Supporting Information for:

An enantio- and diastereoselective approach to indoloquinolizidines in continuous flow

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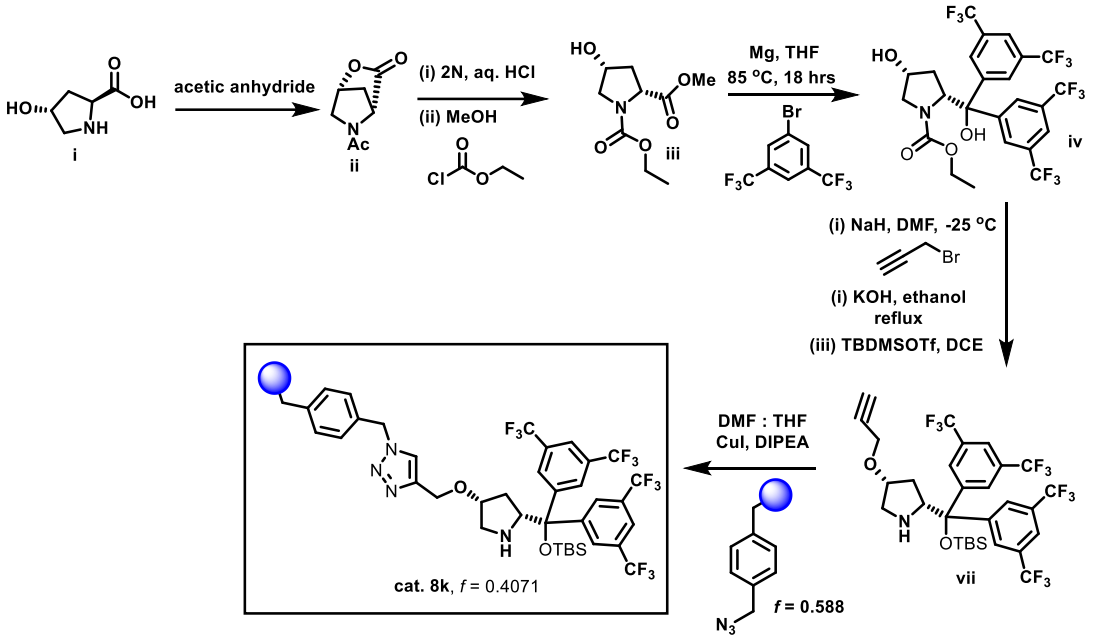
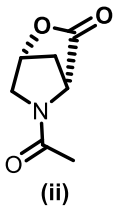
1. General information and data collection:

Column chromatographic separations performed over 100-200 Silica-gel. Visualization of Michael adducts were accomplished by UV light or staining with *p*-anisaldehyde followed by heating. Commercially available regents were purchased from common sources. For sensitive reactions, anhydrous solvent such as THF, CH_2Cl_2, DMF were obtained from the ICIQ's SPS (dry solvent system) and purged using Argon for 30 min to 1 hour before use. Merrifield resin (f = 0.6 mmol/g) was purchased from Iris biotech GMBH. The functionalization of resin was determined by elemental analysis and done using LECO 932 micro-analyzer at Universidad Complutense de Madrid, Spain or at Medac Ltd, United Kingdom. ^{1}H and ^{13}C NMR spectra were recorded on 400 or 500 and 100 or 125 MHz respectively, using a Bruker spectrometer. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded with Waters GCT or LCT- electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a BrukerTensor 27/diamond. High performance Liquid chromatography (HPLC) analysis was performed on Agilent technologies (Series 1200) using Chiralpak OJ-H (for Michael adducts) or AD-H (for Indoloquinolizidines) column with *n*-hexane:IPA. Racemic compounds prepared using 1:1 mixture of (*R*)- and (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether or (*R*)- and (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether. For racemic compound, dimethyl malonate (0.33 mmols, 1 equi), α,β-unsaturated aldehyde (0.66 mmol, 2 equiv), acetic acid (0.5 equiv), Catalyst (7 mol% R + 7 mol% S) catalyst was stirred for 24 h at room temperature in MeOH as solvent. In some cases, enantiomeric excess determined in cyclisation step. The flow chemistry experiments were carried on Vapourtec R-series with coiled reactor (5 mL volume) and glass column (Omnifit, 6.6 x 70 mm or 10 x 70 mm or 10 x 230 mm) or using syringe pump (Legato 200 from KD Scientific) or Vapourtec SF-10 pump.

Preparation of catalyst 8k



Scheme S1. Preparation of catalyst

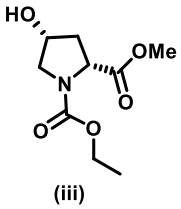


(ii)

1-ethyl 2-methyl (2*R*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (ii):

The brownish suspension of (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (i) (12 g, 91.56 mmol) and acetic anhydride (60 mL) was heated at 90 °C for 24 hours. The solution was cooled to room temperature and again stirred at room temperature for 48 hours. The solution was evaporated to give a thick brown liquid which was precipitated by adding IPA (50 mL) and stirring energetically. A brown precipitate formed which was stirred for 45 minutes at room temperature and then cooled to 0 °C and again stirred for 4 hours (if no precipitation, then stir for overnight at 0 °C). The precipitate was filtered and washed with cold IPA and dried to afford (1*R*,4*R*)-5-acetyl-2-oxa-5-azabicyclo[2.2.1]heptan-3-one (**ii**) (8.2 g, 58%) as brown solid. The NMR data matches with the literature values.[1a,1b]

^{1}H-NMR (300 MHz, Chloroform-d) δ 5.20 – 5.13 (m, 1H), 5.08 (s, 0.34H), 4.51 – 4.42 (m, 0.62H), 3.74 – 3.44 (m, 2H), 2.35 – 2.24 (m, 1H), 2.18 (s, 1.91H), 2.14 – 2.10 (m, 0.7H), 2.05 (s, 1.09H), 2.01 – 1.91 (m, 0.39H).

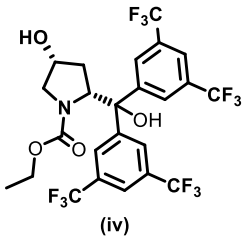


(iii)

1-ethyl 2-methyl (2*R*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (iii):

Compound **ii** (3 g, 1 equiv, 19.34 mmol) was dissolved in 2N aqueous HCl (30 mL) and the solution was heated at reflux (100 ^{o}C) for 2 h. After that the solution was neutralized to pH 6 with 5 N NaOH (~10-12 mL) and then concentrated using rotary evaporator to give the crude product. To this crude product was added methanol (100 mL) and ethyl chloroformate (3 mL, 1.89 equiv, 36.49 mmol) and resulting reaction mixture was stirred at room temperature for 24 hours. Later, the mixture was filtered, and the filtrate was concentrated using rotary evaporator. Finally, added water and organic component was extracted using ethyl acetate to give product (**iii**) (2.28 g, 10.5 mmol, 54% yield). The NMR data matches with its isomer.[1c,2]

^{1}H-NMR (300 MHz, Chloroform-*d*) δ 4.53 – 4.28 (m, 2H), 4.25 – 4.03 (m, 2H), 3.83 – 3.74 (m, 3H), 3.75 – 3.49 (m, 2H), 2.51 – 2.24 (m, 1H), 2.19 – 2.05 (m, 1H), 1.24 (dt, *J* = 18.6, 7.1 Hz, 3H).



(iv)

ethyl (2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (iv):

(Magnesium was washed with dilute HCL followed by with methanol, DCM and dried in oven at 100 ^{o}C).

In a two neck round bottom flask under argon atmosphere was added magnesium (2.18 g, 91.24 mmol, 4 equiv), followed by addition of 50 mL dry THF. Later, 1-bromo-3,5-bis(trifluoromethyl)benzene (20.04 g or 11.8 mL, 68.43 mmol, 3 equiv) was dissolved in 50 mL of dry THF and resulting solution was added to the RB containing Mg under inert atmosphere. The resulting reaction mixture was refluxed at 85 ^{o}C for 3 hours (colourless to brown). The reaction mixture was cooled to room temperature first and later cooled to 0 ^{o}C. Finally, 1-ethyl 2-methyl

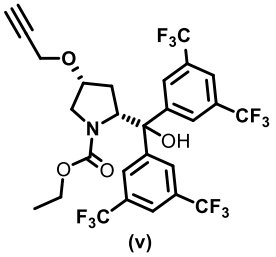
(2*R*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (iii) was dissolved in 80 mL of dry THF and added dropwise into the above Grignard solution at 0 ^{o}C. The resulting mixture was stirred at room temperature (26 ^{o}C) for 6 hours. The reaction progress can be monitored by TLC comparison with staining in *p*-anisaldehyde. The reaction solution was quenched with 50 mL of saturated aqueous NH_4Cl and organic component was extracted using with ethyl acetate. Also add 50 to 100 mL of water if solids do not dissolve. The organic layer was again washed with saturated aqueous NH_4Cl 50 mL x 3 times followed by washing with brine, organic layer evaporated and dried over anhydrous MgSO4 and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was chromatographed on silica gel (90:10 to 80:20% of cyclohexane: ethyl acetate) to give the product ethyl (2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (iv) (3.5 g, 25% yield, 5.71 mmol) as brownish solid. Unreacted starting material can be recovered back. We haven't tried but the yield can be improved with commercially available Grignard reagent. The isomer of the compound is reported by Hayashi and co-workers and our data matches with literature.[2]

^{1}H-NMR (400 MHz, Chloroform-*d*) δ 8.09 (s, 2H), 7.87 (s, 3H), 7.73 (s, 1H), 6.38 (s, 1H), 5.10 (d, *J* = 9.2 Hz, 1H), 4.60 (t, *J* = 6.4 Hz, 1H), 4.09 – 3.92 (m, 1H), 3.85 – 3.71 (m, 1H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.37 – 3.17 (m, 1H), 2.41 (ddd, *J* = 15.2, 9.3, 6.3 Hz, 1H), 1.82 (d, *J* = 14.8 Hz, 1H), 1.15 – 0.78 (m, 3H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ 155.55, 148.04, 146.61, 132.25 (q, *J* = 33.7 Hz), 131.07 (q, *J* = 33.1 Hz), 127.30 – 126.88 (m), 124.75 (d, *J* = 15.9 Hz), 122.27 – 121.78 (m), 121.59 – 121.20 (m), 119.33 (d, *J* = 16.3 Hz), 79.27, 70.16, 65.08, 61.96, 57.21, 37.71, 14.24.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -62.91.

HRMS: (ESI) m/z calculated for $C_{24}H_{19}F_{12}NO_4$ (M+Na)+: 636.1020, found: 636.1036.



(v)

ethyl (2R,4R)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (v):

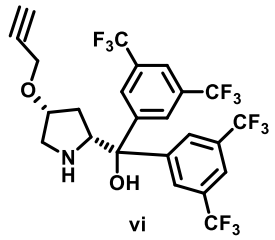
In a typical procedure, a two neck round bottom flask, was equipped with septum and thermometer to maintain the internal temperature. A suspension of sodium hydride (NaH) (60% in mineral oil) (0.2 g, 2 equiv, 4.89 mmol) in anhydrous DMF under nitrogen atmosphere was cooled to -25 ^{o}C using cryobath (internal temperature) and solution of ethyl (2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (iv) (1.5 g, 1 equiv, 2.44 mmol) in 10 mL dry DMF was added dropwise. The reaction mixture was stirred at -25 ^{o}C for 20 minutes. Using a syringe, 3-bromoprop-1-yne (443.6 mg, 334 µL, 80% Wt, 1.22 Eq, 2.983 mmol) was added very slowly and checked temperature time to time and tried to keep it below -15 to -20 ^{o}C. If it started to increase, then stopped the addition of propargyl bromide. After sometime again added slowly, if temp is risen then it forms unwanted allene. After addition, the RM was stirred at 0 ^{o}C for 1.5 hour and checked progress checked by TLC. The reaction mixture was warmed to room temperature naturally and quenched with sat. NH_4Cl and extracted using DCM. The pure compound was obtained after silica gel column chromatography in combiflash using ethyl acetate and cyclohexane (10:90 to 30:70) as an eluent to afford ethyl (2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (v) (640 mg, 982 µmol, 40 % isolated yield as a colorless liquid.

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.03 (m, 2H), 7.89 – 7.82 (m, 3H), 7.78 – 7.70 (m, 1H), 5.77 (bs, 1H), 5.10 (d, *J* = 9.1 Hz, 1H), 4.42 (td, *J* = 6.0, 5.5, 3.5 Hz, 1H), 4.25 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.15 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.07 – 3.95 (m, 1H), 3.86 – 3.77 (m, 1H), 3.69 – 3.59 (m, 1H), 2.46 – 2.34 (m, 2H), 1.96 (d, *J* = 15.0 Hz, 1H), 1.02 – 0.89 (m, 3H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 155.30, 147.63, 146.23, 132.06 (q, *J* = 33.5 Hz), 131.13 (q, *J* = 33.1 Hz), 127.17 – 126.81 (m), 124.34 (d, *J* = 20.5 Hz), 122.00 – 121.77 (m), 121.46 – 121.19 (m), 120.00 (d, *J* = 21.3 Hz), 79.39, 76.10, 64.58, 61.80, 57.09, 54.54 – 53.21 (m), 35.20, 14.20.

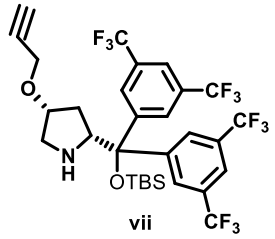
^{19}F-NMR (376 MHz, $CDCl_3$) δ -62.88.

HRMS: (ESI) m/z calculated for $C_{27}H_{21}F_{12}NO_4$ (M+Na)+: 674.1177, found: 674.1176.



vi

Compound (iv) ethyl (2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (640 mg, 1 equiv, 0.982 mmol) was dissolved in 10 mL ethanol and added 4 mL 2.37M KOH solution (KOH solution prepared by dissolving 533 mg KOH in 4 mL H_2O). The resulting reaction mixture was refluxed at 90 ^oC with vigorous stirring for overnight. In the next morning TLC was checked which showed new spot formation which showed violet-pink color after staining in ninhydrin. The reaction mixture was quenched by adding sat. NH_4Cl and extracted using DCM (30 x 3 times). The dark yellow liquid obtained after evaporation which was used for next reaction without further purification.



vii

(2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (vii):

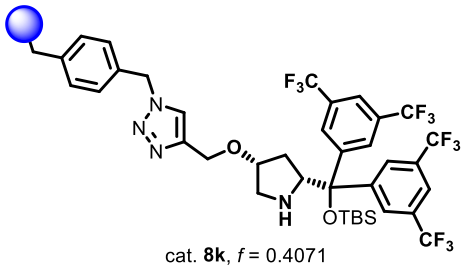
In a round-bottom flask compound (iv) (0.9499 mmol, 1 equiv, 550 mg) was dissolved in dichloroethane (DCE) 16 mL under nitrogen and cooled to 0 ^oC. Then, lutidine (7.599 mmol, 8 equiv, 880 µL) and (*tert*-Butyldimethylsilyl trifluoromethanesulfonate) TBDMSOTf (3.799 mmol, 4 equiv, 872 µL) were added to the reaction mixture slowly, the flask was fitted with reflux condenser and the reaction mixture was refluxed at 80 °C overnight. The day after, conversion was checked by TLC and the reaction mixture was then diluted with saturated NH_4Cl. The aqueous phase was further extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by Combiflash (cyclohexane/EtOAc: 100:00 to 95:05%) to afford (2*R*,4*R*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((tert-butyldimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (vii) (421 mg, 0.60 mmol) as a colorless liquid.

^{1}H-NMR (400 MHz, Chloroform-*d*) δ 8.13 (s, 2H), 7.86 (s, 2H), 7.77 (s, 2H), 4.16 – 4.07 (m, 1H), 4.01 (t, *J* = 8.2 Hz, 1H), 3.90 (d, *J* = 2.4 Hz, 2H), 2.98 (dd, *J* = 12.1, 5.6 Hz, 1H), 2.78 (dd, *J* = 12.1, 3.6 Hz, 1H), 2.34 (t, *J* = 2.4 Hz, 1H), 1.99 – 1.82 (m, 2H), 1.51 – 1.44 (m, 1H), 0.10 (s, 9H), -0.18 (s, 3H), -0.49 (s, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 147.79, 145.99, 131.67 (m, overlapped signals), 131.34 (m, overlapped signals), 129.72 (d, *J* = 3.5 Hz), 128.32 (d, *J* = 3.8 Hz), 124.80, 124.62, 122.10 (m, overlapped signals), 81.83, 79.78, 65.01, 56.29, 52.64, 34.94, 26.02, 19.07, -2.54, -3.31.

^{19}F-NMR (376 MHz, $CDCl_3$) δ -62.93, -63.01.

HRMS (ESI) m/z calculated for $C_{30}H_{31}F_{12}NO_2Si$ (M+H)+: 694.2005, found: 694.2002.



cat. **8k**, *f* = 0.4071

Synthesis of polymer supported catalyst 8k:

In a round bottom flask, azidomethylpolystyrene (*f* = 0.588 mmol g^{-1}, 852.6 mg, 0.501 mmol, 0.8 equiv) was added in mixture of dry THF (5 mL) + dry DMF (15 mL) and shaken using mechanical shaker for 15 minutes at room temperature. Copper iodide (60 mg, 0.66 mmol, 1.05 equiv) and DIPEA (808 mg, 6.26 mmol, 10 equiv) was added in the resin solution. Finally, compound (vii) (411 mg, 0.626 mmol, 1 equiv) was dissolved in dry THF (10 mL) and added to the resin solution and resulting mixture was shaken using mechanical shaker at 45 ^{o}C for 72 hours. Small amount of resin was taken washed with water, methanol + water, methanol, methanol+DCM, DCM, dried and checked using IR to confirm the disappearance of azide peak (2094 cm^{-1}). Once confirmed, whole resin was washed with hot water, water, methanol + water, methanol, methanol + DCM, DCM and dried at 45 ^{o}C under vacuum for overnight to afford brown solid (1.12 g). The catalyst **4** has elemental analysis values- %C =77.93, %H =6.70, %N =2.28 and functionalization (*f* = 0.4071 mmol/g) which was calculated by formula.

f_{exp} = % element X 10^3 / number of elements X molecular weight of element X 100

f_{exp} = 2.28 X 10 / 4 X 14.00

f_{exp} = 22.8 / 56

f_{exp} = 0.4071 mmol/g

Molecular weight of catalyst can be calculated by = 1 / f_{exp} X 1000

Molecular weight of catalyst **8k**= 1/0.4071 X 1000 = 2456.1

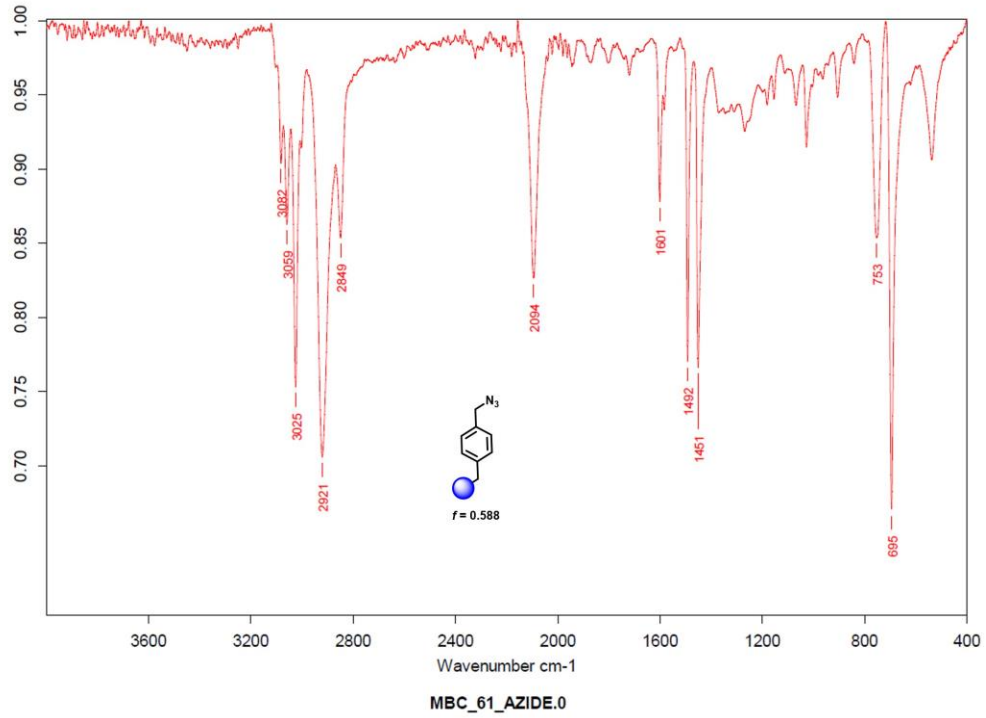


Figure S1. IR spectra of azidomethylpolystyrene (Azide peak at 2094 cm^{-1}).

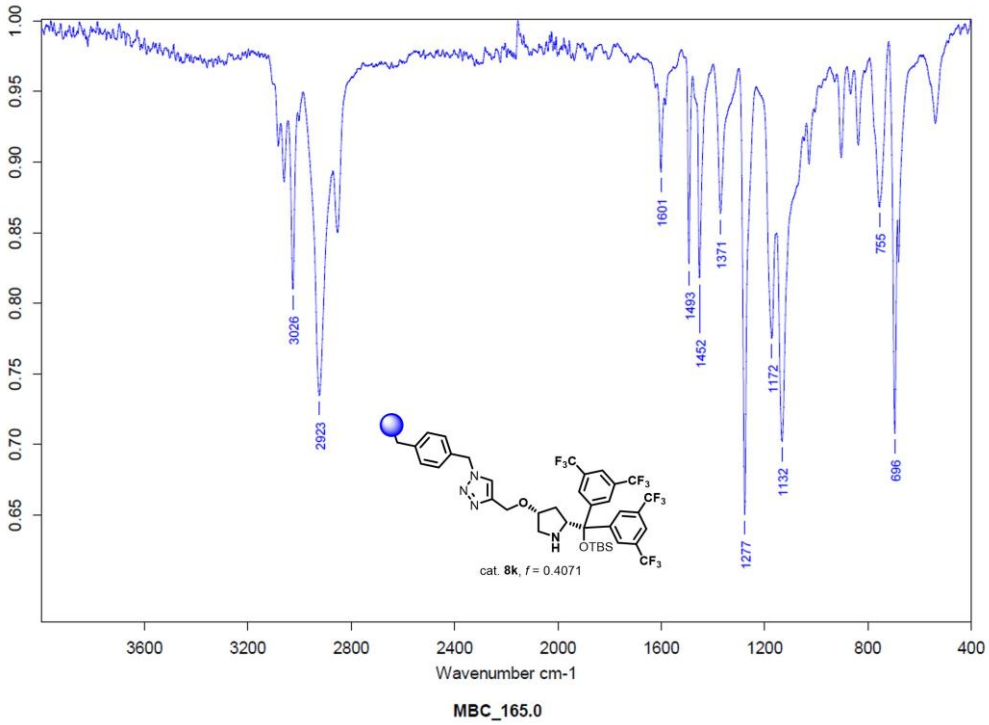
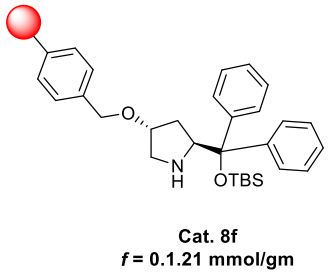


Figure S2. IR spectra of catayst **8k** shows absence of azide peak at 2094 cm^{-1}

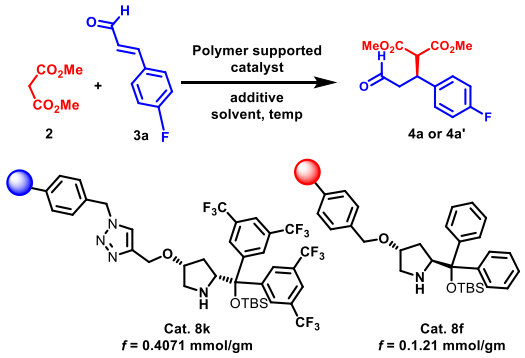


Catalyst **8f** was prepared by us in previously reported work which showed elemental analysis- %C =73.98, %H =7.07, %N =1.70 and functionalization (*f* = 1.21 mmol/g) which was calculated by previously mentioned formula.[3]

2. Michael addition in batch

(A) Optimization of reaction conditions

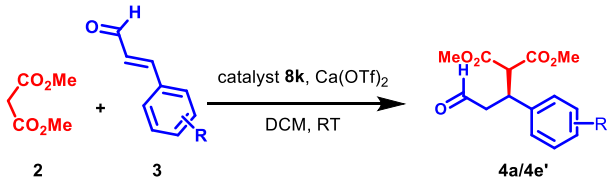
Table S1. Optimization in Batch using polymer-supported catalysts



Entry	Cat	Ratio **2**:**3**	T °C	Additive	Yield[b]	Solvent	Time in h	ee[c]
1	**8k**	3:1	60	AcOH	32	DCM	48	77
2	**8k**	3:1	60	TFA	trace	DCM	48	--
3[d]	**8k**	1:2	25	$Ca(OTf)_2$	48	EA	36	73
4[d]	**8k**	1:2	25	$Ca(OTf)_2$	70	DCM	36	95
5[e]	**8f**	15:1	25	AcOH	55	DCM	36	97
6[e]	**8f**	3:1	25	AcOH	72	DCM	36	97

[a] Reactions performed using 30 mol% of catalyst and additive 0.6 equiv. [b] isolated yields. [C] determined by chiral HPLC using OJ-H column. [d] 1 equi of $Ca(OTf)_2$, [e] opposite enantiomer.

(B) General experimental procedure for the synthesis of 4 in batch using catalyst 8k

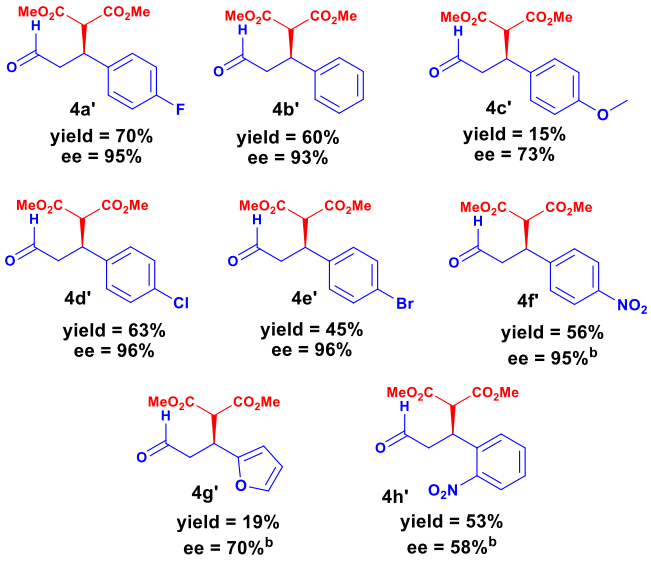


In a 20 mL re-sealable vial was added catalyst **8k** (0.075 mmol, 0.3 equiv, 184.2 mg), dimethyl malonate (0.25 mmol, 1 equiv, 33 mg), α,β-unsaturated aldehyde (0.5 mmol, 2 equiv), $Ca(OTf)_2$ (0.25 mmol, 1 equiv, 84.5 mg) and dichloromethane 1.5 mL, the tube is sealed with a cap using crimper. The reaction mixture was shaken using mechanical shaken at room temperature (25 °C) for 48 hrs. After reaction completion, catalyst **8k** was filtered, washed with DCM and ethyl acetate, and dried in vacuum oven at 40 °C for 4 hours and used for next reaction. Likewise, all optimization and substrate scope were performed using same catalyst. A volatile component was evaporated using a

vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70). Enantiomeric excess was determined using OJ-H column.[4]

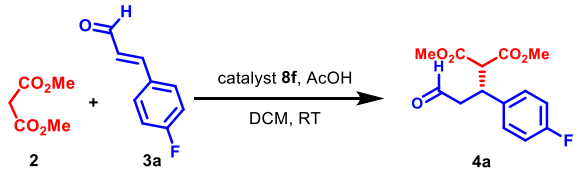
(C) Substrate scope in batch using catalyst 8k[a]

All the substrates shown below were synthesized using same catalyst and followed the procedure mentioned in section 3(B). The spectroscopic data matches with literature reports.[4,6]



Scheme S2. [a]Scope of enantioselective conjugate addition using catalyst **8k**. Conditions: dimethyl malonate **2** (0.25 mmol, 1 equi), substituted cinnamaldehyde **3** (0.5 mmol, 2 equi), Cat. **8k** (184 mg, 30 mol%), $Ca(OTf)_2$ (1 equi, 84.5mg, 0.25 mmol) and DCM (2 mL) was shaken for 48 hours at 25 ^oC, Enatiomeric excess determined using OJ-H column. [c]ee was determined after cyclization with tryptamine using AD-H column.

(D) Experimental procedure for the synthesis of 4a in batch using catalyst 8f



In a 20 mL re-sealable vial was added catalyst **8f** (0.198 mmol, 0.3 equiv, 163 mg), dimethyl malonate (2 mmol, 3 equiv, 264 mg) 4-flurocinnamaldehyde (0.66 mmol, 1 equiv, 0.66 mmol), acetic acid (0.396 mmol, 0.6 equiv, 23.75 mg) and dichloromethane 3 mL, the tube is sealed with a cap using crimper. The reaction mixture was shaken using mechanical shaken at room temperature (25 ^oC) for 36 hrs. After reaction completion, catalyst **8f** was filtered, washed with DCM and ethyl acetate. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford **4a** dimethyl (*R*)-2-

(1-(4-fluorophenyl)-3-oxopropyl)malonate (135 mg, 0.478 mmol, 72%) as a colorless liquid with 97% ee. The spectroscopic data matches with the literature report.

3. Catalytic enantioselective Michael additions in continuous flow

(A) Experimental procedure for conjugate addition in flow with DCM as a solvent with catalyst 8f

A glass column of Omnifit with outer jacket (10 mm bore x 230 mm of adjustable bed height) and Omnifit PTFE frit at the bottom was packed with catalyst **8f** (1 g, 1.21 mmol). The outer jacket was circulated with oil (Ministat-Huber) for heating purpose. A check valve and back pressure regulator of 100 psi was also placed. The catalyst was swelled by passing dichloromethane at a flow rate of 0.2 mL/min for 20 minutes at 50 ^{o}C, bed height = 8 cm. Later, a 0.2M DCM solution of 4-flurocinnamaldehyde (1 equiv) along with dimethyl malonate (15 equiv) and acetic acid (0.6 equiv) was flowed at flow rate of 100 µL/min and 50 ^{o}C using Vaportch SF-10 pump. The residence time was 63 minutes (residence time can be calculated by following formula: reactor volume/flow rate). After reaching a steady state, 5 mL solution was collected. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford **4a** dimethyl (*R*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate as a colorless liquid with 96% ee with 60% isolated yield.

(B) Experimental procedure for conjugate addition in flow with DCM as a solvent with catalyst 8k:

A glass column of Omnifit with outer jacket (10 mm bore X 100 mm of adjustable bed height) and Omnifit PTFE 10 um frit at the bottom was packed with premixed mixture of catalyst **8k** (500 mg, 1.21 mmol) and $Ca(OTf)_2$(169 mg). The outer jacket was circulated with oil (Ministat-Huber) for heating purpose. A check valve and back pressure regulator of 20 psi was also placed. The mixture was swelled by passing dichloromethane at a flow rate of 0.2 mL/min for 20 minutes at 50 ^{o}C, bed height = 4.2 cm. Later, a 0.05M DCM solution of dimethyl malonate (1 equiv) and 4-flurocinnamaldehyde (2 equiv) was flowed at a flow rate of 20 µL/min at 50 ^{o}C. The residence time was 330 minutes (residence time can be calculated by following formula: reactor volume/flow rate). After reaching a steady state, 2 mL solution was collected. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford **4a'** dimethyl (*S*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate as a colorless liquid with 91% ee with 35% isolated yield. In this experiment, in reaction mixture we

observed presence of $Ca(OTf)_2$ also, since it is soluble in dimethyl malonate thus this approach is not suitable due to long residence time and leaching of calcium salt.

(C) Experimental procedure for solvent free conjugate addition in flow using catalyst 8f:

A glass column of Omnifit with outer jacket (10 mm bore X 70 mm of adjustable bed height) and Omnifit PTFE frit at the bottom was packed with catalyst **8f** (1 g, 1.21 mmol, *f* = 1.21 mmol/g). The outer jacket was circulated with oil (Ministat-Huber) for heating purpose. A check valve and back pressure regulator of 75 psi was also placed. The catalyst was swelled by passing dimethyl malonate at a flow rate of 0.2 mL/min for 20 minutes at 60 ^{o}C, bed height ~3.2 cm. Later, dimethyl malonate (**2**) (86.66 mmol, 11.44 g, 2 equiv), 4-flurocinnamaldehyde (**3a**) (43.33 mmol, 6.5 g, 1 equiv), and acetic acid (25.99 mmol, 1.56 g, 0.6 equiv) were mixed in a vial and flowed at flow rate of 100 or 50 or 20 µL/min at 60 ^{o}C using Vapourtec SF-10 pump. The residence time was 25, 50 and 125 minutes (residence time can be calculated by following formula: reactor volume/flow rate). In every experiment, after reaching a steady state, 3 mL solution was collected. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford **4a** dimethyl (*R*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate as a colorless liquid with 98, 98 and 96 % ee with 52, 68 and 73% isolated yield respectively. After each reaction, the catalyst bed was washed with ethyl acetate (0.2 mL/min for 30 min) followed by washing with acetic acid (0.2 mL/min for 30 min) at 60 ^{o}C. The same procedure was followed for all the substrates.

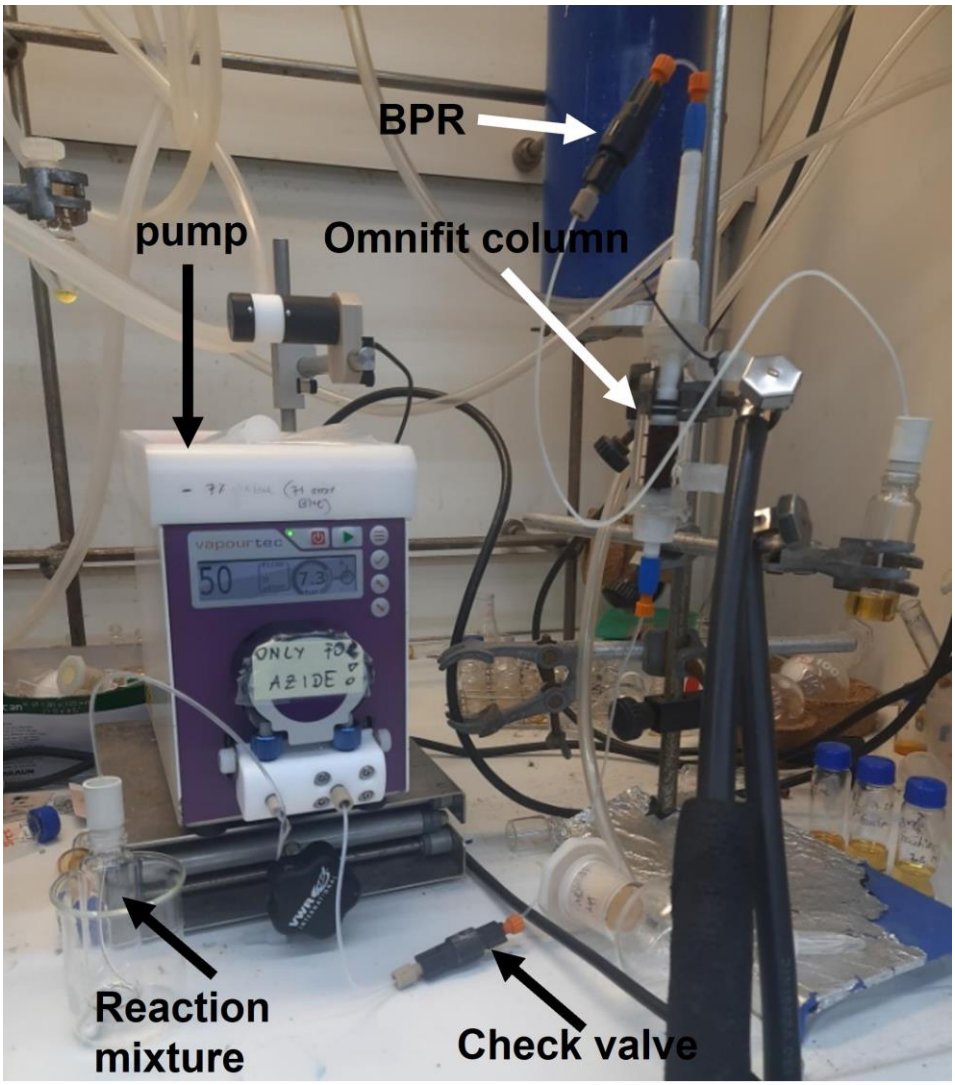
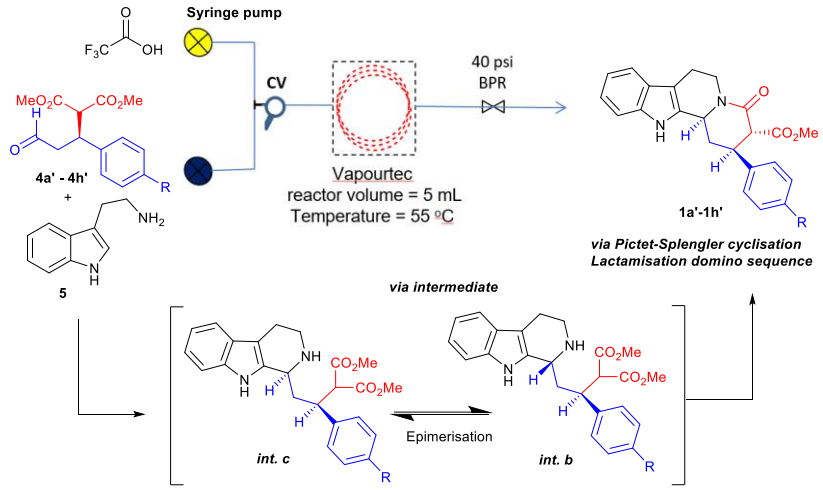


Figure S3. Continuous flow setup for conjugate addition using supported catalyst

4. Diastereoselective continuous flow synthesis of indoloquinolizidines 1

(A) General experimental procedure with 5 mL reactor in continuous flow: All reactions mentioned below are performed with the compounds (**4a'-4e'**) which are obtained from the reaction of **2** and **3a-e** using catalyst **8k** (Section 3(C), Scheme S2).



The continuous flow assembly consist of KD scientific syringe pump and Hamilton gastight syringe, Vapourtec coiled reactor (5 mL) with acid resistant PTFE tubing, check valve, 40 psi back pressure regulator. In a typical procedure, compound **4a'-4e'** (0.1 mmol, 1 equiv) and tryptamine (**5**) (0.15 mmol, 1.5 equiv) was dissolved in 10 mL of dichloromethane (DCM) to make 10 mM solution. On the other hand, trifluoroacetic acid (TFA) (0.25 mmol, 2.5 equiv) was mixed in 10 mL of dichloromethane to make 25 mM solution. The solutions were flowed at a flow rate of 50 µL/min each at 55 ^{o}C through 5 mL reactor. The residence time was 50 minutes (residence time can be calculated by following formula: reactor volume/flow rate). After reaching a steady state, 18 mL of reaction mixture was collected. The reaction mixture was quenched by addition of $NaHCO_3$ and layers were separated. Organic layer was washed with brine, dried over sodium sulfate, evaporated and subjected to column chromatography. The pure compounds were obtained by elution with cyclohexane: ethyl acetate= 20:80 or 40:60 or 50:50.

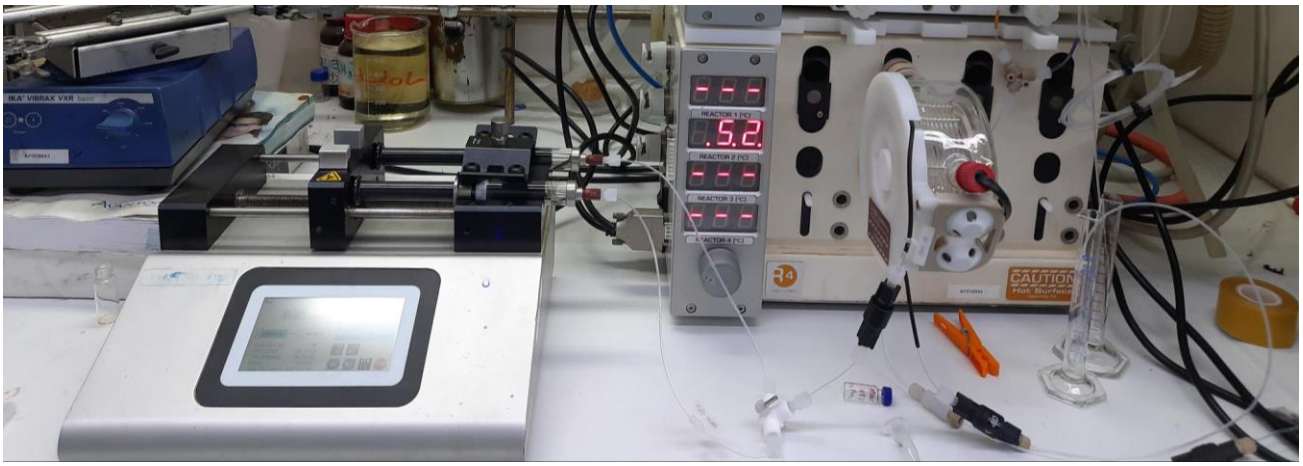


Figure S4. Reaction setup for the continuous-flow synthesis of indoloquinolizidines 1

(B) General experimental procedure with 20 mL reactor in continuous flow: This all reactions performed with the compounds (**4a**-**4g**) (Scheme 2, main article) which were obtained from the reaction of **2** and **3a**-**3g** using catalyst **8f**. The continuous flow assembly consist of Vapourtec R4-series with 3 coiled reactors combined (2 x 5 mL reactors) and (10 mL reactor) having acid resistant PTFE tubing to make overall reactor volume = 20 mL, check valve, 40 psi back pressure regulator.

