Supplemental Material

Amino Acid–Catalyzed Marschalk Reaction and Its Application to an Integrated Continuous-Flow Synthetic Process

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1 General remarks

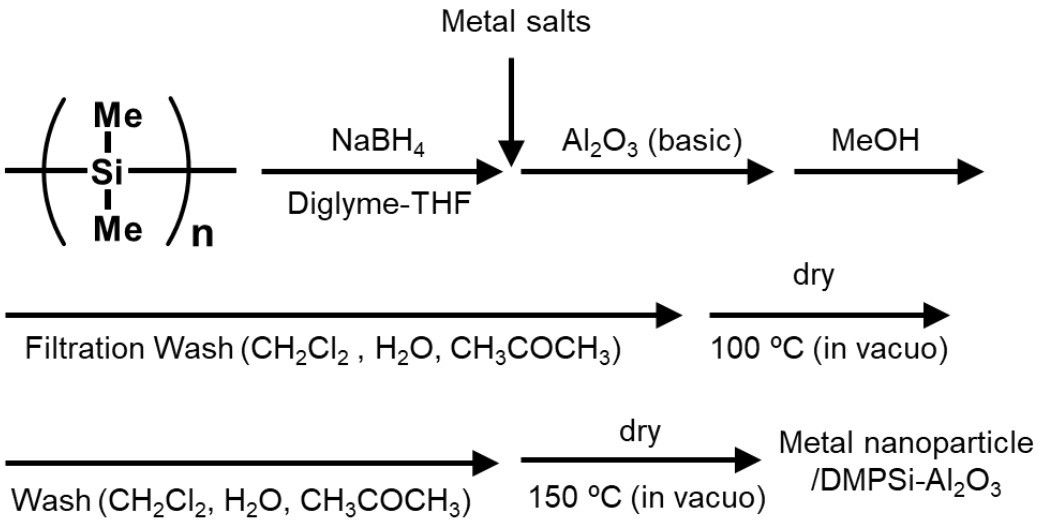
- Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} glass plates purchased from Merck KGaA. Isolation of some products was conducted with PLC Silica gel 60 F_{254}, 1 or 2 mm glass plates purchased from Merck KGaA. Column chromatography was conducted with Silica Gel 60 N (Spherical Neutral) purchased from Kanto Chemical co. inc.
- NMR spectra were recorded with Bruker Advance NEO 400 MHz spectrometer operating at 400 MHz (^{1}H) and 101 MHz (^{13}C) respectively. Chemical shifts were recorded in parts per million (ppm), from relative to internal references of the $CDCl_3$, defined at 7.24 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR) otherwise noted.
- Inductively coupled plasma-atomic emission spectrometry (ICP-AES) analysis was performed on Horiba ULTIMA2 equipment.
- Aqua regia for ICP sample preparation was made by mixing concentrated hydrochloric acid and concentrated nitric acid in a volume of 3:1.
- Energy-dispersive X-ray spectroscopy/Scanning transmission electron microscopes (STEM/EDS) images were obtained using a FEI JTECNAI OSIRIS instrument operated at 200 kV. All STEM specimens were prepared by placing a drop of the solution on carbon-coated copper grids and allowed to dry in air (without staining).
- High Resolution Mass Spectra (HRMS) were recorded using a JEOL JMS-700 (EI) spectrometer. PFK（Perfluorokerosene）was used as a standard.
- FT-IR (ATR) was recorded using a Shimadzu IRSpirit Fourier transform infrared spectrophotometer.
- $NaBH_4$ was purchased from Fujifilm Wako Pure Chemical Industries and it was stored and handled in a glove box.
- Organic reagents were used as purchased, or purified by distillation or

recrystalization following the normal procedures if it is needed.

- Solvents were purchased from Fujifilm Wako Pure Chemical Industries.
- $Na_2PtCl_6 \cdot 6H_2O$ was purchased from Aldrich. $NiCl_2 \cdot 6H_2O$ was purchased from Fujifilm Wako Pure Chemical Industries
- Polisilane (DMPSi) was purchased from NIPPON SODA CO. LTD, and basic Al_2O_3 was purchased from Merck. Pt-Ni/DMPSi-Al_2O_3 were prepared, following a method described in the literature. [1)]

2 Preparation of catalysts

2.1 M/DMPSi-Al_2O_3



Scheme S1. Preparation of DMPSi-Al_2O_3 catalyst

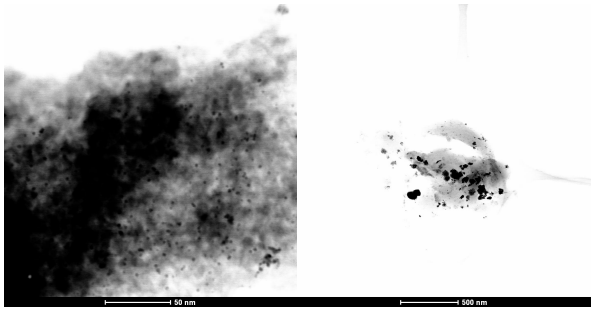
2.1.1 **A procedure for the preparation of Pt-Ni/DMPSi-Al_2O_3 :**

To a suspension of polydimethylsilane (0.501 g) in THF (8 ml) was added $NaBH_4$ (163.4 mg) dissolved in diglyme (6 ml) at room temperature. $Na_2PtCl_6{\cdot}6H_2O$ (134.4 mg) and $NiCl_2{\cdot}6H_2O$ (59.0 mg) dissolved in THF (4 ml) was added dropwise to the solution at room temperature, and the total reaction mixture was stirred at room temperature for 3 h. Then, basic alumina (2.50 g) was added to the mixture, which was then stirred at room temperature for 24 h. MeOH (400 ml) was added slowly to induce coacervation, and the mixture was stirred at room temperature overnight. The resulting solid was collected by filtration and subsequently washed with a large excess of water until no brown solution came out from the filtrate. Afterward, it was washed with 200 ml of acetone, and the catalyst was kept wet with acetone to prevent the catalyst from burning. The collected solid was then dried in a vacuum at 100 ºC for 3 h. Subsequently, the solid was heated to 150 ºC under vacuum for 5 h. The solid was cooled under an

argon atmosphere, after which the solid was washed with acetone (100 mL), water (100 ml), and CH_2Cl_2 (50 ml) then dried *in vacuo* at 150 ºC to afford the Pt-Ni/DMPSi-Al_2O_3 (2.7 g, Pt: 0.012 mmol/g Ni: 0.047 mmol/g).

2.1.2 **STEM analysis of Pt-Ni/DMPSi-Al_2O_3**

Bright field images:



Dark field images:

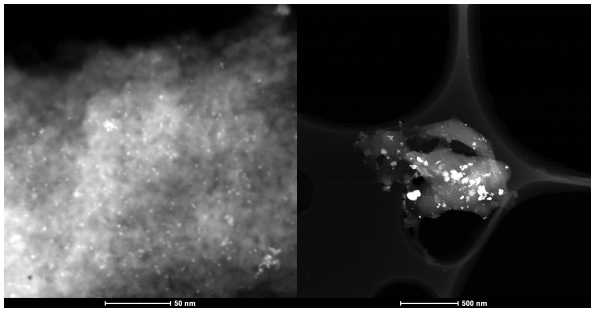
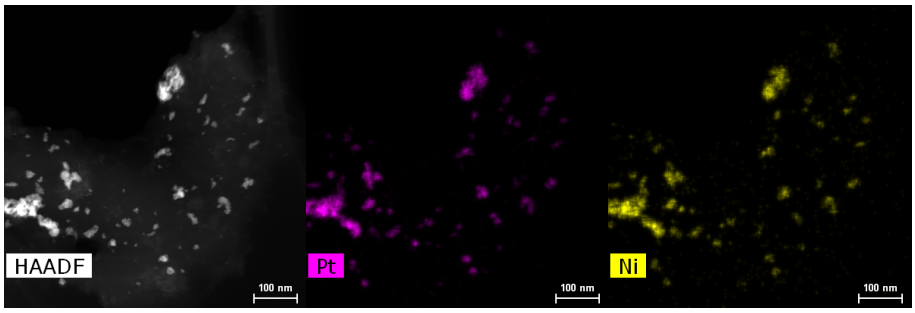


Figure S 1. STEM images of Pt-Ni/DMPSi-Al_2O_3

2.1.3 **EDS mapping of Pt-Ni/DMPSi-Al_2O_3 :**



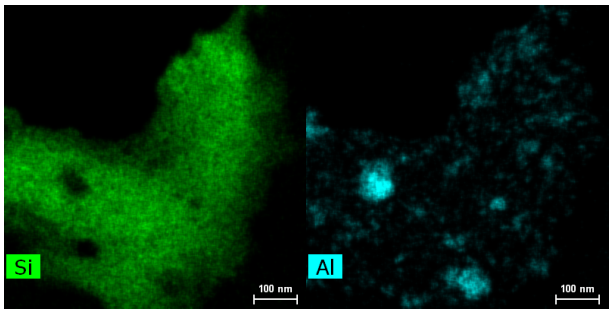


Figure S 2. STEM-EDS mapping of Pt-Ni/DMPSi-Al_2O_3

2.1.4 **Procedure to determine catalyst loading using ICP**

Approximately 2-5 mg of catalyst was measured (with the amount measured being recorded) and placed in a test tube to which 1 mL of sulfuric acid was then added. The test tube was heated to 180 ºC, and nitric acid was added dropwise until all solids had dissolved and no more brown fumes were observed. The mixture was cooled to room temperature and aqua regia (1 mL) was added slowly. The mixture was then treated by sonication until black precipitates were completely dissolved. The resulting mixture was brought up to a final volume of 50 mL with water in a volumetric flask, and the resulting solution was subjected to ICP analysis.

3 Marschalk reaction in batch system

3.1 Reaction apparatus for catalyst screening

Batch reactions were conducted using EYELA PPS-1511 system (*ChemiStation*™) with EYELA PPS-15TC test tube (ϕ15X150 mm) equipped with PTFE cap connected to argon balloon (1 atm).

