 8.0 Hz) (2C), 115.9 (d, *J* = 23.0 Hz), 82.2, 24.5 (2C) ppm.

¹⁹F NMR (376 MHz, CDCl₃) δ -118.86 ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{20}H_{19}FN_3O_2$ 352.1456, found 352.1451.

2-(4-chlorophenoxy)-2-methyl-N-(2-(pyrimidin-5-yl)phenyl)propenamide (1t)



Yield: 202 mg, 55%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.18 (s, 1H), 8.75 (s, 2H), 8.42 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.52-7.47 (m, 1H), 7.36-7.28 (m, 2H), 7.24-7.20 (m, 2H), 6.77-6.72 (m, 2H), 1.46 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 172.6, 157.8, 156.6 (2C), 152.0, 134.4, 132.4, 130.3, 130.1, 129.4 (2C), 129.2, 127.7, 126.0, 123.7, 122.7 (2C), 82.3, 24.6 (2C) ppm.
HRMS (ESI): [M+H]⁺ calcd for C₂₀H₁₉ClN₃O₂ 368.1160, found 368.1155.

Ethyl (E)-3-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy) phenyl)acrylate (3a)



Yield: 68 mg, 73%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.25 (brs, 1H), 9.13 (s, 1H), 8.84 (s, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.52-7.48 (m, 1H), 7.37-7.31 (m, 2H), 7.28-7.22 (m, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 8.0 Hz, 2H), 3.64 (s, 3H), 1.45 (s, 6H), 1.34 (t, *J* = 8.0 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.1, 166.9, 157.5, 156.6 (2C), 154.6, 143.5, 142.8, 134.8, 132.6, 130.3, 130.0, 127.7, 127.5, 125.8, 125.7, 123.9, 122.7, 116.7, 111.8, 83.8, 60.4, 55.6, 24.5 (2C) 14.3 ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{26}H_{28}N_3O_5$ 462.2023, found 462.2025.

Methyl (E)-3-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (3b)



Yield: 74 mg, 82%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.26 (brs, 1H), 9.13 (s, 1H), 8.77 (s, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.54-7.48 (m, 2H), 7.36-7.32 (m, 2H), 7.28-7.24 (m, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 1.45 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.1, 167.3, 157.5, 156.6 (2C), 154.6, 143.7, 142.8, 134.8, 132.6, 130.2, 130.0, 127.7, 127.4, 125.8, 125.7, 123.8, 122.8, 116.2, 111.8, 83.8, 55.6, 51.6, 24.4 (2C) ppm.

HRMS (ESI): [M+Na]⁺ calcd for C₂₅H₂₅N₃O₅Na 470.1686, found 470.1689.

Benzyl (E)-3-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (3c)



Yield: 66 mg, 63%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.25 (brs, 1H), 9.13 (s, 1H), 8.83 (s, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 16.0 Hz, 1H), 7.54-7.46 (m, 1H), 7.42-7.36 (m, 3H), 7.35-7.29 (m, 4H), 7.26-7.22 (m, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.34 (d, *J*=16.0 Hz, 1H), 5.24 (s, 2H), 3.64 (s, 3H), 1.44 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.1, 166.7, 157.6, 156.7 (2C), 154.7, 144.1, 142.8, 136.0, 134.9, 132.7, 130.3, 130.0, 128.5(2C), 128.3 (2C), 128.2, 127.8, 127.5, 125.9, 125.8, 123.9, 122.8, 116.3, 111.8, 83.9, 66.4, 55.7, 24.5 (2C) ppm.

HRMS (ESI): [M+Na]⁺ calcd for C₃₁H₂₉N₃O₅Na 546.1999, found 546.1991.

Methyl (E)-3-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)but-2-enoate (3d)



Yield: 56 mg, 61%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.29 (brs, 1H), 9.13 (s, 1H), 8.85 (s, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.35-7.31 (m, 2H), 7.26-7.22 (m, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 12.0 Hz, 1H), 6.07 (d, *J* = 2.0 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 2.54 (d, *J* = 2.0 Hz, 3H), 1.45 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.2, 167.2, 157.5, 156.7 (2C), 154.3, 153.7, 142.4, 134.9, 134.7, 132.7, 130.3, 130.0, 127.7, 125.8, 123.8, 123.3, 121.9, 115.5, 111.4, 83.8, 55.6, 51.1, 24.5 (2C), 17.6 ppm.

HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{27}N_3O_5Na$ 484.1843, found 484.1842.

Dimethyl (Z)-3-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)pent-2-enedioate (3e)



Yield: 58 mg, 56%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.17 (brs, 1H), 9.13 (s, 1H), 8.83 (s, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.35-7.31 (m, 2H), 7.24-7.18 (m, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 1.44 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.0, 168.2, 165.4, 157.6, 156.7 (2C), 156.6, 154.9, 147.9, 142.9, 134.8, 132.6, 130.3, 130.1, 127.7, 125.8, 124.2, 123.8, 121.9, 115.4, 111.9, 84.0, 55.7, 52.7, 52.0, 24.5 (2C) ppm.

HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{27}N_3O_7Na$ 528.1741, found 528.1746.

Methyl 2-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)benzyl)acrylate (3f)



Yield: 70 mg, 76%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.39 (brs, 1H), 9.13 (s, 1H), 8.84 (s, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.54-7.46 (m, 1H), 7.36-7.28 (m, 2H), 6.93-6.87 (m, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 12.0 Hz, 1H), 6.21 (s, 1H), 5.46-5.43 (m, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 3.53 (s, 2H), 1.41 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.75, 167.2, 157.4, 156.6 (2C), 151.3, 142.3, 140.1, 134.9, 132.7, 131.1, 130.3, 129.9, 128.0, 126.0, 125.8, 125.3, 124.4, 124.1, 111.5, 83.3, 55.4, 51.8, 37.2, 24.5 (2C) ppm.

HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{27}N_3O_5Na$ 484.1843, found 484.1847.

Methyl 5-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-3-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)cyclopent-1-ene-1-carboxylate (3g)



Yield: 62 mg, 63%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.37 (brs, 1H), 9.13 (s, 1H), 8.83 (s, 2H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.54-7.46 (m, 1H), 7.36-7.30 (m, 2H), 6.98-6.92 (m, 1H), 6.90-6.84 (m, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 4.08-4.02 (m, 1H), 3.61 (s, 3H), 3.56 (s, 3H), 2.68-2.44 (m, 3H), 1.90-1.82 (m, 1H), 1.40 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.7, 165.0, 157.5, 156.6 (2C), 151.1, 144.7, 142.4, 139.0, 137.7, 135.0, 132.8, 130.3, 129.9, 128.1, 125.9, 124.2, 123.1, 122.4, 111.5, 83.3, 55.4, 51.3, 49.2, 33.9, 32.1, 24.6, 24.5 ppm.

HRMS (ESI): [M+Na]⁺ calcd for C₂₈H₂₉N₃O₅Na 510.1999, found 510.1991.

(E)-2-(5-(2-cyanovinyl)-2-methoxyphenoxy)-2-methyl-N-(2-(pyrimidin-5-

yl)phenyl)propenamide (3h)



Yield: 56 mg, 68%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.17 (brs, 1H), 9.13 (s, 1H), 8.83 (s, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.53-7.49 (m, 1H), 7.35-7.27 (m, 4H), 7.23-7.15 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.72 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H), 1.45 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 172.9, 157.5, 156.7 (2C), 155.4, 149.3, 143.0, 134.8, 132.6, 130.3, 130.1, 127.6, 126.7, 125.9, 125.3, 123.7, 122.1, 118.2, 111.9, 94.6, 84.0, 55.8, 24.5 (2C) ppm.

HRMS (ESI): $[M+Na]^+$ calcd for $C_{24}H_{22}N_4O_3Na$ 437.1584, found 437.1588.

Diethyl (E)-(4-methoxy-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)styryl)phosphonate (3i)



Yield: 66 mg, 63%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.27 (brs, 1H), 9.12 (s, 1H), 8.84 (s, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.42-7.32 (m, 3H), 7.26-7.22 (m, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 9.84 (d, *J* = 8.0 Hz, 1H), 6.08 (t, *J* = 16.0 Hz, 1H), 4.18-4.08 (m, 4H), 3.65 (s, 3H), 1.45 (s, 6H), 1.36 (t, *J*=8.0 Hz, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.1, 157.4, 156.6 (2C), 154.5, 147.7 (d, *J* = 7.0 Hz), 142.8, 134.8, 132.6, 130.1 (d, *J* = 26.0 Hz), 128.0 (d, *J* = 24.0 Hz), 127.7, 125.8, 125.4, 123.8, 122.4, 112.9, 111.6, 110.9, 83.8, 61.8, 61.7, 55.6, 24.4 (2C), 16.3, 16.2 ppm.

