FtmOx1-Catalyzed Diverse C(sp^3)-H Oxyfunctionalization Enables Versatile Late-stage Diversification of Phenethylamines and Tetrahydroisoquinolines

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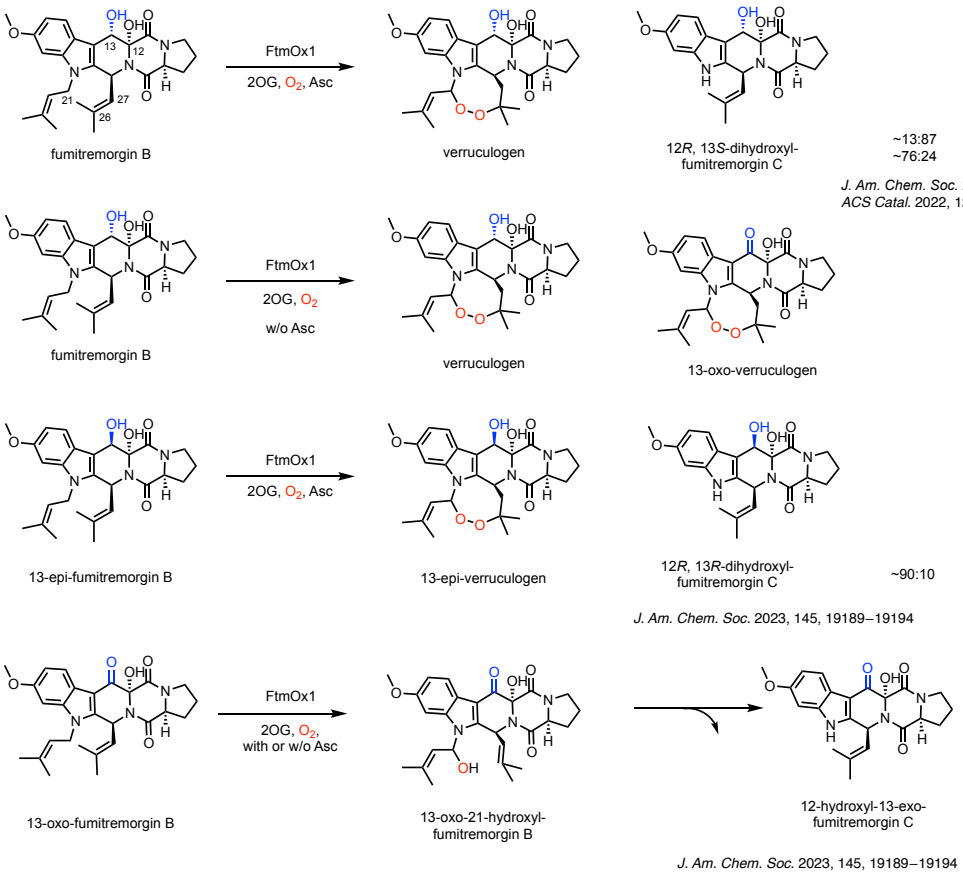


Scheme S1. Various C-H oxidation catalyzed by FtmOx1.

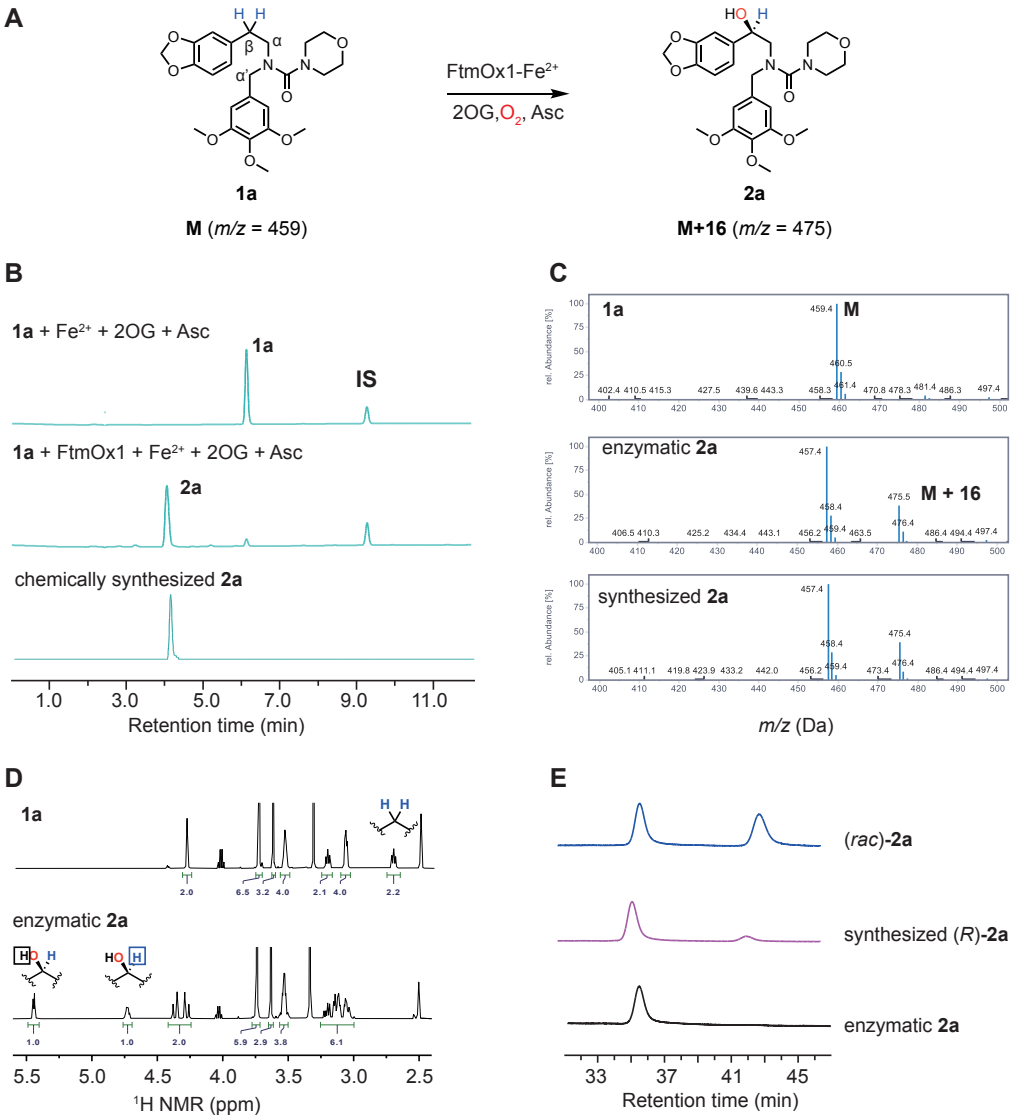


Figure S1. β-C(sp³)-H Hydroxylation Catalyzed by FtmOx1 with Substrate **1a** to Generate (*R*)-**2a**. (A) Schematic of the enzymatic hydroxylation reaction. Reactions were performed at a 100 µL scale using 2 mM **1a**, 0.05 mM FtmOx1, 1 mM Fe^{2+}, 2 mM sodium ascorbate, and 4 mM 2OG. For experimental details, refer to the Supporting Information. (B) LC-MS analysis of the reaction mixture, showing a distinct peak for **2a** that matches the chemically synthesized standard (std.). (C) Mass spectra comparison of enzymatically produced **2a** and synthetic std. **2a**, confirming identical molecular weights. (D) NMR spectra of **1a** and **2a**, demonstrating hydroxylation at the β-C(sp³)-H position. (E) Chiral HPLC chromatograms of enzymatically produced **2a**, synthetic racemate **2a**, and (*R*)-stereomer **2a**, confirming the *R*-configuration of the enzymatic product.

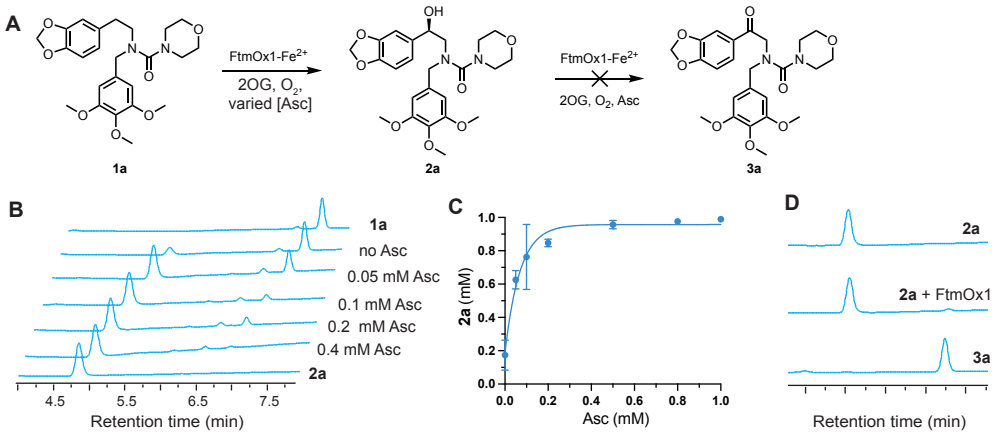


Figure S2. Validation of the Roles of External Ascorbate and the Stability of the Hydroxylated Product in β-C(sp^3)-H Hydroxylation Catalyzed by FtmOx1. (A) Reaction scheme. (B) LC analysis of the reaction of **1a** with FtmOx1. Reactions were conducted at 100 µL scale using 2 mM **1a**, 0.05 mM FtmOx1, 1 mM Fe^{2+}, and 2 mM 2OG, with varying ascorbate concentrations. Each reaction was performed in triplicate. (C) Quantification of product **2a** formation as a function of ascorbate concentration. (D) LC analysis of the reaction of **2a** with FtmOx1 under standard conditions, demonstrating the stability of the hydroxylated product.

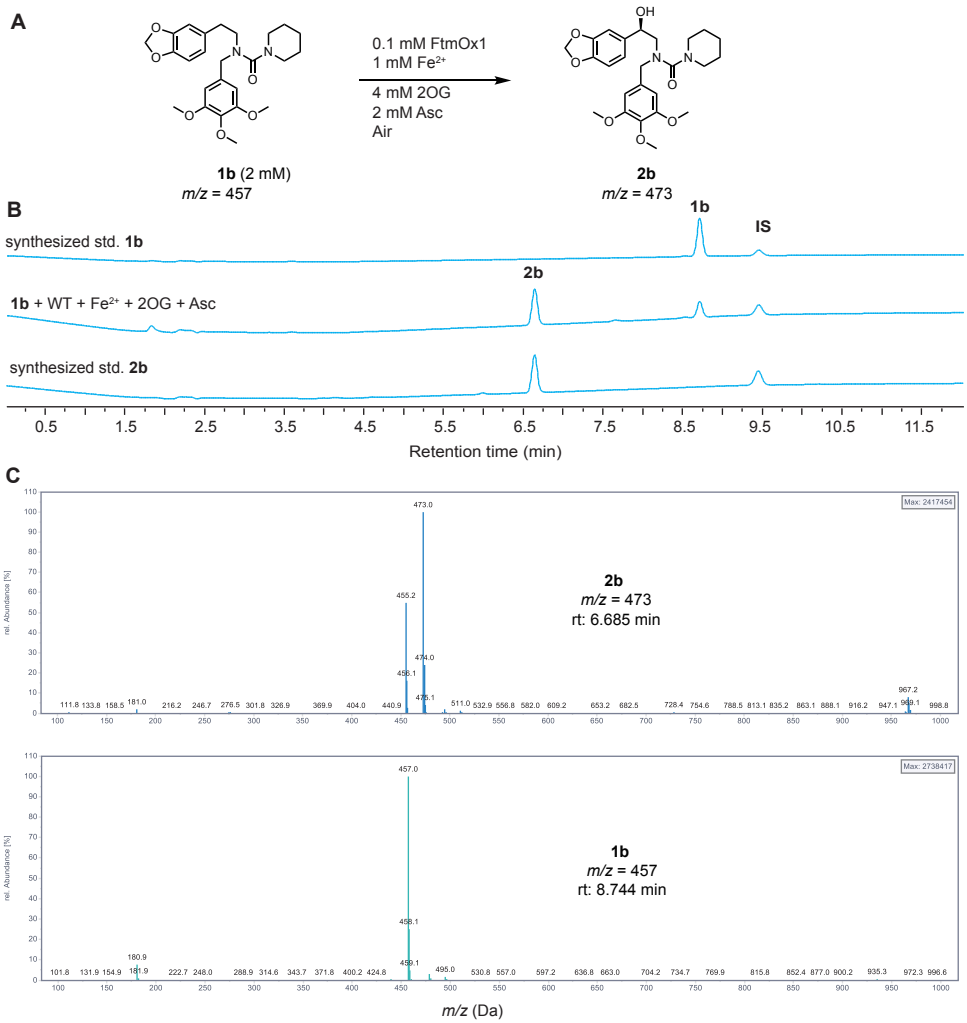


Figure S3. LC-MS analysis of the reaction of FtmOx1 with **1b**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1b** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2b** (*bottom spectrum*). **2b**, **1b** and **IS** were eluted at 6.685 min, 8.744 min, and ~9.5 min, respectively. **C**) mass spectra of **2b** (*top spectrum*) and **1b** (*bottom spectrum*).

