

Generative exploration of fragment-based chemical space via large language models enables the discovery of potent leads for targets lacking bioactive ligands

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Appendix A Detailed results of comparative experiment

We selected a random set of 10 target proteins from the CrossDocked2022 database for evaluation, the PDB ids are 1FMC, 4AAW, 2AZY, 14GS, 1PHK, 3U5Y, 2HCJ, 3KC1, 3O96 and 3HY9. The complete structural characteristics and computational results for each protein target are presented in this section.

Table A1: Result of the de novo design task in the scene of random and prior initialization targeting 1FMC

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	<u>-10.60</u>	<u>-10.30</u>	<u>-9.80</u>	-10.30	-10.00	-9.40
RGA	-7.80	-7.26	-6.38	-7.00	-6.40	-5.30
Reinvent	-10.50	-10.10	-9.50	-10.30	-10.00	-9.40
LMLF	-10.60	-9.80	-8.60	<u>-10.40</u>	<u>-10.20</u>	<u>-9.50</u>
AutoLeadDesign	-12.90	-10.65	-10.60	-12.10	-11.10	-10.40

Table A2: Result of the de novo design task in the scene of random and prior initialization targeting 4AAW

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	<u>-9.40</u>	<u>-9.20</u>	<u>-8.90</u>	-9.40	-8.60	-8.05
RGA	-7.00	-6.59	-5.85	-8.80	-8.40	-7.20
Reinvent	-9.20	-8.80	-8.10	-9.40	-8.60	-8.05
LMLF	-7.60	-7.40	-7.00	-12.50	-11.50	<u>-8.10</u>
AutoLeadDesign	-9.80	-9.20	-8.61	<u>-10.80</u>	<u>-10.46</u>	-9.71

Table A3: Result of the de novo design task in the scene of random and prior initialization targeting 2AZY

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-10.70	-10.50	-10.20	-10.80	-10.60	<u>-10.30</u>
RGA	-8.00	-7.59	-6.64	-10.20	-9.76	-7.64
Reinvent	-11.00	-10.50	-9.70	-11.10	-10.60	-10.10
LMLF	<u>-12.10</u>	<u>-11.80</u>	<u>-10.20</u>	<u>-13.40</u>	<u>-12.00</u>	-10.00
AutoLeadDesign	-13.50	-12.62	-11.81	-13.90	-13.21	-12.40

Table A4: Result of the de novo design task in the scene of random and prior initialization targeting 14GS

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-10.00	-9.70	-9.10	-8.60	-8.20	<u>-7.60</u>
RGA	-7.40	-6.74	-5.91	-8.60	-8.24	-7.20
Reinvent	-8.00	-8.30	-7.70	-8.60	-8.20	-7.60
LMLF	-8.20	-7.40	-6.60	<u>-8.60</u>	<u>-8.40</u>	-7.50
AutoLeadDesign	<u>-9.90</u>	<u>-9.26</u>	<u>-8.60</u>	-9.30	-9.10	-8.40

Table A5: Result of the de novo design task in the scene of random and prior initialization targeting 1PHK

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-10.50	-10.20	-9.90	-11.60	-11.40	-10.90
RGA	-8.70	-7.75	-6.89	-10.70	-10.24	-8.30
Reinvent	<u>-12.60</u>	<u>-11.90</u>	<u>-11.10</u>	<u>-12.40</u>	<u>-11.70</u>	<u>-11.00</u>
LMLF	-10.40	-10.20	-9.40	-10.90	-10.30	-9.30
AutoLeadDesign	-13.90	-12.70	-11.30	-13.20	-12.20	-11.20

Table A6: Result of the de novo design task in the scene of random and prior initialization targeting 3U5Y

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	<u>-11.40</u>	-11.00	-10.50	-11.00	-10.80	-10.40
RGA	-8.60	-8.12	-7.14	-10.70	-10.24	-8.30
Reinvent	-11.30	<u>-11.10</u>	<u>-10.70</u>	<u>-11.70</u>	<u>-11.30</u>	<u>-10.80</u>
LMLF	-8.30	-7.37	-7.07	-11.10	-10.40	-9.80
AutoLeadDesign	-12.60	-11.72	-10.75	-13.00	-12.30	-11.40

Table A7: Result of the de novo design task in the scene of random and prior initialization targeting 2HCJ

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-10.60	-10.40	-10.00	-11.20	-10.70	-10.20
RGA	-6.10	-5.68	-5.07	-7.00	-6.40	-5.30
Reinvent	<u>-9.10</u>	<u>-8.60</u>	<u>-7.90</u>	-9.00	-8.70	-8.00
LMLF	-6.60	-5.90	-5.80	<u>-10.40</u>	<u>-10.00</u>	<u>-9.30</u>
AutoLeadDesign	-8.50	-8.30	-7.40	-9.30	-9.20	-8.5

Table A8: Result of the de novo design task in the scene of random and prior initialization targeting 3KC1

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-11.50	-10.90	-10.50	-10.70	-10.32	-9.31
RGA	-7.00	-6.68	-5.69	-8.80	-8.79	-6.50
Reinvent	<u>-10.10</u>	-9.00	-8.20	-9.10	-8.70	-8.20
LMLF	-7.70	-6.70	-5.02	-9.40	-8.80	-8.00
AutoLeadDesign	-9.10	<u>-8.60</u>	<u>-7.60</u>	<u>-10.00</u>	<u>-9.30</u>	<u>-9.00</u>

Table A9: Result of the de novo design task in the scene of random and prior initialization targeting 3O96

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-12.00	-11.62	-11.20	-12.00	-11.70	-11.10
RGA	-9.30	-8.55	-7.29	-11.00	-10.57	-7.52
Reinvent	<u>-15.00</u>	<u>-14.32</u>	<u>-13.20</u>	<u>-14.40</u>	<u>-13.80</u>	<u>-12.98</u>
LMLF	-10.90	-10.60	-9.92	-14.20	-12.50	-9.72
AutoLeadDesign	-16.50	-15.76	-13.97	-16.50	-15.74	-14.08

Table A10: Result of the de novo design task in the scene of random and prior initialization targeting 3HY9

Methods	Random			Prior		
	Top-1	Top-10	Top-100	Top-1	Top-10	Top-100
ChemGE	-10.90	-10.30	-10.10	-11.60	-11.50	-11.00
RGA	-6.70	-6.15	-5.27	-9.40	-9.14	-7.58
Reinvent	-11.10	-10.54	-9.76	-11.10	-10.82	-9.80
LMLF	-10.40	-9.80	-8.30	-10.40	-10.10	-8.50
AutoLeadDesign	<u>-10.90</u>	<u>-10.54</u>	<u>-9.93</u>	<u>-11.10</u>	<u>-10.87</u>	<u>-9.90</u>

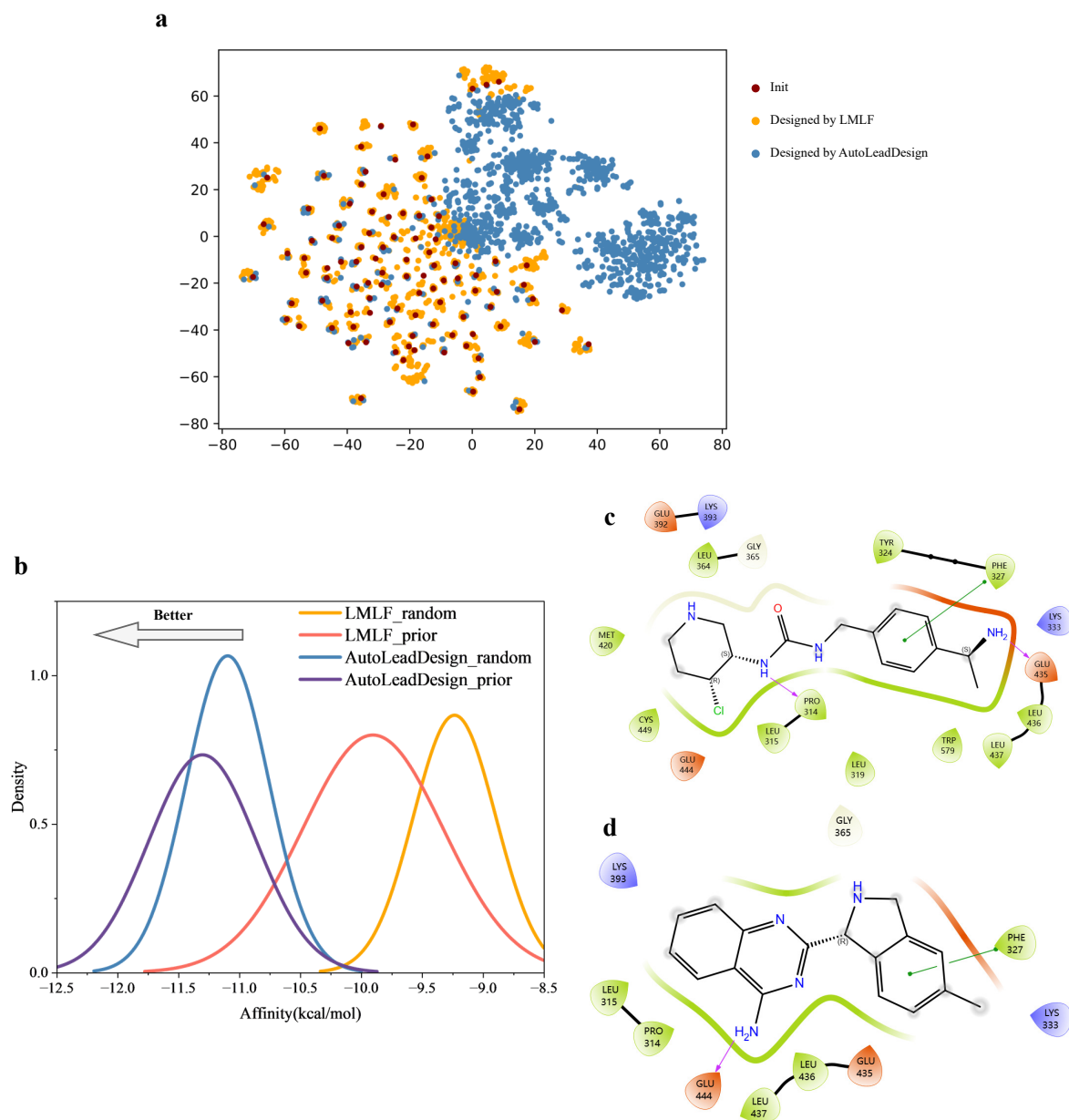
Appendix B Supplementary figures

To assess algorithmic robustness, we conducted experiments targeting PRMT5 using random initialization with 100 compounds. The results (Supplementary Fig. 1a) reveal that LMLF-generated compounds remain confined to the chemical space of their starting points, leading to persistent low bioactivity. This sensitivity to initialization underscores the limitations of local optimization in LLMs for de novo design. Conversely, as detailed in Appendix B and Supplementary Fig. 1c, d, interaction analysis for top-ranked candidates (PRR001 and ADR001) reinforces this finding: while AutoLeadDesign’s ADR001 successfully forms critical hydrogen bonds with key residues like GLU444, the LMLF-designed counterpart fails to engage with pharmacologically significant sites, aligning with our previous observations.

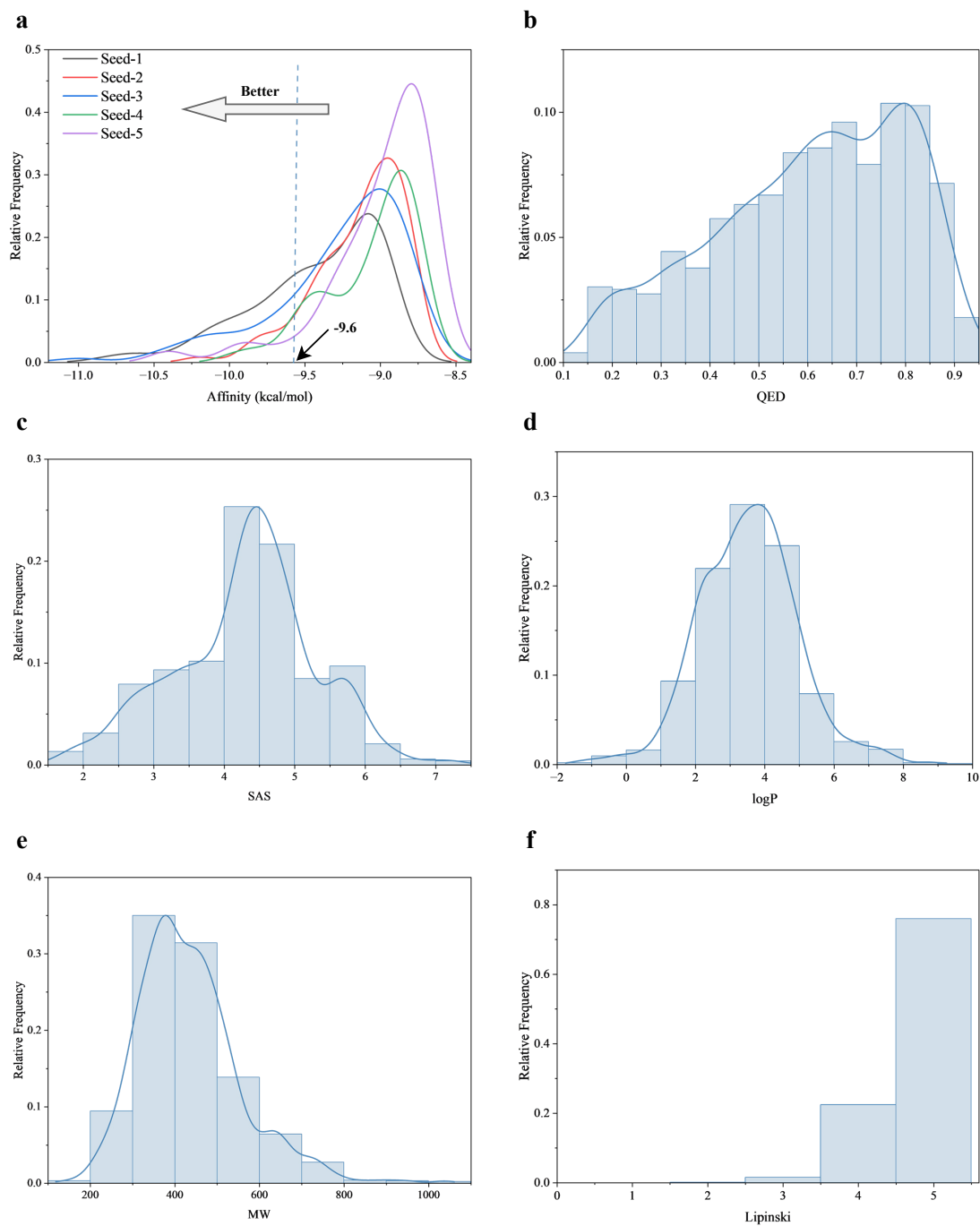
To validate the robustness of our methodology against variations in the initial compound library, we randomly constructed five molecular libraries as the initial library. The distribution of binding energy (Supplementary Fig. 2a) demonstrates that AutoLeadDesign can robustly identify leads (with a standard deviation of 0.16) with significantly higher binding affinity than known bioactive ligand ($\Delta G_{Jun1268} = -9.6 \text{ kcal/mol}$). As demonstrated in Supplementary Figs. 2b-f, the generated molecules also exhibit favorable physicochemical properties. Notably, the majority of compounds display QED scores above 0.5, indicating excellent drug-likeness. The synthetic accessibility assessment reveals that most molecules possess SAScores below 5 (with a subset ≤ 3), suggesting high synthetic feasibility. Furthermore, the calculated logP values fall within the pharmaceutically acceptable range, and molecular weights are predominantly distributed between 300-500 Da, consistent with typical small-molecule drugs. Importantly, over 78% of the generated compounds comply with all the Lipinski five rules, underscoring their potential as drug candidates.

Molecular dynamics simulation of the PLP011-PLpro complex over a 7,000 ps trajectory as shown in Supplementary Figs. 3 reveals a stable binding profile, with the ligand’s root-mean-square deviation (RMSD) primarily fluctuating between 0.10 nm and 0.15 nm after an initial equilibration phase. Atomic stability analysis via root-mean-square fluctuation (RMSF) shows that most atoms maintain low flexibility below 0.2 nm, although higher fluctuations observed in specific terminal regions suggest localized conformational freedom within the binding pocket. The intermolecular interaction is characterized by the transient formation of one to two hydrogen bonds, which provide intermittent stabilization throughout the simulation. Energetic evaluation identifies van der Waals interactions (LJ-SR), ranging from -40 to -60 kJ/mol, as the predominant driving force for complex stability, significantly outweighing the electrostatic contributions (Coul-SR). Overall, these results indicate that PLP011 maintains a robust and energetically favorable binding configuration with PLpro.

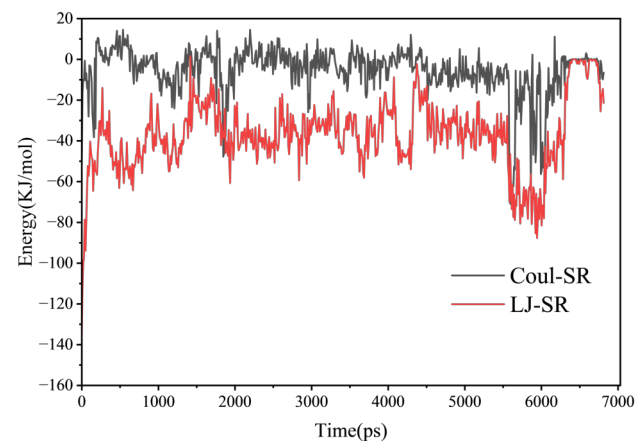
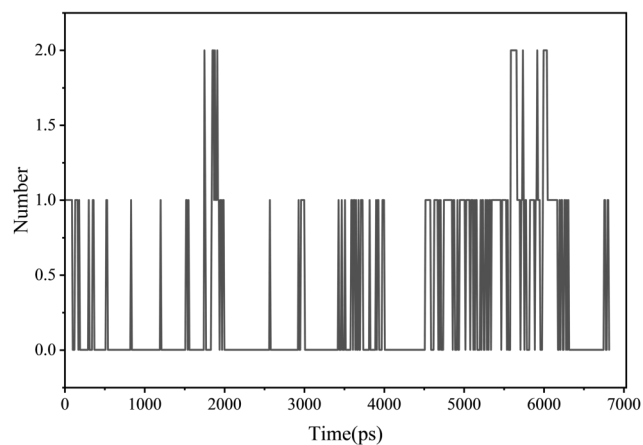
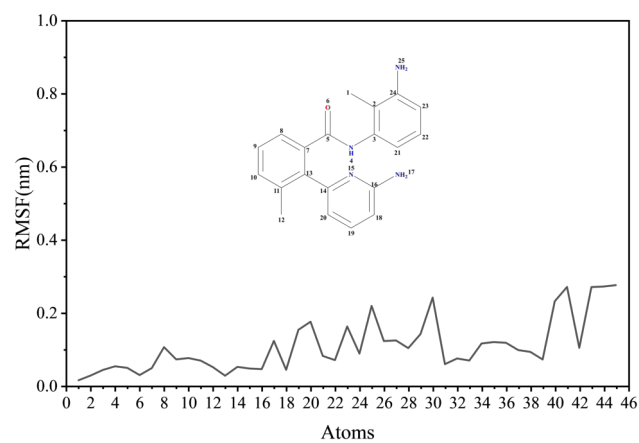
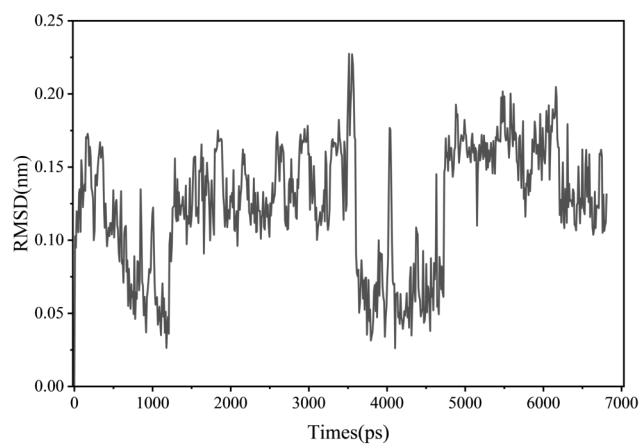
Supplementary Fig. 4 demonstrates another pivotal decision-making process targeting PRMT5. Fragment 1 and Fragment 2 occupy opposite termini of the narrow binding pocket, interacting with LYS-393 and PHE-327 respectively. The overlap between the fragments precluded conventional linker design, prompting strategic replacement of the overlapping region with an amino group to achieve fragment merging. The resulting Mol 3 not only preserves the spatial orientations and binding modes of original fragments but also fully complies with the fundamental principles of fragment merging strategies.



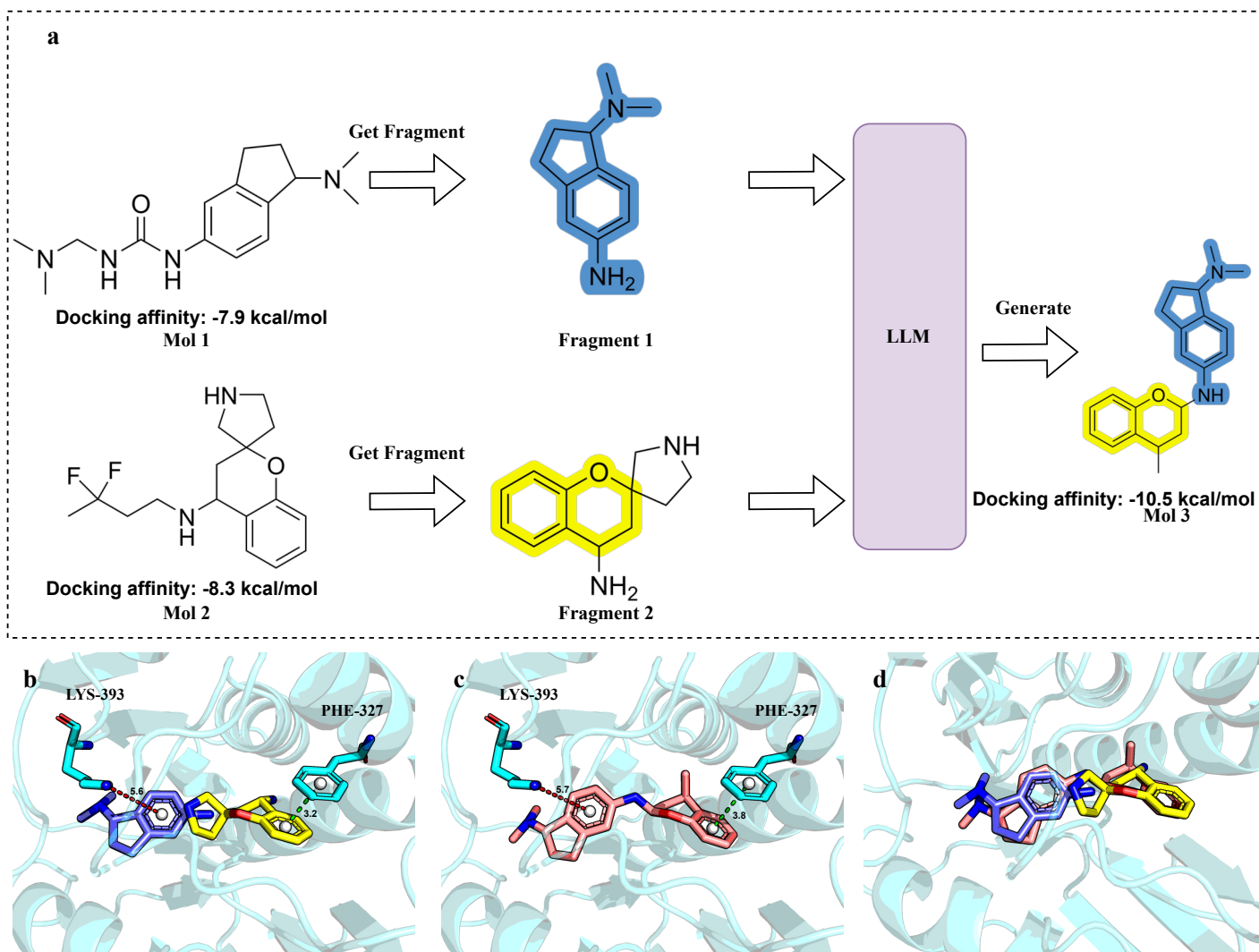
Supplementary Fig. 1 Case study of PRMT5 in the scenario of random initialization. In the visualization of binding interactions, purple lines stands for hydrogen bonds, green lines stands for Pi-Pi Stacking. **a**, The clustering result of designed compounds. **b**, The affinity distribution of designed compounds. **c**, The binding mode of PRR001. **d**, The binding mode of ADR001.



Supplementary Fig. 2 Property distribution of designed compounds. **a**, Docking scores of designed compounds in different random initial library. **b**, Quantitative Estimation of Drug-likeness. **c**, Synthetic Accessibility score. **d**, LogP. **e**, Molecule Weight. **f**, Lipinski.



Supplementary Fig. 3 Molecular Dynamics (MD) of the complex of PLP011 and PLpro. **a**, Root-mean-square deviation (RMSD) values of PLP011 in complex with PLpro. **b**, Root-mean-square fluctuation (RMSF) values of PLP011 atoms in the complex with PLpro. **c**, H-bound numbers between PLP011 and PLpro in complex. **d**, Energy of the complex.

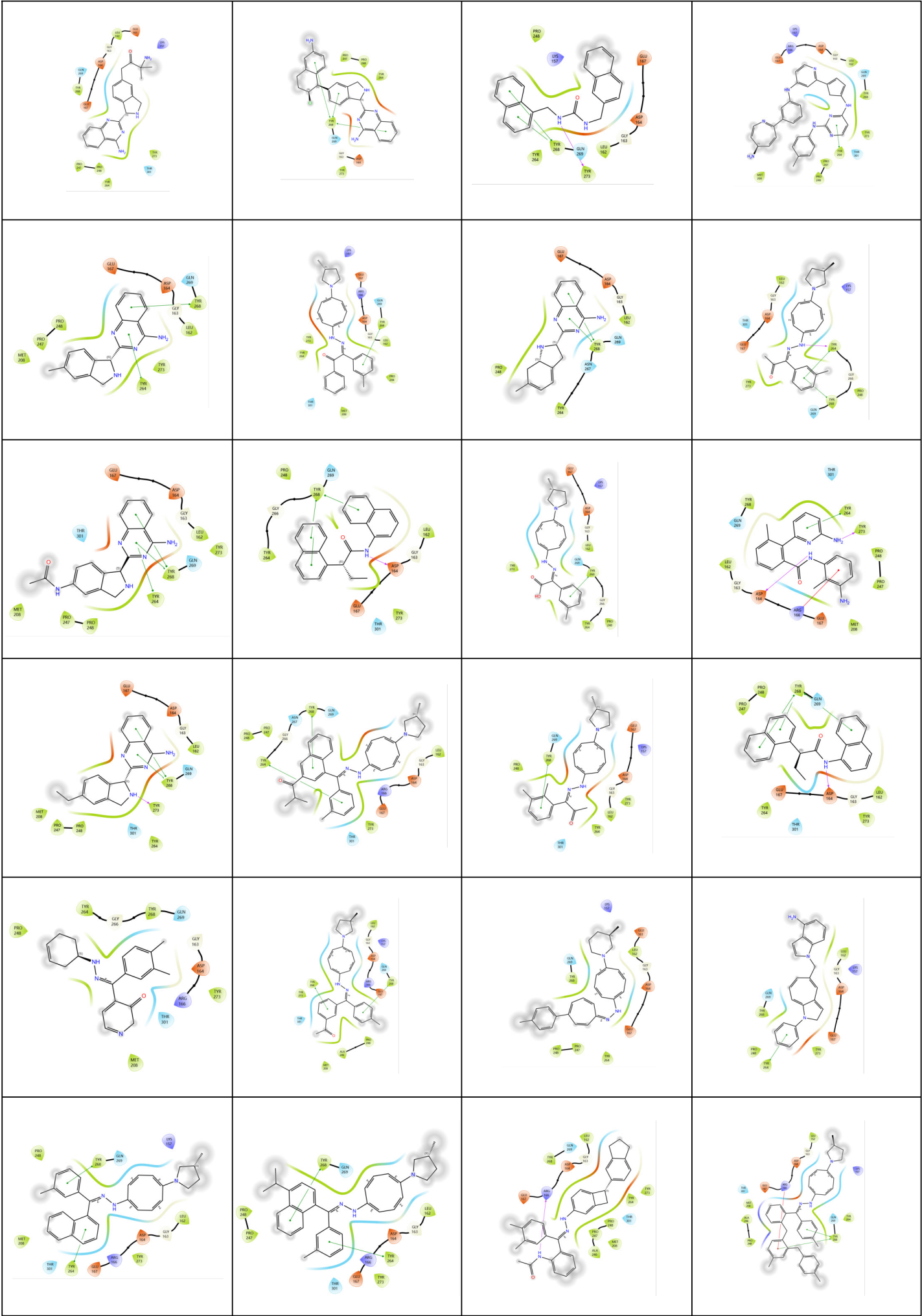


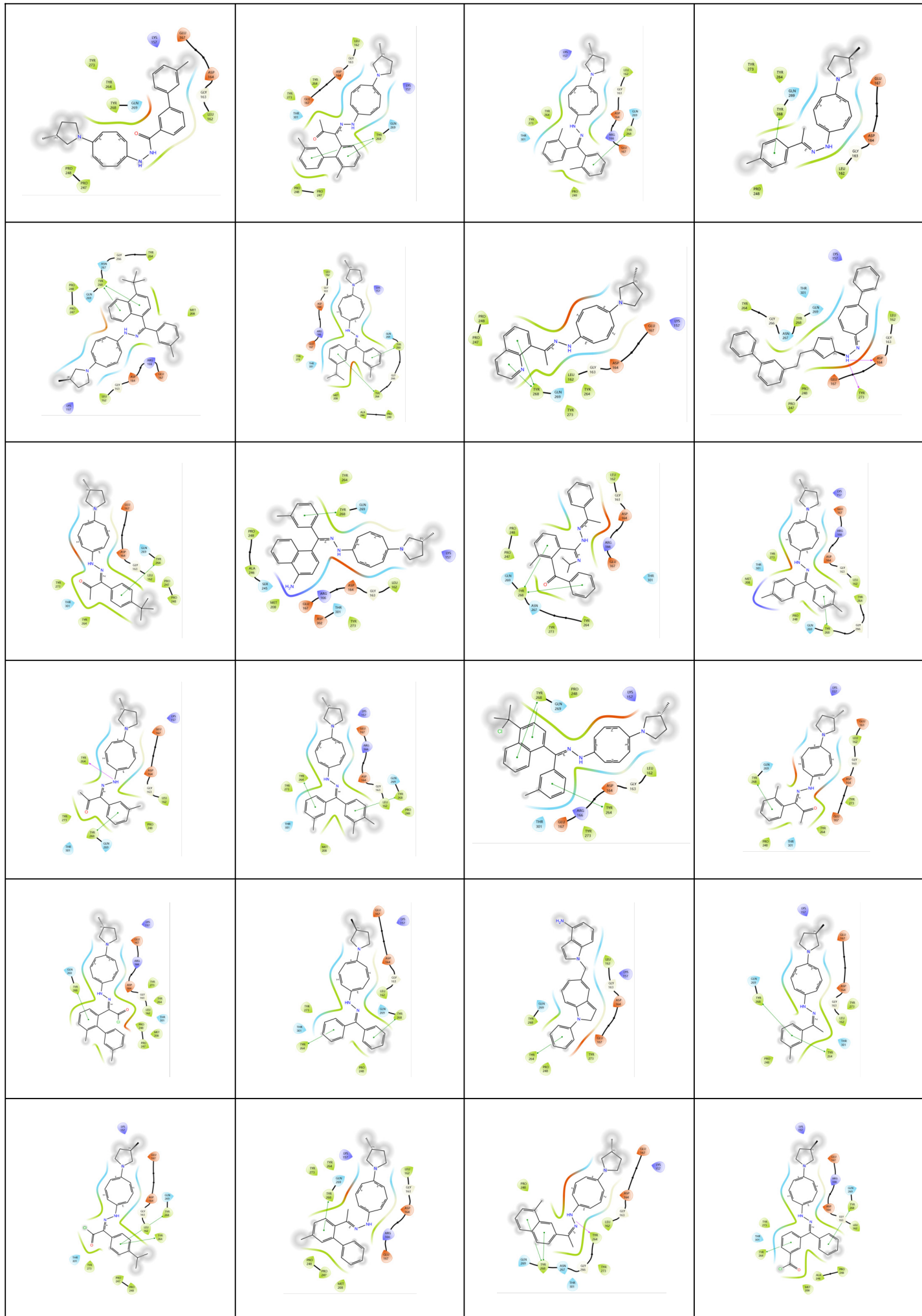
Supplementary Fig. 4 The performance of LLM obey the fragment merging strategy. In the visualization of binding interactions, green lines stands for Pi-Pi Stacking and red lines stand for Pi-cation interactions. **a**, A design process targeting PRMT5. Fragment 1 and Fragment 2 are sampled which are decomposed from Mol 1 and Mol 2 respectively. Then, two fragments are feed to LLM to design Mol 3. **b**, The binding mode of Fragment 1 (blue) and Fragment 2 (yellow). **c**, The binding mode of Mol 3. **d**, The different parts of Mol 3 overlap with two sampled fragments.

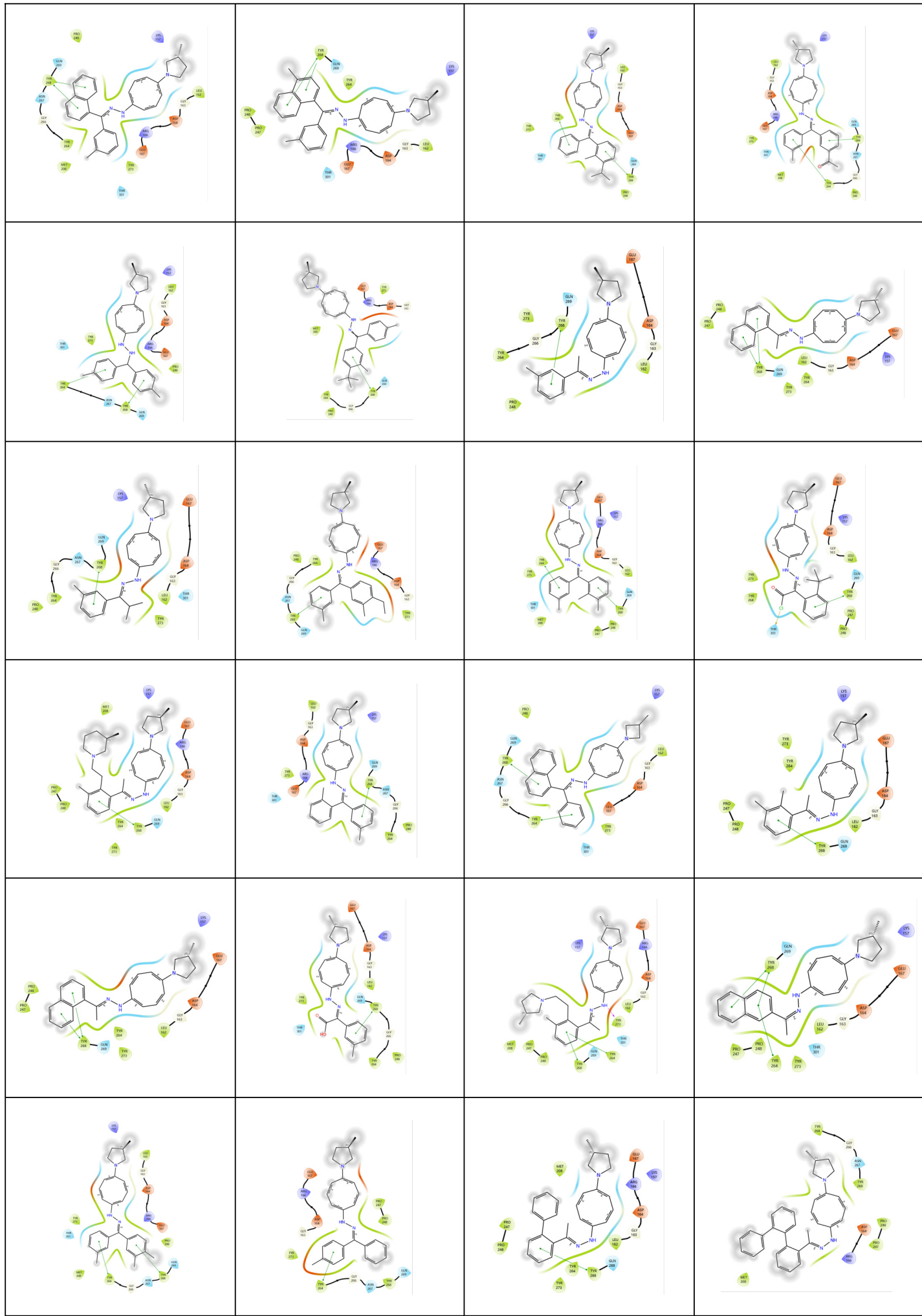
Appendix C Supplementary methods

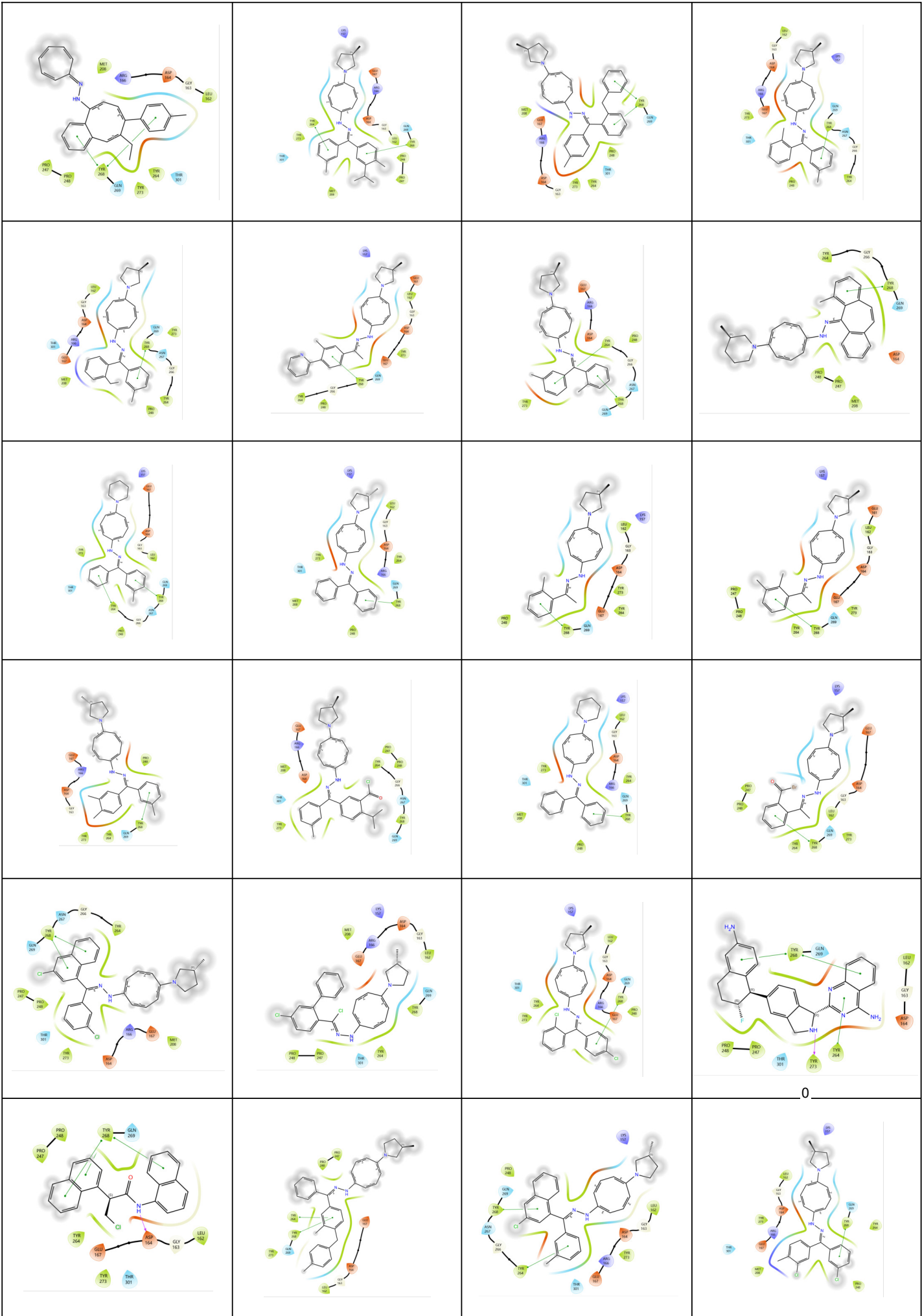
C.1 Filtered compounds

From the generated molecule set, we applied dual criteria of binding affinity ($\leq -9kcal/mol$) and synthetic accessibility ($SAscore \leq 4$), yielding 96 candidate structures that met both requirements. The interaction patterns between the docked conformations of these molecules and the PLpro binding pocket are shown below.









C.2 Antiviral Activity of PLP011 targeting PLpro

C.2.1 The cell line

The cell line used in the experiment is Vero-E6. The cells are cultured in complete DMEM medium supplemented with 10% FBS, 100 *IU/mL* penicillin, and 100 $\mu\text{g/mL}$ streptomycin.

C.2.2 The viruses

SARS-CoV-2/BJ01 (Alpha, BJ01, NCBI: MT291831)

C.2.3 SARS-CoV-2 Inoculation and Detection Protocol

SARS-CoV-2 Inoculation and Detection Protocol: Vero E6 cells in good condition were seeded into 96-well plates and cultured at 37 °C with 5% CO_2 until reaching 70-80% confluence. The in vitro antiviral studies were carried out in an animal biosafety level 3 (ABSL3) in Changchun Veterinary Research Institute, Chinese Academy of Agricultural Sciences. Cells were inoculated with diluted SARS-CoV-2 at an MOI of 0.01–0.1. After 1h, the inoculum was replaced with fresh medium containing the test compounds. Control wells included untreated cells (cell-only control) and virus-infected cells without compound (virus control). After 48h of treatment, 200 μL of supernatant was collected from each well and transferred to a deep-well plate containing VLP lysis buffer.

Viral RNA was extracted from the supernatant using the RNA extraction kit (Tiangen, YDP804-T1) according to the manufacturer’s instructions. Viral RNA load was quantified by RT-qPCR with the SARS-CoV-2 Nucleic Acid Detection Kit (DaAn Gene Co., Ltd., Guangzhou) following the kit protocol. Primers and probes targeting the ORF1ab and N gene regions—recommended by the Chinese Center for Disease Control and Prevention (<https://ivdc.chinacdc.cn/>)—were employed. The reaction setup followed the kit specifications.

Primer and Probe Sequences ORF1ab gene:

Forward (F): CCCTGTGGGTTTTACACTTAA

Reverse (R): ACGATTGTGCATCAGCTGA

Probe (P): 5'-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'

N gene:

Forward (F): GGGGAACCTTCTCCTGCTAGAAT

Reverse (R): CAGACATTTTGCTCTCAAGCTG

Probe (P): 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'

C.2.4 Cell Viability Assay Protocol

Cells in good condition were trypsinized and counted, then seeded into 96-well plates. After incubation at 37°C with 5% CO_2 until a confluent monolayer formed, the cells were inoculated with virus. Two hours post-inoculation, the medium was replaced with fresh medium. Four hours after the medium change, cells were treated with the test compound. Five concentration gradients of the compound were set according to experimental needs. Control wells included blank (cells only), virus-infected (no compound), and compound-treated groups. Each condition was replicated in five wells.

After 36h of treatment, cell morphology was first observed under a microscope. The original medium was then discarded, and 100 μL of serum-free, antibiotic-free DMEM was added to each well. Following this, 10 μL

of CCK-8 solution was added to each well under light-protected conditions. The plate was incubated at 37°C with 5% CO_2 for 1h. Absorbance (OD) was measured at 450nm using a pre-warmed microplate reader, and the data were recorded.

C.3 Biochemical Inhibition of KRAS G12D by KP032.

The detection of interaction between KRAS G12D and cRAF was performed using Human KRAS G12D & cRAF Binding Kit (abs560005, Absin, China) according to the manufacturer's instructions. All reagents were thawed at room temperature and equilibrated for at least 30 min before use. The assay was performed in 384-well shallow-well plates (abs7311) with a final reaction volume of 20 μ L. Briefly, compound A was serially diluted in 1 $\times$ Detection buffer to 10-fold of the final desired concentrations. The tested final concentrations of compound A were 3.125, 6.25, 12.5, 25, 50, and 100 nM. For each well, 4 μ L of Mix-1 (containing Tag2 KRAS G12D and GTP, 1:1), 4 μ L of Tag1 cRAF protein, 2 μ L of diluted Compound A (or 1 $\times$ Detection buffer with equivalent DMSO for the DMSO control), and 10 μ L of Mix-2 (containing anti Tag1 Eu antibody and anti Tag2 Ac antibody, 1:1) were added sequentially. A buffer blank (10 μ L 1 $\times$ Detection buffer + 10 μ L Mix 2) was also included. The plate was sealed and incubated at room temperature for no more than 30 min. Time-resolved fluorescence resonance energy transfer (TR-FRET) signals were measured using a microplate reader equipped with TR FRET capability (excitation at 320 nm; emission at 620 nm and 665 nm).

