Electronic Supplementary Information

An Autonomous Self-Optimizing Flow Machine for the Synthesis of Pyridine-Oxazoline (PyOX) ligands

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Table of Contents

1. General Information

All commercially available chemicals were used as received unless otherwise noted. High-field ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz, respectively. ^{1}H and ^{13}C NMR spectra were referenced to the internal deuterated solvent ($CDCl_3$) at 7.26 and 77.16 ppm, respectively. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance (ν_{max}) are quoted in wave numbers (cm^{-1}). High resolution mass spectrometry (HRMS) was recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates and visualized with a UV lamp at 254 nm or stained with a basic potassium permanganate solution. Flash column chromatography was performed using silica gel 60 (40−63 μm).

2. Details of the experimental setup

HPLC pumps (JASCO PU2080 and JASCO PU4185) equipped with a RS-232 port were employed to flow the solution through the system. A sampler handler (JASCO AS 2055) equipped with a RS-232 port was used to inject reagent in the line. The reactor coil was heated with a heating plate (Heidolph, MR Hei-Connect) equipped with a RS-232 port. A 2-way 6-port valve (VICI, Cheminert C2-3006D) equipped with a RS-232 port was used to inject an aliquot of the crude mixture within the on-line HPLC unit. The HPLC column outlet was connected to a UV detector (JASCO, UV 2075) equipped with a RS-232 port. The flow outlet was connected to a programmable fraction collector (Advantec, CHF 1225C). All units equipped with a RS-232 port were autonomously controlled with MATLAB® through the use of communication protocols provided by the manufacturers.

3. Optimization studies for the synthesis of methyl picolinimidate 2a

The experimental setup consisted in two streams as depicted in Fig. 2. In the first stream, an automatic sample handler injected 750 μL of a solution of 2-cyanopyridine **1a** (0.5 M in MeOH) and 1,2,4-trimethoxybenzene **5** (0.5 M in MeOH) in a stream of MeOH pumped at the required flow rate. The second stream continuously pumped a solution of sodium methoxide (0.05 M) in MeOH at the required flow rate. Both streams merged in a stainless steel T-shaped piece (internal volume: 0.57 μL) and the resulting mixture was introduced in a PEEK reactor coil (10

mL, 0.75 mm id) heated at the desired temperature. The reactor outlet was connected to an automatic 6-port switch valve which inject 0.2 µL of the crude mixture in the HPLC unit while the remaining stream was collected in a fraction collector. A mixture of MeOH/H_2O (45/55, v/v) was used as mobile phase for the HPLC analysis at a flowrate of 0.4 mL/min. A UV detector was connected to the outlet of the HPLC column (Agela Promosil C18, 3.5 mm*150 mm, 5 µm) to follow the absorbance at a wavelength of 274 nm. Peak integration and yield calculation were under full MATLAB automation. The calculated yield was automatically sent to the algorithm which sets new experimental conditions to the units via RS-232 ports. A 3-D optimization of the reaction yield was conducted using the temperature, residence time and stoichiometry as the variables. The initial experiment of the simplex was: 27 °C, 15 min and 0.1 equiv. of MeONa. The *d* value was 10 °C, 15 min and 0.05 equiv. The lower and upper boundaries of the research space were the following: 27-60 °C, 10-120 min and 0.05-0.2 equiv. for the temperature, residence time and stoichiometry, respectively. An optimum giving 82% HPLC yield was found in experiment 10 at 60 °C, 30 min of residence time and 0.1 equiv. of MeONa. Methyl picolinimidate **2a** was not purified and used directly in the next step.

Table S1. Maximization of the reaction yield of methyl picolinimdate 2a

Run	MeONa (equiv.)	Residence time (min)	Temperature (°C)	Yield (%)
1	0.10	15	27	10
2	0.15	15	27	14
3	0.10	30	27	21
4	0.10	15	37	22
5	0.13	25	34	30
6	0.15	30	37	46
7	0.08	35	40	49
8	0.05	45	47	67
9	0.10	30	54	80
10	**0.10**	**30**	**60**	**82**
11	0.10	55	59	84
12	0.10	57	60	85
13	0.07	47	60	84