3.2 Typical procedure of Marschalk reaction and determination of yield by ^{1}H NMR analysis

Piperidine−3−carboxylic acid (**3g**) (2.1 mg), anisaldehyde (**4a**) (337.6 mg) and leuco−quinizarin (**2**) (200.6 mg) were combined in a test tube. 1-Methoxy-2-propanol (4.0 mL) was introduced into the test tube with stirring bar, which was equipped with a three-way cock. The atmosphere of the flask was exchanged to atmospheric Ar using a vacuum pump and a plastic balloon filled with Ar. The reaction mixture was stirred for 3 h at 110 ºC.

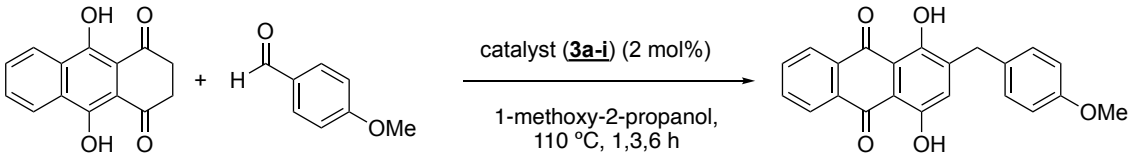
After the reaction mixture were returned to room temperature, dichloromethane (4 mL) and 1,3,5-trimethoxybenzen (38.6 mg) as an internal standard were added to the mixture. Aliquot of the mixture was diluted with $CDCl_3$ (0.5 mL), and the mixture was analyzed by ^{1}H NMR. The yield was calculated by comparing the integration of 2-(4-methoxybenzyl)quinizarin （δ 7.20 − 7.16ppm (m, 2H)) and leuco-quinizarin （δ 8.45 − 8.49ppm (m, 2H)） to that of 1,3,5-trimethoxybenzen (δ 6.09ppm (s, 3H)).

3.3 Representative procedure for observation of reaction profile of Marschalk reaction catalyzed by 3g and determination of yield by ^{1}H NMR analysis

Piperidine−3−carboxylic acid (**3g**) (2.07 mg), anisaldehyde (**4a**) (337.3 mg), leuco−quinizarin (**2**) (200.4 mg) and 1,3,5−trimethoxy benzene (38.7 mg) were combined in a test tube. 1-Methoxy-2-propanol (8.0 mL) was introduced into the test tube with stirring bar, which was equipped with a three-way cock. The atmosphere of the flask was exchanged to atmospheric Ar using a vacuum pump and a plastic balloon filled with Ar. The reaction mixture was stirred for 6 h at 110 ºC.

Aliquot of the mixture was picked up before solidified compounds appeared, and it was diluted with $CDCl_3$ (0.5 mL), and the mixture was analyzed by ^1H NMR. The yield was calculated by comparing the integration of 2-(4-methoxybenzyl)quinizarin （δ 7.20 − 7.16ppm (m, 2H)）and leuco-quinizarin（δ 8.45 − 8.49ppm (m, 2H)）to that of 1,3,5-trimethoxybenzen (δ 6.09ppm (s, 3H)）.

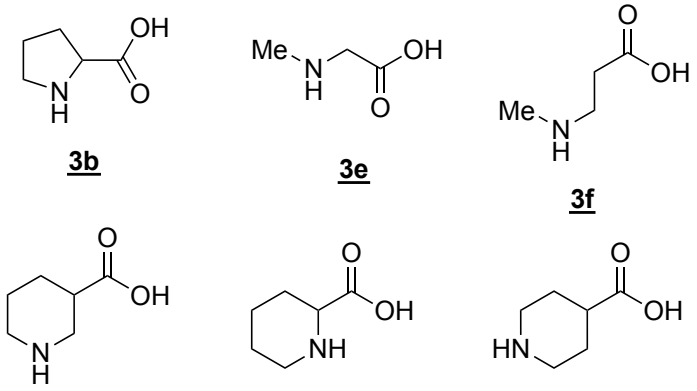
Table S1. Comparison of the Marschalk reaction using amino acids as catalysts at different time points



2 (0.21 M) **4a** (3 equiv.) **1a**

Entry	Catalyst	Yield **1a** (%)[a] at 1 h	Yield **1a** (%)[a] at 3 h	Yield **1a** (%)[a] at 6 h
1	**3b**	5	8	16
2	**3e**	23	38	67
3	**3f**	54	57	99
4	**3g**	51	84	99
5	**3h**	8	11	19
6	**3i**	19	34	79
7[b]	**3g**	21	40	69

[a)] Yield was determined by ^{1}H NMR analysis using trimethoxybenzene as an internal standard. [b)] 1 mol% of **3g** was used.



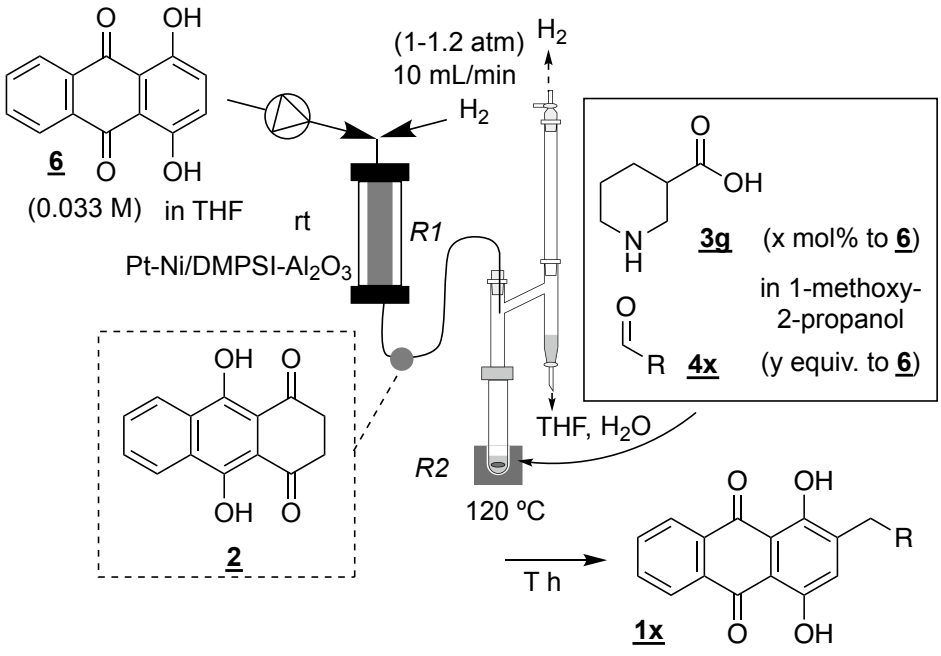
3b **3e** **3f**

3g **3h** **3i**

4 Integrated reactions using Flow-Batch-Separator (FBS) unified reactors

4.1 Direct derivatization of quinizarin to substituted quinizarin

4.1.1 FBS unified reactor system



Scheme S2. FBS unified reactor systems of direct derivatization of quinizarin

The FBS unified reactor systems consisted of a pump units (Minatoconcept MCRP204 peristaltic pump), a column flow reactor (EYELA MCR-1000 (*SynpleFlow*™)), a mass flow controller (EYELA MFC-11GU), a batch reactor with a block heater (EYELA PPS-1511 system (*ChemiStation*™) with an EYELA PPS-25TC test tube (ϕ25X150 mm) equipped with a PTFE cap), and a Dean–Stark apparatus with an air-cooled tube for condensation connected to a Schlenk line. Hydrogen gas was supplied from a PEAK Precision Hydrogen SL200 hydrogen gas generator. A 1/16-inch PTFE tube was used for all liquid and gas lines. Gas and liquid were flowed in a downward direction through a column head with a double-layered structure. Gas was introduced through the outside layer and liquid was introduced through the inside layer. The two phases were mixed well by a PTFE filter or glass wool filter just before the catalyst packing area.

Aldehyde and **3g** that were reacted with leuco-quinizarin were placed at the batch reactor (test tube) in advance. The mixture eluded from flow reactor was introduced to the batch reactor through the Dean–Stark apparatus. The accumulated THF in the Dean–Stark apparatus was regularly drained through a cock.

4.1.2 Representative procedure of integrated reaction using FBS unified reactor (Table 2, entry 2)

Pt-Ni/DMPSi-Al_2O_3 catalyst (0.52 g; 0.020 mmol Pt and 0.042 mmol Ni) and Celite (0.5 g) were mixed in a glass vial by hand shaking. The mixed solid was packed into a glass column (catalyst packing space: 10 cm length x 5 mm inner diameter), and the remaining space was filled with Celite. PTFE filters or glass wool filters were placed at both column ends, and the column was installed into an EYELA MCR-1000 column flow reactor (*SynpleFlow*™) with a double-layered column top unit for the gas-liquid multi-phase reaction.

Benzaldehyde (318.7 mg), **3g** (6.5 mg; 5 mol%) and 1-methoxy-2-propanol (2.0 mL) were combined in a test tube (ϕ25X150 mm) equipped with a PTFE cap and a Dean-Stark apparatus with an air-cooled tube connected to a Schlenk line. The atmosphere of this batch reactor unit was replaced with argon, and the mixture was heated to 120 ºC and stirred.

To the flow reactor column was fed 240 mg of quinizarin (**6**) in THF (30 mL) using a Minatoconcept MCRP204 peristaltic pump unit (9.4 ml/h), and H_2 gas (10 ml/min) was introduced simultaneously using an EYELA MFC-11GU mass flow controller in a downward direction. The flow reaction was conducted at room temperature (no heating) and the eluted mixture was directly introduced into a batch reactor unit.

After all of the THF solution of quinizarin (**1a**) was passed through the column flow reactor, an additional 20 mL of THF was flowed to wash out the remaining compounds in the column flow reactor. The batch reactor units were kept stirred for 12 h and cooled to room temperature, after which 15 mL of dichloromethane was added and washed with saturated $NaHCO_3$ aqueous solution (15 mL). An aqueous layer was washed with 10 mL of dichloromethane for three times. Combined organic layer was dried with Na_2SO_4. After removal of the Na_2SO_4, the solvent was removed by evaporation. The remaining solid was washed by 5 mL of hexane for three times. Remaining solid was dried under vacuum to give analytically pure 2-benzyl quinizarin (**1b**) (290.4 mg). Combined hexane solution was evaporated, and a residue was dissolved in dichloromethane (5 mL) and purified by PLC (toluene) to afford analytically pure 2-benzyl quinizarin (**1b**) (7.3 mg). 297.7 mg of 2-benzyl quinizarin (**1b**) (91% yield) was isolated in total.

