

Supporting Information

Organocatalytic (3+3)-cycloaddition of *ortho*-substituted phenyl nitrones with aryl cyclopropane carbaldehydes: A facile access towards the synthesis of enantioenriched 1,2-oxazinanes

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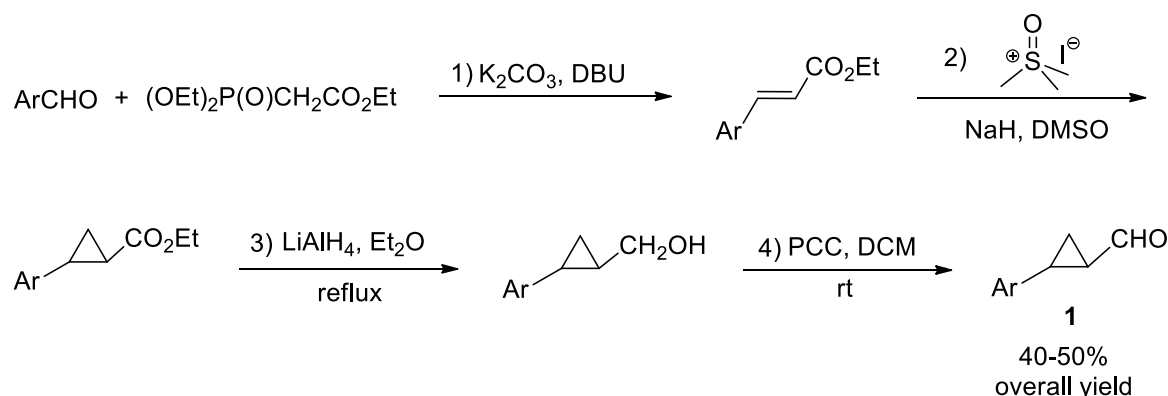
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1. General Information

All reactions were carried out under inert atmosphere with oven-dried glasswares. All solvents and reagents were obtained from commercial sources and were purified following the standard procedure prior to use. Powdered molecular sieves (4Å MS) were dried at 200 °C under vacuum prior to use. Thin-layer chromatography was performed on Merck precoated silica gel 60 F254 aluminum sheets with detection under UV light at 254 nm and charring with *p*-anisaldehyde solution. Chromatographic purifications were performed with silica gel (230-400 mesh) and melting points were taken on Stuart digital melting point apparatus. Nuclear magnetic resonance (NMR) spectroscopy was performed using JEOL 400 MHz and HRMS was recorded on Waters Xevo G2-XS (Q-TOF). The ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃. Chemical shifts of ¹H and ¹³C NMR spectra are expressed in parts per million (ppm). All coupling constants are absolute values and are expressed in Hertz. The description of the signals includes the following: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, br = broad, and m = multiplet. Optical rotations were measured on a Anton Paar MCP 200, [α]^D values are given in deg·cm³·g⁻¹·dm⁻¹; concentration (c) in g (100 mL)⁻¹. The enantiomeric excess (*ee*) values of the products were determined by High Performance Liquid Chromatography (Waters modular system) using Daicel Chiralpak IC, and ASH columns as chiral stationary phase.

2. General procedure for the preparation of *trans*-2-Arylcyclopropanecarbaldehydes (**1**)¹



1) To a mixture of triethyl phosphonoacetate (1.1 equiv.), DBU (0.035 equiv.), and finely ground K₂CO₃ (2 equiv.) was added ArCHO (1 equiv.) and the resulting mixture was stirred using a magnetic stirrer for 4 h at room temperature under argon atmosphere. Ethyl acetate was added to the crude mixture and the solid was filtered off. The solid was rinsed with ethyl acetate and the combined filtrate was concentrated. The resulting oil was distilled under reduced pressure using a bulb-to-bulb apparatus (10 mm Hg/240 °C) to give corresponding alkene (yield 84%) (E:Z = 99:1).

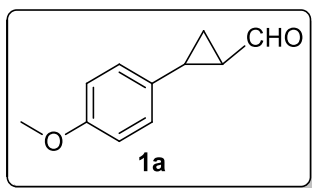
2) A suspension of TMSOI (1.2 equiv.) and NaH (1.5 equiv.) in anhydrous DMSO (15 mL) was stirred for 1 h. A DMSO solution (14 mL) of alkene (14 mmol, 1 equiv) was added at 0 °C. The reaction mixture was stirred at 55 °C for 24 h. Another suspension of TMSOI (0.3 equiv.) and NaH (0.3 equiv.) in DMSO (10 mL) was added to the reaction mixture and reaction was stirred at 65 °C for 84 h. The solution was poured into a brine solution and extracted with

ethyl acetate. Combined organic layer was washed with water and dried over MgSO_4 , concentrated and purified by silica gel column to afford corresponding cyclopropane derivative as a white solid (60-80% yield).

3) To a stirred solution of LAH (1.5 equiv.) in 7 mL diethyl ether was added dropwise a solution of cyclopropane ester (0.90 mmol, 1equiv.) in 3 mL diethyl ether under N_2 atmosphere. After addition was completed the reaction mixture was refluxed for another 6 h. The reaction mixture was then cooled to rt, and the excess LAH was destroyed by water. 15 mL of 10% H_2SO_4 and 8 mL of ether was added and the aqueous layer was extracted several times with diethyl ether. The combined organic layer was washed with water and 5% NaHCO_3 , dried over MgSO_4 and concentrated in a rotary evaporator (90-95% yield). Without any further purification, the crude material (a colorless oil) was used for next step.

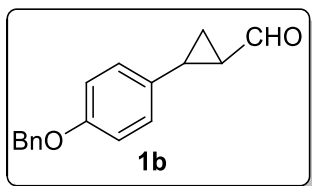
4) To a solution of cyclopropane alcohol (6.8 mmol, 1 equiv.) in dry DCM (14 mL), PCC (2 equiv.) was added in a portion-wise manner through a solid addition tube under N_2 atmosphere. After 3 h reaction mixture was filtered through a small plug of celite and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using ethyl acetate in hexane as an eluent. Starting from aryl aldehyde the 2-arylcyclopropanecarbaldehydes was obtained in 40-55% overall yield.

***trans*-2-(4-methoxyphenyl)cyclopropane-1-carbaldehyde (1a)**



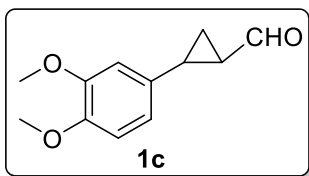
$^1\text{H NMR}$ (400 MHz): δ 9.30 (d, $J = 4.9$ Hz, 1H), 7.05 (d, $J = 8.7$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 3.79 (s, 3H) 2.63-2.56 (m, 1H), 2.13-2.06 (m, 1H), 1.73-1.67 (m, 1H), 1.51-1.45 (m, 1H)

***trans*-2-(4-(benzyloxy)phenyl)cyclopropanecarbaldehyde (1b)**



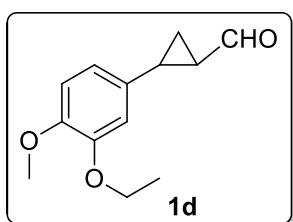
$^1\text{H NMR}$ (400 MHz): δ 9.30 (d, $J = 4.5$ Hz, 1H), 7.44-7.31 (m, 5H), 7.04 (d, $J = 8.5$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 5.04 (s, 2H), 2.62-2.55 (m, 1H), 2.13-2.06 (m, 1H), 1.72-1.67 (m, 1H), 1.51-1.45 (m, 1H)

***trans*-2-(3,4-dimethoxyphenyl)cyclopropanecarbaldehyde (1c)**



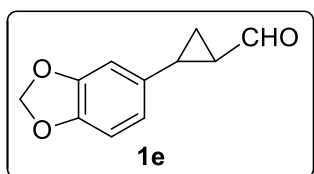
¹H NMR (400 MHz): δ 9.28 (d, J = 4.5 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 6.65 (d, J = 8.2 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.62-2.55 (m, 1H), 2.13-2.06 (m, 1H), 1.71-1.65 (m, 1H), 1.51-1.46 (m, 1H)

***trans*-2-(3-ethoxy-4-methoxyphenyl)cyclopropanecarbaldehyde (1d)**



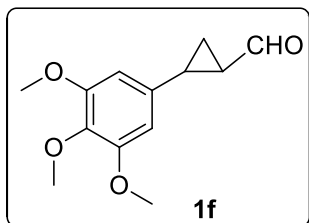
¹H NMR (400 MHz, CDCl₃) δ 9.29 (d, J = 4.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.66-6.63 (m, 2H), 4.07 (q, J = 7.0 Hz, 2H), 3.84 (s, 3H), 2.61-2.54 (m, 1H), 2.12-2.05 (m, 1H), 1.72-1.65 (m, 1H), 1.50-1.46 (m, 1H), 1.45 (t, J = 7.0 Hz, 3H)

***trans*-2-(benzo[*d*][1,3]dioxol-5-yl)cyclopropanecarbaldehyde (1e)**



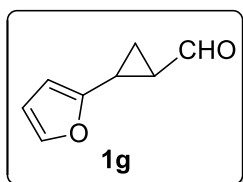
¹H NMR (400 MHz): δ 9.30 (d, J = 4.6 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.57 (s, 1H), 5.93 (s, 2H), 2.60-2.55 (m, 1H), 2.12-2.04 (m, 1H), 1.71-1.66 (m, 1H), 1.49-1.43 (m, 1H)

***trans*-2-(3,4,5-trimethoxyphenyl)cyclopropanecarbaldehyde (1f)**



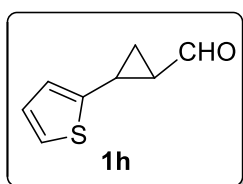
¹H NMR (400 MHz): δ 9.31 (d, J = 4.5 Hz, 1H), 6.33 (s, 2H), 3.84 (s, 6H), 3.81 (s, 3H), 2.62-2.56 (m, 1H), 2.18-2.11 (m, 1H), 1.73-1.67 (m, 1H), 1.53-1.47 (m, 1H)

***trans*-2-(furan-2-yl)cyclopropane-1-carbaldehyde (1g)**



¹H NMR (400 MHz): δ 9.36 (d, J = 4.3 Hz, 1H), 7.27-7.25 (m, 1H), 6.30-6.28 (m, 1H), 6.10 (d, J = 3.3 Hz, 1H), 2.65-2.59 (m, 1H), 2.32-2.26 (m, 1H), 1.69-1.64 (m, 1H), 1.62-1.56 (m, 1H).

***trans*-2-(thiophen-2-yl)cyclopropane-1-carbaldehyde (1h)**

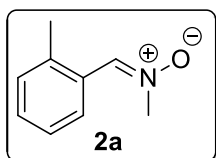


¹H NMR (400 MHz): δ 9.38 (d, J = 4.1 Hz, 1H), 7.13-7.11 (m, 1H), 6.92-6.90 (m, 1H), 6.85-6.84 (m, 1H), 2.84-2.78 (m, 1H), 2.25-2.20 (m, 1H), 1.79-1.74 (m, 1H), 1.55-1.50 (m, 1H).

3. General procedure for the preparation of 2-substituted nitrones (2)²

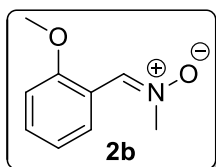
Aldehyde (1.0 equiv), *N*-methylhydroxylamine hydrochloride (2.0 equiv), Na₂CO₃ (2.2 equiv), and Na₂SO₄ (0.5 equiv) were added to a mortar and ground until completion. Et₂O was added, the mixture filtered, and concentrated in vacuo.

(*E*)-*N*-(2-methylbenzylidene)methanamine oxide (2a)



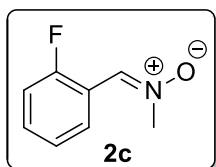
¹H NMR (400 MHz): δ 9.08-9.05 (m, 1H), 7.48 (s, 1H), 7.25-7.13 (m, 3H), 3.85 (s, 3H), 2.32 (s, 3H)

(*E*)-*N*-(2-methoxybenzylidene)methanamine oxide (2b)



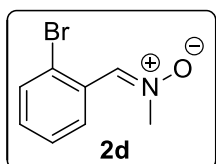
¹H NMR (400 MHz): δ 9.21-9.21 (m, 1H), 7.81 (s, 1H), 7.37-7.33 (m, 1H), 7.02-6.99 (m, 1H), 6.87-6.85 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H)

(*E*)-*N*-(2-fluorobenzylidene)methanamine oxide (2c)



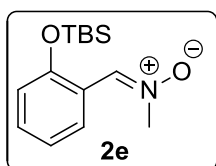
¹H NMR (400 MHz): δ 9.24-9.20 (m, 1H), 7.66 (s, 1H), 7.40-7.35 (m, 1H), 7.23-7.20 (m, 1H), 7.10-7.05 (m, 1H), 3.91 (s, 3H)

(E)-N-(2-bromobenzylidene)methanamine oxide (2d)



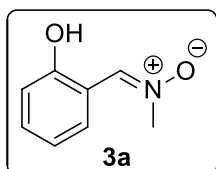
¹H NMR (400 MHz): δ 9.29-9.27 (m, 1H), 7.85 (s, 1H), 7.63-7.60 (m, 1H), 7.42-7.38 (m, 1H), 7.27-7.23 (m, 1H), 3.94 (s, 3H)

(E)-N-(2-((tert-butyldimethylsilyl)oxy)benzylidene)methanamine oxide (2e)



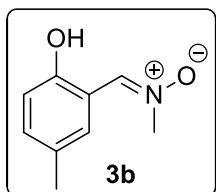
¹H NMR (400 MHz): δ 9.15-9.13 (m, 1H), 7.71 (s, 1H), 7.25-7.21 (m, 1H), 7.00-6.97 (m, 1H), 6.78 (d, $J=8.2$ Hz, 1H), 3.83 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H)

(E)-N-(2-hydroxybenzylidene)methanamine oxide (3a)



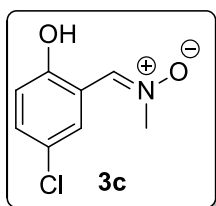
¹H NMR (400 MHz): δ 12.35 (s, 1H), 7.50 (s, 1H), 7.40-7.36 (m, 1H), 7.04 (dd, $J=7.7$ Hz, 1.8 Hz, 1H), 6.95 (d, $J=8.6$ Hz, 1H), 6.85-6.81 (m, 1H), 3.86 (s, 3H)

(E)-N-(2-hydroxy-5-methylbenzylidene)methanamine oxide (3b)



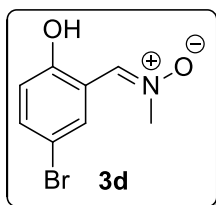
¹H NMR (400 MHz): δ 12.10 (s, 1H), 7.44 (s, 1H), 7.18 (dd, $J=8.2$ Hz, 2.2 Hz, 1H), 6.85 (d, $J=8.2$ Hz, 1H), 6.80-6.79 (m, 1H), 3.83 (s, 3H), 2.23 (s, 3H)

(E)-N-(5-chloro-2-hydroxybenzylidene)methanamine oxide (3c)



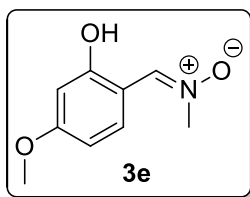
¹H NMR (400 MHz): δ 12.15 (s, 1H), 7.46 (s, 1H), 7.32 (dd, J=8.7 Hz, 2.3 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 6.91 (d, J=8.8 Hz, 1H), 3.89 (s, 3H)

(E)-N-(5-bromo-2-hydroxybenzylidene)methanamine oxide (3d)



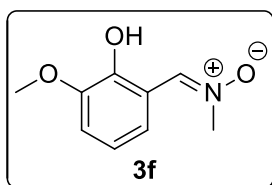
¹H NMR (400 MHz): δ 12.24 (s, 1H), 7.44-7.42 (m, 2H), 7.15 (d, J=2.7 Hz, 1H), 6.83 (d, J=8.7 Hz, 1H), 3.87 (s, 3H)

(E)-N-(2-hydroxy-4-methoxybenzylidene)methanamine oxide (3e)



¹H NMR (400 MHz): δ 13.42 (s, 1H), 7.35 (s, 1H), 6.91 (d, J=8.5 Hz, 1H), 6.44-6.39 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H)

(E)-N-(2-hydroxy-3-methoxybenzylidene)methanamine oxide (3f)



¹H NMR (400 MHz): δ 12.49 (s, 1H), 7.53 (s, 1H), 6.95 (d, J=7.9 Hz, 1H), 6.80-6.76 (m, 1H), 6.66 (d, J=8.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H)

4. Optimization Study

Table S1: Optimization of the reaction conditions

entry	catalyst	solvent	additive	yield ^b (%)	<i>er</i> ^c	<i>dr</i> ^d
1	I	CCl ₄	-	45	75:25	4:1
2	I	DCM	-	n.r. ^e	-	-
3	I	DCE	-	n.r. ^e	-	-
4	I	CHCl ₃	-	n.r. ^e	-	-
5	I	CH ₃ CN	-	n.r. ^e	-	-
6	I	Toluene	-	n.r. ^e	-	-
7	I	CCl ₄	PhCO ₂ H	c.m. ^f	-	-
8	I	CCl ₄	TfOH	c.m. ^f	-	-
9	I	CCl ₄	TFA	c.m. ^f	-	-
10	I	CCl ₄	Et ₃ N	35	56:44	3:2
11	I	CCl ₄	DABCO	36	57:43	3:1
12	I	CCl ₄	DMAP	40	53:47	2.5:1
13	I	CCl ₄	K ₂ CO ₃	10	74:26	1.2:1
14	II	CCl ₄	-	40	62:38	3:1
15	III	CCl ₄	-	Trace	-	-
16	IV	CCl ₄	-	25	60:40	4:1
17	V	CCl ₄	-	n.r. ^e	-	-
18	VI	CCl ₄	-	n.r. ^e	-	-
19 ^g	I	CCl ₄	-	35	55:45	3:1
20 ^h	I	CCl ₄	-	35	75:25	4:1
21 ⁱ	I	CCl ₄	-	30	77:23	4:1
22 ^j	I	CCl ₄	-	35	55:45	1.1:1

^aUnless otherwise all the reactions were carried out with 1 equiv. of 1a, 1.5 equiv. of 2a, 40 mol% of catalyst in the presence of 4 Å molecular sieves at refluxing condition for 10 h; ^bisolated yield by column chromatography; ^cdetermined by chiral HPLC analysis; ^ddetermined from crude nmr; ^eno reaction; ^fcomplex mixture; ^greaction performed at room temperature for 6 d; ^h30 mol% catalyst taken; ⁱ50 mol% catalyst taken, ^junsubstituted nitrone was used.

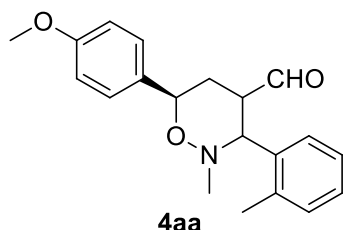
5. Representative procedure and substrate scope for the (3+3)-cycloaddition between cyclopropane carbaldehydes and 2-substituted nitrones

To a round-bottom flask equipped with a magnetic stir bar was charged with cyclopropane carbaldehyde (1 equiv.), 2-substituted nitrone (1.5 equiv.), activated 4 Å MS (200 mol%), and Jørgensen-Hayashi Catalyst I (0.4 equiv.) under nitrogen atmosphere. CCl₄ was added as a

solvent to the reaction mixture and was stirred under reflux conditions for 10-12 hours. After the completion of the reaction (as monitored by TLC), the reaction mixture was passed through a small pad of Celite, and the solvent was removed under reduced pressure by a rotary evaporator. Then the crude product was further purified by column chromatography on silica gel with EtOAc/hexane as eluent.

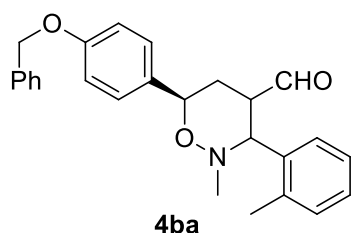
Racemic products were prepared according to the representative procedure 5 by using the racemic catalyst.

(6*R*)-6-(4-methoxyphenyl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4aa)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **2a** (0.036 g, 0.37 mmol), **4aa** (0.036 g, 0.11 mmol); Yellowish sticky liquid, 44% overall yield; $[\alpha]_D^{25} = -86.07$ ($c = 0.7$, CHCl_3); 75:25 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (minor) = 9.36 min, t_R (major) = 11.49 min]; **$^1\text{H NMR}$ (400 MHz):** δ 9.40 (d, $J = 1.8$ Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 2H), 7.22-7.17 (m, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 5.00 (dd, $J = 11.8, 1.8$ Hz, 1H), 3.93 (d, $J = 10.5$ Hz, 1H), 3.81 (m, 1H), 3.34-3.28 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.18-2.15 (m, 1H), 1.99-1.89 (m, 1H); **$^{13}\text{C NMR}$ (100 MHz):** δ 201.7, 159.6, 136.8, 136.6, 132.2, 130.8, 128.1, 128.0, 127.8, 127.3, 127.0, 114.0, 79.3, 65.7, 55.8, 55.4, 43.2, 31.9, 20.5; **HRMS (ESI, Q-TOF) m/z :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{24}\text{NO}_3$ 326.1756, Found 326.1751

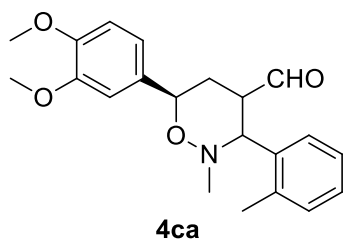
(6*R*)-6-(4-(benzyloxy)phenyl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4ba)



Prepared according to **GP 3. 1a** (0.063 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4ba** (0.036 g, 0.09 mmol); Yellowish sticky liquid, 36% overall yield; $[\alpha]_D^{25} = -49.43$ ($c = 0.7$, CHCl_3); 73.5:26.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (minor) = 17.60 min, t_R (major) = 18.24 min]; **$^1\text{H NMR}$ (400 MHz):** δ 9.39 (d, $J = 1.8$ Hz, 1H), 7.50-7.49 (m, 1H), 7.43-7.35 (m, 8H), 7.19-7.16 (m, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 5.07 (s, 2H), 4.99 (dd, $J = 11.5, 1.8$ Hz, 1H), 3.92 (d, $J = 10.5$ Hz, 1H), 3.33-3.27 (m, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 2.18-2.13 (m, 1H), 1.98-1.89 (m, 1H); **$^{13}\text{C NMR}$ (100 MHz):** δ 201.7, 158.8, 136.9, 136.8, 136.5, 132.4, 130.7, 128.7, 128.1, 128.0, 127.9, 127.5, 127.2, 127.0, 114.9, 79.3, 70.0, 65.7, 55.8, 43.1, 31.8, 20.5; **HRMS (ESI, Q-TOF) m/z :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{28}\text{NO}_3$ 402.2069, Found 402.2068

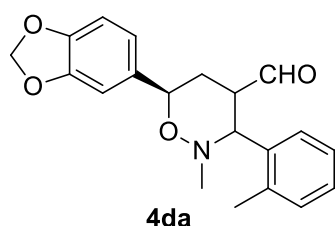
(6*R*)-6-(3,4-dimethoxyphenyl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4ca)

Prepared according to **GP 3. 1c** (0.052 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4ca** (0.048 g, 0.13 mmol); Yellowish sticky liquid, 54% overall yield; $[\alpha]_D^{25} = -60.25$ ($c = 1.0$, CHCl_3); 79.5:20.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC,



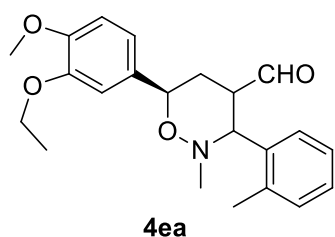
hexane/*i*-PrOH = 80/20, 1.0 mL/min, t_R (major) = 28.98 min, t_R (minor) = 36.04 min]; $^1\text{H NMR}$ (400 MHz): δ 9.41 (d, J = 1.4 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.28-7.17 (m, 4H), 6.99-6.97 (m, 2H), 6.88-6.86 (m, 1H), 4.99 (dd, J = 11.5, 1.9 Hz, 1H), 3.95 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.35-3.28 (m, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 2.20-2.15 (m, 1H), 2.00-1.91 (m, 1H); $^{13}\text{C NMR}$ (100 MHz): δ 201.8, 149.0, 136.8, 136.5, 132.4, 130.8, 128.0, 127.2, 127.0, 119.2, 111.0, 110.0, 79.6, 65.7, 56.0, 56.0, 55.8, 43.2, 31.8, 20.5; **HRMS (ESI, Q-TOF)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{26}\text{NO}_4$ 356.1862, Found 356.1858

(6R)-6-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4ea)



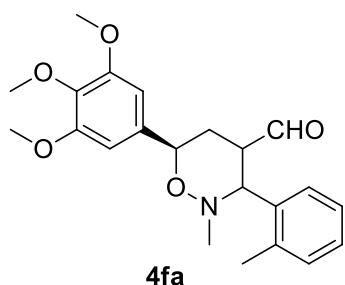
Prepared according to **GP 3. 1d** (0.048 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4da** (0.024 g, 0.07 mmol); Yellowish sticky liquid, 28% overall yield; $[\alpha]_D^{25} = -52.48$ ($c = 0.7$, CHCl_3); 62.5:37.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (minor) = 16.89 min, t_R (major) = 18.63 min]; $^1\text{H NMR}$ (400 MHz): δ 9.39 (d, J = 1.4 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.23-7.16 (m, 3H), 6.94-6.93 (m, 1H), 6.90-6.88 (m, 1H), 6.81-6.79 (m, 1H), 5.96-5.93 (m, 2H), 4.95 (dd, J = 11.4, 2.1 Hz, 1H), 3.91 (d, J = 10.5 Hz, 1H), 3.32-3.26 (m, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 2.17-2.12 (m, 1H), 1.94-1.84 (m, 1H); $^{13}\text{C NMR}$ (100 MHz): δ 201.7, 147.9, 147.6, 136.7, 136.6, 133.9, 130.8, 128.0, 127.3, 127.0, 120.3, 108.3, 107.4, 101.2, 79.5, 65.7, 55.8, 43.2, 32.1, 20.5; **HRMS (ESI, Q-TOF)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_4$ 340.1549, Found 340.1545

(6R)-6-(3-ethoxy-4-methoxyphenyl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4ea)



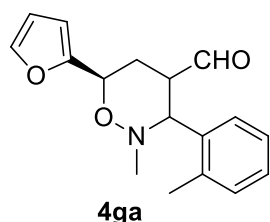
Prepared according to **GP 3. 1e** (0.055 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4ea** (0.032 g, 0.08 mmol); Yellowish sticky liquid, 35% overall yield; $[\alpha]_D^{25} = -84.16$ ($c = 0.4$, CHCl_3); 82.5:17.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 80/20, 1.0 mL/min, t_R (major) = 17.88 min, t_R (minor) = 23.56 min]; $^1\text{H NMR}$ (400 MHz): δ 9.40 (d, J = 1.5 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.23-7.16 (m, 3H), 6.98-6.96 (m, 2H), 6.87-6.85 (m, 1H), 4.97 (dd, J = 11.4, 2.0 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.93 (d, J = 10.0 Hz, 1H), 3.87 (s, 3H), 3.33-3.28 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.19-2.14 (m, 1H), 1.99-1.89 (m, 1H), 1.48 (t, J = 6.8 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz): δ 201.9, 149.3, 148.4, 136.8, 136.6, 132.4, 130.8, 128.0, 127.2, 127.0, 119.2, 111.4, 111.3, 79.6, 65.7, 64.4, 56.1, 55.8, 43.2, 31.8, 20.5, 14.9; **HRMS (ESI, Q-TOF)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{28}\text{NO}_4$ 370.2018, Found 370.2010

(6*R*)-2-methyl-3-(*o*-tolyl)-6-(3,4,5-trimethoxyphenyl)-1,2-oxazinane-4-carbaldehyde (4fa)



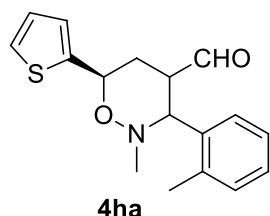
Prepared according to **GP 3**. **1f** (0.060 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4fa** (0.036 g, 0.09 mmol); Yellowish sticky liquid, 37% overall yield; $[\alpha]_D^{25} = -109.54$ ($c = 0.4$, CHCl_3); 62.5:37.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 60/40, 1.0 mL/min, t_R (minor) = 10.74 min, t_R (major) = 21.22 min]; **^1H NMR (400 MHz)**: δ 9.40 (d, $J = 1.3$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.28-7.18 (m, 3H), 6.65 (s, 2H), 4.98 (dd, $J = 11.5$, 2.2 Hz, 1H), 3.95 (d, $J = 10.0$ Hz, 1H), 3.90 (s, 6H), 3.84 (s, 3H), 3.35-3.28 (m, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 2.20-2.16 (m, 1H), 1.99-1.89 (m, 1H); **^{13}C NMR (100 MHz)**: δ 201.8, 153.4, 137.9, 136.7, 136.5, 135.5, 130.8, 128.0, 127.2, 127.0, 103.8, 80.0, 65.7, 60.9, 56.2, 55.7, 43.2, 32.0, 20.5; **HRMS (ESI, Q-TOF)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{28}\text{NO}_5$ 386.1967, Found 386.1964

(6*R*)-6-(furan-2-yl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4ka)



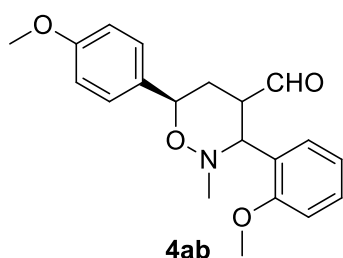
Prepared according to **GP 3**. **1g** (0.034 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4ga** (0.036 g, 0.12 mmol); Yellowish sticky liquid, 45% overall yield; Yellowish sticky liquid, 45% overall yield; $[\alpha]_D^{25} = -45.86$ ($c = 0.6$, CHCl_3); 60.5:39.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiracel ASH, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (major) = 6.93 min, t_R (minor) = 8.16 min]; **^1H NMR (400 MHz)**: δ 9.37 (d, $J = 1.3$ Hz, 1H), 7.49 (d, $J = 7.5$ Hz, 1H), 7.44-7.43 (m, 1H), 7.24-7.16 (m, 3H), 6.43-6.42 (m, 1H), 6.38-6.37 (m, 1H), 5.12-5.09 (m, 1H), 3.92 (d, $J = 10.5$ Hz, 1H), 3.29-3.23 (m, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.19-2.15 (m, 2H); **^{13}C NMR (100 MHz)**: δ 201.5, 152.4, 142.9, 136.5, 130.8, 128.1, 127.2, 127.0, 110.4, 108.4, 73.0, 65.7, 55.4, 43.1, 28.7, 20.5; **HRMS (ESI, Q-TOF)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{20}\text{NO}_3$ 286.1443, Found 286.1437

(6*R*)-2-methyl-6-(thiophen-2-yl)-3-(*o*-tolyl)-1,2-oxazinane-4-carbaldehyde (4la)



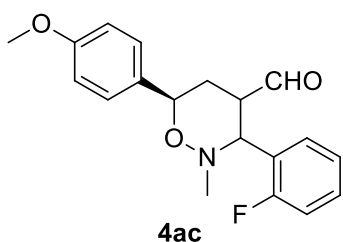
Prepared according to **GP 3**. **1h** (0.038 g, 0.25 mmol), **2a** (0.056 g, 0.37 mmol), **4ha** (0.025 g, 0.08 mmol); Yellowish sticky liquid, 28% overall yield; $[\alpha]_D^{25} = -46.49$ ($c = 0.5$, CHCl_3); 79:21 er of major diastereomer was determined by chiral HPLC analysis, [Chiracel ASH, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (major) = 7.01 min, t_R (minor) = 8.07 min]; **^1H NMR (400 MHz)**: δ 9.38 (d, $J = 1.3$ Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.32-7.31 (m, 1H), 7.24-7.17 (m, 3H), 7.12-7.11 (m, 1H), 7.02-7.00 (m, 1H), 5.28 (dd, $J = 11.6$, 2.0 Hz, 1H), 3.94 (d, $J = 10.6$ Hz, 1H), 3.33-3.26 (m, 1H), 2.44 (s, 3H), 2.39 (s, 3H), 2.35-2.30 (m, 1H), 2.08-1.99 (m, 1H); **^{13}C NMR (100 MHz)**: δ 201.5, 142.5, 136.6, 130.8, 128.1, 127.2, 127.0, 126.7, 125.7, 125.3, 75.3, 65.7, 55.6, 43.1, 32.4, 20.5; **HRMS (ESI, Q-TOF)** m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{20}\text{NO}_2\text{S}$ 302.1215, Found 302.1211

(6R)-3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-2-methyl-1,2-oxazinane-4-carbaldehyde (4ab)



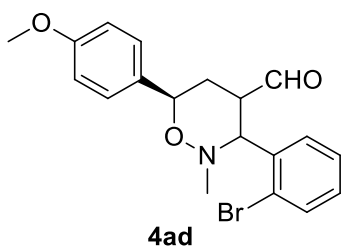
Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **2b** (0.061 g, 0.37 mmol), **4ab** (0.029 g, 0.08 mmol); Yellowish sticky liquid, 34% overall yield; $[\alpha]_{\text{D}}^{25} = -19.50$ ($c = 0.6$, CHCl_3); 62:38 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 95/5, 1.0 mL/min, t_{R} (minor) = 14.93 min, t_{R} (major) = 16.06 min]; **^1H NMR (400 MHz):** δ 9.37 (d, $J = 1.4$ Hz, 1H), 7.48-7.47 (m, 1H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.30-7.27 (m, 1H), 7.03-6.99 (m, 1H), 6.92-6.89 (m, 3H), 4.96 (dd, $J = 11.4, 2.3$ Hz, 1H), 4.26 (d, $J = 10.2$ Hz, 1H), 3.84 (m, 3H), 3.81 (s, 3H), 3.09-3.04 (m, 1H), 2.47 (s, 3H), 2.12-2.07 (m, 1H), 2.01-1.92 (m, 1H); **^{13}C NMR (100 MHz):** δ 202.3, 159.6, 157.1, 132.3, 129.2, 128.1, 121.5, 114.0, 110.8, 79.2, 61.7, 55.6, 55.4, 43.6, 31.8; **HRMS (ESI, Q-TOF) m/z :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{24}\text{NO}_4$ 342.1705, Found 342.1705

(6R)-3-(2-fluorophenyl)-6-(4-methoxyphenyl)-2-methyl-1,2-oxazinane-4-carbaldehyde (4ac)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **2c** (0.057 g, 0.37 mmol), **4ac** (0.027 g, 0.08 mmol); Yellowish sticky liquid, 32% overall yield; $[\alpha]_{\text{D}}^{25} = -96.18$ ($c = 0.3$, CHCl_3); 78.5:21.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_{R} (minor) = 17.2 min, t_{R} (major) = 19.2 min]; **^1H NMR (400 MHz):** δ 9.46 (d, $J = 1.3$ Hz, 1H), 7.50-7.46 (m, 1H), 7.35 (d, $J = 8.7$ Hz, 2H), 7.32-7.28 (m, 1H), 7.21-7.17 (m, 1H), 7.11-7.06 (m, 1H), 6.91 (d, $J = 8.8$ Hz, 2H), 4.98 (dd, $J = 11.4, 1.8$ Hz, 1H), 4.05 (bs, 1H), 3.81 (s, 3H), 3.32-3.16 (m, 1H), 2.47 (s, 3H), 2.19-2.05 (m, 1H), 1.97-1.88 (m, 1H); **^{13}C NMR (100 MHz):** δ 201.1, 162.2, 159.7, 159.5, 132.0, 130.1, 130.0, 128.1, 125.0, 114.0, 55.4, 43.9, 31.9; **HRMS (ESI, Q-TOF) m/z :** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{F}$ 330.1505, Found 330.1500

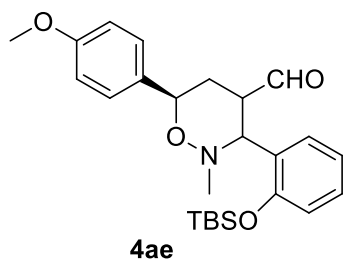
(6R)-3-(2-bromophenyl)-6-(4-methoxyphenyl)-2-methyl-1,2-oxazinane-4-carbaldehyde (4ad)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **2d** (0.079 g, 0.37 mmol), **4ad** (0.027 g, 0.07 mmol); Yellowish sticky liquid, 27% overall yield; $[\alpha]_{\text{D}}^{25} = -46.62$ ($c = 1.0$, CHCl_3); 84:16 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_{R} (minor) = 18.93 min, t_{R} (major) = 20.87 min]; **^1H NMR (400 MHz):** δ 9.47 (d, $J = 1.8$ Hz, 1H), 7.61 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.55 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.40-7.34 (m,

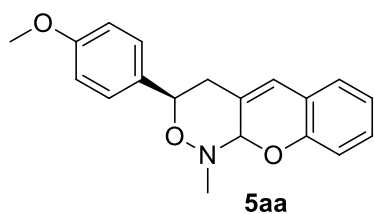
3H), 7.21-7.18 (m, 1H), 6.92 (d, $J = 8.7$ Hz, 2H), 4.97 (dd, $J = 11.4, 2.2$ Hz, 1H), 4.34 (d, $J = 10.7$ Hz, 1H), 3.81 (s, 3H), 3.15-3.08 (m, 1H), 2.47 (s, 3H), 2.16-2.11 (m, 1H), 2.04-1.95 (m, 1H); ^{13}C NMR (100 MHz): δ 201.1, 159.7, 137.8, 133.3, 131.9, 129.8, 129.5, 128.5, 128.1, 125.1, 114.0, 79.3, 68.4, 56.1, 55.4, 43.4, 31.6; HRMS (ESI, Q-TOF) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{Br}$ 390.0705, Found 390.0700

(6R)-3-(2-((tert-butyldimethylsilyloxy)phenyl)-6-(4-methoxyphenyl)-2-methyl-1,2-oxazinane-4-carbaldehyde (4ae)