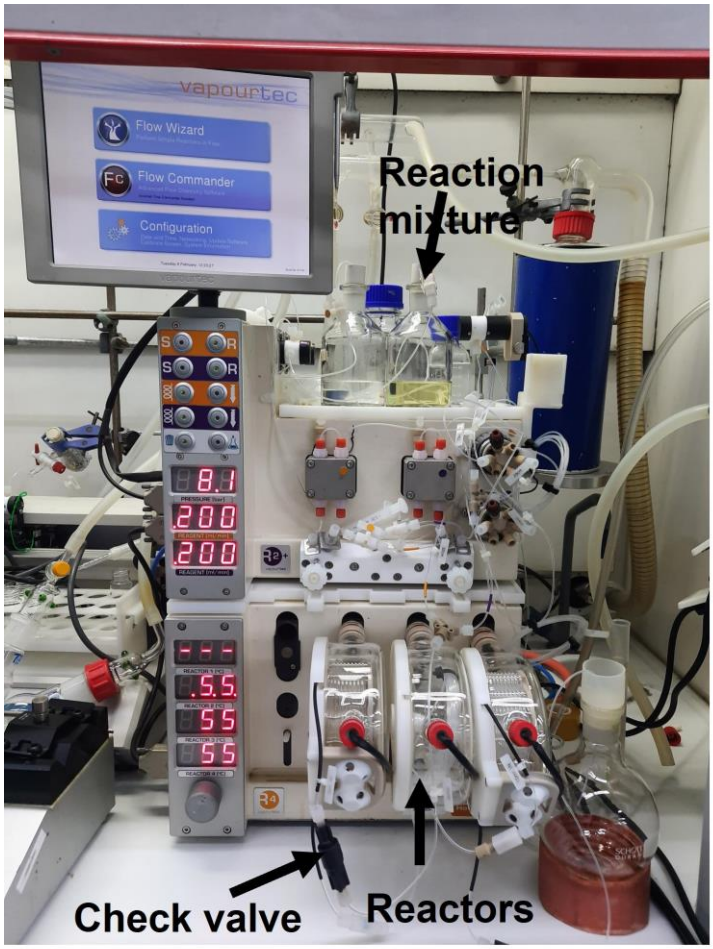


Figure S5. Reaction setup for the scale-up of the continuous-flow synthesis of indoloquinolizidines 1

In a typical procedure, compound **4a**-**4f** (1 mmol, 1 equiv) and tryptamine (**5**) (1.5 mmol, 1.5 equiv) was dissolved in 100 mL of dichloromethane (DCM) to make 10 mM solution. On the other hand, trifluoroacetic acid (TFA) (2.5 mmol, 2.5 equiv) was mixed in 100 mL dichloromethane to make 25 mM solution. The two solutions were flowed separately at a flow rate of 200 µL/min each at 55 ^{o}C through 5 + 5+ 10 mL reactors. The residence time was 50 minutes (residence time can be calculated

by following formula: reactor volume/flow rate). After reaching a steady state, 150 mL of reaction mixture was collected. The reaction mixture was quenched by addition of $NaHCO_3$ and layers were separated. Organic layer was washed with brine, dried over sodium sulfate, evaporated and subjected to column chromatography. Formation of diastereomer in some amount in some cases is possible if the collected reaction mixture kept at room temperature for prolonged time, this is due to cyclisation of unreacted intermediate. The pure compounds were obtained by elution with cyclohexane: ethyl acetate= 80:20 to 60:40 to 50:50.

5. Continuous flow synthesis of δ-lactone 6

The continuous flow assembly consist of Vapourtec R4-series with 5 mL coiled reactor with acid resistant PTFE tubing which is telescoped with Omnifit-packed bed reactor, check valve, 40 psi back pressure regulator.

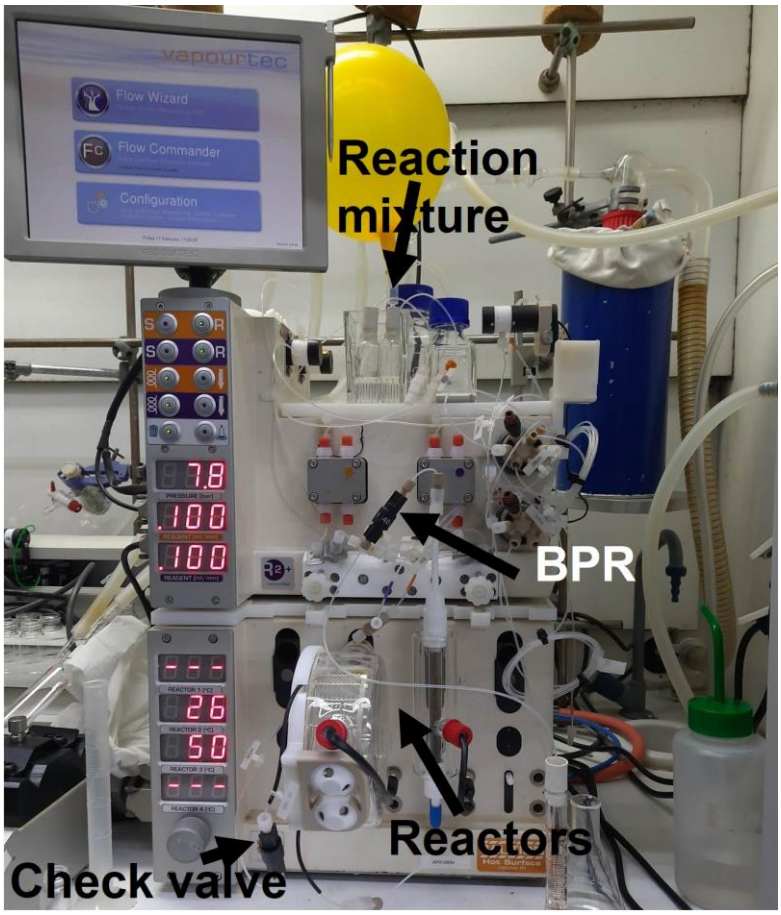
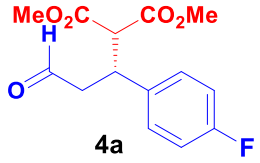


Figure S6. Reaction setup for synthesis of lactone using continuous flow

Experimental procedure for reductive cyclisation:

methyl (3*R*,4*R*)-4-(4-fluorophenyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate: To perform the telescoped reductive-cyclisation, the output of a 5 mL coiled reactor with PTFE tubing was connected to Omnifit© glass column (6.6 mm bore size x 70 mm height) which was filled with 1.5 g Amberlyst-15 (bed height = 9 cm). The temperature of coiled reactor was set to 25 ^{o}C and for packed bed reactor 50 ^{o}C. Dry THF was flown at 0.2 mL/min for 15 min before flowing the actual reactants. The compound **4a** (0.3546 mmol, 100 mg, 1 equiv) and acetic acid (419 µL) was dissolved in 10 mL of dry tetrahydrofuran (THF) to make 35 mM solution. On the other hand, 1M $NaBH_3CN$ (0.5319 mmol, 1.5 equiv, 531 µL) was mixed in 10 mL of dry tetrahydrofuran (THF) to make 53 mM solution and flowed at flow rate of 0.2 mL/min each through the telescoped reactors. Total 17 mL of reaction mixture collected after reaching steady state. THF was evaporated using rotary evaporator and diethyl ether was added. The organic layer washed with $NaHCO_3$ followed by brine to afford crude compound which on column chromatographic separation with eluent diethyl:pentane:DCM (1:1:0.1) to afford methyl (3*R*,4*R*)-4-(4-fluorophenyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate (**6**) (40 mg, 0.158 mmol) as a faint yellow liquid with 53% yield and 95.5% enantiomeric excess (>20/1 d.r). The yield was calculated based on collection of 17 mL of reaction mixture.

6. Analytical data:



4a

(i) dimethyl (*R*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate (4a): Followed the same experimental setup mentioned in section 4C**.** In a vial, 4-fluorocinnamaldehyde (43.33 mmol, 6.5 g, 1 equiv), dimethyl malonate (86.66 mmol, 11.44 g, 2 equiv) and acetic acid (25.99 mmol, 1.56 g, 0.6 equiv) were mixed and flowed at flow rate of 50 µL/min at 60 ^{o}C using Vapourtec SF-10 pump. After reaching a steady state the solution was collected for 4.5 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford (**4a**) dimethyl (*R*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate (18.39 mmol pure product) as a faint yellow liquid with 98% ee. The titled compound is previously reported in the literature and spectroscopic data matches with the literature values.[4]

Productivity=

Turnover frequency (TOF) = Turnover number / time

Turnover frequency (TOF) = 15.19/4.5 = 3.37 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 9.59 (dd, *J* = 2.0, 1.1 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.00 – 6.94 (m, 2H), 4.01 (td, *J* = 9.5, 4.9 Hz, 1H), 3.77 – 3.67 (m, 4H), 3.51 (s, 3H), 3.00 – 2.83 (m, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ 199.68, 168.38, 167.89, 162.13 (d, *J* = 246.4 Hz), 135.64 (d, *J* = 3.4 Hz), 129.80 (d, *J* = 8.1 Hz), 115.80 (d, *J* = 21.5 Hz), 57.34, 52.95, 52.68, 47.46, 38.82.

HPLC (Chiralpak OJ-H, *n*-hexane/IPA (80:20), 1 mL/min, 210 nm): major enantiomer, t_R =15.65 and minor enantiomer, t_R = 19.22.

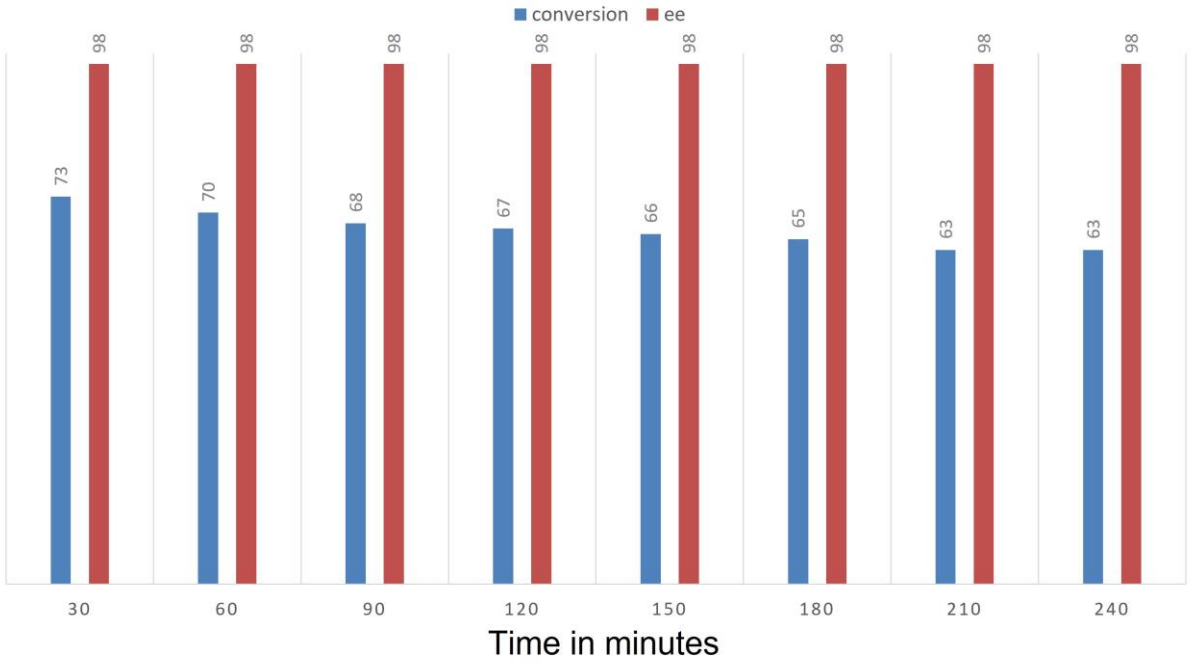
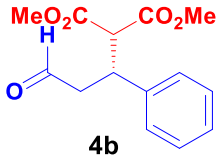


Figure S7. Graph for entry **4a** showing long term monitoring



4b

(ii) dimethyl (*R*)-2-(3-oxo-1-phenylpropyl)malonate (4b): Followed the same experimental setup mentioned in section 4C. In a vial, *trans*-cinnamaldehyde (49.24 mmol, 6.5 g, 1 equiv), dimethyl malonate (98.48 mmol, 13 g, 2 equiv) and acetic acid (25.99 mmol, 1.56 g, 0.6 equiv) were mixed and flowed at flow rate of 50 µL/min at 60 ºC using Vapourtec SF-10 pump. After reaching a steady state the solution was collected for 4.5 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or

30:70) to afford **4b** dimethyl (*R*)-2-(3-oxo-1-phenylpropyl)malonate (19.94 mmol pure product) as a colorless liquid with 97% ee. The titled compound is previously reported in the literature and spectroscopic data matches with the literature values.[4]

Productivity= Turnover frequency (TOF) = 16.47/4.5 = 3.66 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (400 MHz, Chloroform-*d*) δ 9.57 (t, *J* = 1.7 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.24 – 7.16 (m, 3H), 4.01 (ddd, *J* = 9.7, 8.6, 5.6 Hz, 1H), 3.76 – 3.69 (m, 4H), 3.47 (s, 3H), 2.98 – 2.83 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 200.03, 168.47, 167.93, 139.84, 128.87, 128.09, 127.67, 57.37, 52.84, 52.56, 47.31, 39.62.

HPLC (Chiralpak OJ-H, *n*-hexane/IPA (80:20), 1 mL/min, 220 nm): major enantiomer, t_R = 32.57 and minor enantiomer, t_R = 45.19.

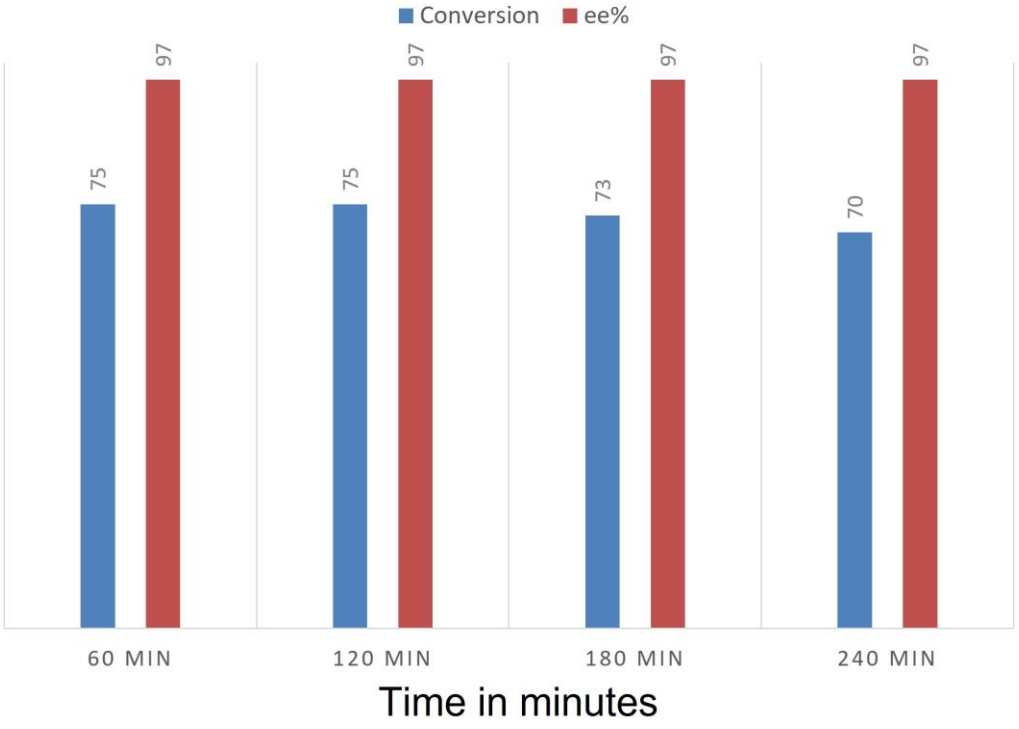
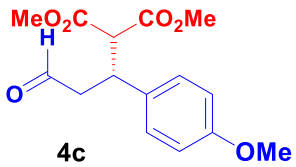


Figure S8. Graph for entry **4b** showing long term monitoring



4c

(iii) dimethyl (*R*)-2-(1-(4-methoxyphenyl)-3-oxopropyl)malonate (4c): Followed the same experimental setup mentioned in section 4C**.** In a vial, 4-methoxycinnamaldehyde (30.86 mmol, 5 g,

1 equiv), dimethyl malonate (75.75 mmol, 10 g, 2.45 equiv) and acetic acid (18.51 mmol, 1.11 g, 0.6 equiv) were mixed and flowed at flow rate of 50 µL/min at 60 °C using Vapourtec SF-10 pump. After reaching a steady state the solution was collected for 4 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford **4c** dimethyl (*R*)-2-(1-(4-methoxyphenyl)-3-oxopropyl)malonate (11.47 mmol pure product) as a faint yellow solid with 96% ee. The titled compound is previously reported in the literature and spectroscopic data matches with the literature values.[4]

Productivity= Turnover frequency (TOF) = 9.48/4 = 2.37 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 9.58 (dd, *J* = 2.2, 1.4 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.98 (td, *J* = 9.5, 5.2 Hz, 1H), 3.77 (s, 3H), 3.74 – 3.67 (m, 4H), 3.52 (s, 3H), 2.94 – 2.79 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 200.27, 168.56, 168.03, 158.98, 131.68, 129.18, 114.27, 57.62, 55.33, 52.86, 52.62, 47.46, 38.97.

HPLC (Chiralpak OJ-H, *n*-hexane/IPA (80:20), 1 mL/min, 220 nm): major enantiomer, t_R =45.06 and minor enantiomer, t_R = 56.09.

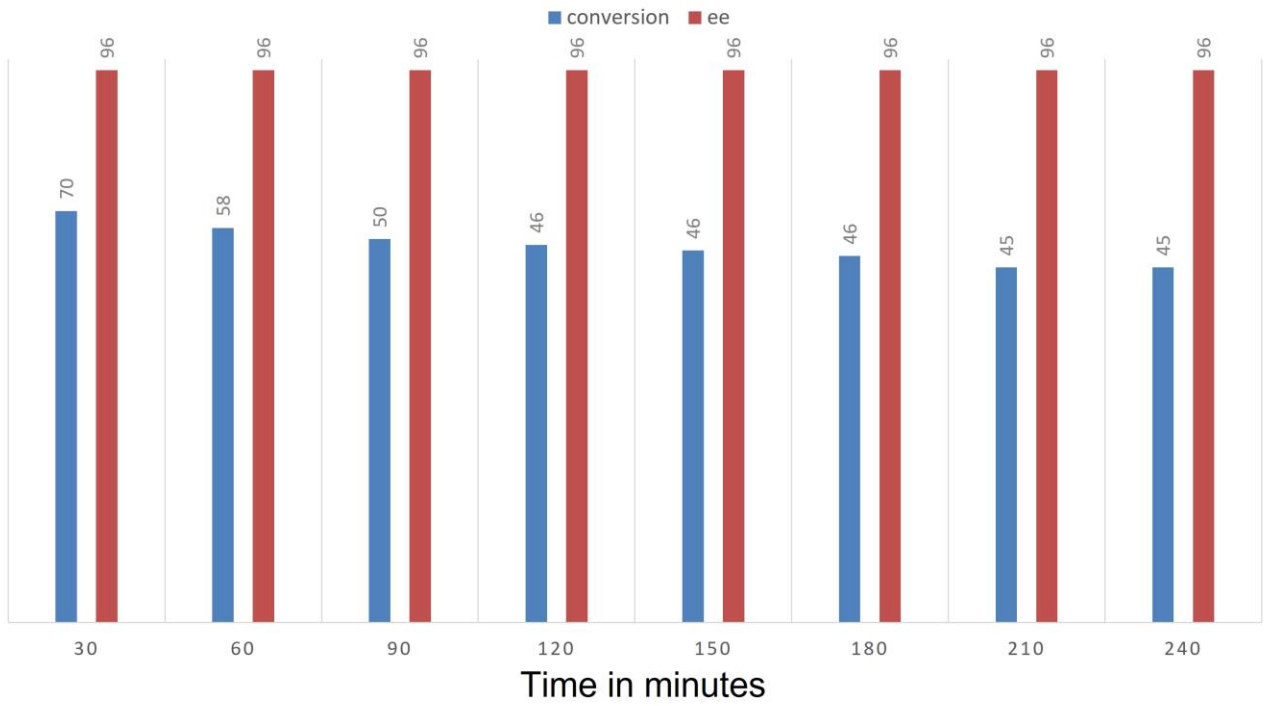
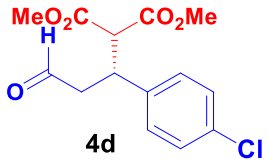


Figure S9. Graph for entry **4c** showing long term monitoring



4d

(iv) dimethyl (*R*)-2-(1-(4-chlorophenyl)-3-oxopropyl)malonate (4d): Followed the same experimental setup mentioned in section 4C**.** In a vial, 4-chlorocinnamaldehyde (27 mmol, 4.5 g, 1 equiv), dimethyl malonate (54.02 mmol, 7.13 g, 2 equiv) and acetic acid (16.2 mmol, 0.97 g, 0.6 equiv) were mixed and flowed at flow rate of 50 µL/min at 60 °C using Vapourtec SF-10 pump. After reaching a steady state the solution was collected for 2.5 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford (**4d**) dimethyl (*R*)-2-(1-(4-chlorophenyl)-3-oxopropyl)malonate (8.10 mmol pure product) as a faint yellow liquid with 97% ee. The titled compound is previously reported in the literature and spectroscopic data matches with the literature values.[4]

Productivity= Turnover frequency (TOF) = 6.69/2.5 = 2.676 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (400 MHz, Chloroform-*d*) δ 9.60 (dd, *J* = 1.8, 1.2 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.01 (td, *J* = 9.3, 5.0 Hz, 1H), 3.76 – 3.67 (m, 4H), 3.53 (s, 3H), 3.07 – 2.79 (m, 2H).

^{13}C-NMR (101 MHz, Chloroform-*d*) δ 199.34, 168.18, 167.68, 138.37, 133.39, 129.43, 128.94, 56.96, 52.84, 52.60, 47.17, 38.74.

HPLC (Chiralpak OJ-H, *n*-hexane/IPA (80:20), 1 mL/min, 220 nm): major enantiomer, t_R =20.10 and minor enantiomer, t_R = 23.60.

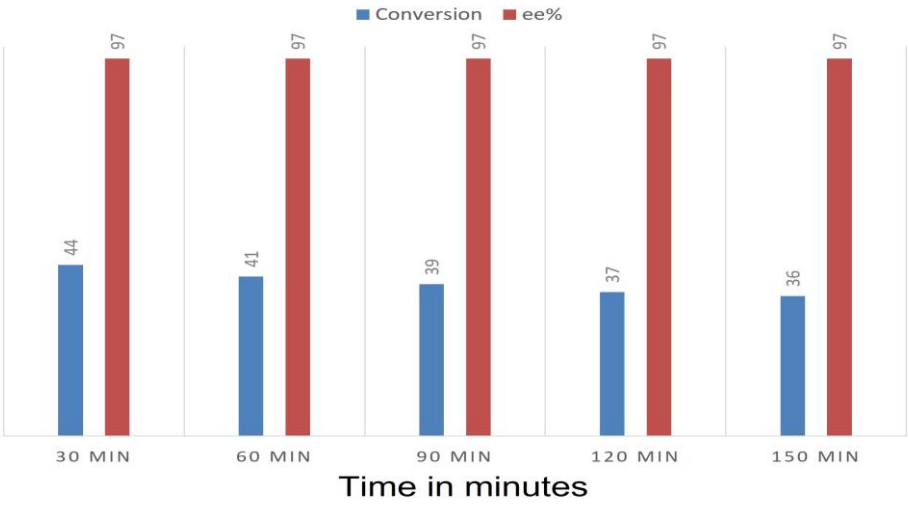
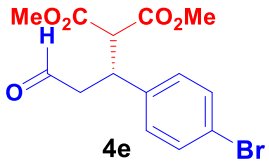


Figure S10. Graph for entry **4d** showing long term monitoring



(v) dimethyl (*R*)-2-(1-(4-bromophenyl)-3-oxopropyl)malonate (4e): Followed the same experimental setup mentioned in section 4C. In a vial, 4-bromocinnamaldehyde (18.95 mmol, 4 g, 1 equiv), dimethyl malonate (113.7 mmol, 15 g, 6 equiv) and acetic acid (11.37 mmol, 0.682 g, 0.6 equiv) were mixed and flowed at flow rate of 50 µL/min at 60 ^{o}C using Vapourtec SF-10 pump. Due to less solubility of 4-bromocinnamaldehyde, 6 equivalents of dimethyl malonate were used. After reaching a steady state the solution was collected for 3.5 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford (**4e**) dimethyl (*R*)-2-(1-(4-bromophenyl)-3-oxopropyl)malonate (4.74 mmol pure product) as a faint yellow liquid with 97% ee. Unreacted 4-bromocinnamaldehyde was recovered back. The titled compound is previously reported in the literature and spectroscopic data matches with the literature values. [5]

Productivity= Turnover frequency (TOF) = 3.91/3.5 = 1.12 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 9.59 (dd, *J* = 1.8, 1.1 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.99 (td, *J* = 9.4, 4.9 Hz, 1H), 3.76 – 3.67 (m, 4H), 3.53 (s, 3H), 3.00 – 2.82 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 199.43, 168.27, 167.78, 139.05, 131.99, 129.90, 121.60, 56.97, 52.95, 52.72, 47.21, 38.89.

HPLC (Chiralpak OJ-H, *n*-hexane/IPA (80:20), 1 mL/min, 220 nm): major enantiomer, t_R = 21.13 and minor enantiomer, t_R = 24.73.

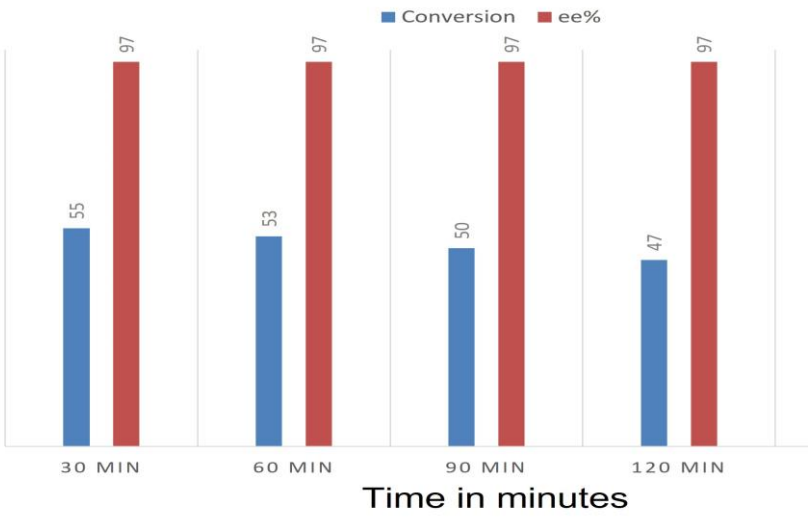
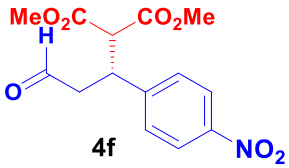


Figure S11. Graph for entry **4e** showing long term monitoring



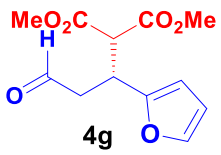
4f

(vi) dimethyl (*R*)-2-(1-(4-nitrophenyl)-3-oxopropyl)malonate (4f): Followed the same experimental setup mentioned in section 4C. In a vial, 4-nitrocinnamaldehyde (15.25 mmol, 2.7 g, 1 equiv), dimethyl malonate (188 mmol, 24.9 g, 11 equiv) and acetic acid (10.1 mmol, 0.61 g, 0.6 equiv) were mixed and flowed at flow rate of 100 µL/min at 60 °C using Vapourtec SF-10 pump. Due to poor solubility of 4-nitrocinnamaldehyde, 11 equivalents of dimethyl malonate were used. After reaching a steady state the solution was collected for 3.18 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford (**4f**) dimethyl (*R*)-2-(1-(4-nitrophenyl)-3-oxopropyl)malonate (1.65 mmol pure product) as a faint yellow liquid with 91% ee. Unreacted 4-nitrocinnamaldehyde was recovered back. The titled compound is previously reported in the literature and spectroscopic data matches with the literature values.[6] Enantiomeric excess was determined after cyclisation with tryptamine.

Productivity= Turnover frequency (TOF) = 1.36/3.18 = 0.43 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 9.62 (t, *J* = 1.1 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 4.14 (td, *J* = 9.2, 4.8 Hz, 1H), 3.82 – 3.63 (m, 4H), 3.54 (s, 3H), 3.12 – 2.93 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 198.62, 167.99, 167.56, 147.79, 147.33, 129.30, 123.97, 56.45, 53.09, 52.85, 47.08.



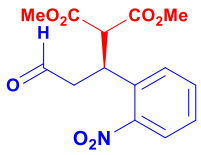
4g

(vii) dimethyl (*R*)-2-(1-(furan-2-yl)-3-oxopropyl)malonate (4g): Followed the same experimental setup mentioned in section 4C. In a vial, (*E*)-3-(furan-2-yl)acrylaldehyde (40.98 mmol, 5 g, 1 equiv), dimethyl malonate (81.95 mmol, 10.818 g, 2 equiv) and acetic acid (24.59 mmol, 1.475 g, 0.6 equiv) were mixed and flowed at flow rate of 50 µL/min at 60 °C using Vapourtec SF-10 pump. Due to poor solubility of 4-nitrocinnamaldehyde, 11 equivalents of dimethyl malonate were used. After reaching a steady state the solution was collected for 3.15 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate= 10:90 or 30:70) to afford (**4g**) dimethyl (*R*)-2-(1-(furan-2-yl)-3-oxopropyl)malonate (6.02 mmol pure product) as a faint yellow liquid with 92% ee. Enantiomeric excess was determined after cyclisation with tryptamine (**5**). The titled compound is previously reported in the literature and spectroscopic data matches with the literature report.[6]

Productivity = Turnover frequency (TOF) = 4.97/3.15 = 1.58 $mmol_{prod}$ $mmol_{resin}^{-1}$ h^{-1}

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 9.67 (dd, *J* = 2.0, 1.2 Hz, 1H), 7.31 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.26 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.13 (dd, *J* = 3.3, 0.7 Hz, 1H), 4.14 (td, *J* = 8.6, 4.8 Hz, 1H), 3.83 (d, *J* = 8.3 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.03 – 2.84 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 199.67, 168.16, 168.03, 152.81, 142.27, 110.49, 107.46, 54.88, 52.87, 52.86, 44.72, 33.13.



4h'

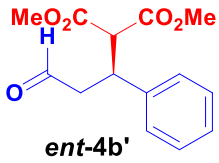
(viii) dimethyl (S)-2-(1-(2-nitrophenyl)-3-oxopropyl)malonate (4h'): Prepared using conditions mentioned in scheme S2. The titled compound is previously reported in the literature and spectroscopic data matches with the literature report.[8]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 9.66 (dd, *J* = 2.0, 1.4 Hz, 1H), 7.81 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.55 (tdd, *J* = 7.3, 1.4, 0.7 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.40 – 7.35 (m, 1H), 4.58 (td, *J* = 8.8, 5.1

Hz, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 3H), 3.10 (ddd, *J* = 17.5, 5.2, 1.4 Hz, 1H), 3.02 (ddd, *J* = 17.6, 8.7, 2.0 Hz, 1H). (ee = 58%) Enantiomeric excess determined after cyclisation with tryptamine (**5**).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 199.41, 168.13, 167.61, 150.38, 134.73, 133.04, 129.14, 128.48, 124.92, 56.14, 53.00, 52.94, 46.68, 33.79.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 220 nm): major enantiomer, t_R = 117.55 and minor enantiomer, t_R = 12.37.

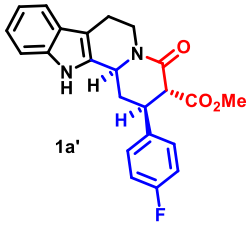


***ent*-4b'**

(ix) dimethyl (*S*)-2-(3-oxo-1-phenylpropyl)malonate (*ent*-4b'): A glass column of Omnifit with outer jacket (10 mm bore X 70 mm of adjustable bed height) and Omnifit PTFE frit at the bottom was packed with catalyst **8k** (500 mg, 0.2 mmol, *f* = 0.407 mmol/g). The outer jacket was circulated with oil (Ministat-Huber) for heating purpose. A check valve and back pressure regulator of 75 psi was also placed. The catalyst was swelled by passing dimethyl malonate at a flow rate of 0.2 mL/min for 20 minutes at 60 ^oC, bed height ~2 cm. In a vial, *trans*-cinnamaldehyde (30.30 mmol, 4 g, 1 equiv), dimethyl malonate (60.60 mmol, 8 g, 2 equiv) and acetic acid (18.18 mmol, 1.09 g, 0.6 equiv) were mixed and flowed at flow rate of 20 µL/min at 60 ^oC using Vapourtec SF-10 pump. After reaching a steady state the solution was collected for 4.5 hours. A volatile component was evaporated using a vacuum and residue was directly purified by silica gel chromatography (cyclohexane: ethyl acetate =10:90 or 30:70) to afford *ent*-**4b'** dimethyl (*S*)-2-(3-oxo-1-phenylpropyl)malonate (3.78 mmol pure product) as a colorless liquid with 92% ee. The unreacted *trans*-cinnamaldehyde was recovered back.

Productivity= Turnover frequency (TOF) = 18.9/4.5 = 4.2 $mmol_{prod}\ mmol_{resin}^{-1}\ h^{-1}$

HPLC (Chiralpak OJ-H, *n*-hexane/IPA (80:20), 1 mL/min, 220 nm): major enantiomer, t_R = 42.99 and minor enantiomer, t_R = 33.99.



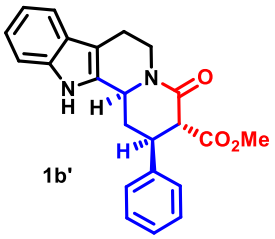
1a'

(x) **methyl (2*S*,3*R*,12b*S*)-2-(4-fluorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1a')**: The title compound prepared using experimental procedure mentioned in section 5(A). Compound **4a'** dimethyl (*S*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate (0.1 mmol, 28.2 mg, 1 equiv), tryptamine (**5**) (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol, 28.5 mg, 2.5 equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-2-(4-fluorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1a'**) (24.8 mg, 0.063 mmol) with 70% isolated yield and 92% ee. Yield was calculated based on collection of 18 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.31 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.22 – 7.08 (m, 4H), 7.01 (t, *J* = 8.6 Hz, 2H), 5.14 (ddd, *J* = 12.1, 4.5, 1.6 Hz, 1H), 4.97 (ddt, *J* = 11.5, 4.3, 1.9 Hz, 1H), 3.62 – 3.48 (m, 5H), 3.00 – 2.89 (m, 1H), 2.89 – 2.73 (m, 2H), 2.59 (ddd, *J* = 13.3, 4.6, 2.4 Hz, 1H), 2.03 (dt, *J* = 13.5, 12.1 Hz, 1H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 170.34, 165.04, 162.21 (d, *J* = 246.4 Hz), 136.78 (d, *J* = 3.3 Hz), 136.50, 132.28, 128.53 (d, *J* = 7.9 Hz), 126.76, 122.61, 120.16, 118.63, 116.05 (d, *J* = 21.5 Hz), 111.20, 109.65, 57.32, 53.98, 52.52, 40.56, 40.20, 35.64, 21.07.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 23.67 and minor enantiomer, t_R = 13.47.



1b'

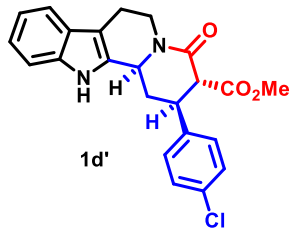
(xi) methyl (2*S*,3*R*,12b*S*)-4-oxo-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1b'): The title compound prepared using experimental procedure mentioned in section 5 (A). Compound **4b'** (dimethyl (*S*)-2-(3-oxo-1-phenylpropyl)malonate) (0.1 mmol, 26.4 mg, 1 equiv), tryptamine (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol, 28.5 mg, 2.5

equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-4-oxo-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1b'**) (20.1 mg, 0.053 mmol) with 60% isolated yield and 89% ee. Yield was calculated based on collection of 18 mL reaction mixture after reaching steady state. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.31 (ddd, *J* = 7.7, 4.9, 3.2 Hz, 3H), 7.27 – 7.21 (m, 1H), 7.17 (ddd, *J* = 7.9, 6.8, 1.4 Hz, 3H), 7.12 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 5.17 – 5.10 (m, 1H), 4.98 – 4.91 (m, 1H), 3.59 – 3.48 (m, 5H) 2.96 – 2.88 (m, 1H), 2.88 – 2.75 (m, 2H), 2.63 – 2.56 (m, 1H), 2.10 – 1.97 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.44, 165.25, 141.00, 136.51, 132.45, 129.14, 127.77, 126.93, 126.78, 122.52, 120.08, 118.59, 111.21, 109.54, 57.17, 54.03, 52.44, 40.89, 40.53, 35.57, 21.09.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 220 nm): major enantiomer, t_R =23.99 and minor enantiomer, t_R = 18.75.



1d'

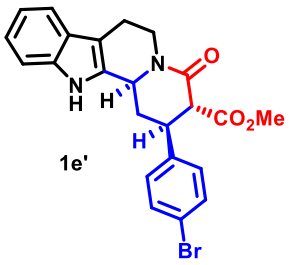
(xii) methyl (2*S*,3*R*,12b*S*)-2-(4-chlorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1d'): The title compound prepared using experimental procedure mentioned in section 5(A). Compound **4d'** dimethyl (*S*)-2-(1-(4-chlorophenyl)-3-oxopropyl)malonate (0.1 mmol, 29.9 mg, 1 equiv), tryptamine (**5**) (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol, 28.5 mg, 2.5 equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-2-(4-chlorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1d'**) (30.2 mg, 0.0738 mmol) with 82% isolated yield and 94% ee. Yield was calculated based on collection of 18 mL reaction mixture.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.46 – 7.35 (m, 5H), 7.30 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.99 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 5.09 (dd, *J* = 11.9, 4.5 Hz, 1H), 4.97 – 4.89 (m, 1H), 3.82 (d, *J* = 12.2 Hz, 1H), 3.58 – 3.44 (m, 4H), 2.95 (td, *J* = 12.4, 4.2 Hz, 1H), 2.77 (ddd, *J* = 13.8, 4.2, 2.5 Hz, 1H), 2.73 – 2.62 (m, 2H), 2.09 (td, *J* = 13.0, 11.6 Hz, 1H).

^{13}C-NMR (126 MHz, DMSO) δ 169.96, 164.36, 140.80, 136.20, 133.76, 131.71, 129.07, 128.60, 126.19, 121.16, 118.71, 117.83, 111.14, 106.93, 56.01, 53.46, 51.72, 34.28, 20.72.

HRMS (ESI) m/z calculated for $C_{23}H_{21}ClN_2O_3$ (M+Na)+: 431.1133, found: 431.1127.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 24.01 and minor enantiomer, t_R = 13.66.

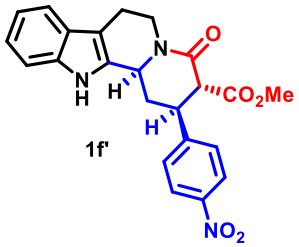


(xiii) methyl (2*S*,3*R*,12b*S*)-2-(4-bromophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1e'): The title compound prepared using experimental procedure mentioned in section 5(A). Compound **4e'** dimethyl (*S*)-2-(1-(4-bromophenyl)-3-oxopropyl)malonate (0.1 mmol, 34.3 mg, 1 equiv), tryptamine (**5**) (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol, 28.5 mg, 2.5 equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-2-(4-bromophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1e'**) (32 mg, 0.07 mmol) with 78% isolated yield and 93% ee. Yield was calculated based on collection of 18 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.57 – 7.49 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.25 (m, 3H), 7.06 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.08 (dd, *J* = 11.6, 4.5 Hz, 1H), 4.95 – 4.88 (m, 1H), 3.82 (d, *J* = 12.2 Hz, 1H), 3.59 – 3.42 (m, 4H), 2.95 (td, *J* = 12.4, 4.2 Hz, 1H), 2.77 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.68 (dddd, *J* = 21.1, 9.8, 5.1, 2.9 Hz, 2H), 2.08 (td, *J* = 13.0, 11.5 Hz, 1H).

^{13}C-NMR (126 MHz, DMSO) δ 169.94, 164.33, 141.21, 136.18, 133.75, 131.51, 129.42, 126.18, 121.15, 120.23, 118.70, 117.82, 111.13, 106.92, 55.93, 53.44, 51.72, 34.22, 20.71.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 28.6 and minor enantiomer, t_R = 15.41.

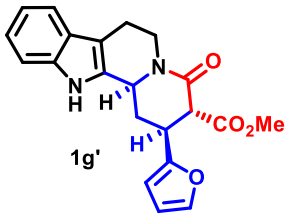


(xiv) methyl (2*S*,3*R*,12b*S*)-2-(4-nitrophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1f'): The title compound prepared using experimental procedure mentioned in section 5(A). Compound **4f'** dimethyl (*S*)-2-(1-(4-nitrophenyl)-3-oxopropyl)malonate (0.1 mmol, 30.9 mg, 1 equiv), tryptamine (**5**) (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol, 28.5 mg, 2.5 equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-2-(4-nitrophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1f'**) (32.5 mg, 0.077 mmol) with 88% isolated yield and 95% ee. Yield was calculated based on collection of 18 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 8.7 Hz, 2H), 8.09 (bs, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.31 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 5.14 (ddd, *J* = 12.3, 4.5, 1.7 Hz, 1H), 5.05 – 4.96 (m, 1H), 3.73 (td, *J* = 12.6, 2.6 Hz, 1H), 3.62 – 3.52 (m, 4H), 2.99 – 2.90 (m, 1H), 2.92 – 2.77 (m, 2H), 2.64 (ddd, *J* = 13.2, 4.6, 2.7 Hz, 1H), 2.10 (td, *J* = 13.1, 11.5 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 169.88, 164.36, 148.33, 147.54, 136.53, 131.84, 128.07, 126.71, 124.41, 122.77, 120.28, 118.68, 111.23, 109.85, 56.57, 53.88, 52.71, 40.74, 40.64, 35.12, 21.07.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 254 nm): major enantiomer, t_R = 74.96 and minor enantiomer, t_R =19.74.



(xv) methyl (2*S*,3*R*,12b*S*)-2-(furan-2-yl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1g'): The title compound prepared using experimental procedure mentioned in section 5(A). Compound **4g'** dimethyl (*S*)-2-(1-(furan-2-yl)-3-oxopropyl)malonate (0.1 mmol, 25.4 mg, 1 equiv), tryptamine (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol,

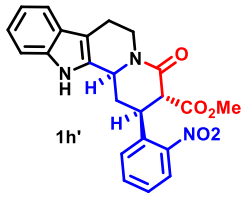
28.5 mg, 2.5 equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-2-(furan-2-yl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1g'**) (mg, 0.085 mmol) with 40% isolated yield and 70% ee. Yield was calculated based on collection of 18 mL reaction mixture.

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.57 – 7.48 (m, 1H), 7.35 (ddd, *J* = 5.0, 2.3, 1.5 Hz, 2H), 7.22 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.16 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.21 – 5.15 (m, 1H), 5.05 – 4.97 (m, 1H), 3.84 – 3.63 (m, 5H), 2.97 (td, *J* = 12.0, 11.5, 4.6 Hz, 1H), 2.92 – 2.78 (m, 3H), 2.01 (td, *J* = 13.0, 11.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.48, 164.65, 154.02, 142.30, 136.51, 132.18, 126.81, 122.61, 120.15, 118.64, 111.18, 110.47, 109.78, 105.70, 54.38, 53.59, 52.76, 40.54, 34.74, 33.45, 21.04.

HRMS (ESI) m/z calculated for $C_{21}H_{21}N_2O_4$ (M+H)+: 365.1496, found: 365.1493.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 14.35 and minor enantiomer, t_R = 10.93.

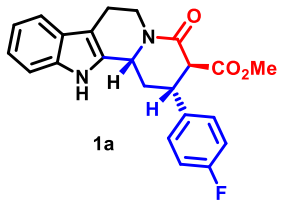


(xvi) methyl (2*S*,3*R*,12b*S*)-2-(2-nitrophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1h'): The title compound prepared using experimental procedure mentioned in section 5(A). Compound **4h'** dimethyl (*S*)-2-(1-(2-nitrophenyl)-3-oxopropyl)malonate (0.1 mmol, 30.9 mg, 1 equiv), tryptamine (0.15 mmol, 24 mg, 1.5 equiv), trifluoroacetic acid (0.25 mmol, 28.5 mg, 2.5 equiv) was used to afford methyl (2*S*,3*R*,12b*S*)-2-(2-nitrophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1h'**) (27 mg, 0.064 mmol) with 71% isolated yield and 58% ee. Yield was calculated based on collection of 18 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.88 (ddd, *J* = 10.7, 8.1, 1.3 Hz, 1H), 7.71 (td, *J* = 7.7, 1.4 Hz, 0H), 7.53 (ddd, *J* = 8.4, 7.4, 1.3 Hz, 0H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 0H), 5.13 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.96 – 4.88 (m, 1H), 4.07 (d, *J* = 12.0 Hz, 1H), 3.88 (td, *J* = 12.4, 2.4 Hz, 1H), 3.45 (s, 1H), 2.99 (td, *J* = 12.4, 4.2 Hz, 1H), 2.86 (ddd, *J* = 13.0, 4.8, 2.5 Hz, 1H), 2.79 (dd, *J* = 15.3, 3.9 Hz, 1H), 2.73 – 2.63 (m, 1H), 2.18 (q, *J* = 12.4 Hz, 1H).