4.1.1 2-benzyl quinizarin (1b) [1)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.44 (d, J = 0.6 Hz, 1H), 12.92 (s, 1H), 8.44 – 8.30 (m, 2H), 7.94 – 7.77 (m, 2H), 7.37 – 7.26 (m, 4H), 7.25 (s, 1H), 7.05 (q, J = 0.8 Hz, 1H), 4.09 (s, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.21, 186.43, 157.77, 156.79, 143.67, 138.08, 134.52, 134.43, 134.31, 133.68, 133.55, 129.40, 129.28, 128.76, 128.71, 127.09, 127.06, 126.95, 126.75, 112.28, 111.44, 35.88.

4.1.2 2-(4-(chloro)benzyl)quinizarin (1c) [1)]

328.0 mg of 2-(4-(chloro)benzyl)quinizarin (**1c**) from remaining solid after hexane washing and 3.5 mg of 2-(4-(chloro)benzyl)quinizarin (**1c**) from PLC purification, 340.7 mg of 2-(4-(chloro)benzyl)quinizarin (**1c**) (95% yield) was

isolated in total

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.40 (s, 1H), 12.90 (s, 1H), 8.46 – 8.22 (m, 2H), 7.92 – 7.72 (m, 2H), 7.35 – 7.27 (m, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 1.0 Hz, 1H), 4.05 (s, 2H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.24, 186.48, 157.66, 156.57, 142.86, 136.62, 134.51, 134.38, 133.64, 133.50, 132.65, 130.57, 128.87, 128.60, 127.09, 127.00, 112.43, 111.61, 35.33.

4.1.3 2-(2-thienylmethyl)quinizarin (1d) [1)]

309.3 mg of 2-(2-thienylmethyl)quinizarin (**1d**) from remaining solid after hexane washing and 16.6 mg of 2-(2-thienylmethyl)quinizarin (**1d**) from PLC purification, 326.3 mg of 2-(2-thienylmethyl)quinizarin (**1d**) (98% yield) was isolated in total

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.43 (d, J = 0.6 Hz, 1H), 12.91 (s, 1H), 8.41 – 8.29 (m, 2H), 7.88 – 7.79 (m, 2H), 7.20 (dd, J = 5.1, 1.3 Hz, 1H), 7.15 (q, J = 0.8 Hz, 1H), 7.01 – 6.92 (m, 2H), 4.29 (s, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.18, 186.46, 157.74, 156.36, 142.55, 139.93, 134.47, 134.35, 133.64, 133.50, 128.41, 127.13, 127.06, 126.97, 126.49, 124.65, 112.36, 111.66, 29.81.

4.1.4 2-(*n*-hexyl)quinizarin (1e) [1)]

262.5 mg of 2-(*n*-hexyl)quinizarin (**1e**) from remaining solid after hexane washing and 46.7 mg of 2-(*n*-hexyl)quinizarin (**1e**) from PLC purification, 309.2 mg of 2-(*n*-hexyl)quinizarin (**1e**) (95% yield) was isolated in total

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.43 (dt, J = 1.3, 0.6 Hz, 1H), 13.06 – 12.90 (m, 1H), 8.35 (ddd, J = 8.1, 4.6, 2.3 Hz, 2H), 7.94 – 7.75 (m, 2H), 7.18 – 7.14 (m, 1H), 2.88 – 2.60 (m, 2H), 1.74 – 1.63 (m, 2H), 1.49 – 1.21 (m, 6H), 0.90 (td, J = 5.9, 3.7 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.24, 186.33, 157.90, 157.26, 145.58, 134.34, 134.21, 133.74, 133.61, 128.08, 127.02, 126.90, 112.02, 111.06, 31.64, 30.18, 29.12, 28.73, 22.58, 14.08.

4.1.5 2-(2-furfulylmethyl)quinizarin (1g)

Pt-Ni/DMPSi-Al_2O_3 catalyst (0.52 g; 0.020 mmol Pt and 0.042 mmol Ni) and Celite (0.5 g) were mixed in a glass vial by hand shaking. The mixed solid was packed

into a glass column (catalyst packing space: 10 cm length x 5 mm inner diameter), and the remaining space was filled with Celite. PTFE filters or glass wool filters were placed at both column ends, and the column was installed into an EYELA MCR-1000 column flow reactor (*SynpleFlow*™) with a double-layered column top unit for the gas-liquid multi-phase reaction.

Furfural (234.0 mg), **3g** (13.2 mg**;** 10 mol%) and 1-methoxy-2-propanol (2.0 mL) were combined in a test tube (ϕ25X150 mm) equipped with a PTFE cap and a Dean-Stark apparatus with an air-cooled tube connected to a Schlenk line. The atmosphere of this batch reactor unit was replaced with argon, and the mixture was heated to 120 ºC and stirred.

To the flow reactor column was fed 246.5 mg of quinizarin (**6**) in THF (30 mL) using a Minatoconcept MCRP204 peristaltic pump unit (9.4 ml/h), and H_2 gas (10 ml/min) was introduced simultaneously using an EYELA MFC-11GU mass flow controller in a downward direction. The flow reaction was conducted at room temperature (no heating) and the eluted mixture was directly introduced into a batch reactor unit.

After all of the THF solution of quinizarin (**1a**) was passed through the column flow reactor, an additional 20 mL of THF was flowed to wash out the remaining compounds in the column flow reactor. The batch reactor units were kept stirred for 3 h and cooled to room temperature, after which 15 mL of dichloromethane was added and washed with saturated $NaHCO_3$ aqueous solution (15 mL). An aqueous layer was washed with 10 mL of dichloromethane for three times. Combined organic layer was dried with Na_2SO_4. After removal of the Na_2SO_4, the solvent was removed by evaporation. The remaining solid dissolved by dichloromethane (10 mL) was passed thorough short silica pad and eluted by dichloromethane (50 mL). The solution was evaporated and dried under vacuum to give 2-(2-furfulymethyl) quinizarin (**1g**) (243.3 mg, 73% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.40 (d, J = 0.6 Hz, 1H), 12.90 (s, 1H), 8.43 – 8.26 (m, 2H), 7.92 – 7.75 (m, 2H), 7.38 (dd, J = 1.9, 0.8 Hz, 1H), 7.10 (q, J = 0.8 Hz, 1H), 6.35 (dd, J = 3.2, 1.9 Hz, 1H), 6.19 (dd, J = 3.2, 0.9 Hz, 1H), 4.11 (d, J = 0.9 Hz, 2H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.19, 186.51, 157.67, 156.50, 151.23, 142.07, 140.49, 134.47, 134.36, 133.65, 133.51, 128.61, 127.08, 126.98, 112.31, 111.66, 110.56, 107.67, 28.25. **HRMS** calc.: 320.06847,

found: 320.0685 (+0.1 ppm). **IR (ATR, ν_{max} /cm^{-1})** 2738, 2678, 2669, 2661, 1622, 1582, 1567, 1561, 1455, 1438, 1418, 1406, 1381, 1363, 1340, 1309, 1260, 1240, 1208, 1177, 1160, 1142, 1119, 1099, 1071, 1045, 1022, 1010, 959, 933, 896, 884, 812, 792, 778, 677, 649, 629, 600, 591, 528, 517, 502, 462, 442, 422, 399, 387, 376, 353, 342. **Mp.** 154-156 ºC.

4.1.6 2-(2-methylphenylmethyl)quinizarin (1g)

Pt-Ni/DMPSi-Al_2O_3 catalyst (0.52 g; 0.020 mmol Pt and 0.042 mmol Ni) and Celite (0.5 g) were mixed in a glass vial by hand shaking. The mixed solid was packed into a glass column (catalyst packing space: 10 cm length x 5 mm inner diameter), and the remaining space was filled with Celite. PTFE filters or glass wool filters were placed at both column ends, and the column was installed into an EYELA MCR-1000 column flow reactor (*SynpleFlow*^{TM}) with a double-layered column top unit for the gas-liquid multi-phase reaction.

o-tolaldehyde (356.8 mg), **3g** (6.5 mg**;** 5 mol%) and 1-methoxy-2-propanol (2.0 mL) were combined in a test tube (ϕ25X150 mm) equipped with a PTFE cap and a Dean-Stark apparatus with an air-cooled tube connected to a Schlenk line. The atmosphere of this batch reactor unit was replaced with argon, and the mixture was heated to 120 ºC and stirred.

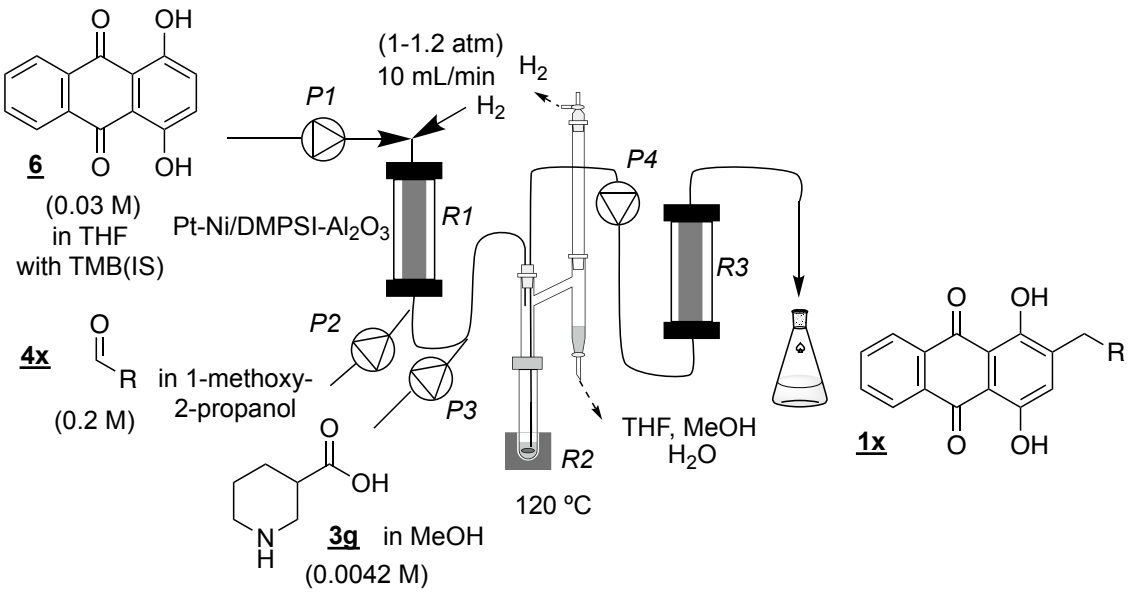
To the flow reactor column was fed 240.1 mg of quinizarin (**6**) in THF (30 mL) using a Minatoconcept MCRP204 peristaltic pump unit (9.4 ml/h), and H_2 gas (10 ml/min) was introduced simultaneously using an EYELA MFC-11GU mass flow controller in a downward direction. The flow reaction was conducted at room temperature (no heating) and the eluted mixture was directly introduced into a batch reactor unit.