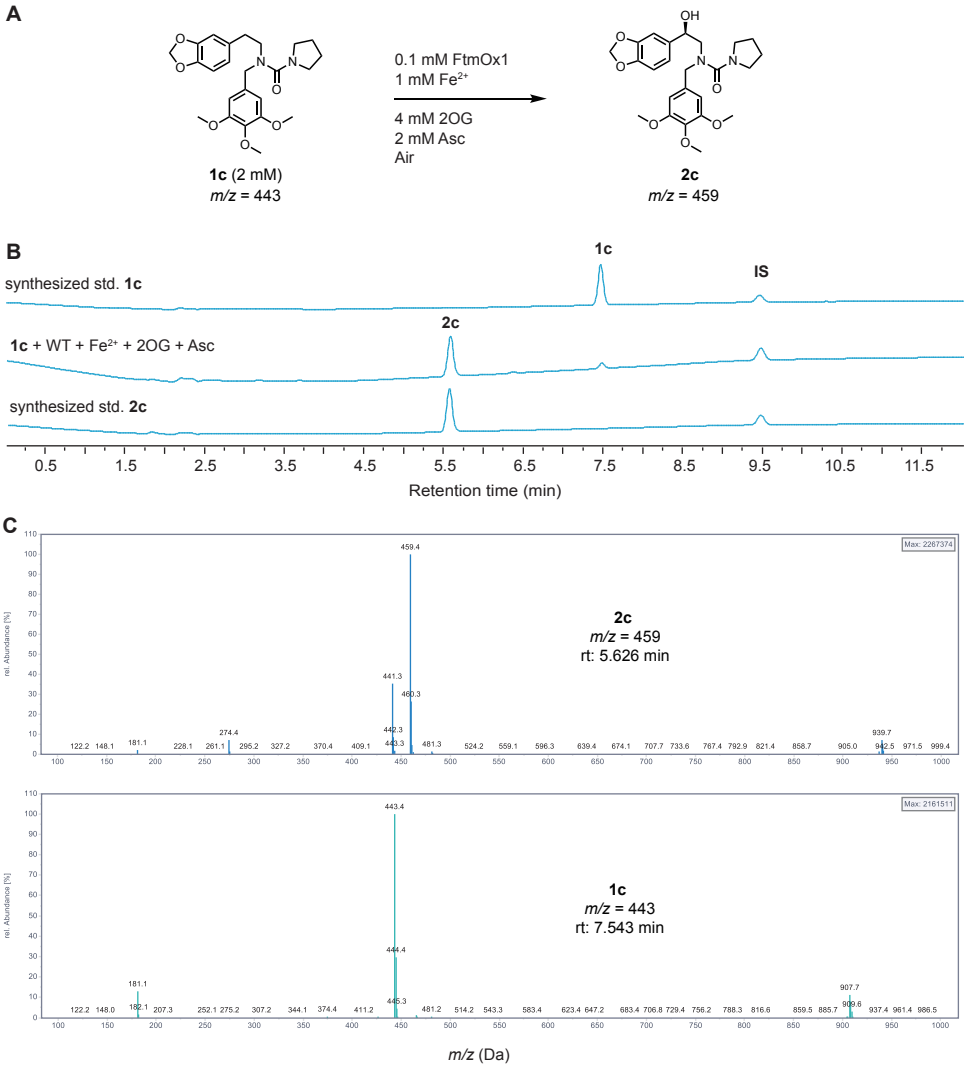


Figure S4. LC-MS analysis of the reaction of FtmOx1 with **1c**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1c** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2c** (*bottom spectrum*). **2c**, **1c** and IS were eluted at 5.626 min, 7.543 min, and ~9.5 min, respectively. **C**) mass spectra of **2c** (*top spectrum*) and **1c** (*bottom spectrum*).

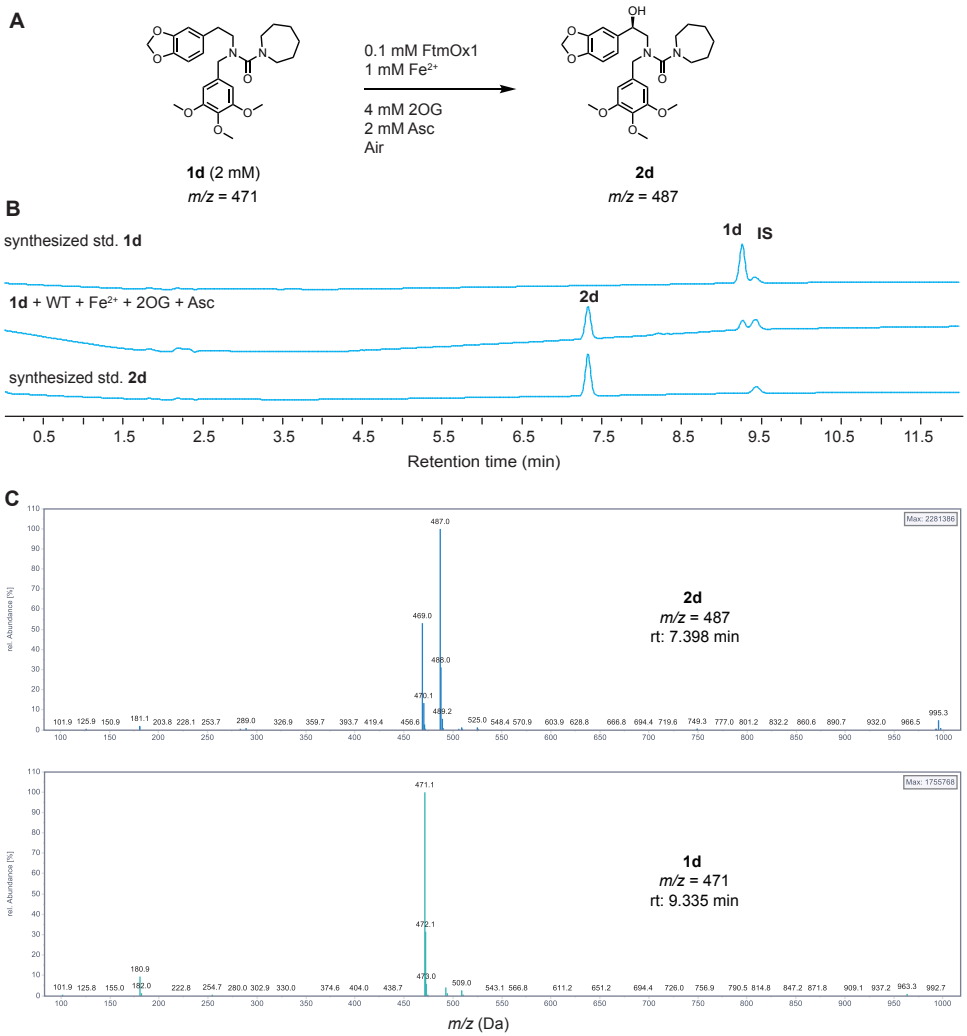


Figure S5. LC-MS analysis of the reaction of FtmOx1 with **1d**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1d** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2d** (*bottom spectrum*). **2d**, **1d** and IS were eluted at 7.398 min, 9.335 min, and ~9.5 min, respectively. **C**) mass spectra of **2d** (*top spectrum*) and **1d** (*bottom spectrum*).

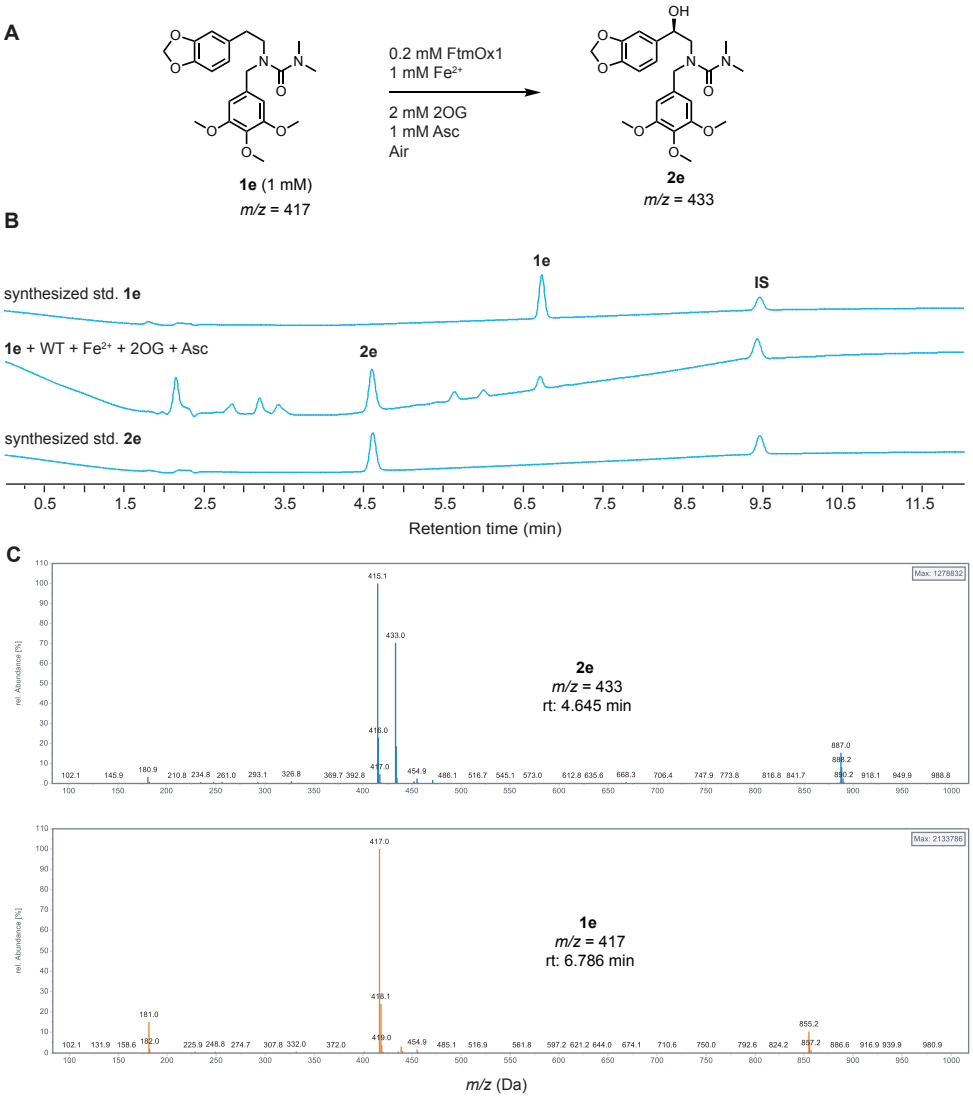


Figure S6. LC-MS analysis of the reaction of FtmOx1 with **1e**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1e** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2e** (*bottom spectrum*). **2e**, **1e** and IS were eluted at 4.645 min, 6.786 min, and ~9.5 min, respectively. **C**) mass spectra of **2e** (*top spectrum*) and **1e** (*bottom spectrum*).