C.4 Synthesis of PLP011

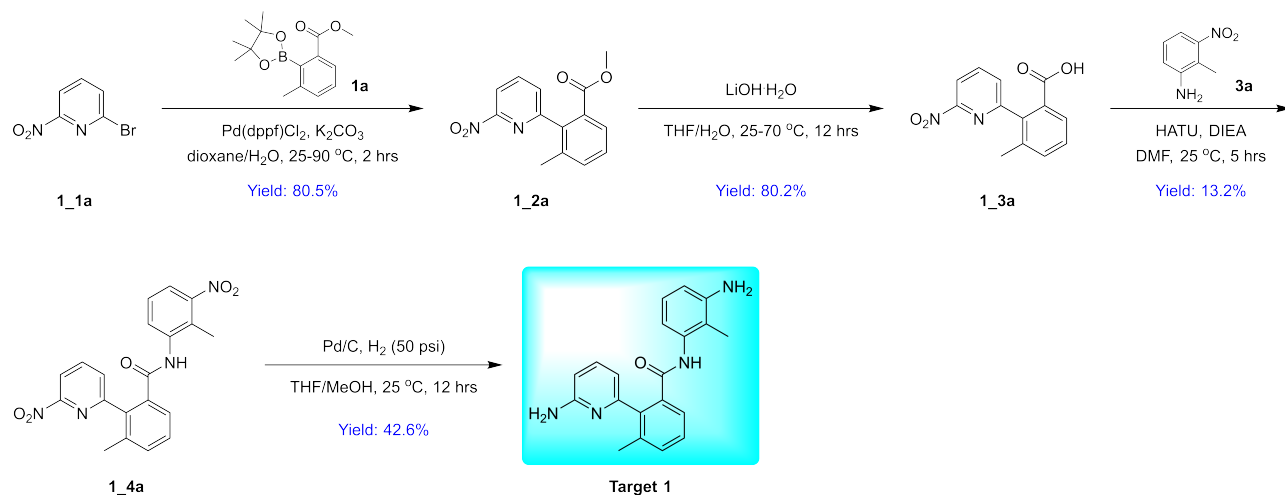


Fig. C1: Synthesis of PLP011

Compound 1_2a. To a mixture of compound 1_1a (500 mg, 2.46 mmol, 1.00 eq) and compound 1a (680 mg, 2.46 mmol, 1.00 eq) in dioxane (10.0 mL) and H_2O (2.00 mL) was added K_2CO_3 (1.02 g, 7.39 mmol, 3.00 eq) and $Pd(dppf)Cl_2$ (180 mg, 246 μ mol, 0.10 eq) at 25 °C under N_2 atmosphere. The mixture was degassed and purged with N_2 for 3 times, and then the mixture was heated to 90 °C and stirred at 90 °C for 2 hrs under N_2 atmosphere. LCMS (EW67459-7-P1A1) showed compound 1_1a was consumed and desired mass (RT = 0.472 min) was detected. TLC (Petroleum ether/Ethyl acetate = 3/1) indicated compound 1_1a was consumed

completely ($R_f = 0.50$) and a new main spot formed ($R_f = 0.35$). The reaction was clean according to TLC. The reaction mixture was poured into H₂O (50.0 mL) and extracted with ethyl acetate (30.0 mL * 2), the organic layers were washed with brine (50.0 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/1 to 10/1, Petroleum ether/Ethyl acetate = 3/1, $R_f = 0.35$) to give compound 1.2a (540 mg, 1.98 mmol, 80.5% yield, 100% purity) as light yellow gum.

Compound 1.3a. To a mixture of compound 1.2a (300 mg, 1.10 mmol, 1.00 eq) in THF (6.00 mL) was added LiOH.H₂O (139 mg, 3.31 mmol, 3.00 eq) in H₂O (1.20 mL) at 25 °C, the mixture was heated to 70 °C and stirred at 70 °C for 12 hrs. LCMS (EW67459-9-P1A) showed compound 1.2a was consumed and desired mass ($RT = 0.412$ min) was detected. The reaction mixture was poured into H₂O (30.0 mL) and adjust to pH = 2 with HCl (1 M) then extracted with ethyl acetate (30.0 mL * 2), the organic layers were washed with brine (30.0 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to compound 1.3a (250 mg, 884 μ mol, 80.2% yield, 91.3% purity) as a light yellow solid.

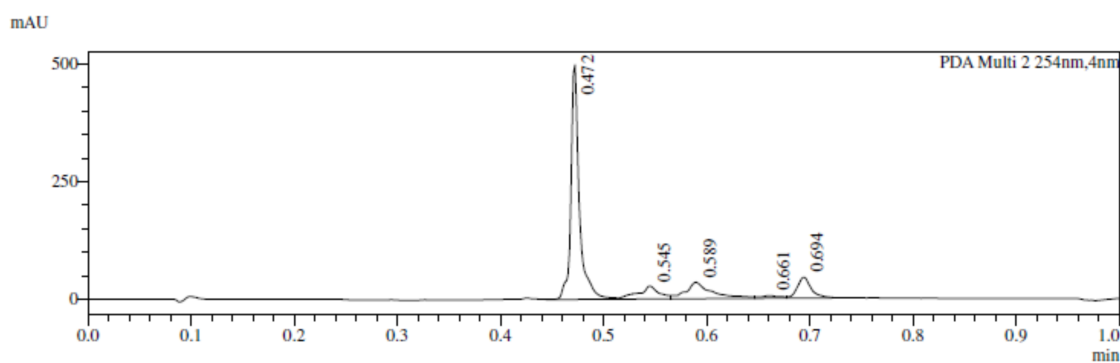
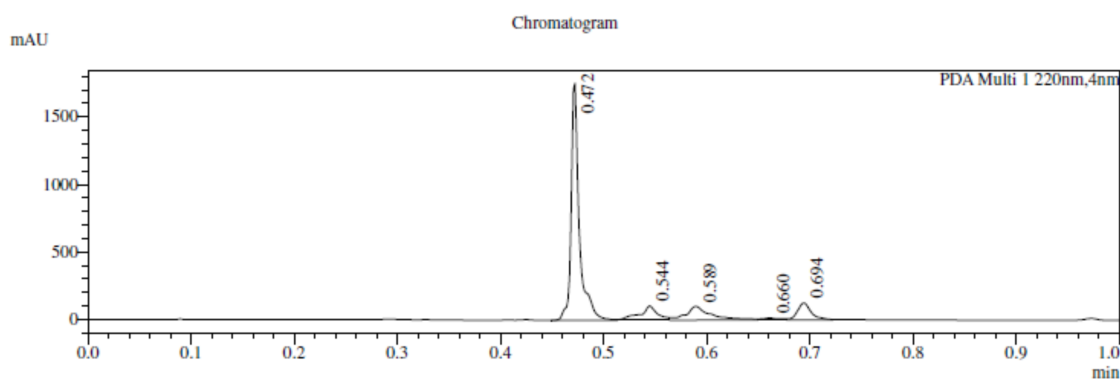
Compound 1.4a. To a mixture of compound 1.3a (100 mg, 387 μ mol, 1.00 eq) and compound 3a (70.7 mg, 465 μ mol, 1.20 eq) in DMF (2.00 mL) was added HATU (221 mg, 581 μ mol, 1.50 eq) and DIEA (150 mg, 1.16 mmol, 202 μ L, 3.00 eq) at 25 °C, the mixture was stirred at 25 °C for 5 hrs. LCMS (EW67459-12-P1A3) showed compound 1.3a was consumed and desired mass ($RT = 1.228$ mins) was detected. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: WePure PrePulite Platinum C18 150*25mm*7 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 17%-47% B over 30.0 min), the eluent was concentrated in vacuum to give compound 1.4a (20.0 mg, 51.0 μ mol, 13.2% yield) as light yellow gum.

Target 1. To a mixture of compound 1.4a (20.0 mg, 51.0 μ mol, 1.00 eq) in THF (2.00 mL) and MeOH (2.00 mL) was Pd/C (20.0 mg, 18.8 μ mol, 10% purity, 0.37 eq) under N₂ at 25 °C. The suspension was degassed under vacuum and purged with H₂ three times. The mixture was stirred under H₂ (50 psi) at 25 °C for 12 hrs. LCMS (EW67459-13-P1A1) showed compound 1.4a was consumed and desired mass ($RT = 0.965$ min) was detected. The reaction mixture was filtered and the filter cake was washed with MeOH (5.00 mL * 3). The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: WePure PrePulite Platinum C18 150*25mm*7 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 17%-47% B over 30.0 min), the eluent was concentrated in vacuum to remove ACN. The residual aqueous solution was lyophilized to give Target 1 (7.23 mg, 21.7 μ mol, 42.6% yield, 99.8% purity) as a white solid.

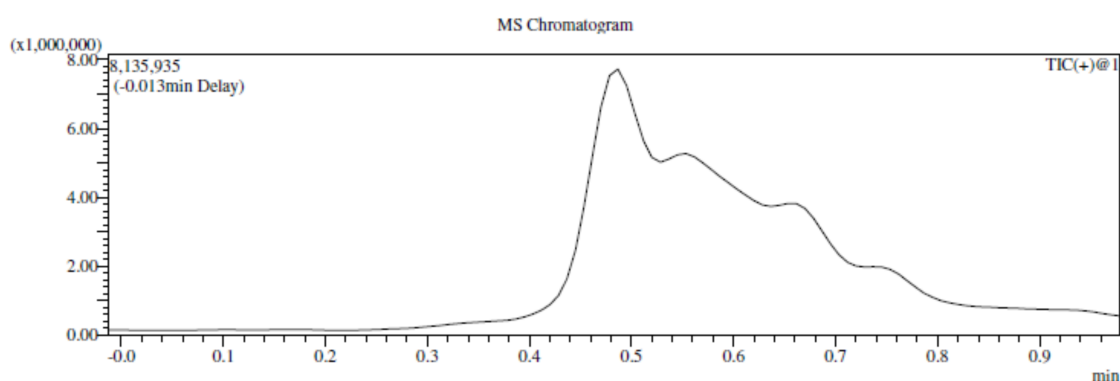
C.5 The LCMS, HPLC and ¹H NMR spectra reports of PLP011

Compound 1.2a:

LCMS of reaction mixture, product: $RT = 0.472$ min, $m/z = 295.0$ ($M + Na$)⁺



1 PDA Multi 1 / 220nm,4nm
2 PDA Multi 2 / 254nm,4nm



Integration Result

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.472	0.014	1754930	83.543	963258	69.360
2	0.544	0.025	103828	4.943	125918	9.067
3	0.589	0.034	102499	4.879	168379	12.124
4	0.660	0.035	14450	0.688	16075	1.157
5	0.694	0.025	124932	5.947	115153	8.292

PDA Ch2 254nm

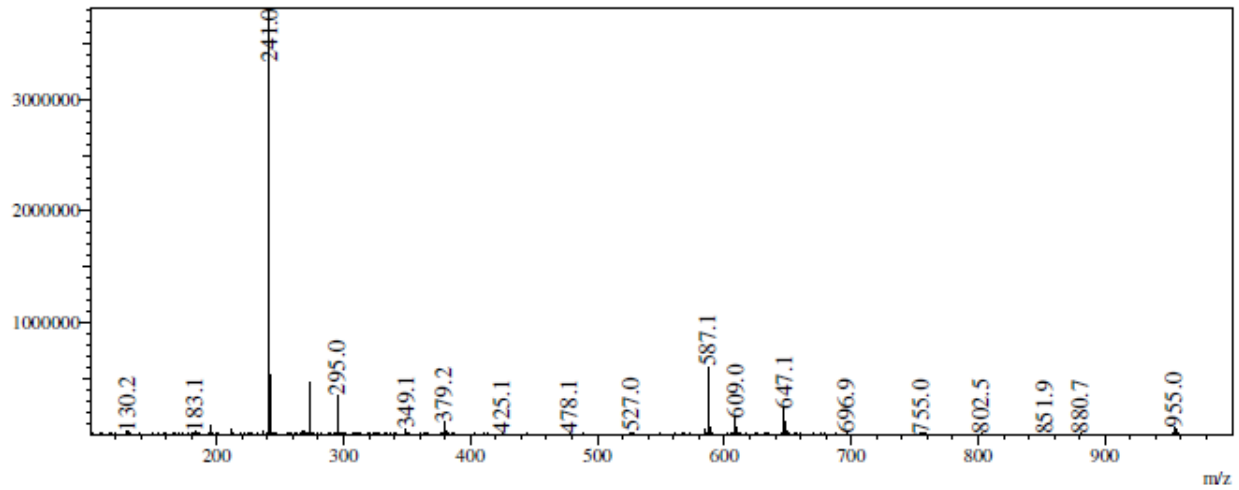
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.472	0.014	499006	81.615	283509	65.460
2	0.545	0.029	27534	4.503	39045	9.015
3	0.589	0.036	35047	5.732	61504	14.201
4	0.661	0.057	5632	0.921	7267	1.678
5	0.694	0.026	44197	7.229	41778	9.646

Fig. C2: LCMS Chromatogram of reaction mixture

MS Spectrum

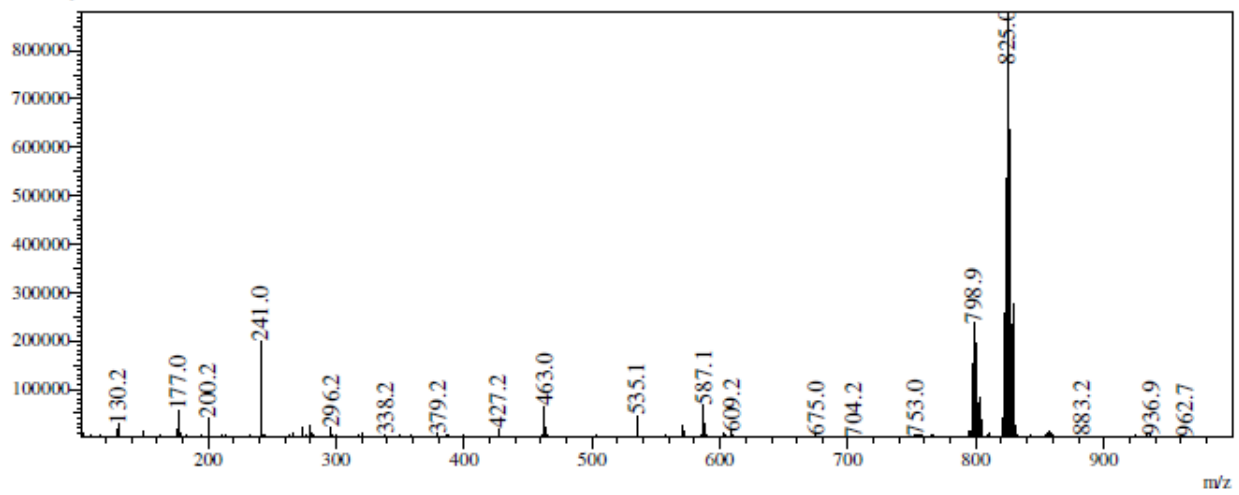
RetTime: 0.470

Intensity



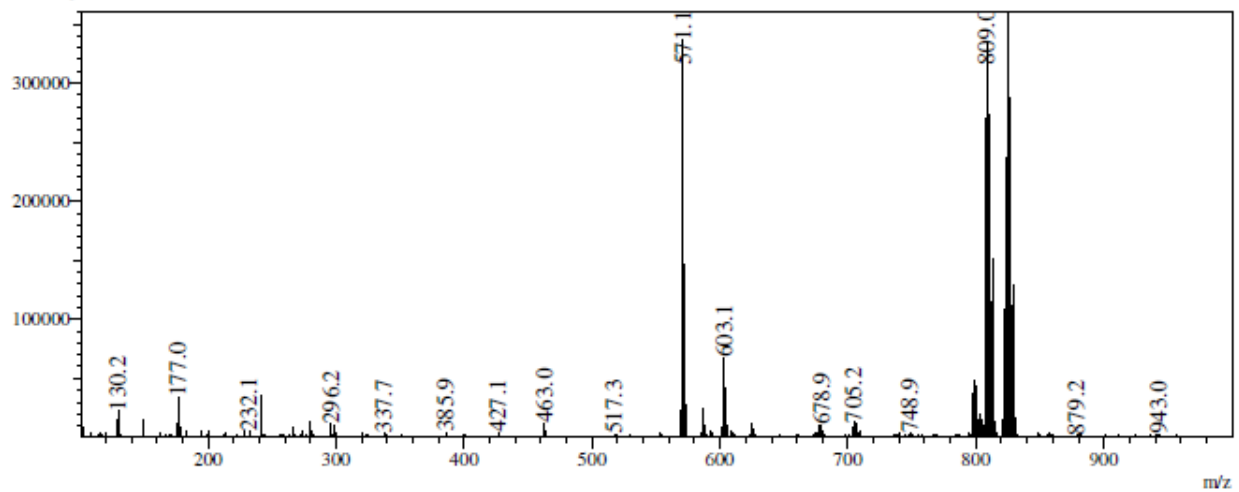
RetTime: 0.545

Intensity



RetTime: 0.587

Intensity



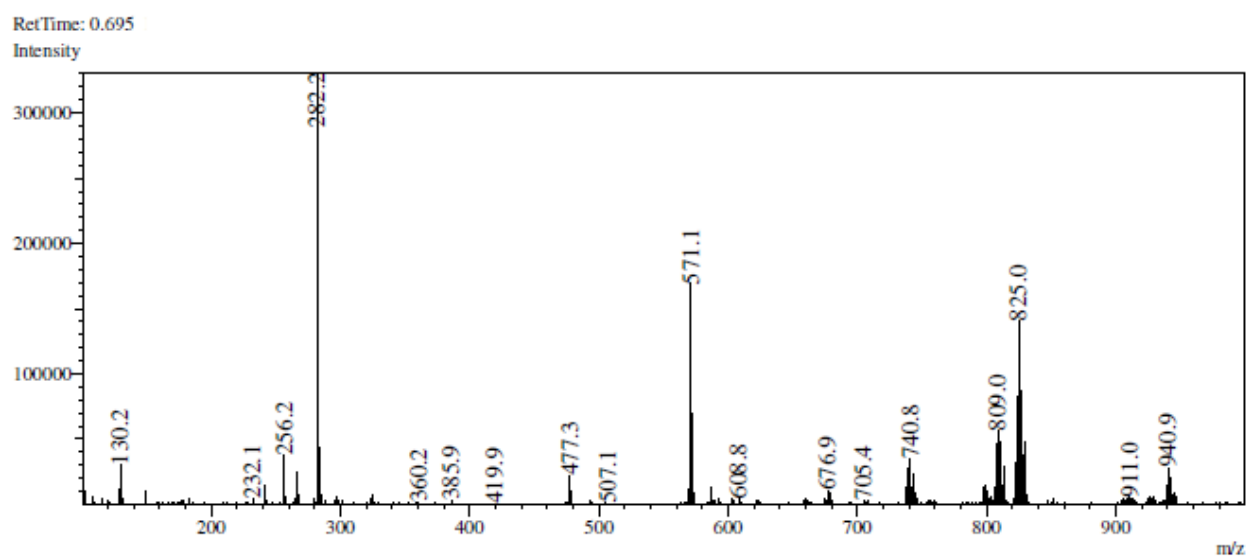
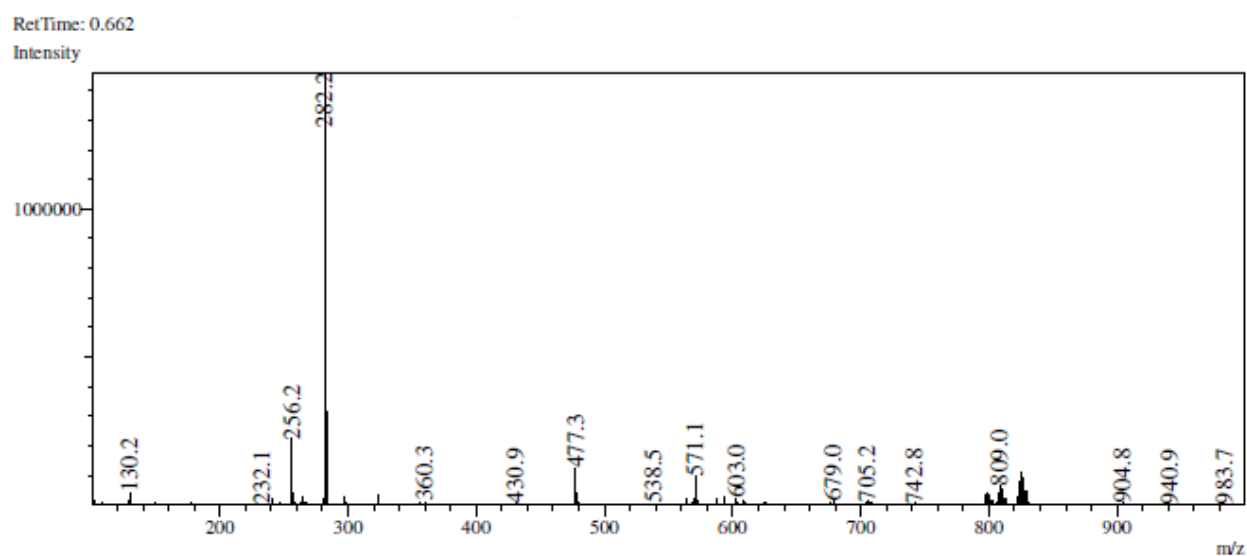
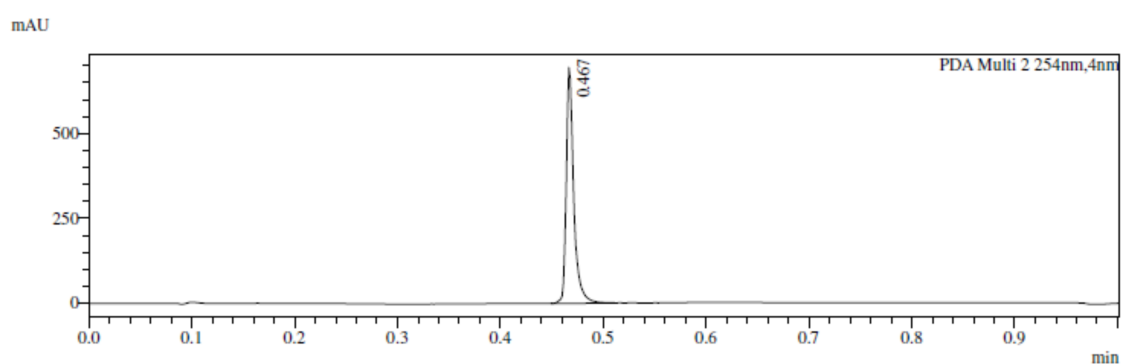
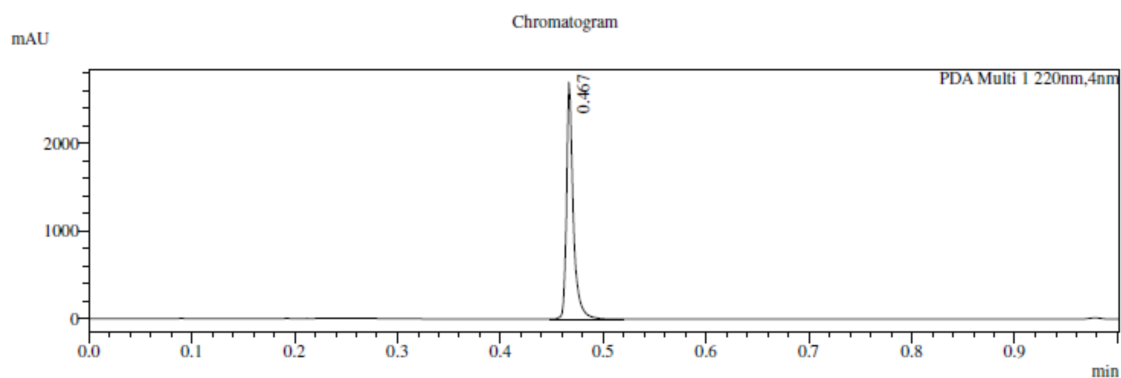
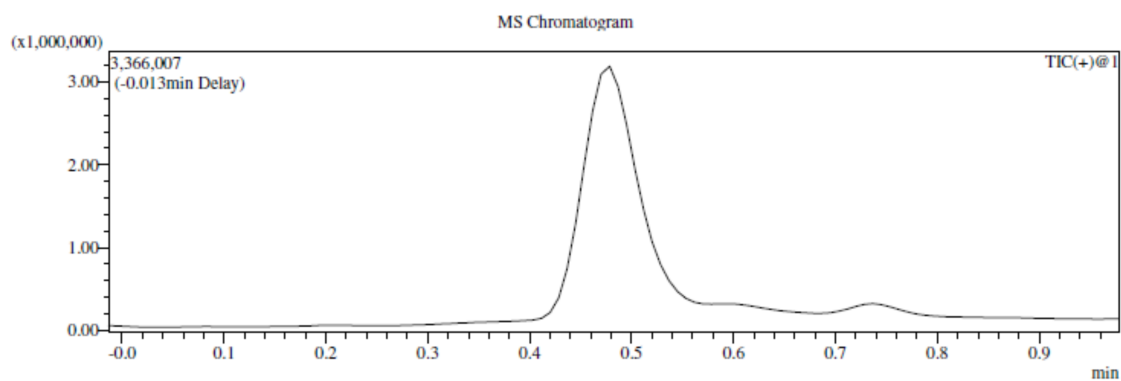


Fig. C3: MS Chromatogram of reaction mixture

LCMS of compound 1_1a, product: RT = 0.467 min, m/z = 295.1 ($M + Na$)⁺



1 PDA Multi 1 / 220nm,4nm
2 PDA Multi 2 / 254nm,4nm



Integration Result

PDA Ch1 220nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.467	0.013	2706692	100.000	1240464	100.000
PDA Ch2 254nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.467	0.014	694749	100.000	350500	100.000

Fig. C4: LCMS Chromatogram of compound 1.2a

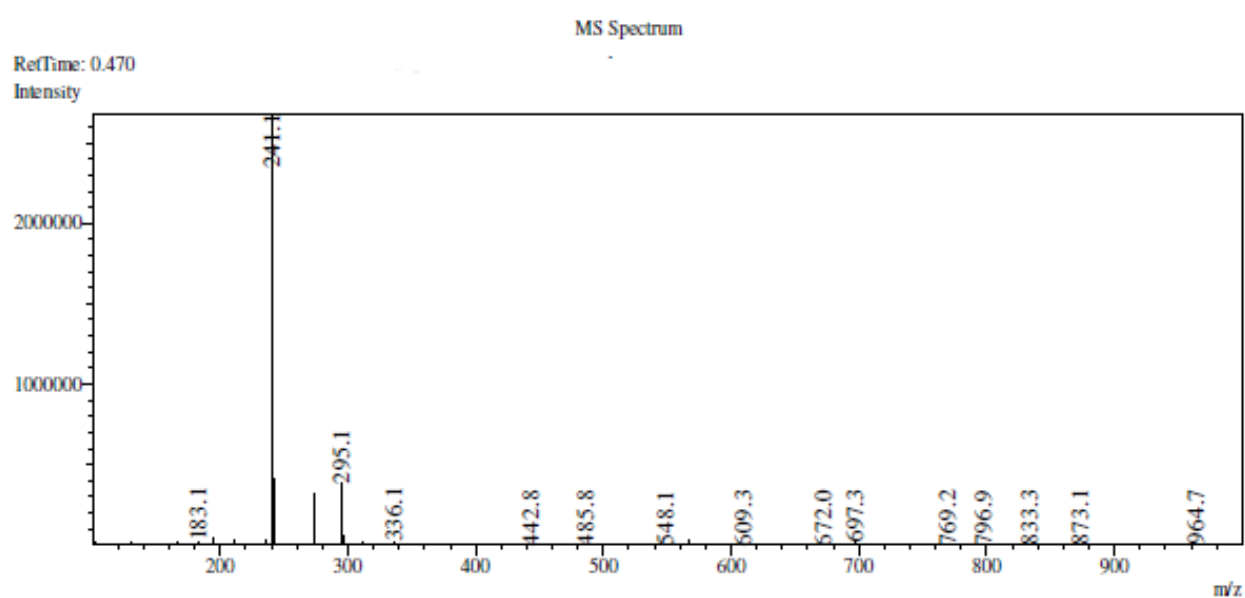


Fig. C5: MS Chromatogram of compound 1.2a

^1H NMR of compound 1_2a (400 MHz, CDCl_3) δ 8.27 (d, $J = 8.0$ Hz, 1H), 8.09 (t, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.52 - 7.40 (m, 2H), 3.66 (s, 3H), 2.12 (s, 3H)

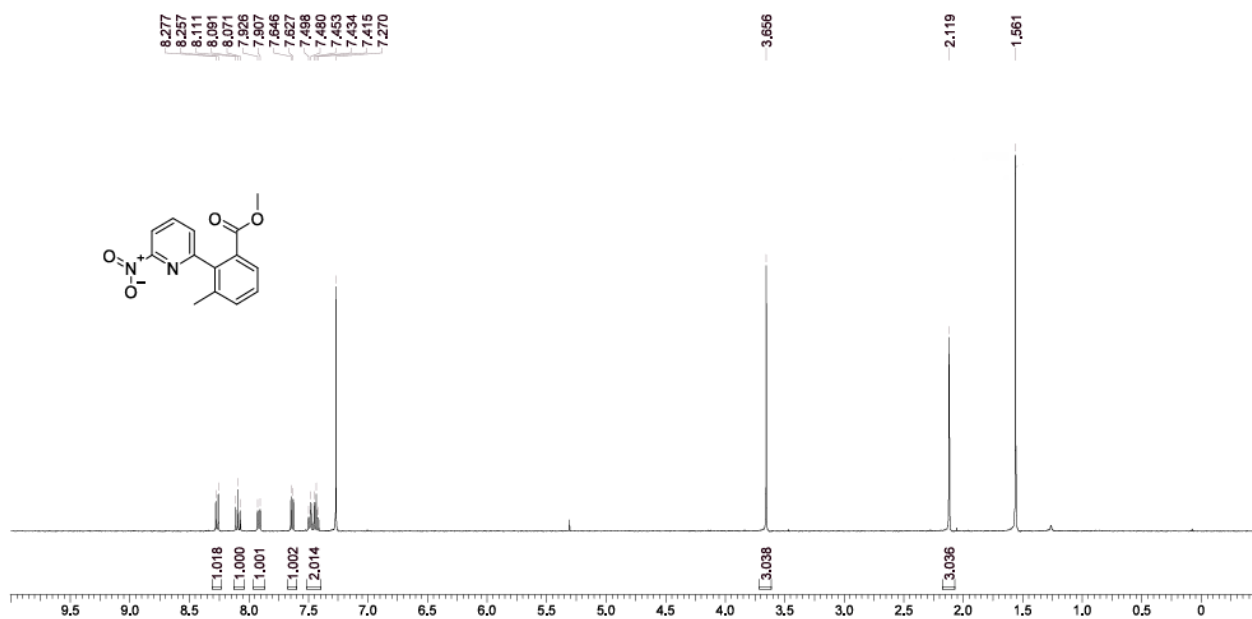
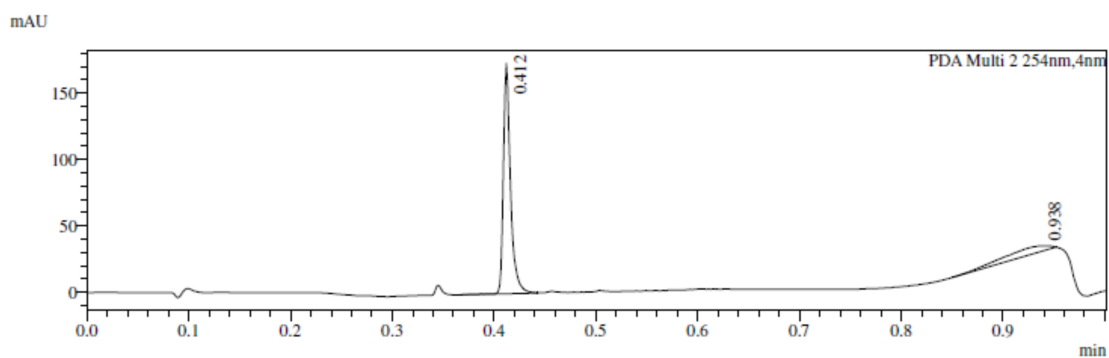
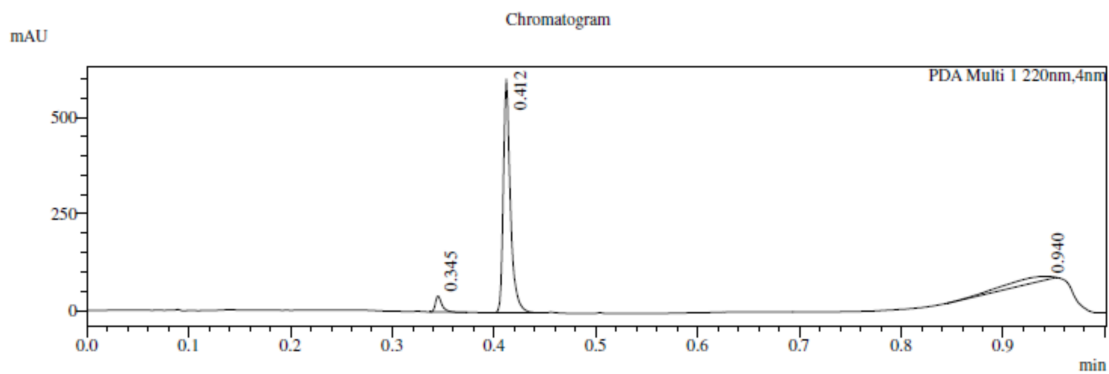


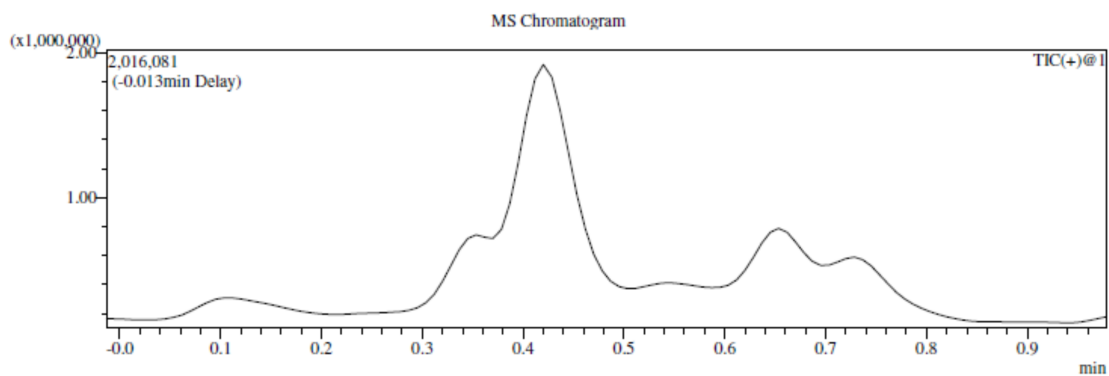
Fig. C6: ^1H NMR of compound 1_2a

Compound 1_3a:

LCMS of reaction mixture, product: RT = 0.412 min, $m/z = 281.0$ ($M + Na$) $^+$



1 PDA Multi 1 / 220nm,4nm
2 PDA Multi 2 / 254nm,4nm



Integration Result

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.345	0.013	40971	6.247	18227	5.045
2	0.412	0.014	604758	92.205	291561	80.692
3	0.940	0.093	10154	1.548	51537	14.263

PDA Ch2 254nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.412	0.014	173607	97.693	84960	82.493
2	0.938	0.089	4100	2.307	18030	17.507

Fig. C7: LCMS Chromatogram of reaction mixture

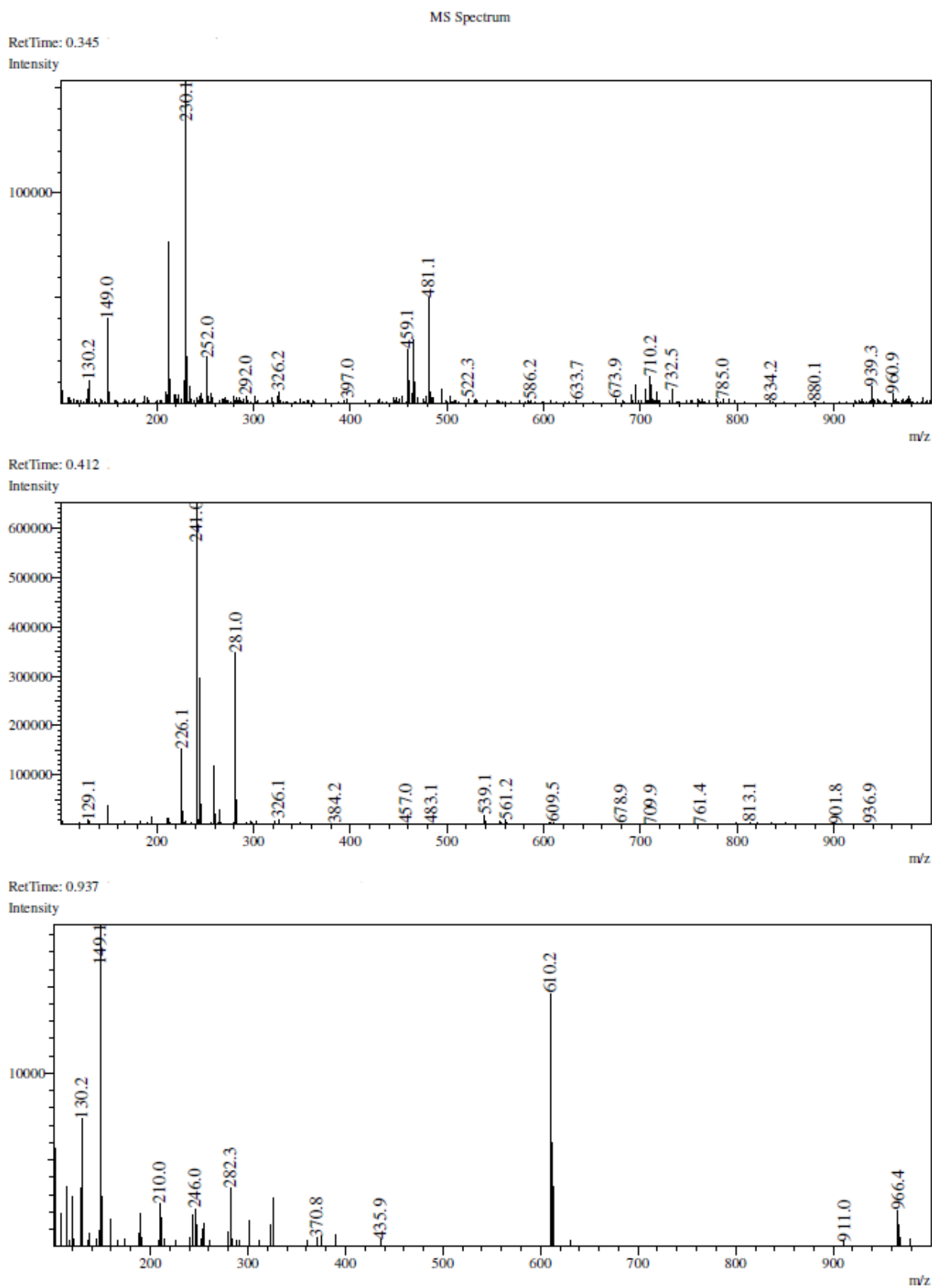
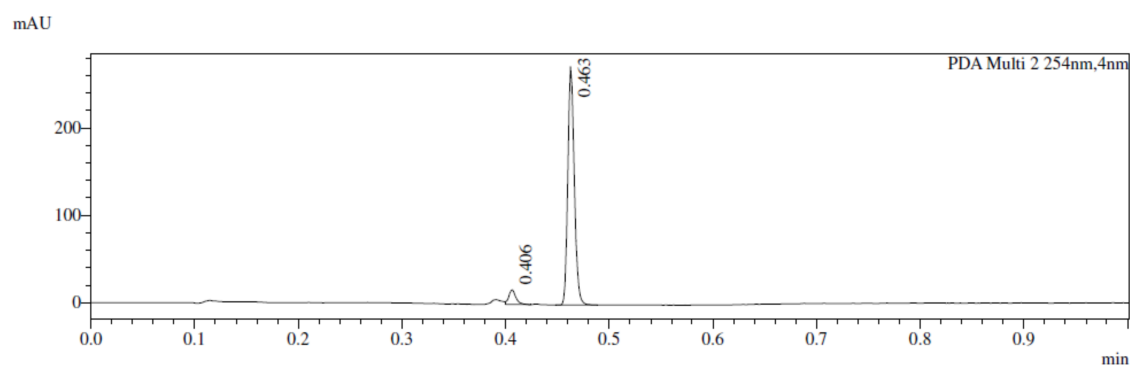
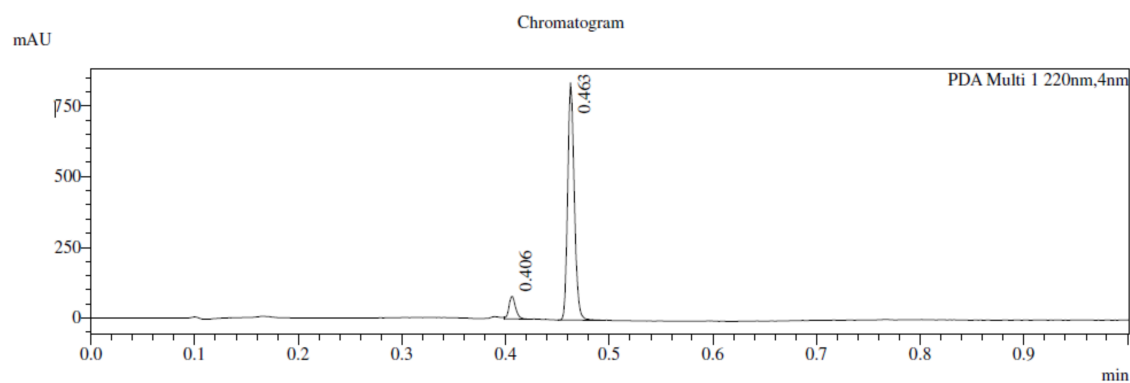
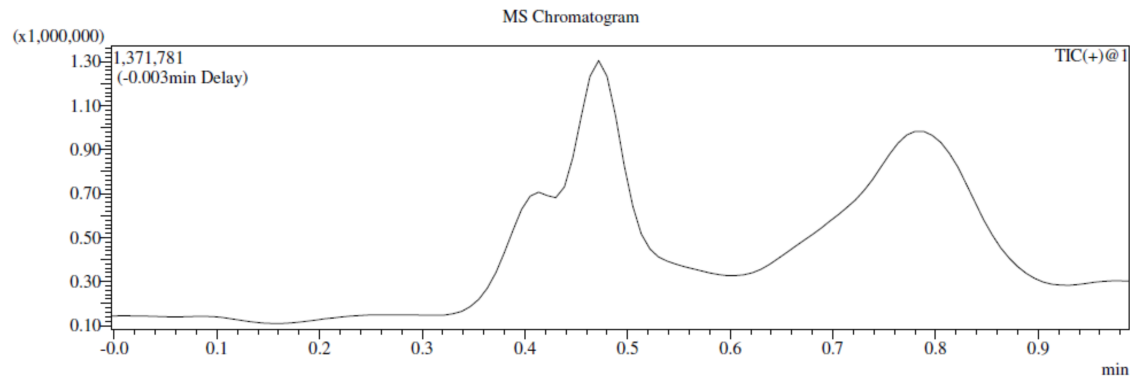


Fig. C8: MS Chromatogram of reaction mixture

LCMS of compound 1_3a, product: RT = 0.463 min, m/z = 281.1 ($M + Na$)⁺



- 1 PDA Multi 1 / 220nm, 4nm
2 PDA Multi 2 / 254nm, 4nm



Integration Result

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.406	0.013	79742	8.668	35514	8.674
2	0.463	0.014	840242	91.332	373904	91.326

PDA Ch2 254nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.406	0.013	16622	5.749	7783	6.149
2	0.463	0.014	272495	94.251	118782	93.851

