Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.
This journal is © The Royal Society of Chemistry 2024

SUPPLEMENTAL MATERIAL

Screening of efficient salicylaldoxime reactivators for DFP and paraoxon-inhibited acetylcholinesterase

Zhao Wei [a,], Dongxu Zhang [a], Xueying Liu [a], Huifang Nie [a], Qin Ouyang [b], Xinlei Zhang [a,*], Zhibing Zheng [c,*]*

[a] *Department of Medicinal Chemistry and Pharmaceutical analysis, School of Pharmacy, Air Force Medical University, Xi'an 300071, China*
[b] Department of Medicinal Chemistry, School of Pharmacy, Third Military Medical University, Chongqing, 400038, China
[c] Department of Medicinal Chemistry, Institute of Pharmacology and Toxicology, Academy of Military Medical Sciences, Beijing 100850, China

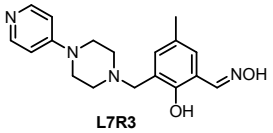
Table of Contents

1. Synthetic information

1.1 General synthetic information

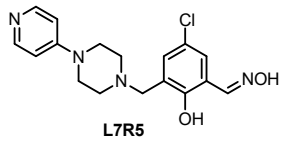
All reagents and solvents were used as received from commercial sources. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz on a Bruker-400 instrument in $CDCl_3$ or DMSO-d6, respectively. Proton and carbon chemical shifts are expressed in parts per million (ppm) relative to internal tetramethylsilane (TMS) and coupling constants (J) are expressed in Hertz (Hz). The splitting pattern abbreviations are as follows: multiplicity (s: singlet, d: doublet, dd: double doublet, ddd: double double doublet, dm: double multiplet, ds: double single, dt: double triplet, t: triplet, td triple doublet, tm, triple multiplet, tt: triple triplet, q: quartet, quint: quintuplet, m: multiplet, br: broad). Low-resolution mass spectra were obtained using an API 3000 LC/MS with an ESI source or an Agilent 620B TOF LC/MS with an ESI source. The chromatography was performed on silica gel (200-300 mesh), compounds were visualized under UV light at 254 nm. All of the following compounds were synthesized using a similar method as described for L7R3 in the text, with the corresponding R3, R5, R6, or R7 moieties and L moieties shown in Table S1. The two-step yields for these compounds ranged from 57% to 95%. All synthesized compounds were determined to possess a purity of more than 90%, as evidenced by high-performance liquid chromatography analysis

1.2 Analysis details



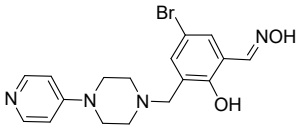
L7R3

General Method for the Preparation of 2-hydroxy-5-methyl- 3-((4-(pyridin-4-yl) piperazin-1-yl) methyl) benzaldehyde oxime (L7R3): The intermediates **R3**、**R5**、**R6** and **R7** was prepared as we described previously by using 2-hydroxy-5-methyl-benzaldehyde, 5-chloro-2-hydroxybenzaldehyde, 5-bromo-2-hydroxybenzaldehyde and 5-fluoro-2-hydroxybenzaldehyde[1]. To a solution of 1-(pyridin-4-yl) piperazine (L7) (0.16 g, 0.98 mmol) in DCM (10 mL) was added triethylamine (0.21 g, 2.07 mmol) and **R3** (0.19 g, 1.03 mmol), the mixture was stirred at room temperature for 2 h. After concentration under reduced pressure, the residue was purified by silica gel chromatography (DCM/MeOH=25/1, *v/v*) to afford the intermediate **L7R3-d1** (0.26 g, 81%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 10.12 (s, 1H), 8.28 (d, *J* = 5.7 Hz, 2H), 7.40 (s, 1H), 7.28 (s, 1H), 6.68 (d, *J* = 5.7 Hz, 2H), 3.71 (s, 2H), 3.50-3.35 (m, 4H), 2.80-2.63 (m, 4H), 2.33 (s, 3H).Then to a solution of **L7R3-d1** (0.25 g, 0.80 mmol) in ethanol (15 mL) was added hydroxylammonium chloride (0.10 g, 1.43 mmol) and anhydrous sodium acetate (0.14 g, 1.70 mmol). The mixture was stirred at room temperature for 3 h. After filtration, the residue was purified by silica gel chromatography (DCM/MeOH=20/1, v/v) to afford the title compound **L7R3** (0.20 g, 76%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 11.32 (s, 1H), 11.07-10.40 (m, 1H), 8.30 (s, 1H), 8.18 (d, *J* = 6.1 Hz, 2H), 7.24 (s, 1H), 7.04 (s, 1H), 6.87 (d, *J* = 6.1 Hz, 2H), 3.65 (s, 2H), 3.45-3.26 (m, 4H), 2.68-2.43 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 155.2, 153.3, 148.6, 147.9, 132.2, 128.2, 127.5, 123.3, 118.2, 108.7, 57.76, 52.1, 45.8, 20.5. MS (ESI+) m/z: 327.18 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{23}N_4O_2^+$ 327.1821 found 327.1815 Da.



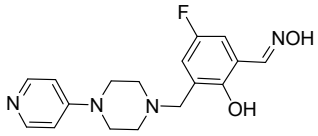
L7R5

5-chloro-2-hydroxy-3-((4-(pyridin-4-yl)piperazin-1-yl)methyl)benzaldehyde oxime (L7R5): The title compound was obtained in a manner similar to that used for **L7R3** as a white solid (0.15 g, 67%) but using **R5**. ^{1}H NMR (400 MHz, DMSO) δ 11.58 (s, 1H), 8.32 (s, 1H), 8.18 (d, J = 4.5 Hz, 2H), 7.47 (s, 1H), 7.28 (s, 1H), 6.85 (d, J = 4.5 Hz, 2H), 3.70 (s, 2H), 3.46-3.21 (m, 4H), 2.70-2.51 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 157.2, 150.7, 148.1, 146.6, 129.2, 126.1, 125.5, 122.3, 117.6, 106.9, 57.7, 54.4, 50.5. MS (ESI+) m/z: 347.13(100.0%), 349.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{17}H_{20}{}^{35}ClN_4O_2^+$ 347.1275 found 347.1269 Da.



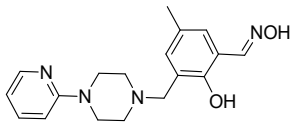
L7R6

5-bromo-2-hydroxy-3-((4-(pyridin-4-yl)piperazin-1-yl)methyl)benzaldehyde oxime (L7R6): The title compound was obtained in a manner similar to that used for **L7R3** as a pale yellow solid (0.07 g, 63%) but using **R6**. ^{1}H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 8.13 (d, J = 5.2 Hz, 2H), 7.57 (s, 1H), 7.38 (s, 1H), 6.87 (d, J = 5.2 Hz, 2H), 3.68 (s, 2H), 3.53-3.30 (m, 4H), 2.71-2.51 (m, 4H).^{13}C NMR (101 MHz, DMSO) δ 155.0, 154.6, 148.5, 147.1, 132.8, 129.6, 125.3, 120.1, 110.9, 108.3, 57.4, 52.1, 45.8. MS (ESI+) m/z: 391.07(100.0%), 393.07(97.3%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{17}H_{20}{}^{79}BrN_4O_2^+$ 391.0770 found 391.0764 Da.



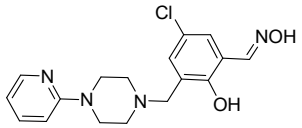
L7R7

5-fluoro-2-hydroxy-3-((4-(pyridin-4-yl)piperazin-1-yl)methyl)benzaldehyde oxime (L7R7): The title compound was obtained in a manner similar to that used for **L7R3** as a pale gray solid (0.05 g, 57%) but using **R7**. ^{1}H NMR (400 MHz, DMSO) δ 8.30 (s, 1H), 8.12 (d, J = 4.8 Hz, 2H), 7.22 (d, J = 9.2 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 4.8 Hz, 2H), 3.67 (s, 2H), 3.57-3.31 (m, 4H), 2.77-2.51 (m, 4H).^{13}C NMR (101 MHz, DMSO) δ 154.9, 151.5, 149.0, 147.0, 124. 6, 118.9, 117.2, 112.7, 112.5, 108.3, 58.5, 52.1, 45.7. MS (ESI+) m/z: 331.15 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{17}H_{20}FN_4O_2^+$ 331.1570 found 331.1565 Da.



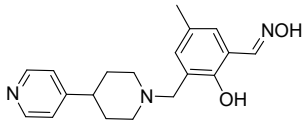
L69R3

2-hydroxy-5-methyl-3-((4-(pyridin-2-yl)piperazin-1-yl)methyl)benzaldehyde oxime (L69R3): The title compound was obtained in a manner similar to that used for **L7R3** as a white solid (0.18 g, 63%) but using **L69** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.23 – 8.14 (m, 1H), 7.49 (ddd, J = 9.0, 7.3, 2.0 Hz, 1H), 7.15 (d, J = 1.4 Hz, 1H), 7.02 (s, 1H), 6.65 (dd, J = 10.5, 3.0 Hz, 2H), 3.75-3.55 (m, 4H), 2.86-2.43 (m, 4H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 154.1, 149.4, 147.9, 137.8, 132.7, 128.6, 128.4, 121.1, 117.8, 113.8, 107.4, 58.4, 52.2, 44.7, 20.4. MS (ESI+) m/z: 327.17 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{23}N_4O_2^+$ 327.1821 found 327.1817 Da.



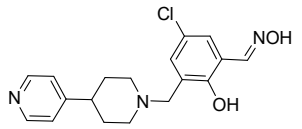
L69R5

5-chloro-2-hydroxy-3-((4-(pyridin-2-yl)piperazin-1-yl)methyl)benzaldehyde oxime (L69R5): The title compound was obtained in a manner similar to that used for **L7R3** as a white solid (0.20 g, 72%) but using **L69** and **R5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 – 10.63 (m, 1H), 8.30 (s, 1H), 8.18 (d, *J* = 4.0 Hz, 1H), 7.59 – 7.47 (m, 1H), 7.42 (d, *J* = 3.1 Hz, 1H), 7.16 (s, 1H), 6.66 (dd, *J* = 10.4, 6.0 Hz, 2H), 3.73 (s, 2H), 3.66-3.41 (m, 4H), 2.91-2.60 (m, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 154.5, 147.8, 146.4, 137.6, 130.0, 125.9, 123.8, 119.9, 117.9, 113.6, 107.1, 58.3, 52.3, 44.8.MS (ESI+) m/z: 347.12(100.0%), 349.13(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{17}H_{20}{}^{35}ClN_4O_2^+$ 347.1275 found 347.1270 Da.



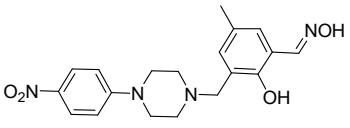
L70R3

2-hydroxy-5-methyl-3-((4-(pyridin-4-yl)piperidin-1-yl)methyl)benzaldehyde oxime (L70R3): The title compound was obtained in a manner similar to that used for **L7R3** as a white solid (0.21 g, 81%) but using **L70** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.5 Hz, 2H), 8.39 – 8.15 (m, 1H), 7.20 (d, *J* = 4.8 Hz, 4H), 4.19 – 3.79 (m, 2H), 3.58 – 3.18 (m, 2H), 2.78 – 2.48 (m, 3H), 2.41-2.06 (m, 5H), 2.03-1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 153.4, 149.7, 148.7, 132.8, 129.2, 128.3, 122.5, 122.2, 117.9, 56.8, 52.4, 30.8, 29.4, 20.2. MS (ESI+) m/z: 326.18 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{24}N_3O_2^+$ 326.1869 found 326.1863 Da.



L70R5

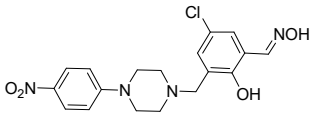
5-chloro-2-hydroxy-3-((4-(pyridin-4-yl)piperidin-1-yl)methyl)benzaldehyde oxime (L70R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.24 g, 85%) but using **L70** and **R5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.41 (m, 2H), 8.32 (s, 1H), 7.47 (d, *J* = 6.4 Hz, 2H), 7.19 (d, *J* = 5.9 Hz, 2H), 3.96 – 3.54 (m, 2H), 3.34 – 2.86 (m, 2H), 2.76 – 2.49 (m, 1H), 2.44 – 2.09 (m, 2H), 1.99 – 1.48 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 149.6, 149.5, 145.4, 129.4, 125.3, 124.7, 123.2, 122.3, 120.4, 59.3, 53.2, 41.1, 32.2. MS (ESI+) m/z: 346.12(100.0%), 348.13(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{21}{}^{35}ClN_3O_2^+$ 346.1322 found 346.1317 Da.



L73R3

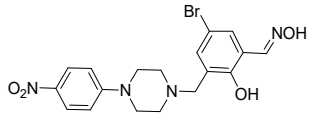
2-hydroxy-5-methyl-3-((4-(4-nitrophenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L73R3): The title compound was obtained in a manner similar to that used for **L7R5** as a pale yellow solid (0.25 g, 91%) but using **L73** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 – 10.40 (m, 1H), 8.39 – 8.19 (m, 1H), 8.19 – 7.93 (m, 2H), 7.57 – 7.38 (m, 1H), 7.12 (s, 2H), 6.98 – 6.43 (m, 2H), 3.81 (s, 2H), 3.55-3.21 (m, 4H), 3.10-2.58 (m, 4H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 153.6, 151.2, 149.5, 138.3, 132.6, 128.9, 128.3, 125.8, 117.6, 112.8, 56.7, 51.7, 46.3, 20.3. MS (ESI+) m/z: 371.16 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}N_4O_4^+$ 371.1719 found 371.1713 Da.



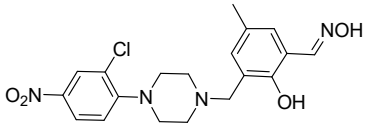
L73R5

5-chloro-2-hydroxy-3-((4-(4-nitrophenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L73R5): The title compound was obtained in a manner similar to that used for **L7R5** as a pale yellow solid (0.25 g, 91%) but using **L73** and **R5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57-10.36 (m, 2H), 8.26 (d, *J* = 11.2 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.70 (s, 2H), 3.59-3.31 (m, 4H), 2.83-2.61 (m, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 154.2, 146.9, 138.0, 129.9, 126.4, 125.8, 125.0, 123.6, 119.8, 112.8, 57.6, 52.1, 46.7.MS (ESI+) m/z: 391.11(100.0%), 393.11(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{20}{}^{35}ClN_4O_4^+$ 391.1173 found 391.1168 Da.



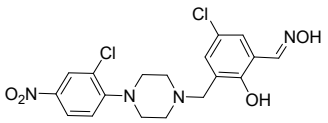
L73R6

5-bromo-2-hydroxy-3-((4-(4-nitrophenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L73R6): The title compound was obtained in a manner similar to that used for **L7R5** as a yellow solid (0.34 g, 75%) but using **L73** and **R6**. [1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53-10.27 (m, 2H), 8.25 (s, 1H), 8.11 (d, *J* = 6.0 Hz, 2H), 7.33 (s, 1H), 7.21 (s, 1H), 6.86 (d, *J* = 6.5 Hz, 2H), 3.69 (s, 3H), 3.62-3.37 (m, 4H), 2.90-2.69 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 154.4, 147.4, 138.4, 130.3, 126.8, 125.9, 125.7, 123.9, 119.8, 112.9, 57.5, 52.2, 46.8. MS (ESI+) m/z: 435.06(100.0%), 437.07(97.3%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{22}{}^{79}BrN_3O_2^+$ ($-NO_2$) 391.0895 found 391.1167 Da.



L74R3

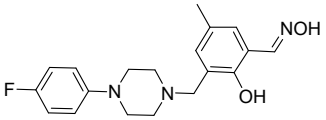
3-((4-(2-chloro-4-nitrophenyl)piperazin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L74R3): The title compound was obtained in a manner similar to that used for **L7R5** as a pale yellow solid (0.28 g, 77%) but using **L74** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.27 (s, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.20 (s, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 2H), 3.51-3.33 (s, 4H), 3.25-2.63 (s, 5H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 154.0, 149.8, 142.5, 133.1, 129.3, 128.7, 127.7, 126.6, 123.5, 120.6, 119.7, 117.6, 58.0, 52.3, 49.7, 20.4.MS (ESI+) m/z: 405.13(100.0%), 407.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{22}{}^{35}ClN_4O_4^+$ 405.1330 found 405.1324 Da.



L74R5

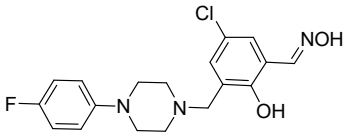
5-chloro-3-((4-(2-chloro-4-nitrophenyl)piperazin-1-yl)methyl)-2-hydroxybenzaldehyde oxime (L74R5): The title compound was obtained in a manner similar to that used for **L7R5** as a yellow solid (0.24 g, 71%) but using **L74** and **R5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.28 (d, *J* = 1.5 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.42 (s,

1H), 7.17 (s, 1H), 7.09 (d, J = 8.8 Hz, 1H), 3.81 (s, 2H), 3.51-3.19 (m, 4H), 3.07-2.89 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 154.2, 147.0, 142.2, 135.5, 130.0, 127.5, 127.1, 126.5, 123.8, 123.4, 119.8, 119.6, 57.5, 52.4, 50.2.MS (ESI+) m/z: 425.07(100.0%), 427.07(63.9%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{19}{}^{35}Cl_2N_4O_4^+$ 425.0783 found 425.0779 Da.



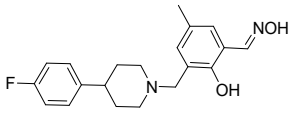
L76R3

3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L76R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.23 g, 82%) but using **L76** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.97 (t, J = 8.3 Hz, 2H), 6.90 (d, J = 4.2 Hz, 2H), 3.94 (s, 2H), 3.41-3.13 (m, 4H), 3.07-2.79 (m, 4H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ156.0, 153.80, 148.8, 147.3, 132.5, 128.7, 128.3, 118.2, 117.9, 115.6, 115.4, 57.2, 52.1, 49.3, 20.3. MS (ESI+) m/z: 425.07 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{23}FN_3O_2^+$ 344.1774 found 344.1771 Da.



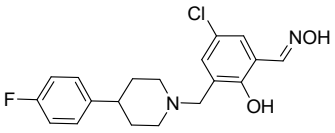
L76R5

5-chloro-3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-2-hydroxybenzaldehyde oxime (L76R5): The title compound was obtained in a manner similar to that used for **L7R5** as a gray solid (0.17 g, 77%) but using **L76** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 11.83 – 11.25 (m, 1H), 8.31 (s, 1H), 7.49 (s, 1H), 7.29 (s, 1H), 7.05 (d, J = 7.4 Hz, 2H), 6.97 (s, 2H), 3.76 (s, 2H), 3.25-2.97 (m, 4H), 2.81-2.61 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 147.4, 146.2, 129.9, 126.1, 123.7, 120.0, 118.0, 117.9, 115.5, 115.3, 58.2, 52.4, 49.6. MS (ESI+) m/z: 364.11(100.0%), 466.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{20}{}^{35}ClFN_3O_2^+$ 364.1228 found 364.1223 Da.



L77R3

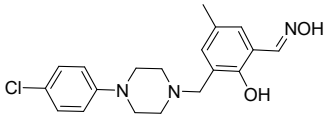
3-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L77R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.25 g, 91%) but using **L77** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.21 (dd, J = 12.0, 5.1 Hz, 3H), 7.00 (t, J = 7.9 Hz, 3H), 3.85(s, 2H), 3.40 – 3.03 (m, 2H), 2.70 – 2.50 (m, 1H), 2.50 – 2.30 (m, 2H), 2.28 (s, 3H), 2.06 – 1.71 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 160.3, 154.5, 148.9, 140.8, 132.4, 128.3, 128.2, 128.2, 118.0,115.4, 115.2, 53.3, 41.1, 32.7, 29.7, 20.4. MS (ESI+) m/z: 343.17 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{20}H_{24}FN_2O_2^+$ 343.1882 found 343.1818 Da.



L77R5

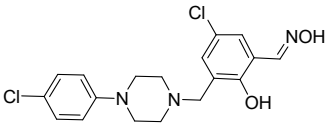
5-chloro-3-((4-(4-fluorophenyl)piperidin-1-yl)methyl)-2-hydroxybenzaldehyde oxime (L77R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.28 g, 87%) but using **L77**

and **R5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.39 (s, 1H), 7.20 (s, 3H), 7.00 (t, *J* = 8.2 Hz, 2H), 3.93 (s, 2H), 3.31 (d, *J* = 10.5 Hz, 2H), 2.81 – 2.34 (m, 3H), 2.13 – 1.64 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 160.4, 155.3, 147.7, 140.2, 131.3, 128.2, 128.2, 124.1, 119.7, 115.5, 115.3, 53.1, 40.7, 32.3, 29.8. MS (ESI+) m/z: 363.12(100.0%), 365.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{21}{}^{35}ClFN_2O_2^+$ 363.1276 found 363.1271 Da.



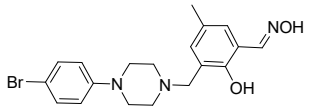
L78R3

3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L78R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.29 g, 93%) but using **L78** and **R3**. ^{1}H NMR (400 MHz, DMSO) δ 11.65 – 11.12 (m, 1H), 11.02 – 10.31 (m, 1H), 8.31 (s, 1H), 7.24 (d, *J* = 8.9 Hz, 3H), 7.13 – 6.99 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 3.69 (s, 2H), 3.24-2.95 (m, 4H), 2.91 – 2.55 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.2, 149.0, 147.8, 139.1, 131.7, 129.6, 128.4, 127.7, 123.9, 117.6, 116.9, 57.5, 51.7, 48.1, 19.9. MS (ESI+) m/z: 360.14(100.0%), 362.15(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}{}^{35}ClN_3O_2^+$ 360.1479 found 360.1475 Da.



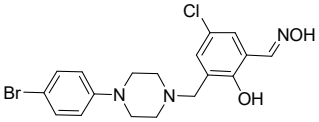
L78R5

5-chloro-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-2-hydroxybenzaldehyde oxime (L78R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.35 g, 88%) but using **L78** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 12.33 – 11.61 (m, 1H), 11.43 – 10.58 (m, 1H), 8.43 (s, 1H), 7.65 (d, *J* = 21.8 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 4.29 (s, 2H), 3.89 – 2.73 (m, 8H). ^{13}C NMR (101 MHz, DMSO) δ 149.6, 146.4, 129.7, 128.6, 128.6, 125.7, 125.4, 123.7, 123.1, 120.1, 117.1, 58.0, 52.3, 48.6. MS (ESI+) m/z: 380.09(100.0%), 382.10(63.9%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{20}{}^{35}Cl_2N_3O_2^+$ 380.0933 found 380.0928 Da.



L79R3

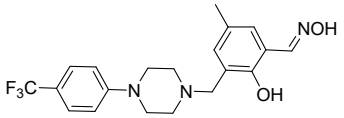
3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L79R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.33 g, 85%) but using **L79** and **R3**. ^{1}H NMR (400 MHz, DMSO) δ 11.67 – 11.15 (m, 1H), 11.17 – 10.44 (m, 1H), 8.30 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.26 (s, 1H), 7.03 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.68 (s, 2H), 3.31 – 2.97 (m, 4H), 2.87 – 2.53 (m, 4H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 149.7, 148.4, 132.4, 132.1, 131.7, 131.62, 128.08, 117.93, 117.71, 111.68, 57.60, 51.95, 48.03, 20.28. MS (ESI+) m/z: 404.09(100.0%), 406.10(97.3%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}{}^{79}BrN_3O_2^+$ 404.0974 found 404.0968 Da.



L79R5

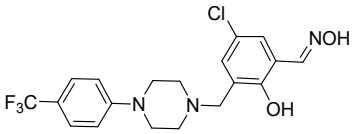
3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-5-chloro-2-hydroxybenzaldehyde oxime (L79R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.23 g, 76%) but using **L79**

and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 12.20 – 11.50 (m, 1H), 11.25 – 10.33 (m, 1H), 8.40 (s, 1H), 7.59 (s, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.22 (s, 2H), 3.76 – 2.72 (m, 8H). ^{13}C NMR (101 MHz, DMSO) δ 154.3, 150.0, 145. 9, 131.7, 129.7, 125.8, 124.8, 123.6, 120.2, 117.7, 111.4, 58.4, 52.4, 48.6. MS (ESI+) m/z: 426.04(100.0%), 424.03(77.3%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{20}{}^{81}Br^{35}ClN_3O_2^+$ 426.0407 found 426.0400 Da.



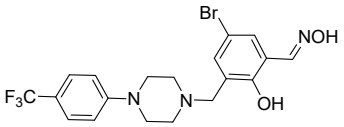
L80R3

2-hydroxy-5-methyl-3-((4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L80R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.34 g, 89%) but using **L80** and **R3**. ^{1}H NMR (400 MHz, DMSO) δ 11.75 – 10.18 (m, 2H), 8.32 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.26 (s, 1H), 7.07 (d, *J* = 8.2 Hz, 3H), 3.69 (s, 2H), 3.48 – 2.91 (m, 6H), 2.89-5.51 (s, 2H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.6, 152.8, 148.6, 132.0, 128.1, 126.2, 126.2, 125.9, 123.2, 117.8, 114.5, 114.5, 57.5, 52.0, 47.3, 20.3. MS (ESI+) m/z: 394.17 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{20}H_{23}F_3N_3O_2^+$ 394.1742 found 394.1736 Da.



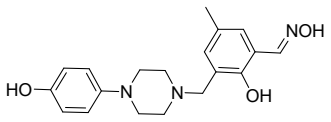
L80R5

5-chloro-2-hydroxy-3-((4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L80R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.31 g, 83%) but using **L80** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 11.61 (s, 1H), 8.33 (s, 1H), 7.65 – 7.36 (m, 3H), 7.30 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 2H), 3.43-3.05 (m, 4H), 2.92-2.53 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 154.4, 152.85, 146.6, 129.9, 126.3, 126.2, 126.0, 123.7, 123.3, 120.3, 119.9, 114.6, 57.8, 52.1, 47.4. MS (ESI+) m/z: 414.11(100.0%), 416.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{20}{}^{35}ClF_3N_3O_2^+$ 414.1196 found 414.1191 Da.



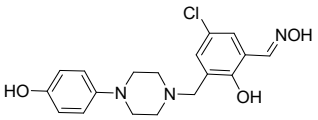
L80R6

5-bromo-2-hydroxy-3-((4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L80R6): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.23 g, 66%) but using **L80** and **R6**. ^{1}H NMR (400 MHz, DMSO) δ 11.59 (s, 1H), 8.32 (s, 1H), 7.67 – 7.37 (m, 3H), 7.29 (s, 1H), 7.07 (d, *J* = 8.3 Hz, 2H), 3.74 (s, 2H), 3.46-3.07 (m, 4H), 2.87-2.51 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 154.4, 152.9, 146.8, 130.0, 126.3, 126.3, 126.2, 126.0, 123.7, 123.3, 119.9, 114.6, 57.8, 52.2, 47.6. MS (ESI+) m/z: 458.06(100.0%), 460.07(97.3%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{20}{}^{79}BrF_3N_3O_2^+$ 458.0961 found 458.0965 Da.



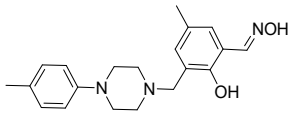
L81R3

2-hydroxy-3-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-5-methylbenzaldehyde oxime (L81R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.25 g, 70%) but using **L81** and **R3**. ^{1}H NMR (400 MHz, DMSO) δ 11.24 (s, 1H), 8.89 (s, 1H), 8.29 (s, 1H), 7.26 (s, 1H), 7.00 (s, 1H), 6.79 (d, *J* = 7.5 Hz, 2H), 6.65 (d, *J* = 7.4 Hz, 2H), 3.68 (s, 2H), 3.17-2.81 (m, 4H), 2.75-2.52 (m, 4H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.7, 151.5, 147.6, 144.2, 131.5, 127.9, 127.0, 122.0, 118.6, 118.2, 115.8, 58.9, 52.7, 50.7, 20.3. MS (ESI+) m/z: 342.17 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{24}N_3O_3^+$ 342.1818 found 342.1812 Da.



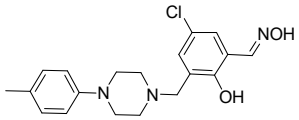
L81R5

5-chloro-2-hydroxy-3-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)benzaldehyde oxime (L81R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.29 g, 68%) but using **L81** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 11.52 (s, 1H), 8.93 (s, 1H), 8.29 (s, 1H), 7.47 (s, 1H), 7.26 (s, 1H), 6.79 (d, *J* = 6.3 Hz, 2H), 6.65 (d, *J* = 6.8 Hz, 2H), 3.75 (s, 2H), 3.19-2.83 (m, 4H), 2.77-2.51 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 154.3, 151.4, 145.5, 144.1, 129.6, 125.4, 124.5, 123.6, 120.2, 118.6, 115.7, 58.8, 52.7, 50.7. MS (ESI+) m/z: 362.12(100.0%), 364.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{21}{}^{35}ClN_3O_2^+$ 362.1271 found 362.1266 Da.



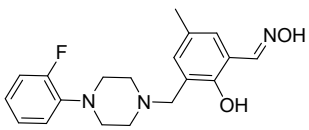
L82R3

2-hydroxy-5-methyl-3-((4-(p-tolyl)piperazin-1-yl)methyl)benzaldehyde oxime (L82R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.33 g, 78%) but using **L82** and **R3**. ^{1}H NMR (400 MHz, DMSO) δ 8.29 (s, 1H), 7.25 (s, 1H), 7.08 (s, 1H), 7.02 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.55 – 3.25 (m, 4H), 3.25-2.90 (m, 4H), 2.20 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 149.1, 148.7, 131.5, 129.6, 129.6, 128.8, 126.5, 124.8, 124.0, 120.0, 116.3, 58.0, 52.8, 49.4, 20.5, 20.4. MS (ESI+) m/z: 340.19 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{20}H_{26}N_3O_2^+$ 340.2025 found 340.2020 Da.



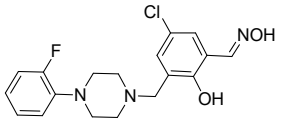
L82R5

5-chloro-2-hydroxy-3-((4-(p-tolyl)piperazin-1-yl)methyl)benzaldehyde oxime (L82R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.32 g, 70%) but using **L82** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 8.29 (s, 1H), 7.46 (s, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.73 (s, 3H), 3.23-2.98 (m, 4H), 2.76-2.54 (m, 4H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 154.2, 148.8, 145.8, 129.7, 129.6, 129.3, 125.7, 124.5, 123.7, 120.2, 116.5, 58.8, 52.6, 20.4. MS (ESI+) m/z: 360.14(100.0%), 362.14(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}{}^{35}ClN_3O_2^+$ 360.1479 found 360.1473 Da.



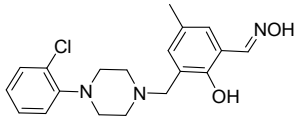
L83R3

3-((4-(2-fluorophenyl)piperazin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L83R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.28 g, 74%) but using **L83** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.11 – 6.71 (m, 5H), 3.87 (s, 2H), 3.43-3.10 (m, 4H), 3.05-2.69 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 154.2, 153.7, 148.2, 139.4, 132.0, 128.1, 124.5, 122.7, 119.0, 118.0, 116.0, 115.8, 57.5, 52.3, 49.8, 20.3. MS (ESI+) m/z: 344.17 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}FN_3O_2^+$ 344.1774 found 344.1769 Da.



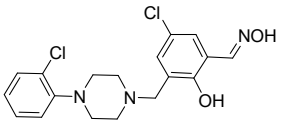
L83R5

5-chloro-3-((4-(2-fluorophenyl)piperazin-1-yl)methyl)-2-hydroxybenzaldehyde oxime (L83R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.19 g, 60%) but using **L83** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 11.58 (s, 1H), 8.32 (s, 1H), 7.49 (s, 1H), 7.28 (d, *J* = 14.2 Hz, 1H), 7.21 – 6.83 (m, 4H), 3.79 (s, 2H), 3.30-2.87 (m, 4H), 2.87-2.55 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 156.7, 154.7, 146.2, 139.5, 129.8, 125.9, 124.4, 123.3, 122.6, 120.2, 118.9, 116.0, 115.8, 58.7, 52.6, 50.2. MS (ESI+) m/z: 364.11(100.0%), 366.12(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{20}{}^{35}ClFN_3O_2^+$ 364.1228 found 364.1224 Da.



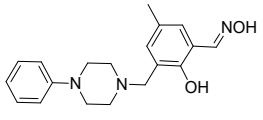
L84R3

3-((4-(2-chlorophenyl)piperazin-1-yl)methyl)-2-hydroxy-5-methylbenzaldehyde oxime (L84R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.22 g, 65%) but using **L84** and **R3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.28 (s, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 10.4 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (dd, *J* = 18.8, 11.3 Hz, 2H), 3.96 (s, 2H), 3.44-3.12 (m, 4H), 3.12-2.69 (m, 4H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 148.7, 148.4, 132.7, 130.5, 128.9, 128.6, 128.4, 127.7, 124.1, 120.6, 120.5, 118.0, 57.4, 52.3, 50.0, 20.3. MS (ESI+) m/z: 360.14(100.0%), 362.14(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{23}{}^{35}ClN_3O_2^+$ 360.1479 found 360.1475 Da.



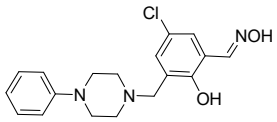
L84R5

5-chloro-3-((4-(2-chlorophenyl)piperazin-1-yl)methyl)-2-hydroxybenzaldehyde oxime (L84R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.32 g, 77%) but using **L84** and **R5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.71 – 9.89 (m, 1H), 8.31 (s, 1H), 7.44 (s, 1H), 7.35 (d, *J* = 5.1 Hz, 2H), 7.28-7.12 (m, 2H), 7.10 – 7.03 (m, 1H), 6.99 (dd, *J* = 13.3, 6.6 Hz, 1H), 3.79 (s, 2H), 3.36-3.05 (m, 4H), 2.97-2.63 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 148.6, 146.5, 130.7, 130.6, 130.1, 128.7, 127.7, 126.3, 124.1, 123.9, 120.51, 120.2, 58.4, 52.6, 50.6. MS (ESI+) m/z: 380.09(100.0%), 382.10(63.9%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{20}{}^{35}Cl_2N_3O_2^+$ 380.0933 found 380.0927 Da.



L85R3

2-hydroxy-5-methyl-3-((4-phenylpiperazin-1-yl)methyl)benzaldehyde oxime (L85R3): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.29 g, 88%) but using **L85** and **R3**. ^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 7.28 (d, *J* = 33.2 Hz, 4H), 7.08 – 6.54 (m, 3H), 4.56 – 3.95 (m, 2H), 3.81-2.70 (m, 8H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 151.0, 147.5, 131.5, 129.0, 128.9, 127.8, 127.1, 122.6, 119.6, 115.9, 115.7, 58.7, 52.5, 48.8, 20.3. MS (ESI+) m/z: 326.18 $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{19}H_{24}N_3O_2^+$ 326.1869 found 326.1863 Da.



L85R5

5-chloro-2-hydroxy-3-((4-phenylpiperazin-1-yl)methyl)benzaldehyde oxime (L85R5): The title compound was obtained in a manner similar to that used for **L7R5** as a white solid (0.28 g, 82%) but using **L85** and **R5**. ^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 7.52 (s, 1H), 7.39 (s, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.82 (t, *J* = 7.2 Hz, 1H), 3.99 (s, 2H), 3.39-3.10 (m, 4H), 3.06-2.71 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 151.1, 148.6, 130.3, 130.3, 128.9, 127.4, 126.5, 121.0, 119.2, 116.9, 115.7, 58.1, 52.8, 48.5. MS (ESI+) m/z: 346.12(100.0%), 348.13(32.0%) $[M+H]^+$. HRMS (ESI+) *m/z* calcd for $C_{18}H_{21}{}^{35}ClN_3O_2^+$ 346.1322 found 346.1317 Da.

2. Biological evaluation

2.1 General in vitro AChE screening information

The *in vitro* experiments were conducted with human acetylcholinesterase (hAChE, 20 U/mL, dissolved in 20 mM HEPES, pH 8.0, contain 0.1% TRITON X-100, from Sigma-Aldrich) serving as enzyme source. Organophosphates (DFP and paraoxon) were from commercial sources. Obidoxime, TMB-4 and HI-6 were synthesized according to the literature protocols[2-4]. A solution of oxime (10 mM) were prepared in water containing 10% acetic acid and 20% methanol and it was further diluted by PBS (0.1 M, pH=7.4) to the required concentrations. The final concentration of acetic acid was <1% and a control experiment revealed that acetic acid and methanol had no impact on the biological essay. Biological evaluation experiment were conducted in 96-well plate, the enzyme activity was measured by the time-dependent hydrolysis of acetylthiocholine (ATCh) in which the product (thiocholine) was detected by reaction with the Ellman's reagent DTNB and absorbance at 412 nm[5]. No oximolysis of ATCh by the tested oximes was detected, and the enzyme activity in the control remained constant during the experiment.

2.2 hAChE inhibition experiments with oximes

The procedure of inhibition experiments was as followings:

1) A stock solution of hAChE (dissolved in 20 mM HEPES, pH=8.0, contain 0.1% RITON X-100, from sigma) was diluted 2000-fold with PBS (0.1 M, pH=7.4, 0.1% BSA);

2) To 20 μL of the diluted enzyme, 20 μL oximes solutions (oxime final concentrations: 1, 4, 20, 100, 200 and 400 μM, each sample was measured duplicate in parallel in 96-well plate) were added and the mixture was incubated for 30 min at 25 ˚C. A positive control was run in parallel by adding 20 μL of PBS instead of oxime solution to the enzyme. A blank control was run in parallel

in which oxime and AChE were replaced by PBS.

