Supporting Information

Short Electrochemical Asymmetric Synthesis of (+)-*N*-Acetylcolchinol

Yi Du,[a] Adelaide Lunga,[a] Aleksandr E. Rubtsov[a,b] and Andrei V. Malkov,*[,a]

[a] Department of Chemistry, Loughborough University, Loughborough, LE11 3TU, UK.

E-mail: A.Malkov@lboro.ac.uk

[b] Department of Chemistry, Perm State University, Bukireva 15, Perm 614990, Russia

Contents

1. General and Experimental Details

The electrochemical reactions were performed using ElectraSyn (IKA) in a constant current mode, unless stated otherwise. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra.

^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded at room temperature; the chemical shifts (δ) were measured in ppm with respect to the solvent ($CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm; DMSO-d_6, ^{1}H: δ = 2.5 ppm, ^{13}C: δ = 39.51 ppm; or tetramethylsilane (TMS), δ = 0 ppm). Coupling constants are given in Hertz. Data are reported as follows: chemical shift (in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*, in Hz), and integration. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The high-resolution mass spectra (HRMS) were recorded in a positive or negative ion mode using electrospray ionization (ESI) from methanol or acetonitrile. Enantiomeric excess (ee) was determined by HPLC on columns with chiral sorbents. All chromatographic manipulations used silica gel (40-63 μm) as the adsorbent.

Melting points were determined on a Kofler block and are uncorrected.

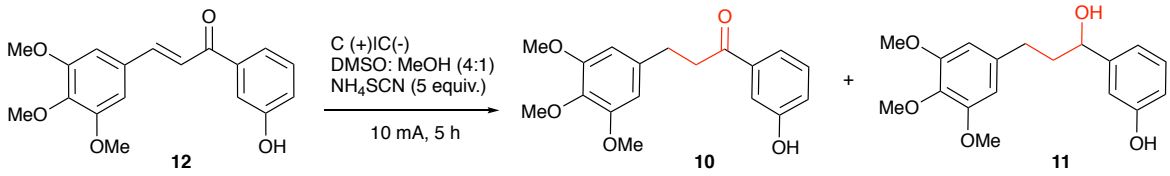
The reaction progress was monitored by GCMS and LCMS analysis and by thin layer chromatography (TLC) on aluminium backed plates with Merck Kiesel 60 F254 silica gel. TLCs were either visualized by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid.

All solvents and reagents for the reactions were of reagent grade and were used as received without further purification.

2. General protocol for the electrochemical reduction

Unsaturated ketone (0.5 mmol) and electrolyte (2 equiv) were added to an undivided 10 mL glass cell equipped with two graphite electrodes, followed by 8 mL of DMSO and 2 mL of MeOH. The mixture was stirred at room temperature for 5 hours under constant current of 10 mA. The progress was monitored by TLC and LCMS. After completion, the reaction mixture was extracted with EtOAc (3x10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The resulting mixture was purified by column chromatography on silica gel eluting with a 2:1 mixture of Hexane/EtOAc.

Table S1. Optimisation of conditions for the reduction of chalcone 12[a]



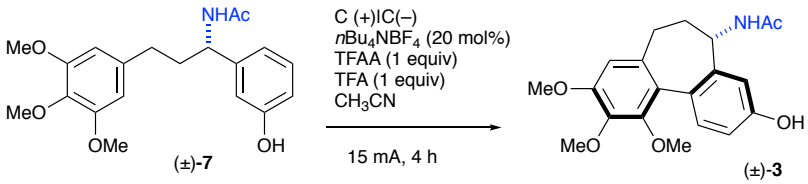
Entry	Variation from standard condition	Yield[b] of **10** (%)	Yield[b] of **11** (%)
1	none	trace	(92)
2	*n*Bu_4NI instead of NH_4SCN	52	42
3	*n*Bu_4NF instead of NH_4SCN	54	40
4	Et_4BF_4 instead of NH_4SCN	80	12
5	NH_4OAc instead of NH_4SCN	56	41
6	NH_4Cl instead of NH_4SCN	60	38
7	DCM as solvent	NR	NR
8	DMF as solvent	NR	NR
9	MeOH as solvent	NR	NR
10	CH_3CN as solvent	95 (92)	trace
11	CH_3CN anhydrous as solvent	93	trace
12	DMF as solvent	98	trace
13	DMF anhydrous as solvent	94	trace
14	MeOH: H_2O (1:4) as solvent	NR	NR
15	DMSO: MeOH (1:4) as solvent	21	20
16	DMSO: MeOH (1:1) as solvent	20	23
17	DMSO: MeOH (2:1) as solvent	32	62
18	Ni (+)/Ni (-) as electrodes	92 (82)	trace
19	C (+)/Ni (-) as electrodes	50	trace
20	C (+)/Fe (-) as electrodes	68	trace
21[c]	Scale up reaction	56	35

*[a]Reaction conditions: Carbon plate anode, Carbon plate cathode, substrate 0.2 mmol, 5 equiv of electrolyte in 10 mL of DMSO/MeOH (4:1), constant current (10 mA), undivided cell, reaction time 5 hours. [b] Conversions by LCMS (isolated yields given in parentheses). [c]Carbon plate anode, Carbon plate cathode, 10 mmol chalcone **12**, 5 equiv NH_4SCN in 500 mL of DMSO/MeOH (4:1), constant current (10 mA), undivided cell, reaction time 5 hours.*

3. General protocol for the electrochemical oxidative cyclization of acetamide 7

A 15 mL undivided cell was charged with with acetamide **7** (0.0359 g, 0.1 mmol) in 7 mL of acetonitrile, electrolyte (20 mmol%), TFAA (13 µL, 1 equiv) and additive (7.6 µL, 1 equiv). The cell was equipped with two graphite electrodes and a constant current of 15 mA was applied; the mixture was stirred at room temperature for 4 hours. The process was monitored by TLC. After completion, a saturated aqueous solution of $NaHCO_3$ was added to the mixture, which was then extracted with EtOAc (3x10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated in vacuum and purified by chromatography on silica eluting with a 30:1 mixture of DCM/MeOH to give the title compound as an off-white solid.

Table S2. Optimisation of the oxidative coupling of 7[a]



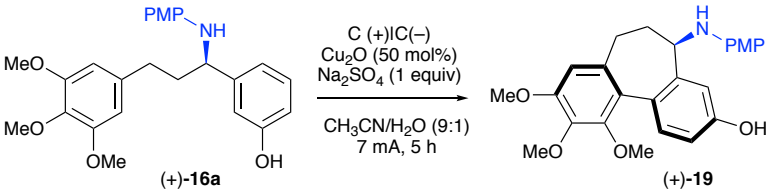
Entry	Variation from standard condition	Yield[b] of **3** (%)
1	none	68
2	nBu$_4$NI instead of nBu$_4$NBF$_4$	trace
3	nBu$_4$NBr instead of nBu$_4$NBF$_4$	trace
4	nBu$_4$NHSO$_4$ instead of nBu$_4$NBF$_4$	trace
5	nBu$_4$NF instead of nBu$_4$NBF$_4$	28
6	DCM as solvent	32
7	iPrOH as solvent	NR
8	MeOH as solvent	trace
9	THF as solvent	NR
10	HIFP as solvent	NR
11	Without TFAA and TFA	46
12	TFA instead of TFAA	22
13	H_2O_2 instead of TFAA	trace
14	H_2O instead of TFAA	NR
15	Without TFAA	21
16	Without TFA	59
17	Glassy Carbon plate electrodes	54
18	Cu_2O (50 mol%) as additive	52
19[c]	CH_3CN/H_2O (9:1), Na_2SO_4 (1 equiv), Cu_2O (50 mol%)	<5
20	CH_3CN, Na_2SO_4 (1 equiv), Cu_2O (50 mol%)	10

[a]Reaction conditions: Carbon plate anode, Carbon plate cathode, substrate 0.1 mmol, 20 mol% of electrolyte in 7 mL of solvent, constant current (15 mA), additive 1.0 equiv, undivided cell, reaction time 4 hours. [b]Isolated yield. [c]Standard conditions from Table S3 were used.

4. General protocol for the electrochemical oxidative cyclization of aniline 16a

Sodium sulphate (0.0142 g, 1 equiv) was added to the solution of **16** (0.0424 g, 0.1 mmol) in 18 mL of acetonitrile and 2 mL of water in an undivided electrochemical cell. Then, copper(I) oxide (0.0071 g, 50 mol%) was added, the setup was equipped with two carbon plate electrodes; the mixture was electrolised under constant current (7 mA) for 5 hours. After completion, the reaction mixture was extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica eluting with a 3:1 mixture of hexane: ethyl acetate to give the title product as a thick brown oil.

Table S3. Optimisation of the oxidative coupling of 16a[a]



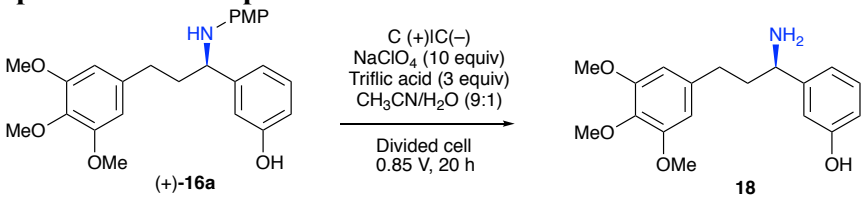
Entry	Variation from standard conditions	Yield[b]
1	none	82 (74[c])
2	$CuSO_4$ instead of Cu_2O	50
3	Cu instead of Cu_2O	NR
4	CuCl instead of Cu_2O	56
5	CuBr instead of Cu_2O	60
6	$[Cu(MeCN)_4]BF_4$ of Cu_2O	53
7	$NaClO_4$ instead of Cu_2O	NR
8	With triflic acid	70 (56[c])
9	Without H_2O	20
10	K_2SO_4 instead of Na_2SO_4	76 (63[c])
11	Pt/Pt instead of C/C	48
12	Cu/Cu instead of C/C	NR

[a] *Carbon plate anode, Carbon plate cathode, 0.1 mmol of* ***16a****, electrolyte 1 equiv, additive 50 mol%, acid 3 equiv, solvent CH_3CN/H_2O 9:1, current 7 mA;* [b] *conversion based on LC-MS;* [c] *isolated yield.*

5. General protocol for the electrochemical deprotection of 16a

In a divided electrochemical glass cell, the protected amine **16a** (0.0422 g, 0.1 mmol) dissolved in the mixture of CH_3CN (9 mL) and triflic acid (13 µL, 3 equiv) was loaded in the anode chamber. The cathode chamber was charged with a solution of $NaClO_4$ (0.0610 g, 10 equiv) in CH_3CN (9 mL) and 2 mL of water. The cell was equipped with two carbon plate electrodes, the potential was maintained at constant voltage of 0.85 V for 20 hours at room temperature. The process was monitored by TLC and LCMS. Upon completion, most of the organic solvent was removed under reduced pressure; a 0.1N aqueous HCl was added dropwise to adjust pH to 3.5. After that, the aqueous solution was washed with DCM (20 mL), the mixture was made alkaline (0.1N NaOH) and then extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford primary amine as a white solid, which was used in the next step without additional purification.

