Electronic Supplementary Information

Stereoselective Synthesis of Enamino Ketones Through Aza-Michael/Hydrolysis Cascade

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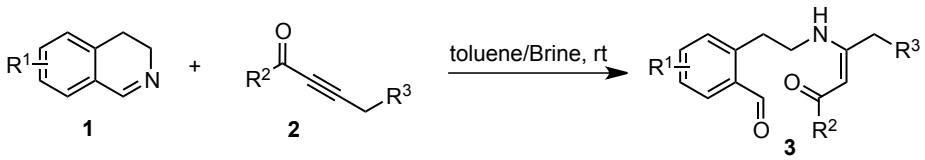
1. **General methods:**

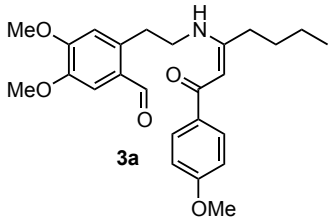
^{1}H NMR and ^{13}C NMR spectra were recorded at Bruker Avance 400. Chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants are given in Hz. ESI-MS analysis was performed using a Finnigan LCQ^{DECA} ion trap mass spectrometer.

All reagents and solvents were obtained from commercial sources and used without further purification. Toluene was distilled from CaH_2. Isoquinoline imines **1** and ynones **2** were prepared according to reported procedure.[1,2]

2. **General procedure for the synthesis of enamino ketones 3:**

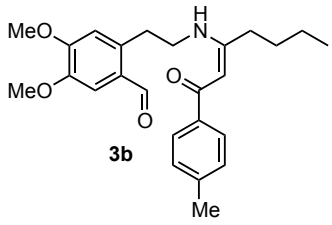


A mixture of isoquinoline imine **1** (0.2 mmol, 1.0 eq), ynone **2** (0.30 mmol, 1.5 eq), toluene (0.2 mL) and brine (0.5 mL) was stirred at room temperature (or stirred at 50 ^{o}C). On the consumption of isoquinoline imine **1** (monitored by TLC), the mixture was extracted by DCM (x 2). The combined organic layers was concentrated and purified directly by a silica gel flash chromatography (Hexane/EtOAc/Et_3N) affording compound **3 (***Enamino ketones **3** are unstable under acidic conditions***)**.



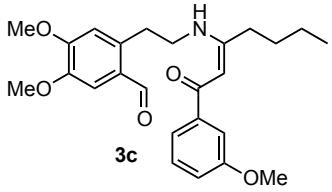
(*Z*)-4,5-imethoxy-2-(2-((1-(4-methoxyphenyl)-1-oxohept-2-en-3-yl)amino)ethyl)benzaldehyde (3a). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 68.1 mg; 80% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62

(brs, 1H), 10.09 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.31 (s, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 5.57 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.60 (q, J = 6.4 Hz, 2H), 3.30 (t, J = 6.4 Hz, 2H), 2.14-2.10 (m, 2H), 1.45-1.39 (m, 2H), 1.36-1.28 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 187.1, 168.3, 161.6, 153.6, 148.1, 135.8, 133.3, 128.6, 126.7, 114.8, 114.5, 113.4, 90.6, 56.2, 56.1, 55.3, 44.4, 33.6, 32.0, 30.2, 22.6, 13.8; ESI-HRMS: calcd. for $C_{25}H_{32}NO_5^+$ $(M+H)^+$ 426.2275, found 426.2275.



3b

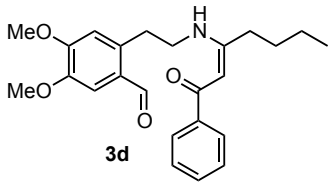
(*Z*)-4,5-Dimethoxy-2-(2-((1-oxo-1-(*p*-tolyl)hept-2-en-3-yl)amino)ethyl)benzaldehyde (3b). At 50 ^{o}C for 10 h; Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 67.6 mg; 83% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (brs, 1H), 10.09 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.31 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.86 (s, 1H), 5.59 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.60 (q, J = 6.4 Hz, 2H), 3.31 (t, J = 6.4 Hz, 2H), 2.37 (s, 3H), 2.12 (t, J = 8.0 Hz, 2H), 1.45-1.39 (m, 2H), 1.36-1.25 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 187.7, 168.6, 153.6, 148.1, 140.7, 137.9, 135.8, 128.8, 126.8, 126.7, 114.9, 114.6, 91.0, 56.2, 56.1, 44.4, 33.6, 32.0, 30.1, 22.5, 21.4, 13.7; ESI-HRMS: calcd. for $C_{25}H_{32}NO_4^+$ $(M+H)^+$ 410.2326, found 410.2326.



