Title: Novel TRPV1 modulators with reduced pungency induce analgesic effects in mice.

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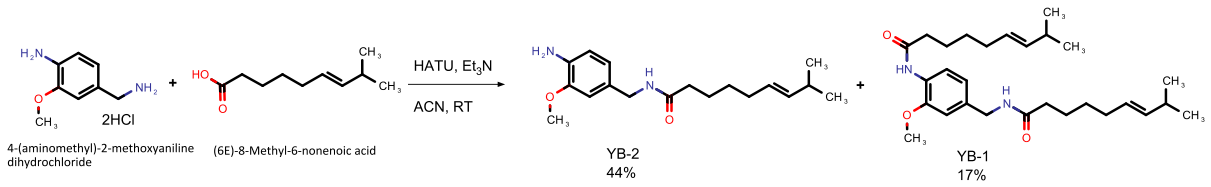
Supporting Information

Scheme S1 – Supporting Documentation for Synthesis

[0001] Example 1: Procedure of the preparation of **YB-1** and **YB-2**



[0002] A mixture of (6E)-8-Methyl-6-nonenoic acid (10 mg, 0.059 mmol; Order Number LN01303052 from LabNetwork), 4-(aminomethyl)-2-methoxyaniline dihydrochloride (13 mg, 0.059 mmol; Order Number EN300-1721327 from Enamine) in ACN (0.5 mL) was treated with Et_3N (26 uL, 0.19 mmol) and HATU (24 mg, 0.062 mmol) at rt for 0.5 h, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 15 min, then diluted with EtOAc (3 mL) and H_2O (3 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (1 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude brown oil, which was purified by chromatography (2:1 EtOAc/Hexane) to afford 4.7 mg of YB-1 (0.010 mmol, 17%), R_f 0.42 (2:1 EtOAc/Hexane), 98% purity (HPLC) and 7.9 mg of YB-2 (0.026 mmol, 44%), R_f 0.33 (2:1 EtOAc/Hexane), 97% purity (HPLC).

[0003] **YB-1**

[0004] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 6.83 (d, J = 9.8 Hz, 1H, ArH), 6.82 (s, 1H, Amide NH), 5.70 (s, 1H, amide NH), 5.19-5.39 (m, 4H, olefin Hs), 4.38 (d, J = 5.5 Hz, 2H, ArCH2NH), 3.86 (s, 3H, ArOCH3), 2.38 (t, J = 7.3 Hz, 2H, alkyl Hs), 2.18-2.24 (m, 4H, alkyl Hs), 1.95-2.04 (m, 4H, alkyl Hs), 1.63-1.76 (m, 4H, alkyl Hs), 1.24-1.47 (m, 4H, alkyl Hs), 0.92-0.96 (m, 12H, alkyl CH3).

[0005] MS m/e 457 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{45}N_2O_3$ 457.3430; Found 457.3418.

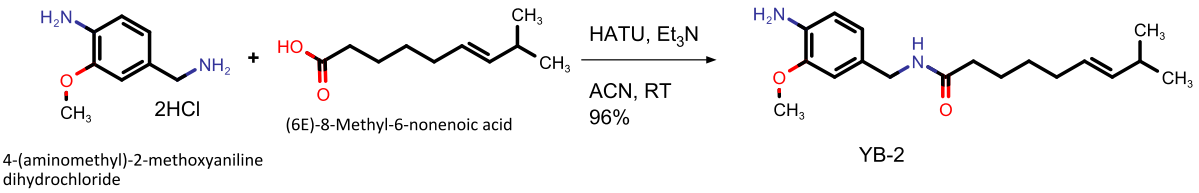
[0006] **YB-2**

[0007] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.63-6.71 (m, 3H, ArH), 5.62 (s, 1H, amide NH), 5.28-5.39 (m, 2H, olefin Hs), 4.31-4.32 (m, 2H, ArCH2NH), 4.11 (br s, 1H, amine NH2), 3.83 (s, 3H, ArOCH3), 3.82 (br s, 1H, amine NH2), 2.16-2.23 (m, 3H, alkyl Hs), 2.03-2.06 (m, 1H,

alkyl Hs),1.95-2.00 (m, 1H, alkyl Hs), 1.60-1.68 (m, 2H, alkyl Hs), 1.33-1.41 (m, 2H, alkyl Hs), 0.91-0.95 (m, 6H, alkyl CH3).

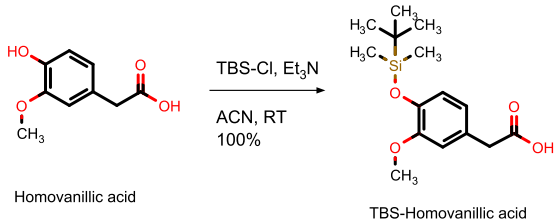
[0008] MS m/e 305 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{29}N_2O_2$ 305.2229; Found 305.2240.

[0009] Example 2: Modified procedure of the preparation of **YB-2**



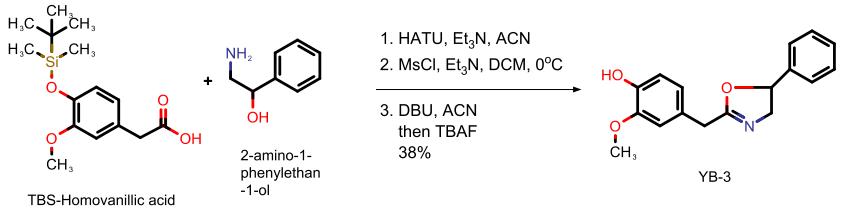
[0010] A mixture of (6E)-8-Methyl-6-nonenoic acid (100 mg, 0.59 mmol; Order Number LN01303052 from LabNetwork), 4-(aminomethyl)-2-methoxyaniline dihydrochloride (143 mg, 0.65 mmol; Order Number EN300-1721327 from Enamine) in ACN (5 mL) was treated with Et_3N (260 uL, 1.9 mmol) and HATU (240 mg, 0.62 mmol) at 0°C for 20 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 15 min, then diluted with DCM (25 mL) and H_2O (20 mL). The organic phase was separated, and the aqueous phase was extracted with DCM (10 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:1 EtOAc/Hexane) to afford 172 mg of YB-2 (0.57 mmol, 96%), R_f 0.33 (2:1 EtOAc/Hexane), 98% purity (HPLC). NMR and MS data same as YB-2 from the previous procedure in Example 1.

[0011] Example 3: Procedure of the preparation of **YB-3**



[0012] Et_3N (540 uL, 3.9 mmol) was added dropwise to a mixture of the Homovanillic acid (200 mg, 1.1 mmol; Order Number EN300-179380 from Enamine) and TBDMS-Cl (360

mg, 2.4 mmol) in ACN (5 mL) at rt. The resulting mixture was stirred vigorously at rt for 12h, then quenched with MeOH (0.44 mL, 11 mmol). The solution was stirred at rt for 10 min, then concentrated. The residue was stirred in EtOAc (10 mL) at 0°C, and added 0.3N HCl (11 mL, 3.3 mmol). The mixture was stirred vigorously at rt for 1.5 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organics were dried (Na_2SO_4) and concentrated to give 0.33 g of TBS-Homovanillic acid (1.1 mmol, 100%), which was carried into the next step without purification, R_f = 0.50 (2:1 EtOAc/Hexane).



[0013] Et_3N (18 uL, 0.13 mmol) was added dropwise to a mixture of crude TBS-Homovanillic acid (33 mg, 0.11 mmol), 2-amino-1-phenylethan-1-ol (16 mg, 0.12 mmol; Order Number EN300-19918 from Enamine) and HATU (45 mg, 0.12 mmol) in ACN (1 mL) at rt. The mixture was stirred at rt for 20 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 15 min, then diluted with DCM (5 mL) and H_2O (2 mL) . After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give 46 mg of alcohol intermediate (0.11 mmol, 100%).

[0014] Crude alcohol intermediate (46 mg, 0.11 mmol) in DCM (2 mL) was treated with Et_3N (39 uL, 0.28 mmol) and MsCl (17 uL, 0.22 mmol) at 0°C for 10 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 30 min, then diluted with DCM (3 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give 54 mg of mesylate intermediate (0.11 mmol, 100%).

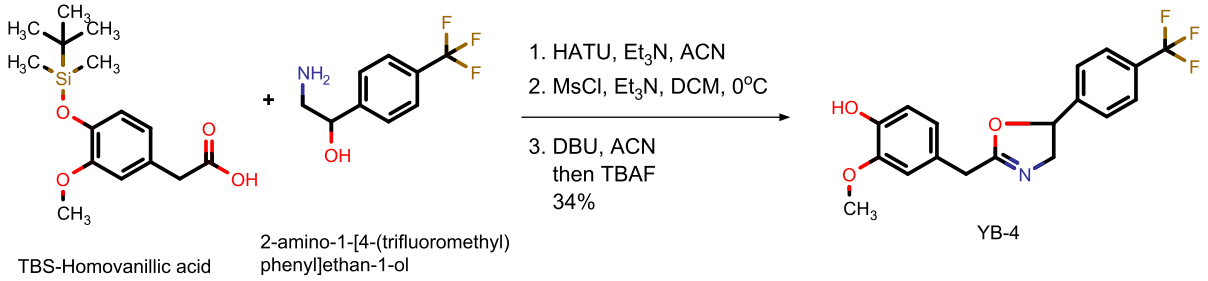
[0015] Crude Mesylate (54 mg, 0.11 mmol) in 1 mL of ACN was treated with DBU (33 uL, 0.22 mmol) for 10 min, followed by TBAF, 70-75% in water (79 mg, 0.22 mmol) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.22 mL, 0.22 mmol) at 0°C, then diluted with EtOAc (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with EtOAc (2 mL). The combined organics were dried (Na_2SO_4) and

concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to afford 12 mg of YB-3 (0.042 mmol, 38%), R_f 0.09 (2:3 EtOAc/Hexane), 95% purity (HPLC).

[0016] ^{1}H-NMR (400 MHz, CDCl3) δ 7.25-7.31 (m, 5H, phenyl ArH), 6.84 (d, J = 8.0 Hz, 1H, vanillyl ArH), 6.68 (s, 1H, vanillyl ArH), 6.65 (d, J = 8.0 Hz, 1H, vanillyl ArH), 5.86 (m, 1H, oxazoline), 4.78 (dd, J = 7.3, 3.2 Hz, 1H, oxazoline), 3.84 (s, 3H, ArOCH3), 3.82 (m, 1H, oxazoline), 3.48 (s, 2H, ArCH2CO).

[0017] MS m/e 284 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_3$ 284.1287; Found 284.1294.

[0018] Example 4: Procedure of the preparation of **YB-4**



[0019] Et_3N (18 uL, 0.13 mmol) was added dropwise to a mixture of crude TBS-Homovanillic acid (33 mg, 0.11 mmol), 2-amino-1-[4-(trifluoromethyl)phenyl]ethan-1-ol (25 mg, 0.12 mmol; Order Number EN300-42624 from Enamine) and HATU (45 mg, 0.12 mmol) in ACN (1 mL) at rt. The mixture was stirred at rt for 20 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 15 min, then diluted with DCM (5 mL) and H_2O (2 mL) . After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give 53 mg of alcohol intermediate (0.11 mmol, 100%).