^{13}C-NMR (126 MHz, DMSO) δ 169.42, 163.88, 149.70, 136.20, 134.55, 133.52, 133.22, 128.67, 128.53, 126.16, 123.83, 121.20, 118.73, 117.85, 111.14, 107.07, 55.26, 53.44, 51.81, 34.61, 33.99, 20.75, 20.71.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 117.55 and minor enantiomer, t_R = 12.37.



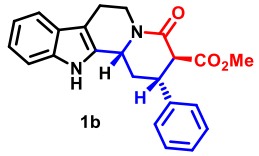
1a

(xvii) methyl (2*R*,3*S*,12b*R*)-2-(4-fluorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1a): The title compound prepared using experimental procedure mentioned in section 5(B). Compound **4a** dimethyl (*R*)-2-(1-(4-fluorophenyl)-3-oxopropyl)malonate (1 mmol, 282 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) was used to afford methyl (2*R*,3*S*,12b*R*)-2-(4-fluorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1a**) (255 mg, 0.649 mmol) with 72% isolated yield and 97% ee. Yield was calculated based on collection of 150 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.31 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.21 – 7.11 (m, 4H), 7.04 – 6.99 (m, 2H), 5.19 – 5.12 (m, 1H), 5.02 – 4.94 (m, 1H), 3.69 – 3.43 (m, 5H) 2.94 (td, *J* = 11.6, 4.4 Hz, 1H), 2.90 – 2.76 (m, 2H), 2.59 (ddd, *J* = 13.3, 4.6, 2.4 Hz, 1H), 2.14 – 1.93 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.19, 164.86, 163.08, 161.12, 136.66, 136.63, 136.35, 132.11, 128.43, 128.37, 126.67, 122.53, 120.09, 118.54, 116.02, 115.85, 111.03, 109.67, 57.15, 53.82, 52.39, 40.41, 40.10, 35.62, 20.95.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 11.70 and minor enantiomer, t_R = 18.78. The difference between the retention time of **1a** and ***ent-1a'*** is due to temperature.



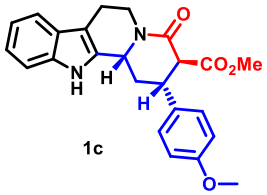
1b

(xviii) methyl (2*R*,3*S*,12b*R*)-4-oxo-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1b): The title compound prepared using experimental procedure mentioned in section 5(B). Compound **4b** (dimethyl (*R*)-2-(3-oxo-1-phenylpropyl)malonate) (1 mmol, 264 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) with flow rate = 0.1 mL/min each and residence time of 100 min to afford methyl (2*R*,3*S*,12b*R*)-4-oxo-2-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1b**) (200 mg, 0.587 mmol) with 65% isolated yield and 96% ee. Low yield was observed when same reaction performed with high flow rate of 0.2 mL/min each. Yield was calculated based on collection of 150 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.55 – 7.46 (m, 1H), 7.33 – 7.28 (m, 3H), 7.26 – 7.22 (m, 2H), 7.20 – 7.09 (m, 4H), 5.17 – 5.10 (m, 1H), 4.98 – 4.90 (m, 1H), 3.60 – 3.50 (m, 5H), 2.96 – 2.72 (m, 3H), 2.66 – 2.53 (m, 1H), 2.09 – 1.97 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.45, 165.26, 141.01, 136.51, 132.45, 129.14, 127.77, 126.93, 126.79, 122.53, 120.09, 118.60, 111.21, 109.55, 57.16, 54.03, 52.44, 40.89, 40.53, 35.58, 21.09.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 220 nm): major enantiomer, t_R = 18.26 and minor enantiomer, t_R = 23.83.



1c

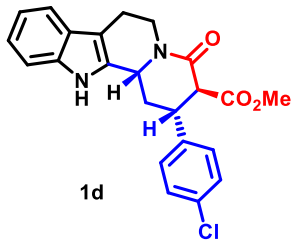
(xvix) methyl (2*R*,3*S*,12b*R*)-2-(4-methoxyphenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1c): The title compound prepared using experimental procedure mentioned in section 5(B). Compound **4c** dimethyl (*R*)-2-(1-(4-methoxyphenyl)-3-oxopropyl)malonate (1 mmol, 294 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) was used to afford methyl (2*R*,3*S*,12b*R*)-2-(4-methoxyphenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylat (**1c**) (200

mg, 0.494 mmol) with 55% isolated yield and 95% ee. Yield was calculated based on collection of 150 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.31 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.18 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.15 – 7.09 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.20 – 5.13 (m, 1H), 5.00 – 4.92 (m, 1H), 3.77 (s, 3H), 3.63 – 3.47 (m, 5H), 2.93 (td, *J* = 11.7, 4.1 Hz, 1H), 2.90 – 2.76 (m, 2H), 2.61 – 2.53 (m, 1H), 2.10 – 1.98 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.54, 165.31, 159.07, 136.48, 133.09, 132.48, 127.95, 126.84, 122.58, 120.16, 118.64, 114.50, 111.16, 109.70, 57.41, 55.40, 54.00, 52.48, 40.50, 40.14, 35.90, 21.10.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 220 nm): major enantiomer, t_R = 13.98 and minor enantiomer, t_R = 20.98.



1d

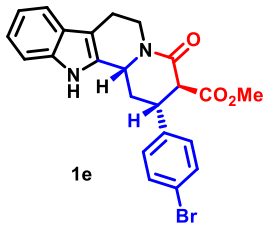
(xx) methyl (2*R*,3*S*,12b*R*)-2-(4-chlorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1d): The title compound prepared using experimental procedure mentioned in section 5(B). Compound **4d** dimethyl (*R*)-2-(1-(4-chlorophenyl)-3-oxopropyl)malonate (1 mmol, 298.7 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) was used to afford methyl (2*R*,3*S*,12b*R*)-2-(4-chlorophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1d**) (280 mg, 0.684 mmol) with 76% isolated yield and 97% ee. Yield was calculated based on collection of 150 mL reaction mixture.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.46 – 7.34 (m, 5H), 7.32 – 7.25 (m, 1H), 7.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 5.09 (dd, *J* = 11.6, 4.3 Hz, 1H), 4.97 – 4.86 (m, 1H), 3.83 (d, *J* = 12.2 Hz, 1H), 3.63 – 3.43 (m, 4H), 2.95 (td, *J* = 12.4, 4.2 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.74 – 2.62 (m, 2H), 2.14 – 2.04 (m, 1H).

^{13}C-NMR (126 MHz, DMSO) δ 169.95, 164.35, 140.79, 136.18, 133.76, 131.69, 129.06, 128.59, 126.18, 121.15, 118.70, 117.82, 111.13, 106.91, 55.99, 54.90, 53.45, 51.71, 34.27, 20.71.

HRMS (ESI) m/z calculated for $C_{23}H_{21}ClN_2O_3$ (M + Na): 431.1127, found: 411.1133

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 13.39 and minor enantiomer, t_R = 23.99.



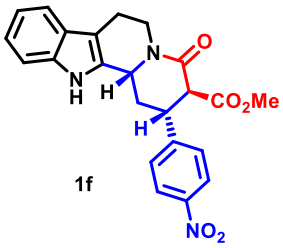
1e

(xxi) methyl (2*R*,3*S*,12b*R*)-2-(4-bromophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1e): The title compound prepared using experimental procedure mentioned in section 5(B). Compound **4e** dimethyl (*R*)-2-(1-(4-bromophenyl)-3-oxopropyl)malonate (1 mmol, 343 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) was used to afford methyl (2*R*,3*S*,12b*R*)-2-(4-bromophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1e**) (305 mg, 0.672 mmol) with 76% isolated yield and 92% ee. Yield was calculated based on collection of 150 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.26 (m, 3H), 7.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.98 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 5.12 – 5.05 (m, 1H), 4.97 – 4.88 (m, 1H), 3.82 (d, *J* = 12.2 Hz, 1H), 3.58 – 3.45 (m, 4H), 2.95 (td, *J* = 12.4, 4.2 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.73 – 2.61 (m, 2H), 2.17 – 2.01 (m, 1H).

^{13}C-NMR (126 MHz, DMSO) δ 169.94, 164.33, 141.21, 136.18, 133.75, 131.51, 129.42, 129.37, 126.18, 121.15, 120.22, 118.70, 117.82, 111.13, 106.91, 55.92, 53.44, 51.72, 34.21, 20.71.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 254 nm): major enantiomer, t_R = 14.83 and minor enantiomer, t_R = 28.51.



1f

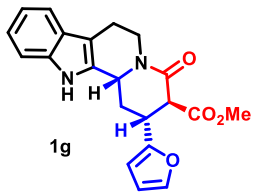
(xxii) methyl (2*R*,3*S*,12b*R*)-2-(4-nitrophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1f): The title compound prepared using experimental procedure

mentioned in section 5(B). Compound **4f,** dimethyl (*R*)-2-(1-(4-nitrophenyl)-3-oxopropyl)malonate (1 mmol, 309 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) was used to afford methyl (2*R*,3*S*,12b*R*)-2-(4-nitrophenyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1f**) (276 mg, 0.658 mmol) with 73% isolated yield and 91% ee. Yield was calculated based on collection of 150 mL reaction mixture. The spectroscopic data matches with previous report.[7]

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.8 Hz, 1H), 7.83 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.31 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 5.20 – 5.13 (m, 1H), 5.08 – 5.02 (m, 1H), 3.75 (td, *J* = 12.6, 2.7 Hz, 1H), 3.64 – 3.60 (m, 3H), 2.97 (td, *J* = 11.6, 4.5 Hz, 1H), 2.93 – 2.79 (m, 1H), 2.63 (ddd, *J* = 13.2, 4.6, 2.7 Hz, 1H), 2.19 – 2.09 (m, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 169.88, 164.31, 148.26, 147.61, 136.50, 131.76, 128.07, 126.78, 124.47, 122.87, 120.37, 118.76, 111.17, 110.14, 56.53, 53.84, 52.77, 40.78, 40.62, 35.32, 21.08.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 19.35 and minor enantiomer, t_R = 77.50.



1g

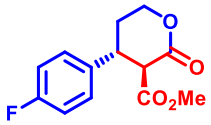
(xxiii) methyl (2*R*,3*S*,12b*R*)-2-(furan-2-yl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (1g): The title compound prepared using experimental procedure mentioned in section 5(B). Compound **4g** dimethyl (*R*)-2-(1-(furan-2-yl)-3-oxopropyl)malonate (1 mmol, 254 mg, 1 equiv), tryptamine (1.5 mmol, 240 mg, 1.5 equiv), trifluoroacetic acid (2.5 mmol, 285 mg, 2.5 equiv) was used to afford methyl (2*R*,3*S*,12b*R*)-2-(furan-2-yl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-3-carboxylate (**1g**) (174 mg, 0.477 mmol) with 53% isolated yield and 92% ee. Yield was calculated based on collection of 150 mL reaction mixture.

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.57 – 7.48 (m, 1H), 7.35 (ddd, *J* = 5.0, 2.3, 1.5 Hz, 2H), 7.22 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.16 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.21 – 5.15 (m, 1H), 5.05 – 4.97 (m, 1H), 3.84 – 3.63 (m, 5H), 2.97 (td, *J* = 12.0, 11.5, 4.6 Hz, 1H), 2.92 – 2.78 (m, 3H), 2.01 (td, *J* = 13.0, 11.7 Hz, 1H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 170.48, 164.65, 154.02, 142.30, 136.51, 132.18, 126.81, 122.61, 120.15, 118.64, 111.18, 110.47, 109.78, 105.70, 54.38, 53.59, 52.76, 40.54, 34.74, 33.45, 21.04.

HRMS (ESI) m/z calculated for $C_{21}H_{21}N_2O_4$ (M+H)+: 365.1496, found: 365.1493.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 0.6 mL/min, 280 nm): major enantiomer, t_R = 10.99 and minor enantiomer, t_R = 14.76.



6

(xxiv) methyl (3*R*,4*R*)-4-(4-fluorophenyl)-2-oxotetrahydro-2*H*-pyran-3-carboxylate (6): The titled compound prepared using experimental procedure shown in section 6.

^{1}H-NMR (500 MHz, Chloroform-*d*) δ 7.21 – 7.14 (m, 2H), 7.07 – 6.97 (m, 2H), 4.54 (ddd, *J* = 11.6, 5.0, 3.9 Hz, 1H), 4.47 (ddd, *J* = 11.6, 10.2, 4.0 Hz, 1H), 3.70 – 3.53 (m, 5H), 2.24 – 2.06 (m, 2H).

^{13}C-NMR (126 MHz, Chloroform-*d*) δ 162.22 (d, *J* = 246.7 Hz), 136.81 (d, *J* = 3.3 Hz), 128.49 (d, *J* = 8.2 Hz), 116.13 (d, *J* = 21.5 Hz), 68.91, 55.38, 52.88, 40.61, 30.02.

^{19}F-NMR (471 MHz, $CDCl_3$) δ -114.44 (multiple signals).

HRMS (ESI) m/z calculated for $C_{13}H_{13}FO_4$ (M+Na)+ :275.0690, found: 275.0693.

HPLC (Chiralpak AD-H, *n*-hexane/IPA (70:30), 1 mL/min, 280 nm): major enantiomer, t_R = 8.62 and minor enantiomer, t_R = 10.90.

7. NMR Spectra and HPLC chromatograms:

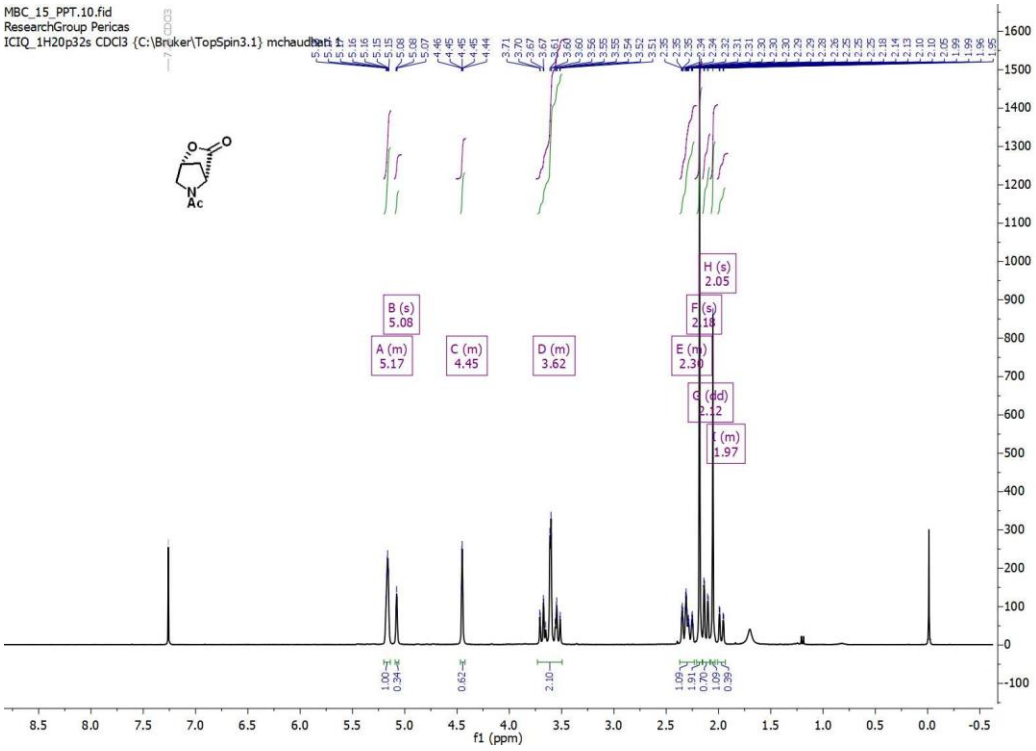


Figure S12. ^{1}H-NMR of compound **ii** (Scheme S1)

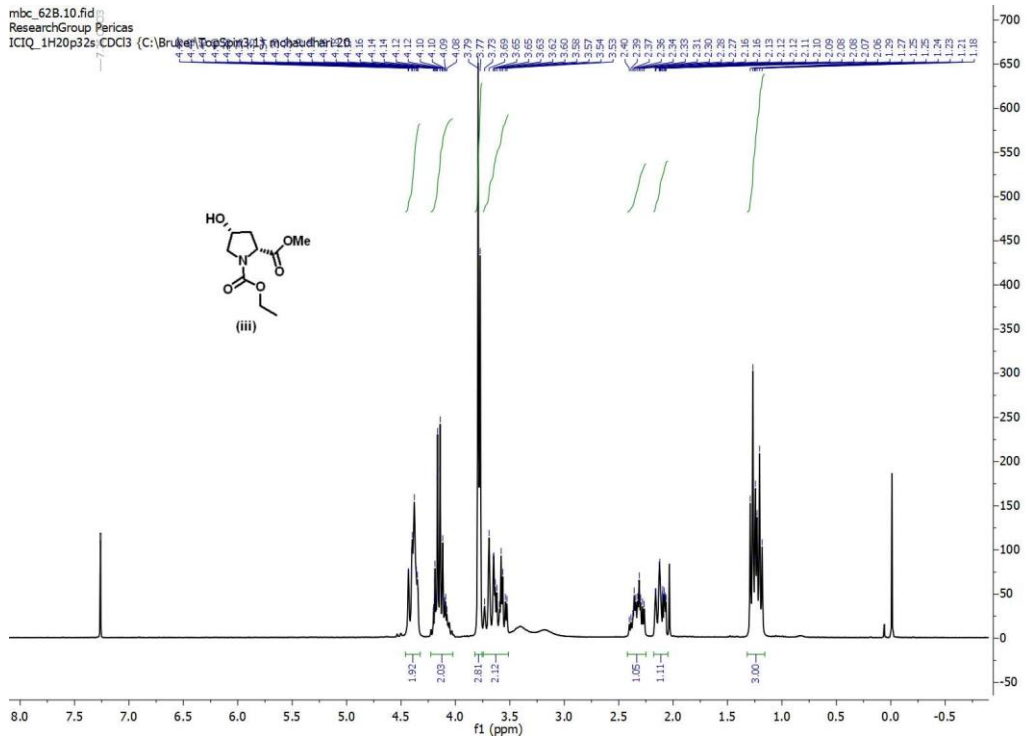


Figure S13. ^{1}H-NMR of compound **iii** (Scheme S1)

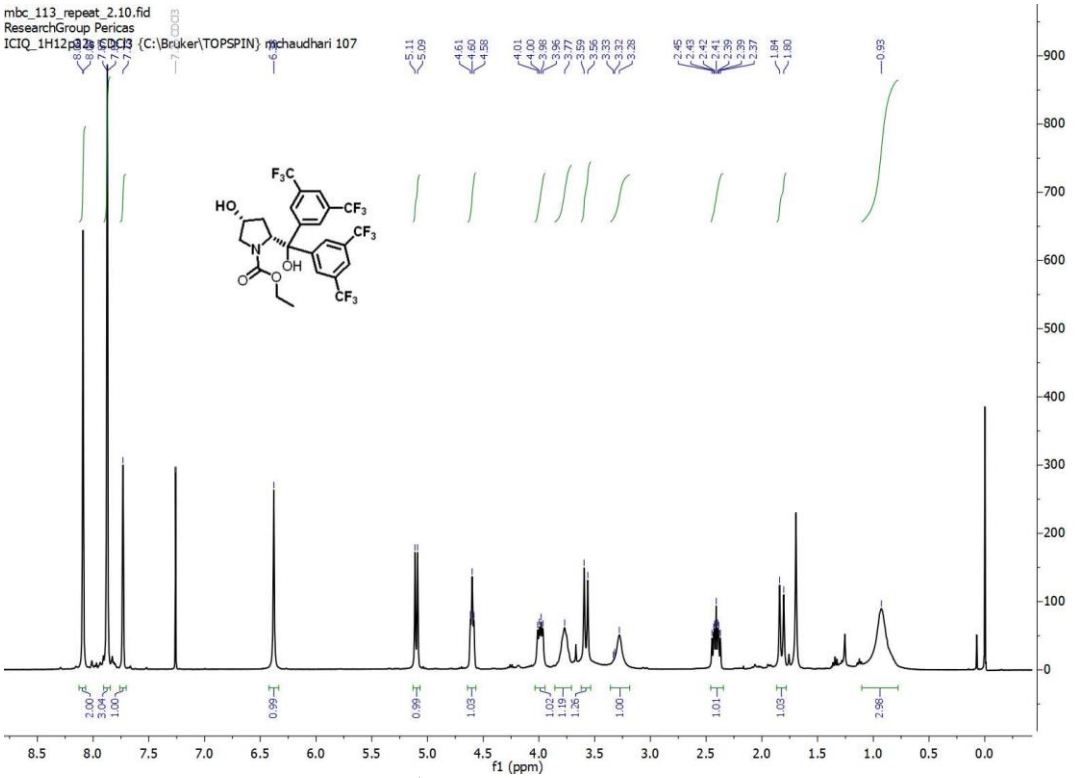


Figure S14. ^{1}H-NMR of compound **iv** (Scheme S1)

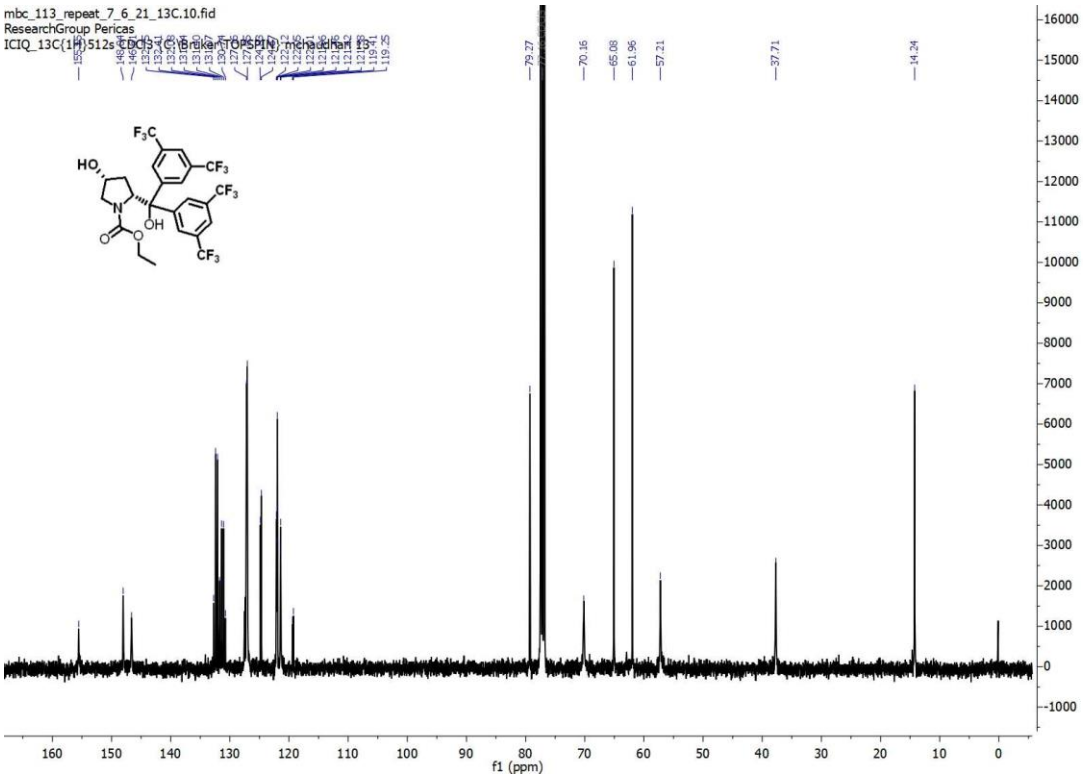


Figure S15. ^{13}C-NMR of compound **iv** (Scheme S1)

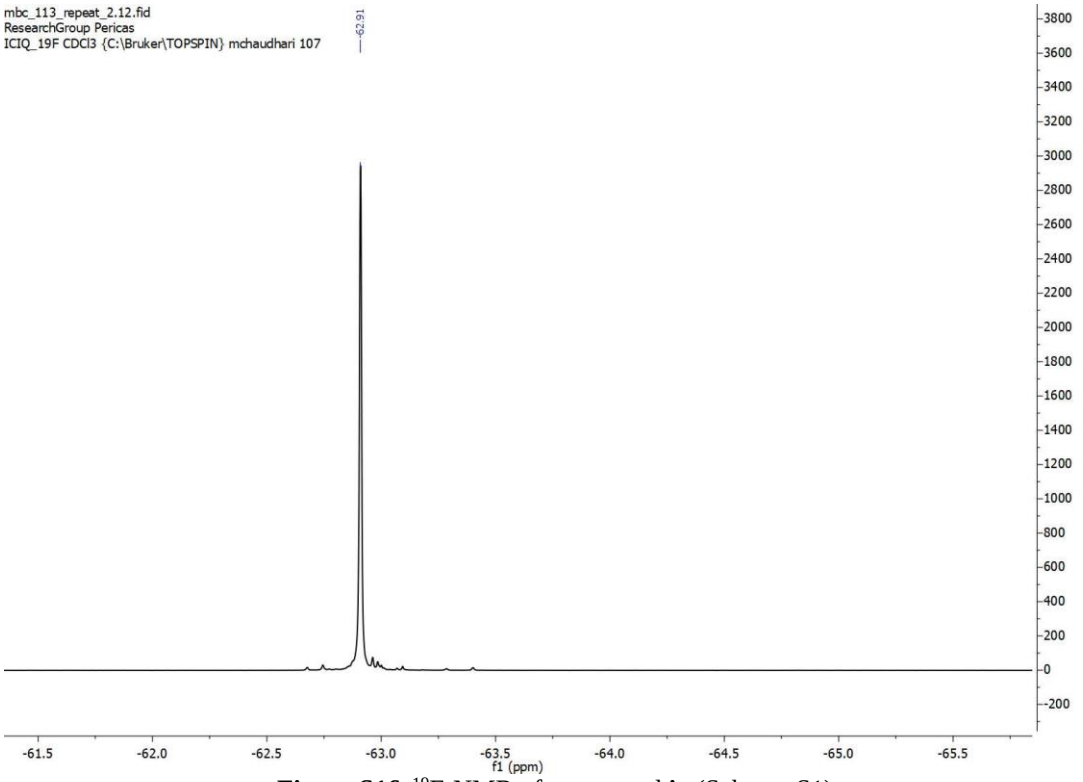


Figure S16. ^{19}F-NMR of compound **iv** (Scheme S1)

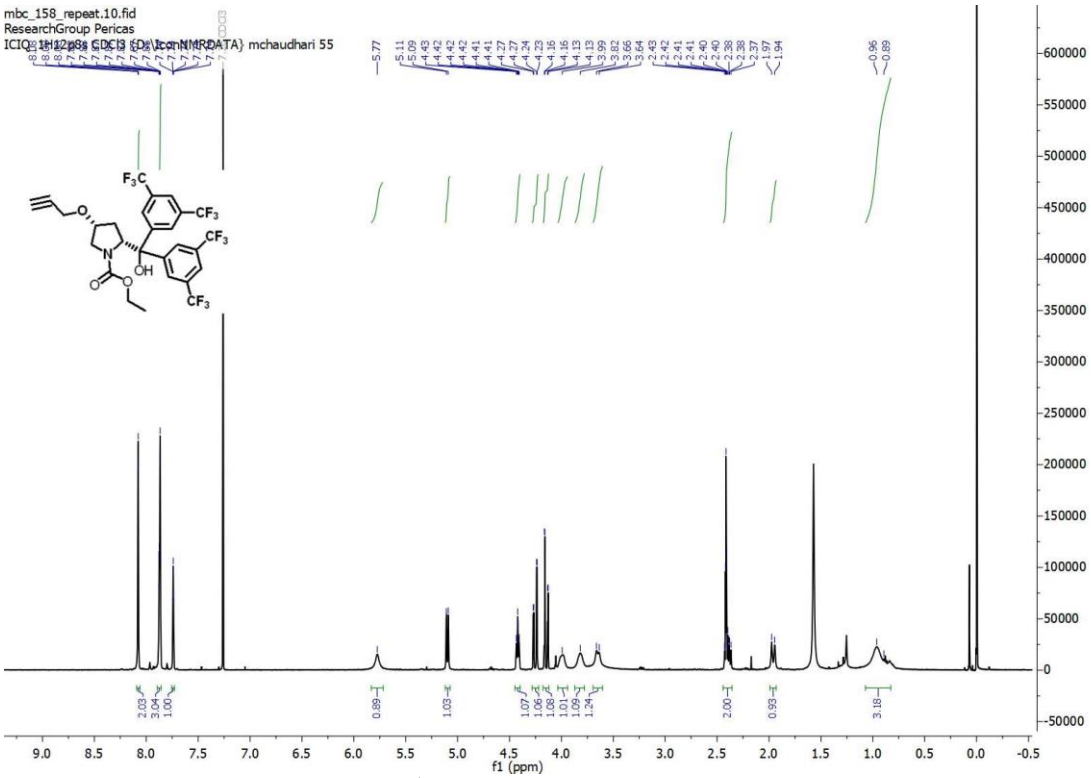


Figure S17. ^{1}H-NMR of compound **vi** (Scheme S1)

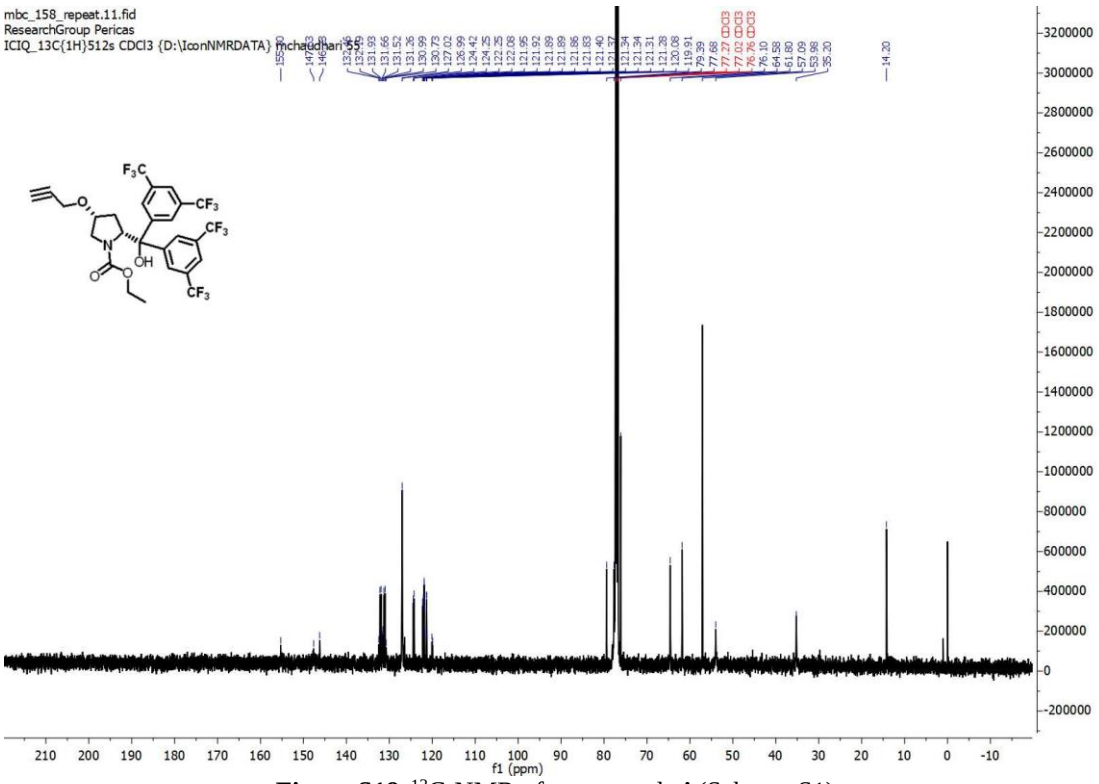


Figure S18. ^{13}C-NMR of compound **vi** (Scheme S1)

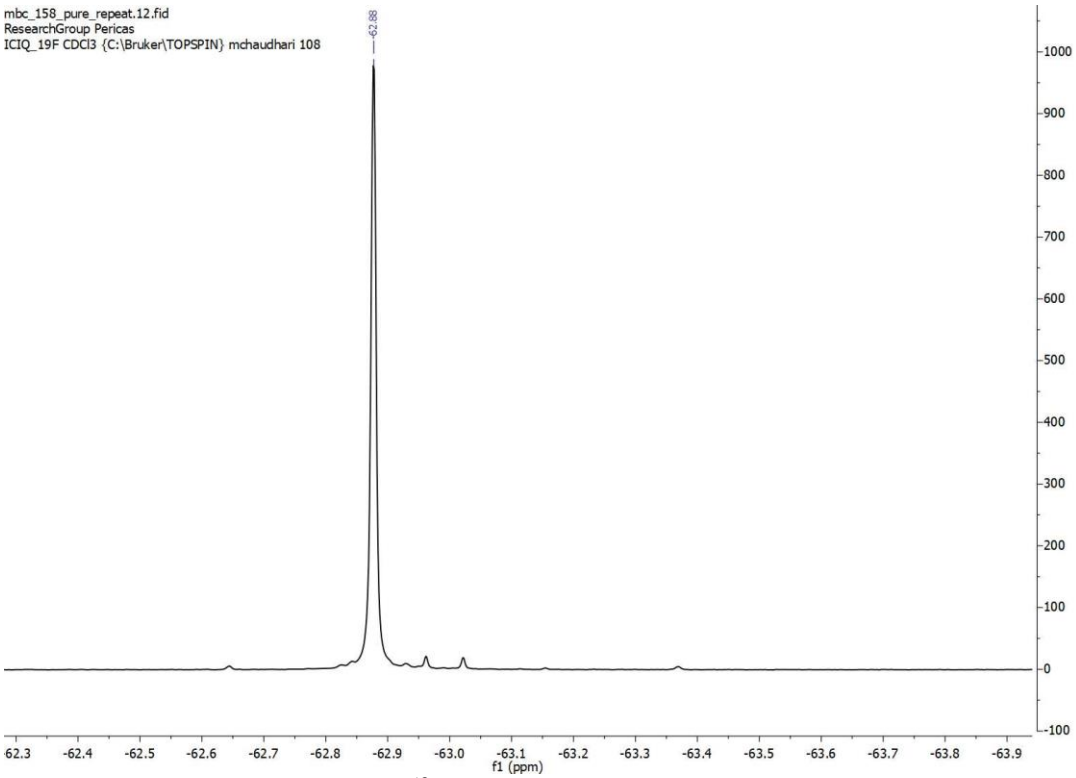


Figure S19. ^{19}F-NMR of compound **vi** (Scheme S1)

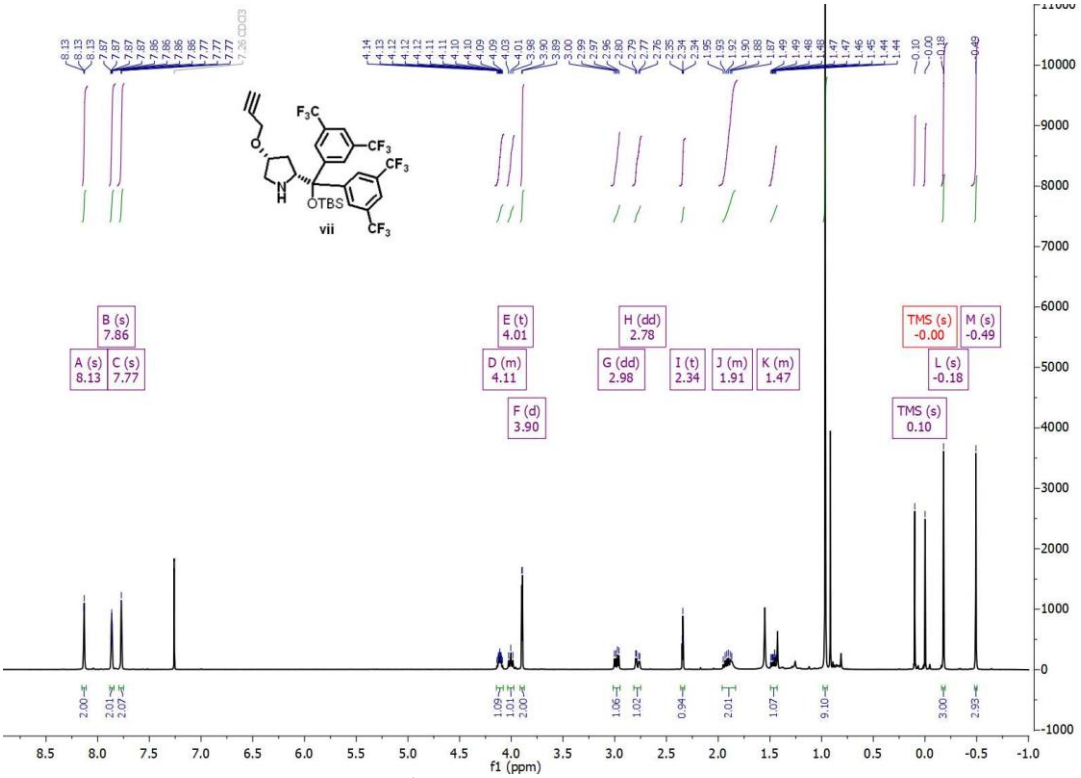


Figure S20. ^{1}H-NMR of compound **vii** (Scheme S1)

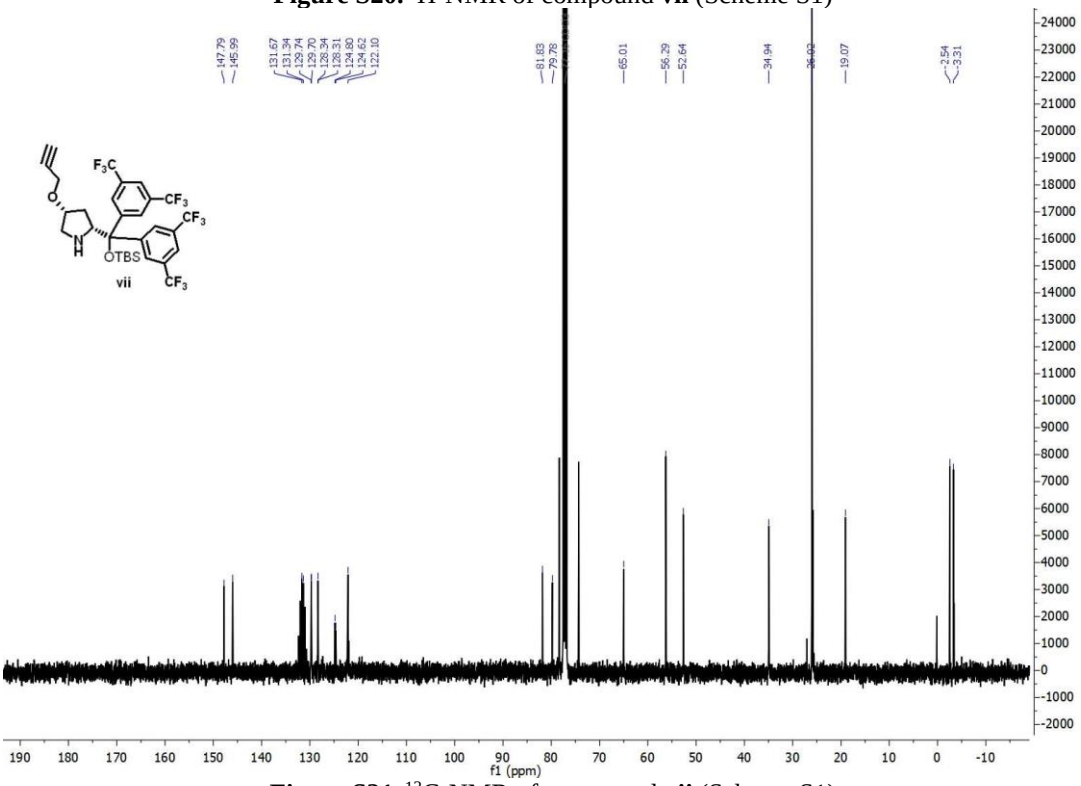


Figure S21. ^{13}C-NMR of compound **vii** (Scheme S1)

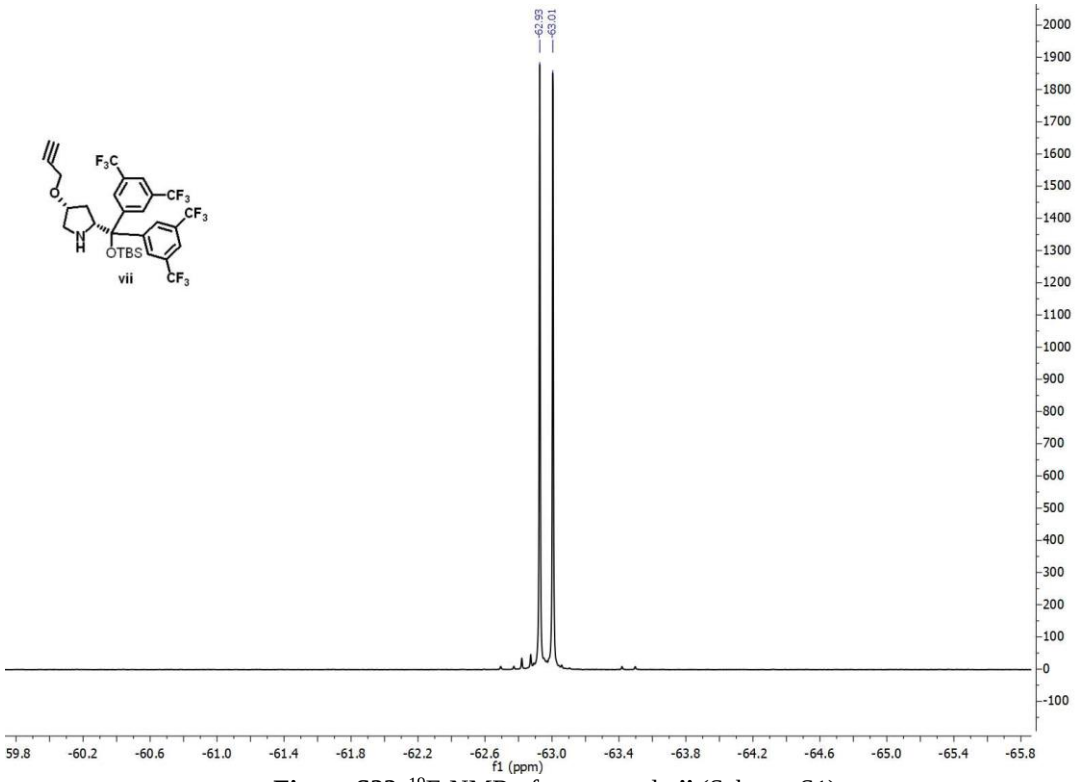


Figure S22. ^{19}F-NMR of compound **vii** (Scheme S1)