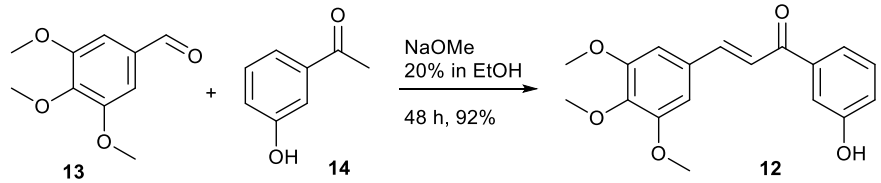
Table S4. Optimisation of deprotection of 16a[a]



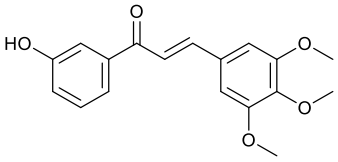
Entry	Variation from standard condition	Yield[b]
1	none	76(70[c])
2	TFA instead of triflic acid	trace
3	HCl instead of triflic acid	NR
4	H_2SO_4 instead of triflic acid	NR
6	$CuSO_4$ as additive	50[c]
7	Without triflic acid	NR
8	Without H_2O	NR
9	Pt (+)/Pt (-) instead of C (+)/C(+)	30

*[a] Carbon plate anode, Carbon plate cathode in a divided cell, 0.1mmol of **16a**, additive 50 mol%, acid 3 equiv, 20 mL of solvent CH_3CN/H_2O 9:1, voltage 0.85 V, reaction time 20 hours, rt; [b]Conversion based on LC-MS; [c]isolated yield.*

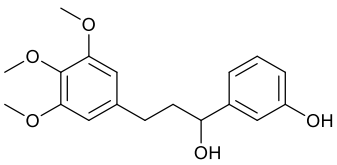
6. Synthetic protocols



(*E*)-1-(3-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one[S1] (12). A solution of NaOH (260 mg, 6.5 mmol, 1.3 equiv) in water (10 mL) was added to a solution of 3-hydroxyacetophenone (0.69 g, 5 mmol) in ethanol (6 mL). Then, 3,4,5-trimethoxybenzaldehyde (0.98 g, 5 mmol, 1.0 equiv) was added portion-wise to the resulting mixture at 0 °C with stirring. The mixture was allowed to warm to room temperature and stirred for 48 hours. After completion of the reaction (as indicated by TLC), the mixture was poured onto crushed ice and acidified with a dilute HCl, the precipitate formed was separated by filtration under suction and washed until the filtrate showed neutral pH. The solid was recrystallized from EtOH to give the title compounds as a yellow solid (1.44 g, yield 92%). M.p. = 175-177 °C (Lit. 174-176 °C), R_f = 0.2 (hexane/ethyl acetate 5:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.68 (s, 3H), 3.82 (s, 6H), 7.03 (m, 1H), 7.18 (s, 2H), 7.34 (m, 1H), 7.44 (m, 1H), 7.59 (m, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.77 (d, J = 15.6 Hz, 1H), 9.76 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 56.0, 60.0, 106.4, 114.5, 119.4, 120.0, 121.3, 129.6, 130.1, 139.0, 139.6, 144.2, 153.0, 157.6, 189.0. IR ν 3219, 2998, 2943, 2828, 1648, 1573, 1502, 1459, 1416 cm^{-1}. The data are in agreement with literature.[S1]

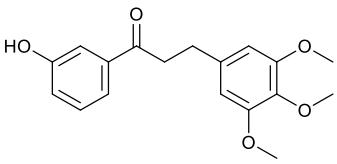


3-(1-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl)phenol (11). To an undivided 10 mL glass cell, unsaturated ketone **12** (63.2 mg, 0.2 mmol) and NH_4SCN (5 equiv, 76 mg) were added, followed by 8 mL of DMSO and 2 mL of MeOH. The cell was equipped with two carbon plate electrodes. The constant current (10 mA) electrolysis was performed at room temperature for 5 hours. The reaction mixture was extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The resulting mixture was purified by column chromatography on silica gel eluting with Hexane/EtOAc (2:1) to afford **11** (58 mg) of as a white solid. Yield 92%, M.p. = 136.8-137.3 °C. R_f = 0.45 (hexane/ethyl acetate 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.87 (q, J = 7.7 Hz, 2H), 2.59 (m, 2H), 3.62 (s, 3H), 3.74 (s, 6H), 4.46 (q, J = 6.0 Hz, 1H), 5.19 (d, J = 4.3 Hz, 1H), 6.47 (s, 2H), 6.63 (m, 1H), 6.75 (m, 1H), 6.79 (s, 1H), 7.10 (m, 1H), 9.27 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 32.1, 40.9, 55.8, 60.0, 71.8, 105.4, 112.8, 113.6, 116.6, 129.0, 135.5, 137.9, 147.8,

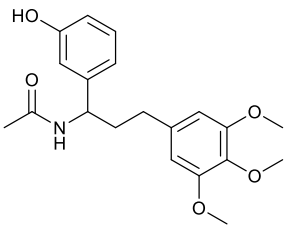


152.8, 157.2. IR ν 3452, 3258, 2963, 2935, 2835, 1591, 1507, 1451, 1419 cm^{-1}. HRMS: $[C_{18}H_{22}NaO_5]^+$ $[M+Na]^+$: calculated 341.1359; found 341.1359.

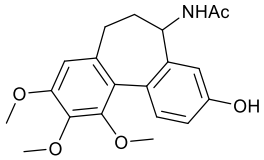
1-(3-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propan-1-one (10). Obtained by the general procedure using MeCN as a solvent. Yield 92%, 0.1453g. M.p. = 142.2-142.5 °C. R_f = 0.2 (Hexane/Ethyl acetate 5:1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.86 (t, J = 7.6 Hz, 2H), 3.30 (t, J = 7.6 Hz, 2H), 3.62 (s, 3H), 3.75 (s, 6H), 6.58 (s, 2H), 7.02 (m, 1H), 7.31 (m, 1H), 7.34 (m, 1H), 7.45 (m, 1H), 9.75 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 30.0, 55.8, 59.9, 105.7, 114.1, 118.9, 120.2, 129.8, 135.7, 136.9, 138.1, 152.7, 157.6, 199.2. The data are in agreement with literature.[1]



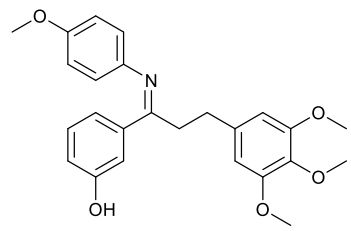
***N*-(1-(3-hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propyl)acetamide (7).** A 25 mL round-bottomed flask was charged with 3-(1-hydroxy-3-(3,4,5-trimethoxyphenyl)propyl)phenol (1.59 g, 5 mmol) in a 1.5 mL of acetonitrile and 0.3 mL of water. The mixture was cooled on an ice bath followed by a slow addition of sulfuric acid (0.15 mL). The ice bath was removed, and the mixture was stirred at room temperature for 36 hours. After the reaction was completed, the mixture was quenched by adding 2.5 mL of a 50% aqueous NaOMe. Then, it was extracted with DCM (3x10 mL). The combined organic layers were passed through a plug of anhydrous magnesium sulfate, concentrated under reduced pressure and purified by a short column chromatography on silica gel eluting with EtOAc to afford the title compound as a white solid (1.31 g). Yield 73%, M.p. = 53-54 °C. R_f = 0.32 (ethyl acetate). ^{1}H NMR (500 MHz, DMSO-d_6) δ1.87 (s, 3H), 1.91 (m, 1H), 2.47 (m, 1H), 2.54 (m, 1H), 3.62 (s, 3H), 3.74 (s, 6H), 4.68 (q, J = 8.5 Hz, 1H), 6.46 (s, 2H), 6.62 (m, 1H), 6.69 (m, 2H), 7.09 (m, 1H), 8.28 (m, 1H), 9.33 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 22.7, 32.9, 37.7, 51.9, 55.7, 59.9, 105.5, 113.5, 113.6, 117.1, 129.2, 135.5, 137.2, 145.3, 152.7, 157.3, 168.5. IR ν 3423, 3238, 3080, 2938, 1593, 1508, 1457, 1420. HRMS: $[C_{20}H_{25}NaNO_5]^+$ $[M+Na]^+$: calculated 382.1625; found: 382.1624.



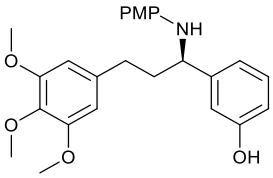
(±)-*N*-(3-hydroxy-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulen-5-yl)acetamide (3). Acetamide **7** (35.9 mg, 0.1 mmol) in a 7 mL of acetonitrile, nBu$_4$NBF$_4$ (0.0043 g, 20 mmol%), TFAA (13.8 µL, 1 equiv) and TFA (7.6 µL, 1 equiv) were added to a 15 mL undivided glass cell equipped with carbon plate electrodes; the mixture was electrolised under constant current of 15 mA at room temperature for 4 hours. The process was monitored by TLC and LCMS. After completion, aqueous solution of $NaHCO_3$ was added to the mixture, which was extracted with ethyl acetate (3x10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica eluting with a 30:1 mixture of DCM/MeOH to give the product as an off-white solid, 24.3 mg (68%). ^{1}H NMR (400 MHz, DMSO-d_6) 1.87 (m, 4H), 2.09 (m, 2H), 2.46 (s, 1H), 3.45 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 4.45 (m, 1H), 6.68 (m, 1H), 6.74 (m, 2H), 7.11 (m, 1H), 8.32 (m, 1H), 9.38 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 22.6, 30.1, 38.4, 48.1, 55.8, 60.4, 60.5, 108.0, 110.2, 112.9, 124.4, 124.7, 130.4, 134.7, 140.5, 141.7, 150.3, 151.8, 156.4, 168.2. The data are in agreement with literature.[S2]



3-(1-((4-methoxyphenyl)imino)-3-(3,4,5-trimethoxyphenyl)propyl)phenol (15a). 5Å molecular sieves (7.25 g) were added to a solution of **10** (1.688 g, 4 mmol) and *p*-anisidine (0.7688 g, 1.05 equiv) in 25 mL of anhydrous toluene. The solution was heated to reflux with a Dean-Stark adapter for 72 hours. The hot reaction mixture was filtered from the sieves, the solvent was removed under reduced pressure and the residue was purified by flash chromatography of a short silica gel column with a 2:1 mixture of hexane/ethyl acetate to give the title compound as a yellow solid. It can also be used directly in the next step, without further purification. Yield 82%, ^{1}NMR (500 MHz, DMSO-d_6) δ 2.82 (t, J = 7.6 Hz, 2H), 3.23 – 3.29 (t, J = 7.6 Hz, 2H), 3.57 (s, 3H), 3.58 (s, 3H), 3.71 (s, 6H), 6.49 – 6.45 (m, 2H), 6.54 (s, 2H), 6.61 – 6.58 (m, 2H), 6.98 (ddd, J = 8.1, 2.5, 0.9 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.30 (dd, J = 2.3, 1.7 Hz, 1H), 7.41 (ddd, J = 7.7, 1.5, 1.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.56, 55.79, 56.29, 60.45, 106.20, 114.62, 115.01, 115.49, 119.47, 120.70, 130.29, 136.21, 137.47, 138.61, 142.82, 151.21, 153.23, 158.13, 199.73.

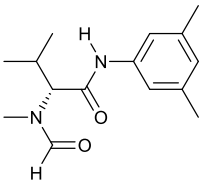


(+)-3-(1-((4-methoxyphenyl)amino)-3-(3,4,5-trimethoxyphenyl)propyl)phenol (16a).



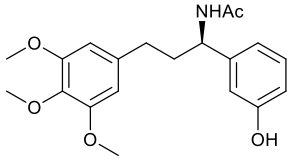
Trichlorosilane (70 µL, 3 equiv) was added dropwise to a solution of imine **15a** (0.0848 g, 0.2 mmol) and catalyst **17a** (5 mg, 5 mol%) in an anhydrous toluene (2 mL) at -30 °C, the reaction mixture was stirred at -30 °C for 4 hours. Then it was quenched with a saturated solution of $NaHCO_3$ (10 mL) and the resulting mixture was extracted with ethyl acetate (3x20 mL). The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc (3:1) to give **16a** as a white solid. Yield 0.077g, 91%, M.p = 178.6°C, R_f = 0.08 (Hexane: Ethyl acetate 3:1); $[\alpha]_D$ = +40 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 – 1.99 (m, 2H), 2.49 – 2.67 (m, 2H), 3.53 (s, 3H), 3.57 (s, 3H), 3.66 (s, 6H), 4.09 – 3.98 (m, 1H), 5.71 (d, J = 7.4 Hz, 1H), 6.39 (s, 1H), 6.41 (s, 3H), 6.50 – 6.54 (m, 1H), 6.55 – 6.59 (m, 2H), 6.71 (dd, J = 9.9, 4.9 Hz, 2H), 7.02 (t, J = 7.8 Hz, 1H), 9.18 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 33.21, 40.53, 55.81, 56.19, 57.49, 60.48, 105.97, 113.75, 113.96, 114.07, 114.98, 117.80, 129.65, 136.02, 138.05, 142.99, 147.34, 150.97, 153.21, 157.85. HPLC analysis [Chiralpak IC, hexane / propan-2-ol (65:35), 0.75 mL/min, t_{minor} = 19.40 min, t_{major} = 22.30 min] showed 99 % ee. HRMS: $[C_{25}H_{27}NNaO_5]^+$ $[M+Na]^+$: calculated 446.1943; found 446.1938.