After all of the THF solution of quinizarin (**1a**) was passed through the column flow reactor, an additional 20 mL of THF was flowed to wash out the remaining compounds in the column flow reactor. The batch reactor units were kept stirred for 12 h and cooled to room temperature, after which 15 mL of dichloromethane was added and washed with saturated $NaHCO_3$ aqueous solution (15 mL). An aqueous layer was washed with 10 mL of dichloromethane for three times. Combined organic layer was dried with Na_2SO_4. After removal of the Na_2SO_4, the solvent was removed by evaporation. The remaining solid was washed by 5 mL

of hexane for three times. The remaining solid dissolved by dichloromethane (10 mL) was passed thorough short silica pad and eluted by dichloromethane (50 mL). The solution was evaporated and dried under vacuum to give 2-(2-methylphenylmethyl) quinizarin (**1h**) (253.7 mg). Combined hexane solution was evaporated, and a residue was dissolved in dichloromethane (5 mL) and purified by PLC (toluene) to afford analytically pure 2-(2-methylphenylmethyl) quinizarin (**1h**) (14.0 mg). 267.7 mg of 2-(2-methylphenylmethyl) quinizarin (**1h**) (78% yield) was isolated in total.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.50 (d, J = 0.6 Hz, 1H), 12.92 (s, 1H), 8.36 (ddd, J = 10.8, 6.0, 3.3 Hz, 2H), 7.83 (dd, J = 5.8, 3.3 Hz, 2H), 7.24 – 7.12 (m, 4H), 6.80 (d, J = 0.8 Hz, 1H), 4.09 (d, J = 1.1 Hz, 2H), 2.26 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.29, 186.43, 157.86, 156.83, 143.30, 136.81, 135.89, 134.45, 134.31, 133.71, 133.56, 130.64, 130.27, 128.11, 127.22, 127.07, 126.96, 126.39, 112.04, 111.27, 33.22, 19.49. **HRMS** calc.: 344.1049, found: 344.1044 (-1.3 ppm). **IR (ATR, ν_{max} /cm^{-1})** 3014, 2948, 2919, 2902, 1630, 1590, 1567, 1455, 1420, 1403, 1375, 1355, 1335, 1309, 1280, 1246, 1226, 1206, 1165, 1114, 1099, 1051, 1039, 1016, 973, 956, 947, 930, 901, 870, 852, 827, 807, 752, 738, 680, 652, 631, 620, 597, 551, 522, 502, 462, 439, 425, 393, 385, 376, 362, 353, 344. **Mp.** 164-166 ºC.

4.1.7 Full continuous-flow hydrogenation-Marschalk reaction



Scheme S2. Full continuous-flow hydrogenation-Marschalk reaction

Full continuous-flow Marschalk reaction was conducted using a combined reactor system of two flow reactors (*R1* and *R3*) and a FBS unified reactor (*R2*) (Figure S2). Reaction monitoring profiles of different substrates were shown in Figures S3-S5. Almost two hours were needed to reach steady state to afford **1x** in stable yields. Representative experimental procedure of Entry 1 in Table 3 were described in below.

Pt-Ni/DMPSi-Al_2O_3 catalyst (0.277 g; 0.008 mmol Pt) and Celite (0.5 g) were mixed in a glass vial by hand shaking. The mixed solid was packed into a glass column (catalyst packing space: 10 cm length x 5 mm inner diameter), and the remaining space was filled with Celite. PTFE filters or glass wool filters were placed at both column ends, and the column was installed into an EYELA MCR-1000 column flow reactor (*SynpleFlow*™) (*R1*) with a double-layered column top unit for the gas-liquid multi-phase reaction.

9 mL of 1-methoxy-2-propanol solution containing anisaldehyde (**4a**; 0.2 M), 18 mL of methanol solution containing **3g** (0.0042 M), 18 mL of 1-methoxy-2-propanol, and a stirring bar were placed in a batch reactor (ϕ25 x 150 mm) equipped with a PTFE cap and a Dean-Stark apparatus with an air-cooled tube connected to a Schlenk line (*R2*). The atmosphere of this batch reactor unit (*R2*)

was replaced with argon, and the mixture was heated to 125 ºC and stirred. The reaction mixture was kept under heating for almost 1 h, and MeOH was distilled out from the reactor (R2) to Dean-Stark apparatus.

To the flow reactor column (*R1*) was fed THF solution containing quinizarin (**1a**; 0.03 M) and 1,3,5-trimethoxybenzene (internal standard; 0.01 M), using a Minatoconcept MCRP204 peristaltic pump unit (*P1*; 14 ml/h), and H_2 gas (10 ml/min) was introduced simultaneously using an EYELA MFC-11GU mass flow controller in a downward direction. The flow reaction was conducted at room temperature (no heating). The eluted mixture was combined with 1-methoxy-2-propanol solution containing anisaldehyde (0.2 M) from (*P2*; 6 ml/h) and methanol solution containing **3g** (0.0042 M) from (*P3*; 6 ml/h), and the combined stream was directly introduced into a batch reactor unit (*R2*).

The mixture of the batch reactor (*R2*) was fed to a glass column (10 cm length x 5 mm inner diameter) which was heated at 110 ºC in an EYELA MCR-1000 column flow reactor (*SynpleFlow*™) (*R3*), using a Minatoconcept MCRP204 peristaltic pump unit (*P4*; 6 ml/h) in upward direction. Flow rate of the pump unit (*P2*) and the pump unit (*P3*) was equal, and constant volume of solution in a batch reactor unit (*R2*) was maintained at steady state.

Eluted solution from the column flow reactor (*R3*) was collected as fractions. An aliquot of a fraction was diluted with $CDCl_3$ to be analyzed by ^1H NMR, and yield of **1a** was calculated using an integration of a peaks of 1,3,5-trimethoxybenzene and **1a** (δ 6.09 ppm (s, 3H) of 1,3,5-trimethoxybenzene and 7.23 – 7.16 (m, 2H) of **1a**).

To two collected fractions for 1.6 h during steady state (Plots at 3.08 h and 3.96 h in Figure S4) was added fixed amount of decane as an internal standard for GC analysis to determine the amount of 1,3,5-trimethoxybenzene inside the fraction. An aliquot was taken from the fraction, which was analyzed by GC. The amount of 1,3,5-trimethoxybenzene inside the fraction was found to be 15.0 mg, and thus 64.2 mg of **6** as a starting material was estimated to be fed to this fraction.

5 mL of hexane was added to the fraction and red solid appeared. Generated solid was collected by filtration and the solid was washed by 10 mL of hexane. Remaining solid was dissolved in 5 mL of dichloromethane and it was washed by

$NaHCO_3$ aq. (10 mL). An aqueous phase was washed by 5 mL of dichloromethane for three times. Combined organic layer was dried by Na_2SO_4 and dichloromethane was evaporated. 85.7 mg of red solid was obtained (87% yield) as analytically pure **1a**.

4.1.8 2-(4-methoxyphenylmethyl) quinizarin (1a) [1)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.39 (d, J = 1.1 Hz, 1H), 12.88 (d, J = 1.1 Hz, 1H), 8.30 (dtd, J = 6.5, 3.2, 1.4 Hz, 2H), 7.85 – 7.72 (m, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.00 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 3.99 (s, 2H), 3.78 (s, 3H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.13, 186.34, 158.47, 157.80, 156.77, 144.18, 134.39, 134.26, 133.65, 133.51, 130.28, 130.01, 128.52, 127.02, 126.91, 114.20, 112.21, 111.31, 55.29, 35.03.

Yield of a collected fraction from time point A (h) to time point B (h) was plotted at [(A+B)/2] (h). Time point 0 (h) was defined as the time when the reaction mixture began to appear from reactor *R3*.

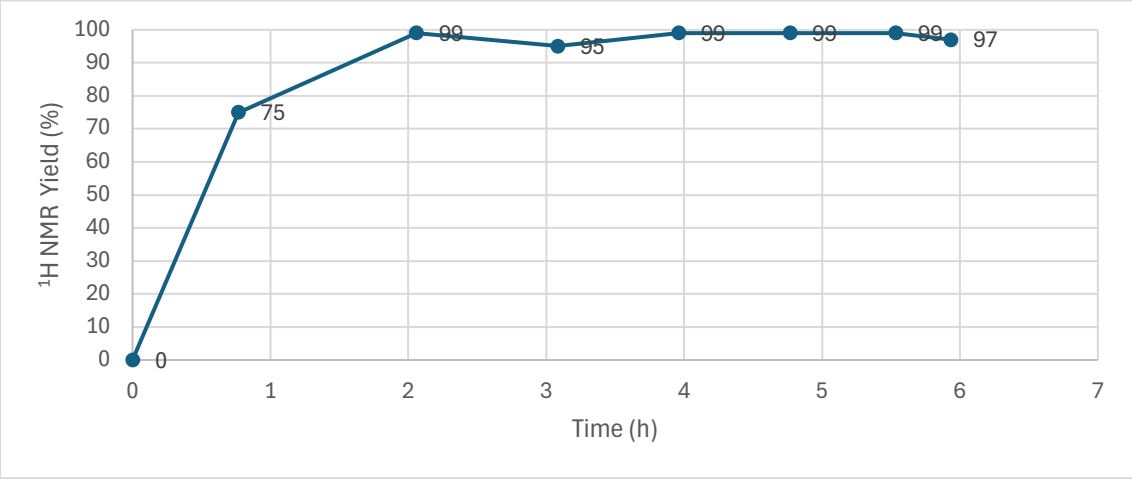


Figure S3. Time course of reaction output using combined full continuous-flow system. (Table 3, Entry 1)

Table3, Entry 3:

Flow rate of **6** solution (*P1*): 14 mL/h

Flow rate of aldehyde **4c** solution (*P2 & P4*): 6 mL/h

Flow rate of **3g** solution (*P3*): 7 mL/h

A fraction collected for 0.83 h (A plot at 2.08 h in Figure S5): 43.2 mg of **6** as a starting material was estimated to be fed to this fraction. 55.1 mg of **1c** was obtained (83% yield).