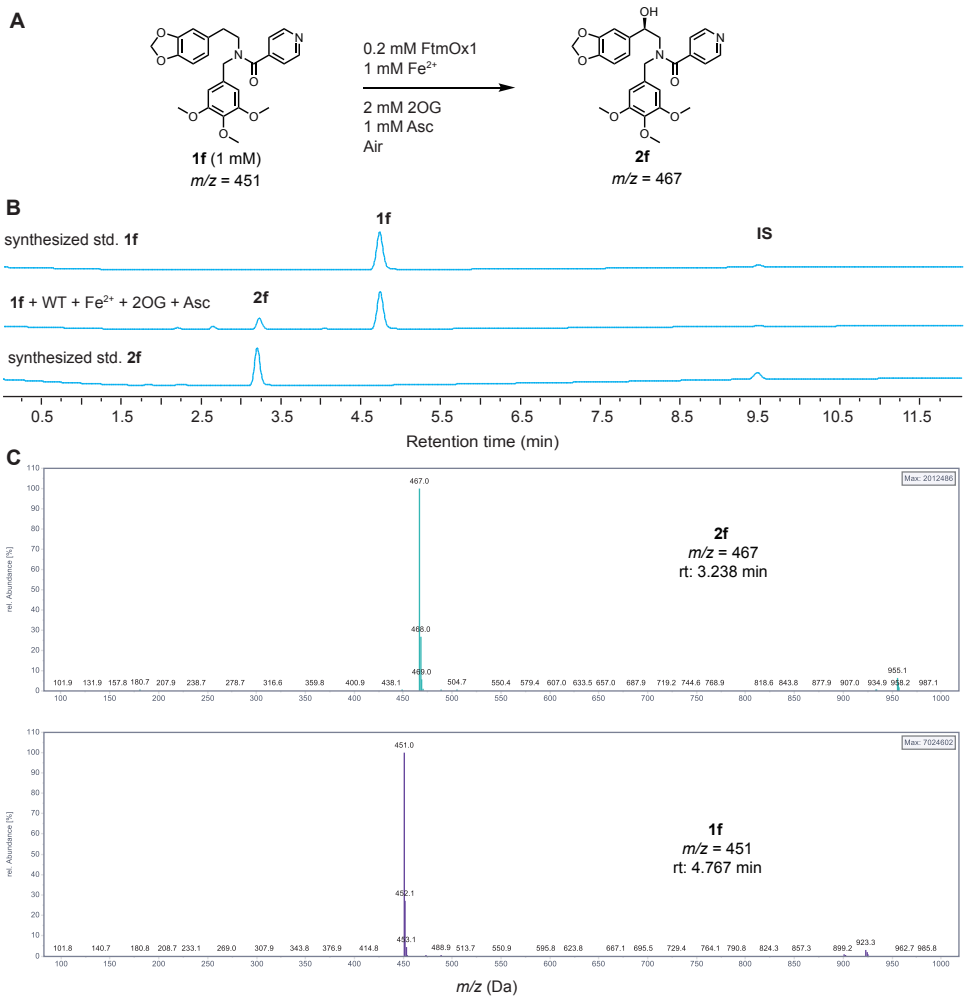


Figure S7. LC-MS analysis of the reaction of FtmOx1 with **1f**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1f** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2f** (*bottom spectrum*). **2f**, **1f** and IS were eluted at 3.238 min, 4.767 min, and ~9.5 min, respectively. **C**) mass spectra of **2f** (*top spectrum*) and **1f** (*bottom spectrum*).

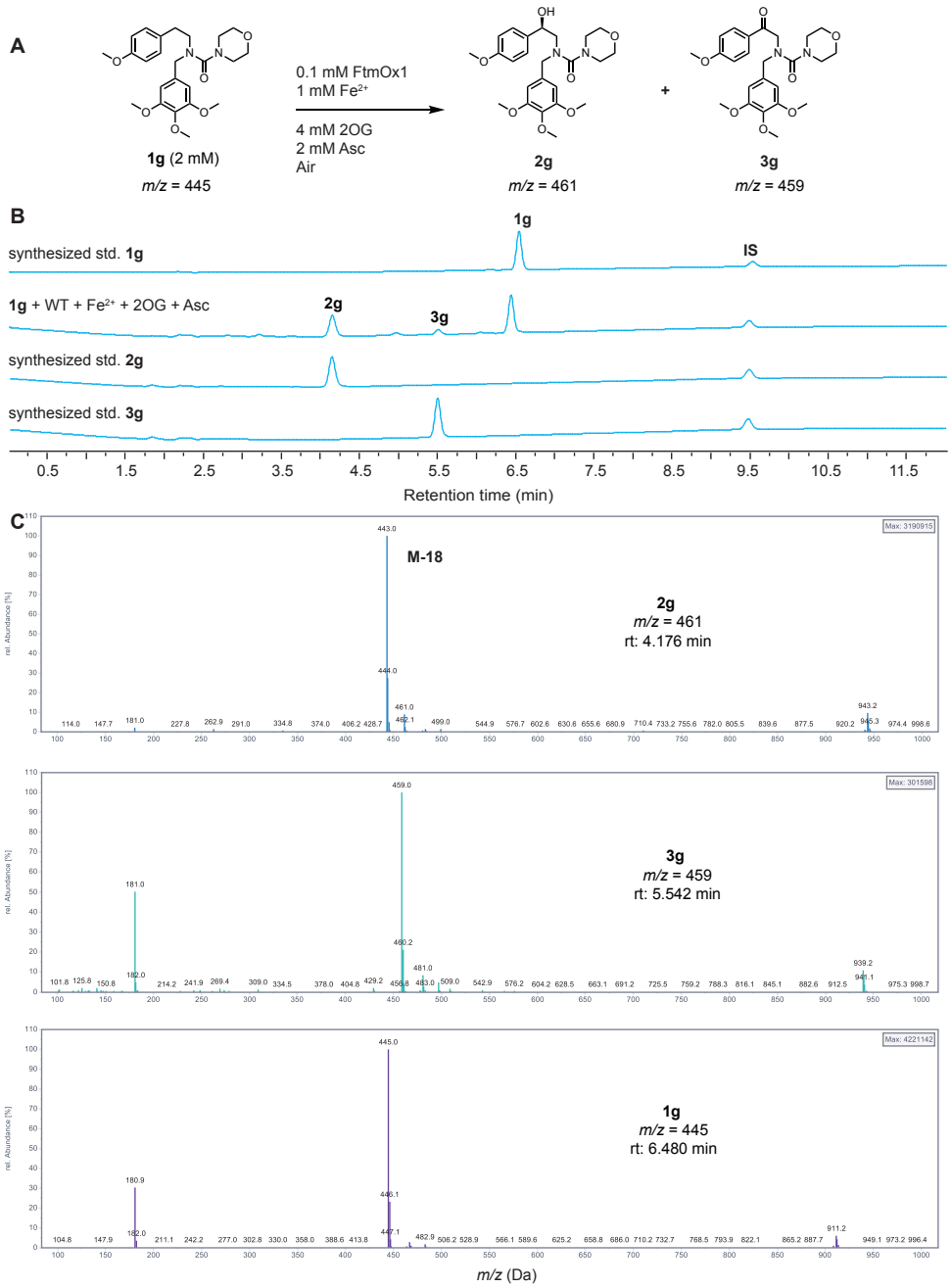


Figure S8. LC-MS analysis of the reaction of FtmOx1 with **1g**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1g** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2g**, **3g** (*second from bottom, bottom spectrum*). **2g**, **3g**, **1g** and IS were eluted at 4.176 min, 5.542 min, 6.480 min and ~9.5 min, respectively. **C**) mass spectra of **2g** (*top spectrum*), **3g** (*middle spectrum*) and **1g** (*bottom spectrum*).

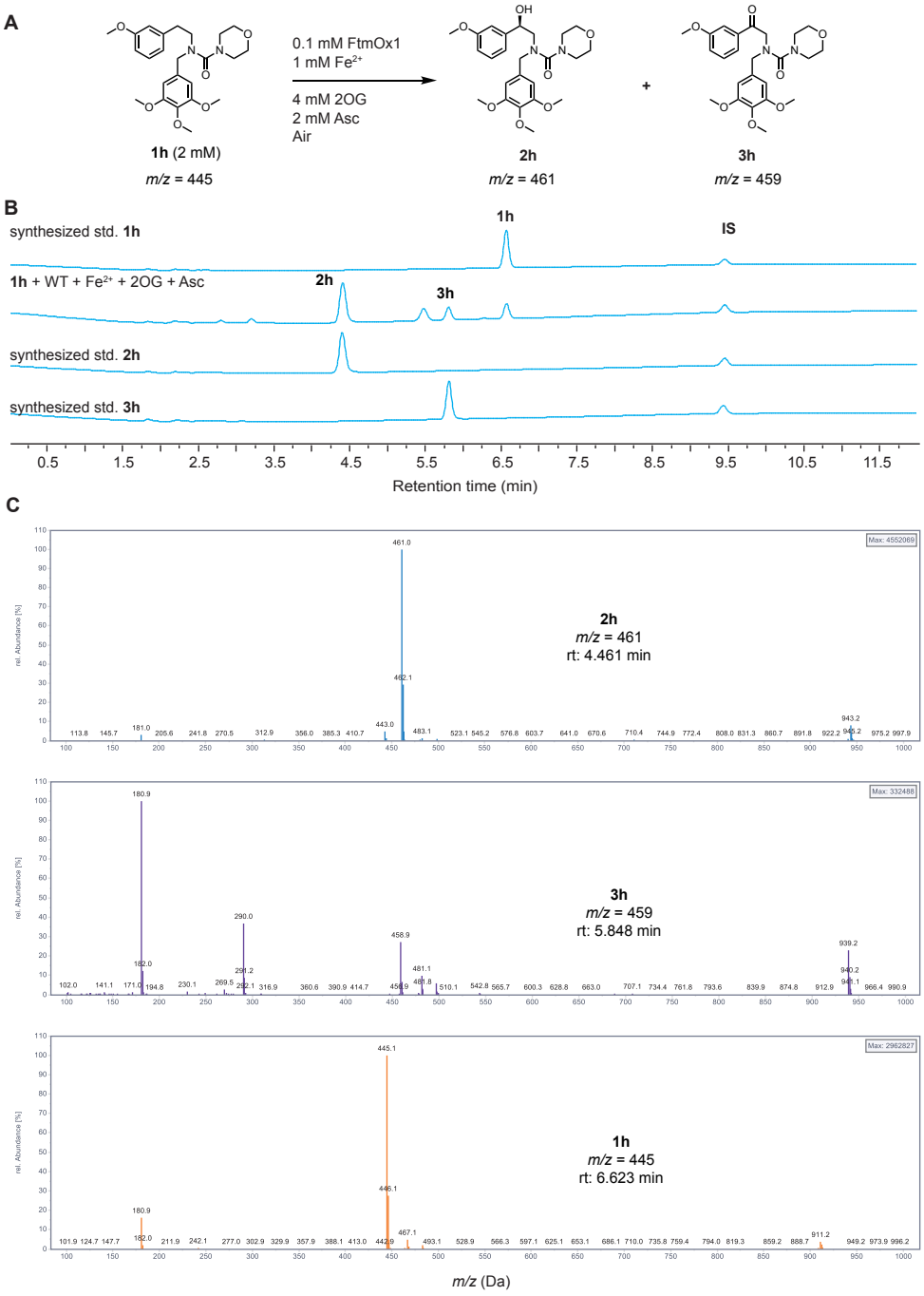


Figure S9. LC-MS analysis of the reaction of FtmOx1 with **1h**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1h** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2h**, **3h** (*second from bottom, bottom spectrum*). **2h**, **3h**, **1h** and IS were eluted at 4.461 min, 5.848, 6.623 min and ~9.5 min, respectively. **C**) mass spectra of **2h** (*top spectrum*), **3h** (*middle spectrum*) and **1h** (*bottom spectrum*).