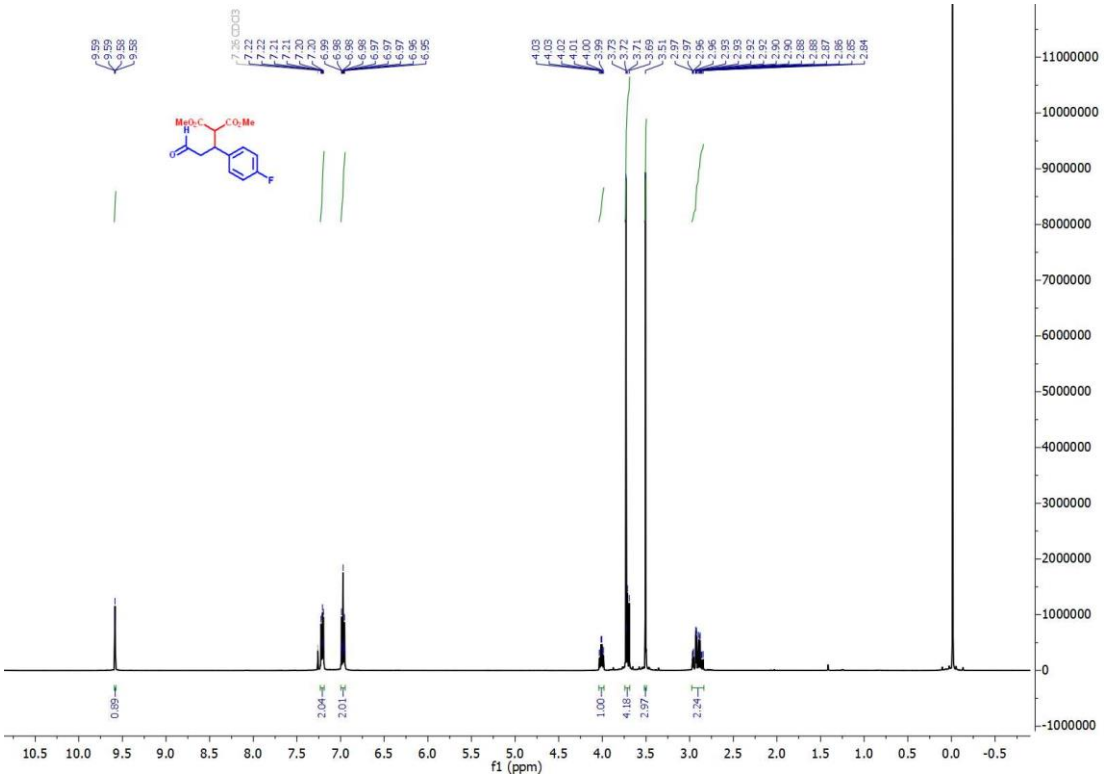


Figure S23. ^{1}H NMR of Compound **4a**

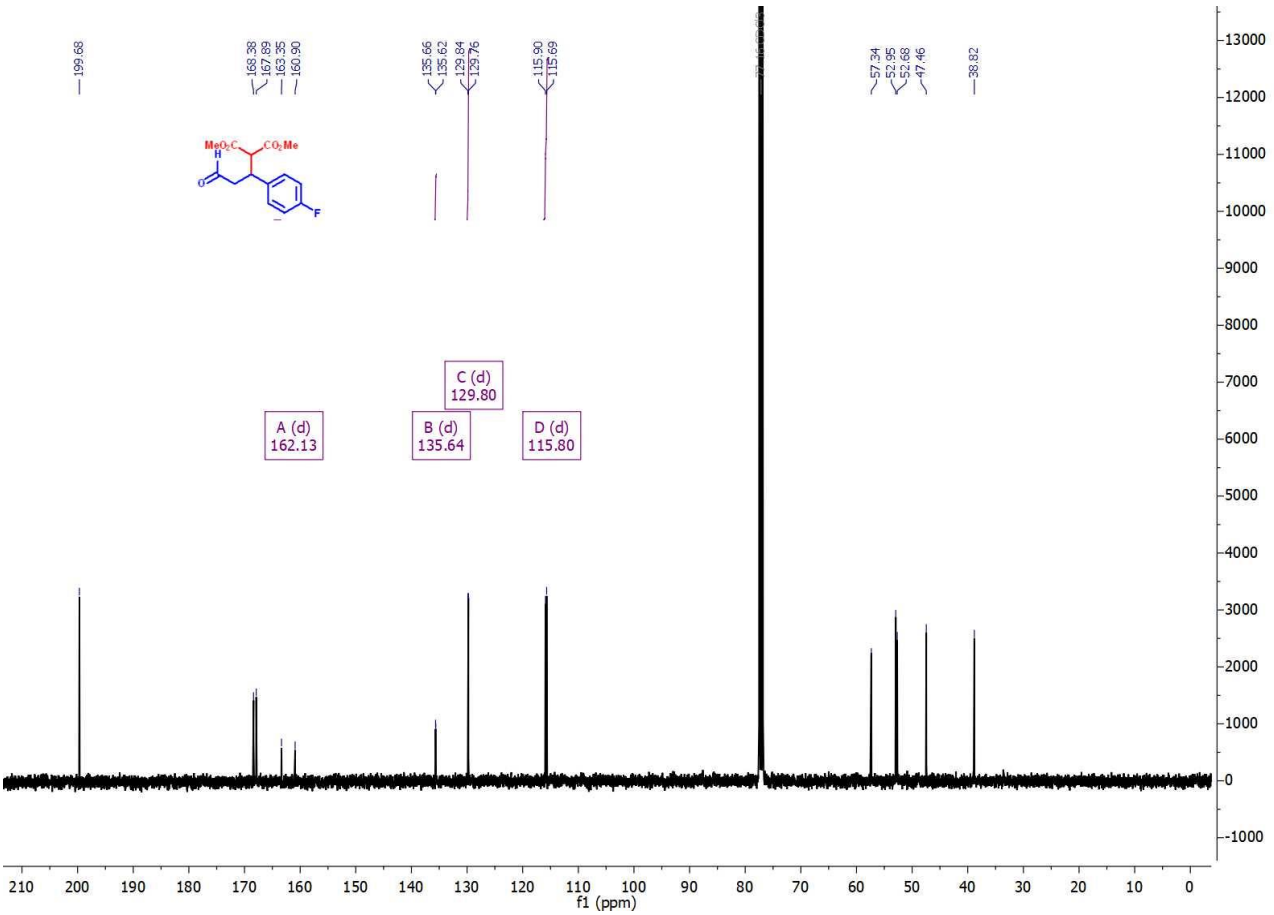


Figure S24. ^{13}C NMR of Compound **4a**

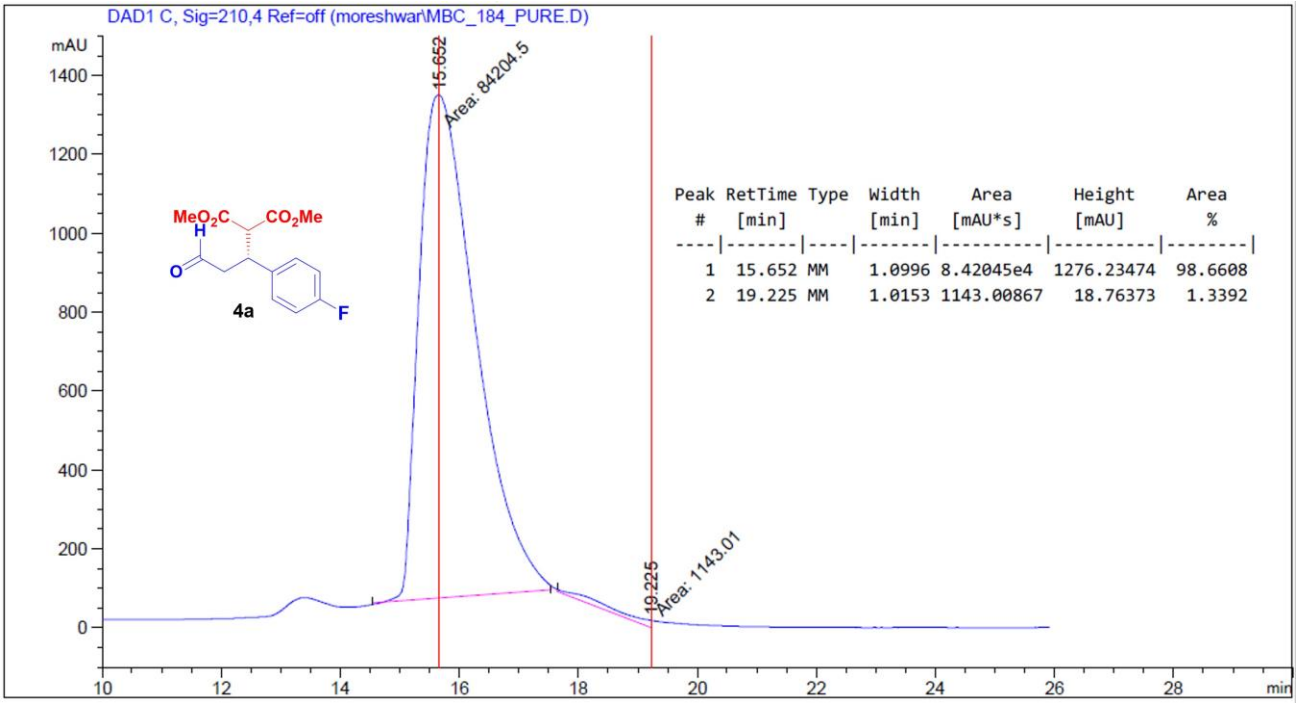


Figure S25. HPLC chromatogram for **4a**

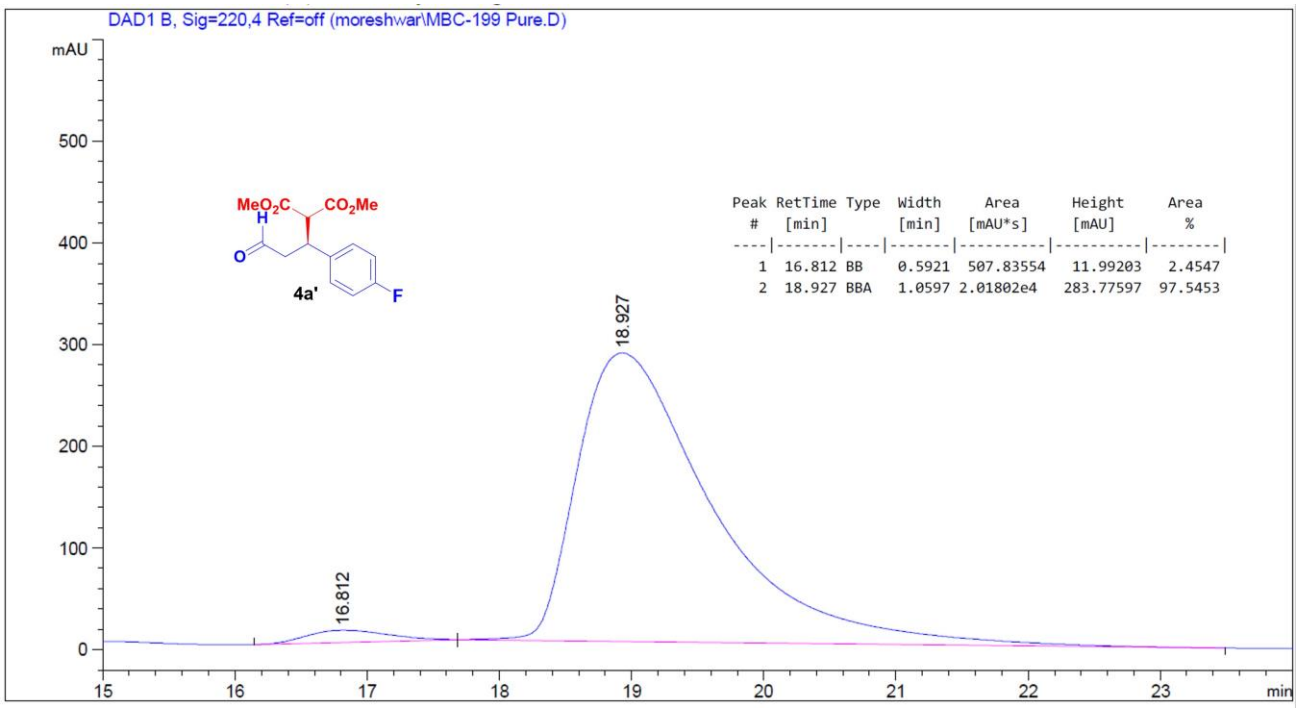


Figure S26. HPLC chromatogram for **4a'**

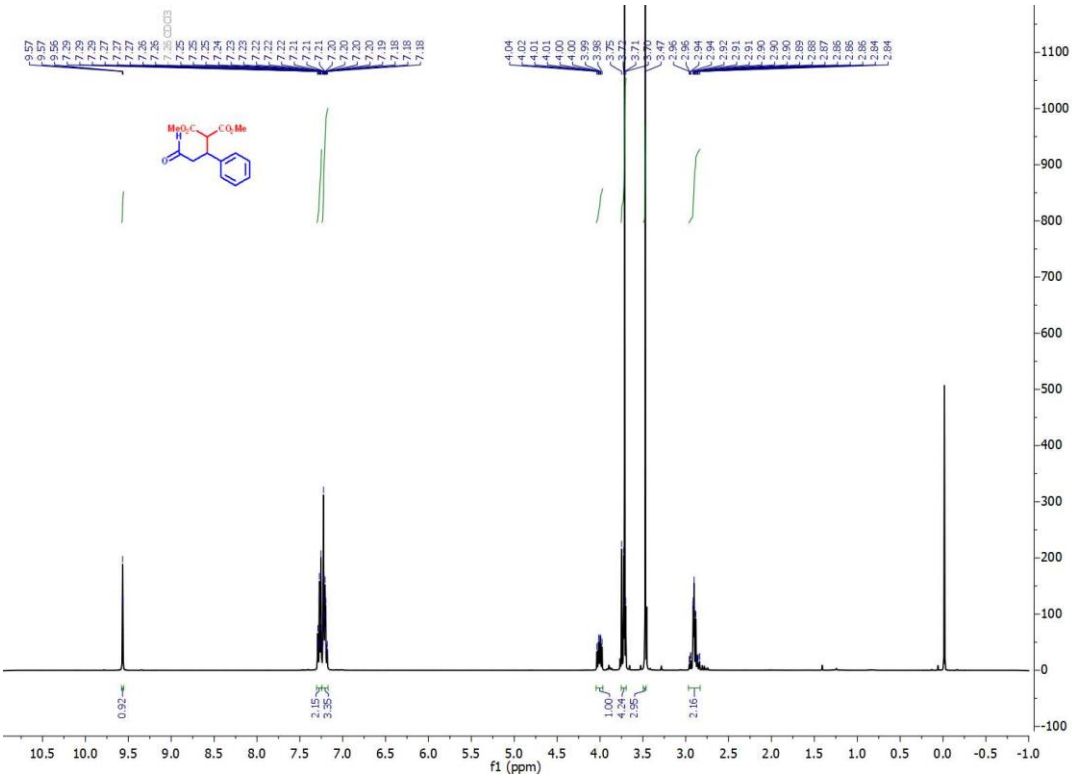


Figure S27. ^{1}H NMR of Compound **4b**

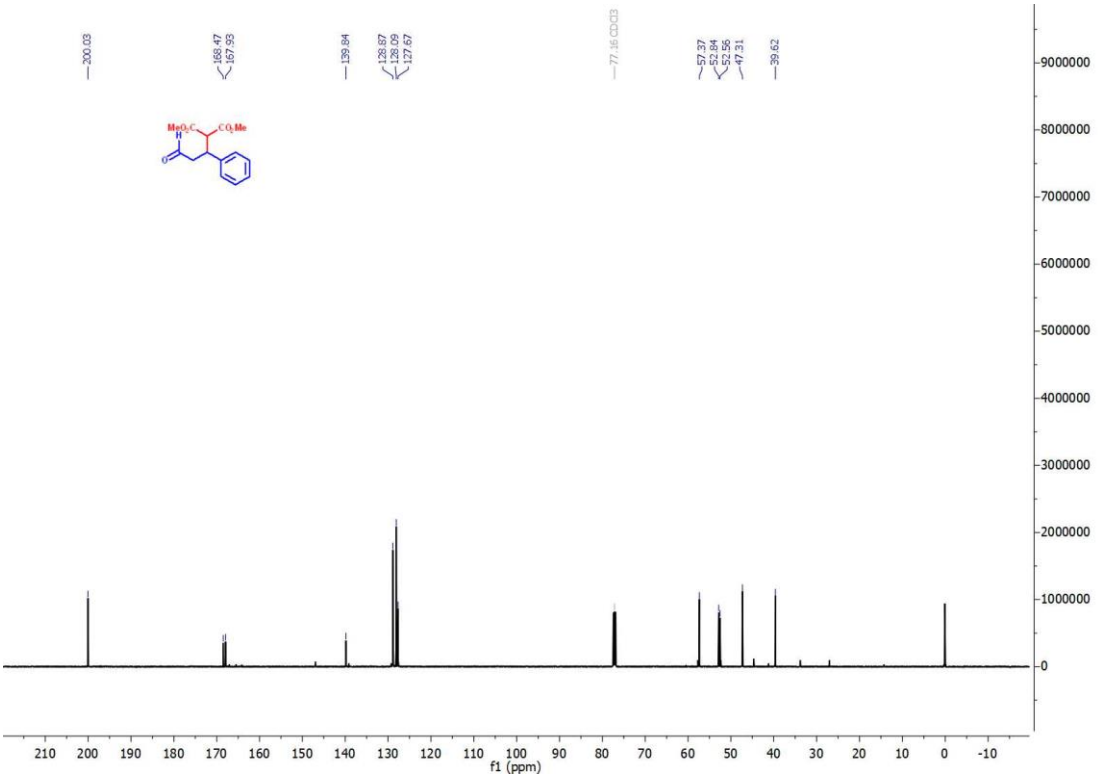


Figure S28. ^{13}C NMR of Compound **4b**

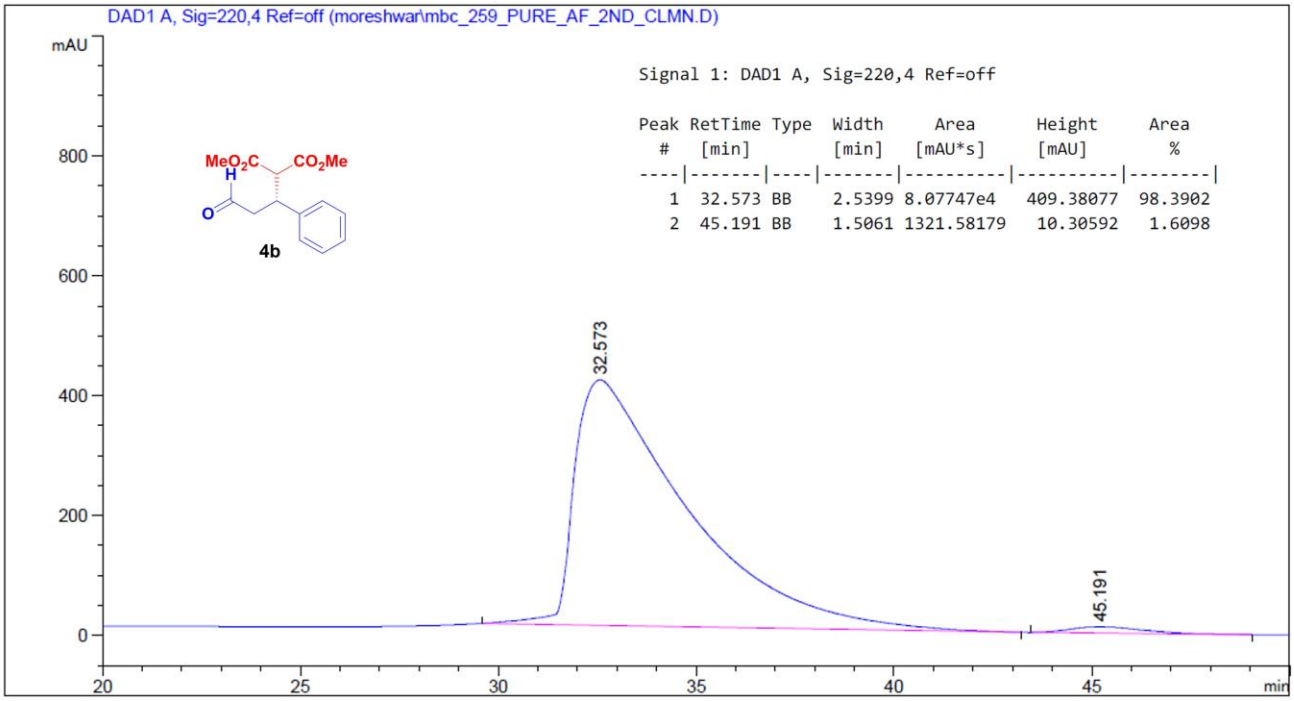


Figure S29. HPLC chromatogram for **4b**

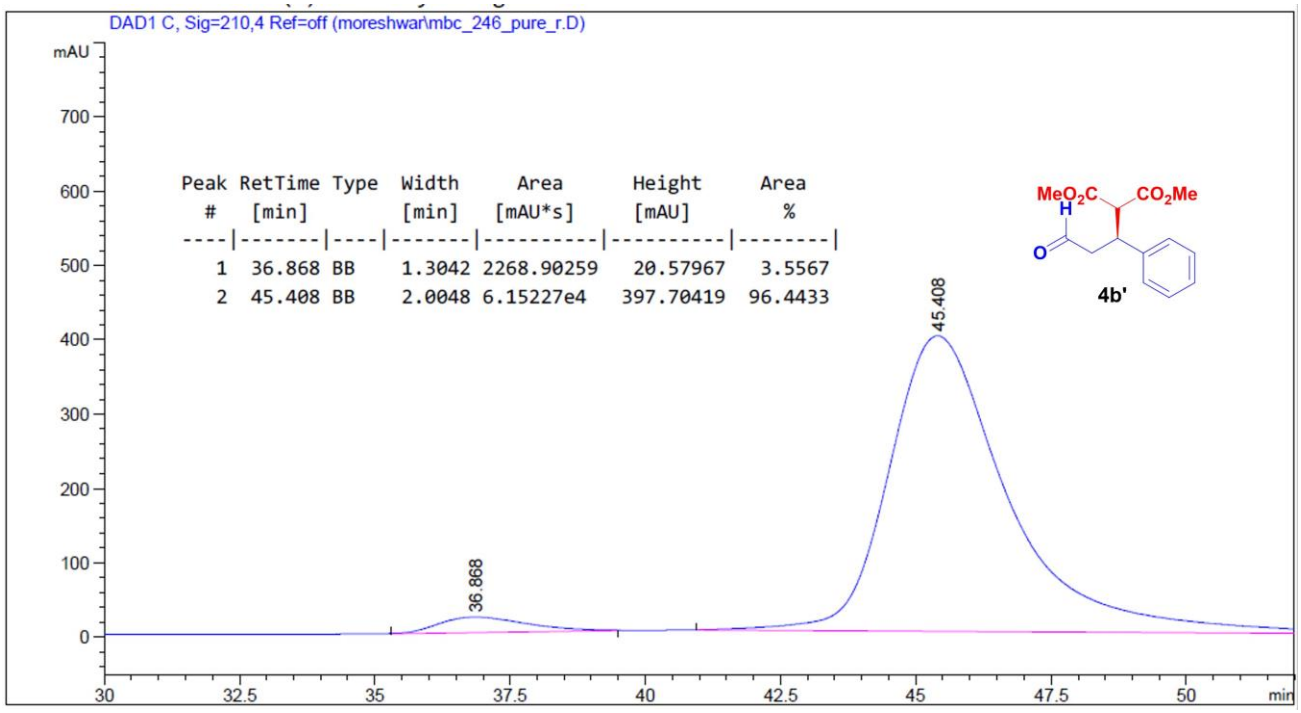


Figure S30. HPLC chromatogram for **4b'**

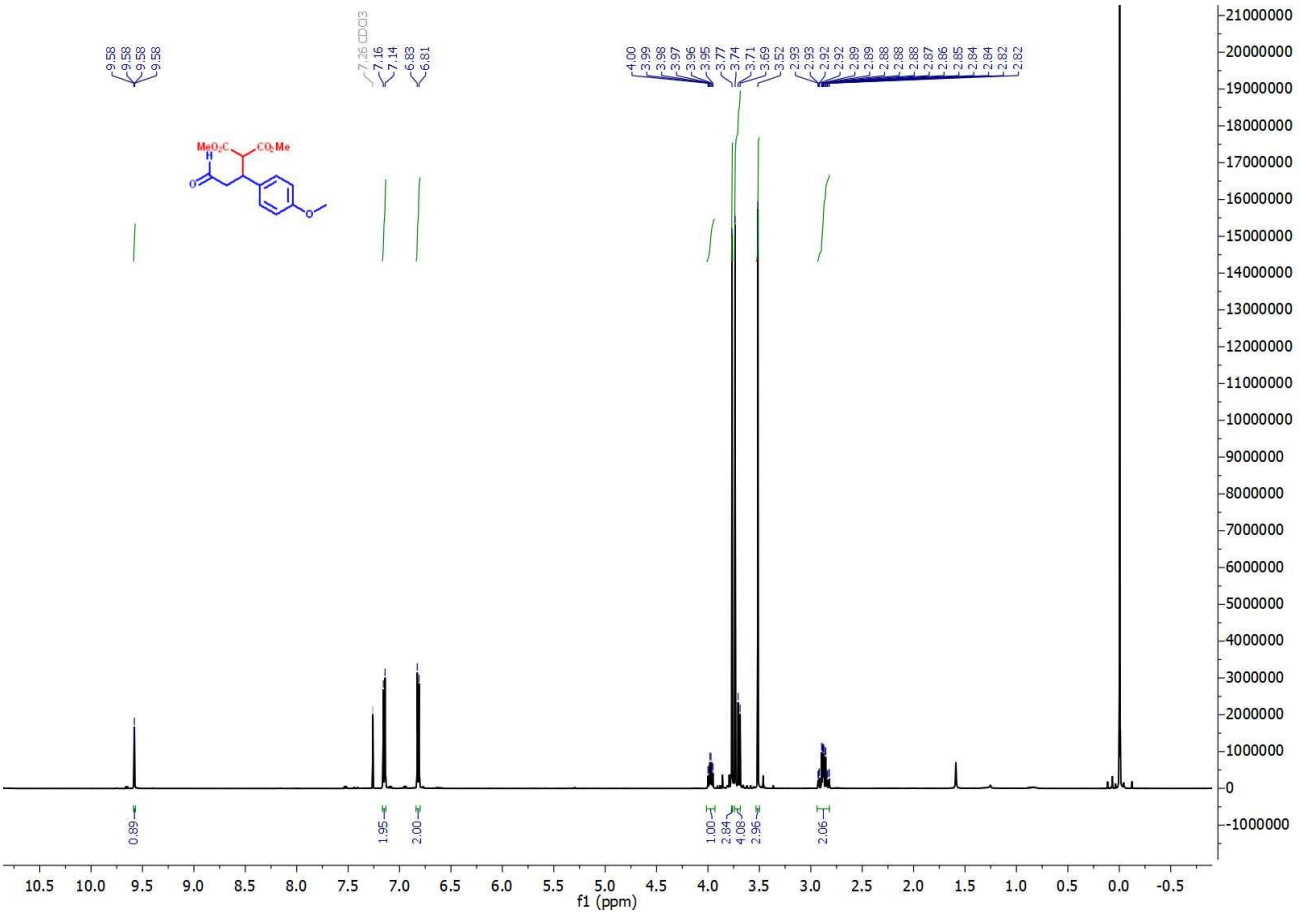


Figure S31. ^{1}H NMR of Compound **4c**

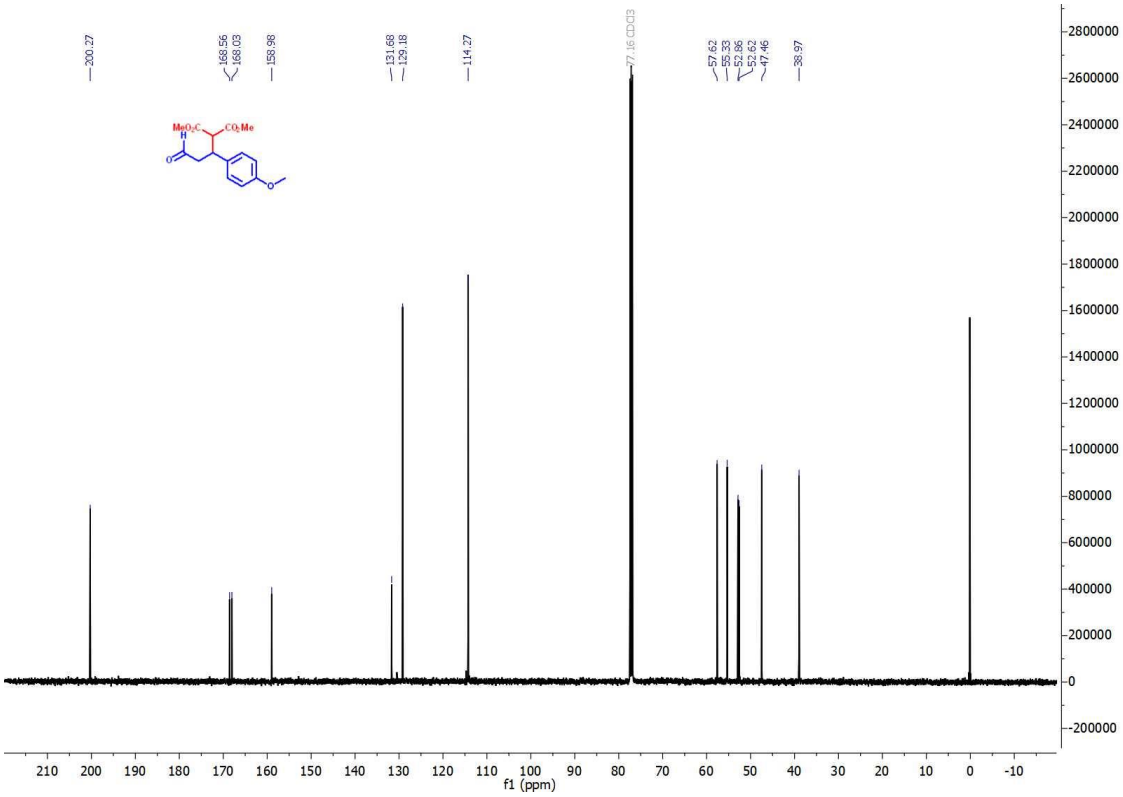


Figure S32. ^{13}C NMR of Compound **4c**

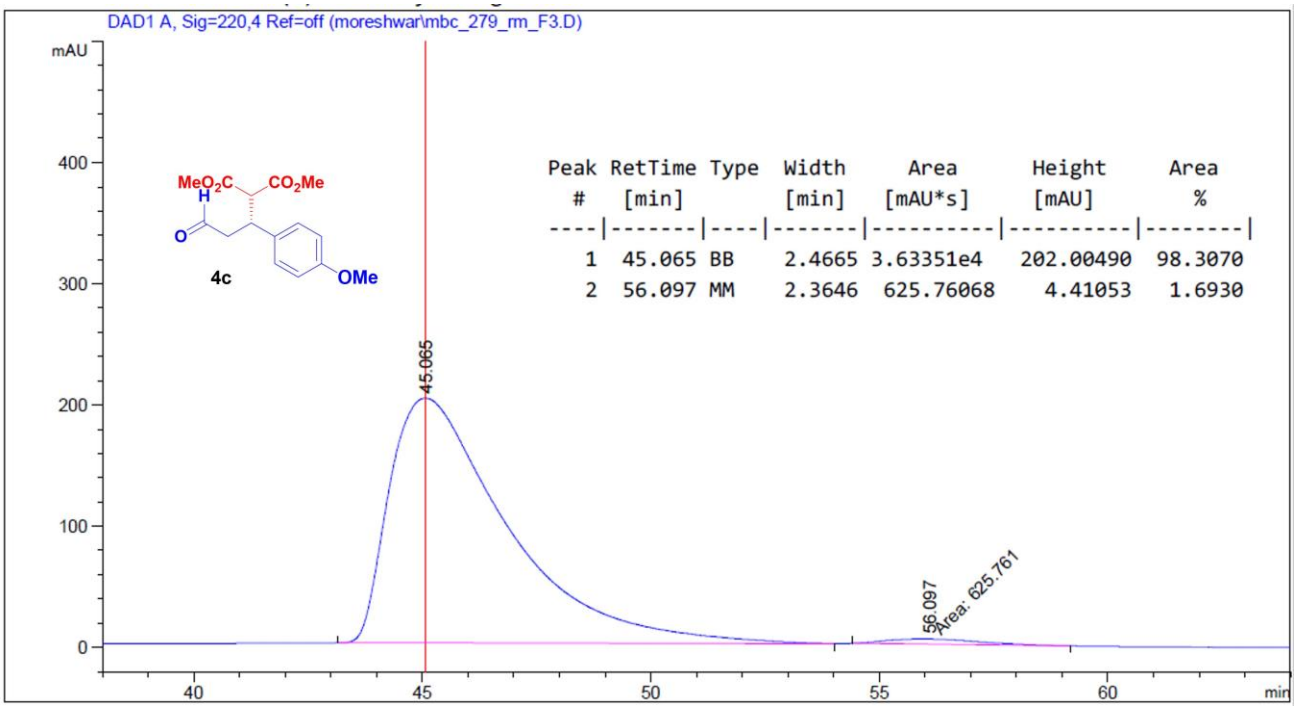


Figure S33. HPLC chromatogram for **4c**

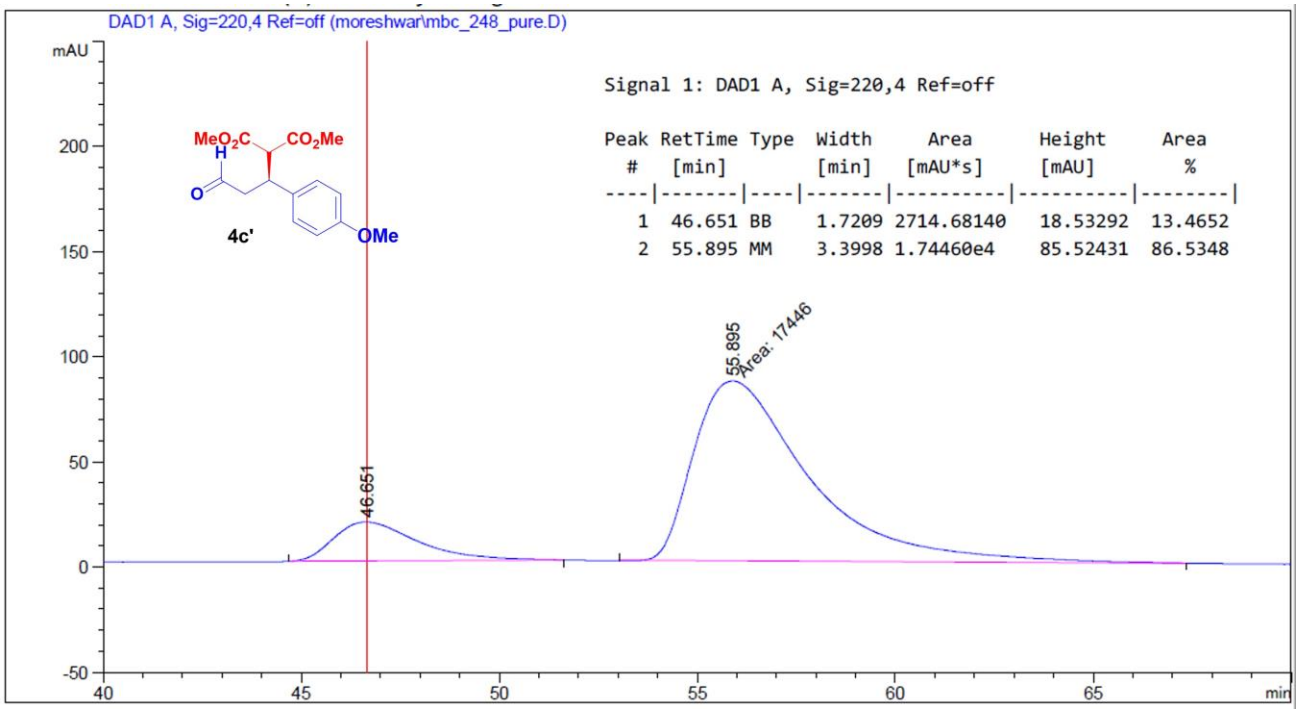


Figure S34. HPLC chromatogram for **4c'**

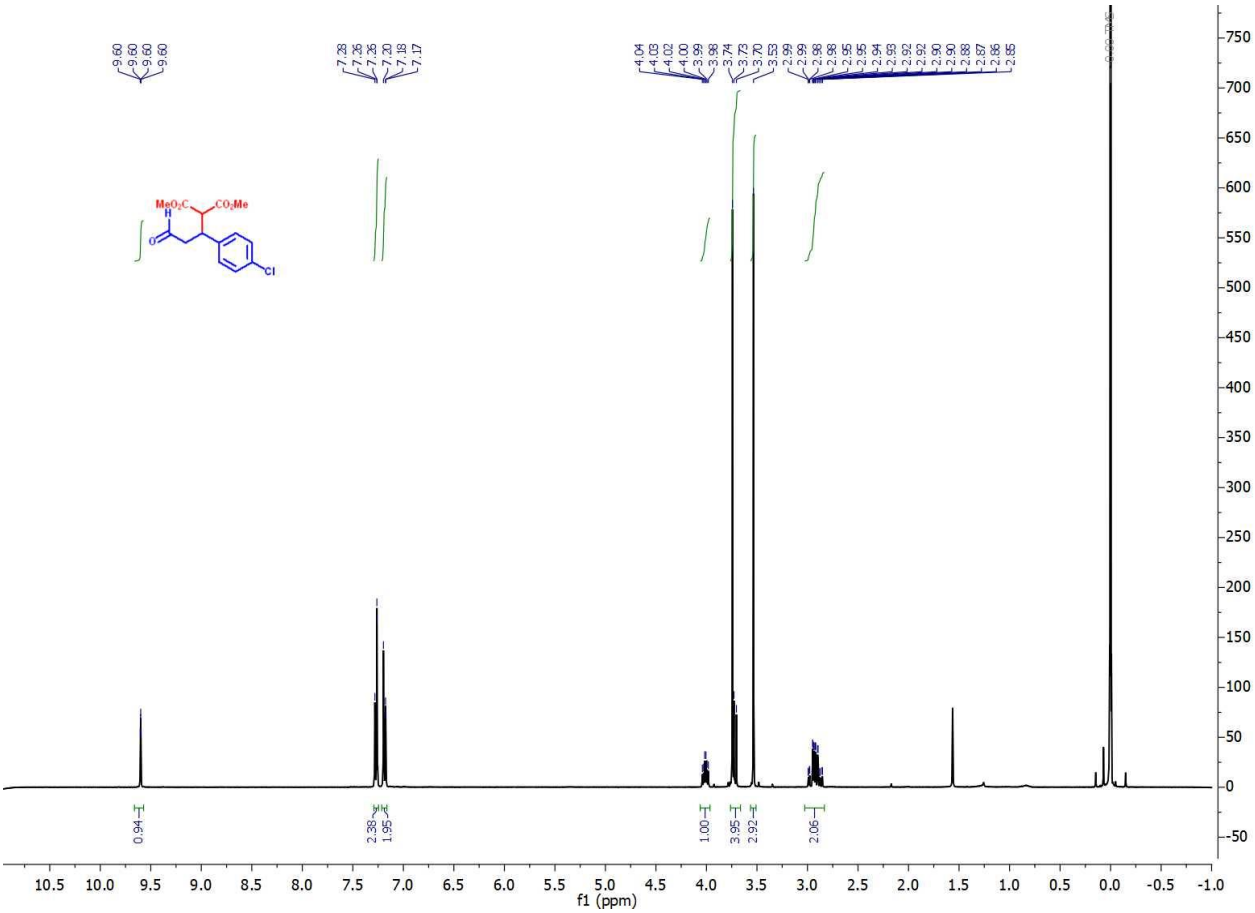


Figure S35. ^{1}H NMR of Compound **4d**

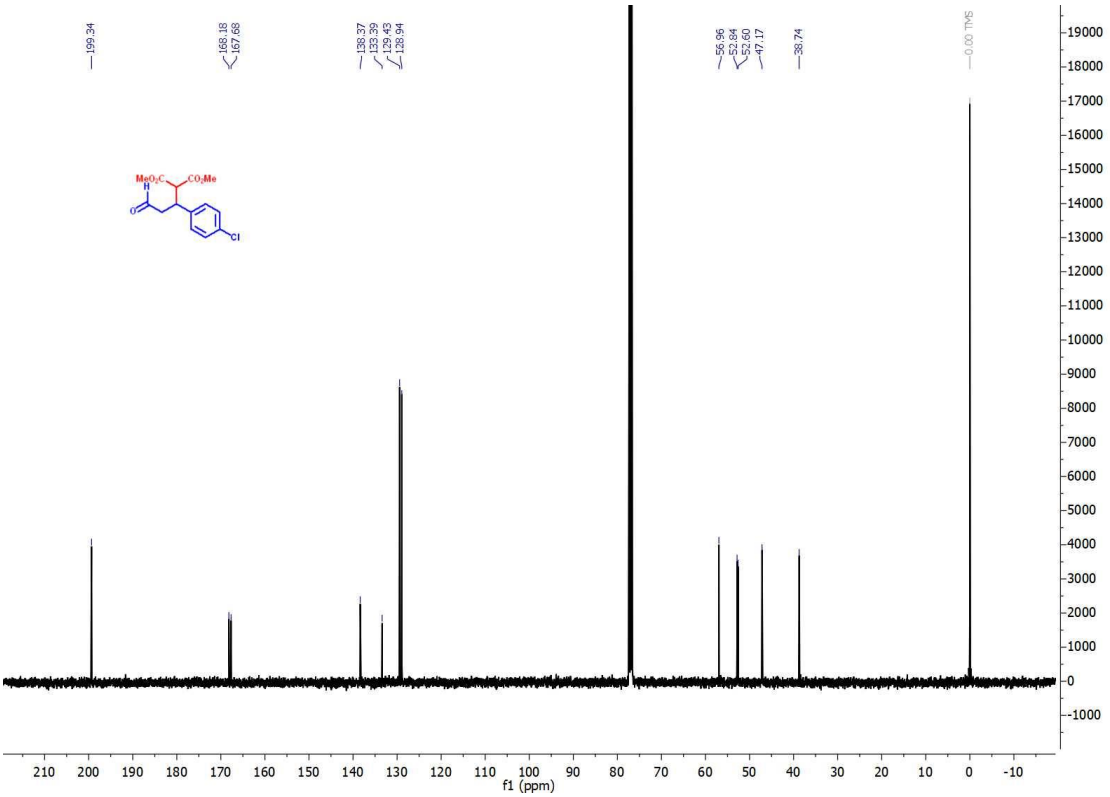


Figure S36. ^{13}C NMR of Compound **4d**

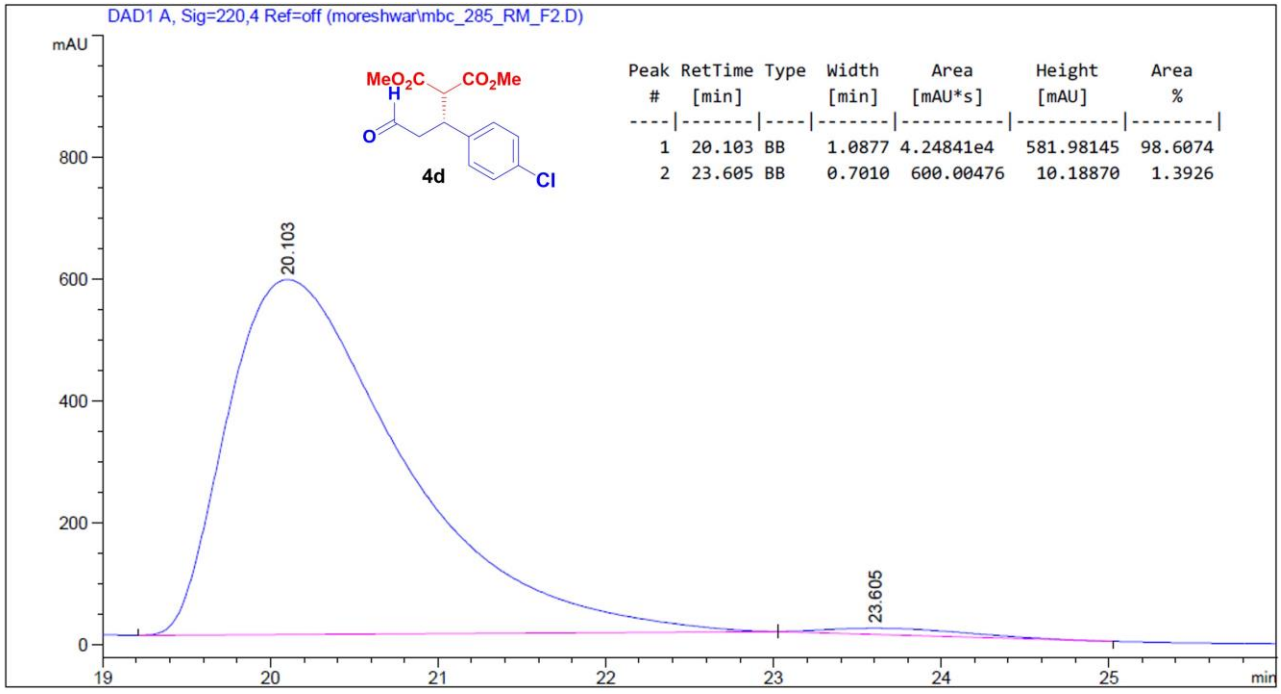


Figure S37. HPLC chromatogram for **4d**

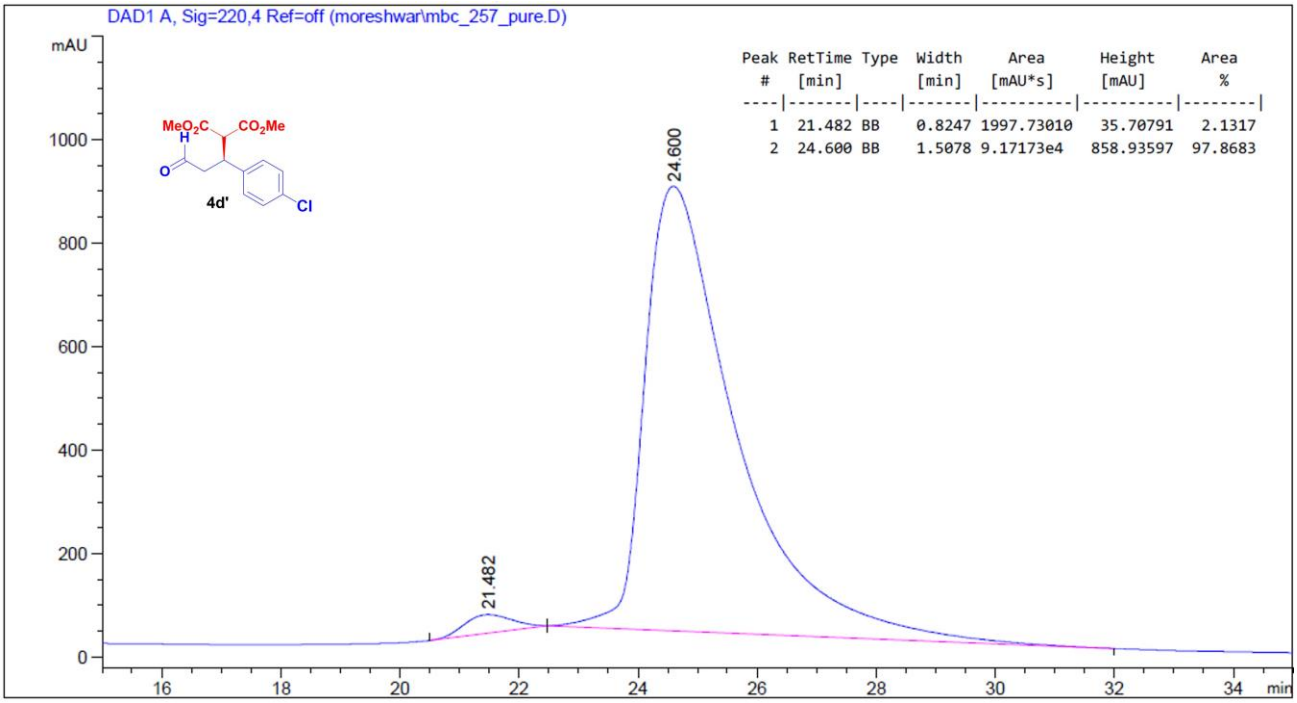