4.1.9 **2-(4-chlorophenylmethyl) quinizarin (1c)** [1)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.33 (s, 1H), 12.82 (s, 1H), 8.31 – 8.23 (m, 2H), 7.79 – 7.72 (m, 2H), 7.26 – 7.12 (m, 4H), 6.98 (d, J = 0.9 Hz, 1H), 3.98 (s, 2H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.23, 186.46, 157.65, 156.56, 142.85, 136.62, 134.50, 134.37, 133.63, 133.49, 132.64, 130.56, 128.87, 128.59, 127.08, 126.98, 112.42, 111.60, 35.32.

Yield of a collected fraction from time point A (h) to time point B (h) was plotted at [(A+B)/2] (h). Time point 0 (h) was defined as the time when the reaction mixture began to appear from reactor *R3*.

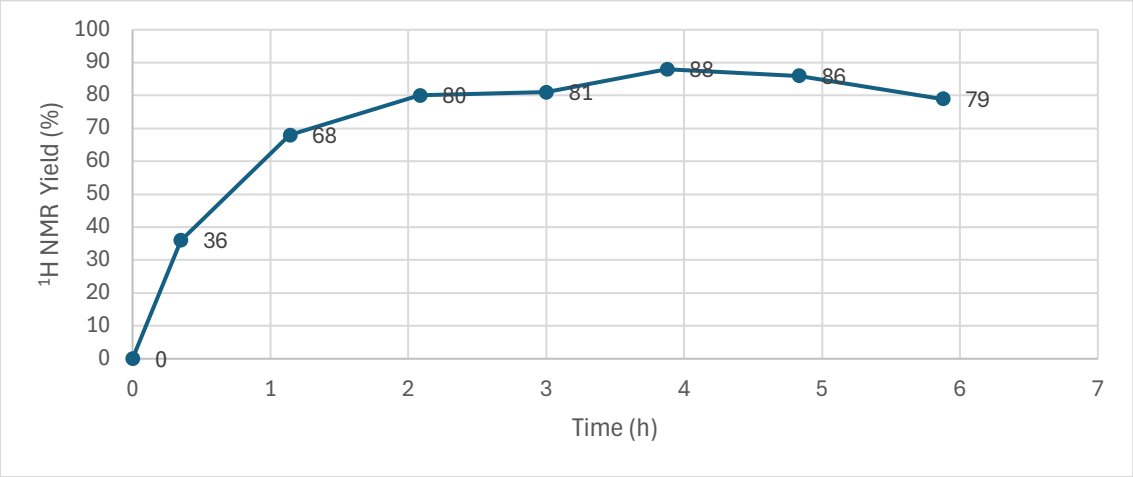


Figure S4. Time course of reaction output using combined full continuous-flow system. (Table 3, Entry 3)

Table3, Entry 4:

Flow rate of **6** solution (*P1*): 15 mL/h

Flow rate of aldehyde **4f** solution (*P2 & P4*): 7 mL/h

Flow rate of **3g** solution (*P3*): 9 mL/h (0.0126 M)

A fraction collected for 1.0 h (A plot at 7.7 h in Figure S6): 96.3 mg of **6** as a

starting material was estimated to be fed to this fraction. 120.5 mg of **1f** was obtained (89% yield).

4.1.10 **2-(cyclohexylmethyl) quinizarin (1a)** [1)]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.45 (d, J = 0.6 Hz, 1H), 13.01 (d, J = 1.1 Hz, 1H), 8.48 – 8.29 (m, 2H), 7.93 – 7.72 (m, 2H), 7.14 (d, J = 0.8 Hz, 1H), 2.66 (d, J = 6.7 Hz, 2H), 1.82 – 1.64 (m, 6H), 1.33 – 1.17 (m, 3H), 1.05 (q, J = 11.8 Hz, 2H).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 187.23, 186.33, 157.59, 157.46, 144.14, 134.32, 134.21, 133.71, 133.60, 129.16, 127.01, 126.88, 112.06, 111.17, 38.03, 37.67, 33.29, 26.42, 26.23.

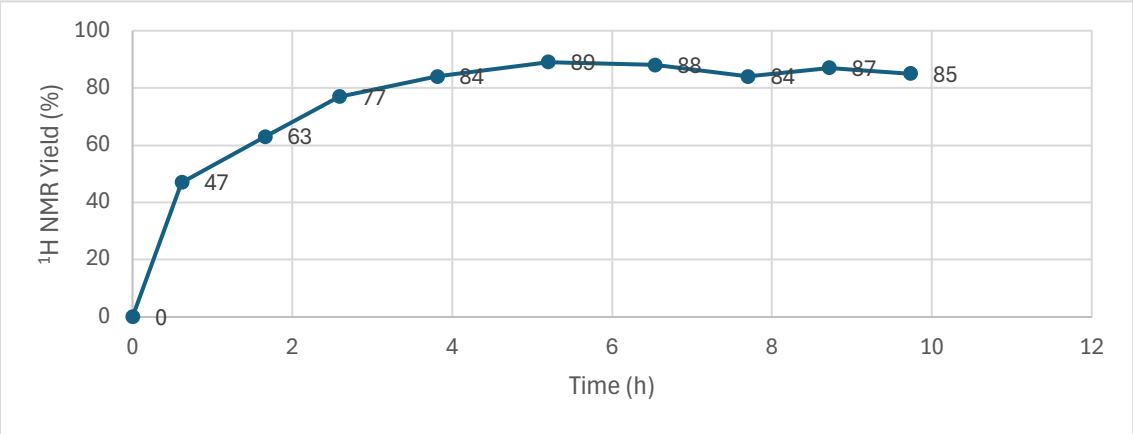
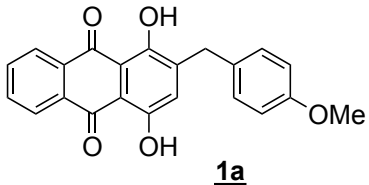


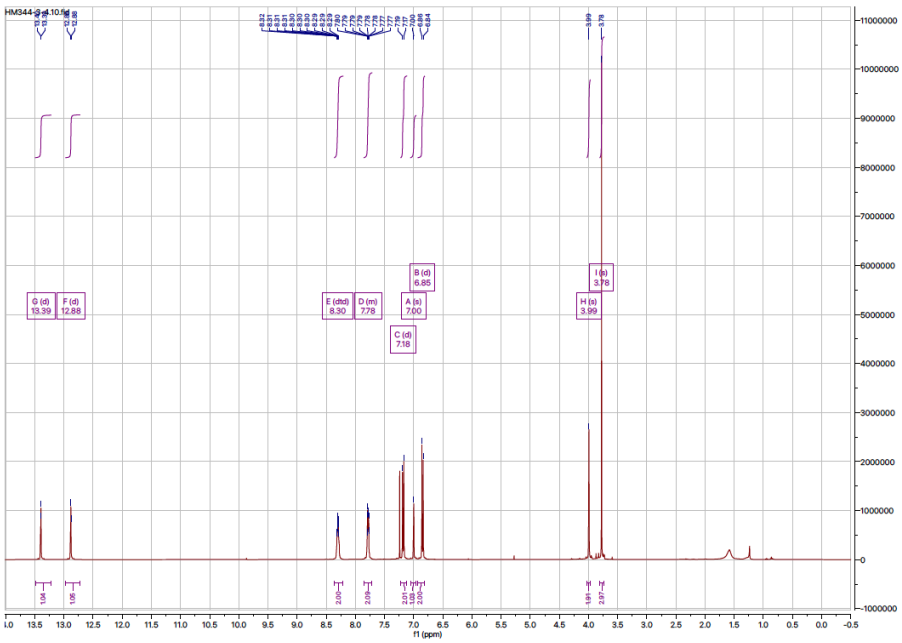
Figure S5. Time course of reaction output using combined full continuous-flow system. (Table 3, Entry 4)

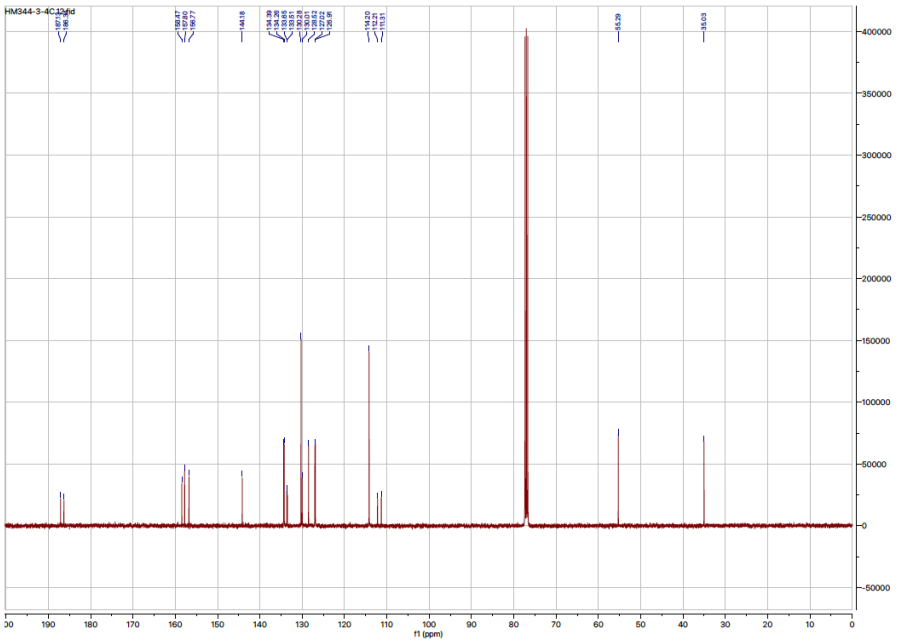
6 ^{1}H & ^{13}C NMR Charts of Isolated Compounds