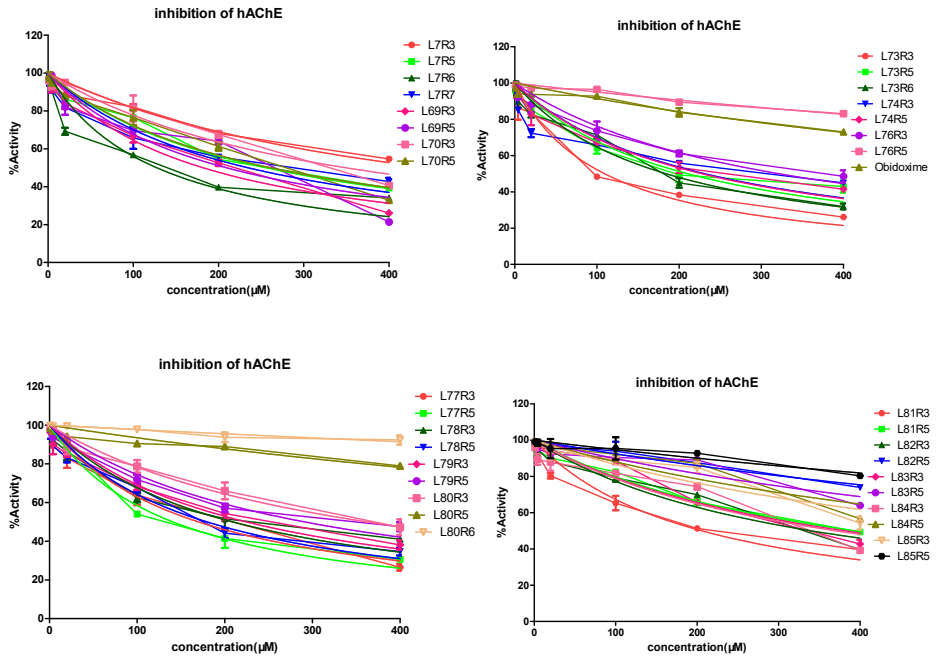
3) For each sample in 96-well plate, 30 μL of ATCh (3.0 mM, pH=7.4 PBS, 0.1% BSA) and 150 μL of DTNB (0.75 mM, pH=7.0 PBS) was added followed by incubation 37 ˚C for 20 min.

The reaction product was monitored immediately by testing the absorption value at 412 nm (0<OD<2.5).

Enzyme activity was calculated by using the formula: %Activity= 100*(S-B)/(P-B).

Where S=absorption value of tested sample; P = absorption value of positive control (100% activity), B= absorption value of blank control.

IC_{50} values were calculated by non-linear fitting using the standard IC_{50} equation: %Activity = $100*IC_{50}/(IC_{50}+[Ox])$. The non-linear fitting results of the tested compounds in the inhibition experiment were depicted by the following pictures.



2.3 hAChE reactivation experiments with oximes

The procedures of reactivation experiments were as followings:

1) A stock solution of hAChE (dissolved in 20 mM HEPES, pH=8.0, contain 0.1% RITON X-100, from sigma) was diluted 2000-fold with PBS (0.1 M, pH=7.4, 0.1% BSA). The concentrations of various organophosphates were determined through a pre-experiment that was similar to the inhibition experiment, aiming to achieve an inhibition plateau ranging from 90% to 97%. The final concentration of DFP and paraoxon in the incubation mixture were $2*10^{-6}$ M and $3*10^{-6}$M.

2) The diluted hAChE (20 μL) was incubated with different organophosphates (20 μL) at 25 °C for 15 min. Then the inhibited enzyme was incubated with oximes (20 μL, final concentrations of oximes were 100 μM and 10 μM) at 37 °C for 30 min (t = 0 corresponds to the incubation of the inhibited enzyme with oxime).

3) In each well of the 96-well plate, 30 μL of ATCh (3.0 mM, pH=7.4 PBS, 0.1% BSA) and 150 μL of DTNB (0.75 mM, pH=7.0 PBS) was added followed by incubation for 20 minutes (the final volume of the reactivation mixture was 240 μL and the final ATCh concentration was 0.375 mM).

The reaction product was monitored immediately by measuring the absorbance at 412 nm (0<OD<2.5).

Blank samples were run in parallel and consisted of: (a) A positive control (P): uninhibited enzyme (20 μL) was used instead of the inhibited enzyme; (b) a negative control (N): PBS (20 μL, 0.1 M, pH 7.4, 0.1% BSA) was used instead of oximes. %Reactivation was calculated using the formula: %Reactivation 100*(S-N)/(P-N).

2.4 Determination of reactivation kinetics

The procedures of reactivation kinetics experiments were as followings:

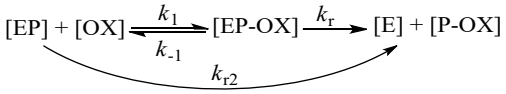
1) A stock solution of hAChE (dissolved in 20 mM HEPES, pH=8.0, contain 0.1% RITON X-100, from sigma) was diluted 2000-fold with PBS (0.1 M, pH=7.4, 0.1% BSA). The diluted hAChE (20 μL) was incubated with different organophosphates (20 μL) at 25 °C for 15 min to attain an inhibition plateau between 90% to 97%.

2) Different oximes at different concentrations (20 μL) was added, and 30 μL of ATCh (3.0 mM, pH=7.4 PBS, 0.1% BSA) and 150 μL of DTNB (0.75 mM, pH=7.0 PBS) were added immediately (the final volume of the reactivation mixture was 240 μL and the final ATCh concentration was 0.375 mM). The final concentrations of the oximes were presented in **Table S1**.

3) The reaction product was promptly monitored by measuring the absorbance at 412 nm (0<OD<2.8) at 37 °C for a period of 120 min (t = 0 corresponds to the incubation of the inhibited enzyme with oxime). The absorbance values were measured at 5 or 10 minute intervals.

Blank samples were run in parallel and consisted of: (a) A positive control (P): uninhibited enzyme (20 μL) was used instead of the inhibited enzyme; (b) a negative control (N): PBS (20 μL, 0.1 M, pH 7.4, 0.1% BSA) was used instead of oximes.

The observed first-order rate constant $\boldsymbol{k_{obs}}$ for each oxime concentration, the dissociation constant $\boldsymbol{K_D}$ of inhibited enzyme-oxime conjugates (**EP-OX**) and the maximal reactivation rate constant $\boldsymbol{k_r}$ were calculated by non-linear fitting using the standard oxime concentration dependent reactivation equation derived from the following scheme. [6]



$$\%\text{Reactivation} = 100*(1-e^{-k_{obs}*t})$$

$$k_{obs} = k_r[OX]/(K_D+[OX])$$

In this scheme, EP is the phosphylated enzyme, [EP-OX] is the reversible Michaelis-type complex between EP and the oxime [OX], E is the active enzyme and P-OX the phosphylated oxime. K_D is equal to the ratio $(k_{-1}+ \boldsymbol{k_r})/k_1$, and it typically approximates the dissociation constant of the [EP-OX] complex, where from it follows that: $\boldsymbol{k_{r2}} = \boldsymbol{k_r} / K_D$.

To provide further details, we conducted a reactivation experiment using different oxime concentrations and measured enzyme activity at various reactivation intervals. Basically, the concentration of the reactivated AChE is proportional to the enzyme activity, k_{obs} was calculated from the continuous recording of d[S]/dt, the velocity of substrate hydrolysis (v) can be described as pseudo-first-order process of reactivation, , as shown in Eq. 1.

$$\ln\left(\frac{v_0 - v_t}{v_0 - v_i}\right) = -k_{obs}t \qquad \mathbf{1}$$

In which v_t represents velocity at time t, v_0 represents maximum velocity (positive control) and v_i represents minimum velocity (negative control). Alternatively, for each oxime concentration, k_{obs} value was determined using linear regression analysis, applying Eq. 2.

$$v_t = v_0(1 - e^{-k_{obs}t}) \qquad \mathbf{2}$$

Integration of (2) results in Eq. 3.

$$-d[S] = \int_0^t v dt = v_o t + \frac{v_o}{k_{obs}}(e^{-k_{obs}t} - 1) \qquad \mathbf{3}$$

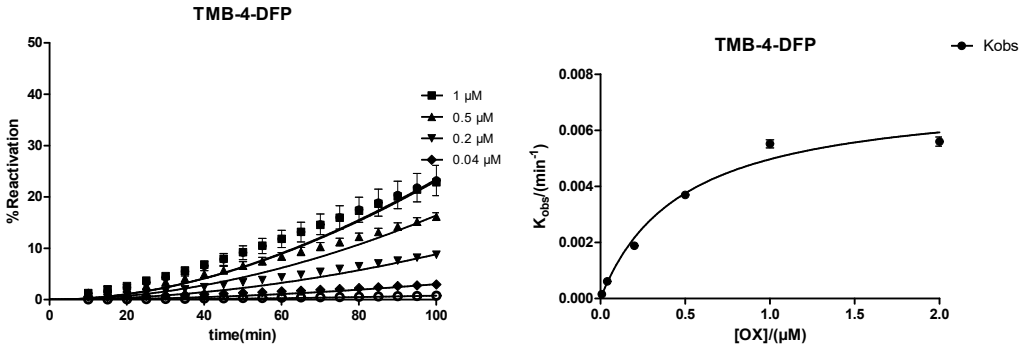
which was used for non-linear regression analysis of the data points obtained from individual oxime concentrations.

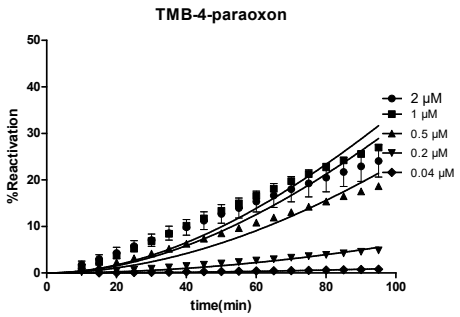
Concentrations of the oximes used to determine the concentration dependence of the apparent reactivation rate $\boldsymbol{k_{obs}}$ for the reactivation of OPs inhibited *h*AChE were show in **Table S1**.

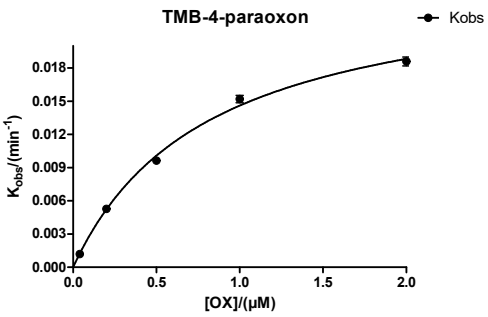
Table S1. Oxime concentrations (μM) for determination of the observed first-order rate constant k_{obs}.

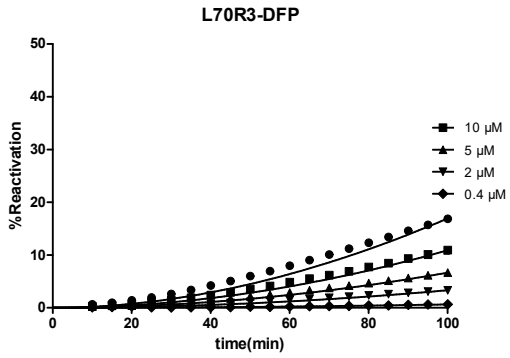
oximes	DFP-hAChE	paraoxon-hAChE
Obidoxime	20-10-5-2-0.4-0.08	20-10-5-2-0.4-0.08
TMB-4	2-1-0.5-0.2-0.04	2-1-0.5-0.2-0.04
L7R3	2-1-0.5-0.2-0.04	2-1-0.5-0.2-0.04
L7R5	20-10-5-2-0.4-0.08	2-1-0.5-0.2-0.04
L7R6	20-10-5-2-0.4-0.08	2-1-0.5-0.2-0.04
L70R3	20-10-5-2-0.4-0.08	20-10-5-2-0.4-0.08
L70R5	20-10-5-2-0.4-0.08	10-5-2-1-0.4-0.08
L73R3	20-10-5-2-0.4-0.08	10-5-2-1-0.4-0.08
L73R5	20-10-5-2-0.4-0.08	10-5-2-1-0.4-0.08
L73R6	20-10-5-2-0.4-0.08	10-5-2-1-0.4-0.08
L74R3	20-10-5-2-0.4-0.08	20-10-5-2-0.4-0.08
L74R5	20-10-5-2-0.4-0.08	10-5-2-1-0.4-0.08
L77R5	200-100-50-20-4-0.8	10-5-2-1-0.4-0.08
L80R3	200-100-50-20-4-0.8	10-5-2-1-0.4-0.08

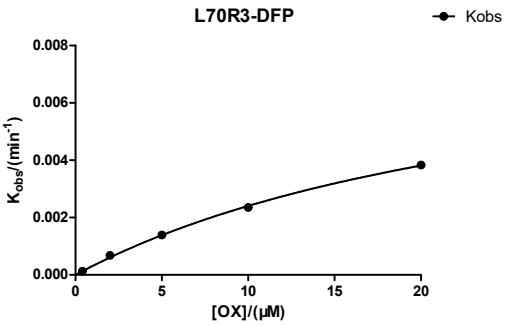
Reactivation of OP-inhibited hAChE: Plot of k_{obs} *vs* obidoxime, HI-6 and new synthesized oximes.

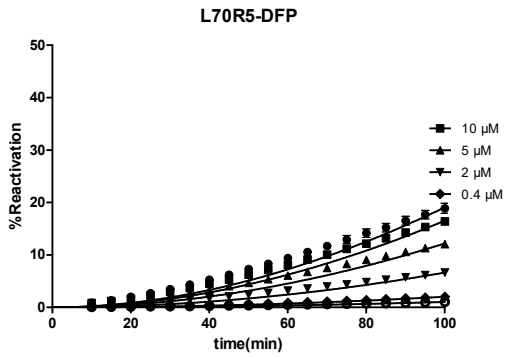


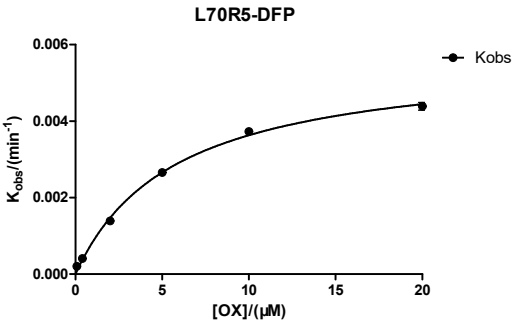

TMB-4-paraoxon
%Reactivation
time(min)
2 μM
1 μM
0.5 μM
0.2 μM
0.04 μM

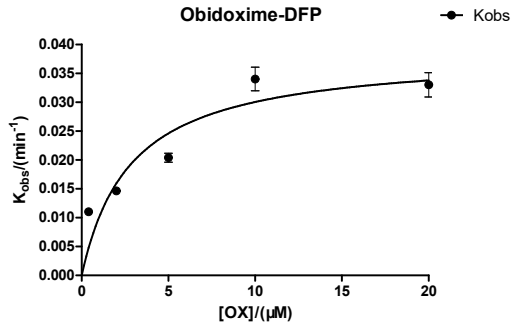

TMB-4-paraoxon
Kobs
K_{obs}/(min^{-1})
[OX]/(μM)

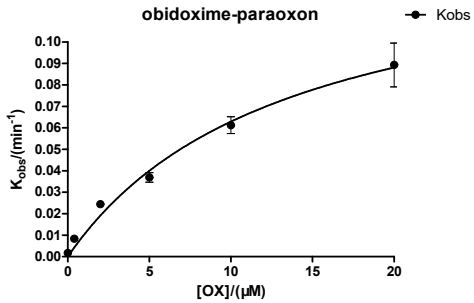

L70R3-DFP
%Reactivation
time(min)
10 μM
5 μM
2 μM
0.4 μM

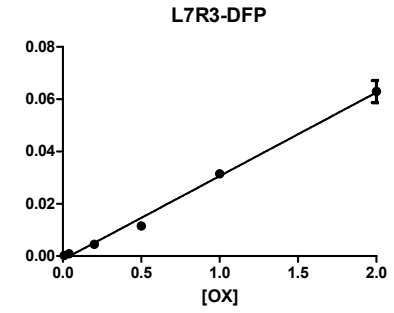

L70R3-DFP
Kobs
K_{obs}/(min^{-1})
[OX]/(μM)

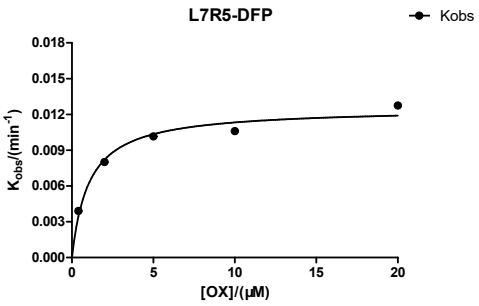

L70R5-DFP
%Reactivation
time(min)
10 μM
5 μM
2 μM
0.4 μM

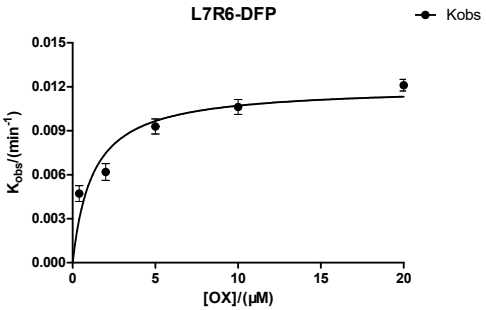

L70R5-DFP
Kobs
K_{obs}/(min^{-1})
[OX]/(μM)

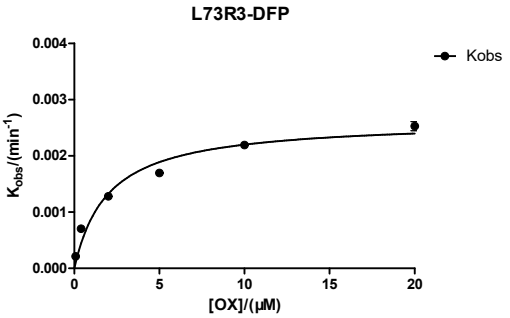

Obidoxime-DFP
Kobs
K_{obs}/(min^{-1})
[OX]/(μM)

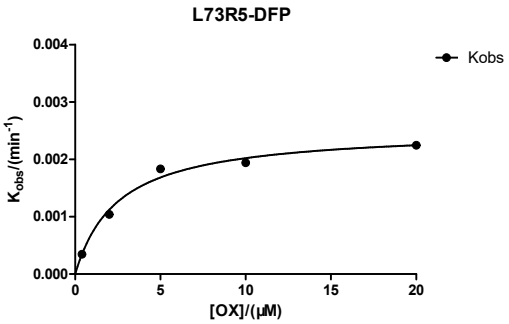

obidoxime-paraoxon
Kobs
K_{obs}/(min^{-1})
[OX]/(μM)

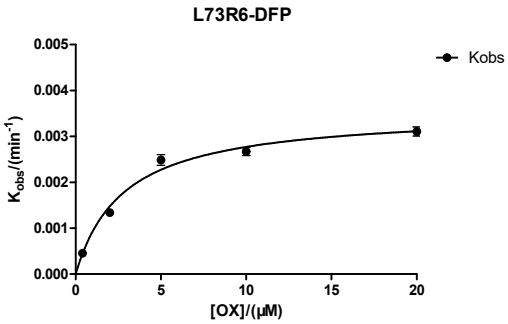

L7R3-DFP
0.08
0.06
0.04
0.02
0.00
0.0
0.5
1.0
1.5
2.0
[OX]

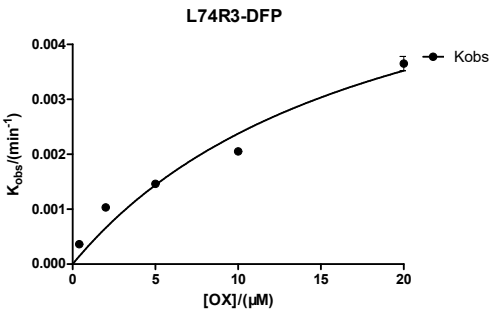

L7R5-DFP
Kobs
0.018
0.015
0.012
0.009
0.006
0.003
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

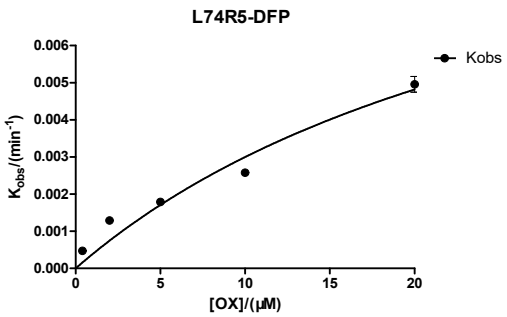

L7R6-DFP
Kobs
0.015
0.012
0.009
0.006
0.003
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

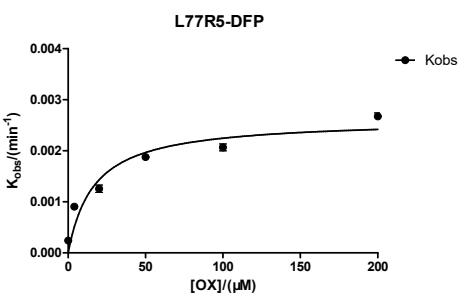

L73R3-DFP
Kobs
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

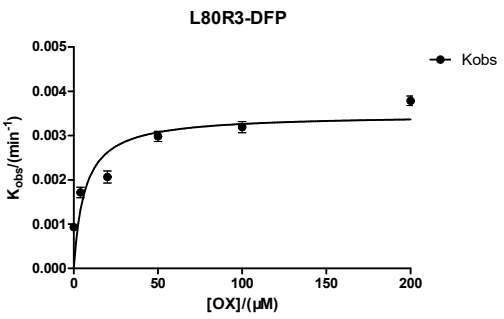

L73R5-DFP
Kobs
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

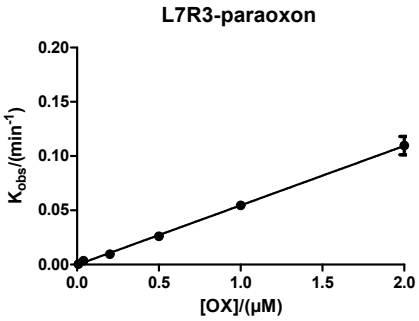

L73R6-DFP
Kobs
0.005
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

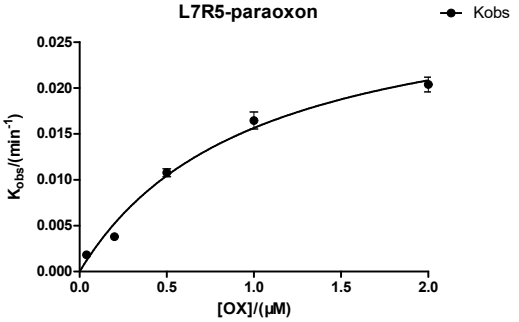

L74R3-DFP
Kobs
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

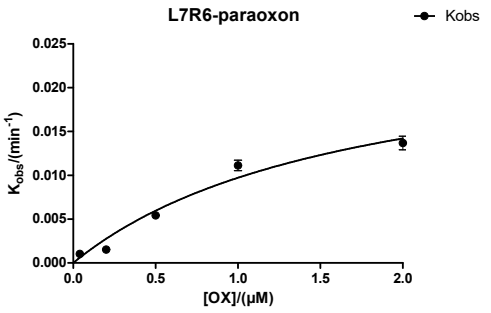

L74R5-DFP
Kobs
0.006
0.005
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
5
10
15
20
[OX]/(μM)

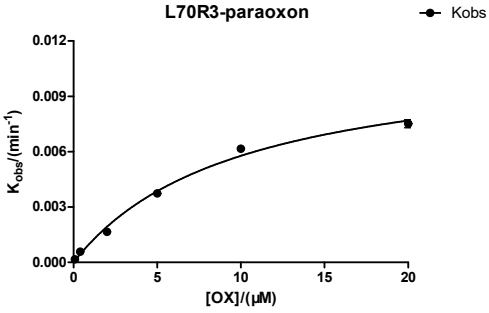

L77R5-DFP
Kobs
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
50
100
150
200
[OX]/(μM)

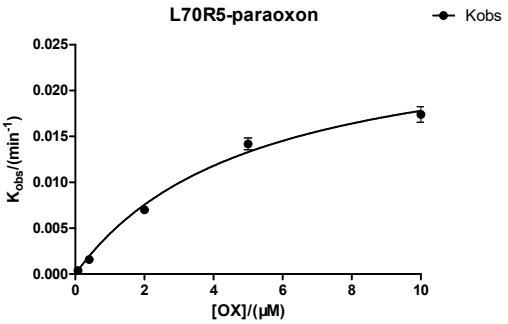

L80R3-DFP
Kobs
0.005
0.004
0.003
0.002
0.001
0.000
$K_{obs}/(min^{-1})$
0
50
100
150
200
[OX]/(μM)

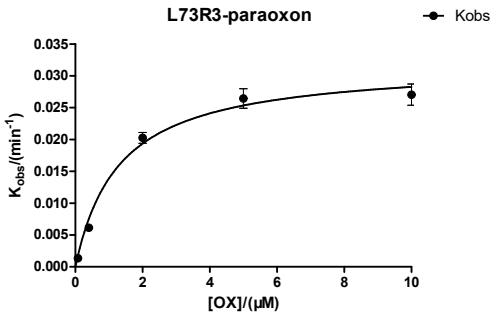

L7R3-paraoxon
$K_{obs}/(min^{-1})$
0.20
0.15
0.10
0.05
0.00
0.0
0.5
1.0
1.5
2.0
[OX]/(μM)

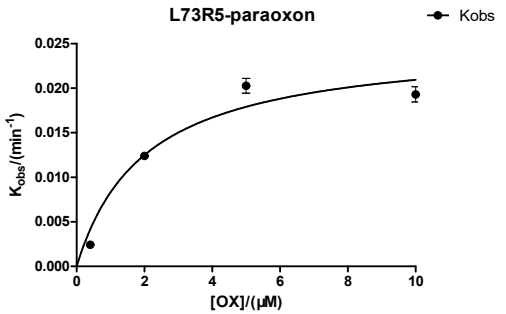

L7R5-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.025
0.020
0.015
0.010
0.005
0.000
0.0
0.5
1.0
1.5
2.0
[OX]/(μM)

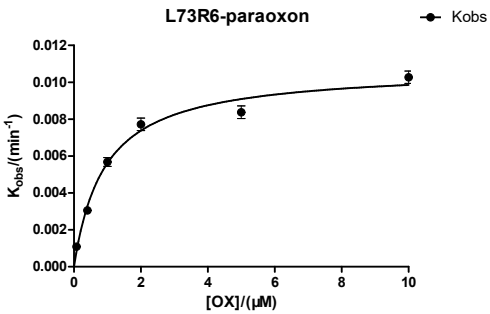

L7R6-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.025
0.020
0.015
0.010
0.005
0.000
0.0
0.5
1.0
1.5
2.0
[OX]/(μM)

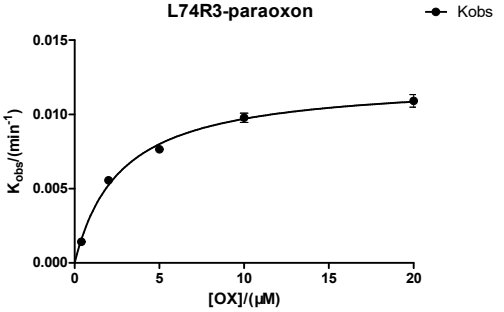

L70R3-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.012
0.009
0.006
0.003
0.000
0
5
10
15
20
[OX]/(μM)

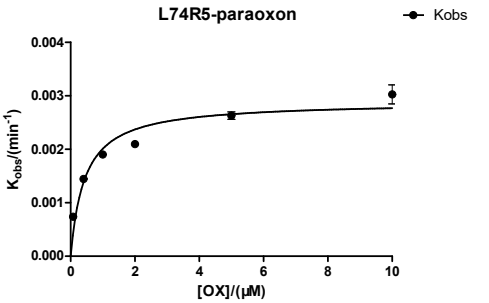

L70R5-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.025
0.020
0.015
0.010
0.005
0.000
0
2
4
6
8
10
[OX]/(μM)

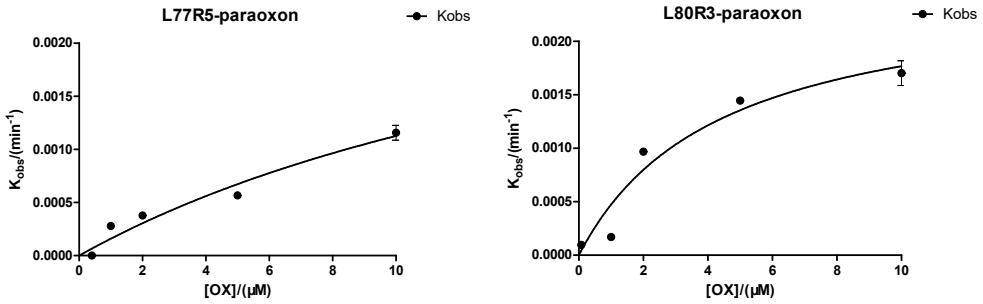

L73R3-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
0
2
4
6
8
10
[OX]/(μM)


L73R5-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.025
0.020
0.015
0.010
0.005
0.000
0
2
4
6
8
10
[OX]/(μM)


L73R6-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
2
4
6
8
10
[OX]/(μM)


L74R3-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.015
0.010
0.005
0.000
0
5
10
15
20
[OX]/(μM)


L74R5-paraoxon
Kobs
$K_{obs}/(min^{-1})$
0.004
0.003
0.002
0.001
0.000
0
2
4
6
8
10
[OX]/(μM)



References

[1] Edward JP, Brennie EH Jr, George MS. Pyridinium Aldoximes. *J. Org. Chem.* 1958, *23*, 714-717. doi: 10.1021/jo01099a019.

[2] Hsiao LYY, Getzville NY, Musallam HA, Damascus Md. Bis-methylene ether pyridinium compound preparation. *U.S. Patent.* 5130438 1992.

[3] Eddolls J, Mccormack P, Hodgson A. Process for the manufacture of HI-6 dimethanesulfonate. *H.K. Patent.* 1137422, 2013.

[4] Wei Z, Liu YQ, Wang SZ, Yao L, Nie HF, Wang YA, Liu XY, Zheng ZB, Li S. Conjugates of salicylaldoximes and peripheral site ligands: Novel efficient nonquaternary reactivators for nerve agent-inhibited acetylcholinesterase. *Bioorg Med Chem.* 2017; 25(16):4497-4505. doi: 10.1016/j.bmc.2017.06.041.

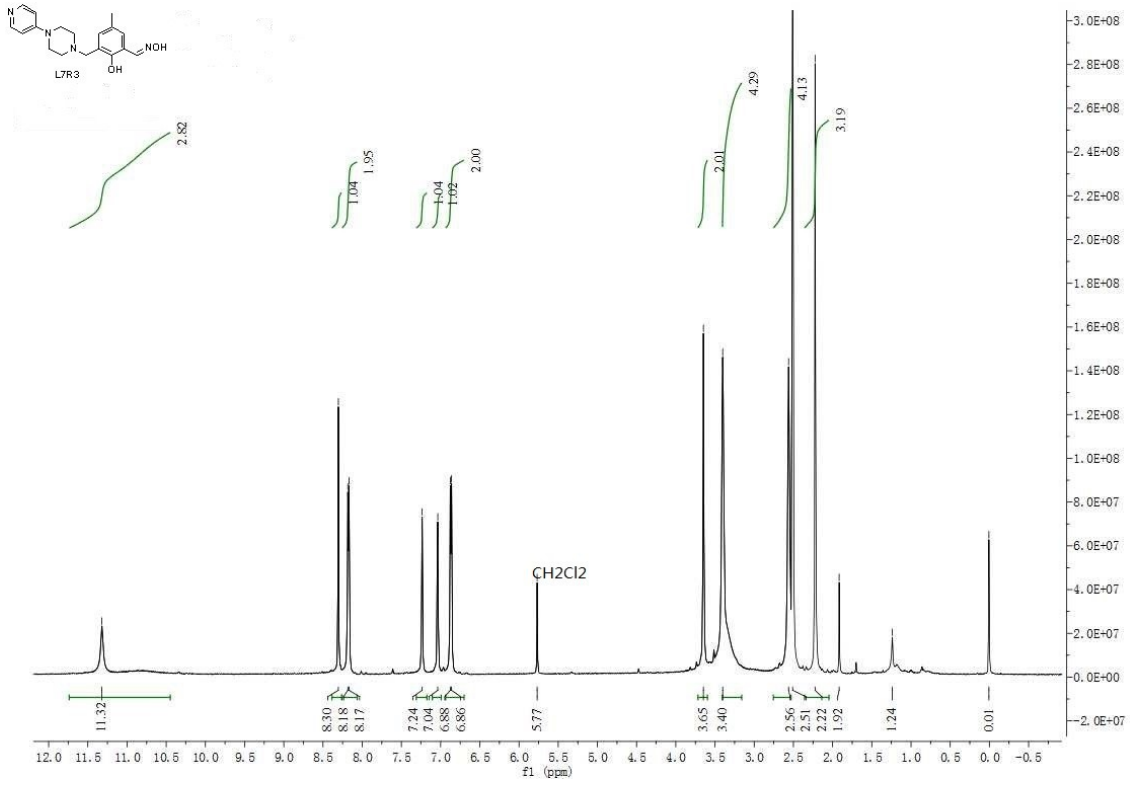
[5] Ellman GL, Courtney KD, Andres V Jr, Feather-stone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem Pharmacol.* 1961; 7:88-95.

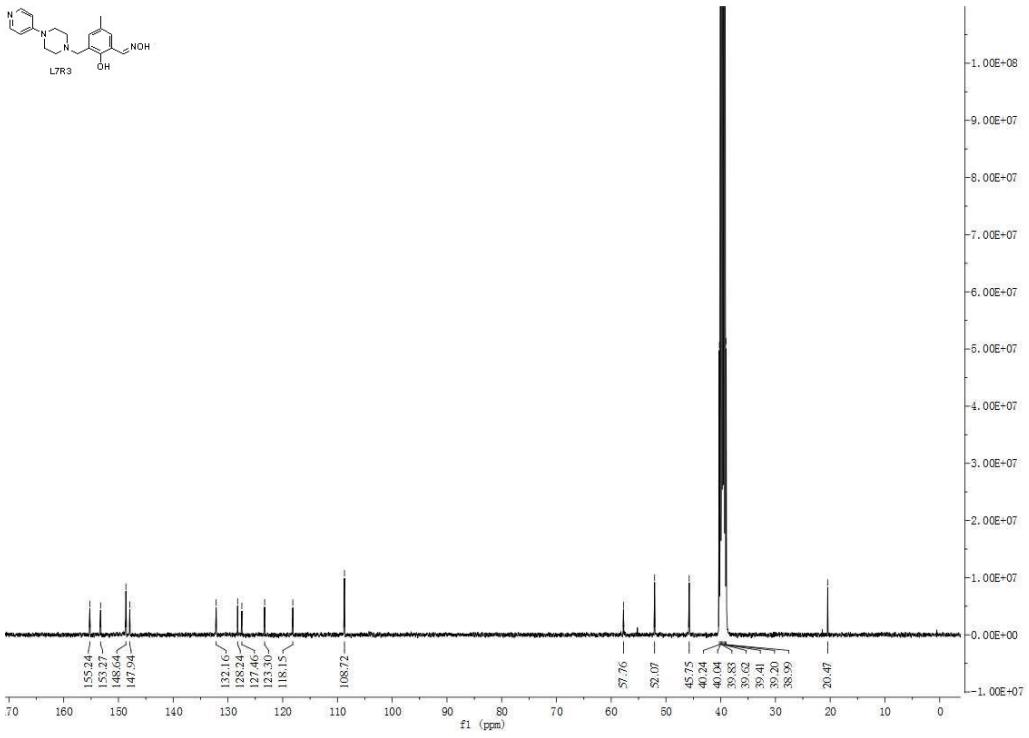
[6] Worek F, Thiermann H, Szinicz L, Eyer P. Kinetic analysis of interactions between human acetylcholinesterase, structurally different organophosphorus compounds and oximes. *Biochem Pharmacol.* 2004; 68(11):2237-2248.

[7] Gray AP. Design and structure-activity relationships of antidotes to organophosphorus anticholinesterase agents. *Drug Metab Rev.* 1984;15(3):557-589.