Kenamide (+)-17. The catalysts was synthesized following the literature method.[SP3] Yield 80%,



M.p = 101.4°C , R_f = (hexane/ethyl acetate 3:1), $[\alpha]_D$ = +19.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.04 (d, J = 6.5 Hz, 3H), 2.26 (s, 6H), 2.44 (dt, J = 19.6, 6.6 Hz, 1H), 2.99 (s, 3H), 4.41 (dd, J = 11.2, 3.7 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 8.13 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.66, 19.62, 21.39, 25.37, 31.64, 63.23, 117.74, 126.25, 137.61, 138.77, 164.04, 167.30.[S3]

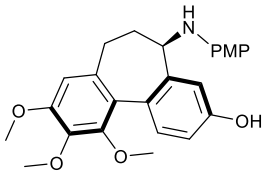
(+)-3-(1-amino-3-(3,4,5-trimethoxyphenyl)propyl)phenol (7). In a divided electrochemical



glass cell, amine **16a** (0.0422 g, 0.1 mmol) was dissolved in a mixture of CH_3CN (9 mL) and triflic acid (13 µL, 3 eq) in the anode chamber. The cathode chamber was charged with a solution of $NaClO_4$ (0.1220 g, 10 equiv) in CH_3CN (9 mL) and 2 mL of water. The cell was equipped with two carbon plate electrodes, the potential was maintained at constant voltage of 0.85 V for 20 hours at room temperature. The process was monitored by TLC and LCMS. After completion,

most of the organic solvent was removed under reduced pressure; a 0.1N aqueous HCl was added dropwise to adjust pH to 3.5. Then, the aqueous solution was washed with DCM (20 mL), the mixture was made alkaline (0.1N NaOH) and extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford primary amine as an off-white solid (0.0221 g), which used for the next step without additional purification. It was dissolved in DCM (2 mL) in a round-bottomed flask, followed by a dropwise addition of acetic anhydride (7.8 μL, 1.2 eq) under stirring, the mixture was left stirring at room temperature for 20 minutes. After that, the reaction mixture was treated with a saturated solution of Na_2CO_3 (10 mL), the organic phase then washed by three times with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the title compound as a light-yellow solid. Yield 0.0222 g, 62%, $[\alpha]_D$ = + 42 (c 0.5, $CHCl_3$). ^{1}H NMR spectrum matched that of racemic sample **7**.

(+)-9,10,11-trimethoxy-5-((4-methoxyphenyl)amino)-6,7-dihydro-5H-dibenzo-[*a,c*][7]annulen-3-ol (19). Na_2SO_4 (0.0142 g, 1 equiv) was added to a solution of **16a** (0.0424 g, 0.1 mmol) in 18 mL acetonitrile and 2 mL water in an undivided cell, followed by the addition of copper(I) oxide (0.0071 g, 50 mol%). The mixture was equipped with carbon plate electrodes and electrolysed under a constant current of 7 mA for 5 hours. After the reaction was complete, the mixture was extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by column chromatography on silica eluting with a 3:1 mixture of hexane: ethyl acetate to give the title product as a thick brown oil. Yield 0.0312g, 74%. R_f = 0.29 (hexane/ethyl acetate 3:1); $[\alpha]_D$ = +293 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-*d*6) 1.85 (dd, *J* = 13.1, 5.8 Hz, 1H), 2.14 (dt, *J* = 9.9, 5.6 Hz, 1H), 2.40 – 2.43 (m, 1H), 2.51 – 2.57 (m, 1H), 3.44 (s, 3H), 3.63 (d, *J* = 1.8 Hz, 6H), 3.69 (s, 3H), 4.54 (q, *J* = 5.3 Hz, 1H), 6.47 (s, 1H), 6.55 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 2H), 6.71 (d, *J* = 9.1 Hz, 2H), 6.76 (d, *J* = 6.6 Hz, 2H), 7.07 – 7.02 (m, 1H), 9.23 (s, 1H); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 24.89, 28.30, 31.23, 55.67, 56.24, 59.85, 60.94, 64.89, 107.68, 113.69, 113.93, 114.35, 117.19, 121.88, 126.38, 129.77, 130.17, 141.52, 145.87, 145.93, 146.80, 148.59, 154.49, 157.89. HRMS: $[C_{25}H_{27}NNaO_5]^+$ $[M+Na]^+$: calculated 444.1787; found 444.1782.



(+)- *N*-Acetylcolchinol (3). In a divided glass cell, amine **19** (42 mg, 0.1 mmol) dissolved in a mixture of CH_3CN (9 mL) and triflic acid (13 µL, 3 equiv) was loaded into the anode chamber. The cathode chamber was charged with a solution of $NaClO_4$ (61 mg, 10 equiv) in CH_3CN (9 mL) and 2 mL of water. The cell was equipped with two carbon plate electrodes, the potential was maintained at a constant voltage of 0.7 V for 15 hours at room temperature. Most of the organic solvent was removed under reduced pressure; a 0.1N aqueous HCl was added dropwise to adjust pH to 3.5. Then, the aqueous solution was washed with DCM (20 mL), the mixture was made alkaline (0.1N NaOH) and extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford primary amine as a white solid, which was dissolved in DCM (2 mL) in a round bottomed flask, followed by a dropwise addition of acetic anhydride (7.8 µL, 1.2 equiv) under stirring. The mixture was left stirring at room temperature for 8 h. After that, the reaction mixture was treated with a saturated solution of Na_2CO_3 (10 mL), the organic phase then washed three times with water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to afford the title product as a white solid. Yield 0.0249 g, 70%. $[\alpha]_D$ = +48.2 (c 0.5, $CHCl_3$) (Lit:[S2] $[\alpha]_D$ = –55.8 (c 0.135, $CHCl_3$)). ^{1}H NMR spectrum matched that of racemic sample **3**.

7. General protocol for Cyclic Voltammetry

Cyclic voltammetry was recorded using a Princeton Applied Research VersaSTAT 3. A glassy carbon disk, Pt wire, and Ag/Ag^+ ($AgNO_3$ in acetonitrile) were used as the working, counter, and reference electrodes, respectively. Anhydrous acetonitrile was used as the solvent with 10 mM $[NBu_4][BF_4]$ as supporting electrolyte. The solution was deoxygenated by bubbling with Ar as appropriate and experiments were run under a blanket of Ar. The CV curves of linear acetamide **7** and *N*-acetylcolchonol **3** are shown in Figure S1.

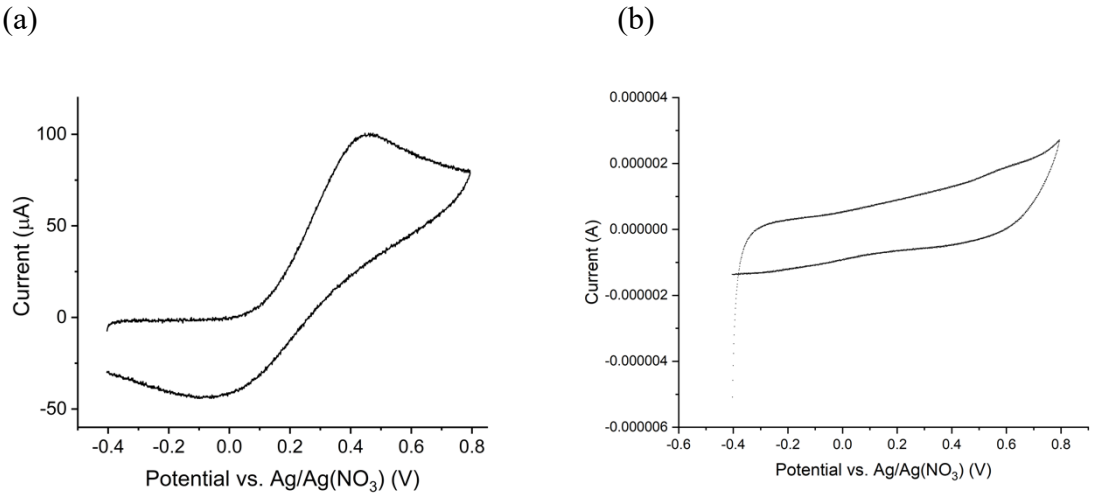
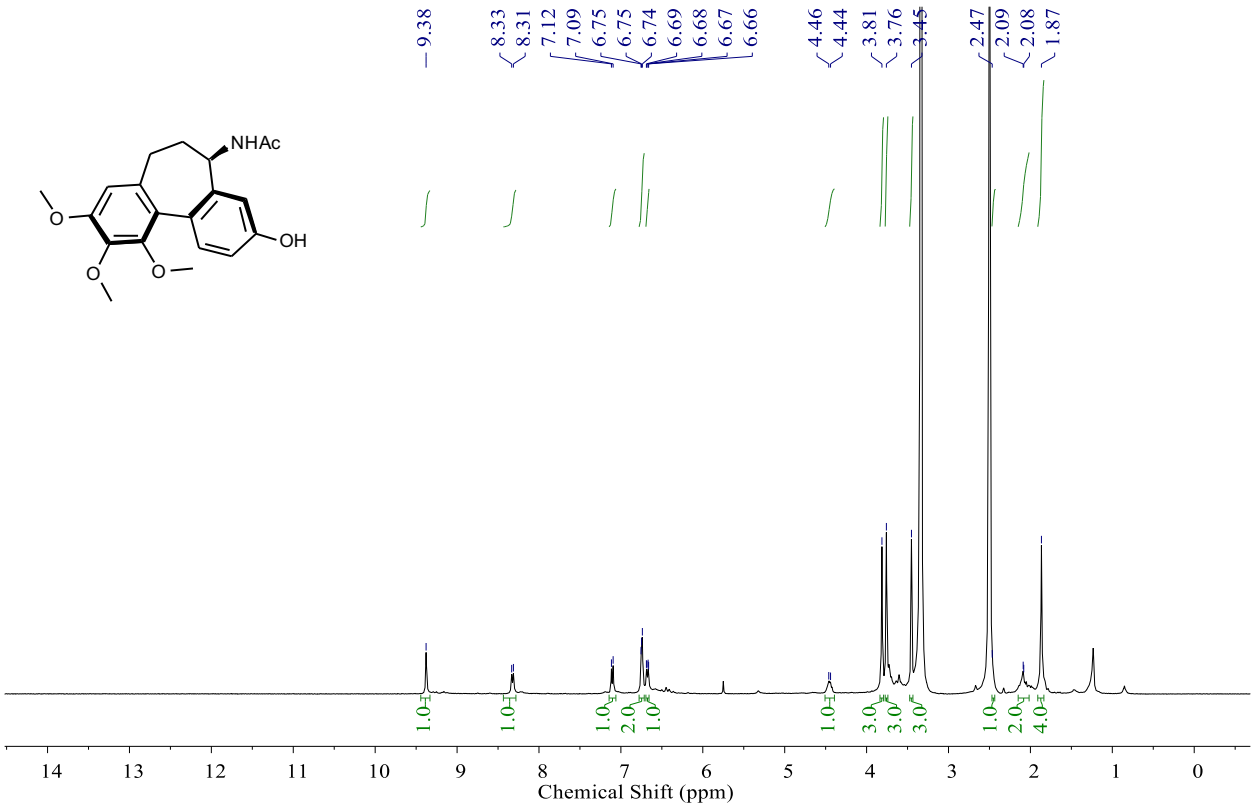