6.1 2-(4-(methoxy)benzyl)quinizarin (1a)

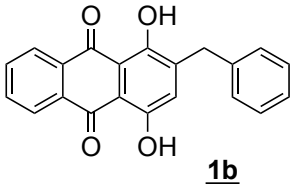


1a

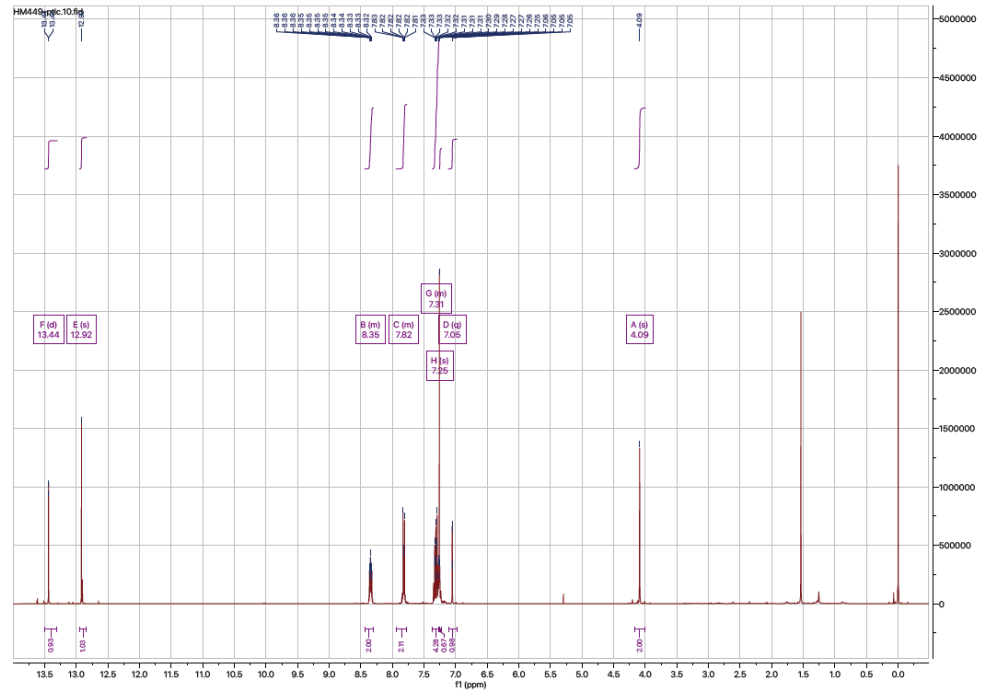


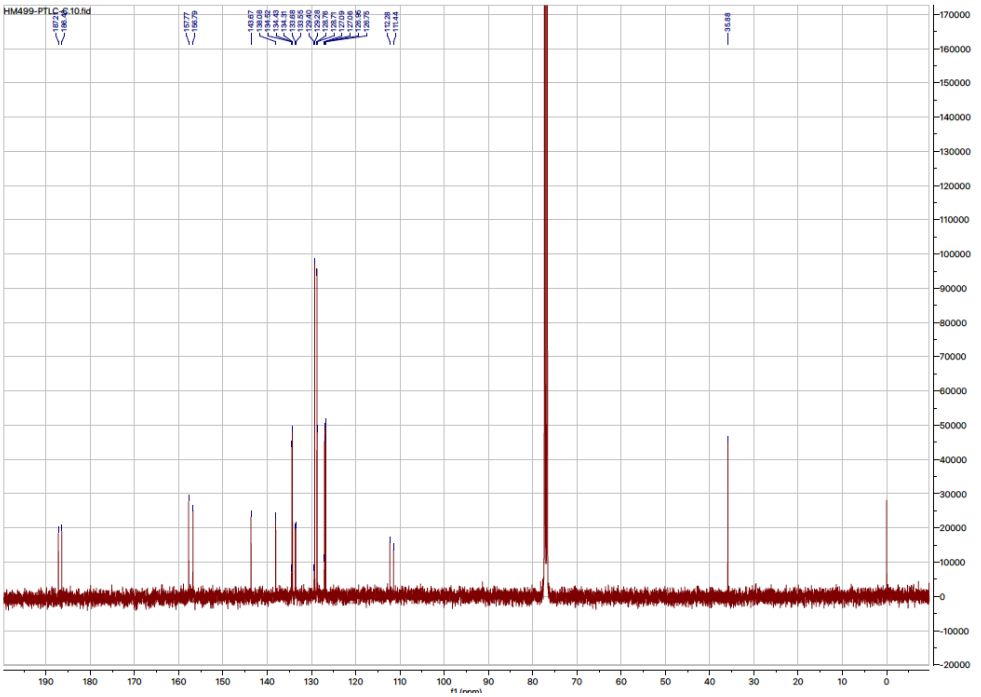


6.2 2-benzyl quinizarin (1b)

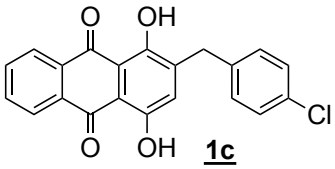


1b

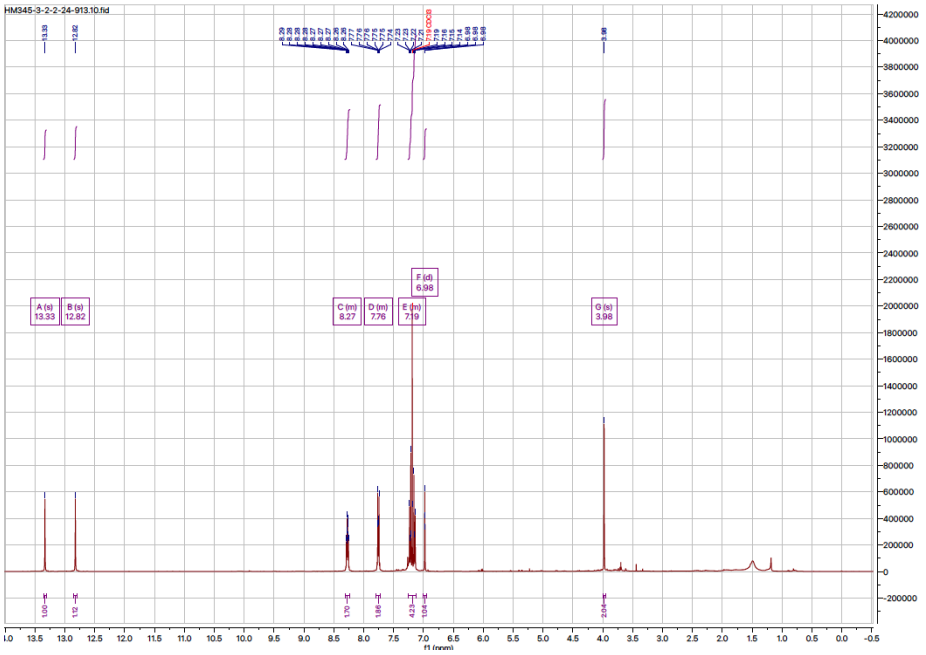


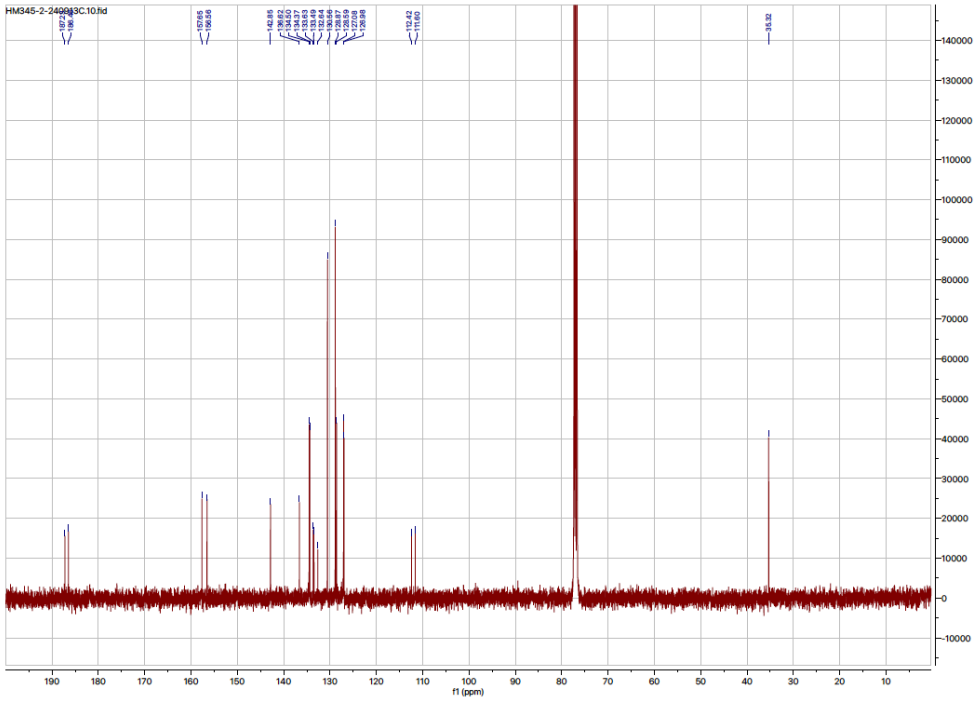


6.3 2-(4-(chloro)benzyl)quinizarin (1c)