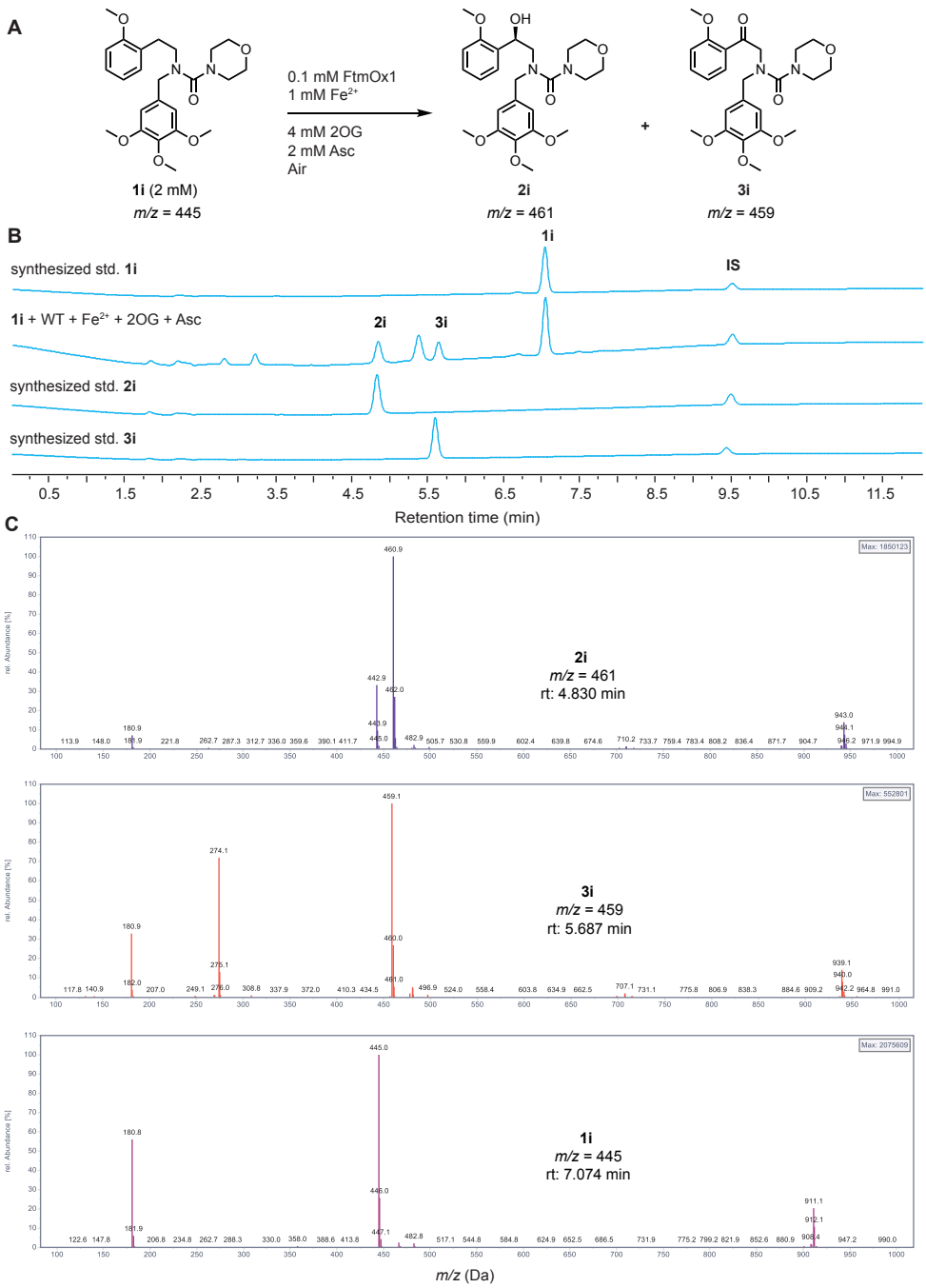


Figure S10. LC-MS analysis of the reaction of FtmOx1 with **1i**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1i** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2i**, **3i** (*second from bottom, bottom spectrum*). **2i**, **3i**, **1i** and IS were eluted at 4.830 min, 5.687, 7.704 min and ~9.5 min, respectively. **C**) mass spectra of **2i** (*top spectrum*), **3i** (*middle spectrum*) and **1i** (*bottom spectrum*).

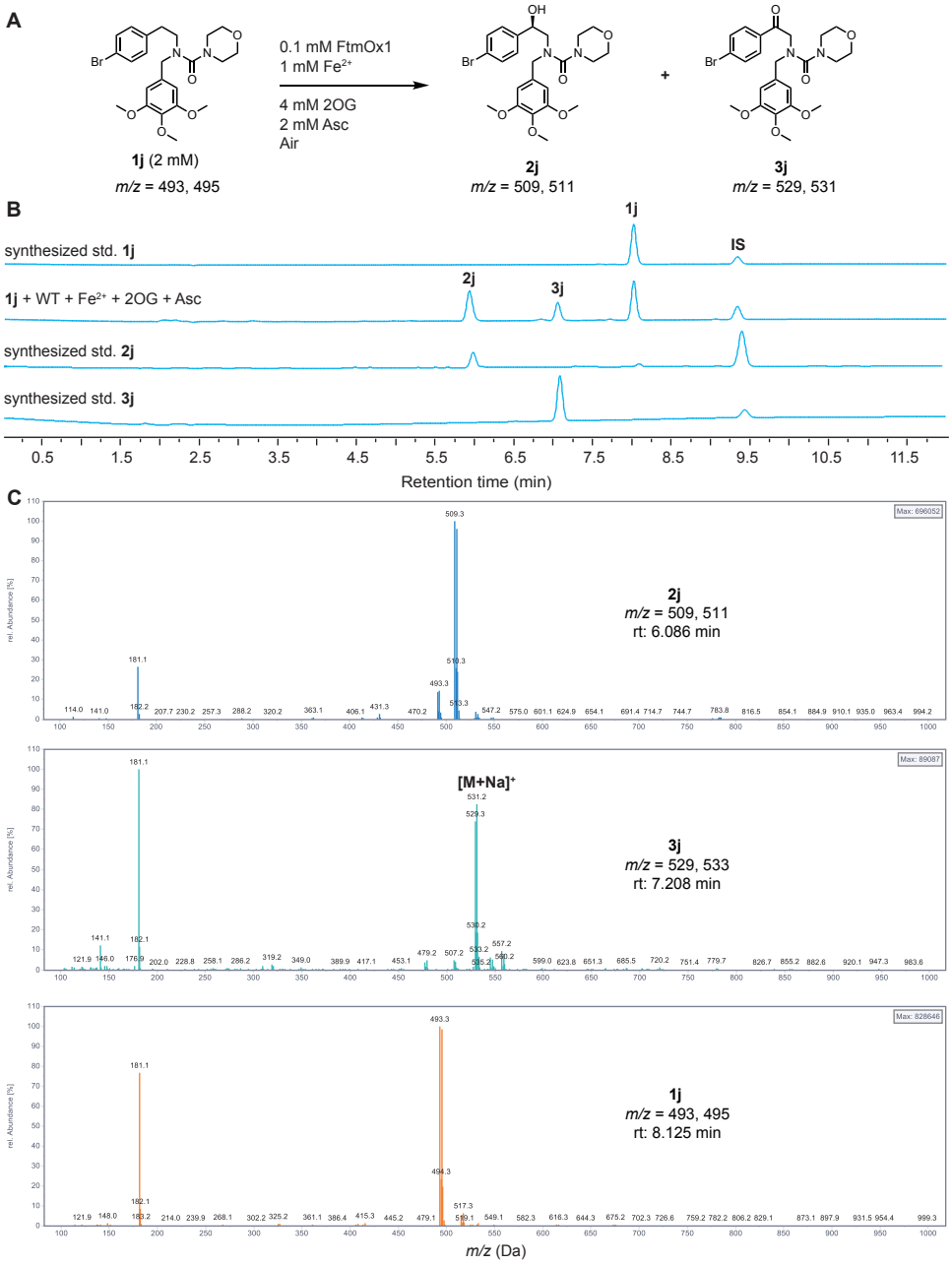


Figure S11. LC-MS analysis of the reaction of FtmOx1 with **1j**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1j** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2j**, **3j** (*second from bottom, bottom spectrum*). **2j**, **3j**, **1j** and IS were eluted at 6.086 min, 7.208, 8.125 min and ~9.5 min, respectively. **C**) mass spectra of **2j** (*top spectrum*), **3j** (*middle spectrum*) and **1j** (*bottom spectrum*).

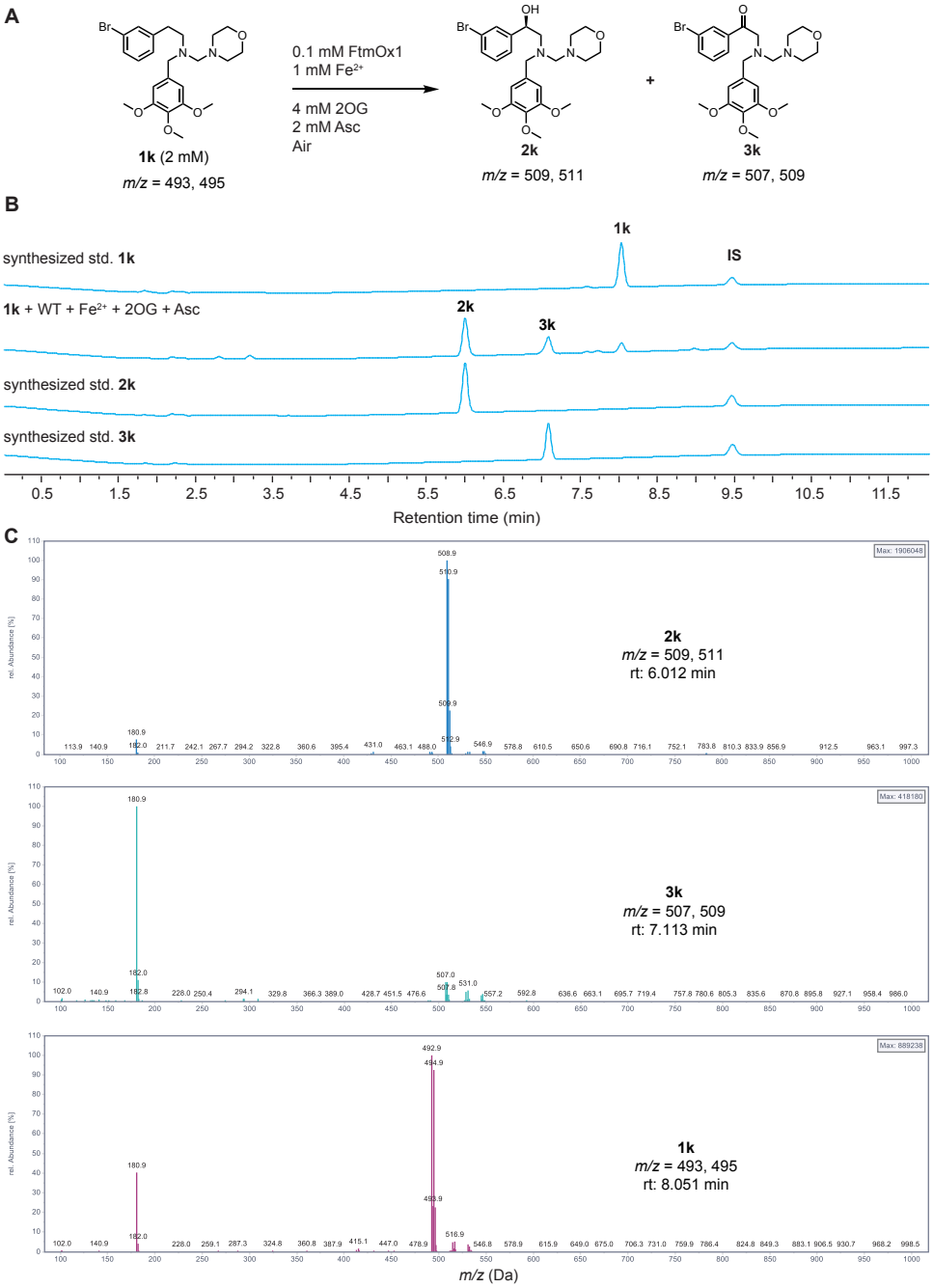


Figure S12. LC-MS analysis of the reaction of FtmOx1 with **1k**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1k** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2k**, **3k** (*second from bottom, bottom spectrum*). **2k**, **3k**, **1k** and IS were eluted at 6.012 min, 7.113, 8.051 min and ~9.5 min, respectively. **C**) mass spectra of **2k** (*top spectrum*), **3k** (*middle spectrum*) and **1k** (*bottom spectrum*).