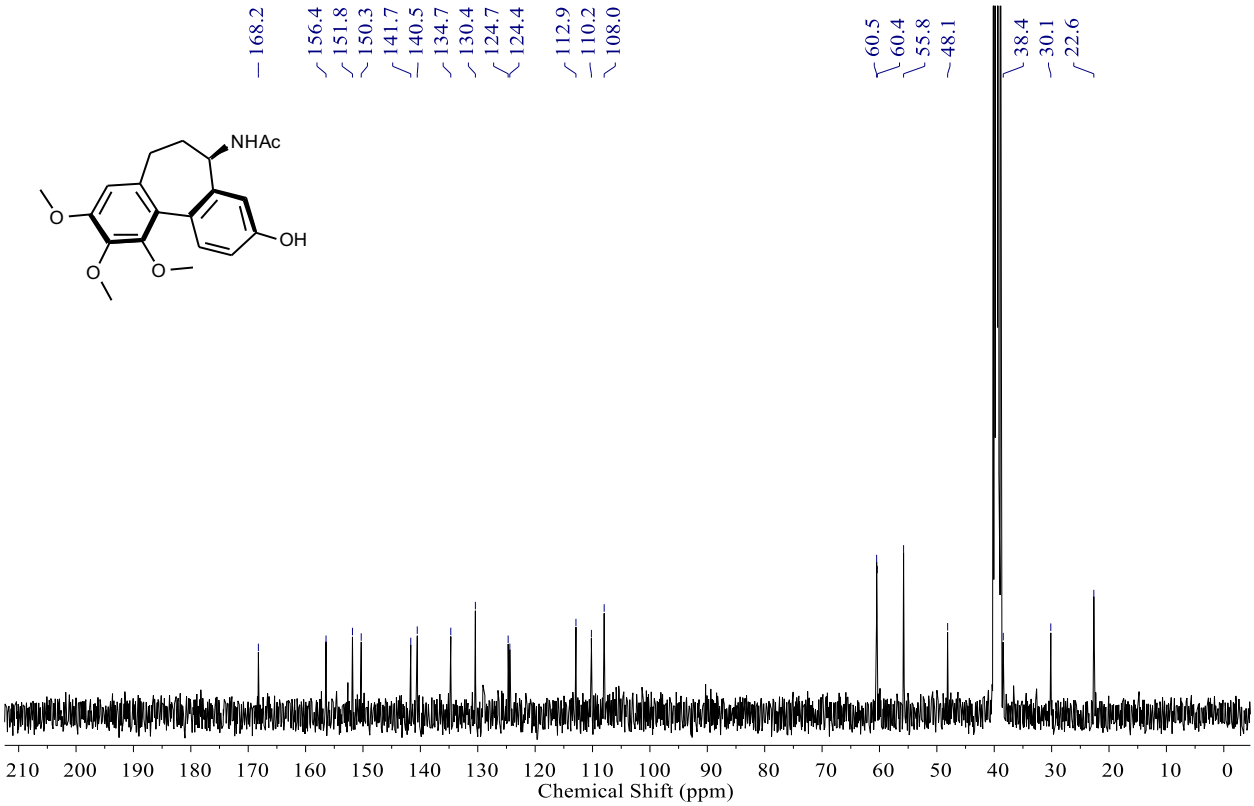
Figure S1. The redox behaviour of (a) acetamide 7 and (b) *N*-acetylcolchonol 3.

8. ^{1}H and ^{13}C-NMR Spectra

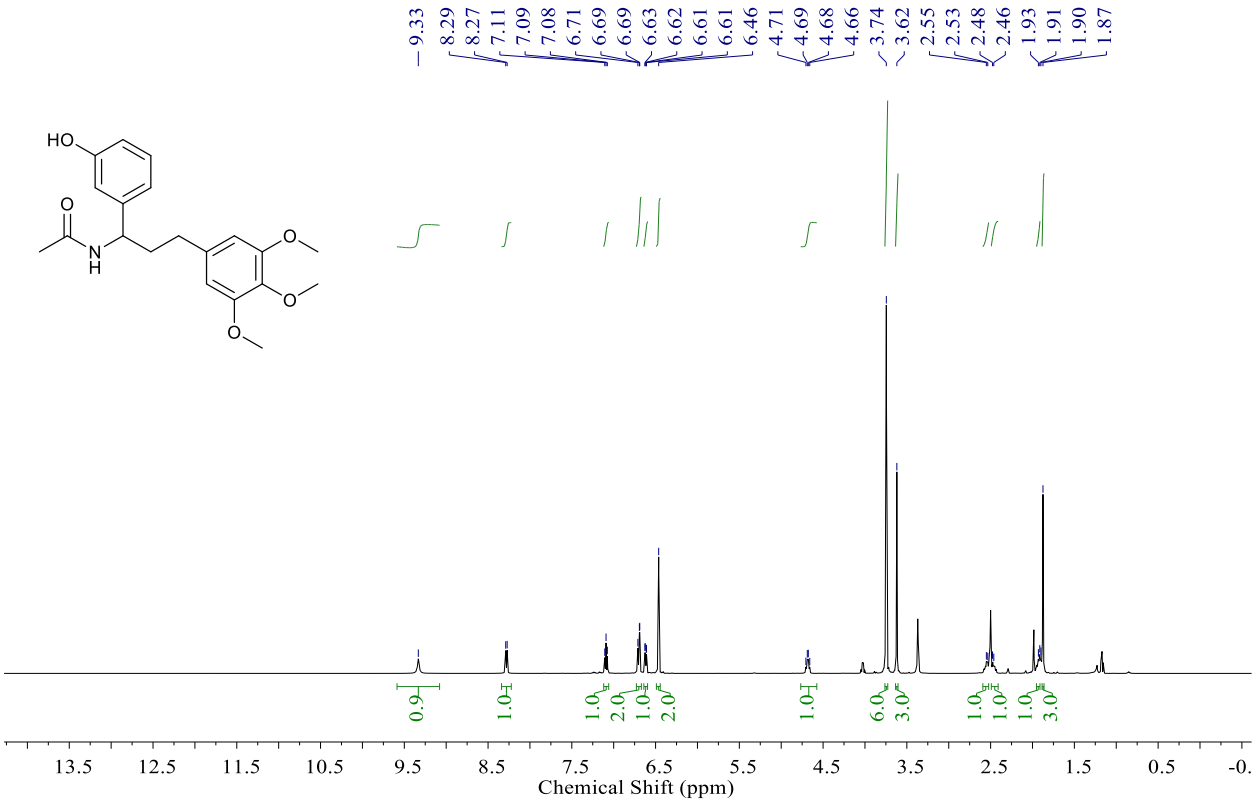
3, ^{1}H NMR (400 MHz, DMSO)



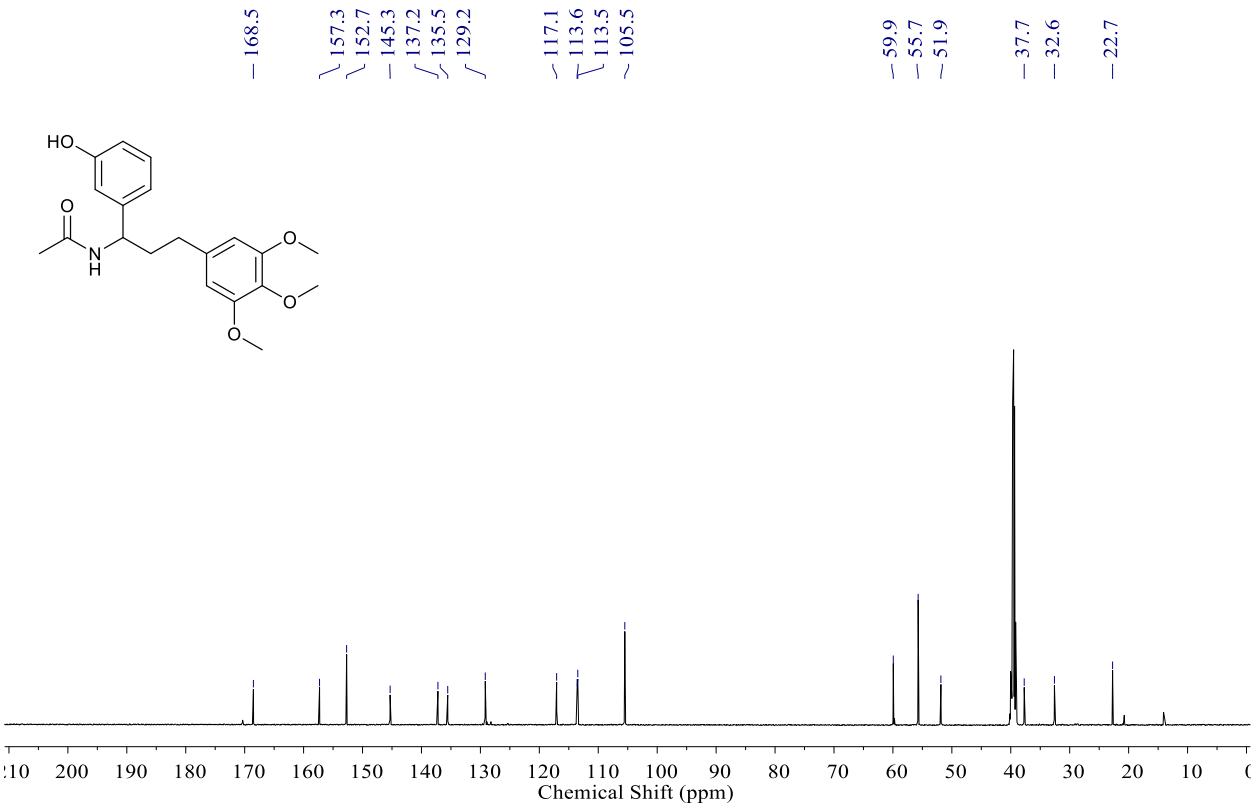
3, ^{13}C NMR (100 MHz, DMSO)



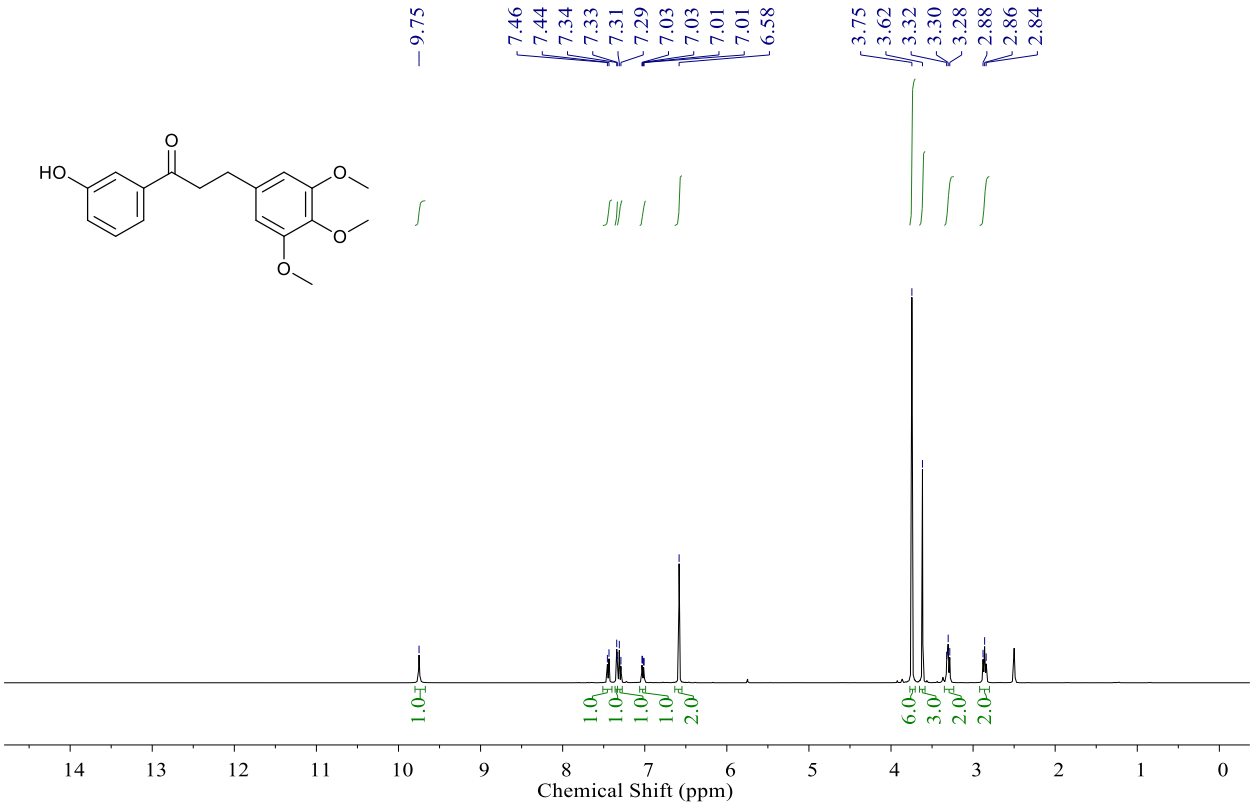
7, ^{1}H NMR (500 MHz, DMSO)