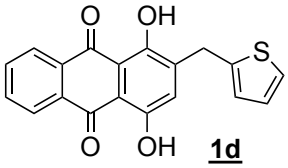


1c

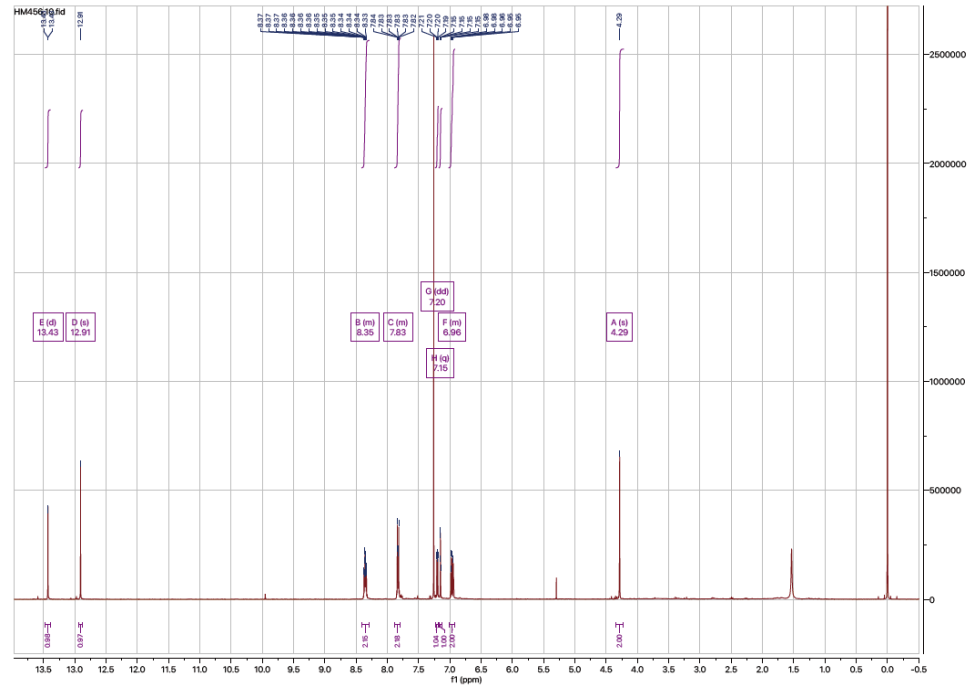


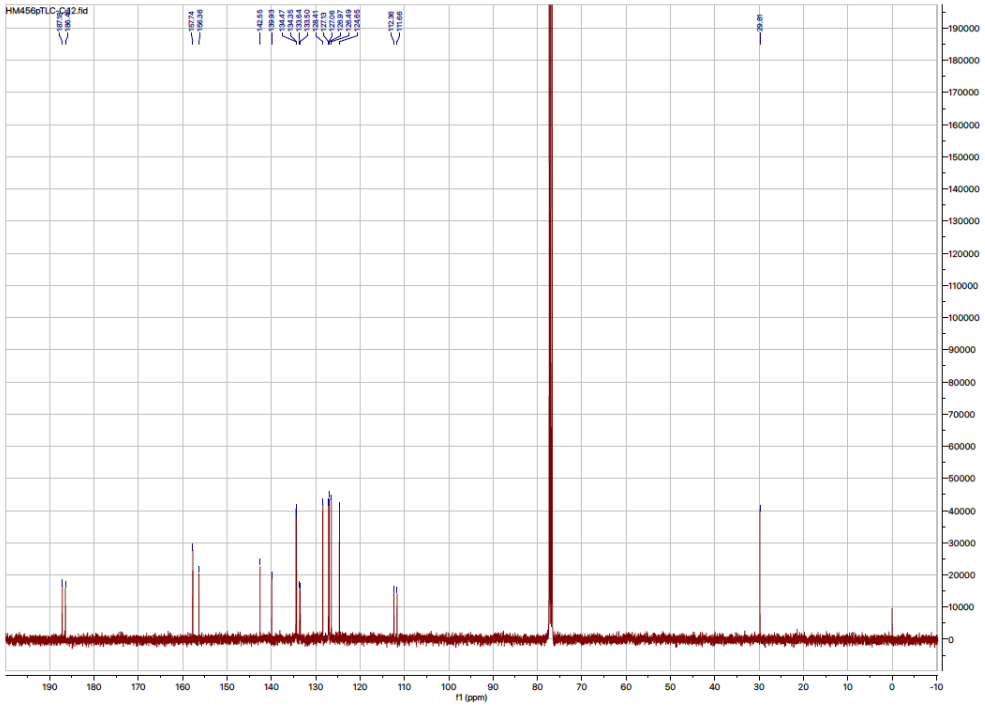


6.4 2-(2-thienylmethyl)quinizarin (1d)

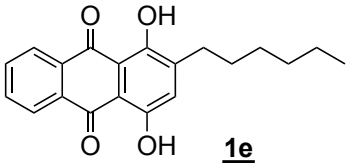


1d

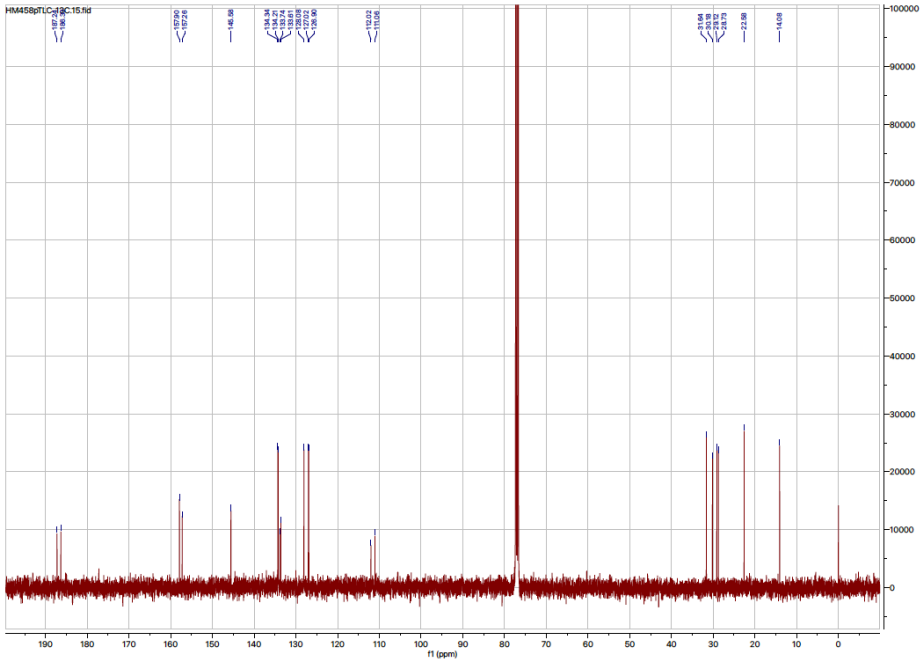




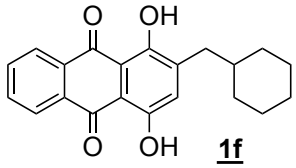
6.1 2-(*n*-hexyl)quinizarin (1e)



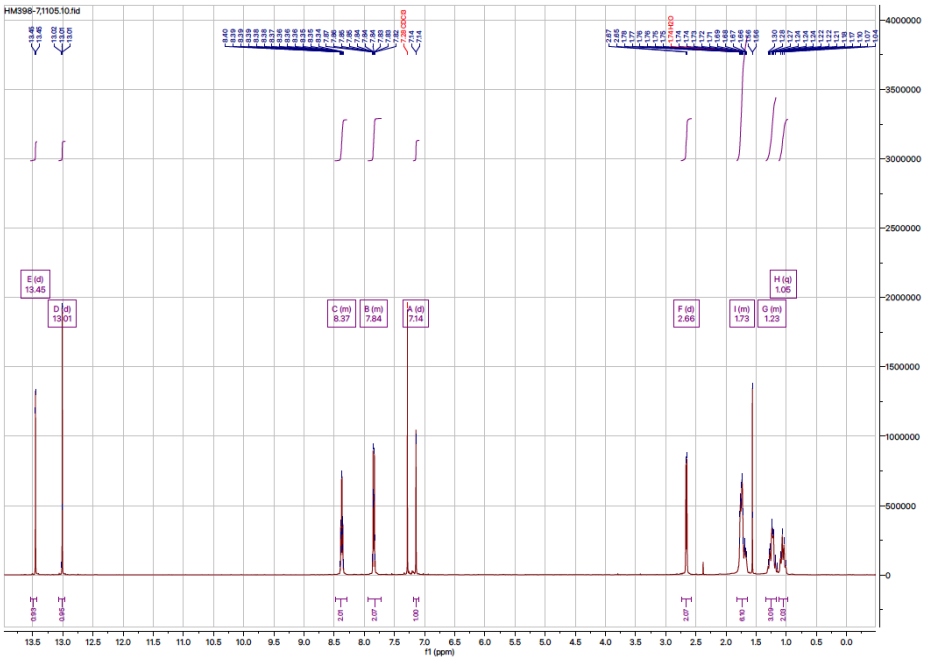
1e

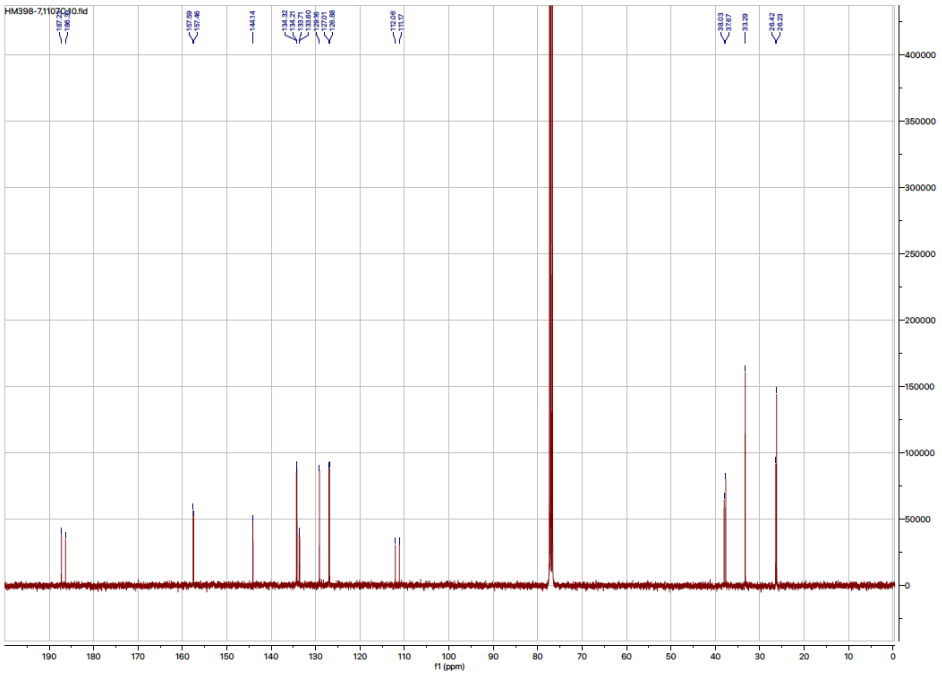


6.2 2-(cyclohexylmethyl)quinizarin (1f)