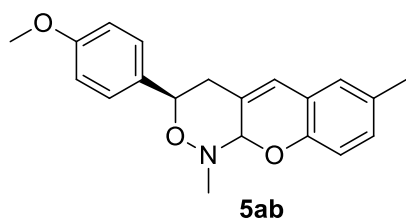
Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **2e** (0.098 g, 0.37 mmol), **4ae** (0.022 g, 0.05 mmol); Yellowish sticky liquid, 20% overall yield; $[\alpha]_{\text{D}}^{25} = 79.26$ ($c = 0.8$, CHCl_3); 78:22 er of major diastereomer was determined by chiral HPLC analysis, [Chiracel ASH, hexane/*i*-PrOH = 90/10, 0.2 mL/min, t_{R} (minor) = 12.90 min, t_{R} (major) = 17.74 min]; ^1H NMR (400 MHz): δ 9.38 (d, $J = 1.6$ Hz, 1H), 7.49-7.47 (m, 1H), 7.36 (d, $J = 8.7$ Hz, 2H), 7.19-7.15 (m, 1H), 7.02-6.98 (m, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 6.84-6.82 (m, 1H), 4.95 (dd, $J = 11.5, 1.9$ Hz, 1H), 4.19 (d, $J = 10.8$ Hz, 1H), 3.81 (s, 3H), 3.10-3.03 (m, 1H), 2.47 (s, 3H), 2.15-2.10 (m, 1H), 1.97-1.87 (m, 1H), 1.03 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (100 MHz): δ 202.2, 159.6, 153.6, 132.2, 128.9, 128.7, 128.5, 128.2, 121.9, 118.3, 114.0, 79.0, 62.6, 55.5, 55.4, 43.5, 31.6, 26.0, 18.4, -3.8; HRMS (ESI, Q-TOF) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{36}\text{NO}_4\text{Si}$ 442.2414, Found 442.2411

(3R)-3-(4-methoxyphenyl)-1-methyl-1,3,4,10a-tetrahydrochromeno[2,3-*c*][1,2]oxazine (5aa)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **3a** (0.056 g, 0.37 mmol), **5aa** (0.020 g, 0.06 mmol); White solid; 26% overall yield; Melting point: 118-121 °C $[\alpha]_{\text{D}}^{25} = 256.04$ ($c = 0.3$ CHCl_3); 74:26 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_{R} (major) = 14.61 min, t_{R} (minor) = 15.47 min]; ^1H NMR (400 MHz): δ 7.33 (d, $J = 8.3$ Hz, 2H), 6.96-6.94 (m, 1H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.88-6.86 (m, 1H), 6.80-6.78 (m, 1H), 6.30 (s, 1H), 5.18 (s, 1H), 4.92 (dd, $J = 9.3, 4.3$ Hz, 1H), 3.80 (s, 3H), 2.81 (s, 3H), 2.76-2.73 (m, 1H), 2.71-2.69 (m, 1H); ^{13}C NMR (100 MHz): δ 159.7, 151.6, 131.8, 129.8, 128.9, 128.2, 127.9, 126.3, 121.7, 120.1, 119.3, 115.2, 114.0, 92.8, 80.9, 55.4, 41.7, 40.1; HRMS (ESI, Q-TOF) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{20}\text{NO}_3$ 310.1443, Found 310.1434

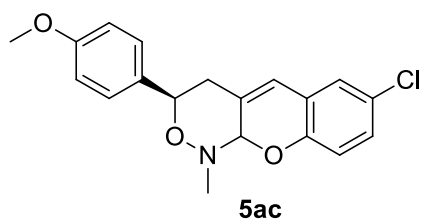
(3R)-3-(4-methoxyphenyl)-1,7-dimethyl-1,3,4,10a-tetrahydrochromeno[2,3-*c*][1,2]oxazine (5ab)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **3b** (0.061 g, 0.37 mmol), **5ab** (0.019 g, 0.06 mmol); Colourless sticky liquid, 23% overall yield; $[\alpha]_D^{25} = 75.25$ ($c = 0.9$, CHCl_3); 60:40 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (major) = 14.61 min, t_R (minor) = 15.47 min]; **$^1\text{H NMR}$ (400**

MHz): δ 7.33 (d, $J = 8.7$ Hz, 2H), 6.91-6.87 (m, 3H), 6.76 (d, $J = 1.8$ Hz, 1H), 6.70 (d, $J = 8.2$ Hz, 1H), 6.26 (s, 1H), 5.14 (s, 1H), 4.91 (dd, $J = 9.8, 4.3$ Hz, 1H), 3.80 (s, 3H), 2.81 (s, 3H), 2.76-2.72 (m, 1H), 2.70-2.69 (m, 1H); **$^{13}\text{C NMR}$ (100 MHz):** δ 159.6, 149.5, 131.9, 130.8, 129.8, 129.3, 127.9, 126.7, 119.9, 119.4, 114.9, 92.8, 80.9, 55.4, 41.8, 40.1, 20.6; **HRMS (ESI, Q-TOF) m/z:** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{NO}_3$ 324.1600, Found 324.1617

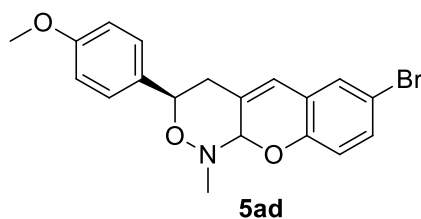
(3R)-7-chloro-3-(4-methoxyphenyl)-1-methyl-1,3,4,10a-tetrahydrochromeno[2,3-c][1,2]oxazine (5ac)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **3c** (0.068 g, 0.37 mmol), **5ac** (0.018 g, 0.05 mmol); Colourless sticky liquid, 20% overall yield; $[\alpha]_D^{25} = 80.98$ ($c = 0.8$, CHCl_3); 67.5:32.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (major) = 13.18 min, t_R (minor) = 14.45 min]; **$^1\text{H NMR}$**

(400 MHz): δ 7.32 (d, $J = 8.7$ Hz, 2H), 7.04 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.93 (d, $J = 2.5$ Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 2H), 6.73 (d, $J = 8.6$ Hz, 1H), 6.24 (s, 1H), 5.17 (s, 1H), 4.91 (dd, $J = 9.6, 4.5$ Hz, 1H), 3.80 (s, 3H), 2.80 (s, 3H), 2.77-2.73 (m, 1H), 2.71-2.70 (m, 1H); **$^{13}\text{C NMR}$ (100 MHz):** δ 159.7, 150.1, 131.5, 131.2, 128.4, 127.9, 126.3, 125.8, 121.5, 118.4, 116.5, 114.0, 92.8, 80.8, 55.4, 41.7, 40.0; **HRMS (ESI, Q-TOF) m/z:** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{Cl}$ 344.1053, Found 344.1080

(3R)-7-bromo-3-(4-methoxyphenyl)-1-methyl-1,3,4,10a-tetrahydrochromeno[2,3-c][1,2]oxazine (5ad)

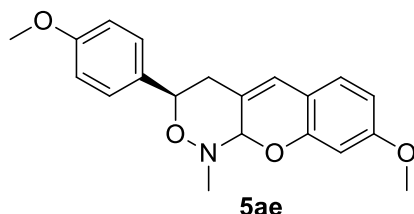


Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **3d** (0.085 g, 0.37 mmol), **5ad** (0.026 g, 0.06 mmol); Colourless sticky liquid, 27% overall yield; $[\alpha]_D^{25} = 102.64$ ($c = 0.6$, CHCl_3); 65.5:34.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (major) = 12.75 min, t_R (minor) = 13.74 min]; **$^1\text{H NMR}$**

(400 MHz): δ 7.31 (d, $J = 8.2$ Hz, 2H), 7.17 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.07 (d, $J = 2.3$ Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.68 (d, $J = 8.4$ Hz, 1H), 6.23 (s, 1H), 5.17 (s, 1H), 4.90 (dd, $J = 9.9, 4.1$ Hz, 1H), 3.80 (s, 3H), 2.80 (s, 3H), 2.77-2.73 (m, 1H), 2.71-2.70 (m, 1H); **$^{13}\text{C NMR}$ (100 MHz):** δ 159.5, 150.5, 131.2, 131.0, 128.5, 127.8, 121.9, 118.1, 116.8, 113.8,

113.4, 92.6, 80.7, 55.3, 41.6, 39.8; **HRMS (ESI, Q-TOF)** m/z: [M+H]⁺ calculated for C₁₉H₁₉NO₃Br 388.0548, Found 388.0563

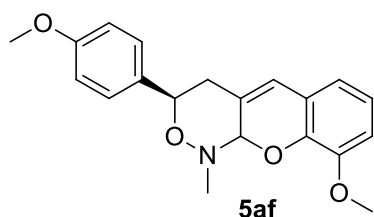
(3R)-8-methoxy-3-(4-methoxyphenyl)-1-methyl-1,3,4,10a-tetrahydrochromeno[2,3-c][1,2]oxazine (5ae)



Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **3e** (0.067 g, 0.37 mmol), **5ae** (0.022 g, 0.06 mmol); Colourless sticky liquid, 26% overall yield; [α]_D²⁵ = 59.82 (c = 0.9, CHCl₃); 70.5:29.5 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (minor) = 22.29 min, t_R (major) = 22.29 min]; **¹H NMR**

(400 MHz): δ 7.32 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.43 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 6.25 (s, 1H), 5.15 (s, 1H), 4.90 (dd, *J* = 10.2, 3.9 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.80 (s, 3H), 2.74-2.71 (m, 1H), 2.68-2.67 (m, 1H); **¹³C NMR (100 MHz):** δ 160.4, 159.6, 152.7, 131.8, 128.2, 127.9, 126.8, 126.7, 118.9, 113.9, 113.3, 107.3, 101.3, 92.8, 80.0, 55.5, 53.4, 41.7, 39.9; **HRMS (ESI, Q-TOF)** m/z: [M+H]⁺ calculated for C₂₀H₂₂NO₄ 340.1549, Found 340.1549

(3R)-9-methoxy-3-(4-methoxyphenyl)-1-methyl-1,3,4,10a-tetrahydrochromeno[2,3-c][1,2]oxazine (5af)

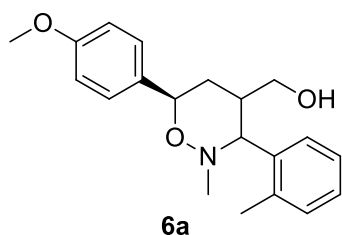


Prepared according to **GP 3. 1a** (0.044 g, 0.25 mmol), **3f** (0.067 g, 0.37 mmol), **5af** (0.021 g, 0.06 mmol); Colourless sticky liquid, 25% overall yield; [α]_D²⁵ = 125.24 (c = 0.4, CHCl₃); 68:32 er of major diastereomer was determined by chiral HPLC analysis, [Chiralpak IC, hexane/*i*-PrOH = 90/10, 0.5 mL/min, t_R (minor) = 22.29 min, t_R (major) = 22.29 min]; **¹H NMR (400 MHz):** δ 7.33 (d, *J* = 8.7 Hz,

1H), 6.91-6.87 (m, 3H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.26 (s, 1H), 5.14 (s, 1H), 4.92 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.80 (s, 3H), 2.81 (s, 3H), 2.76-2.72 (m, 1H), 2.70-2.69 (m, 1H), 2.24 (s, 3H); **¹³C NMR (100 MHz):** δ 159.6, 149.4, 131.8, 130.8, 129.8, 129.3, 127.9, 126.7, 119.8, 119.4, 114.9, 114.0, 92.8, 80.9, 55.4, 41.8, 40.0, 20.6; **HRMS (ESI, Q-TOF)** m/z: [M+H]⁺ calculated for C₂₀H₂₂NO₄ 340.1549, Found 340.1552

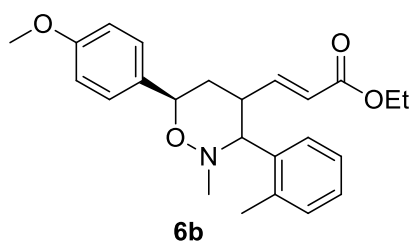
6. Chemical transformations

((6R)-6-(4-methoxyphenyl)-2-methyl-3-(*o*-tolyl)-1,2-oxazinan-4-yl)methanol (6a)³



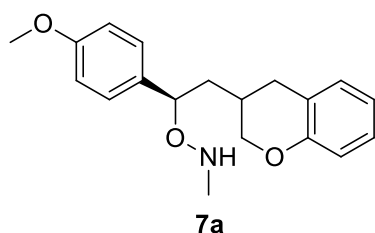
Prepared according to the literature procedure.³ **4aa** (0.022 g, 0.06 mmol), **NaBH₄** (0.005 g, 0.12 mmol), **6a** (0.015 g, 0.04 mmol); Colourless liquid, 67% yield; **¹H NMR (400 MHz):** δ 7.45 (d, $J = 7.3$ Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 2H), 7.24-7.19 (m, 1H), 7.18-7.16 (m, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.01 (dd, $J = 11.7, 2.0$ Hz, 1H), 3.81 (s, 3H), 3.70 (d, $J = 10.5$ Hz, 1H), 3.44 (dd, $J = 10.5, 3.6$ Hz, 1H), 3.31 (dd, $J = 10.7, 6.1$ Hz, 1H), 2.41 (s, 3H), 2.40 (s, 3H), 2.38-2.32 (m, 1H), 2.16-2.12 (m, 1H), 1.86-1.77 (m, 1H); **¹³C NMR (100 MHz):** δ 159.2, 138.1, 136.7, 132.8, 130.3, 128.0, 127.3, 127.0, 126.7, 113.7, 79.7, 67.8, 64.1, 55.2, 45.2, 43.6, 34.9, 29.6, 20.3; **HRMS (ESI, Q-TOF) m/z:** $[M+H]^+$ calculated for C₂₀H₂₆NO₃ 328.1913, Found 328.1911

(E)-ethyl 3-((6R)-6-(4-methoxyphenyl)-2-methyl-3-(o-tolyl)-1,2-oxazinan-4-yl)acrylate (6b)⁴



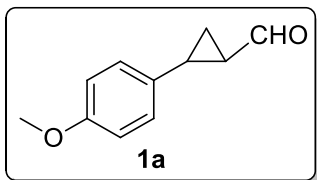
Prepared according to the literature procedure.⁴ **4aa** (0.020 g, 0.06 mmol); **6b** (0.018 g, 0.04 mmol), 74% yield; **¹H NMR (400 MHz):** δ 7.44 (d, $J = 8.1$ Hz, 1H), 7.37 (d, $J = 8.7$ Hz, 2H), 7.24-7.20 (m, 1H), 7.18-7.16 (m, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.64 (dd, $J = 16.0, 7.7$ Hz, 1H), 5.61 (dd, $J = 16.0, 1.3$ Hz, 1H), 5.02 (dd, $J = 11.4, 1.8$ Hz, 1H), 4.12-4.06 (m, 2H), 3.81 (s, 3H), 3.66 (d, $J = 10.0$ Hz, 1H), 3.03-2.95 (m, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.09-2.04 (m, 1H), 1.93-1.84 (m, 1H), 1.21 (t, $J = 6.9$ Hz, 3H); **¹³C NMR (100 MHz):** δ 166.3, 159.5, 147.8, 137.6, 136.5, 132.5, 130.5, 128.1, 127.5, 126.9, 126.7, 122.2, 114.0, 79.4, 69.4, 60.3, 55.4, 46.3, 43.9, 36.8, 20.4, 14.2; **HRMS (ESI, Q-TOF) m/z:** $[M+H]^+$ calculated for C₂₄H₃₀NO₄ 396.2175, Found 396.2179

O-((1R)-2-(chroman-3-yl)-1-(4-methoxyphenyl)ethyl)-N-methylhydroxylamine (7a)⁵

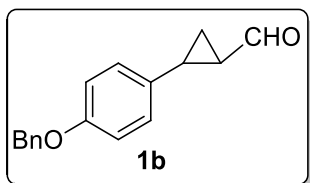
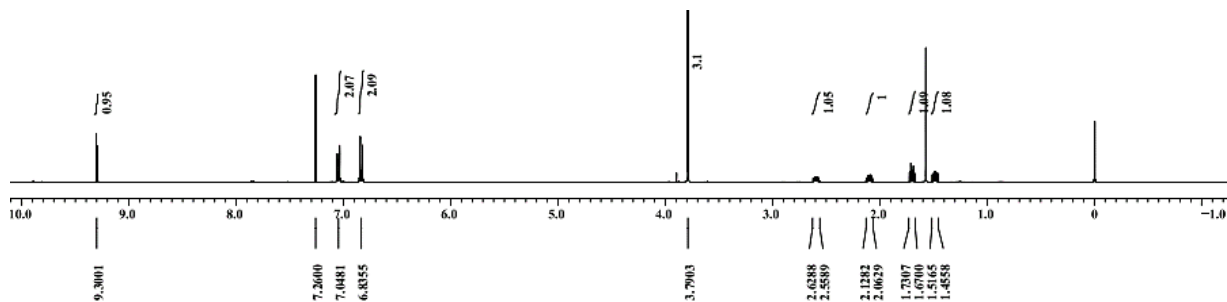


Prepared according to the literature procedure.⁵ **5aa** (0.025 g, 0.08 mmol), **7a** (0.018 g, 0.05 mmol), colorless liquid, 71% yield, **¹H NMR (400 MHz):** δ 8.32 (bs, 1H), 7.33 (d, $J = 8.7$ Hz, 2H), 7.17-7.10 (m, 2H), 6.94-6.85 (m, 4H), 5.29 (dd, $J = 11.7, 2.0$ Hz, 1H), 3.80 (s, 3H), 3.36-3.29 (m, 1H), 2.68 (dd, $J = 13.8, 6.3$ Hz, 1H), 2.62 (s, 3H), 2.58 (d, $J = 2.3$ Hz, 2H), 2.30-2.23 (m, 1H), 2.06-1.98 (m, 1H), 1.80-1.77 (m, 1H); **¹³C NMR (100 MHz):** δ 159.6, 155.8, 132.5, 130.7, 128.2, 128.1, 126.6, 120.6, 117.4, 114.0, 76.5, 58.3, 55.4, 46.4, 35.9, 34.0, 31.4; **HRMS (ESI, Q-TOF) m/z:** $[M+H]^+$ calculated for C₁₉H₂₄NO₃ 314.1756, Found 314.1754

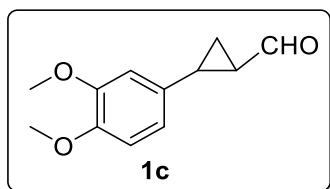
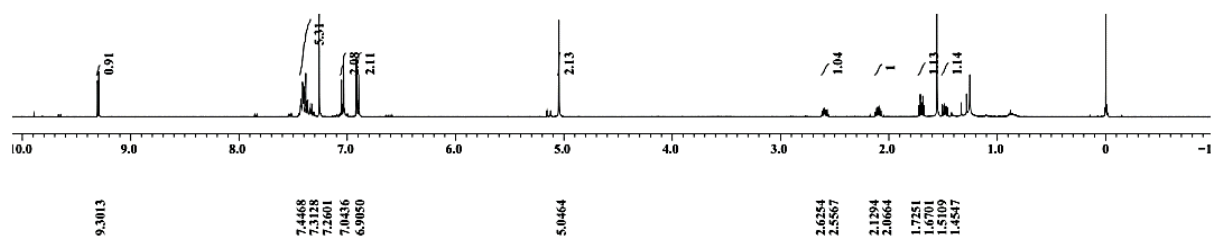
7. NMR, Mass spectra and HPLC data of the compounds



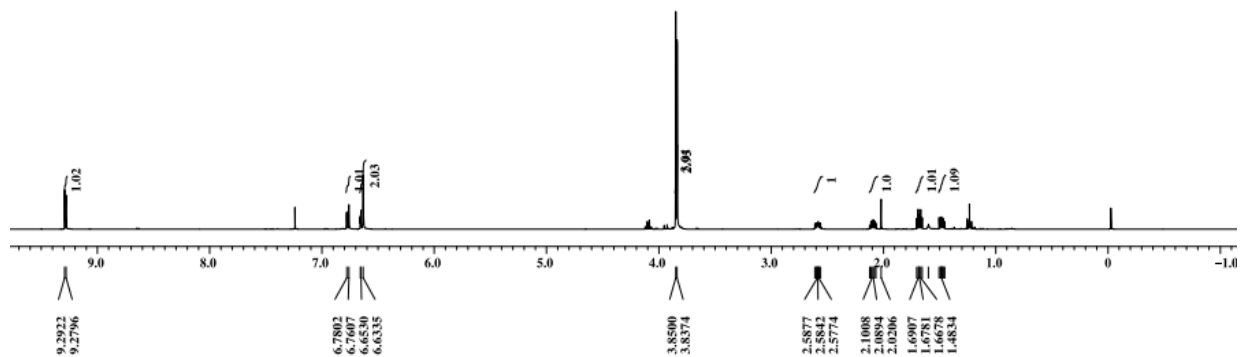
¹H-NMR (CDCl₃, 400MHz) of 1a

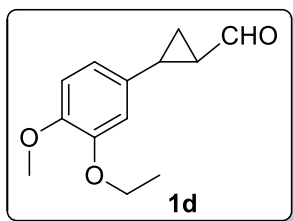


¹H-NMR (CDCl₃, 400MHz) of 1b

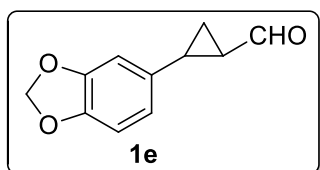
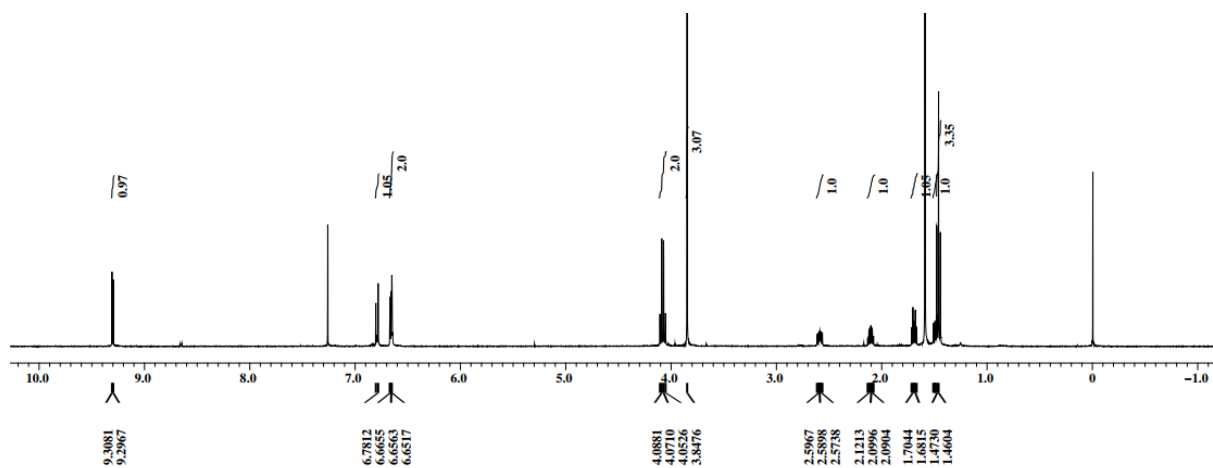


¹H-NMR (CDCl₃, 400MHz) of 1c

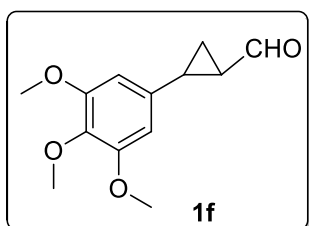
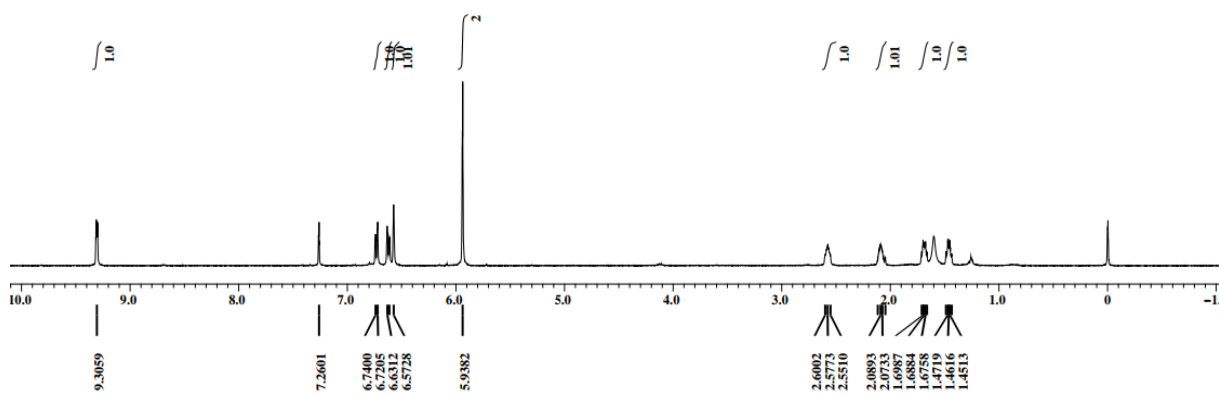




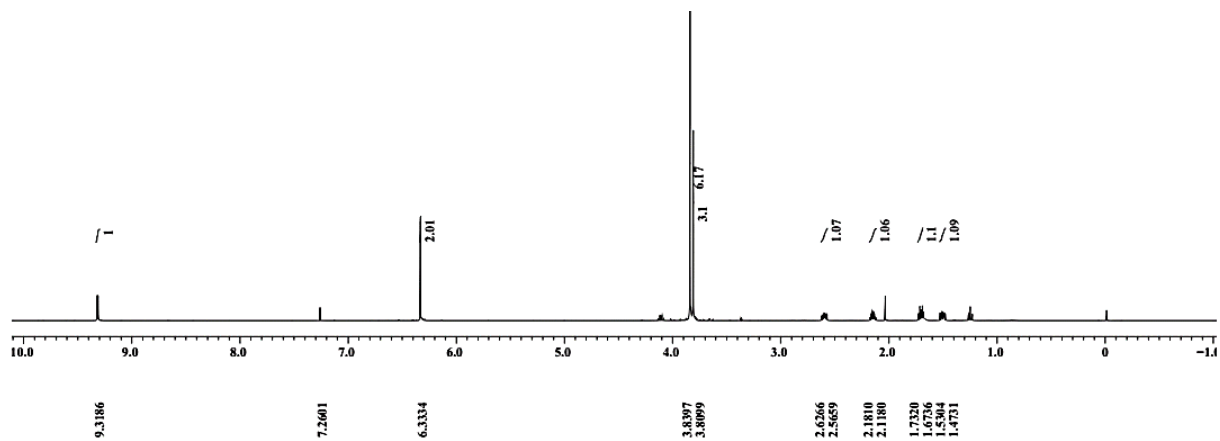
¹H-NMR (CDCl₃, 400MHz) of 1d



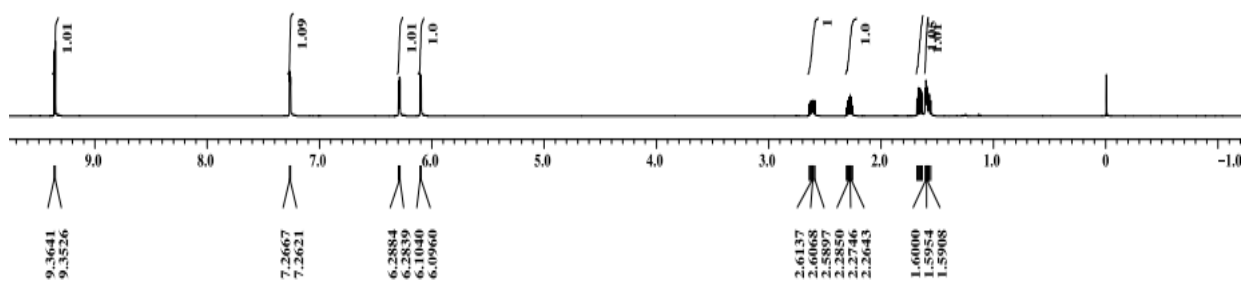
¹H-NMR (CDCl₃, 400MHz) of 1e



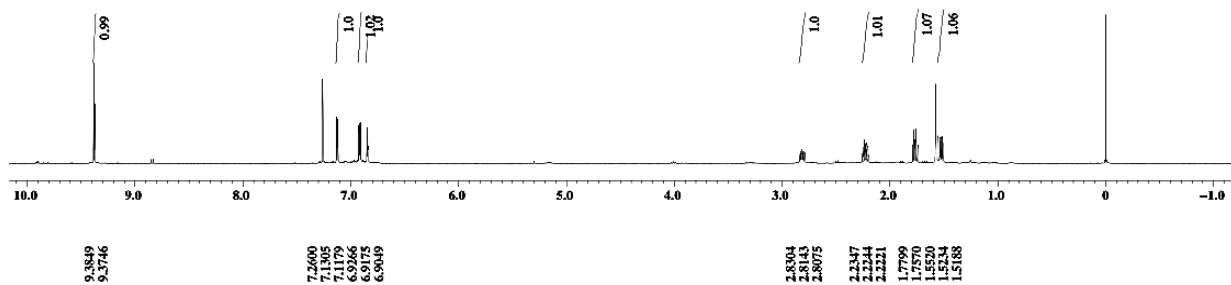
¹H-NMR (CDCl₃, 400MHz) of 1f

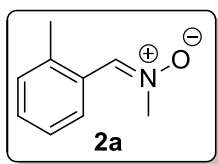


¹H-NMR (CDCl₃, 400MHz) of 1i

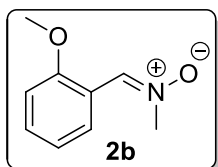
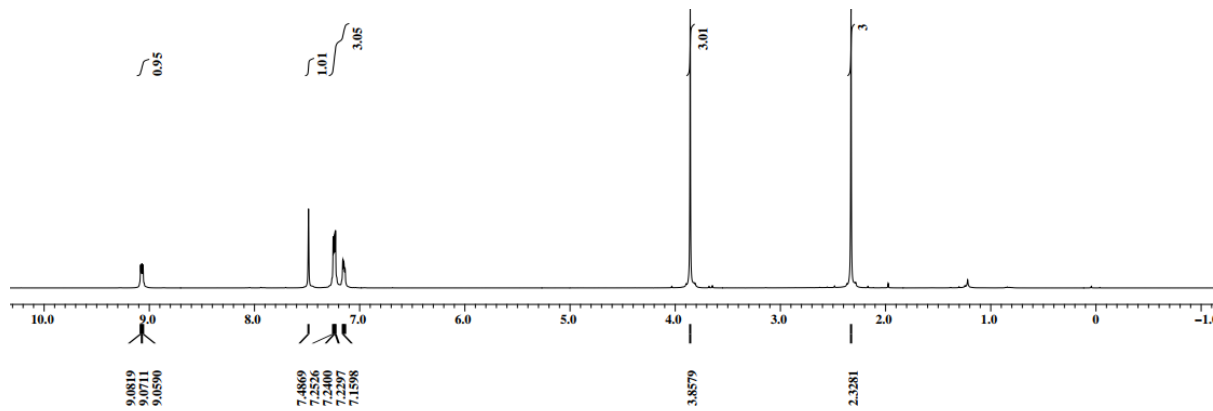


¹H-NMR (CDCl₃, 400MHz) of 1j

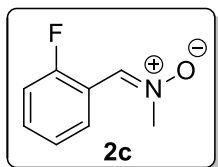
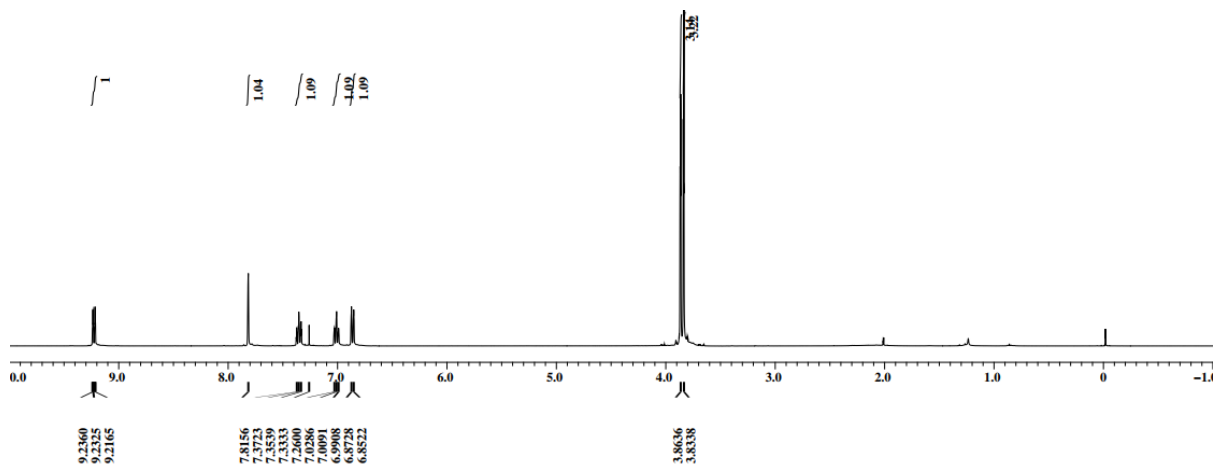




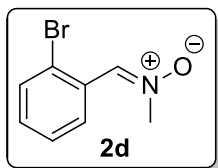
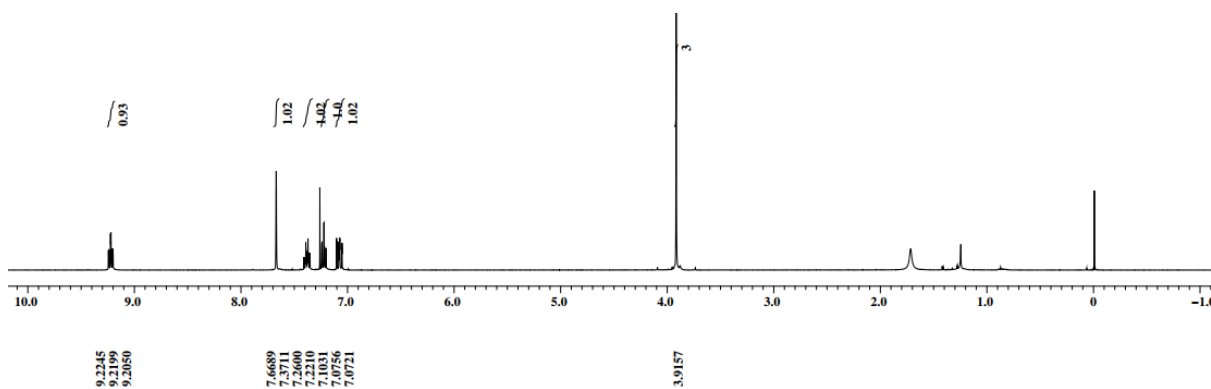
¹H-NMR (CDCl₃, 400MHz) of 2a



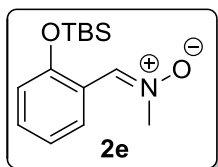
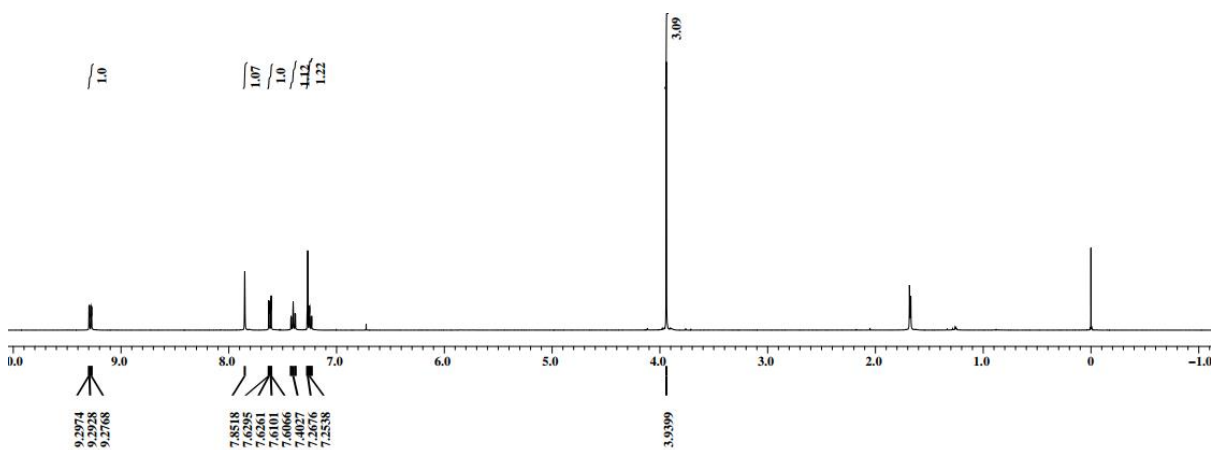
¹H-NMR (CDCl₃, 400MHz) of 2b