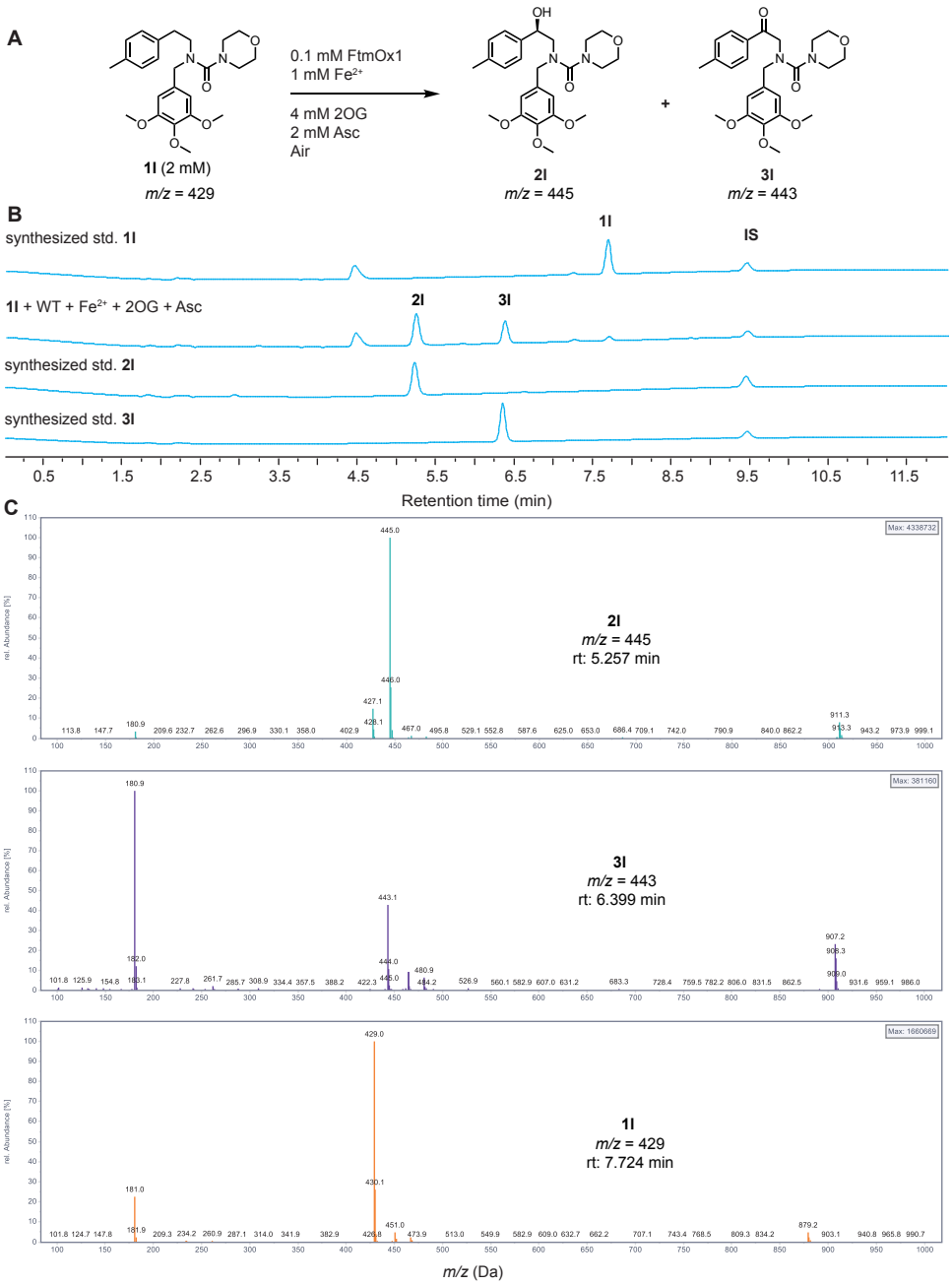


Figure S13. LC-MS analysis of the reaction of FtmOx1 with **1l**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1l** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2l**, **3l** (*second from bottom, bottom spectrum*). **2l**, **3l**, **1l** and IS were eluted at 5.257 min, 6.399, 7.724 min and ~9.5 min, respectively. **C**) mass spectra of **2l** (*top spectrum*), **3l** (*middle spectrum*) and **1l** (*bottom spectrum*).

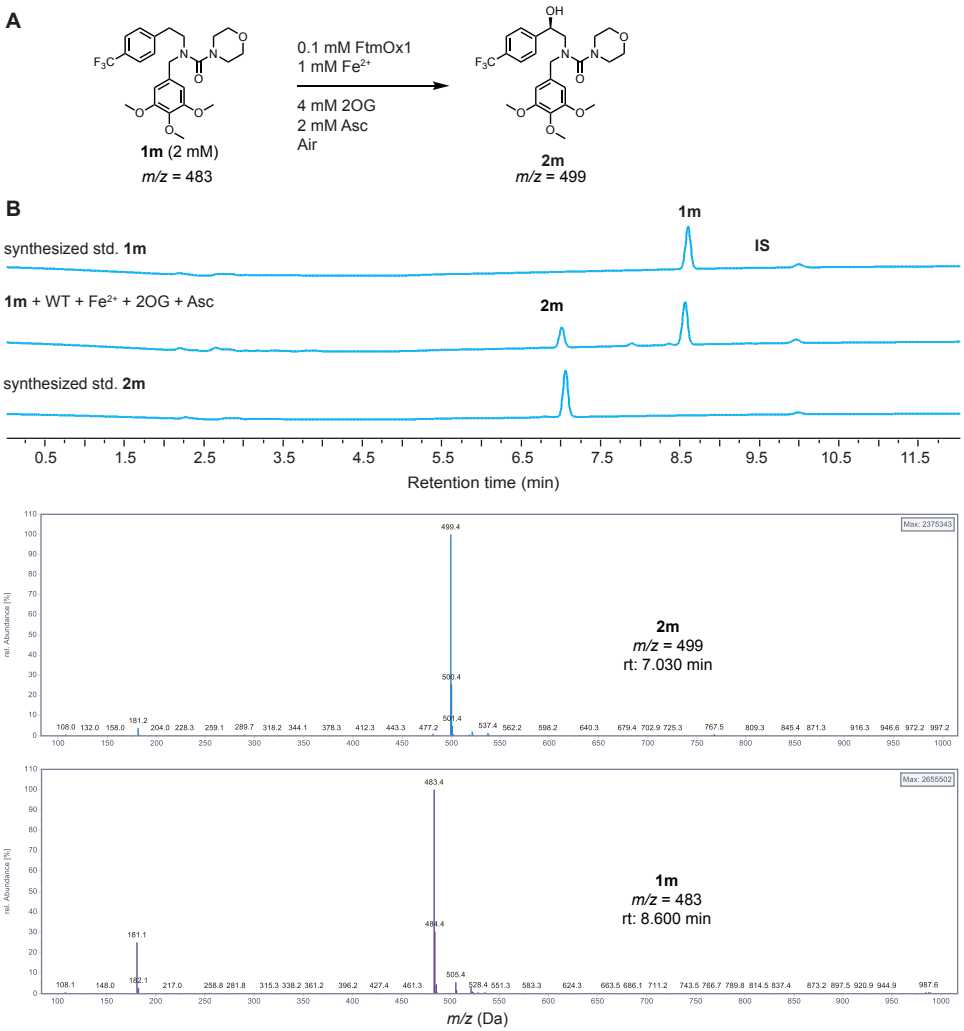


Figure S14. LC-MS analysis of the reaction of FtmOx1 with **1m**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1m** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2m** (*bottom spectrum*). **2m**, **1m** and IS were eluted at 7.030 min, 8.600 min, and ~9.5 min, respectively. **C**) mass spectra of **2m** (*top spectrum*) and **1m** (*bottom spectrum*).

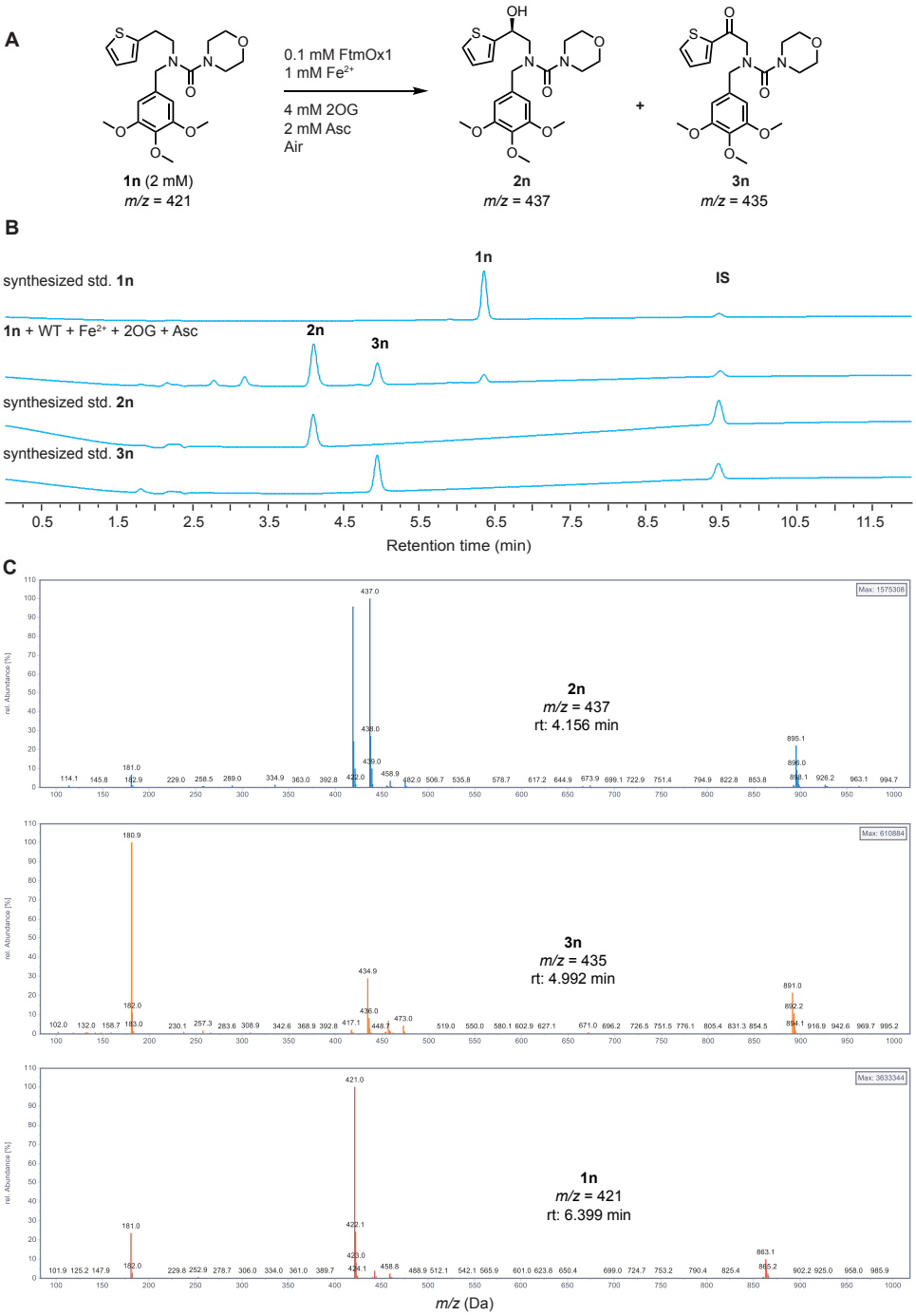


Figure S15. LC-MS analysis of the reaction of FtmOx1 with **1n**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1n** (*top spectrum*), the full reaction (*second form top spectrum*), and the synthetic product std. **2n**, **3n** (*second from bottom, bottom spectrum*). **2n**, **3n**, **1n** and IS were eluted at 4.156 min, 4.992, 6.399 min and ~9.5 min, respectively. **C**) mass spectra of **2n** (*top spectrum*), **3n** (*middle spectrum*) and **1n** (*bottom spectrum*).

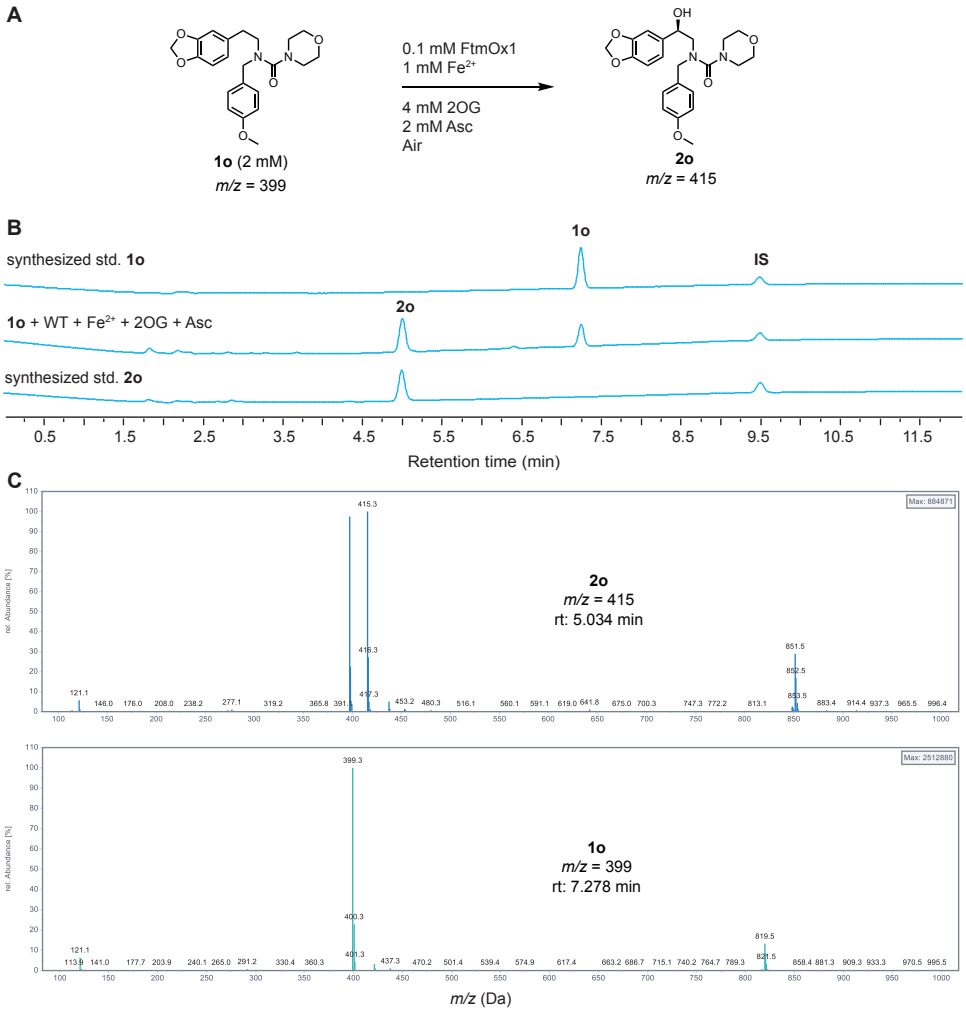


Figure S16. LC-MS analysis of the reaction of FtmOx1 with **1o**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1o** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2o** (*bottom spectrum*). **2o**, **1o** and IS were eluted at 5.034 min, 7.278 min, and ~9.5 min, respectively. **C**) mass spectra of **2o** (*top spectrum*) and **1o** (*bottom spectrum*).