Fig. C9: LCMS Chromatogram of compound 1_3a

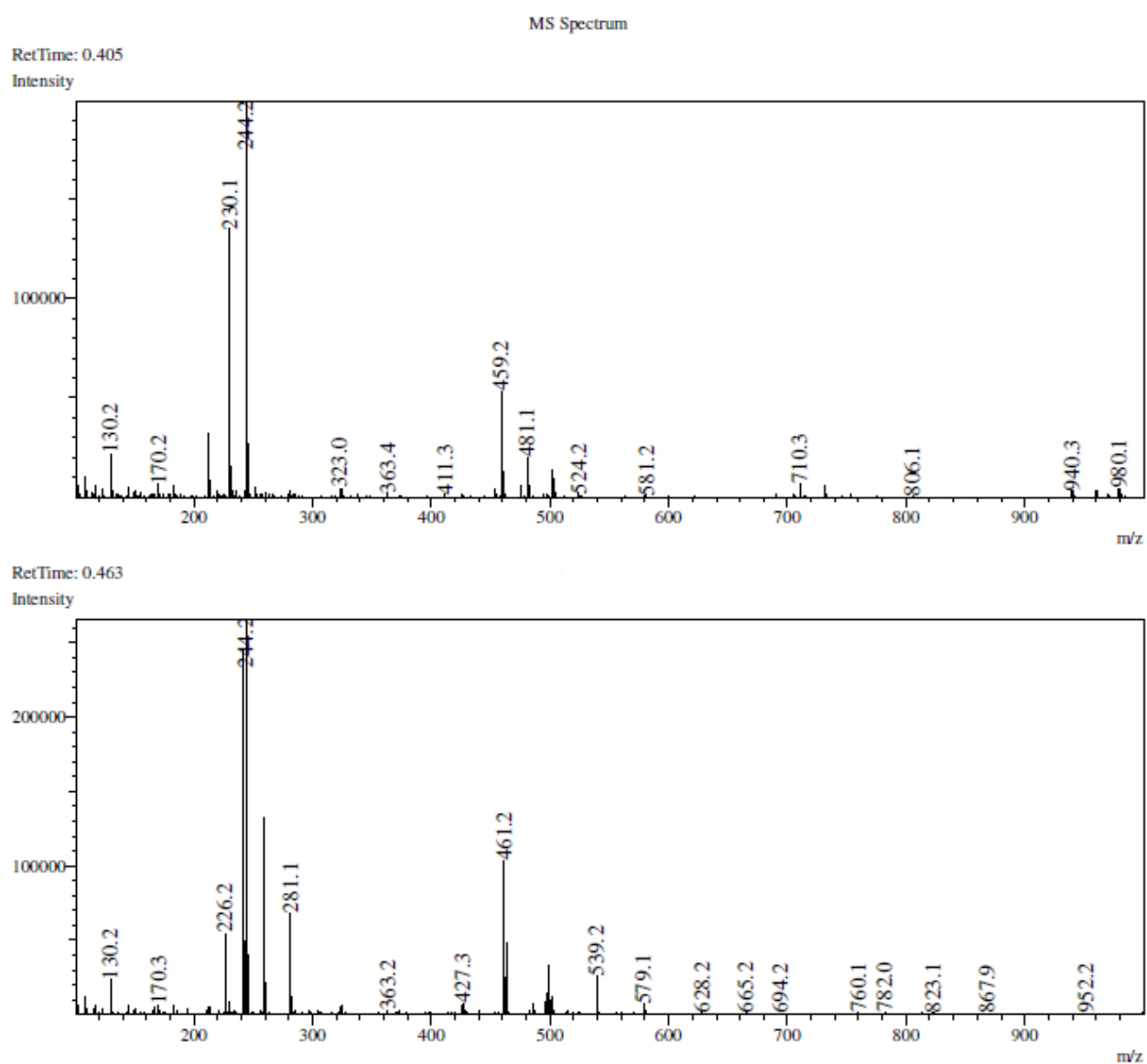


Fig. C10: MS Chromatogram of compound 1.3a

^1H NMR of compound 1_3a(400 MHz, CDCl_3) δ 8.24 (d, $J = 8.0$ Hz, 1H), 8.05 (t, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 7.6$ Hz, 1H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.54 - 7.49 (m, 1H), 7.46 - 7.42 (m, 1H), 2.10 (s, 3H)

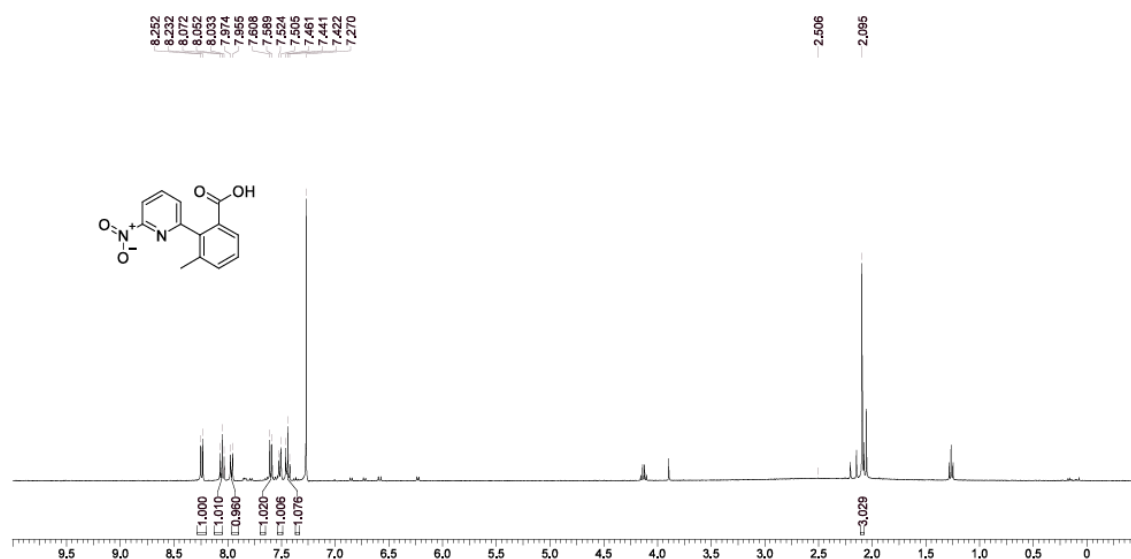
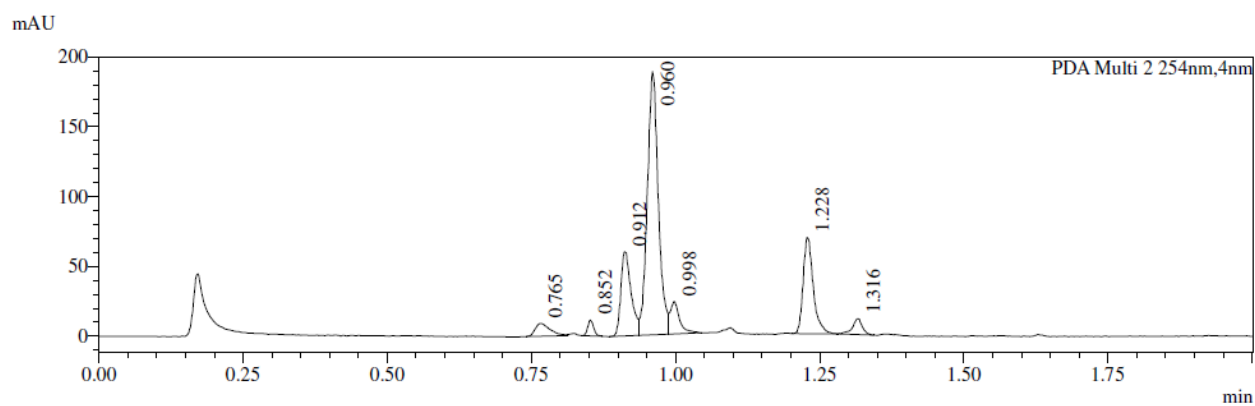
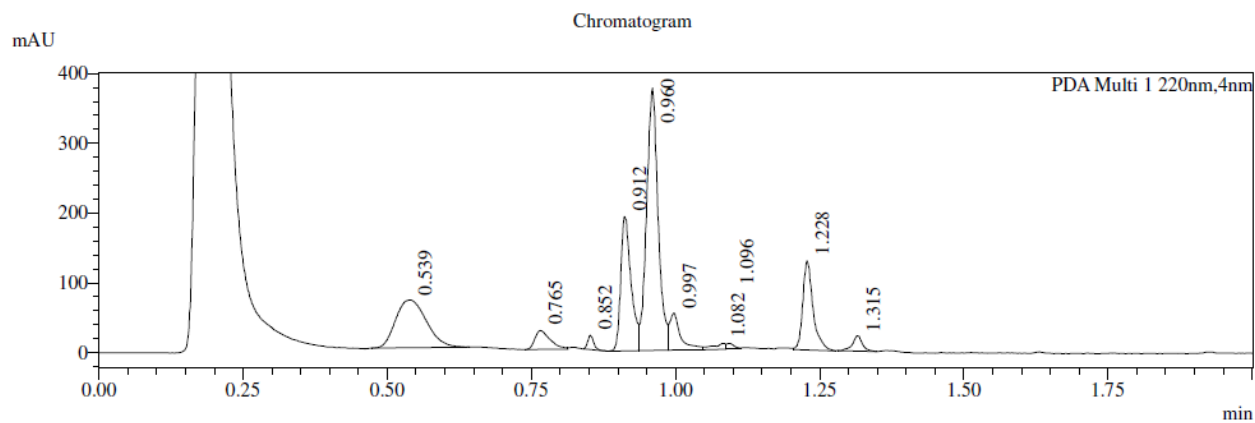


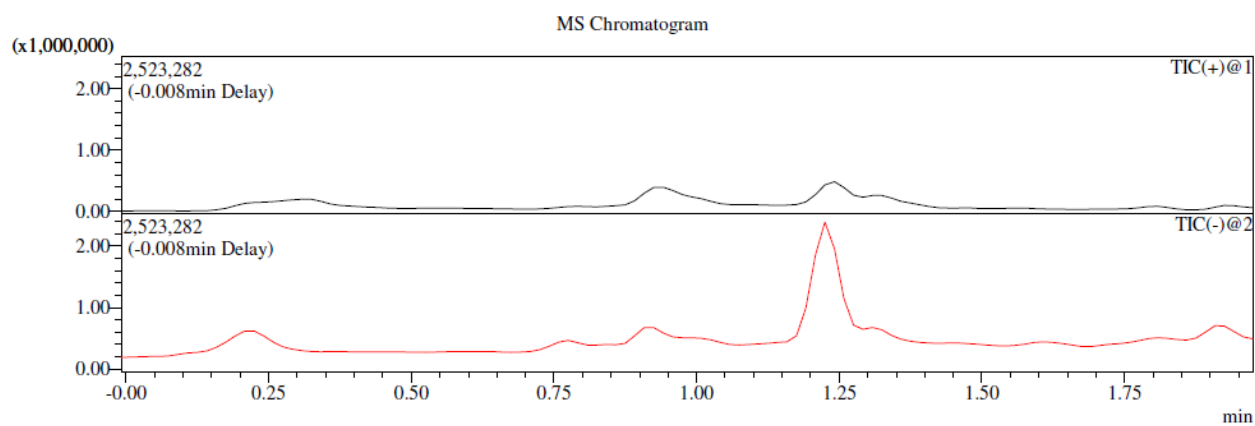
Fig. C11: ^1H NMR of compound 1_3a

Compound 1_4a:

LCMS of reaction mixture, product: RT = 1.228 mins, $m/z = 391.0$ ($M - H$) $^+$



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



Integration Result

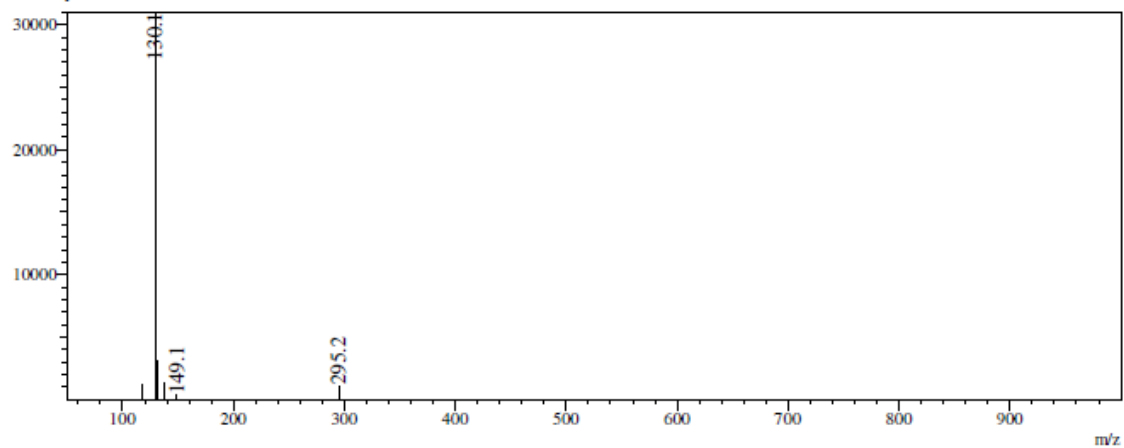
PDA Ch1 220nm							
Peak#	Ret. Time	Width	Height	Height%	Area	Area%	
1	0.539	0.096	68360	7.555	253554	18.715	
2	0.765	0.049	27103	2.995	49832	3.678	
3	0.852	0.022	20804	2.299	14774	1.090	
4	0.912	0.033	192471	21.272	240967	17.786	
5	0.960	0.038	376099	41.567	522650	38.576	
6	0.997	0.042	53187	5.878	67583	4.988	
7	1.082	0.057	8808	0.973	13561	1.001	
8	1.096	0.067	8086	0.894	7570	0.559	
9	1.228	0.033	127809	14.126	157777	11.645	
10	1.315	0.031	22074	2.440	26580	1.962	
PDA Ch2 254nm							
Peak#	Ret. Time	Width	Height	Height%	Area	Area%	
1	0.765	0.048	9135	2.450	16804	3.547	
2	0.852	0.022	11262	3.020	8049	1.699	
3	0.912	0.033	60482	16.220	75138	15.859	
4	0.960	0.036	188471	50.545	250380	52.847	
5	0.998	0.039	23301	6.249	25732	5.431	
6	1.228	0.032	68957	18.493	84240	17.780	
7	1.316	0.031	11272	3.023	13444	2.838	

Fig. C12: MS Chromatogram of reaction mixture

MS Spectrum

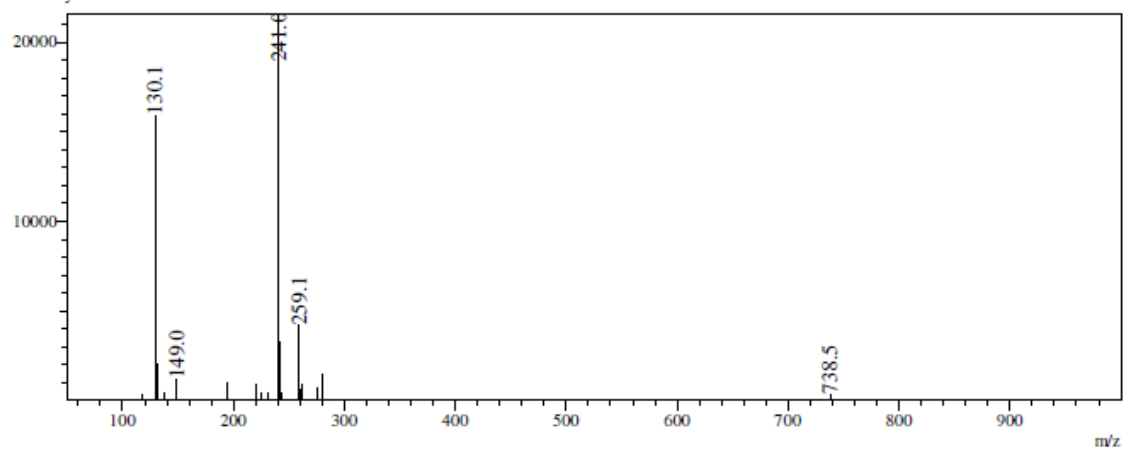
RetTime: 0.525

Intensity



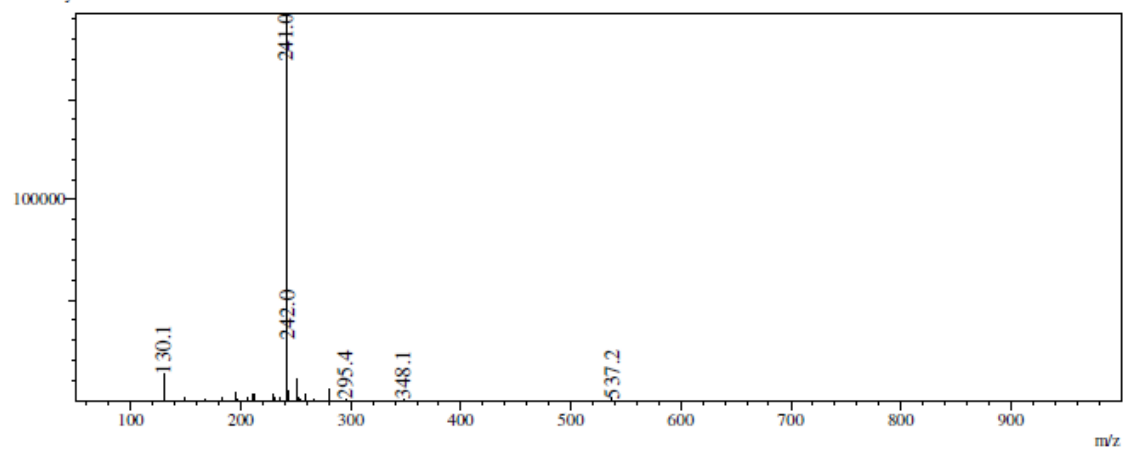
RetTime: 0.758

Intensity



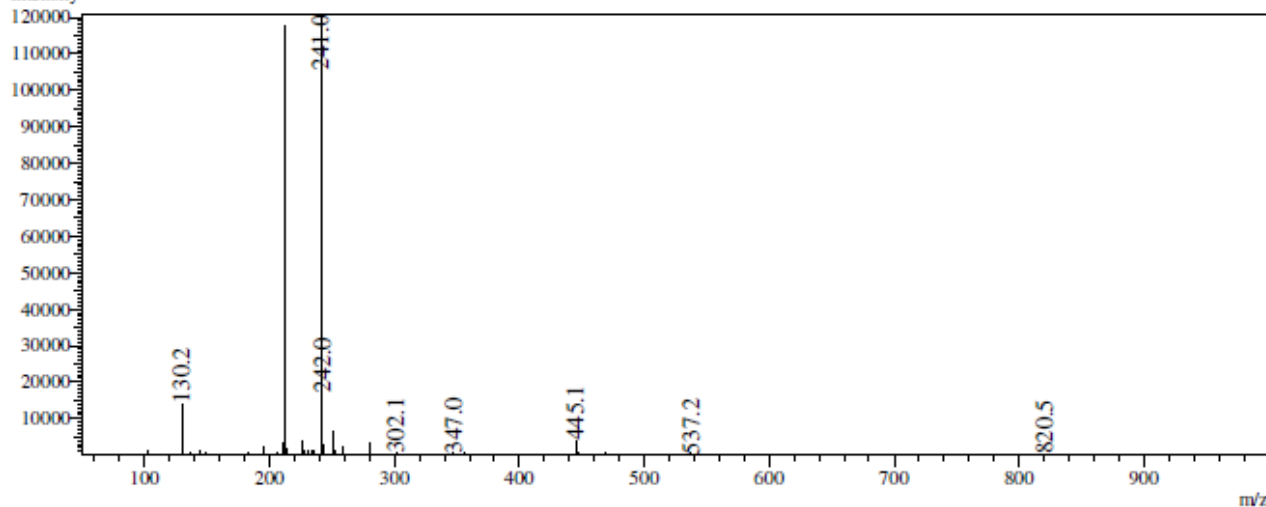
RetTime: 0.908

Intensity



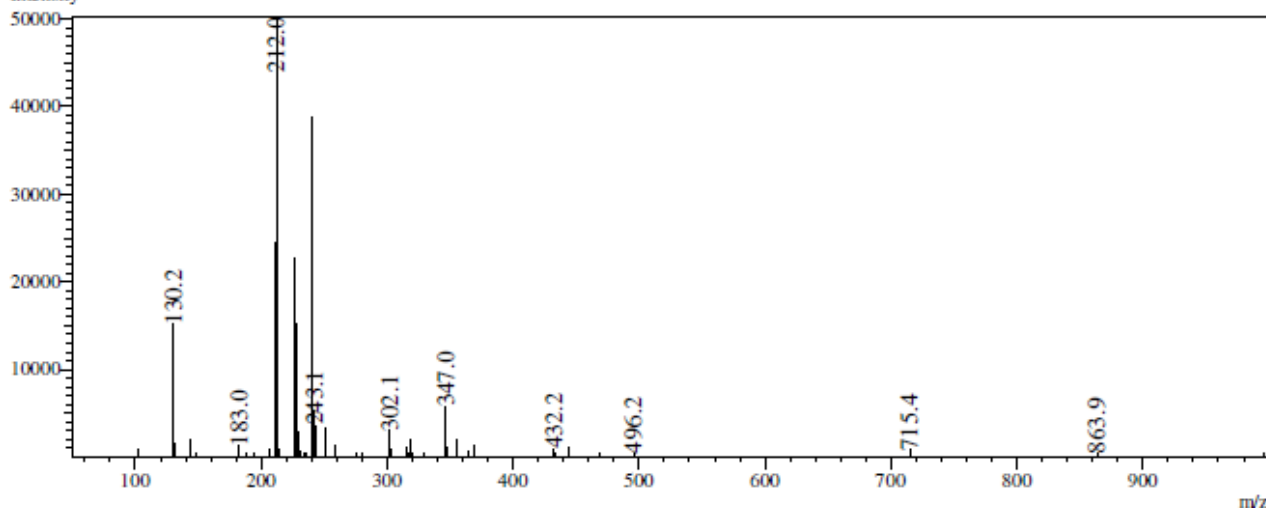
RetTime: 0.958

Intensity



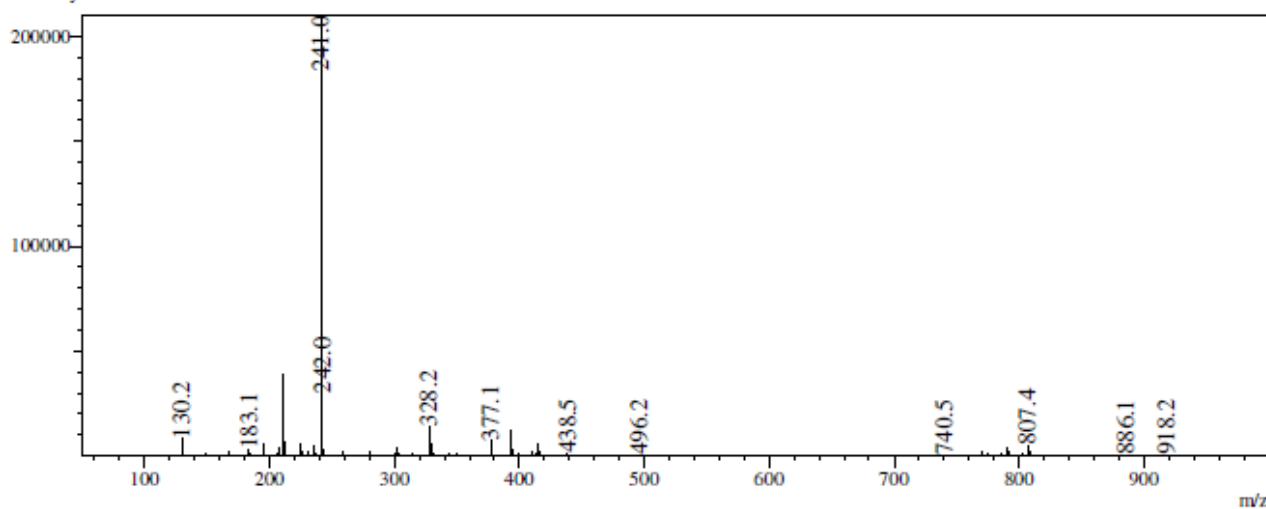
RetTime: 0.992

Intensity



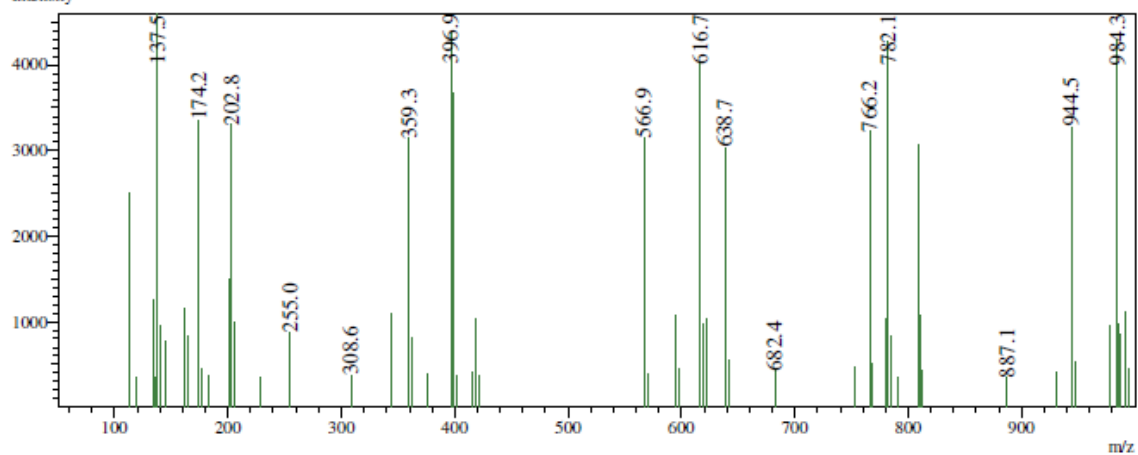
RetTime: 1.225

Intensity



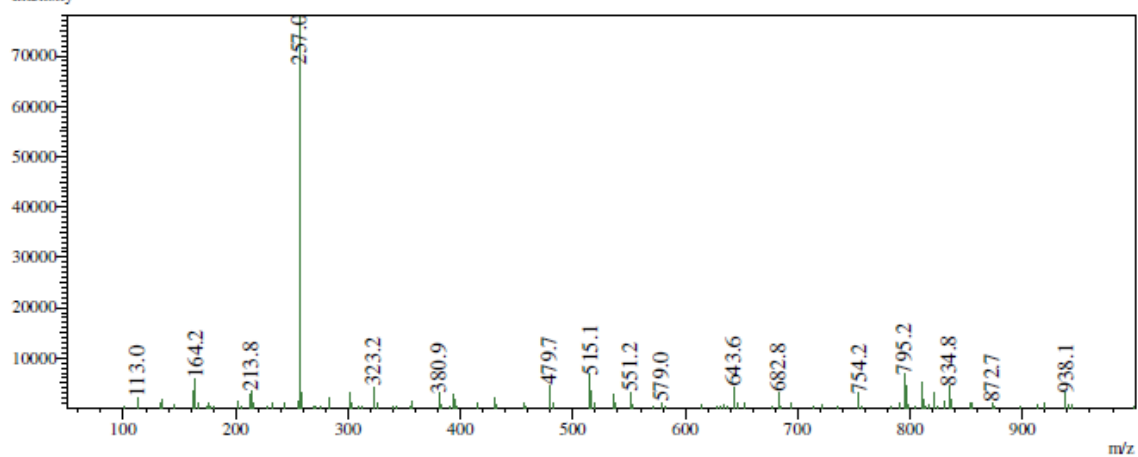
RetTime: 0.533

Intensity



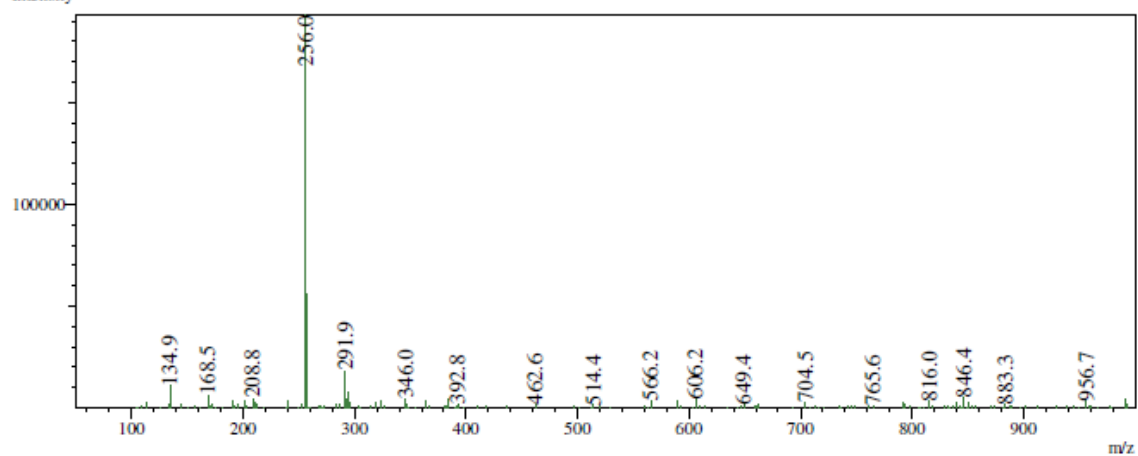
RetTime: 0.766

Intensity



RetTime: 0.916

Intensity



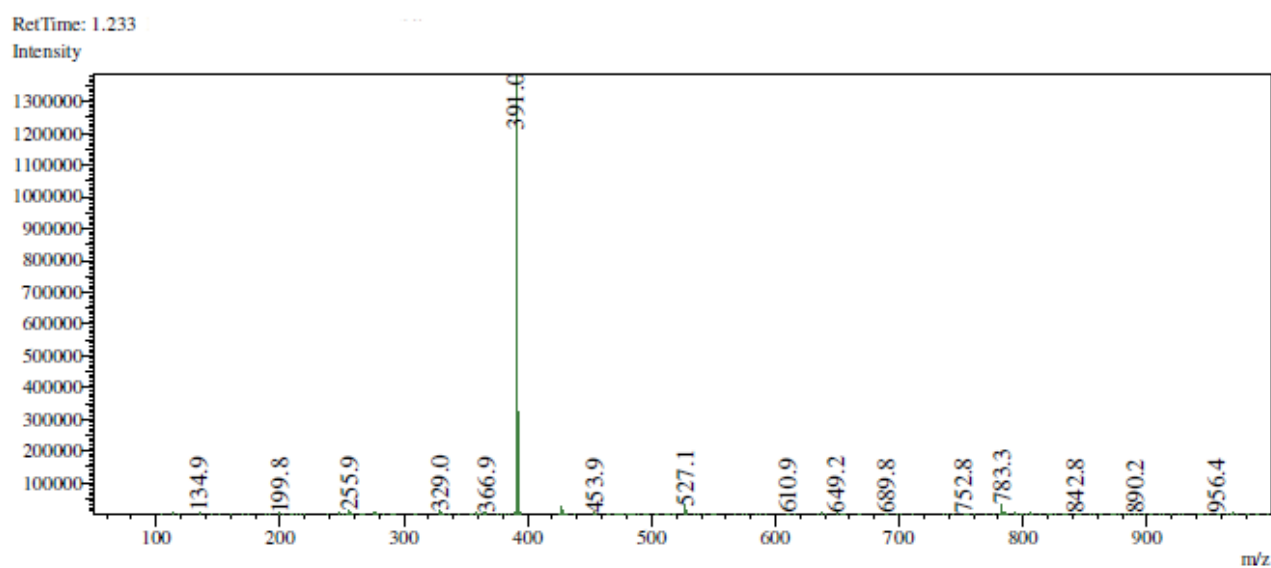
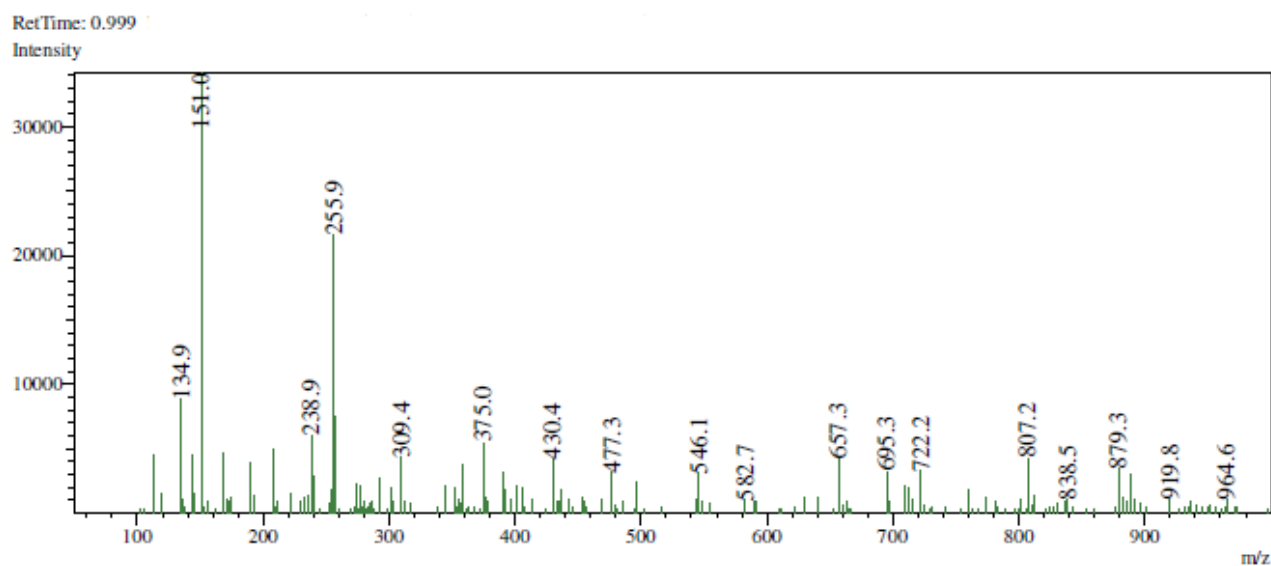
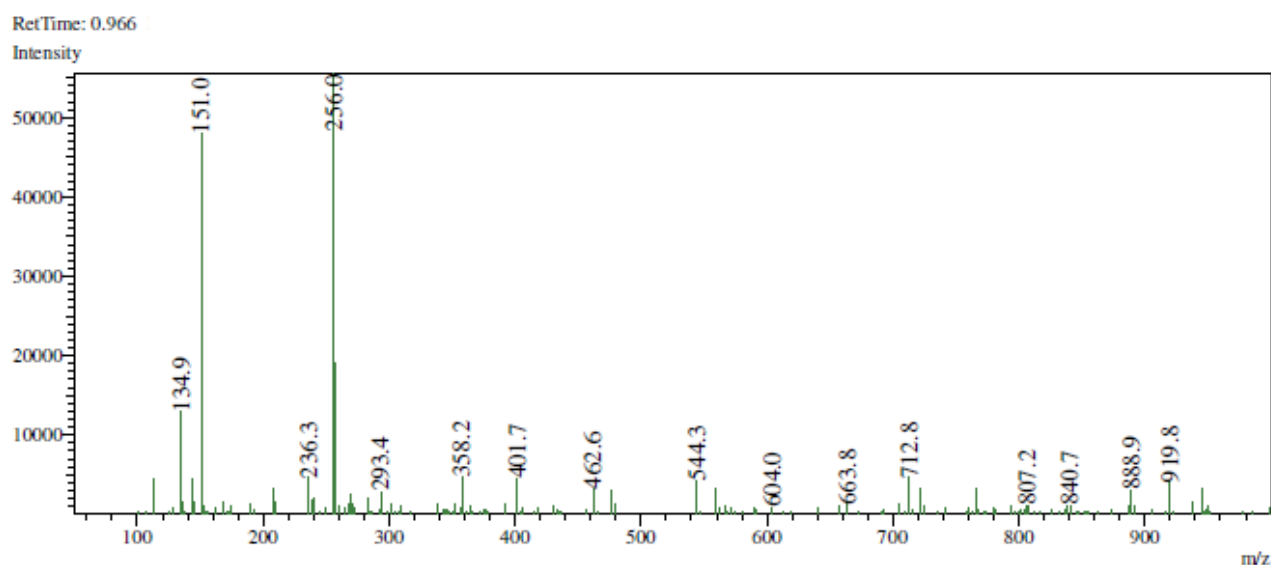


Fig. C13: MS Chromatogram of reaction mixture

^1H NMR of compound 1_4a (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.0$ Hz, 1H), 8.12 (t, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.72 (br d, $J = 8.4$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H), 7.59 (br d, $J = 2.0$ Hz, 1H), 7.49 (br d, $J = 4.4$ Hz, 2H), 7.31 - 7.28 (m, 1H), 2.32 (s, 3H), 2.25 (s, 3H)

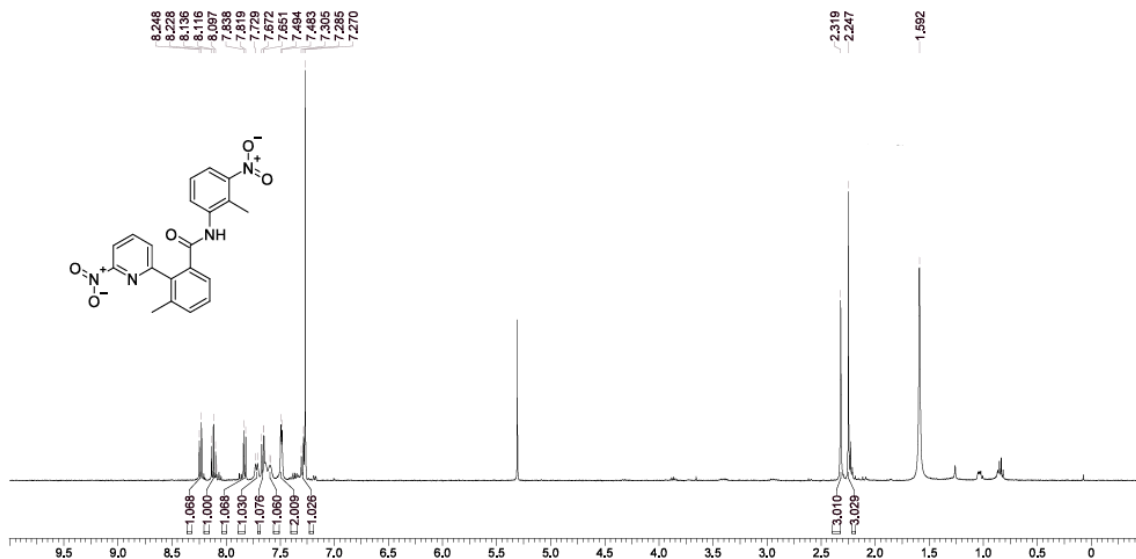
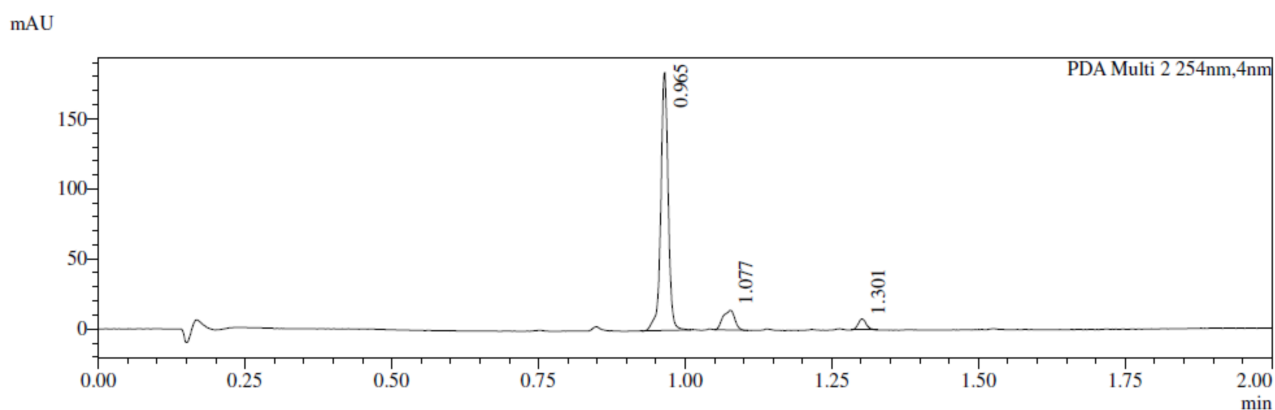
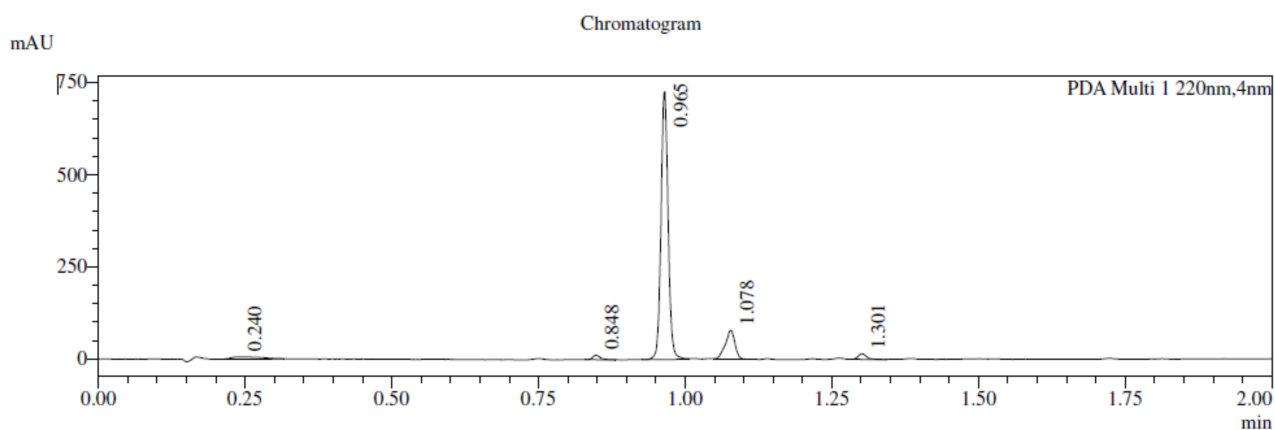


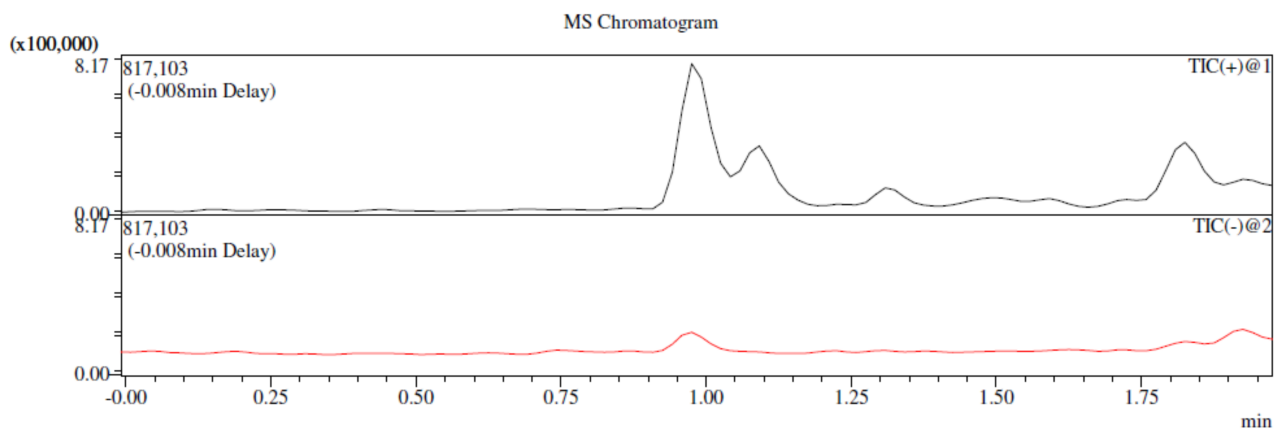
Fig. C14: ^1H NMR of compound 1_4a

Target:

LCMS of reaction mixture, product: RT = 0.965 min, $m/z = 333.1$ ($M + H$) $^+$



- 1 PDA Multi 1 / 220nm,4nm
2 PDA Multi 2 / 254nm,4nm



Integration Result

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.240	0.098	6676	0.795	23997	3.177
2	0.848	0.025	12118	1.443	10839	1.435
3	0.965	0.024	726107	86.484	614065	81.296
4	1.078	0.032	79079	9.419	90993	12.047
5	1.301	0.028	15604	1.859	15449	2.045

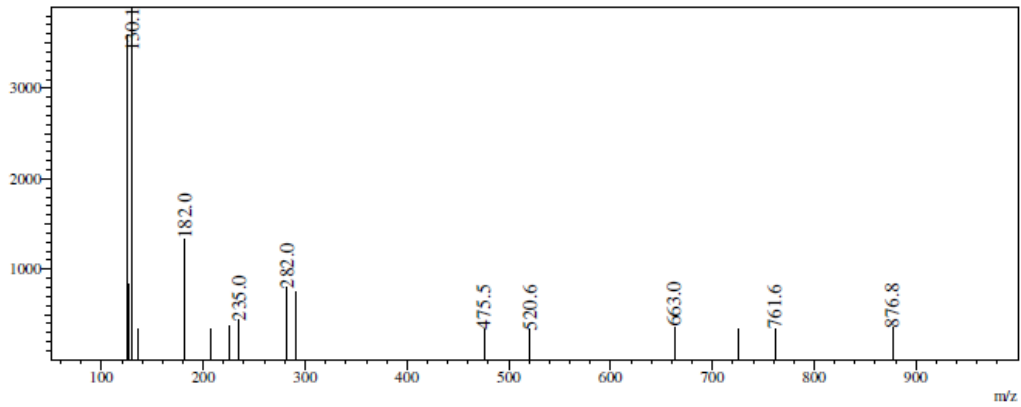
PDA Ch2 254nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.965	0.024	184123	89.346	161471	85.629
2	1.077	0.037	14097	6.841	19495	10.338
3	1.301	0.027	7860	3.814	7604	4.032