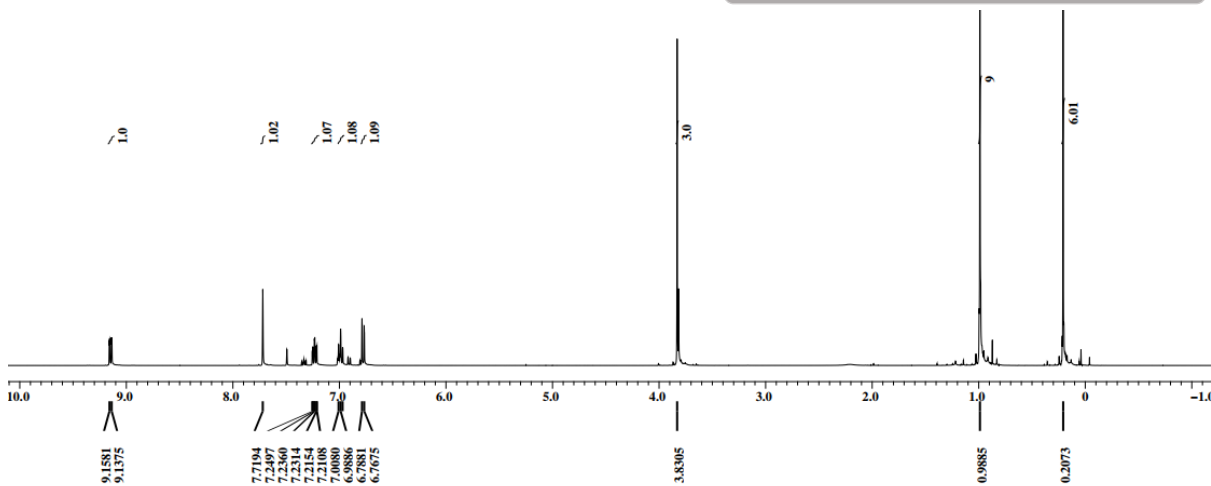
¹H-NMR (CDCl₃, 400MHz) of 2c

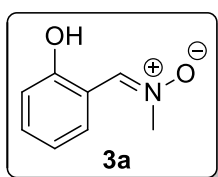


¹H-NMR (CDCl₃, 400MHz) of 2d

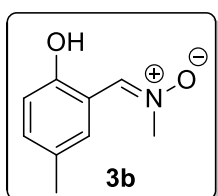
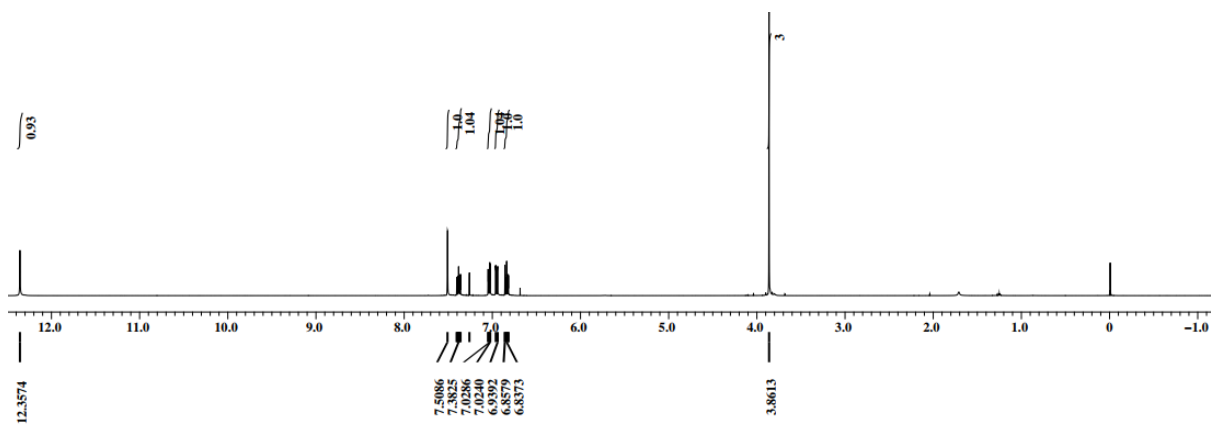


¹H-NMR (CDCl₃, 400MHz) of 2e

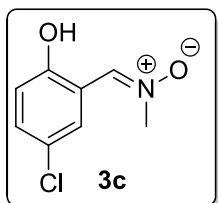
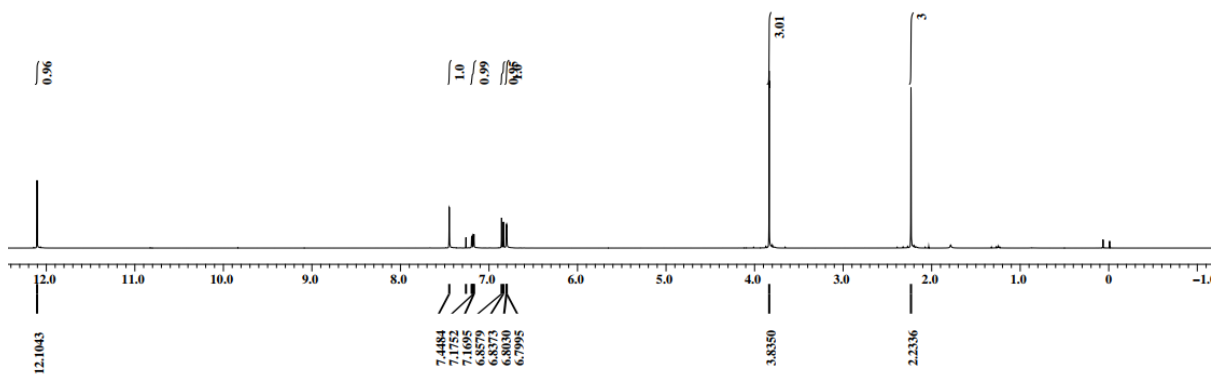




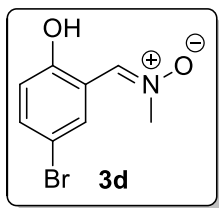
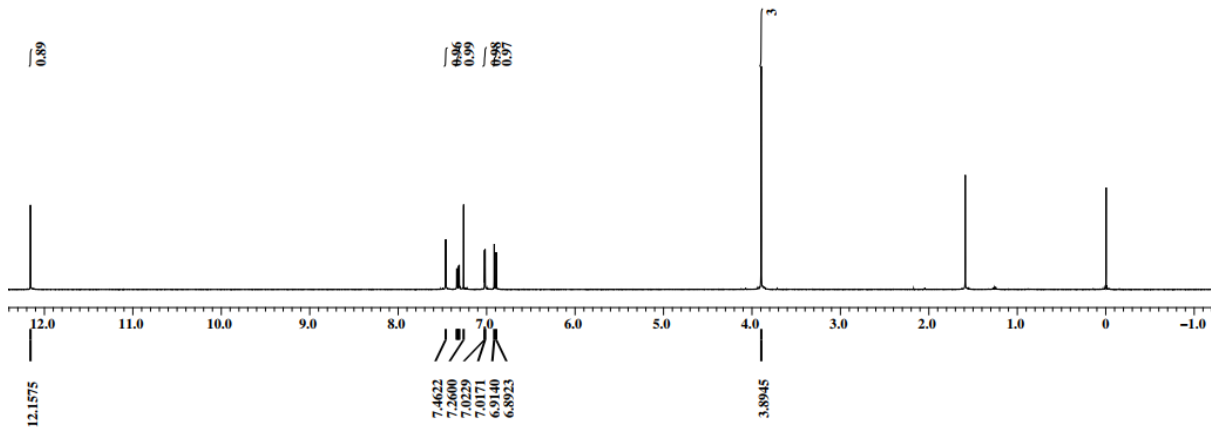
¹H-NMR (CDCl₃, 400MHz) of 3a



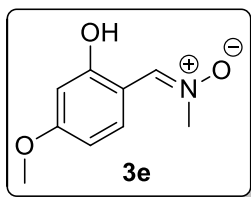
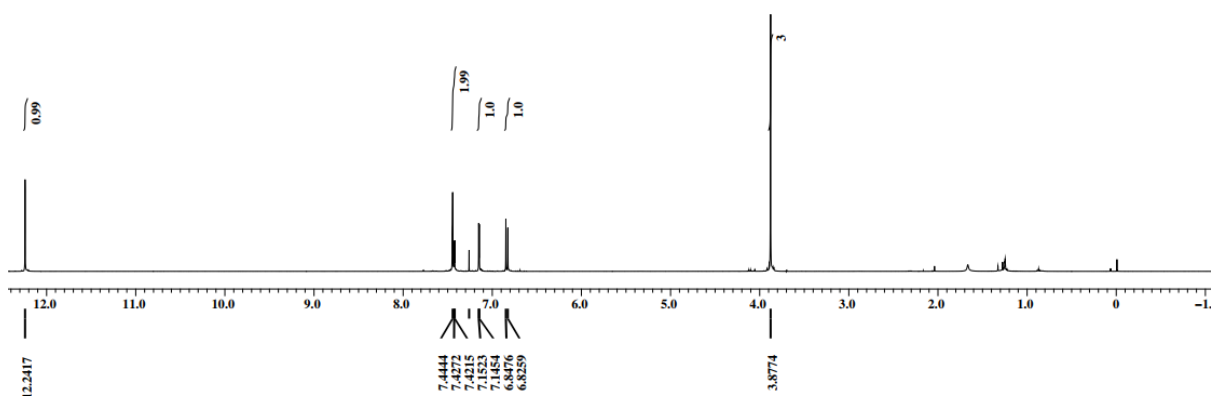
¹H-NMR (CDCl₃, 400MHz) of 3b



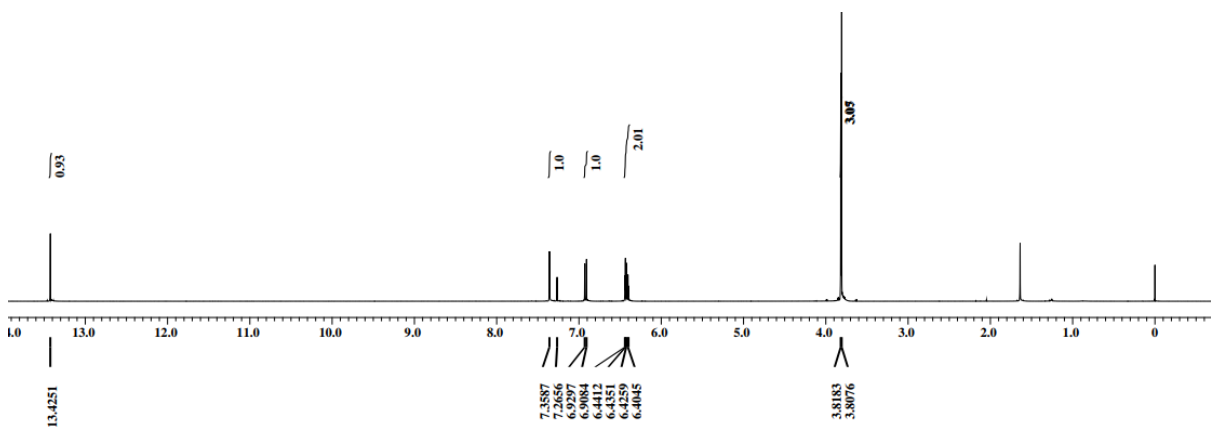
¹H-NMR (CDCl₃, 400MHz) of 3c

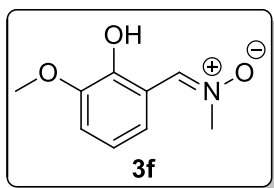


¹H-NMR (CDCl₃, 400MHz) of 3d

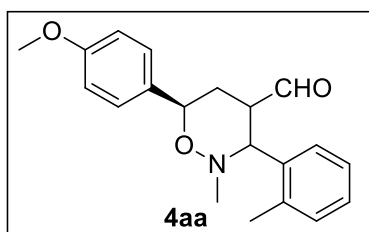
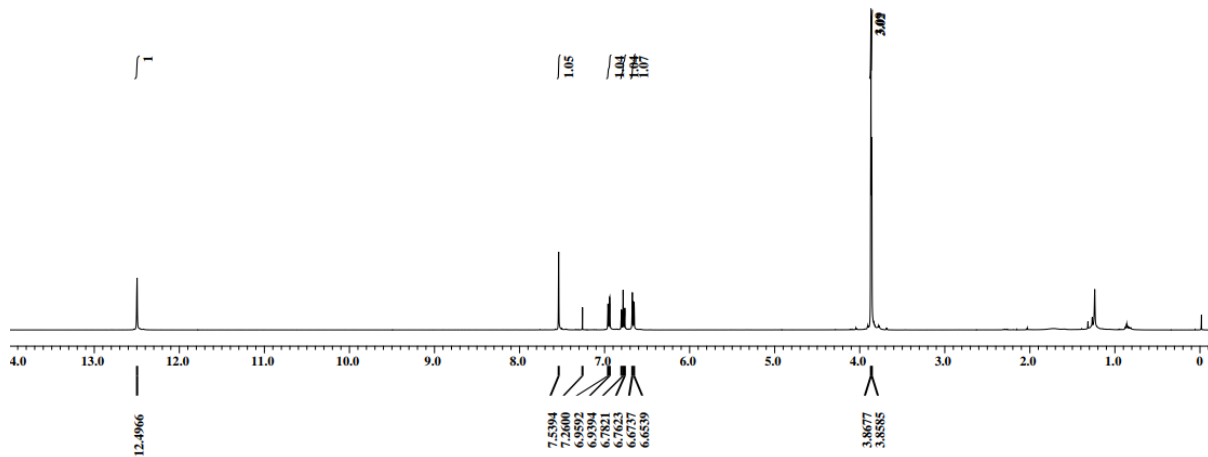


¹H-NMR (CDCl₃, 400MHz) of 3e

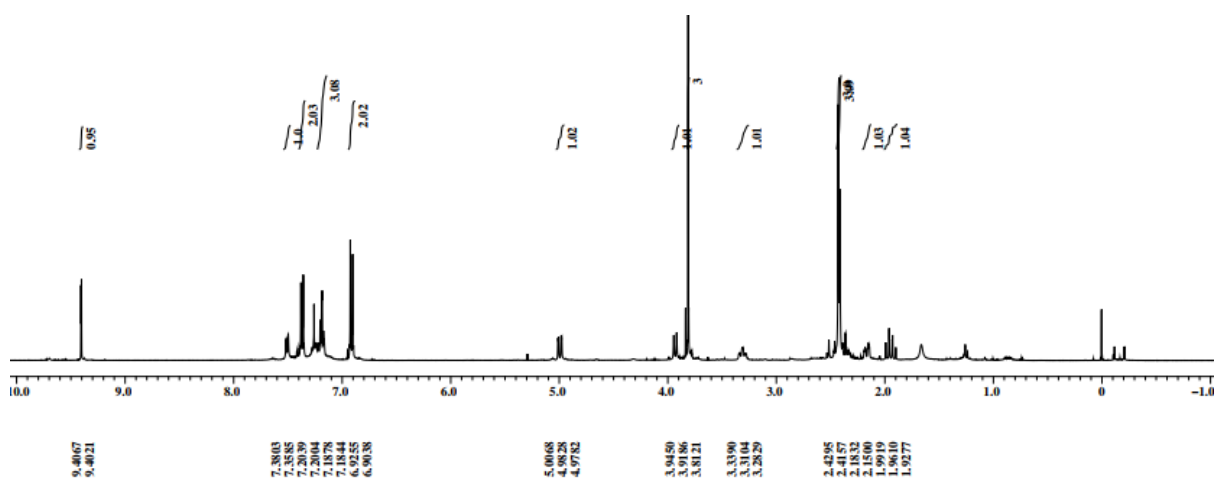




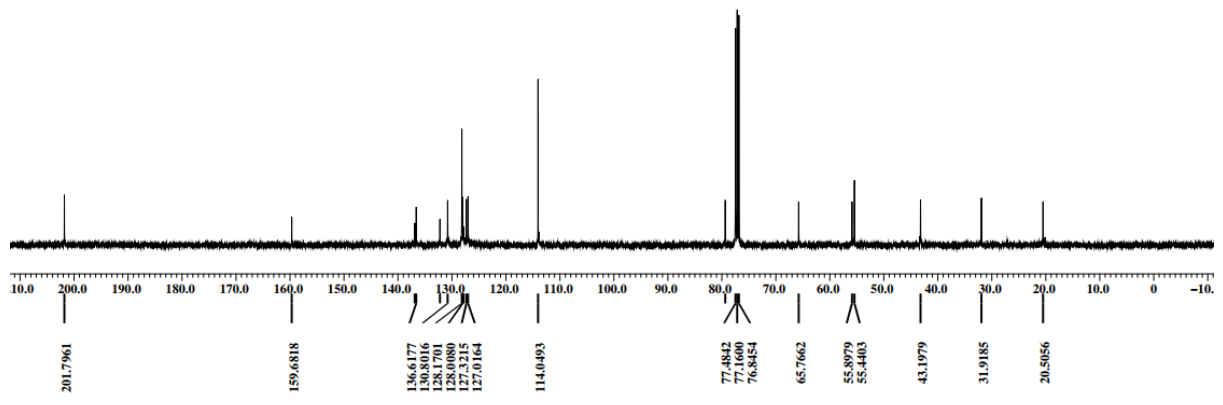
¹H-NMR (CDCl₃, 400MHz) of 3f



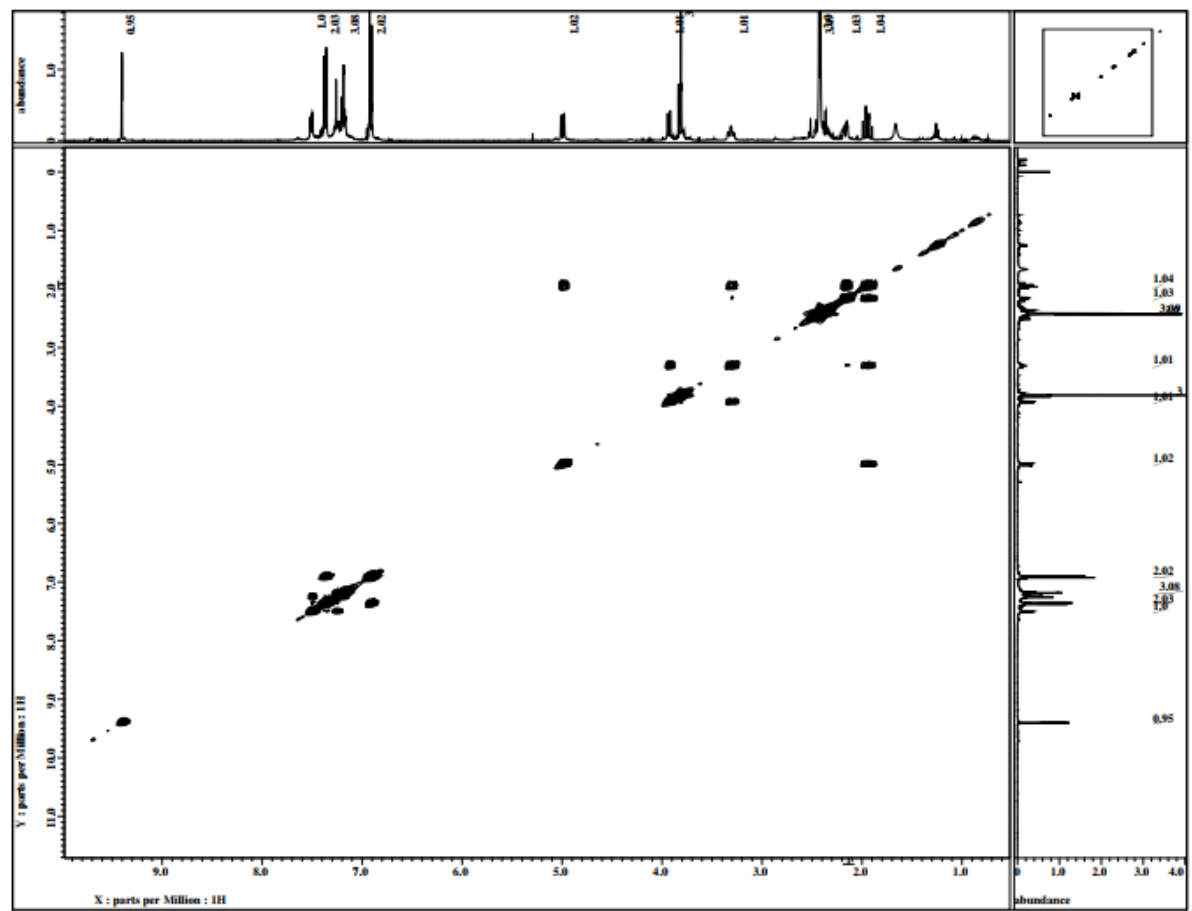
¹H-NMR (CDCl₃, 400MHz) of 4aa



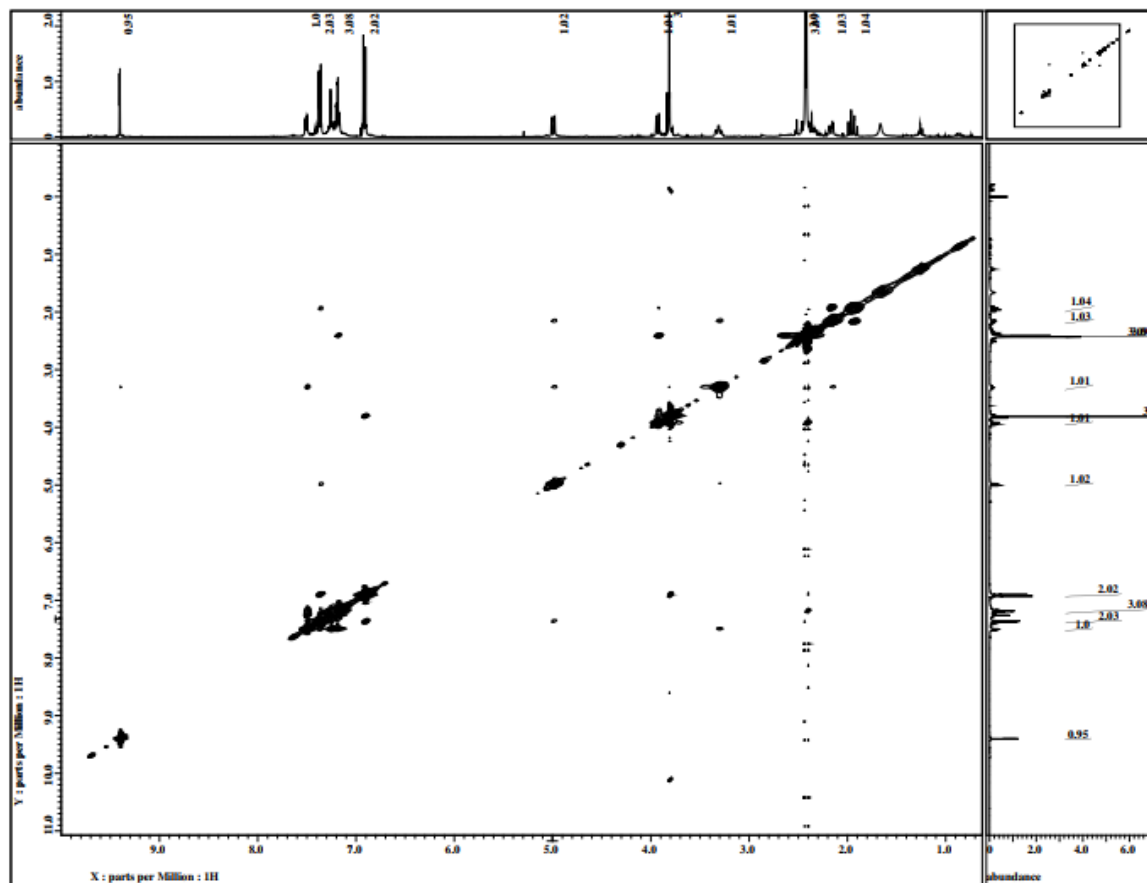
¹³C-NMR (CDCl₃, 100MHz) of 4aa



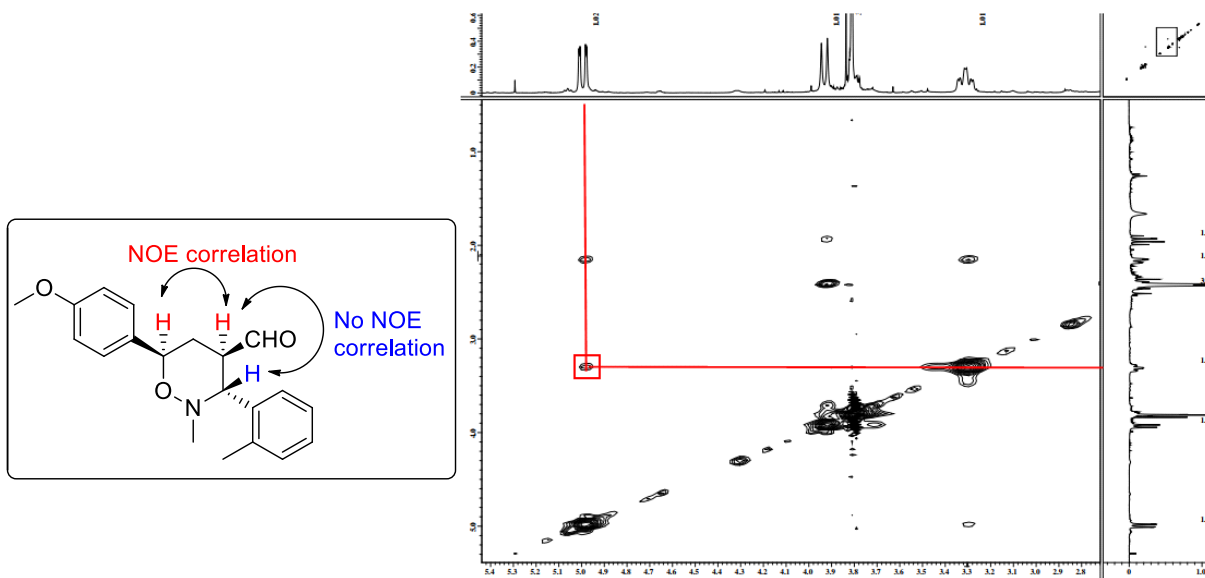
¹H-¹H COSY NMR (CDCl₃, 400MHz) of 4aa



^1H - ^1H NOESY NMR (CDCl_3 , 400MHz) of 4aa



^1H - ^1H NOESY NMR (CDCl_3 , 400MHz) of 4aa ZOOM



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

61 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

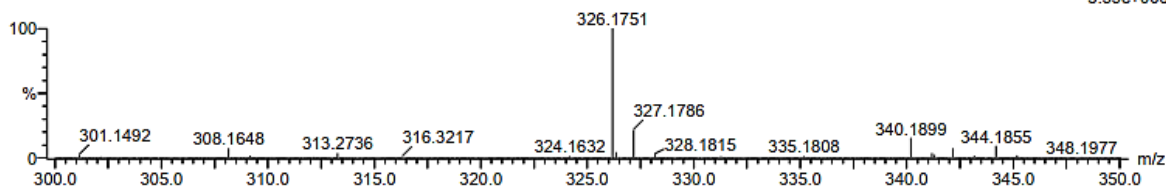
C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_233
 Test Name :
 110822_25_02_233 21 (0.231)

IITRPR

XEVO G2-XS QTOF

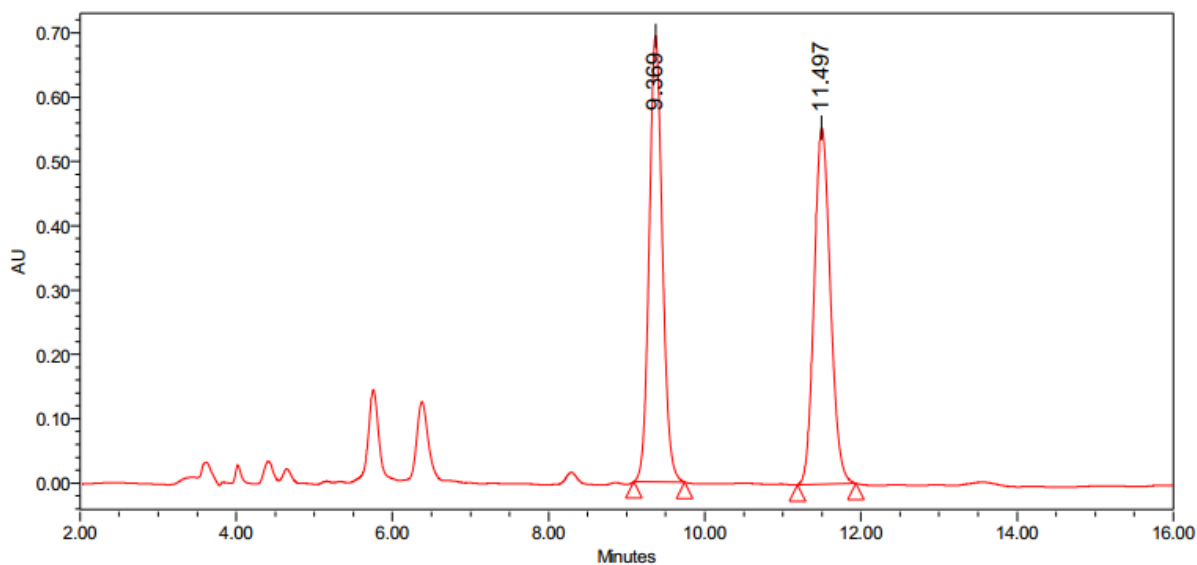
1: TOF MS ES+
 5.33e+006



Minimum: -1.5
 Maximum: 2.0 5.0 50.0

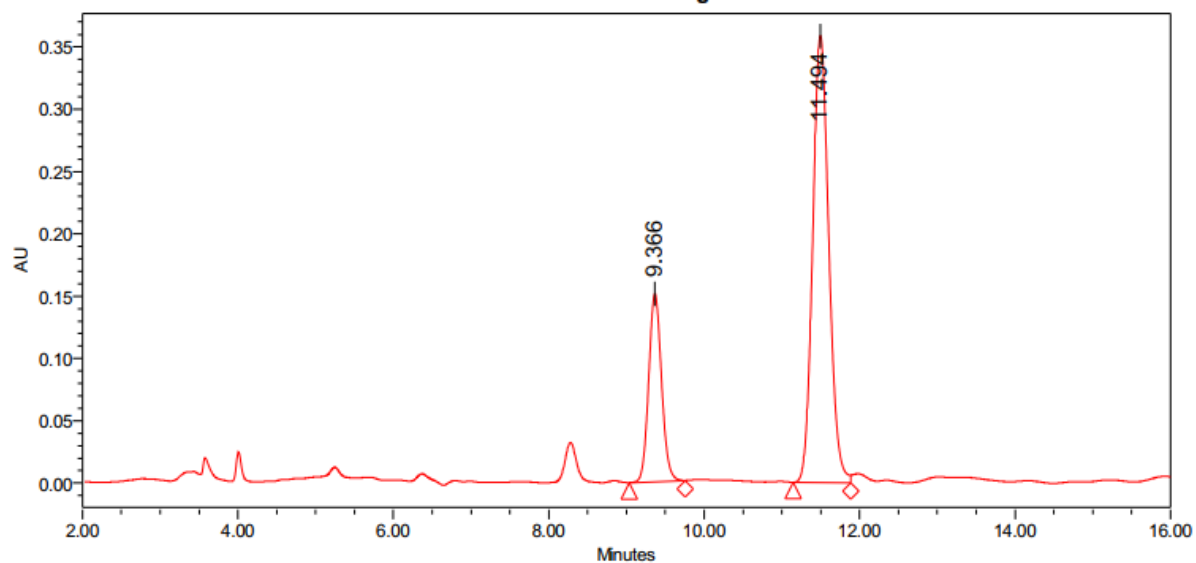
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
326.1751	326.1756	-0.5	-1.5	9.5	623.9	n/a	n/a	C20 H24 N O3

HPLC spectra of racemic 4aa

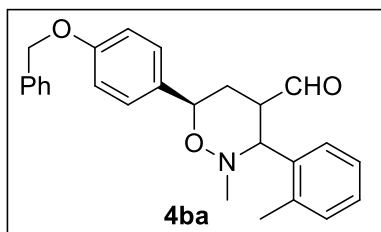


Name	RT	Area	% Area
1	9.369	8137460	50.34
2	11.497	8026886	49.66

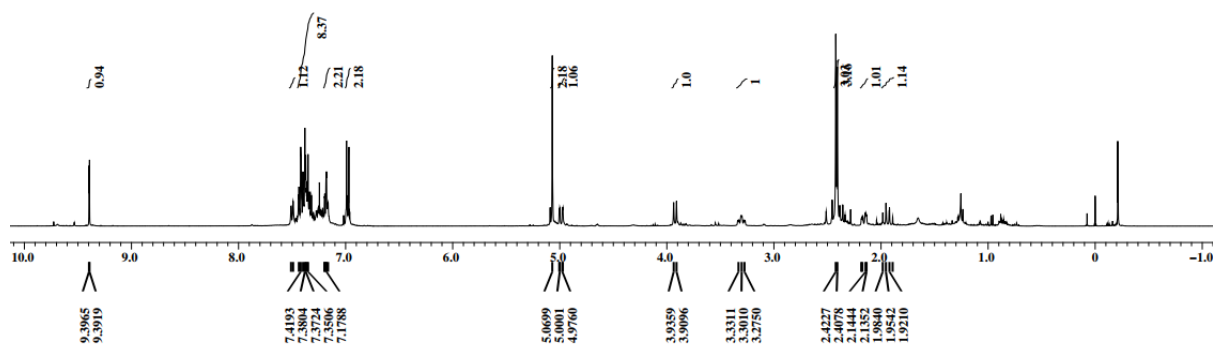
HPLC spectra of chiral 4aa



Peak Results			
Name	RT	Area	% Area
1	9.366	1744152	25.21
2	11.494	5174913	74.79

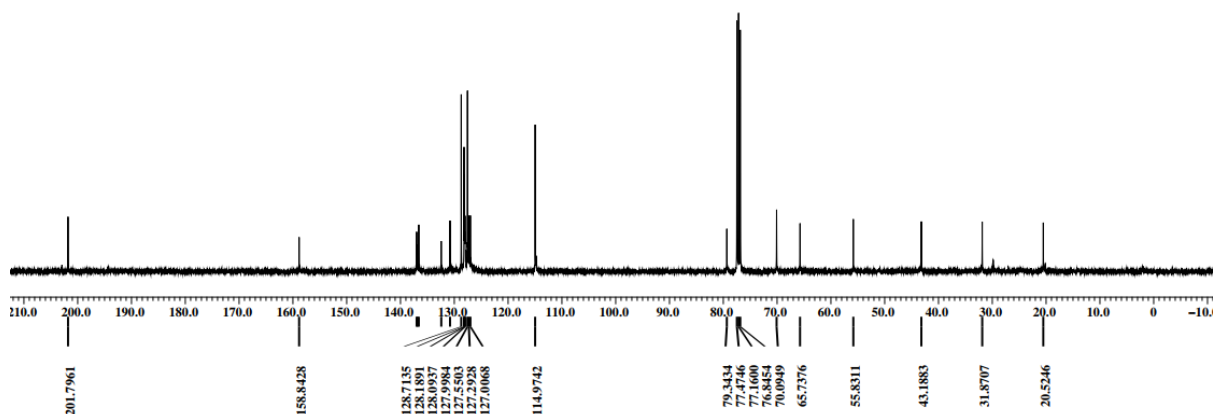


¹H-NMR (CDCl₃, 400MHz) of 4ba



¹³C-NMR (CDCl₃, 100MHz) of 4ba





HRMS of 4ba

Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

79 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_285

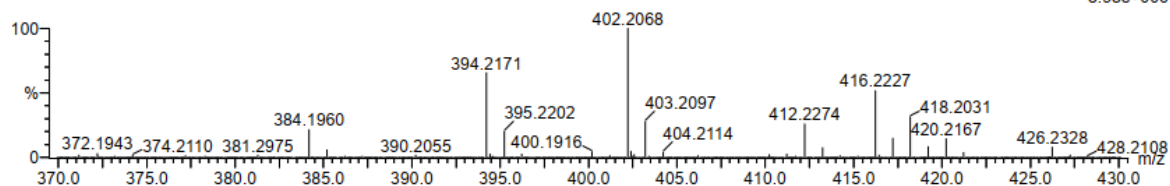
IITRPR

XEVO G2-XS QTOF

Test Name :

1: TOF MS ES+
8.98e+006

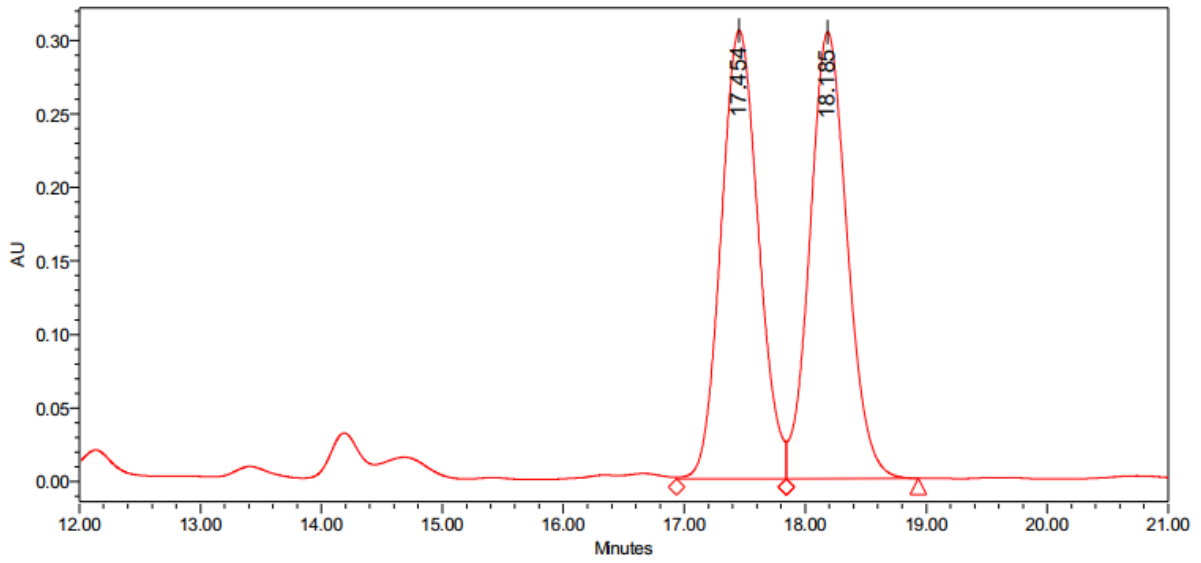
110822_25_02_285 8 (0.097)



Minimum: -1.5
Maximum: 2.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
402.2068	402.2069	-0.1	-0.2	13.5	485.8	n/a	n/a	C26 H28 N O3