Copies of ^{1}H NMR, ^{13}C NMR and HRMS spectra

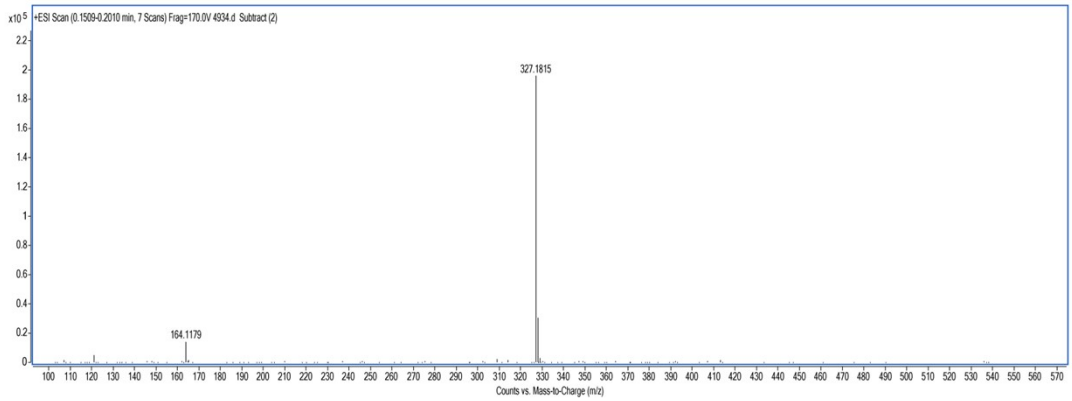
L7R3


L7R3
NOH
OH
CH2Cl2
f1 (ppm)

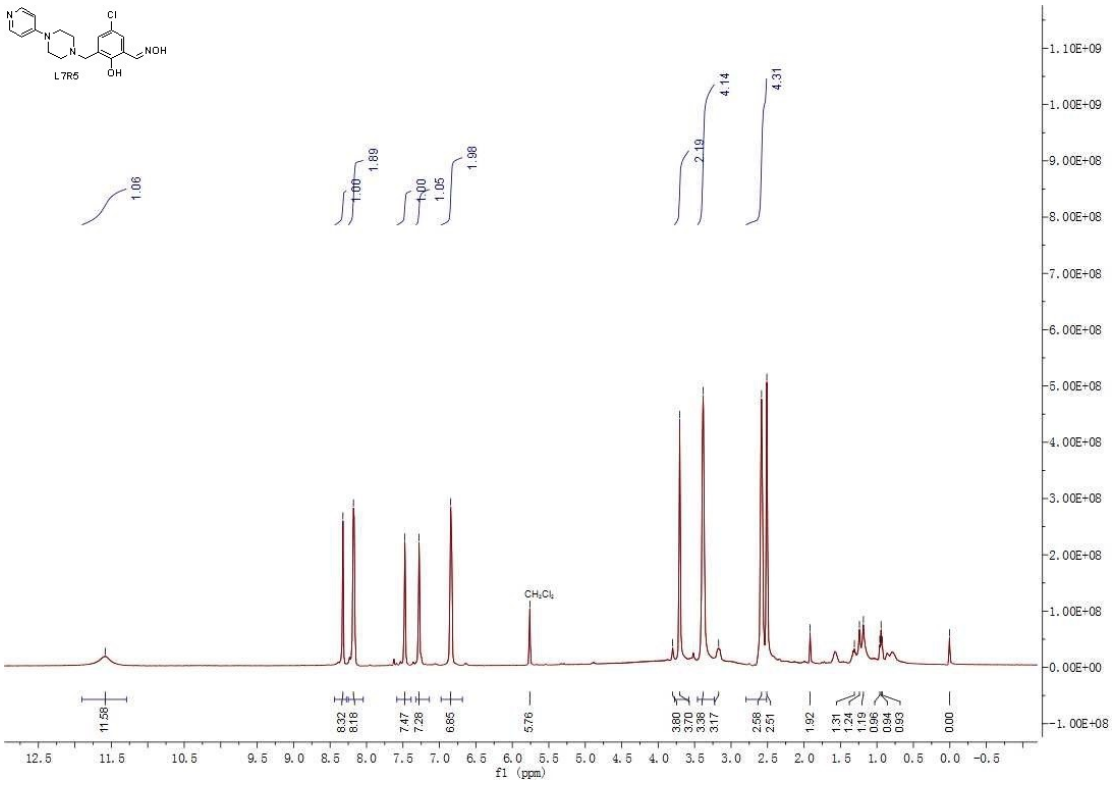

L7R3
NOH
OH
f1 (ppm)

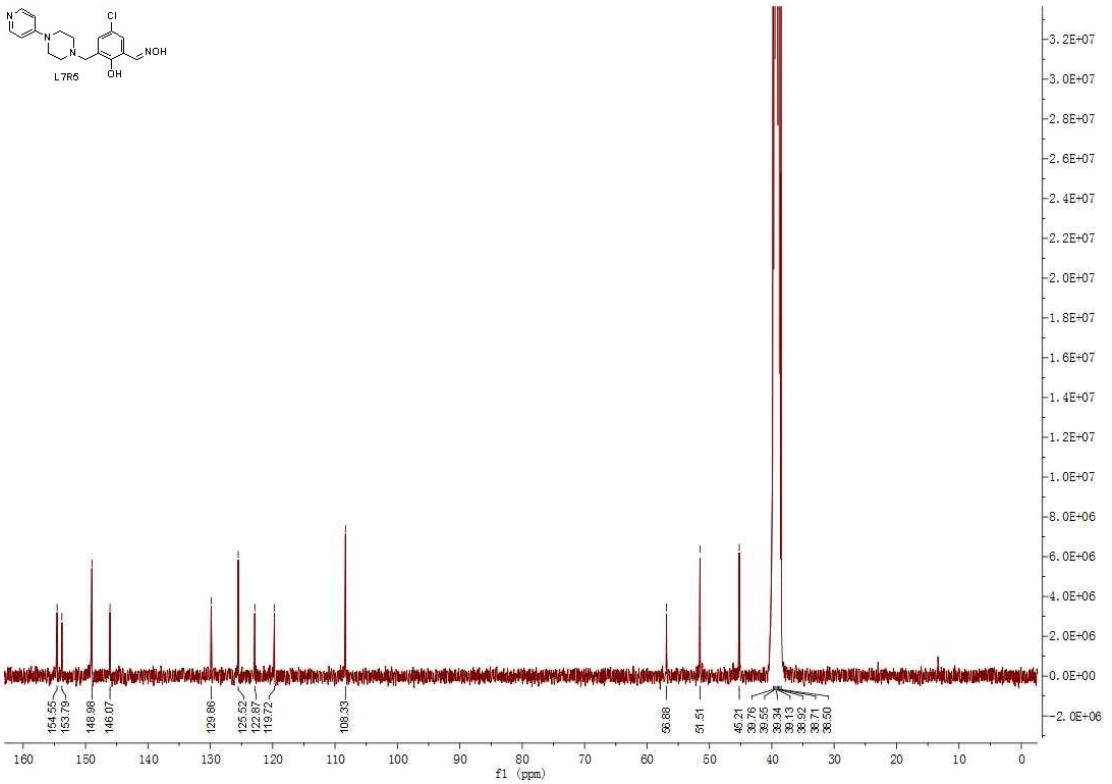
Data Filename	4934.d	**Sample Name**	130
Instrument Name	TOF G6230A	**Acquired Time**	2019-07-29
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



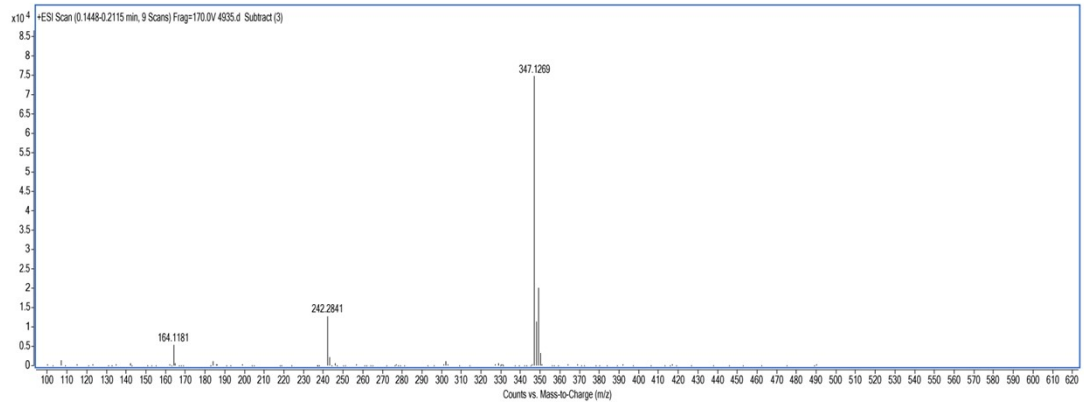
L7R5


L7R5
1.06
1.00
1.89
1.00
1.05
1.98
2.19
4.14
4.31
CH2Cl2
11.58
8.32
8.18
7.47
7.29
6.85
5.76
3.80
3.70
3.38
3.17
2.58
2.51
1.92
1.31
1.24
1.19
0.96
0.94
0.93
0.00
f1 (ppm)

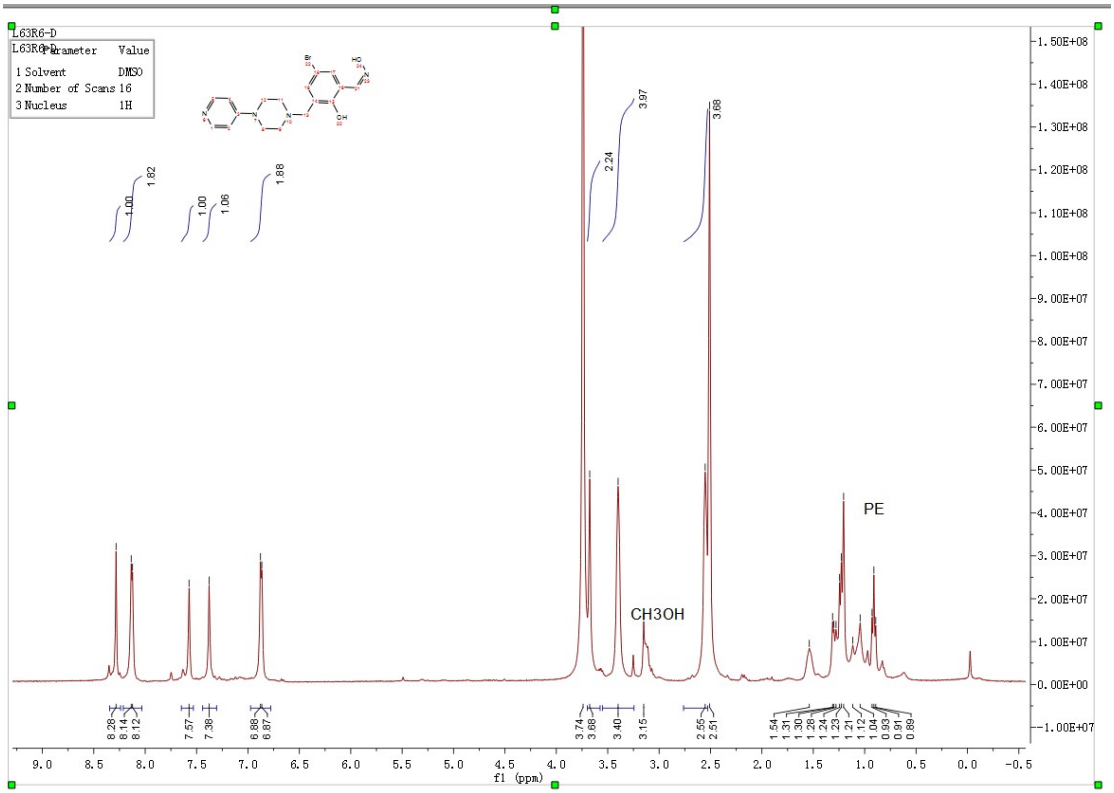

L7R5
154.55
153.79
148.98
146.07
129.86
125.52
122.87
119.72
108.33
66.88
51.51
46.21
39.76
39.55
39.34
39.13
38.92
38.71
38.50
f1 (ppm)

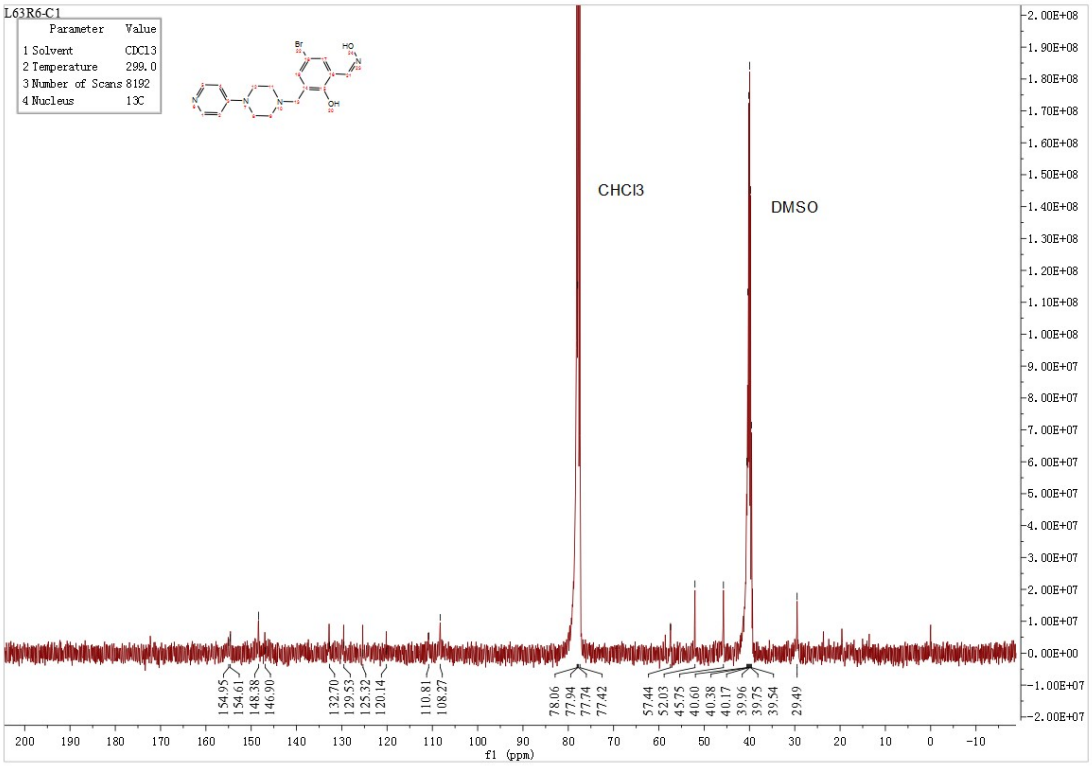
Data Filename	4935.d	**Sample Name**	131
Instrument Name	TOF G6230A	**Acquired Time**	2019-07-29
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



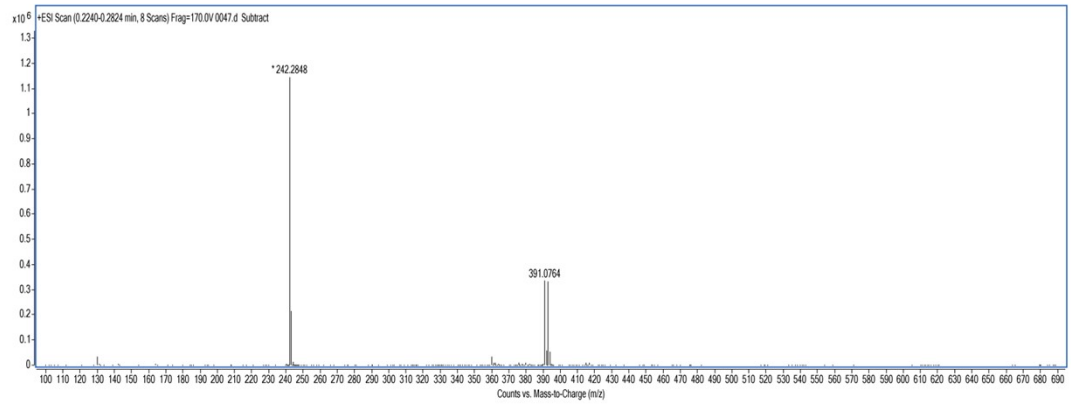
L7R6



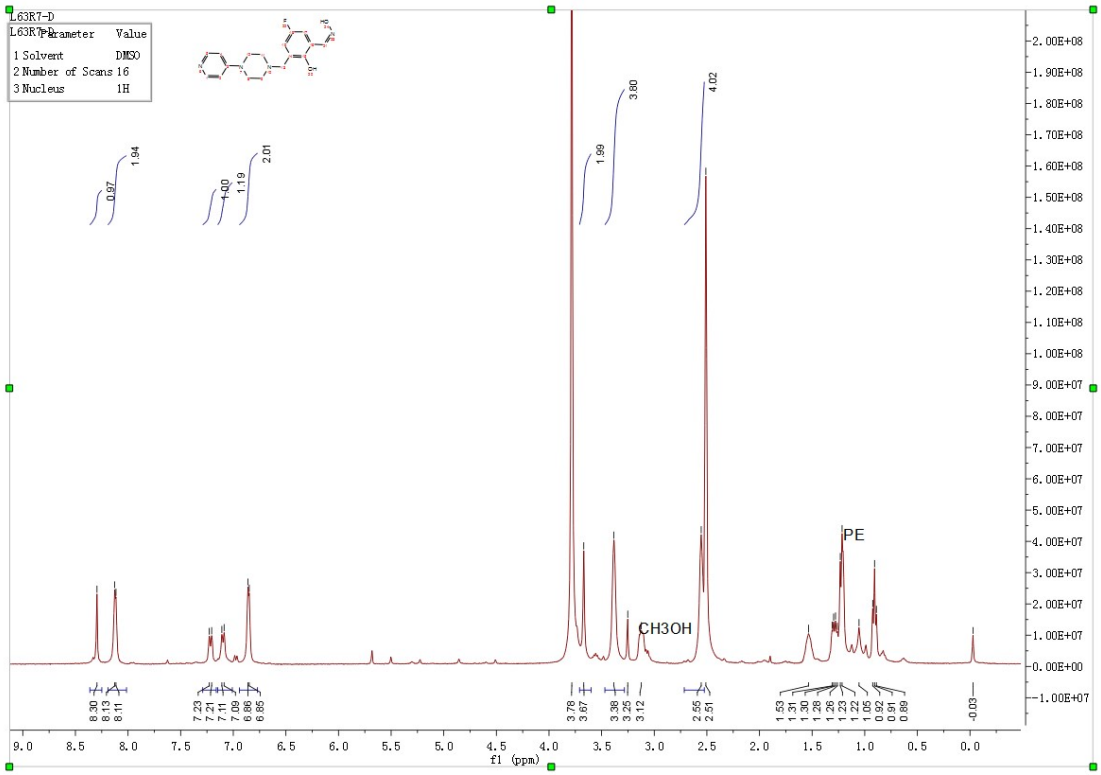


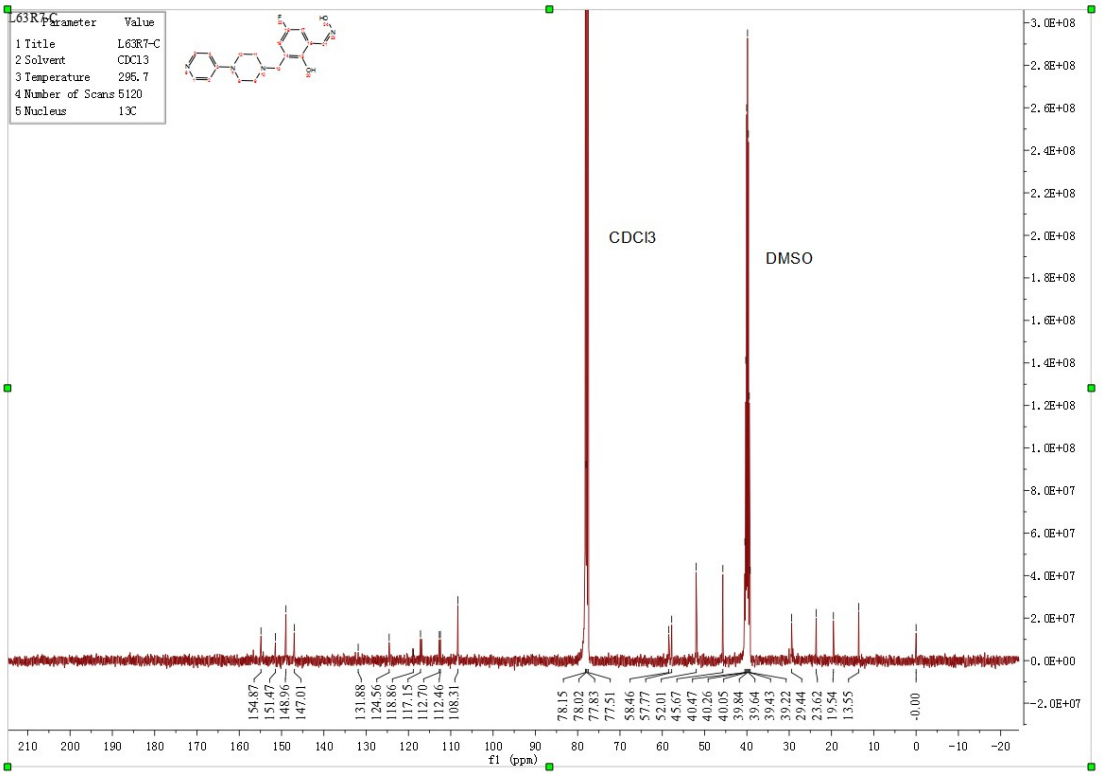
Data Filename	0047.d	**Sample Name**	L63R6
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

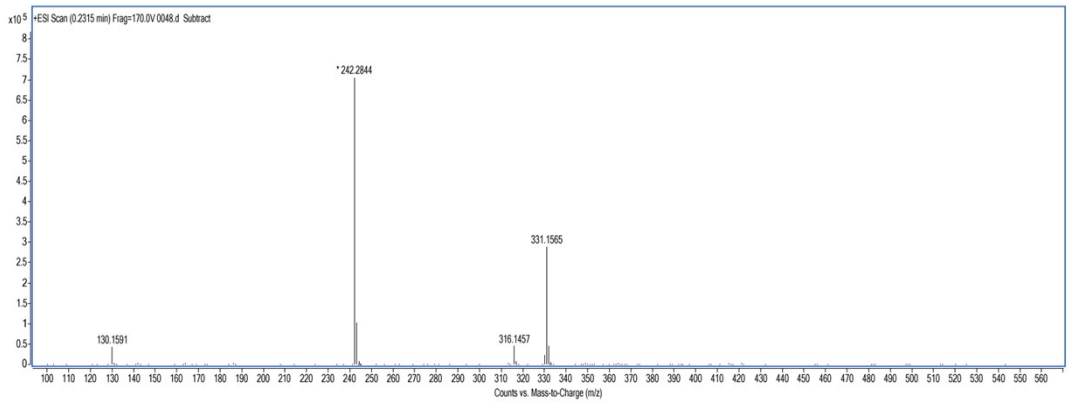


L7R7

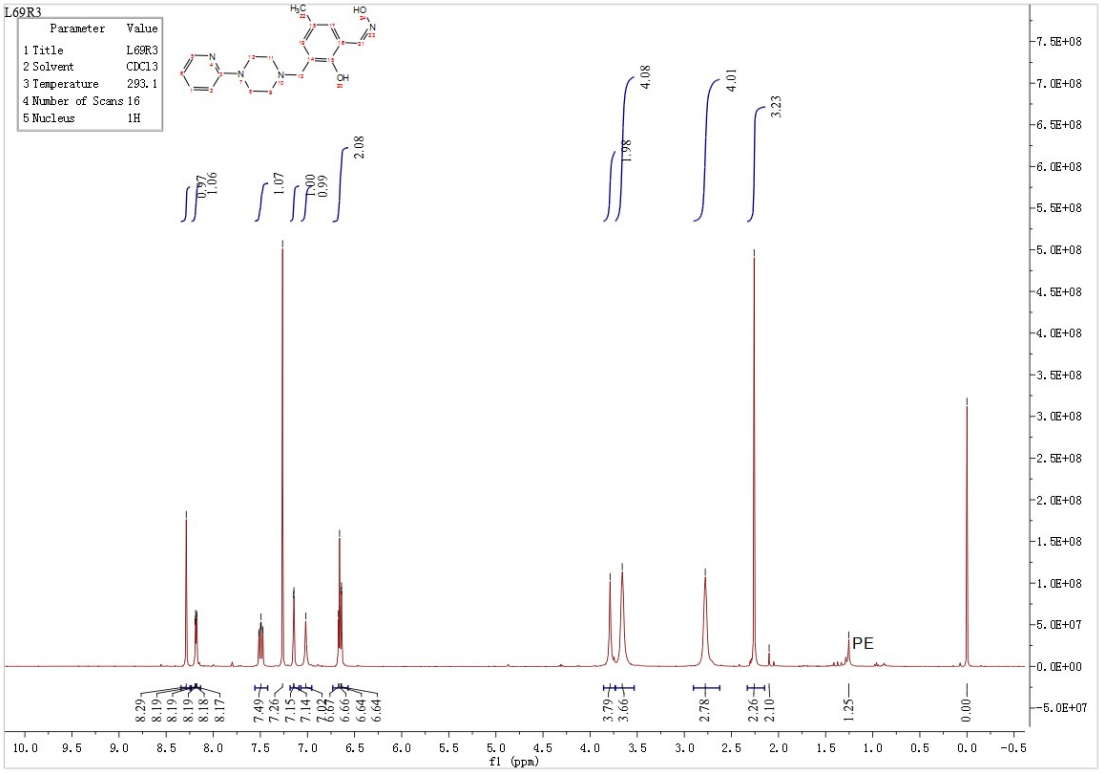

L63R7-D
Parameter Value
1 Solvent DMSO
2 Number of Scans 16
3 Nucleus 1H
PE
CH3OH
f1 (ppm)

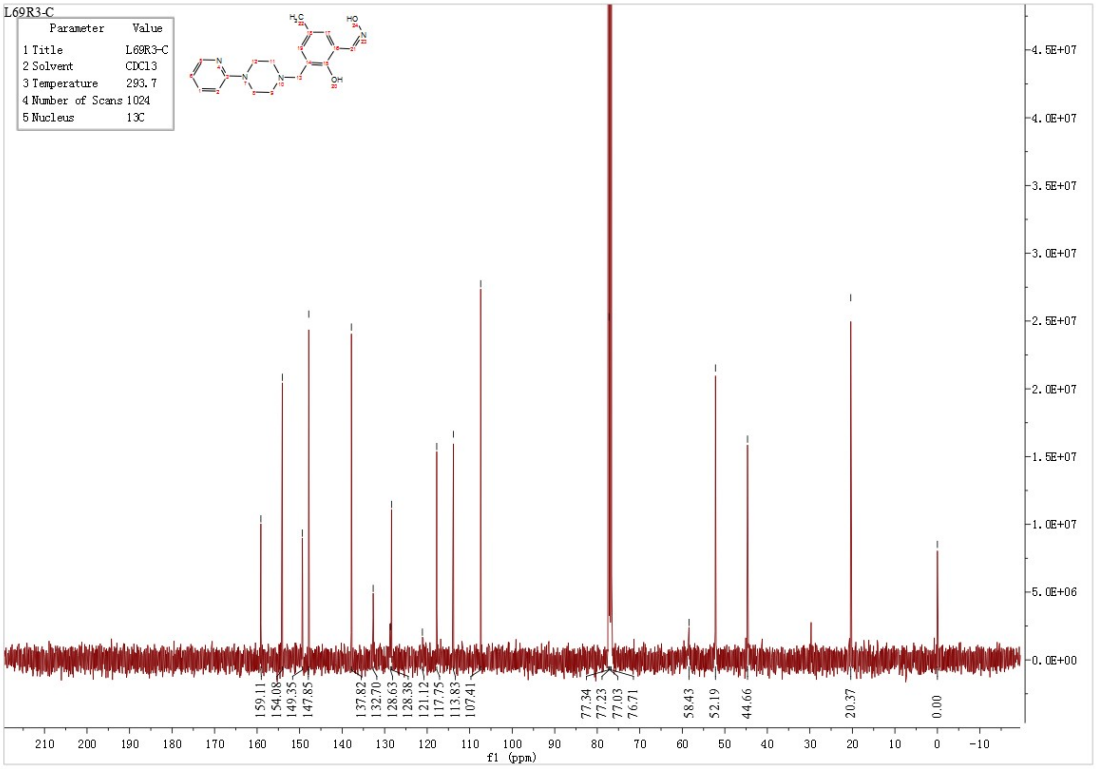

L63R7-C
Parameter Value
1 Title L63R7-C
2 Solvent CDCl3
3 Temperature 295.7
4 Number of Scans 5120
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0048.d	**Sample Name**	L63R7
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



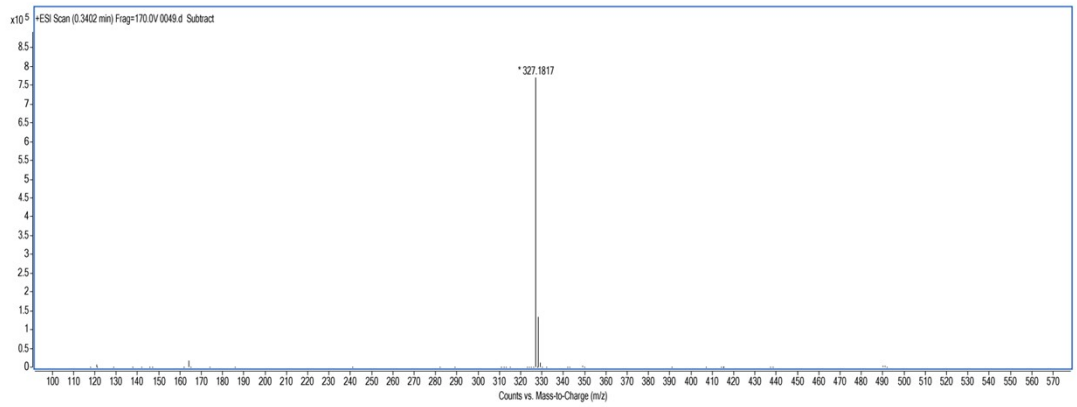
L69R3



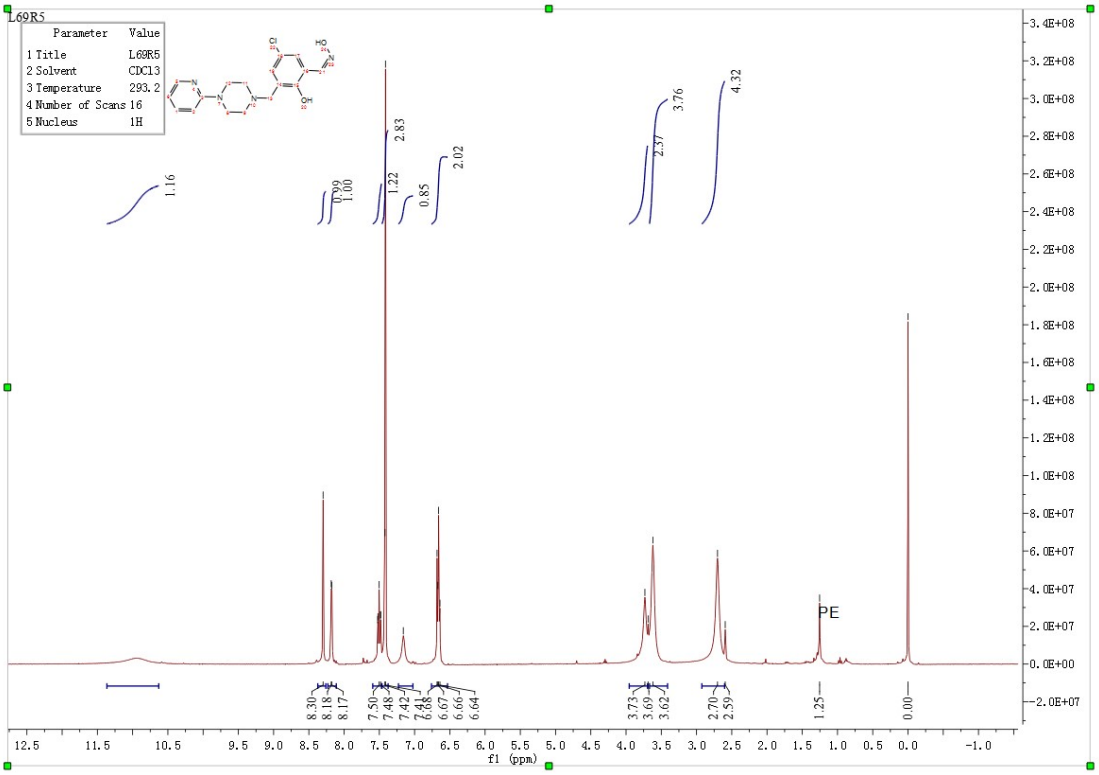


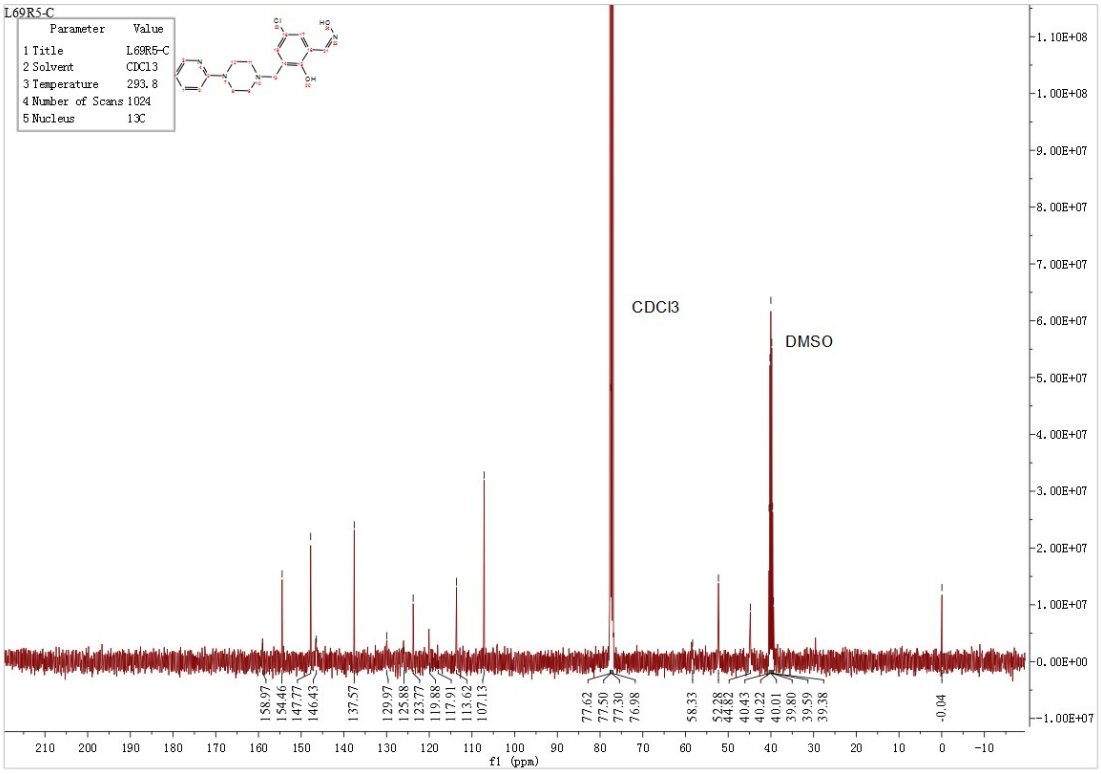
Data Filename	0049.d	**Sample Name**	L69R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



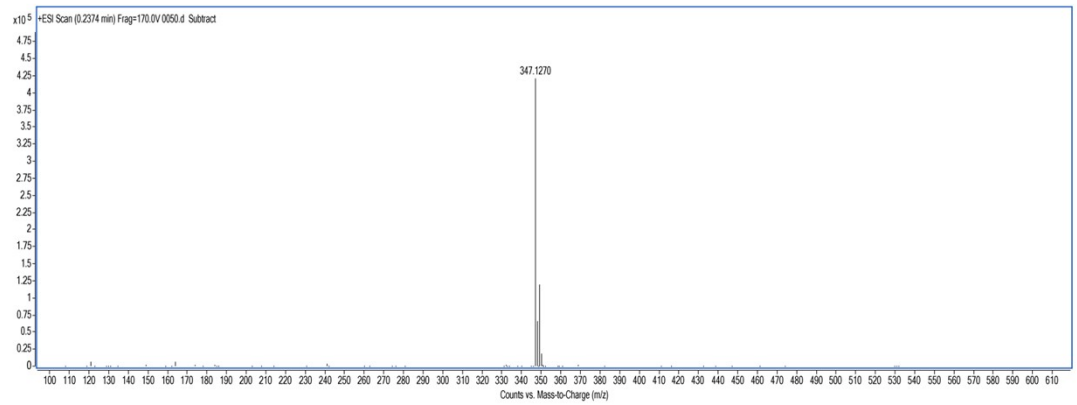
L69R5


L69R5
Parameter Value
1 Title L69R5
2 Solvent CDCl3
3 Temperature 293.2
4 Number of Scans 16
5 Nucleus 1H
PE
f1 (ppm)

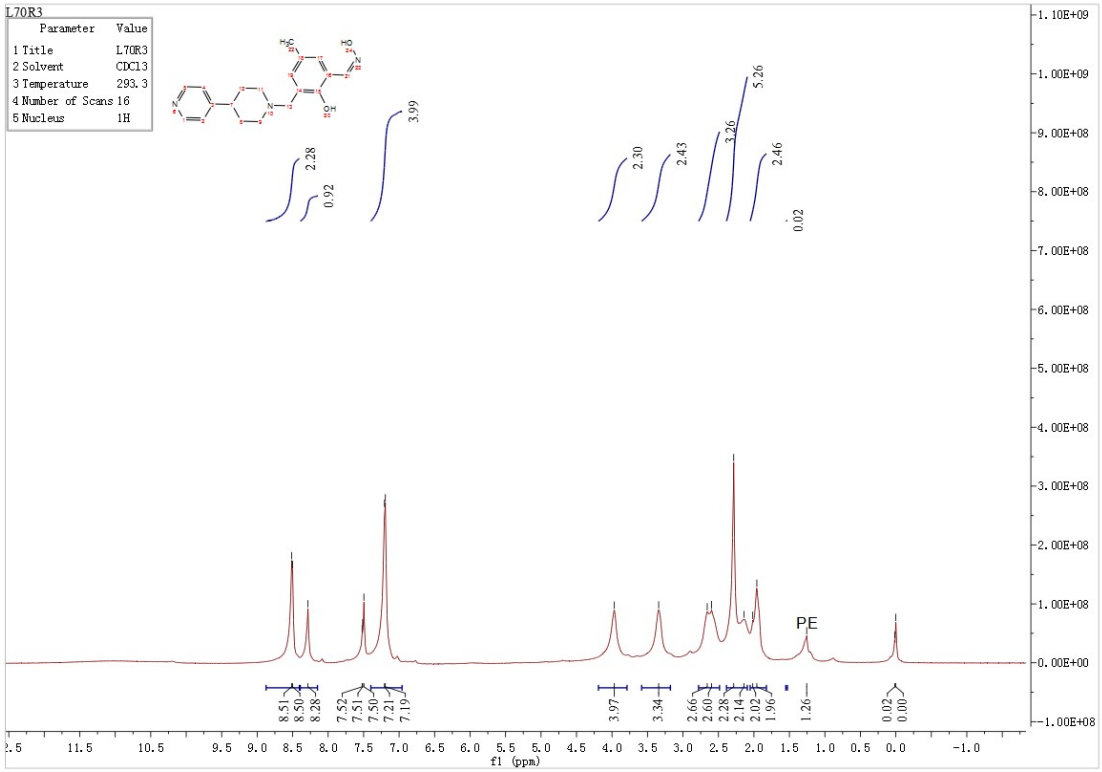

L69R5-C
Parameter Value
1 Title L69R5-C
2 Solvent CDCl3
3 Temperature 293.8
4 Number of Scans 1024
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