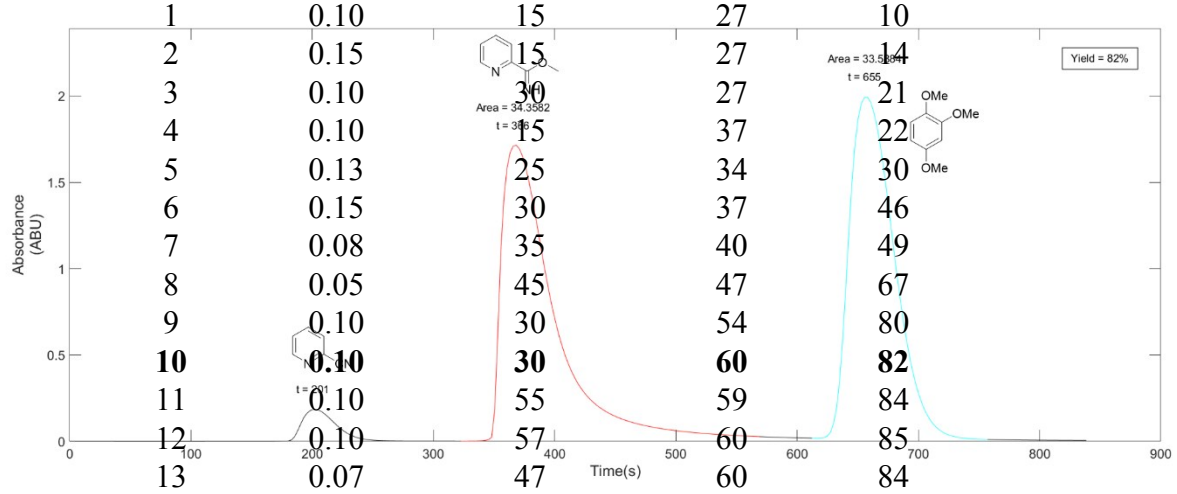

Fig. S1 HPLC chromatogram of the crude mixture of experiment 10.

4. Optimization studies for the synthesis of (*S*)-*i*-PrPyOX 4a

The experimental setup consisted in three streams as depicted in Fig. 4. In the first stream, a solution of (*S*)-valinol **3a** (1 M) and chlorobenzene **6** (5.5 M) in $C_2H_4Cl_2$ was continuously pumped at the required flow rate. In the second stream, a solution of $BF_3.Et_2O$ (0.04 M) in $C_2H_4Cl_2$ was continuously pumped at the required flow rate. In the third stream, a solution of methyl picolinimdate **2a** (1.2 M) in $C_2H_4Cl_2$ was continuously pumped at the required flow rate. All three lines merged in a stainless steel cross-shaped mixer (internal volume: 0.72 µL) and the resulting mixture was introduced in a PEEK reactor coil (5 mL, 0.75 mm id) heated at the desired temperature. The reactor outlet was connected to an automatic 6-port switch valve which inject 0.2 µL of the crude mixture in the HPLC unit while the remaining stream was collected in a fraction collector. A mixture of MeOH/H_2O (50/50, v/v) was used as mobile phase for the HPLC analysis at a flowrate of 0.9 mL/min. A UV detector was connected to the outlet of the HPLC column (Agela Promosil C18, 4.5 mm*150 mm, 5 µm) to follow the absorbance at a wavelength of 260 nm. Peak integration and yield calculation were under full MATLAB automation. The calculated yield was automatically sent to the algorithm which sets new experimental conditions to the units via RS-232 ports. A 4-D optimization of the reaction yield was conducted using the temperature, residence time loading of acid and equivalent of imidate **2a** as the input variables. The initial experiment of the simplex was: 35 °C, 10 min of residence time, 2 mol% of $BF_3.Et_2O$ and 1 equivalent of imidate **2a** with delta values of 15 °C, 25 min. The *d* value was 15 °C, 25 min, 2.5 mol% and 0.25 equivalent, respectively. The lower and upper boundaries of the research space were the following: 25-80 °C, 10-90 min, 1-10 mol% and 1-2 equiv. for the temperature, residence time, acid loading and equivalent of imidate **2a**, respectively. An optimum giving 101% HPLC yield was found in experiment 21 at 75 °C, 73 min of residence time, 1 mol% of $BF_3.Et_2O$ and 1.54 equivalents of imidate **2a**.