MS Spectrum

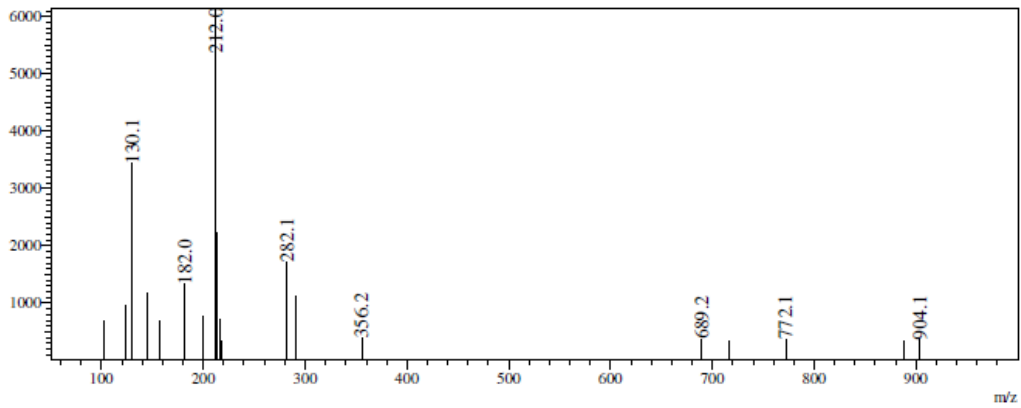
RetTime: 0.225

Intensity



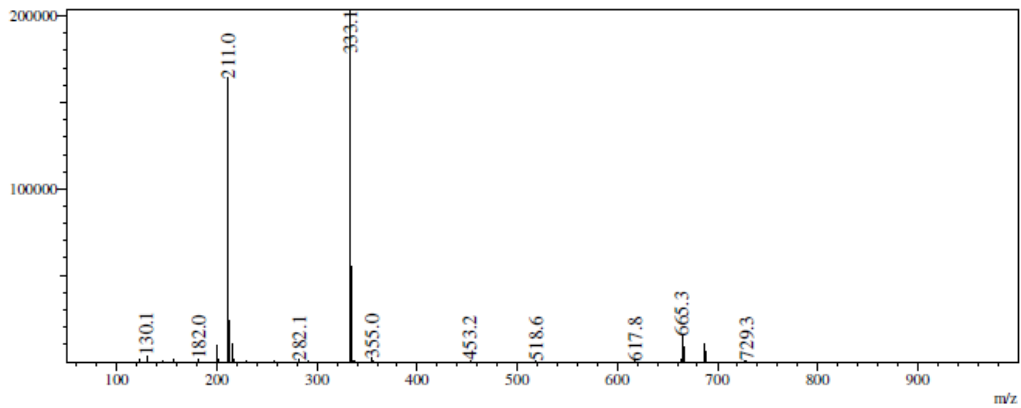
RetTime: 0.842

Intensity



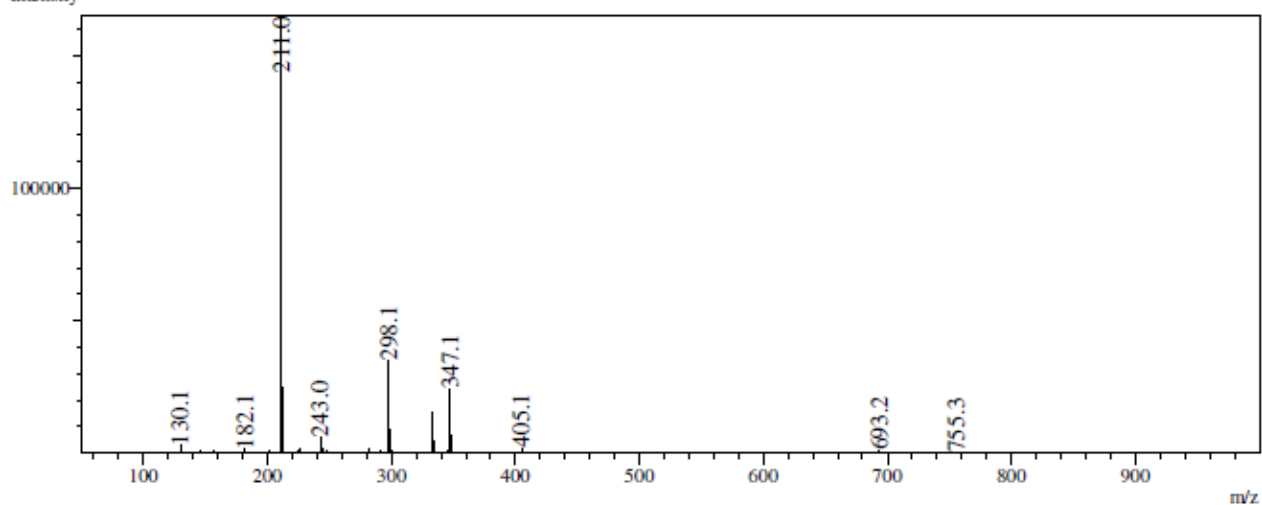
RetTime: 0.958

Intensity



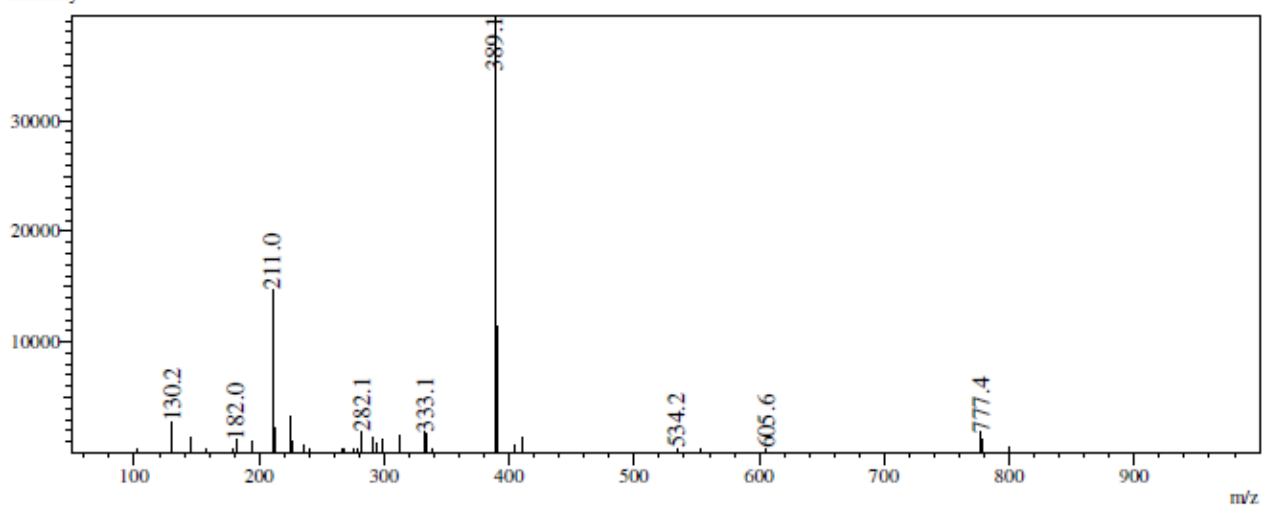
RetTime: 1.075

Intensity



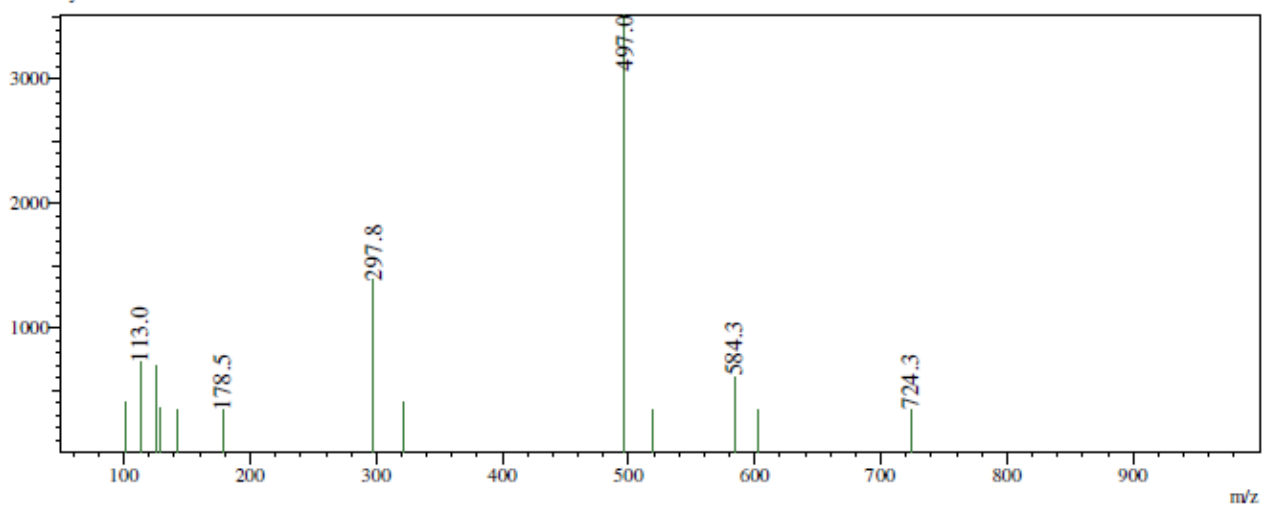
RetTime: 1.292

Intensity



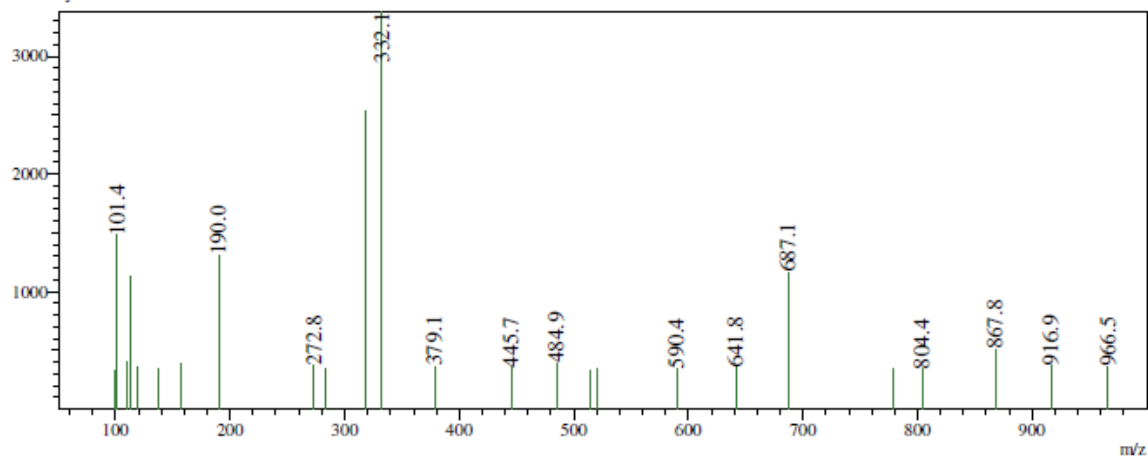
RetTime: 0.233

Intensity



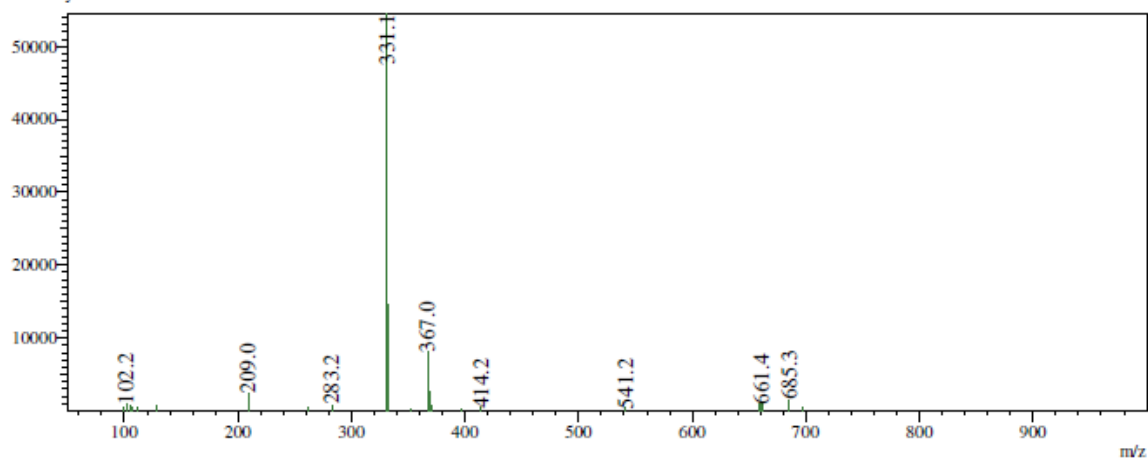
RetTime: 0.849

Intensity



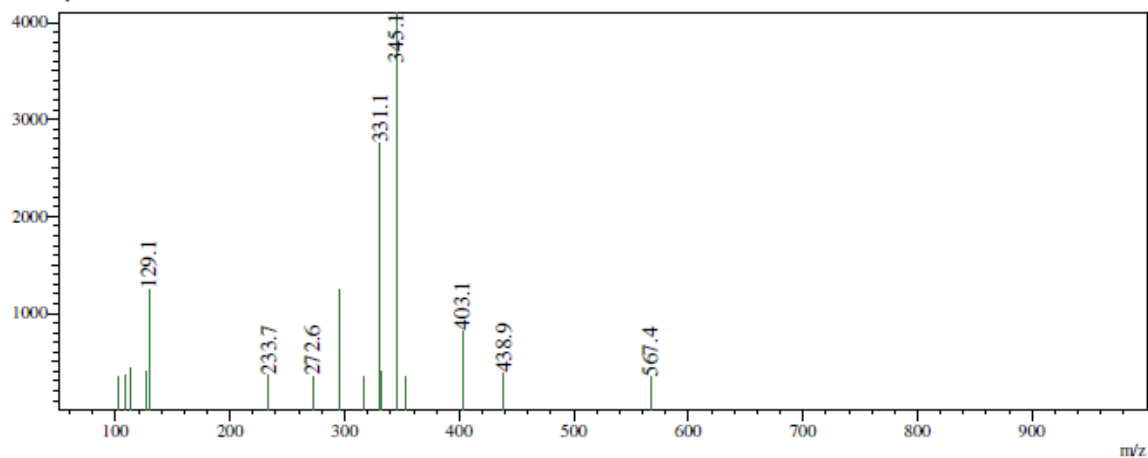
RetTime: 0.966

Intensity



RetTime: 1.083

Intensity



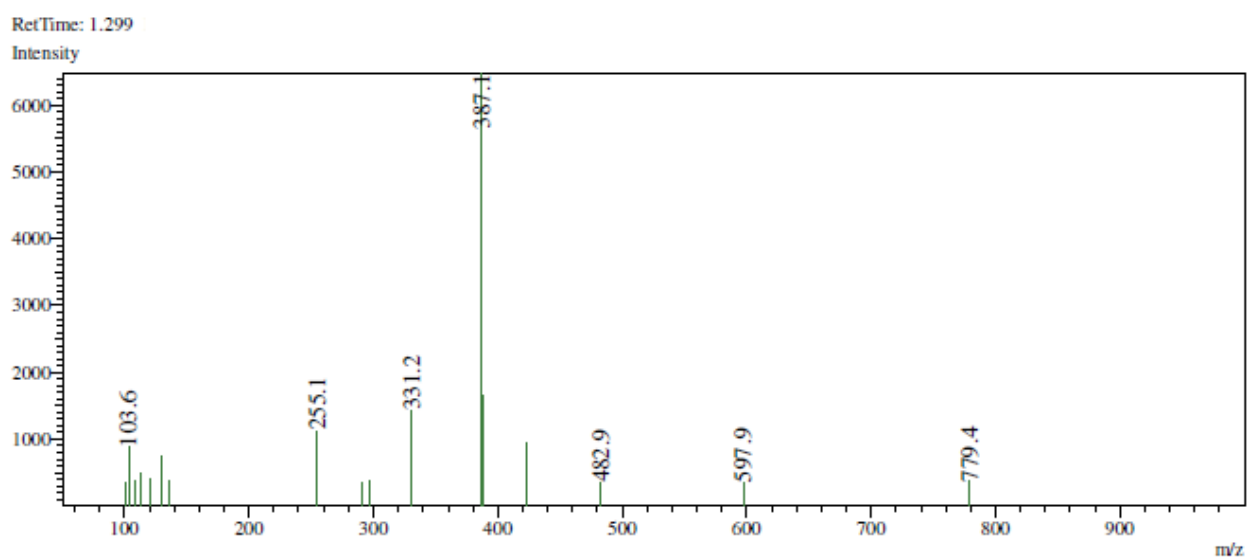
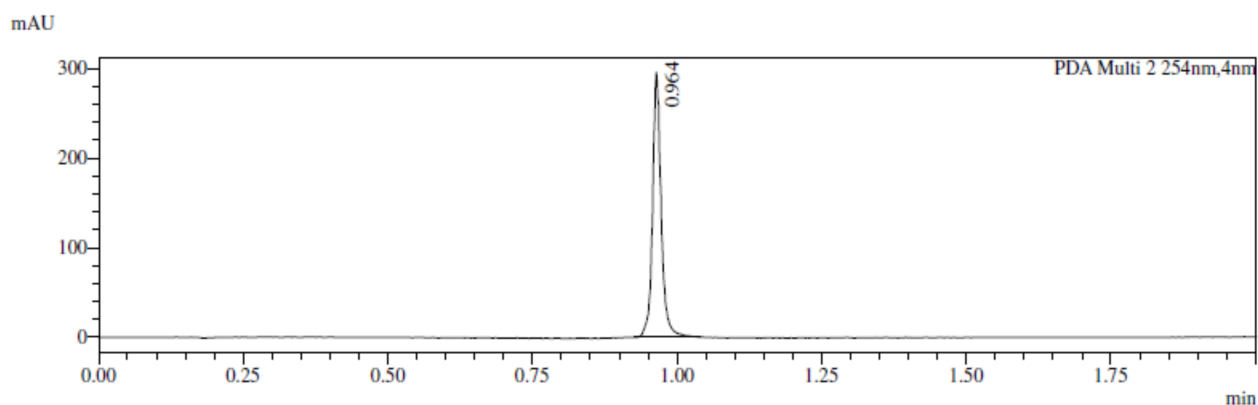
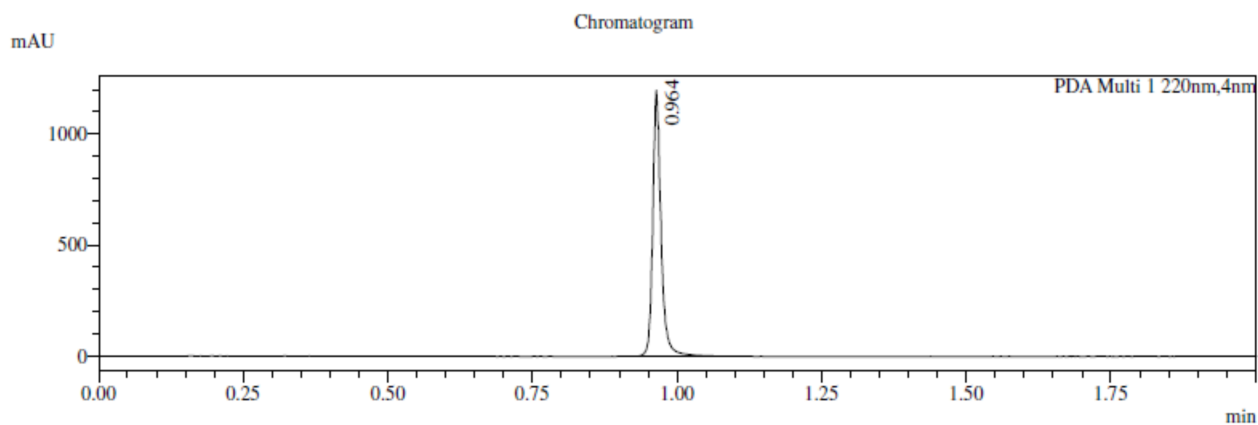
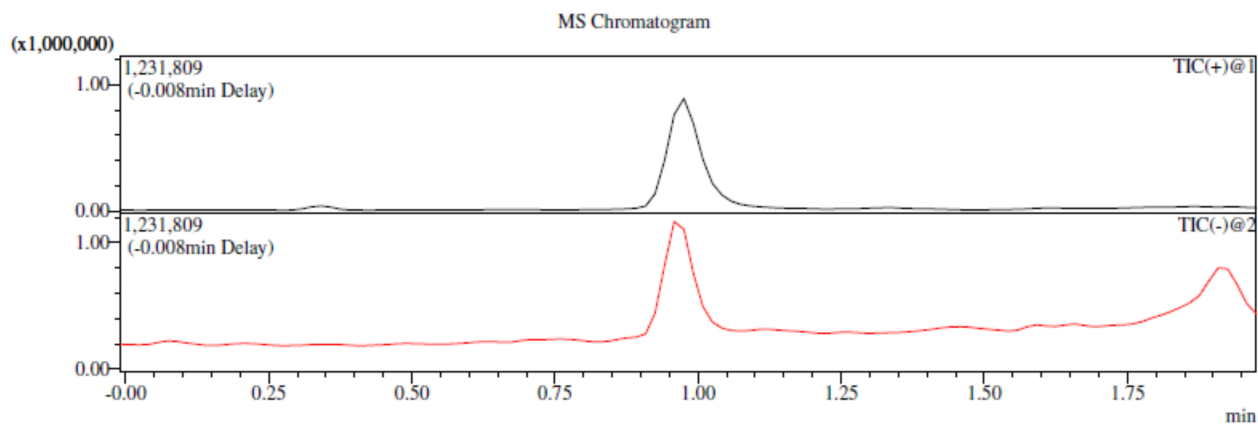


Fig. C16: MS Chromatogram of reaction mixture

LCMS of Target 1, product: RT = 0.637 min, m/z = 320.8 ($M + H$)⁺



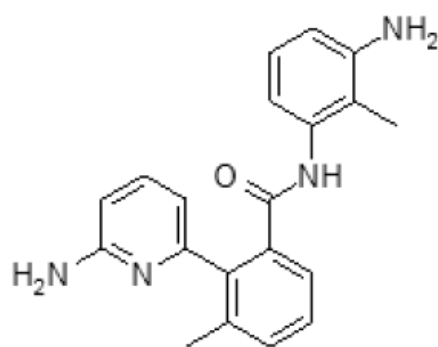
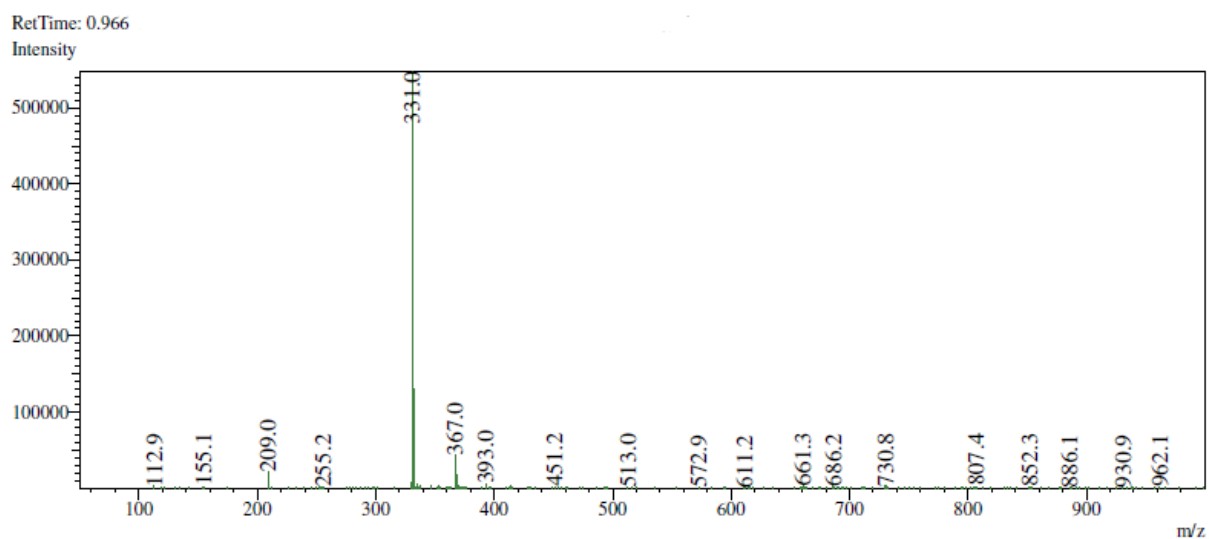
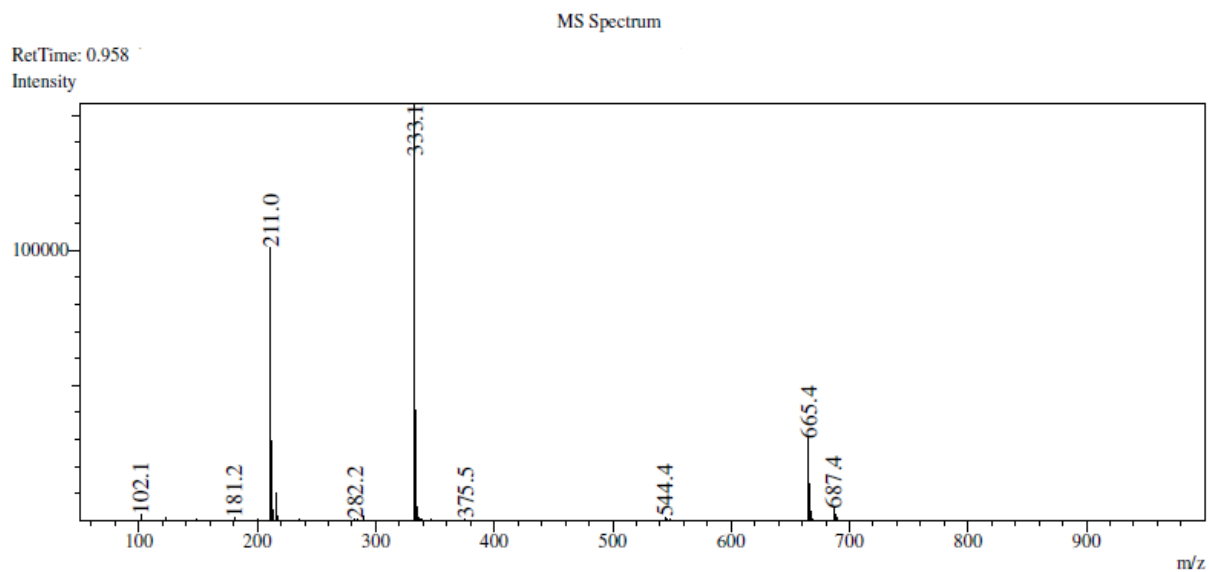
- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



Integration Result

PDA Ch1 220nm							
Peak#	Ret. Time	Width	Height	Height%	Area	Area%	
1	0.964	0.027	1197689	100.000	1191637	100.000	
PDA Ch2 254nm							
Peak#	Ret. Time	Width	Height	Height%	Area	Area%	
1	0.964	0.028	296232	100.000	306096	100.000	

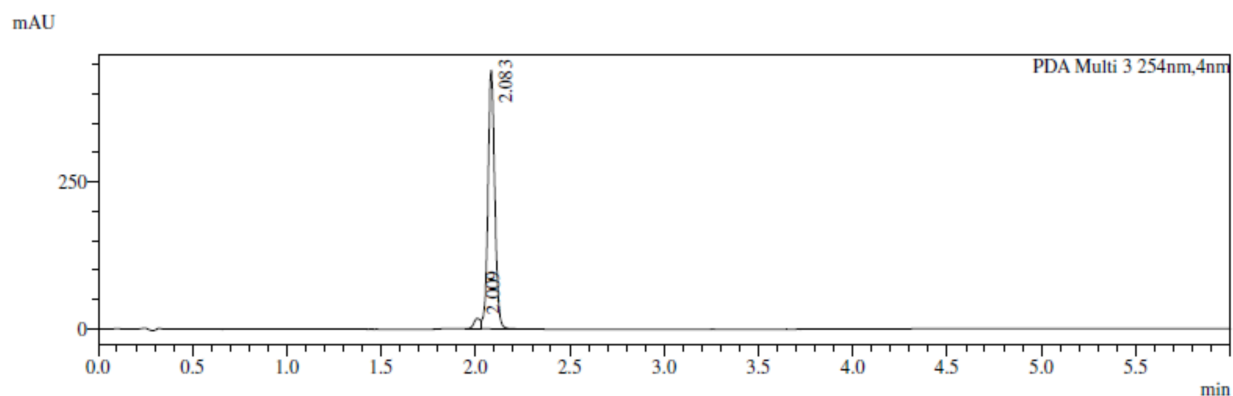
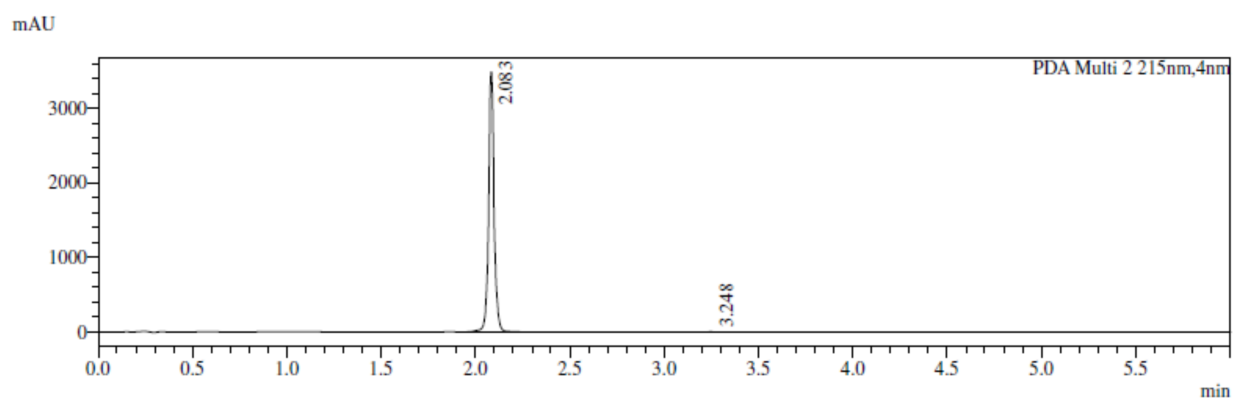
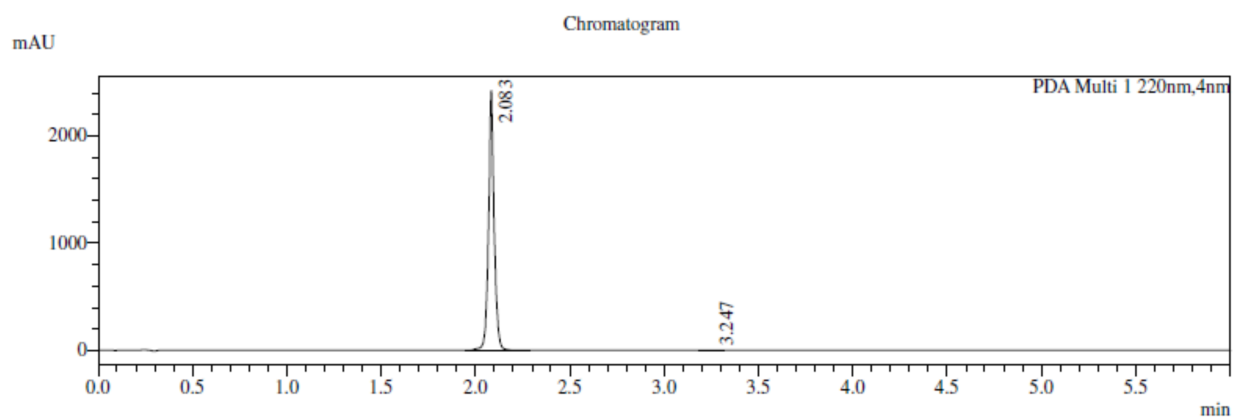
Fig. C17: LCMS Chromatogram of Target 1



Chemical Formula: $C_{20}H_{20}N_4O$
Exact Mass: 332.16

Fig. C18: MS Chromatogram of Target 1

HPLC of Target 1, product: RT = 3.638 mins, 99.1% purity under 220 nm.



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 215nm,4nm
- 3 PDA Multi 3 / 254nm,4nm

=====
Integration Result
=====

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	2.083	0.051	2422195	99.877	5032172	99.816
2	3.247	0.081	2973	0.123	9268	0.184

PDA Ch2 215nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	2.083	0.046	3493506	99.929	7133488	99.896
2	3.248	0.078	2485	0.071	7438	0.104

PDA Ch3 254nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	2.009	0.103	17707	3.872	41211	3.582
2	2.083	0.066	439542	96.128	1109390	96.418

Fig. C19: HPLC Chromatogram of Target 1

¹H NMR of Target 1: EW67459-13-P1A (400 MHz, DMSO-d₆) δ 9.08 (s, 1H), 7.42 - 7.32 (m, 4H), 6.76 (t, J = 8.0 Hz, 1H), 6.54 - 6.42 (m, 2H), 6.41 - 6.30 (m, 2H), 5.85 (s, 2H), 4.78 (s, 2H), 2.14 (s, 3H), 1.74 (s, 3H)

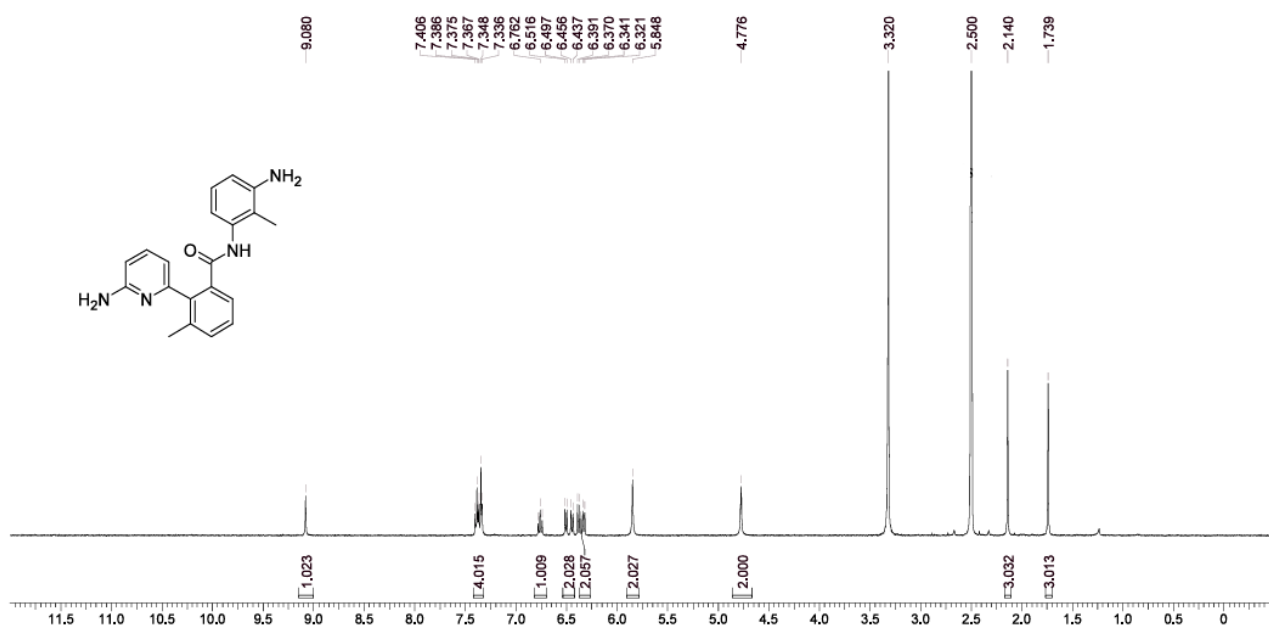


Fig. C20: ¹H NMR of Target 1

C.6 Synthesis of KP032

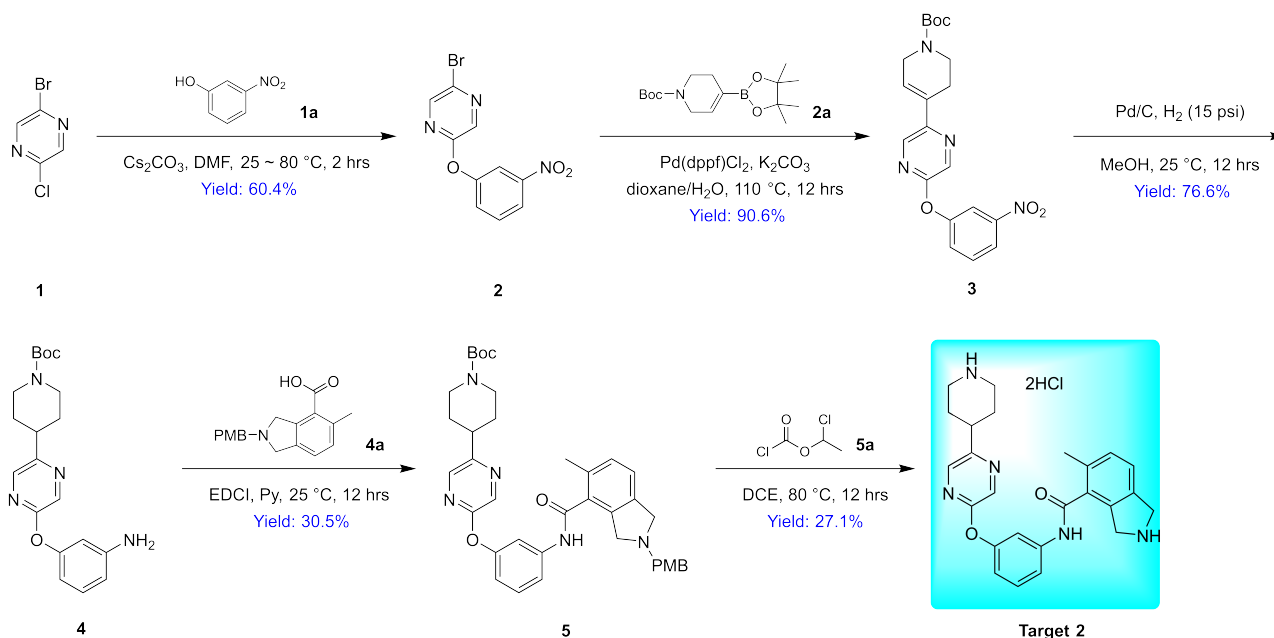


Fig. C21: Synthesis of KP032

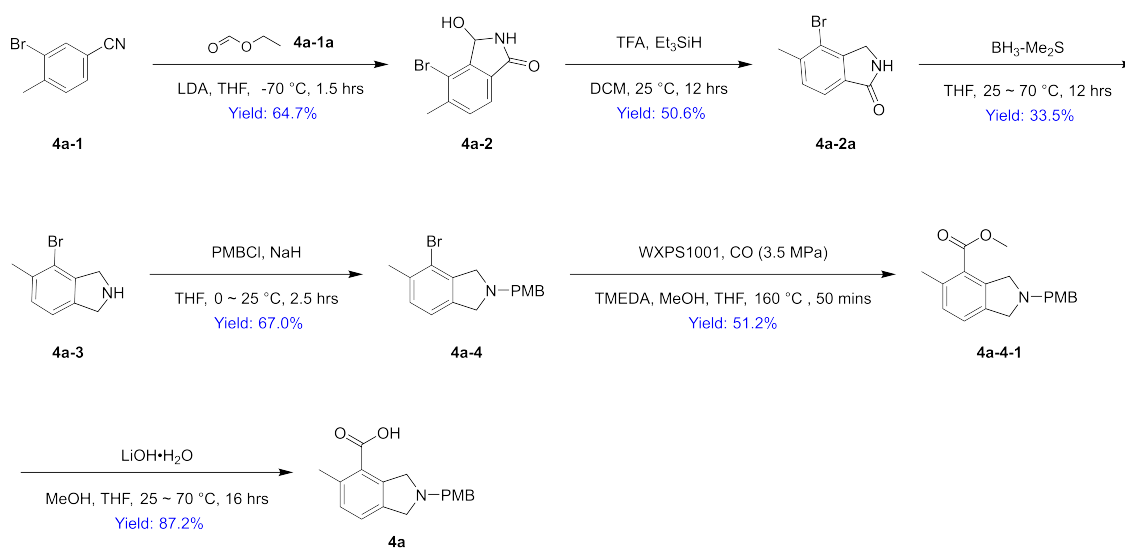


Fig. C22: Synthesis of Compound 4a

Compound 2. To a solution of compound 1 (4.00 g, 20.6 mmol, 1.00 eq), compound 1a (3.16 g, 22.7 mmol, 4.52 mL, 1.10 eq) in DMF (40.0 mL) was added Cs₂CO₃ (10.1 g, 31.0 mmol, 1.50 eq) at 25 °C, the mixture was stirred at 80 °C for 2 hrs. TLC (Petroleum ether/Ethyl acetate = 3/1) showed compound 1 (R_f = 0.60) was consumed completely and a major spot (R_f = 0.50) was detected. The mixture was poured into H₂O (400 mL), the aqueous phase was extracted with ethyl acetate (100 mL * 2). The combined organic phase was washed with brine (300 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 30/1 to 5/1, Petroleum ether/Ethyl acetate = 3/1, R_f = 0.50) to give the product. Compound 2 (3.70 g, 12.5 mmol, 60.4% yield) was obtained as a white solid.

Compound 3. To a solution of compound 2 (3.00 g, 10.1 mmol, 1.00 eq), compound 2a (3.76 g, 12.1 mmol, 1.20 eq) and K₂CO₃ (2.80 g, 20.2 mmol, 2.00 eq) in dioxane (30.0 mL) and H₂O (3.00 mL) was added Pd(dppf)Cl₂ (741 mg, 1.01 mmol, 0.100 eq), then the mixture was stirred at 110 °C for 12 hrs under N₂. TLC (Petroleum ether/Ethyl acetate = 5/1) showed compound 2 (R_f = 0.50) was consumed completely and a major spot (R_f = 0.30) was detected. The mixture was concentrated to give the product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 30/1 to 5/1, Petroleum ether/Ethyl acetate = 5/1, R_f = 0.30) to give the product. Compound 3 (4.50 g, 11.2 mmol, 90.6% yield) was obtained as a white solid.

Compound 4. To a solution of compound 3 (2.00 g, 5.02 mmol, 1.00 eq) in MeOH (20.0 mL) was added Pd/C (0.500 g, 469 μmol, 10.0% purity, 9.36e-2 eq), the mixture was stirred at 25 °C for 12 hrs under H₂ (15 psi). LCMS (EW67434-6-P1A2) showed the desired product MS (RT = 0.491 min) was detected. The mixture was filtered through celite and the filtrate was concentrated under vacuum to get the product. The crude product was purified by reversed-phase HPLC (column: Welch Ultimate XB-SiOH 250*50mm*10μm; mobile phase: [Heptane-EtOH (0.1% NH₃H₂O)]; gradient: 5%-45% B over 15.0 min). Compound 4 (1.50 g, 3.85 mmol, 76.6% yield, 94.9% purity) was obtained as a yellow oil.

Compound 5. To a solution of compound 4 (89.7 mg, 242 μ mol, 1.20 eq), compound 4a (60.0 mg, 201 μ mol, 1.00 eq) and EDCI (77.3 mg, 403 μ mol, 2.00 eq) in Py (1.50 mL), the mixture was stirred at 25 °C for 12 hrs. LCMS (EW67434-26-P1A1) showed the desired product MS (RT = 2.139 min) was detected. The mixture was concentrated. The crude product was purified by prep-HPLC (column: Phenomenex Luna C8 150*25mm*10um;mobile phase: [H₂O (0.225% FA)-ACN]; gradient: 31%-61% B over 10.0 min). The eluent was concentrated in vacuum to remove ACN. The residual aqueous solution was lyophilized to give a product. Compound 5 (40.0 mg, 61.5 μ mol, 30.5% yield) was obtained as a yellow solid.

Target 2. To a solution of compound 5 (40.0 mg, 61.5 μ mol, 1.00 eq) in DCE (1.00 mL) and was added compound 5a (26.4 mg, 184 μ mol, 3.00 eq), the mixture was stirred at 80 °C for 12 hr. LCMS (EW67434-33-P1B1) showed the desired product MS (RT = 1.204 min) was detected. The reaction was concentrated and dissolved in MeOH to pre-HPCL purification. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um;mobile phase: [H₂O (0.05% HCl)-ACN]; gradient: 0%-25% B over 13.0 min). The eluent was concentrated in vacuum to remove ACN. The residual aqueous solution was lyophilized to give a product. Target 2 (8.55 mg, 16.7 μ mol, 27.1% yield, 98.3% purity, 2HCl) was obtained as a colorless oil.

Compound 4a-2. To a solution of compound 4a-1 (4.00 g, 20.4 mmol, 1.00 eq) in THF (40.0 mL) was slowly added LDA (2.00 M, 13.2 mL, 1.30 eq) at -70 °C, the mixture was stirred at -70 °C for 0.5 hr, then compound 4a-1a (1.66 g, 22.4 mmol, 1.81 mL, 1.10 eq) in THF (8.00 mL) was added to the mixture and the mixture was stirred at -70 °C for 1 hr. TLC (Petroleum ether/Ethyl acetate = 1/1) showed EW67434-8-R1 (R_f = 0.80) was consumed completely and a major spot (R_f = 0.10) was detected. The mixture was poured into NH₄Cl (100 mL), the aqueous phase was adjust pH = 5-6 with 1.00 N HCl solution and extracted with ethyl acetate (80.0 mL * 2). The combined organic phase was washed with brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with Petroleum ether/Ethyl acetate = 1/1 (30.0 mL) at 25 °C for 30 mins. Compound 4a-2 (3.20 g, 13.2 mmol, 64.7% yield) was obtained as a yellow solid.