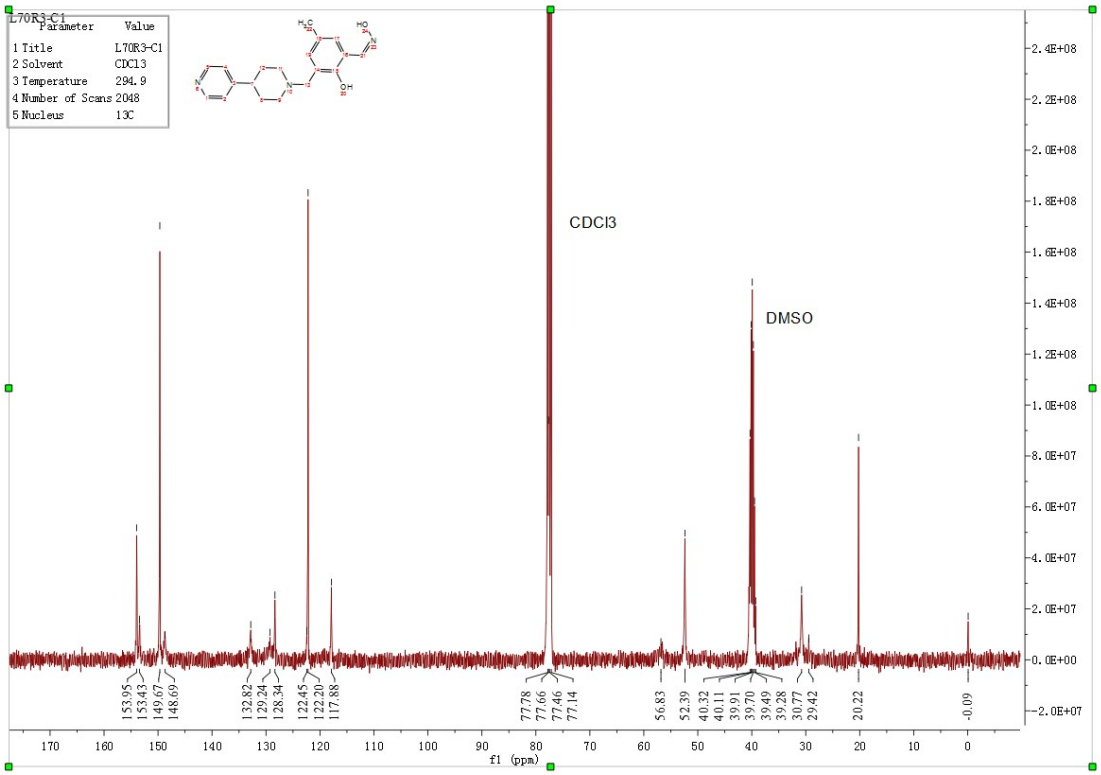
Data Filename	0050.d	**Sample Name**	L69R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

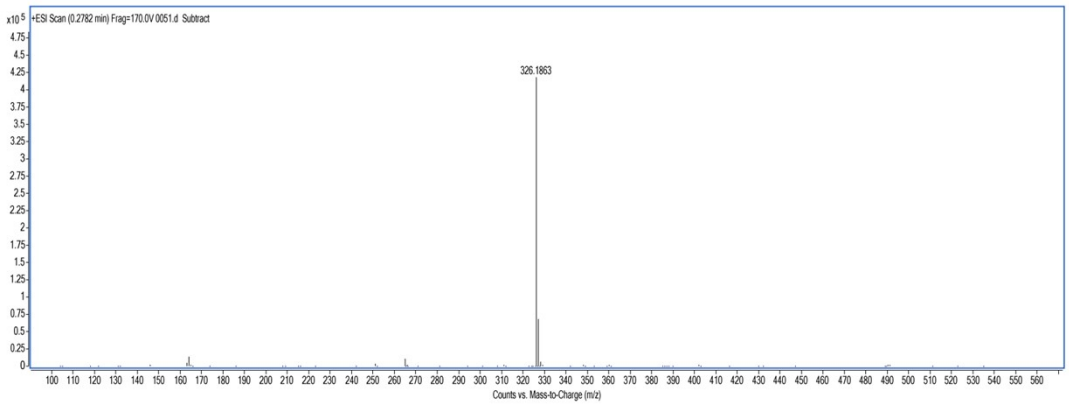


L70R3

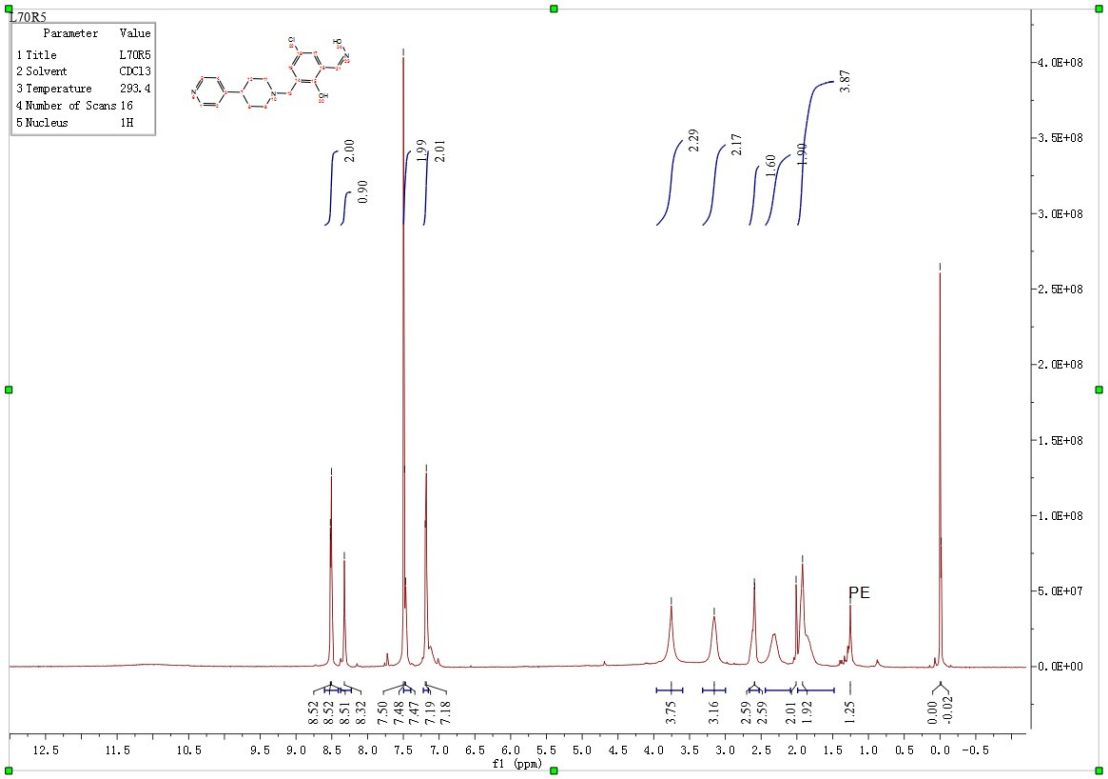


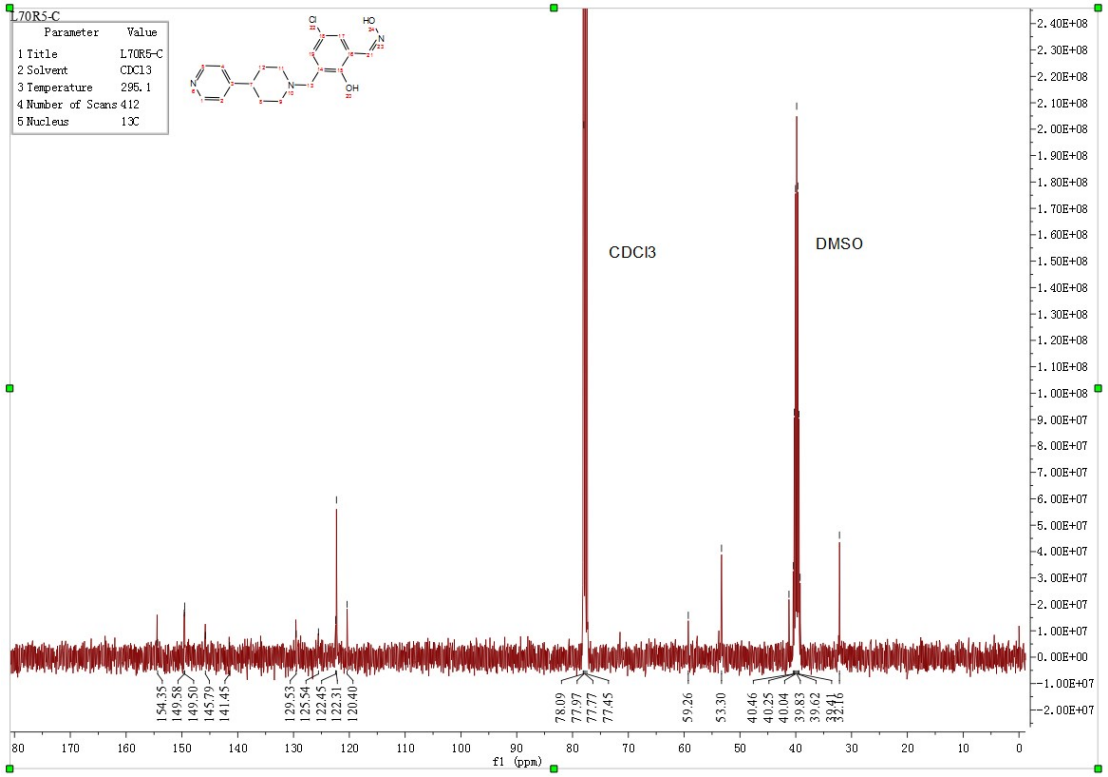


Data Filename	0051.d	**Sample Name**	L70R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			

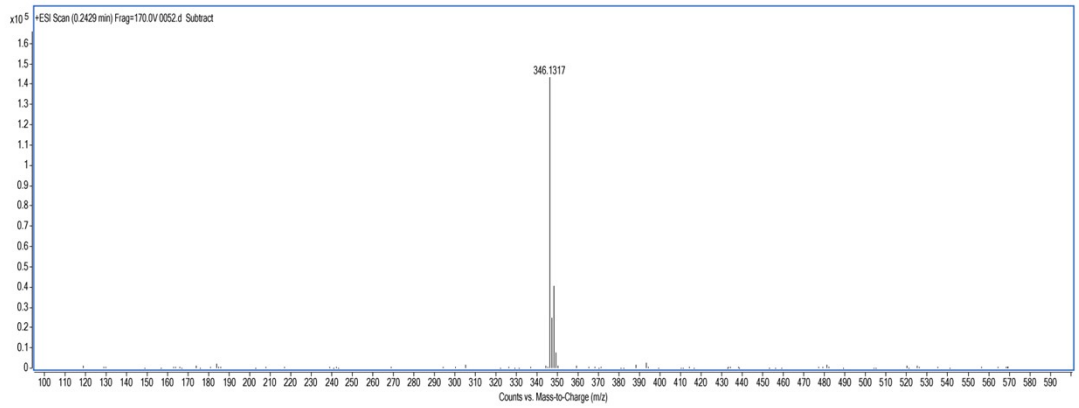


L70R5

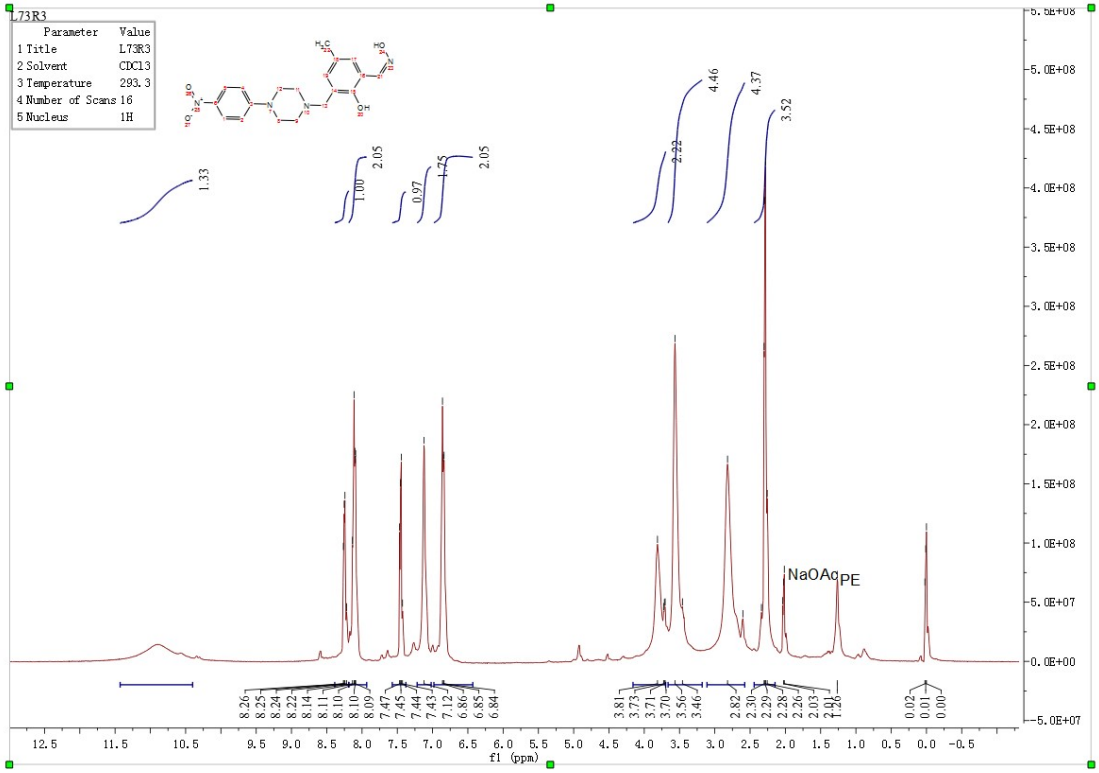

L70R5
Parameter Value
1 Title L70R5
2 Solvent CDCl3
3 Temperature 293.4
4 Number of Scans 16
5 Nucleus 1H
PE
f1 (ppm)

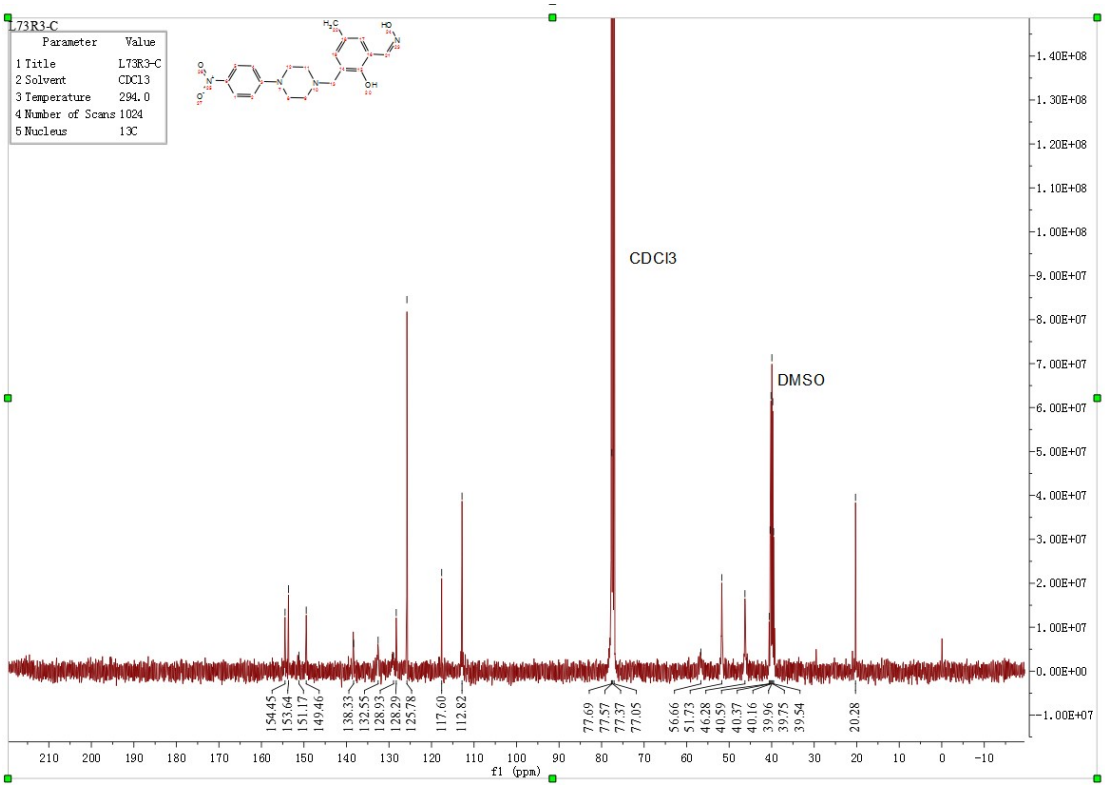

L70R5-C
Parameter Value
1 Title L70R5-C
2 Solvent CDCl3
3 Temperature 295.1
4 Number of Scans 412
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0052.d	**Sample Name**	L70R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chromatograms			

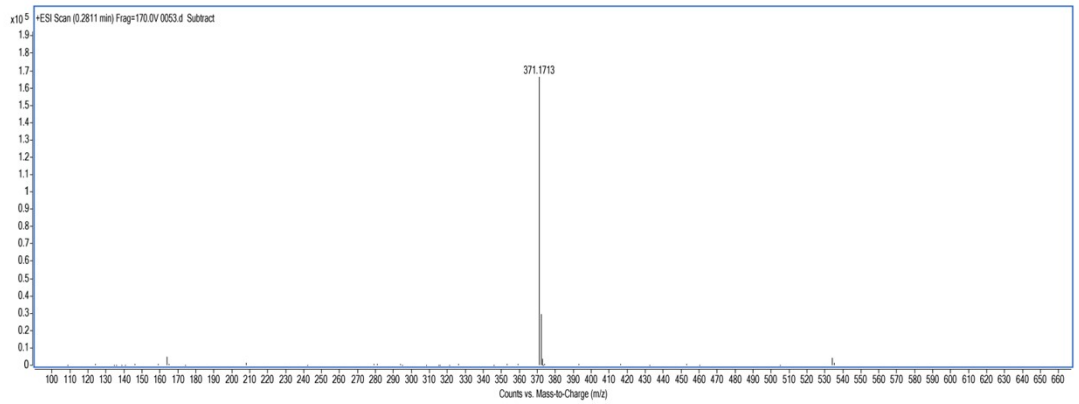


L73R3

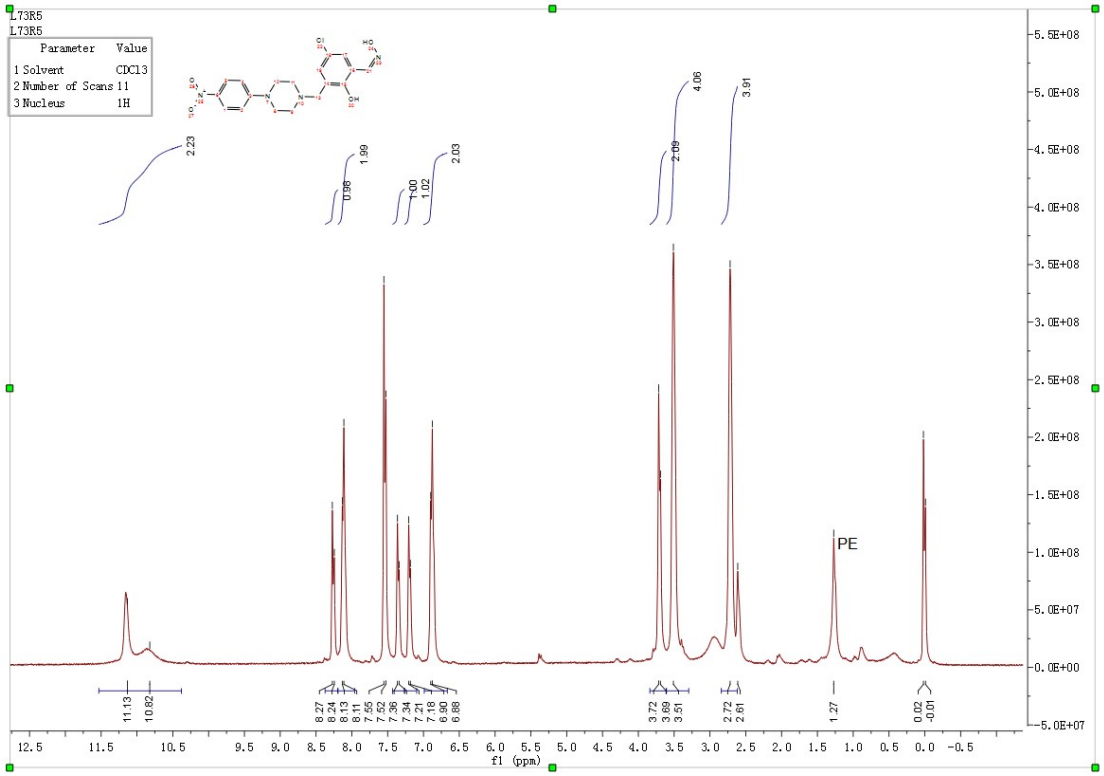


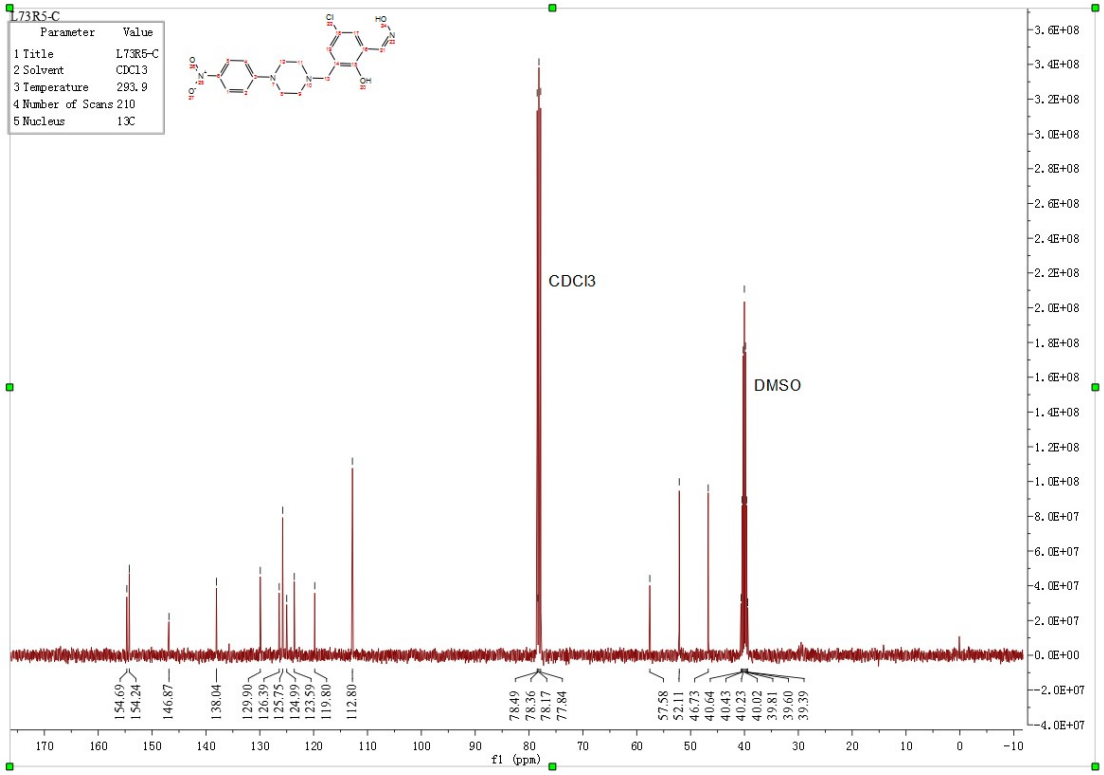


Data Filename	0053.d	**Sample Name**	L73R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			

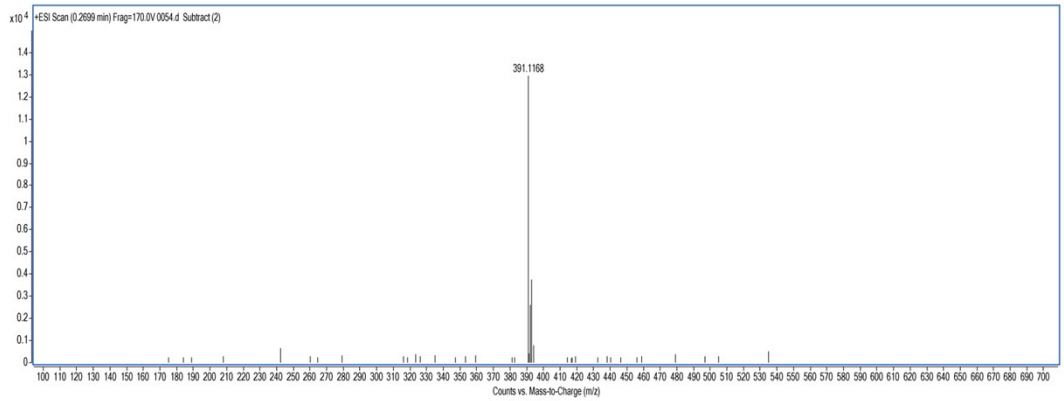


L73R5

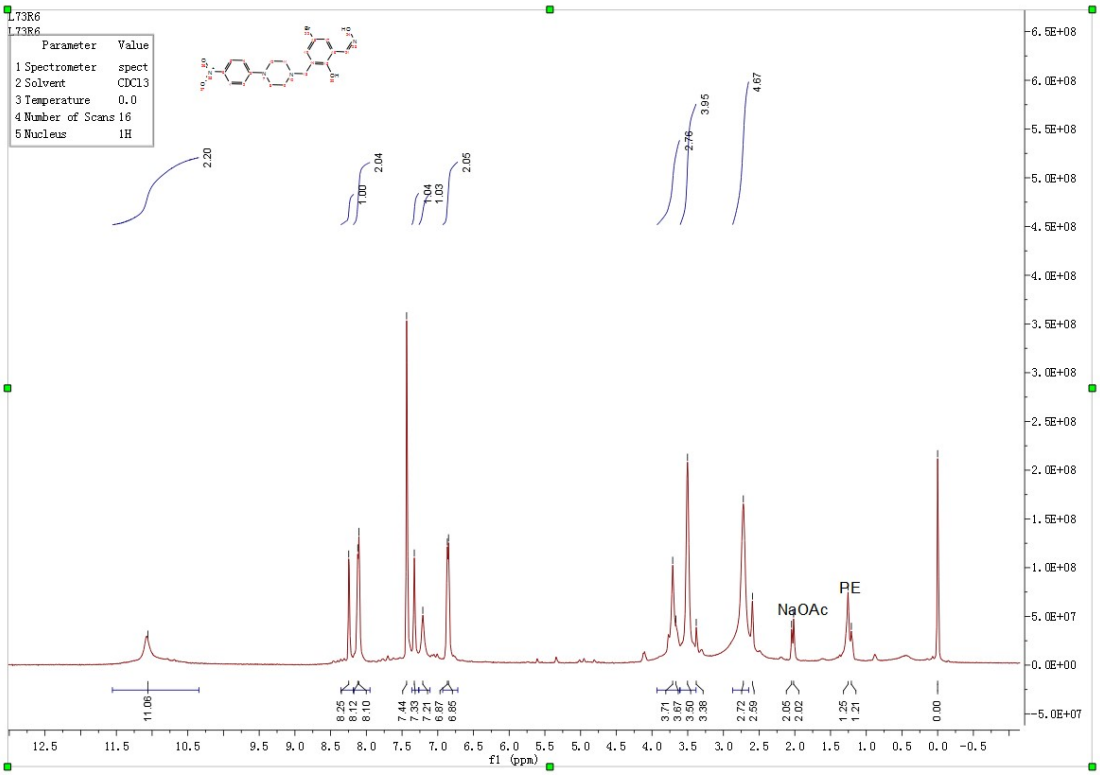

L73R5
L73R5
Parameter Value
1 Solvent CDCl3
2 Number of Scans 11
3 Nucleus 1H
PE
f1 (ppm)

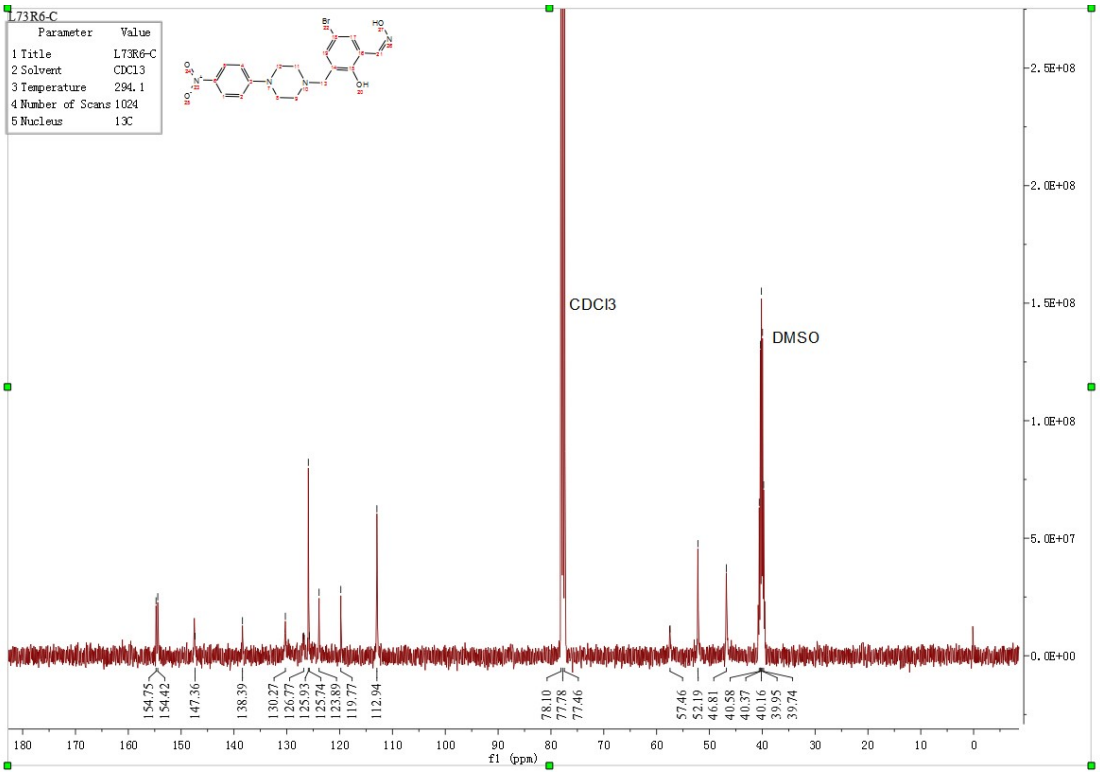

L73R5-C
Parameter Value
1 Title L73R5-C
2 Solvent CDCl3
3 Temperature 293.9
4 Number of Scans 210
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0054.d	**Sample Name**	L73R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



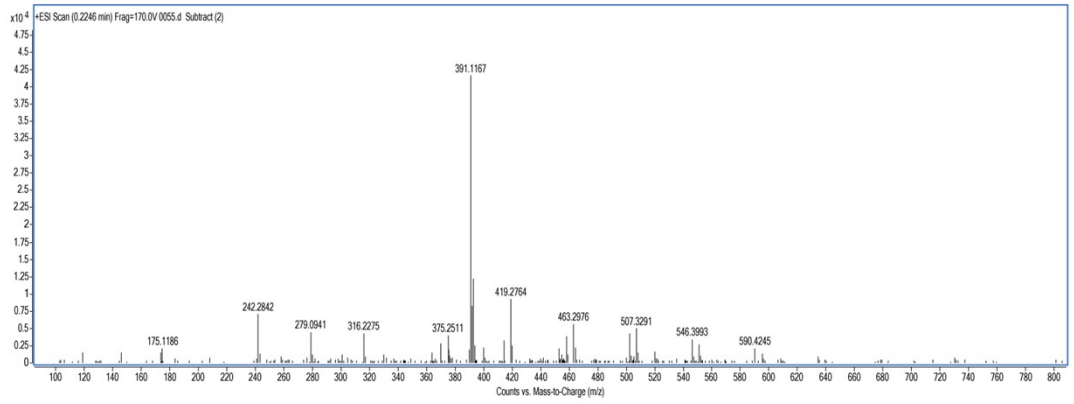
L73R6



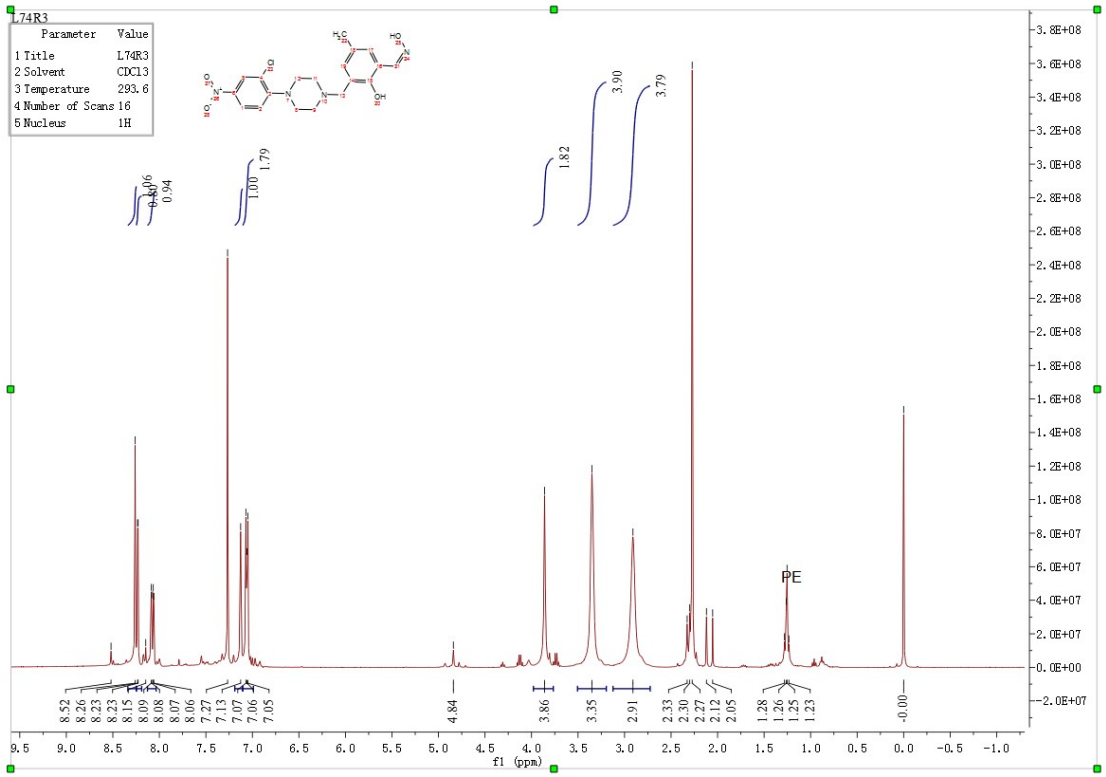


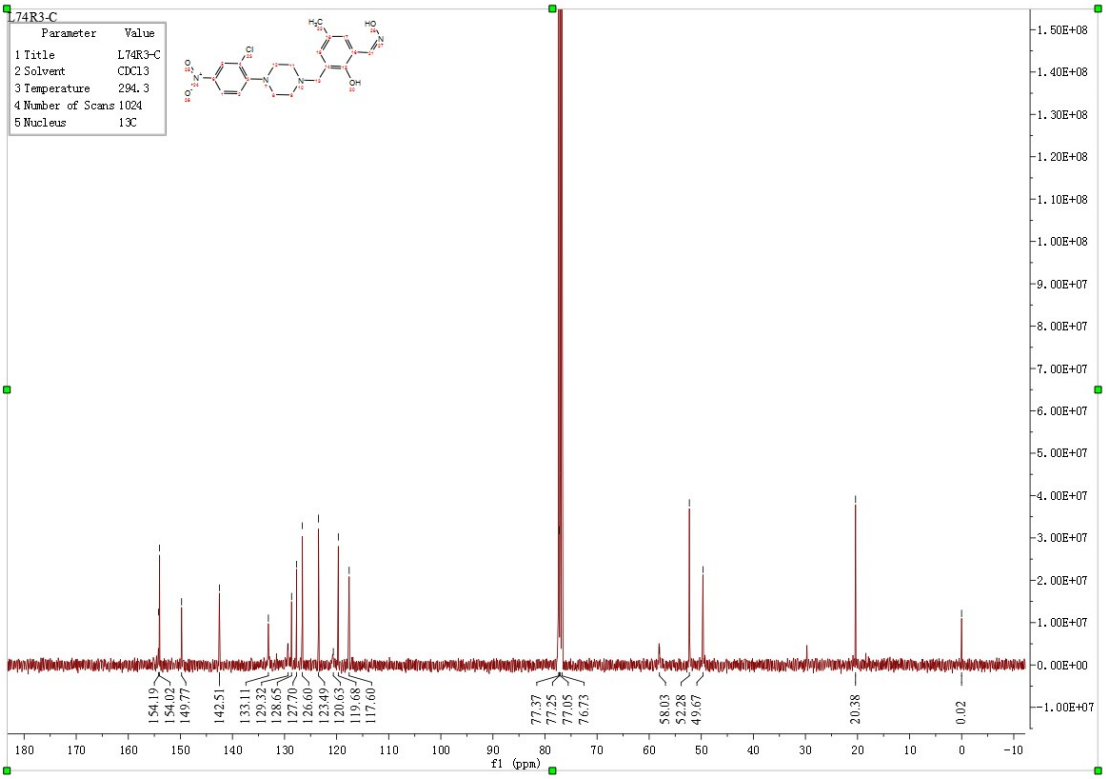
Data Filename	0055.d	**Sample Name**	L73R6
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



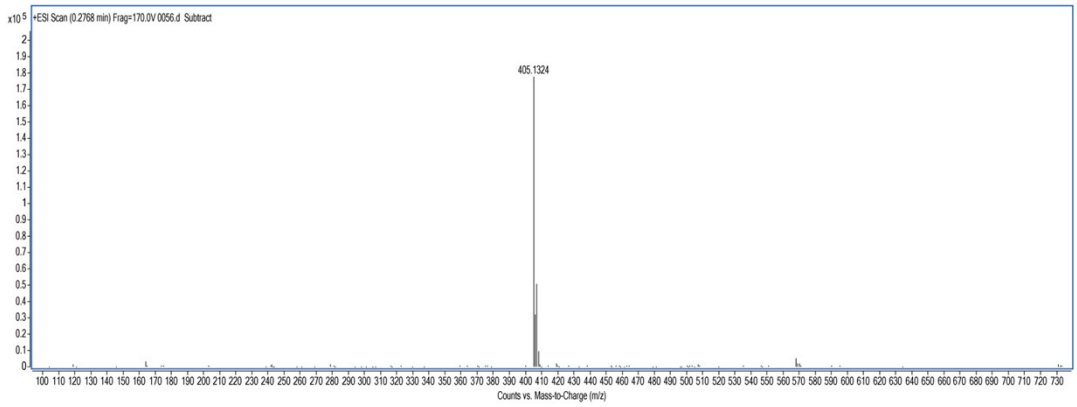
L74R3


L74R3
Parameter Value
1 Title L74R3
2 Solvent CDCl3
3 Temperature 293.6
4 Number of Scans 16
5 Nucleus 1H
PE
f1 (ppm)