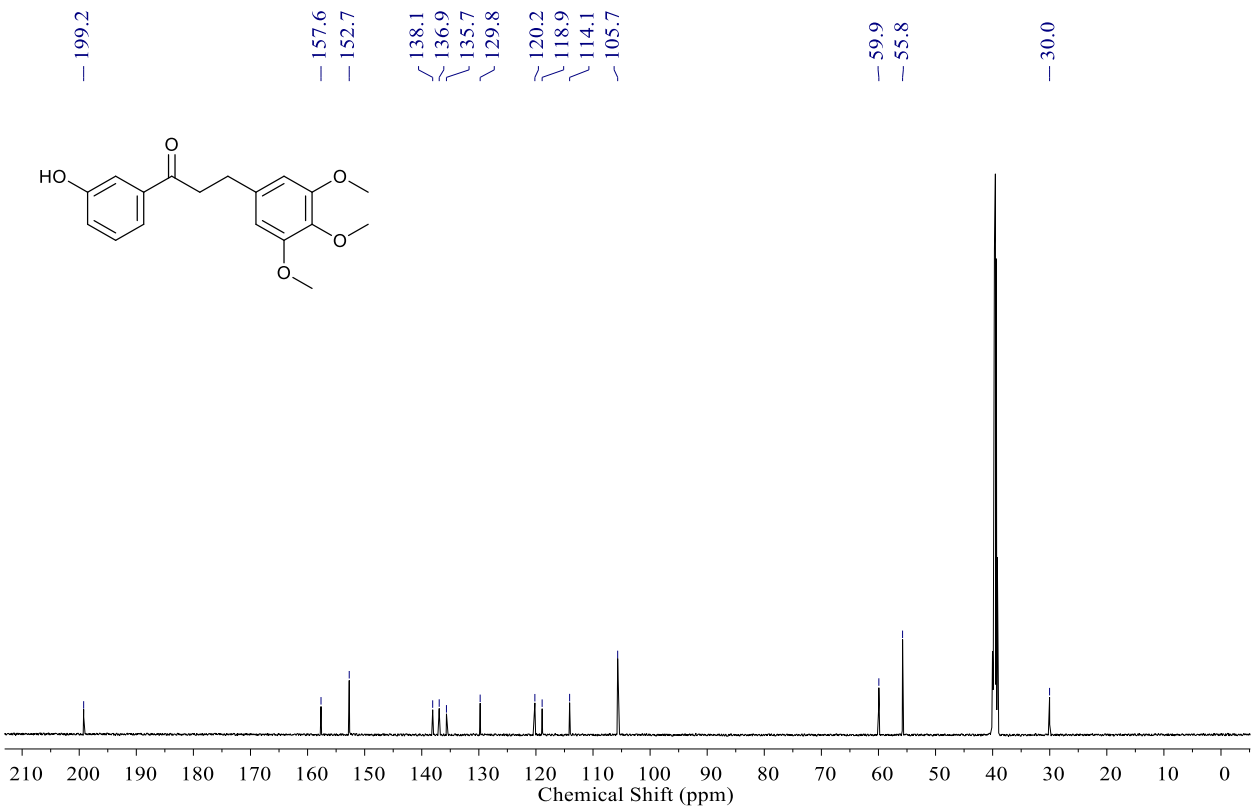
7, ^{13}C NMR (125 MHz, DMSO)



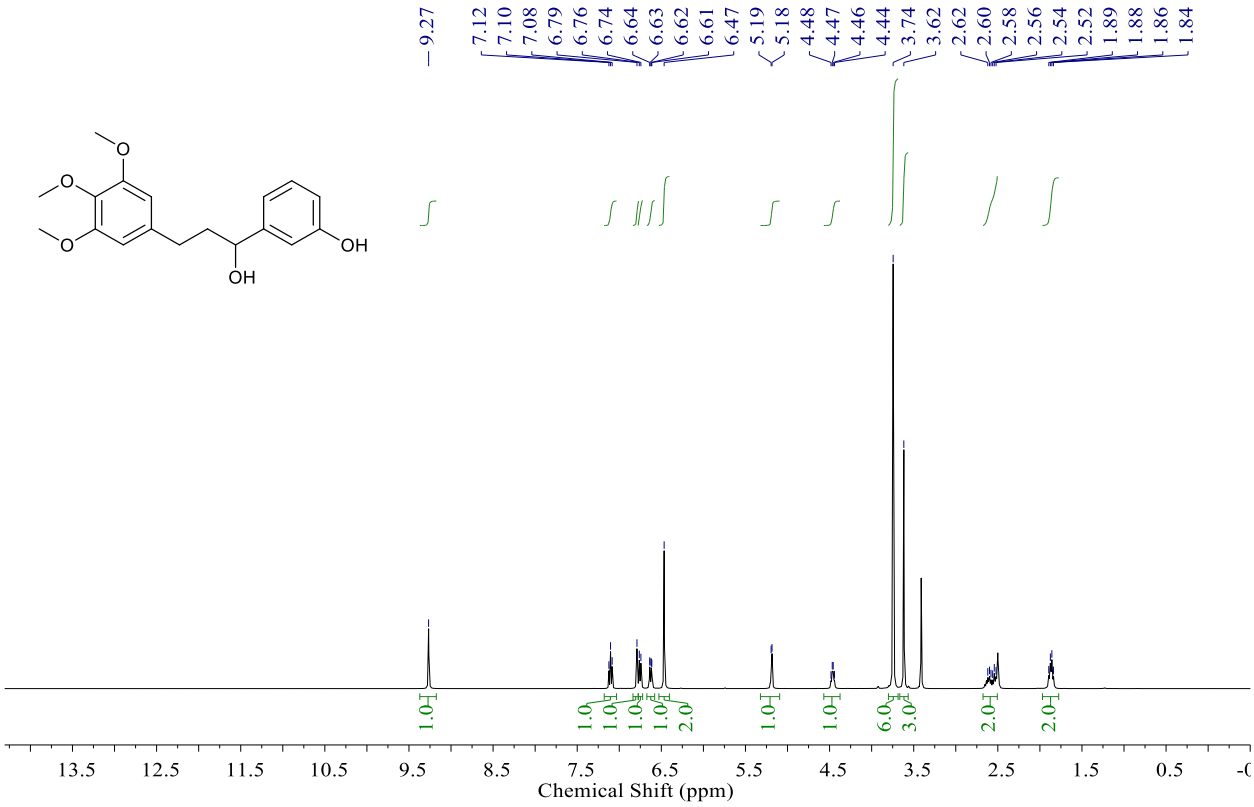
10, ^{1}H NMR (500 MHz, DMSO)



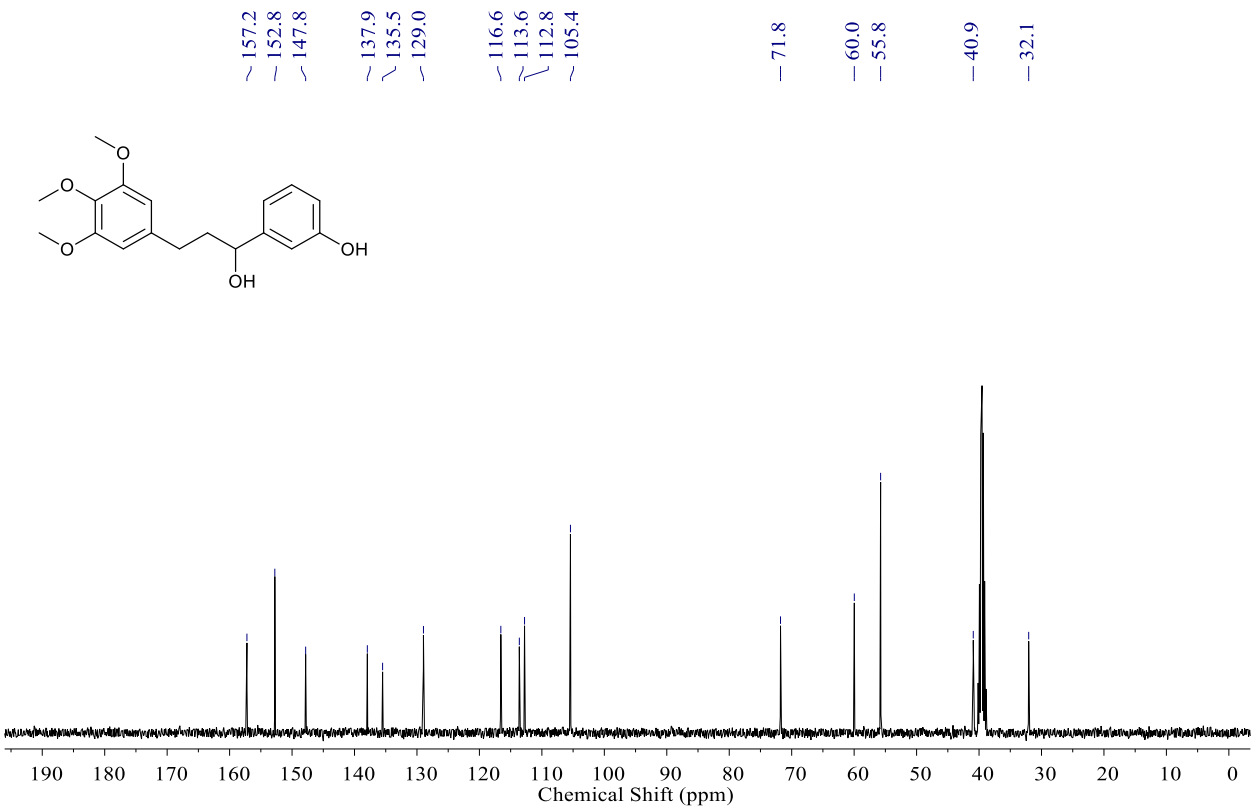
10, ^{13}C NMR (125 MHz, DMSO)



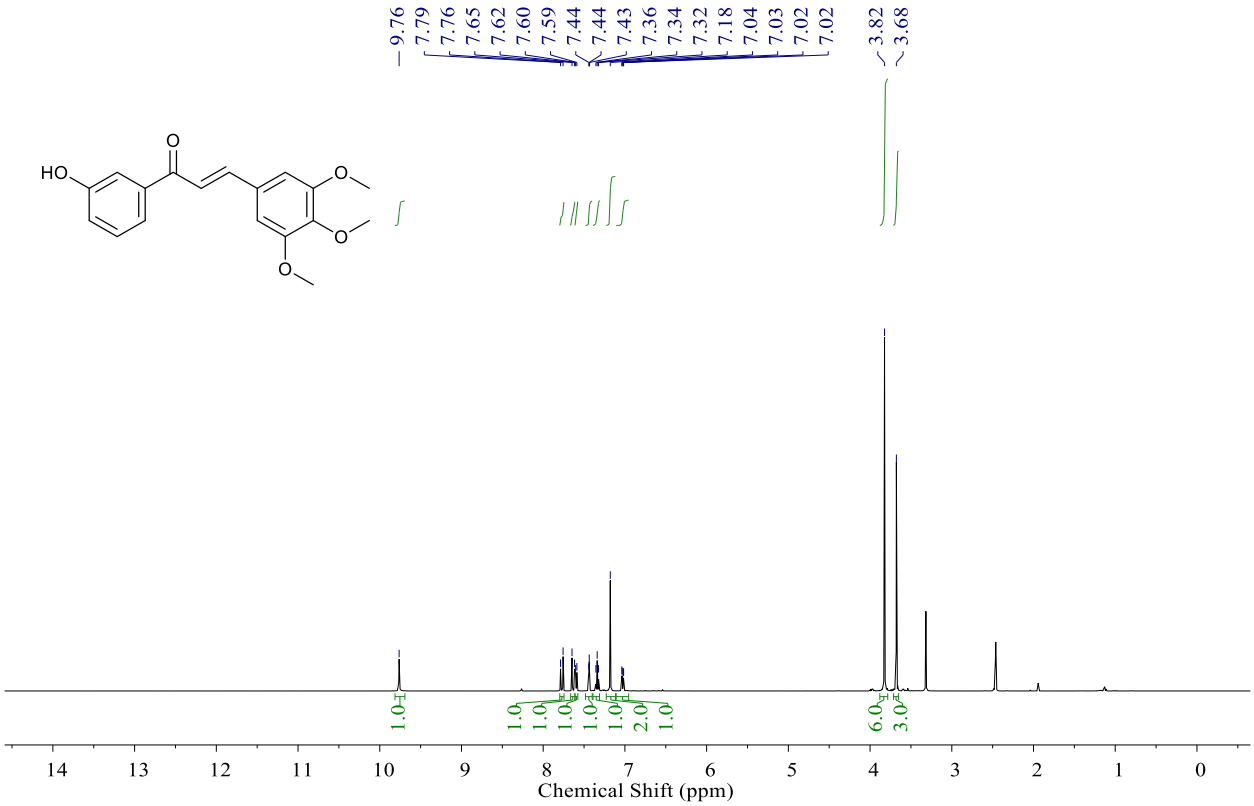
11, ^{1}H NMR (500 MHz, DMSO)