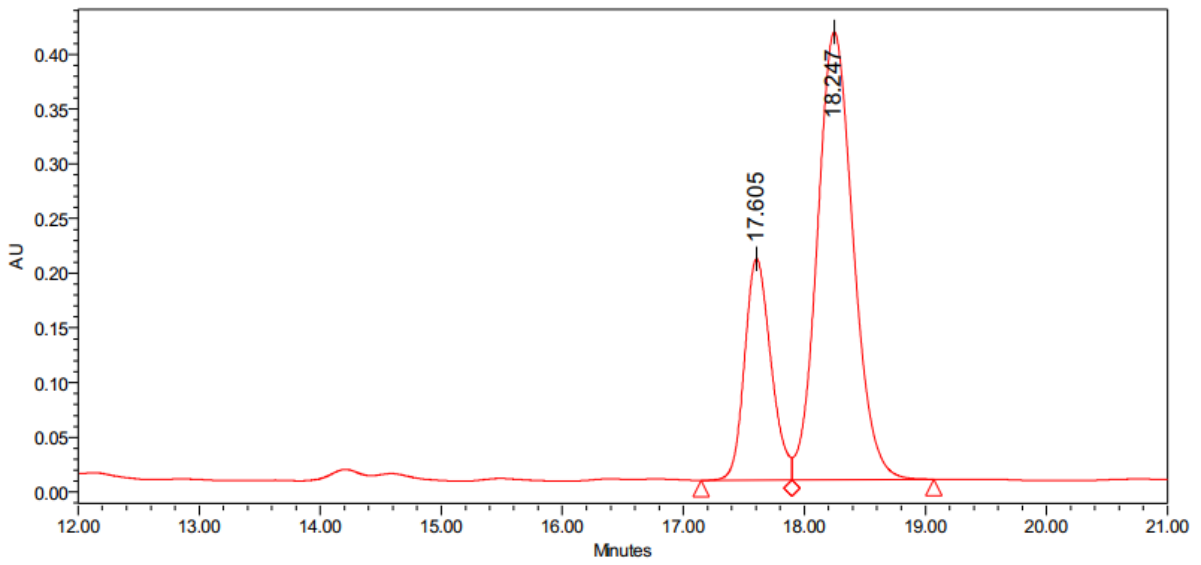
HPLC spectra of racemic 4ba



Peak Results

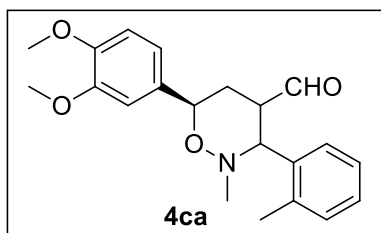
Name	RT	Area	% Area
1	17.454	6537031	50.05
2	18.185	6523167	49.95

HPLC spectra of chiral 4ba

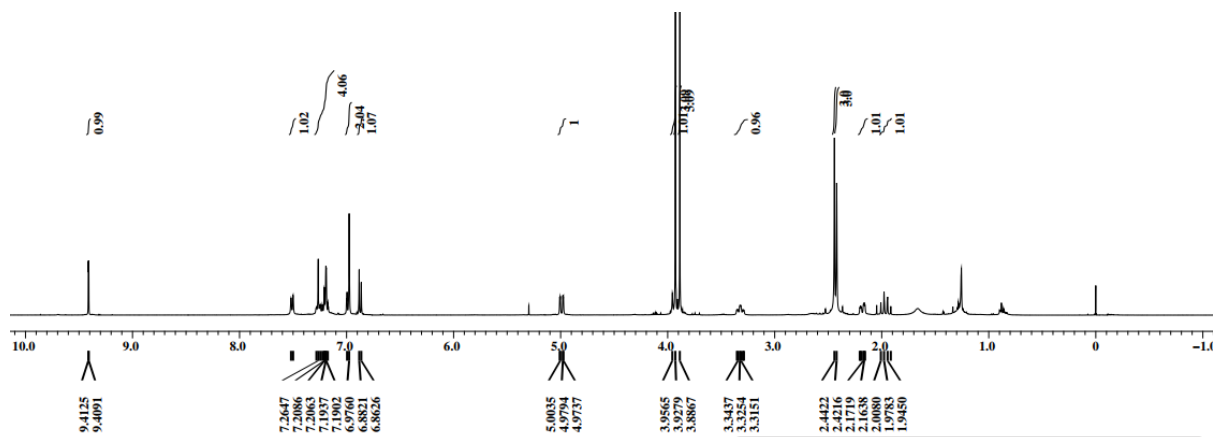


Peak Results

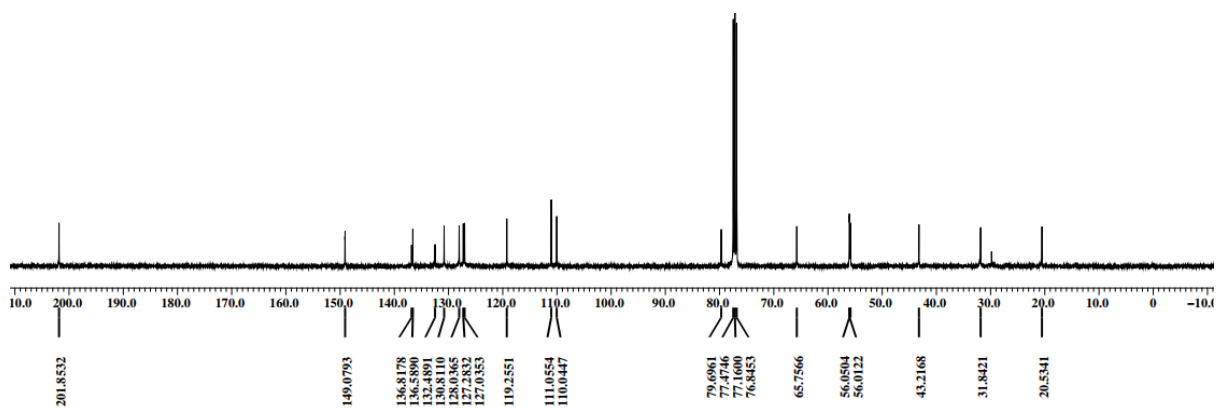
Name	RT	Area	% Area
1	17.605	3052717	26.59
2	18.247	8429311	73.41



$^1\text{H-NMR}$ (CDCl_3 , 400MHz) of 4ca



$^{13}\text{C-NMR}$ (CDCl_3 , 100MHz) of 4ca



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

96 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

C: 1-22 H: 1-100 N: 0-5 O: 1-5

Sample Name : 25_02_288

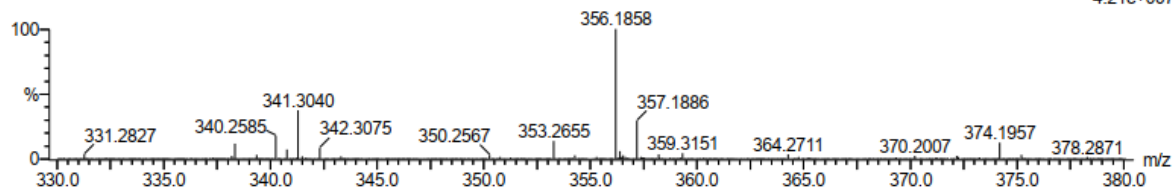
Test Name :

080822_25_02_288 11 (0.134)

IITRPR

XEVO G2-XS QTOF

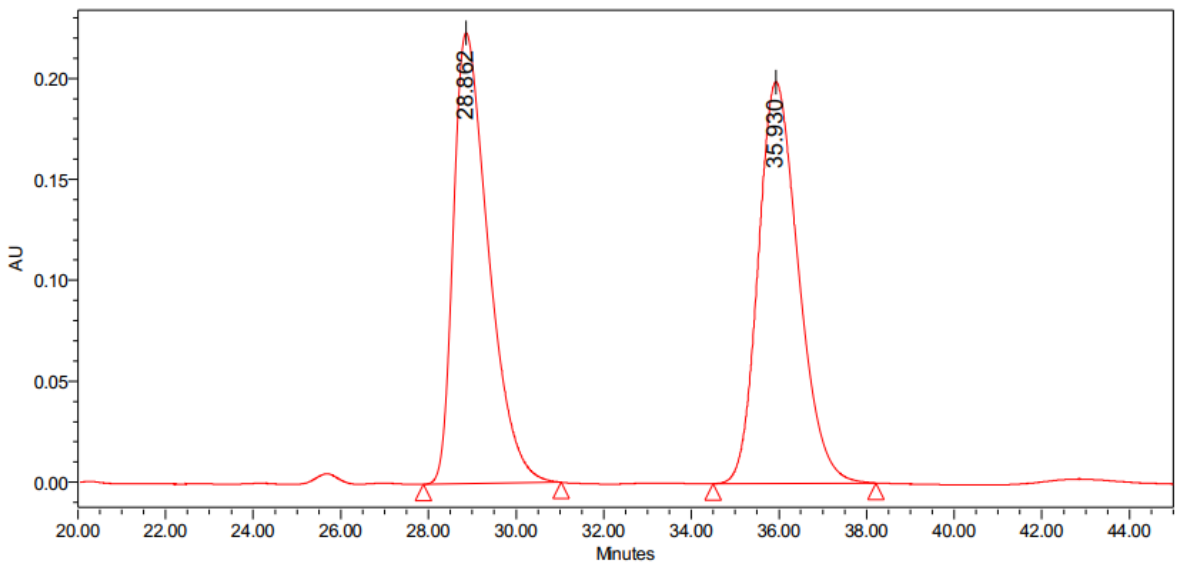
1: TOF MS ES+
4.21e+007



Minimum: -1.5
Maximum: 2.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
356.1858	356.1862	-0.4	-1.1	9.5	675.7	n/a	n/a	C21 H26 N O4

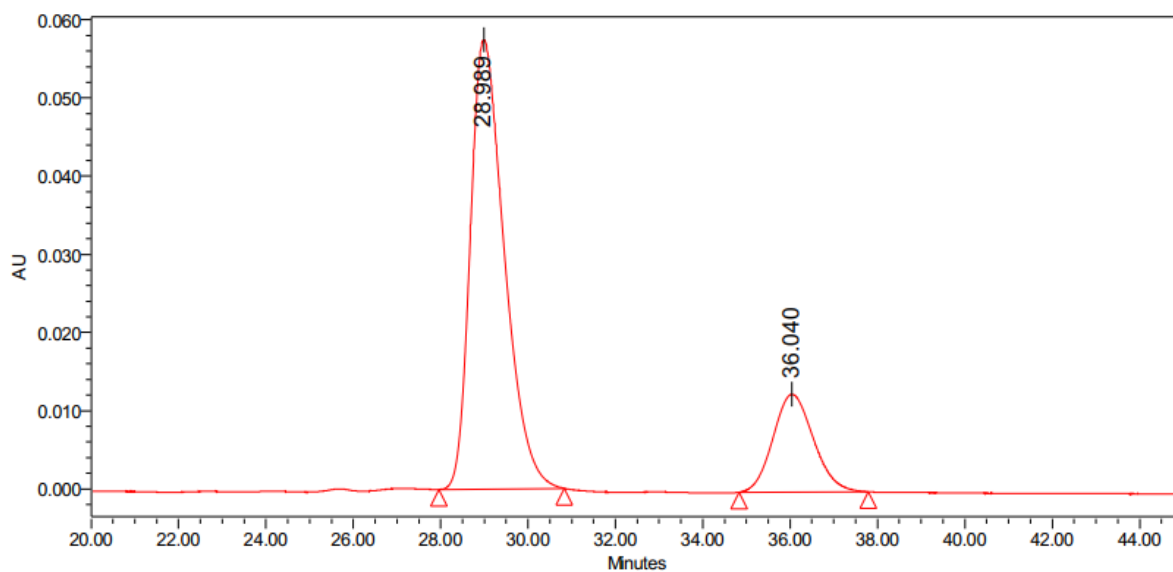
HPLC spectra of racemic 4ca



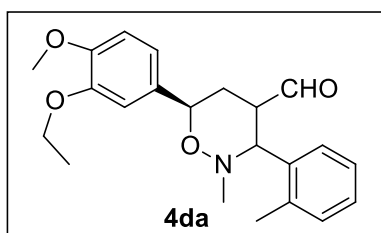
Peak Results

Name	RT	Area	% Area
1	28.862	12434799	49.55
2	35.930	12660008	50.45

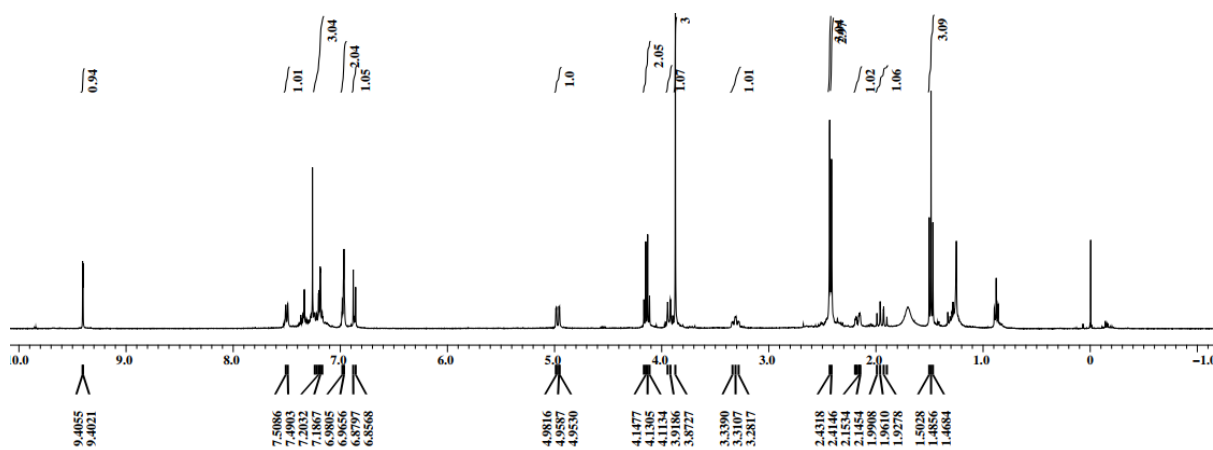
HPLC spectra of chiral 4ca



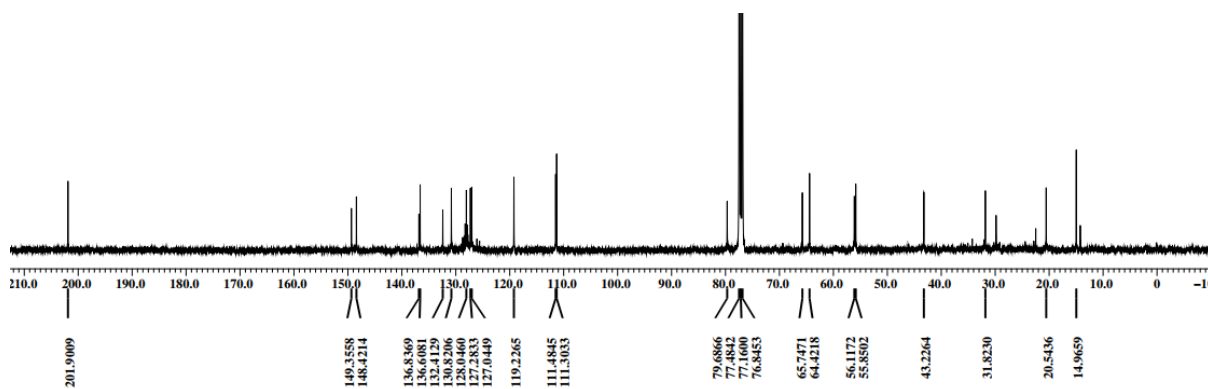
Peak Results			
Name	RT	Area	% Area
1	28.989	3129184	79.65
2	36.040	799360	20.35



¹H-NMR (CDCl₃, 400MHz) of 4da



¹³C-NMR (CDCl₃, 100MHz) of 4da



HRMS of 4da

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Odd and Even Electron Ions

34 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

C: 22-22 H: 1-100 N: 0-5 O: 0-5

Sample Name : 25_02_291

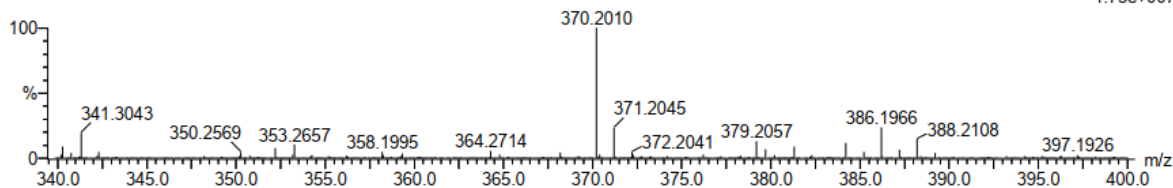
Test Name :

080822_25_02_291 22 (0.240)

IITRPR

XEVO G2-XS QTOF

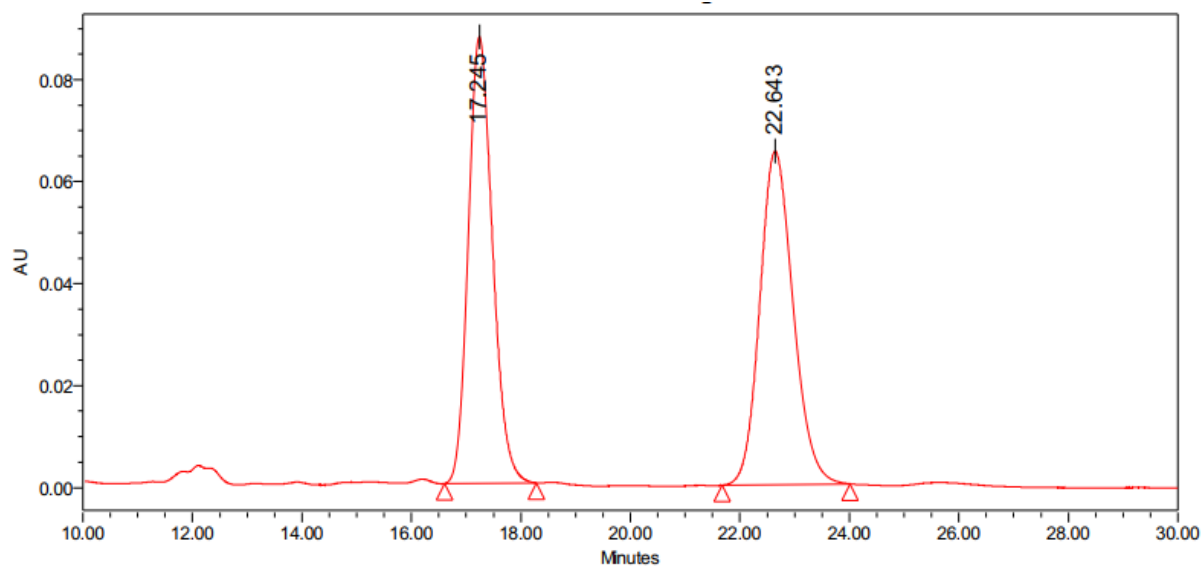
1: TOF MS ES+
1.75e+007



Minimum: -1.5
Maximum: 2.0 5.0 50.0

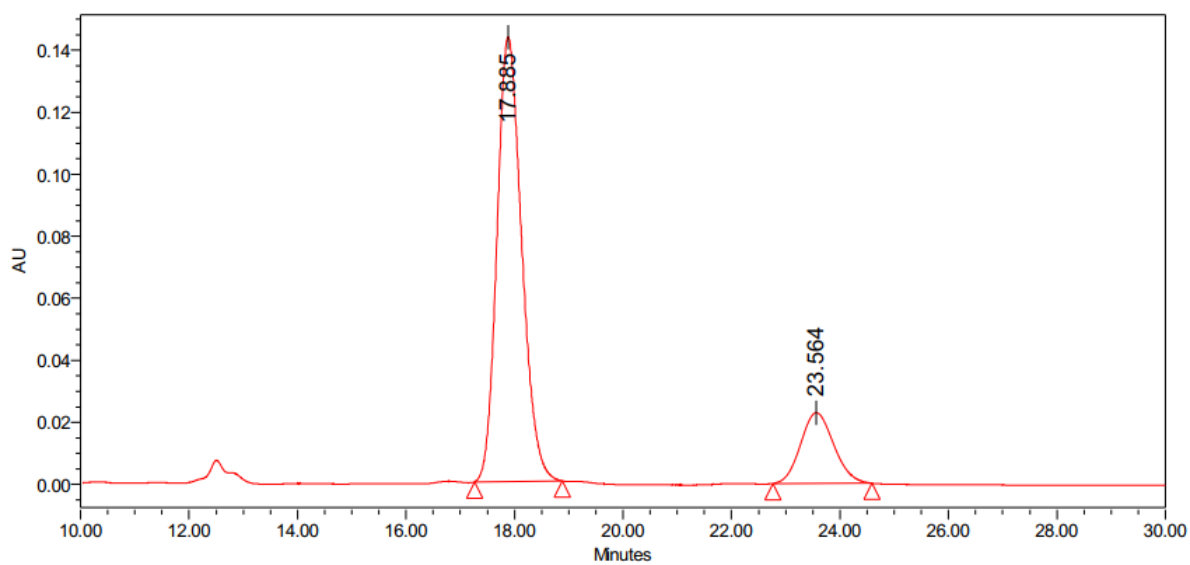
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
370.2010	370.2018	-0.8	-2.2	9.5	728.6	n/a	n/a	C22 H28 N O4

HPLC spectra of racemic 4da

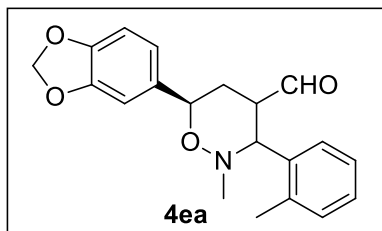


Peak Results			
Name	RT	Area	% Area
1	17.245	2688440	49.39
2	22.643	2754392	50.61

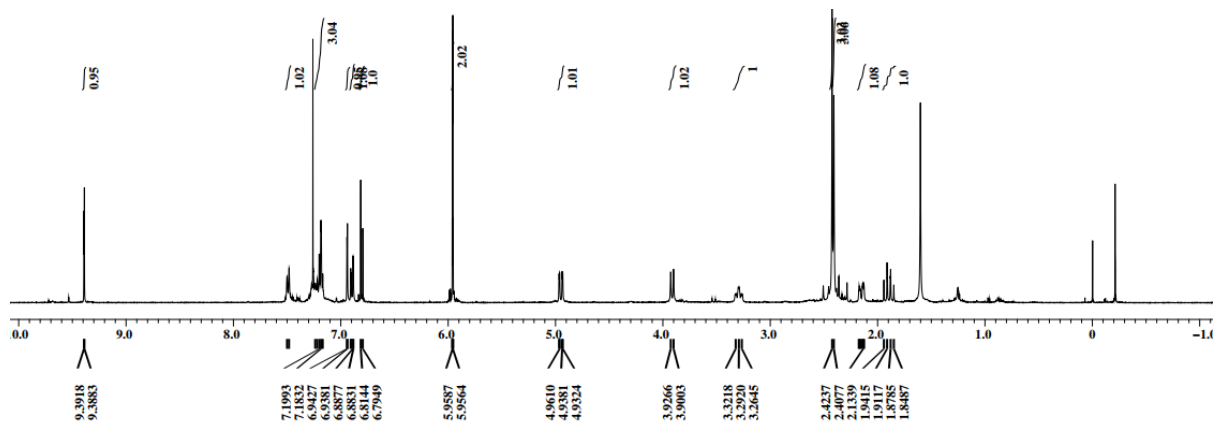
HPLC spectra of chiral 4da



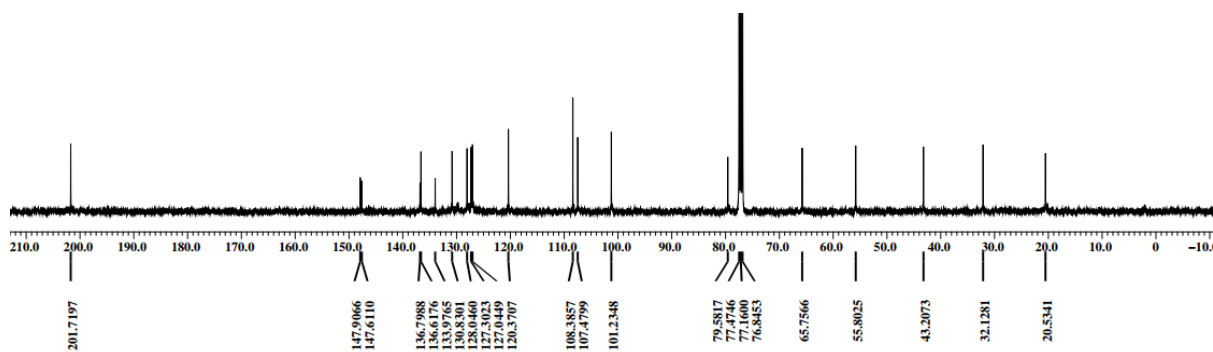
Peak Results			
Name	RT	Area	% Area
1	17.885	4516387	82.34
2	23.564	968732	17.66



¹H-NMR (CDCl₃, 400MHz) of 4ea



¹³C-NMR (CDCl₃, 100MHz) of 4ea



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
 Element prediction: Off
 Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

64 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

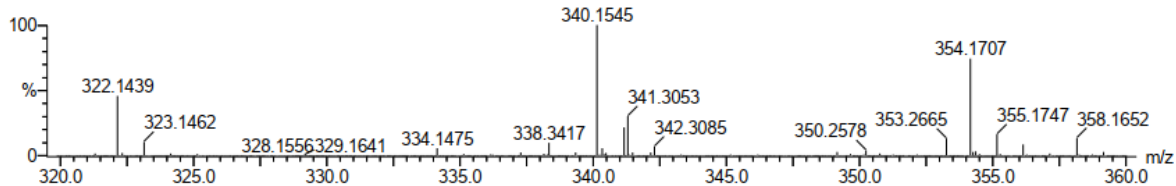
C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_312
 Test Name :
 110822_25_02_312 9 (0.117)

IITRPR

XEVO G2-XS QTOF

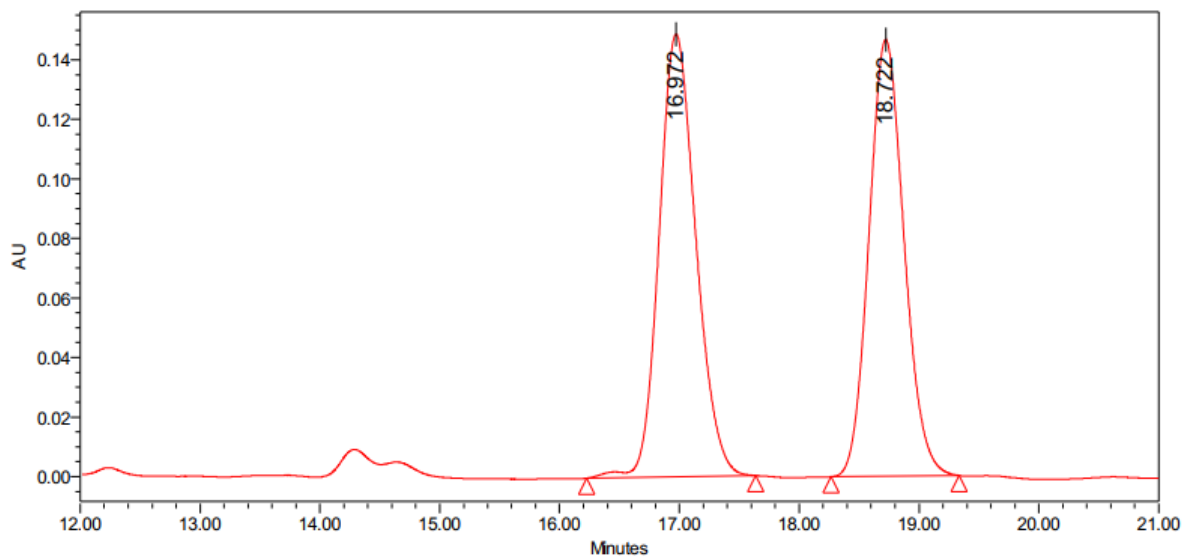
1: TOF MS ES+
 1.07e+007



Minimum: -1.5
 Maximum: 2.0 5.0 50.0

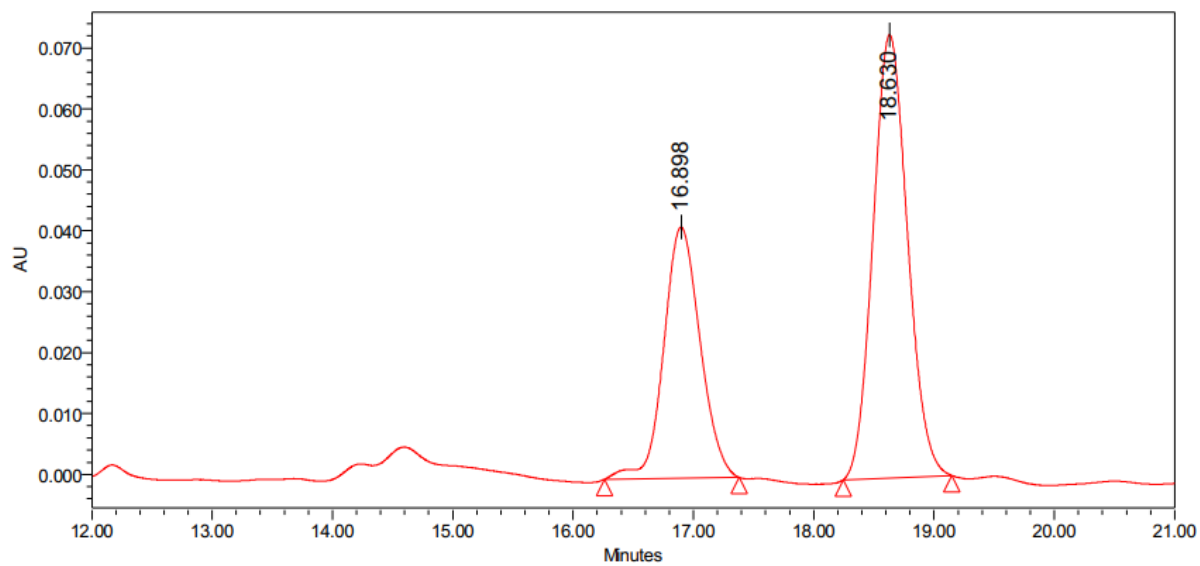
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
340.1545	340.1549	-0.4	-1.2	10.5	657.4	n/a	n/a	C20 H22 N O4

HPLC spectra of racemic 4ea



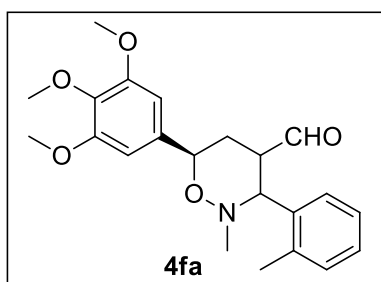
Name	RT	Area	% Area
1	16.972	3172593	51.51
2	18.722	2987108	48.49

HPLC spectra of chiral 4ea

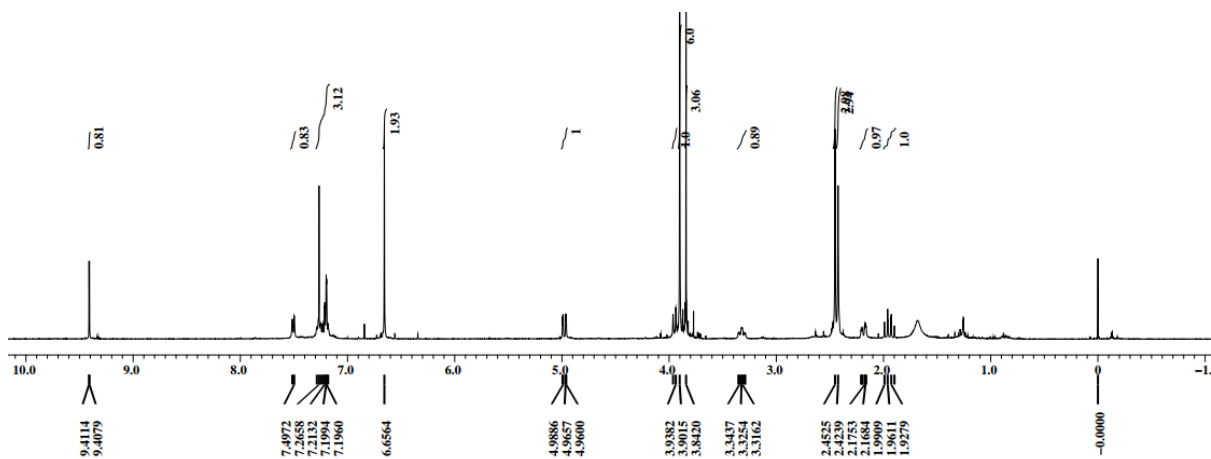


Peak Results

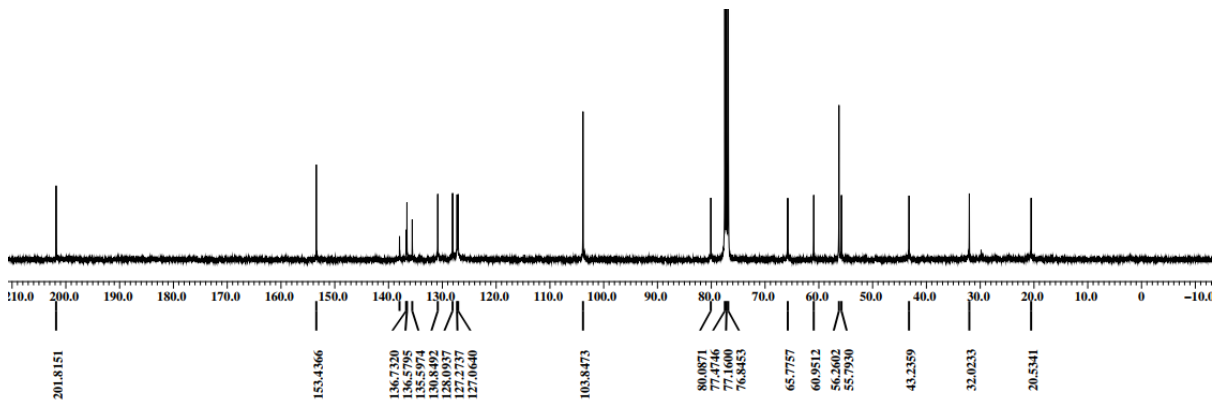
Name	RT	Area	% Area
1	16.898	868034	37.44
2	18.630	1450514	62.56



¹H-NMR (CDCl₃, 400MHz) of 4fa



¹³C-NMR (CDCl₃, 100MHz) of 4fa



HRMS of 4fa

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

76 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_310

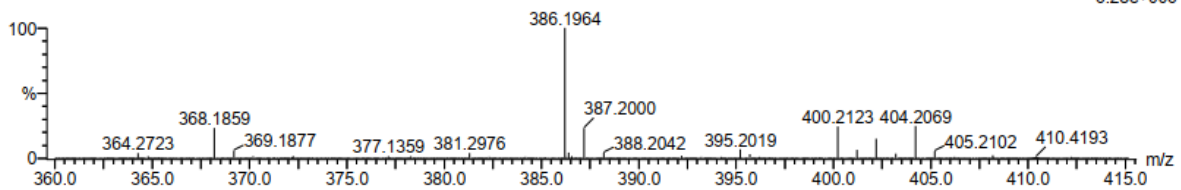
IITRPR

XEVO G2-XS QTOF

Test Name :

110822_25_02_310 8 (0.097)

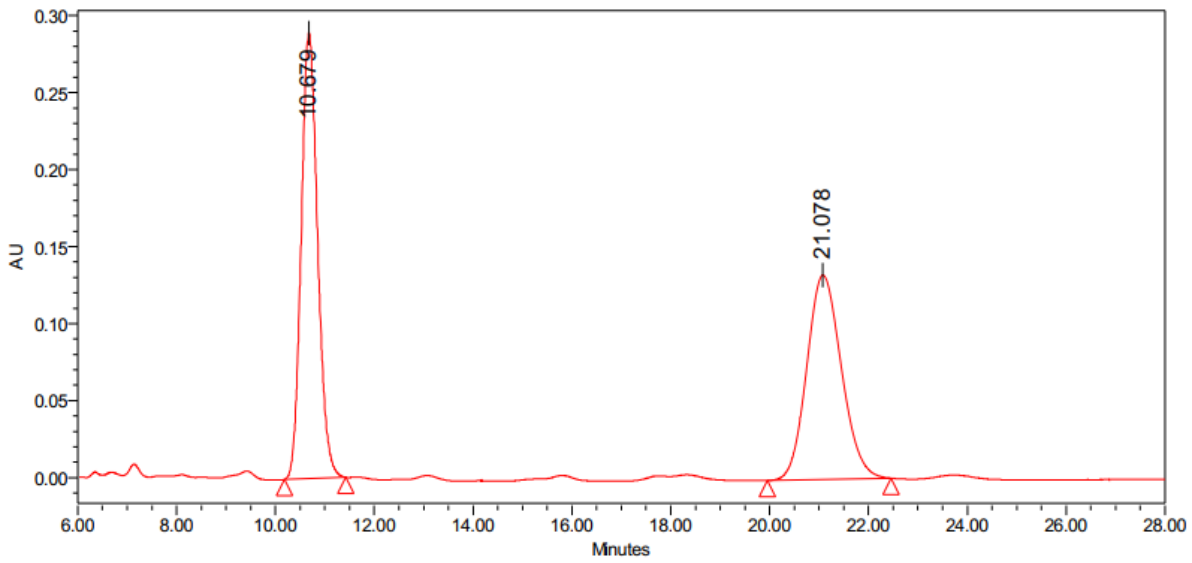
1: TOF MS ES+
6.28e+006



Minimum: -1.5
Maximum: 2.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
386.1964	386.1967	-0.3	-0.8	9.5	530.1	n/a	n/a	C22 H28 N O5