[0020] Crude alcohol intermediate (53 mg, 0.11 mmol) in DCM (2 mL) was treated with Et_3N (39 uL, 0.28 mmol) and MsCl (17 uL, 0.22 mmol) at 0°C for 10 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 30 min, then diluted with DCM (3 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined

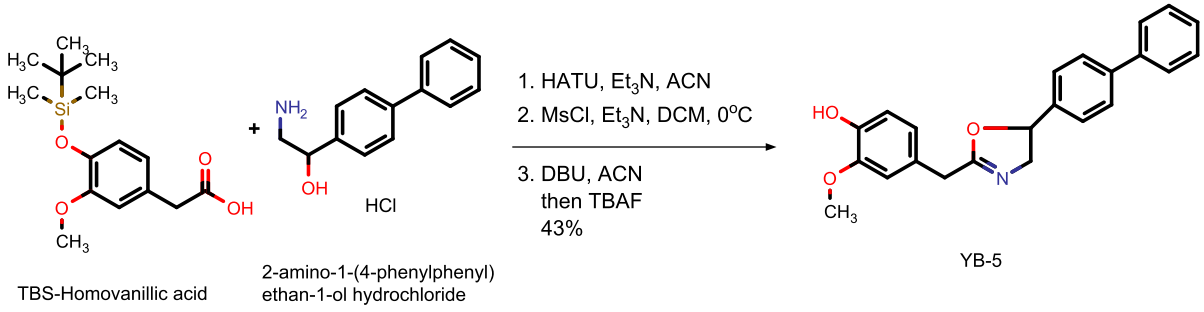
organics were dried (Na_2SO_4) and concentrated to give 62 mg of mesylate intermediate (0.11 mmol, 100%).

[0021] Crude Mesylate (62 mg, 0.11 mmol) in 1 mL of ACN was treated with DBU (33 uL, 0.22 mmol) for 10 min, followed by TBAF, 70-75% in water (79 mg, 0.22 mmol) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.22 mL, 0.22 mmol) at 0°C, then diluted with EtOAc (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with EtOAc (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:1 EtOAc/Hexane) to afford 13 mg of YB-4 (0.037 mmol, 34%), R_f 0.33 (2:1 EtOAc/Hexane), 96% purity (HPLC).

[0022] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.2 Hz, 2H, CF_3-ArHs), 7.26 (d, J = 8.2 Hz, 2H, CF_3-ArHs), 6.84-6.89 (m, 3H, vanillyl ArHs), 5.52 (dd, J = 10.2, 7.7 Hz, 1H, oxazoline), 4.31 (dd, J = 14.4, 10.3 Hz, 1H, oxazoline), 3.84 (s, 3H, ArOCH3), 3.73 (q, J = 7.2 Hz, 1H, oxazoline), 3.64 (s, 2H, ArCH2CO).

[0023] MS m/e 352 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}F_3NO_3$ 352.1161; Found 352.1152.

[0024] Example 5: Procedure of the preparation of **YB-5**



[0025] Et_3N (18 uL, 0.13 mmol) was added dropwise to a mixture of crude TBS-Homovanillic acid (33 mg, 0.11 mmol), 2-amino-1-(4-phenylphenyl)ethan-1-ol hydrochloride (30 mg, 0.12 mmol; Order Number EN300-139453 from Enamine) and HATU (45 mg, 0.12 mmol) in ACN (1 mL) at rt. The mixture was stirred at rt for 20 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 15 min, then diluted with DCM (5 mL) and H_2O (2 mL) . After separation, the aqueous layer was extracted with DCM (2 mL). The

combined organics were dried (Na_2SO_4) and concentrated to give 54 mg of alcohol intermediate (0.11 mmol, 100%).

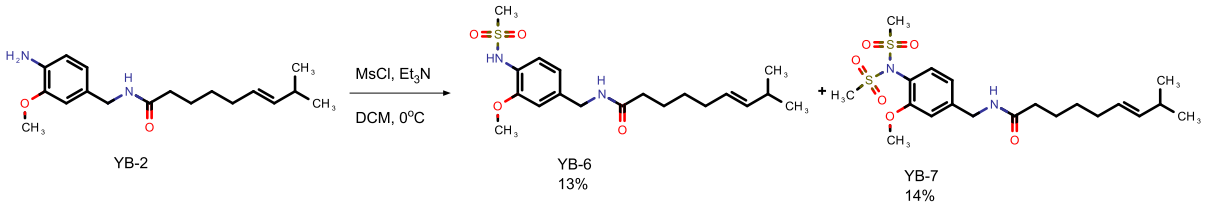
[0026] Crude alcohol intermediate (54 mg, 0.11 mmol) in DCM (2 mL) was treated with Et_3N (39 uL, 0.28 mmol) and MsCl (17 uL, 0.22 mmol) at 0°C for 10 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 30 min, then diluted with DCM (3 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give 63 mg of mesylate intermediate (0.11 mmol, 100%).

[0027] Crude Mesylate (63 mg, 0.11 mmol) in 1 mL of ACN was treated with DBU (33 uL, 0.22 mmol) for 10 min, followed by TBAF, 70-75% in water (79 mg, 0.22 mmol) for 20 min. The mixture was quenched with pH 7 buffer (1 mL)and 1N HCl (0.22 mL, 0.22 mmol) at 0°C, then diluted with EtOAc (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with EtOAc (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (EtOAc) to afford 17 mg of YB-5 (0.047 mmol, 43%), R_f 0.40 (EtOAc), 95% purity (HPLC).

[0028] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53-7.58 (m, 4H, ArHs), 7.43 (t, J = 7.5 Hz, 2H, ArHs), 7.34 (t, J = 7.3 Hz, 1H, ArHs), 7.24-7.26 (m, 2H, ArHs), 6.83-6.88 (m, 3H, vanillyl ArHs), 5.50 (dd, J = 10.1, 7.8 Hz, 1H, oxazoline), 4.28 (dd, J = 14.2, 10.3 Hz, 1H, oxazoline), 3.83 (s, 3H, ArOCH3), 3.80 (t, 1H, J=7.4Hz, oxazoline), 3.64 (s, 2H, ArCH2CO)

[0029] MS m/e 360 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}NO_3$ 360.1600; Found 360.1591.

[0030] Example 6: Procedure of the preparation of **YB-6** and **YB-7**



[0031] A solution of YB-2 (23 mg, 0.076 mmol) and Et_3N (26 uL, 0.19 mmol) in DCM (1 mL) at 0°C was treated with MsCl (12 uL, 0.15 mmol) for 10 min, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 30 min, then diluted with DCM (3 mL).

After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:1 EtOAc/Hexane) to provide 3.9 mg of YB-6 (0.010 mmol, 13%), R_f 0.26 (2:1 EtOAc/Hexane), 97% purity (HPLC) and 5.0 mg of YB-7 (0.011 mmol, 14%), R_f 0.46 (2:1 EtOAc/Hexane), 95% purity (HPLC).

[0032] **YB-6**

[0033] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 1H, ArH), 6.86 (d, J = 7.3 Hz, 2H, ArH), 6.74 (s, 1H, MeSO2NH), 5.74 (s, 1H, amide NH), 5.19-5.40 (m, 2H, olefin Hs), 4.41 (d, J = 6.0 Hz, 2H, ArCH2N), 3.87 (s, 3H, ArOCH3), 2.95 (s, 3H, MeSO2N), 2.17-2.26 (m, 3H, alkyl Hs), 1.96-2.03 (m, 2H, alkyl Hs), 1.62-1.70 (m, 2H, alkyl Hs), 1.35-1.45 (m, 2H, alkyl Hs), 0.95 (d, J = 6.8 Hz, 6H, alkyl CH3).

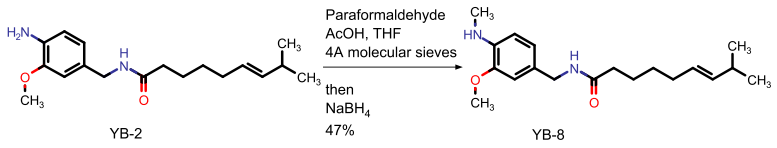
[0034] MS m/e 383 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{31}N_2O_4S$ 383.2005; Found 383.1992.

[0035] **YB-7**

[0036] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 1H, ArH), 6.95 (s, 1H, ArH), 6.91 (d, J = 8.0 Hz, 1H, ArH), 5.73 (s, 1H, amide NH), 5.19-5.41 (m, 2H, olefin Hs), 4.46 (d, J = 5.7 Hz, 2H, ArCH2N), 3.90 (s, 3H, ArOCH3), 3.42 (s, 6H, MeSO2N), 2.14-2.25 (m, 3H, alkyl Hs), 1.97-2.07 (m, 2H, alkyl Hs), 1.63-1.71 (m, 2H, alkyl Hs), 1.34-1.43 (m, 2H, alkyl Hs), 0.95 (d, J = 6.8 Hz, 6H, alkyl CH3)

[0037] MS m/e 461 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{33}N_2O_6S_2$ 461.1780; Found 461.1795.

[0038] Example 7: Procedure of the preparation of **YB-8**



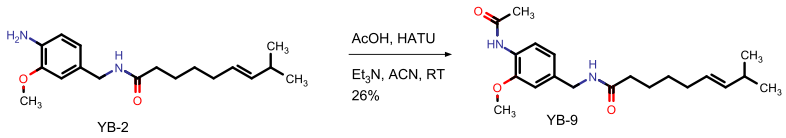
[0039] A mixture of YB-2 (7.9 mg, 0.026 mmol), Paraformaldehyde (4 mg, 0.13 mmol), AcOH (0.1 uL, 0.0026 mmol) and small amount of 4Å molecular sieves in THF (1 mL) was stirred at rt for 12 h. The resulting mixture was carefully treated with solid $NaBH_4$ (3 mg,

0.078 mmol) and stirred at rt for 10 min. The reaction was quenched with H_2O (2 mL) at 0°C. The mixture was vigorously stirred at rt for 5 min, then diluted with DCM (3 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a clear oil, which was purified by chromatography (2:1 EtOAc/Hexane) to furnish 3.9 mg of YB-8 (0.012 mmol, 47%), R_f 0.62 (2:1 EtOAc/Hexane), 96% purity (HPLC).

[0040] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 7.8 Hz, 1H, ArH), 6.69 (s, 1H, ArH), 6.51 (d, J = 7.8, 1H, ArH), 5.57 (s, 1H, amide NH), 5.18-5.40 (m, 2H, olefin Hs), 4.33 (br.s, 2H, ArCH2N), 4.12 (dd, J = 7.1, 3.0 Hz, 1H, aniline NH), 3.82 (s, 3H, ArOCH3), 2.85 (s, 3H, ArNCH3), 2.16-2.23 (m, 2H, alkyl Hs), 1.95-2.05 (m, 2H, alkyl Hs), 1.61-1.68 (m, 2H, alkyl Hs), 1.34-1.41 (m, 2H, alkyl Hs), 1.25 (m, 1H, alkyl H), 0.94 (dd, J = 6.8 Hz, 2.8 Hz, 6H, alkyl CH3).

[0041] MS m/e 319 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{31}N_2O_2$ 319.2386; Found 319.2373.

[0042] Example 8: Procedure of the preparation of **YB-9**



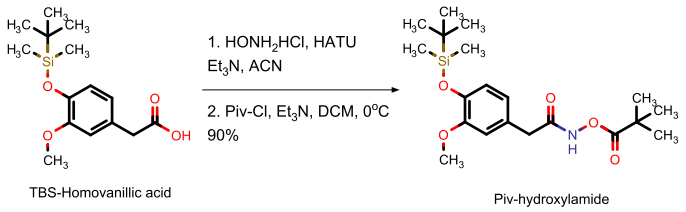
[0043] A mixture of YB-2 (6.0 mg, 0.020 mmol) and AcOH (1.3 uL, 0.0023 mmol) in ACN (0.5 mL) was treated with Et_3N (5 uL, 0.036 mmol) and HATU (15 mg, 0.039 mmol) at rt for 10 min, then quenched with aq. $NaHCO_3$ (2 mL) at 0°C. The mixture was vigorously stirred at rt for 15 min, then diluted with EtOAc (3 mL). After separation, the aqueous layer was extracted with EtOAc (1 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a yellow oil, which was purified by chromatography (2:1 EtOAc/Hexane) to furnish 1.8 mg of YB-9 (0.0052 mmol, 26%), R_f 0.17 (2:1 EtOAc/Hexane), 95% purity (HPLC).