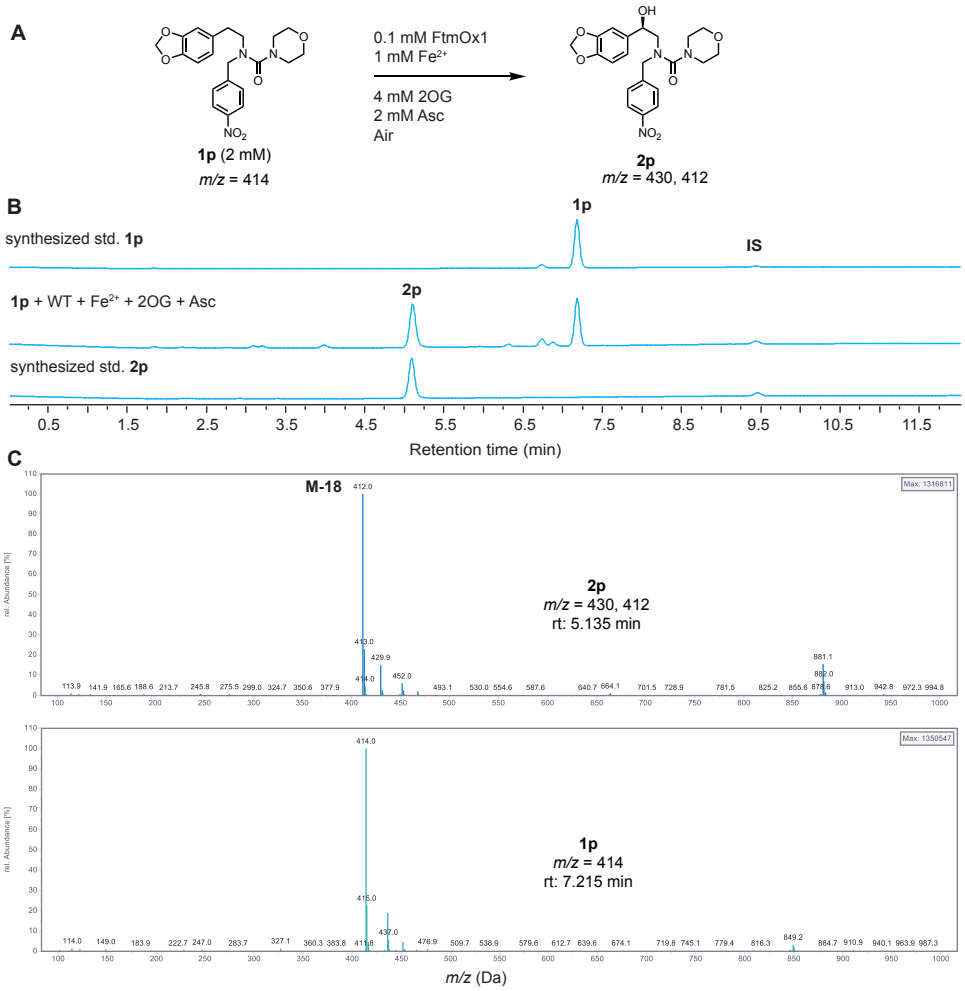


Figure S17. LC-MS analysis of the reaction of FtmOx1 with **1p**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1p** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2p** (*bottom spectrum*). **2p**, **1p** and IS were eluted at 5.135 min, 7.215 min, and ~9.5 min, respectively. **C**) mass spectra of **2p** (*top spectrum*) and **1p** (*bottom spectrum*).

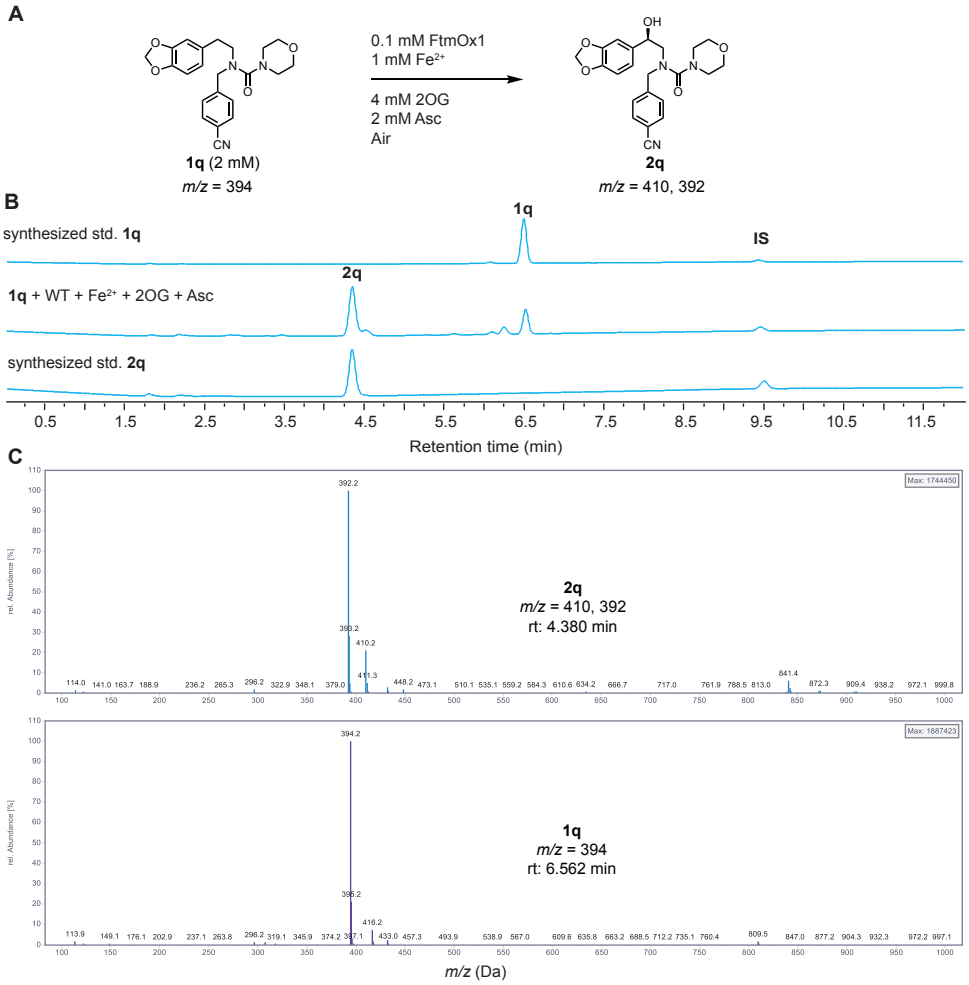


Figure S18. LC-MS analysis of the reaction of FtmOx1 with **1q**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1q** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2q** (*bottom spectrum*). **2q**, **1q** and IS were eluted at 4.38 min, 6.562 min, and ~9.5 min, respectively. **C**) mass spectra of **2q** (*top spectrum*) and **1q** (*bottom spectrum*).

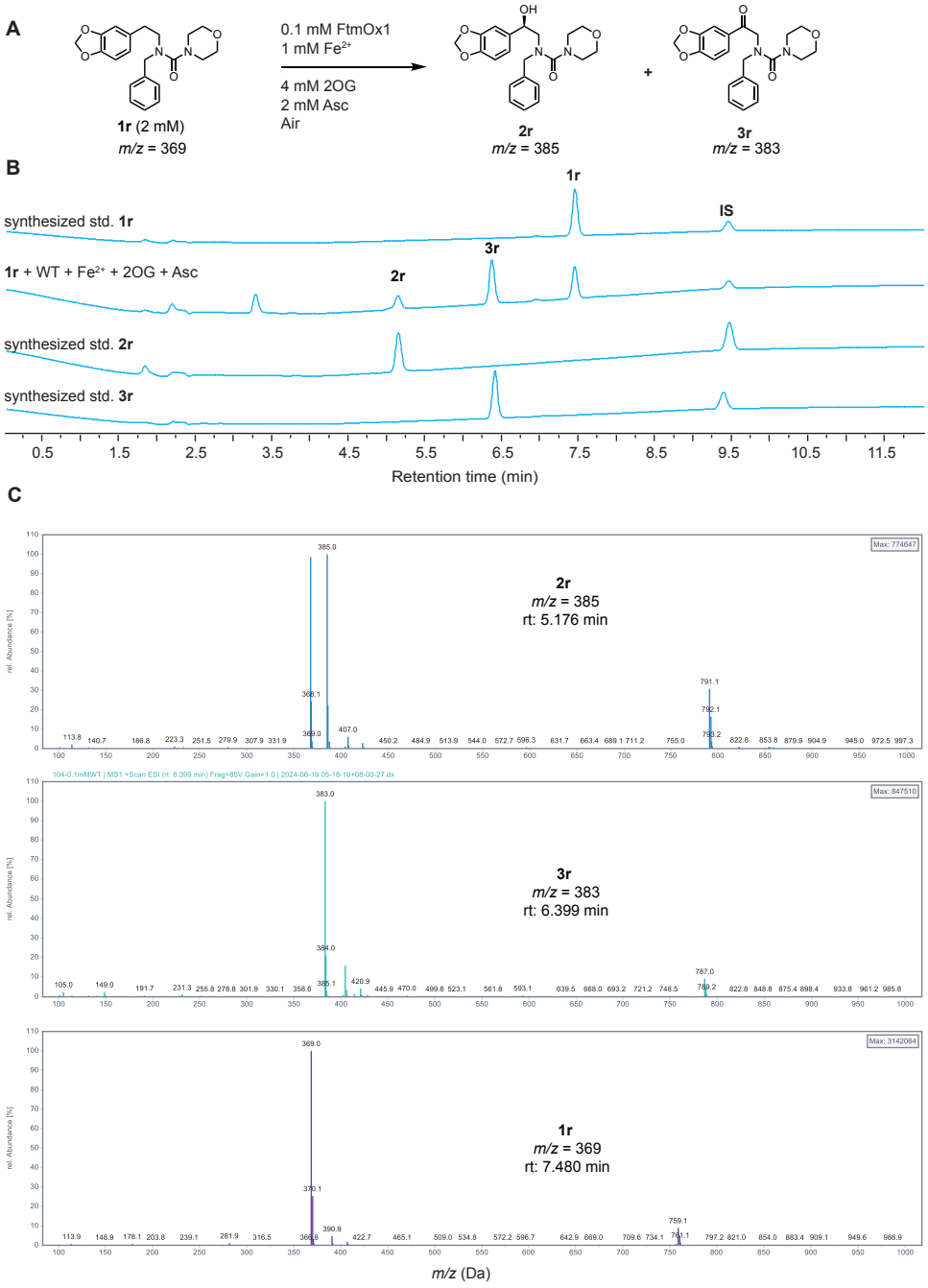


Figure S19. LC-MS analysis of the reaction of FtmOx1 with **1r**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1r** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2r**, **3r** (*second from bottom, bottom spectrum*). **2r**, **3r**, **1r** and IS were eluted at 5.176 min, 6.399, 7.480 min and ~9.5 min, respectively. **C**) mass spectra of **2r** (*top spectrum*), **3r** (*middle spectrum*) and **1r** (*bottom spectrum*).