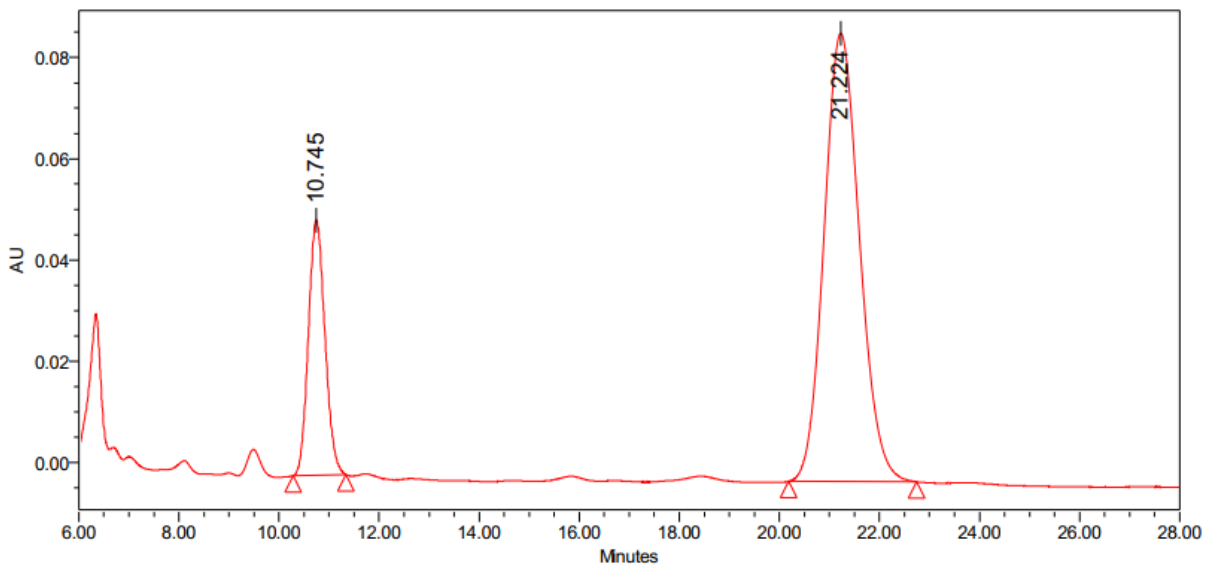
HPLC spectra of racemic 4fa



Peak Results

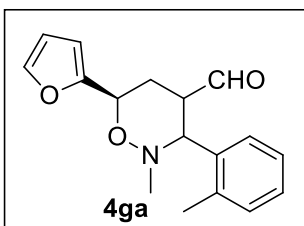
Name	RT	Area	% Area
1	10.679	6637235	50.63
2	21.078	6471619	49.37

HPLC spectra of chiral 4fa

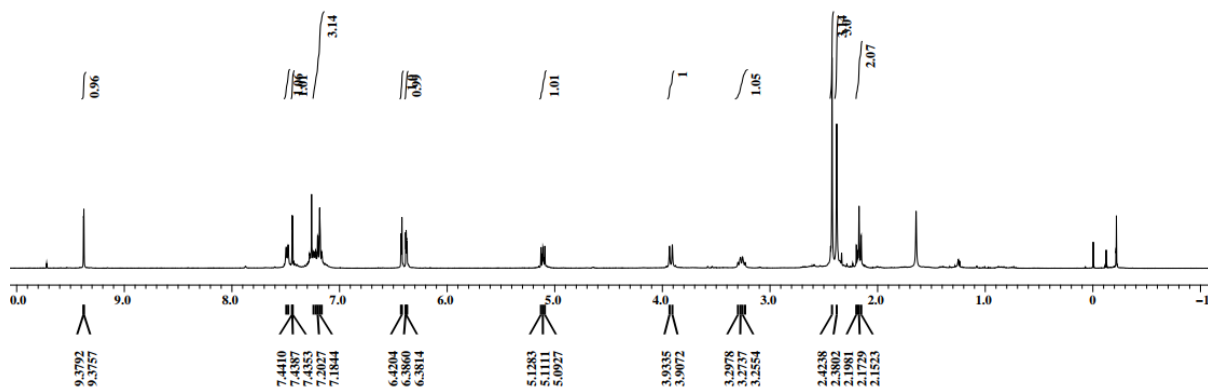


Peak Results

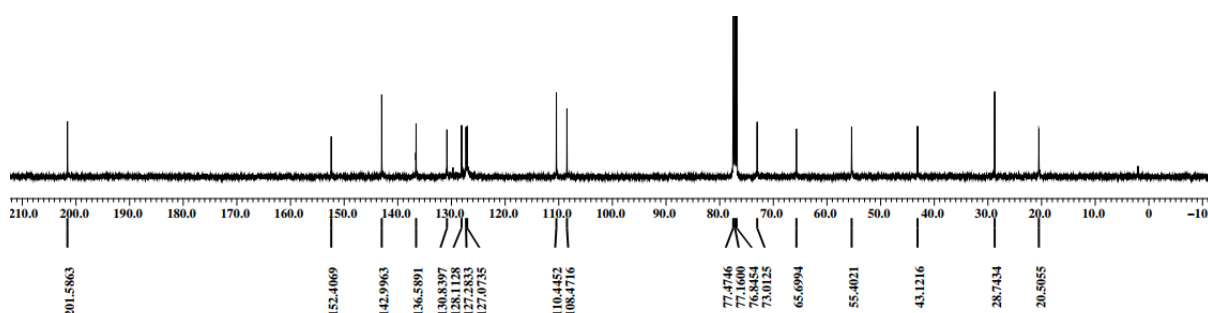
Name	RT	Area	% Area
1	10.745	1151929	20.89
2	21.224	4362202	79.11



¹H-NMR (CDCl₃, 400MHz) of 4ga



¹³C-NMR (CDCl₃, 100MHz) of 4ga



HRMS of 4ga

Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

51 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_308

IITRPR

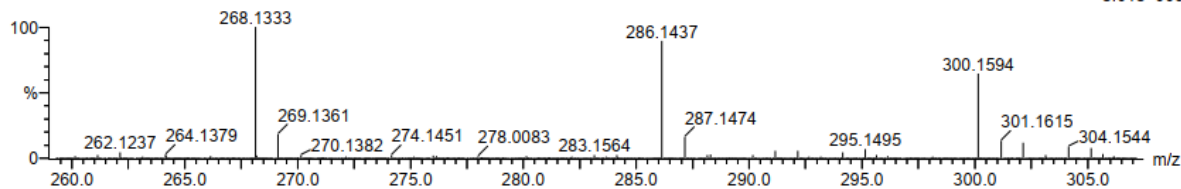
XEVO G2-XS QTOF

Test Name :

110822_25_02_308 16 (0.177)

1: TOF MS ES+

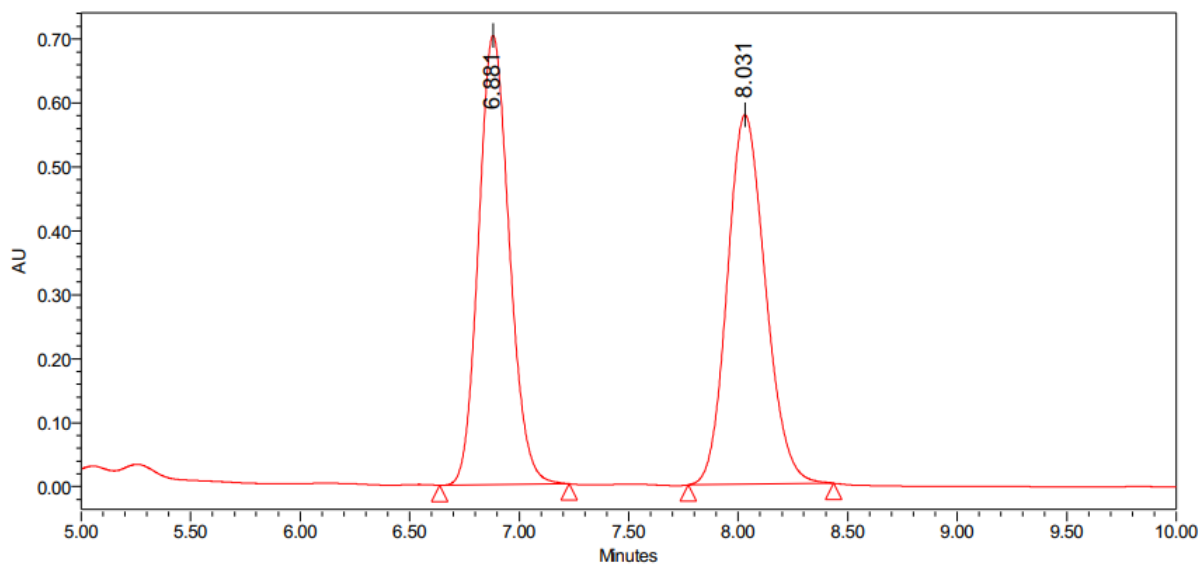
5.01e+006



Minimum: -1.5
Maximum: 2.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
286.1437	286.1443	-0.6	-2.1	8.5	771.9	n/a	n/a	C17 H20 N O3

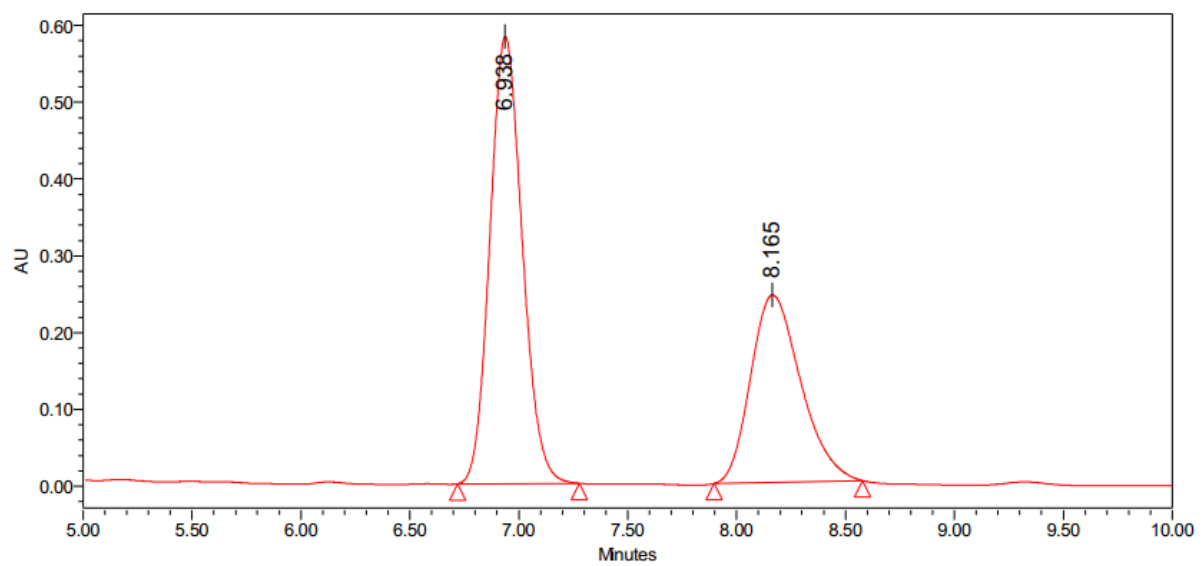
HPLC spectra of racemic 4ga



Peak Results

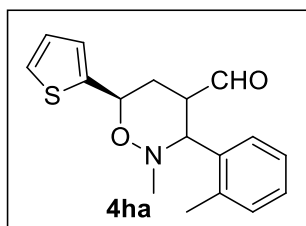
Name	RT	Area	% Area
1	6.881	6863940	49.50
2	8.031	7003882	50.50

HPLC spectra of chiral 4ga

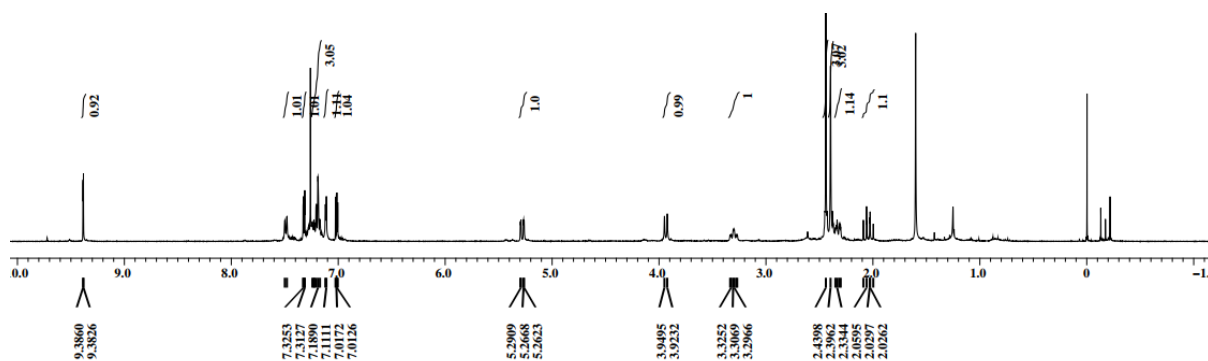


Peak Results

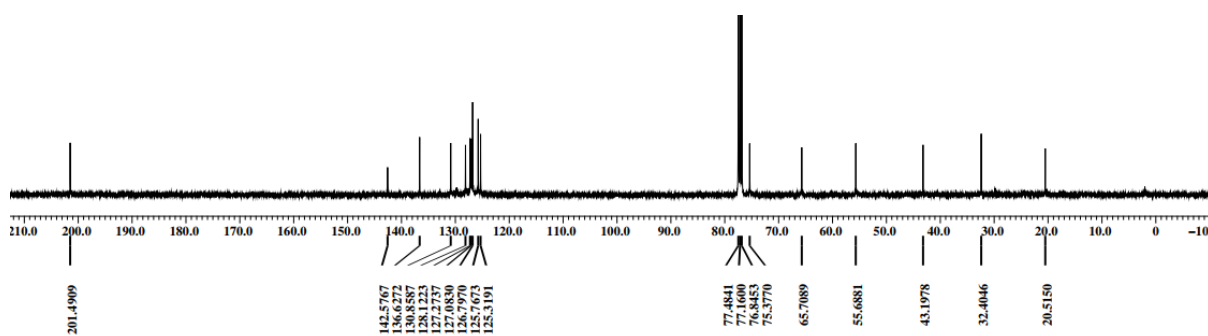
Name	RT	Area	% Area
1	6.938	5999199	60.60
2	8.165	3899658	39.40



¹H-NMR (CDCl₃, 400MHz) of 4ha



¹³C-NMR (CDCl₃, 100MHz) of 4ha



HRMS of 4ha

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
 Element prediction: Off
 Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

27 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

C: 1-50 H: 1-100 N: 1-1 O: 1-10 S: 1-1

Sample Name : 25_02_329

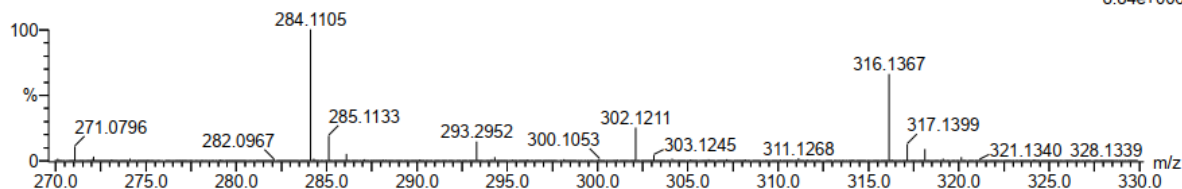
IITRPR

XEVO G2-XS QTOF

Test Name :

110822_25_02_329 12 (0.143)

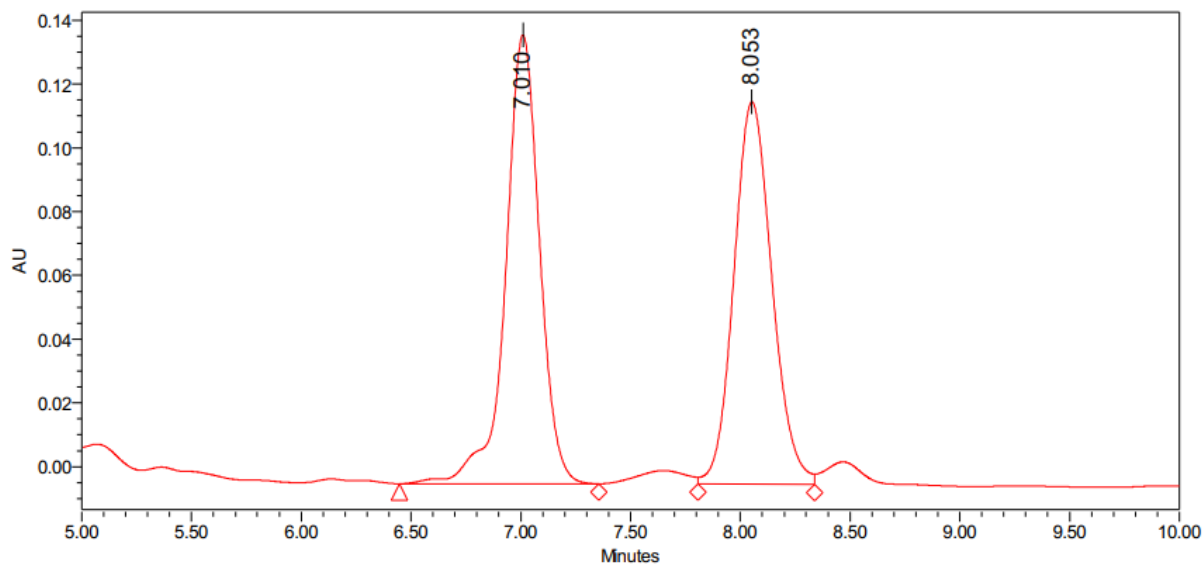
1: TOF MS ES+
8.84e+006



Minimum: -1.5
 Maximum: 2.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
302.1211	302.1215	-0.4	-1.3	8.5	787.5	n/a	n/a	C17 H20 N O2 S

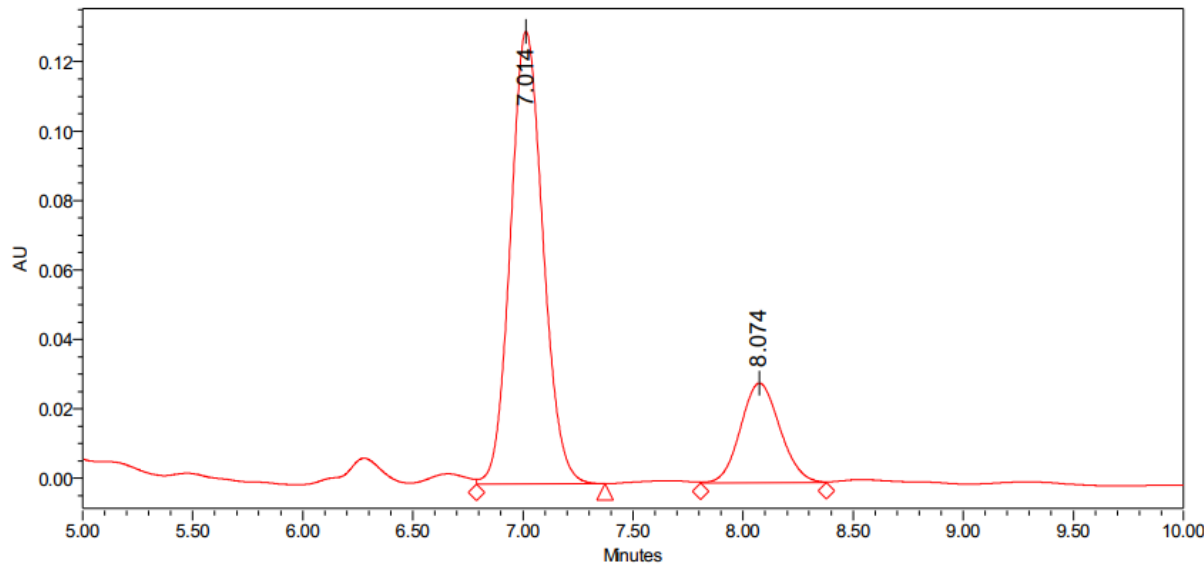
HPLC spectra of racemic 4ha



Peak Results

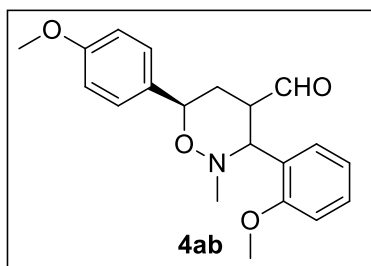
Name	RT	Area	% Area
1	7.010	1519581	51.22
2	8.053	1447373	48.78

HPLC spectra of chiral 4ha

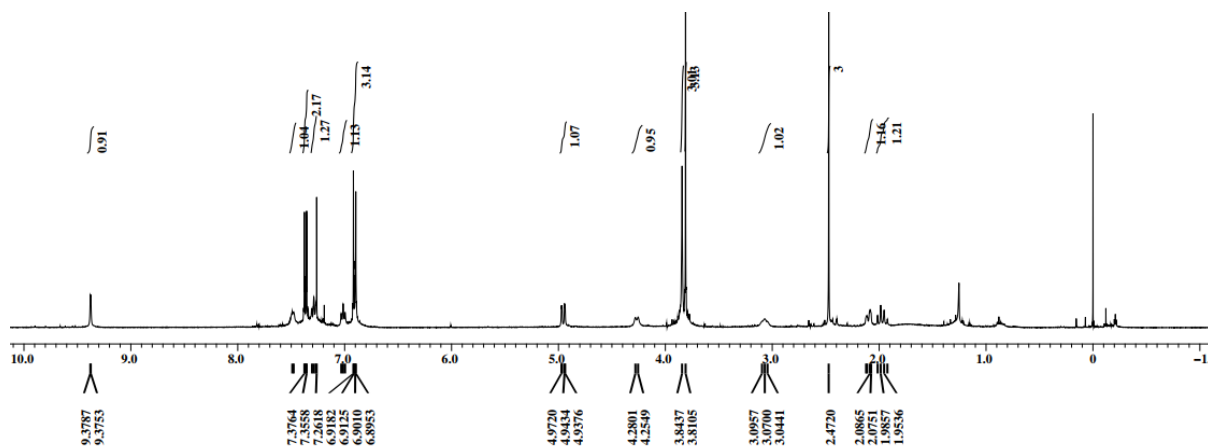


Peak Results

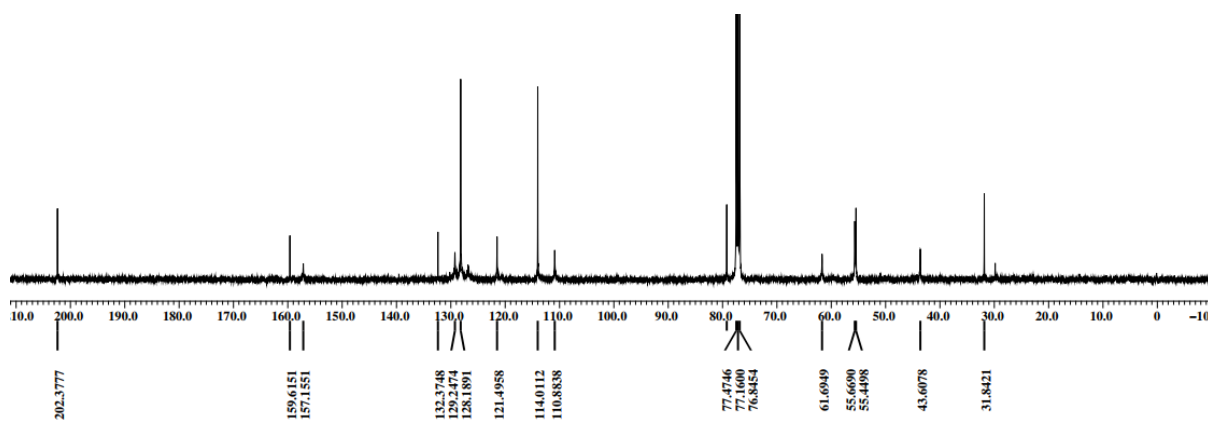
Name	RT	Area	% Area
1	7.014	1344097	79.01
2	8.074	356979	20.99



¹H-NMR (CDCl₃, 400MHz) of 4ab



¹³C-NMR (CDCl₃, 100MHz) of 4ab



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
 Element prediction: Off
 Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

64 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

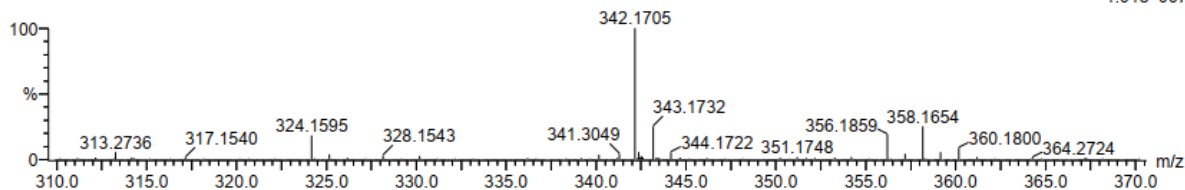
C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_232
 Test Name :
 110822_25_02_232 8 (0.097)

IITRPR

XEVO G2-XS QTOF

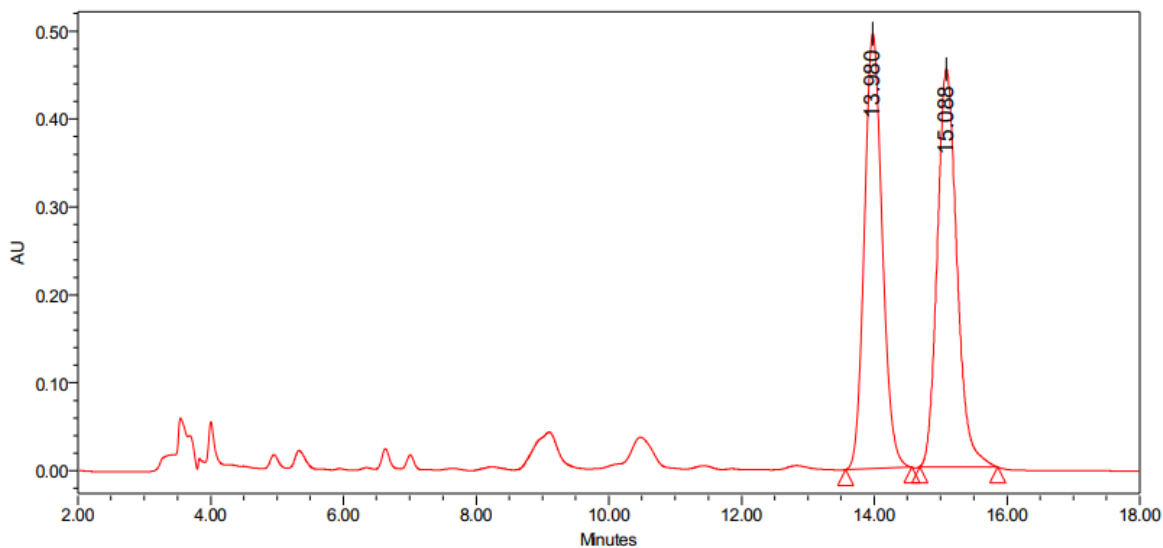
1: TOF MS ES+
 1.01e+007



Minimum: -1.5
 Maximum: 2.0 5.0 50.0

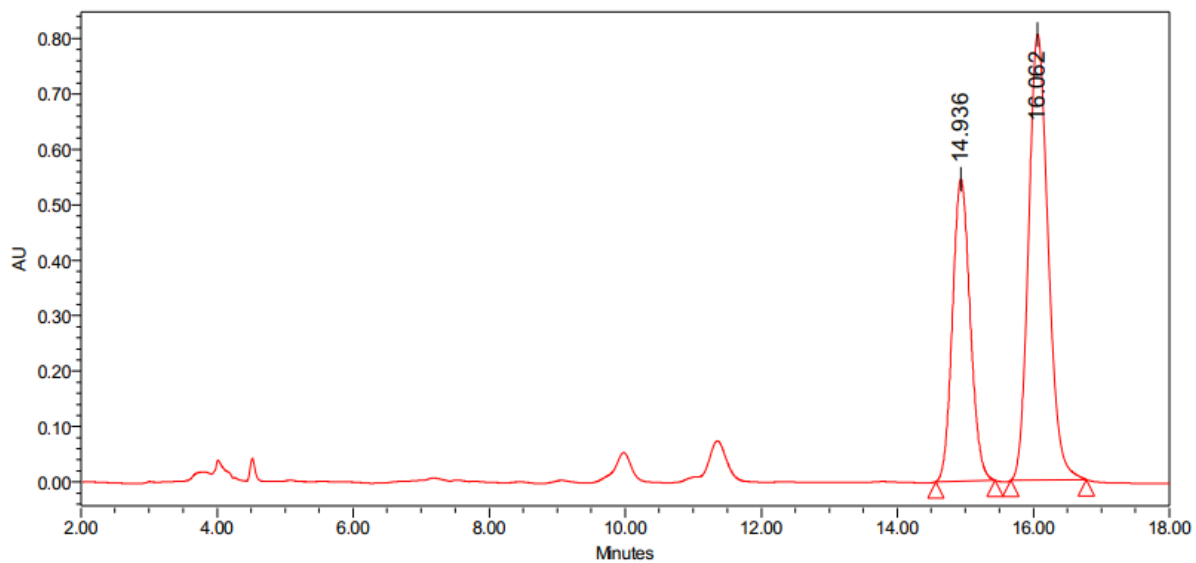
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
342.1705	342.1705	0.0	0.0	9.5	604.2	n/a	n/a	C20 H24 N O4

HPLC spectra of racemic 4ab



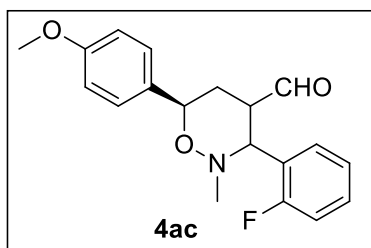
Name	RT	Area	% Area
1	13.980	9249099	49.91
2	15.088	9281271	50.09

HPLC spectra of chiral 4ab

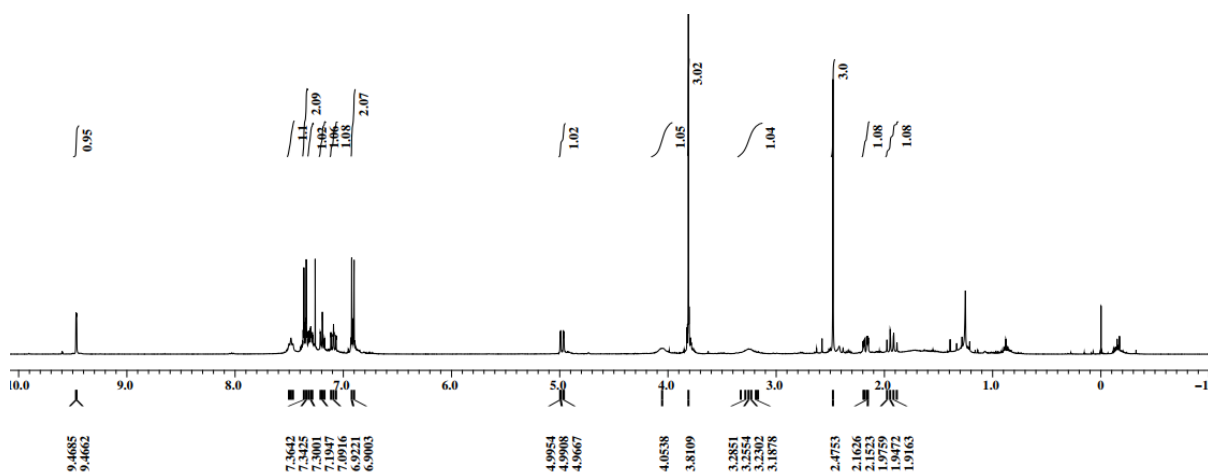


Peak Results

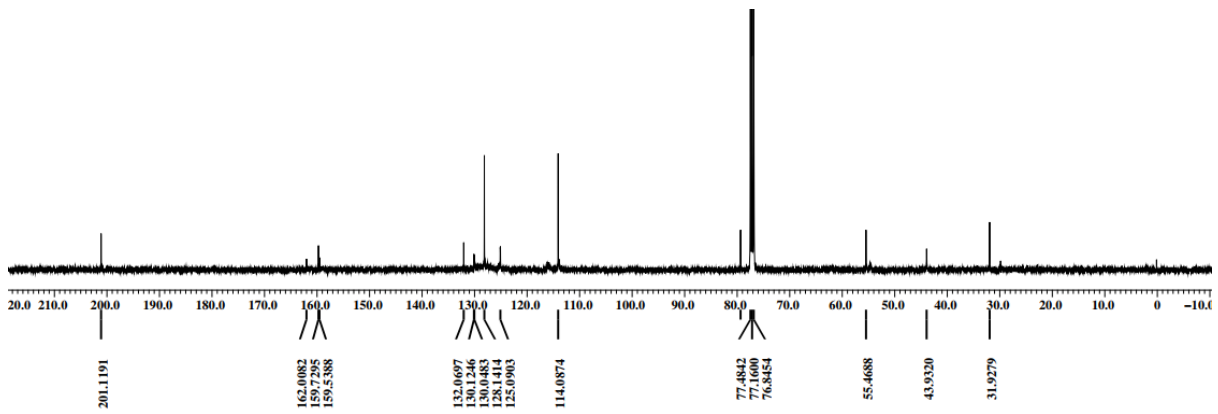
Name	RT	Area	% Area
1	14.936	9810358	37.87
2	16.062	16093781	62.13



¹H-NMR (CDCl₃, 400MHz) of 4ac



¹³C-NMR (CDCl₃, 100MHz) of 4ac



HRMS of 4ac

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

110 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

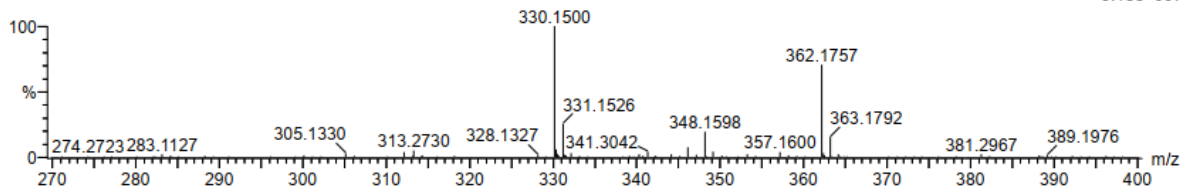
C: 1-22 H: 1-100 N: 0-5 O: 1-5 F: 1-1

Sample Name : 25_02_284
Test Name :
080822_25_02_284 21 (0.231)

IITRPR

XEVO G2-XS QTOF

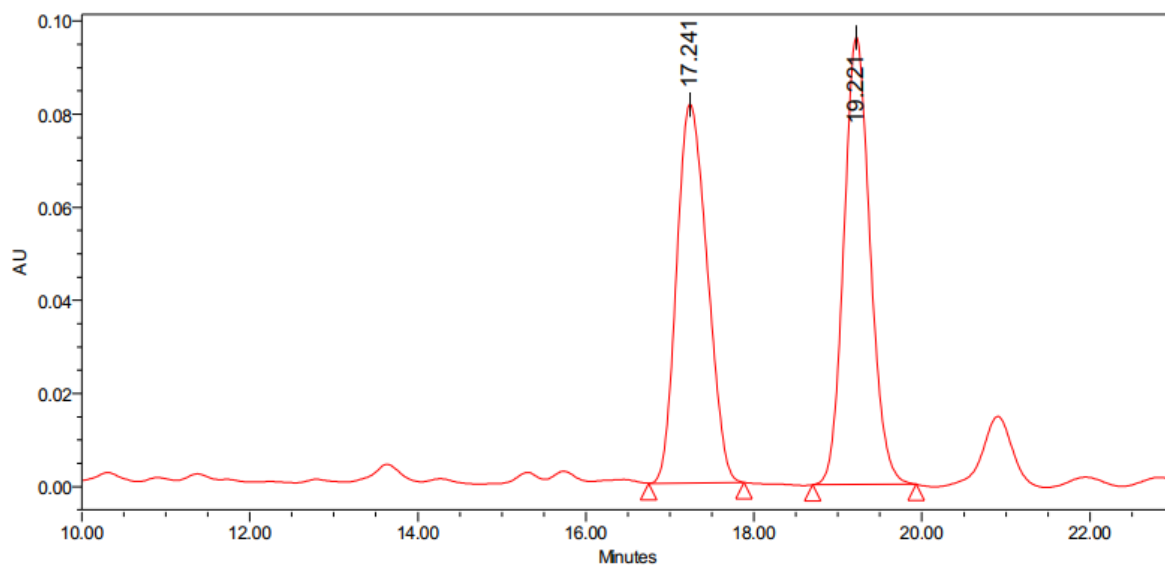
1: TOF MS ES+
9.13e+007



Minimum: -1.5
Maximum: 2.0 5.0 50.0

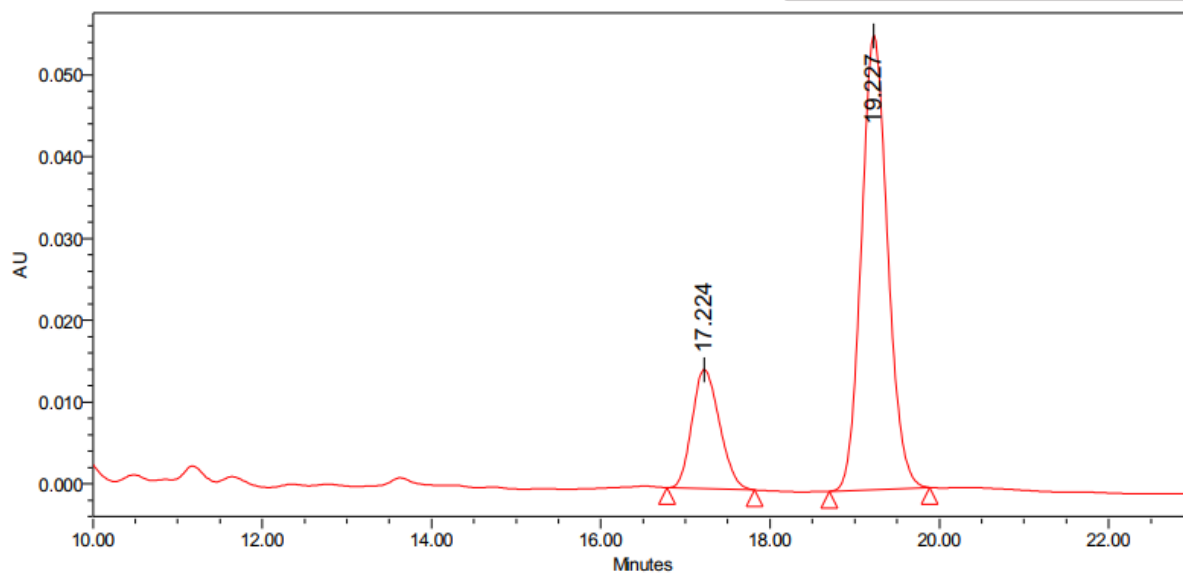
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
330.1500	330.1505	-0.5	-1.5	9.5	810.9	n/a	n/a	C19 H21 N O3 F