3c

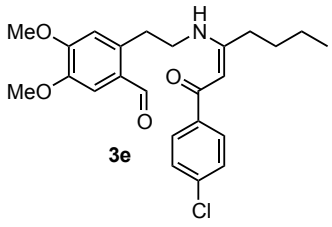
(*Z*)-4,5-Dimethoxy-2-(2-((1-(3-methoxyphenyl)-1-oxohept-2-en-3-yl)amino)ethyl) benzaldehyde (3c). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 68.9 mg; 81% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ

11.71 (brs, 1H), 10.09 (s, 1H), 7.41-7.29 (m, 5H), 6.98-6.96 (m, 1H), 6.86 (s, 1H), 5.60 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.85 (s, 3H), 3.62 (q, J = 6.4 Hz, 2H), 3.32 (t, J = 6.4 Hz, 2H), 2.14 (t, J = 8.0 Hz, 2H), 1.46-1.40 (m, 2H), 1.36-1.31 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 187.4, 169.1, 159.7, 153.5, 148.1, 142.1, 135.7, 129.1, 126.7, 119.3, 116.6, 114.8, 114.7, 111.7, 91.3, 56.2, 56.1, 55.3, 44.5, 33.6, 31.9, 30.1, 22.6, 13.8; ESI-HRMS: calcd. for $C_{25}H_{32}NO_5^+$ $(M+H)^+$ 426.2275, found 426.2275.



3d

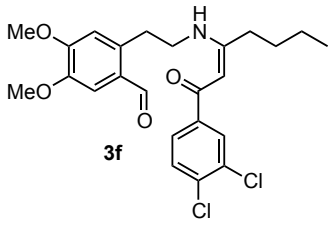
(*Z*)-4,5-Dimethoxy-2-(2-((1-oxo-1-phenylhept-2-en-3-yl)amino)ethyl)benzaldehyde (3d). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 55.9 mg; 71% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.71 (brs, 1H), 10.09 (s, 1H), 7.82 (dd, J = 8.0, 1.6 Hz, 2H), 7.41-7.37 (m, 3H), 7.32 (s, 1H), 6.86 (s, 1H), 5.61 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.62 (q, J = 6.4 Hz, 2H), 3.32 (t, J = 6.4 Hz, 2H), 2.16-2.12 (m, 2H), 1.46-1.40 (m, 2H), 1.36-1.29 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 187.8, 169.0, 153.5, 148.1, 140.6, 135.7, 130.4, 128.1, 126.8, 126.7, 114.9, 114.6, 91.1, 56.3, 56.1, 44.4, 33.6, 31.9, 30.1, 22.6, 13.8; ESI-HRMS: calcd. for $C_{24}H_{30}NO_4^+$ $(M+H)^+$ 396.2169, found 396.2170.



3e

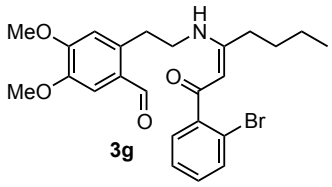
(*Z*)-2-(2-((1-(4-Chlorophenyl)-1-oxohept-2-en-3-yl)amino)ethyl)-4,5-dimethoxybenzaldehyde (3e). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 68.3 mg; 79% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (brs, 1H), 10.08 (s, 1H), 7.76-7.75 (m, 2H), 7.36-7.31 (m, 4H), 6.85 (s, 1H), 5.55 (s,

1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.62 (q, *J* = 6.4 Hz, 2H), 3.31 (t, *J* = 6.4 Hz, 2H), 2.14 (t, *J* = 8.0 Hz, 2H), 1.46-1.40 (m, 2H), 1.36-1.25 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 186.2, 169.4, 153.5, 148.1, 139.0, 136.5, 135.5, 128.9, 128.4, 128.2, 126.7, 114.8, 90.9, 56.2, 56.1, 44.5, 33.6, 32.0, 30.2, 22.6, 13.8; ESI-HRMS: calcd. for $C_{24}H_{29}ClNO_4^+$ $(M+H)^+$ 430.1780, found 430.1779.