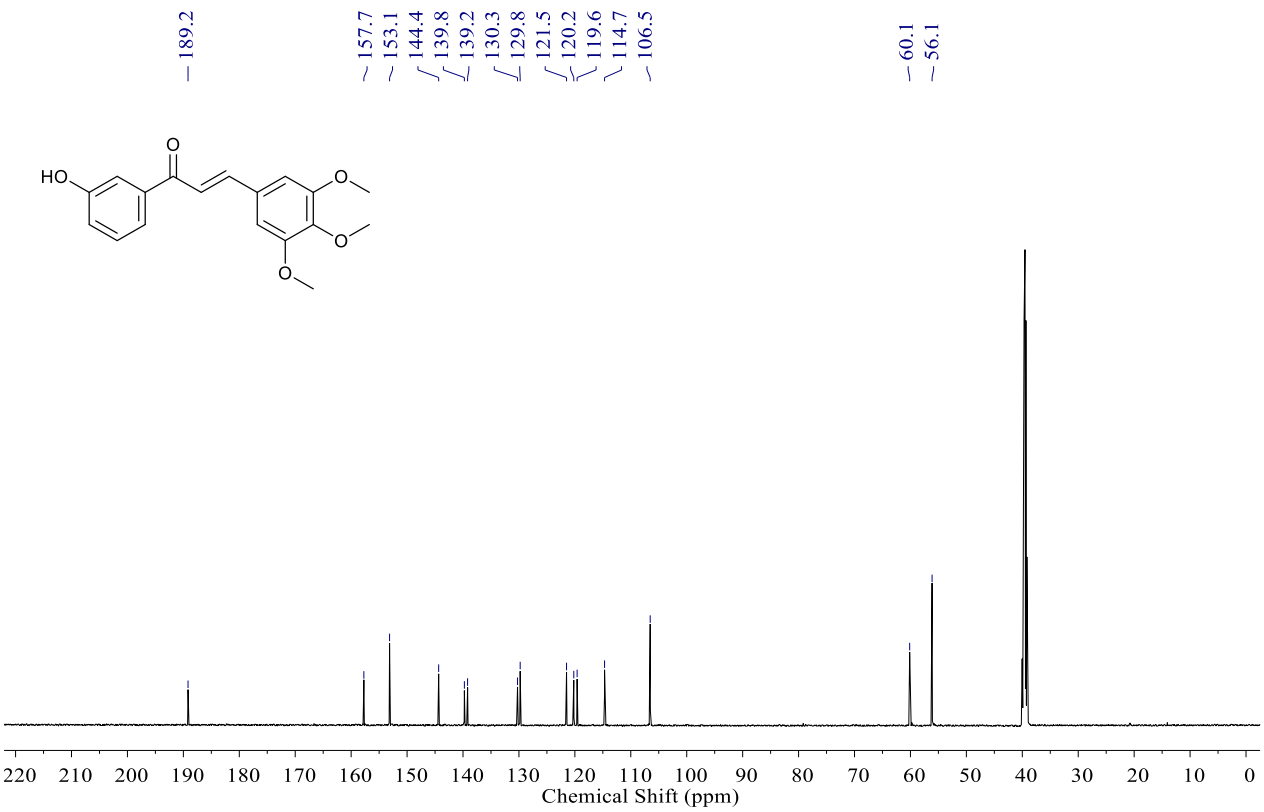
11, ^{13}C NMR (125 MHz, DMSO)



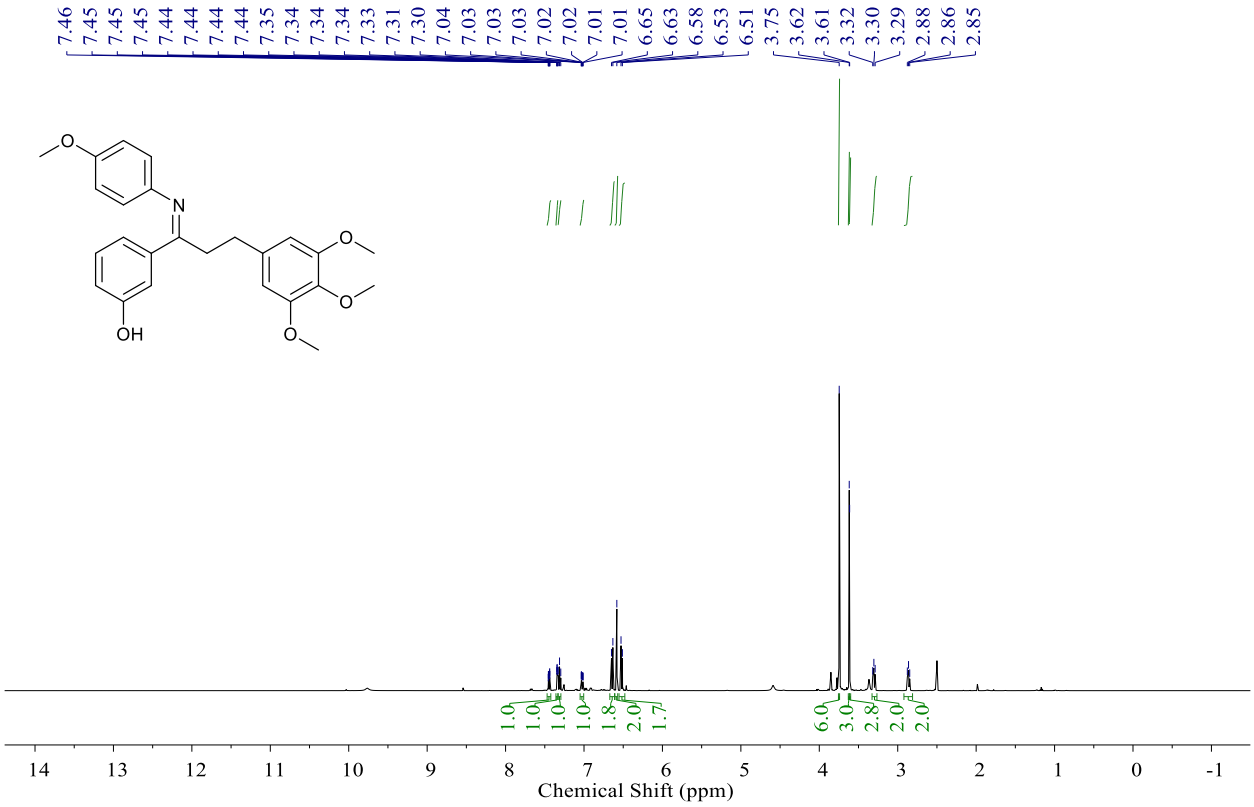
12, ^{1}H NMR (500 MHz, DMSO)



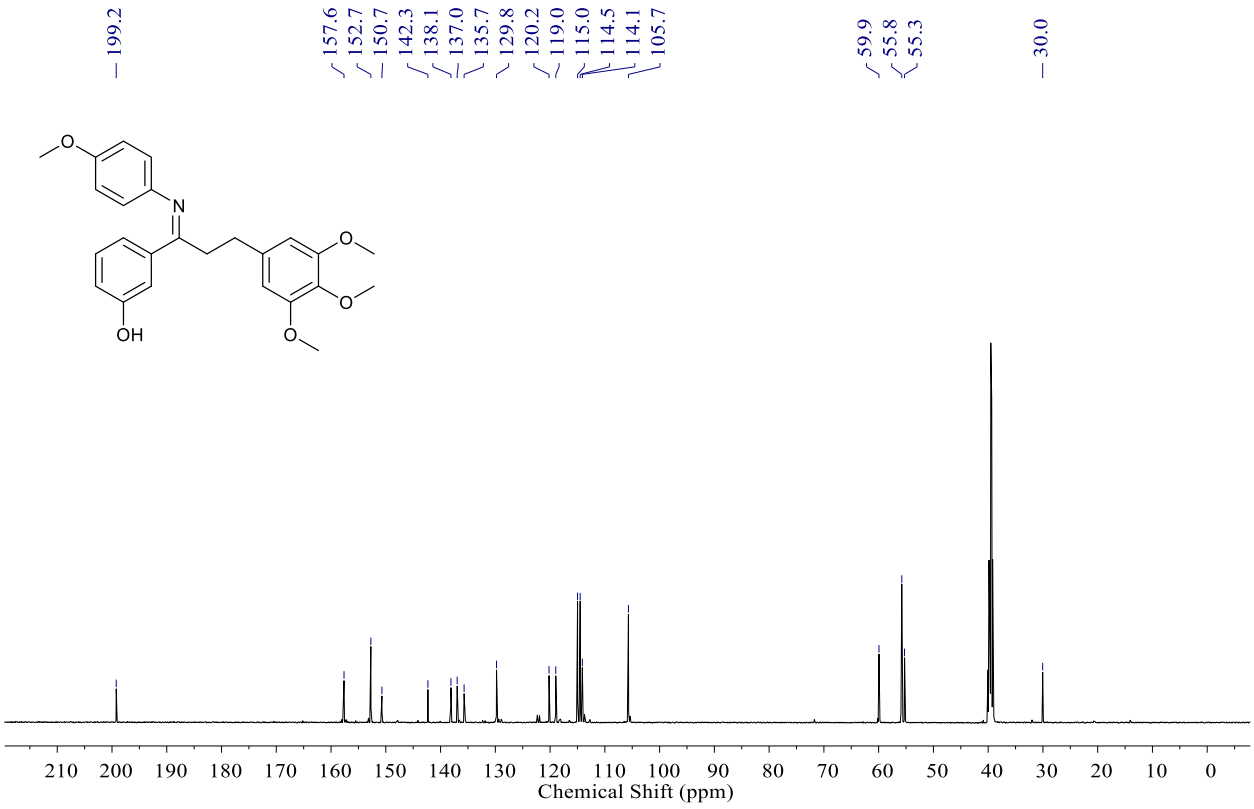
12, ^{13}C NMR (125 MHz, DMSO)



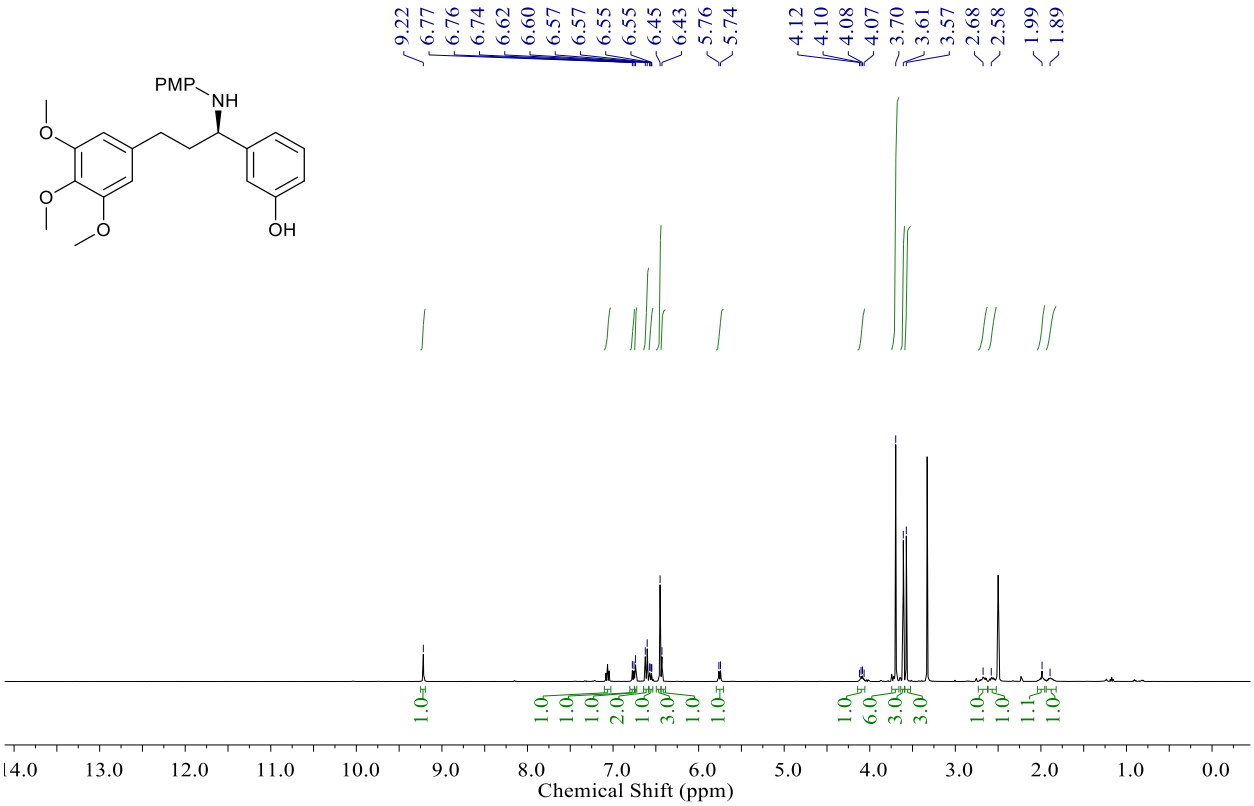
15, ^{1}H NMR (400 MHz, DMSO)