HPLC spectra of racemic 4ac

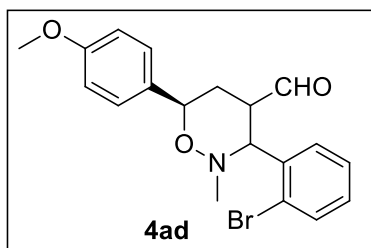


Peak Results			
Name	RT	Area	% Area
1	17.241	2054329	49.55
2	19.221	2091329	50.45

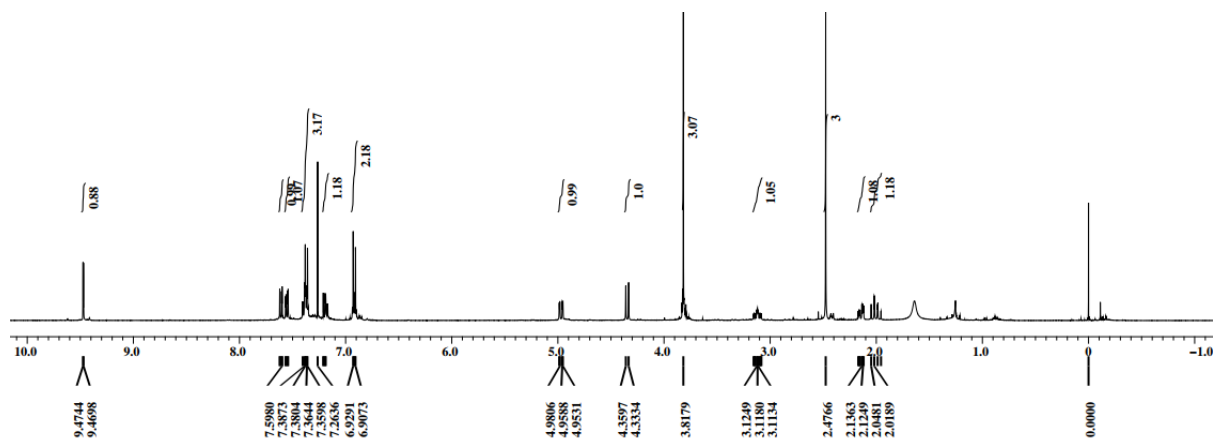
HPLC spectra of chiral 4ac



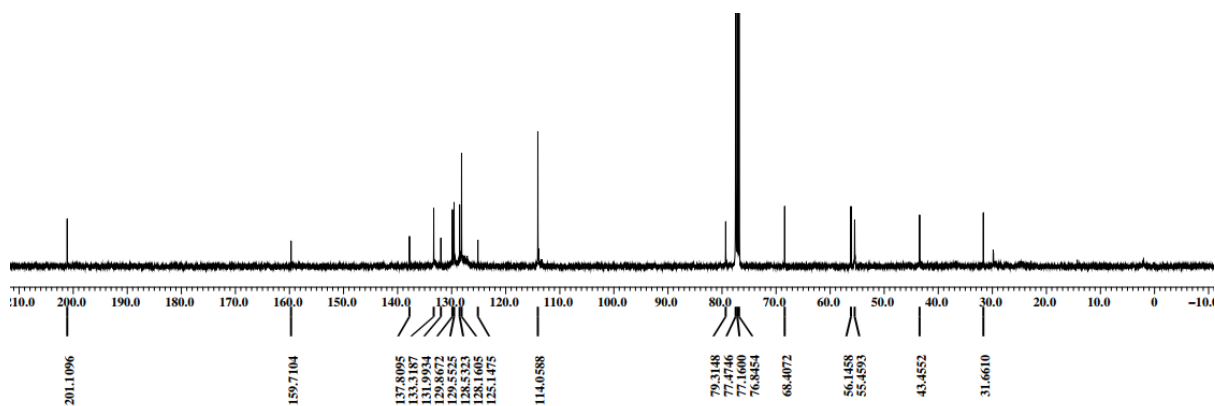
Peak Results			
Name	RT	Area	% Area
1	17.224	329205	21.52
2	19.227	1200389	78.48



¹H-NMR (CDCl₃, 400MHz) of 4ad



¹³C-NMR (CDCl₃, 100MHz) of 4ad



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
 Element prediction: Off
 Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

76 formula(e) evaluated with 1 results within limits (up to 1 closest results for each mass)

Elements Used:

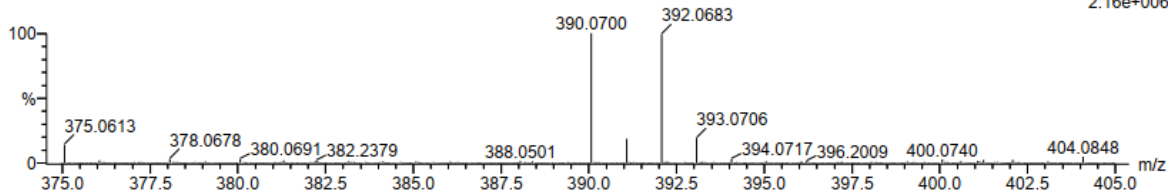
C: 1-50 H: 1-100 N: 1-1 O: 1-10 79Br: 0-1

Sample Name : 25_02_320
 Test Name :
 110822_25_02_320 20 (0.223)

IITRPR

XEVO G2-XS QTOF

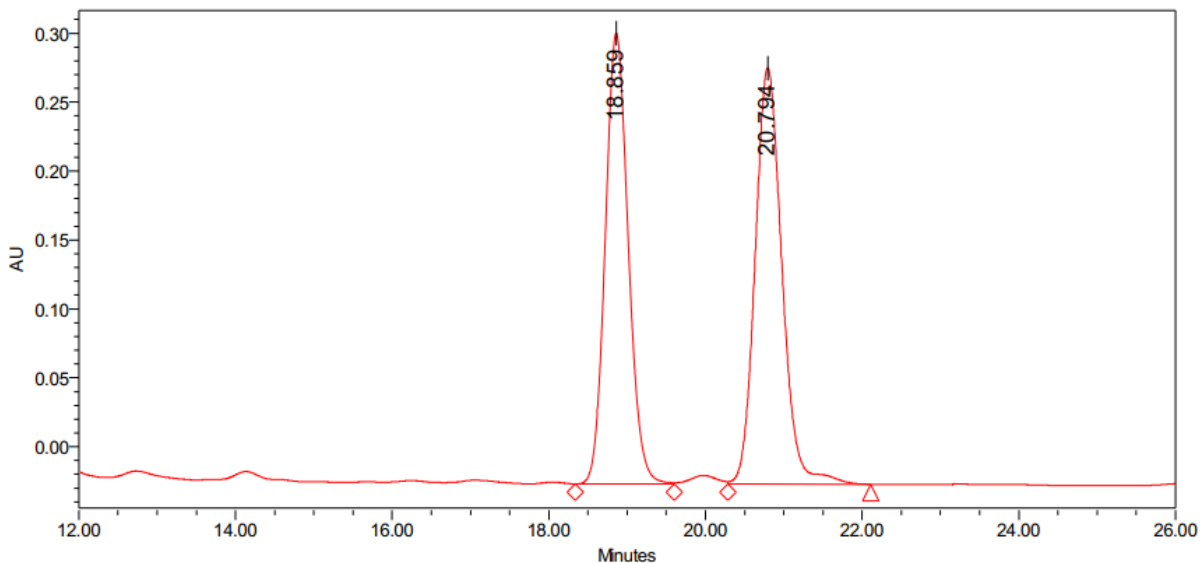
1: TOF MS ES+
 2.16e+006



Minimum: -1.5
 Maximum: 2.0 5.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
390.0700	390.0705	-0.5	-1.3	9.5	580.9	n/a	n/a	C19 H21 N O3 79Br

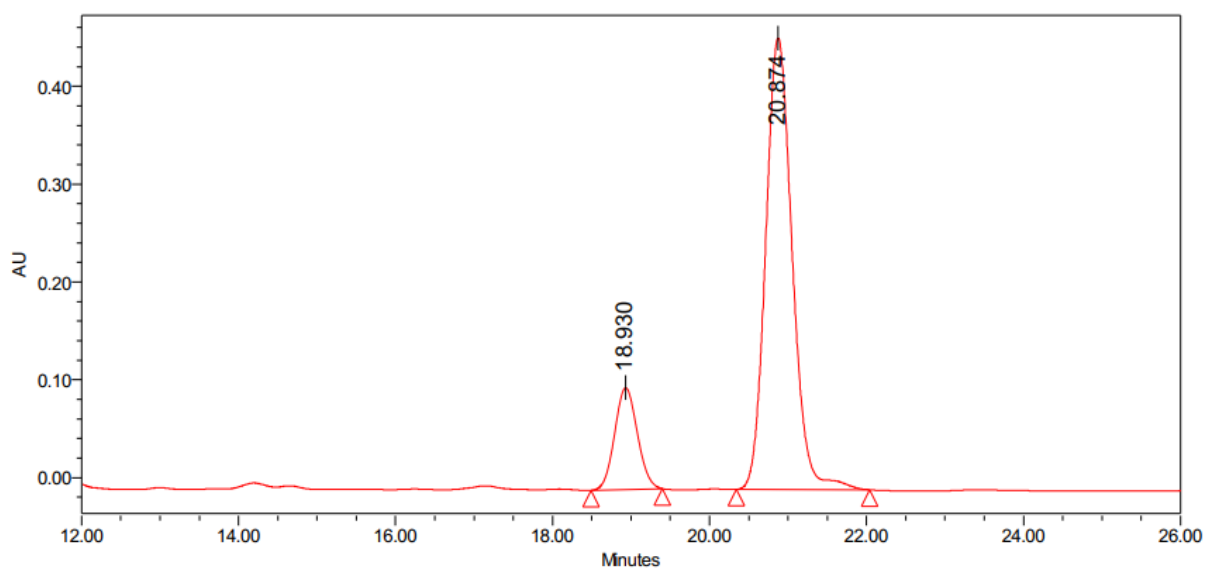
HPLC spectra of racemic 4ad



Peak Results

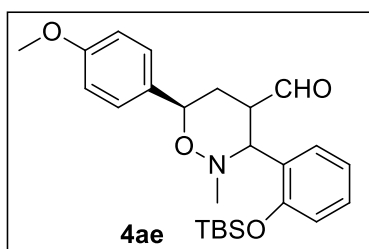
Name	RT	Area	% Area
1	18.859	6668118	48.17
2	20.794	7174643	51.83

HPLC spectra of chiral 4ad

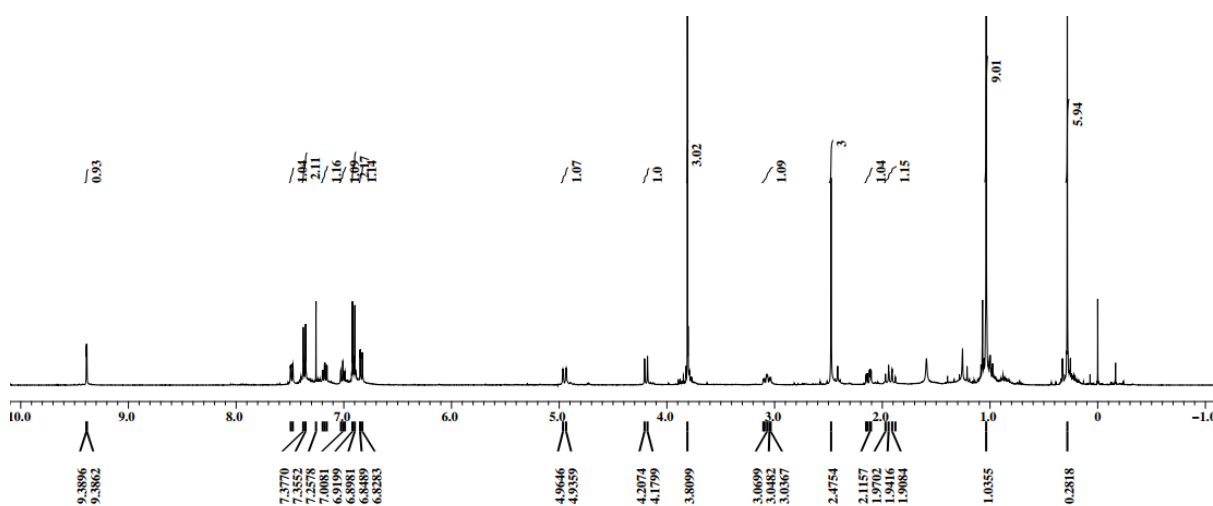


Peak Results

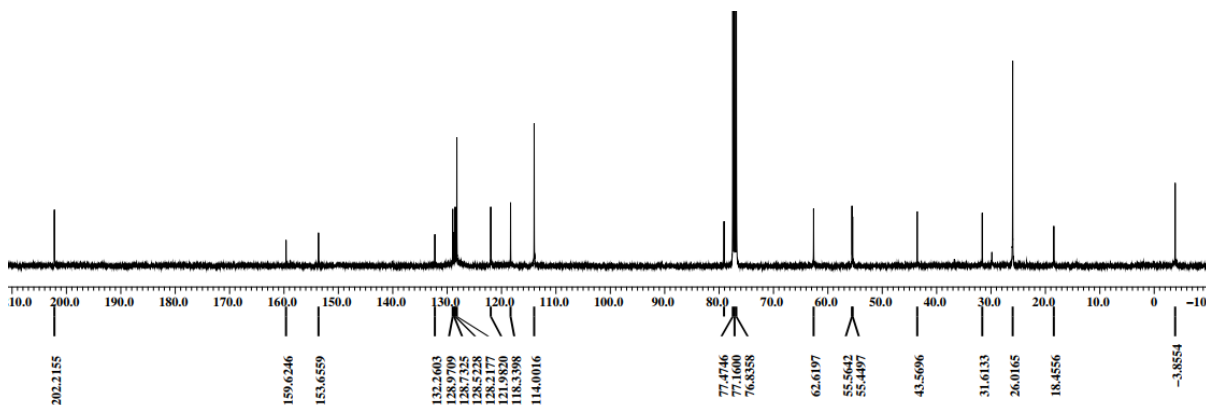
Name	RT	Area	% Area
1	18.930	2091214	16.22
2	20.874	10801903	83.78



¹H-NMR (CDCl₃, 400MHz) of 4ae



¹³C-NMR (CDCl₃, 100MHz) of 4ae



HRMS of 4ae

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

127 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-25 H: 0-50 N: 0-4 O: 0-4 Si: 0-2

050423_25_03_14 20 (0.223)

IITRPR

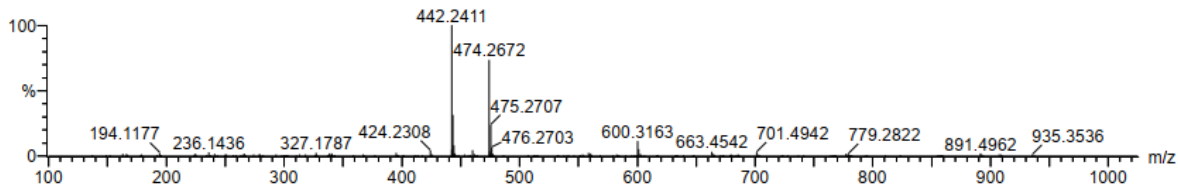
XEVO G2-XS QTOF

Test Name :

050423_25_03_14

1: TOF MS ES+

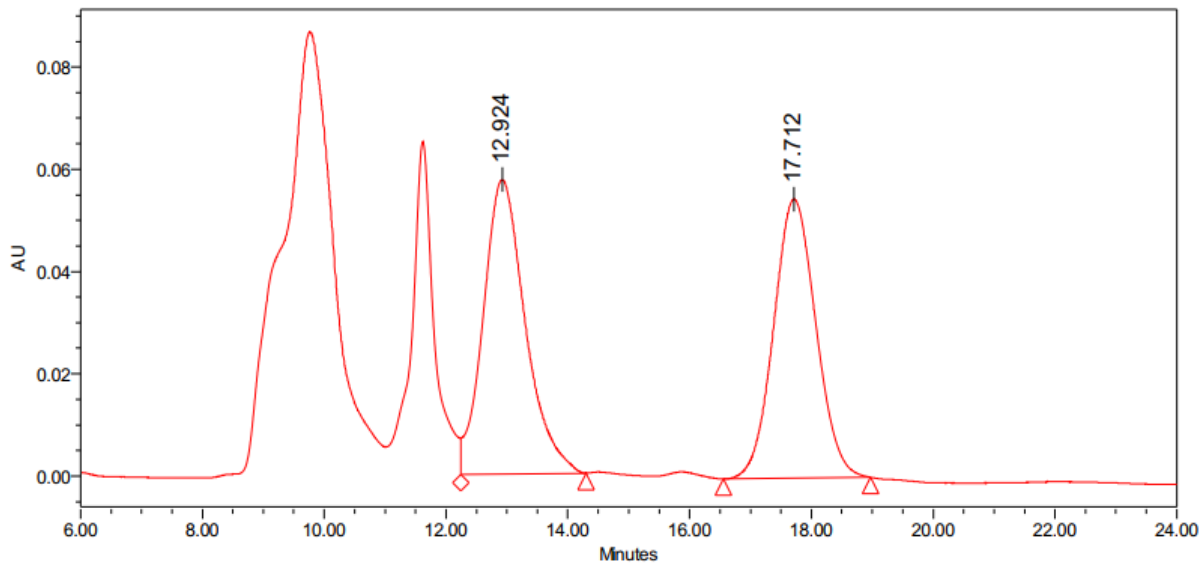
5.17e+006



Minimum: -1.5
Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
442.2411	442.2414	-0.3	-0.7	9.5	822.4	n/a	n/a	C25 H36 N O4 Si

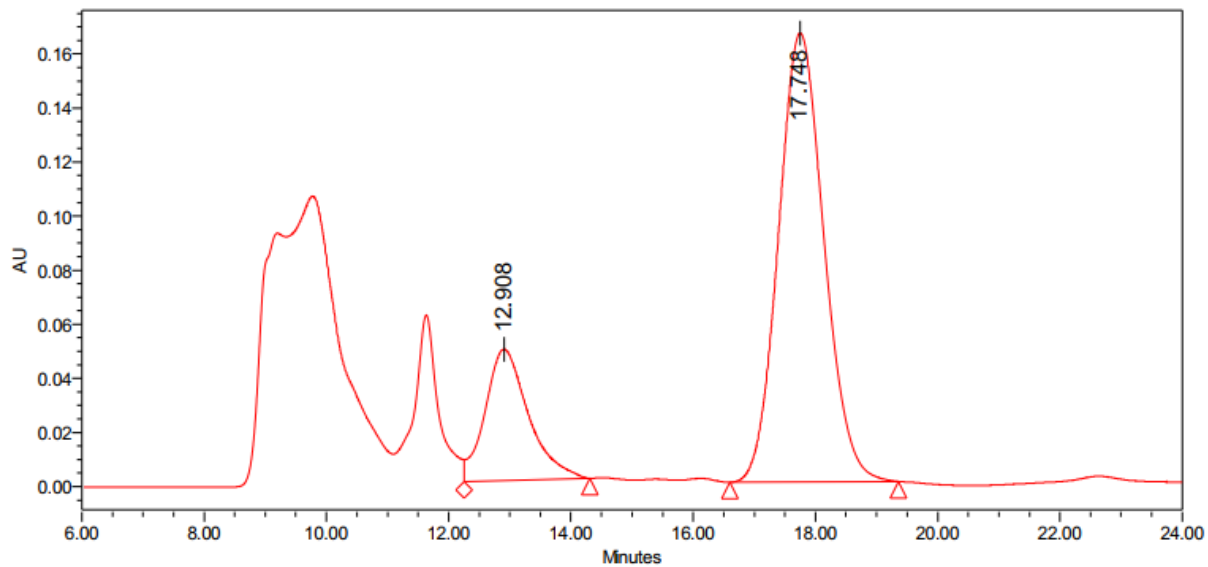
HPLC spectra of racemic 4ae



Peak Results

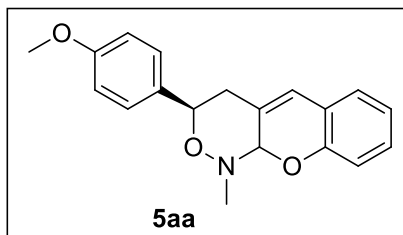
Name	RT	Area	% Area
1	12.924	2758075	51.22
2	17.712	2626177	48.78

HPLC spectra of chiral 4ae

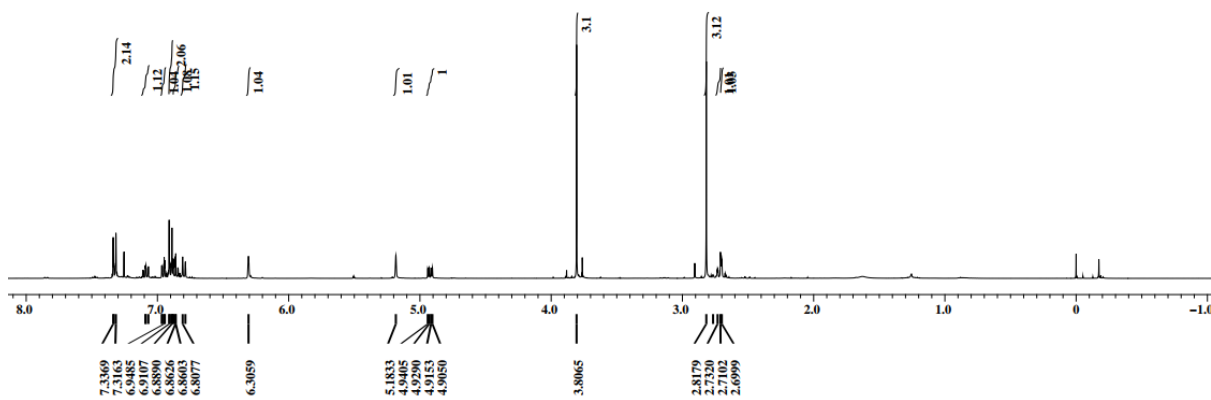


Peak Results

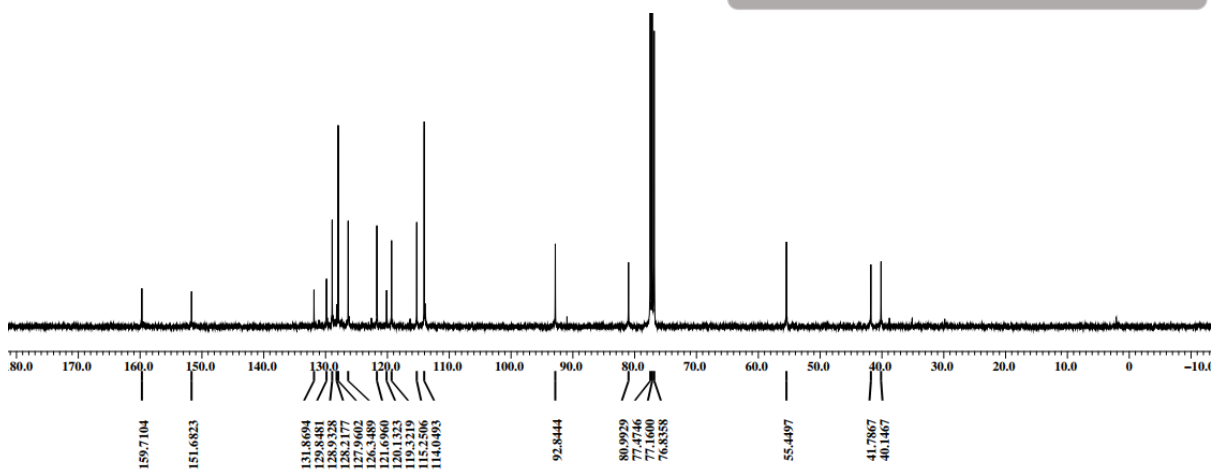
Name	RT	Area	% Area
1	12.908	2385729	21.77
2	17.748	8575536	78.23



¹H-NMR (CDCl₃, 400MHz) of 5aa



¹³C-NMR (CDCl₃, 100MHz) of 5aa



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

15 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

C: 0-19 H: 0-40 N: 0-2 O: 0-3

281222_25_02_373 18 (0.205)

IITRPR

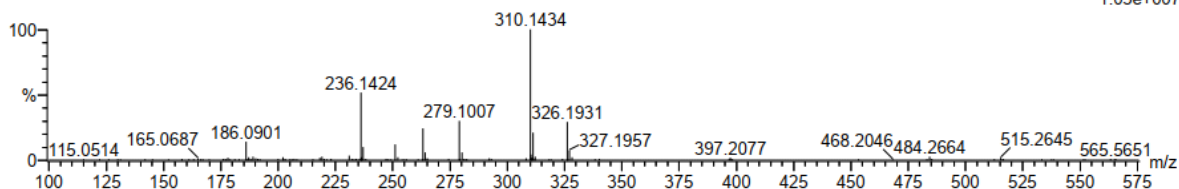
XEVO G2-XS QTOF

Test Name :

25_02_373

1: TOF MS ES+

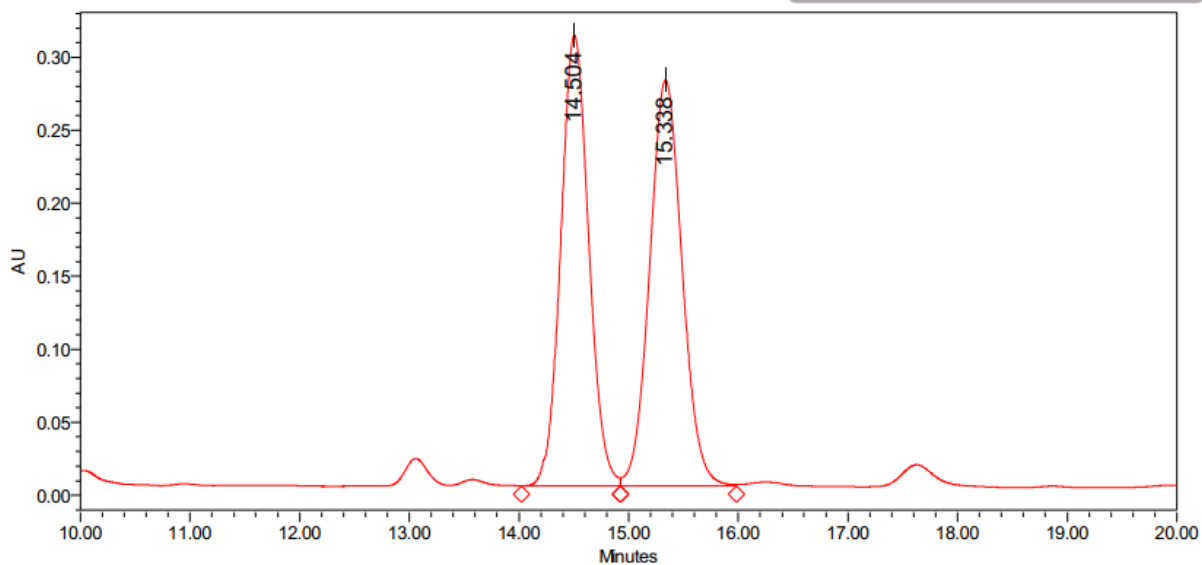
1.03e+007



Minimum: -1.5
Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
310.1434	310.1443	-0.9	-2.9	10.5	1179.9	n/a	n/a	C19 H20 N O3

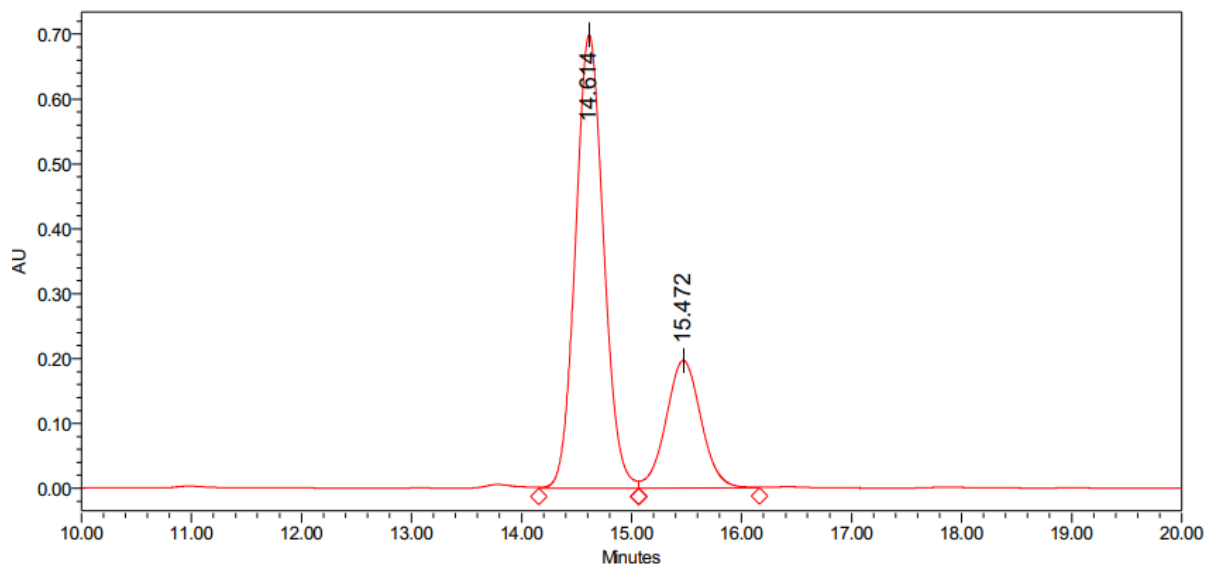
HPLC spectra of racemic 5aa



Peak Results

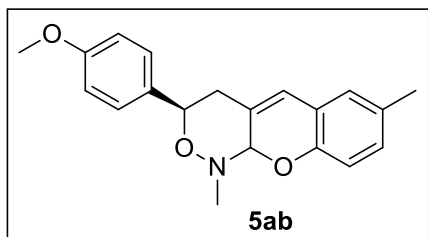
Name	RT	Area	% Area
1	14.504	5478043	48.91
2	15.338	5722825	51.09

HPLC spectra of chiral 5aa

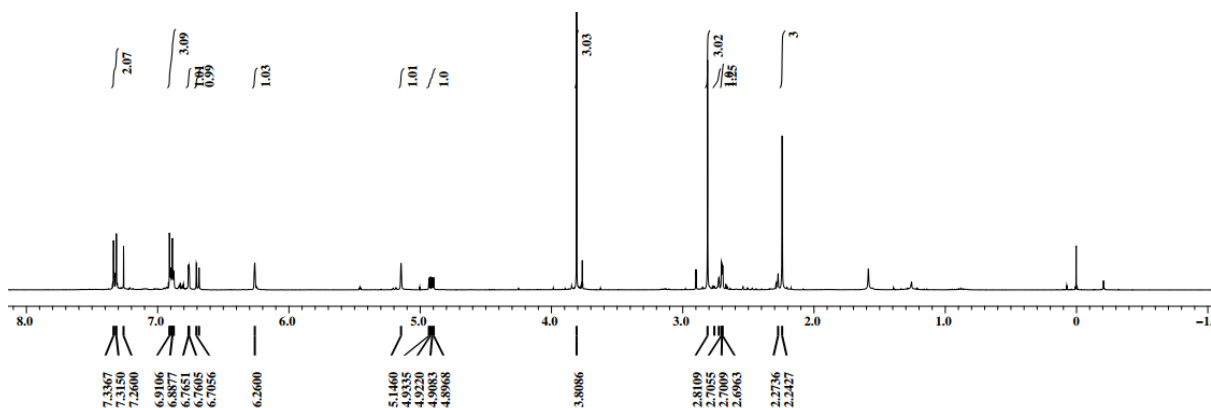


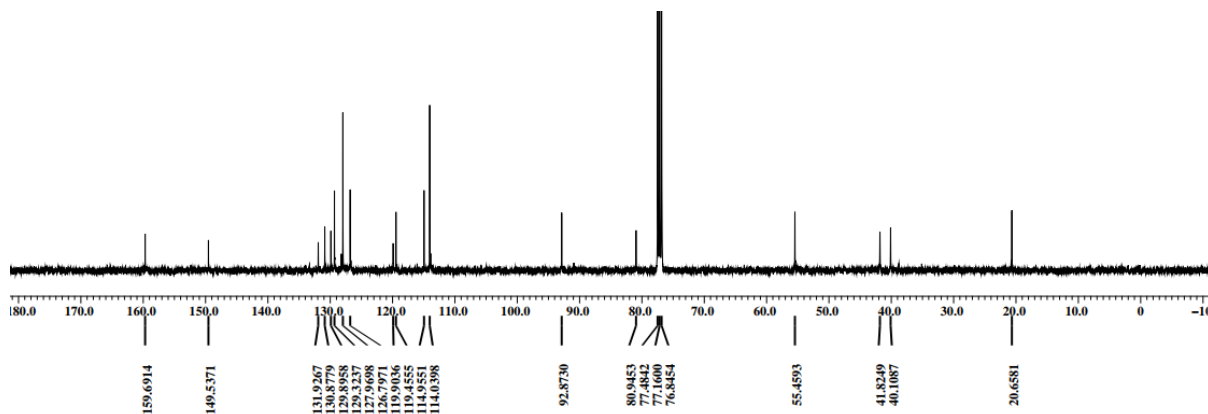
Peak Results

Name	RT	Area	% Area
1	14.614	12404132	74.06
2	15.472	4345400	25.94



¹H-NMR (CDCl₃, 400MHz) of 5ab





HRMS of 5ab

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

76 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-21 H: 0-50 N: 0-4 O: 0-4

130123_25_02_385 71 (0.729)

IITRPR

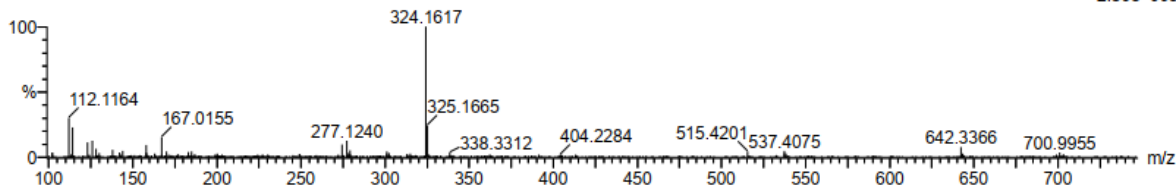
XEVO G2-XS QTOF

130123_25_02_385

Test Name :

1: TOF MS ES+

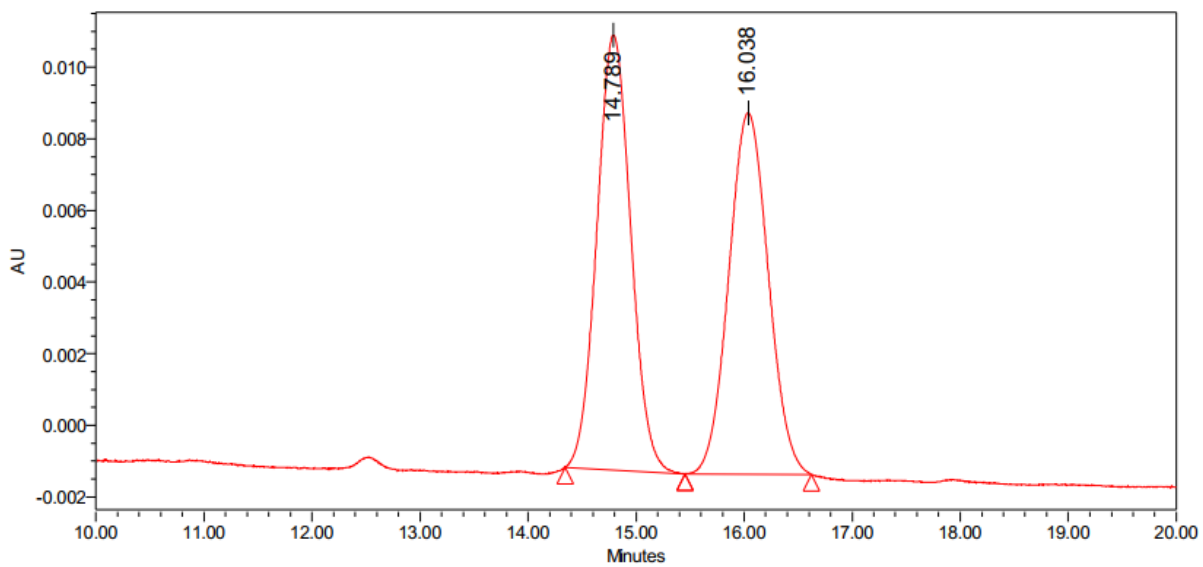
2.86e+005



Minimum: -1.5
Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
324.1617	324.1600	1.7	5.2	10.5	687.4	n/a	n/a	C20 H22 N O3