3f

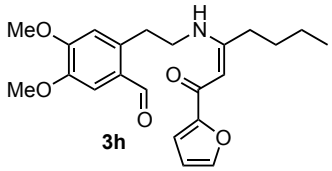
(*Z*)-2-(2-((1-(3,4-Dichlorophenyl)-1-oxohept-2-en-3-yl)amino)ethyl)-4,5-dimethoxybenzaldehyde (3f). At 50 °C for 11 h; Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 84.2 mg; 91% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (brs, 1H), 10.07 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 6.85 (s, 1H), 5.52 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.63 (q, *J* = 6.4 Hz, 2H), 3.32 (t, *J* = 6.4 Hz, 2H), 2.18-2.14 (m, 2H), 1.46-1.39 (m, 2H), 1.37-1.25 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 184.5, 169.9, 153.5, 148.1, 140.4, 135.3, 134.4, 132.5, 130.2, 128.9, 126.7, 126.0, 115.0, 114.8, 90.8, 56.2, 56.1, 44.5, 33.6, 32.0, 30.1, 22.6, 13.7; ESI-HRMS: calcd. for $C_{24}H_{28}Cl_2NO_4^+$ $(M+H)^+$ 464.1390, found 464.1389.



3g

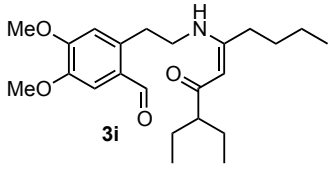
(*Z*)-2-(2-((1-(2-Bromophenyl)-1-oxohept-2-en-3-yl)amino)ethyl)-4,5-dimethoxybenzaldehyde (3g). At 50 °C for 18 h; Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 48.5 mg; 51% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (brs, 1H), 10.09 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.32-7.27 (m, 2H), 7.17 (td, *J* = 8.0, 1.6 Hz, 1H), 6.87 (s, 1H),

5.20 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.63 (q, J = 8.4 Hz, 2H), 3.34 (t, J = 6.4 Hz, 2H), 2.14-2.10 (m, 2H), 1.43-1.40 (m, 2H), 1.34-1.26 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 189.7, 169.2, 153.6, 148.1, 143.6, 135.6, 133.3, 129.8, 129.0, 127.1, 126.8, 119.5, 114.8, 95.0, 56.5, 56.1, 44.5, 33.5, 31.6, 29.9, 22.5, 13.8; ESI-HRMS: calcd. for $C_{24}H_{30}BrN_2O_4^+$ $(M+H)^+$ 489.1384, found 489.1383.



3h

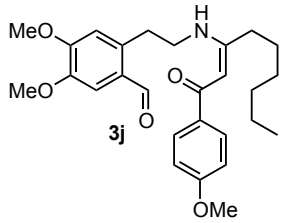
(*Z*)-2-(2-((1-(Furan-2-yl)-1-oxohept-2-en-3-yl)amino)ethyl)-4,5-dimethoxybenzaldehyde (3h). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 55.4 mg; 72% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (brs, 1H), 10.08 (s, 1H), 7.45 (s, 1H), 7.31 (s, 1H), 6.94 (d, J = 3.2 Hz, 1H), 6.84 (s, 1H), 6.45 (dd, J = 3.2, 1.6 Hz, 1H), 5.52 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.60 (q, J = 6.4 Hz, 2H), 3.30 (t, J = 6.4 Hz, 2H), 2.13-2.09 (m, 2H), 1.45-1.39 (m, 2H), 1.38-1.28 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 177.3, 169.3, 154.7, 153.6, 148.1, 143.7, 135.6, 126.7, 114.8, 114.7, 111.9, 111.7, 90.6, 56.3, 56.1, 44.5, 33.6, 31.8, 30.1, 22.6, 13.8; ESI-HRMS: calcd. for $C_{22}H_{28}NO_5^+$ $(M+H)^+$ 386.1962, found 386.1962.