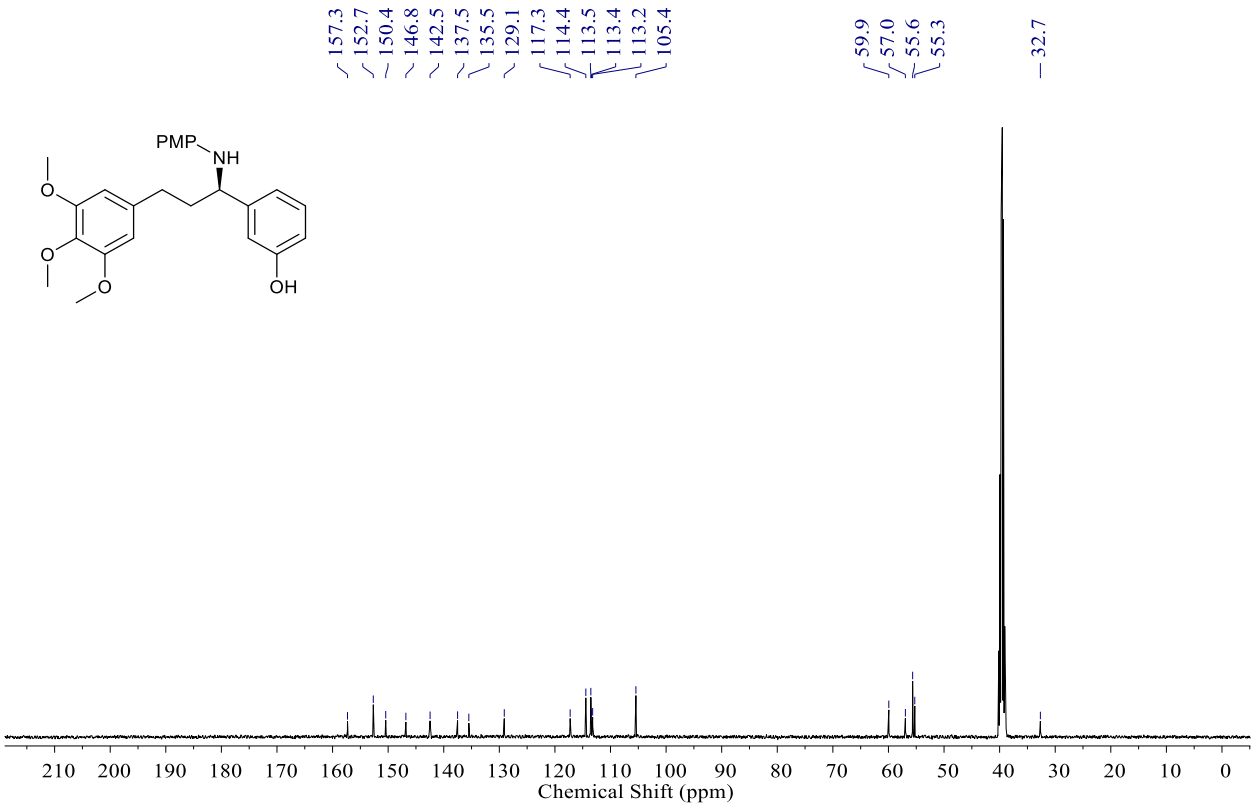
15, ^{13}C NMR (100 MHz, DMSO)



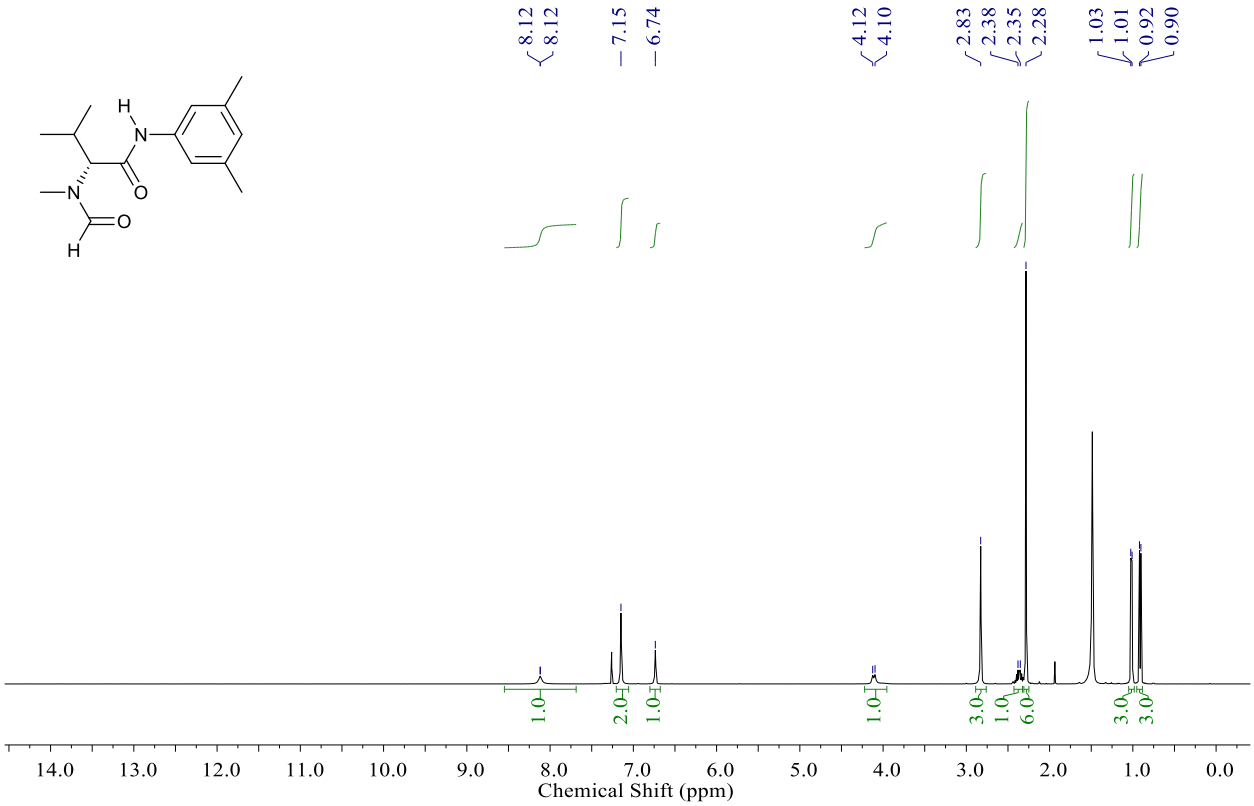
16, ^{13}H NMR (400 MHz, DMSO)



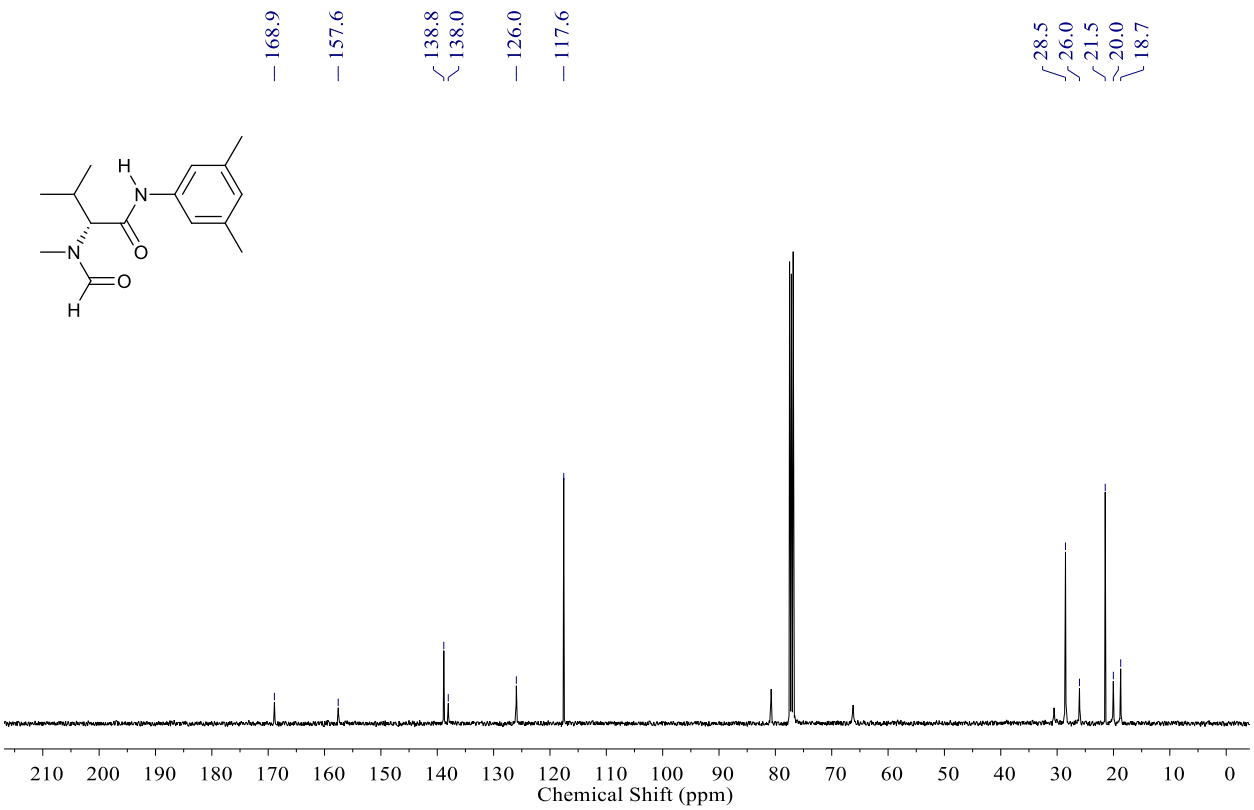
16, ^{13}C NMR (100 MHz, DMSO)



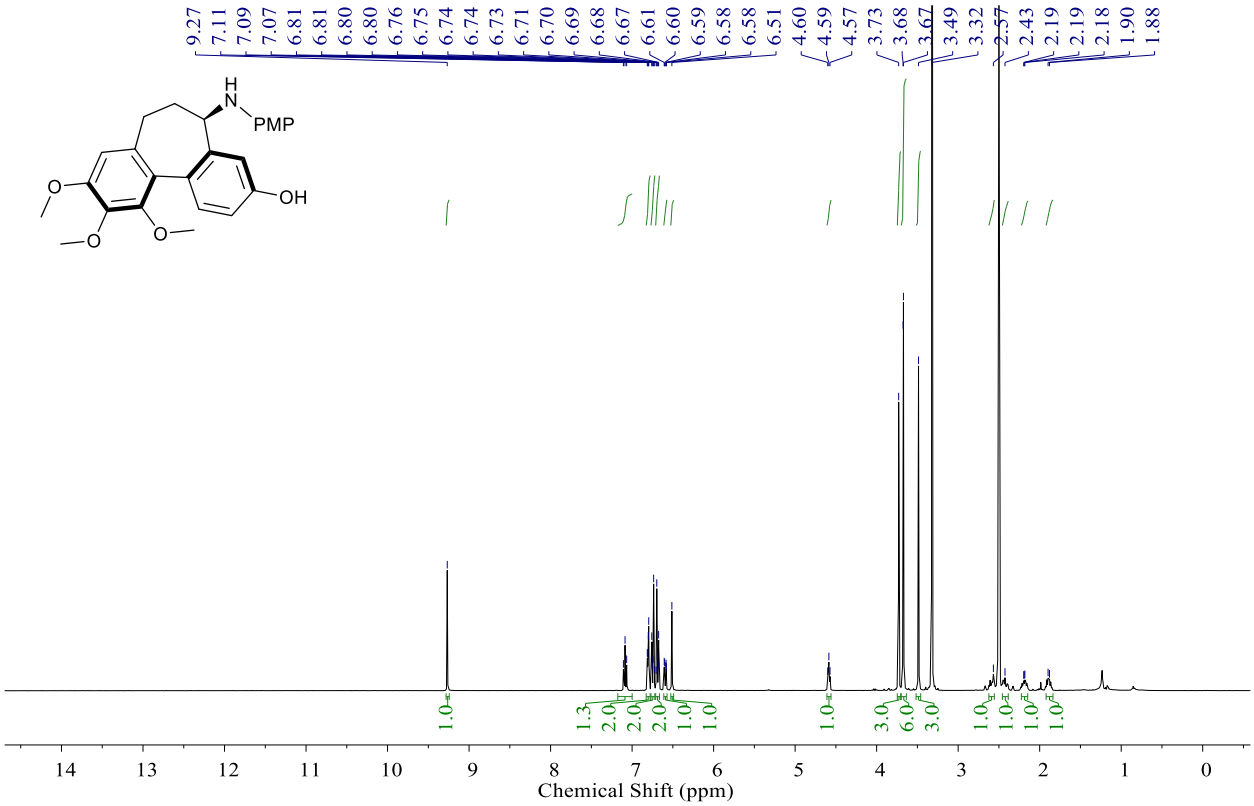
17, ^{1}H NMR (400 MHz, $CDCl_3$)