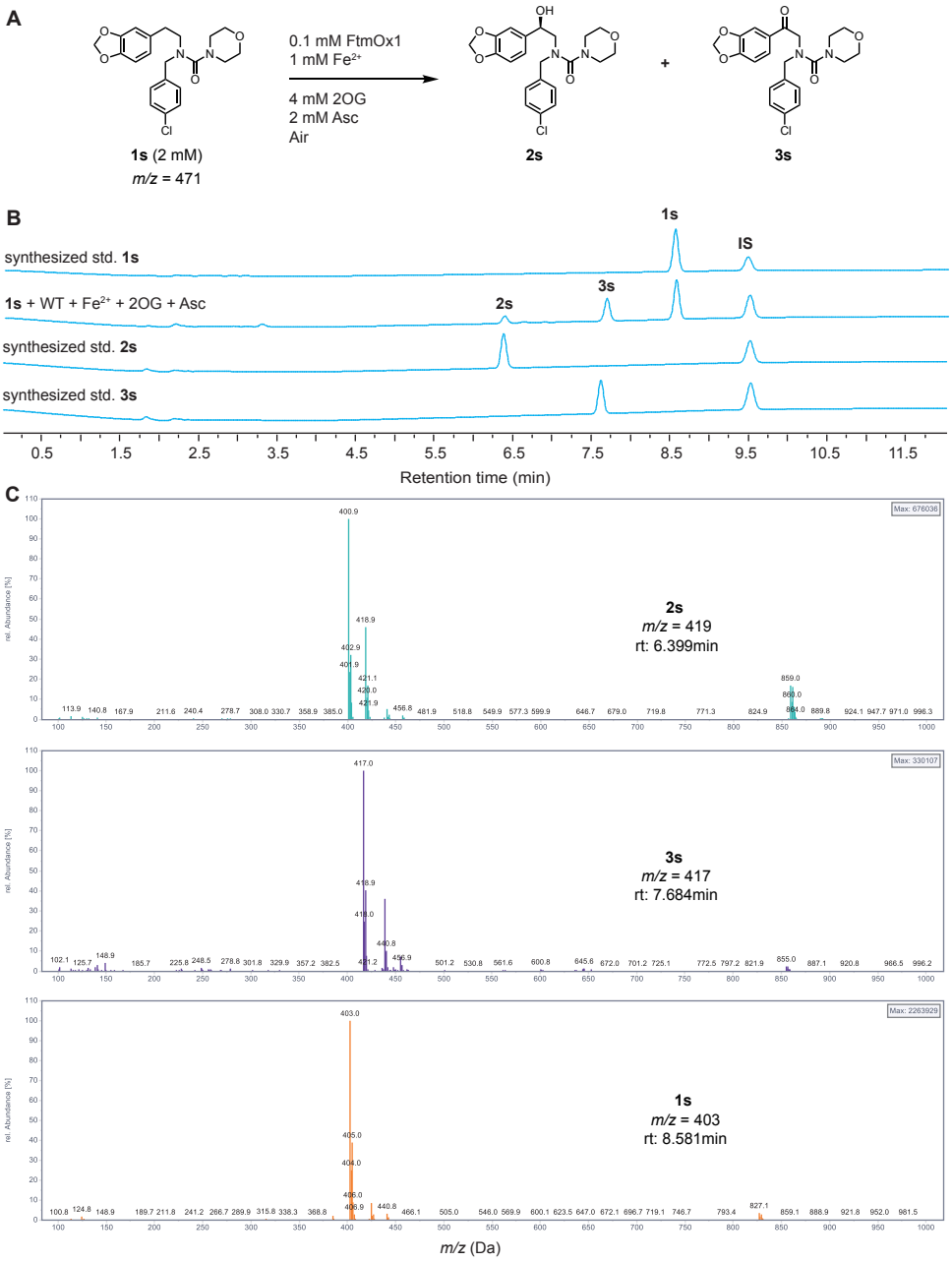


Figure S20. LC-MS analysis of the reaction of FtmOx1 with **1s**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1s** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2s**, **3s** (*second from bottom, bottom spectrum*). **2s**, **3s**, **1s** and IS were eluted at 6.399 min, 7.684, 8.581 min and ~9.5 min, respectively. **C**) mass spectra of **2s** (*top spectrum*), **3s** (*middle spectrum*) and **1s** (*bottom spectrum*).

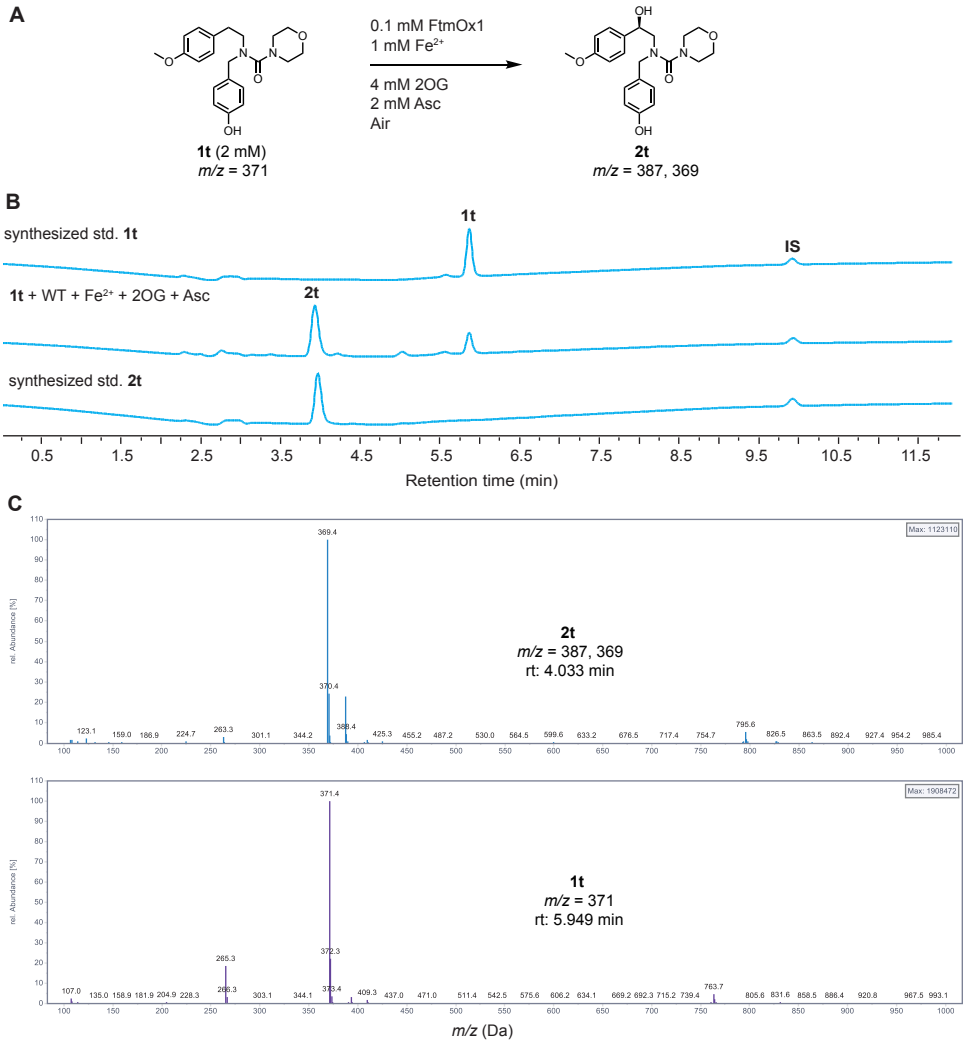


Figure S21. LC-MS analysis of the reaction of FtmOx1 with **1t**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1t** (*top spectrum*), the full reaction (*middle spectrum*), and the synthetic product std. **2t** (*bottom spectrum*). **2t**, **1t** and IS were eluted at 4.033 min, 5.949 min, and ~9.5 min, respectively. **C**) mass spectra of **2t** (*top spectrum*) and **1t** (*bottom spectrum*).

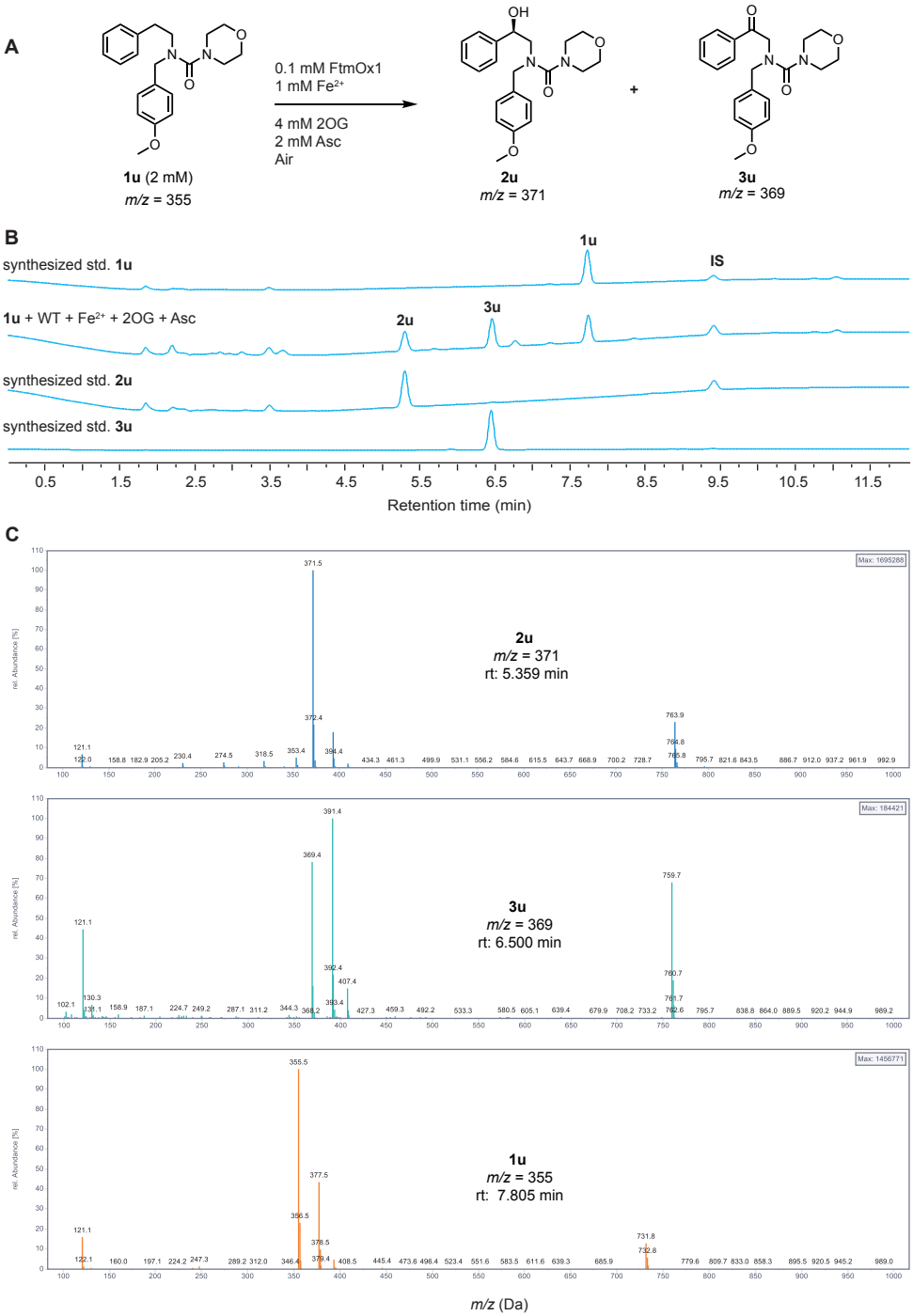


Figure S22. LC-MS analysis of the reaction of FtmOx1 with **1u**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1u** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2u**, **3u** (*second from bottom, bottom spectrum*). **2u**, **3u**, **1u** and IS were eluted at 5.359 min, 6.500, 7.805 min and ~9.5 min, respectively. **C**) mass spectra of **2u** (*top spectrum*), **3u** (*middle spectrum*) and **1u** (*bottom spectrum*).