3i

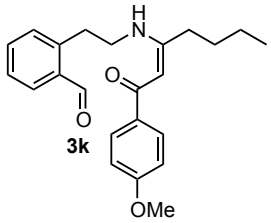
(*Z*)-2-(2-((8-Ethyl-7-oxodec-5-en-5-yl)amino)ethyl)-4,5-dimethoxybenzaldehyde (3i). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 60.9 mg; 78% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (brs, 1H), 10.07 (s, 1H), 7.30 (s, 1H), 6.81 (s, 1H), 4.88 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.50 (q, J = 6.4 Hz, 2H), 3.24 (t, J = 6.4 Hz, 2H), 2.03-1.99 (m, 2H), 1.98-1.94 (m, 1H), 1.56-1.39 (m, 2H), 1.38-1.25 (m, 6H), 0.88-0.81 (m, 9H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 201.2, 190.3, 166.8, 153.6, 148.0, 136.0, 126.7, 114.6, 114.2, 94.6, 56.3, 56.1, 54.9, 44.3, 33.4, 31.5, 30.0, 25.9, 22.4, 13.7, 12.2; ESI-HRMS: calcd. for $C_{23}H_{36}NO_4^+$ $(M+H)^+$ 390.2639, found 390.2639.



3j

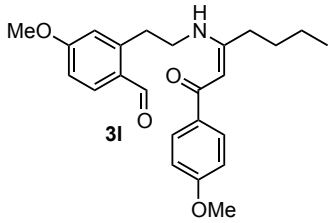
(*Z*)-4,5-Dimethoxy-2-(2-((1-(4-methoxyphenyl)-1-oxonon-2-en-3-yl)amino)ethyl)benzaldehyde (3j). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 38.6 mg; 43% yield; colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (brs, 1H), 10.09 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.32 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.85 (s, 1H), 5.57 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.60 (q, *J* = 6.4 Hz, 2H), 3.30 (t, *J* = 6.4 Hz, 2H), 2.13-2.09 (m, 2H), 1.44-1.42 (m, 2H), 1.32-1.25 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 187.1, 168.4, 161.6, 153.6, 148.1, 135.8, 133.3, 128.6, 126.7, 114.8, 114.4, 113.4, 90.6, 56.2, 56.1, 55.3, 44.4, 33.6, 32.3, 31.5, 29.1, 28.1, 22.5, 14.0; ESI-HRMS: calcd. for $C_{27}H_{36}NO_5^+$ $(M+H)^+$ 454.2588, found 454.2587.



3k

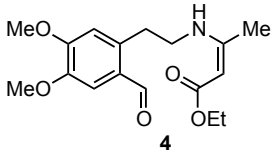
(*Z*)-2-(2-((1-(4-Methoxyphenyl)-1-oxohept-2-en-3-yl)amino)ethyl)benzaldehyde (3k). At 50 ^{o}C for 27 h; Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 44.2 mg; 60% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (brs, 1H), 10.16 (s, 1H), 7.85-7.31 (m, 3H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.59 (s, 1H), 3.84 (s, 3H), 3.58 (q, *J* = 6.4 Hz, 2H), 3.35 (t, *J* = 6.8 Hz, 2H), 2.22 (t, *J* = 8.0 Hz, 2H), 1.52-1.45 (m, 2H), 1.42-1.25 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 193.0, 187.2, 168.3, 161.5, 140.5, 134.6, 134.1, 133.9, 133.4, 132.3, 128.7, 127.5, 113.4, 90.7, 55.3, 44.0, 34.7, 32.0, 30.3, 22.6, 13.8; ESI-HRMS: calcd. for $C_{23}H_{28}NO_3^+$ $(M+H)^+$ 366.2064, found 366.2066.



3l

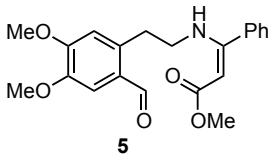
(*Z*)-4-Methoxy-2-(2-((1-(4-methoxyphenyl)-1-oxohept-2-en-3-yl)amino)ethyl)benz aldehyde (3l). Purified by flash column chromatography (Hexane/EtOAc/Et_3N = 70/30/1); 38.7 mg; 49% yield; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 11.57 (brs, 1H), 10.01 (s, 1H), 7.84-7.82 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 6.94-6.86 (m, 4H), 5.59 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.60 (q, *J* = 6.8 Hz, 2H), 3.34 (t, *J* = 6.8 Hz, 2H), 2.22-2.18 (m, 2H), 1.49-1.45 (m, 2H), 1.39-1.33 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 187.0, 168.5, 163.7, 161.5, 143.2, 137.4, 133.4, 128.6, 127.5, 117.3, 113.3, 113.2, 90.6, 55.6, 55.3, 43.8, 35.0, 32.0, 30.3, 22.6, 13.8; ESI-HRMS: calcd. for $C_{24}H_{30}NO_4^+$ $(M+H)^+$ 396.2169, found 396.2170.