Table S2. Maximization of the reaction yield of *(S)*-*i*-PrPyOX 4a

Run	$BF_3.Et_2O$ (equiv.)	Imidate **2a** (equiv.)	Residence time (min)	Temperature (°C)	Yield (%)
1	0.020	1	10	35	0
2	0.045	1	10	35	1
3	0.020	1.25	10	35	1
4	0.020	1	35	35	2
5	0.020	1	10	50	3
6	0.032	1.12	23	43	6
7	0.039	1.19	29	46	14
8	0.010	1.19	29	46	5
9	0.023	1.00	35	50	18
10	0.026	1.19	16	61	22

11	0.028	1.25	10	70	17
12	0.029	1.28	45	52	23
13	0.034	1.42	62	53	40
14	0.051	1.21	42	59	49
15	0.072	1.22	49	65	69
16	0.039	1.23	52	69	65
17	0.062	1.53	54	74	91
18	0.070	1.66	59	80	85
19	0.075	1.50	90	69	91
20	0.080	1.33	61	80	91
21	**0.100**	**1.54**	**73**	**75**	**101**

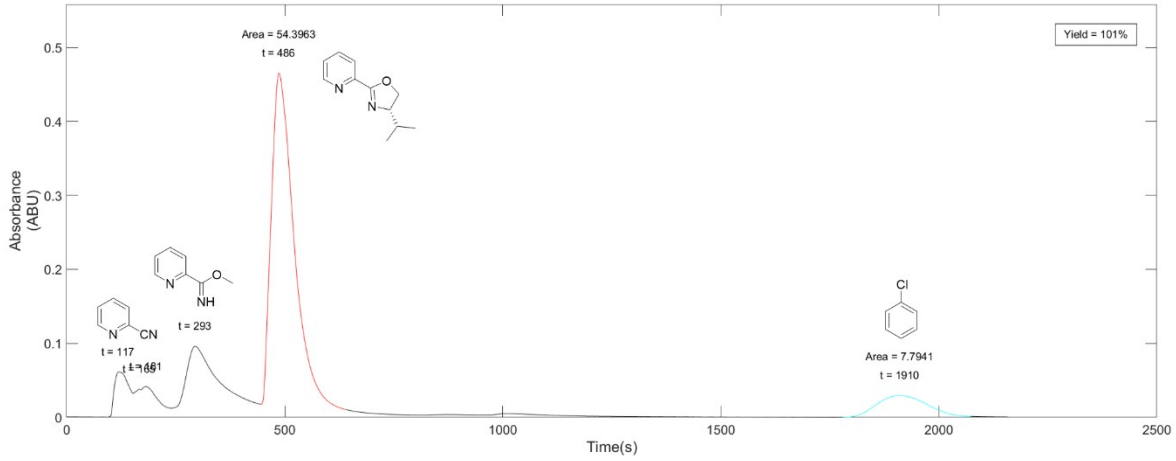

Fig. S2 HPLC chromatogram of the crude mixture of experiment 21.

5. Synthesis of imidates 2a-c

The experimental setup consisted in two streams as depicted in Fig. 6B. The first stream (flow rate: 0.167 mL/min), equipped with a PEEK injection loop (1 mL) loaded with a solution of cyanopyridine **1a-c** in MeOH (0.5 M), meet in a stainless steel T-shaped piece (internal volume 0.57 µL) a second stream (flow rate: 0.167 mL/min) consisting of a solution of MeONa in MeOH (0.05 M). The merged streams entered in a stainless steel reactor coil (10 mL, 0.75 mm id, 60 °C) at a flow rate of 0.334 mL/min and the resulting imidates **2a-c** were collected in vials containing AcOH (10 µL per mmol of imidate) to instantaneously quench the reaction. Volatiles were removed under reduced pressure and the crude imidates **2a-c** were dissolved in CH_2Cl_2, washed with brine and dried over anhydrous $MgSO_4$. The organic phase was concentrated under vacuum to give with imidates **2a-c** which were used for the next step without further purification.

Methyl picolinimidate ***2a.*** The process furnished a mixture of methyl picolinimidate **2a** and picolonitrile **1a** in a ratio of *ca*. 90/10 as the only detectable compounds on the crude ^{1}H NMR. IR (ATR) *v* 3289, 2947, 1650, 1577, 1434, 1361, 1186, 1081 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (broad s, 1H), 6.64 (dd, 1H, J = 1.2, 6.4 Hz), 7.75-7.86 (m, 2H) 7.34-7.39 (m, 1H), 4.01 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 149.3, 137.3, 125.5, 121.1, 54.1. HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_7H_9N_2O$ 137.0715; Found 137.0709.

Methyl 5-(trifluoromethyl)picolinimidate ***2b.*** The process furnished imidate **2b** as the only detectable compound on the crude ^{1}H NMR. IR (ATR) *v* 3417, 3299, 3153, 1701, 1653, 1605, 1573, 1323, 1165, 1121, 1076 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (broad s, 1H), 8.91 (broad s, 1H), 8.05 (dd, 1H, J = 1.5, 8.1 Hz), 7.97 (d, 1H, J = 8.1 Hz), 4.04 (s, 3H). HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_8H_8N_2OF_3$ 205.0589; Found 205.0596.