[0044] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.8 Hz, 1H, ArH), 7.71 (s, 1H, ArH), 6.81 (d, J = 8.2 Hz, 1H, ArH), 6.80 (s, 1H, Amide NH), 5.73 (s, 1H, amide NH), 5.18-5.34 (m, 2H, olefin Hs), 4.37 (d, J = 5.7 Hz, 2H, ArCH2NH), 3.85 (s, 3H, ArOCH3), 2.17-2.21 (m, 3H,

alkyl Hs), 2.18 (s, 3H, CH3CO Hs), 1.96-2.03 (m, 2H, alkyl Hs), 1.60-1.70 (m, 2H, alkyl Hs), 1.33-1.41 (m, 2H, alkyl Hs), 0.93 (d, J = 6.8 Hz, 6H, alkyl CH3).

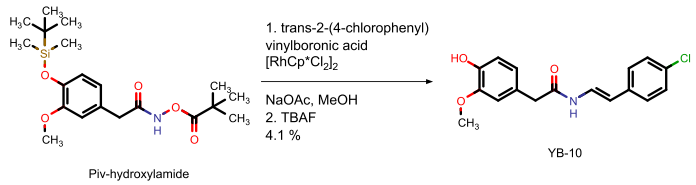
[0045] MS m/e 347 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{31}N_2O_3$ 347.2335; Found 347.2326.

[0046] Example 9: Procedure of the preparation of **YB-10**



[0047] Et_3N (0.24 mL, 1.7 mmol) was added dropwise to a suspension of TBS-Homovanillic acid (0.23 g, 0.78 mmol), Hydroxylamine hydrochloride (59 mg, 0.86 mmol; Order Number H158125G from Fisher) and HATU (0.31 g, 0.82 mmol) in ACN (2 mL) at rt. The mixture was stirred at rt for 2h, then quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at rt for 15 min, then diluted with DCM (5 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil product, R_f 0.33 (2:1 EtOAc/Hexane).

[0048] A solution of the crude product from the previous step in DCM (2 mL) was treated with Et_3N (0.14 mL, 1.0 mmol) and Piv-Cl (0.11 mL, 0.86 mmol; Order Number T72605 from Sigma-Aldrich) at 0°C for 10 min. The reaction was quenched with aq. $NaHCO_3$. The mixture was vigorously stirred at 0°C for 10 min, then at rt for 15 min. The mixture was diluted with DCM (3 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a crude yellow oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 0.28 g of Piv-hydroxylamide (0.70 mmol, 90% over 2 steps), R_f 0.62 (2:3 EtOAc/Hexane).



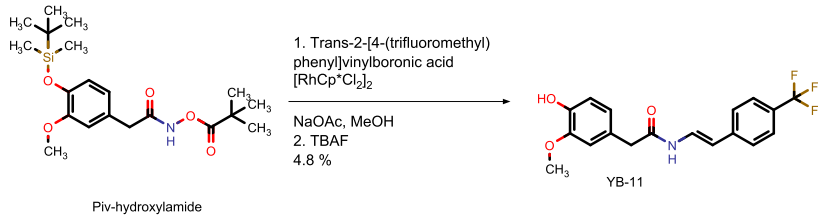
[0049] A mixture of Piv-hydroxylamide prepared in the previous step (40 mg, 0.10 mmol), alkenyl boronic acid: trans-2-(4-chlorophenyl)vinylboronic acid (27 mg, 0.15 mmol; Order Number AC431340010 from Fisher), NaOAc (12 mg. 0.15 mmol), $[RhCp^*Cl_2]_2$ (0.8 mg, 0.00125 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (72 mg, 0.20 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 1.3 mg of YB-10 (0.0041 mmol, 4.1% over 2 steps), R_f 0.62 (2:1 EtOAc/Hexane), 97% purity (HPLC).

[0050] **YB-10**

[0051] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 14.4 and 10.8 Hz, 1H, -C=CH-), 7.18-7.24 (m, 4H, Cl-ArHs), 6.77-6.95 (m, 3H, vanillyl ArHs), 5.91 (d, J = 14.8 Hz, 1H, -CH=C-), 5.65 (s, 1H, amide NH), 4.29 (d, J = 5.6 Hz, 1H, Ar-OH), 3.91 (s, 3H, ArOCH3), 3.62 (s, 2H, ArCH2CO).

[0052] MS m/e 318 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}ClNO_3$ 318.0897; Found 318.0906.

[0053] Example 10: Procedure of the preparation of **YB-11**



[0054] A mixture of Piv-hydroxylamide (40 mg, 0.10 mmol), alkenyl boronic acid: Trans-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (32 mg, 0.15 mmol; Order Number BB-8104 from Combi-Blocks), NaOAc (12 mg. 0.15 mmol), $[RhCp^*Cl_2]_2$ (0.8 mg, 0.00125 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5

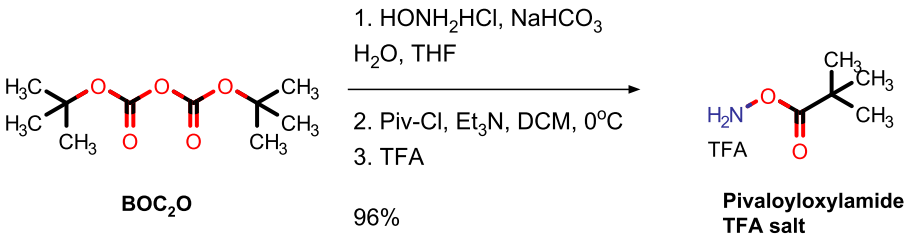
mL) and treated with a solution of TBAF, 70-75% in water (72 mg, 0.20 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 1.7 mg of YB-11 (0.0048 mmol, 4.8% over 2 steps), R_f 0.23 (2:3 EtOAc/Hexane), 97% purity (HPLC).

[0055] **YB-11**

[0056] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 14.6 and 11.0 Hz, 1H, -C=CH-), 7.51 (d, 2H, J = 8.2 Hz, CF3-ArHs), 7.35 (d, 2H, J = 8.0 Hz, CF3-ArHs), 7.15 (br. d, J = 10.3 Hz, 1H, Phenol OH), 6.95 (d, J = 7.5 Hz, 1H, vanillyl ArH), 6.78 (d, J = 7.8 Hz, 2H, vanillyl ArHs), 5.98 (d, J = 14.6 Hz, 1H, -CH=C-), 5.68 (br.d, J=9.6 Hz, 1H, amide NH), 3.91 (s, 3H, ArOCH3), 3.63 (s, 2H, ArCH2CO).

[0057] MS m/e 352 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}F_3NO_3$ 352.1161; Found 352.1148.

[0058] Example 11: Modified procedure of the preparation of **YB-11**



[0059] A solution of BOC_2O (1.1 g, 5.0 mmol) in THF (4 mL) was added to a solution of Hydroxylamine hydrochloride (0.52 g, 7.5 mmol; Order Number H158125G from Fisher), $NaHCO_3$ (1.05 g, 12.5 mmol) in H_2O (4 mL) at rt. The mixture was vigorously stirred overnight, then concentrated to afford a white solid. The residue was suspended in $CHCl_3$ (10 mL), dried (Na_2SO_4) and filtered. The resulted solution was concentrated to give crude N-Boc-hydroxylamine.

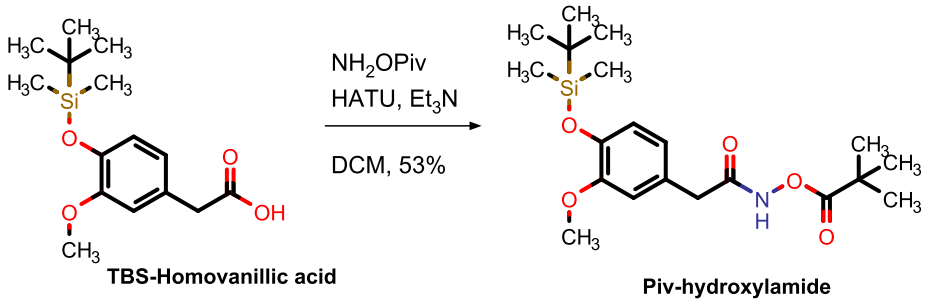
[0060] Et_3N (0.84 mL, 6.0 mmol) was introduced to a mixture of N-Boc-hydroxylamine and small amount of 4Å molecular sieves in DCM (16 mL). The mixture was stirred at rt for

10 min before being cooled to 0°C. After the addition of Piv-Cl (0.65 mL, 5.3 mmol; order Number T72605 from Sigma-Aldrich) dropwise via syringe, the mixture was stirred at 0°C for 15 min, then quenched with aq. $NaHCO_3$. The resulted suspension was vigorously stirred at rt for 5 min. After separation, the aq. layer was extracted with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated to give a crude solid, which was dissolved in DCM and passed through a short plug of silica gel (2:1 EtOAc/hexane) to obtain BOC-NH-O-Piv.

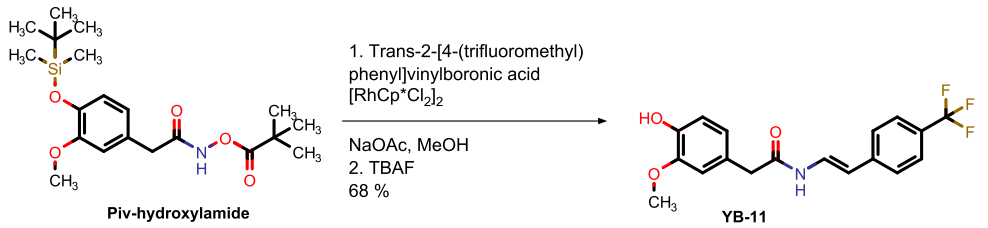
[0061] **BOC-NH-O-Piv**

[0062] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H, CONH), 1.49 (s, 9H, Boc 3 CH3s), 1.30 (s, 9H, Piv 3 CH3s).

[0063] BOC-NH-O-Piv was treated with a solution of TFA (2 mL) in DCM (2 mL) at rt for 10 min, then concentrated to remove the volatiles. The residue was diluted with DCM, evaporated and repeated one more time to give 1.1 g of TFA NH2-O-Piv (4.8 mmol, 96% yield).

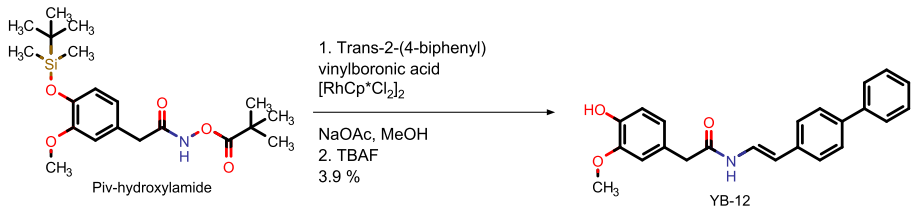


TBS-Homovanillic acid (0.33 g, 1.1 mmol) in DCM (55 mL) at 0°C was treated with Et_3N (0.40 mL, 2.9 mmol), 0.25M of TFA NH_2-O-Piv in DCM (6.0 mL, 1.5 mmol), then HATU (0.61 g, 1.6 mmol) in 3 portions over 30 min. The mixture was stirred at 0°C for 10 min, then warmed up to rt. After 40 min, the mixture was quenched with aq. $NaHCO_3$ at 0°C, and the resulted suspension was vigorously stirred at rt for 15 min. After separation, the aqueous layer was extracted with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography (2:3 EtOAc/Hexane) to furnish 0.23 g of Piv-hydroxylamide (0.58 mmol, 53%), R_f 0.21 (1:4 EtOAc/Hexane). TLC showed Piv-hydroxylamide prepared using this route had better purity than the material prepared using the previous route in Example 9.