4

(*Z*)-Ethyl 3-((2-formyl-4,5-dimethoxyphenethyl)amino)but-2-enoate (4). A mixture of isoquinoline imine **1** (0.2 mmol, 1.0 eq, 38.2 mg), methyl but-2-ynoate (1.0 mmol, 5.0 eq, 116.6 μL), Tol (0.2 mL) and brine (0.5 mL) was stirred at room temperature for 6 days (monitored by TLC), the mixture was extracted by DCM (x 2). The combined organic layers was concentrated and purified directly by a silica gel flash chromatography (Hexane/EtOAc/Et_3N = 70/30/1) affording compound **4** as pale yellow gum (25.4 mg, 41% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.71 (brs, 1H), 7.32 (s, 1H), 6.75 (s, 1H), 4.40 (s, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.48 (q, *J* = 6.4 Hz, 2H), 3.21 (t, *J* = 6.4 Hz, 2H), 1.76 (s, 3H), 1.23

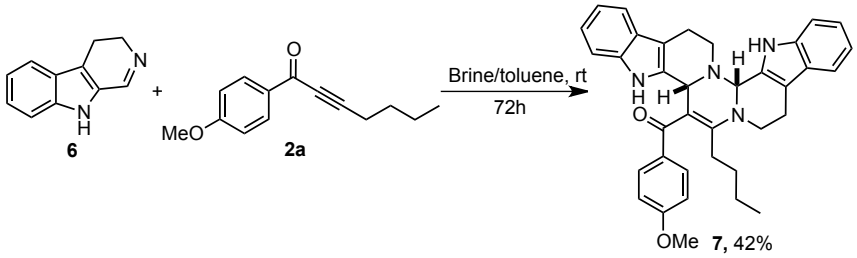
(t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 170.6, 161.6, 153.6, 148.1, 136.0, 126.8, 114.4, 114.0, 82.6, 58.3, 56.1, 56.1, 44.6, 33.7, 19.1, 14.6; ESI-HRMS: calcd. for $C_{17}H_{24}NO_5^+$ $(M+H)^+$ 322.1649, found 322.1650.



5

(*Z*)-Methyl 3-((2-formyl-4,5-dimethoxyphenethyl)amino)-3-phenylacrylate (5). A mixture of isoquinoline imine **1** (0.2 mmol, 1.0 eq, 38.2 mg), methyl 3-phenylpropiolate (0.30 mmol, 1.5 eq, 48.1 mg), Tol (0.2 mL) and brine (0.5 mL) was stirred at 50 ^{o}C for 27 h. Then the mixture was extracted by DCM (x 2). The combined organic layers was concentrated and purified directly by a silica gel flash chromatography (Hexane/EtOAc/Et_3N = 70/30/1) affording compound **5** as white foam solid (29.1 mg, 39% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.65 (brs, 1H), 7.37-7.28 (m, 4H), 7.13 (d, J = 6.8 Hz, 2H), 6.59 (s, 1H), 4.56 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.67 (s, 3H), 3.37 (q, J = 6.8 Hz, 2H), 3.08 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 170.6, 164.8, 153.6, 148.0, 136.2, 135.7, 129.3, 128.3, 127.8, 127.0, 114.0, 112.8, 85.5, 56.1, 56.0, 50.2, 46.1, 33.9; ESI-HRMS: calcd. for $C_{21}H_{24}NO_5^+$ $(M+H)^+$ 370.1649, found 370.1649.