Compound 4a-2a. To a solution of compound 4a-2 (3.00 g, 12.3 mmol, 1.00 eq) in DCM (30.0 mL) was added Et₃SiH (11.5 g, 99.1 mmol, 15.8 mL, 8.00 eq) and TFA (11.3 g, 99.1 mmol, 7.36 mL, 8.00 eq) at 25 °C, then the mixture was stirred at 25 °C for 12 hrs. TLC (Petroleum ether/Ethyl acetate = 2/1) showed compound 4a-2 (R_f = 0.20) was consumed completely and a major spot (R_f = 0.30) was detected. The reaction mixture was diluted with H₂O (50.0 mL), adjust pH = 8-9 with Na₂CO₃ solution and extracted with DCM (30.0 mL * 2). The combined organic layers were washed with brine (50.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 15/1 to 0/1, Petroleum ether/Ethyl acetate = 1/1, R_f = 0.3) to give the product. Compound 4a-2a (1.42 g, 6.28 mmol, 50.6% yield) was obtained as a yellow solid.

Compound 4a-3. To a solution of compound 4a-2a (1.27 g, 5.62 mmol, 1.00 eq) in THF (12.0 mL) was added slowly added BH₃-Me₂S (10.0 M, 1.40 mL, 2.50 eq) at 25 °C, after addition, the mixture was stirred at 70 °C for 12 hrs under N₂. LCMS (EW67434-15-P1B1) showed the desired product MS (RT = 1.082 min) was detected. The mixture was cooled to 25 °C, and 2.00 M HCl/MeOH (15.0 mL) was slowly added to the mixture under N₂. Finally, the mixture was stirred at 25 °C for 30 mins. then the mixture was filtered, the wet cake was

washed with THF (20.0 mL * 2) concentrated to give the product. The crude product was purified by prep-HPLC (column: Welch Ultimate XB-SiOH 250*100mm*10um;mobile phase: [Heptane-EtOH (0.1% NH₃H₂O)]; gradient: 1%-40% B over 16.0 min). The eluent was concentrated in vacuum to give a product. Compound 4a-3 (0.400 g, 1.89 mmol, 33.5% yield) was obtained as a yellow solid.

Compound 4a-4. To a solution of compound 4a-3 (0.400 g, 1.89 mmol, 1.00 eq) in THF (4.00 mL) was slowly added NaH (113 mg, 2.83 mmol, 60.0% purity, 1.50 eq) at 0 °C, the mixture was stirred at 0 °C for 30 mins, PMB-Cl (354 mg, 2.26 mmol, 307 μ L, 1.20 eq) was slowly added dropwise, then the mixture was stirred at 25 °C for 2 hrs. LCMS (EW67434-17-P1A) showed the desired product MS (RT = 1.640 min) was detected. The mixture was poured into NH₄Cl (10.0 mL) and extracted with ethyl acetate (20.0 mL * 2). The combined organic phase was washed with brine (30.0 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 20/1 to 5/1, Petroleum ether/Ethyl acetate = 3/1, R_f = 0.50) to give the product. Compound 4a-4 (420 mg, 1.26 mmol, 67.0% yield) was obtained as a yellow oil.

Compound 4a-4-1. Solution 1: compound 4a-4 (250 mg, 752 μ mol, 1.00 eq) and TMEDA (262 mg, 2.26 mmol, 340 μ L, 3.00 eq) in MeOH (2.50 mL) and THF (2.50 mL). The fixed bed (named FLR1, volume 100 mL) was completely packed with granular catalyst WXPS1001 (190 g, 1.79 mol, 2372.66 eq). The CO back pressure regulator was adjusted to 3.5 Mpa, and the CO flow rate was 1.60 eq, 10.3 sccm. The solution 1 was pumped by Pump 1 S1, P1, 2.00 mL/min to flow reactor 1 FLR1, SS, Fixed bed, 12.700(1/2")mm, 100 mL, 160°C LCMS (EW67434-22-P1A) showed the desired product MS (RT = 1.559 min) was detected. The mixture was concentrated to give the residue. The crude product was purified by prep-HPLC (column: Phenomenex Luna C8 150*25mm*10um; mobile phase: [H₂O (0.225% FA)-ACN]; gradient: 8%-38% B over 15.0 min). The eluent was concentrated in vacuum to remove ACN. The residual aqueous solution was lyophilized to give a product. Compound 4a-4-1 (120 mg, 385 μ mol, 51.2% yield) was obtained as a yellow oil.

Compound 4a. To a solution of compound 4a-4-1 (120 mg, 385 μ mol, 1.00 eq) in MeOH (2.00 mL) and THF (2.00 mL) was added LiOH•H₂O (2.00 M, 578 μ L, 3.00 eq) at 25 °C, after addition, the mixture was stirred at 70 °C for 16 hrs. LCMS (EW67434-23-P1A2) showed the desired product MS (RT = 1.353 min) was detected. The mixture was added H₂O (5.00 mL), adjust pH to 2-3 with 1.00 N HCl solution, then extracted with ethyl acetate (5.00 mL * 3), the combined organic layers were washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound 4a (100 mg, 336 μ mol, 87.2% yield) was obtained as a yellow solid.

C.7 The LCMS, HPLC and ¹H NMR spectra reports of KP032

compound 2:

¹H NMR of compound 2, (400 MHz, DMSO-d₆) δ 8.56 - 8.50 (m, 1H), 8.47 - 8.36 (m, 1H), 8.19 - 8.10 (m, 2H), 7.81 - 7.70 (m, 2H)

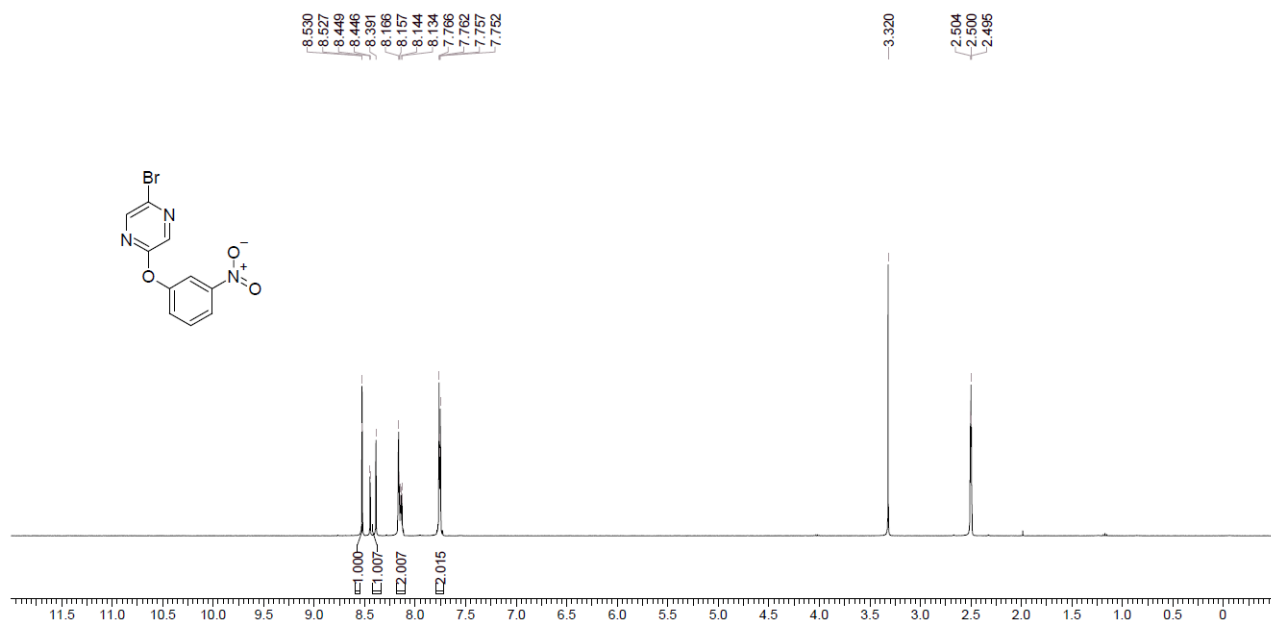


Fig. C23: ¹H NMR of compound 2

compound 3:

¹H NMR of compound 3, (400 MHz, DMSO-d₆) δ 8.58 (d, J = 1.2 Hz, 1H), 8.39 (d, J = 1.2 Hz, 1H), 8.17 - 8.07 (m, 2H), 7.79 - 7.67 (m, 2H), 6.69 (br s, 1H), 4.05 (br s, 2H), 3.55 (br t, J = 5.6 Hz, 2H), 2.55 (br d, J = 1.6 Hz, 2H), 1.42 (s, 9H)

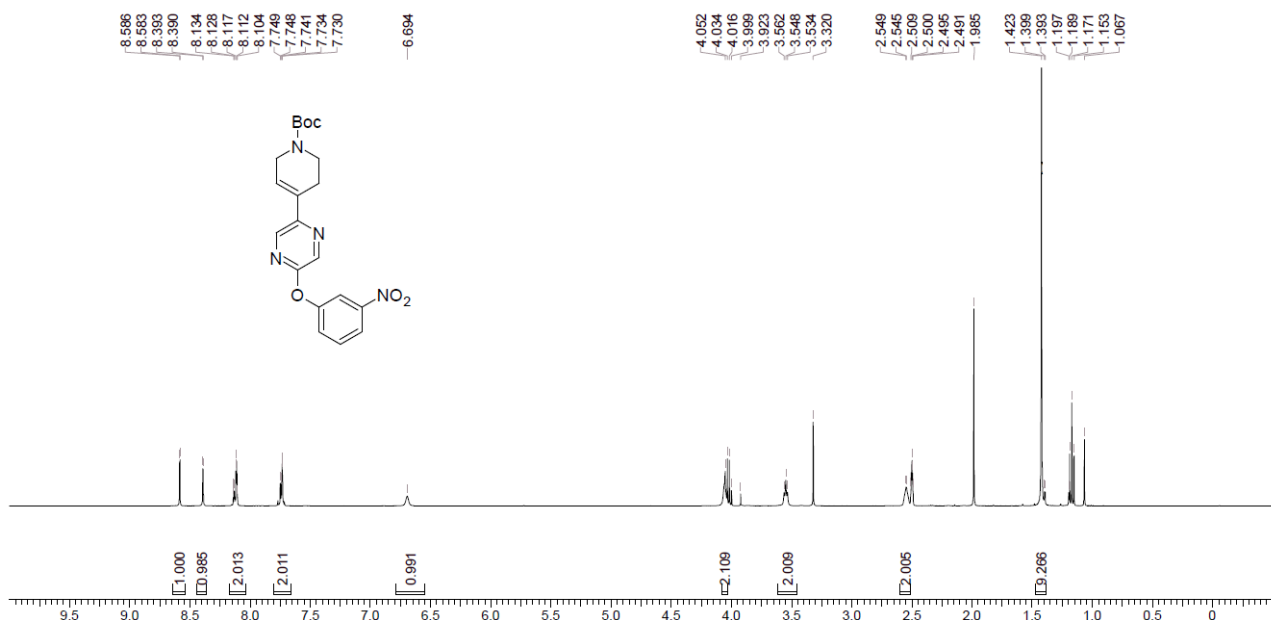
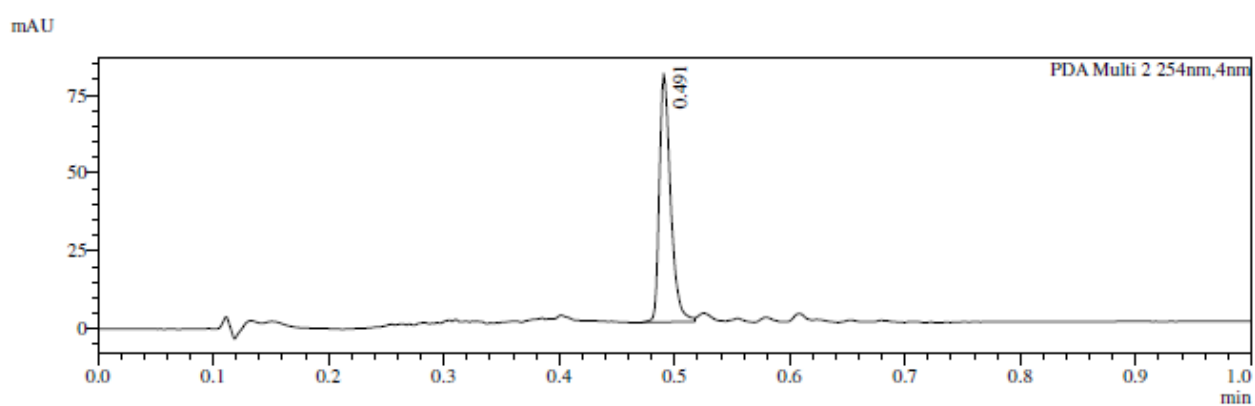
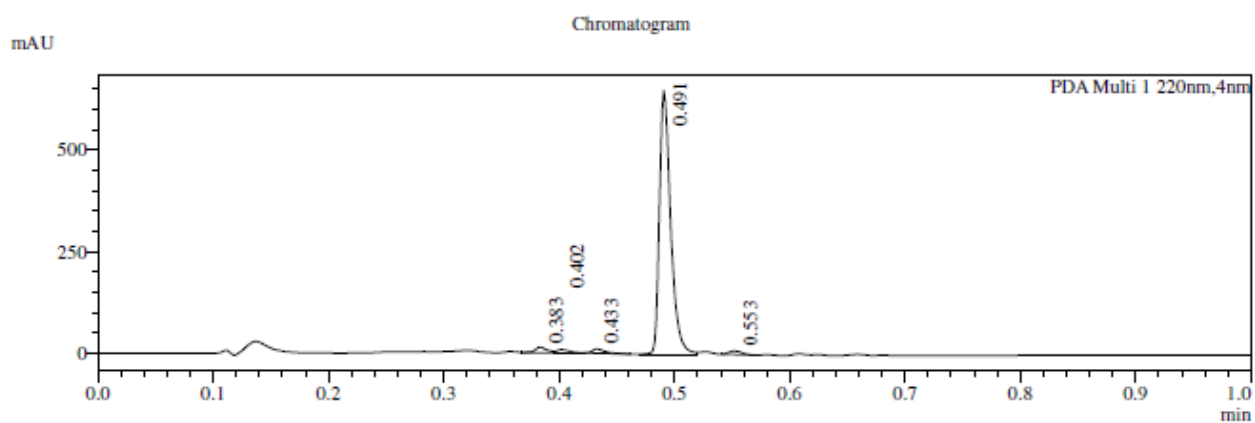


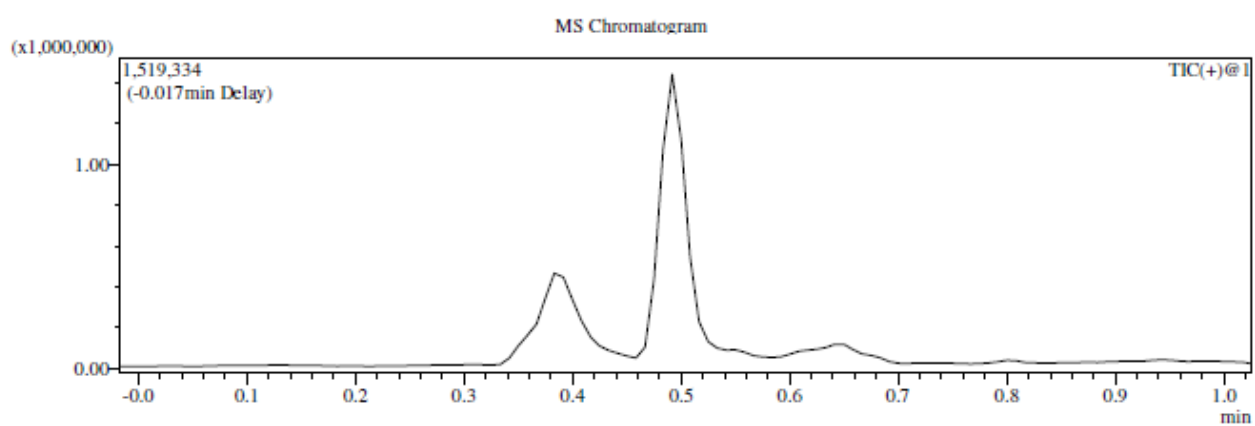
Fig. C24: ¹H NMR of compound 2

compound 4:

LCMS of reaction mixture, product: RT = 0.491 min, m/z = 393.2 (M+Na)+



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



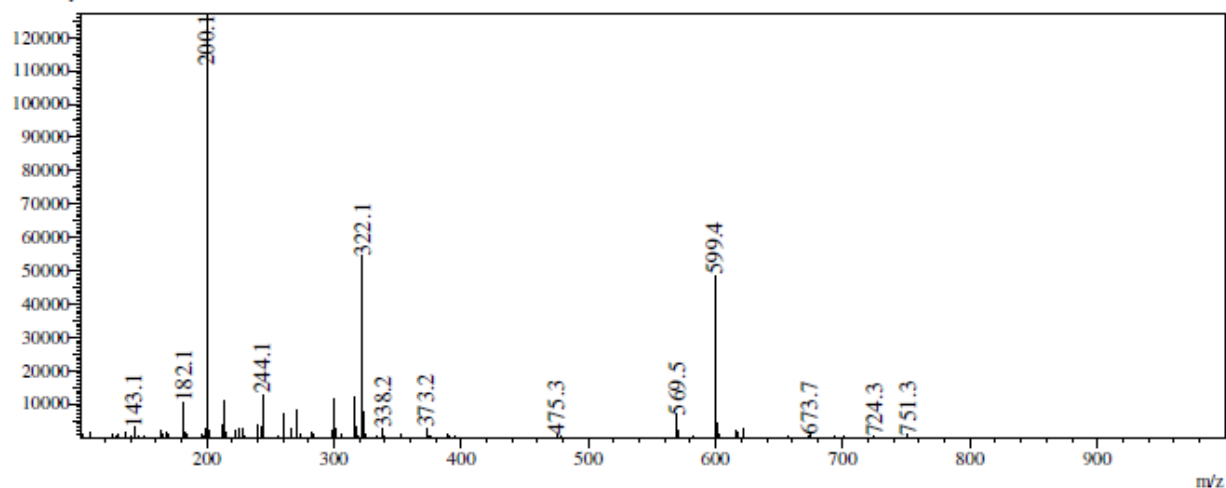
Integration Result						
PDA Ch1 220nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.383	0.021	13635	1.976	10138	2.165
2	0.402	0.026	7694	1.115	6004	1.282
3	0.433	0.021	10507	1.523	7877	1.682
4	0.491	0.020	649661	94.138	437606	93.461
5	0.553	0.022	8621	1.249	6598	1.409
PDA Ch2 254nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.491	0.020	79785	100.000	54242	100.000

Fig. C25: LCMS Chromatogram of reaction mixture

MS Spectrum

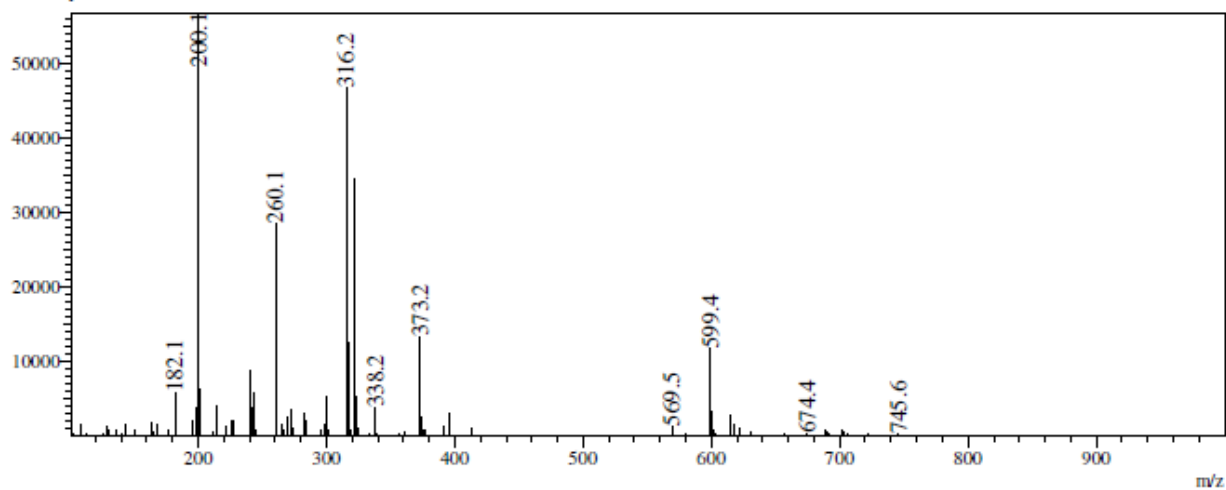
RetTime: 0.383

Intensity



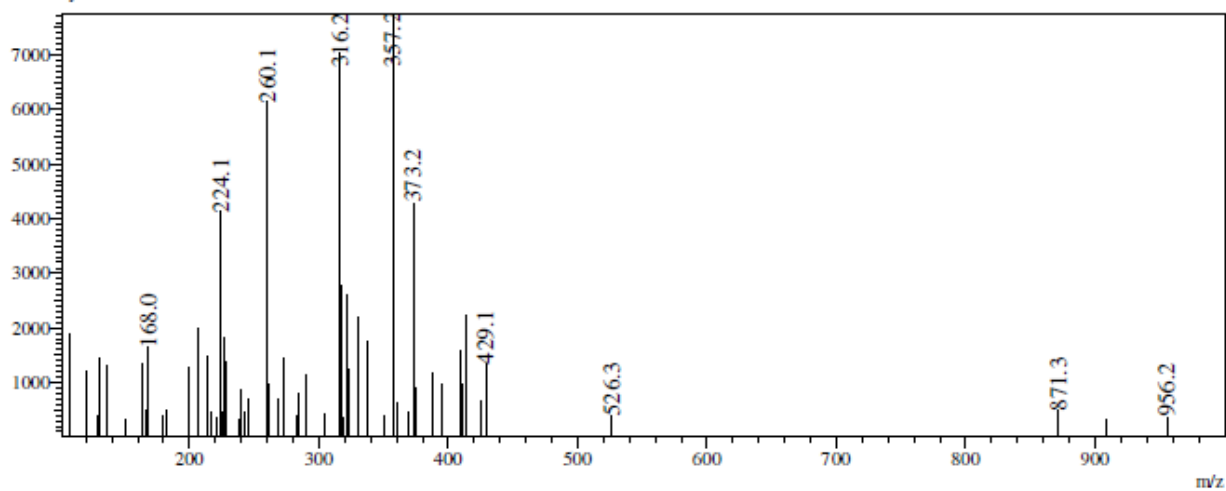
RetTime: 0.400

Intensity



RetTime: 0.433

Intensity



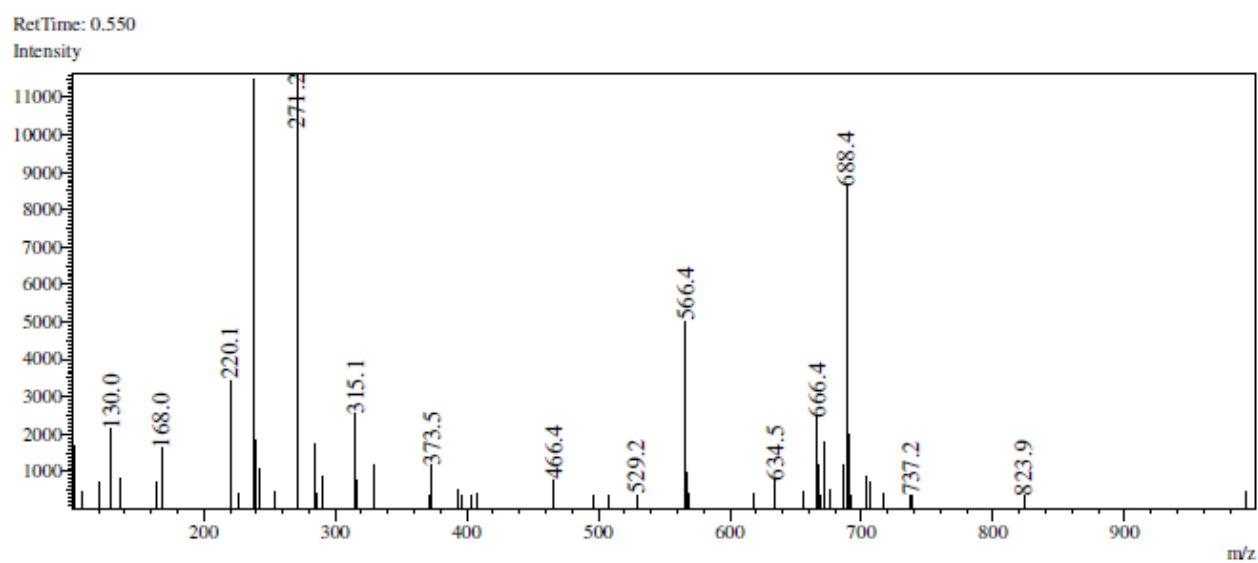
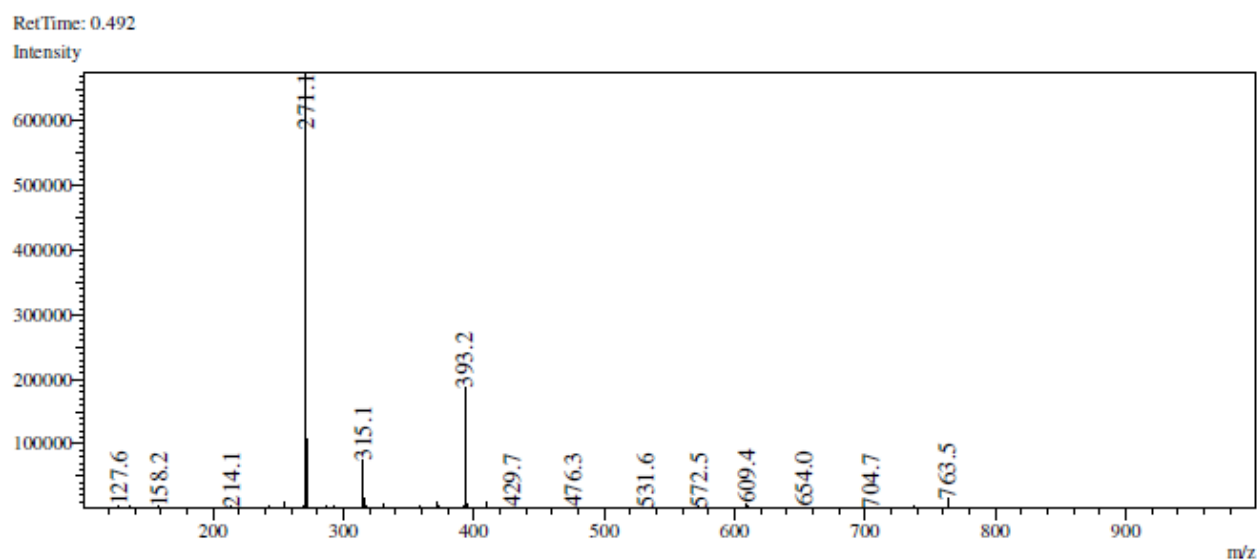


Fig. C26: MS Chromatogram of reaction mixture

^1H NMR of compound 4, (400 MHz, DMSO-d_6) δ 8.35 (d, $J = 1.2$ Hz, 1H), 8.15 (d, $J = 1.2$ Hz, 1H), 7.02 (t, $J = 8.0$ Hz, 1H), 6.41 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.29 (t, $J = 2.4$ Hz, 1H), 6.23 (dd, $J = 7.2, 1.6$ Hz, 1H), 5.25 (s, 2H), 4.06 (br d, $J = 12.0$ Hz, 2H), 2.97 - 2.72 (m, 3H), 1.81 (br d, $J = 11.6$ Hz, 2H), 1.61 - 1.50 (m, 2H), 1.41 (s, 9H)

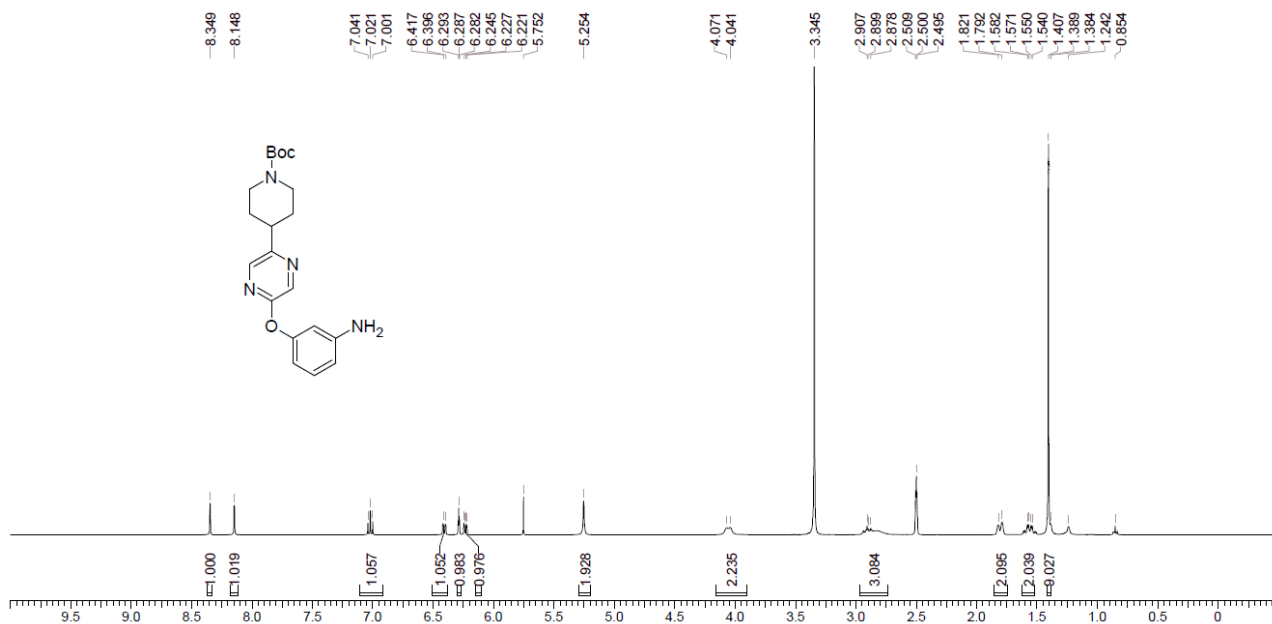
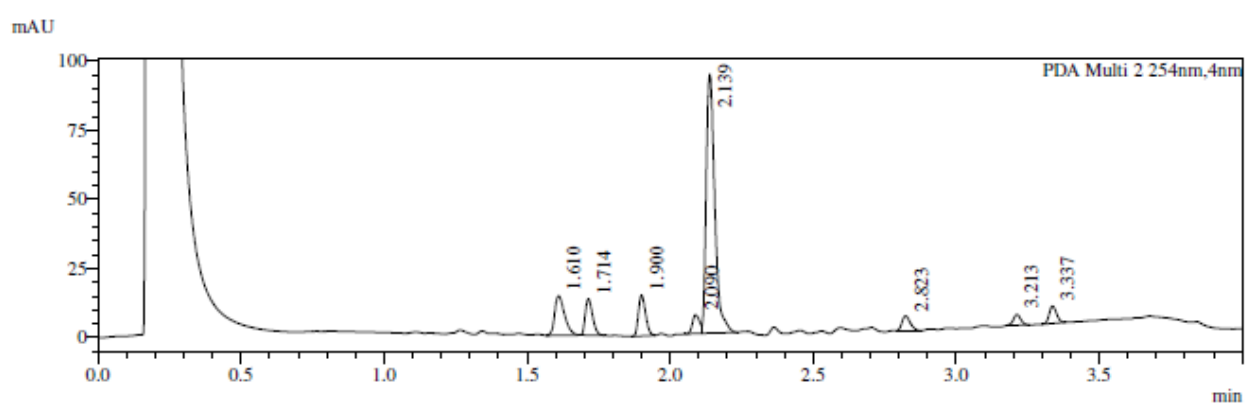
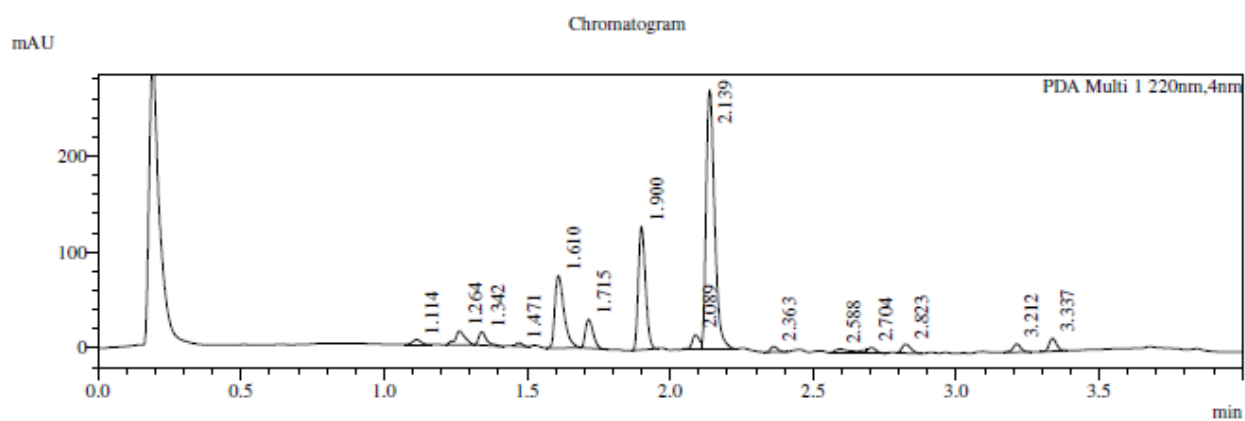
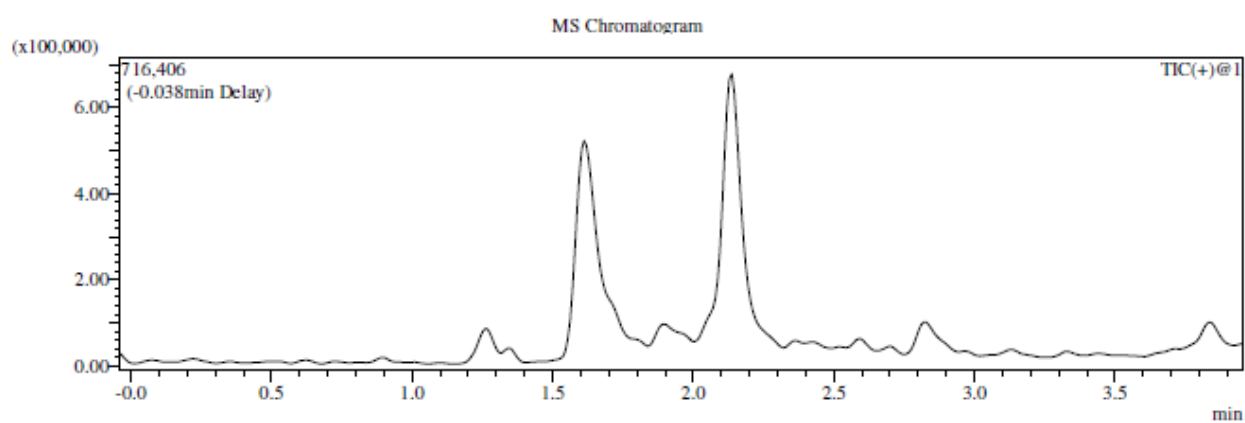


Fig. C27: ^1H NMR of compound 4

compound 5: LCMS of reaction mixture, product: RT = 2.139 min, $m/z = 650.3$ ($\text{M}+\text{H}$) $^+$



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



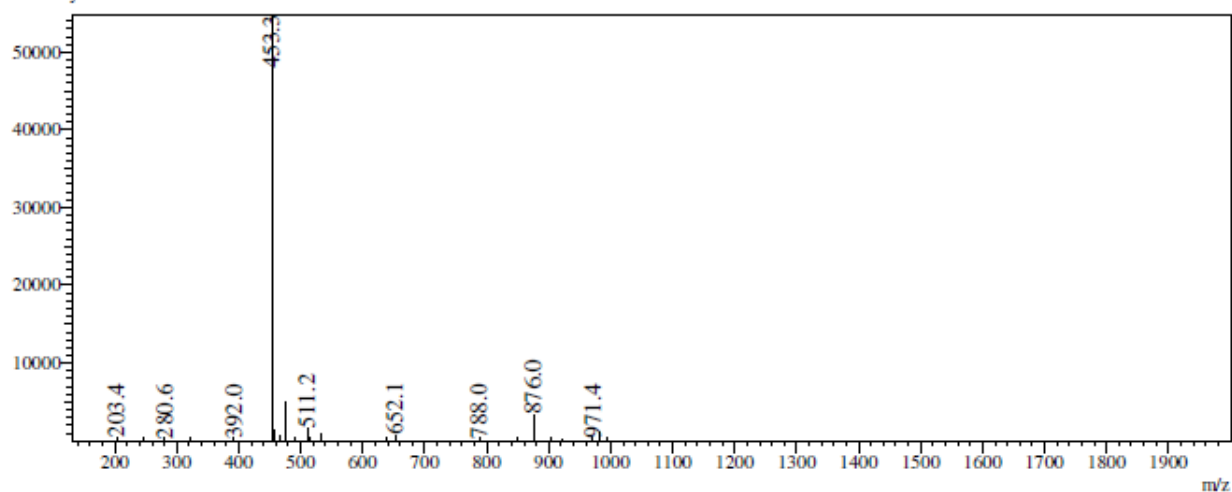
Integration Result								
PDA Ch1 220nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	1.114	0.053	1.081	--	5023	0.842	9800	0.817
2	1.264	0.059	0.999	2.669	14203	2.380	34450	2.873
3	1.342	0.047	1.788	1.463	13554	2.271	25610	2.136
4	1.471	0.041	1.282	2.945	3714	0.622	5545	0.462
5	1.610	0.058	1.595	2.799	74926	12.555	167864	13.998
6	1.715	0.051	1.386	1.941	29757	4.986	55661	4.642
7	1.900	0.048	1.280	3.738	126961	21.274	224335	18.707
8	2.089	0.054	--	3.729	14531	2.435	26441	2.205
9	2.139	0.053	1.419	0.924	268684	45.023	551807	46.015
10	2.363	0.047	1.247	4.453	5631	0.944	9857	0.822
11	2.588	0.104	--	2.976	3622	0.607	18351	1.530
12	2.704	0.063	--	1.394	5490	0.920	10221	0.852
13	2.823	0.057	1.380	1.992	9207	1.543	19523	1.628
14	3.212	0.050	0.962	7.283	8367	1.402	15885	1.325
15	3.337	0.049	1.196	2.531	13106	2.196	23847	1.989
PDA Ch2 254nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	1.610	0.063	1.385	--	14246	9.061	34479	10.824
2	1.714	0.048	1.362	1.871	13131	8.352	23094	7.250
3	1.900	0.047	1.261	3.915	14602	9.288	25688	8.064
4	2.090	0.053	--	3.791	6685	4.252	11948	3.751
5	2.139	0.053	1.541	0.929	93276	59.329	194421	61.034
6	2.823	0.054	1.314	12.766	5328	3.389	10783	3.385
7	3.213	0.049	0.980	7.613	3774	2.401	7024	2.205
8	3.337	0.049	1.182	2.566	6176	3.928	11106	3.487

Fig. C28: LCMS Chromatogram of reaction mixture

MS Spectrum

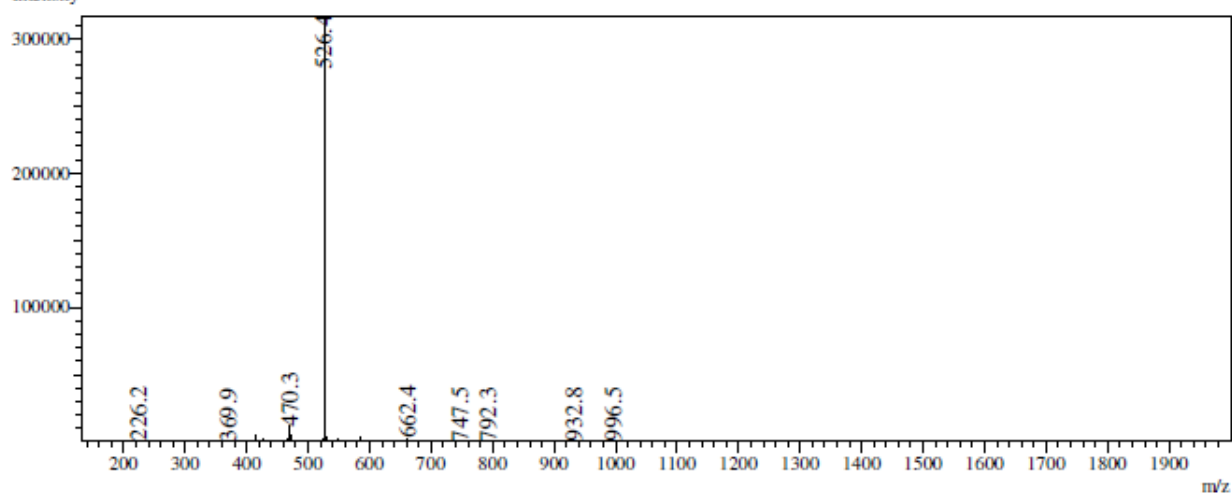
RetTime: 1.262

Intensity



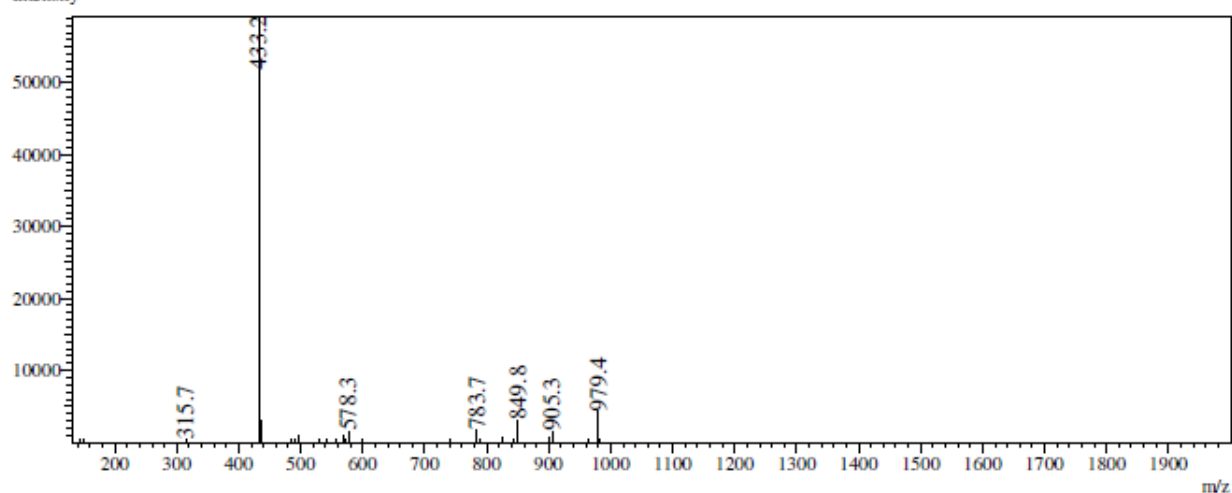
RetTime: 1.612

Intensity



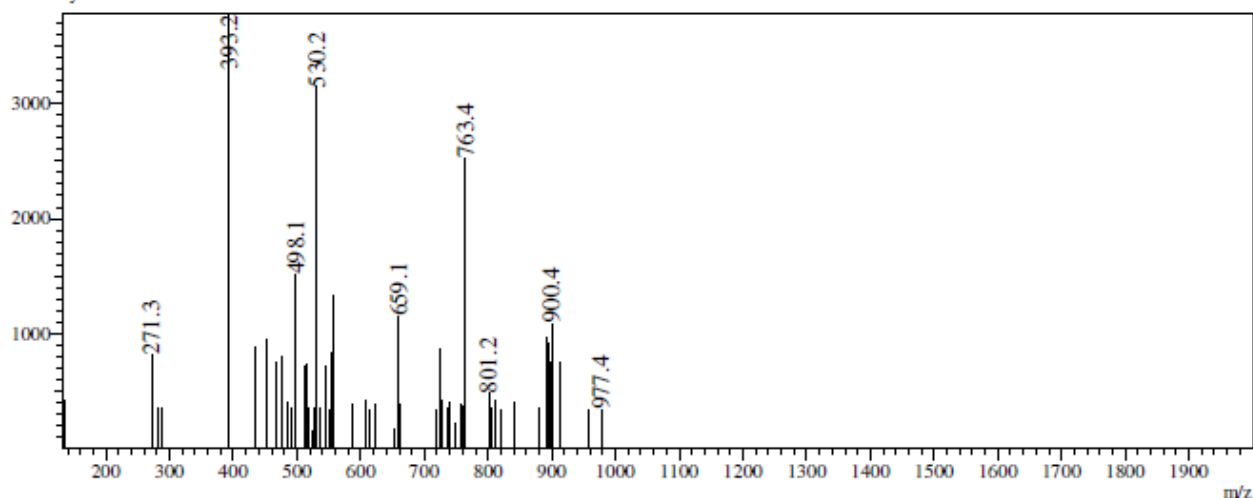
RetTime: 1.712

Intensity



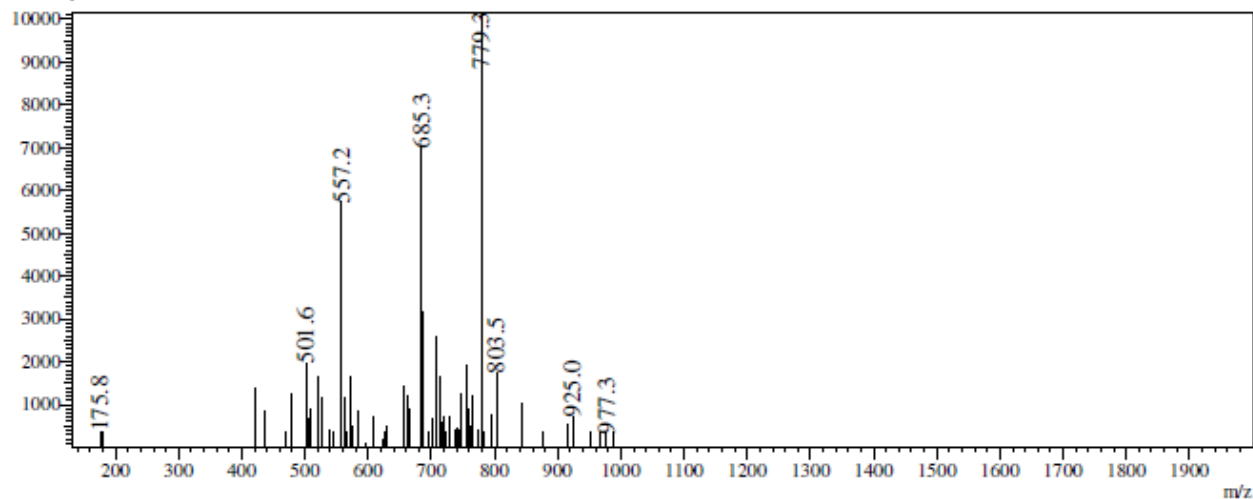
RetTime: 1.903

Intensity



RetTime: 2.087

Intensity



RetTime: 2.137

Intensity

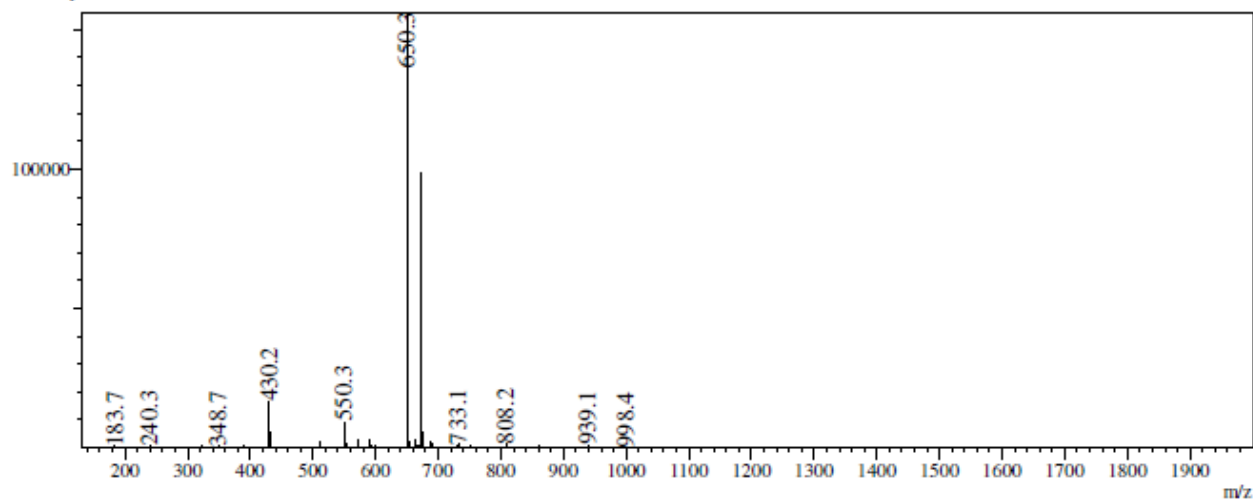


Fig. C29: MS Chromatogram of reaction mixture

^1H NMR of compound 5, (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.47 (s, 1H), 8.15 (s, 1H), 7.61 (s, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.28 - 7.20 (m, 3H), 7.15 - 7.09 (m, 1H), 6.92 - 6.85 (m, 3H), 4.11 - 4.00 (m, 2H), 3.83 - 3.76 (m, 6H), 3.73 (s, 3H), 2.99 - 2.77 (m, 3H), 2.29 (s, 3H), 1.83 - 1.80 (m, 2H), 1.63 - 1.52 (m, 2H), 1.41 (s, 9H)