³¹P NMR (162 MHz, CDCl₃) δ 19.69 ppm.

HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{32}N_3O_6PNa$ 548.1921, found 548.1921.

(E)-2-(2-methoxy-5-(2-(phenylsulfonyl)vinyl)phenoxy)-2-methyl-N-(2-(pyridin-3-

yl)phenyl)propenamide (3j)



Yield: 57 mg, 54%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.17 (brs, 1H), 9.09 (s, 1H), 8.82 (s, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.98-7.94 (m, 2H), 7.63-7.51 (m, 5H), 7.34-7.31 (m, 2H), 7.25-7.22 (m, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 16.0 Hz, 1H), 3.65 (s, 3H), 1.43 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 172.9, 157.5, 156.6 (2C), 155.4, 142.9, 141.5, 140.8, 134.8, 133.2, 132.6, 130.3, 130.0, 129.3 (2C), 127.6, 127.5 (2C), 126.7, 125.8, 125.5, 125.3, 123.8, 123.3, 111.9, 84.0, 55.7, 24.4 (2C) ppm.

HRMS (ESI): $[M+Na]^+$ calcd for $C_{29}H_{27}N_3O_5SNa$ 552.1564, found 552.1570.

2-((4-methoxy-2',5'-dioxo-2',5'-dihydro-[1,1'-biphenyl]-3-yl)oxy)-2-methyl-N-(2-(pyrimidin-5-yl)phenyl)propenamide (3k)



Yield: 38 mg, 40%, red oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.10 (brs, 1H), 9.07 (s, 1H), 8.75 (s, 2H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.54-7.46 (m, 1H), 7.35-7.28 (m, 2H), 7.24-7.20 (m, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.72-6.64 (m, 2H), 3.68 (s, 3H), 1.49 (s, 6H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 172.4, 166.4, 157.8, 156.7 (2C), 149.3, 136.3, 136.2, 134.2, 132.3, 130.2, 130.1, 127.6, 126.1, 124.7, 124.6, 123.7, 121.83, 121.80, 121.7, 121.6, 116.9, 116.6, 82.6, 60.7, 24.6 (2C) ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_5$ 470.1710, found 470.1708.

Ethyl (E)-3-(4-methoxy-2-methyl-5-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (3l)



Yield: 61 mg, 64%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.28 (brs, 1H), 9.14 (s, 1H), 8.85 (s, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 16.0 Hz, 1H), 7.54-7.50 (m, 1H), 7.36-7.30 (m, 2H), 7.17 (s, 1H), 6.64 (s, 1H) 6.21 (d, *J* = 16.0 Hz, 1H), 4.30-4.22 (m, 2H), 3.62 (s, 3H), 2.40 (s, 3H), 1.43 (s, 6H), 1.34 (t, *J* = 8.0 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.3, 167.1, 157.6, 156.7 (2C), 154.2, 141.1, 140.7 (2C), 135.5, 134.9, 130.3, 130.0, 127.6, 125.7 (2C), 123.7, 121.5, 117.3, 113.7, 83.6, 60.4, 55.5, 24.5 (2C), 19.6, 14.3 ppm.

HRMS (ESI): [M+Na]⁺ calcd for C₂₇H₂₉N₃O₅Na 498.1999, found 498.1997.

Ethyl (E)-3-(2-ethyl-4-methoxy-5-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (3m)



Yield: 58 mg, 60%, yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.28 (brs, 1H), 9.14 (s, 1H), 8.85 (s, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.34-7.28 (m, 2H), 7.17 (s, 1H), 6.65 (s, 1H), 6.22 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 8.0 Hz, 2H), 3.63 (s, 3H), 2.75 (q, J = 8.0 Hz, 2H), 1.43 (s, 6H), 1.34 (t, J = 7.6 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H) ppm.
¹³C NMR (100 MHz, CDCl₃) δ 173.3, 167.1, 157.5, 156.6 (2C), 154.3, 141.7, 140.8, 140.7, 134.8, 132.6, 130.3, 130.0, 127.7, 125.8, 125.0, 123.9, 121.6, 117.5, 112.2, 83.6, 60.3, 55.5, 26.3, 24.5 (2C), 16.0, 14.3 ppm.