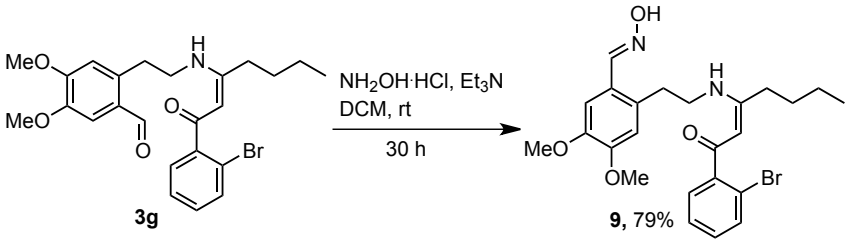
3. **Synthesis of compound 7:**



A mixture of 3,4-dihydro-β-carboline imine **6** (0.2 mmol, 1.0 eq, 34.0 mg), ynone **2a** (0.3 mmol, 1.5 eq, 64.9 mg), toluene (0.2 mL) and brine (0.5 mL) was stirred at room temperature for 72 h. Then the mixture was extracted by DCM (x 2). The combined organic layers was concentrated and purified directly by a silica gel flash

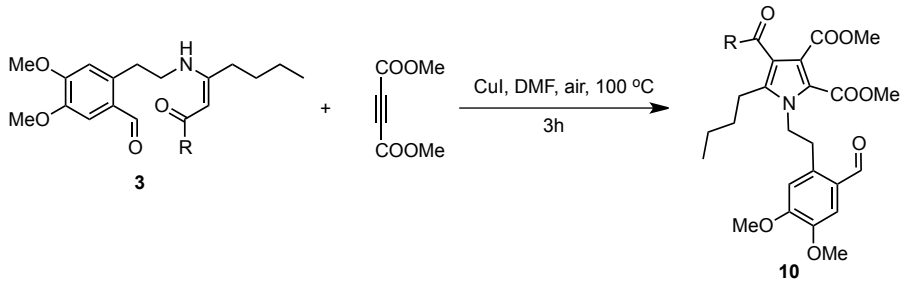
chromatography (Hexane/EtOAc/Et_3N = 70/30/1) affording compound **7** as yellow solid (23.4 mg, 42% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.50 (s, 1H), 7.60-7.56 (m, 3H), 7.43-7.40 (m, 2H), 7.25-7.22 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 2H), 7.06-7.03 (m, 1H), 7.01-6.97 (m, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.81 (s, 1H), 5.72 (s, 1H), 3.84-3.80 (m, 1H), 3.79 (s, 3H), 3.44-3.38 (m, 1H), 3.14 (td, *J* = 7.2, 4.0 Hz, 1H), 3.01-2.95 (m, 1H), 2.89-2.83 (m, 2H), 2.81-2.77 (m, 1H), 2.71 (dd, *J* = 15.2, 3.6 Hz, 1H), 2.17 (t, *J* = 8.0 Hz, 2H), 1.41-1.29 (m, 2H), 1.08-0.88 (m, 2H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 162.6, 152.5, 136.4, 136.0, 135.5, 133.6, 130.6, 130.4, 126.6, 126.2, 122.5, 121.2, 119.8, 118.7, 118.4, 118.0, 113.7, 112.0, 111.4, 111.1, 110.6, 108.8, 72.8, 56.3, 55.4, 44.3, 40.3, 30.9, 30.5, 22.5, 22.1, 21.9, 13.5; ESI-HRMS: calcd. for $C_{36}H_{37}N_4O_2^+$ $(M+H)^+$ 557.2911, found 557.2911.

4. **Synthesis of compound 9:**

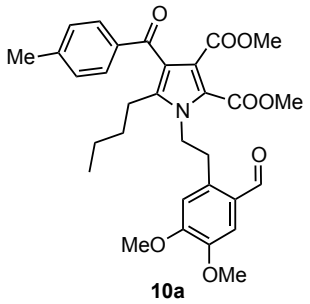


To a solution of compound **3g** (0.11 mmol, 1.0 eq, 52.7 mg), NEt_3 (0.22 mmol, 2.0 eq, 32.0 μL) and DCM (1 mL) was added hydroxylamine hydrochloride (0.22 mmol, 2.0 eq, 16.0 mg) and the resulting suspention was stirred at room temperature for 30 h. Then the mixture was purified directly by a silica gel flash chromatography (Hexane/EtOAc = 7/3) affording compound **9** as pale yellow amorphous solid (44.6 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (brs, 1H), 8.29 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.17 (td, *J* = 7.6, 1.6 Hz, 1H), 7.09 (s, 1H), 6.75 (s, 1H), 5.21 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.53 (q, *J* = 6.8 Hz, 2H), 3.11 (t, *J* = 6.8 Hz, 2H), 2.13 (t, *J* = 7.6 Hz, 2H), 1.47-1.43 (m, 2H), 1.37-1.31 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 169.0, 150.0, 148.7, 147.9, 143.6, 133.3, 130.8, 129.8, 129.0, 127.1, 122.6, 119.5, 114.0, 111.1, 95.0, 56.1, 56.0, 44.5, 34.5, 31.8, 29.9, 22.6, 13.8; ESI-HRMS: calcd. for $C_{24}H_{30}BrN_2O_4^+$ $(M+H)^+$ 489.1384, found 489.1383.