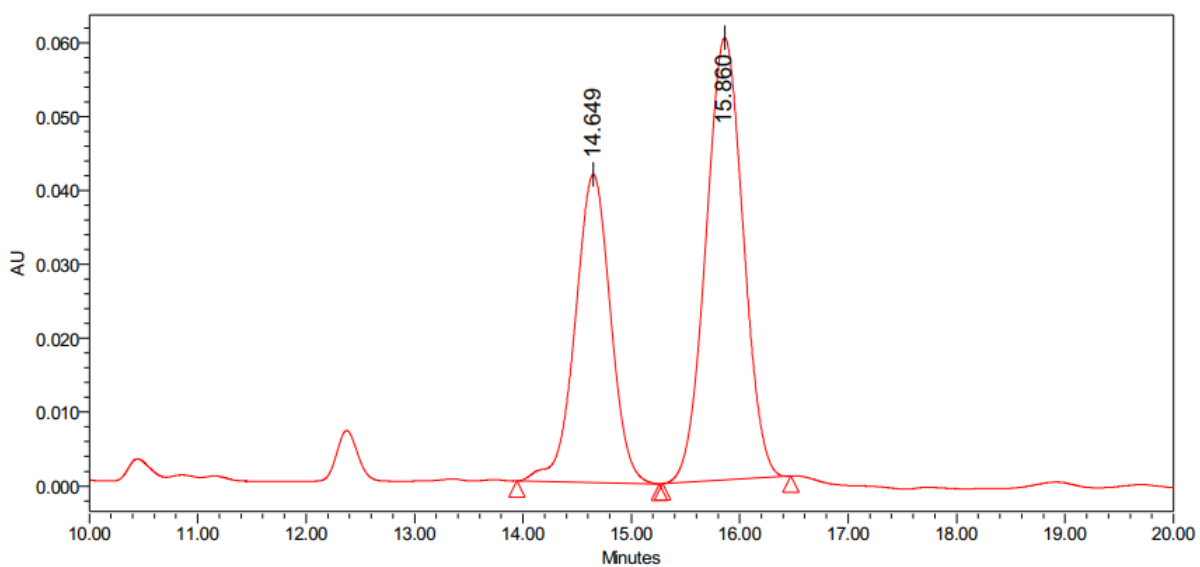
HPLC spectra of racemic 5ab



Peak Results

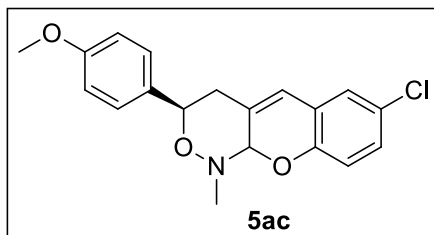
Name	RT	Area	% Area
1	14.789	264946	50.77
2	16.038	256866	49.23

HPLC spectra of chiral 5ab

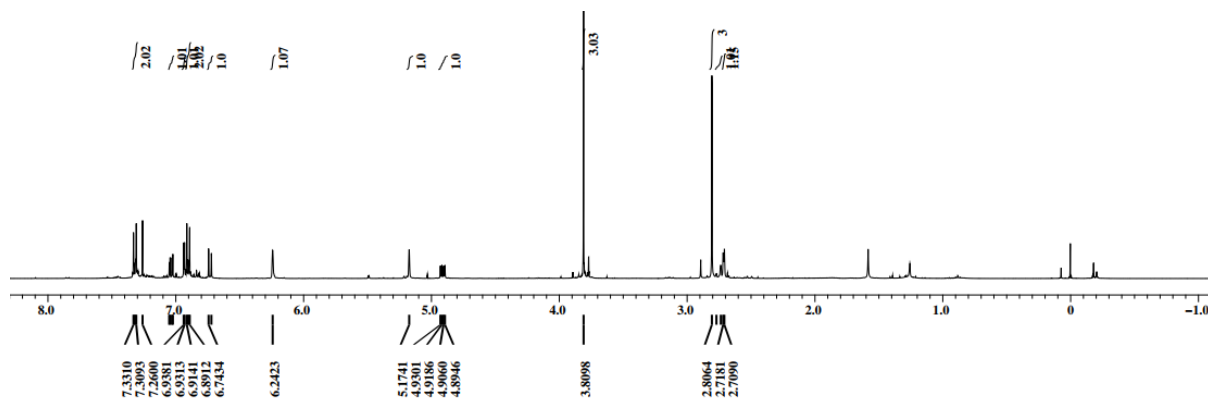


Peak Results

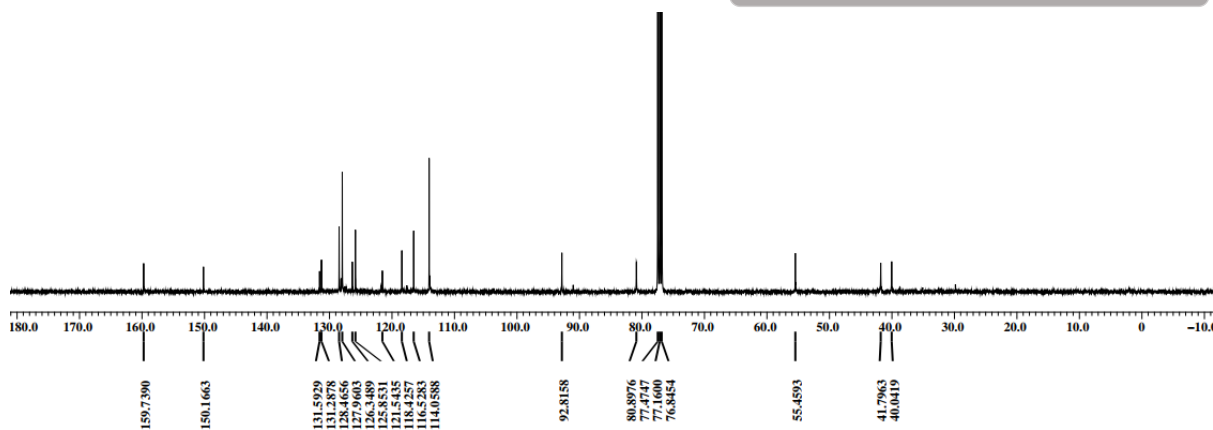
Name	RT	Area	% Area
1	14.649	947804	39.88
2	15.860	1428604	60.12



¹H-NMR (CDCl₃, 400MHz) of 5ac



¹³C-NMR (CDCl₃, 100MHz) of 5ac



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
 Element prediction: Off
 Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

16 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-19 H: 0-40 N: 0-1 O: 0-3 Cl: 0-1

090123_25_02_380 20 (0.223)

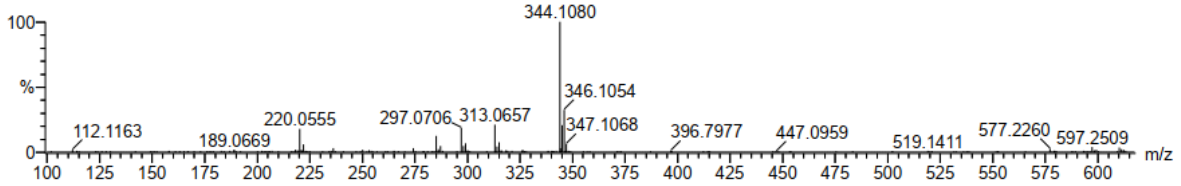
Test Name :

1: TOF MS ES+

IITRPR

XEVO G2-XS QTOF
 090123_25_02_380

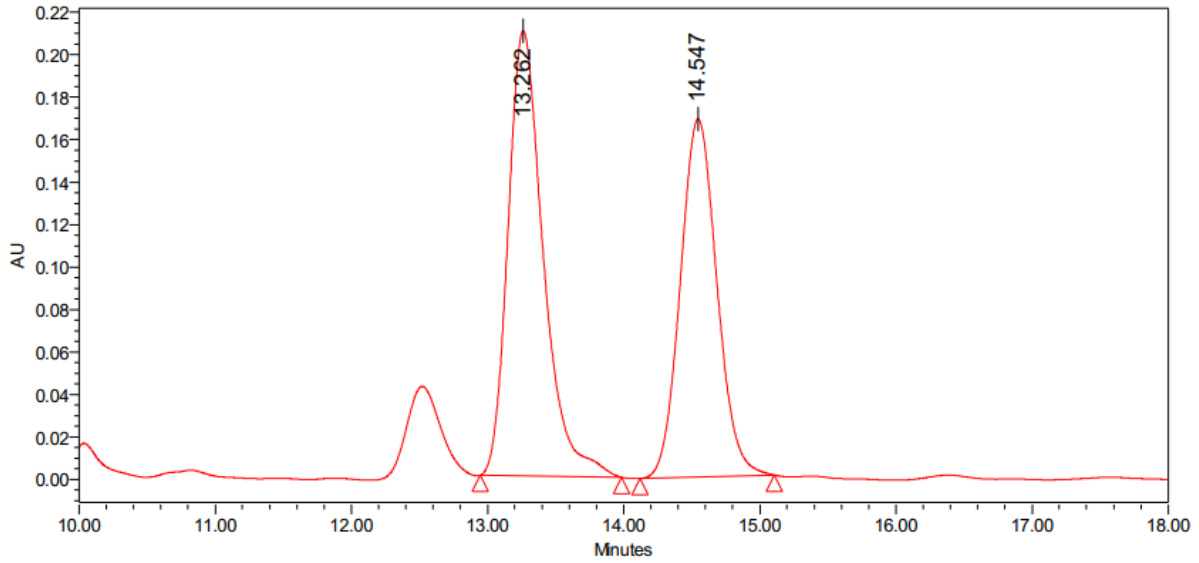
2.79e+006



Minimum: -1.5
 Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
344.1080	344.1053	2.7	7.8	10.5	974.0	n/a	n/a	C19 H19 N O3 Cl

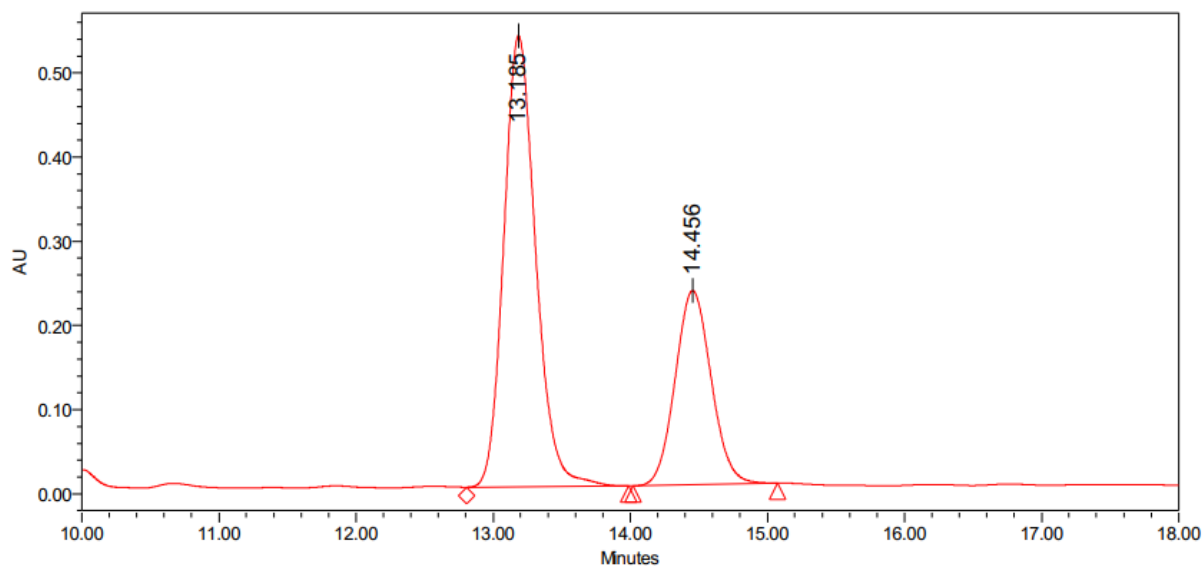
HPLC spectra of racemic 5ac



Peak Results

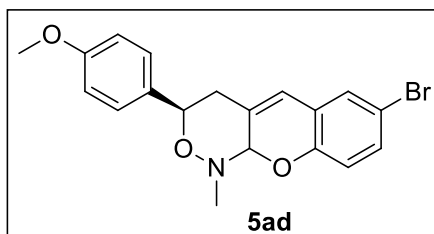
Name	RT	Area	% Area
1	13.262	3769812	54.53
2	14.547	3144090	45.47

HPLC spectra of chiral 5ac

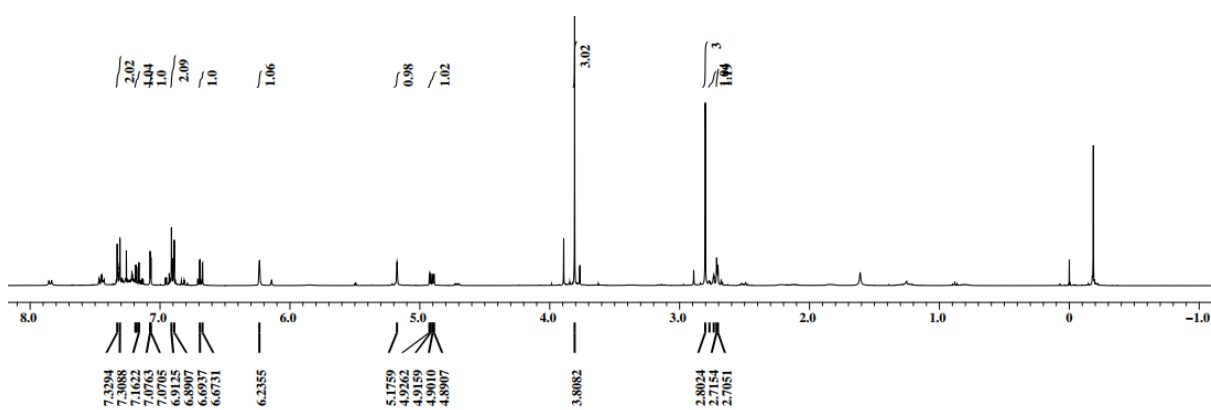


Peak Results

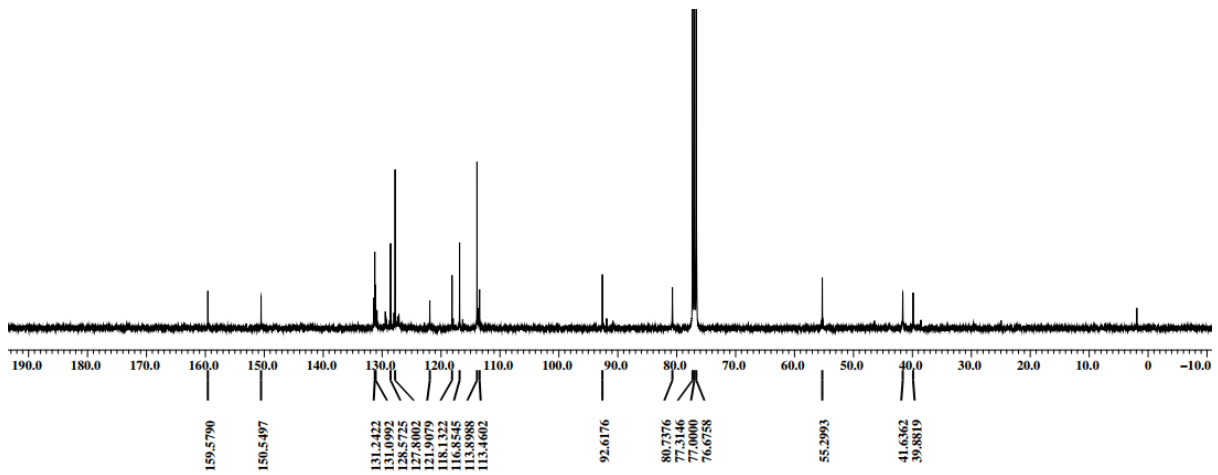
Name	RT	Area	% Area
1	13.185	8662641	67.37
2	14.456	4196042	32.63



¹H-NMR (CDCl₃, 400MHz) of 5ad



¹³C-NMR (CDCl₃, 100MHz) of 5ad



HRMS of 5ad

Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

71 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-19 H: 0-50 N: 0-2 O: 0-3 Br: 0-2

300123_25_03_03 40 (0.417)

IITRPR

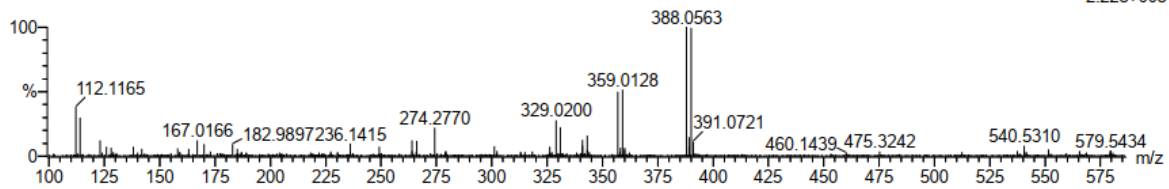
XEVO G2-XS QTOF

Test Name :

300123_25_03_03

1: TOF MS ES+

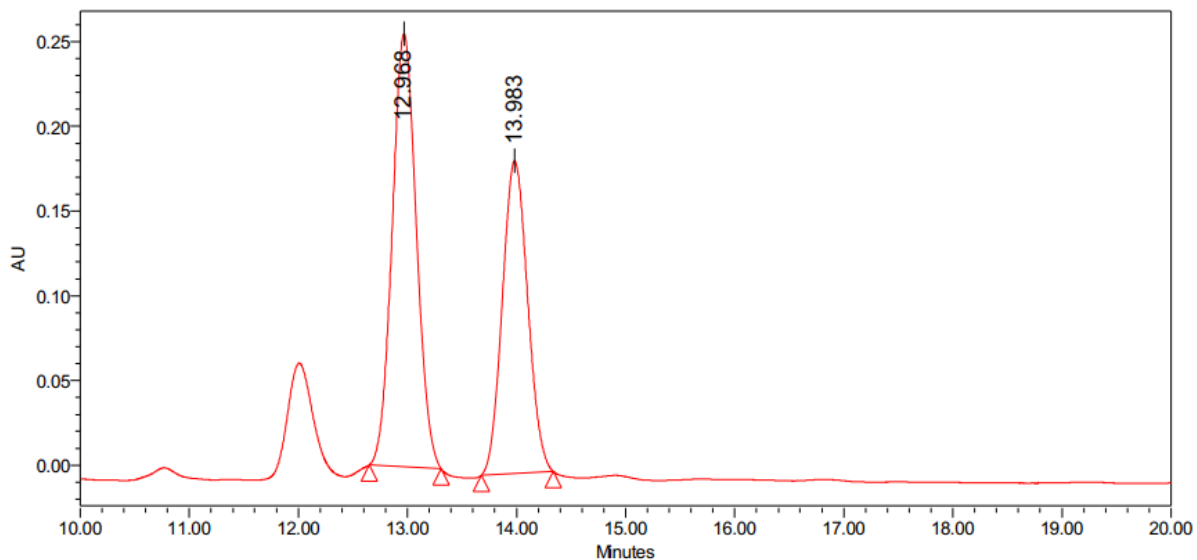
2.22e+005



Minimum: -1.5
Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
388.0563	388.0548	1.5	3.9	10.5	713.8	n/a	n/a	C19 H19 N O3 Br

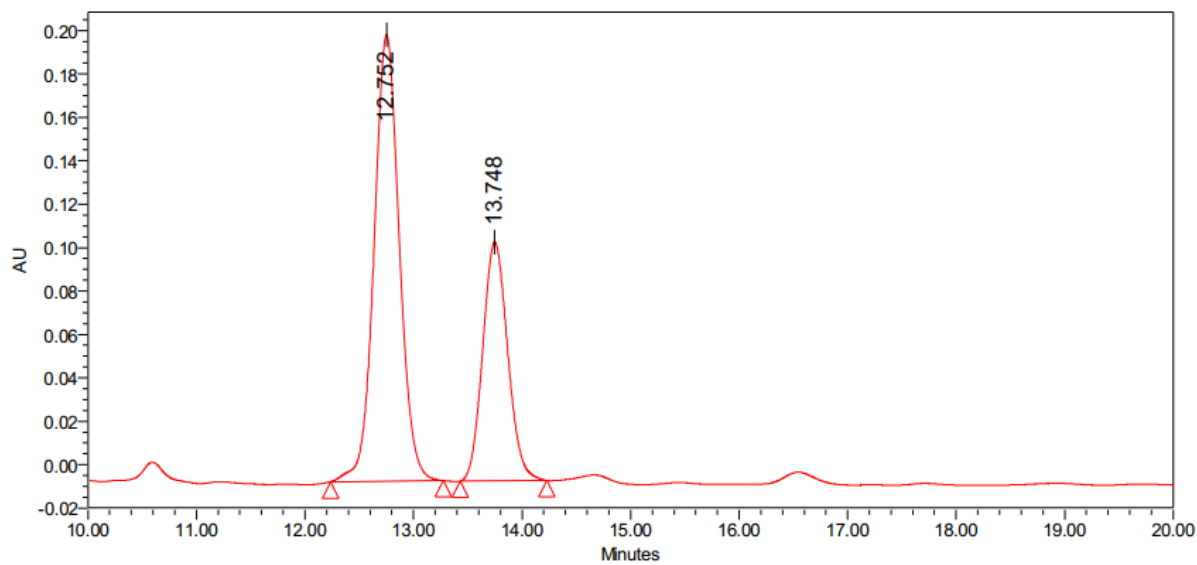
HPLC spectra of racemic 5ad



Peak Results

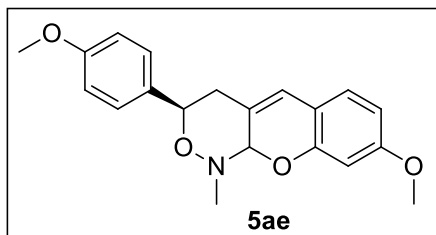
Name	RT	Area	% Area
1	12.968	3921290	57.01
2	13.983	2956730	42.99

HPLC spectra of chiral 5ad

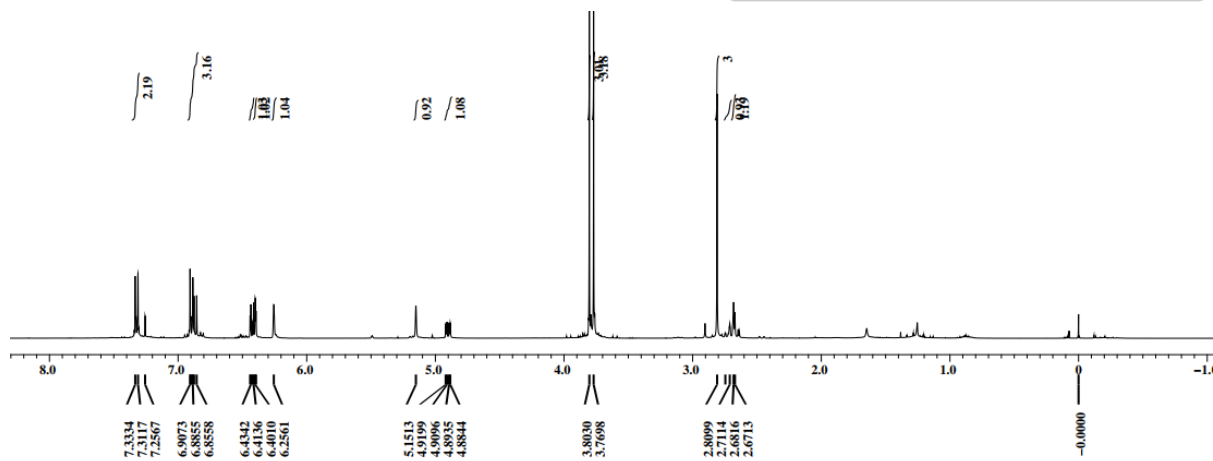


Peak Results

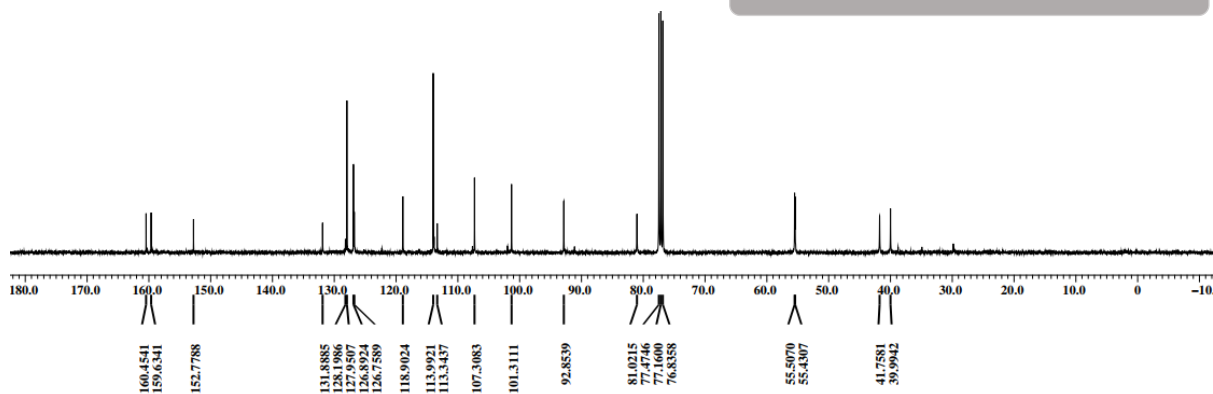
Name	RT	Area	% Area
1	12.752	3314501	65.37
2	13.748	1755519	34.63



¹H-NMR (CDCl₃, 400MHz) of 5ae



¹³C-NMR (CDCl₃, 100MHz) of 5ae



Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
38 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-20 H: 0-100 N: 0-3 O: 0-4

130223_25_03_07 53 (0.551)

IITRPR

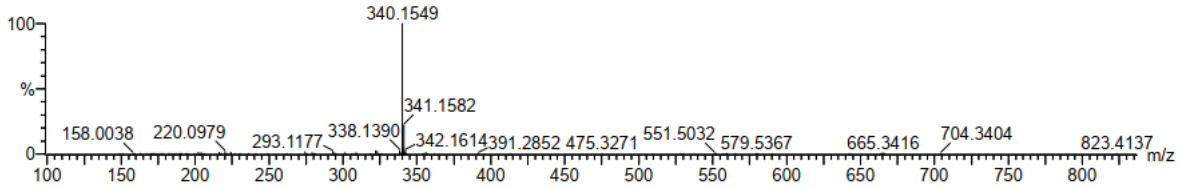
XEVO G2-XS QTOF

Test Name :

130223_25_03_07

1: TOF MS ES+

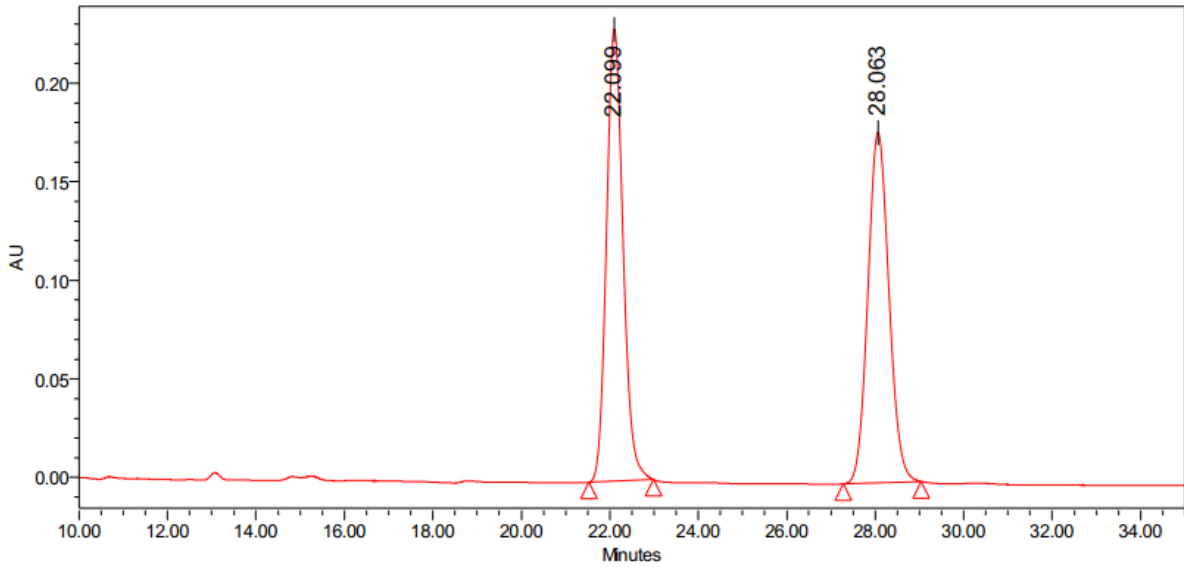
6.73e+006



Minimum: -1.5
Maximum: 5.0 10.0 50.0

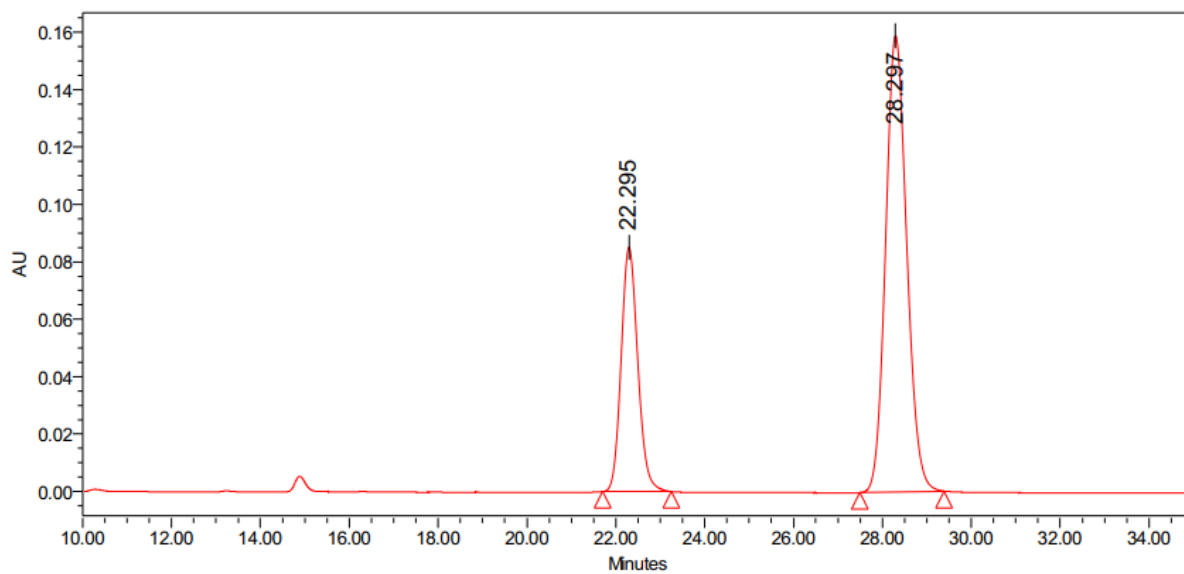
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
340.1549	340.1549	0.0	0.0	10.5	1038.2	n/a	n/a	C20 H22 N O4

HPLC spectra of racemic 5ae



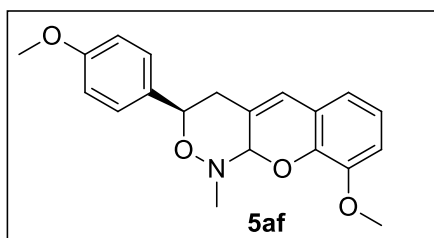
Name	RT	Area	% Area
1	22.099	5972657	50.40
2	28.063	5876945	49.60

HPLC spectra of chiral 5ae

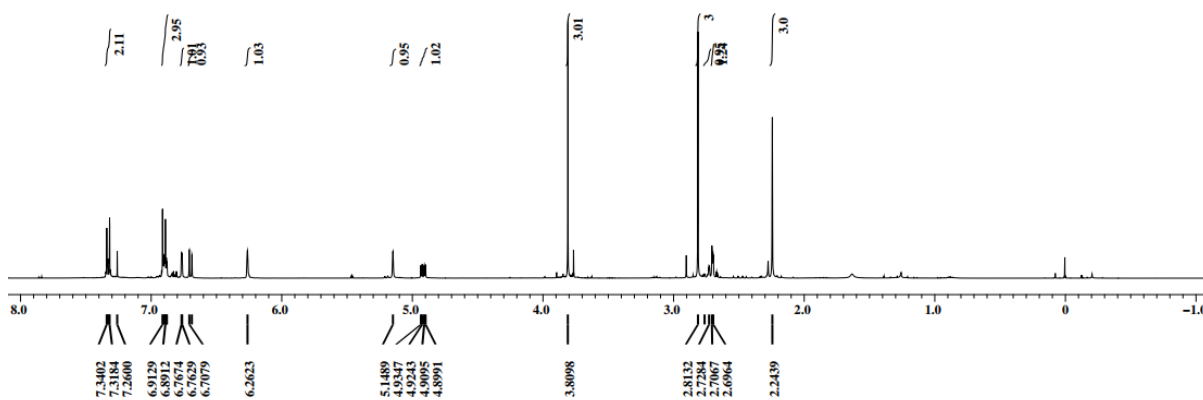


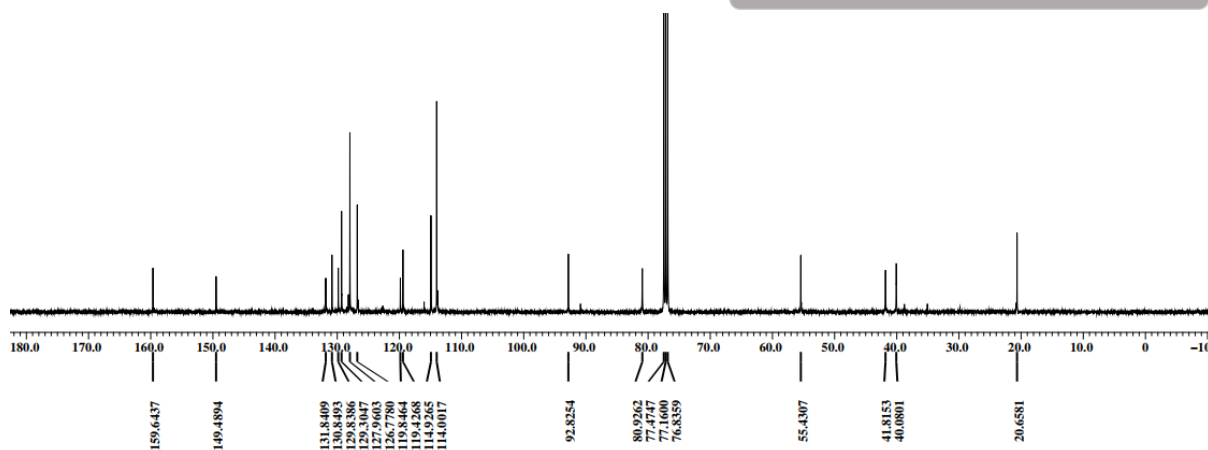
Peak Results

Name	RT	Area	% Area
1	22.295	2215293	29.65
2	28.297	5255553	70.35



¹H-NMR (CDCl₃, 400MHz) of 5af





HRMS of 5af

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

38 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-20 H: 0-100 N: 0-3 O: 0-4

130223_25_03_08 51 (0.534)

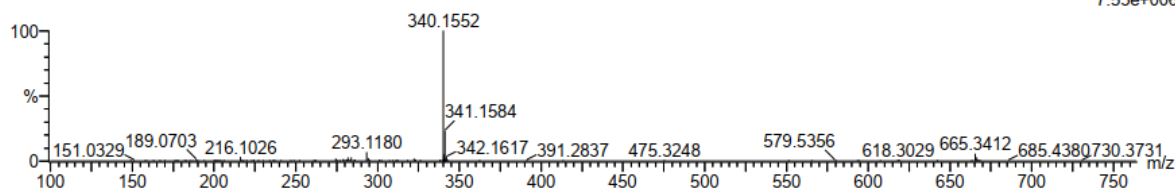
IITRPR

XEVO G2-XS QTOF

130223_25_03_08

Test Name :
1: TOF MS ES+

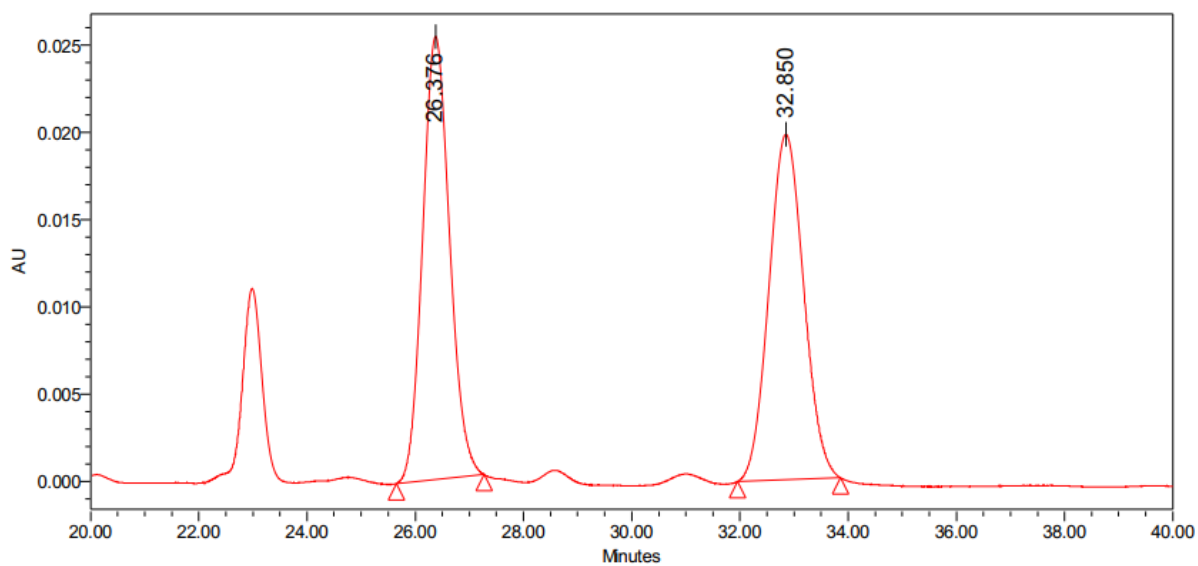
7.53e+006



Minimum: -1.5
Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
340.1552	340.1549	0.3	0.9	10.5	1092.8	n/a	n/a	C20 H22 N O4