[0064] A mixture of Piv-hydroxylamide (40 mg, 0.10 mmol) prepared in the previous step, alkenyl boronic acid: Trans-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (32 mg, 0.15 mmol; Order Number BB-8104 from Combi-Blocks), NaOAc (12 mg. 0.15 mmol), $[RhCp^*Cl_2]_2$ (0.8 mg, 0.00125 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (72 mg, 0.20 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 24 mg of YB-11 (0.068 mmol, 68% over 2 steps), R_f 0.23 (2:3 EtOAc/Hexane), 98% purity (HPLC). NMR and MS data same as YB-11 from the previous procedure in Example 10.

[0065] Example 12: Procedure of the preparation of **YB-12**



[0066] A mixture of Piv-hydroxylamide (40 mg, 0.10 mmol) prepared using the route in Example 9, alkenyl boronic acid: Trans-2-(4-biphenyl)vinylboronic acid (34 mg, 0.15 mmol; Order Number BB-8214 from Combi-Blocks), NaOAc (12 mg. 0.15 mmol), $[RhCp^*Cl_2]_2$ (0.8 mg, 0.00125 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (1.0 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (72 mg, 0.20 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL)

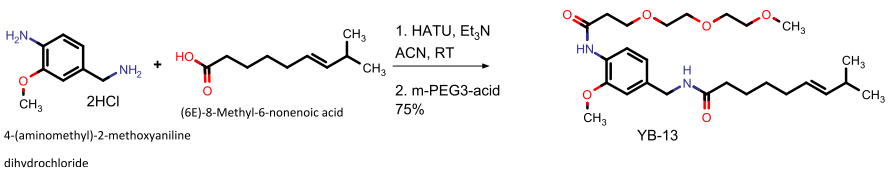
and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 1.4 mg of YB-12 (0.0039 mmol, 3.9% over 2 steps), R_f 0.22 (2:3 EtOAc/Hexane), 95% purity (HPLC).

[0067] **YB-12**

[0068] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.56 (m, 10H, -C=CH-, Ar-ArHs), 6.79-6.97 (m, 3H, vanillyl ArHs), 6.00 (d, J = 14.8 Hz, 1H, -CH=C-), 5.65 (br.s, 1H, amide NH), 4.29 (d, J = 5.6 Hz, 1H, Ar-OH), 3.92 (s, 3H, ArOCH3), 3.63 (s, 2H, ArCH2CO).

[0069] MS m/e 360 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}NO_3$ 360.1600; Found 360.1592.

[0070] Example 13: Procedure of the preparation of **YB-13**



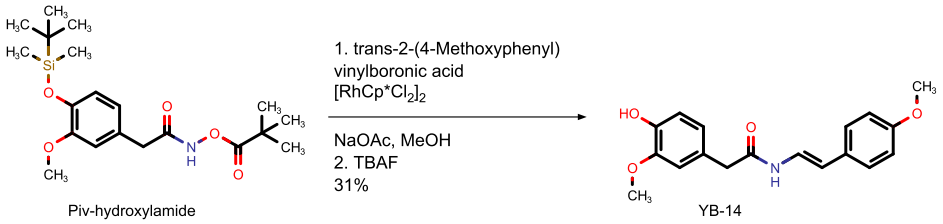
[0071] Et_3N (39 uL, 0.28 mmol) was added dropwise to a suspension of (6E)-8-Methyl-6-nonenoic acid (10 mg, 0.059 mmol; Order Number LN01303052 from LabNetwork), 4-(aminomethyl)-2-methoxyaniline dihydrochloride (14.3 mg, 0.065 mmol; Order Number EN300-1721327 from Enamine) and HATU (46 mg, 0.12 mmol) in ACN (1 mL) at 0°C. The mixture was stirred at 0°C for 20 min. After the addition of m-PEG3-acid (17 mg, 0.089 mmol; Cat # BP-20981 from Broadpharm), the mixture was stirred at rt for 40 min, then quenched with aq. $NaHCO_3$ at 0°C. The resulted mixture was vigorously stirred at rt for 15 min, then diluted with DCM (2 mL). After separation, the aqueous phase was extracted with DCM (1 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (1:13 MeOH/DCM) to furnish 20.8 mg of YB-13 (0.044 mmol, 75% over 2 steps), R_f 0.20 (1:20 MeOH/DCM), 97% purity (HPLC).

[0072] **YB-13**

[0073] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H, Ar-NH-CO), 8.31 (d, J = 8.0 Hz, 1H, ArH), 6.83 (d, J = 9.8 Hz, 2H, ArHs), 5.68 (s, 1H, Amide NH), 5.19-5.40 (m, 2H, olefin Hs), 4.38 (d, J = 5.7 Hz, 2H, ArCH2NH), 3.86 (s, 3H, ArOCH3), 3.82 (t, J = 5.6 Hz, 2H, CH2O), 3.71 (s, 4H, 2 CH2O), 3.63-3.65 (m, 2H, CH2O), 3.48-3.53 (m, 2H, CH2O), 3.36 (s, 3H, OCH3), 2.66 (t, J = 5.7 Hz, 2H, COCH2), 2.18-2.23 (m, 3H, alkyl Hs), 1.98 (q, J = 6.9 Hz, 1H, alkyl H), 1.61-1.69 (m, 3H, alkyl Hs), 1.34-1.42 (m, 2H, alkyl Hs), 0.92-0.95 (d, J = 3.4 Hz, 6H, alkyl CH3s).

[0074] MS m/e 479 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{43}N_2O_6$ 479.3121; Found 479.3108.

[0075] Example 14: Procedure of the preparation of **YB-14**



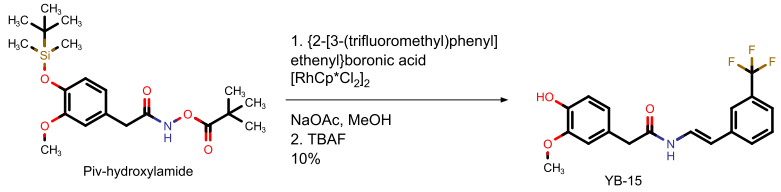
[0076] A mixture of Piv-hydroxylamide (20 mg, 0.05 mmol) prepared using the route in Example 9, alkenyl boronic acid: trans-2-(4-Methoxyphenyl)vinylboronic acid (13.5 mg, 0.075 mmol; Order Number BB-8136 from Combi-blocks), NaOAc (6 mg. 0.075 mmol), $[RhCp^*Cl_2]_2$ (0.4 mg, 0.000625 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (72 mg, 0.20 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 4.8 mg of YB-14 (0.015 mmol, 31% over 2 steps), R_f 0.13 (2:3 EtOAc/Hexane), 97% purity (HPLC).

[0077] **YB-14**

[0078] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 14.6, 10.7 Hz, 1H, -C=CH-), 7.20 (d, 2H, J = 8.7 Hz, MeO-ArHs), 7.05 (br.d, J = 10.3 Hz, 1H, Phenol OH), 6.94 (d, J = 8.5 Hz, 1H, vanillyl ArH), 6.81 (d, J = 8.7 Hz, 2H, MeO-ArHs), 6.78 (d, J = 5.9 Hz, 2H, vanillyl ArHs), 5.92 (d, J = 14.6 Hz, 1H, -CH=C-), 5.30 (s, 1H, amide NH), 3.91 (s, 3H, vanillyl ArOCH3), 3.78 (s, 3H, CH3O-Ar), 3.61 (s, 2H, ArCH2CO).

[0079] MS m/e 314 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_4$ 314.1392; Found 314.1403.

[0080] Example 15: Procedure of the preparation of **YB-15**



[0081] A mixture of Piv-hydroxylamide (20 mg, 0.05 mmol) prepared using the route in Example 9, alkenyl boronic acid: {2-[3-(trifluoromethyl)phenyl]ethenyl}boronic acid (E/Z mixture) (16 mg, 0.075 mmol; Order Number EN300-310386 from Enamine), NaOAc (6 mg. 0.075 mmol), $[RhCp^*Cl_2]_2$ (0.4 mg, 0.000625 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (72 mg, 0.20 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with DCM (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 1.7 mg of YB-15 (0.0048 mmol, 10% over 2 steps), R_f 0.20 (2:3 EtOAc/Hexane), 98% purity (HPLC).

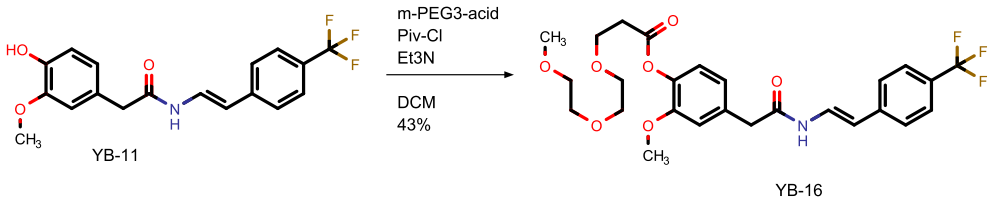
[0082] **YB-15**

[0083] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 14.6 and 11.0 Hz, 1H, -C=CH-), 7.49 (s, 1H, CF3-ArH), 7.37-7.45 (m, 3H, CF3-ArHs), 7.14 (br. d, J = 10.3 Hz, 1H, Phenol OH), 6.95 (d, J = 8.0 Hz, 1H, vanillyl ArH), 6.79 (d, J = 7.3 Hz, 2H, vanillyl ArHs), 5.99 (d, J =

14.6 Hz, 1H, -CH=C-), 5.65 (s, 1H, amide NH), 3.91 (s, 3H, ArOCH3), 3.64 (s, 2H, ArCH2CO).

[0084] MS m/e 352 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}F_3NO_3$ 352.1161; Found 352.1174.

[0085] Example 16: Procedure of the preparation of **YB-16**



[0086] Et_3N (4.7 uL, 0.034 mmol) was introduced to a mixture of m-PEG3-acid (11 mg, 0.059 mmol; Cat # BP-20981 from Broadpharm) and small amount of 4Å molecular sieves in DCM (1 mL). The mixture was stirred at rt for 10 min before the addition of Piv-Cl (7.1 uL, 0.058 mmol; order Number T72605 from Sigma-Aldrich). The mixture was stirred at rt for 10 min to form the mixed anhydride.