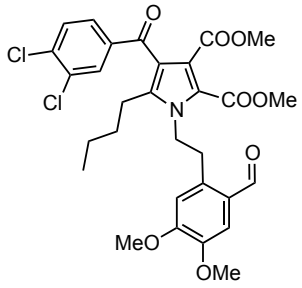
5. **General procedure for the synthesis of fully substituted pyrrole.**



To a solution of compound **3** (1.0 eq) in DMF (0.2 M) was added dimethyl acetylenedicarboxylate (1.2 eq) and CuI (0.1 eq) and the resulting mixture was stirred at 120 ^{o}C for 3 h under air. Then the mixture was cooled to room temperature, diluted with DCM, washed with water (x 2) and concentrated. The residue was purified directly by a silica gel flash chromatography (Hexane/EtOAc) affording fully substituted pyrroles **10**.

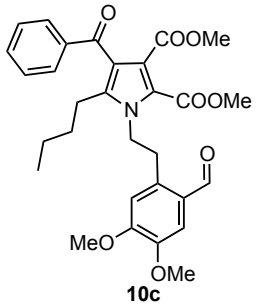


Dimethyl 5-butyl-1-(2-formyl-4,5-dimethoxyphenethyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2,3-dicarboxylate (10a). Performed at 0.154 mmol scale; Purified by flash column chromatography (Hexane/EtOAc = 3/1); 45.5 mg; 54% yield; pale yellow foam solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.30 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.62 (s, 1H), 4.52 (t, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.78 (s, 3H), 3.42 (t, *J* = 7.2 Hz, 2H), 3.33 (s, 3H), 2.56 (t, *J* = 8.0 Hz, 2H), 2.39 (s, 3H), 1.44-1.40 (m, 2H), 1.27-1.21 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 190.7, 165.2, 160.9, 153.6, 148.2, 143.0, 142.8, 136.7, 134.6, 129.0, 128.9, 127.3, 124.0, 121.0, 120.4, 114.4, 114.1, 56.2, 56.1, 51.9, 51.8, 46.3, 34.0, 32.2, 24.3, 22.5, 21.6, 13.6; ESI-HRMS: calcd. for $C_{31}H_{36}NO_8^+$ $(M+H)^+$ 550.2435, found 550.2435.



10b

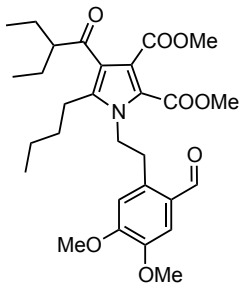
Dimethyl 5-butyl-4-(3,4-dichlorobenzoyl)-1-(2-formyl-4,5-dimethoxyphenethyl)-1*H*-pyrrole-2,3-dicarboxylate (10b). Performed at 0.160 mmol scale; Purified by flash column chromatography (Hexane/EtOAc = 4/1); 41.3 mg; 43% yield; pale yellow foam solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.51-7.48 (m, 2H), 7.30 (s, 1H), 6.68 (s, 1H), 4.52 (t, *J* = 7.2 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.80 (s, 3H), 3.45-3.39 (m, 5H), 2.62 (t, *J* = 8.0 Hz, 2H), 1.48-1.42 (m, 2H), 1.33-1.28 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 189.6, 165.1, 160.7, 153.7, 148.3, 144.0, 139.0, 136.7, 134.4, 132.7, 130.7, 130.4, 127.9, 127.3, 123.8, 120.8, 119.5, 114.7, 114.1, 56.2, 56.2, 52.1, 51.9, 46.4, 34.1, 32.2, 24.4, 22.6, 13.6; ESI-HRMS: calcd. for $C_{30}H_{32}Cl_2NO_8^+$ $(M+H)^+$ 604.1500, found 604.1499.