Methyl quinoline-2-carbimidate ***2c.*** The process furnished a mixture of methyl quinoline-2-carbimidate **2c** and quinoline-2-carbonitrile **1c** in a ratio of *ca*. 85/15 as the only detectable compounds on the crude. ^{1}H NMR. IR (ATR) *v* 3266, 2988, 2941, 1647, 1433, 1359, 1186, 1087 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, 1H, J = 8.7 Hz), 8.17 (d, 1H, J = 8.4 Hz), 7.97 (d, 1H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.7 Hz), 7.75-7.80 (m, 1H), 7.61 (dd, 1H, J = 6.9, 8.1 Hz), 4.13 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 54.1, 118.1, 127.6, 127.7, 128.7, 130.0, 130.1, 137.5, 147.4, 147.5, 167.0. HRMS (ESI) *m/z* $[M + H]^+$ Calcd for $C_{11}H_{11}N_2O$ 187.0871; Found 187.0868.

6. Synthesis of PyOX ligand 4a-f

The experimental setup consisted in two streams as depicted in Fig. 6C. The first stream (flow rate : 0.033 mL/min), equipped with a PEEK injection loop (0.5 mL) loaded with a solution of imidates **2a-c** (0.44 M) and amino alcohol **3a-d** (0.67 M) in $C_2H_4Cl_2$, meet in a stainless steel T-shaped piece (internal volume 0.57 µL) a second stream (flow rate: 0.036 mL/min) consisting of a solution of BF_3Et_2O in $C_2H_4Cl_2$ (0.04 M). The merged streams entered in a PEEK reactor coil (5 mL, 0.75 mm id, 75 °C) at a flow rate of 0.069 mL/min and the resulting PyOX ligand **4a-f** were collected in vials containing a saturated solution of $NaHCO_3$ to instantaneously quench the reaction. The organic layer was separated. The aqueous layer was extracted three times with EtOAc. The collected organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude PyOX ligands **2a-c** were purified

by flash chromatography (from 1% Et_3N – 15% EtOAc – 84% petroleum ether to 1% Et_3N – 30% EtOAc – 69% petroleum ether).

(S)-4-(iso-propyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole **4a**.[1] IR (ATR) *v* 2962, 2867, 1641, 1468, 1440, 1353, 1093, 963 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (dm, 1H, *J* = 4.8 Hz), 8.05 (dt, 1H, *J* = 1.0, 7.9 Hz), 7.75 (dt, 1H, *J* = 1.8, 7.8 Hz), 7.37 (ddd, 1H, *J* = 1.2, 4.8, 7.6 Hz), 4.48-4.52 (m, 1H), 4.13-4.23 (m, 2H), 1.88 (oct, 1H, *J* = 6.5 Hz), 1.05 (d, 3H, *J* = 6.7 Hz), 0.94 (d, 3H, *J* = 6.7 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 149.8, 147.1, 136.7, 125.5, 124.0, 73.1, 70.9, 32.9, 19.2, 18.3. $[\alpha]^{25}_D$ -70.1° (*c* 3.2, toluene). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{15}N_2O$ 191.1184; Found 191.1176.

(S)-4-(tert-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole **4b**.[2] IR (ATR) *v* 3059, 2959, 2870, 1641, 1468, 1441, 1360, 1095, 967 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (dm, 1H, *J* = 4.8 Hz), 8.05 (dm, 1H, *J* = 8.0 Hz), 7.75 (dt, 1H, *J* = 1.8, 7.8 Hz), 7.37 (ddd, 1H, *J* = 1.2, 4.8, 7.6 Hz), 4.44 (dd, 1H, *J* = 8.7, 10.2 Hz), 4.30 (t, 1H, *J* = 8.5 Hz), 4.11 (dd, 1H, *J* = 8.5, 10.2 Hz), 0.97 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 149.8, 147.2, 136.7, 125.5, 124.1, 76.7, 69.4, 34.1, 26.1. $[\alpha]^{25}_D$ -62.1° (*c* 2.4, $CHCl_3$). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{17}N_2O$ 205.1341; Found 205.1340.