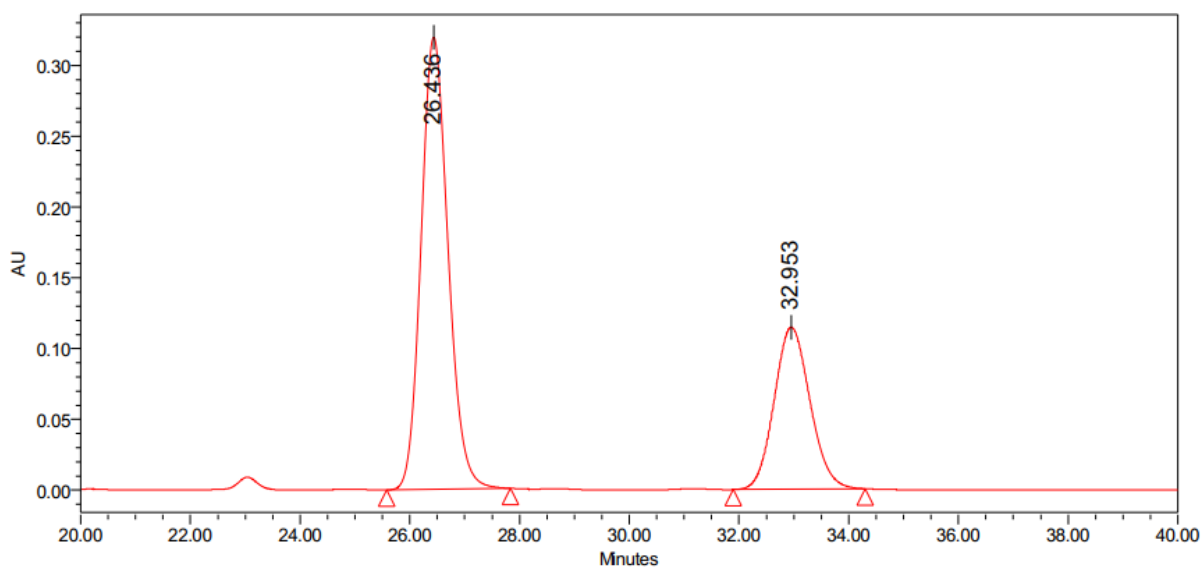
HPLC spectra of racemic 5af



Peak Results

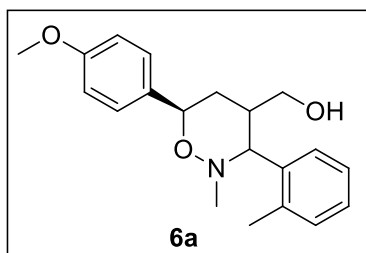
Name	RT	Area	% Area
1	26.376	873597	49.82
2	32.850	879805	50.18

HPLC spectra of chiral 5af

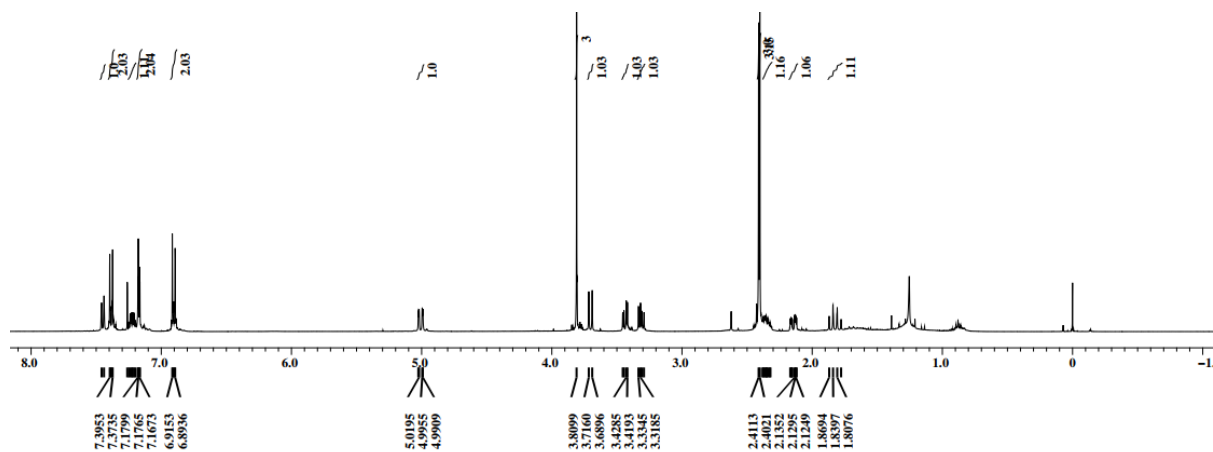


Peak Results

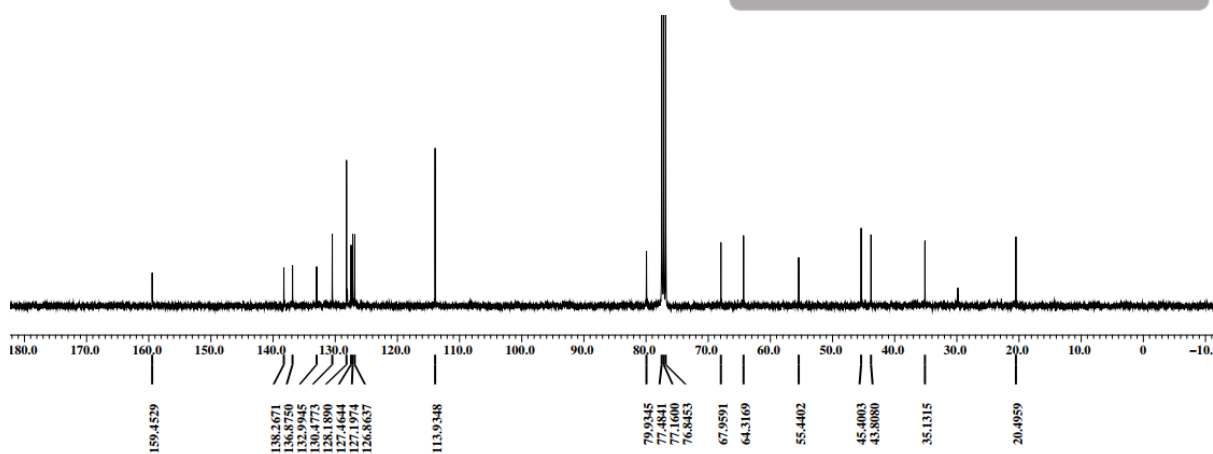
Name	RT	Area	% Area
1	26.436	10929958	67.82
2	32.953	5186484	32.18



¹H-NMR (CDCl₃, 400MHz) of 6a



¹³C-NMR (CDCl₃, 100MHz) of 6a



Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

153 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-23 H: 0-100 N: 0-3 O: 0-4 Cl: 0-1

240223_25_03_19 25 (0.277)

IITRPR

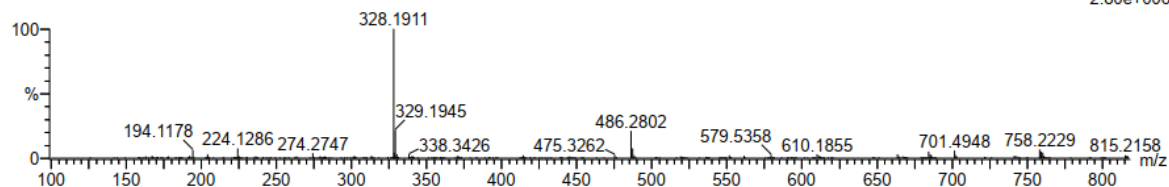
XEVO G2-XS QTOF

240223_25_03_19

Test Name

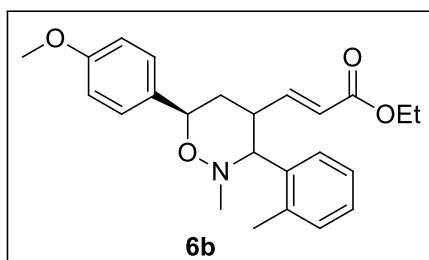
1: TOF MS ES+

2.80e+006

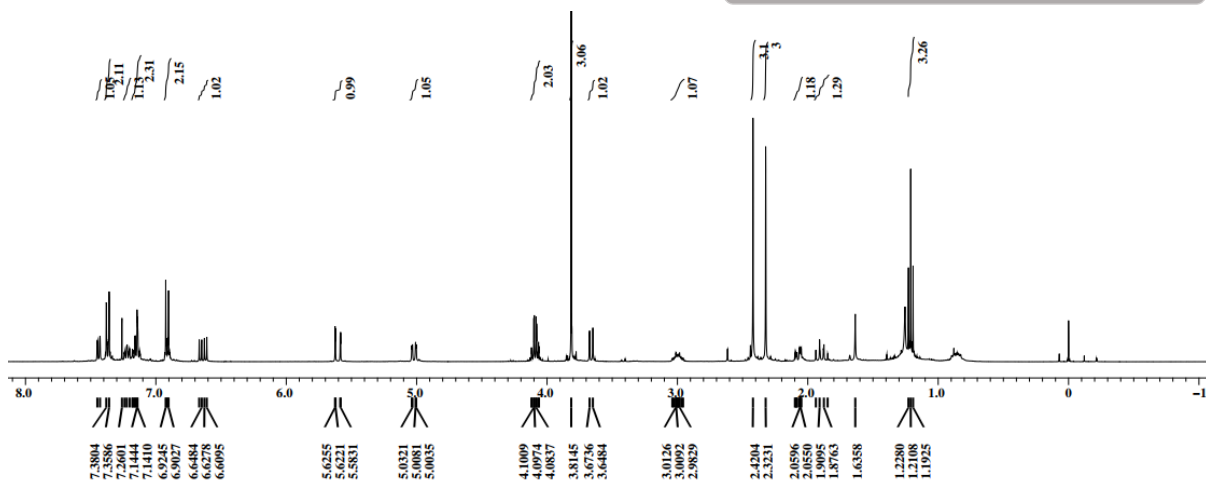


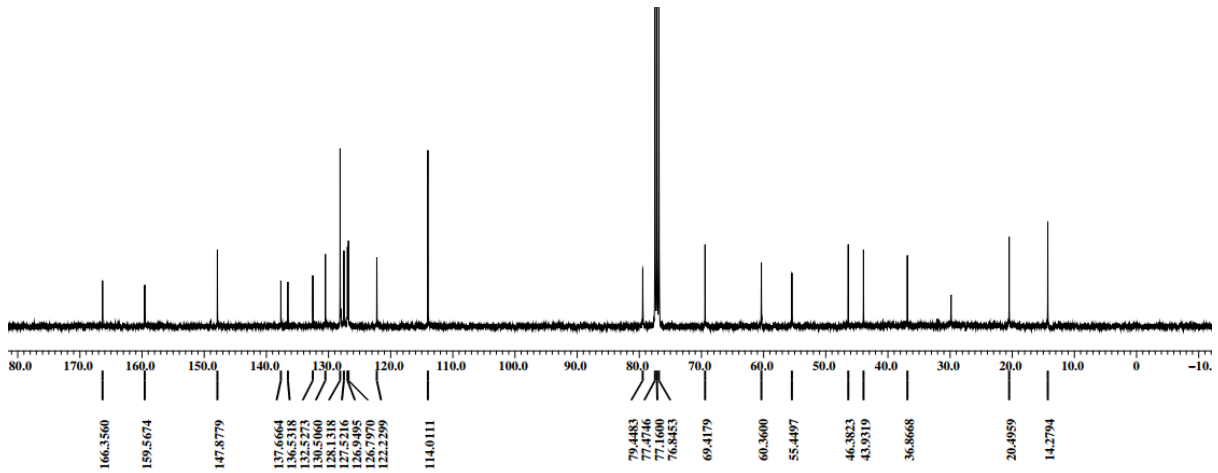
Minimum: -1.5
Maximum: 5.0 10.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
328.1911	328.1913	-0.2	-0.6	8.5	987.9	n/a	n/a	C20 H26 N O3



¹H-NMR (CDCl₃, 400MHz) of 6b





HRMS of 6b

Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

11 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-24 H: 0-30 N: 0-2 O: 0-4

100323_25_03_18 26 (0.285)

IITRPR

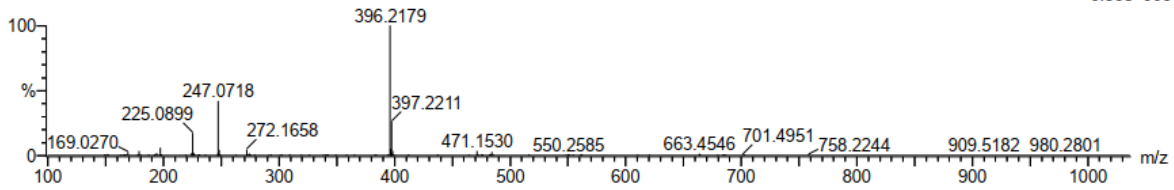
XEVO G2-XS QTOF

100323_25_03_18

Test Name :

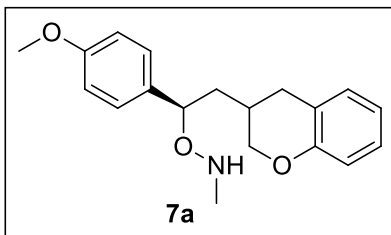
6.36e+006

1: TOF MS ES+

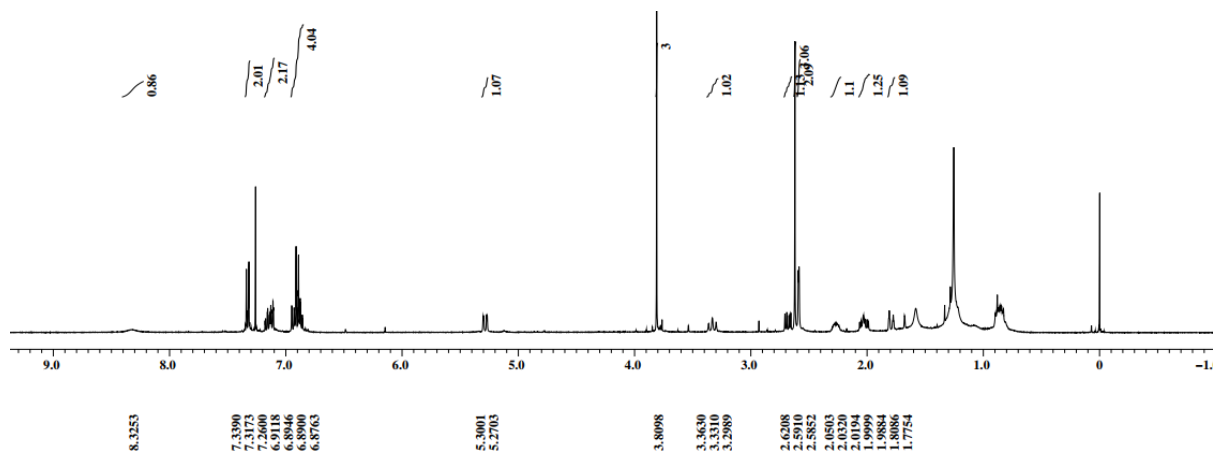


Minimum: -1.5
Maximum: 50.0

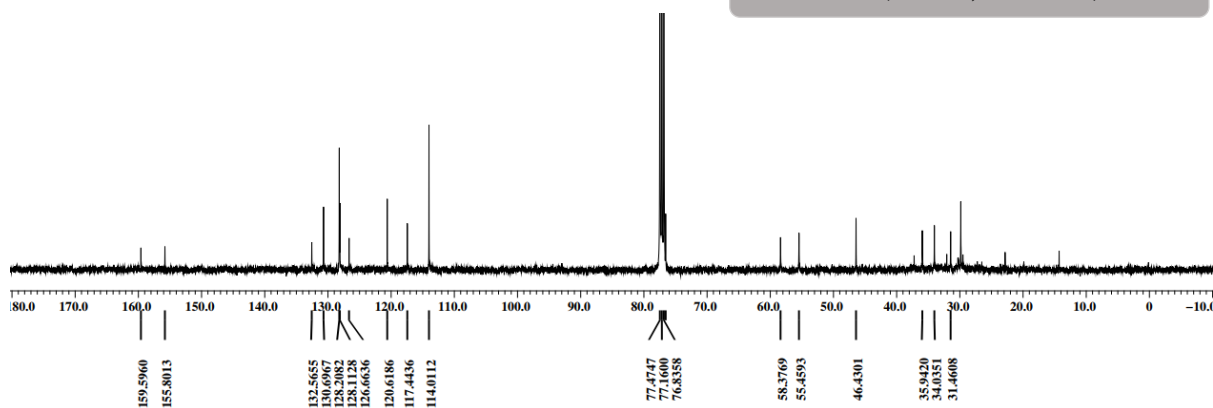
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
396.2179	396.2175	0.4	1.0	10.5	935.6	n/a	n/a	C24 H30 N O4



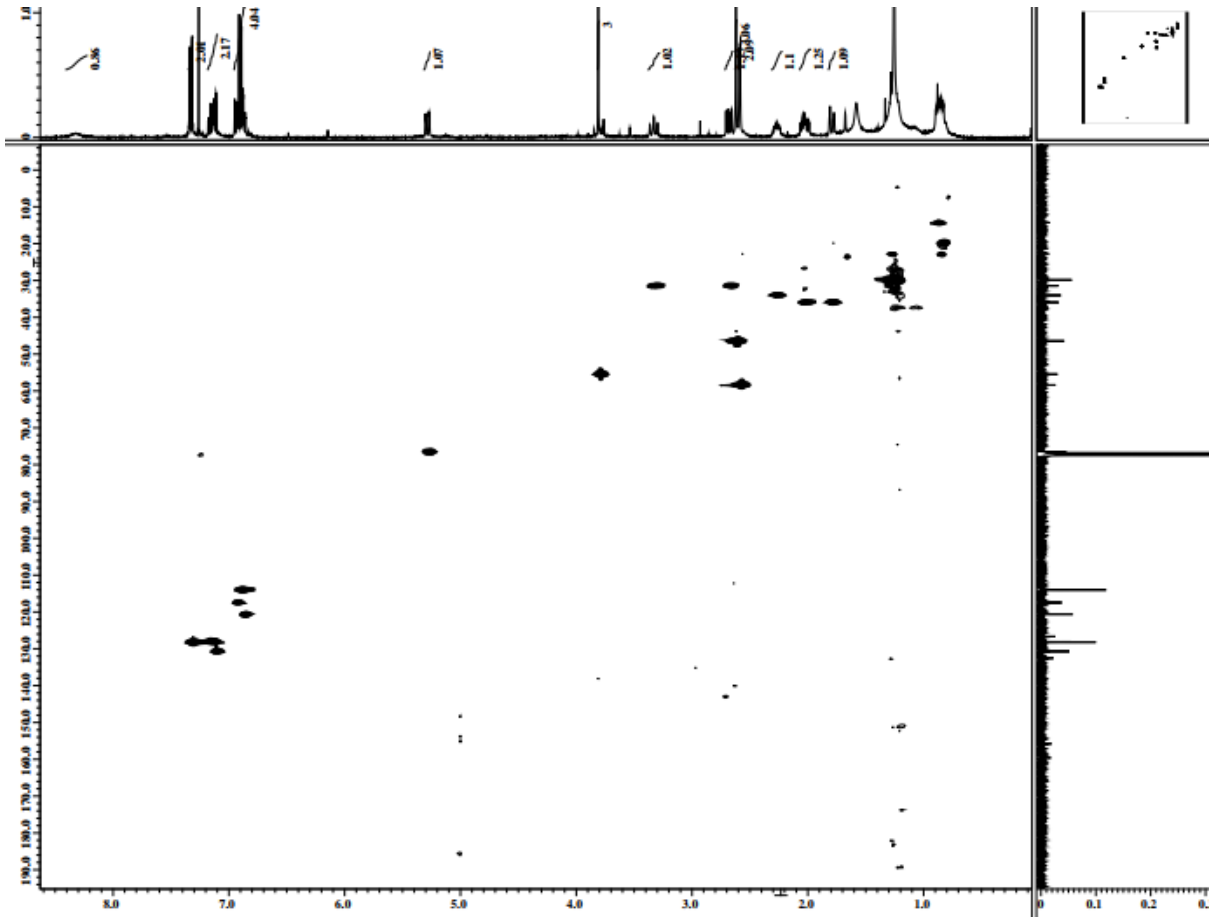
¹H-NMR (CDCl₃, 400MHz) of 7a



¹³C-NMR (CDCl₃, 100MHz) of 7a



¹³C, ¹H HSQC NMR (CDCl₃, 100, 400 MHz) of 7a



HRMS of 7a

Elemental Composition Report

Page 1

Single Mass Analysis

Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

74 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 0-26 H: 0-50 N: 0-2 O: 0-5

120423_25_03_22 20 (0.223)

IITRPR

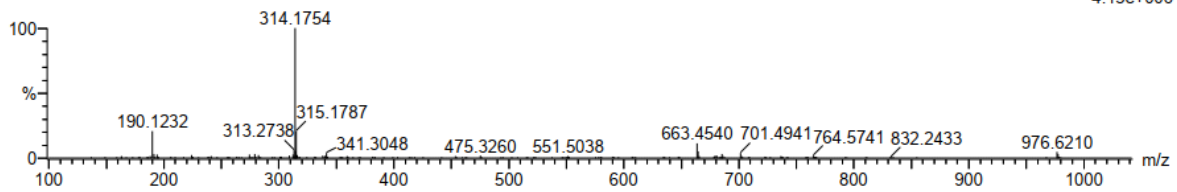
XEVO G2-XS QTOF

Test Name :

120423_25_03_22

1: TOF MS ES+

4.13e+006



Minimum: -1.5
Maximum: 5.0 20.0 50.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf (%)	Formula
314.1754	314.1756	-0.2	-0.6	8.5	1025.7	n/a	n/a	C19 H24 N O3

8. X-ray data of 5aa

For the determination of X-ray crystal structures of **5aa** single crystal was selected and mounted with paratone oil on a glass fiber using gum. The data was collected at 293K on a CMOS based Bruker D8 Venture PHOTON 100 diffractometer equipped with a INCOATEC micro-focus source with graphite monochromatic Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$) operation at 50 kV and 30 mA. For the integration of diffraction profiles SAINT program⁶ was used. Absorption correction was done applying SADABS program.⁷ The crystal structure was solved by SIR 92⁸ and refined by full matrix least square method using SHELXL-97⁹ WinGX system, Ver 1.70.01.¹⁰ All the non-hydrogen atoms in the structure were located the Fourier map and refined anisotropically. The hydrogen atoms were fixed by HFIX in their ideal positions and refined using riding model with isotropic thermal parameters. The crystal structure (excluding structure factor) has been deposited to Cambridge Crystallographic Data Centre and allocated deposition number: **5aa: CCDC 2237741**.

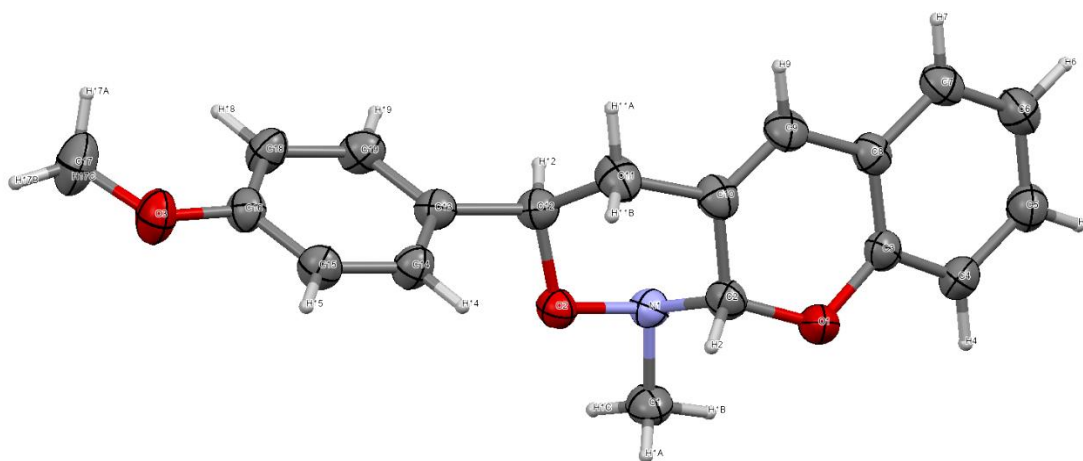


Table S2. Crystal data and structure refinement for 5aa.

Ccdc no.	2237741
Empirical formula	C ₁₉ H ₁₉ NO ₃
Formula weight	309.35
Temperature/K	298.0
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	5.8734(3)
b/Å	15.4556(7)
c/Å	17.6587(7)
α /°	90
β /°	90
γ /°	90
Volume/Å ³	1603.00(13)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.282

μ/mm^{-1}	0.087
F(000)	656.0
Crystal size/ mm^3	$0.35 \times 0.236 \times 0.123$
Radiation	MoK α ($\lambda = 0.71073$)
2Θ range for data collection/ $^\circ$	4.614 to 52.79
Index ranges	$-7 \leq h \leq 7, -19 \leq k \leq 19, -22 \leq l \leq 22$
Reflections collected	33944
Independent reflections	3289 [$R_{\text{int}} = 0.0505, R_{\text{sigma}} = 0.0225$]
Data/restraints/parameters	3289/0/210
Goodness-of-fit on F^2	1.087
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0360, wR_2 = 0.0859$
Final R indexes [all data]	$R_1 = 0.0444, wR_2 = 0.0908$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.12/-0.10
Flack parameter	0.2(5)

Table S3: Selected bond lengths of 5aa

Atoms	Length/ \AA	Atoms	Length/ \AA
O2- N1	1.475(2)	C13- C12	1.509(3)
O2- C12	1.435(3)	C13- C19	1.370(3)
O1- C3	1.377(3)	C14- C15	1.380(3)
O1- C2	1.417(3)	C7- C6	1.381(3)
N1- C1	1.455(3)	C15- C16	1.382(3)
N1- C2	1.481(3)	C10- C2	1.493(3)
O3- C16	1.366(3)	C10- C11	1.498(3)
O3- C17	1.418(4)	C3- C4	1.376(3)
C8- C9	1.453(3)	C12- C11	1.523(3)
C8- C9	1.390(3)	C18- C16	1.382(3)
C8- C3	1.390(3)	C18- C19	1.391(3)
C9- C10	1.320(3)	C4- C5	1.384(3)
C13- C14	1.393(3)	C5- C6	1.376(4)

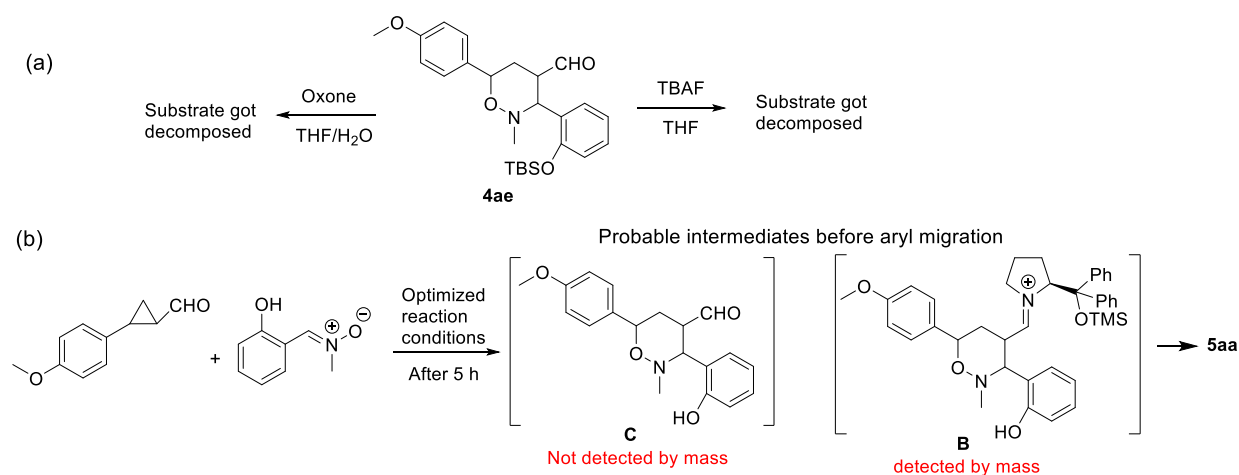
Table S4: Selected bond angles of 5aa

Atom	Angle/ $^\circ$	Atom	Angle/ $^\circ$
C12- O2- N1	108.46(14)	O1- C3- C8	121.3(2)
C3- O1- C2	120.09(18)	C4- C3- O1	116.8(2)
O2- N1- C2	103.21(15)	C4- C3- C8	121.9(2)
C1- N1- O2	103.55(16)	O2- C12- C13	106.62(18)
C1- N1- C2	112.55(19)	O2- C12- C11	109.18(19)
C16- O3- C17	117.7(2)	C13- C12- C11	113.76(18)

Atom	Angle/°	Atom	Angle/°
C7- C8- C9	123.9(2)	C16- C18- C19	119.3(2)
C3- C8- C9	118.3(2)	O1- C2- N1	108.86(18)
C3- C8- C7	117.7(2)	O1- C2- C10	115.90(18)
C10- C9- C8	121.2(2)	N1- C2- C10	105.93(19)
C14- C13-	121.0(2)	C3- C4- C5	119.2(2)
C19- C12	117.9(2)	O3- C16- C15	115.6(2)
C19- C13- C12	121.2(2)	O3- C16- C18	124.8(2)
C15- C14- C13	121.0(2)	C15- C16- C18	119.6(2)
C6- C7- C8	120.8(2)	C13- C19- C18	122.0(2)
C14- C15- C16	120.2(2)	C10- C11- C12	109.39(18)
C9- C10- C2	120.6(2)	C6- C5- C4	120.1(2)
C9- C10- C11	126.3(2)	C5- C6- C7	120.3(2)
C2- C10- C11	112.3(2)		

9. Control experiments

To check whether the aryl migration was occurring under catalytic or non-catalytic conditions, some control experiments have been performed. First, the TBS-protected product **4ae** was subjected to hydrolysis in both TBAF/THF condition and Oxone/water condition but the product got decomposed without forming neither the free OH-containing product nor the aryl migrated product (from the ¹H-NMR study). Additionally the authors tried to get HRMS data of the crude reaction mixture at half completion time for the preparation of **5aa** and the in situ generated intermediate **B** was detected instead of intermediate **C** prior to the aryl migration. Which indicates that the aryl migration occurs under catalytic conditions.



Scheme S1: Control experiments; (a) hydrolysis of **4ae**, (b) trapping of intermediates

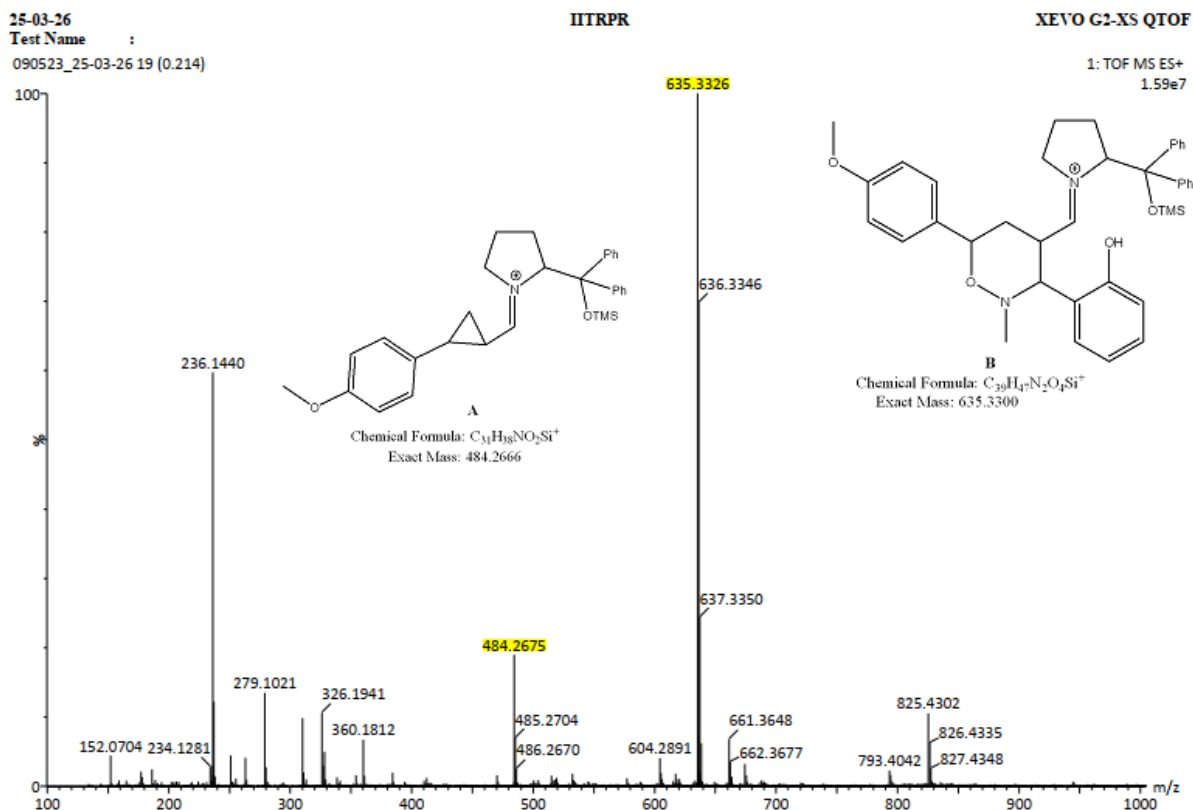


Figure S1: Mass traces of probable intermediates

10. Rearrangement reaction for the production of aryl aldehydes

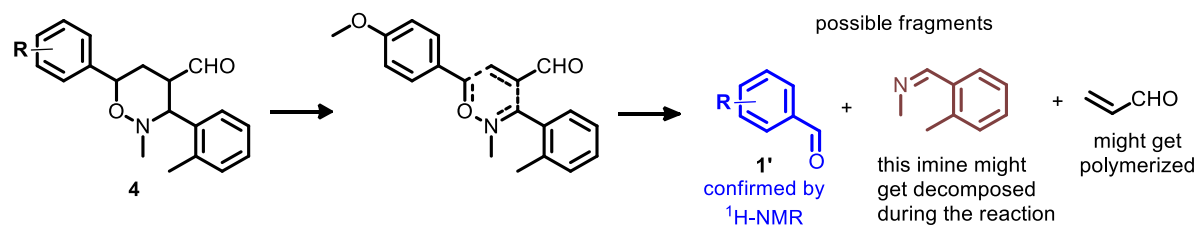


Figure S2: Rearrangement pathway for the aryl aldehyde formation

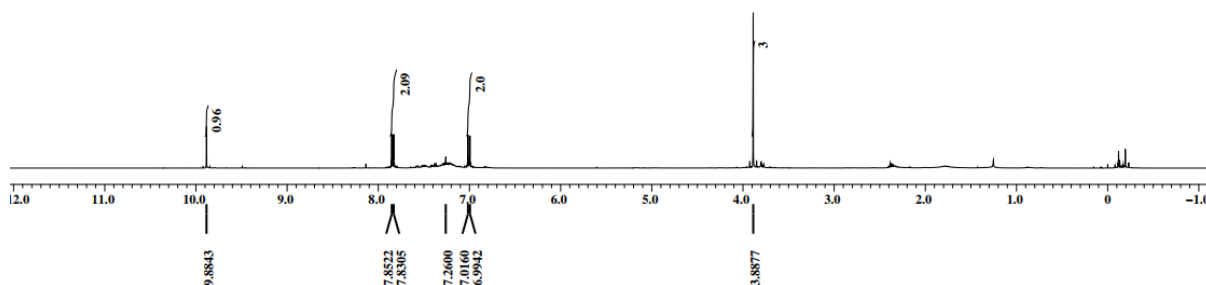


Figure S3: ¹H-NMR of isolated **1a'** (4-methoxy benzaldehyde)

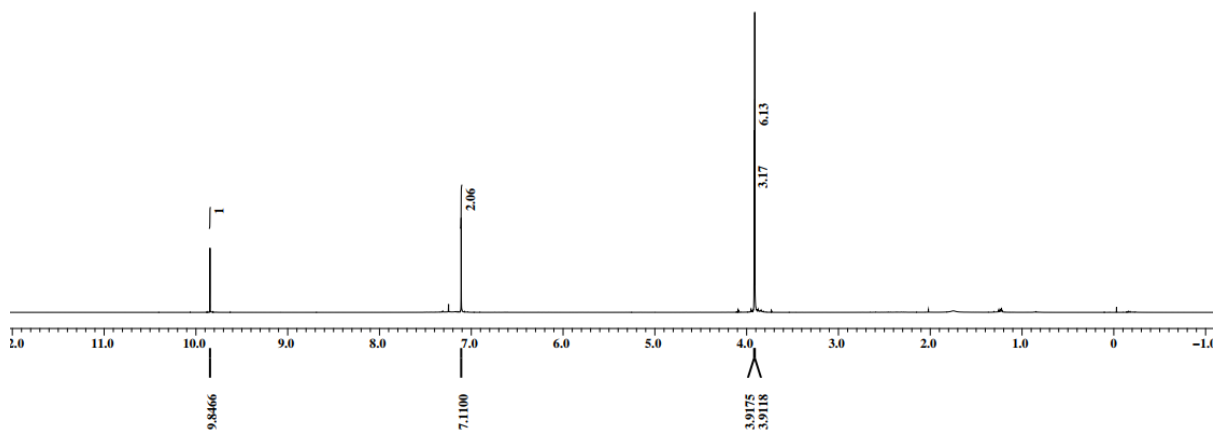


Figure S4: ¹H-NMR of isolated **1f** (3,4,5-trimethoxy benzaldehyde)

11. References

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