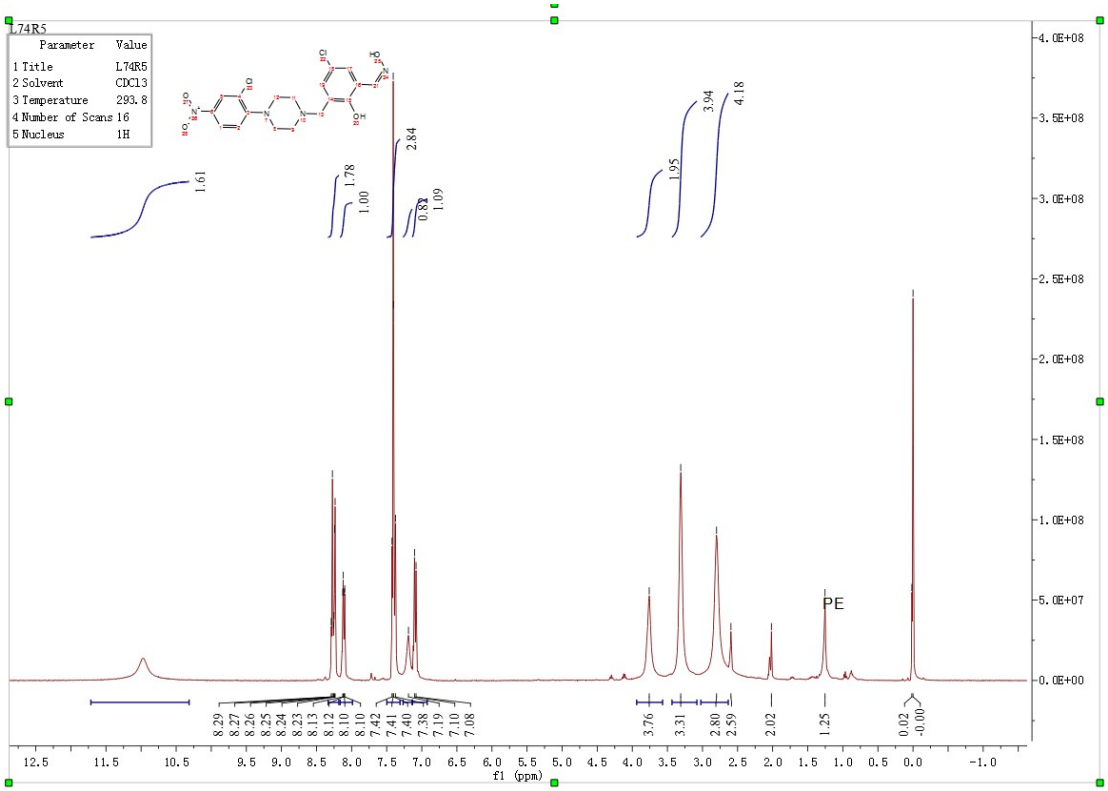

L74R3-C
Parameter Value
1 Title L74R3-C
2 Solvent CDCl3
3 Temperature 294.3
4 Number of Scans 1024
5 Nucleus 13C
f1 (ppm)

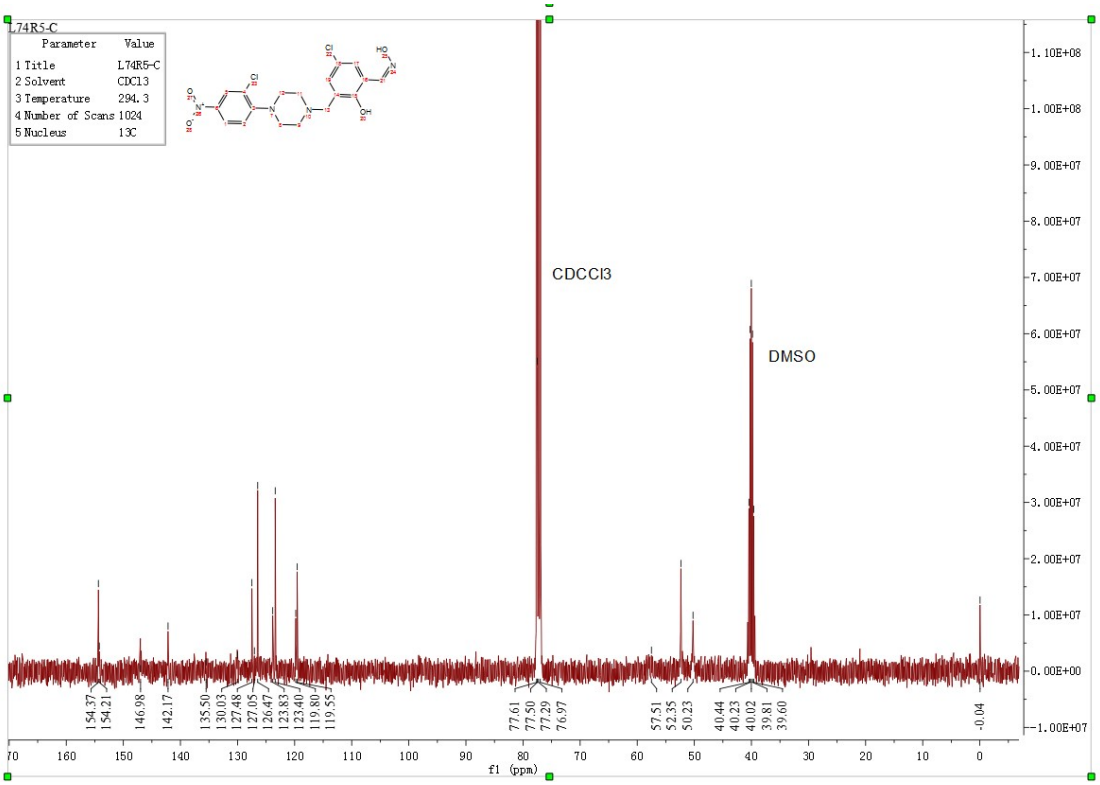
Data Filename	0056.d	**Sample Name**	L74R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



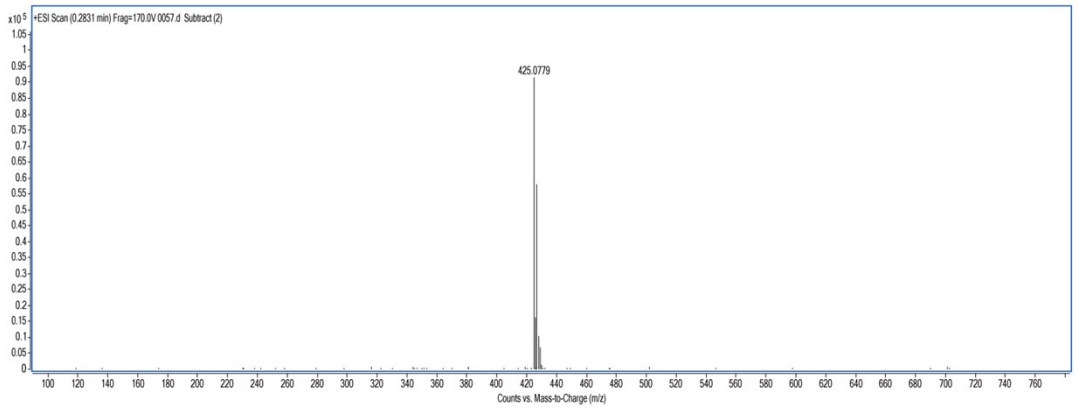
L74R5



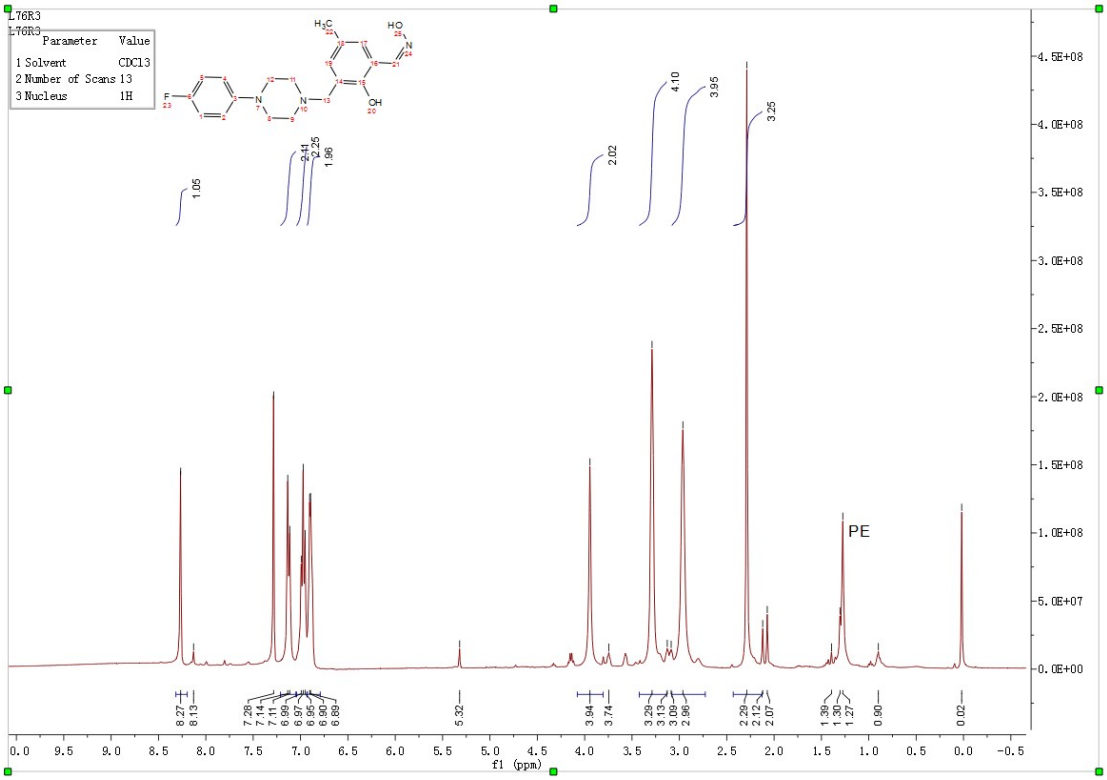


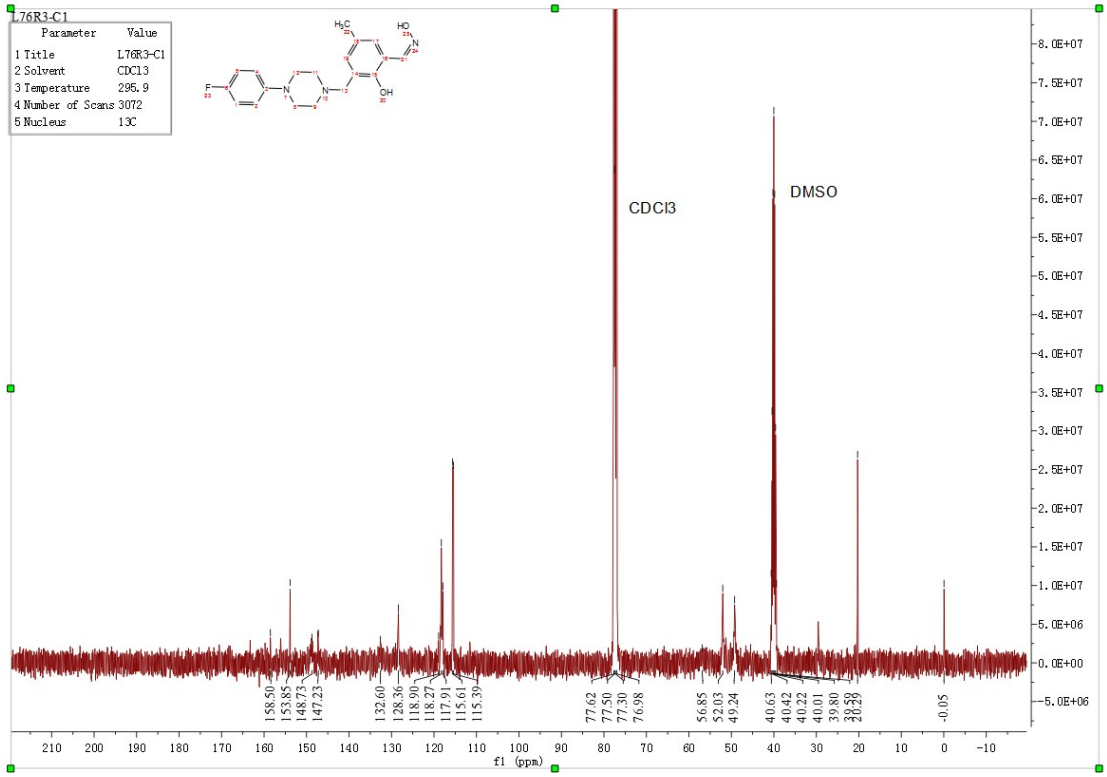
Data Filename	0057.d	**Sample Name**	L74R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

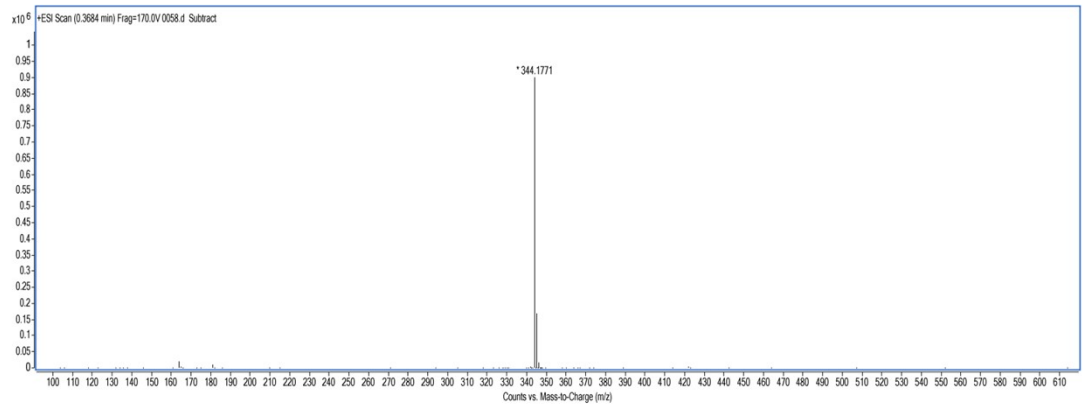


L76R3

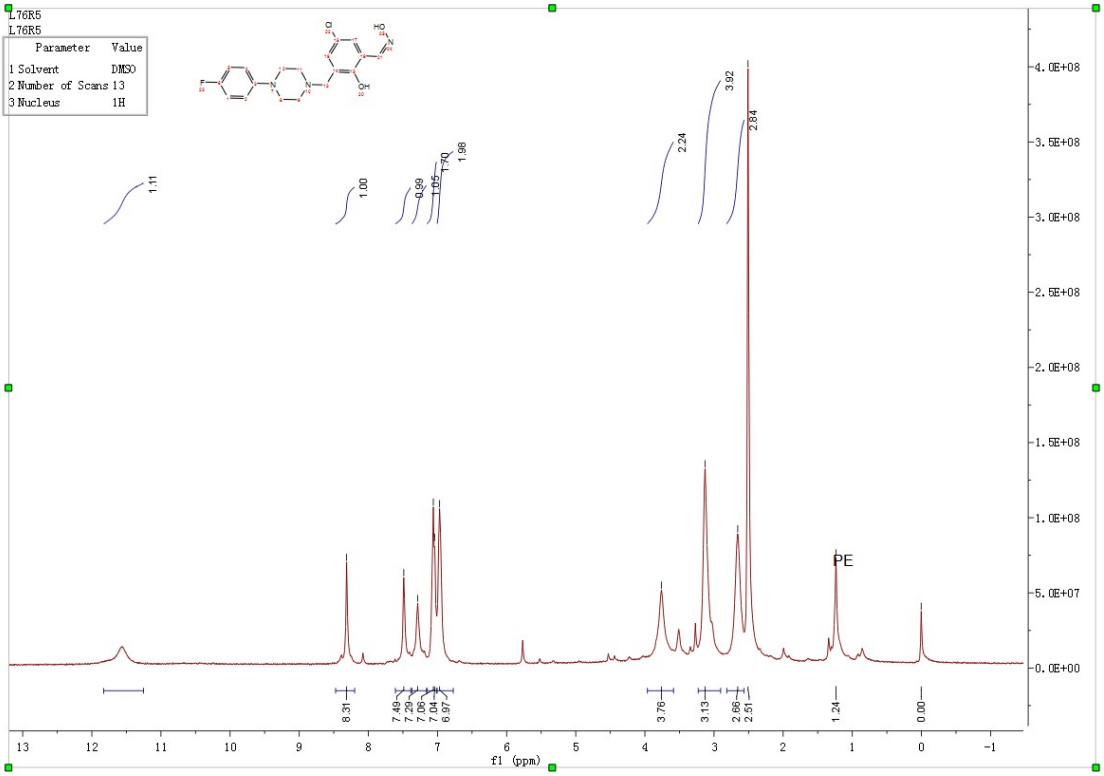

L76R3
L76R3
Parameter Value
1 Solvent CDCl3
2 Number of Scans 13
3 Nucleus 1H
PE
f1 (ppm)

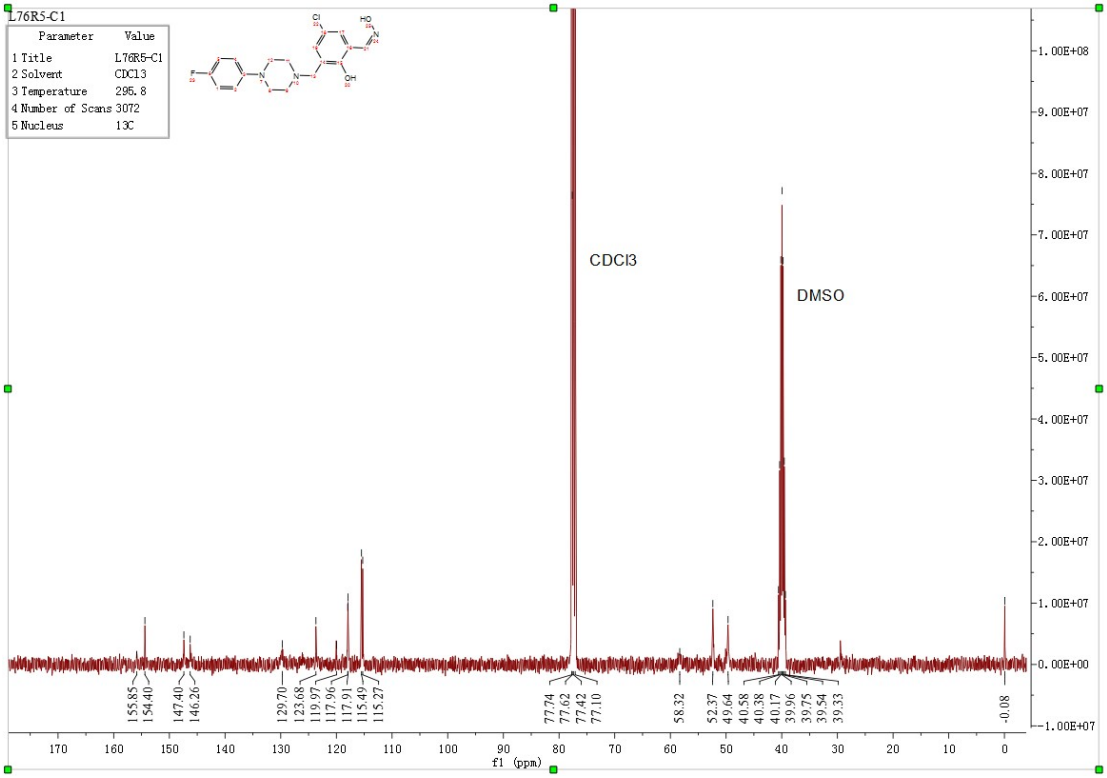

L76R3-C1
Parameter Value
1 Title L76R3-C1
2 Solvent CDCl3
3 Temperature 295.9
4 Number of Scans 3072
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0058.d	**Sample Name**	L76R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



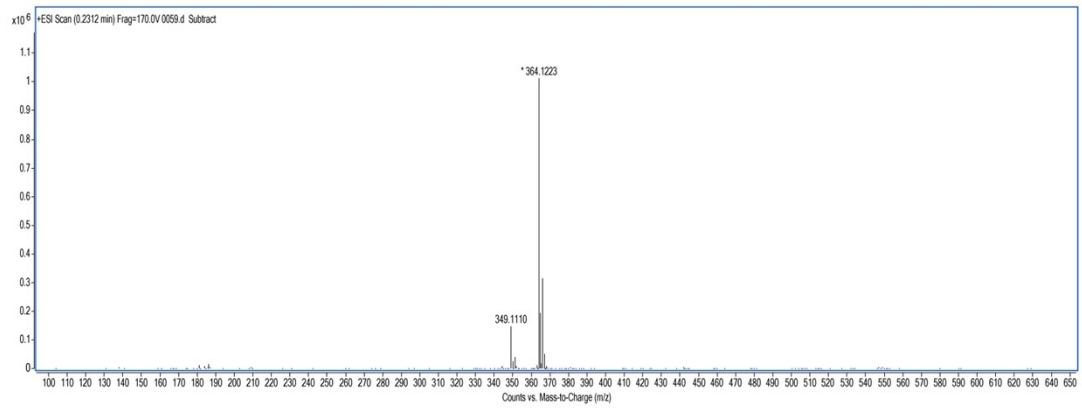
L76R5



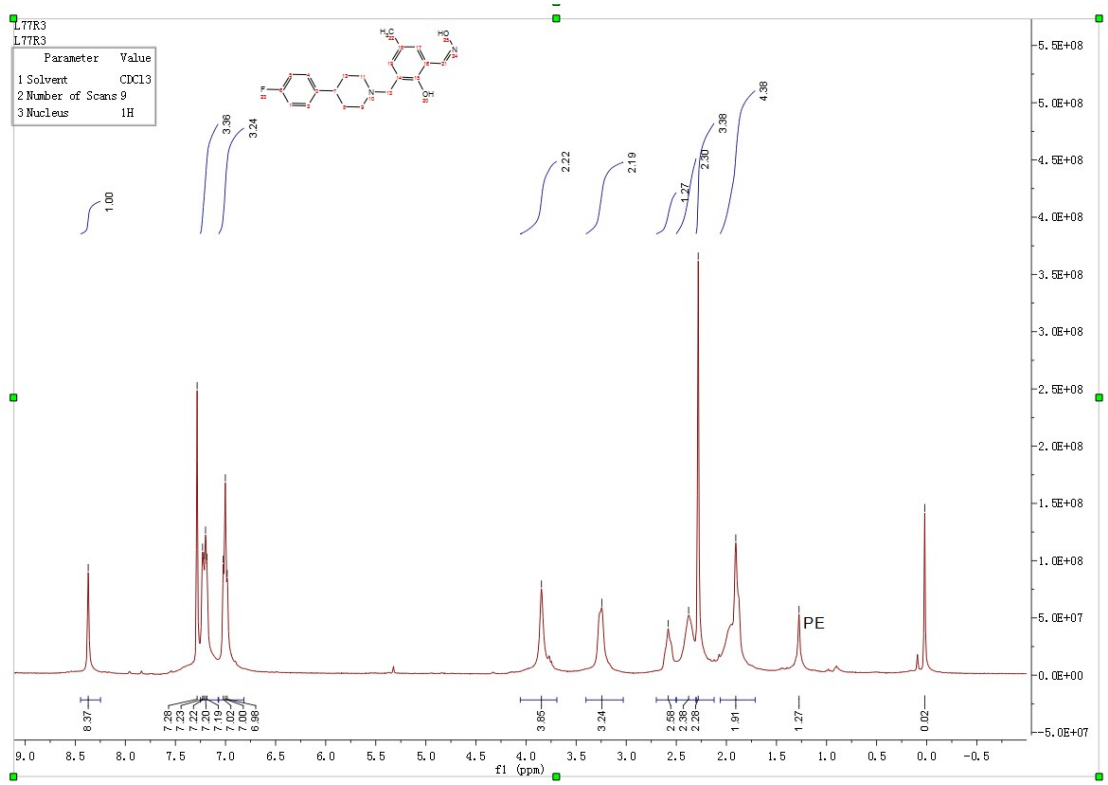


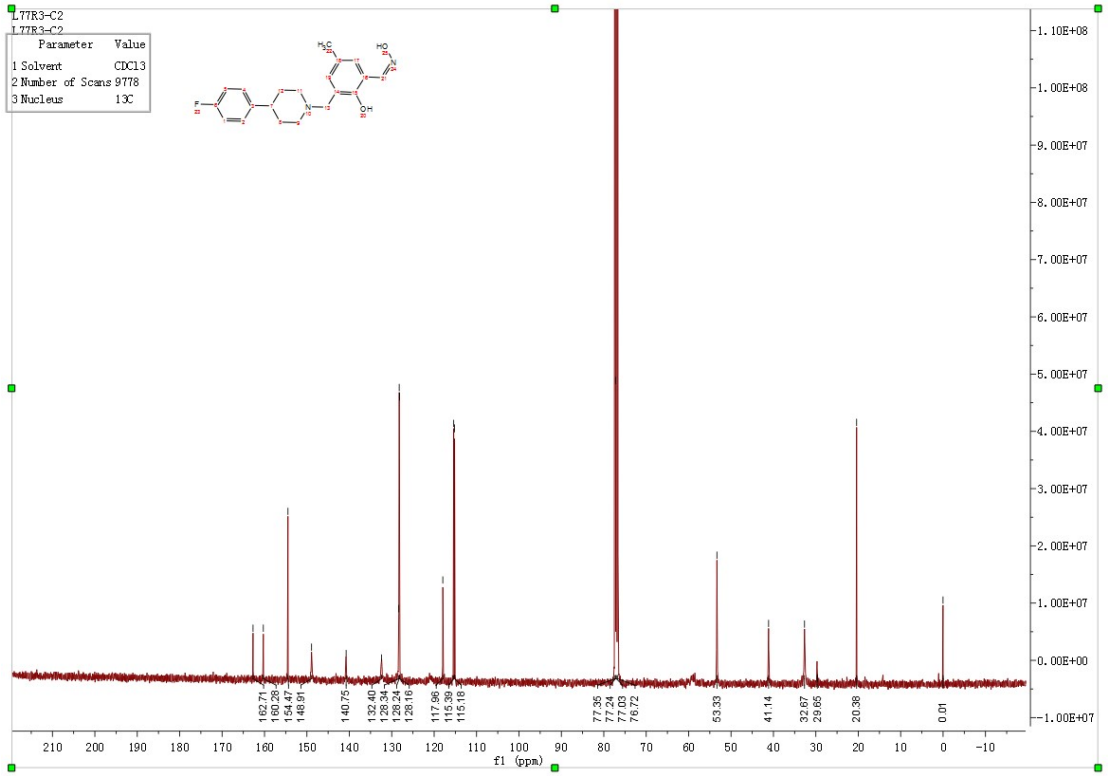
Data Filename	0059.d	**Sample Name**	L76R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



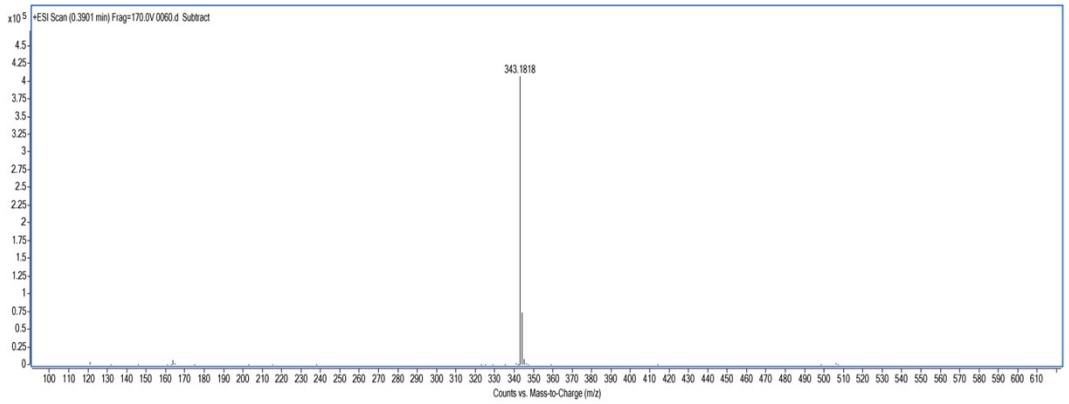
L77R3


L77R3
L77R3
Parameter Value
1 Solvent CDCl3
2 Number of Scans 9
3 Nucleus 1H
PE
f1 (ppm)

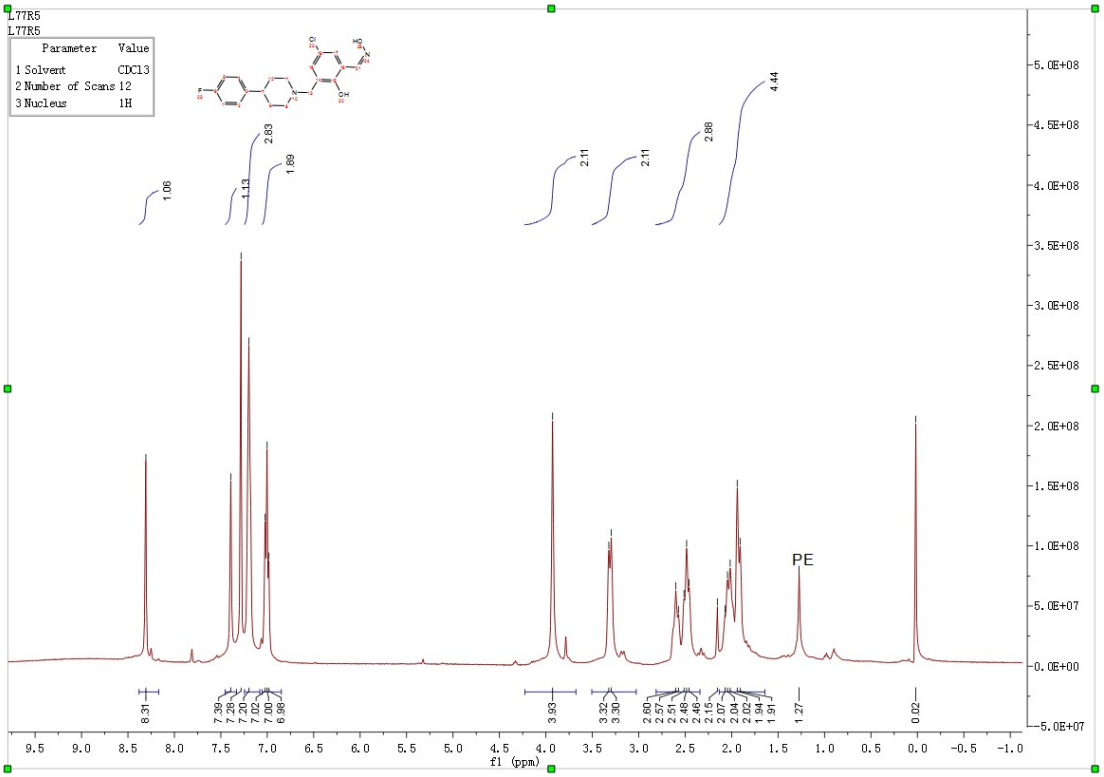

L77R3-C2
L77R3-C2
Parameter Value
1 Solvent CDCl3
2 Number of Scans 9778
3 Nucleus 13C
f1 (ppm)

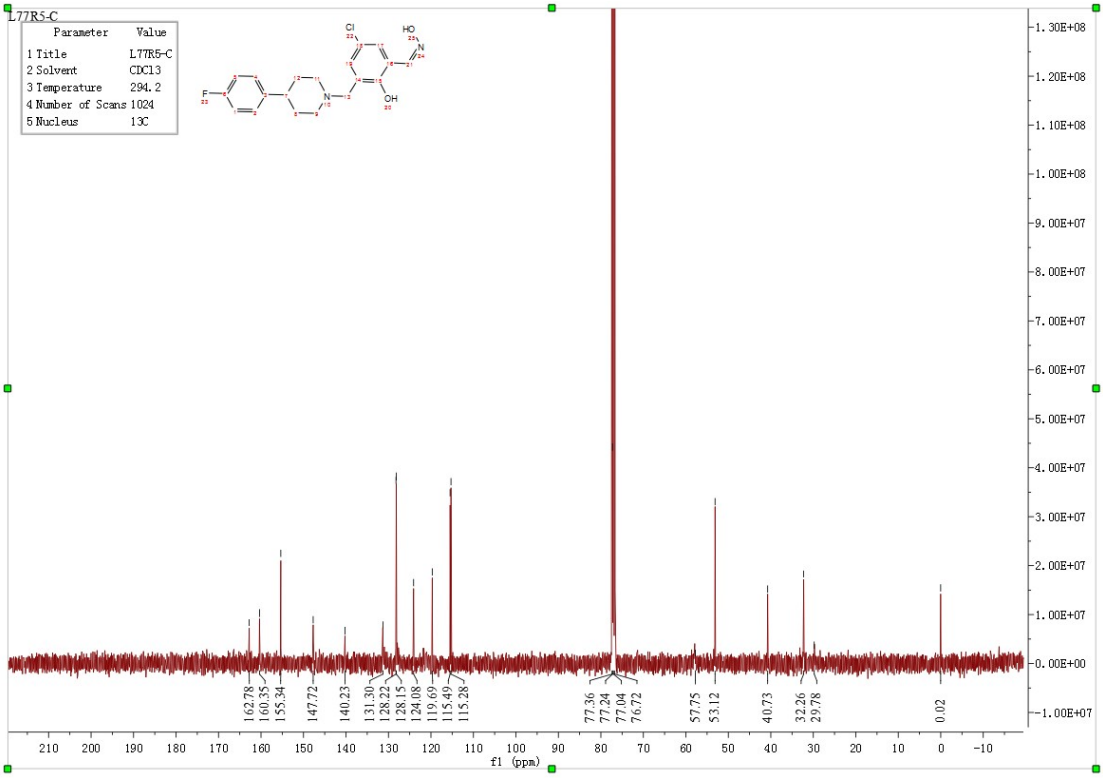
Data Filename	0060.d	**Sample Name**	L77R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



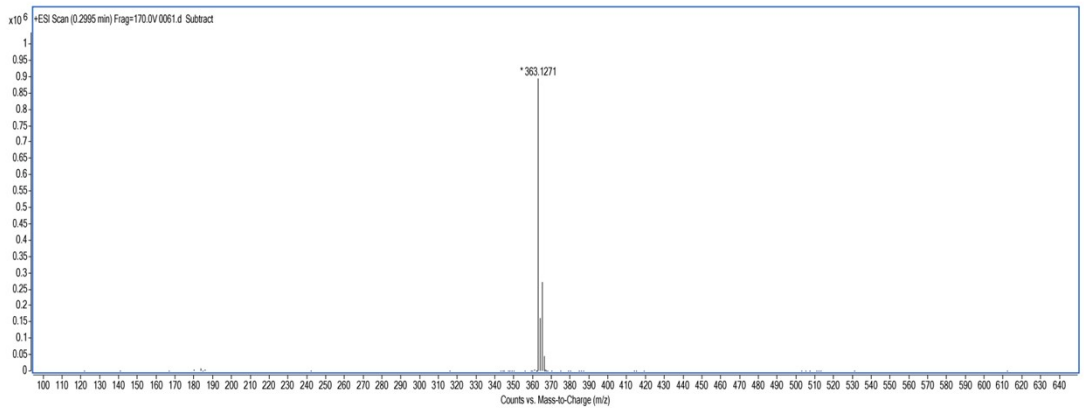
L77R5



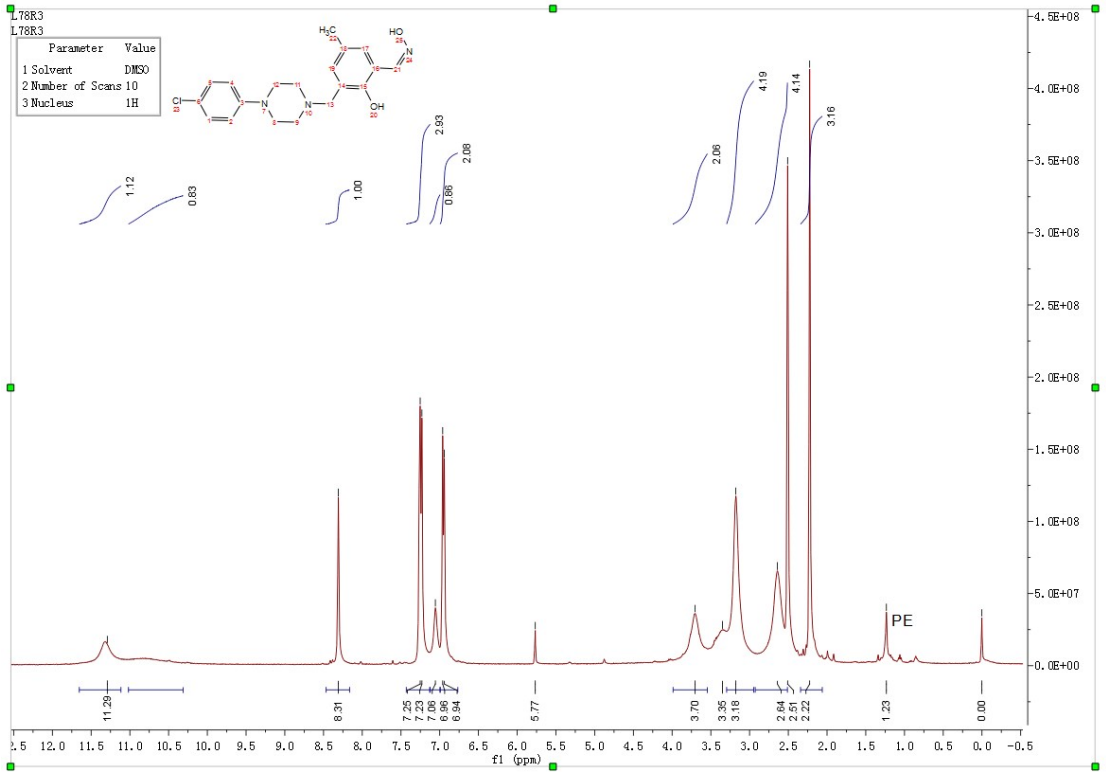


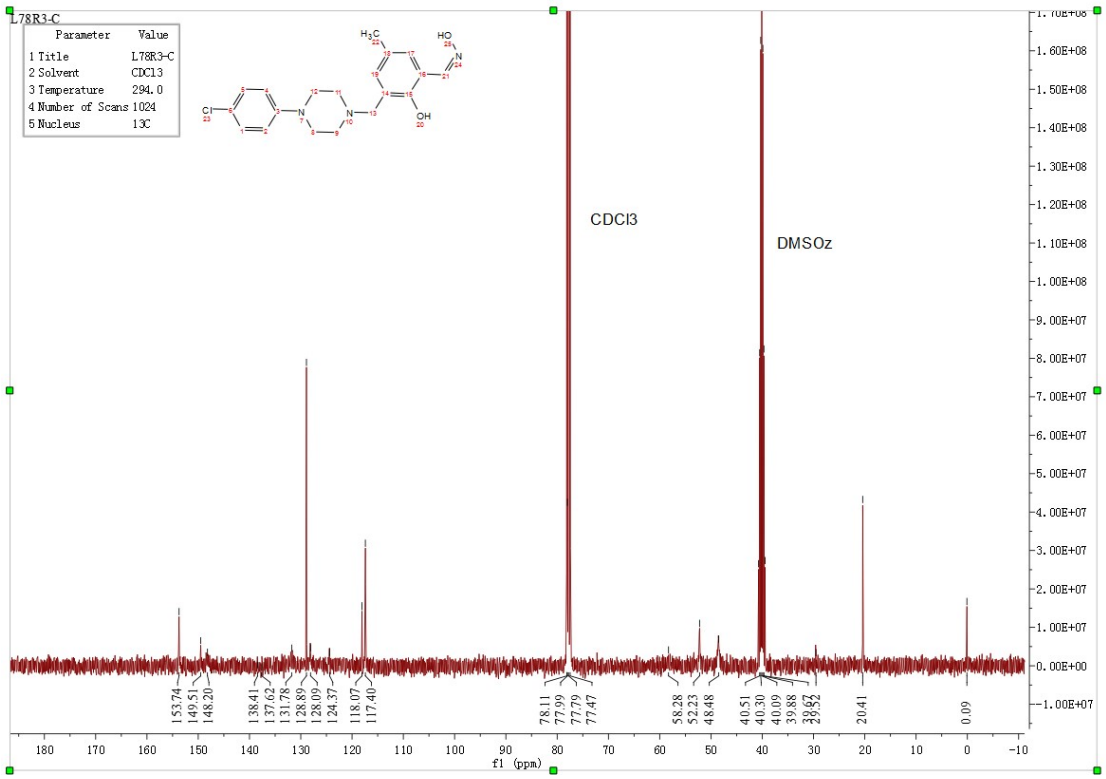
Data Filename	0061.d	**Sample Name**	L77R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