(S)-4-(benzyl)-2-(5-trifluoromethylpyridin-2-yl)-4,5-dihydrooxazole **4c**.[3] IR (ATR) *v* 3084, 3034, 2925, 1647, 1603, 1574, 1325, 1121, 1094, 1072, 1011, 871 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (br s, 1H), 8.19 (d, 2H, *J* = 8.3 Hz), 8.03 (dd, 1H, *J* = 2.3, 8.1 Hz), 7.24-7.34 (m, 5H), 4.66-4.74 (m, 1H), 4.49 (dd, 1H, *J* = 8.7, 9.5 Hz), 4.26 (dd, 1H, *J* = 7.8, 8.6 Hz), 3.28 (dd, 1H, *J* = 5.3, 13.9 Hz), 2.79 (dd, 1H, *J* = 8.7, 13.9 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 150.0, 146.8 (q, *J* = 3.9 Hz), 137.6, 134.1 (q, *J* = 3.5 Hz), 129.4, 128.8, 128.2 (q, *J* = 33.4 Hz), 126.8, 123.8, 123.3 (q, *J* = 273.0 Hz), 72.9, 68.4, 41.6. $[\alpha]^{25}_D$ -29.8° (*c* 5.4, EtOH). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}N_2OF_3$ 307.1058; Found 307.1047.

(S)-4-(iso-propyl)-2-(5-trifluoromethylpyridin-2-yl)-4,5-dihydrooxazole **4d**.[3] IR (ATR) *v* 2967, 2892, 1639, 1603, 1576, 1399, 1328, 1121, 1094, 1075, 1013, 872 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.18 (d, 2H, *J* = 8.3 Hz), 8.01 (dd, 1H, *J* = 2.3, 8.4 Hz), 4.54 (dd, 1H, *J* = 8.1, 9.4 Hz), 4.24 (t, 1H, *J* = 8.4 Hz), 4.16-4.22 (m, 1H), 1.90 (oct, 1H, *J* = 6.7 Hz), 1.05 (d, 3H, *J* = 6.7 Hz), 0.95 (d, 3H, *J* = 6.7 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 150.2, 146.7 (q, *J* = 4.1 Hz), 134.0 (q, *J* = 3.6 Hz), 128.1 (q, *J* = 33.0 Hz), 123.8, 123.2 (q, *J* = 273.3 Hz),

73.3, 71.2, 32.9, 19.1, 18.3. $[\alpha]^{25}_{D}$ -41.3° (c 4.8, EtOH). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{14}N_2OF_3$ 259.1058; Found 259.1050.

(S)-4-(iso-propyl)-2-(quinolin-2-yl)-4,5-dihydrooxazole **4e**.[4] IR (ATR) *v* 2956, 1635, 1503, 1462, 1364, 1121, 1085, 971 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.23-8.29 (m, 1H), 8.21 (br s, 2H), 7.84 (dd, 1H, *J* = 0.8, 8.1 Hz), 7.74 (tm, 1H, *J* = 7.8 Hz), 7.59 (t, 1H, 7.5 Hz), 4.58 (dd, 1H, *J* = 8.3, 9.4 Hz), 4.30 (t, 1H, *J* = 8.3 Hz), 4.19-4.25 (m, 1H), 1.94 (oct, 1H, *J* = 6.7 Hz), 1.08 (d, 3H, *J* = 6.7 Hz), 0.97 (d, 3H, *J* = 6.7 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 147.7, 147.2, 136.8, 130.5, 130.1, 128.9, 128.0, 127.6, 121.0, 77.2, 71.1, 33.0, 19.2, 18.3. $[\alpha]^{25}_{D}$ -72.2° (c 4.3, $CHCl_3$). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O$ 241.1341; Found 241.1332.

(R)-4-(phenyl)-2-(quinolin-2-yl)-4,5-dihydrooxazole **4f**.[5] IR (ATR) *v* 3028, 2925, 1634, 1503, 1364, 1124, 1087, 970 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.31 (m, 3H), 7.86 (d, 1H, *J* = 8.5 Hz), 7.77 (tm, 1H, *J* = 7.4 Hz), 7.62 (tm, 1H, *J* = 7.1 Hz), 7.33-7.37 (m, 4H), 7.26-7.32 (m, 1H), 5.51 (dd, 1H, *J* = 8.5, 10.2 Hz), 4.97 (dd, 1H, *J* = 8.5, 10.2 Hz), 4.47 (t, 1H, *J* = 8.6 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 147.8, 146.9, 141.9, 136.9, 130.5, 130.2, 129.0, 129.0, 128.2, 127.9, 127.7, 127.0, 75.7, 70.6. $[\alpha]^{25}_{D}$ +73.5° (c 5.6, $CHCl_3$). HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{15}N_2O$ 275.1184; Found 275.1175.

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