HRMS (ESI): [M+Na]⁺ calcd for C₂₈H₃₁N₃O₅Na 512.2156, found 512.2154.

Ethyl (E)-3-(4-methoxy-5-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)-2-propylphenyl)acrylate (3n)



Yield: 50 mg, 50%, yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.27 (brs, 1H), 9.14 (s, 1H), 8.85 (s, 2H), 8.08 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.34-7.30 (m, 2H), 7.18 (s, 1H), 6.63 (s, 1H), 6.21 (d, J = 12.0 Hz, 1H), 4.27 (q, J = 8.0 Hz, 2H), 3.63 (s, 3H), 2.68 (t, J = 8.0 Hz, 1H), 1.59 (q, J = 8.0 Hz, 2H), 1.43 (s, 6H), 1.34 (t, J = 7.6 Hz, 3H) ppm.
¹³C NMR (100 MHz, CDCl₃) δ 173.4, 167.2, 157.6, 156.7 (2C), 154.3, 141.1, 140.9, 140.4, 134.9, 132.8, 130.4, 130.1, 127.8, 125.9, 125.4, 124.0, 121.6, 117.4, 113.0, 83.7, 60.4, 55.6, 35.2, 24.9, 24.5 (2C), 14.4, 13.9 ppm.

HRMS (ESI): [M+Na]⁺ calcd for C₂₉H₃₃N₃O₅Na 526.2312, found 526.2313.

Ethyl (E)-3-(4-methoxy-2-methyl-3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (30)



Yield: 51 mg, 55%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.12 (s, 1H), 8.85 (s, 1H), 8.82 (s, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 16.0 Hz, 1H), 7.53-7.46 (m, 1H), 7.35-7.30 (m, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 8.0 Hz, 2H), 3.65 (s, 3H), 2.22 (s, 3H), 1.39 (s, 6H), 1.33 (t, *J* = 7.2 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 173.7, 166.9, 157.5, 156.6 (2C), 152.9, 144.0, 143.8, 135.2, 133.7, 132.9, 130.7, 130.4, 130.0, 127.7, 125.6, 123.8, 123.2, 117.6, 107.9, 83.8, 60.5, 55.3, 25.1 (2C), 17.3, 14.3 ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{27}H_{30}N_3O_5$ 476.2180, found 476.2183.

Ethyl (E)-3-(3-((2-methyl-1-oxo-1-((2-(pyrimidin-5-yl)phenyl)amino)propan-2yl)oxy)phenyl)acrylate (3r)



Yield: 39 mg, 45%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.17 (s, 1H), 8.74 (s, 2H), 8.46 (s, 1H), 8.08-8.02 (m, 1H), 7.63-7.58 (m, 1H), 7.53-7.49 (m, 1H), 7.36-7.28 (m, 4H), 6.98-6.96 (m, 1H), 6.84-6.81 (m, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.31-4.25 (m, 2H), 1.50 (s, 6H), 1.35 (t, *J* = 8.0 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) δ 172.7, 166.7, 157.8, 156.6 (2C), 153.9, 143.6, 142.7, 136.5, 136.0, 134.4, 130.3, 130.1, 129.7, 126.0, 123.6, 123.5, 122.6, 120.6, 119.2, 82.1, 60.5, 24.7 (2C), 14.2 ppm.

HRMS (ESI): [M+H]⁺ calcd for C₂₅H₂₆N₃O₄ 432.1918, found 432.1921.

Ethyl (E)-3-(2-fluoro-5-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (3s)



Yield: 28 mg, 31%, yellow oil.

¹**H NMR (400 MHz, CDCl₃)** δ 9.19 (s, 1H), 8.78 (s, 2H), 8.49 (s, 1H), 8.05 (d, *J* = 8.0, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.56-7.49 (m, 1H), 7.36-7.29 (m, 2H), 7.03-6.97 (m, 2H), 6.88-6.78 (m, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.47 (s, 6H), 1.35 (t, *J* = 7.2 Hz, 3H) ppm.

¹³C NMR (100 MHz, CDCl₃) 172.3, 166.4, 157.7, 156.7, 156.6 (2C), 149.3 (d, J = 2.0 Hz), 136.2, 134.1, 132.3, 130.2, 130.0, 127.6, 126.1, 124.6 (d, J = 7.0 Hz), 123.8, 123.1 (d, J = 11.0 Hz), 121.7 (d, J = 3.0 Hz), 121.5 (d, J = 5.0 Hz), 116.7 (d, J = 19.0 Hz), 82.5, 60.6, 24.5 (2C), 14.2 ppm.