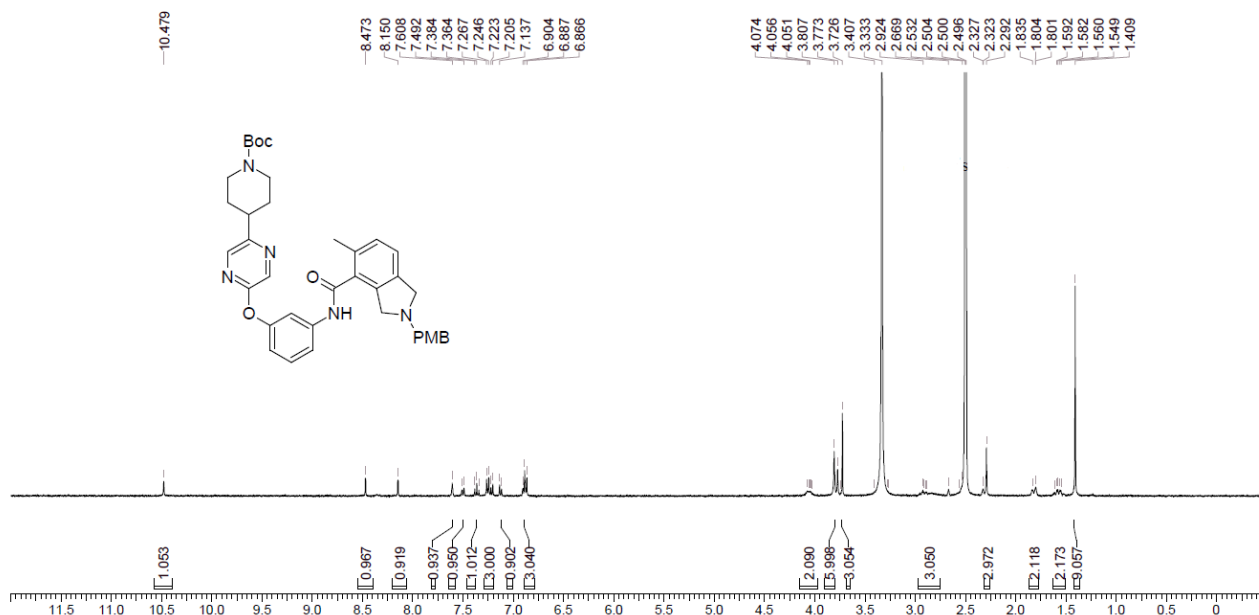
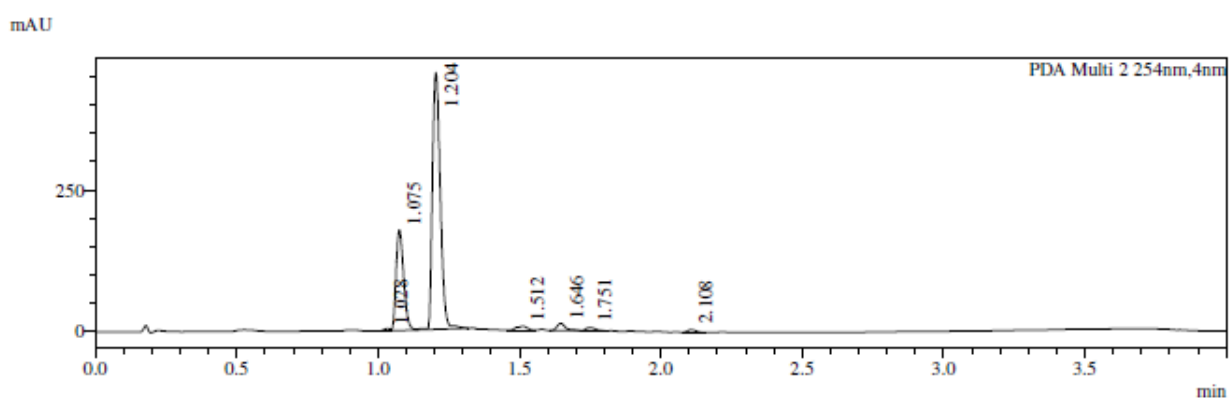
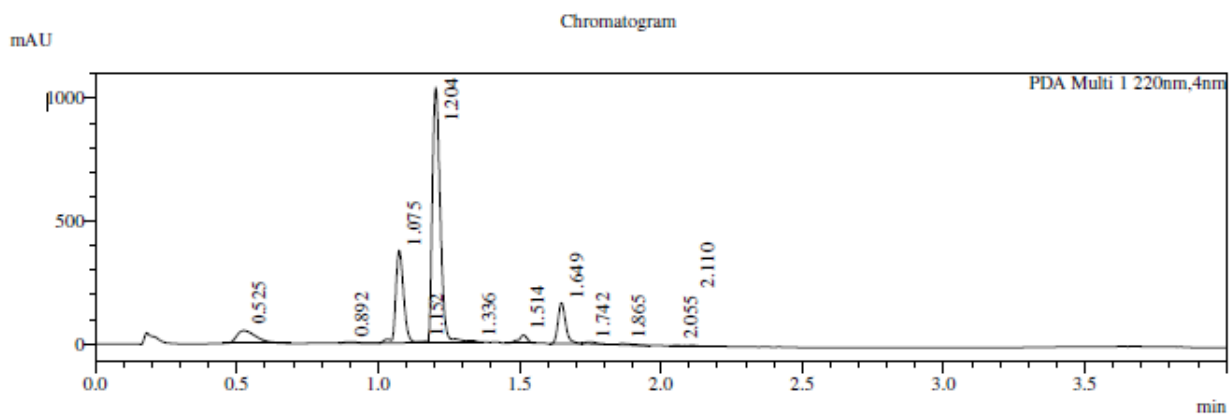


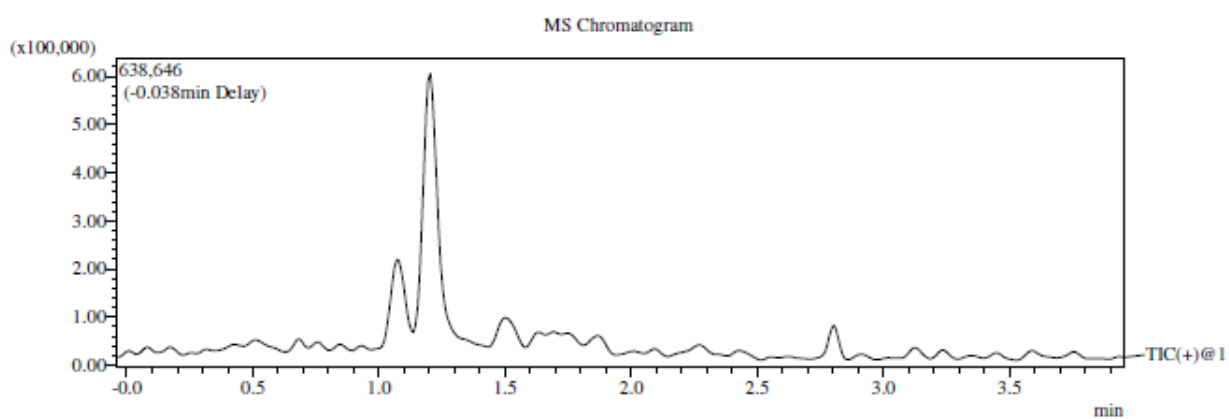
Fig. C30: ^1H NMR of compound 5

Target 2:

LCMS of reaction mixture, product: RT = 1.204 min, $m/z = 430.2$ ($\text{M}+\text{H}$) $^+$



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm

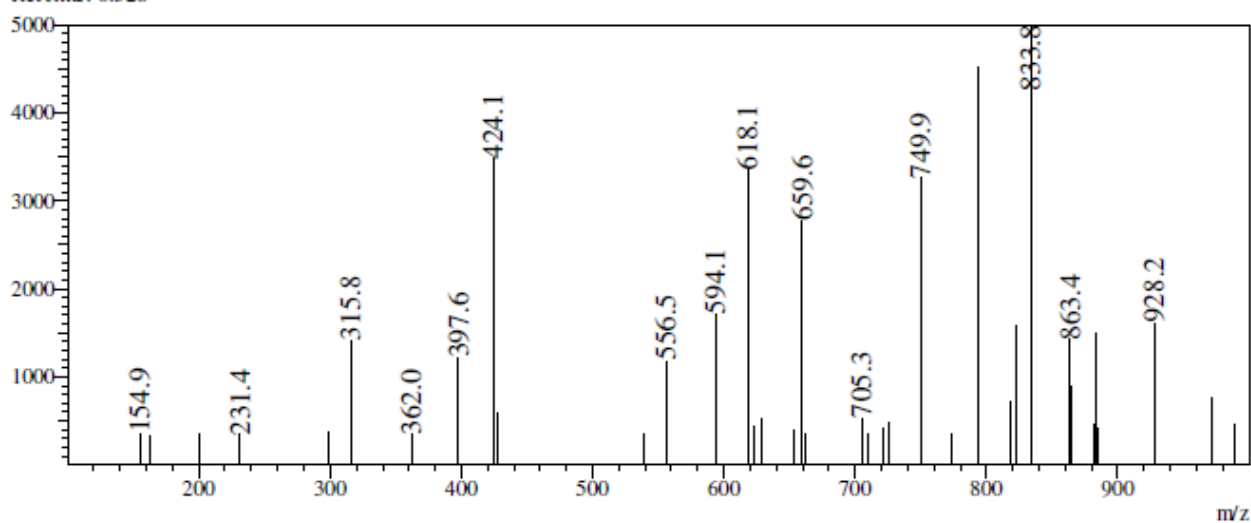


Integration Result							
PDA Ch1 220nm							
Peak#	Ret. Time	USP Width	Height	Height%	Area	Area%	
1	0.525	0.126	51889	3.078	252956	7.352	
2	0.892	0.075	2890	0.171	7467	0.217	
3	1.075	0.050	375045	22.246	728981	21.187	
4	1.152	0.168	5241	0.311	11891	0.346	
5	1.204	0.052	1029409	61.059	2004291	58.251	
6	1.336	0.058	7267	0.431	11447	0.333	
7	1.514	0.051	32586	1.933	69554	2.021	
8	1.649	0.049	163218	9.681	310843	9.034	
9	1.742	0.063	6695	0.397	17825	0.518	
10	1.865	0.081	5392	0.320	15397	0.447	
11	2.055	0.041	2818	0.167	4091	0.119	
12	2.110	0.049	3481	0.206	6016	0.175	
PDA Ch2 254nm							
Peak#	Ret. Time	USP Width	Height	Height%	Area	Area%	
1	1.028	0.070	3329	0.507	6303	0.494	
2	1.075	0.050	176532	26.900	328727	25.742	
3	1.204	0.052	447273	68.156	876668	68.649	
4	1.512	0.067	7227	1.101	18371	1.439	
5	1.646	0.052	12624	1.924	26892	2.106	
6	1.751	0.060	4922	0.750	12179	0.954	
7	2.108	0.049	4338	0.661	7881	0.617	

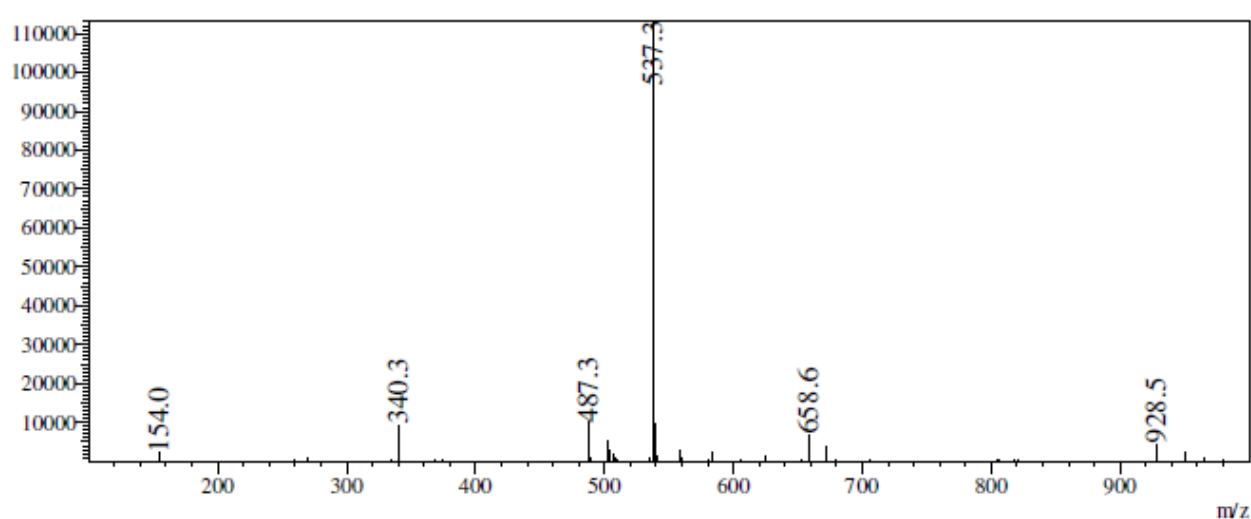
Fig. C31: LCMS Chromatogram of reaction mixture

Mass Spectrum

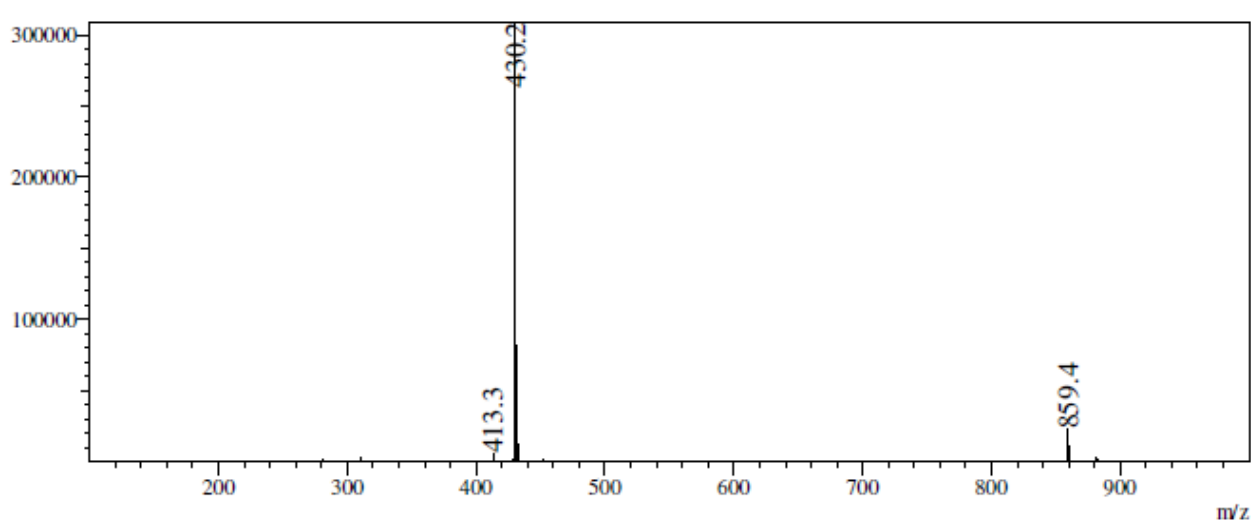
RetTime: 0.528



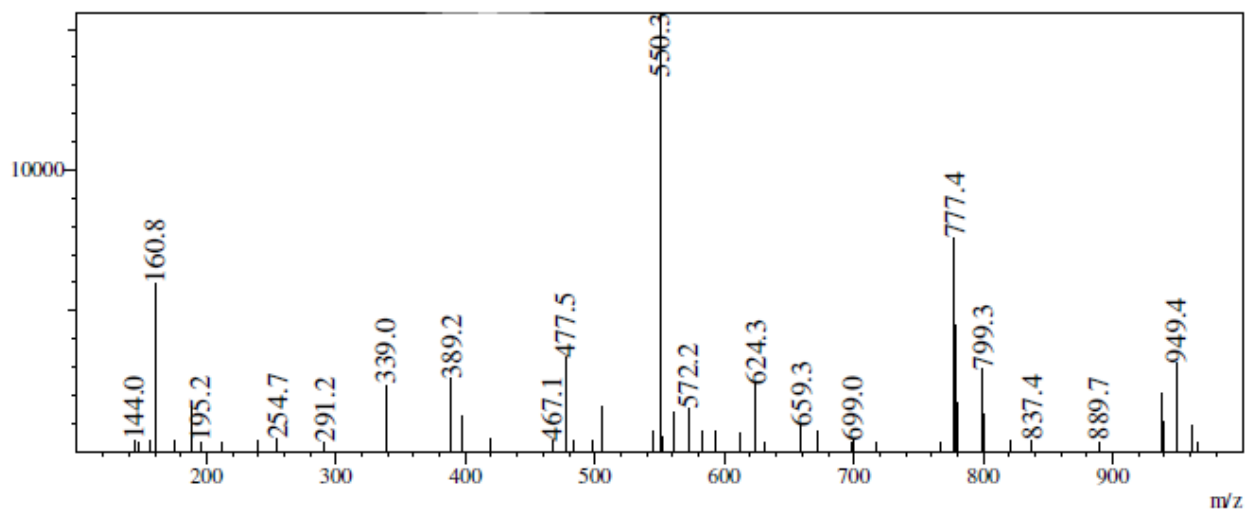
RetTime: 1.078



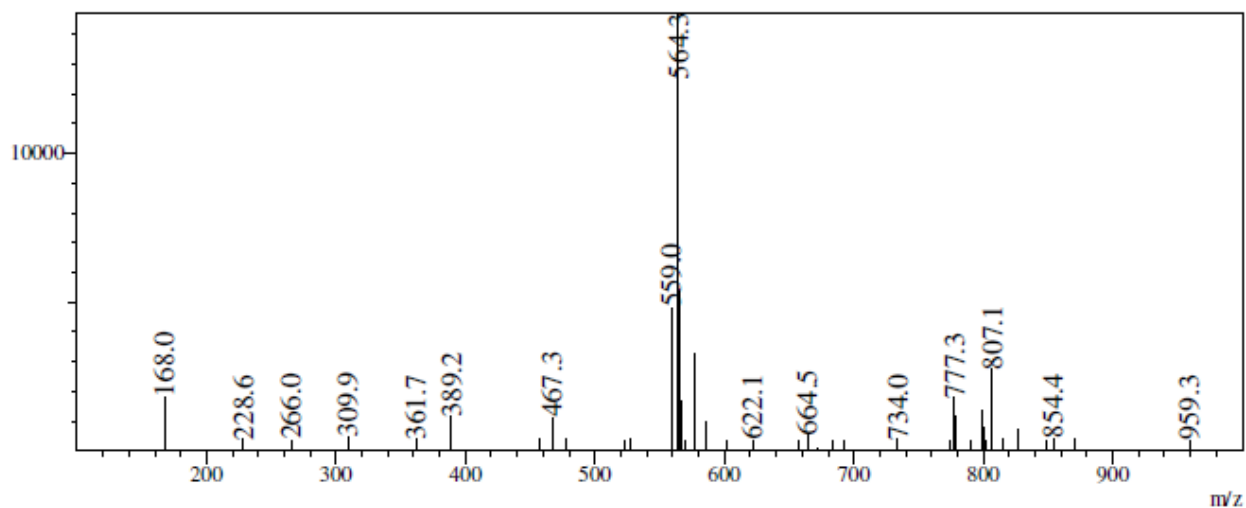
RetTime: 1.203



RetTime: 1.512



RetTime: 1.645



RetTime: 1.745

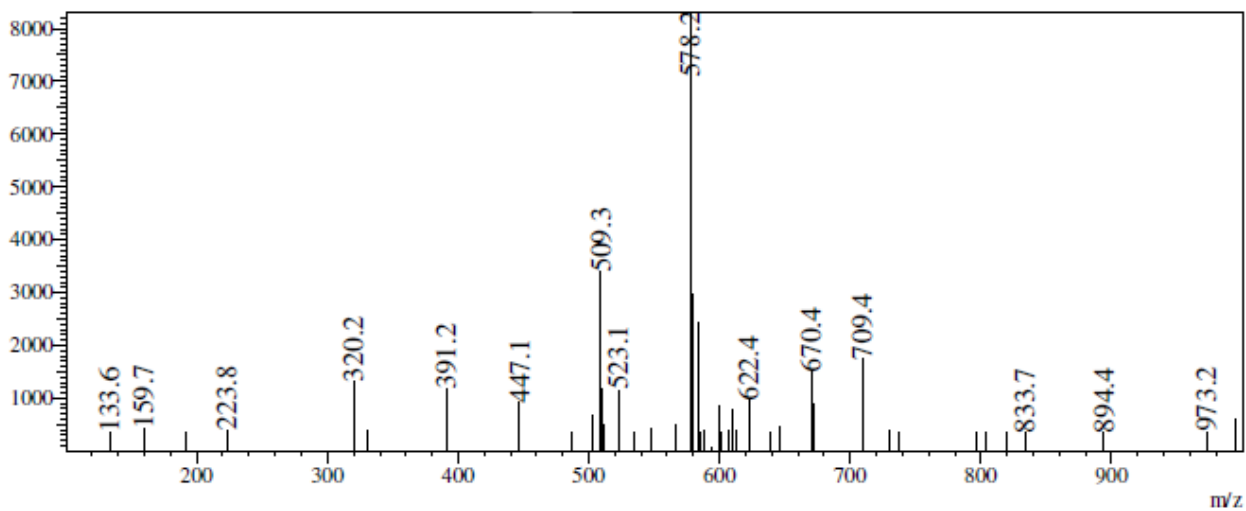
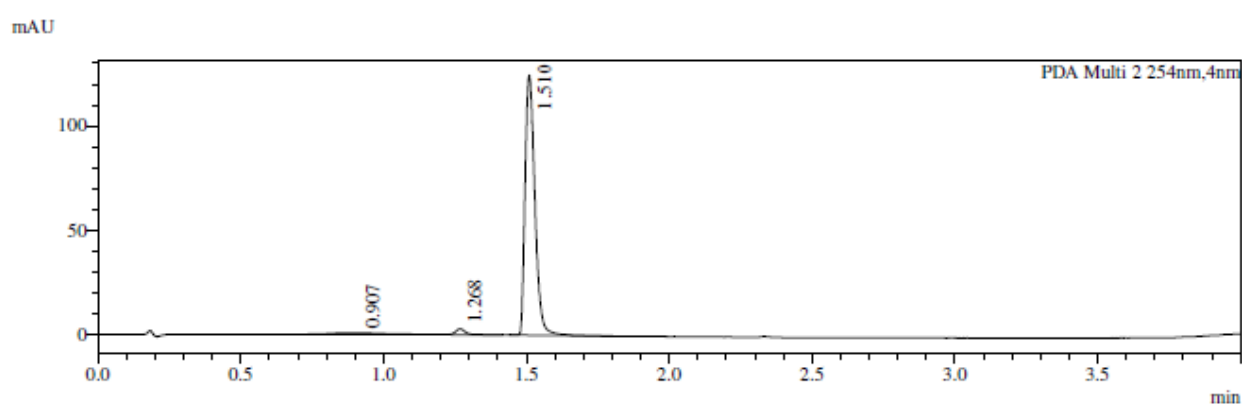
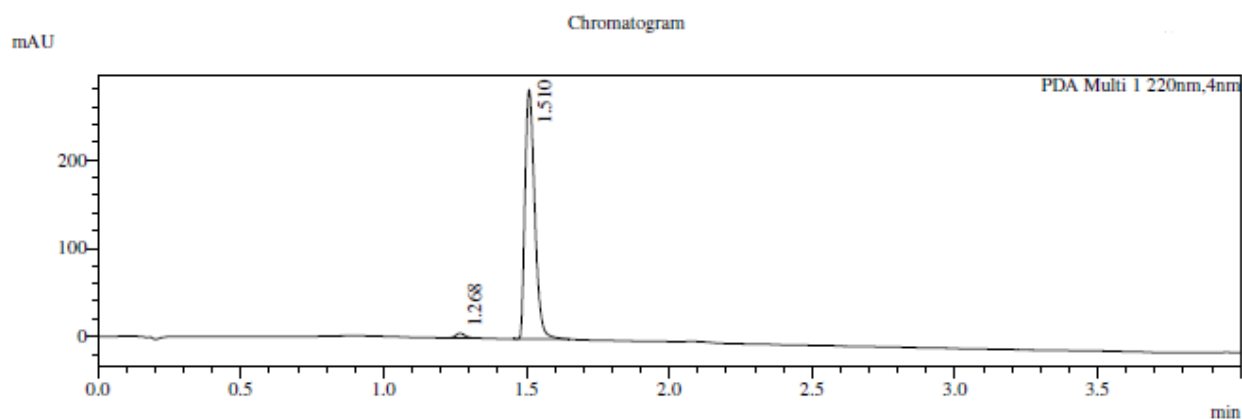
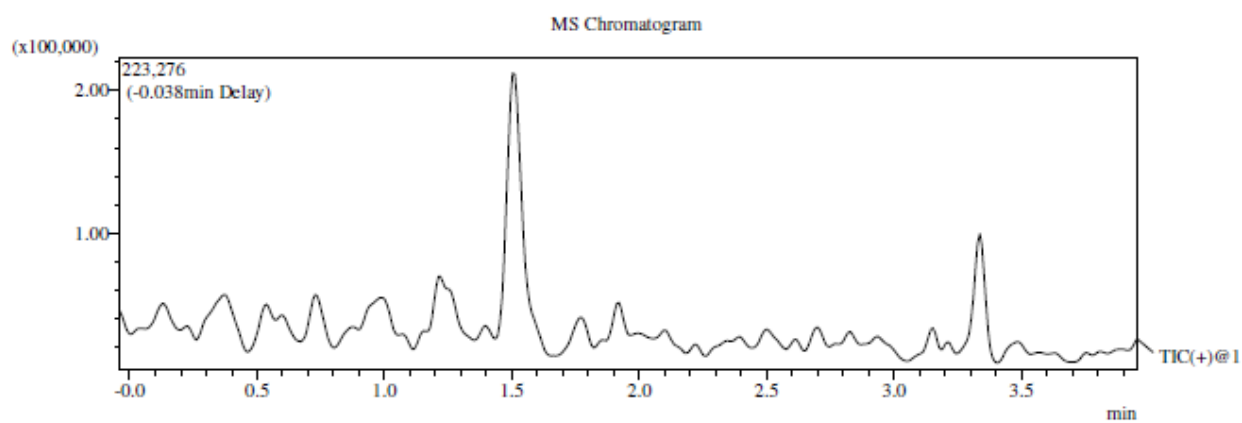


Fig. C32: MS Chromatogram of reaction mixture

LCMS of Target 2, product: RT = 1.510 min, m/z = 430.2 (M+H)⁺



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



Integration Result						
PDA Ch1 220nm						
Peak#	Ret. Time	USP Width	Height	Height%	Area	Area%
1	1.268	0.060	5342	1.870	11839	1.739
2	1.510	0.063	280328	98.130	668868	98.261
PDA Ch2 254nm						
Peak#	Ret. Time	USP Width	Height	Height%	Area	Area%
1	0.907	0.336	657	0.520	9966	3.160
2	1.268	0.061	2706	2.142	6316	2.003
3	1.510	0.063	123000	97.338	299113	94.838

Fig. C33: LCMS Chromatogram of Target 2

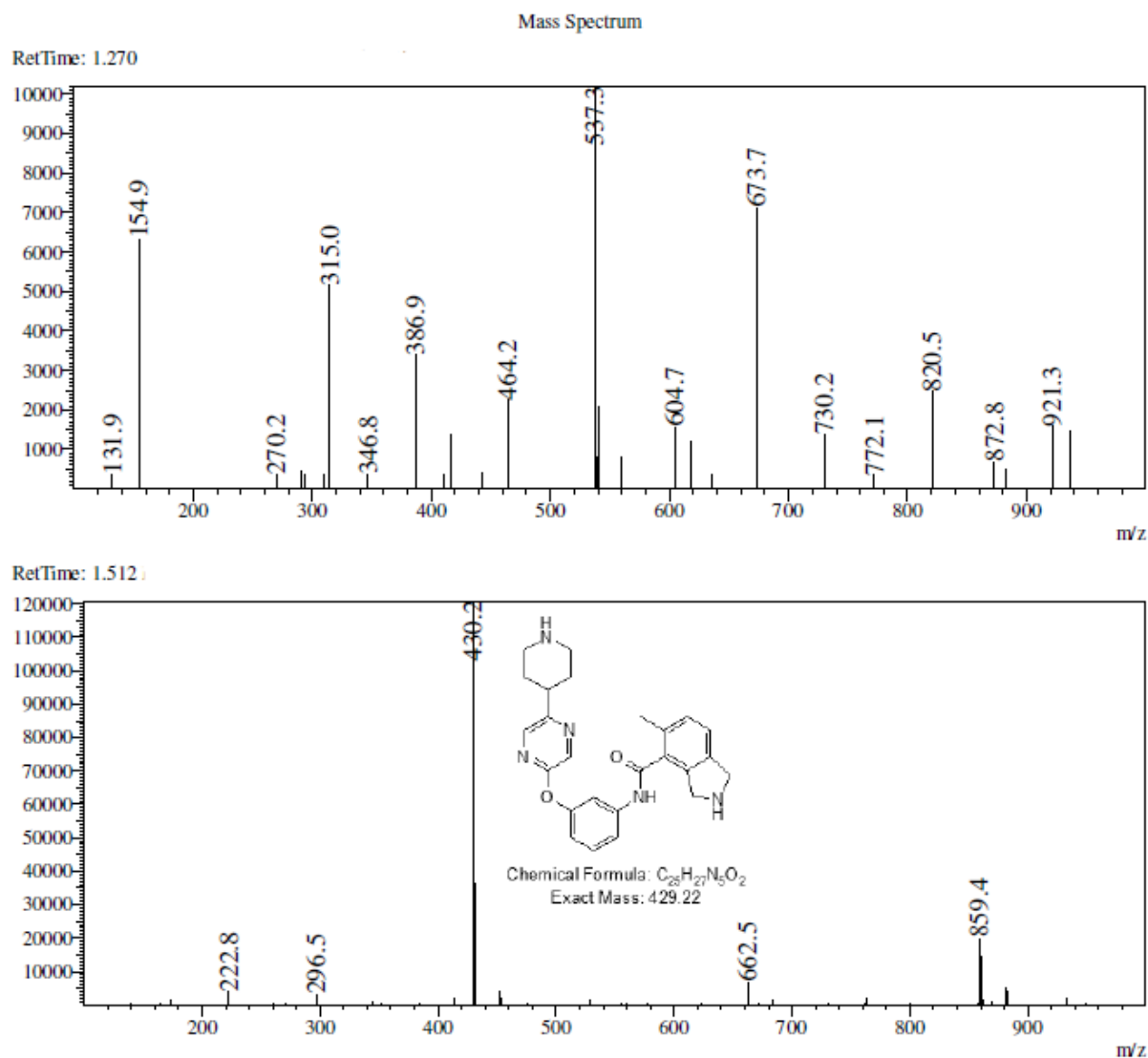
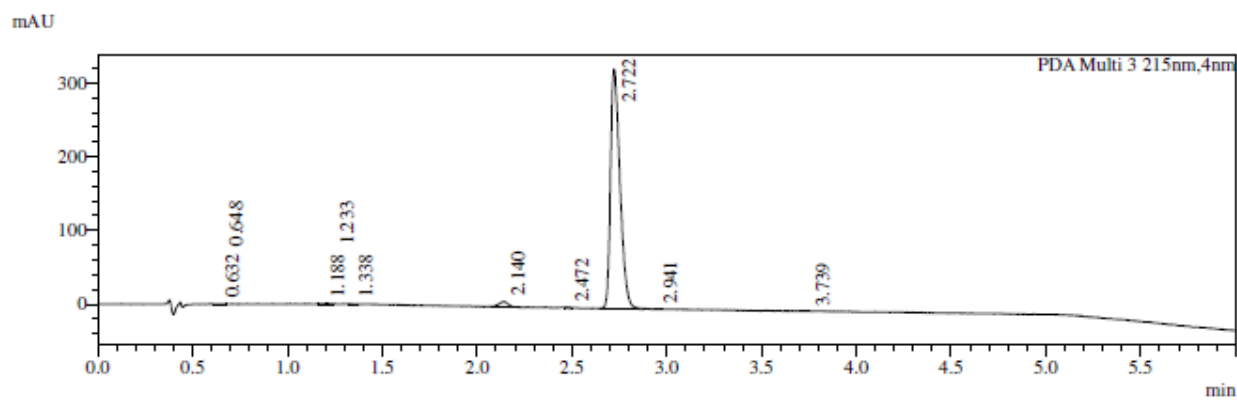
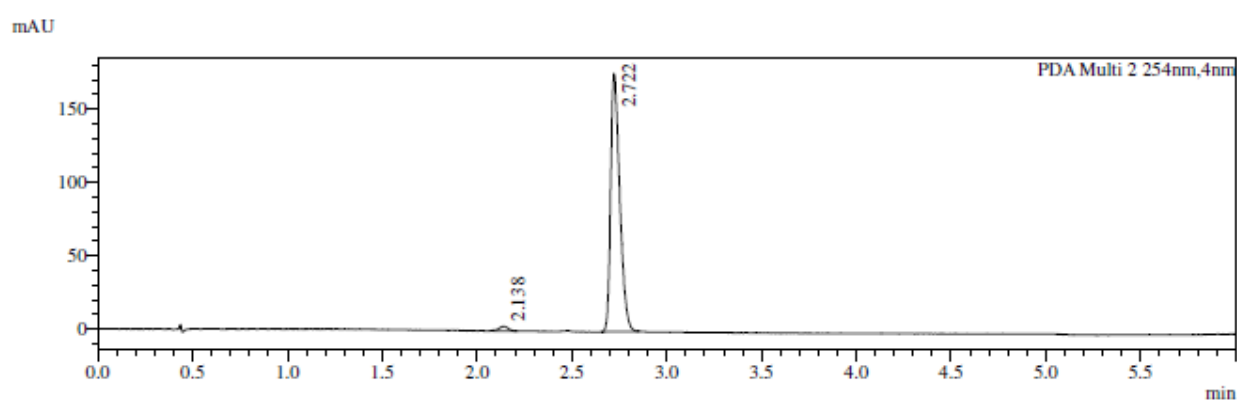
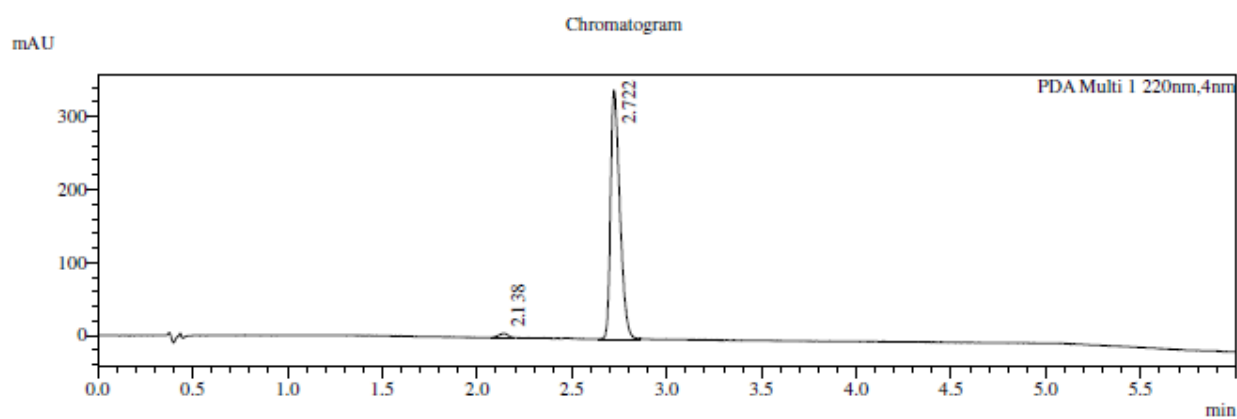


Fig. C34: MS Chromatogram of Target 2

HPLC of target 2, product: RT = 2.722 min, 98.3% purity under 220 nm.