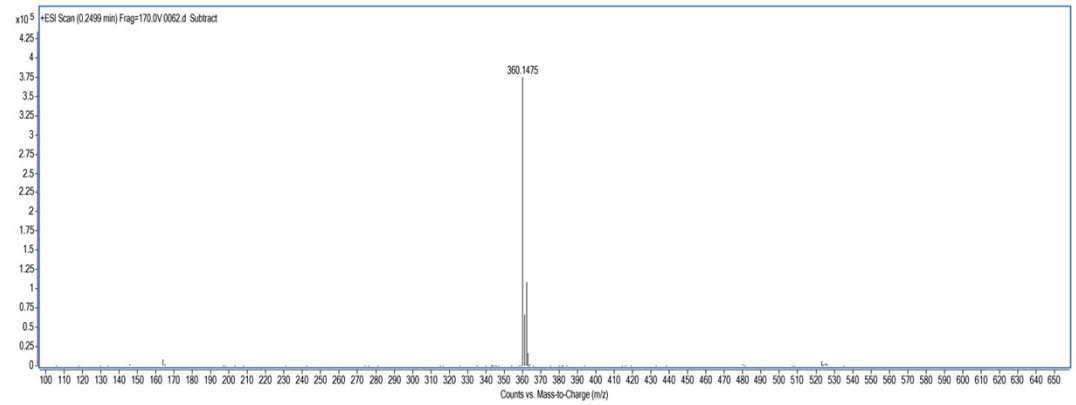


L78R3

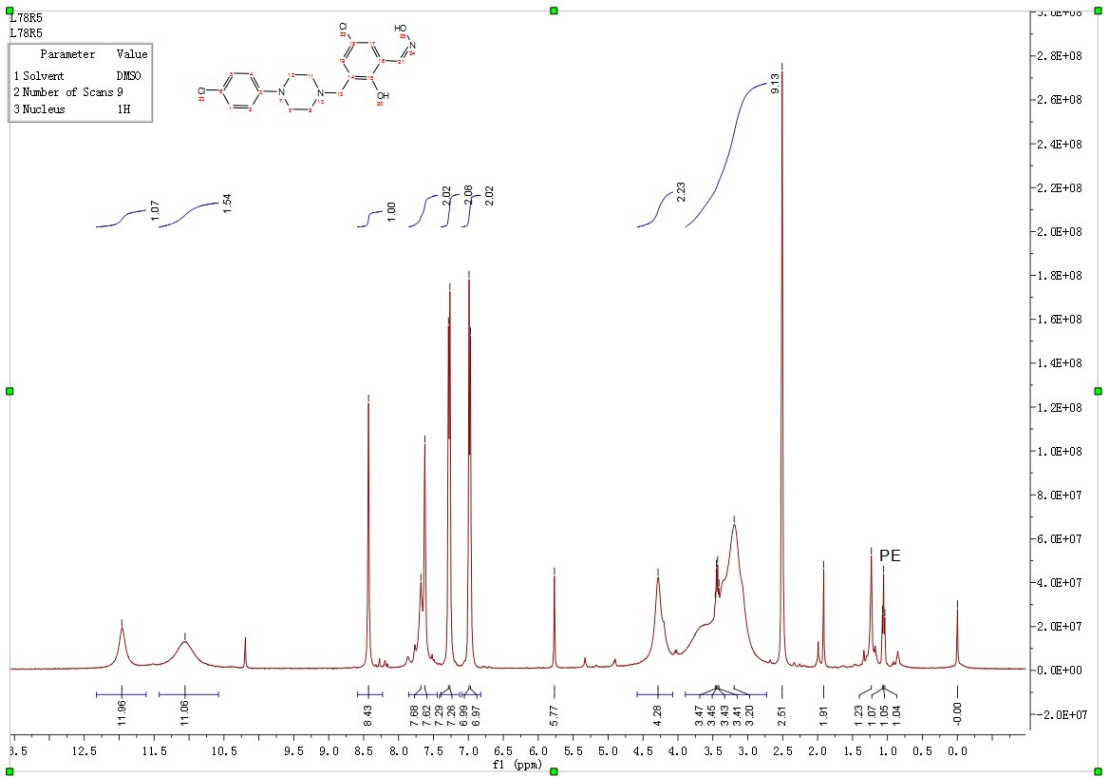

L78R3
L78R3
Parameter Value
1 Solvent DMSO
2 Number of Scans 10
3 Nucleus 1H
PE
f1 (ppm)

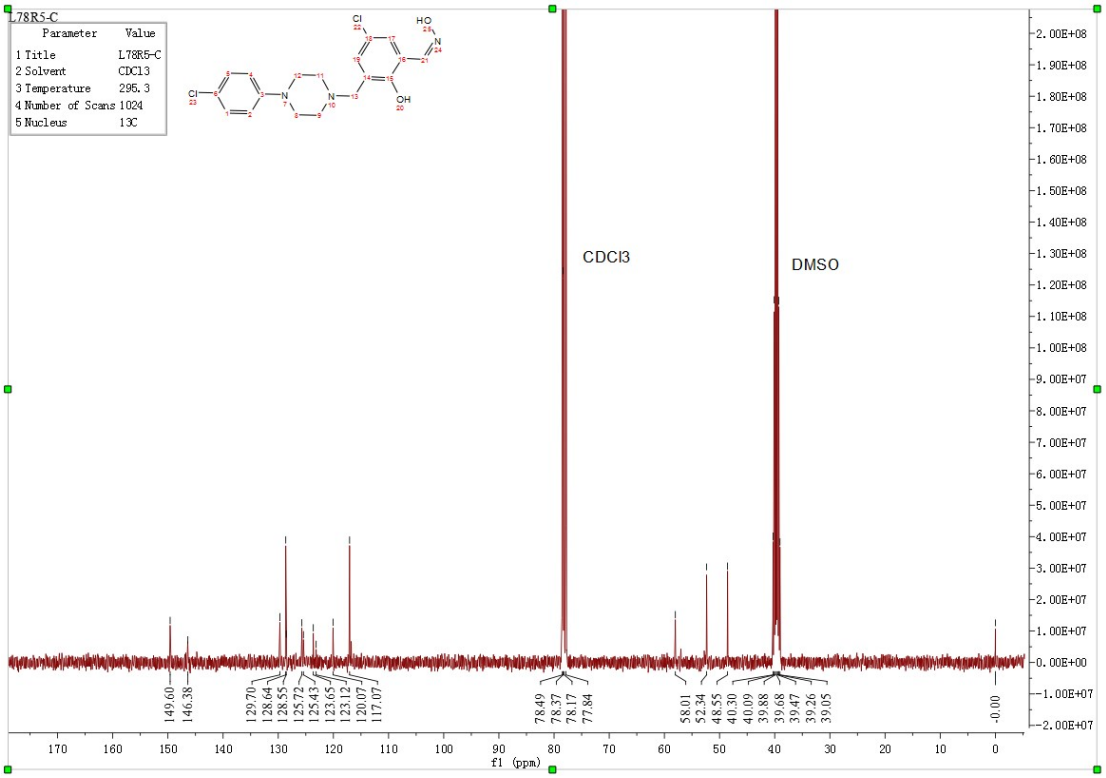

L78R3-C
Parameter Value
1 Title L78R3-C
2 Solvent CDCl3
3 Temperature 294.0
4 Number of Scans 1024
5 Nucleus 13C
CDCl3
DMSOz
f1 (ppm)

Data Filename	0062.d	**Sample Name**	L78R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



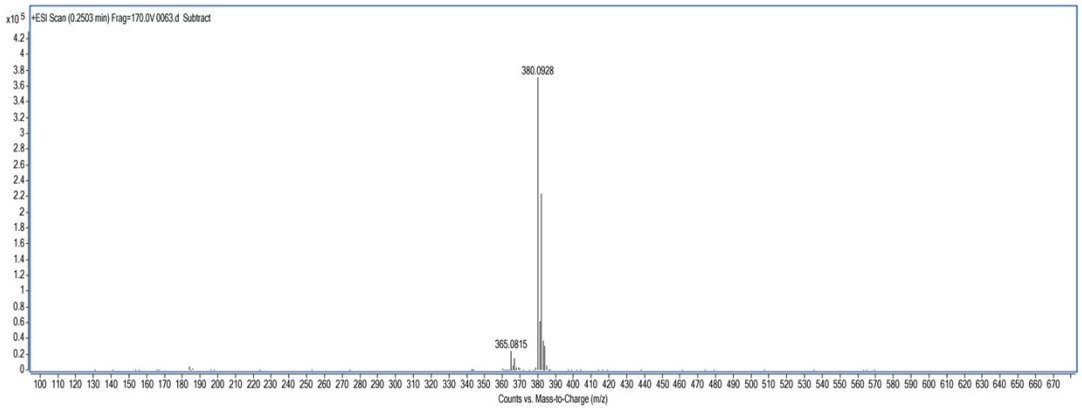
L78R5



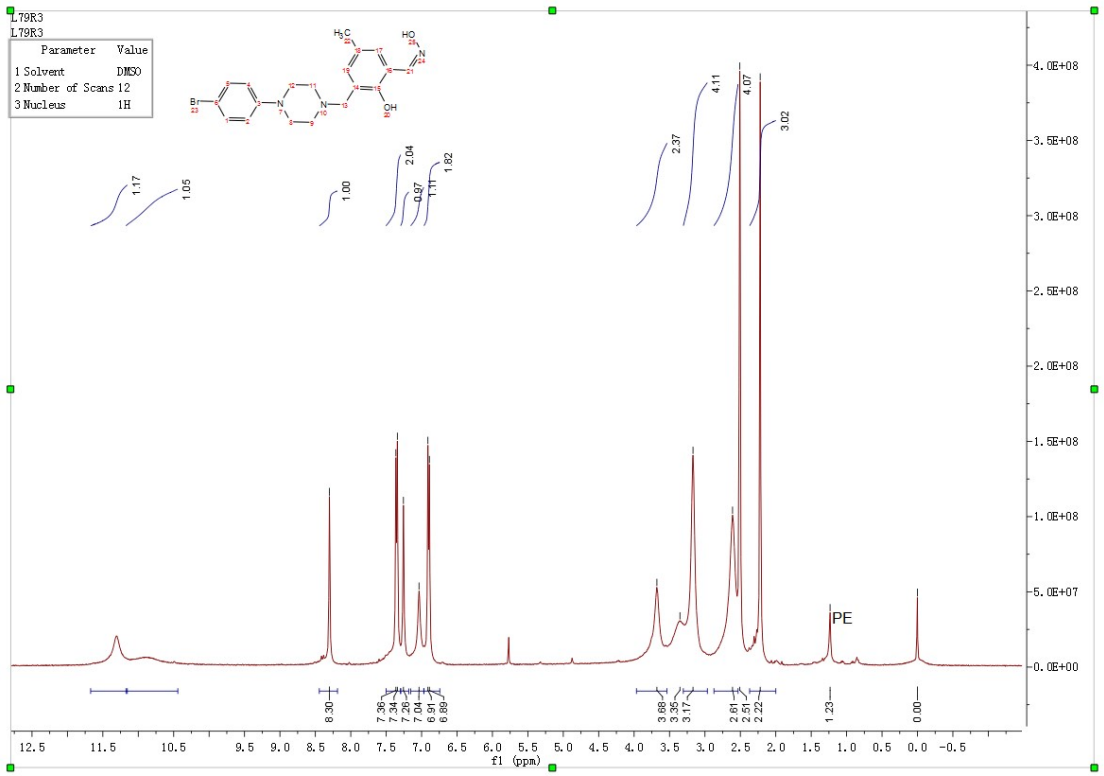


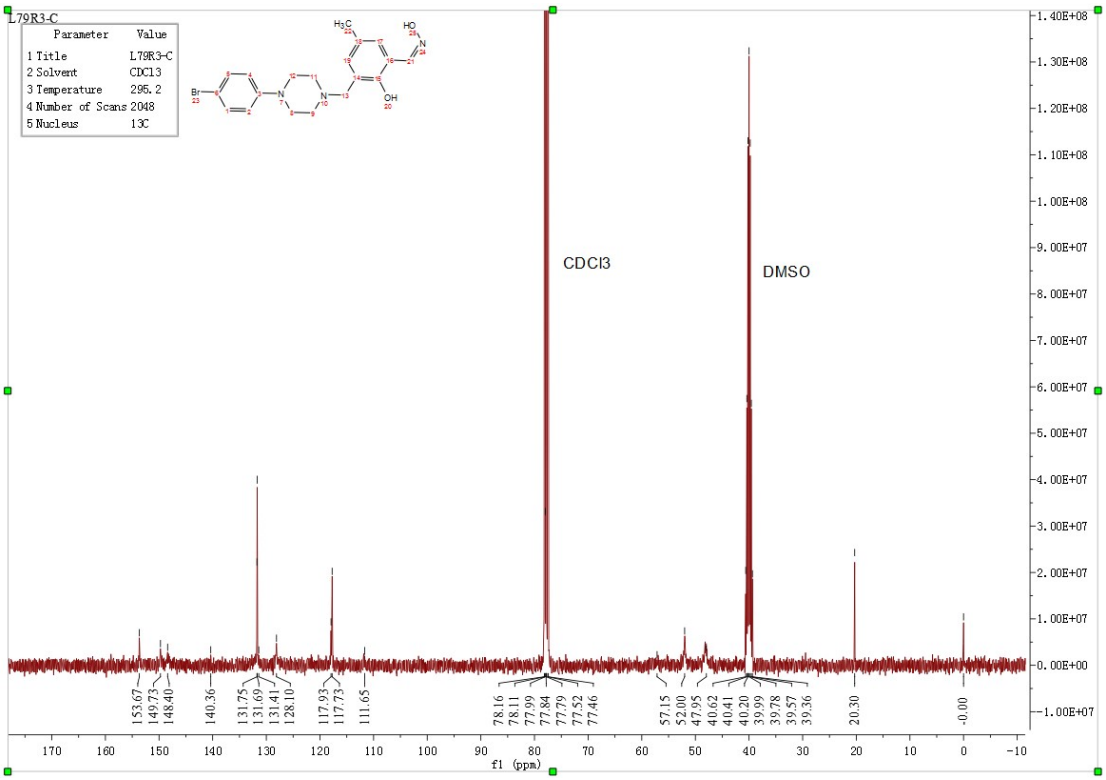
Data Filename	0063.d	**Sample Name**	L78R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

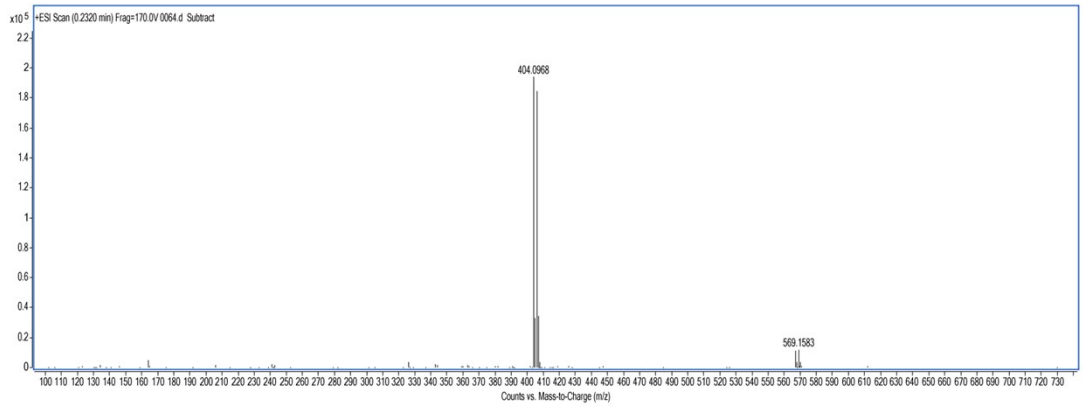


L79R3

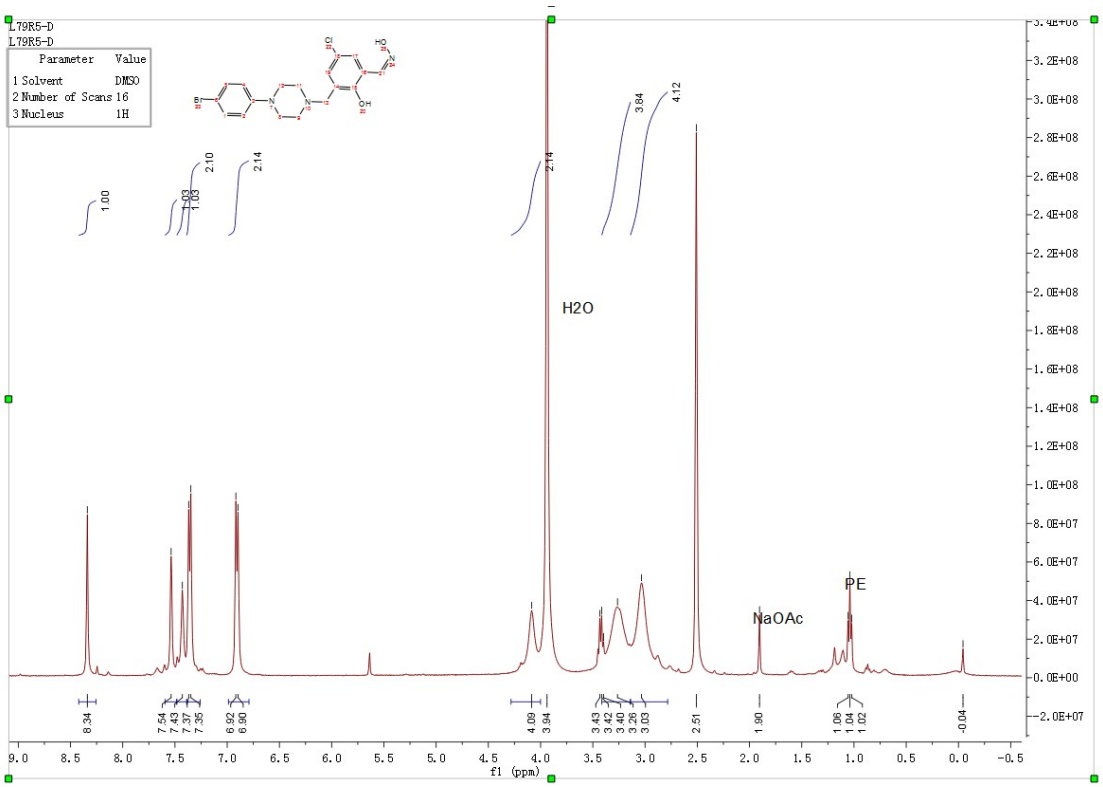

L79R3
L79R3
Parameter Value
1 Solvent DMSO
2 Number of Scans 12
3 Nucleus 1H
PE
f1 (ppm)

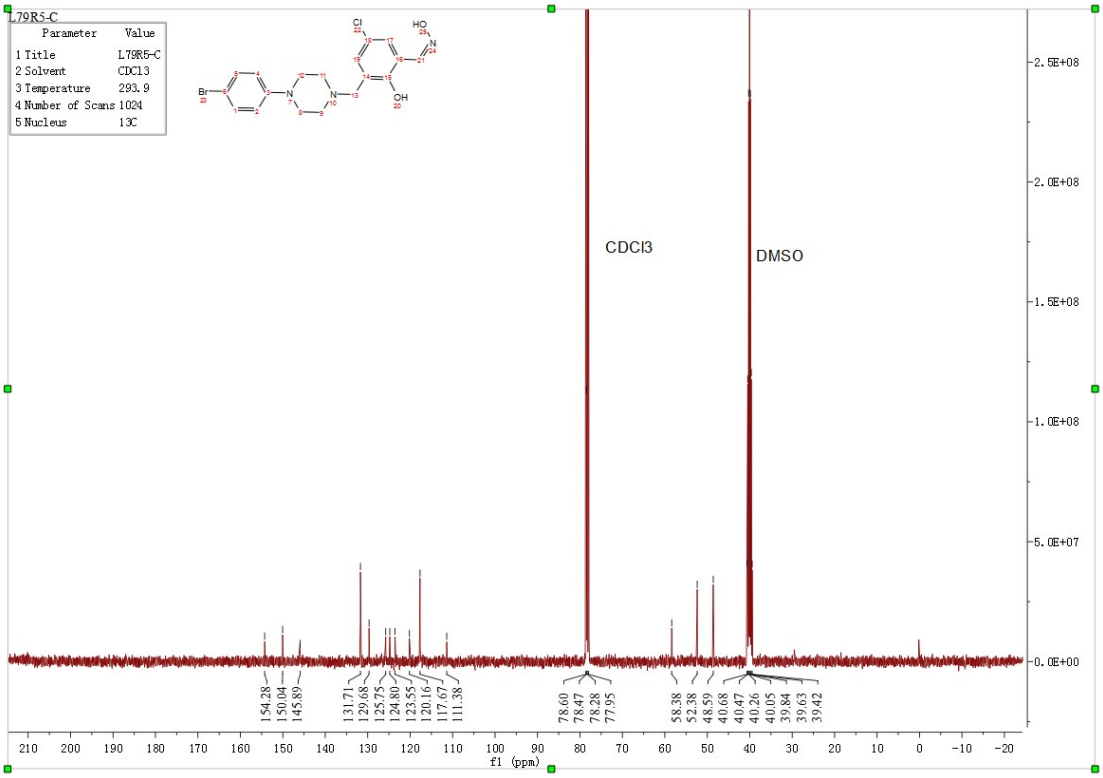

L79R3-C
Parameter Value
1 Title L79R3-C
2 Solvent CDCl3
3 Temperature 295.2
4 Number of Scans 2048
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0064.d	**Sample Name**	L79R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



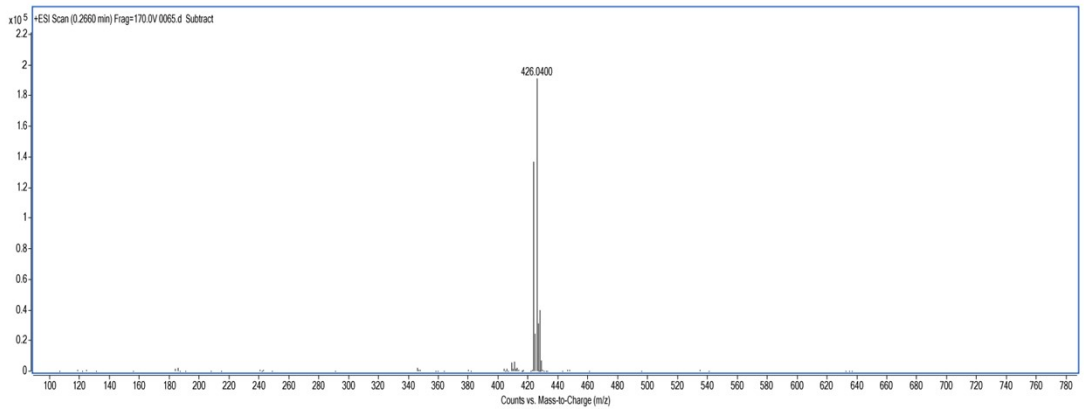
L79R5



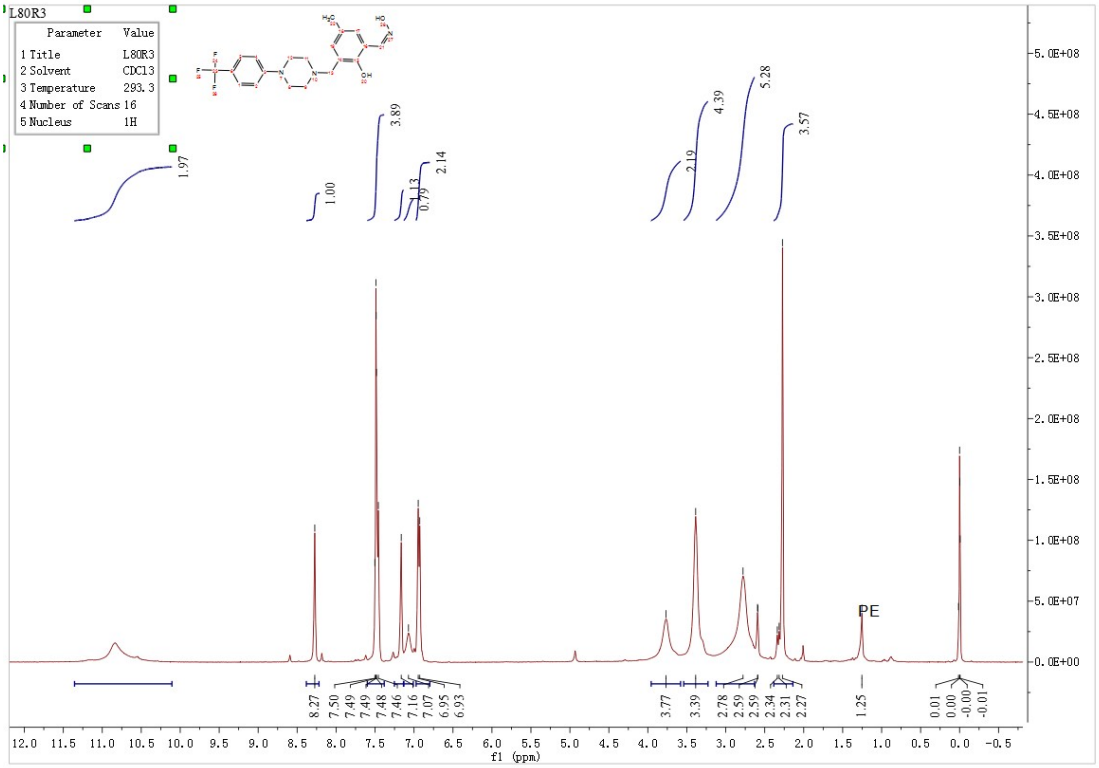


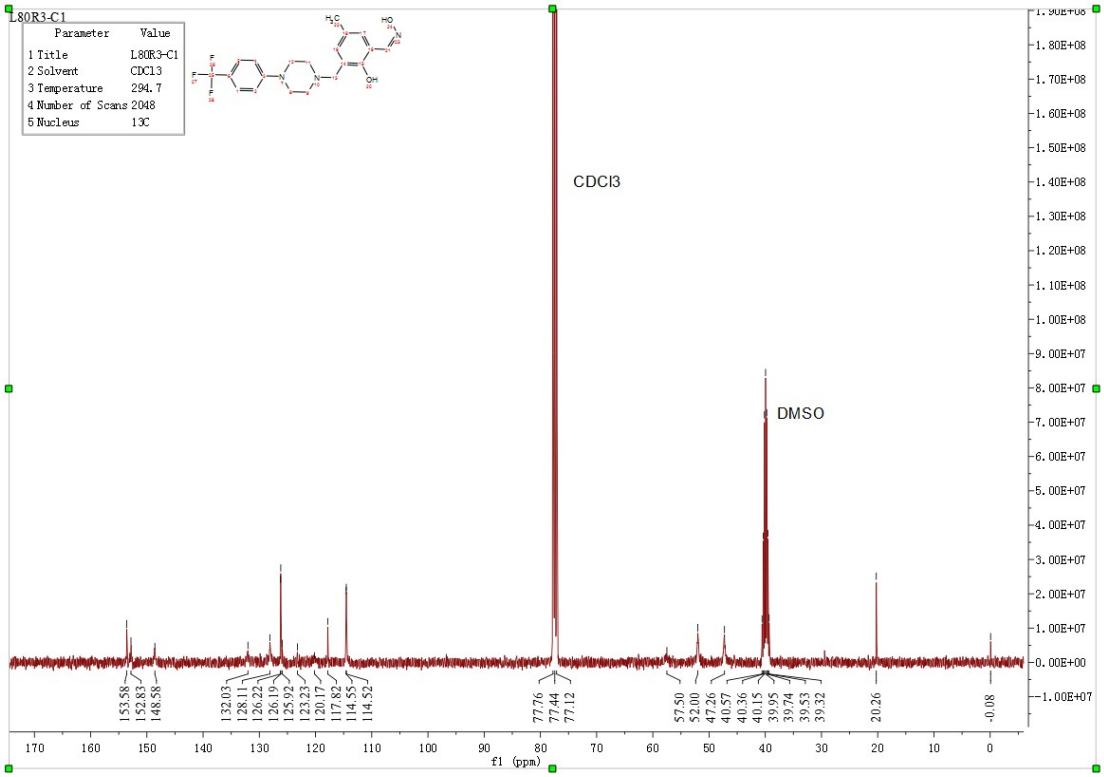
Data Filename	0065.d	**Sample Name**	L79R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



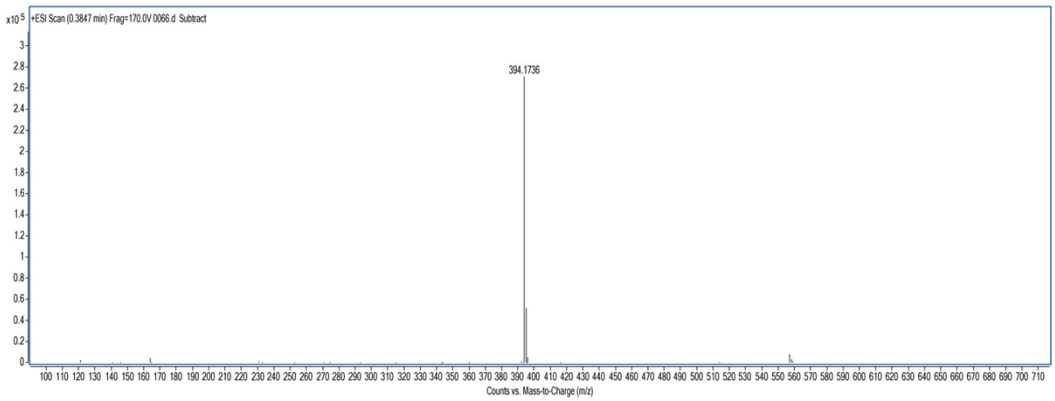
L80R3


L80R3
Parameter Value
1 Title L80R3
2 Solvent CDCl3
3 Temperature 293.3
4 Number of Scans 16
5 Nucleus 1H
PE

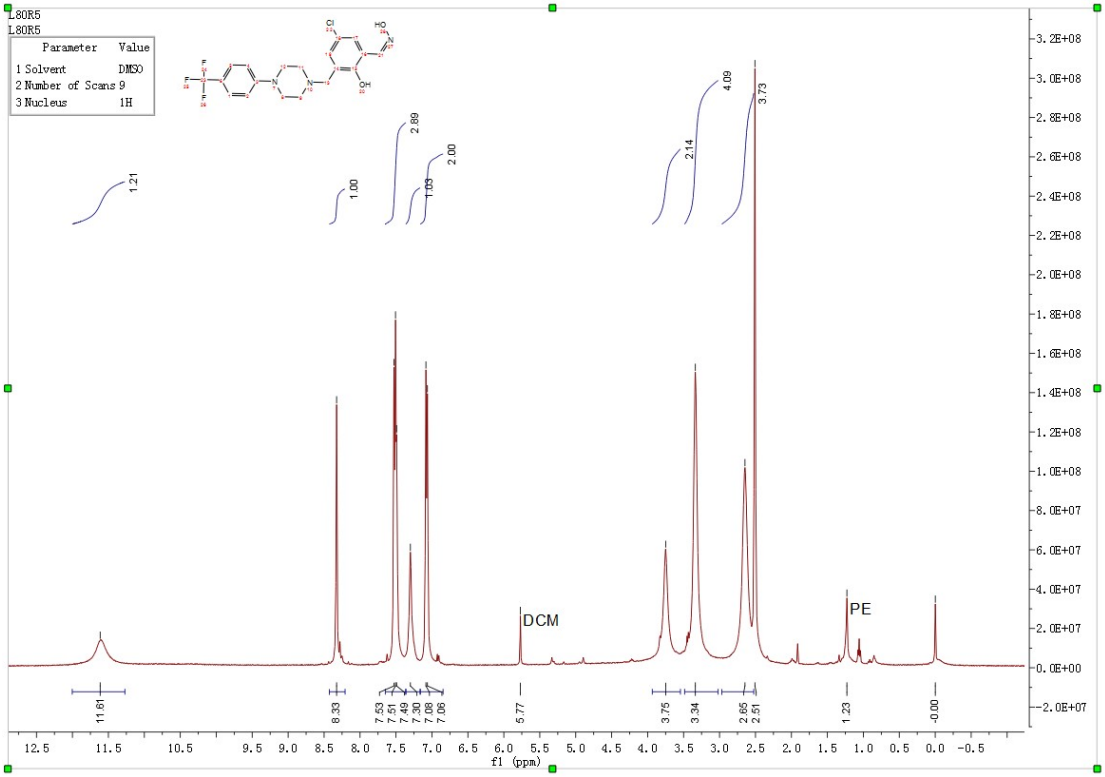

L80R3-C1
Parameter Value
1 Title L80R3-C1
2 Solvent CDCl3
3 Temperature 294.7
4 Number of Scans 2048
5 Nucleus 13C
CDCl3
DMSO

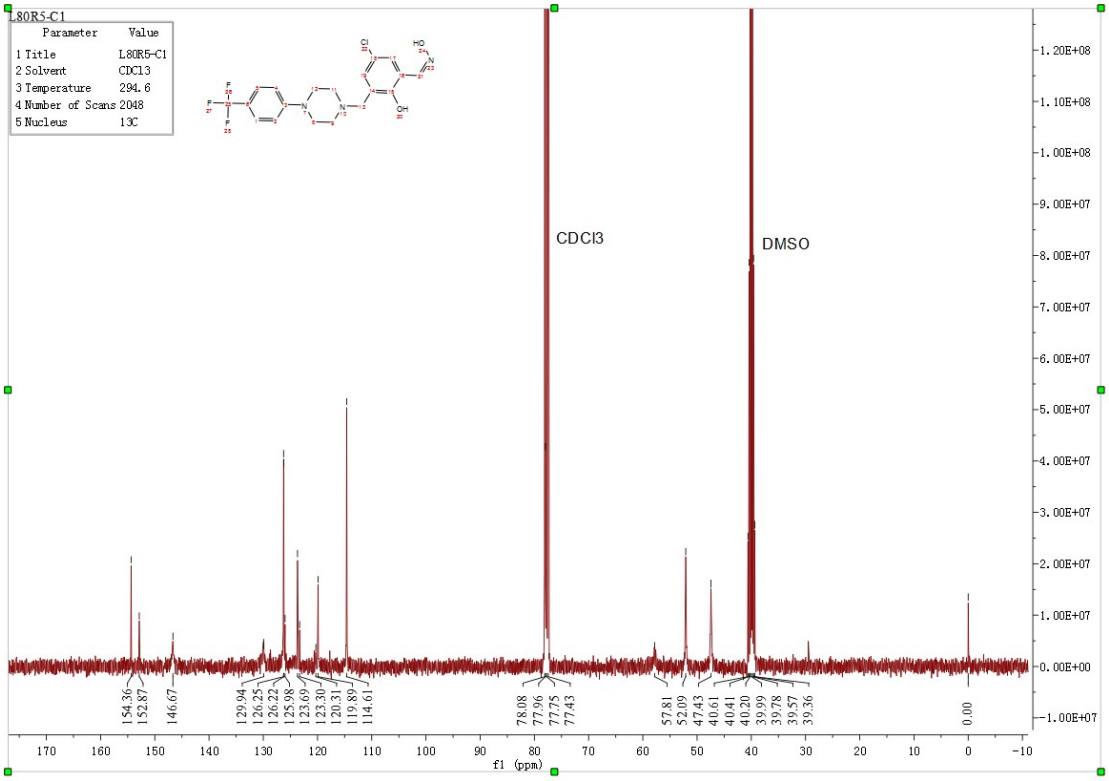
Data Filename	0066.d	**Sample Name**	L80R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