10c

Dimethyl 4-benzoyl-5-butyl-1-(2-formyl-4,5-dimethoxyphenethyl)-1H-pyrrole-2,3-dicarboxylate (10c). Performed at 0.10 mmol scale; Purified by flash column chromatography (Hexane/EtOAc = 7/3); 35.8 mg; 67% yield; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42-7.39 (m, 2H), 7.30 (s, 1H), 6.65 (s, 1H), 4.53 (t, *J* = 7.6 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.79 (s, 3H), 3.43 (t, *J* = 7.2 Hz, 2H), 3.31 (s, 3H), 2.59 (t, *J* = 7.6

Hz, 2H), 1.43-1.40 (m, 2H), 1.30-1.24 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 190.7, 165.2, 160.8, 153.7, 148.3, 143.3, 139.5, 134.6, 132.2, 128.8, 128.2, 127.3, 124.2, 120.7, 120.5, 114.5, 114.1, 56.2, 51.9, 51.7, 46.4, 34.0, 32.2, 24.3, 22.5, 13.6; ESI-HRMS: calcd. for $C_{30}H_{34}NO_8^+$ $(M+H)^+$ 536.2279, found 536.2278.



10d

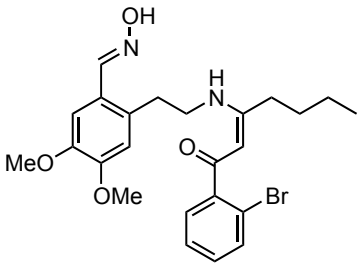
Dimethyl 5-butyl-4-(2-ethylbutanoyl)-1-(2-formyl-4,5-dimethoxyphenethyl)-1H-pyrrole-2,3-dicarboxylate (10d). Performed at 0.190 mmol scale; Purified by flash column chromatography (Hexane/EtOAc = 7/3); 27.6 mg; 27% yield; yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.29 (s, 1H), 6.63 (s, 1H), 4.51 (t, J = 7.2 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 6H), 3.83 (s, 3H), 3.38 (t, J = 7.2 Hz, 2H), 2.75-2.72 (m, 2H), 2.64-2.61 (m, 1H), 1.71-1.64 (m, 2H), 1.49-1.38 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H), 0.83 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 190.8, 167.5, 160.3, 153.6, 148.2, 144.7, 134.6, 127.3, 125.0, 120.6, 118.8, 114.5, 114.1, 56.2, 56.1, 52.6, 52.1, 51.9, 46.1, 33.9, 31.9, 25.0, 24.4, 22.9, 13.7, 11.6; ESI-HRMS: calcd. for $C_{29}H_{40}NO_8^+$ $(M+H)^+$ 530.2748, found 530.2749.

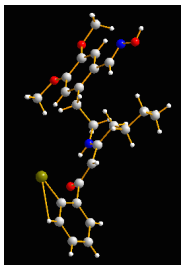
Reference:

1 M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2013, **135,** 1891.

2 (*a*) R. Shintani and T. Hayashi, *Org. Lett.,* 2005, **7,** 2071. (*b*) W. Li and X.-F. Wu, *Org. Biomol. Chem.,* 2015, **13,** 5090.

6. **Crystal data of Compound 9：**





Bond precision: C-C = 0.0037 A Wavelength=0.71073

Cell: a=7.8755(4) b=11.9538(6) c=13.5136(8)
alpha=66.584(3) beta=88.943(3) gamma=81.445(3)
Temperature: 296 K

	Calculated	Reported
Volume	1153.28(11)	1153.28(11)
Space group	P -1	P-1
Hall group	-P 1	?
Moiety formula	C24 H29 Br N2 O4	?
Sum formula	C24 H29 Br N2 O4	C24 H29 Br N2 O4
Mr	489.39	489.40
Dx,g cm-3	1.409	1.409
Z	2	2
Mu (mm-1)	1.815	1.815
F000	508.0	508.0
F000'	507.63	
h,k,lmax	10,15,17	10,15,17
Nref	5318	5292
Tmin,Tmax	0.639,0.721	0.760,0.810
Tmin'	0.596	

Correction method= # Reported T Limits: Tmin=0.760 Tmax=0.810
AbsCorr = MULTI-SCAN

Data completeness= 0.995 Theta(max)= 27.530

R(reflections)= 0.0424(3950) wR2(reflections)= 0.1439(5292)

S = 1.007 Npar= 287