Figure S38. HPLC chromatogram for **4d'**

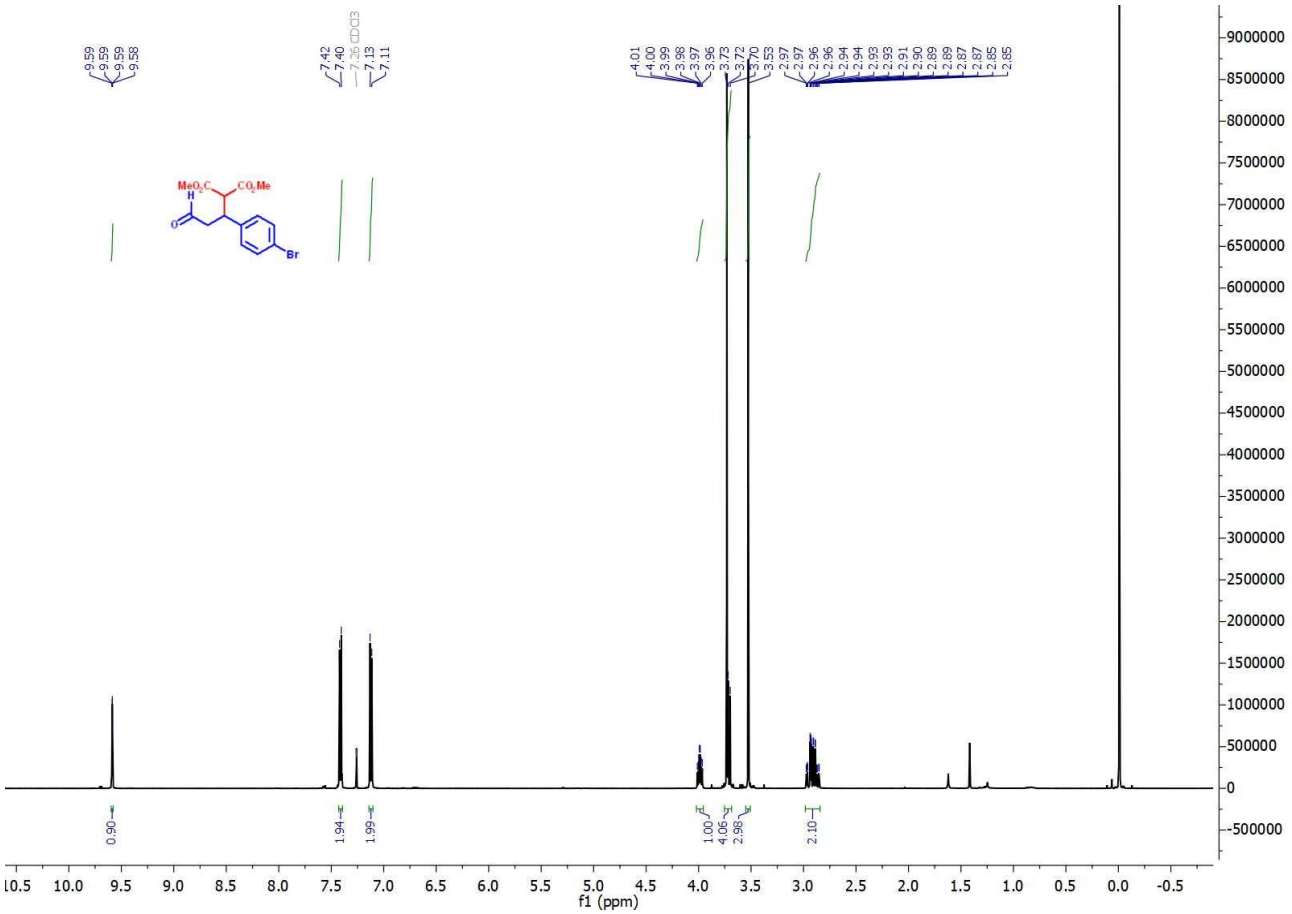


Figure S39. ^{1}H NMR of Compound **4e**

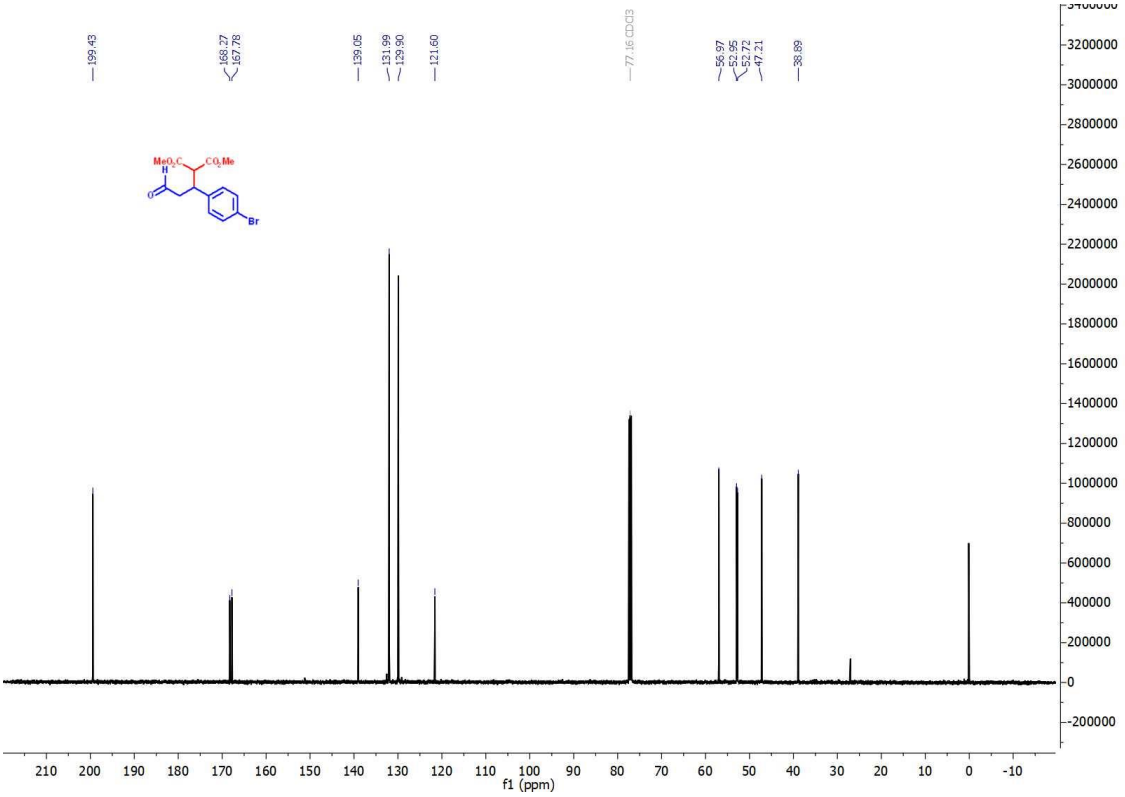
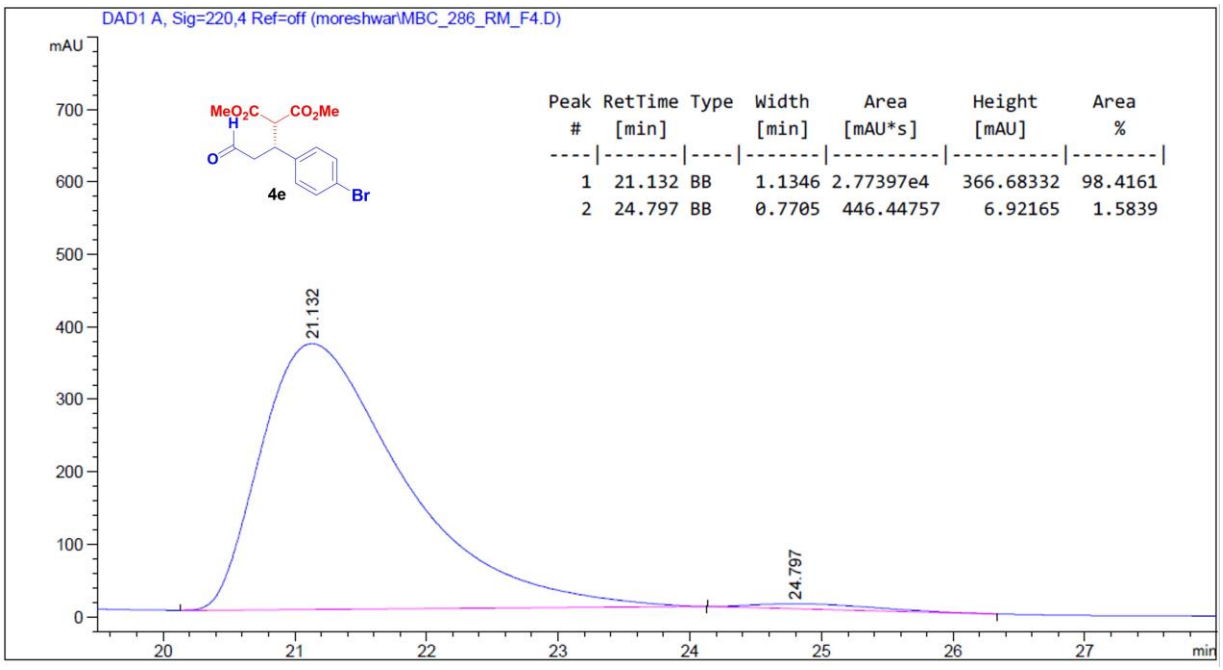


Figure S40. ^{13}C NMR of Compound **4e**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.132	BB	1.1346	2.77397e4	366.68332	98.4161
2	24.797	BB	0.7705	446.44757	6.92165	1.5839

Figure S41. HPLC chromatogram for **4e**

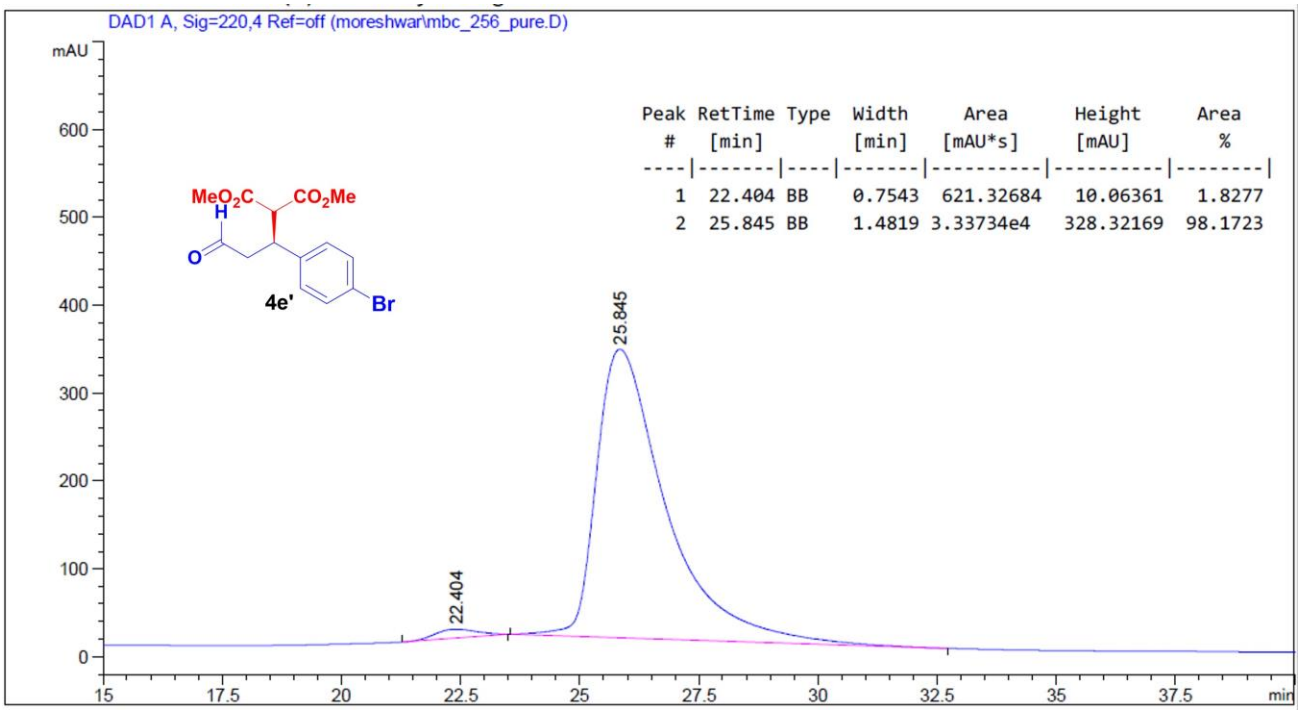


Figure S42. HPLC chromatogram for **4e'**

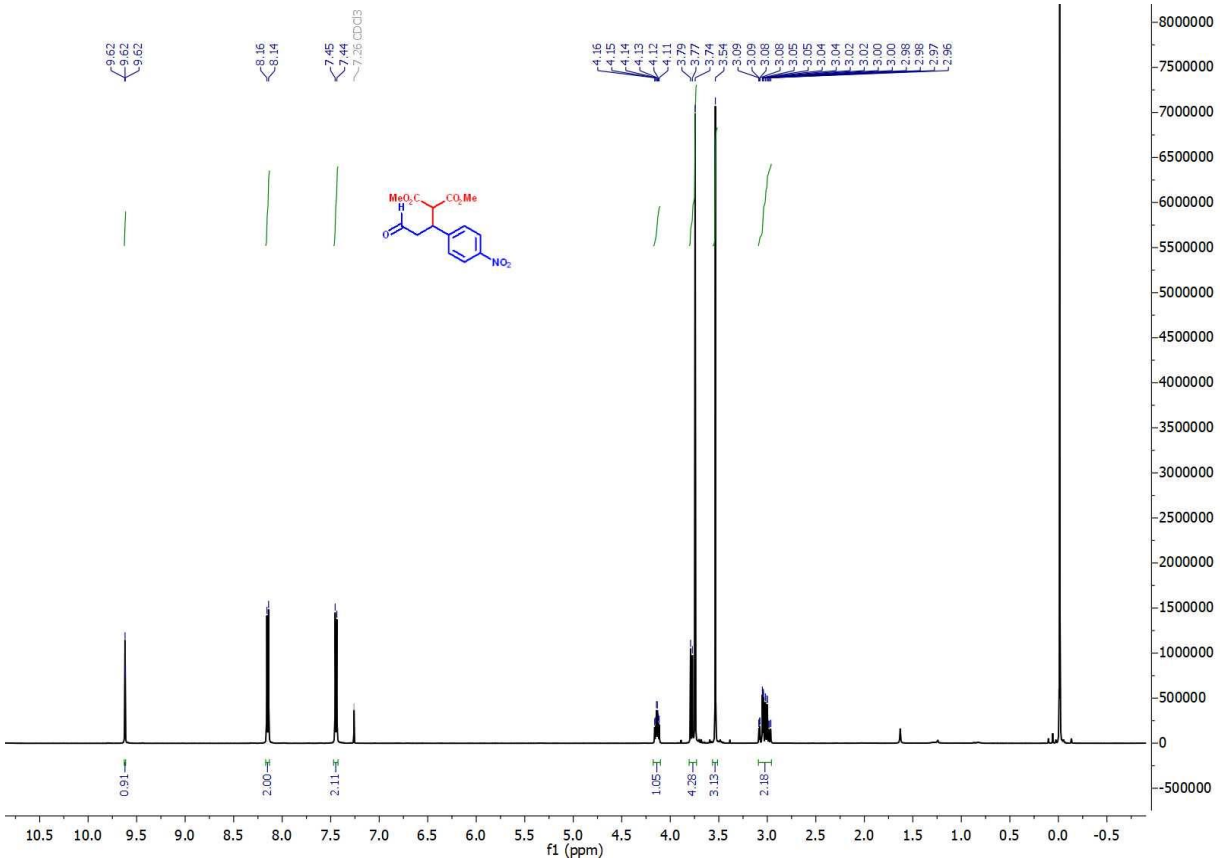


Figure S43. ^{1}H NMR of Compound **4f**

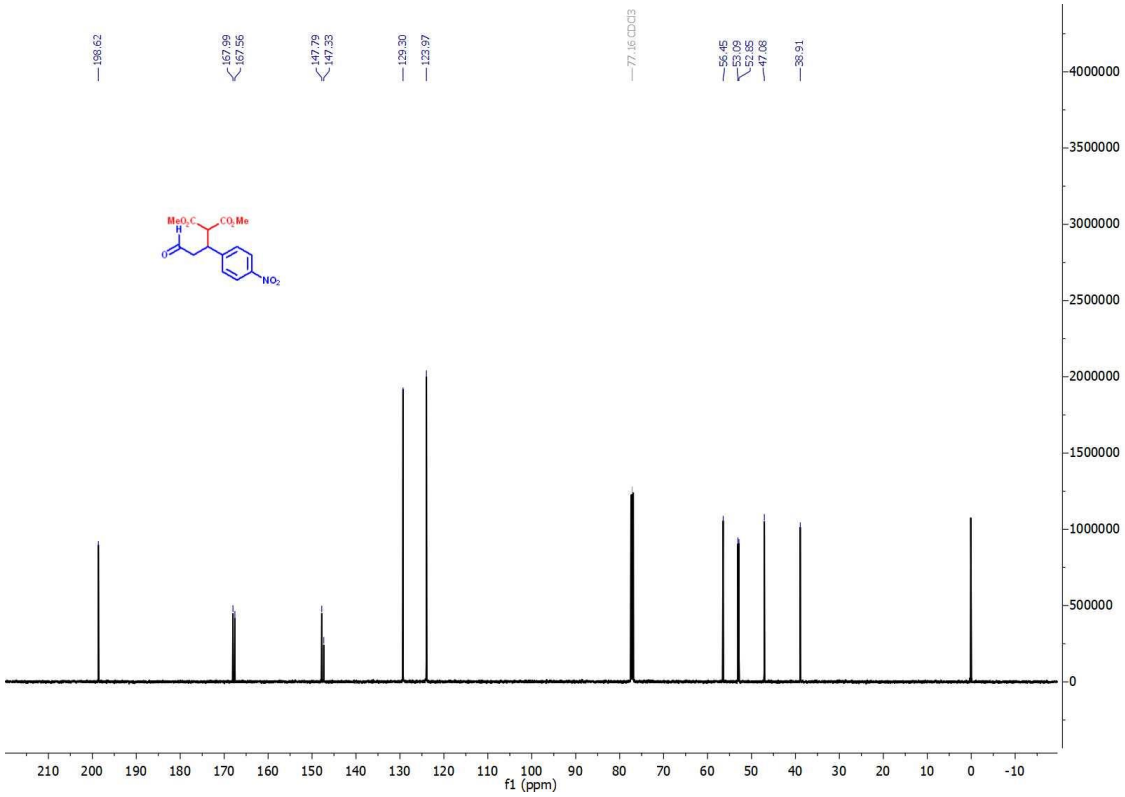


Figure S44. ^{13}C NMR of Compound **4f**

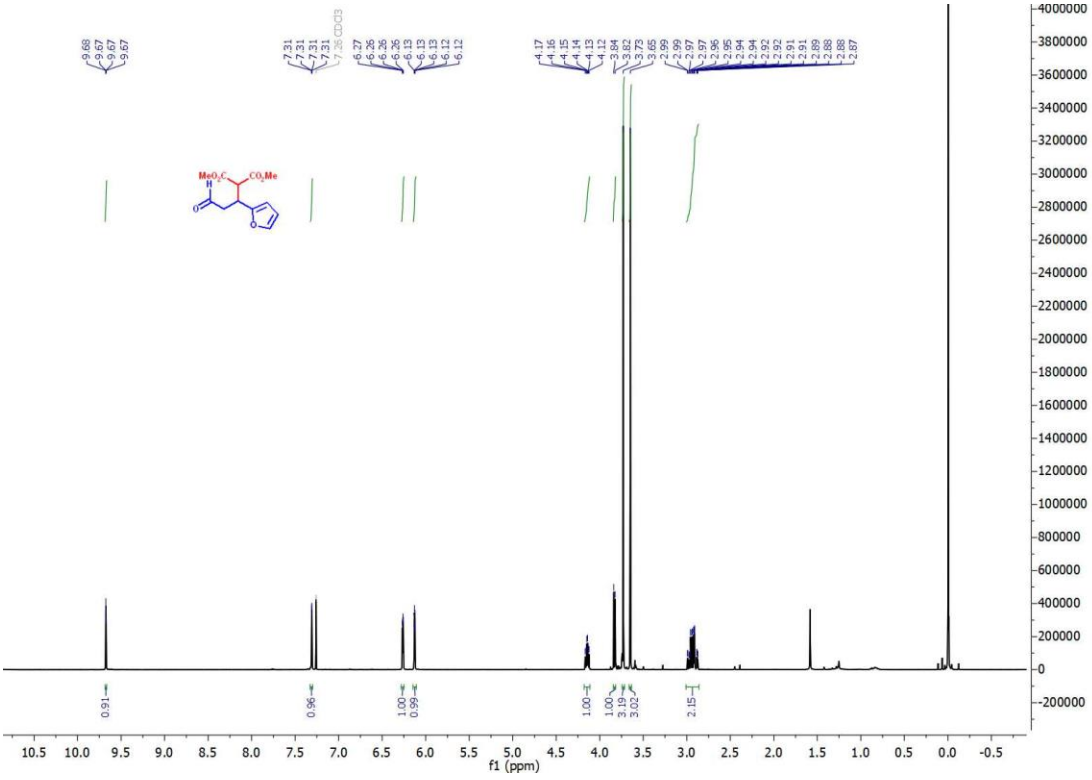


Figure S45. ^{1}H NMR of Compound **4g**

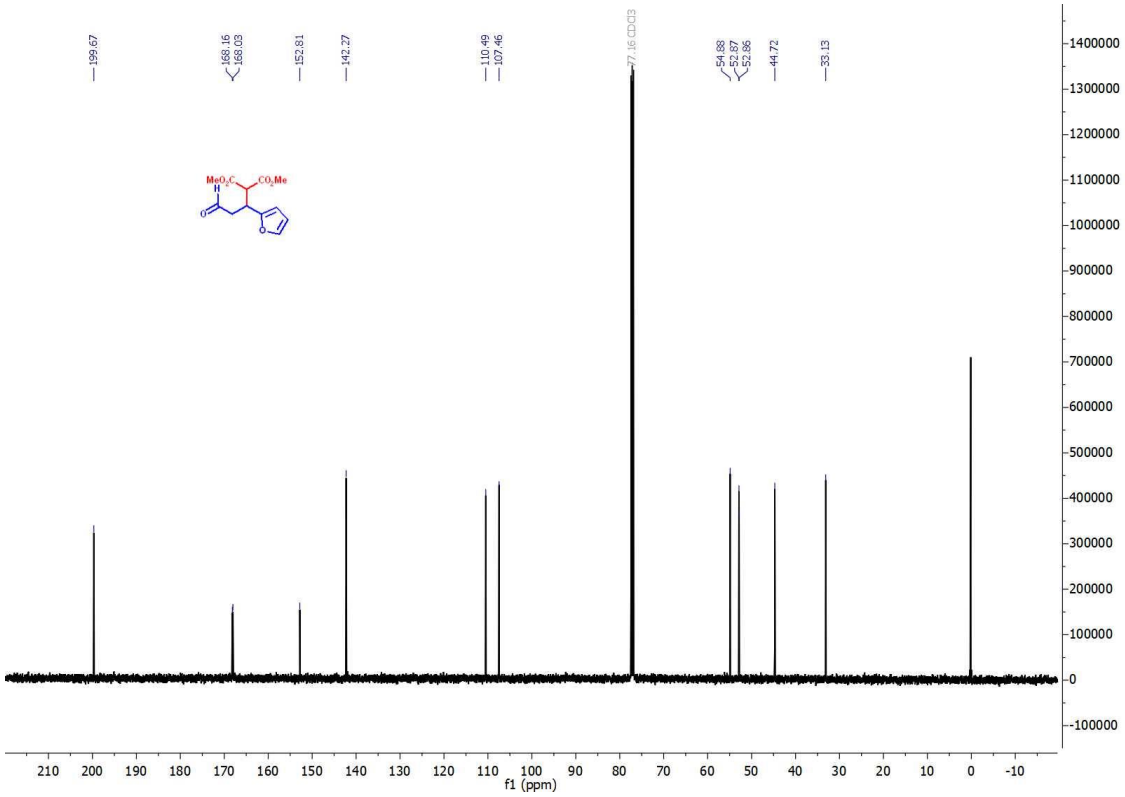


Figure S45. ^{13}C NMR of Compound **4g**

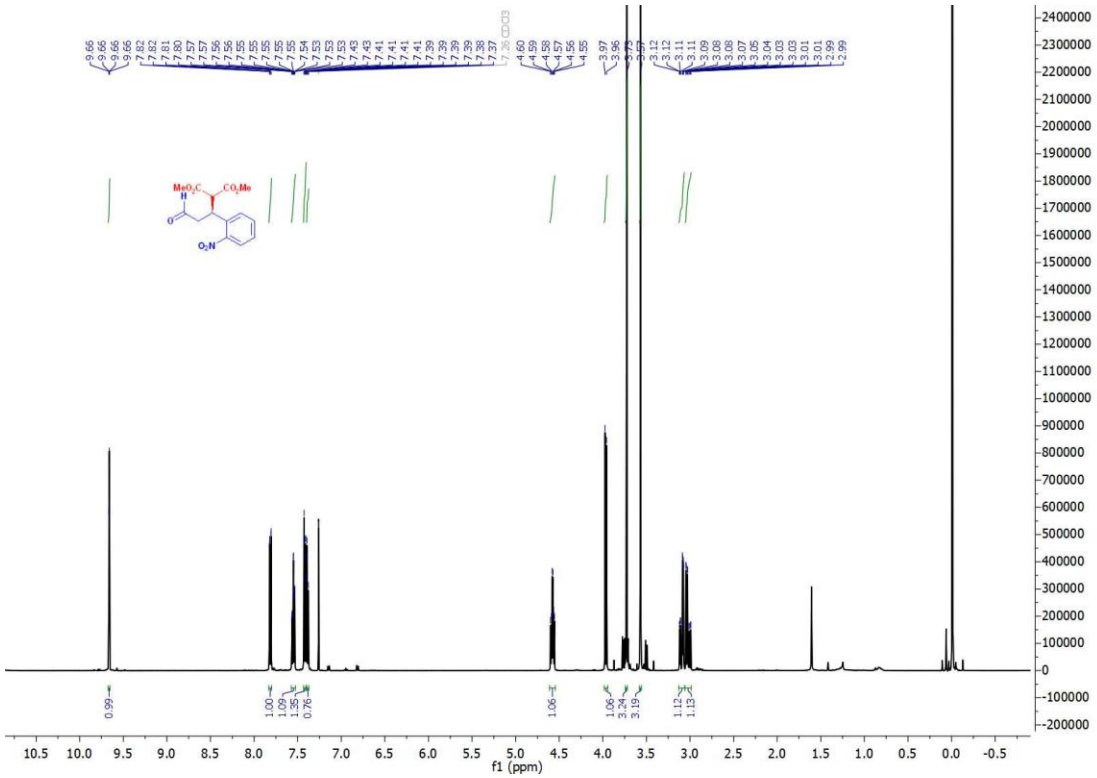


Figure S46. ^{1}H NMR of Compound **4h**

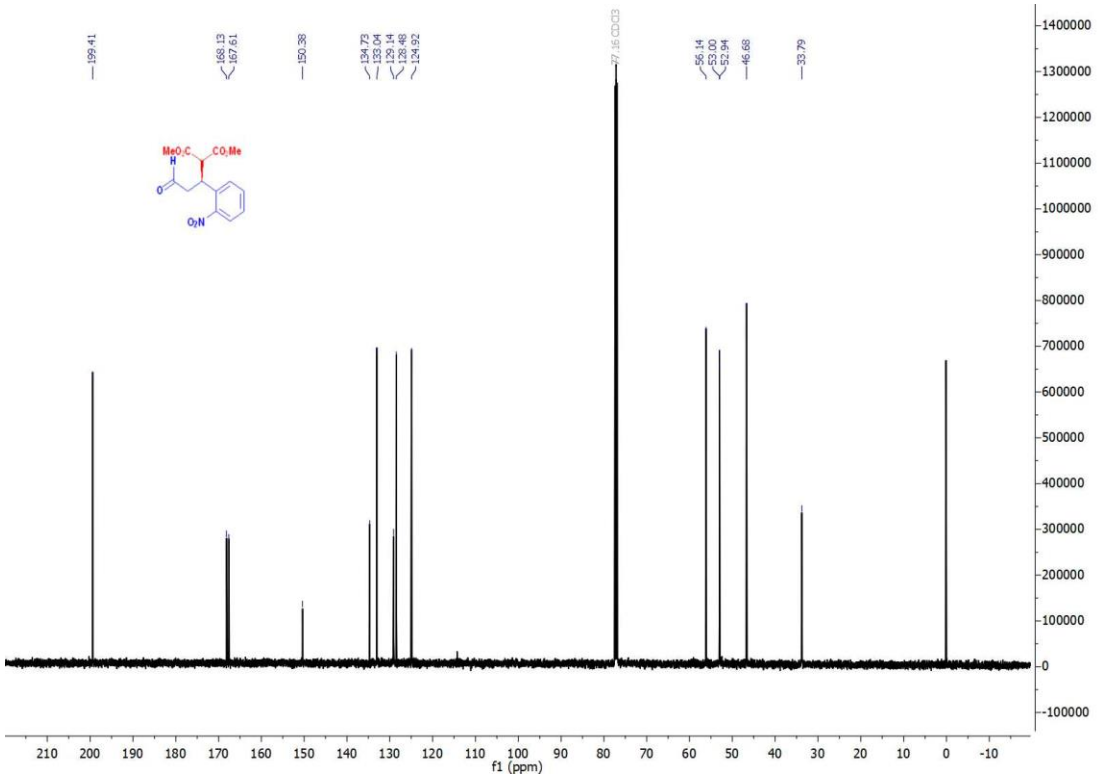


Figure S47. ^{13}C NMR of Compound **4h**

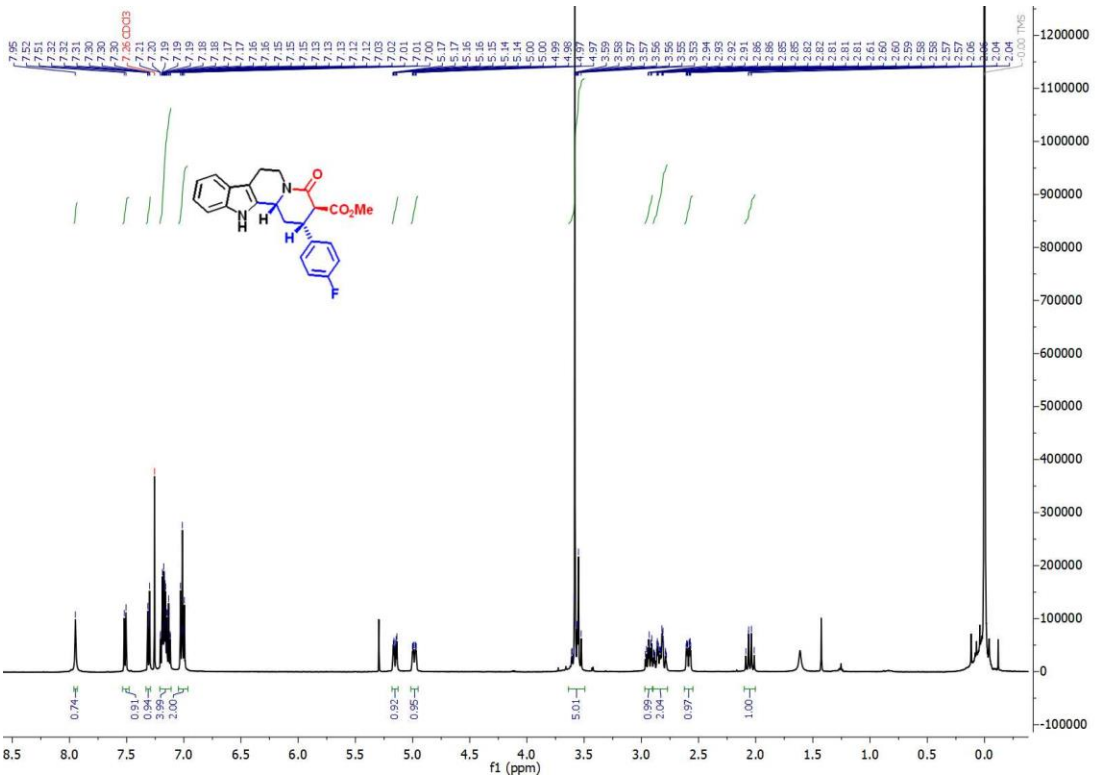


Figure S48. ^{1}H NMR of Compound **1a**

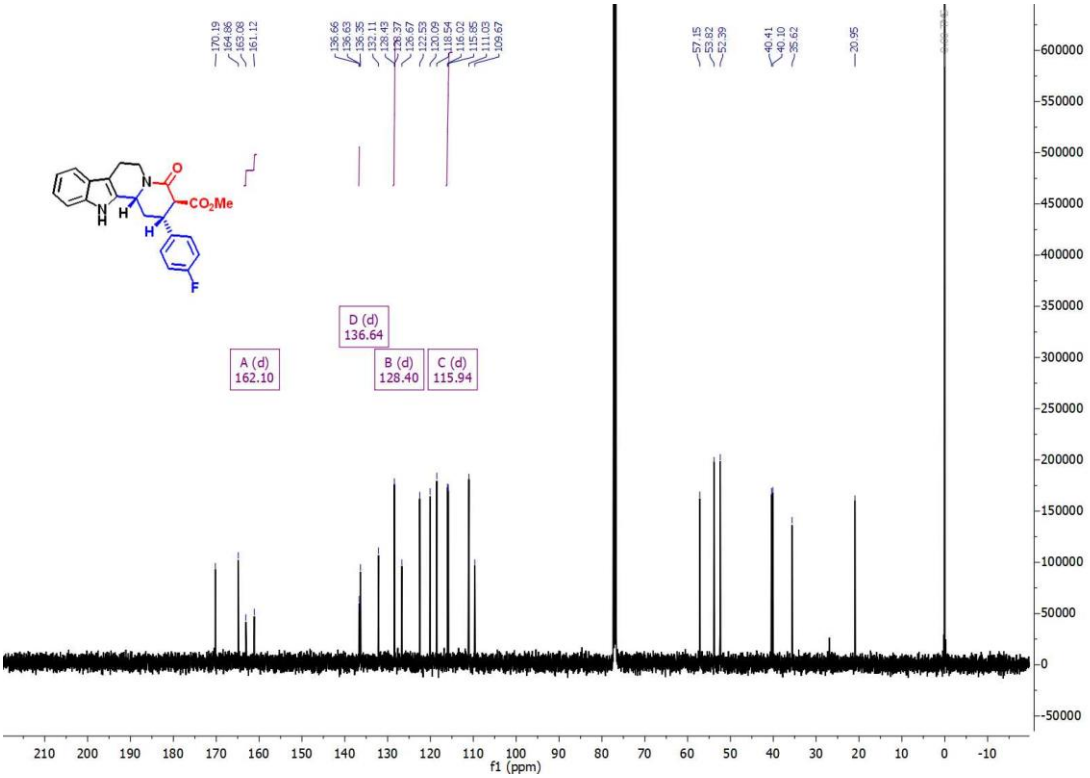


Figure S49. ^{13}C NMR of Compound **1a**

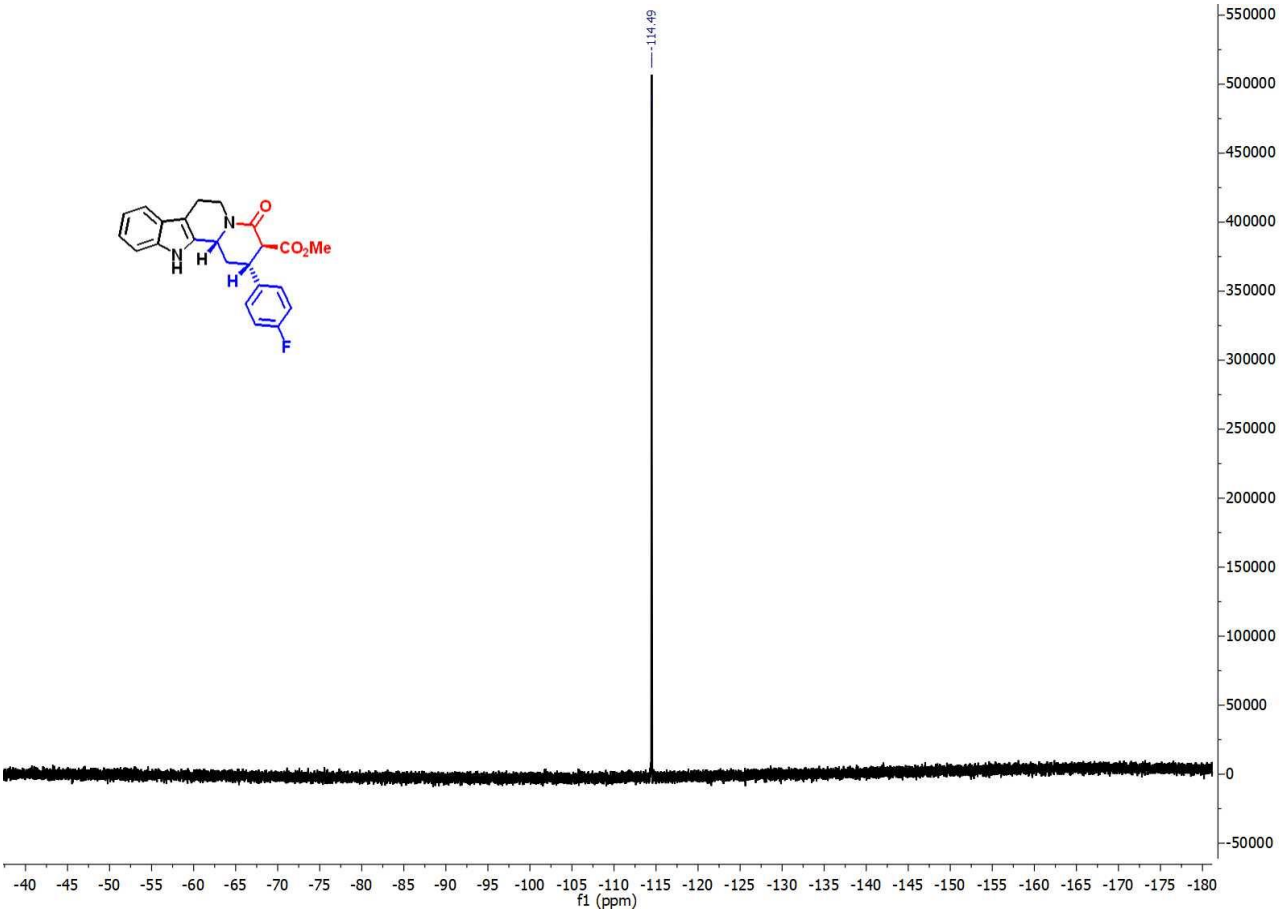
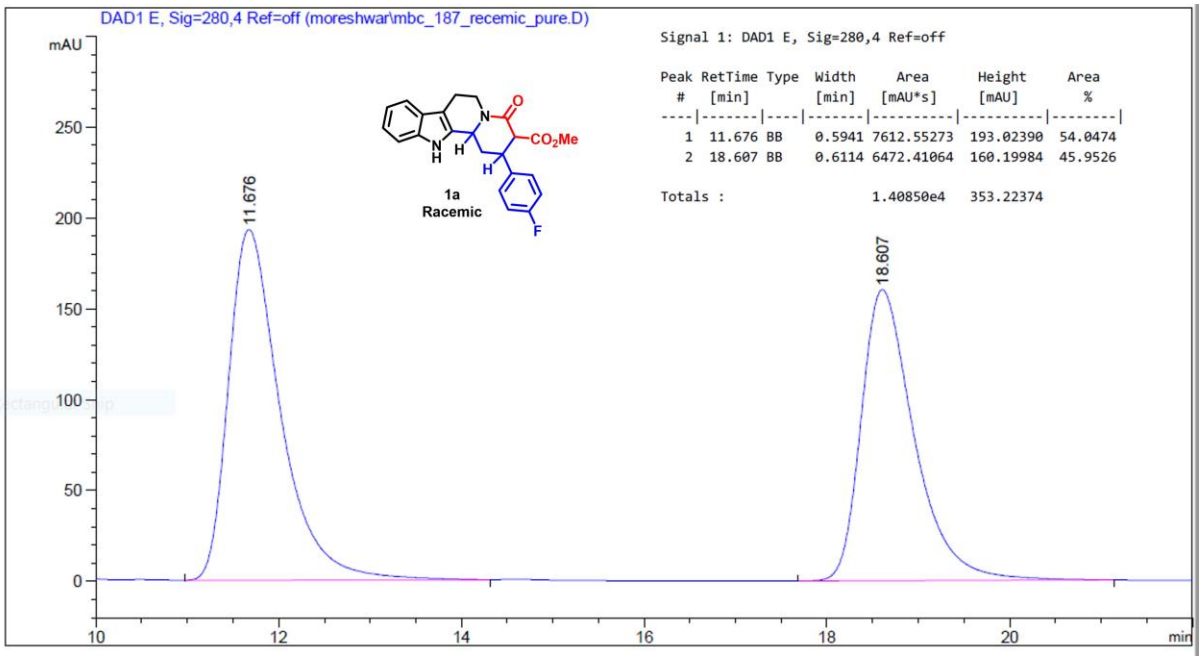