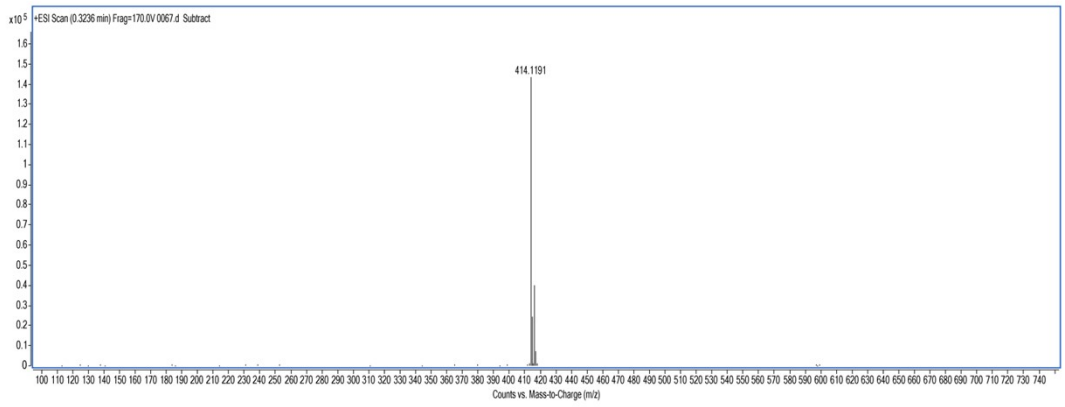


L80R5

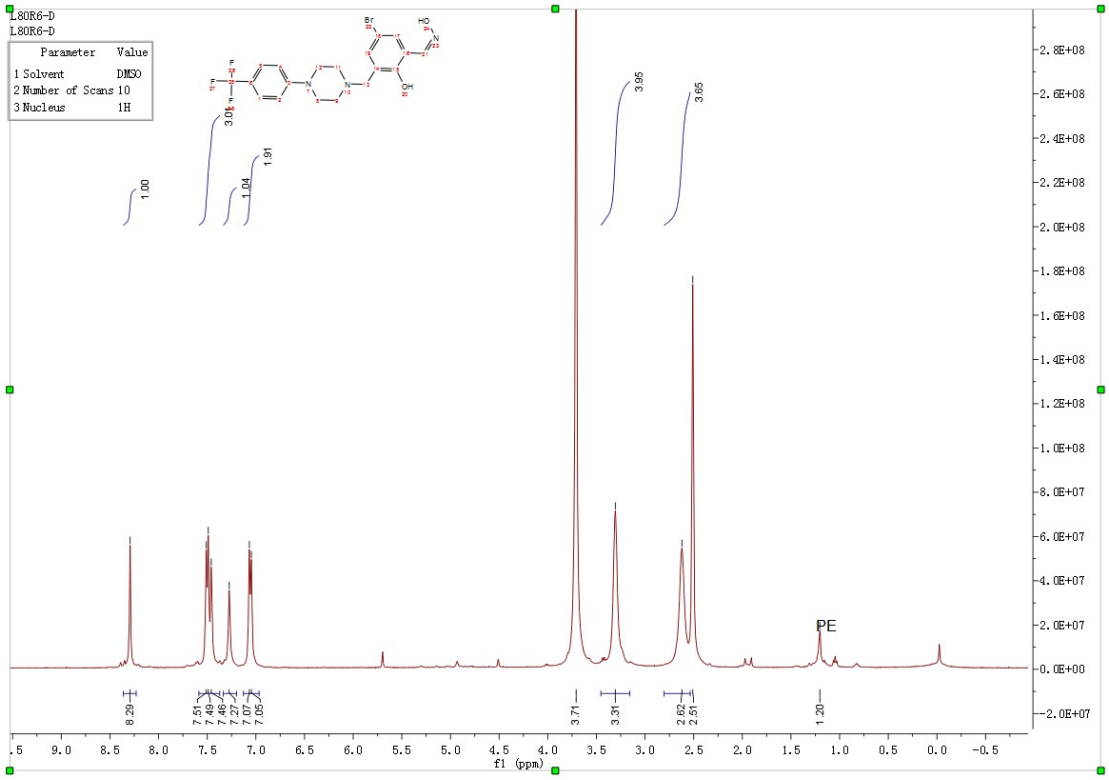


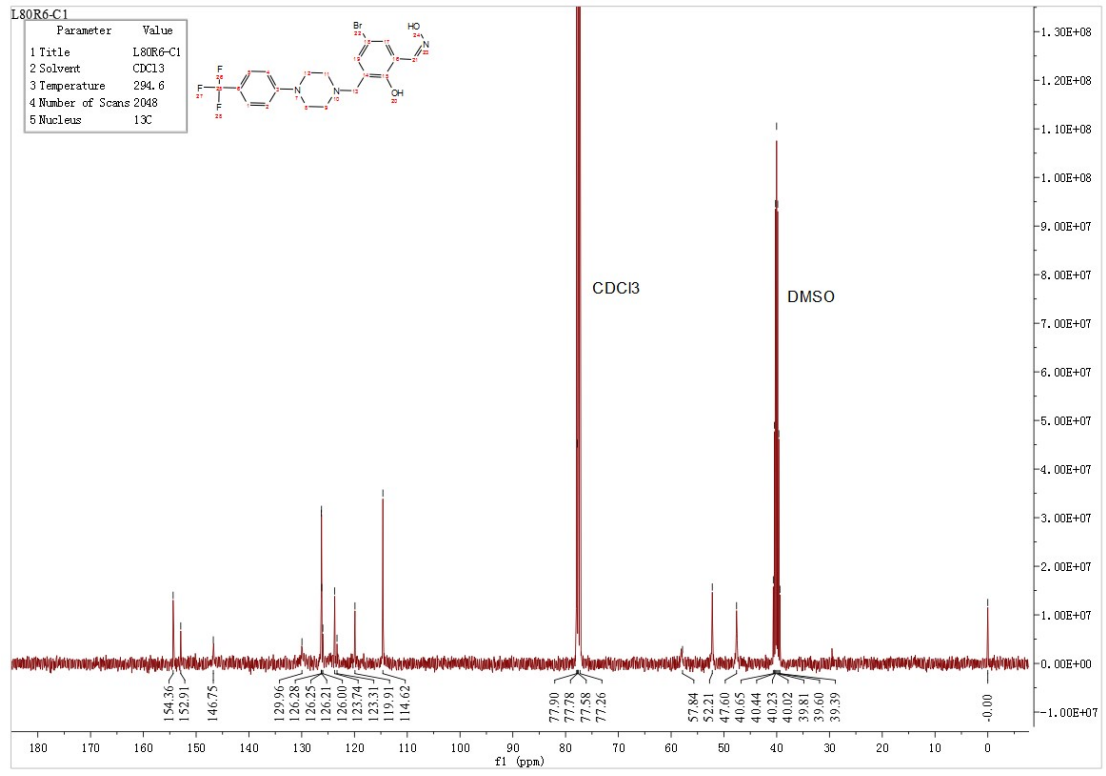


Data Filename	0067.d	**Sample Name**	L80R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			

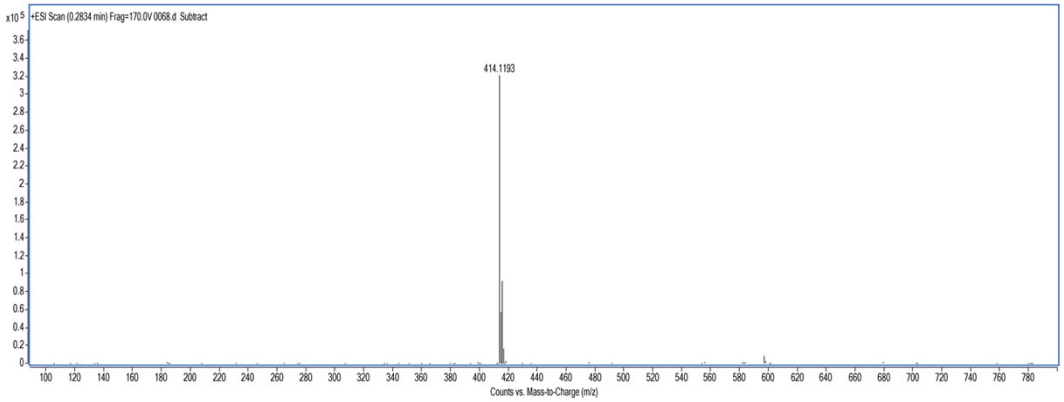


L80R6

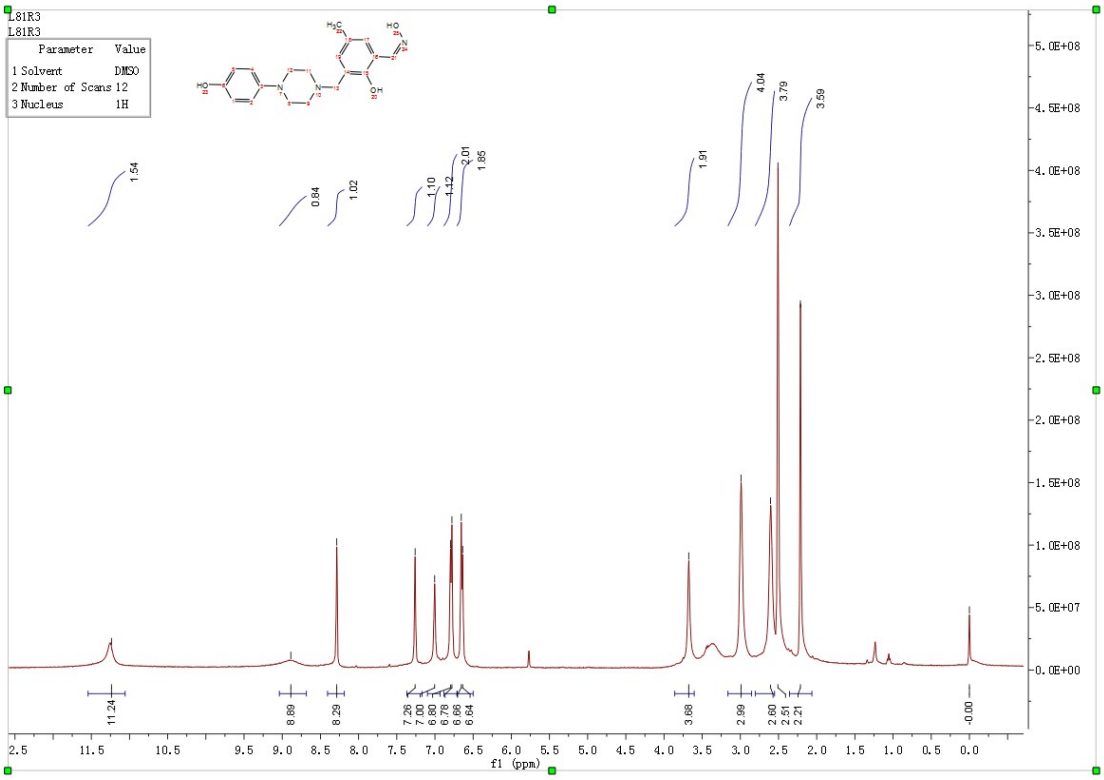

L80R6-D
L80R6-D
Parameter Value
1 Solvent DMSO
2 Number of Scans 10
3 Nucleus 1H
PE
f1 (ppm)

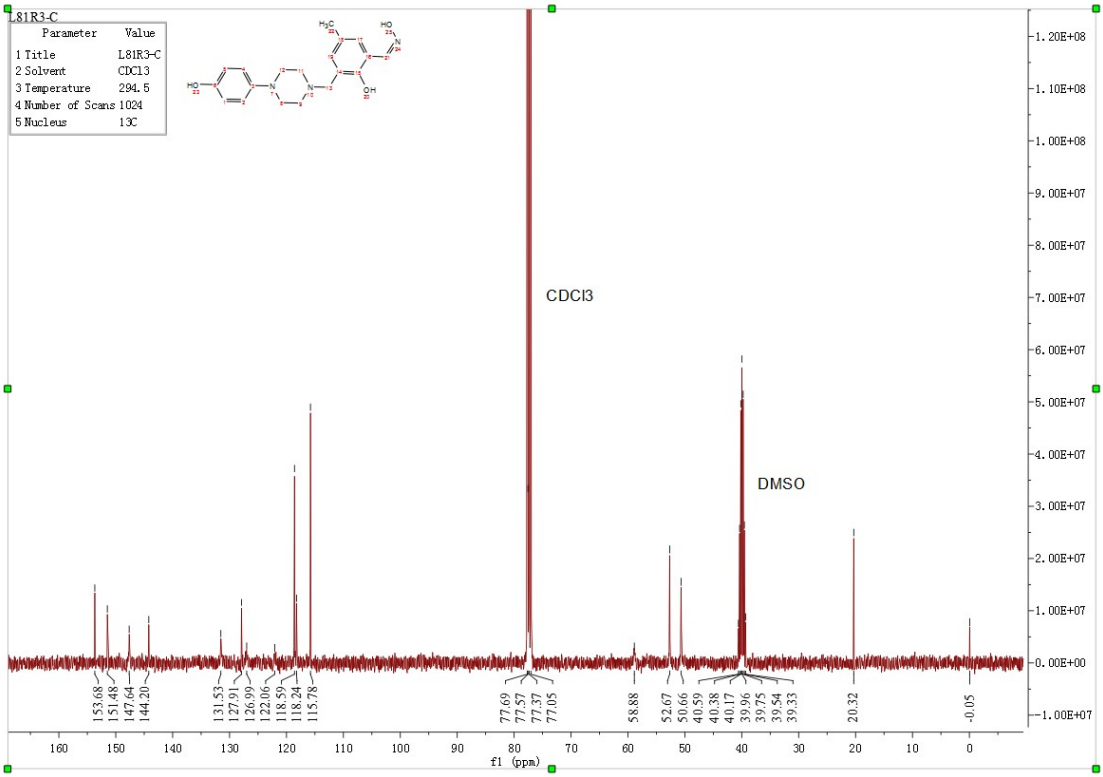

L80R6-C1
Parameter Value
1 Title L80R6-C1
2 Solvent CDCl3
3 Temperature 294.6
4 Number of Scans 2048
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0068.d	**Sample Name**	L80R6
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



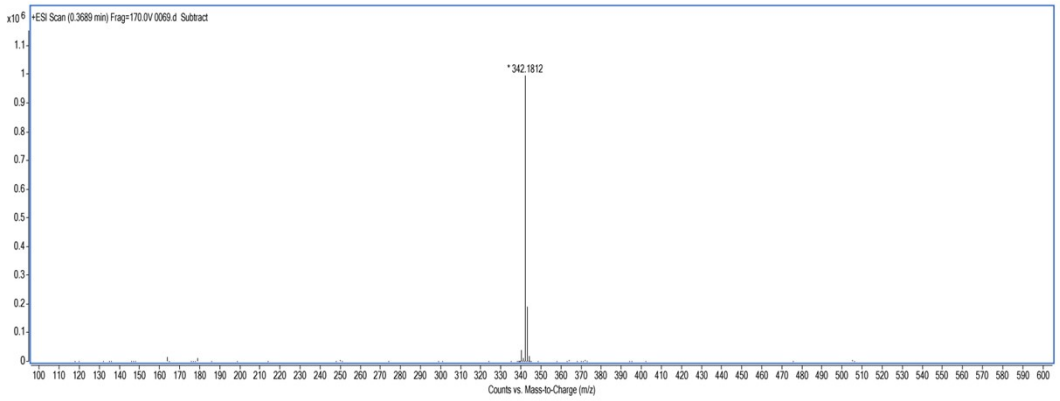
L81R3



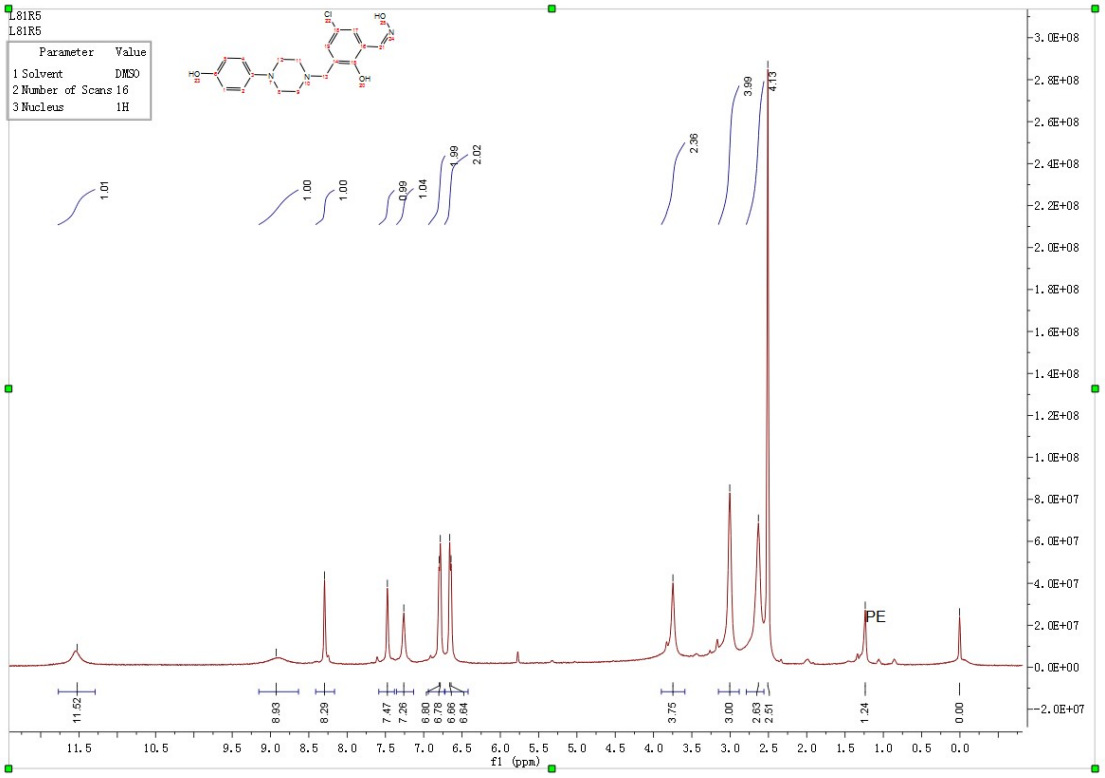


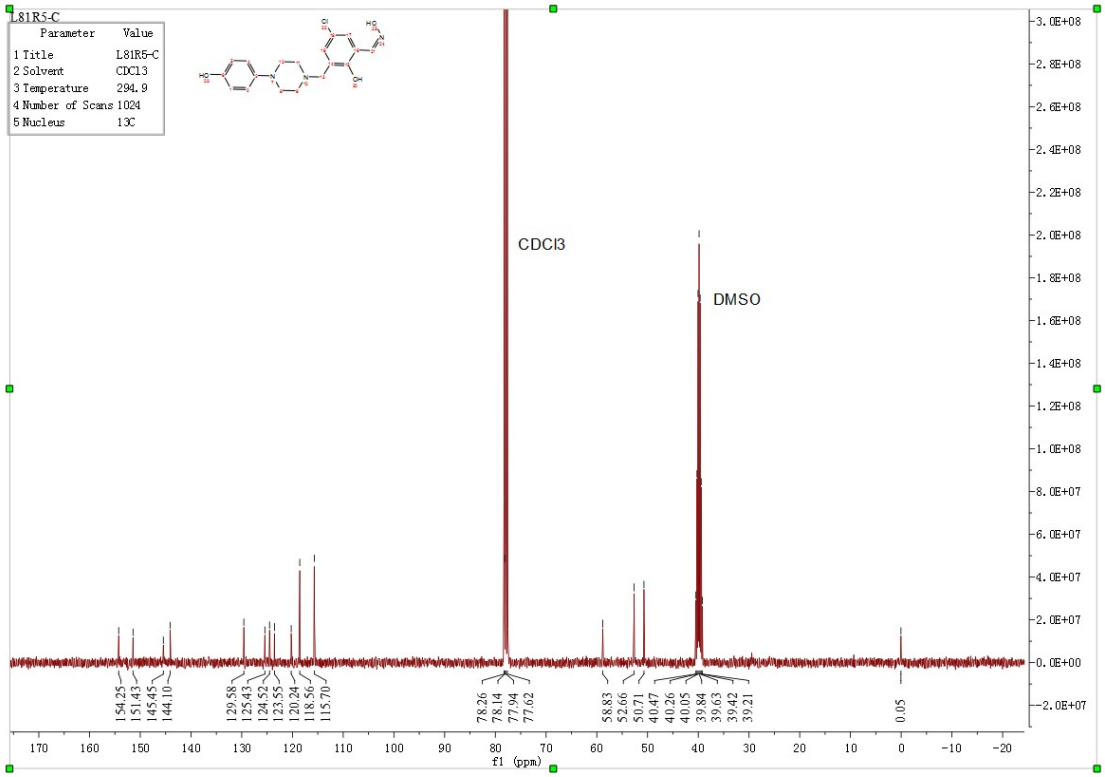
Data Filename	0069.d	**Sample Name**	L81R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms



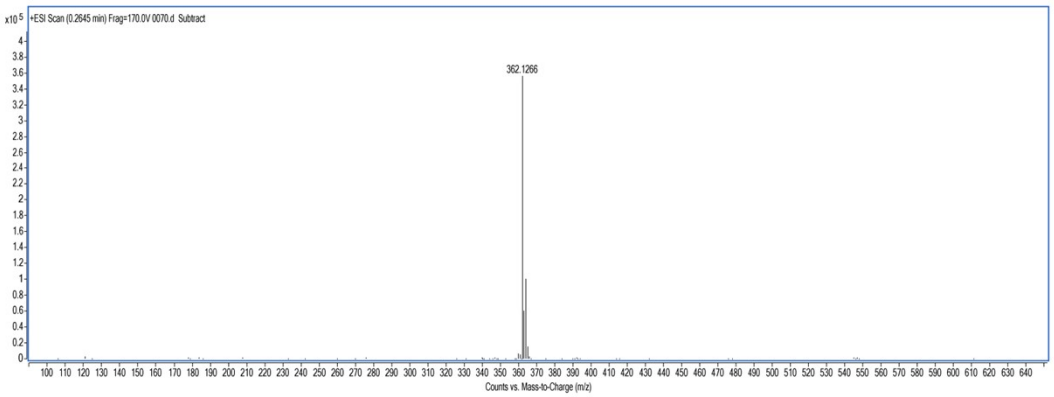
L81R5


L81R5
L81R5
Parameter Value
1 Solvent DMSO
2 Number of Scans 16
3 Nucleus 1H
PE
f1 (ppm)

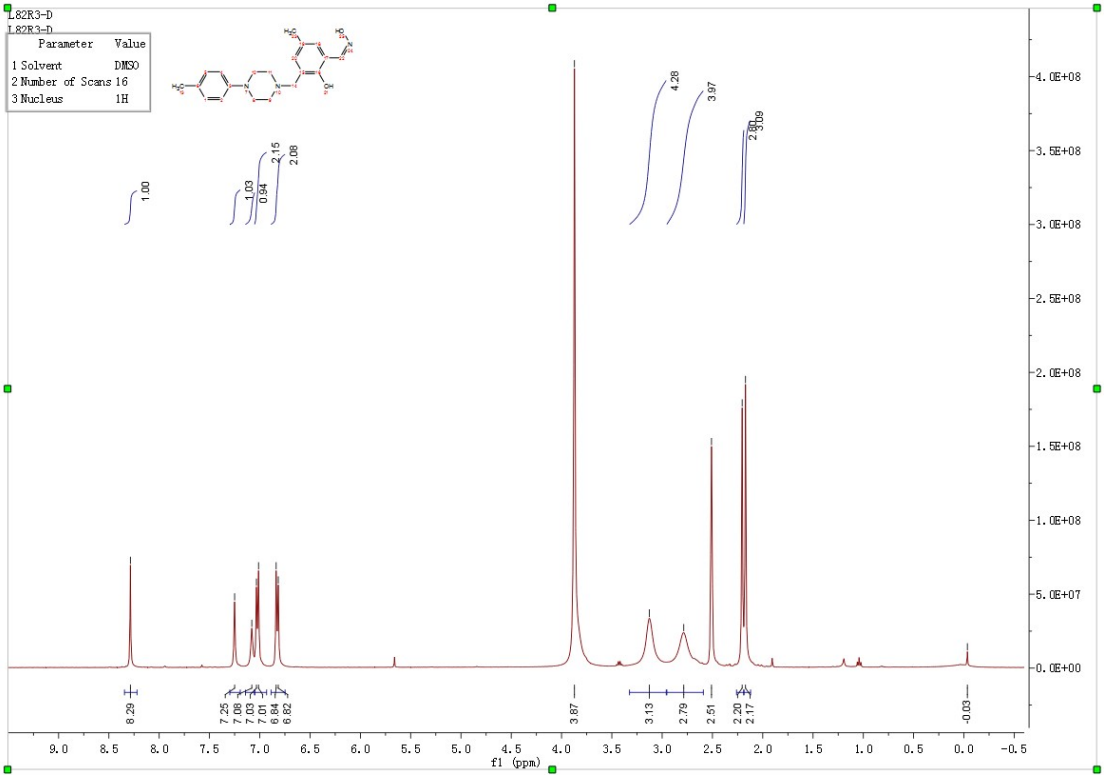

L81R5-C
Parameter Value
1 Title L81R5-C
2 Solvent CDCl3
3 Temperature 294.9
4 Number of Scans 1024
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

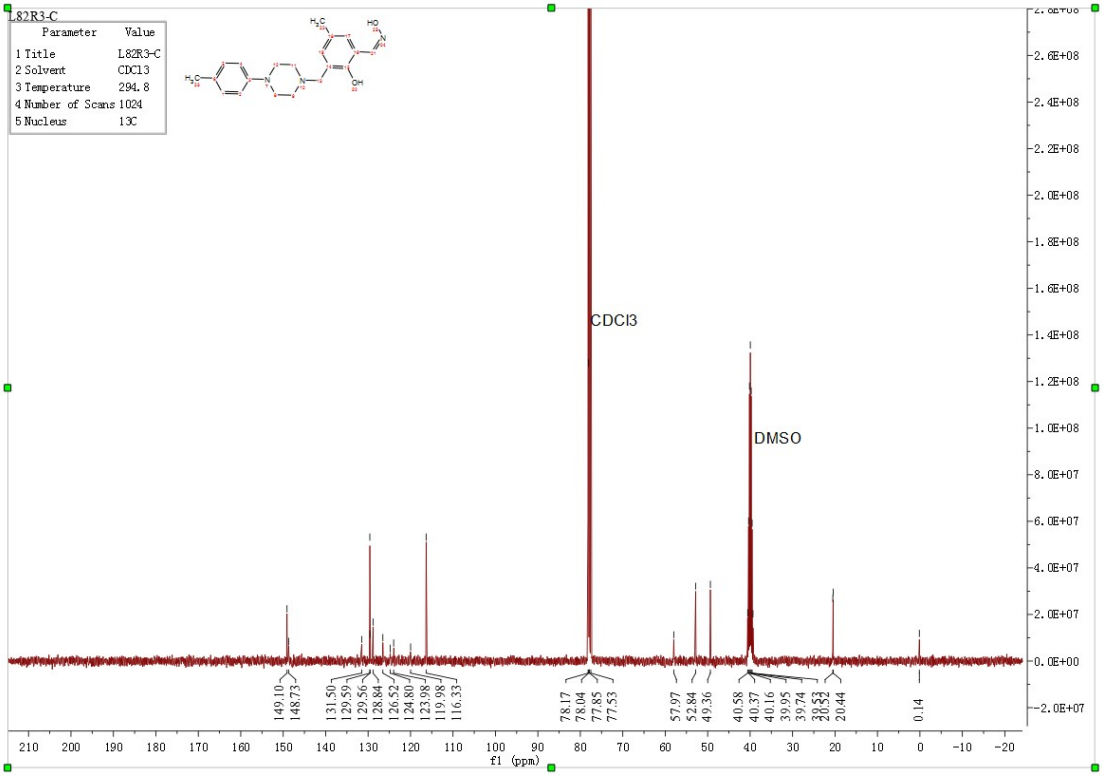
Data Filename	0070.d	**Sample Name**	L81R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

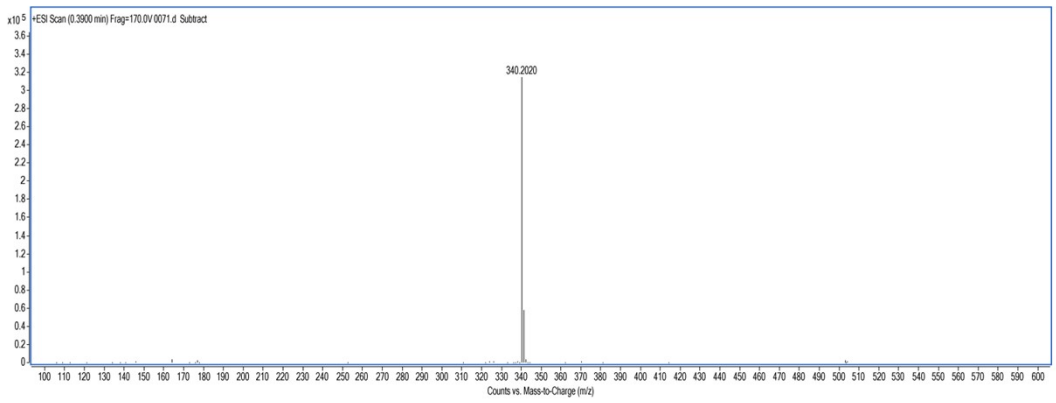


L82R3

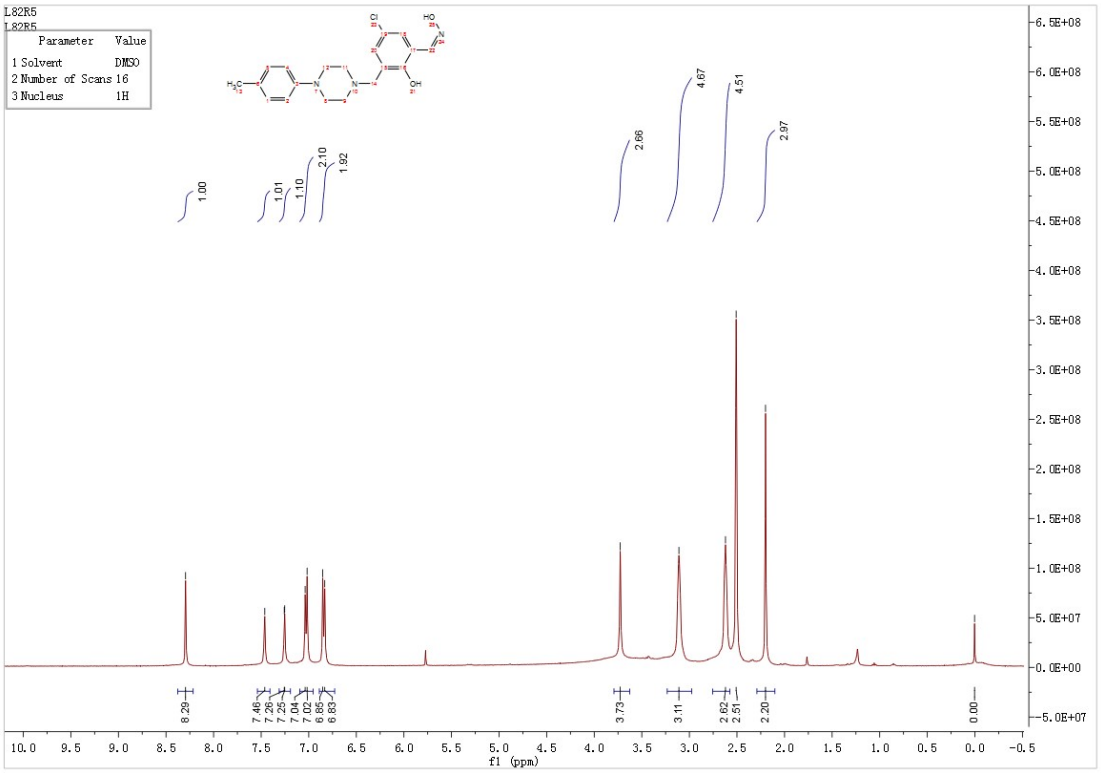


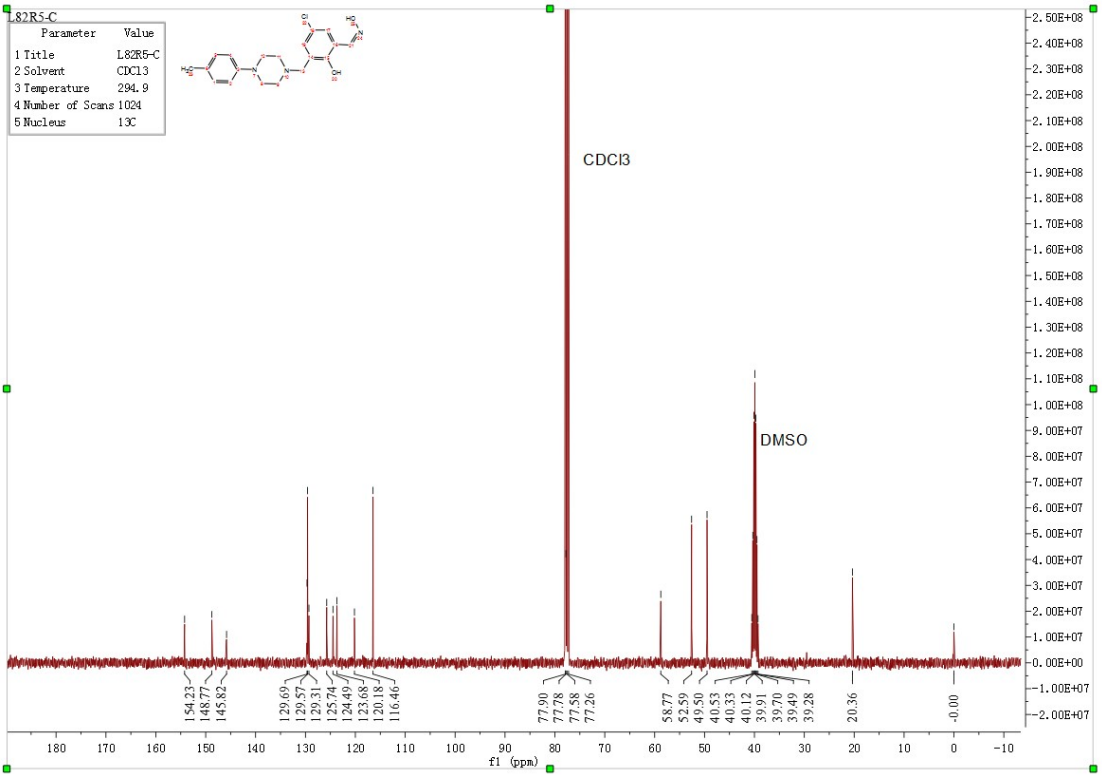


Data Filename	0071.d	**Sample Name**	L82R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			

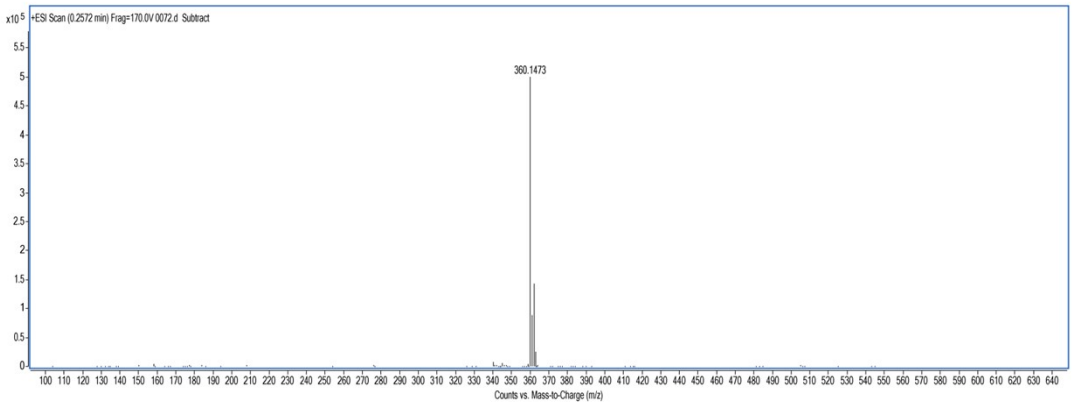


L82R5

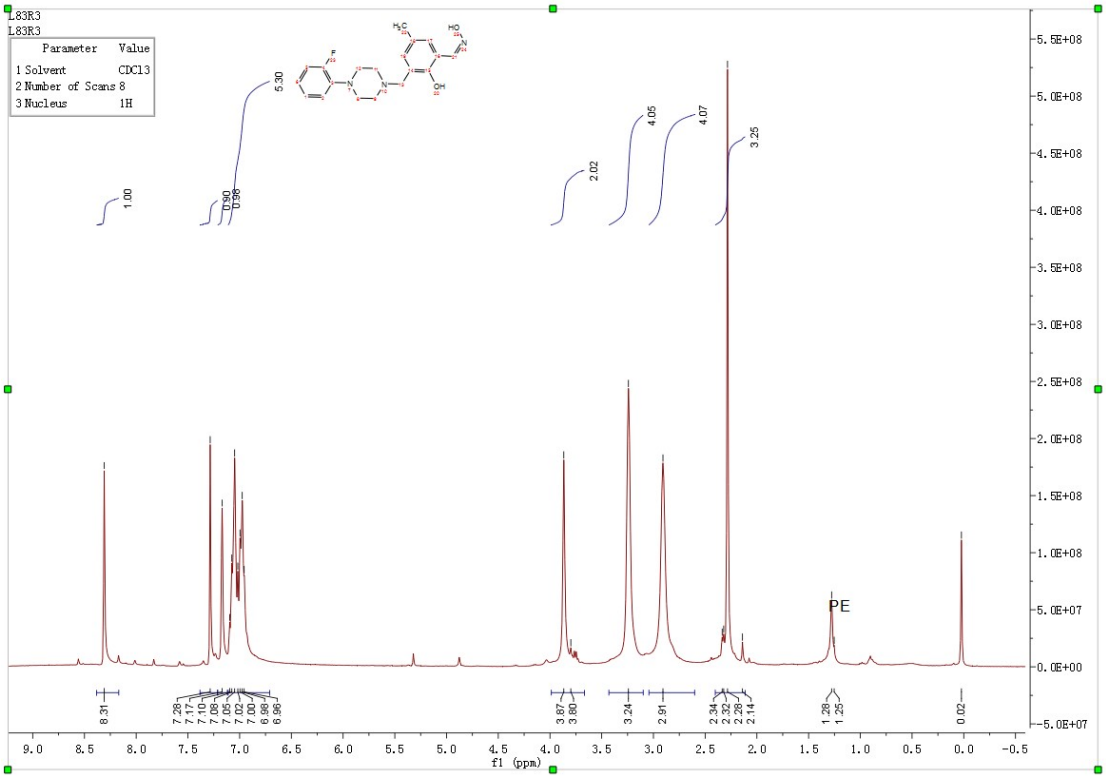

L82R5
L82R5
Parameter Value
1 Solvent DMSO
2 Number of Scans 16
3 Nucleus 1H
f1 (ppm)