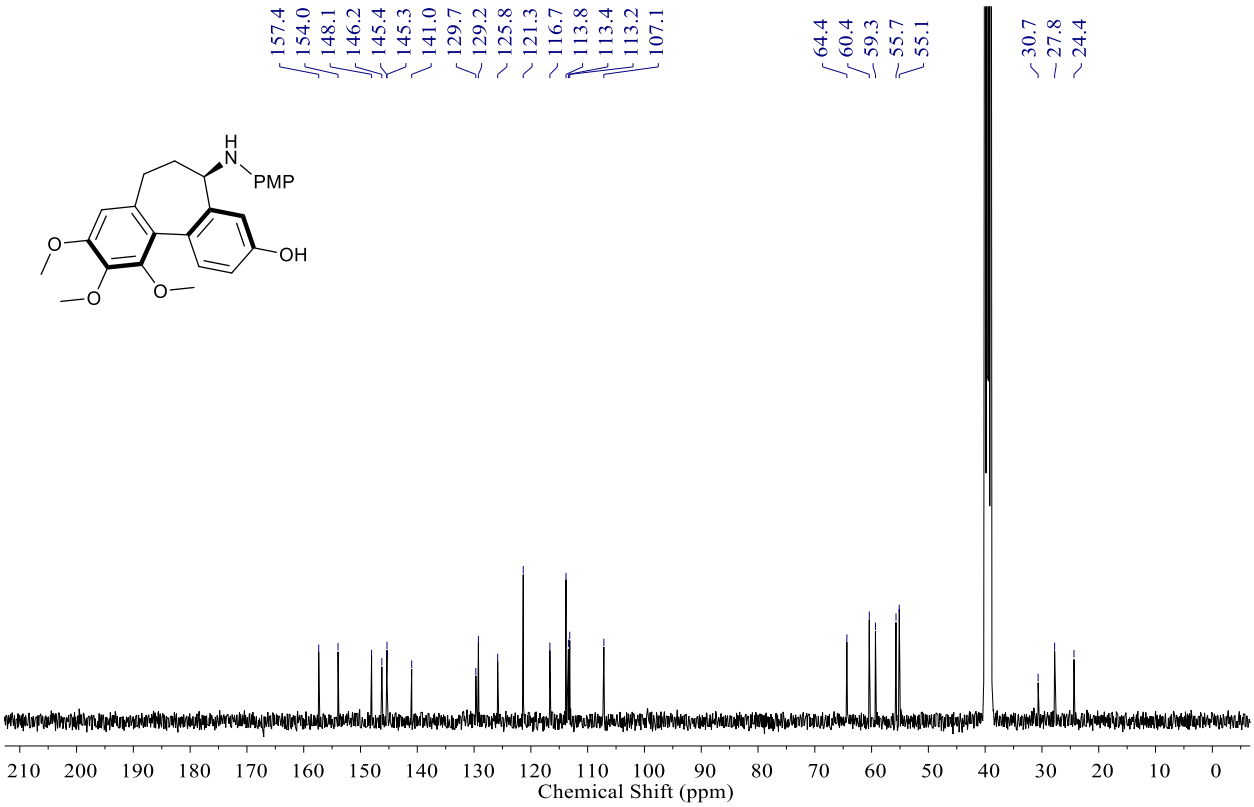
17, ^{13}C NMR (100 MHz, $CDCl_3$)



19, ^{1}H NMR (400 MHz, DMSO)



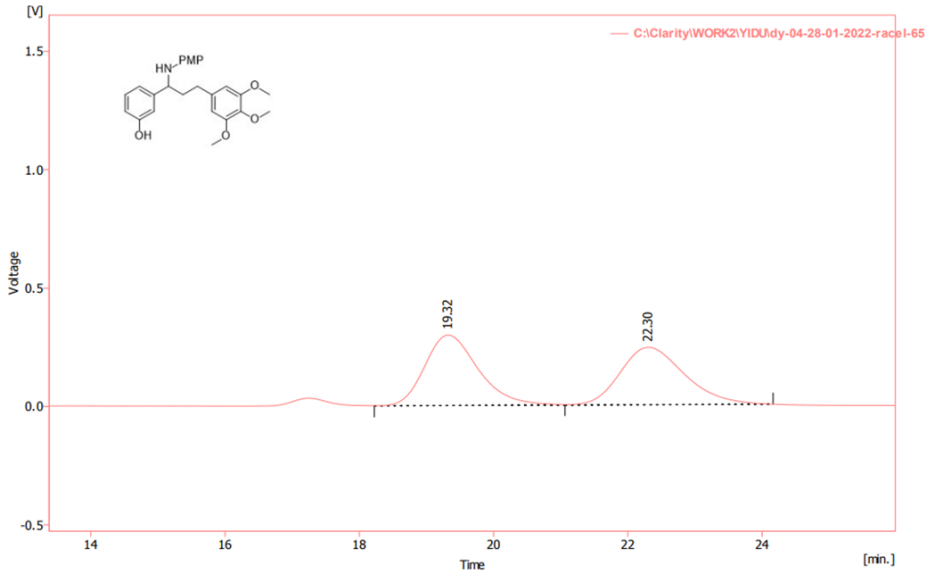
19, ^{13}C NMR (100 MHz, DMSO)



9. Chiral HPLC traces

HPLC Condition: Chiralpak IC, eluent: Hexane/Propan-2-ol (65:35); flow rate: 0.75 mL/min,

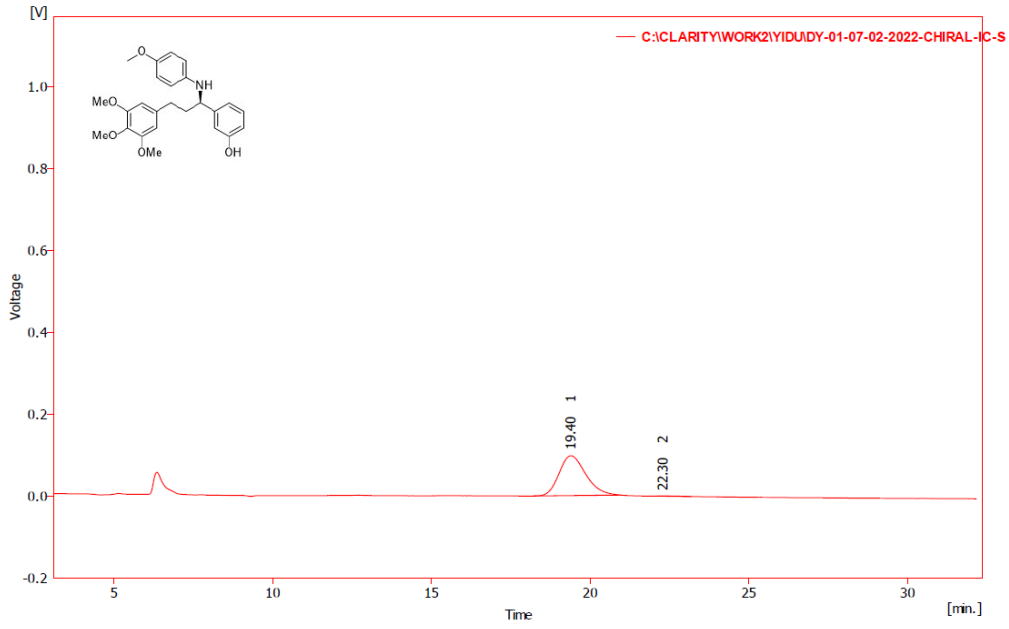
Racemic standard (±)-16a



Result Table (Uncal - C:\Clarity\WORK2\YIDU\dy-04-28-01-2022-racel-65)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.324	16437.922	297.594	50.4	55.1	0.84
2	22.304	16150.713	242.393	49.6	44.9	1.03
	Total	32588.636	539.986	100.0	100.0	

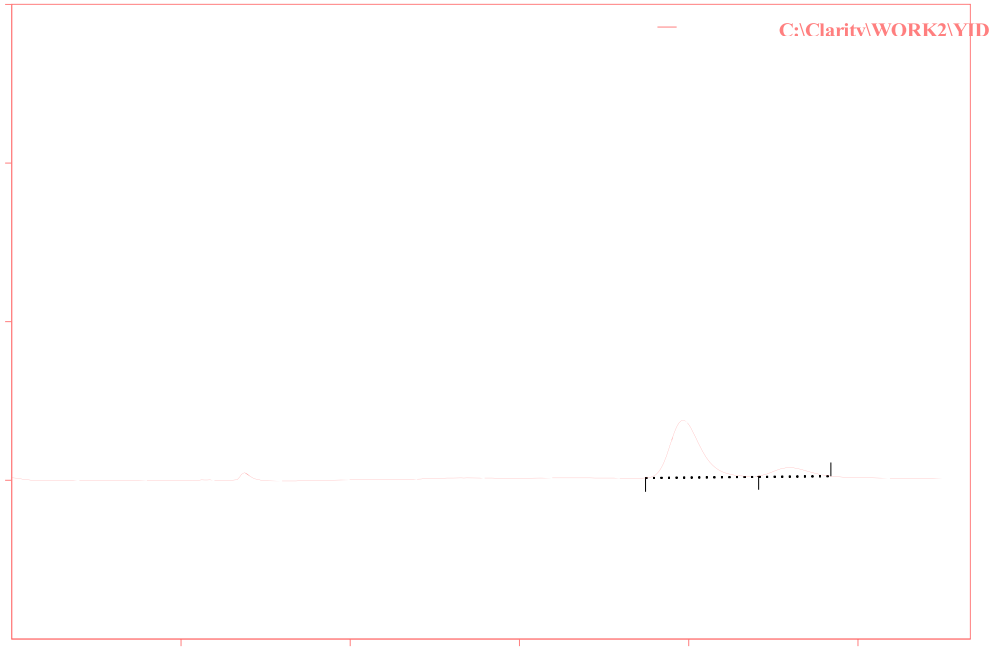
Enantioenriched (+)-16a, the reaction run at –30 ºC



Result Table (Uncal - C:\CLARITY\WORK2\YIDU\DY-01-07-02-2022-CHIRAL-IC-S)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.396	5705.325	97.596	99.6	99.6	0.91
2	22.300	23.691	0.392	0.4	0.4	0.30
	Total	5729.016	97.988	100.0	100.0	

Enantioenriched (+)-16a, the reaction run at RT



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	19.836	22947.729	362.829	85.5	86.5	0.96
2	22.968	3905.325	56.560	14.5	13.5	1.14
	Total	26853.053	419.389	100.0	100.0	

References

S1. K. Silbermann, C. P. Shah, N. U. Sahu, K. Juvale, S. M. Stefan, P. S. Kharkar and M. Wiese, *Eur. J. Med. Chem.*, 2019, **164**, 193-213.

S2. N. Nicolaus, J. Reball, N. Sitnikov, J. Velder, A. Termath, A. Y. Fedorov and H.-G. Schmalz, *Heterocycles*, 2011, **82**, 1585-1600.

S3. A. V. Malkov, S. Stončius, K. N. MacDougall, A. Mariani, G. D. McGeoch and P. Kočovský, *Tetrahedron*, 2006, **62**, 264-284.