Figure S50. ^{19}F NMR of Compound **1a**



Signal 1: DAD1 E, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.676	BB	0.5941	7612.55273	193.02390	54.0474
2	18.607	BB	0.6114	6472.41064	160.19984	45.9526
Totals :				1.40850e4	353.22374	

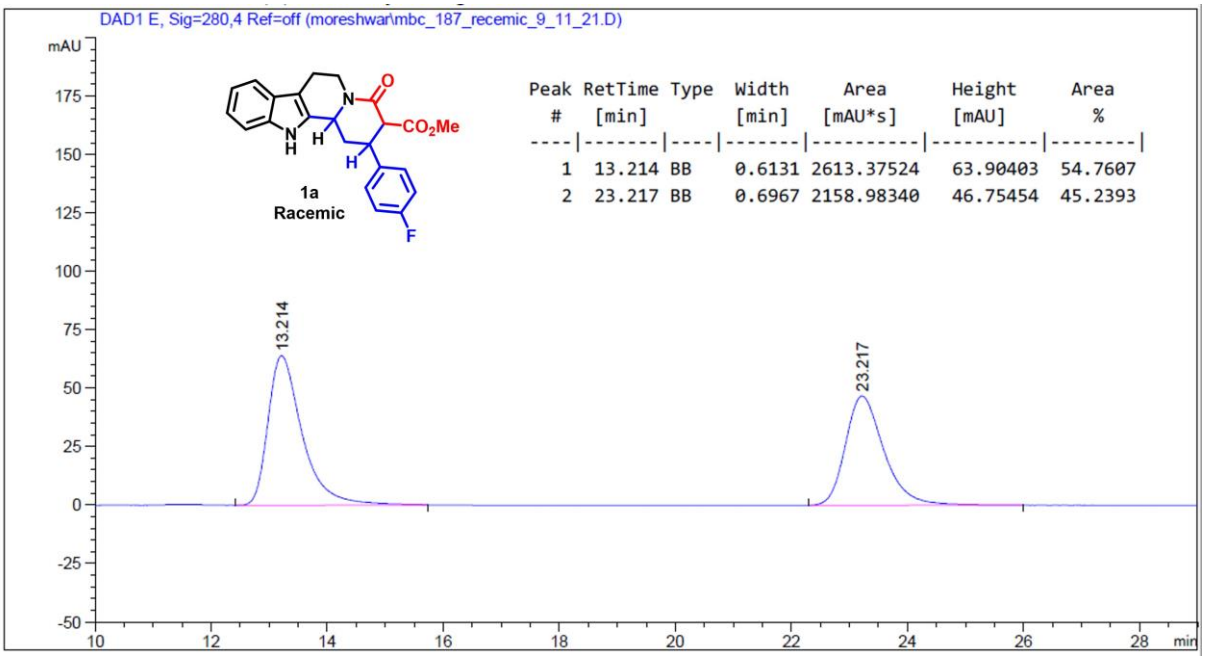


Figure S51. HPLC chromatogram for **1a** (Racemic)

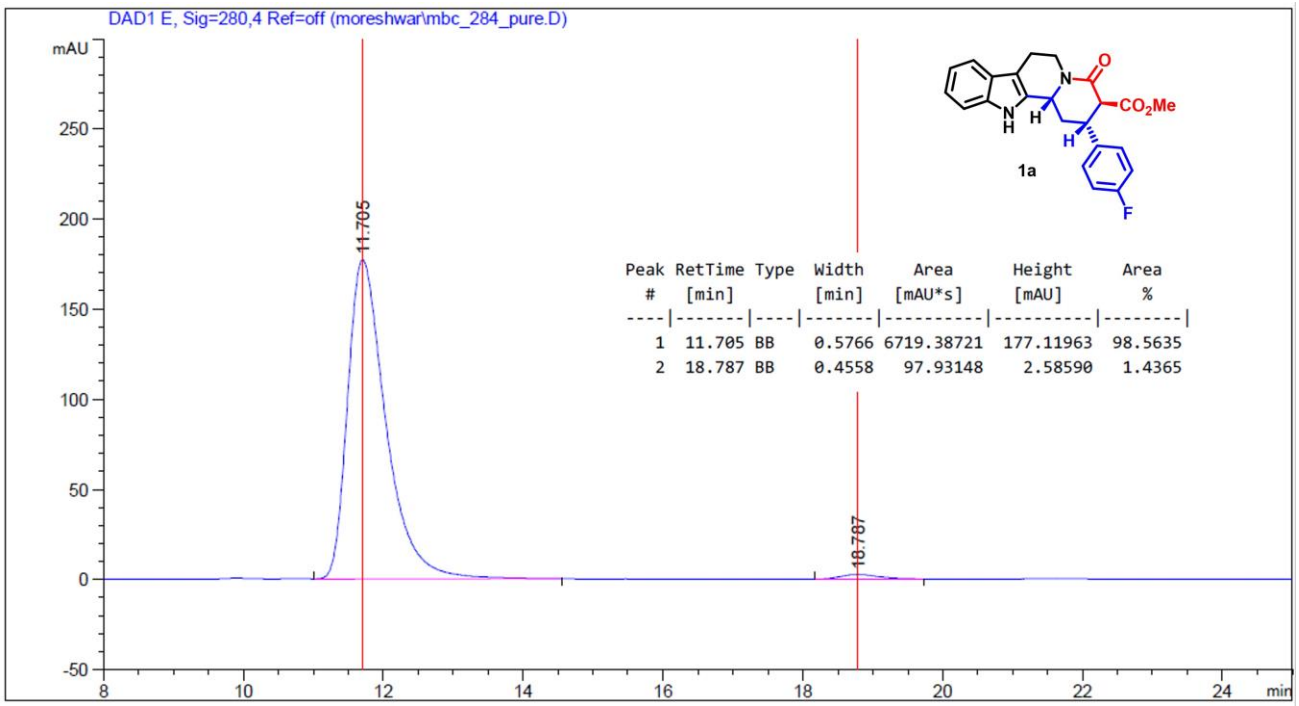


Figure S52. HPLC chromatogram for **1a**

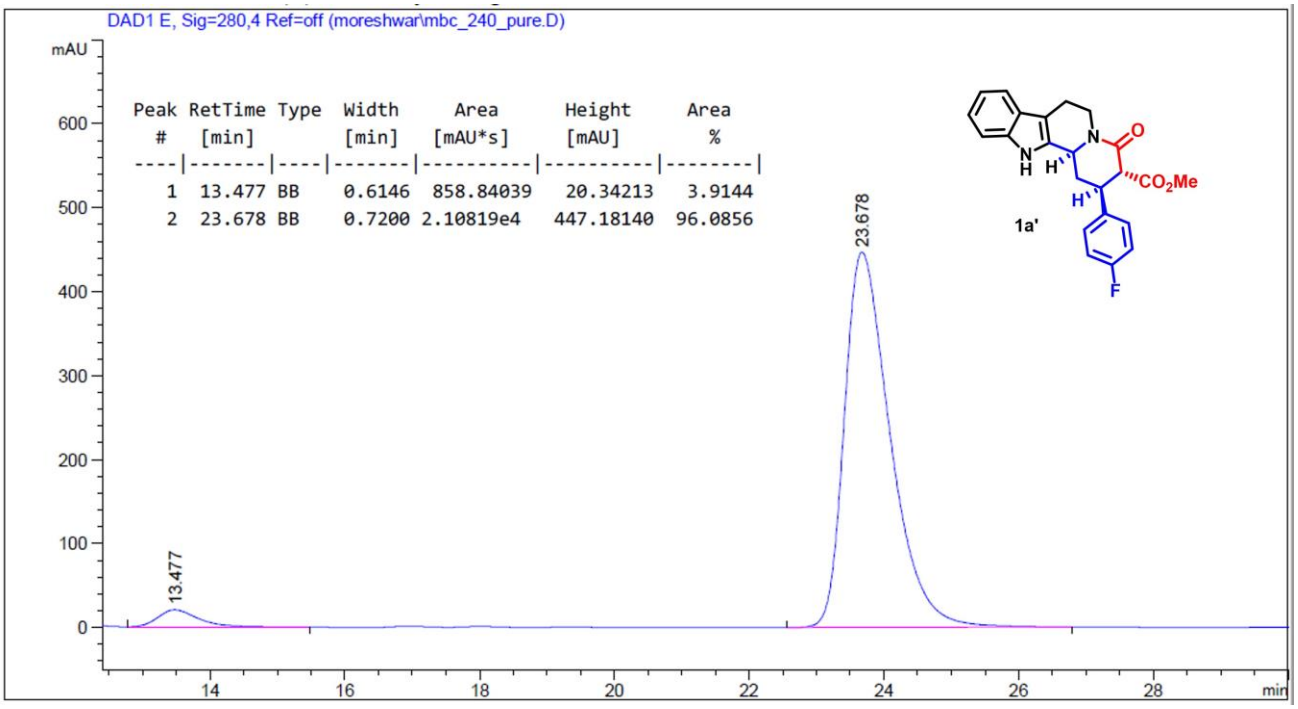


Figure S53. HPLC chromatogram for **1a'**

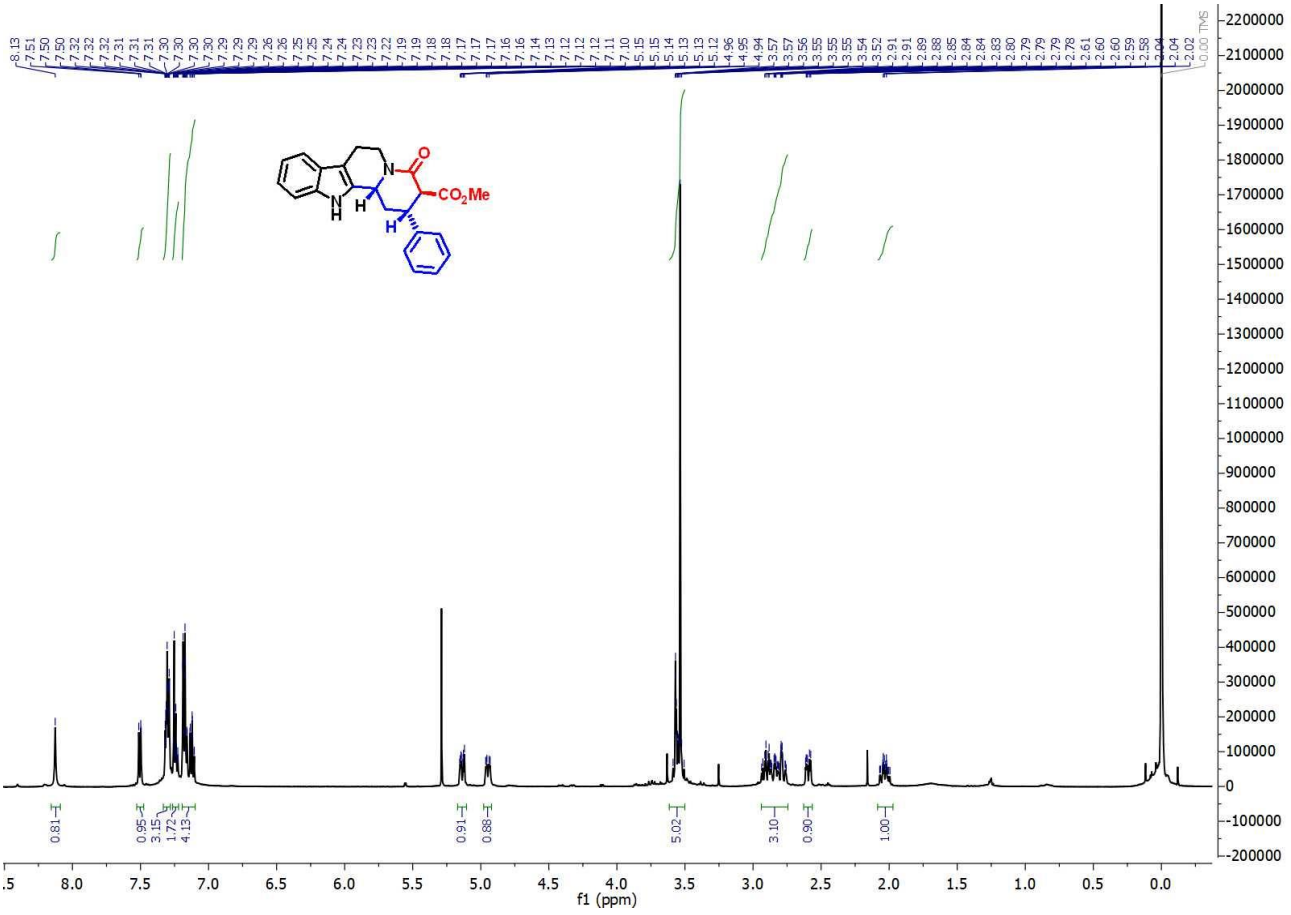


Figure S54. ^{1}H NMR of Compound **1b**

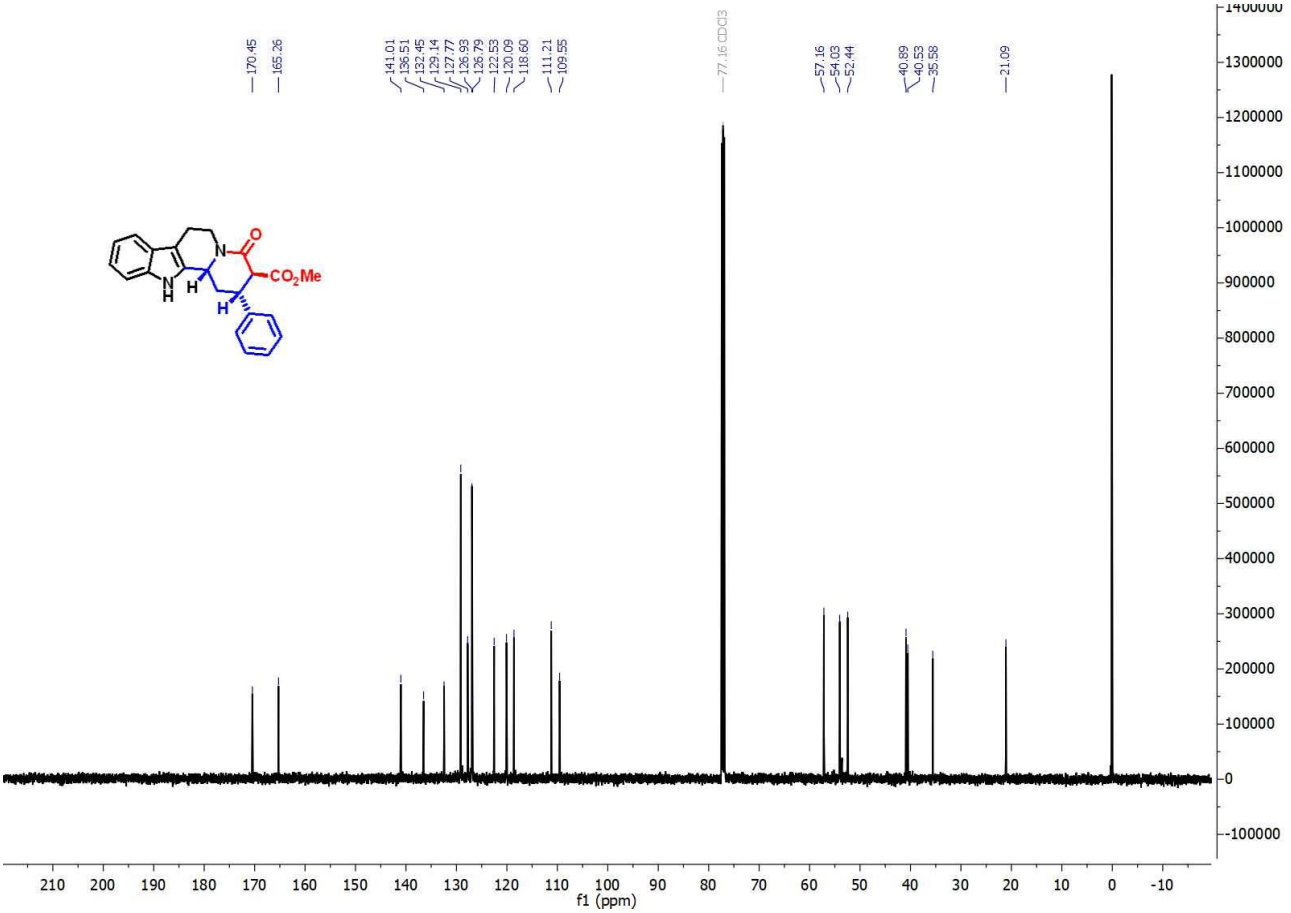


Figure S55. ^{13}C NMR of Compound **1b**

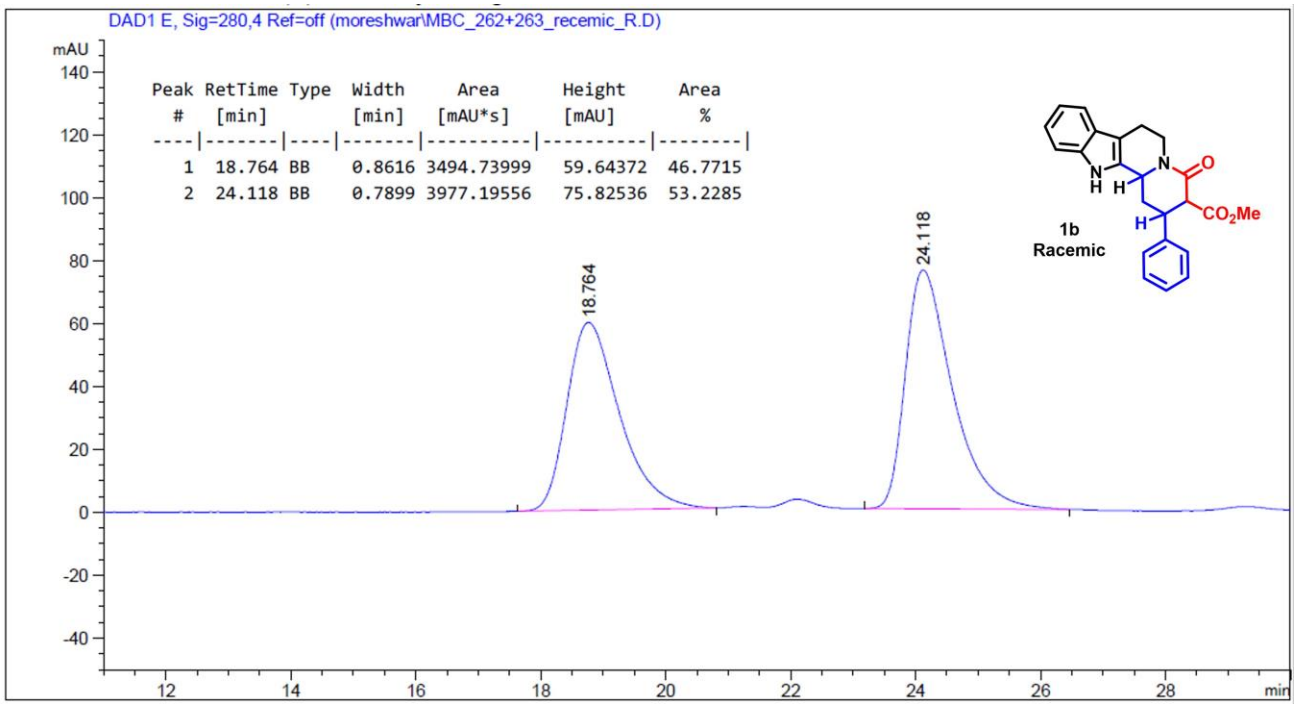


Figure S56. HPLC chromatogram for **1b** (Racemic)

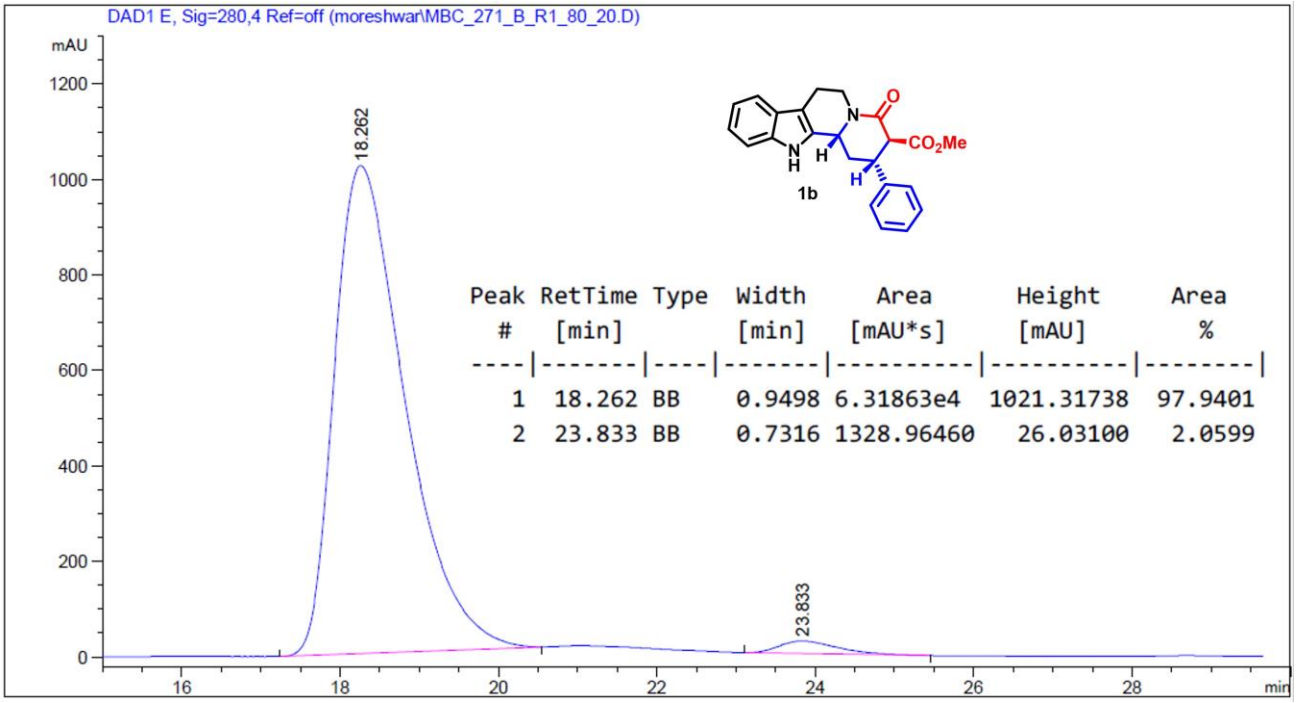


Figure S57. HPLC chromatogram for **1b**

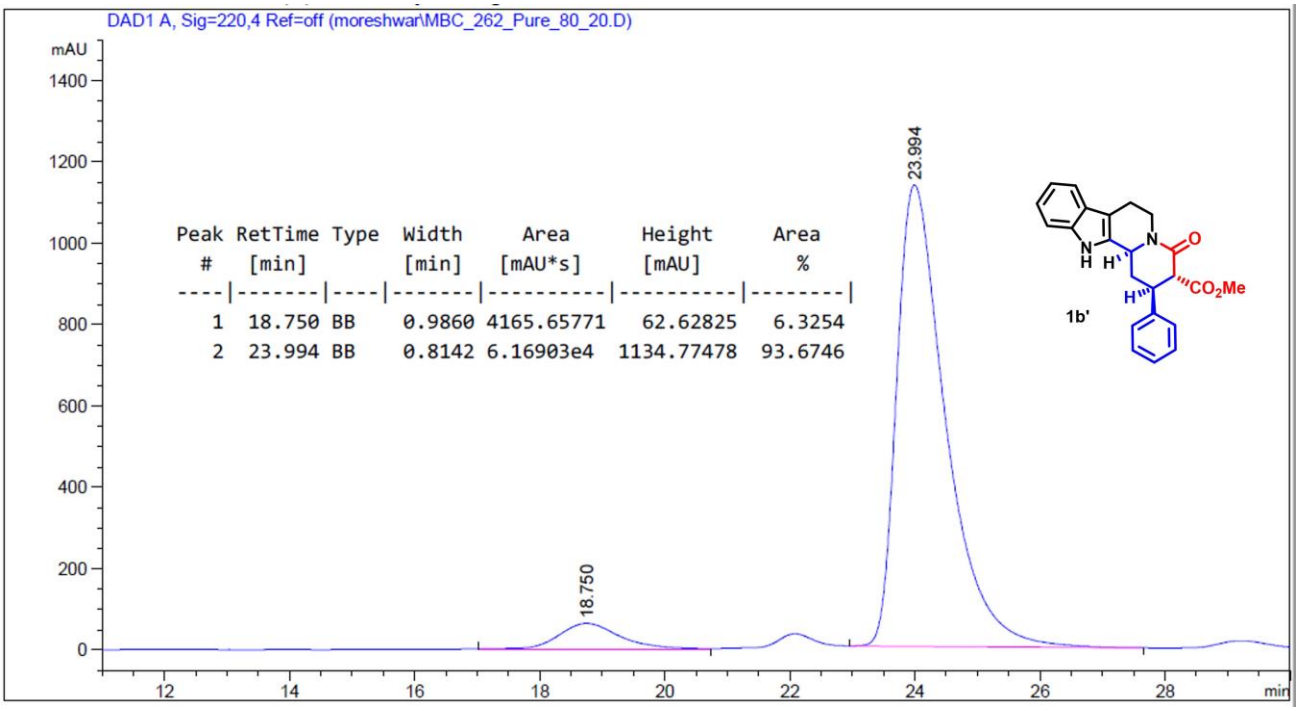


Figure S58. HPLC chromatogram for **1b'**

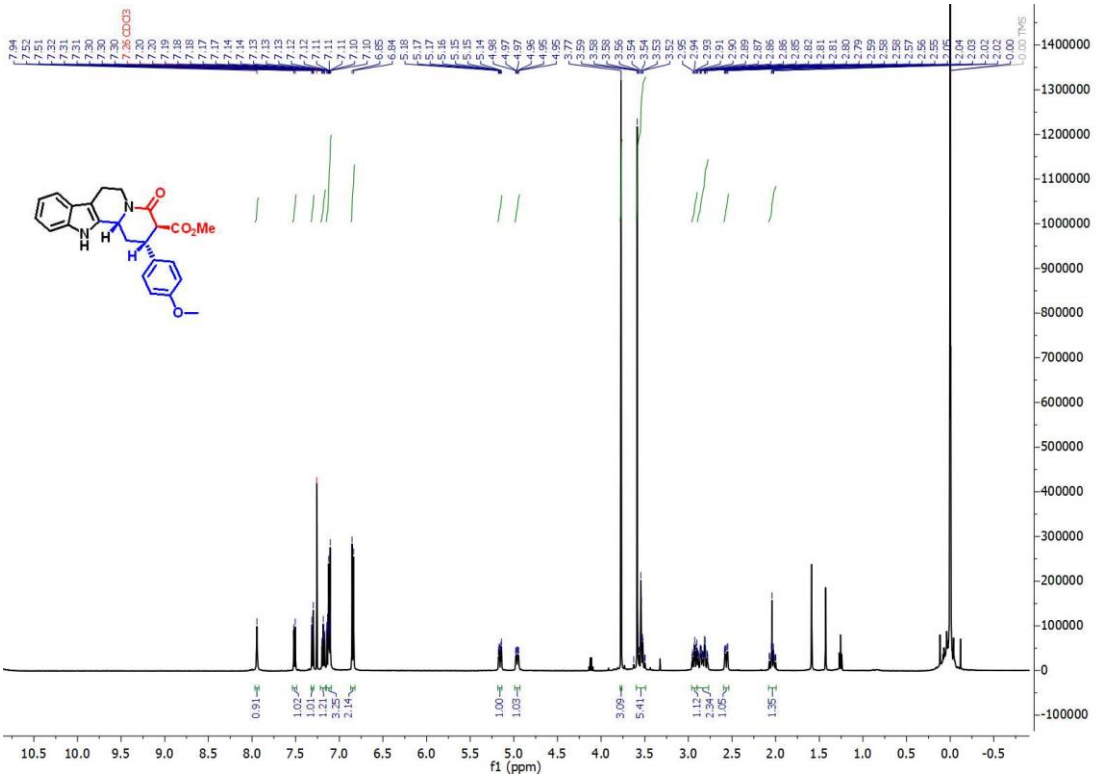


Figure S59. ^{1}H NMR of Compound **1c**

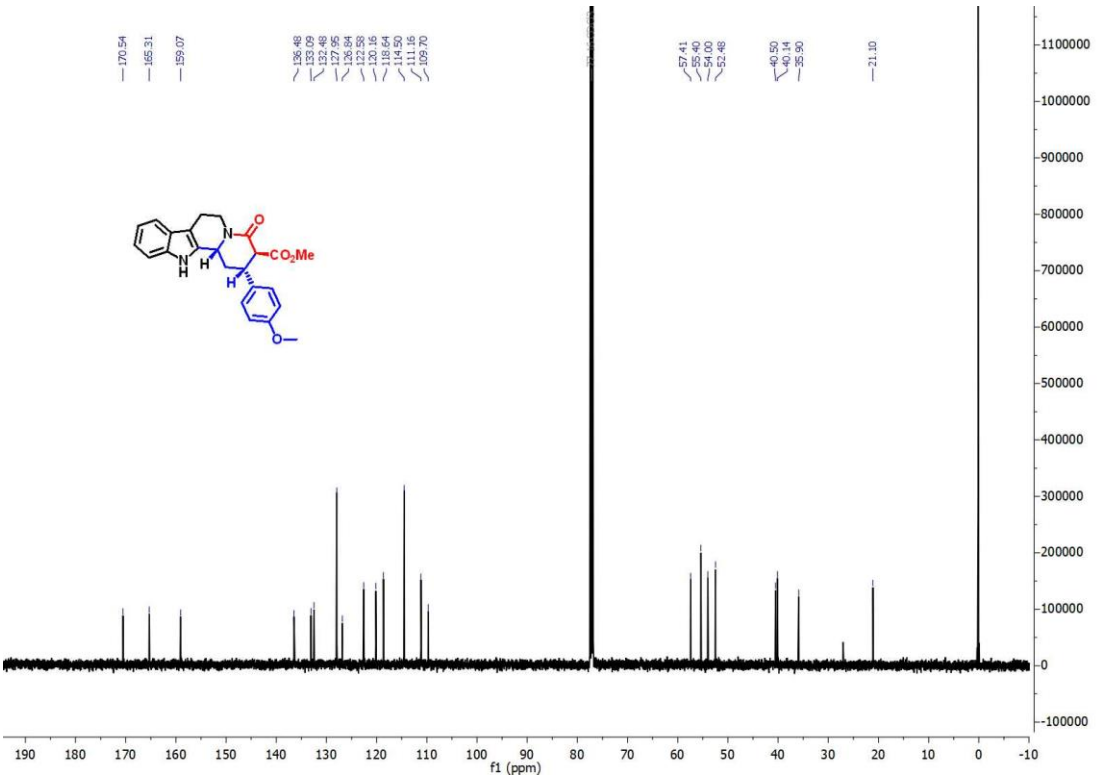


Figure S60. ^{13}C NMR of Compound **1c**

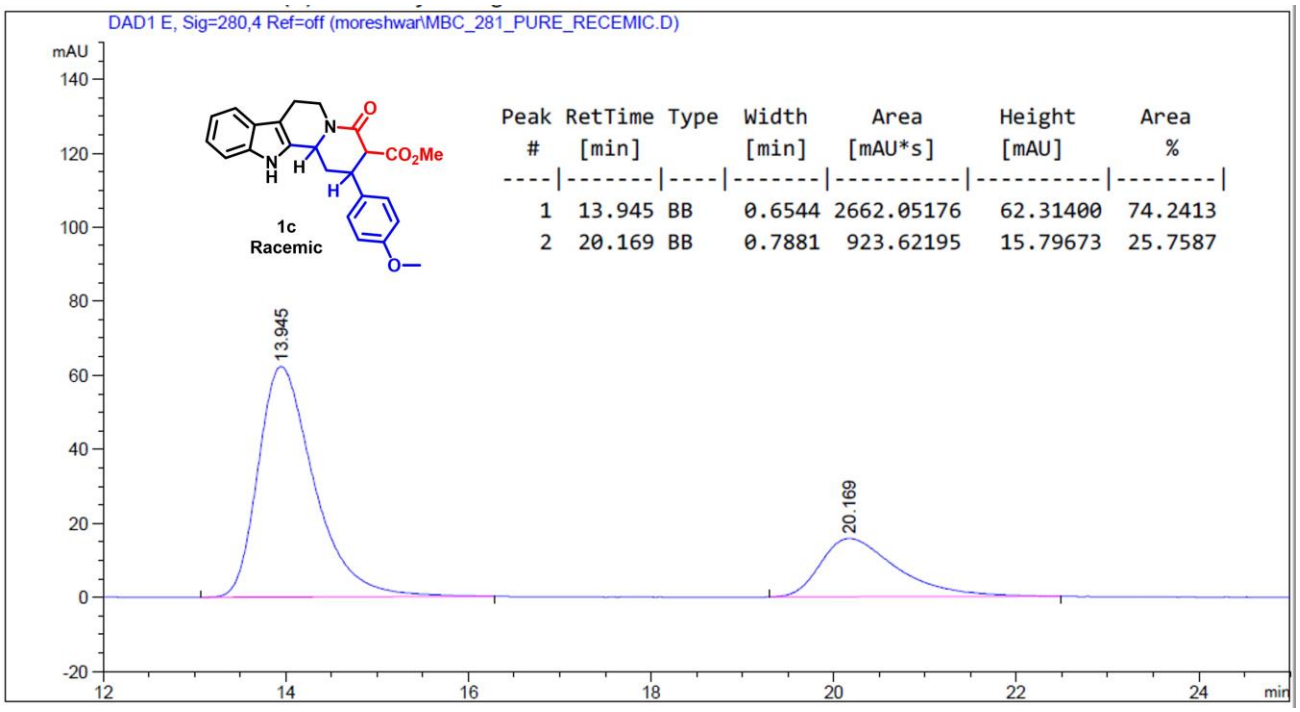


Figure S61. HPLC chromatogram for **1c** (Racemic)

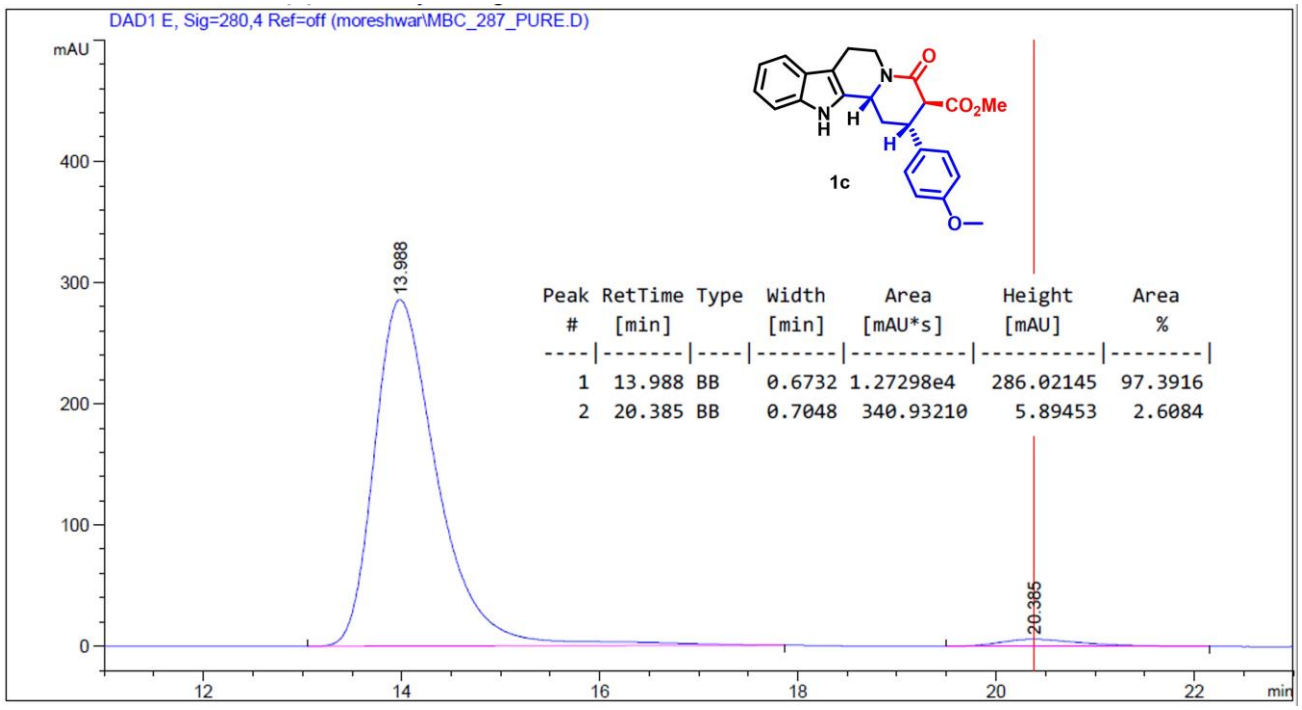


Figure S62. HPLC chromatogram for **1c**

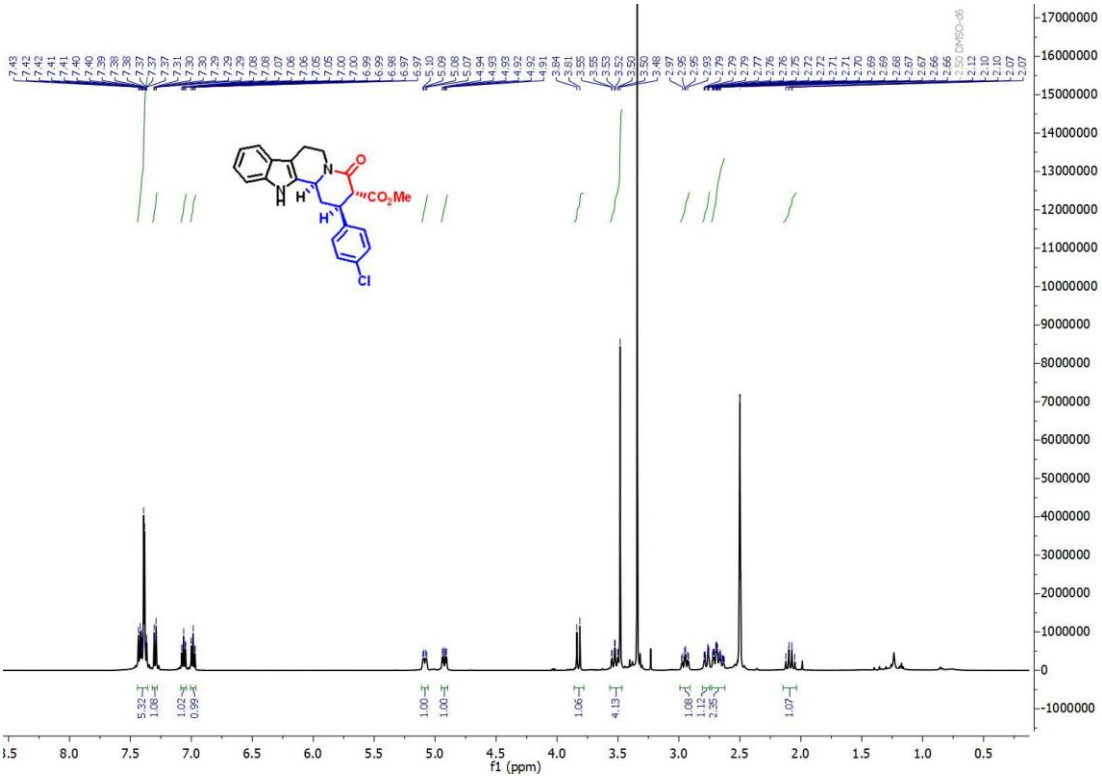


Figure S63. ^{1}H NMR of Compound **1d'**

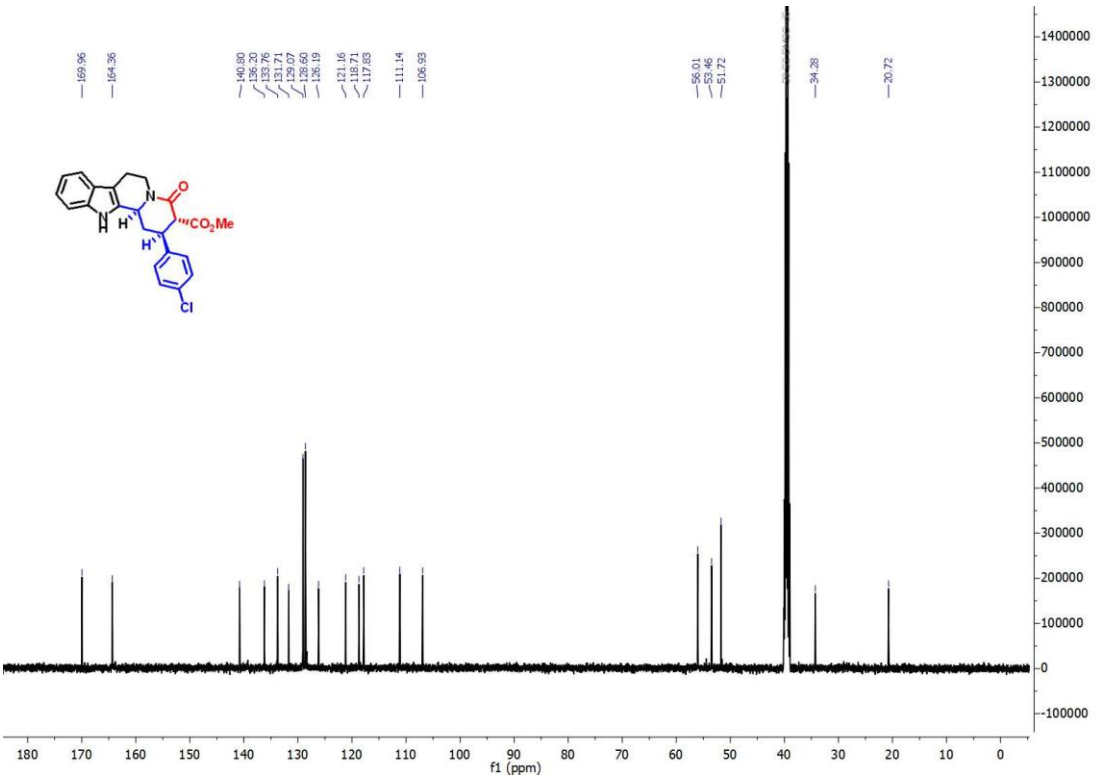


Figure S64. ^{13}C NMR of Compound **1d'**

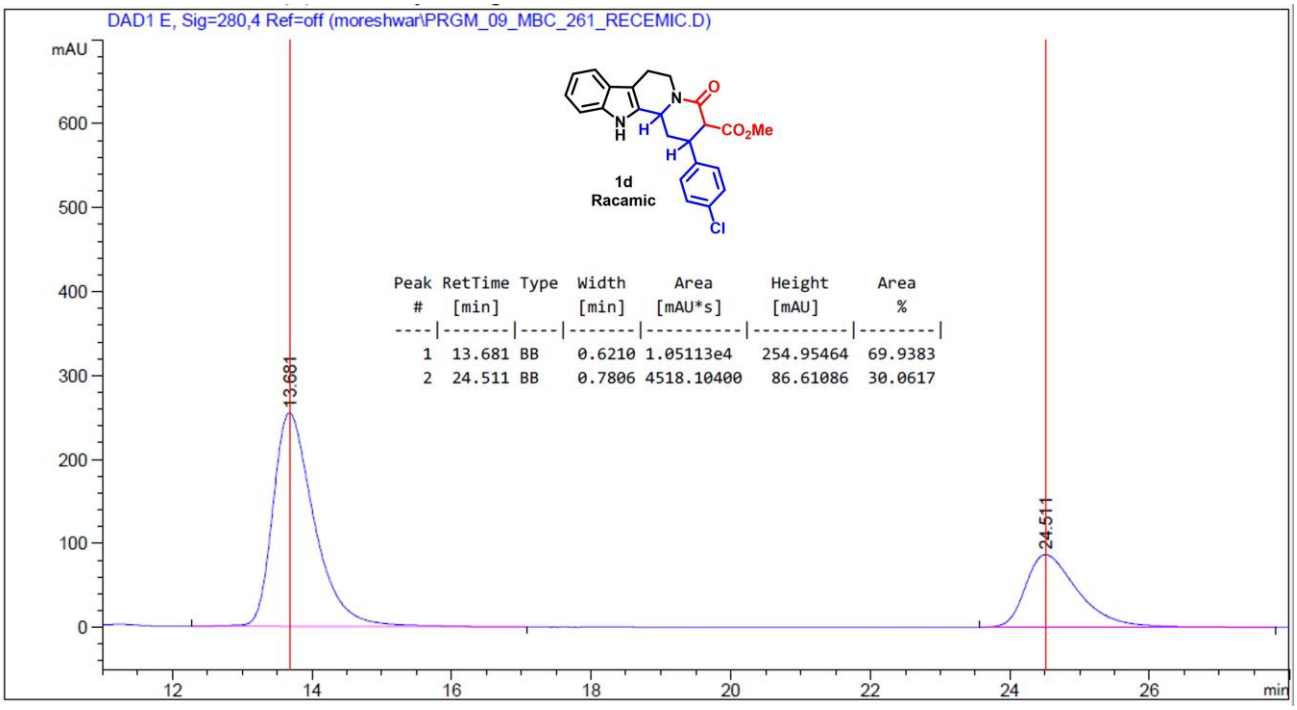


Figure S65. HPLC chromatogram for **1d** (Racemic)