Integration Result						
PDA Ch1 220nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	2.138	0.090	6085	1.751	19807	1.675
2	2.722	0.090	341431	98.249	1163065	98.325
PDA Ch2 254nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	2.138	0.086	3136	1.749	10524	1.762
2	2.722	0.088	176123	98.251	586637	98.238
PDA Ch3 215nm						
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	0.632	0.035	815	0.240	1092	0.094
2	0.648	0.050	728	0.214	1186	0.102
3	1.188	0.024	1037	0.305	1404	0.121
4	1.233	0.036	791	0.233	1080	0.093
5	1.338	0.019	926	0.273	1325	0.114
6	2.140	0.082	7341	2.161	23245	2.001
7	2.472	0.020	1181	0.348	1449	0.125
8	2.722	0.091	325311	95.756	1128818	97.168
9	2.941	0.037	604	0.178	1067	0.092
10	3.739	0.009	996	0.293	1048	0.090

Fig. C35: HPLC Chromatogram of Target 2

¹H NMR of Target2, (400 MHz, MeOD) δ 8.42 (s, 1H), 8.10 (s, 1H), 7.73 (s, 1H), 7.46 - 7.38 (m, 4H), 7.02 - 6.94 (m, 1H), 4.65 (br d, J = 4.8 Hz, 4H), 3.54 - 3.48 (m, 2H), 3.19 - 3.14 (m, 2H), 2.48 (s, 3H), 2.16 - 2.04 (m, 4H)

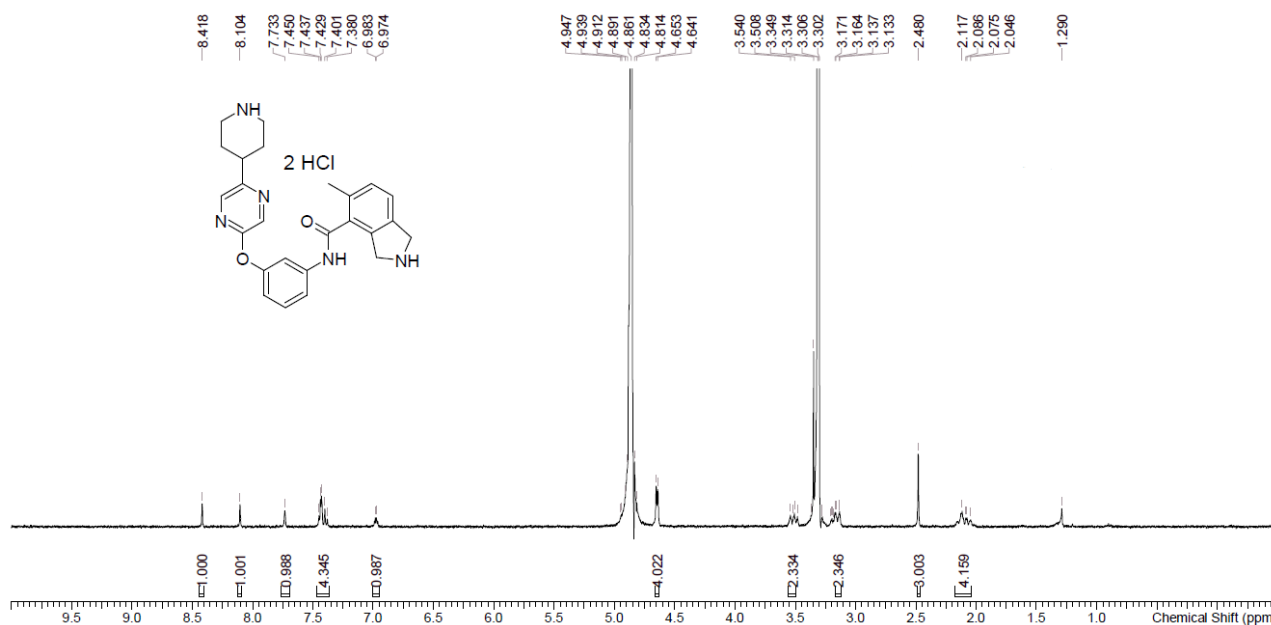


Fig. C36: ¹H NMR of Target 2

Compound 4a-2:

^1H NMR of compound 4a-2, (400 MHz, DMSO- d_6) δ 8.98 (s, 1H), 7.52 - 7.47 (m, 2H), 6.38 (d, J = 9.6 Hz, 1H), 5.79 (d, J = 8.8 Hz, 1H), 2.43 (s, 3H)

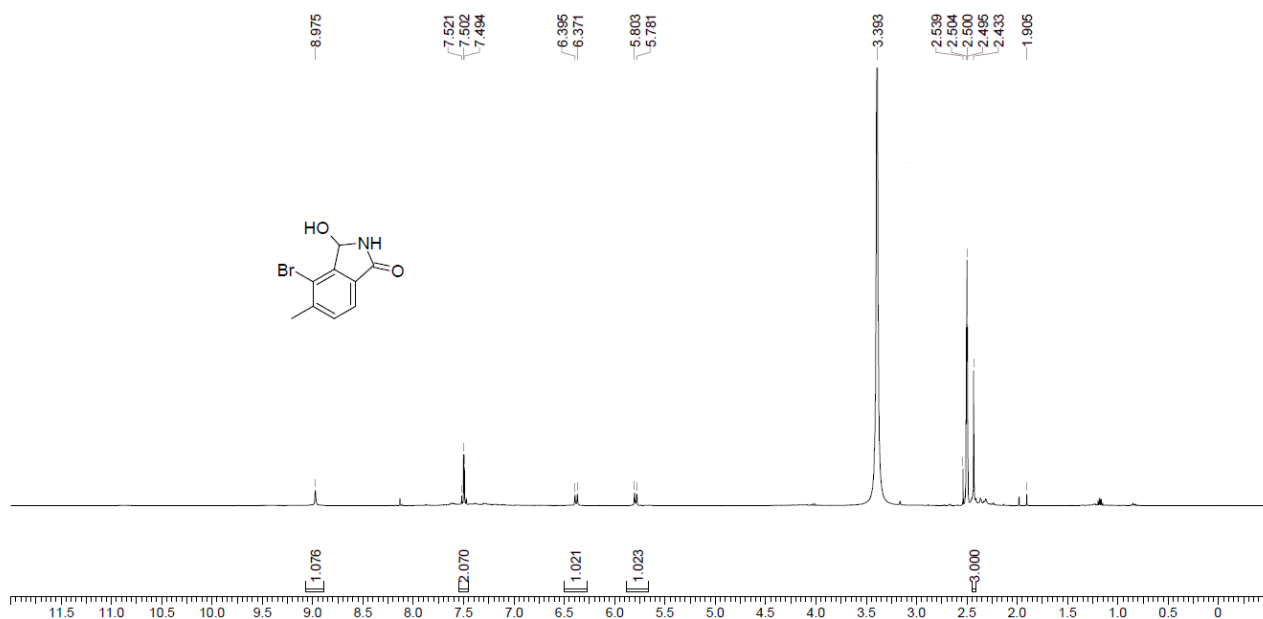


Fig. C37: ^1H NMR of compound 4a-2a

Compound 4a-2a:

^1H NMR: EW67434-10-P1A, (400 MHz, DMSO- d_6) δ 8.69 (br s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 4.27 (s, 2H), 2.45 (s, 3H)

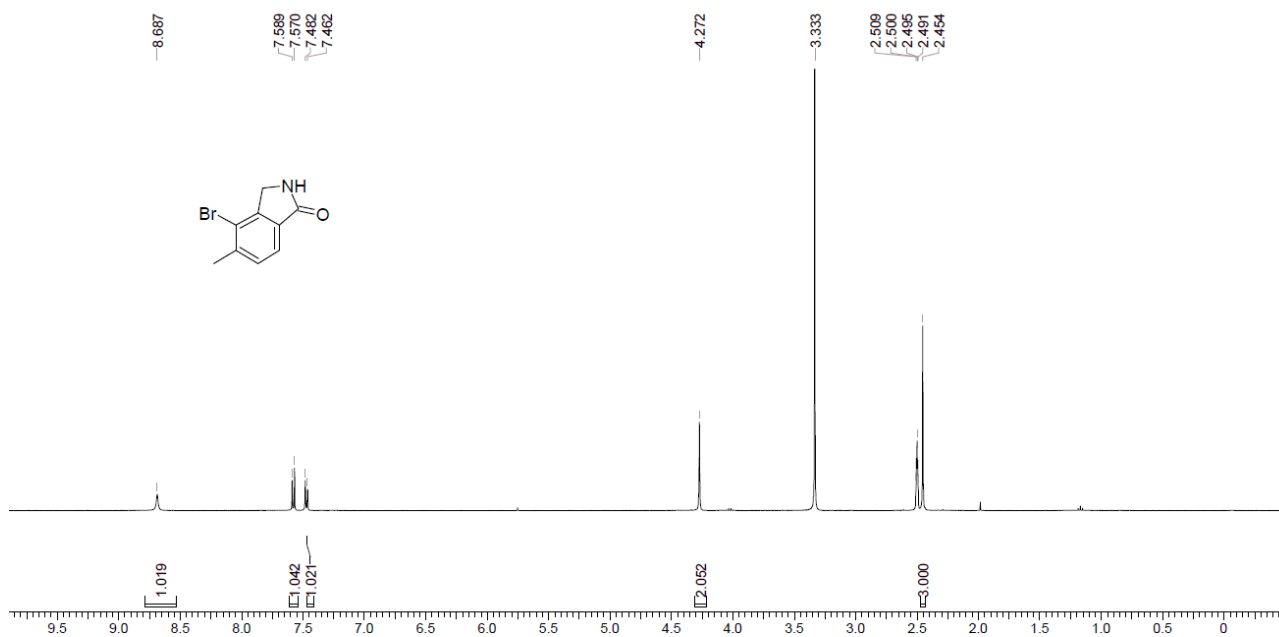
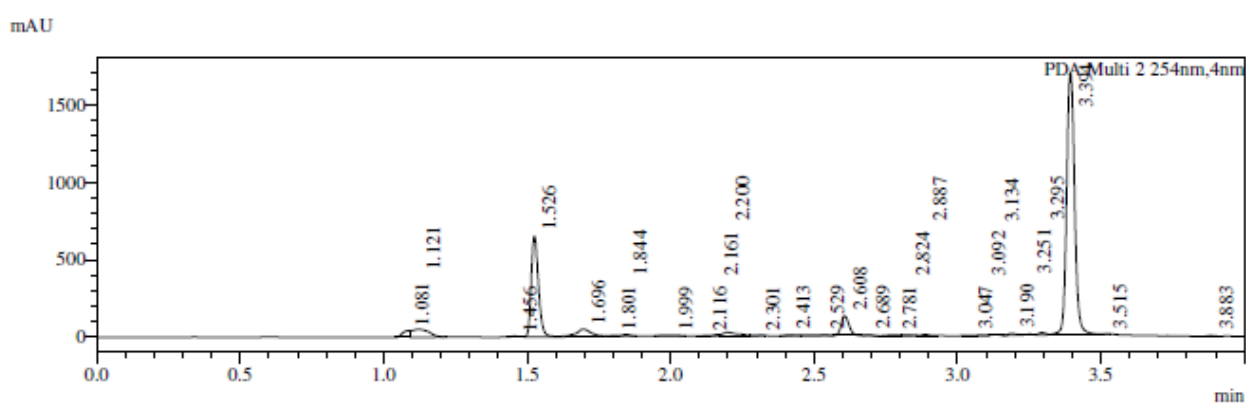
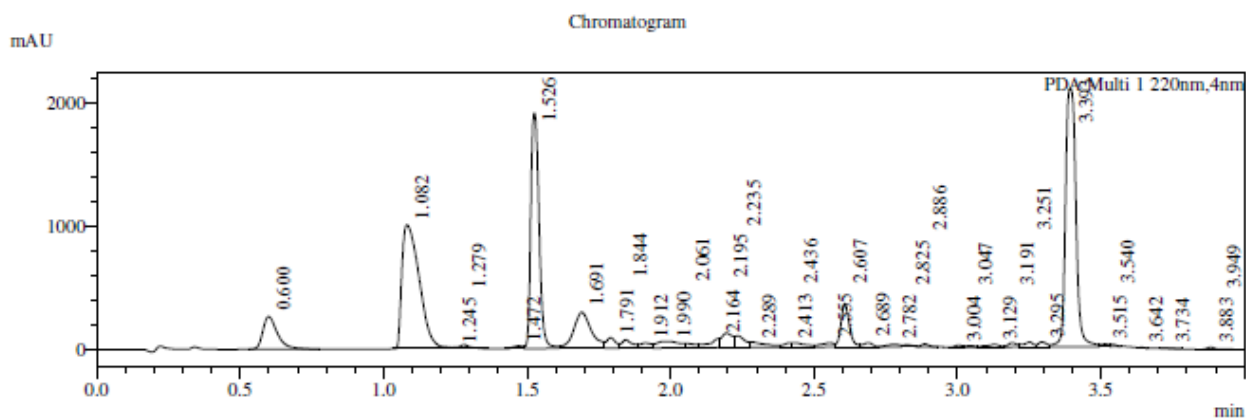


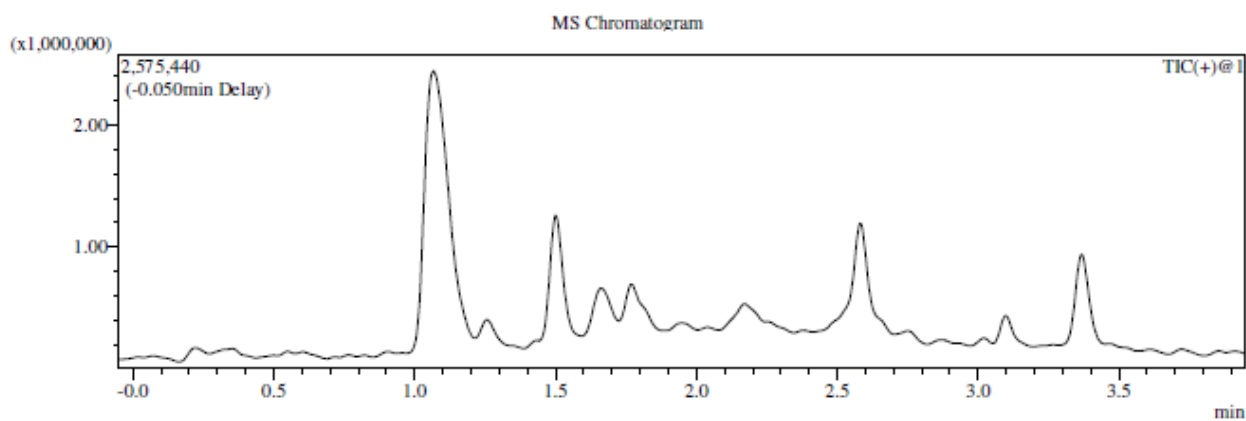
Fig. C38: ^1H NMR of compound 4a-2a

Compound 4a-3:

LCMS of reaction mixture, product: RT = 1.082 min, m/z = 212.1 (M+H)+

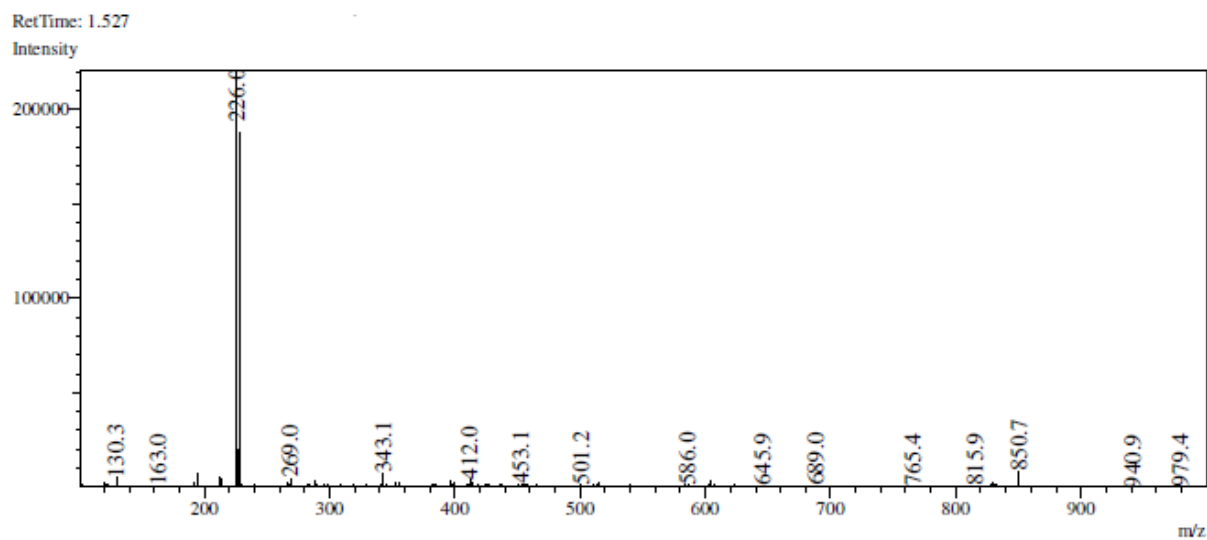
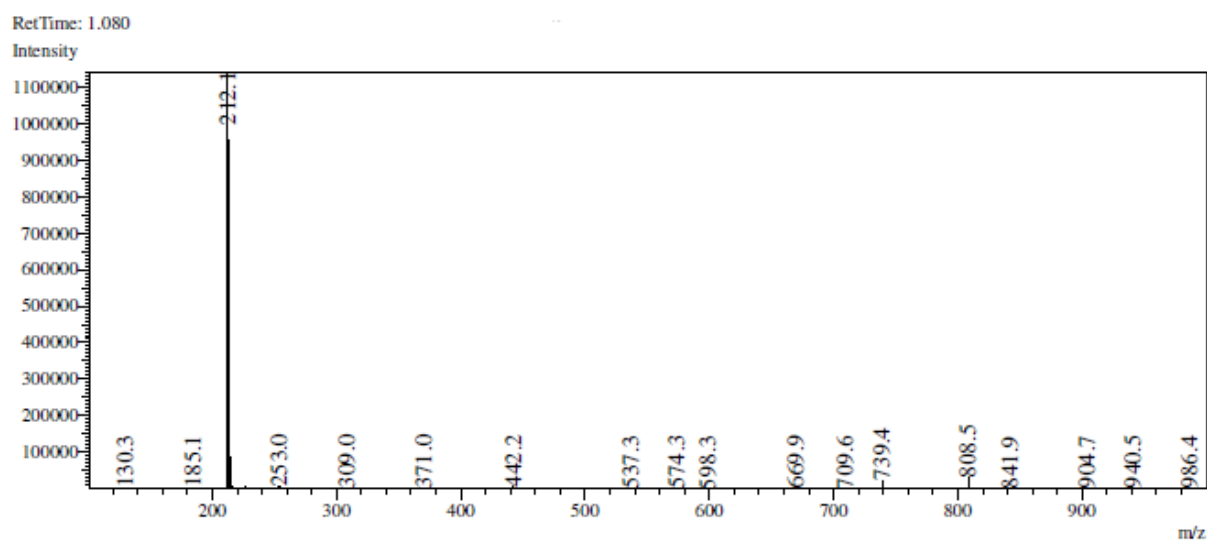
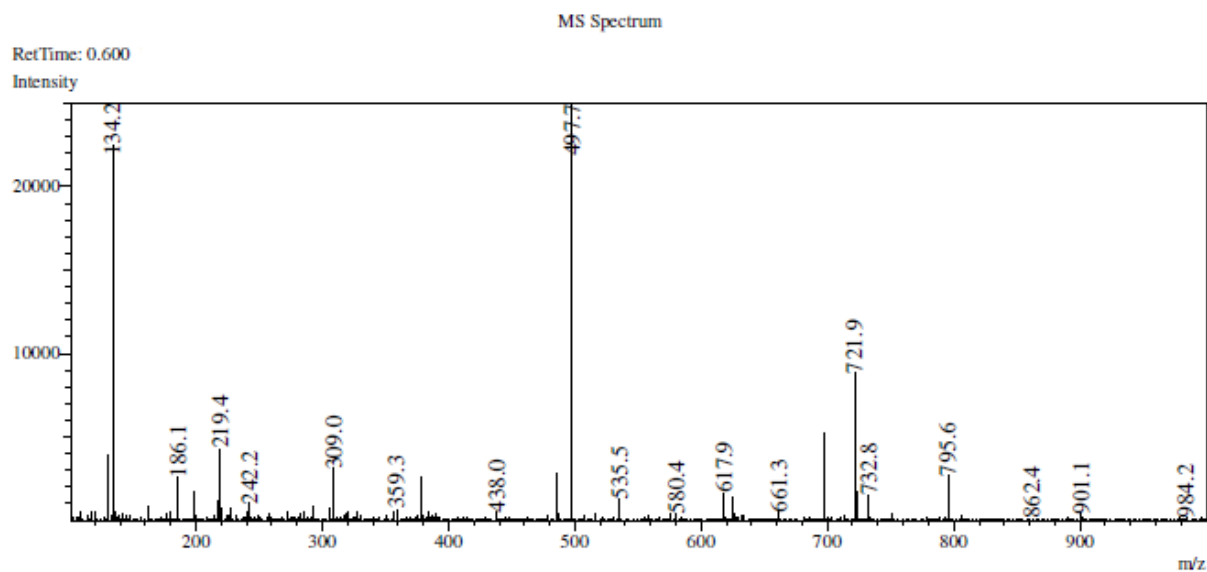


- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



Integration Result								
PDA Ch1 220nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	0.600	0.089	1.511	--	264922	3.767	924847	4.838
2	1.082	0.111	2.035	4.821	1008328	14.339	4249120	22.228
3	1.245	0.737	--	0.386	10157	0.144	10372	0.054
4	1.279	0.062	--	0.085	31926	0.454	82541	0.432
5	1.472	0.106	--	2.289	20774	0.295	51871	0.271
6	1.526	0.051	1.283	0.687	1917423	27.267	3842912	20.103
7	1.691	0.108	--	2.086	293436	4.173	1251113	6.545
8	1.791	0.071	--	1.121	86866	1.235	189477	0.991
9	1.844	0.073	--	0.734	66516	0.946	172841	0.904
10	1.912	0.144	--	0.628	39681	0.564	104743	0.548
11	1.990	0.178	--	0.486	53223	0.757	297592	1.557
12	2.061	0.000	--	--	32750	0.466	79740	0.417
13	2.164	0.453	--	--	71527	1.017	180081	0.942
14	2.195	0.128	--	0.106	118043	1.679	319256	1.670
15	2.235	0.285	--	0.195	94252	1.340	226955	1.187
16	2.289	0.567	--	0.128	41806	0.595	165495	0.866
17	2.413	3.190	--	0.066	34157	0.486	71597	0.375
18	2.436	0.384	--	0.013	35598	0.506	112723	0.590
19	2.555	0.120	--	0.475	35252	0.501	105344	0.551
20	2.607	0.053	--	0.600	352841	5.018	721383	3.774
21	2.689	0.065	--	1.389	33159	0.472	73452	0.384
22	2.782	0.090	--	1.187	19314	0.275	56792	0.297
23	2.825	0.079	--	0.507	13867	0.197	27946	0.146
24	2.886	0.046	1.266	0.985	21591	0.307	36249	0.190
25	3.004	0.057	--	2.289	17003	0.242	31716	0.166
26	3.047	0.067	--	0.695	13127	0.187	24659	0.129
27	3.129	0.071	--	1.196	22011	0.313	68364	0.358
28	3.191	0.067	--	0.894	34309	0.488	71779	0.375
29	3.251	0.065	--	0.906	39119	0.556	94174	0.493
30	3.295	0.061	--	0.693	40378	0.574	81004	0.424
31	3.393	0.058	1.186	1.653	2106085	29.950	5280641	27.624
32	3.515	0.110	--	1.450	19519	0.278	38168	0.200
33	3.540	0.151	--	0.198	16045	0.228	20978	0.110
34	3.642	0.029	1.385	1.130	2175	0.031	2229	0.012
35	3.734	0.054	1.364	2.213	3287	0.047	6661	0.035
36	3.883	0.049	--	2.889	18101	0.257	32598	0.171
37	3.949	0.083	--	0.998	3519	0.050	8944	0.047
PDA Ch2 254nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	1.081	0.000	--	--	39978	1.463	72549	1.351
2	1.121	0.180	--	--	49654	1.818	207793	3.870
3	1.456	0.085	--	2.528	5295	0.194	11732	0.219
4	1.526	0.046	1.254	1.064	647125	23.688	1132963	21.102
5	1.696	0.083	0.993	2.631	47327	1.732	166652	3.104
6	1.801	0.054	--	1.525	4493	0.164	7752	0.144
7	1.844	0.045	--	0.884	9971	0.365	16225	0.302
8	1.999	0.093	0.968	2.239	5701	0.209	21200	0.395
9	2.116	0.076	--	1.387	2440	0.089	5098	0.095
10	2.161	0.304	--	0.239	8487	0.311	11465	0.214
11	2.200	0.094	--	0.193	22562	0.826	82631	1.539
12	2.301	0.524	--	0.329	2109	0.077	4842	0.090
13	2.413	0.061	--	0.380	5897	0.216	13215	0.246
14	2.529	0.052	1.649	2.069	2600	0.095	6641	0.124
15	2.608	0.051	1.142	1.519	124363	4.552	231855	4.318
16	2.689	0.043	1.135	1.735	3577	0.131	5325	0.099
17	2.781	0.106	--	1.237	6001	0.220	19169	0.357
18	2.824	0.084	--	0.453	5276	0.193	10585	0.197
19	2.887	0.047	1.275	0.966	7771	0.284	13427	0.250
20	3.047	0.041	0.868	3.671	2592	0.095	3846	0.072
21	3.092	0.086	--	0.704	1958	0.072	3500	0.065
22	3.134	0.050	--	0.619	5616	0.206	9648	0.180
23	3.190	0.050	--	1.109	11490	0.421	23551	0.439
24	3.251	0.055	--	1.176	5303	0.194	8961	0.167
25	3.295	0.047	--	0.849	14693	0.538	24468	0.456
26	3.394	0.049	1.125	2.076	1682813	61.598	3243408	60.410
27	3.515	0.037	--	2.826	1941	0.071	2459	0.046
28	3.883	0.046	0.977	8.950	4874	0.178	7998	0.149

Fig. C39: LCMS Chromatogram of reaction mixture



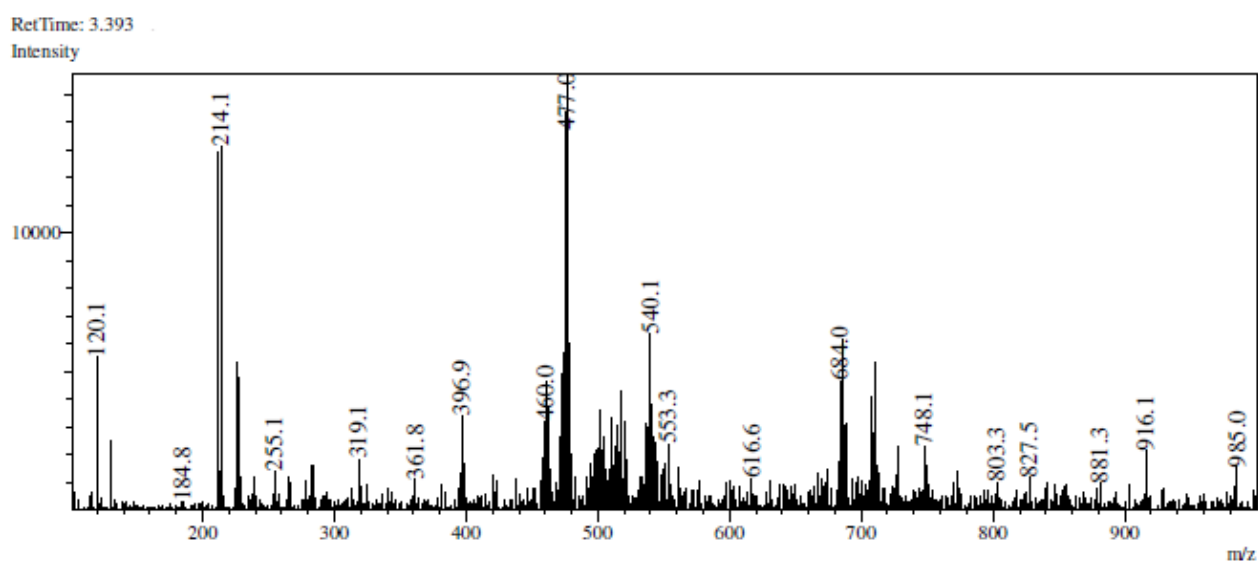
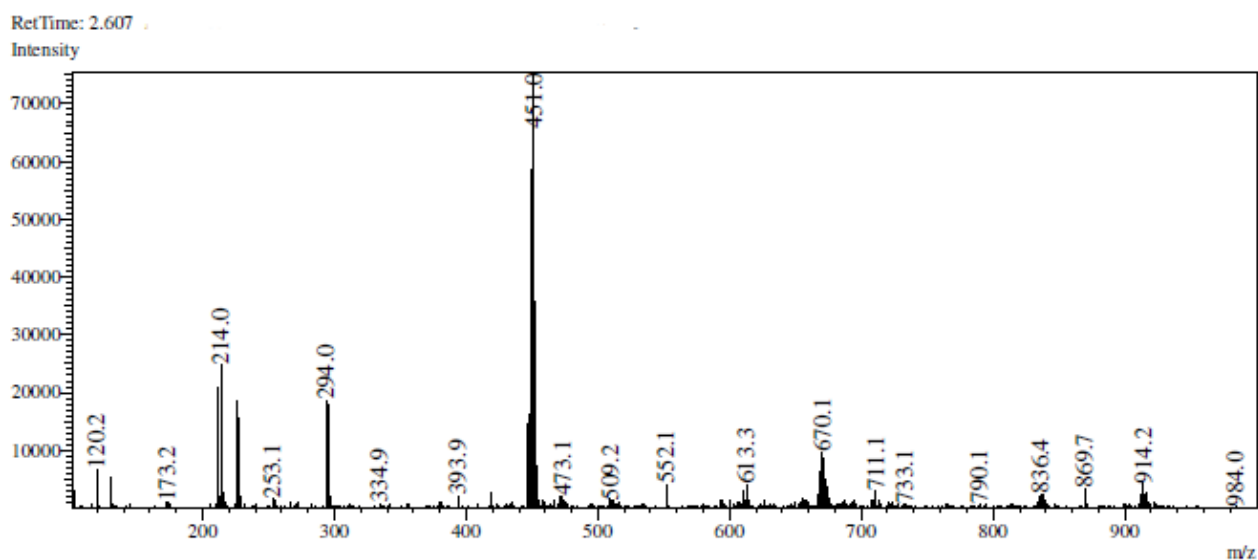
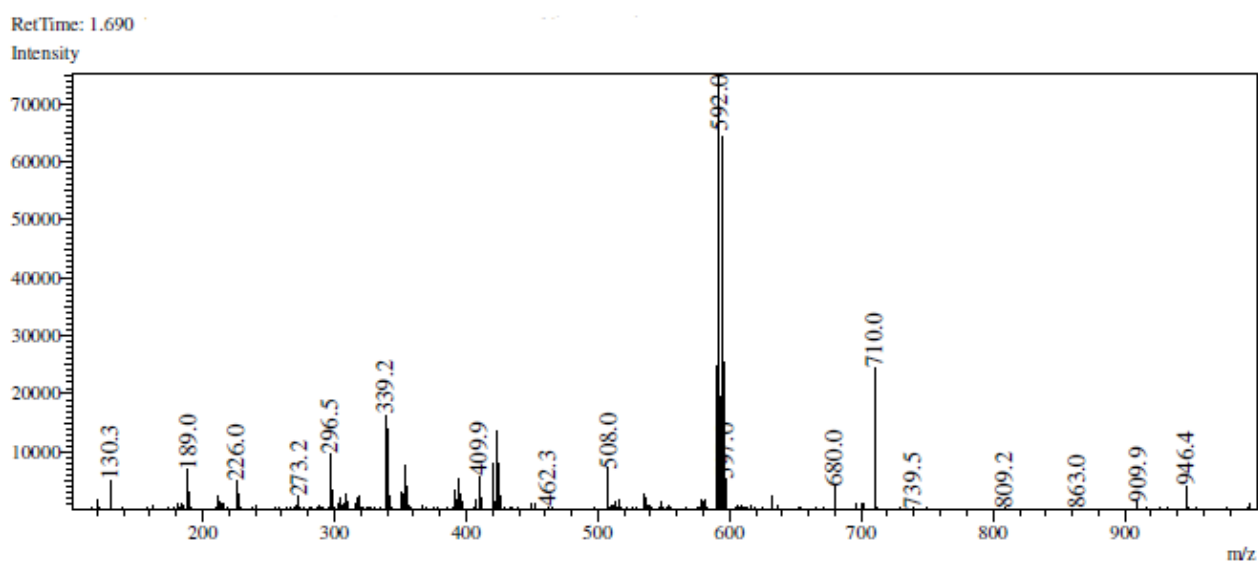


Fig. C40: MS Chromatogram of reaction mixture

^1H NMR of compound 4a-3, (400 MHz, DMSO- d_6) δ 7.22 - 7.08 (m, 2H), 4.14 (s, 2H), 4.02 (s, 2H), 2.32 (s, 3H)

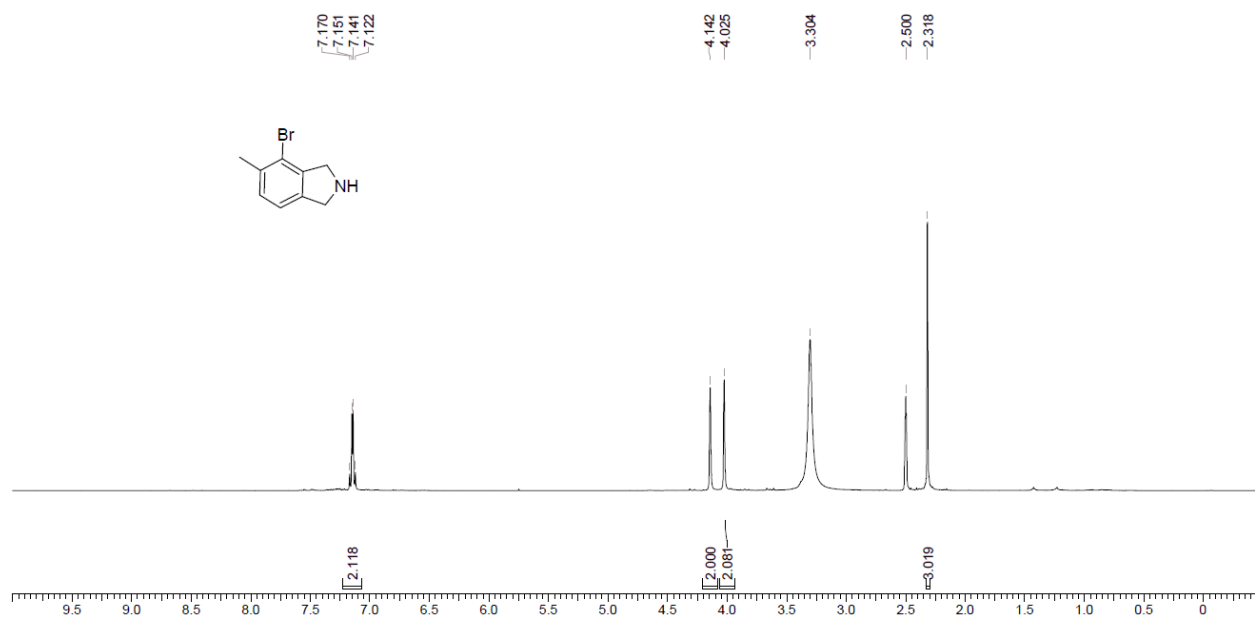
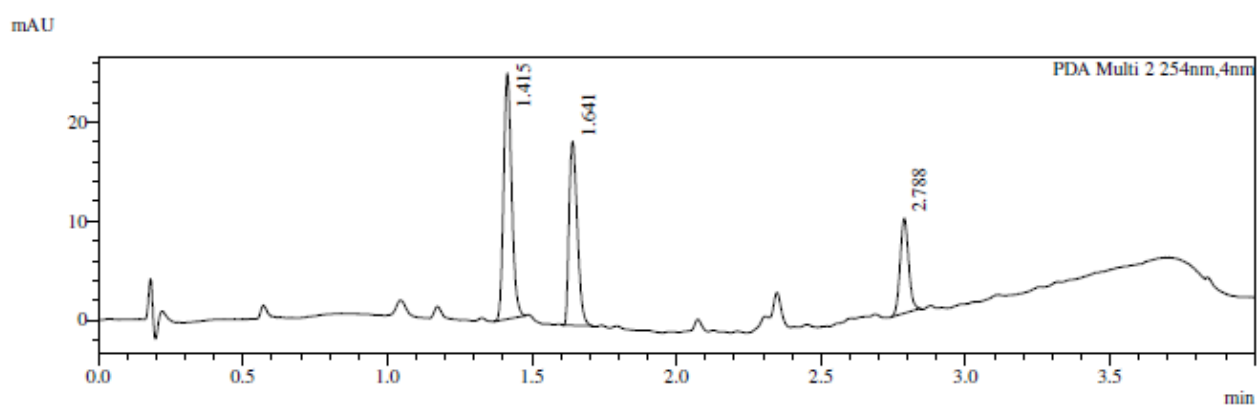
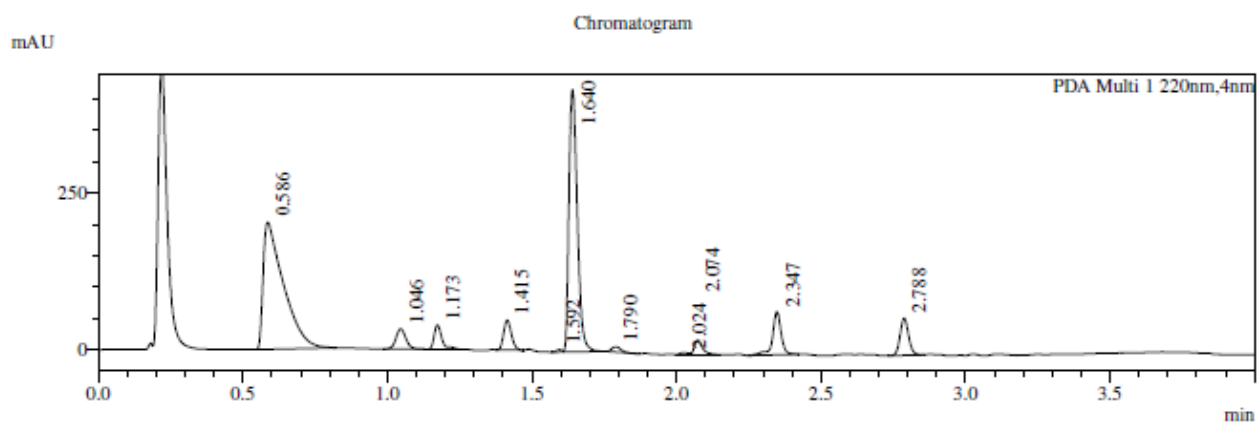


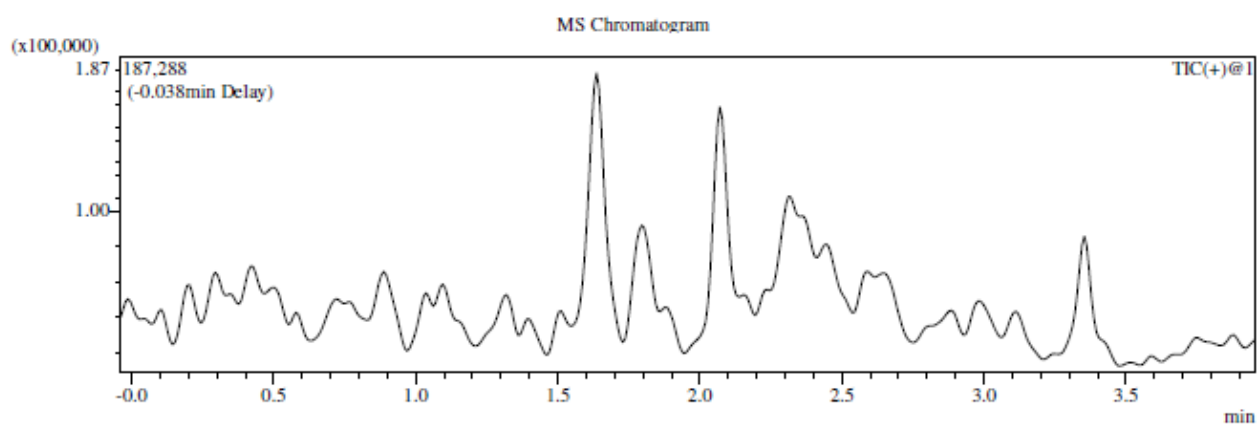
Fig. C41: ^1H NMR of compound 4a-3

Compound 4a-4:

LCMS of reaction mixture, product: RT = 1.640 min, m/z = 334.1 ($\text{M}+\text{H}$) $^+$



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



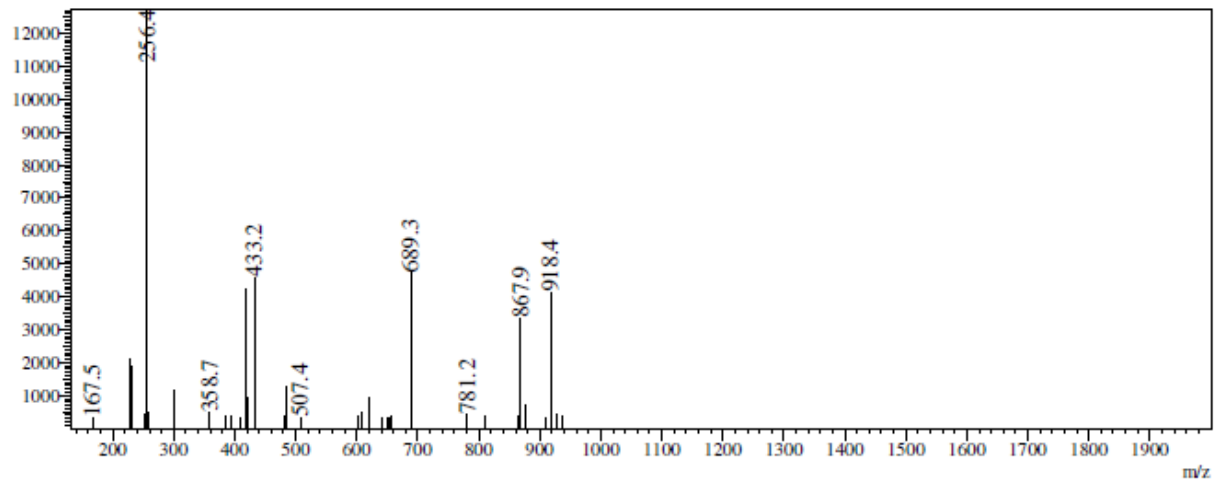
Integration Result									
PDA Ch1 220nm									
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%	
1	0.586	0.142	2.930	--	202417	22.484	990416	41.112	
2	1.046	0.063	1.119	4.500	32019	3.557	75532	3.135	
3	1.173	0.047	1.802	2.314	37949	4.215	72094	2.993	
4	1.415	0.051	1.190	4.936	47543	5.281	90138	3.742	
5	1.592	0.046	--	3.663	3473	0.386	5181	0.215	
6	1.640	0.054	1.386	0.969	415218	46.122	843623	35.019	
7	1.790	0.059	1.224	2.663	8487	0.943	18235	0.757	
8	2.024	0.053	--	4.181	3226	0.358	5846	0.243	
9	2.074	0.049	--	0.972	22762	2.528	43991	1.826	
10	2.347	0.050	0.810	5.518	68126	7.567	143018	5.937	
11	2.788	0.054	1.117	8.432	59052	6.559	120986	5.022	
PDA Ch2 254nm									
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%	
1	1.415	0.052	1.189	--	24775	47.012	48152	45.866	
2	1.641	0.054	1.376	4.261	18400	34.914	37176	35.412	
3	2.788	0.054	1.098	21.205	9525	18.075	19655	18.722	

Fig. C42: LCMS Chromatogram of reaction mixture

MS Spectrum

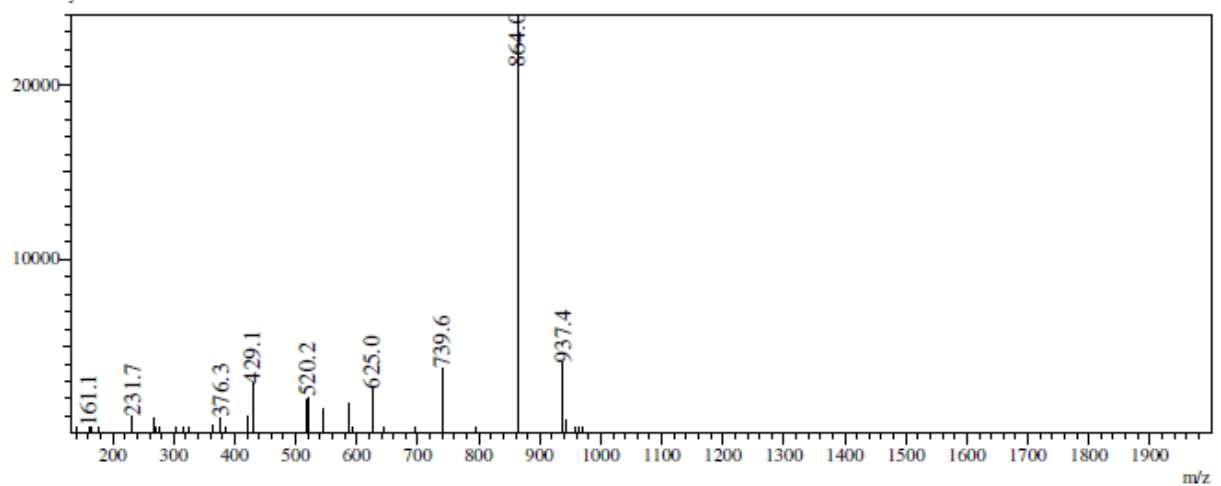
RefTime: 0.587

Intensity



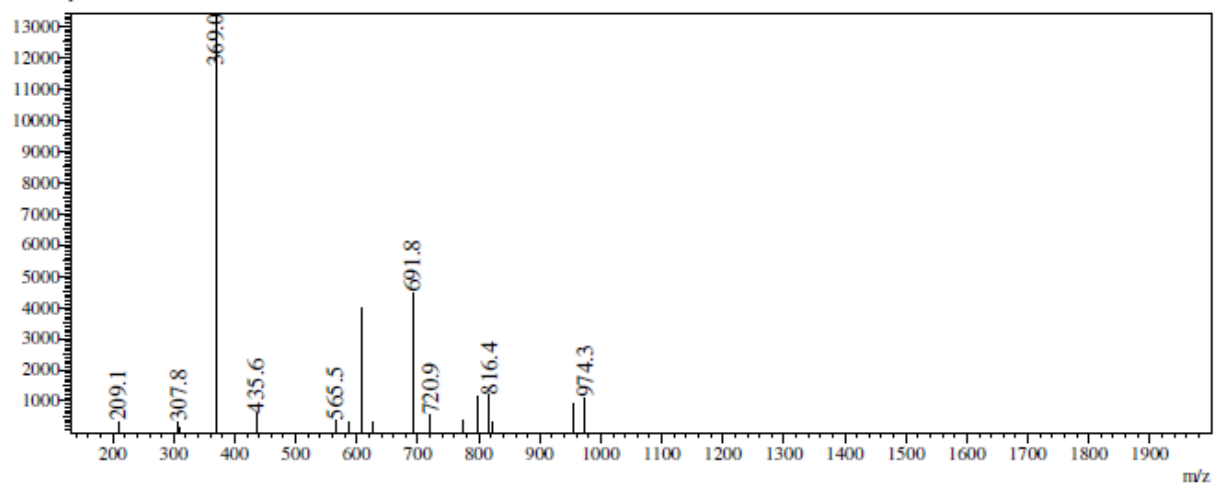
RefTime: 1.045

Intensity



RefTime: 1.412

Intensity



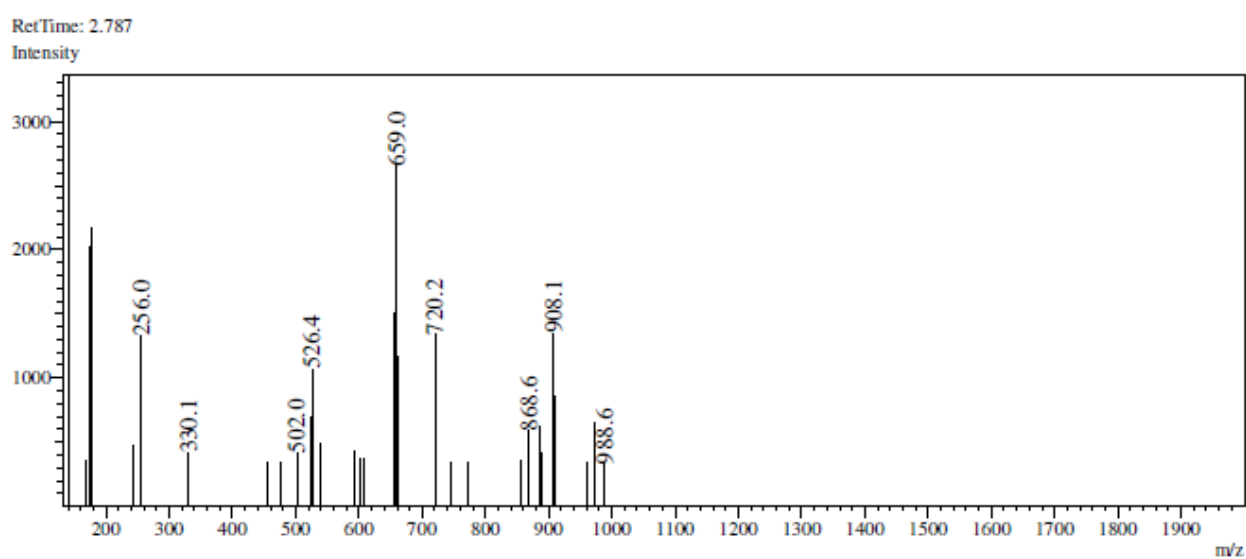
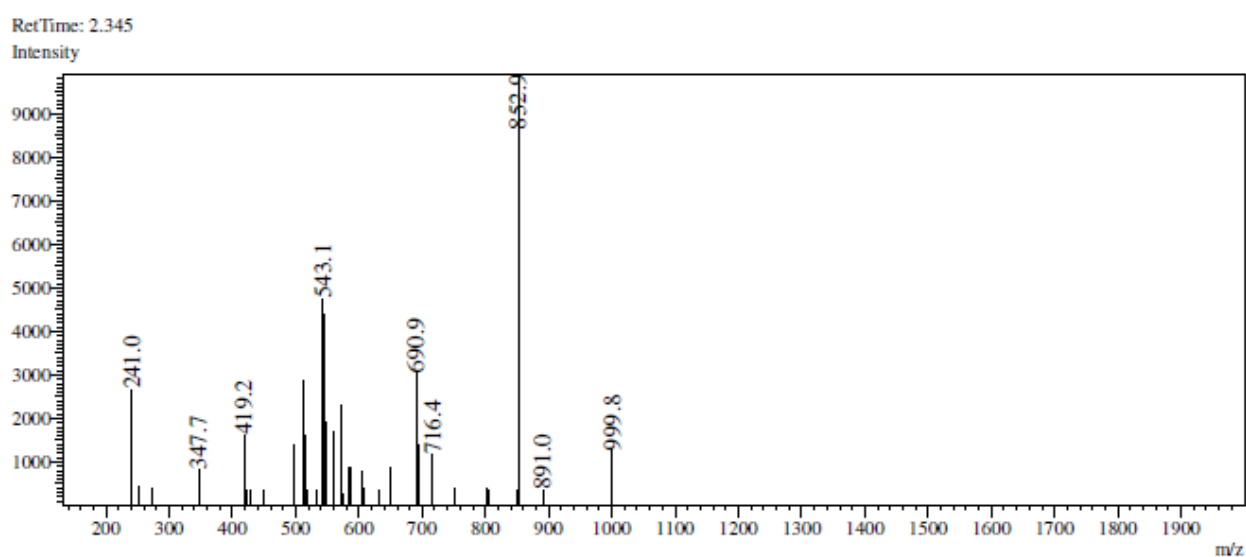
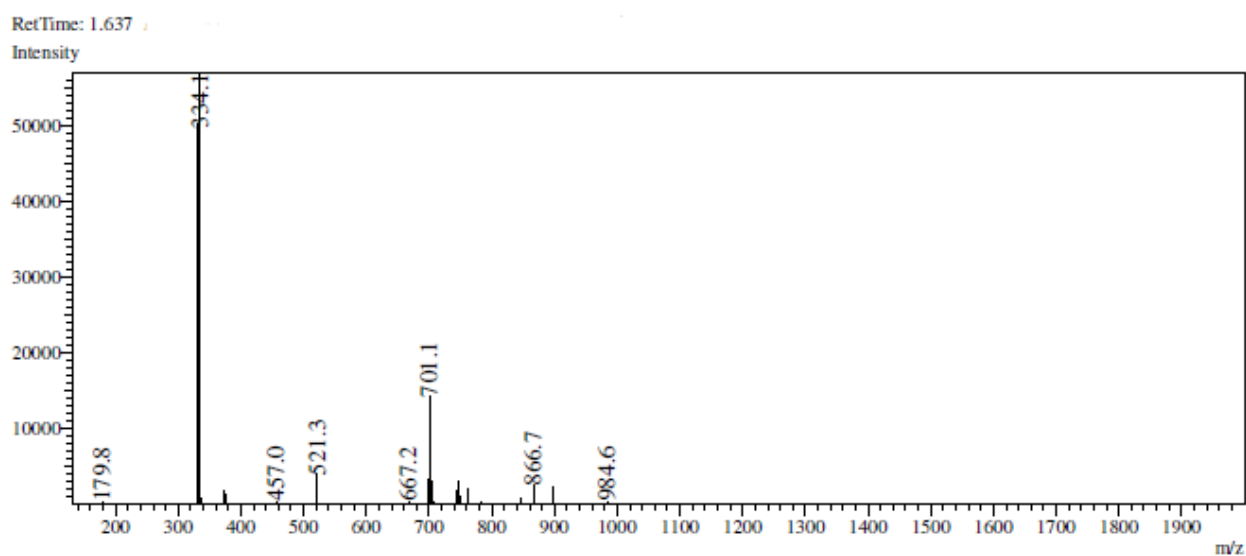