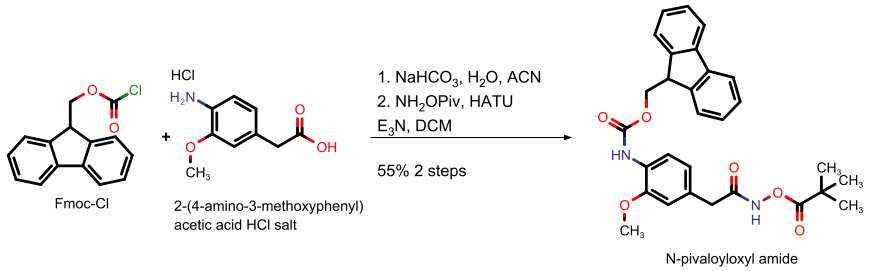
[0087] Et_3N (4.9 uL, 0.035 mmol) was introduced to a mixture of YB-11 (10 mg, 0.028 mmol) and small amount of 4Å molecular sieves in DCM (1 mL) at 0°C. The mixture was stirred at 0°C for 10 min before the addition of the freshly prepared mixed anhydride. The resulted mixture was stirred for 12h at rt and purified by chromatography (2:1 EtOAc/Hexane) to furnish 6.4 mg of YB-16 (0.012 mmol, 43%), R_f 0.17 (2:1 EtOAc/Hexane), 95% purity (HPLC).

[0088] **YB-16**

[0089] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 14.6 and 11.0 Hz, 1H, -C=CH-), 7.51 (d, J = 8.0 Hz, 2H, CF3-ArHs), 7.36 (d, J = 8.2 Hz, 2H, CF3-ArHs), 7.07 (d, J = 8.0 Hz, 1H, vanillyl ArH), 6.84-6.88 (m, 2H, vanillyl ArHs), 6.04 (d, J = 14.9 Hz, 1H, -CH=C-), 3.89 (t, J = 6.5 Hz, 2H, CH2O), 3.83 (s, 3H, ArOCH3), 3.65-3.73 (m, 8H, ArCH2CO, 3 CH2O), 3.55-3.57 (m, 2H, CH2O), 3.38 (s, 3H, OCH3), 2.90 (t, J = 6.4 Hz, 2H, COCH2).

[0090] MS m/e 526 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{31}F_3NO_7$ 526.2053; Found 526.2037.

[0091] Example 17: Procedure of the preparation of **YB-17**

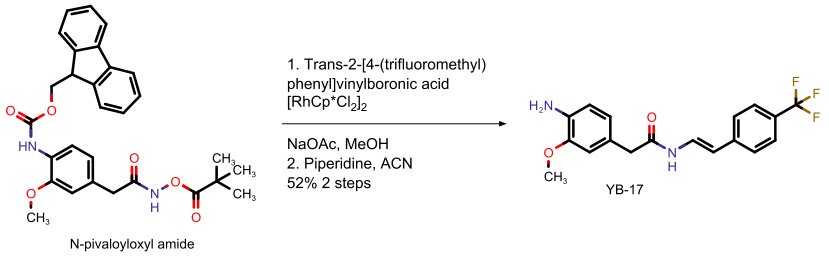


[0092] A solution of $NaHCO_3$ (50 mg, 0.60 mmol) in H_2O (2 mL) was added to a suspension of 2-(4-amino-3-methoxyphenyl) acetic acid hydrochloride (44 mg, 0.20 mmol; Order Number FCH886354 from Chem-space) and Fmoc-Cl (78 mg, 0.30 mmol) in ACN (2 mL) at rt. The suspension was completely dissolved after the addition. After the solution was vigorously stirred overnight, white solid precipitated out. The mixture was diluted with 1:3 EtOAc/Hexane (6 mL), stirred at 0°C for 5 min, then filtered to give 85 mg of 2-[4-(Fmoc-amino)-3-methoxyphenyl]acetic acid sodium salt (0.20 mmol, 100%).

[0093] A suspension of 2-[4-(Fmoc-amino)-3-methoxyphenyl]acetic acid sodium salt (85 mg, 0.20 mmol) in DCM (10 mL) at 0°C was treated with 0.25 M of TFA NH_2-O-Piv in DCM (1.2 mL, 0.30 mmol), Et_3N (49 uL, 0.35 mmol), then HATU (80 mg, 0.21 mmol) in 3 portions over 30 min. The mixture was stirred at 0°C for 10 min, then warmed up to rt for 1h 20 min. The mixture was quenched with aq. $NaHCO_3$ at 0°C, and the resulted suspension was vigorously stirred at rt for 15 min. After separation, the aqueous layer was extracted with EtOAc (5 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude solid, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 53 mg of N-Pivaloyloxylamide (0.11 mmol, 55% over 2 steps), R_f 0.28 (2:3 EtOAc/Hexane).

[0094] **N-Pivaloyloxylamide**

[0095] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (br.s,1H, NH), 8.05 (br. s, 1H NH), 7.78 (d, J = 7.3 Hz, 2H, Fmoc ArHs), 7.63 (d, J = 7.3 Hz, 2H, Fmoc ArHs), 7.41 (t, J = 7.4 Hz, 2H, Fmoc ArHs), 7.32 (t, J = 7.4 Hz, 2H, Fmoc ArHs), 7.27 (m, 1H, ArH), 6.85 (m, 2H, ArHs), 4.50 (d, J = 6.2 Hz, 2H, Fmoc CH2), 4.29 (t, J = 6.9 Hz, 1H, Fmoc CH), 3.90 (s, 3H, ArOCH3), 3.61 (s, 2H, ArCH2CO), 1.28 (s, 9H, Piv 3 CH3s).



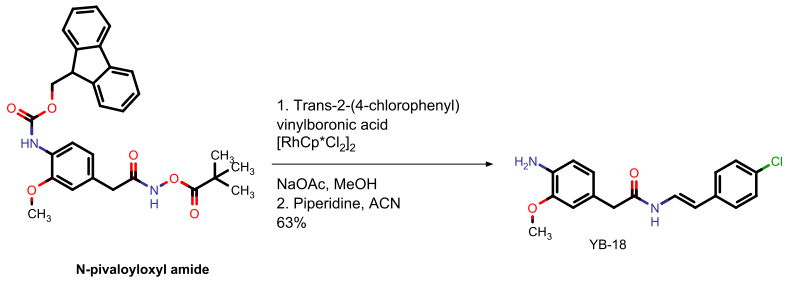
[0096] A mixture of N-Pivaloyloxylamide (21 mg, 0.042 mmol), alkenyl boronic acid: Trans-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (16 mg, 0.075 mmol; Order Number BB-8104 from Combi-Blocks), NaOAc (6 mg. 0.075 mmol), $[RhCp^*Cl_2]_2$ (0.4 mg, 0.000625 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (1.0 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was treated with a 20% solution of piperidine in ACN (1.0 mL) at rt for 20 min, then concentrated to give a crude solid, which was purified by chromatography (2:1 EtOAc/Hexane) to furnish 7.6 mg of YB-17 (0.022 mmol, 52% over 2 steps), R_f 0.44 (2:1 EtOAc/Hexane), 98% purity (HPLC).

[0097] **YB-17**

[0098] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 14.6 and 11.2 Hz, 1H, -C=CH-), 7.50 (d, J = 8.2 Hz, 2H, CF3-ArHs), 7.35 (d, J = 8.2 Hz, 2H, CF3-ArHs), 7.20 (br.d, J=10.3 Hz, 1H, NH), 6.68-6.75 (m, 3H, vanillyl ArHs), 5.95 (d, J = 14.6 Hz, 1H, -CH=C-), 3.87 (s, 3H, ArOCH3), 3.61 (s, 2H, ArCH2CO).

[0099] MS m/e 351 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}F_3N_2O_2$ 351.1320; Found 351.1305.

[00100] Example 18: Procedure of the preparation of **YB-18**



[00101] A mixture of N-Pivaloyloxylamide (10.5 mg, 0.021 mmol), alkenyl boronic acid: trans-2-(4-chlorophenyl)vinylboronic acid (5.8 mg, 0.032 mmol; Order Number

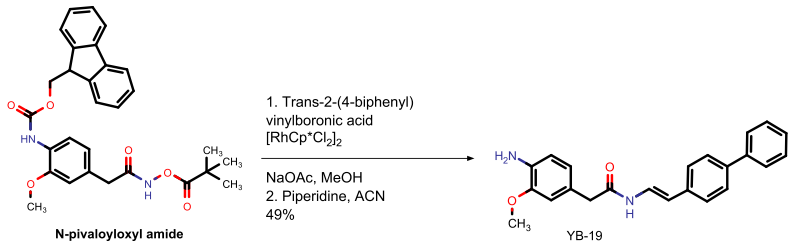
AC431340010 from Fisher), NaOAc (2.6 mg. 0.032 mmol), $[RhCp^*Cl_2]_2$ (0.2 mg, 0.00026 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (1.0 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was treated with a 20% solution of piperidine in ACN (1.0 mL) at rt for 20 min, then concentrated to give a crude solid, which was purified by chromatography (3:2 EtOAc/Hexane) to furnish 4.2 mg of YB-18 (0.013 mmol, 63% over 2 steps), R_f 0.44 (2:1 EtOAc/Hexane), 97% purity (HPLC).

[00102] **YB-18**

[00103] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 14.6 and 10.7 Hz, 1H, -C=CH-), 7.12-7.23 (m, 4H, Cl-ArHs), 6.67-6.74 (m, 3H, vanillyl ArHs), 5.88 (d, J = 14.6 Hz, 1H, -CH=C-), 3.86 (s, 3H, ArOCH3), 3.59 (s, 2H, ArCH2CO).

[00104] MS m/e 317 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}ClN_2O_2$ 317.1057; Found 317.1069.

[00105] Example 19: Procedure of the preparation of **YB-19**



[00106] A mixture of N-Pivaloyloxylamide (10.5 mg, 0.021 mmol), alkenyl boronic acid: Trans-2-(4-biphenyl)vinylboronic acid (7.2 mg, 0.032 mmol; Order Number BB-8214 from Combi-Blocks), NaOAc (2.6 mg. 0.032 mmol), $[RhCp^*Cl_2]_2$ (0.2 mg, 0.00026 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (1.0 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was treated with a 20% solution of piperidine in ACN (1.0 mL) at rt for 20 min, then concentrated to give a crude solid, which was purified by chromatography (3:2 EtOAc/Hexane) to furnish 3.7 mg of YB-19 (0.010 mmol, 49% over 2 steps), R_f 0.46 (2:1 EtOAc/Hexane), 97% purity (HPLC).

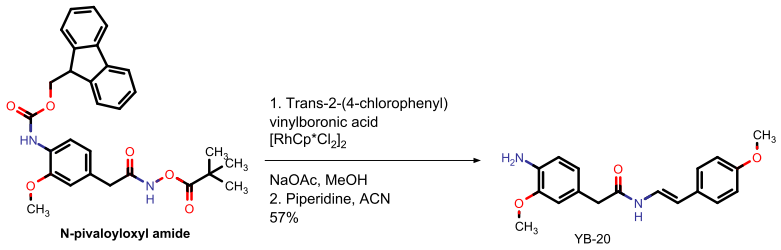
[00107] **YB-19**

[00108] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 2H, Ar-ArHs), 7.50-7.53 (m, 3H, -C=CH-, Ar-ArHs), 7.42 (t, J = 7.5 Hz, 2H, Ar-ArHs), 7.30-7.35 (m, 3H, Ar-ArHs), 7.16

(br. d, J = 10.7 Hz, 1H, NH), 6.69-6.75 (m, 3H, vanillyl ArHs), 5.97 (d, J = 14.6 Hz, 1H, -CH=C-), 3.87 (s, 3H, ArOCH3), 3.61 (s, 2H, ArCH2CO).

[00109] MS m/e 359 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{23}N_2O_2$ 359.1760; Found 359.1744.