¹⁹F NMR (376 MHz, CDCl₃) δ -119.89 ppm.

HRMS (ESI): [M+H]⁺ calcd for C₂₅H₂₅FN₃O₄ 450.1824, found 450.1820.

Ethyl

(E)-3-(2-chloro-5-((2-methyl-1-oxo-1-((2-(pyrimidin-5-

yl)phenyl)amino)propan-2-yl)oxy)phenyl)acrylate (3t)



Yield: 44 mg, 47%, yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.76 (s, 2H), 8.46 (s, 1H), 8.06-7.98 (m, 2H), 7.54-7.48 (m, 1H), 7.36-7.29 (m, 3H), 7.12-7.06 (m, 1H), 6.82-6.75 (m, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 4.33-4.26 (m, 2H), 1.50 (s, 6H), 1.36 (t, *J* = 8.0 Hz, 3H) ppm.
¹³C NMR (100 MHz, CDCl₃) δ 172.2, 166.2, 157.8, 156.6 (2C), 152.2, 139.6, 134.2, 133.8, 132.3, 130.8, 130.3, 130.1, 129.8, 127.6, 126.1, 123.8, 123.7, 121.7, 120.4, 82.6, 60.8, 24.7 (2C), 14.3 ppm.

HRMS (ESI): $[M+H]^+$ calcd for $C_{25}H_{25}ClN_3O_4$ 466.1528, found 466.1525.

3-Hydroxy-4-methoxycinnamic acid



Yield: 16 mg, 41%, white solid.

¹**H NMR (400 MHz, DMSO)** δ 12.19 (brs, 1H), 9.17 (s, 1H), 7.46 (d, *J* = 12.0 Hz, 1H), 7.12-7.06 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H) ppm.

¹³C NMR (100 MHz, DMSO) δ 168.3, 150.3, 147.1, 144.7, 127.5, 121.5, 116.7, 114.6, 112.4, 56.0 ppm.

7. The removal of template



Step1: 3a (0.138 mmol), LiOH (1.38 mmol, 10 equiv), ethylene glycol (1 mL), and water (0.3 mL) were mixed together. The mixture was stirred at 165 °C under a nitrogen atmosphere for 8 hours. The recovery rate of the directing group was 25 %, and the yield of (E)-3-(3-((2-carboxypropan-2-yl)oxy)-4-methoxyphenyl)acrylic acid was 83 %.

Step2: (E)-3-(3-((2-Carboxypropan-2-yl)oxy)-4-methoxyphenyl)acrylic acid (0.2 mmol), DPPA (0.2 mmol), triethylamine (0.2 mmol), DMF (2.5 mL), and toluene (2.5 mL) were mixed together and heated under reflux for 4 h. The 3-Hydroxy-4-methoxycinnamic acid was obtained in a 41 % yield.

8. NMR spectra





























 ^{13}C NMR (100 MHz, CDCl₃) of compound 3d



 ^{13}C NMR (100 MHz, CDCl₃) of compound 3e



¹³C NMR (100 MHz, CDCl₃) of compound **3f**



 ^{13}C NMR (100 MHz, CDCl_3) of compound 3g



 $^{13}\mathrm{C}$ NMR (100 MHz, CDCl_3) of compound $\boldsymbol{3h}$



 ^{13}C NMR (100 MHz, CDCl₃) of compound 3i



¹H NMR (400 MHz, CDCl₃) of compound **3**j



 ^1H NMR (400 MHz, CDCl_3) of compound 3k



¹H NMR (400 MHz, CDCl₃) of compound **3**l



¹H NMR (400 MHz, CDCl₃) of compound **3m**



¹H NMR (400 MHz, CDCl₃) of compound **3n**



¹H NMR (400 MHz, CDCl₃) of compound **30**



 ^1H NMR (400 MHz, CDCl₃) of compound 3r



¹H NMR (400 MHz, CDCl₃) of compound **3s**



 ^{19}F NMR (376 MHz, CDCl₃) of compound 3s



 ^{13}C NMR (100 MHz, CDCl₃) of compound 3t





190 180 170 100 90 f1 (ppm)