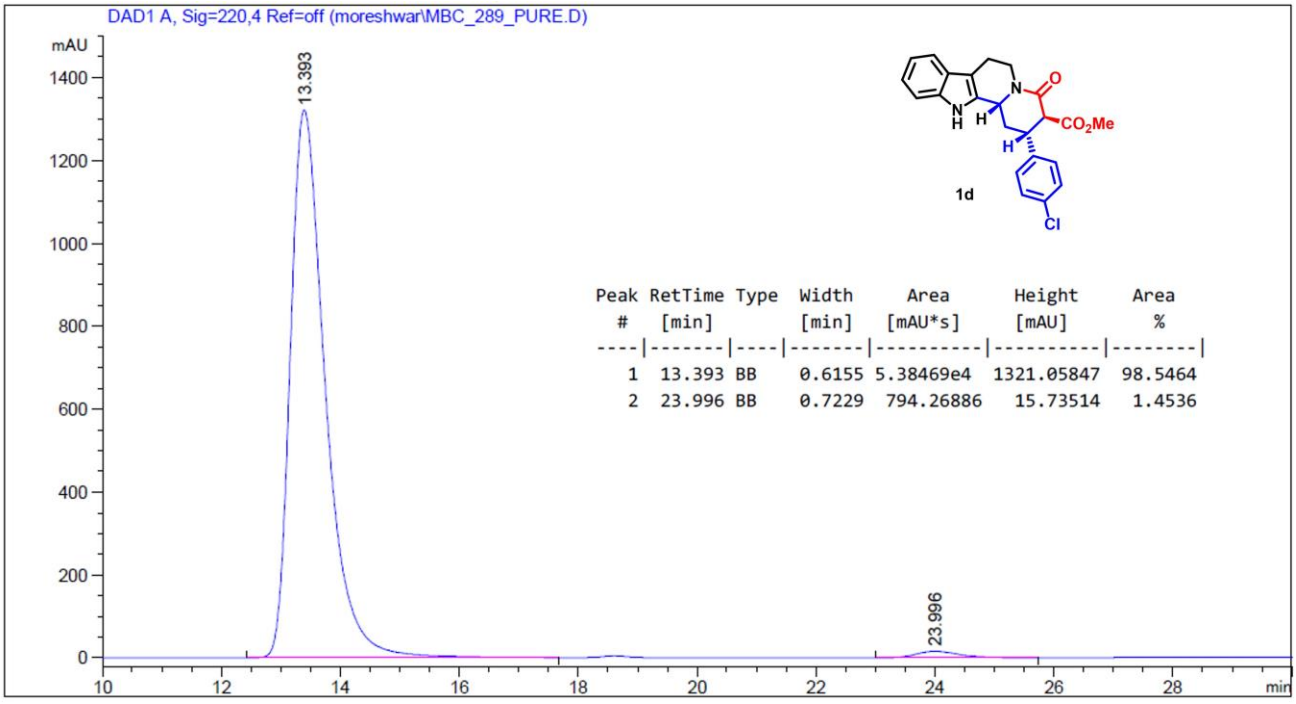


Figure S66. HPLC chromatogram for **1d**

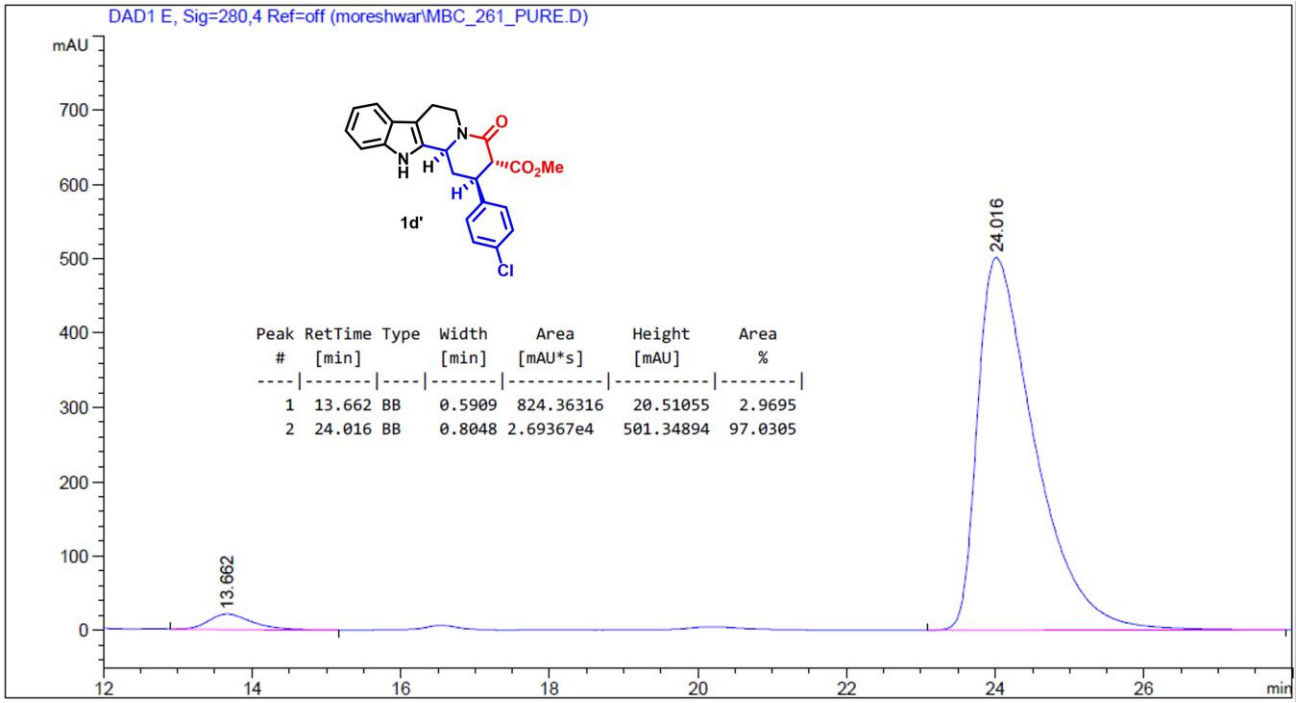


Figure S67. HPLC chromatogram for **1d'**

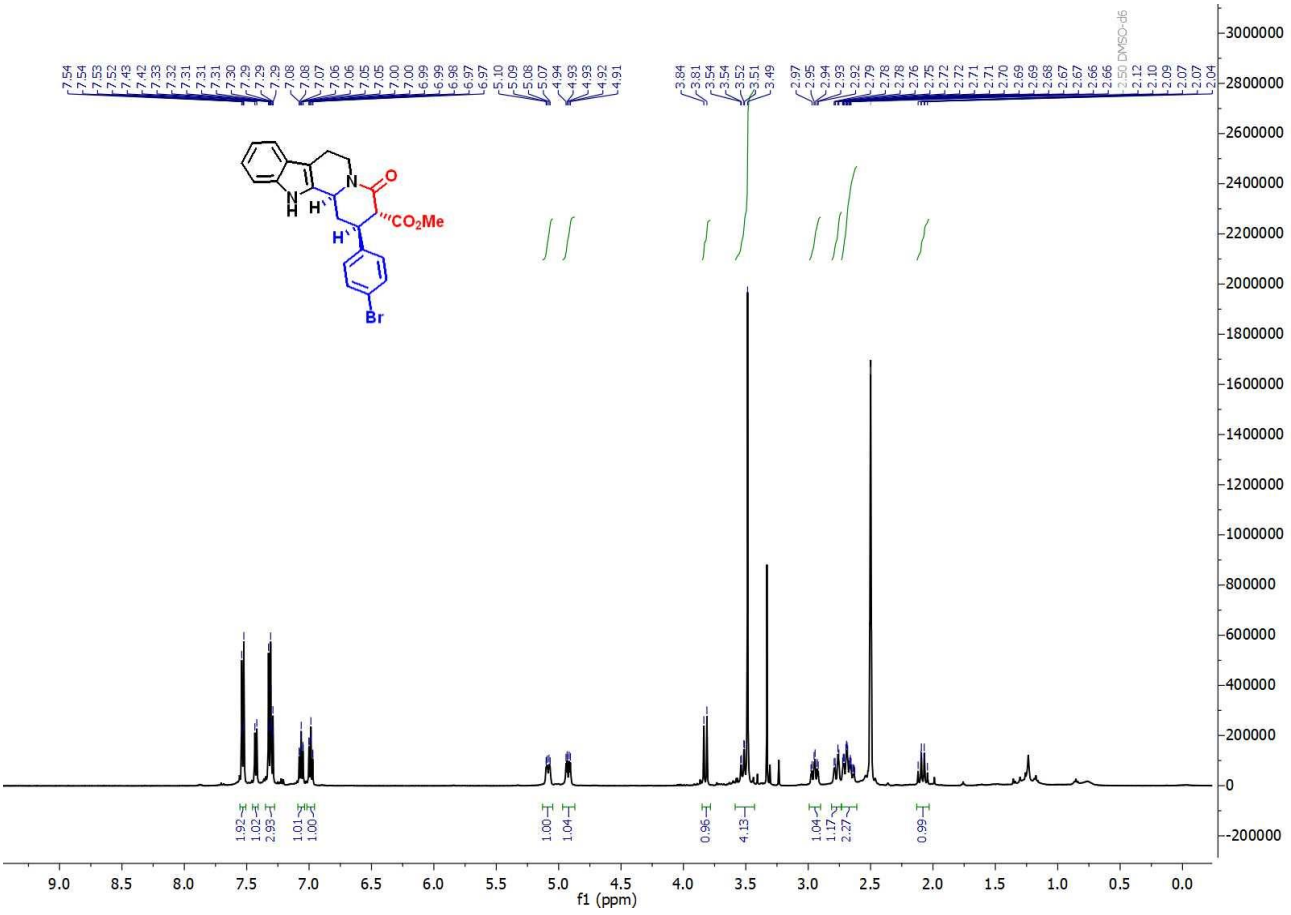


Figure S68. ^{1}H NMR of Compound **1e'**

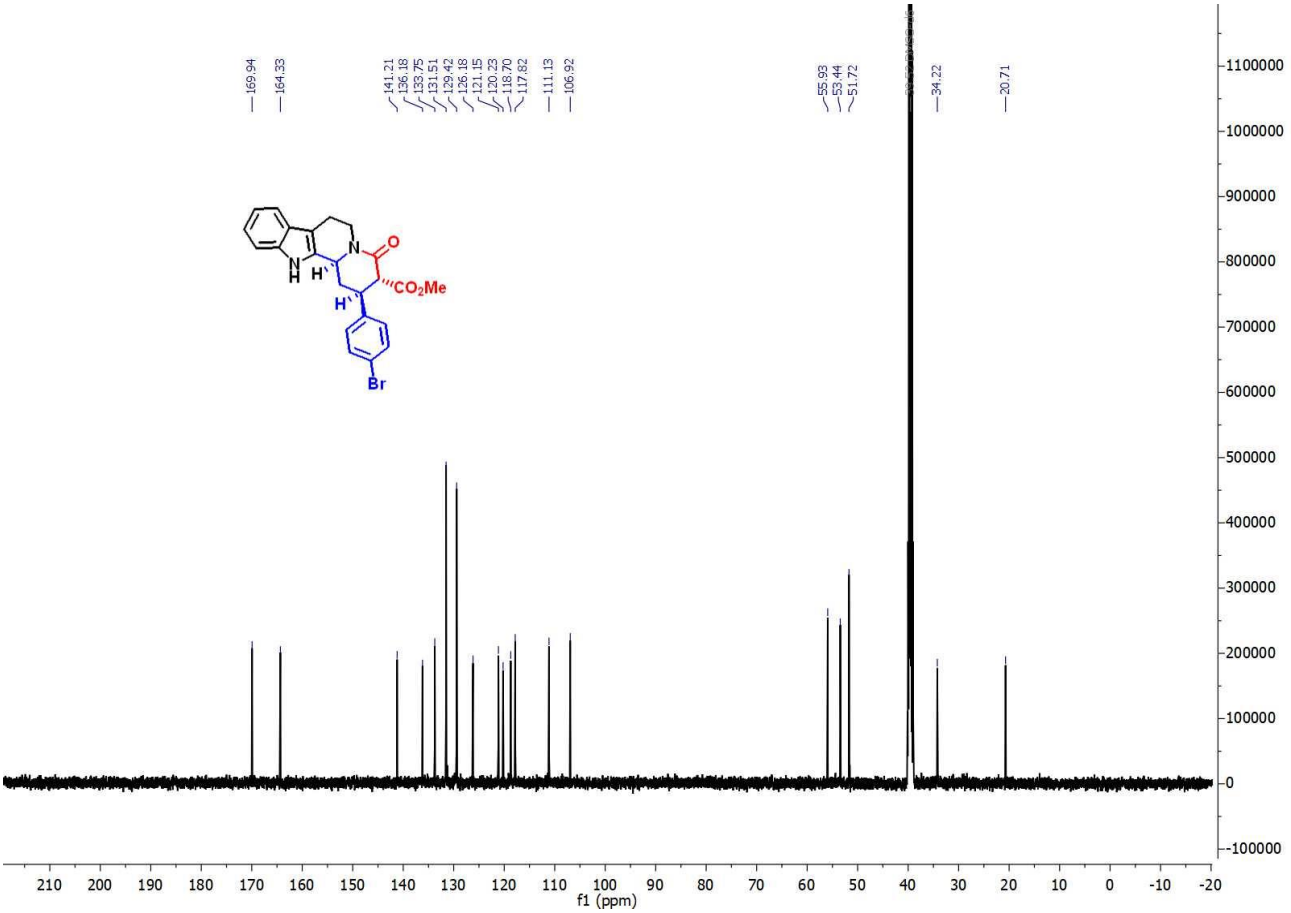


Figure S69. ^{13}C NMR of Compound **1e'**

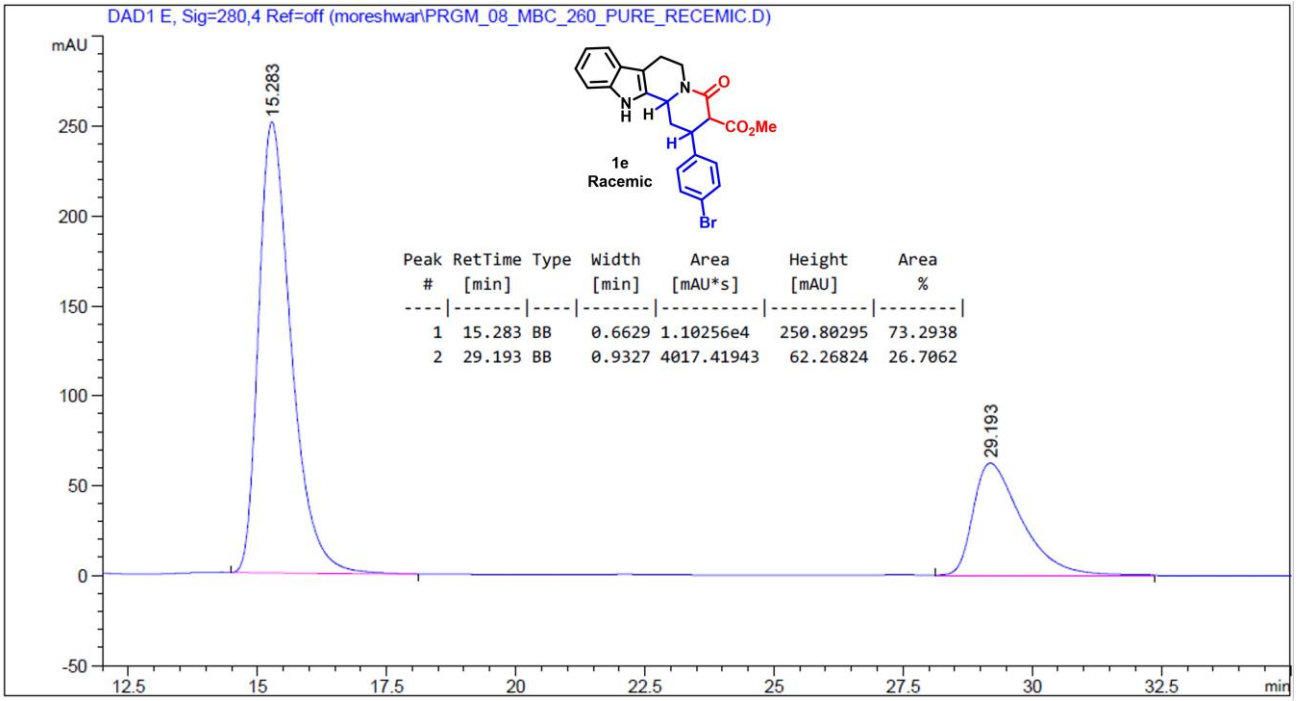


Figure S70. HPLC chromatogram for **1e** (Racemic)

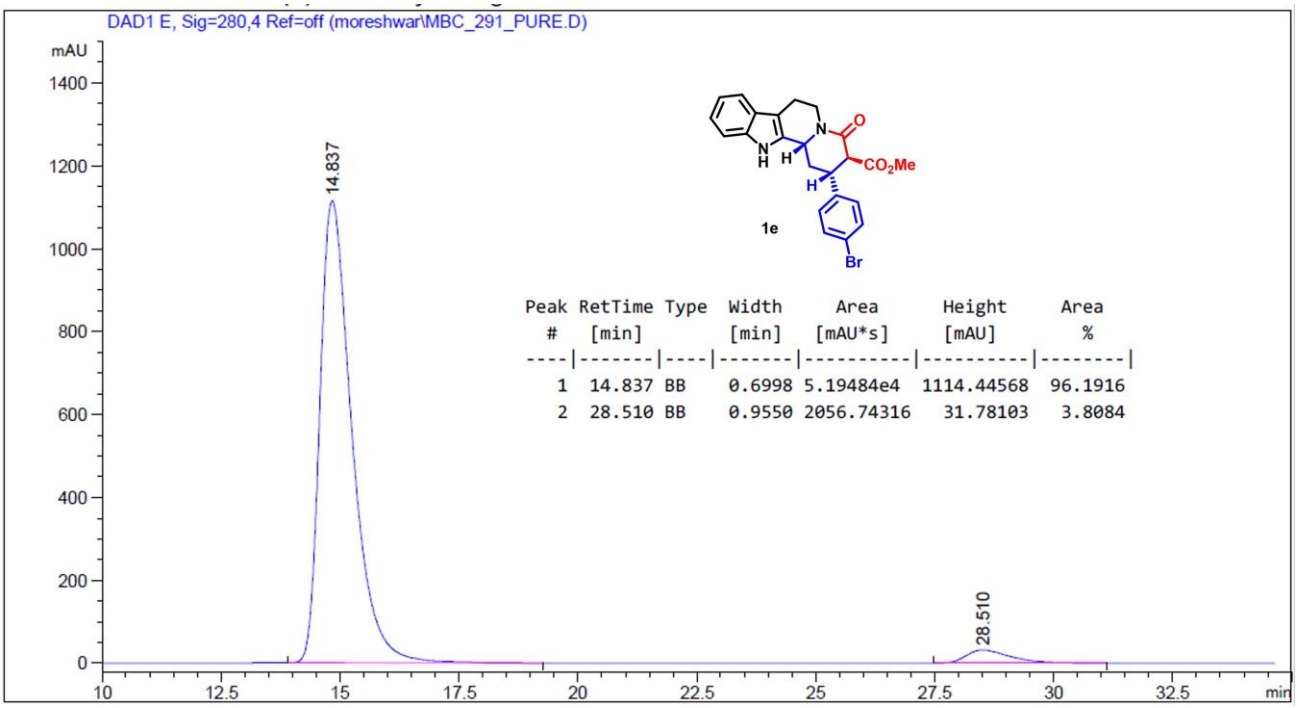


Figure S71. HPLC chromatogram for **1e**

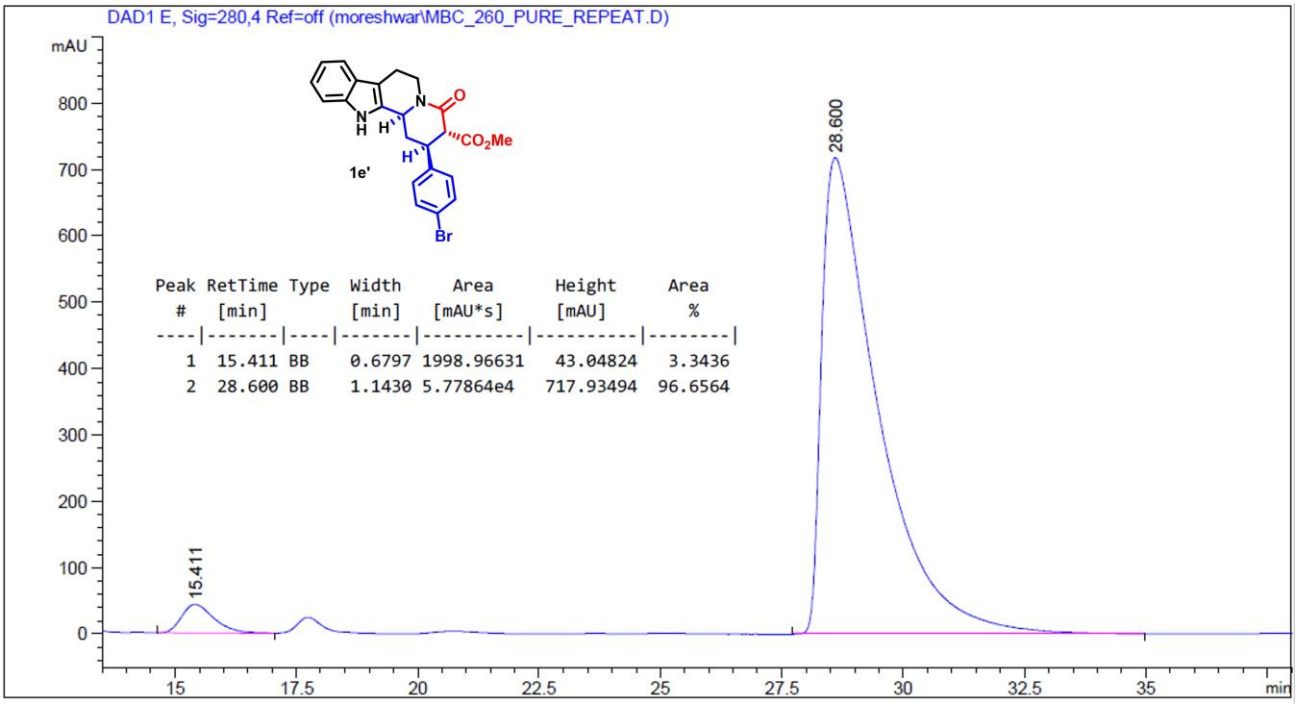


Figure S72. HPLC chromatogram for **1e'**

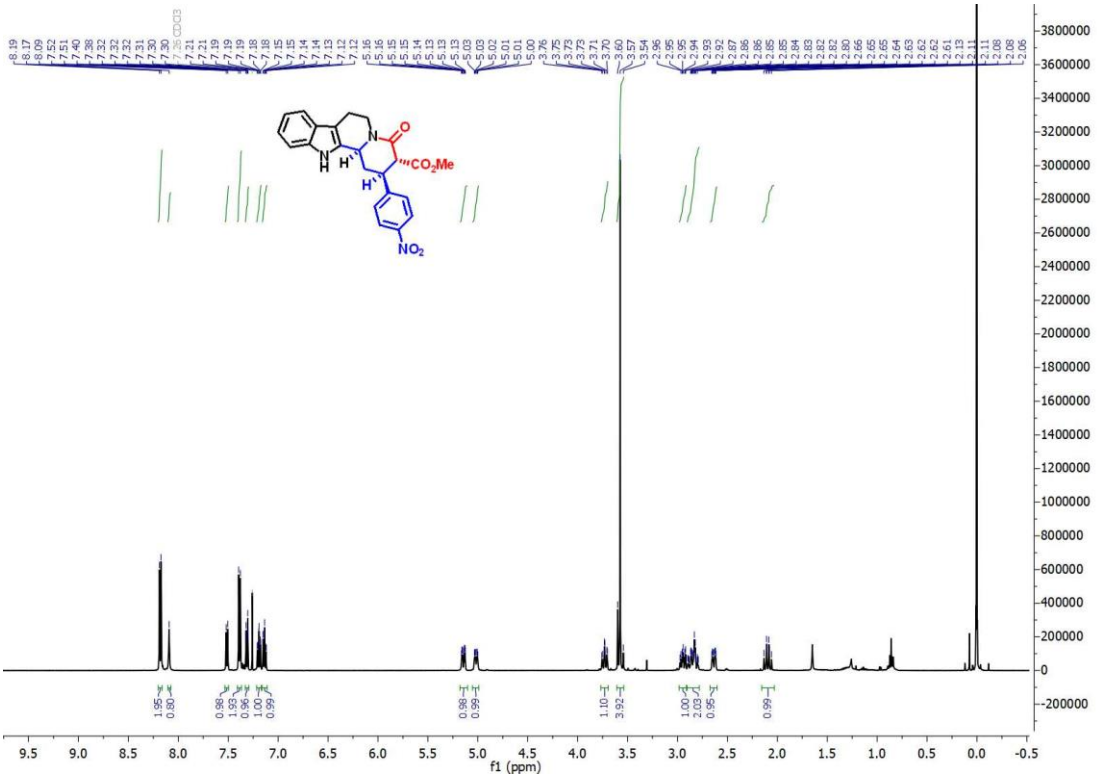


Figure S73. ^{1}H NMR of Compound **1f'**

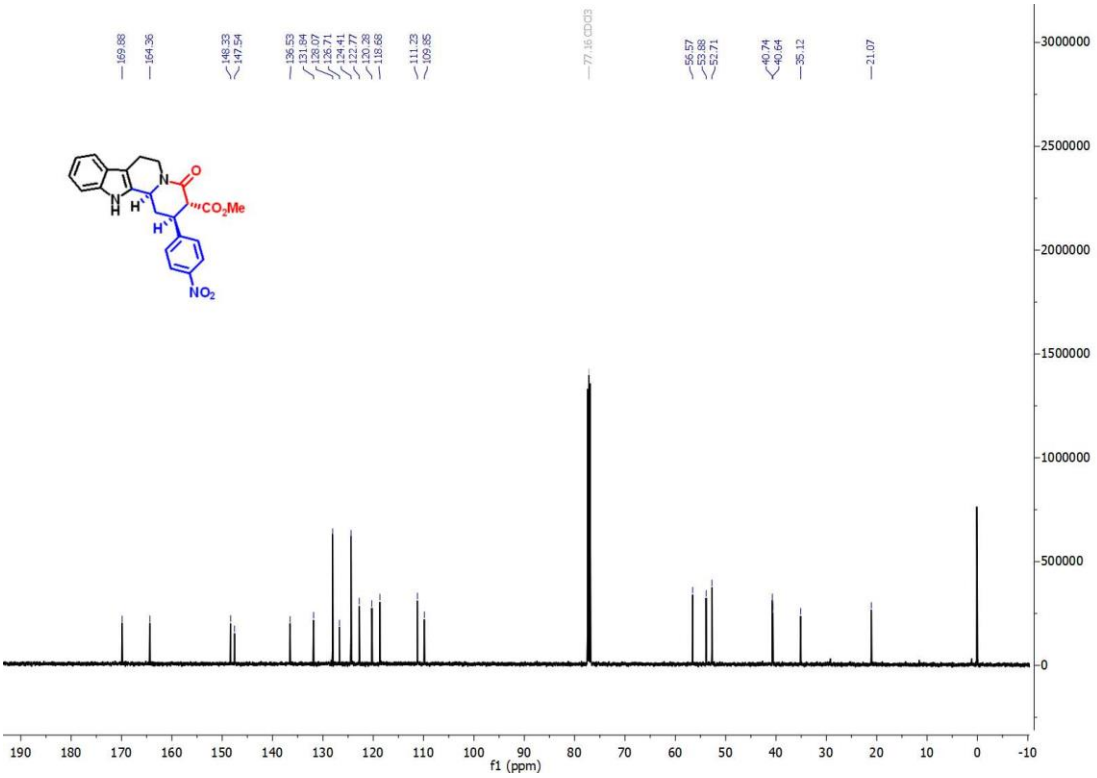


Figure S74. ^{13}C NMR of Compound **1f'**

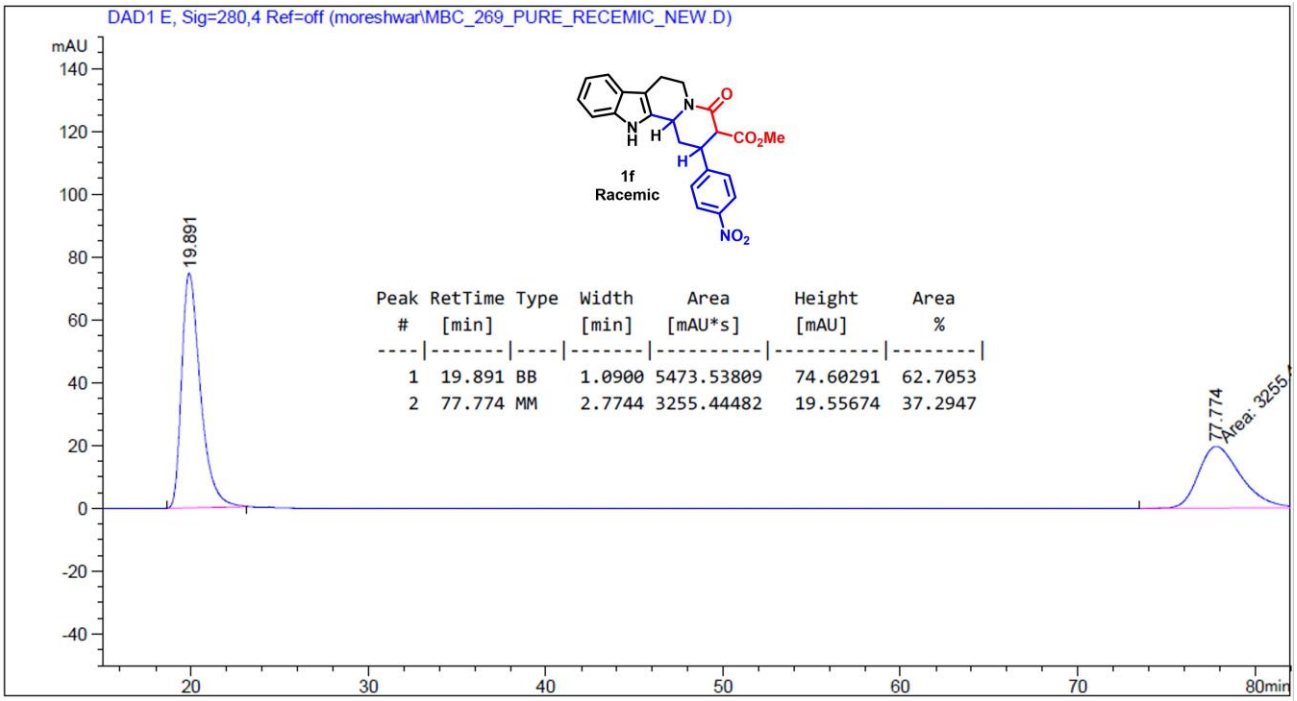


Figure S75. HPLC chromatogram for **1f** (Racemic)