[00110] Example 20: Procedure of the preparation of **YB-20**



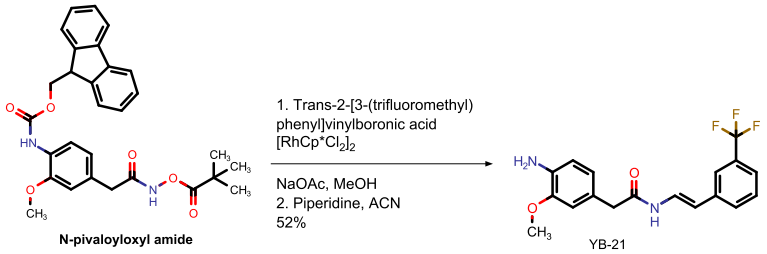
[00111] A mixture of N-Pivaloyloxylamide (10.5 mg, 0.021 mmol), alkenyl boronic acid: trans-2-(4-Methoxyphenyl)vinylboronic acid (5.7 mg, 0.032 mmol; Order Number BB-8136 from Combi-block), NaOAc (2.6 mg. 0.032 mmol), $[RhCp^*Cl_2]_2$ (0.2 mg, 0.00026 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (1.0 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was treated with a 20% solution of piperidine in ACN (1.0 mL) at rt for 20 min, then concentrated to give a crude solid, which was purified by chromatography (3:2 EtOAc/Hexane) to furnish 3.9 mg of YB-20 (0.012 mmol, 57% over 2 steps), R_f 0.35 (2:1 EtOAc/Hexane), 97% purity (HPLC).

[00112] **YB-20**

[00113] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 14.5, 10.9 Hz, 1H, -C=CH-), 7.20 (d, 2H, J = 8.5 Hz, MeO-ArHs), 7.08 (br.d, J = 10.7 Hz, 1H, NH), 6.81 (d, J = 8.7 Hz, 2H, MeO-ArHs), 6.68-6.74 (m, 3H, vanillyl ArHs), 5.89 (d, J = 14.6 Hz, 1H, -CH=C-), 3.86 (s, 3H, vanillyl ArOCH3), 3.78 (s, 3H, CH3O-Ar), 3.58 (s, 2H, ArCH2CO).

[00114] MS m/e 313 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{21}N_2O_3$ 313.1552; Found 313.1563.

[00115] Example 21: Procedure of the preparation of **YB-21**



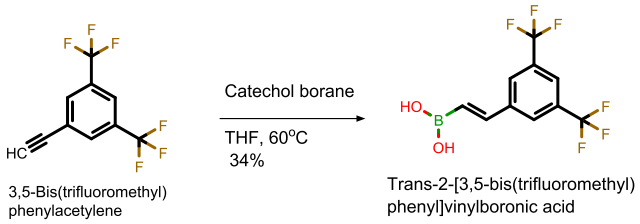
[00116] A mixture of N-Pivaloyloxylamide (10.5 mg, 0.021 mmol), alkenyl boronic acid: {2-[3-(trifluoromethyl)phenyl]ethenyl}boronic acid (E/Z mixture) (6.9 mg, 0.032 mmol; Order Number EN300-310386 from Enamine), NaOAc (2.6 mg. 0.032 mmol), $[RhCp^*Cl_2]_2$ (0.2 mg, 0.00026 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (1.0 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was treated with a 20% solution of piperidine in ACN (1.0 mL) at rt for 20 min, then concentrated to give a crude solid, which was purified by chromatography (3:2 EtOAc/Hexane) to furnish 4.0 mg of YB-21 (0.011 mmol, 52% over 2 steps), R_f 0.50 (2:1 EtOAc/Hexane), 98% purity (HPLC).

[00117] **YB-21**

[00118] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 14.6 and 11.0 Hz, 1H, -C=CH-), 7.48 (s, 1H, CF3-ArH), 7.36-7.44 (m, 3H, CF3-ArHs), 7.19 (br. d, J = 11.0 Hz, 1H, NH), 6.68-6.75 (m, 3H, vanillyl ArHs), 5.95 (d, J = 14.6 Hz, 1H, -CH=C-), 3.86 (s, 3H, ArOCH3), 3.61 (s, 2H, ArCH2CO).

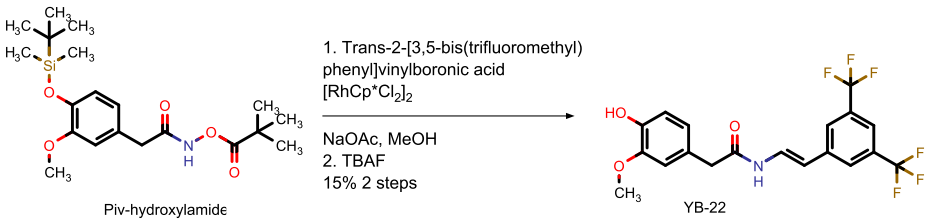
[00119] MS m/e 351 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}F_3N_2O_2$ 351.1320; Found 351.1332.

[00120] Example 22: Procedure of the preparation of **YB-22**



[00121] A terminal aromatic alkyne 3,5-Bis(trifluoromethyl)phenylacetylene (119 mg, 0.5 mmol; Order Number SS-4899 from Combi-Blocks) was treated with 1 M solution of catechol borane in THF (0.75 mL, 0.75 mmol) under nitrogen atmosphere at 60 °C for 17 h. The

mixture was quenched with water (2.5 mL) and vigorously stirred at rt for 4 h, then concentrated to give a white solid residue, which was purified by chromatography (EtOAc) to furnish 49 mg of Trans-2-[3,5-bis(trifluoromethyl)phenyl]vinylboronic acid (0.17 mmol, 34%), R_f 0.43 (EtOAc).



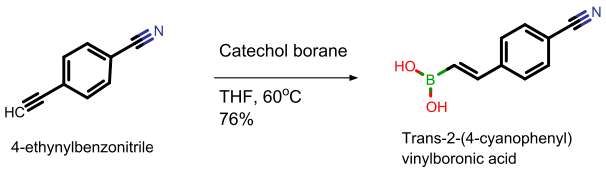
[00122] A mixture of Piv-hydroxylamide (11 mg, 0.028 mmol) prepared using the route in Example 9, alkenyl boronic acid: Trans-2-[3,5-bis(trifluoromethyl)phenyl]vinylboronic acid (12 mg, 0.042 mmol), NaOAc (3.4 mg. 0.042 mmol), $[RhCp^*Cl_2]_2$ (0.2 mg, 0.00035 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (20 mg, 0.056 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with EtOAc (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 1.7 mg of YB-22 (0.0041 mmol, 15% over 2 steps), R_f 0.25 (2:3 EtOAc/Hexane), 96% purity (HPLC).

[00123] **YB-22**

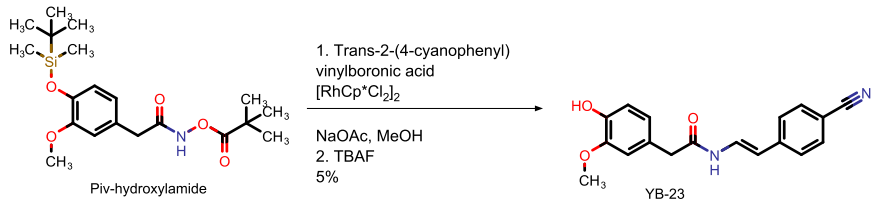
[00124] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 2H, CF3-ArHs), 7.63 (s, 1H, CF3-ArH), 7.61 (dd, J = 14.8 and 10.8 Hz, 1H, -C=CH-), 7.45 (br. s, 1H, Phenol OH), 6.95 (d, J = 8.5 Hz, 1H, vanillyl ArH), 6.78-6.80 (m, 2H, vanillyl ArHs), 6.02 (d, J = 14.6 Hz, 1H, -CH=C-), 5.69 (s, 1H, amide NH), 3.91 (s, 3H, ArOCH3), 3.64 (s, 2H, ArCH2CO).

[00125] MS m/e 420 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}F_6NO_3$ 420.1034; Found 420.1050.

[00126] Example 23: Procedure of the preparation of **YB-23**



[00127] A terminal aromatic alkyne 4-ethynylbenzonitrile (127 mg, 1.0 mmol; Order Number QA-3961 from Combi-Blocks) was treated with 1 M solution of catechol borane in THF (2.0 mL, 2.0 mmol) under nitrogen atmosphere at 60 °C for 3 days. The mixture was quenched with water (4 mL) and vigorously stirred at rt for 4 h, then concentrated to obtain a residue, which was purified by chromatography (EtOAc) to furnish 132 mg of Trans-2-(4-cyanophenyl)vinylboronic acid (0.76 mmol, 76%), R_f 0.34 (EtOAc).



[00128] A mixture of Piv-hydroxylamide (11 mg, 0.028 mmol) prepared using the route in Example 9, alkenyl boronic acid: Trans-2-(4-cyanophenyl)vinylboronic acid (7.3 mg, 0.042 mmol), NaOAc (3.4 mg. 0.042 mmol), $[RhCp^*Cl_2]_2$ (0.2 mg, 0.00035 mmol; Order Number 50-536-096 from Fisher) in anhydrous MeOH (0.5 mL) was stirred at rt for 12 h, then concentrated to remove the solvent. The crude residue was suspended in ACN (0.5 mL) and treated with a solution of TBAF, 70-75% in water (20 mg, 0.056 mmol) in ACN (0.2 mL) for 20 min. The mixture was quenched with pH 7 buffer (1 mL) and 1N HCl (0.20 mL, 0.20 mmol) at 0°C, then diluted with DCM (4 mL) and H_2O (2 mL). After separation, the aqueous layer was extracted with EtOAc (2 mL). The combined organics were dried (Na_2SO_4) and concentrated to give a crude oil, which was purified by chromatography (2:3 EtOAc/Hexane) to furnish 0.4 mg of YB-23 (0.0013 mmol, 5% over 2 steps), R_f 0.10 (2:3 EtOAc/Hexane), 95% purity (HPLC).