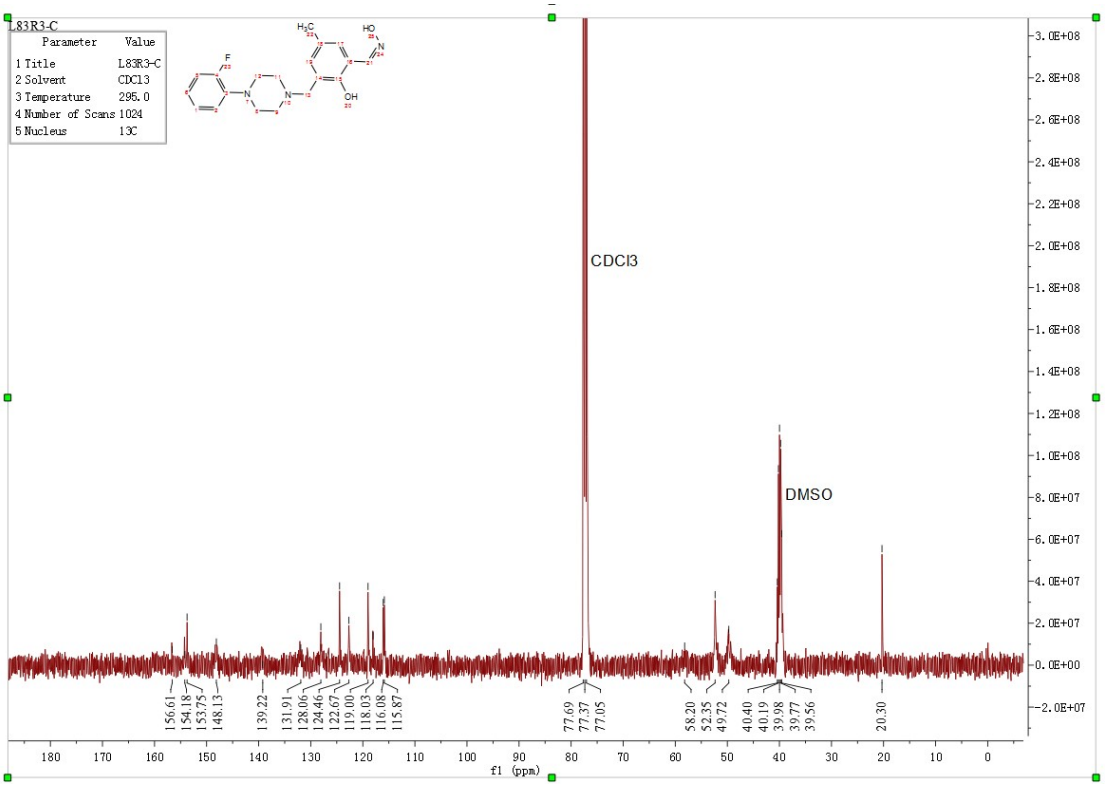

L82R5-C
Parameter Value
1 Title L82R5-C
2 Solvent CDCl3
3 Temperature 294.9
4 Number of Scans 1024
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0072.d	**Sample Name**	L82R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



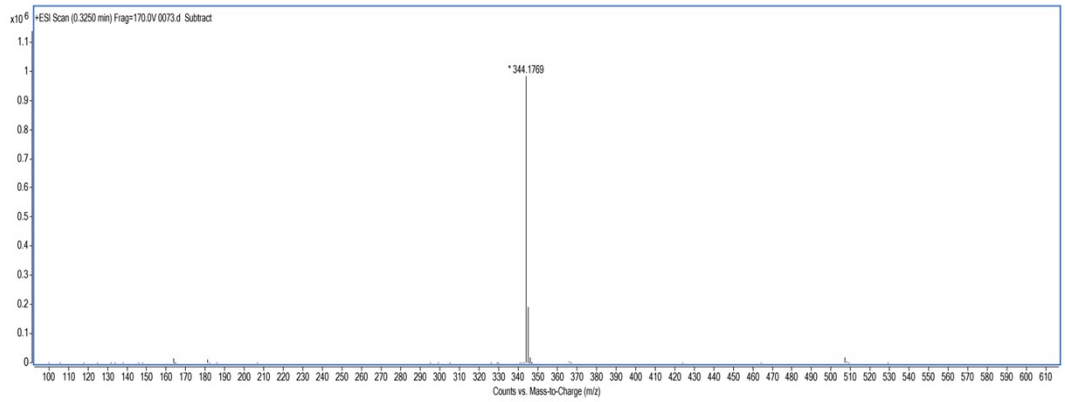
L83R3



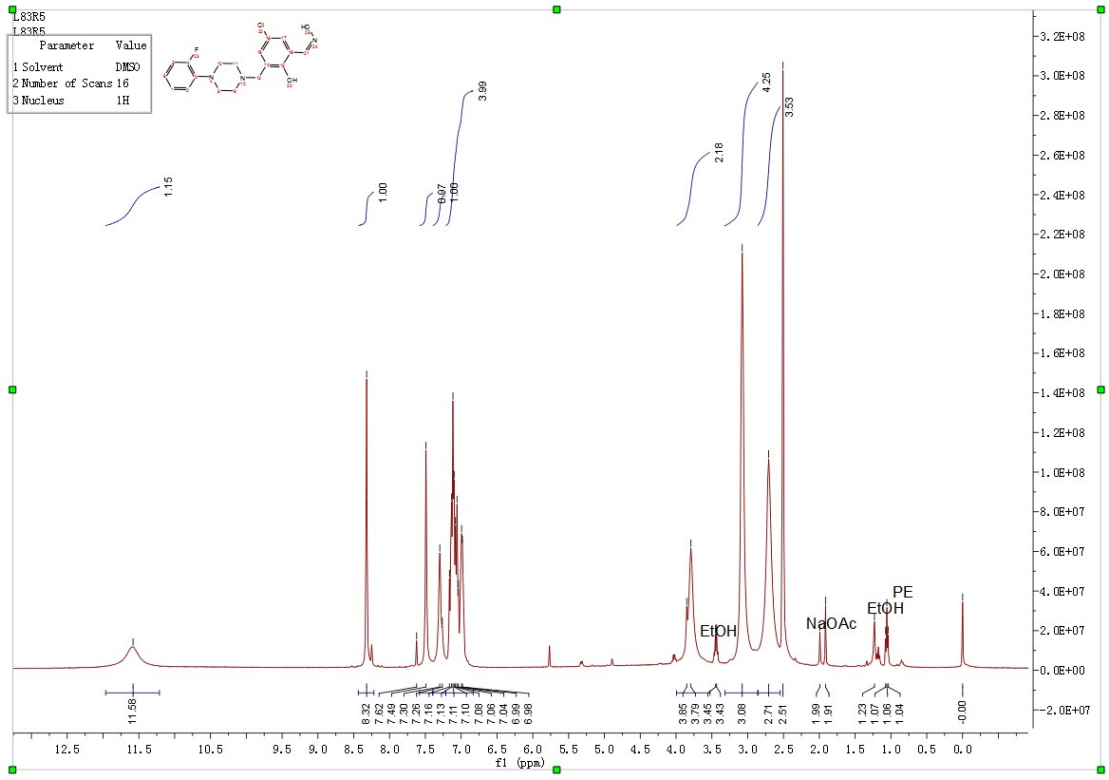


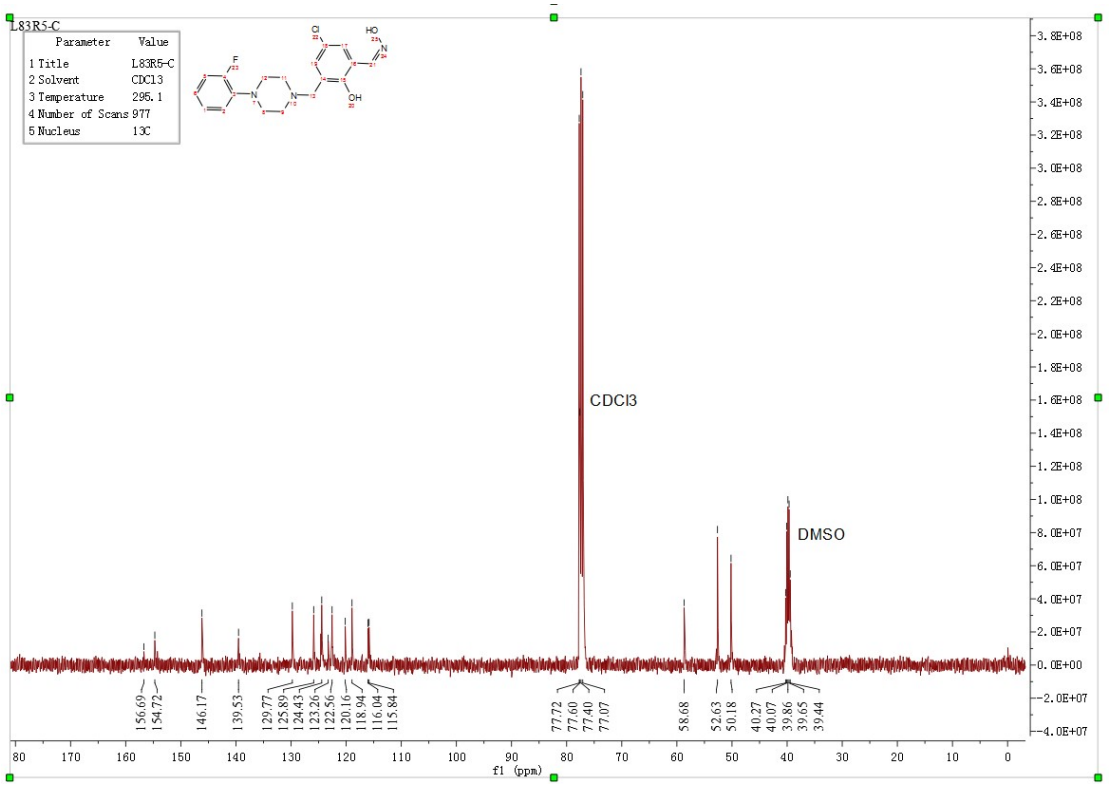
Data Filename	0073.d	**Sample Name**	L83R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

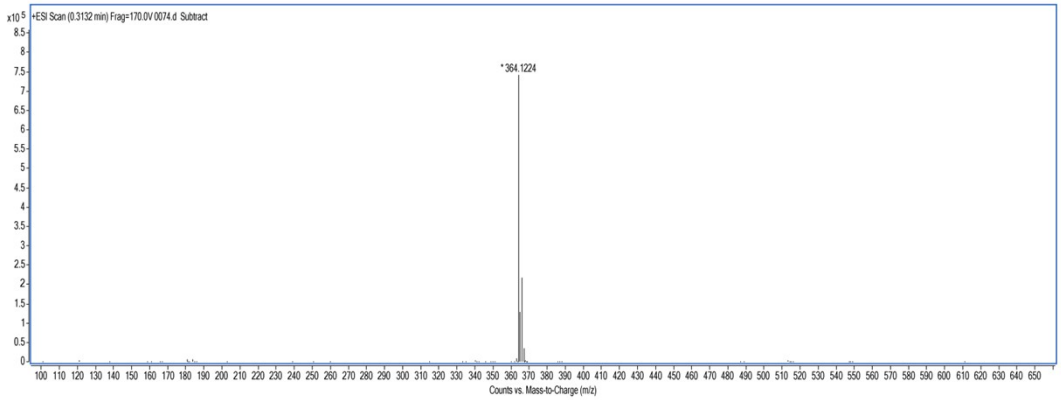


L83R5

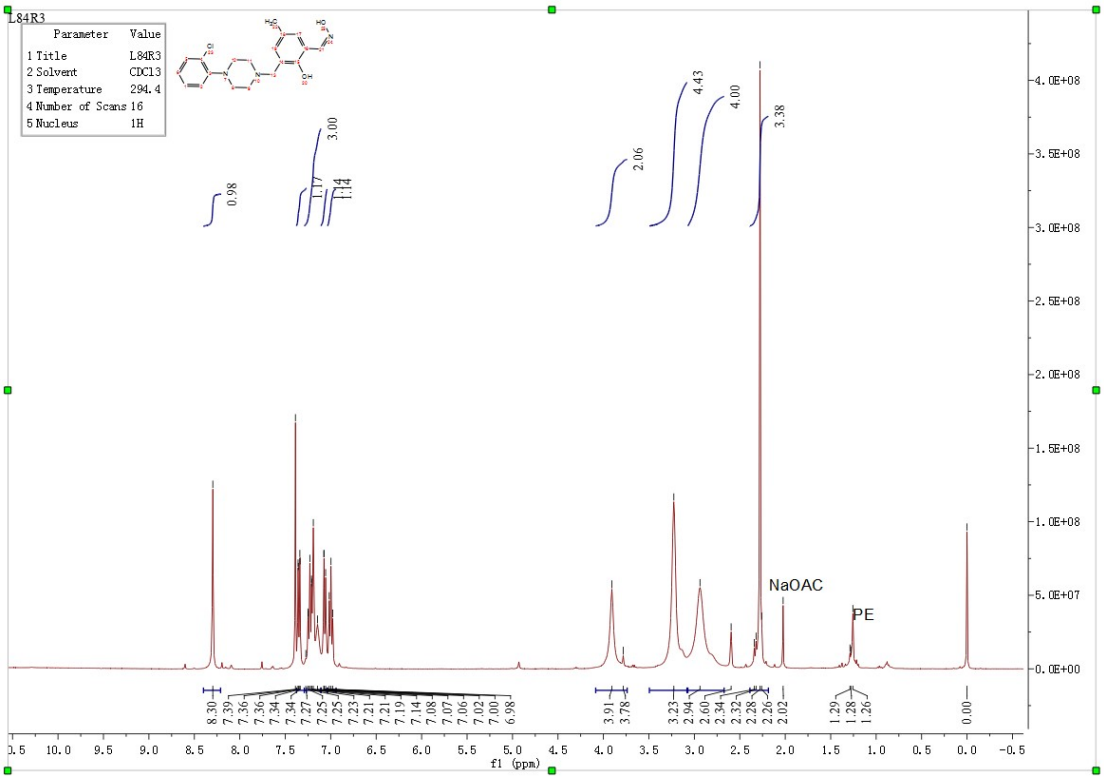

L83R5
L83R5
Parameter Value
1 Solvent DMSO
2 Number of Scans 16
3 Nucleus 1H
EtOH
NaOAc
EtOH
PE
f1 (ppm)

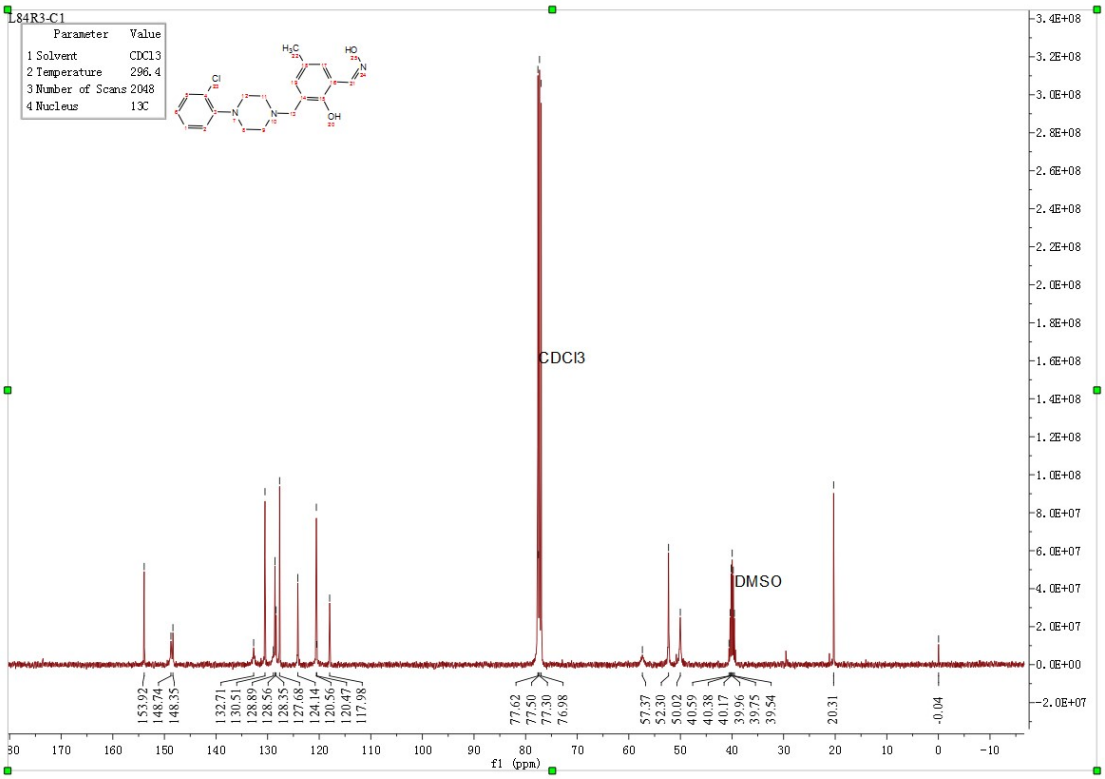

L83R5-C
Parameter Value
1 Title L83R5-C
2 Solvent CDCl3
3 Temperature 295.1
4 Number of Scans 977
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0074.d	**Sample Name**	L83R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



L84R3

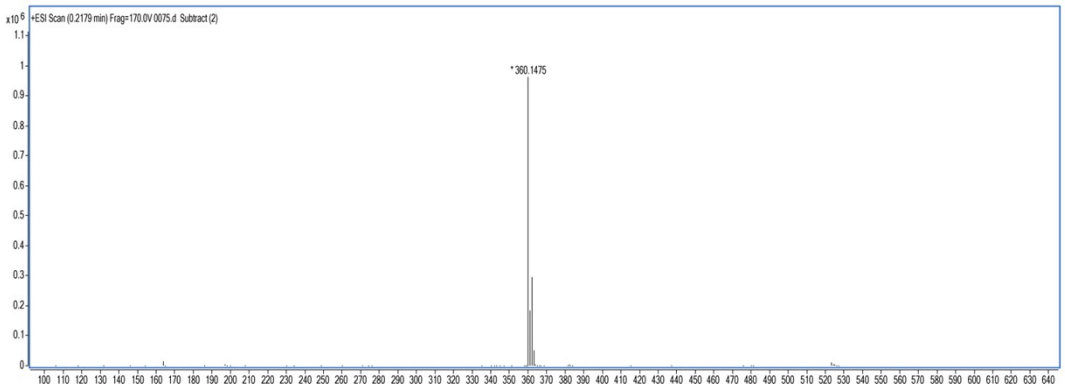




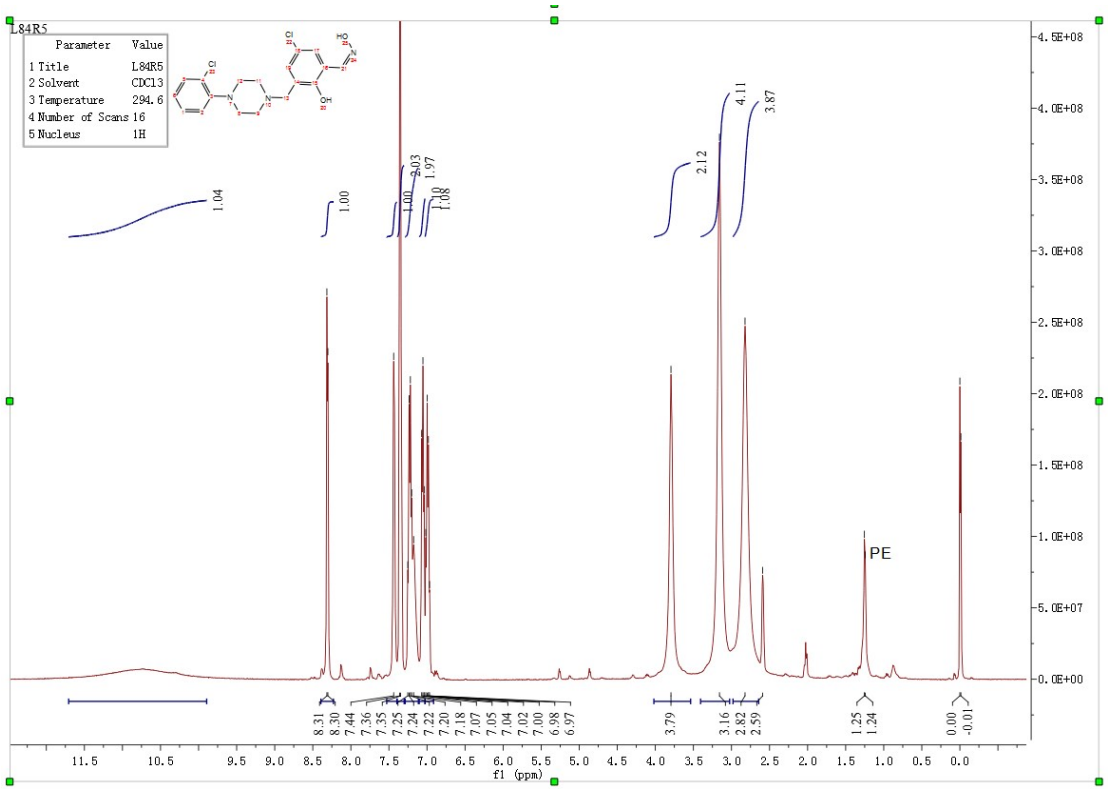
Qualitative Analysis Report

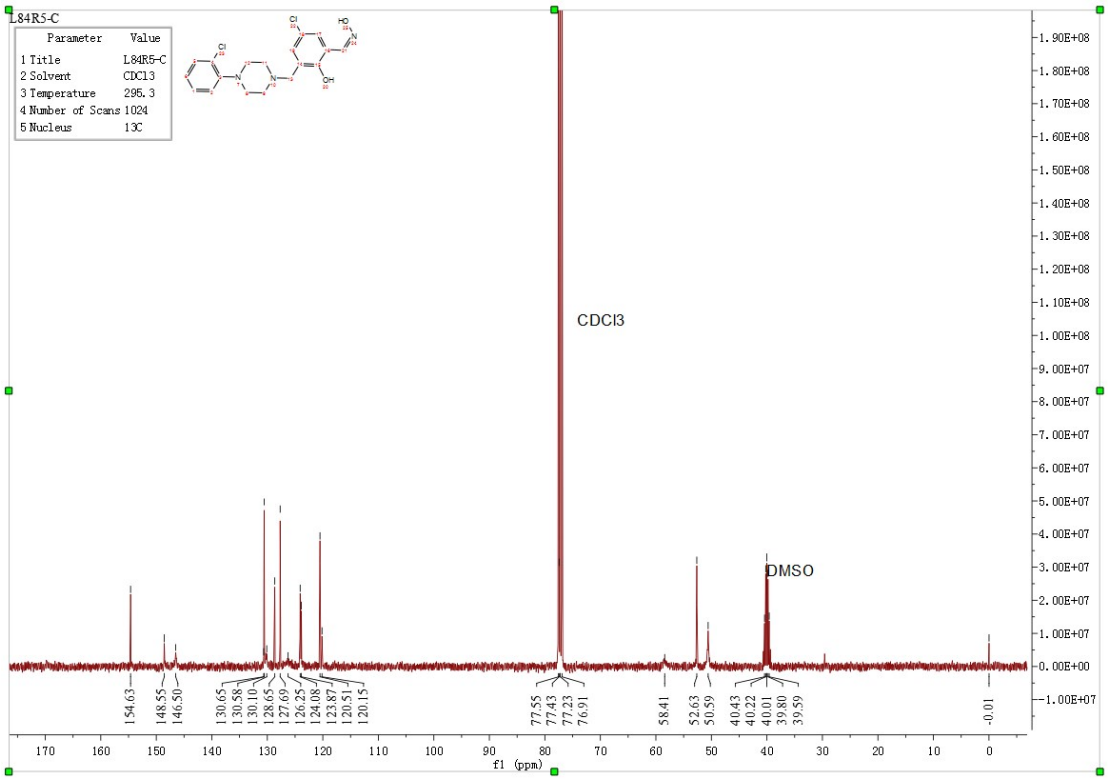
Data Filename	0075.d	**Sample Name**	L84R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms

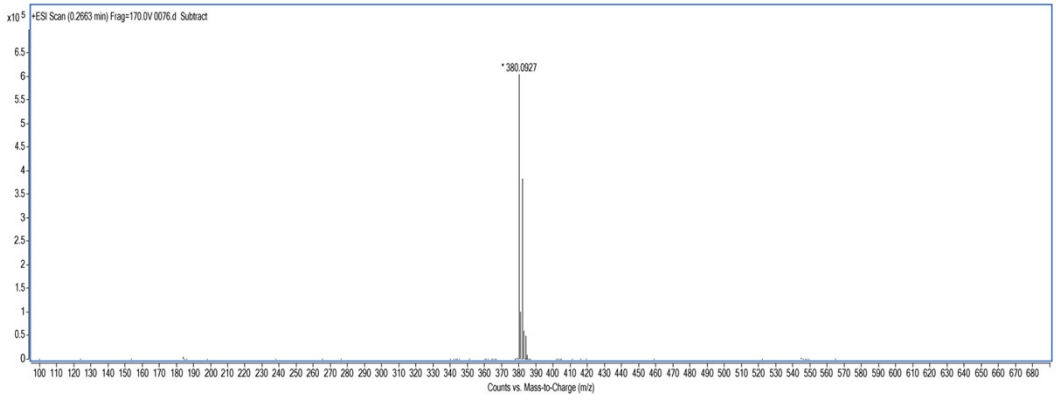


L84R5

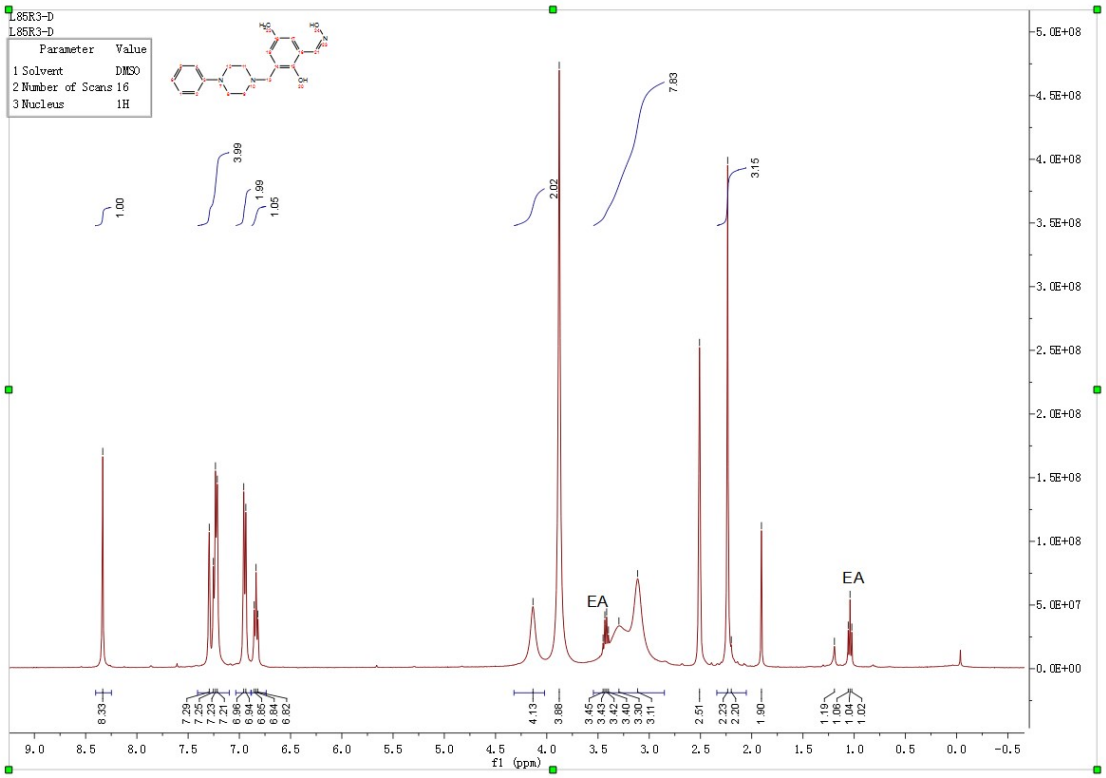

L84R5
Parameter Value
1 Title L84R5
2 Solvent CDCl3
3 Temperature 294.6
4 Number of Scans 16
5 Nucleus 1H
PE
f1 (ppm)

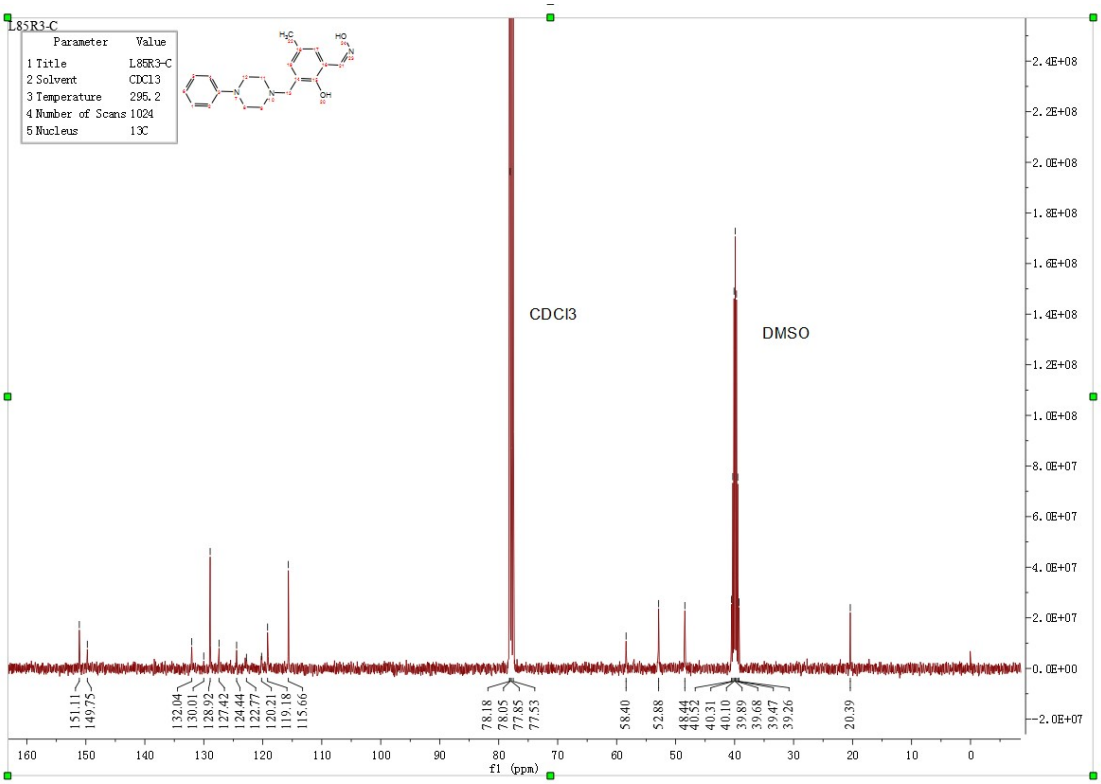

L84R5-C
Parameter Value
1 Title L84R5-C
2 Solvent CDCl3
3 Temperature 295.3
4 Number of Scans 1024
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0076.d	**Sample Name**	L84R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		
User Chormatograms			



L85R3

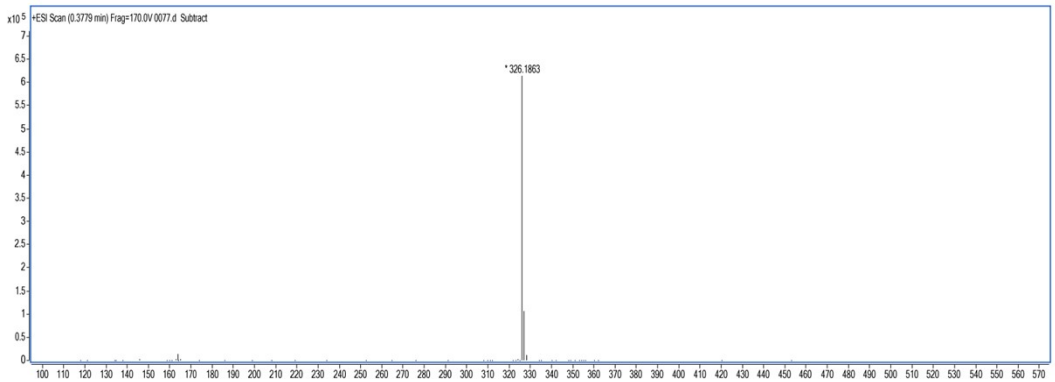




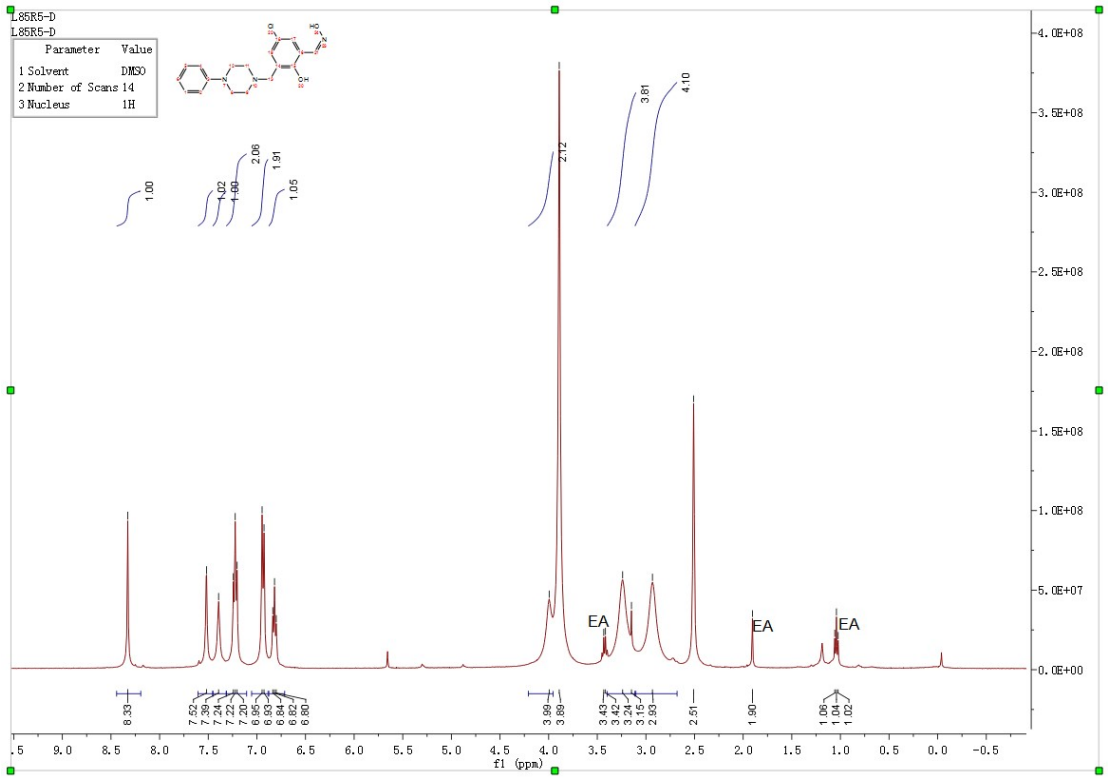
Qualitative Analysis Report

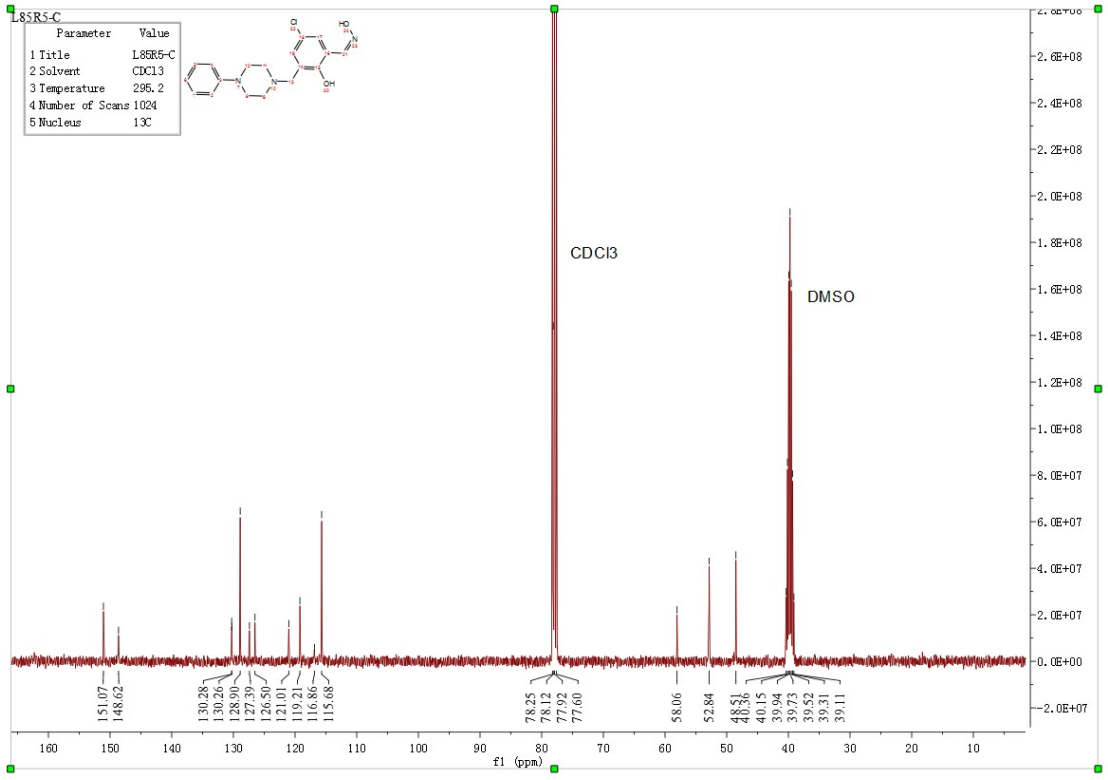
Data Filename	0077.d	**Sample Name**	L85R3
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	Success		

User Chormatograms



L85R5


L85R5-D
L85R5-D
Parameter Value
1 Solvent DMSO
2 Number of Scans 14
3 Nucleus 1H
EA
EA
EA
f1 (ppm)


L85R5-C
Parameter Value
1 Title L85R5-C
2 Solvent CDCl3
3 Temperature 295.2
4 Number of Scans 1024
5 Nucleus 13C
CDCl3
DMSO
f1 (ppm)

Data Filename	0078.d	**Sample Name**	L85R5
Instrument Name	TOF G6230A	**Acquired Time**	2024-01-16
Acq Method	YCL.M	**Acquired SW**	6200 series TOF/6500 series
IRM Calibration Status	**Success**		

User Chormatograms