Fig. C43: MS Chromatogram of reaction mixture

¹H NMR of compound 4a-4, (400 MHz, DMSO-d₆) δ 7.28 (d, J = 8.4 Hz, 2H), 7.18 - 7.10 (m, 2H), 6.93 - 6.89 (m, 2H), 3.91 (s, 2H), 3.78 (s, 4H), 3.75 (s, 3H), 2.31 (s, 3H)

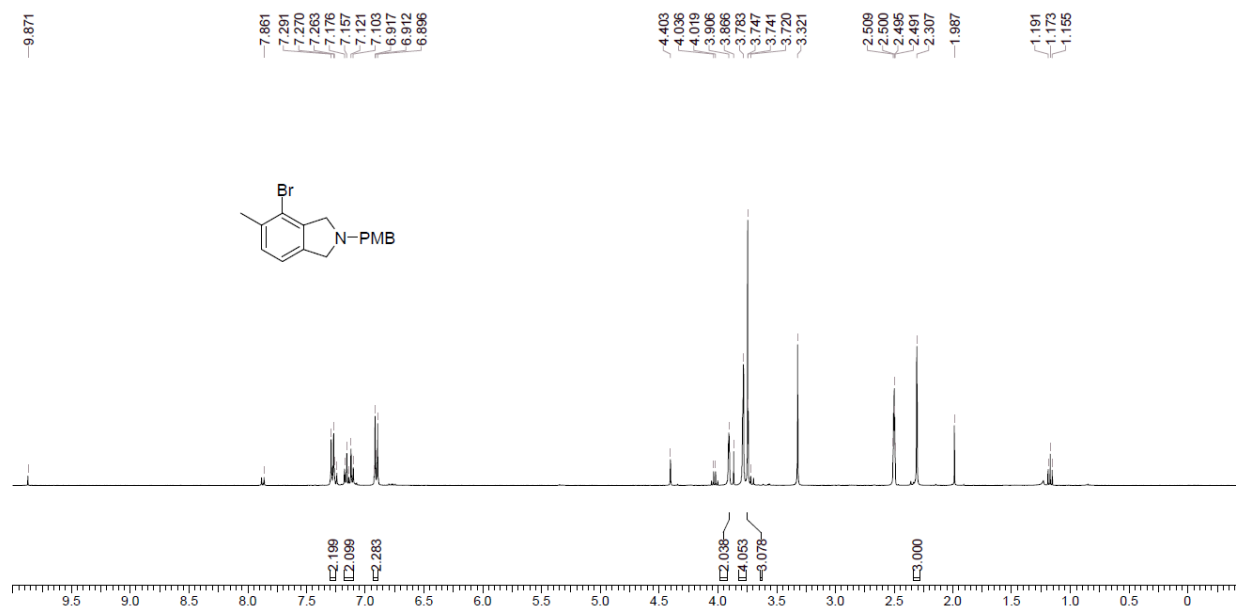
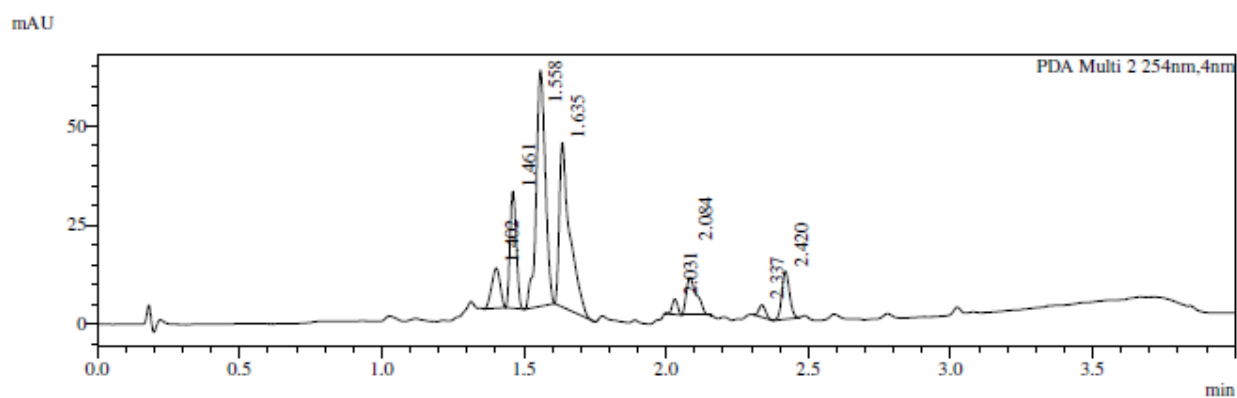
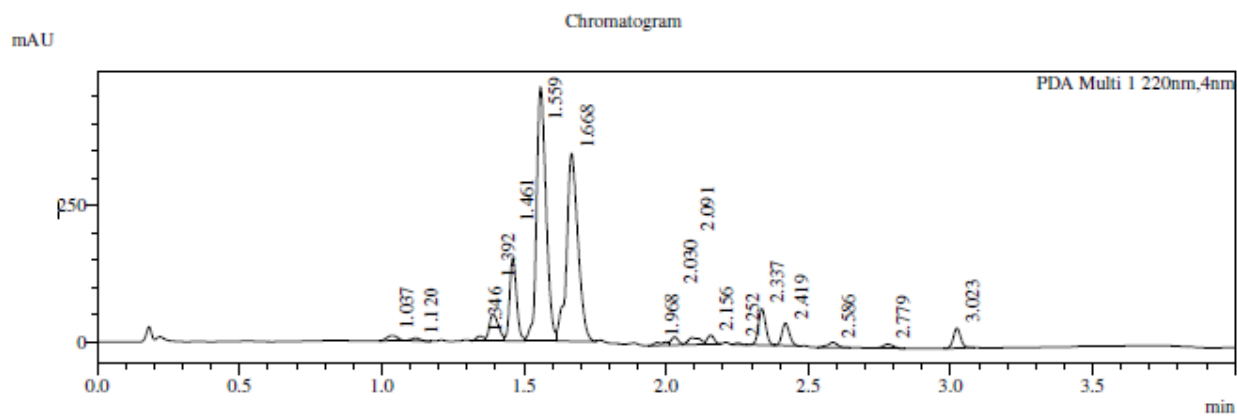


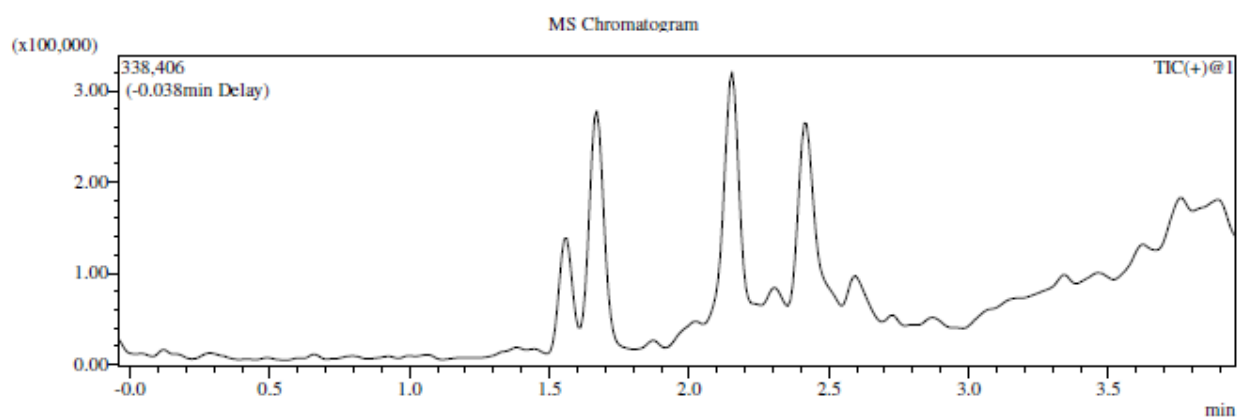
Fig. C44: ¹H NMR of compound 4a-4

Compound 4a-4-1:

LCMS of reaction mixture, product: RT = 1.559 min, m/z = 312.2 (M+H)⁺



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



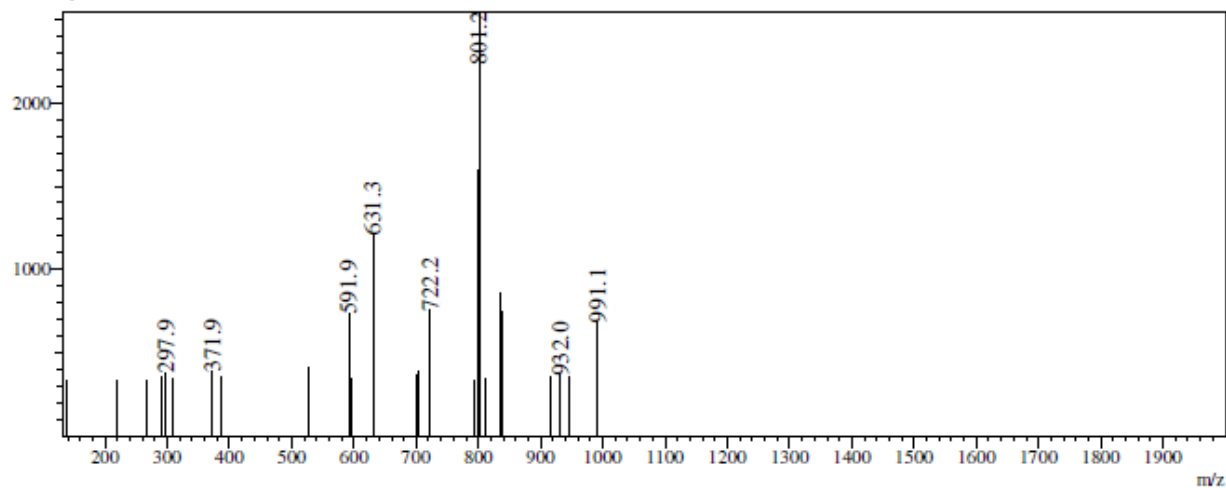
Integration Result								
PDA Ch1 220nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	1.037	0.069	1.017	--	9206	0.741	24192	0.842
2	1.120	0.055	1.068	1.334	5226	0.421	10583	0.368
3	1.346	0.059	--	3.989	8483	0.683	14709	0.512
4	1.392	0.062	--	0.763	48764	3.926	110251	3.835
5	1.461	0.045	1.137	1.302	149834	12.063	257568	8.960
6	1.559	0.061	1.109	1.841	465295	37.461	1078854	37.529
7	1.668	0.071	1.016	1.647	343604	27.664	966198	33.610
8	1.968	0.180	--	2.397	5323	0.429	17930	0.624
9	2.030	0.051	--	0.539	14953	1.204	25515	0.888
10	2.091	0.077	--	0.953	12586	1.013	38404	1.336
11	2.156	0.049	--	1.034	16133	1.299	27551	0.958
12	2.252	0.036	1.128	2.256	2941	0.237	3787	0.132
13	2.337	0.049	1.066	1.993	65560	5.278	119585	4.160
14	2.419	0.050	1.157	1.678	40828	3.287	75490	2.626
15	2.586	0.059	0.908	3.059	9374	0.755	21996	0.765
16	2.779	0.065	1.146	3.117	7353	0.592	17092	0.595
17	3.023	0.048	1.065	4.333	36606	2.947	65043	2.263
PDA Ch2 254nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	1.402	0.059	0.899	--	10049	6.000	20937	5.785
2	1.461	0.042	1.139	1.167	29038	17.337	44920	12.411
3	1.558	0.058	0.940	1.930	59117	35.295	132664	36.656
4	1.635	0.054	2.252	1.362	41085	24.530	106706	29.483
5	2.031	0.037	1.030	8.667	3844	2.295	5176	1.430
6	2.084	0.061	1.602	1.085	9420	5.624	24206	6.688
7	2.337	0.045	1.131	4.787	2976	1.777	4775	1.319
8	2.420	0.050	1.098	1.744	11962	7.142	22536	6.227

Fig. C45: LCMS Chromatogram of reaction mixture

MS Spectrum

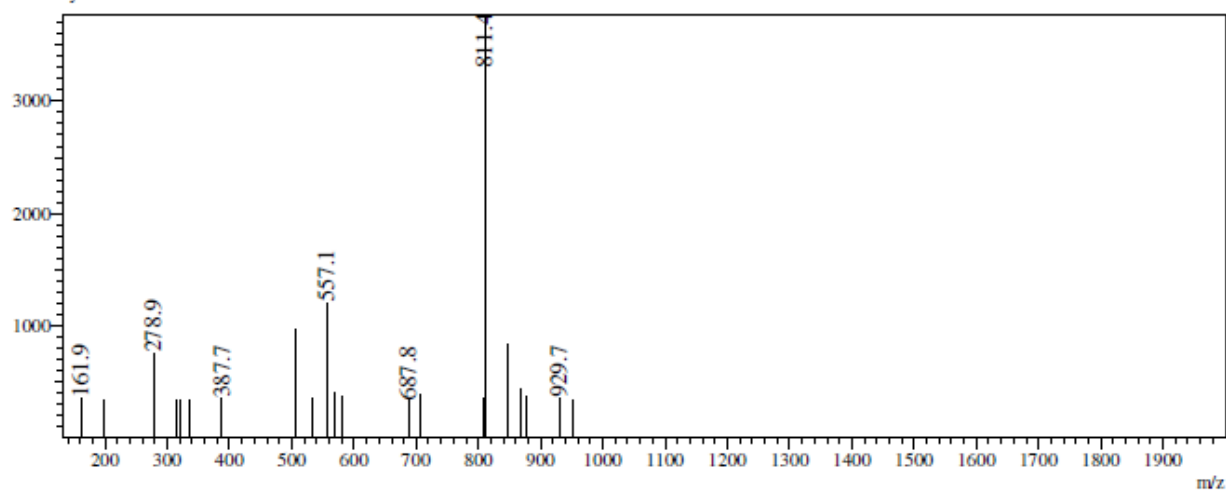
RefTime: 1.395

Intensity



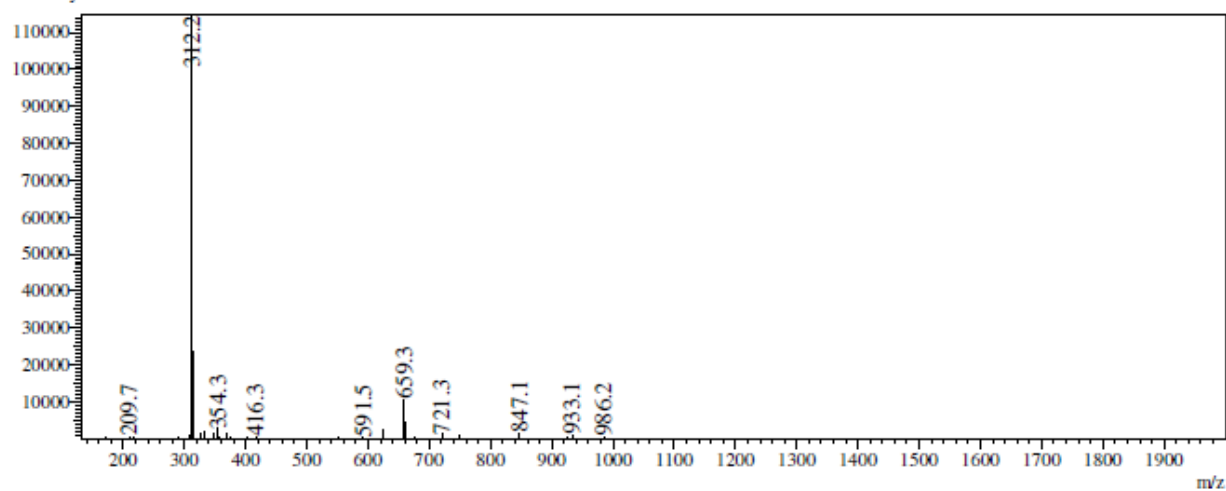
RefTime: 1.462

Intensity



RefTime: 1.562

Intensity



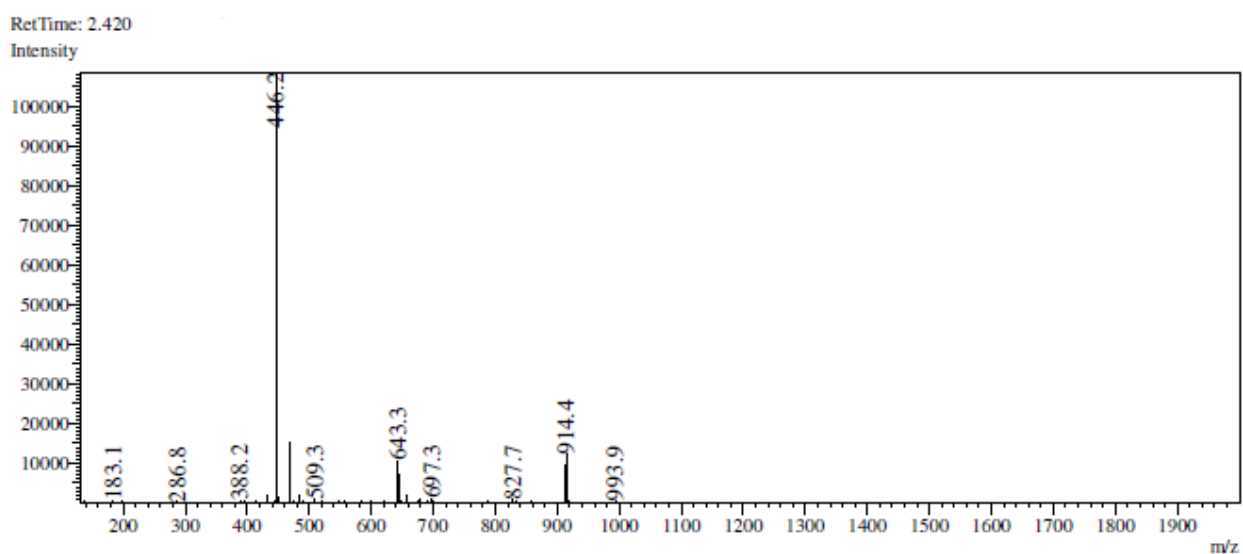
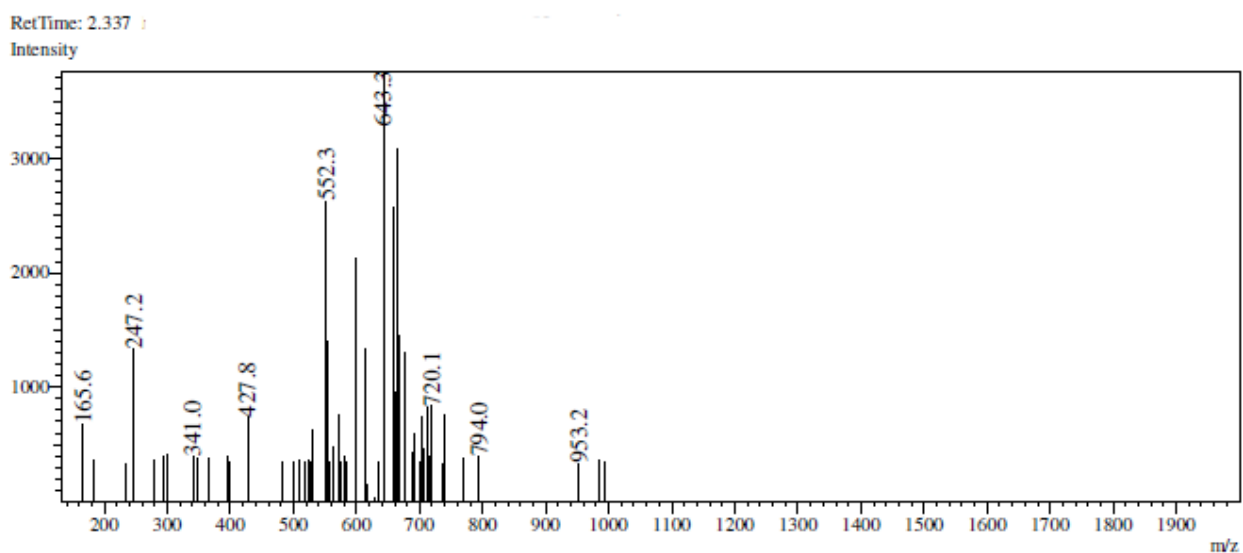
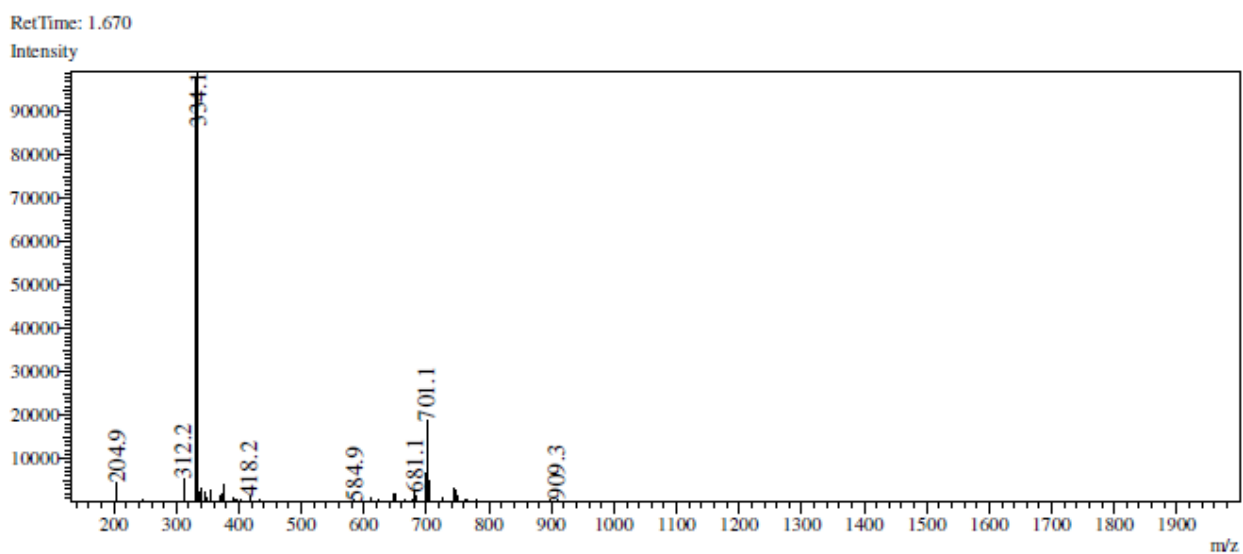


Fig. C46: MS Chromatogram of reaction mixture

¹H NMR of compound 4a-4-1, (400 MHz, DMSO-d₆) δ 7.27 (d, J = 8.4 Hz, 3H), 7.14 (d, J = 7.6 Hz, 1H), 6.94 - 6.87 (m, 2H), 3.92 (s, 2H), 3.79 (s, 3H), 3.77 (s, 4H), 3.74 (s, 3H), 2.40 (s, 3H)

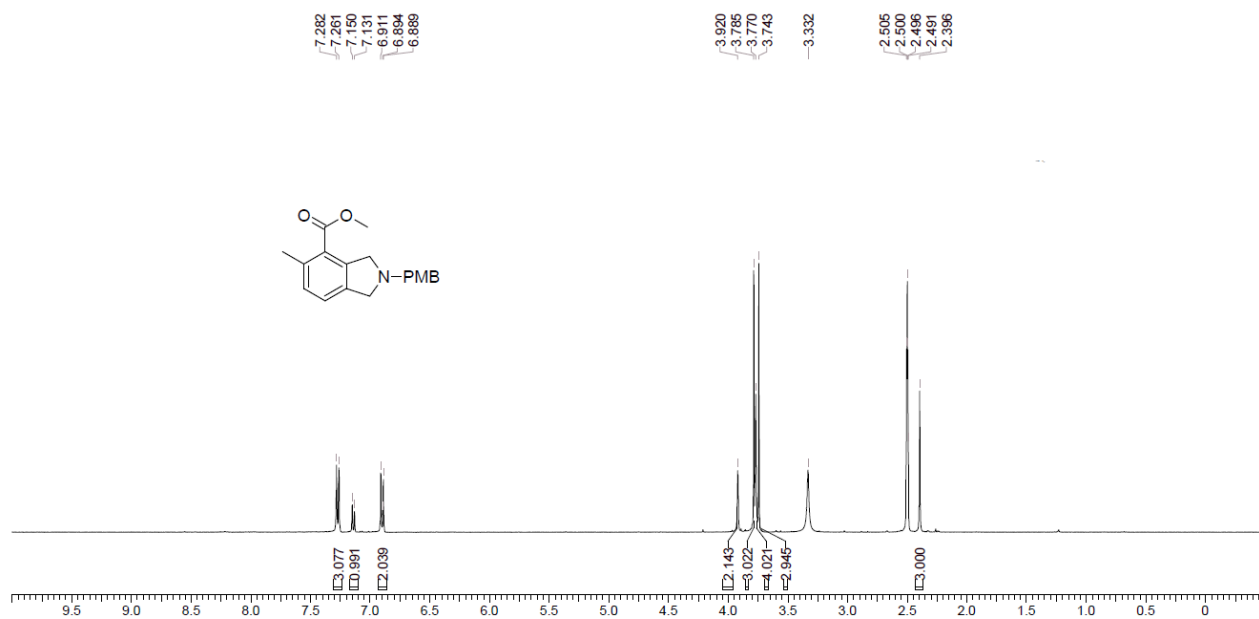
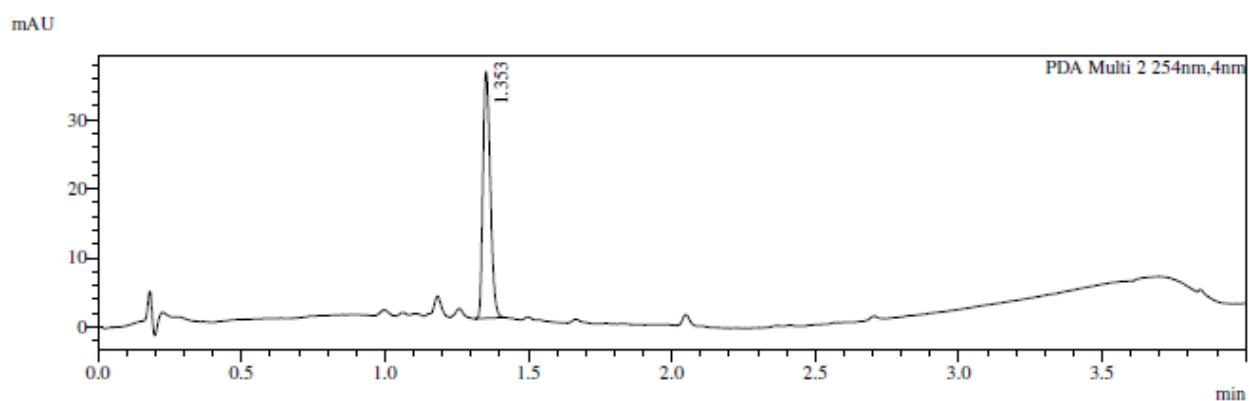
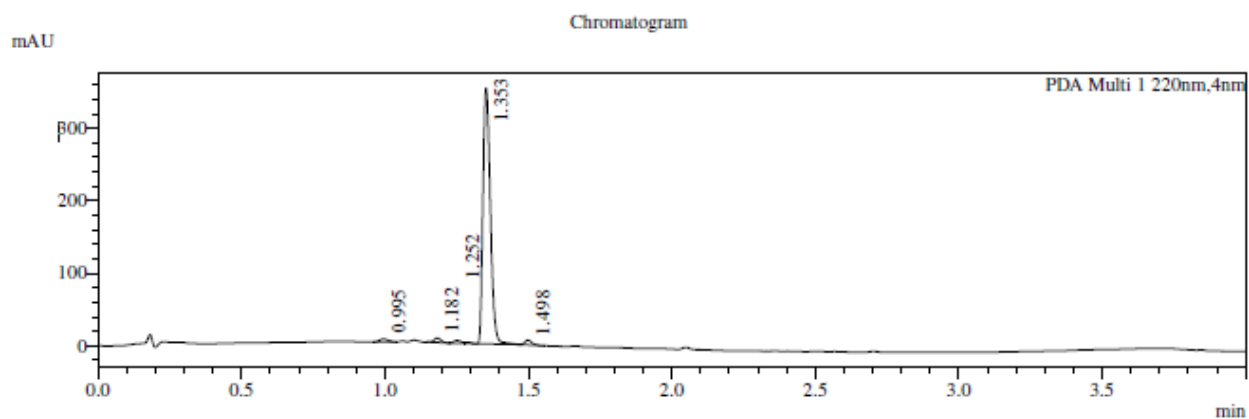


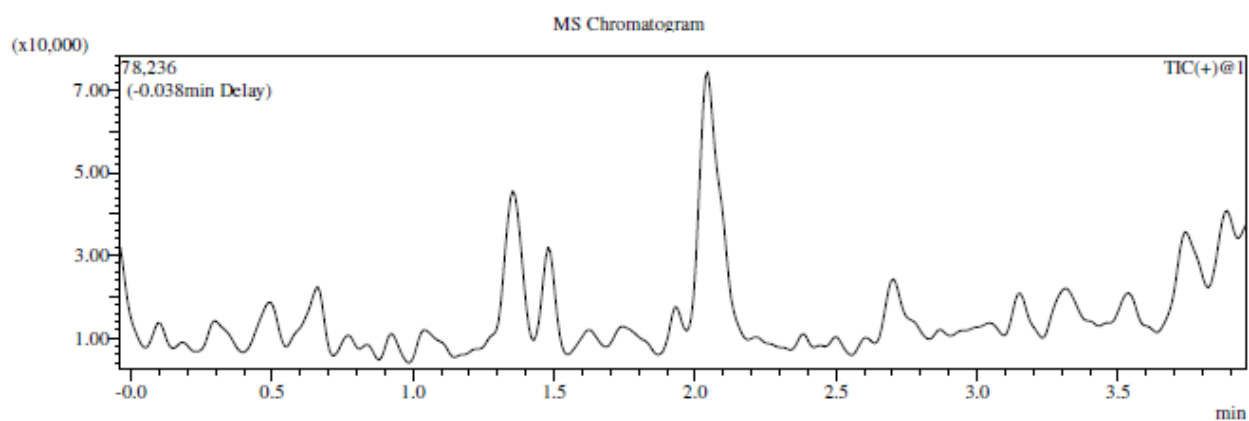
Fig. C47: ¹H NMR of compound 4a-4-1

Compound 4a:

LCMS of reaction mixture, product: RT = 1.353 min, m/z = 298.2 (M+H)⁺



- 1 PDA Multi 1 / 220nm,4nm
- 2 PDA Multi 2 / 254nm,4nm



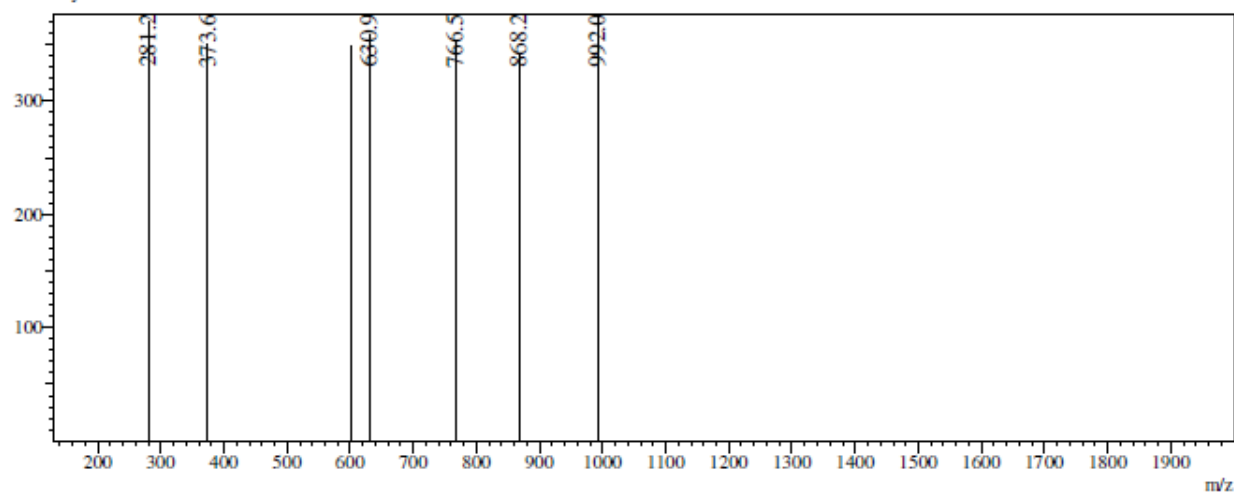
Integration Result								
PDA Ch1 220nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	0.995	0.054	1.114	--	3842	1.047	7561	1.137
2	1.182	0.045	0.960	3.770	5805	1.582	9710	1.460
3	1.252	0.051	--	1.454	3604	0.982	6861	1.032
4	1.353	0.048	1.302	2.031	347277	94.627	630414	94.824
5	1.498	0.044	1.293	3.163	6469	1.763	10281	1.546
PDA Ch2 254nm								
Peak#	Ret. Time	Width	Tailing Factor	Resolution	Height	Height%	Area	Area%
1	1.353	0.049	1.277	--	35251	100.000	63731	100.000

Fig. C48: LCMS Chromatogram of reaction mixture

MS Spectrum

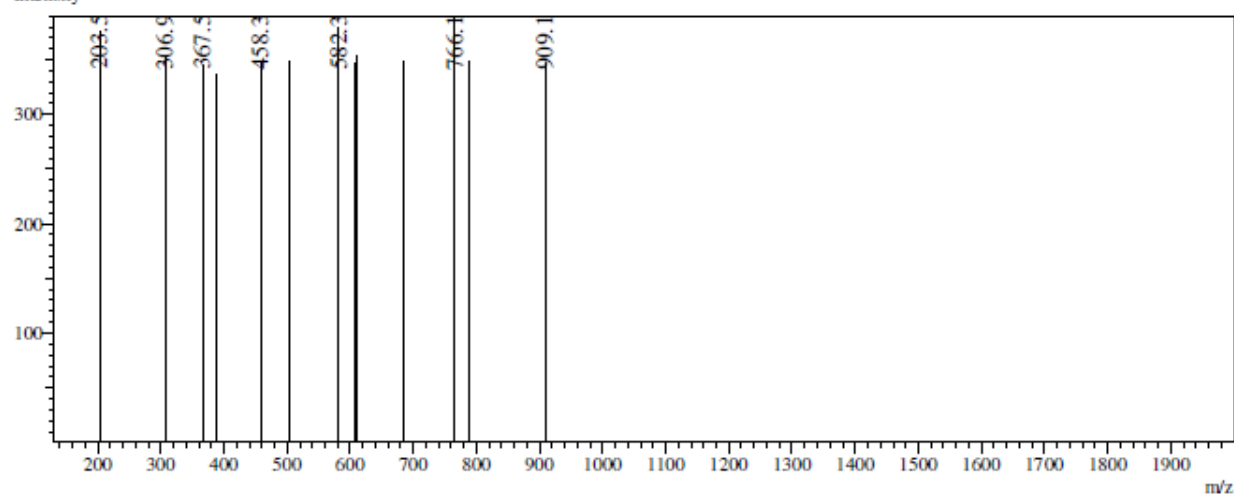
RetTime: 0.995

Intensity



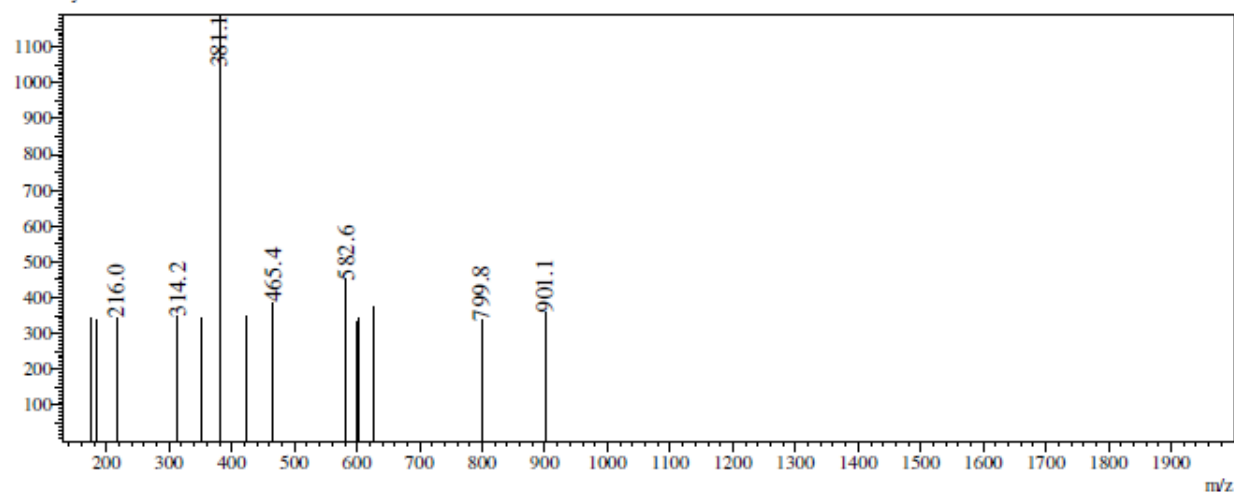
RetTime: 1.178

Intensity



RetTime: 1.253

Intensity



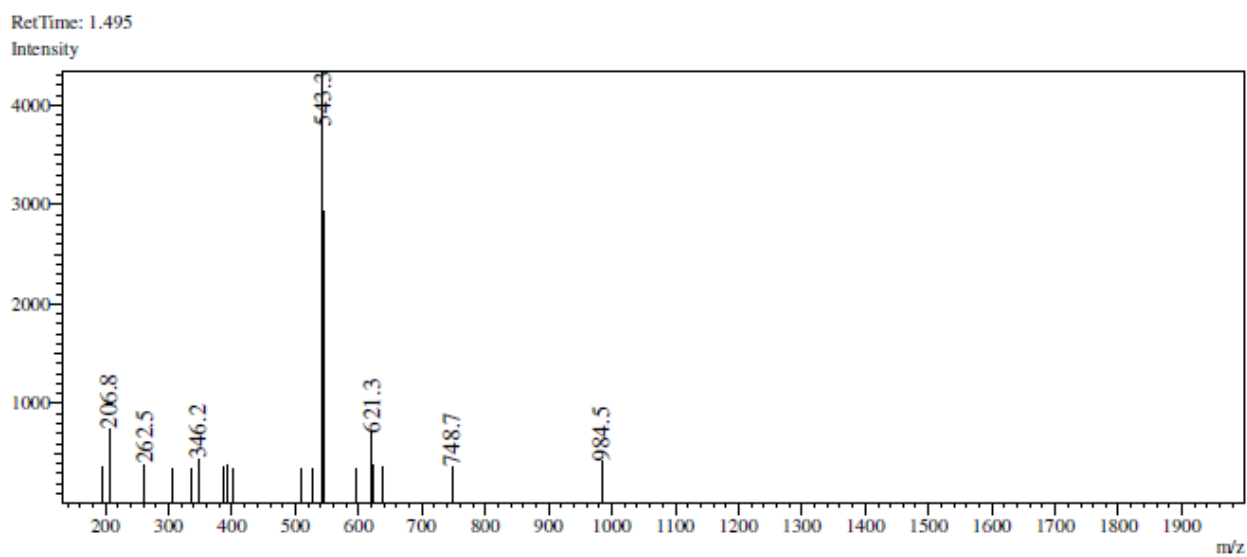
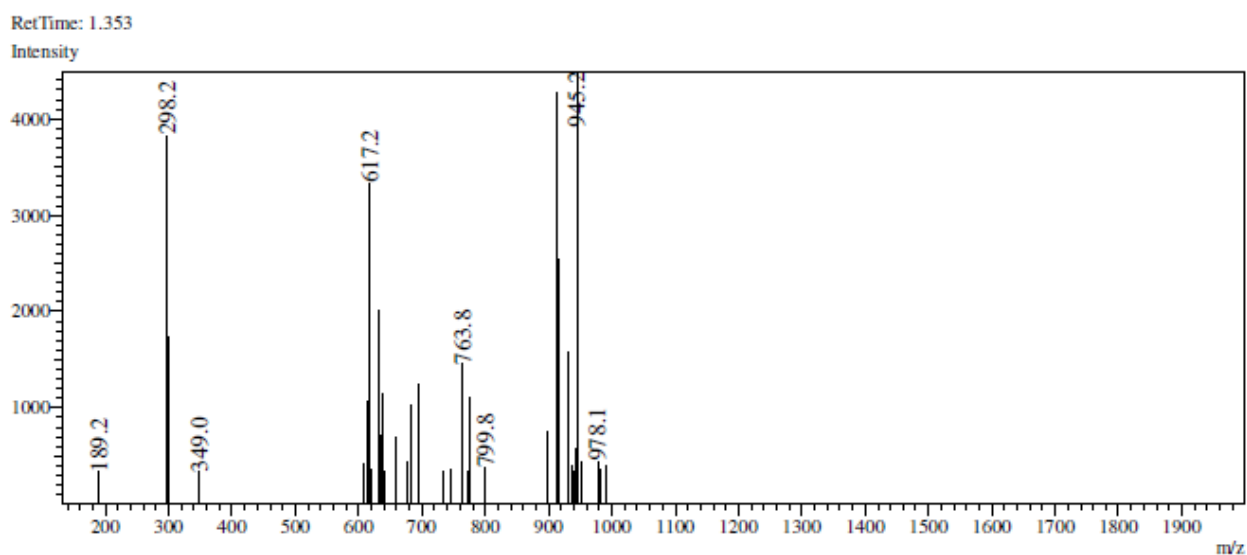


Fig. C49: MS Chromatogram of reaction mixture