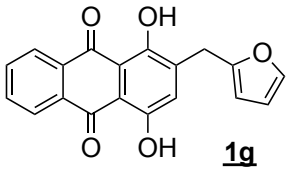


1f

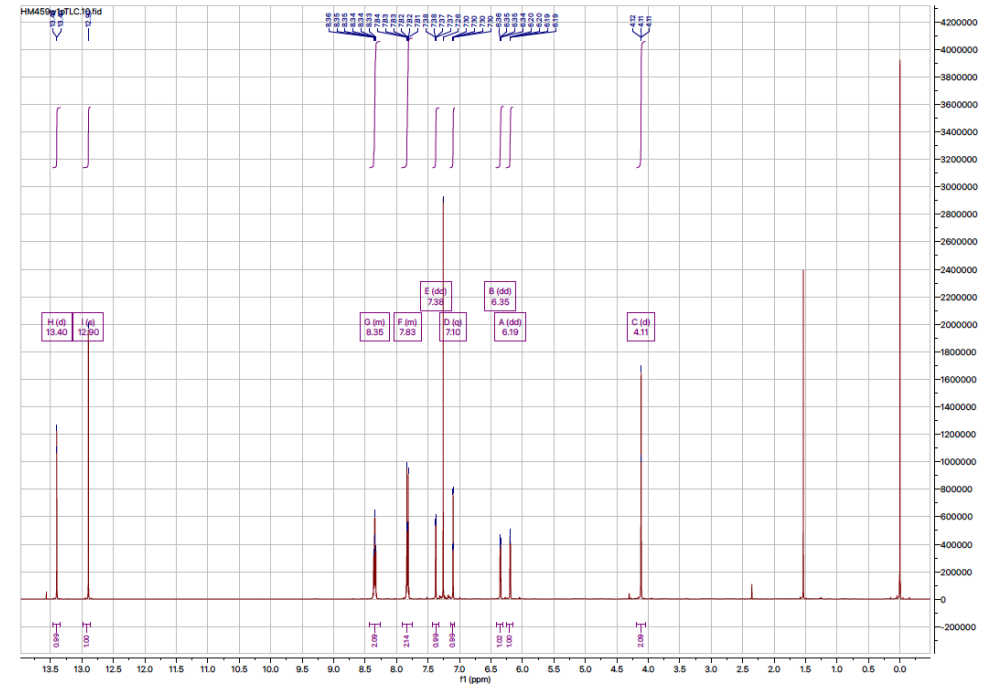


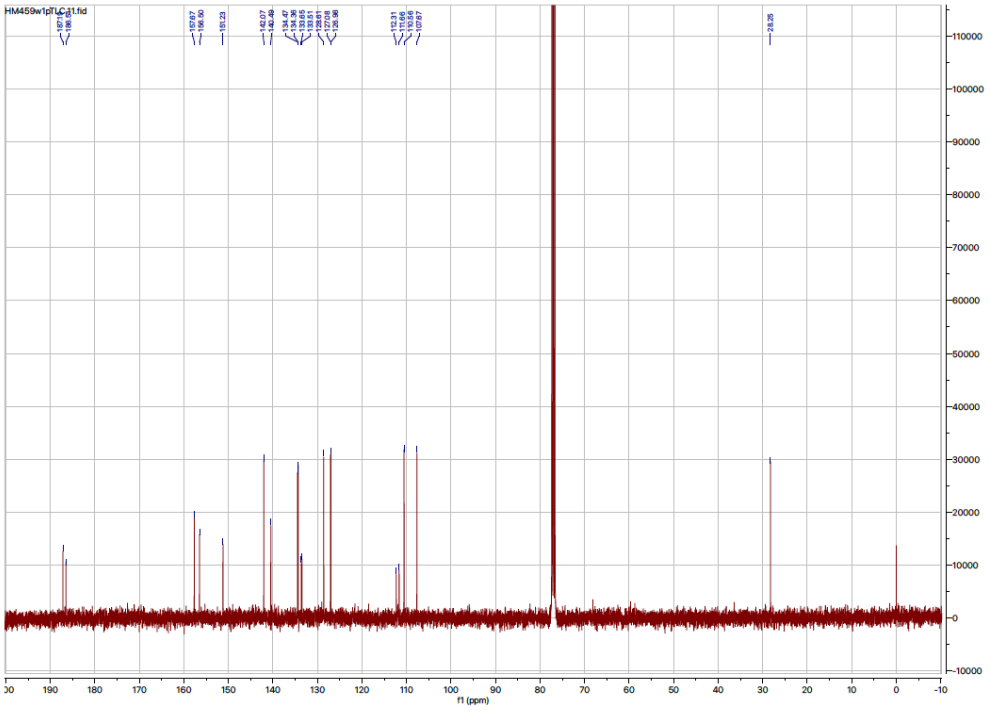


6.3 2-(2-furfulylmethyl)quinizarin (1g)

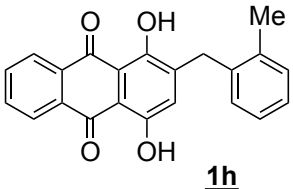


1g

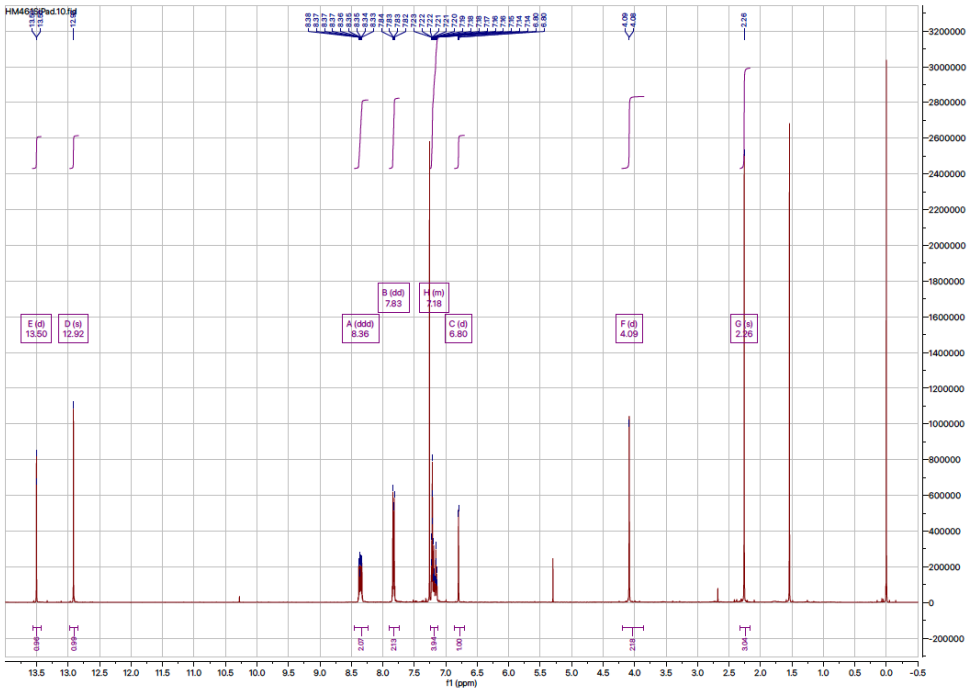


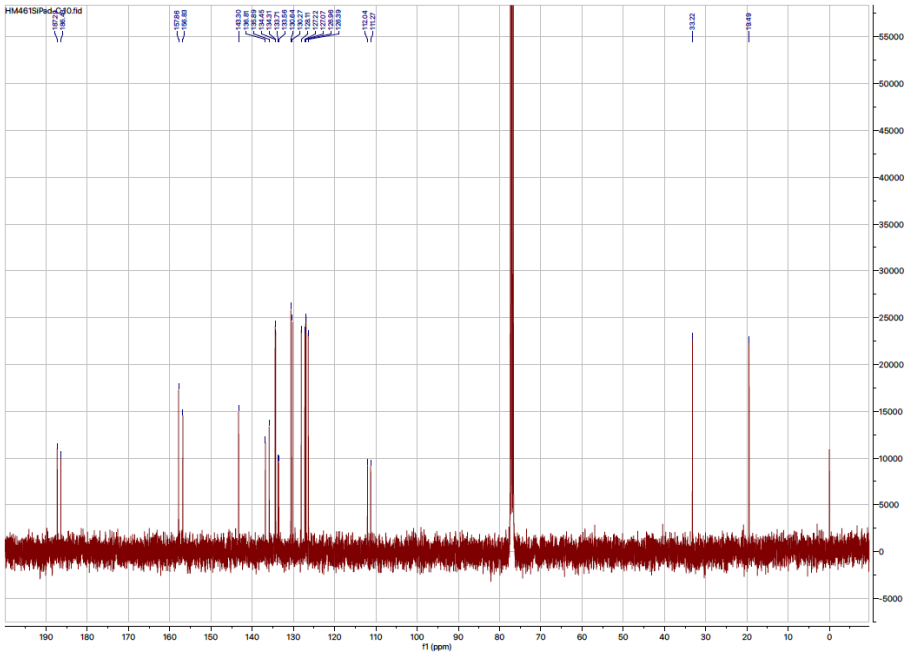


6.1 2-(2-methylphenylmethyl)quinizarin (1h)



1h





7 References

1) H. Miyamura, A. Sharma, M. Takata, R. Kajiyama, S. Kobayashi, Y. Kon, *ACS Catal.* **2024**, *14*, 10317-10323.