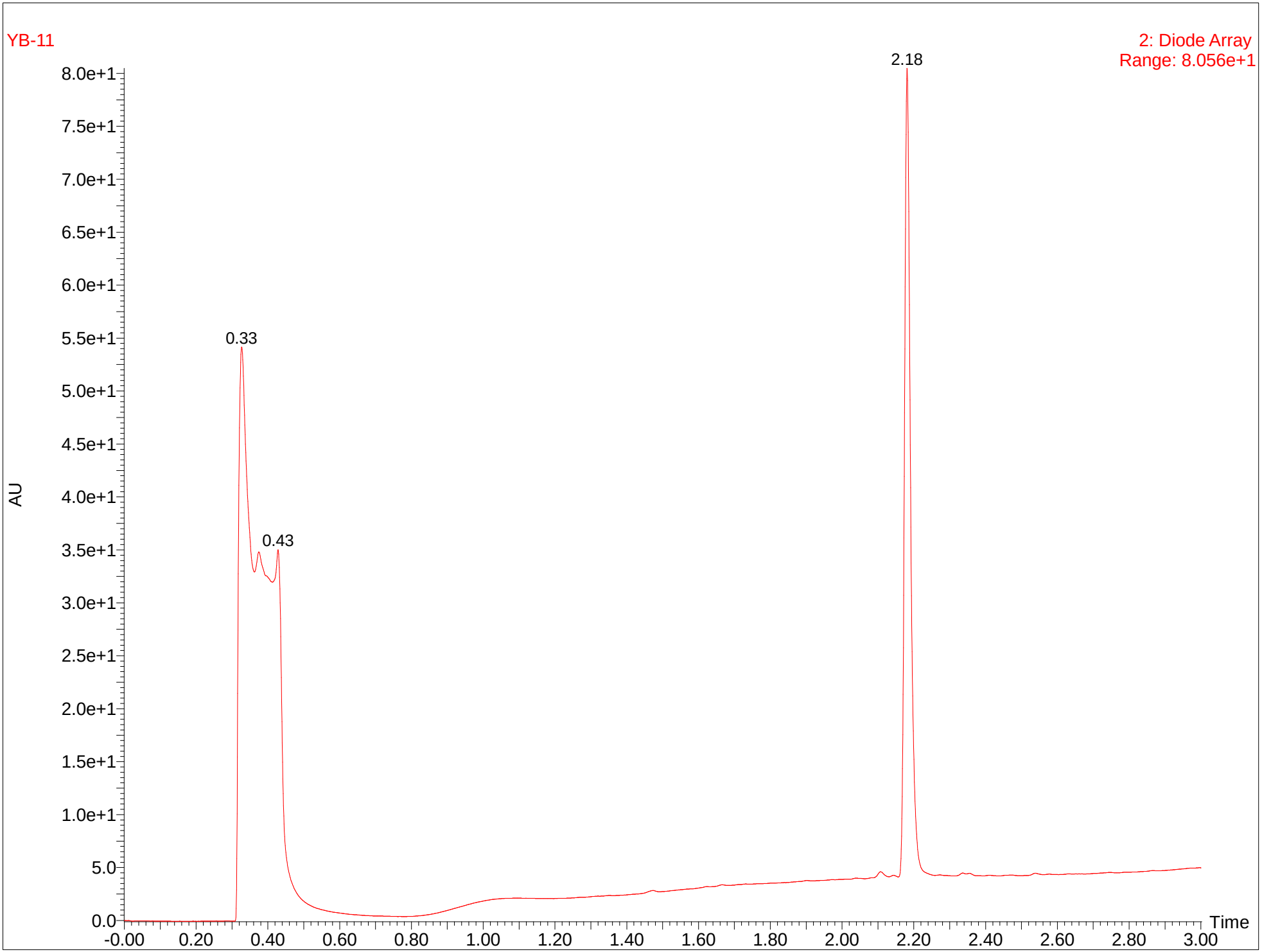
[00129] **YB-23**

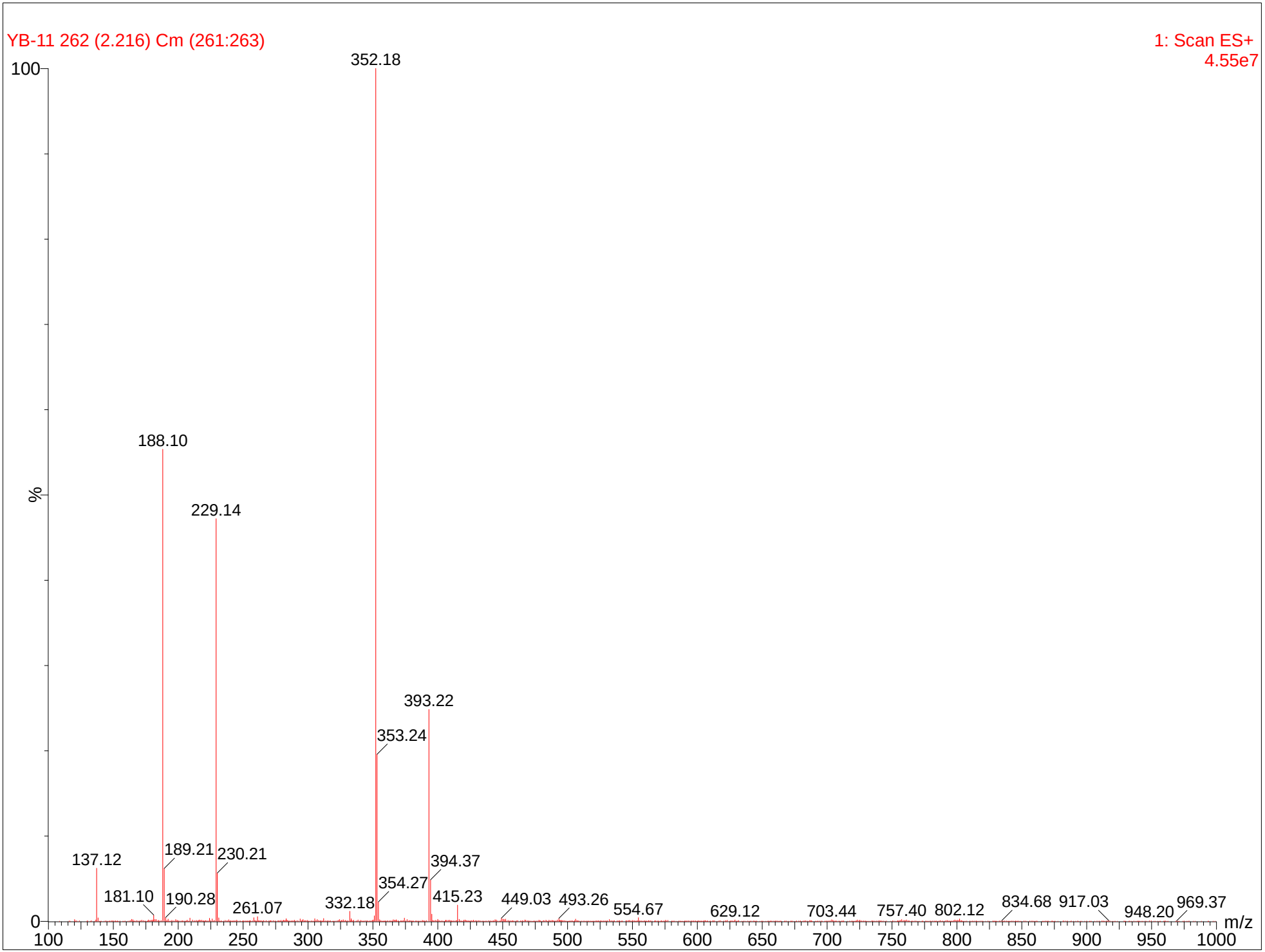
[00130] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 14.8 and 11.2 Hz, 1H, -C=CH-), 7.54 (d, 2H, J = 8.4 Hz, CN-ArHs), 7.33 (d, 2H, J = 8.2 Hz, CN-ArHs), 6.91-6.97 (m, 1H, vanillyl

ArH), 6.77-6.79 (m, 2H, vanillyl ArHs), 5.95 (d, J = 14.4 Hz, 1H, -CH=C-), 5.66 (s, 1H, amide NH), 3.91 (s, 3H, ArOCH3), 3.64 (s, 2H, ArCH2CO).

[00131] MS m/e 309 (M^++H). HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1239; Found 309.1223.

Figure S1 - Supporting Data (HPLC, UV, MS) for YB11 and YB16

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%
0
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188.10
229.14
393.22
353.24
137.12
189.21
230.21
394.37
354.27
181.10
190.28
261.07
332.18
415.23
449.03
493.26
554.67
629.12
703.44
757.40
802.12
834.68
917.03
948.20
969.37
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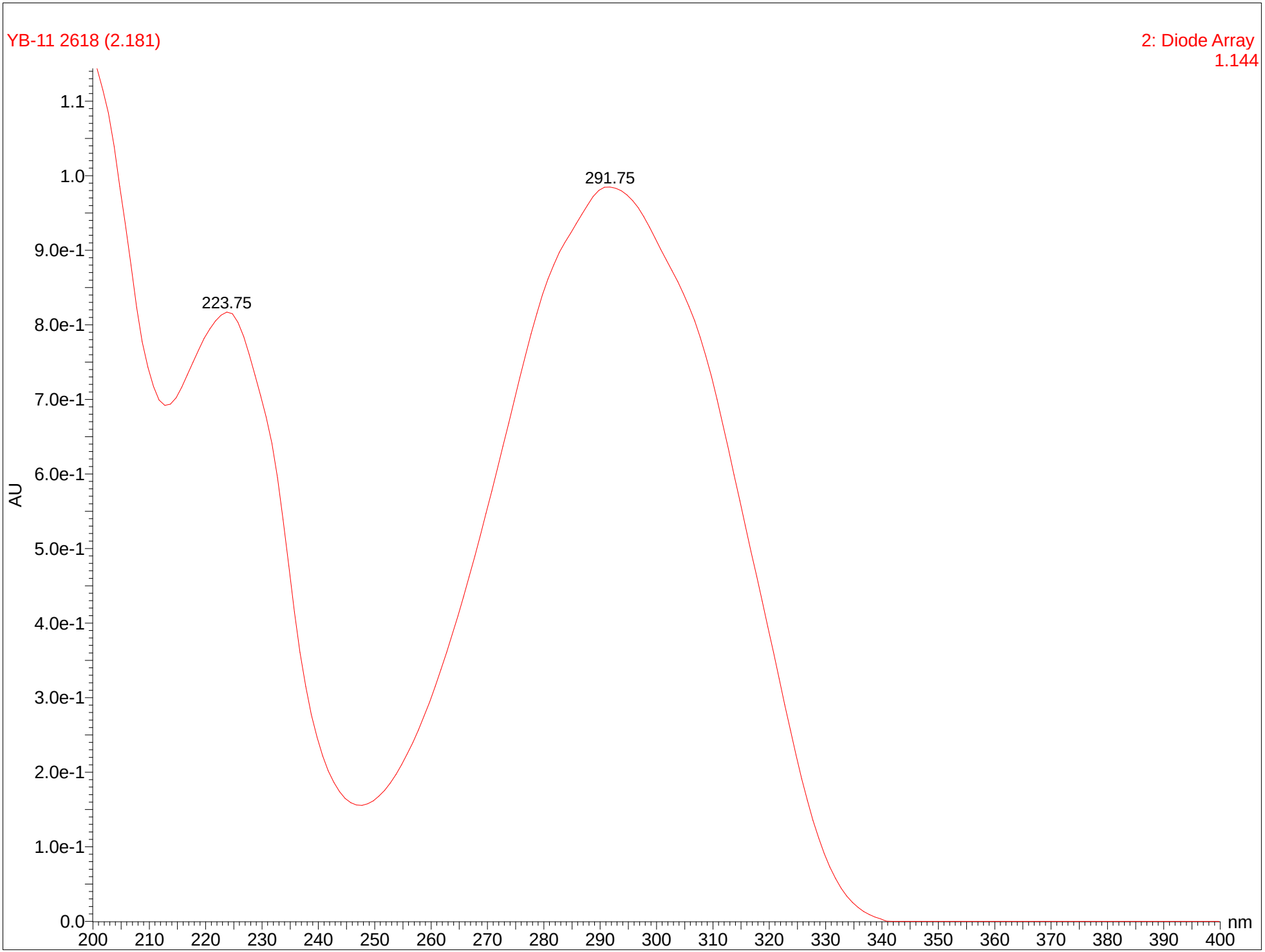
550
600
650
700
750
800
850
900
950
1000