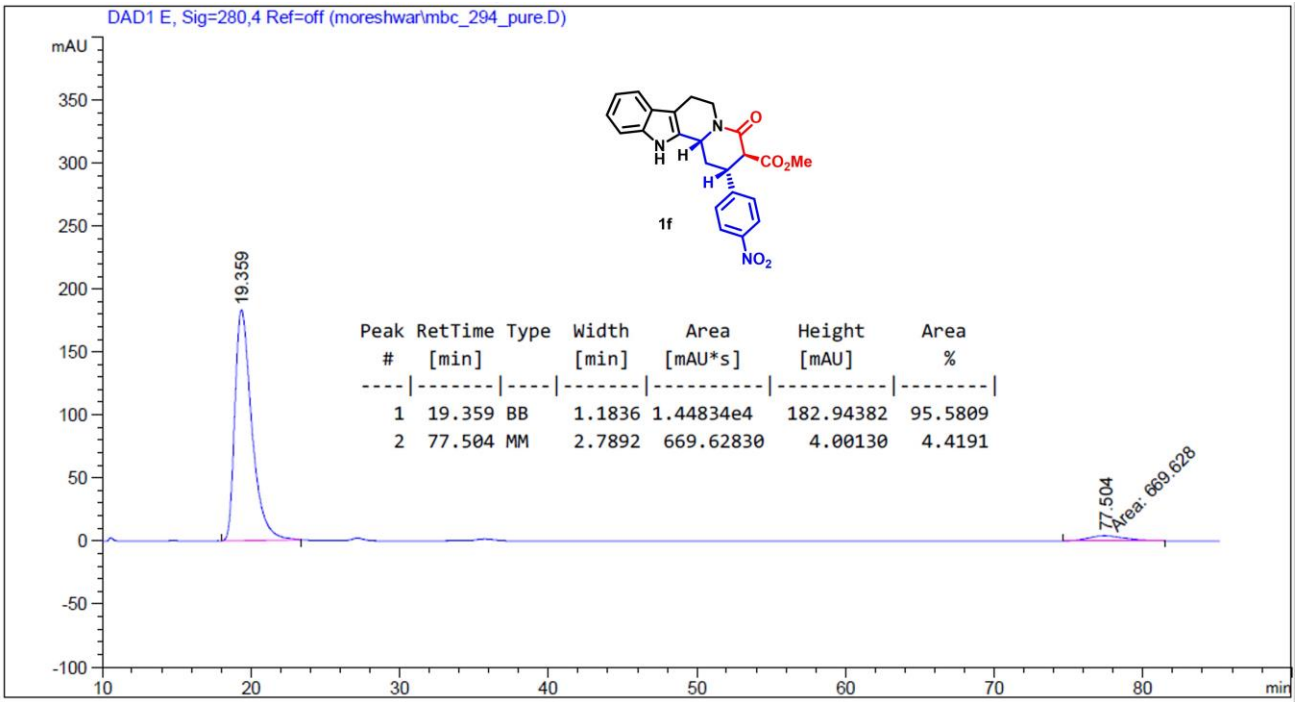


Figure S76. HPLC chromatogram for **1f**

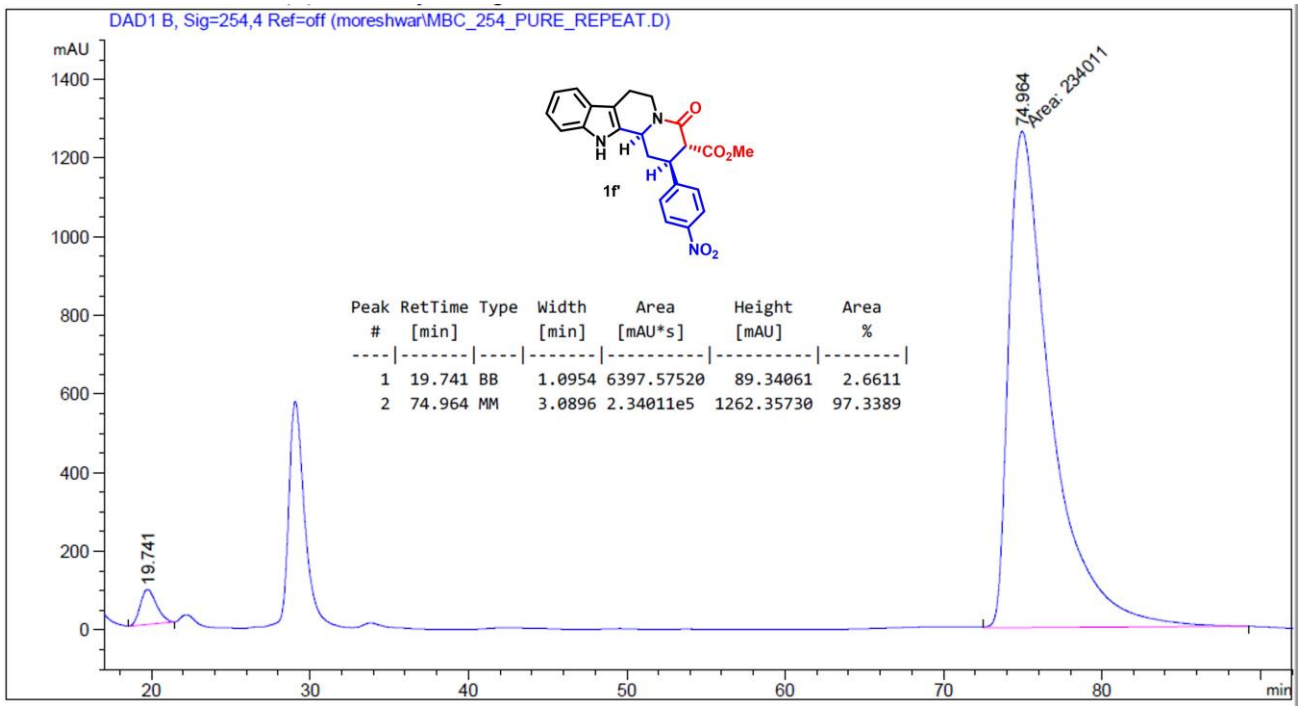


Figure S77. HPLC chromatogram for **1f'**

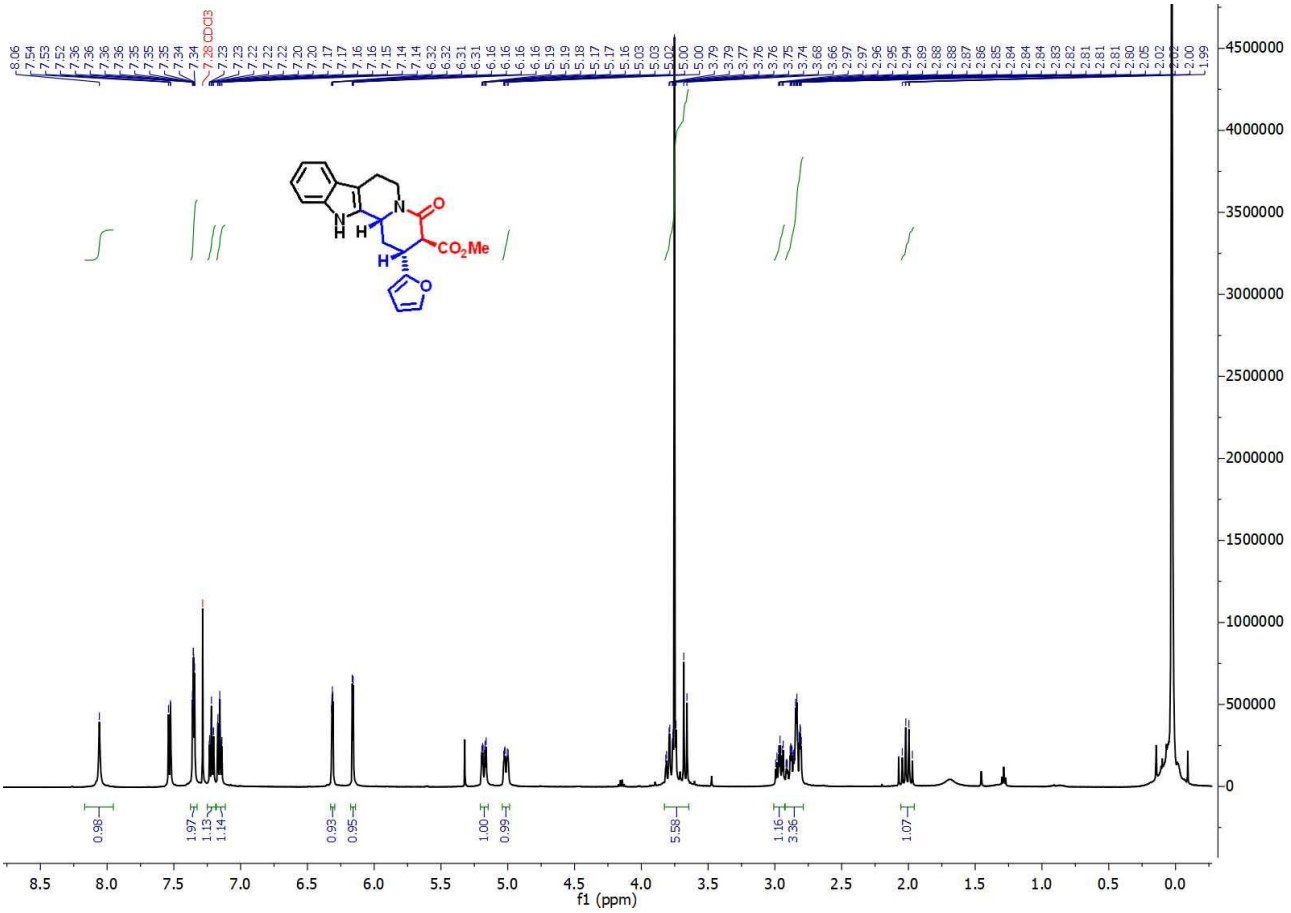


Figure S78. ^{1}H NMR of Compound **1g**

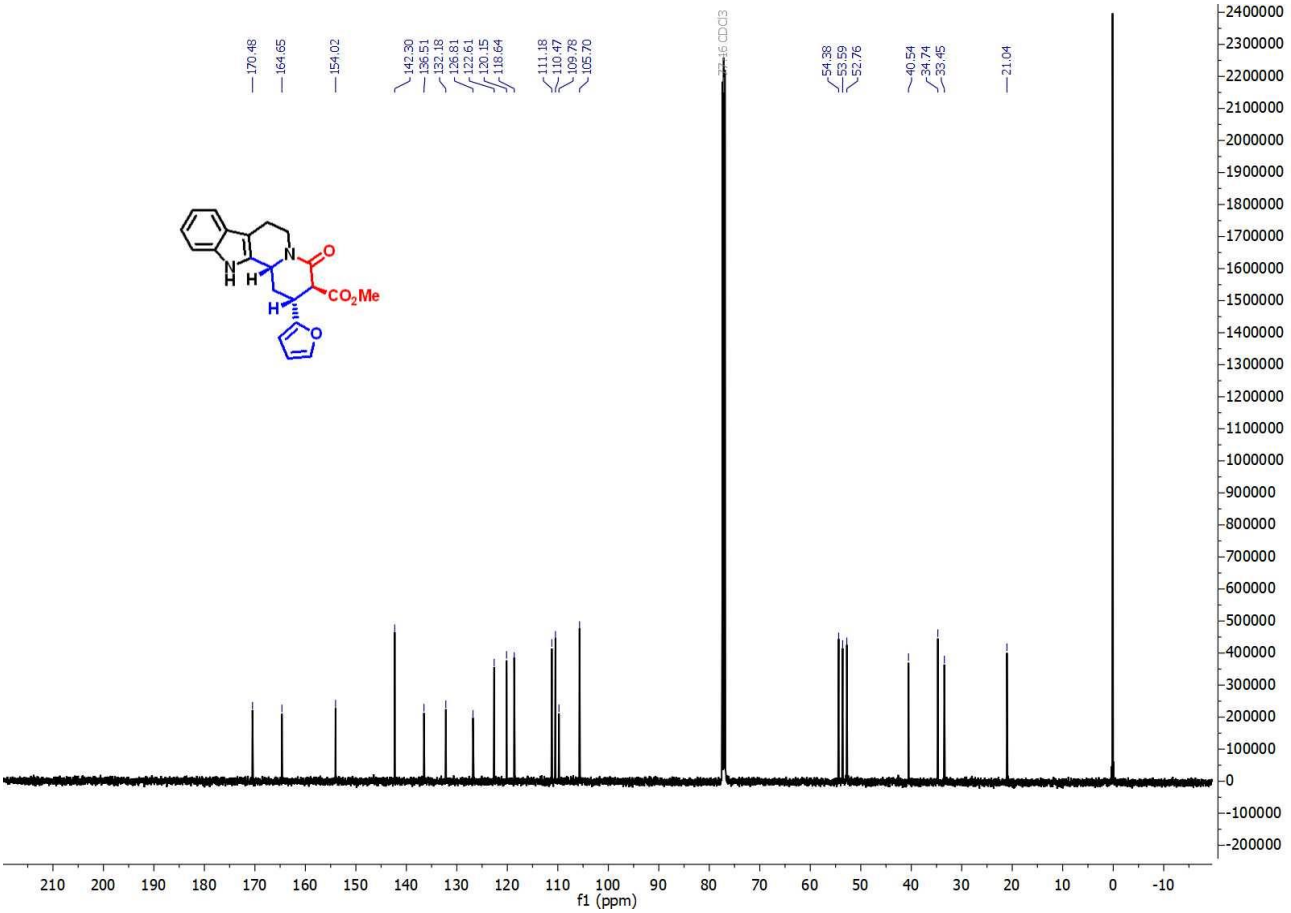
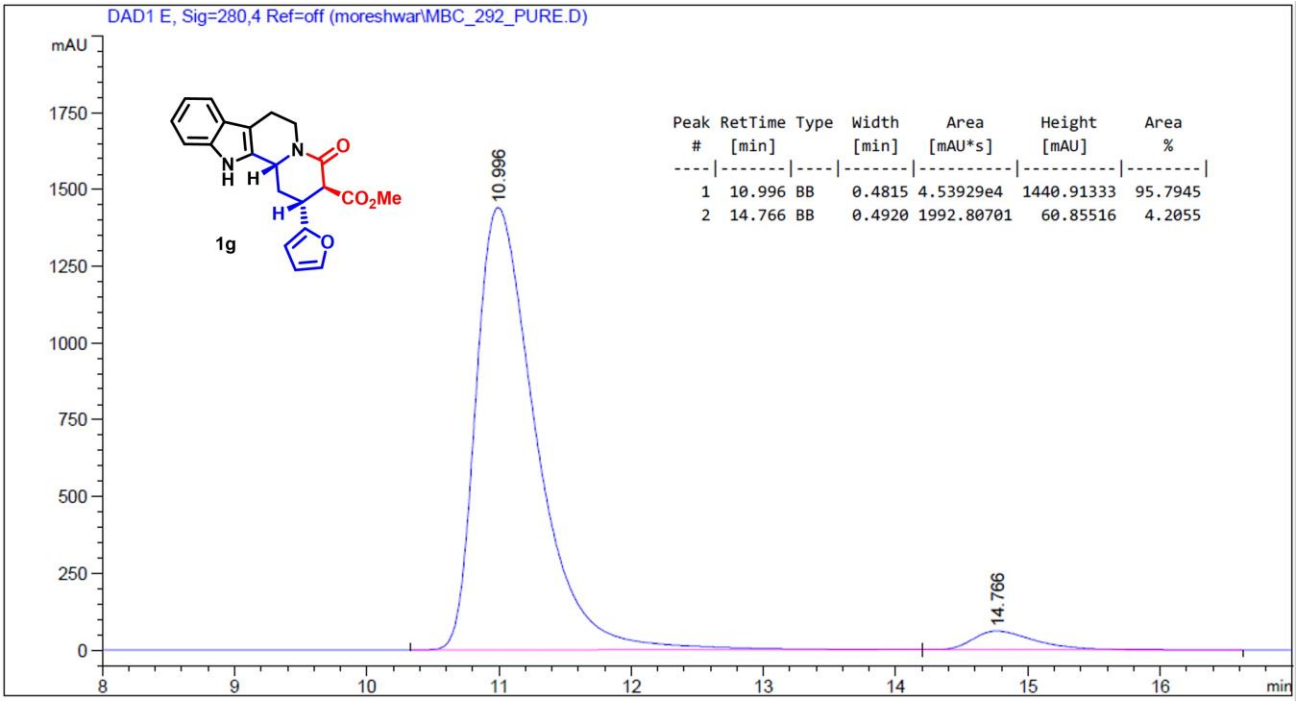


Figure S79. ^{13}C NMR of Compound **1g**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.996	BB	0.4815	4.53929e4	1440.91333	95.7945
2	14.766	BB	0.4920	1992.80701	60.85516	4.2055

Figure S80. HPLC chromatogram for **1g**

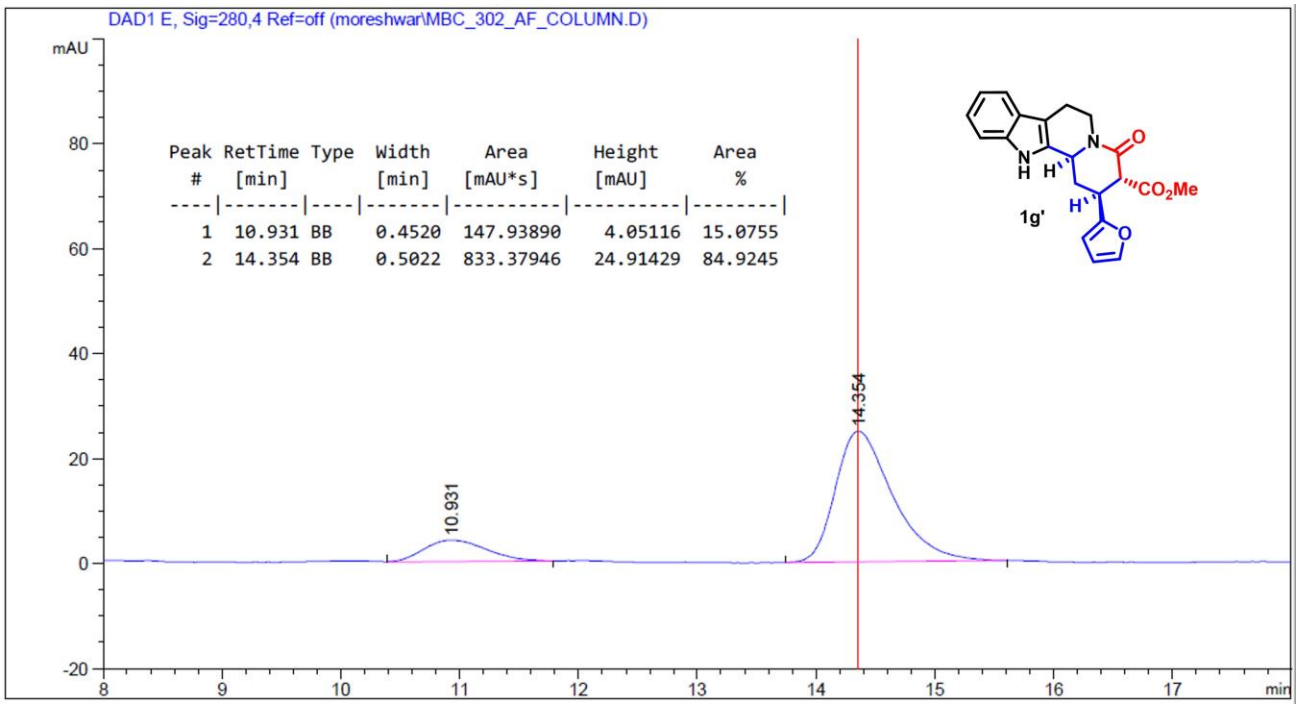


Figure S81. HPLC chromatogram for **1g'**

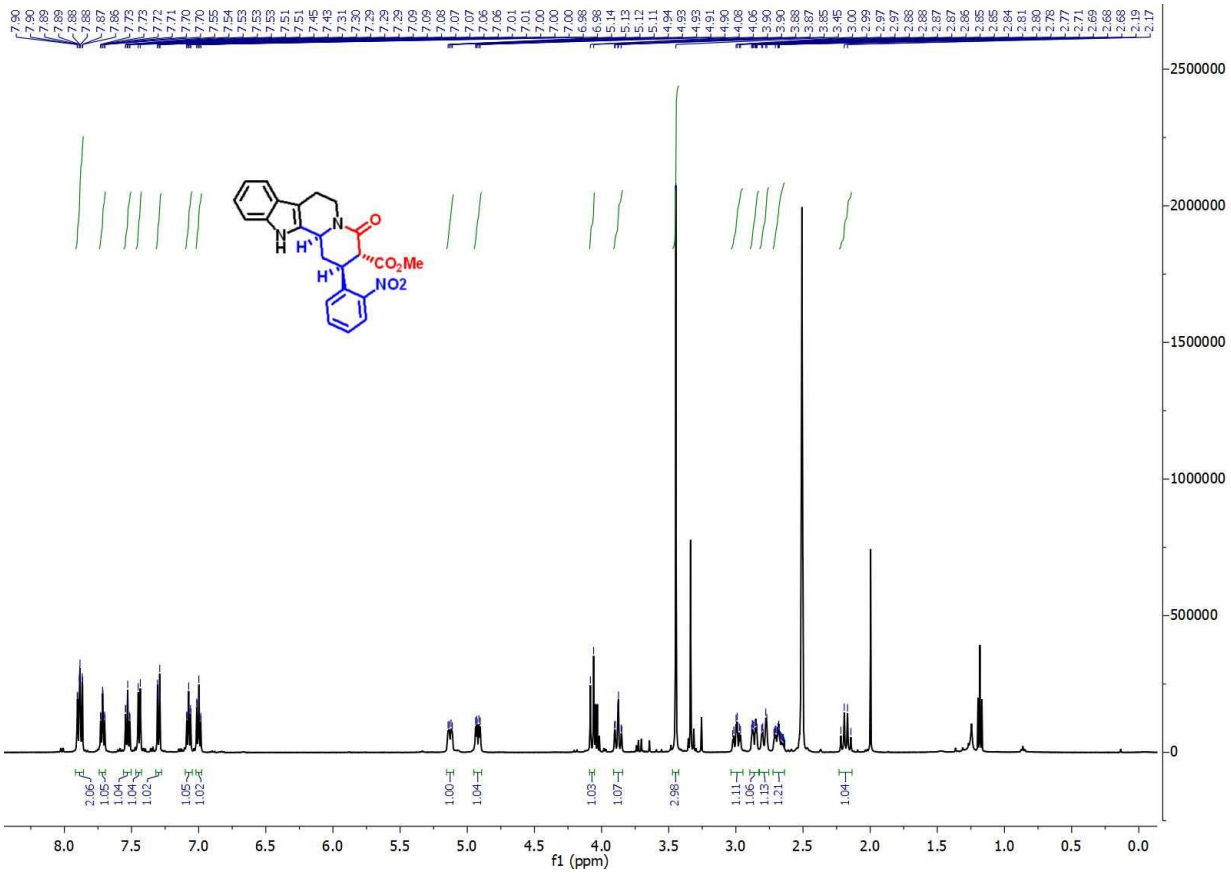


Figure S82. ^{1}H NMR of Compound **1h'**

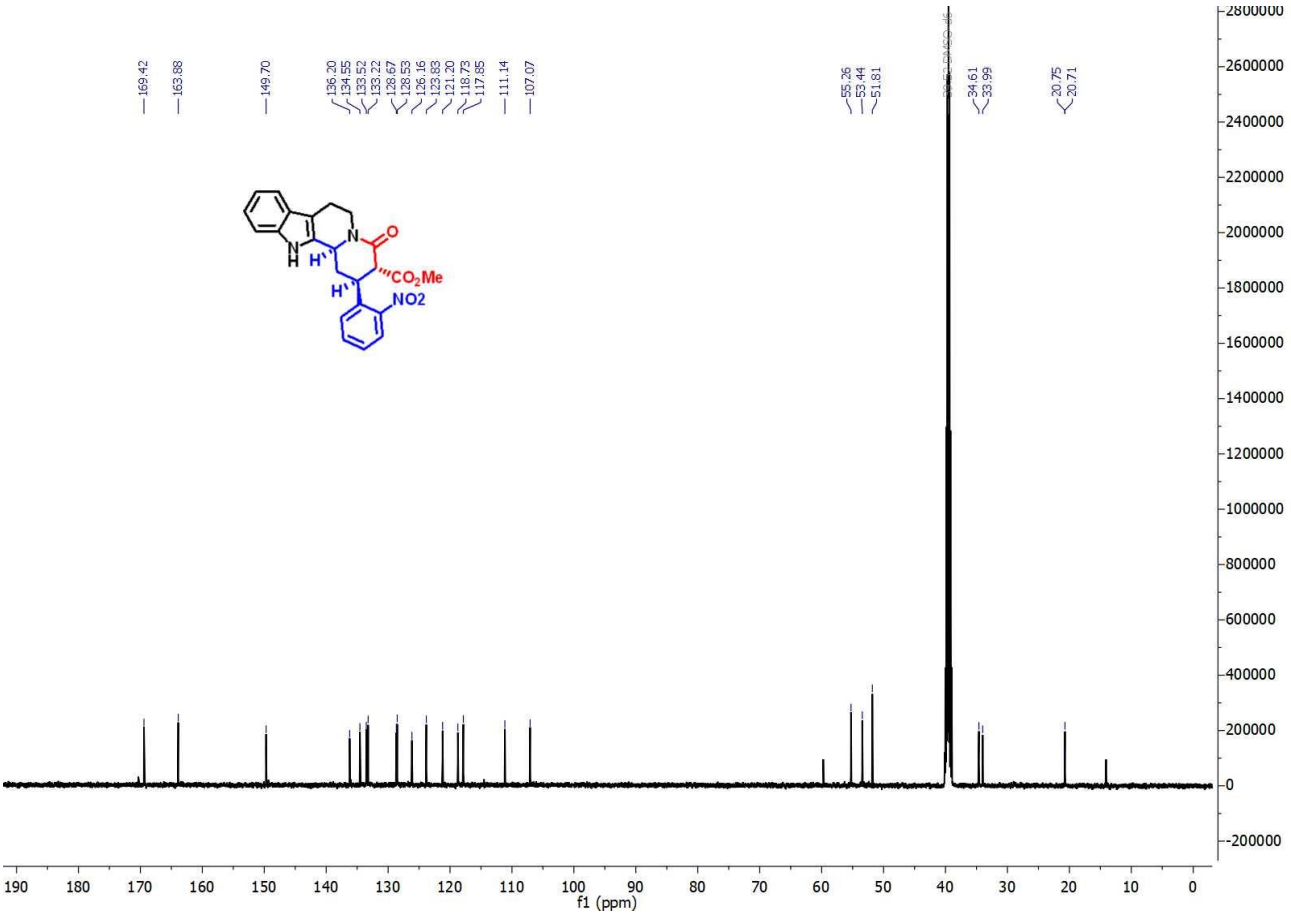


Figure S83. ^{13}C NMR of Compound **1h'**

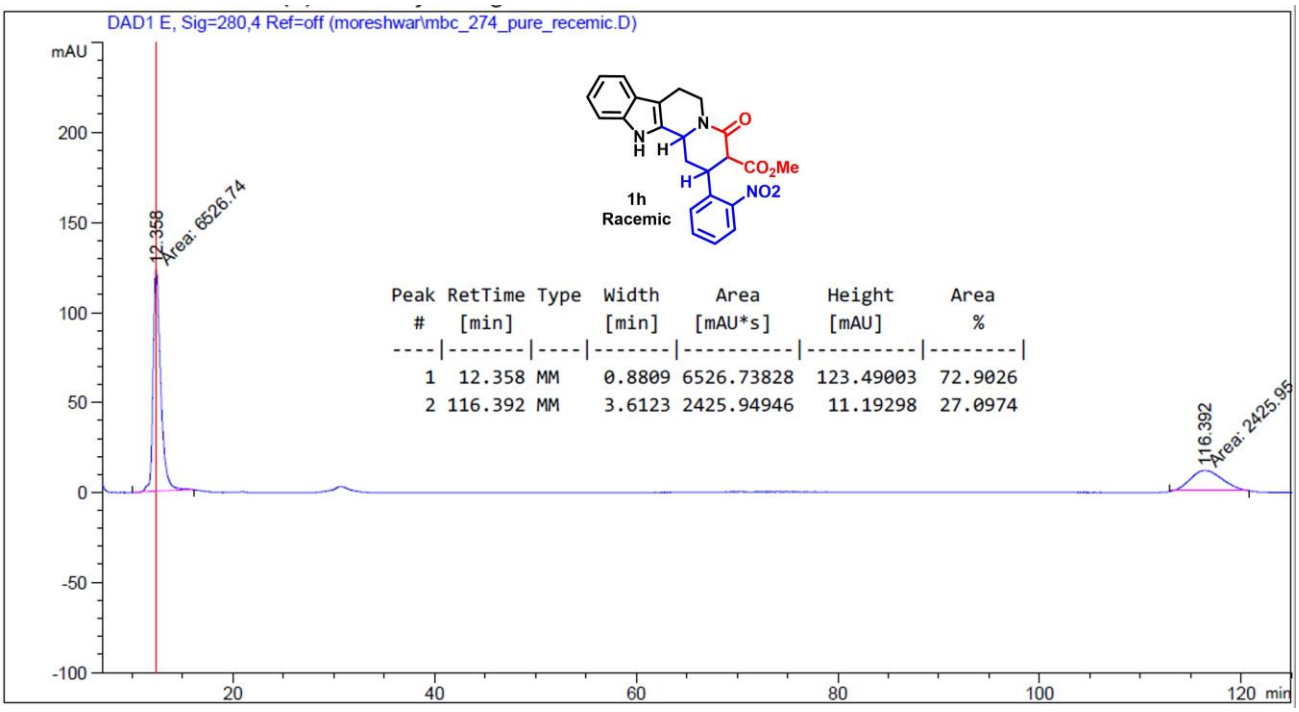


Figure S84. HPLC chromatogram for **1h** (Racemic)

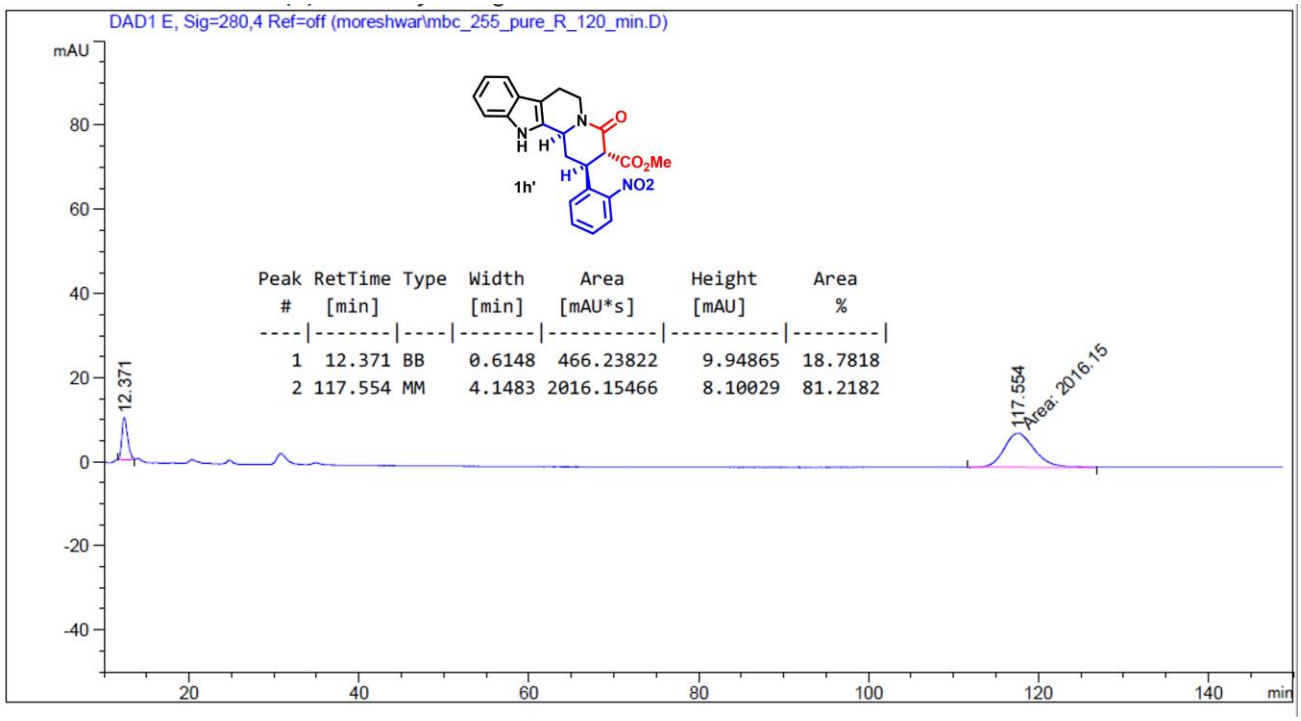


Figure S85. HPLC chromatogram for **1h'**

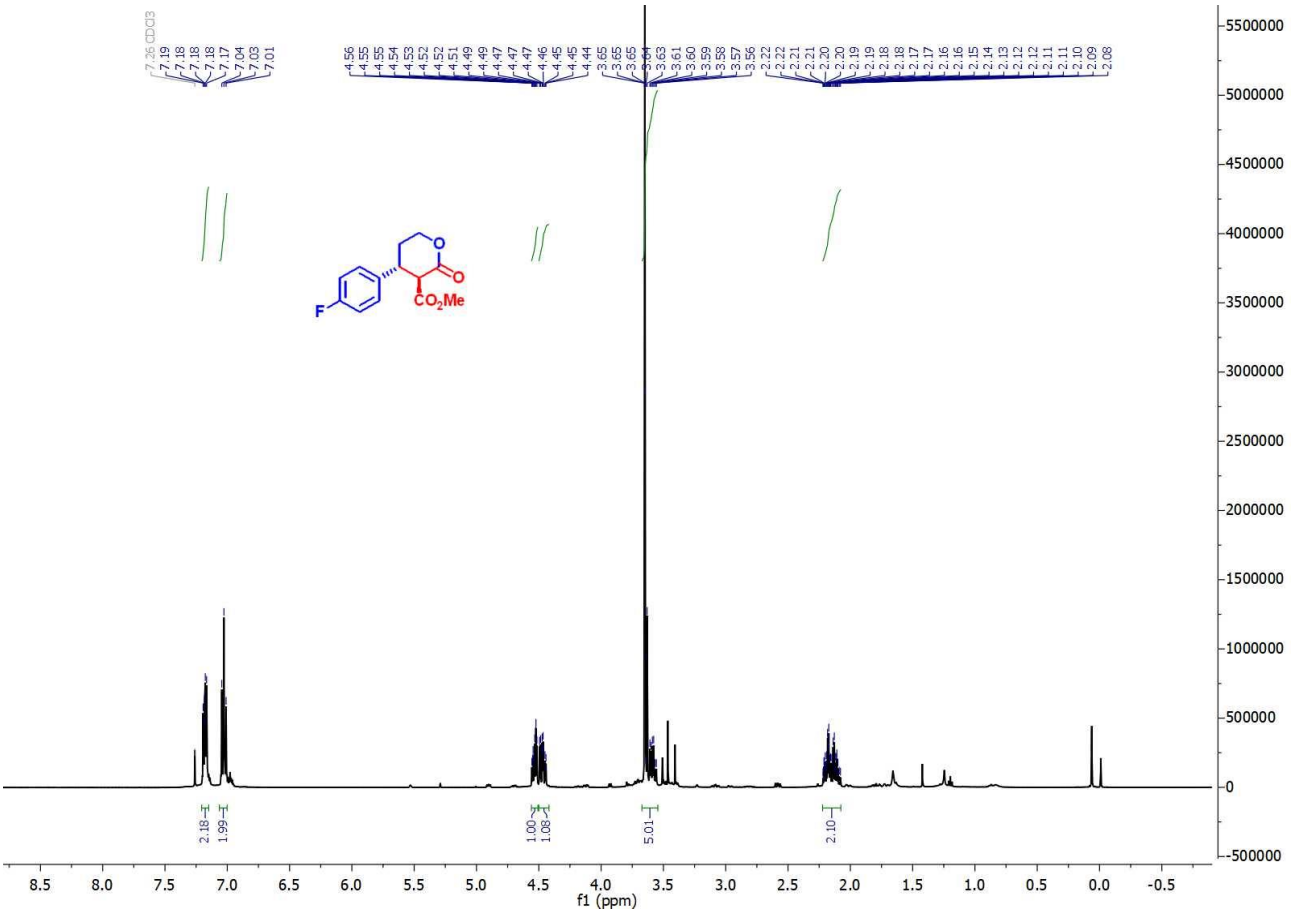


Figure S86. ^{1}H NMR of Compound **6**

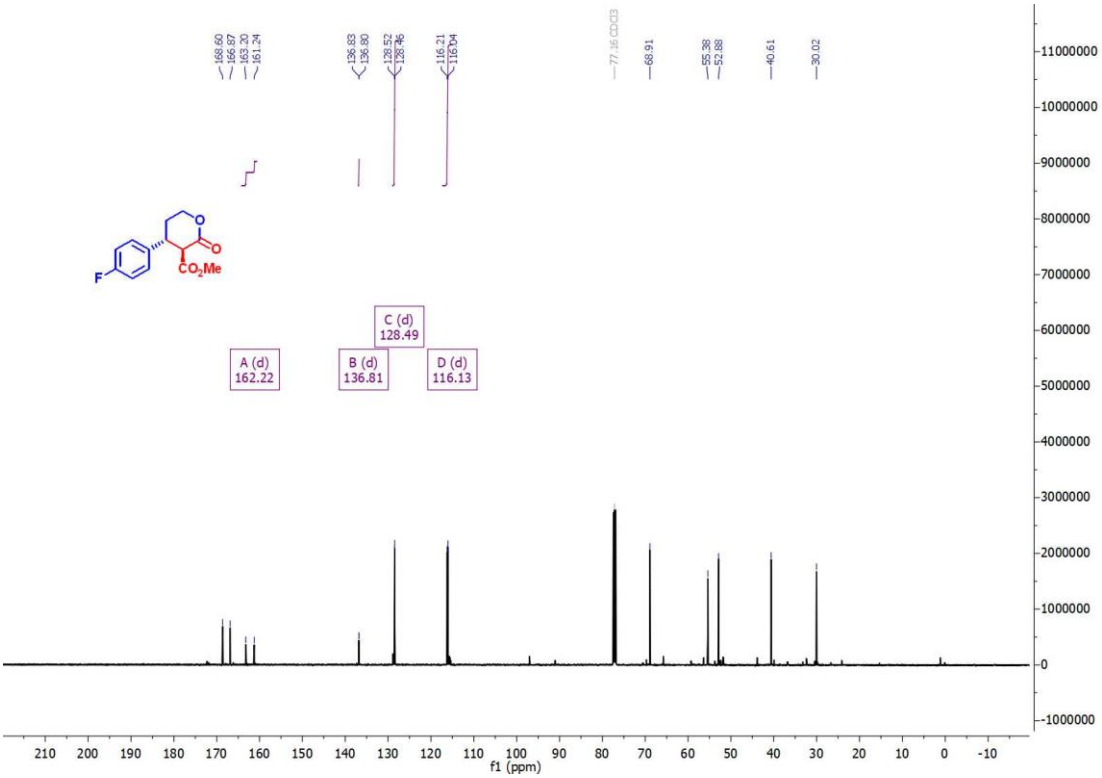


Figure S87. ^{13}C NMR of Compound **6**

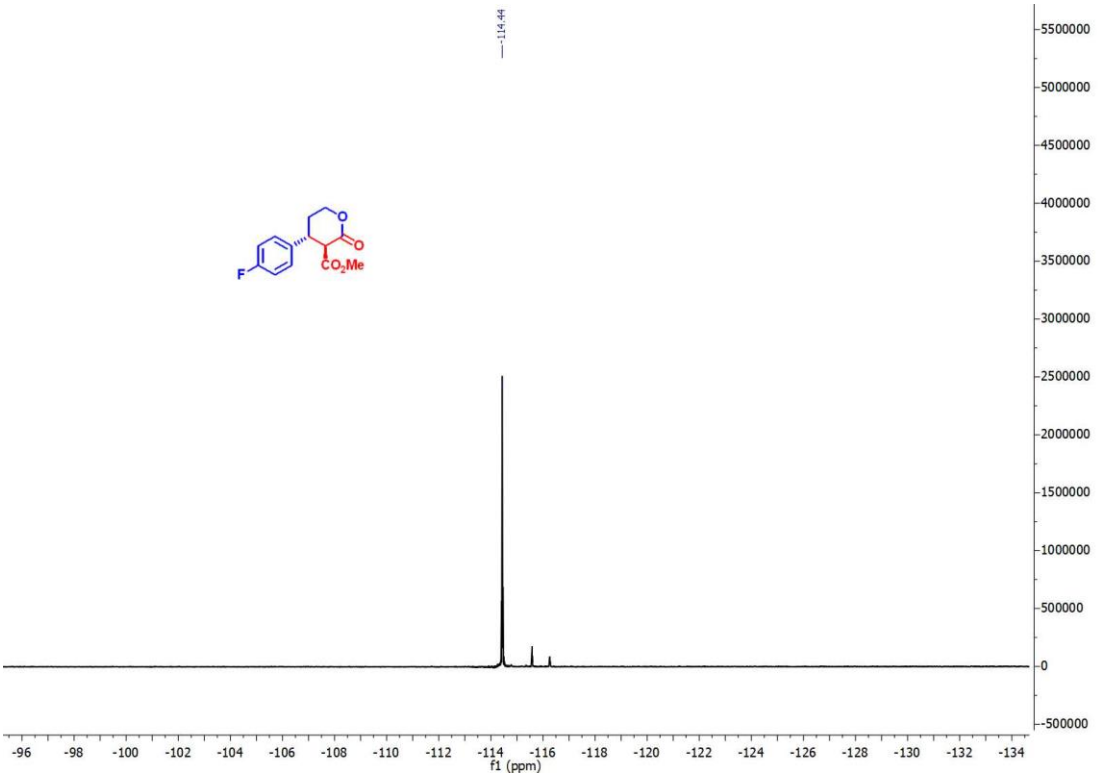


Figure S88. ^{19}F NMR of Compound **6**

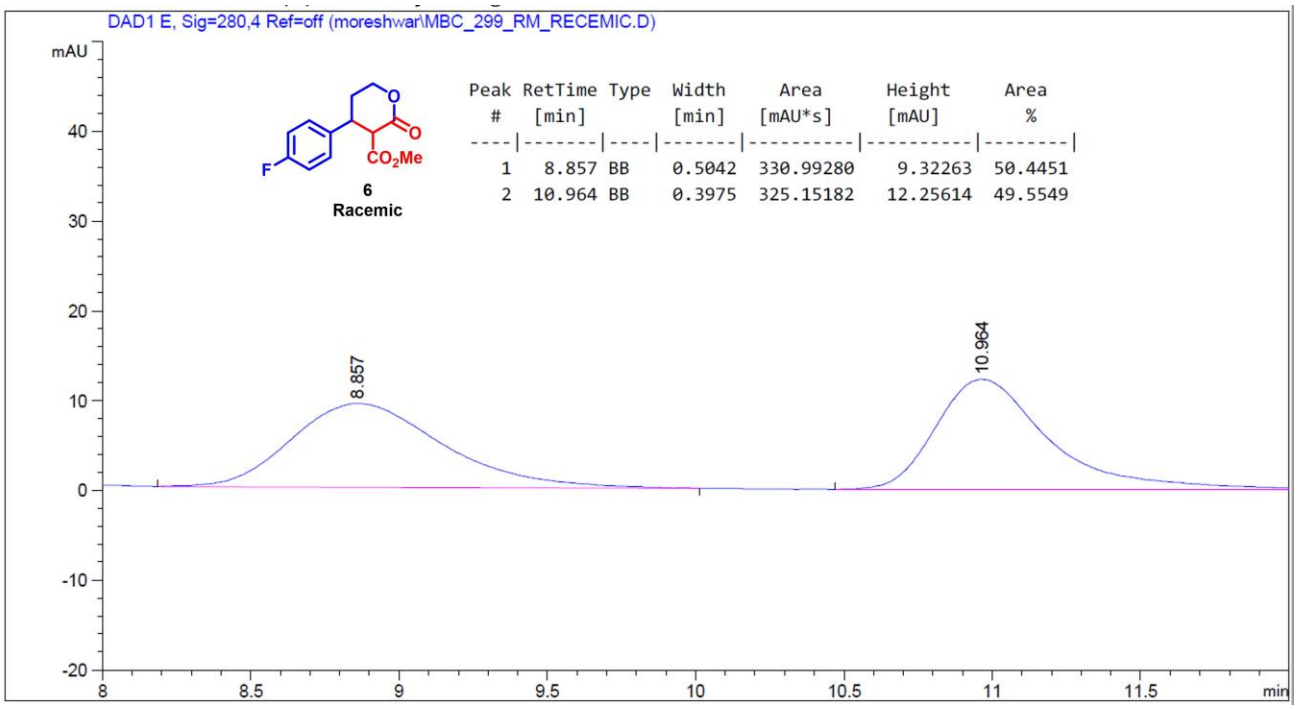


Figure S89. HPLC chromatogram for **6** (Racemic)

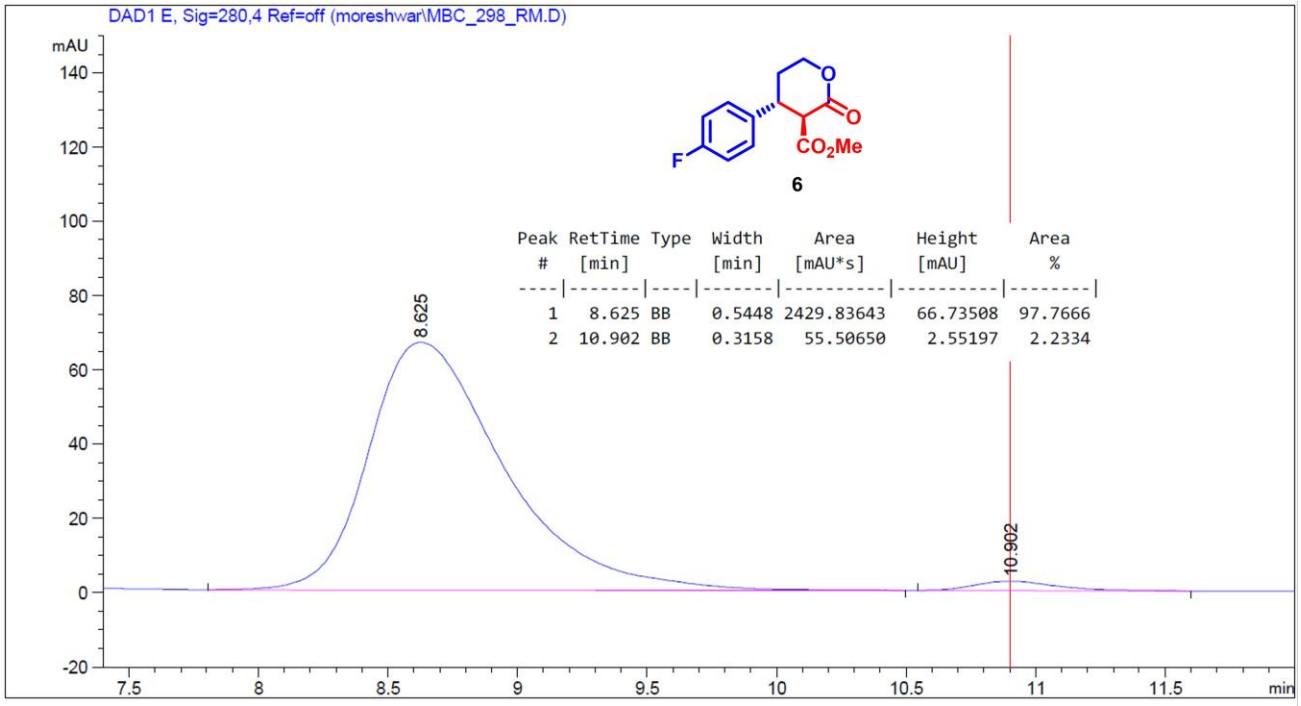


Figure S90. HPLC chromatogram for **6**

8. Crystal data of 1a'

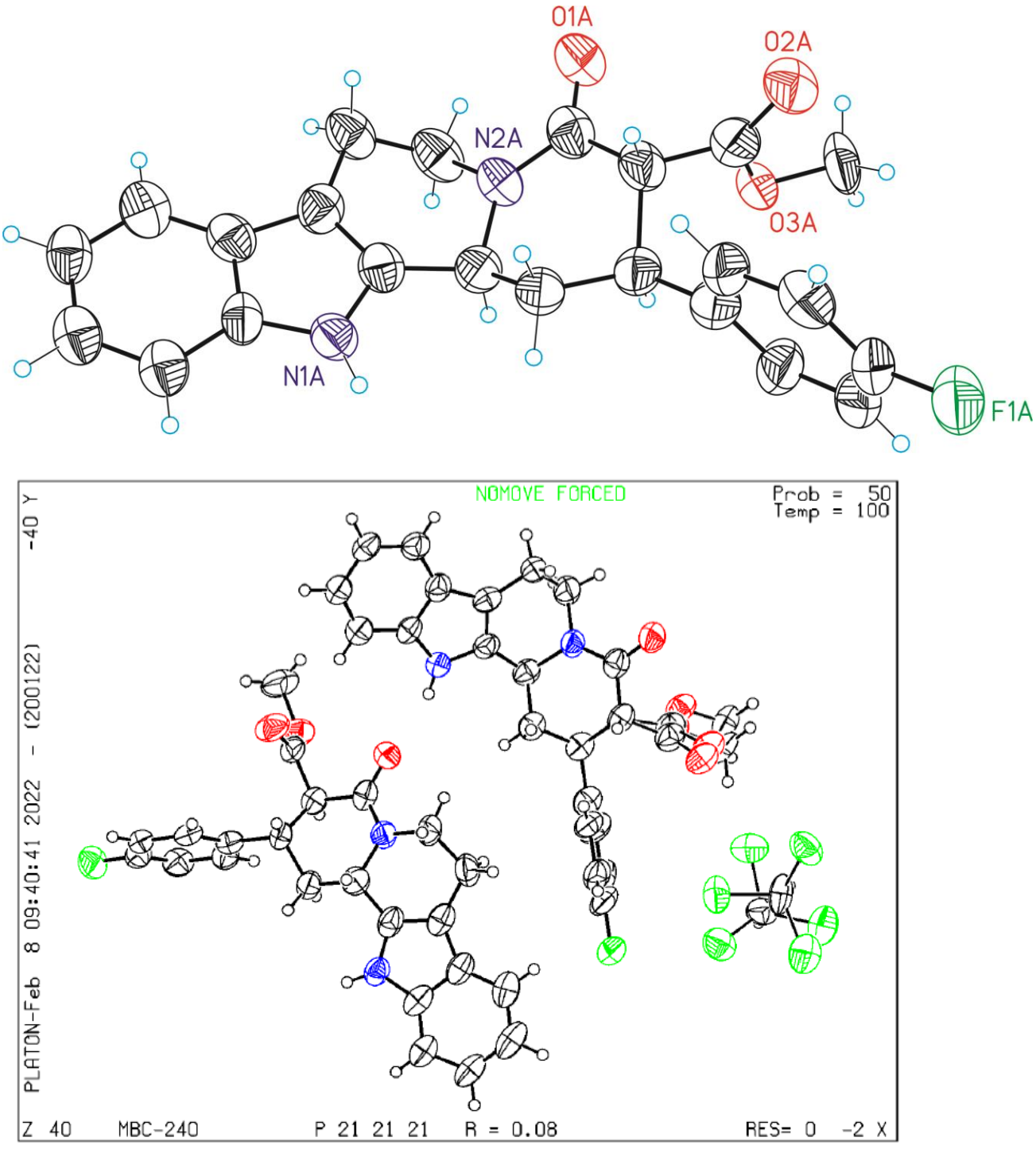


Figure S91. Single crystal data for entry **1a'**

Table 1. Crystal data and structure refinement for entry **1a'**.

Identification code	Entry **1a'**	
Empirical formula	C23.50 H21.50 Cl1.50 F N2 O3	
Formula weight	452.10	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.8581(16)Å	α= 90°.
	b = 14.632(2)Å	β = 90°.
	c = 27.589(4)Å	γ = 90°.
Volume	4383.3(11) $Å^3$	
Z	8	
Density (calculated)	1.370 Mg/m^3	
Absorption coefficient	0.272 mm^{-1}	
F(000)	1880	
Crystal size	0.100 x 0.050 x 0.050 mm^3	
Theta range for data collection	2.336 to 26.236°.	
Index ranges	-13<=h<=12,-18<=k<=15,-29<=l<=34	
Reflections collected	35993	
Independent reflections	8576[R(int) = 0.1429]	
Completeness to theta =26.236°	98.6%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.52	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8576/ 120/ 622	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0762, wR2 = 0.1689	
R indices (all data)	R1 = 0.1856, wR2 = 0.2042	
Flack parameter	x =0.01(7)	
Largest diff. peak and hole	0.216 and -0.258 $e.Å^{-3}$	

10. References:

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