YB-11 2618 (2.181)
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291.75
223.75
AU
1.1
1.0
9.0e-1
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7.0e-1
6.0e-1
5.0e-1
4.0e-1
3.0e-1
2.0e-1
1.0e-1
0.0
200
210
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340
350
360
370
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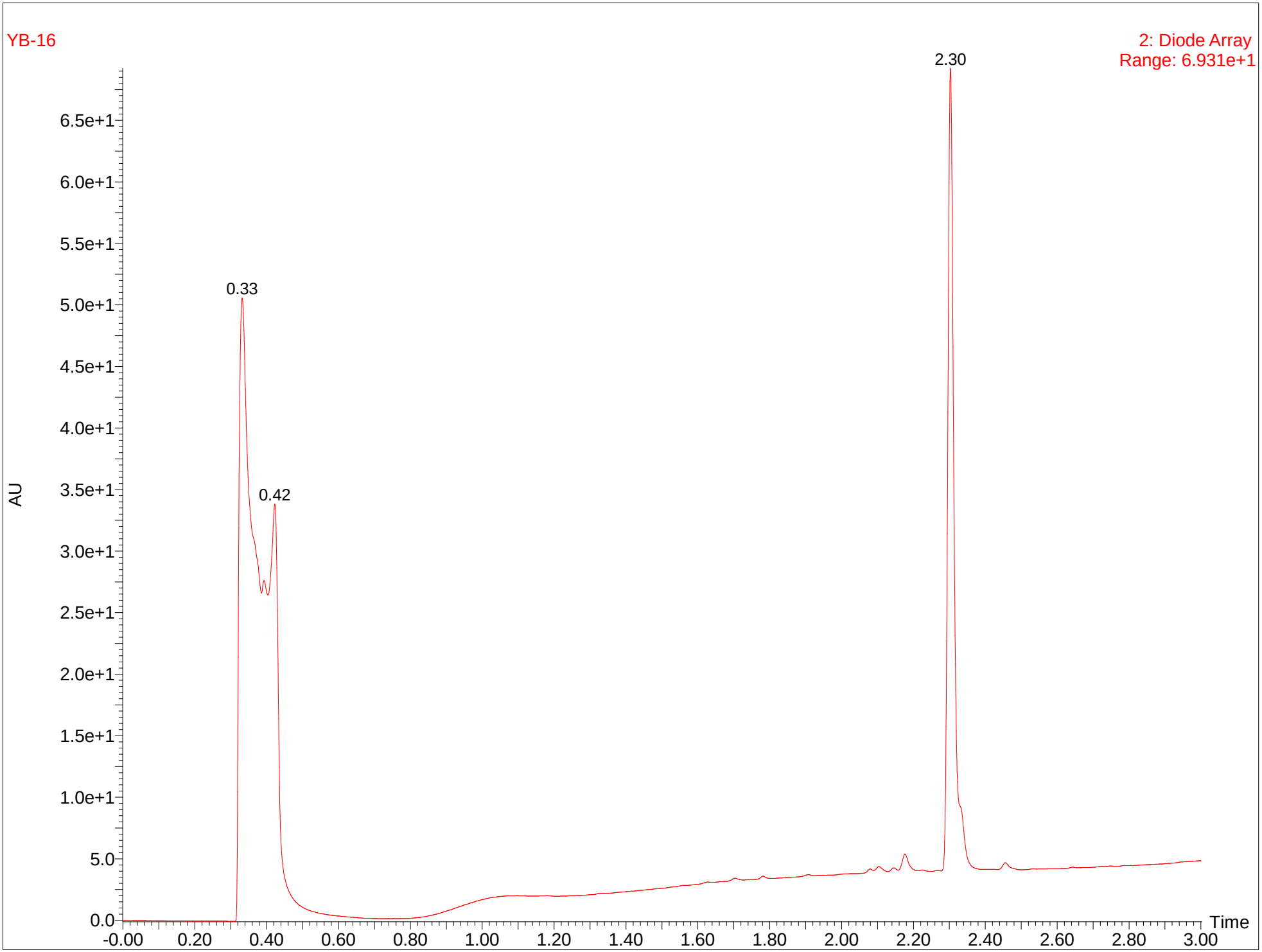
390
400
nm


YB-16
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Range: 6.931e+1
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AU
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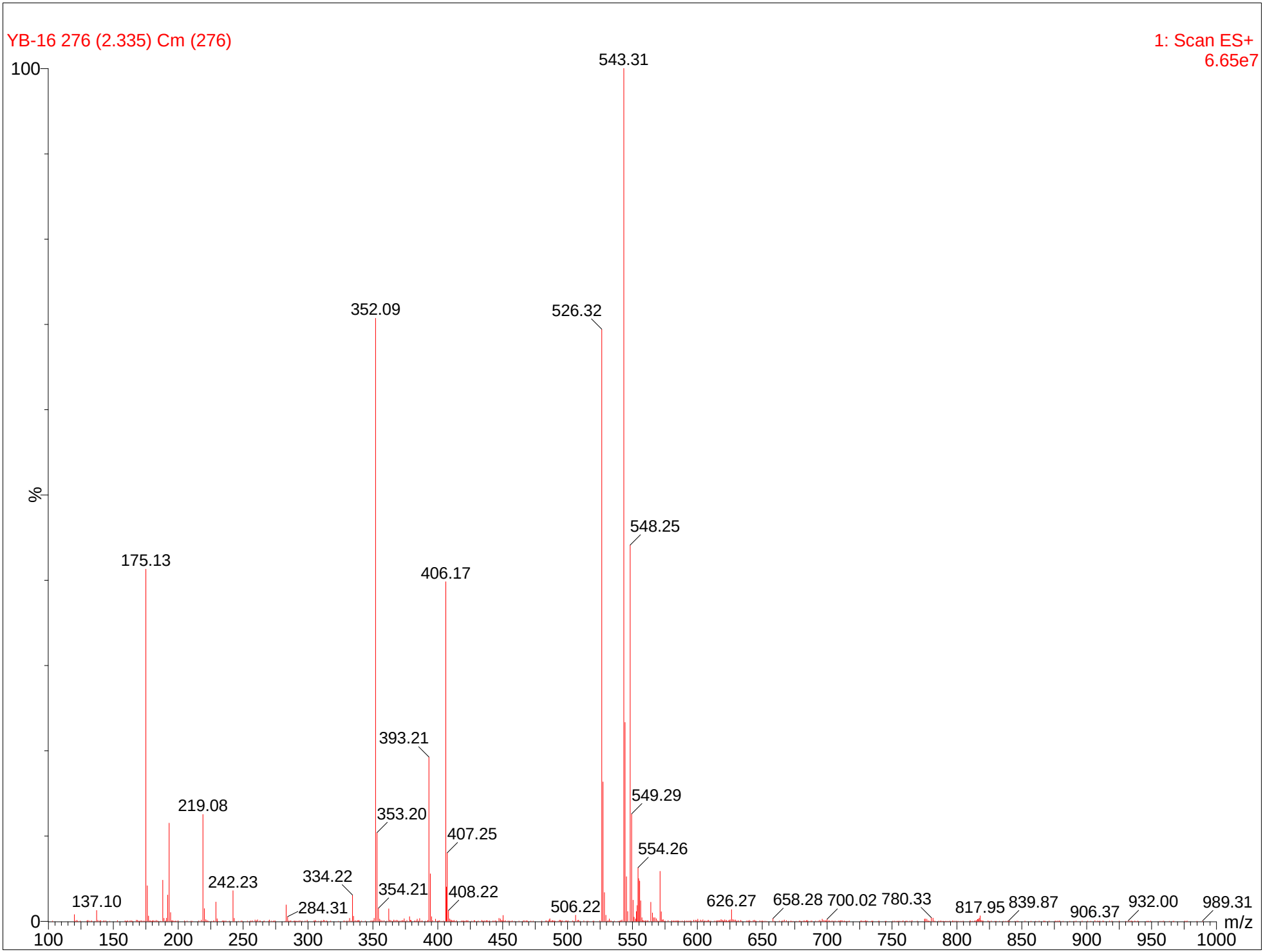
3.0e+1
2.5e+1
2.0e+1
1.5e+1
1.0e+1
5.0
0.0
-0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
1.60
1.80
2.00
2.20
2.40
2.60
2.80
3.00
Time

S30


YB-16 276 (2.335) Cm (276)
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%
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352.09
526.32
548.25
175.13
406.17
393.21
549.29
219.08
353.20
407.25
554.26
242.23
334.22
354.21
408.22
137.10
284.31
506.22
626.27
658.28
700.02
780.33
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932.00
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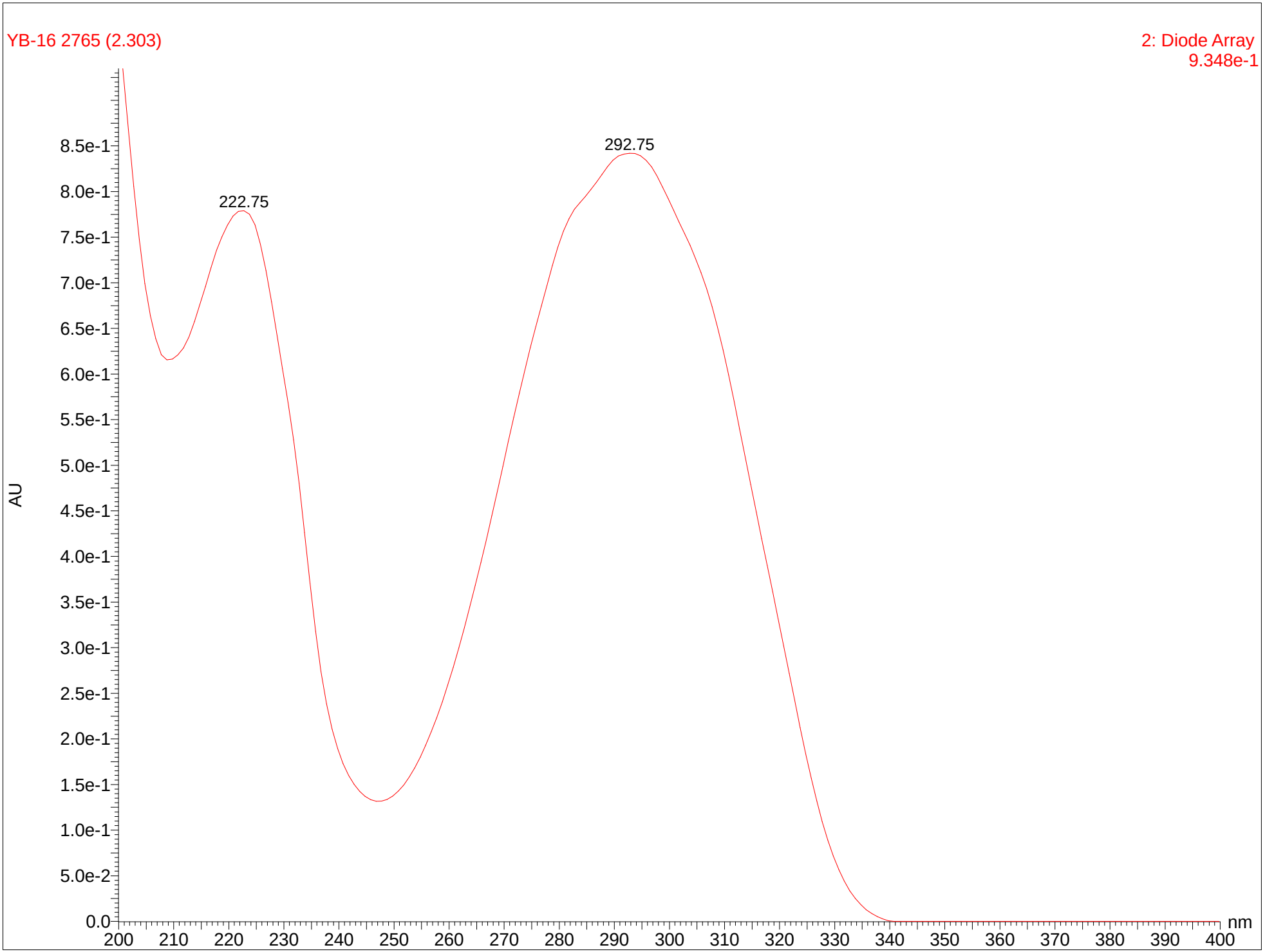
1000

S31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3.5e-1
3.0e-1
2.5e-1
2.0e-1
1.5e-1
1.0e-1
5.0e-2
0.0
200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400
nm

S32