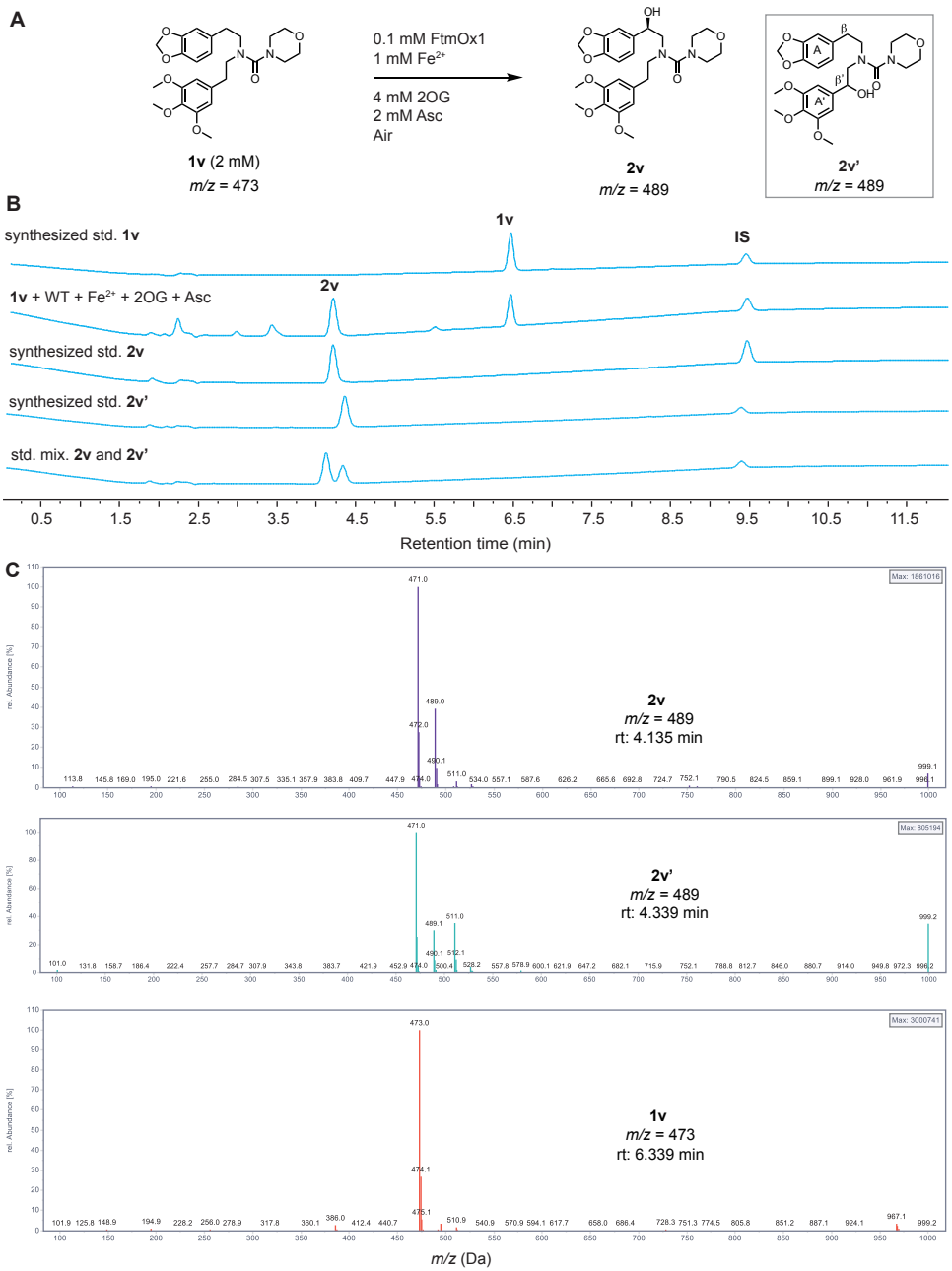


Figure S23. LC-MS analysis of the reaction of FtmOx1 with **1v**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1v** (*top spectrum*), the full reaction (*second from top spectrum*), and the synthetic product std. **2v**, **2v**' and their co-inject (*middle*, *second from bottom, bottom spectrum*). **2v**, **2v**', **1v** and IS were eluted at 4.135 min, 4.339, 6.339 min and ~9.5 min, respectively. **C**) mass spectra of **2v** (*top spectrum*), **3v** (*middle spectrum*) and **1v** (*bottom spectrum*).

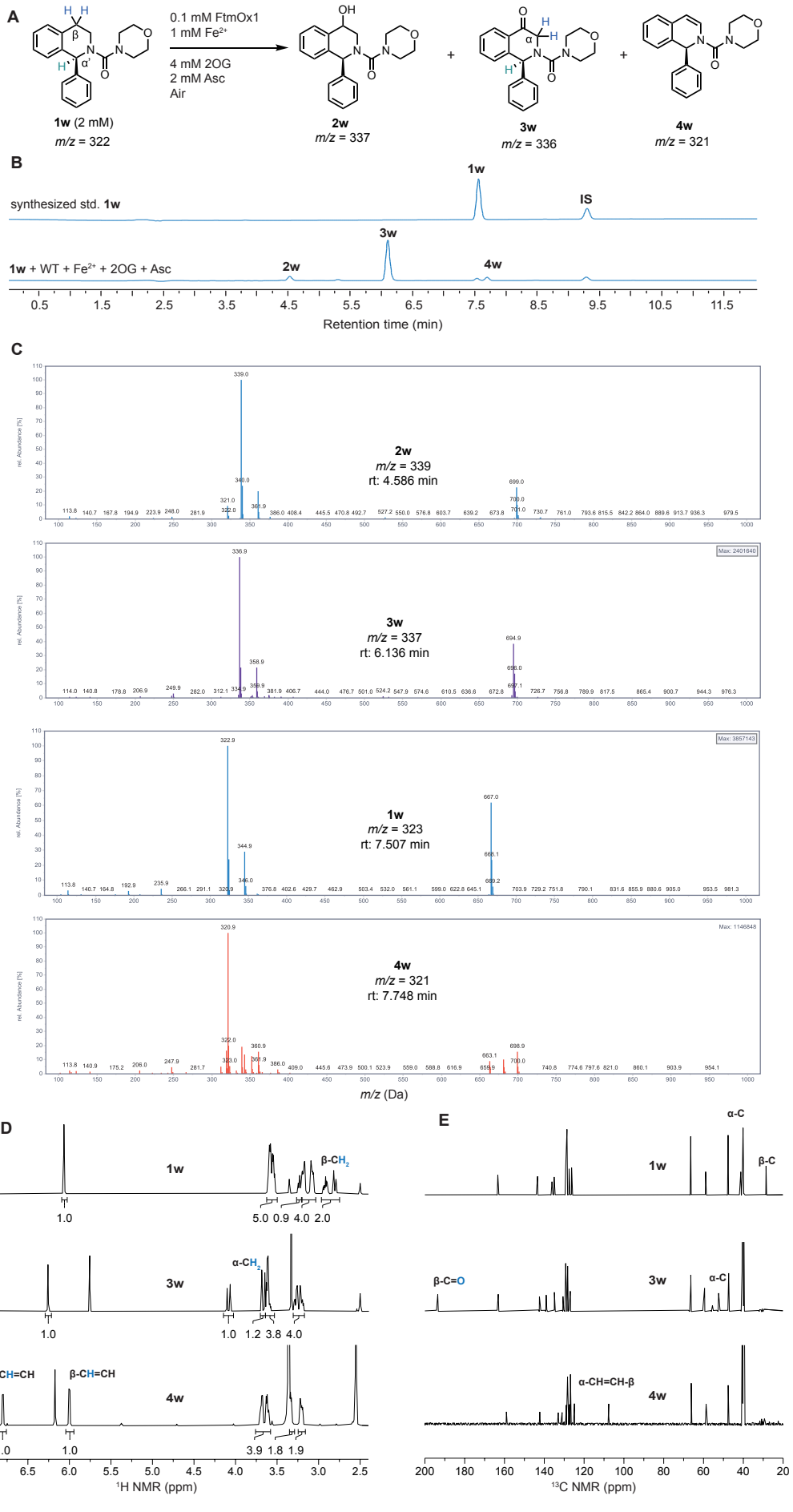

A
0.1 mM FtmOx1
1 mM Fe2+
4 mM 2OG
2 mM Asc
Air
1w (2 mM)
m/z = 322
2w
m/z = 337
3w
m/z = 336
4w
m/z = 321
B
synthesized std. 1w
1w + WT + Fe2+ + 2OG + Asc
1w
IS
2w
3w
4w
Retention time (min)
C
2w
m/z = 339
rt: 4.586 min
3w
m/z = 337
rt: 6.136 min
1w
m/z = 323
rt: 7.507 min
4w
m/z = 321
rt: 7.748 min
m/z (Da)
D
1w
β-CH2
α-CH2
α-CH=CH
β-CH=CH
1H NMR (ppm)
E
α-C
β-C
β-C=O
α-CH=CH-β
13C NMR (ppm)

Figure S24. LC-MS analysis of the reaction of FtmOx1 with **1w**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1w** (*top spectrum*) and the full reaction (*bottom spectrum*). **2w**, **3w**, **1w** **4w** and IS were eluted at 4.586 min, 6.136 min, 7.507 min, 7.748 min and ~9.5 min, respectively. **C**) mass spectra of **2w** (*top spectrum*), **3w** (*second from top spectrum*) and **1w, 4w** (*second from bottom*, *bottom spectrum*). **D**) ^{1}H NMR spectra of **1w, 2w** and **3w**, demonstrating β-C(sp^{3})-H carbonylation and and the generation of olefin products. **E**) ^{13}C NMR spectra of **1w, 2w** and **3w**, demonstrating carbonylation at the β-C(sp^{3})-H position and the generation of olefin products.

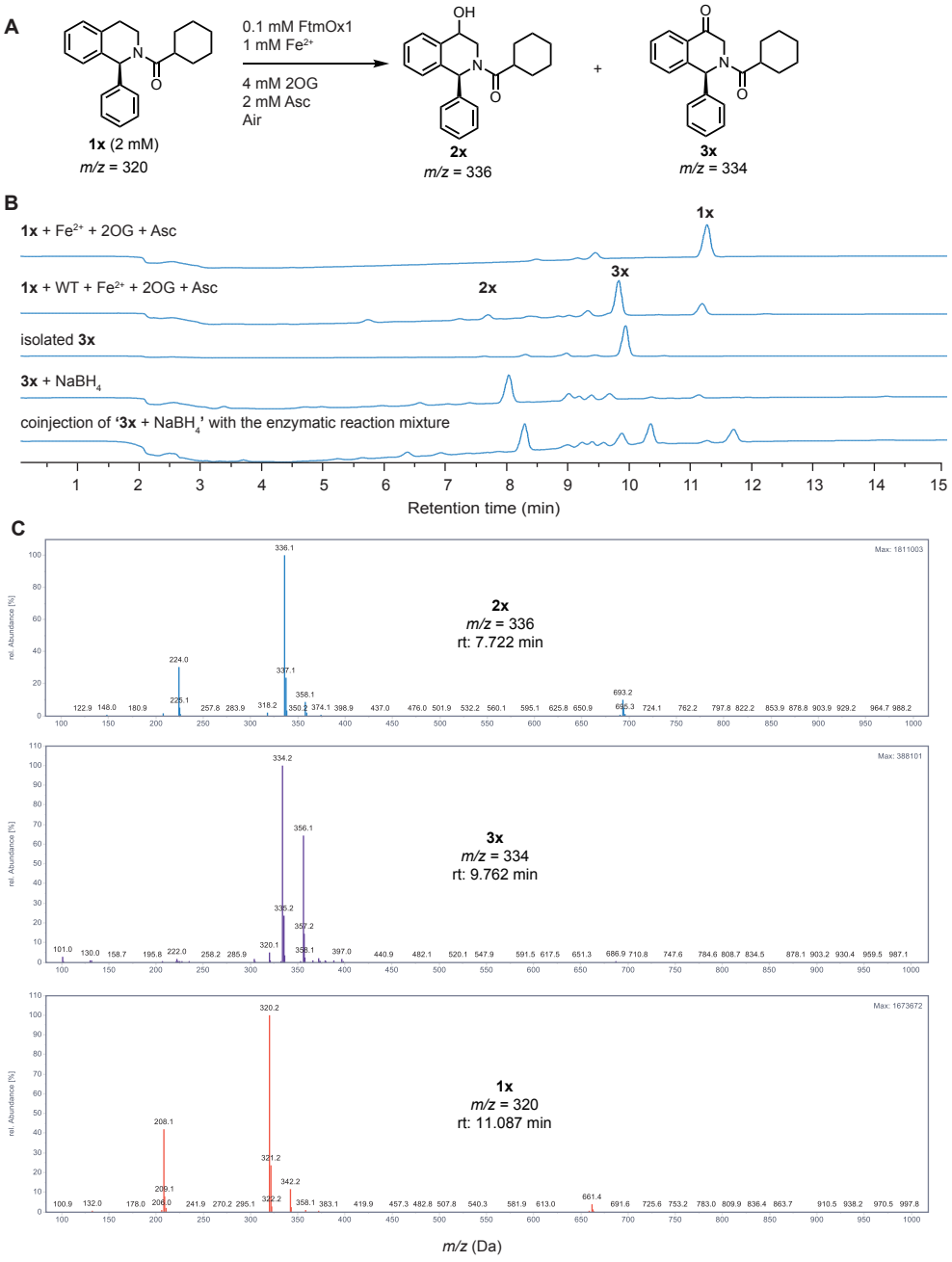


Figure S25. LC-MS analysis of the reaction of FtmOx1 with **1x**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1x** (*top spectrum*), the full reaction (*second from top spectrum*) and the isolated **3x** (*middle spectrum*)**,** product reduced by $NaBH_4$ from **3x** (*second from bottom*)**,**

and the co-injection of '**3x** + $NaBH_4$' with the enzymatic reaction mixture (*bottom spectrum*). **2x**, **3x**, **1x** and IS were eluted at 7.722 min, 9.762 min, 11.087 min and ~11.5 min, respectively. **C**) mass spectra of **2x** (*top spectrum*), **3x** (*middle spectrum*) and **1x** (*bottom spectrum*).

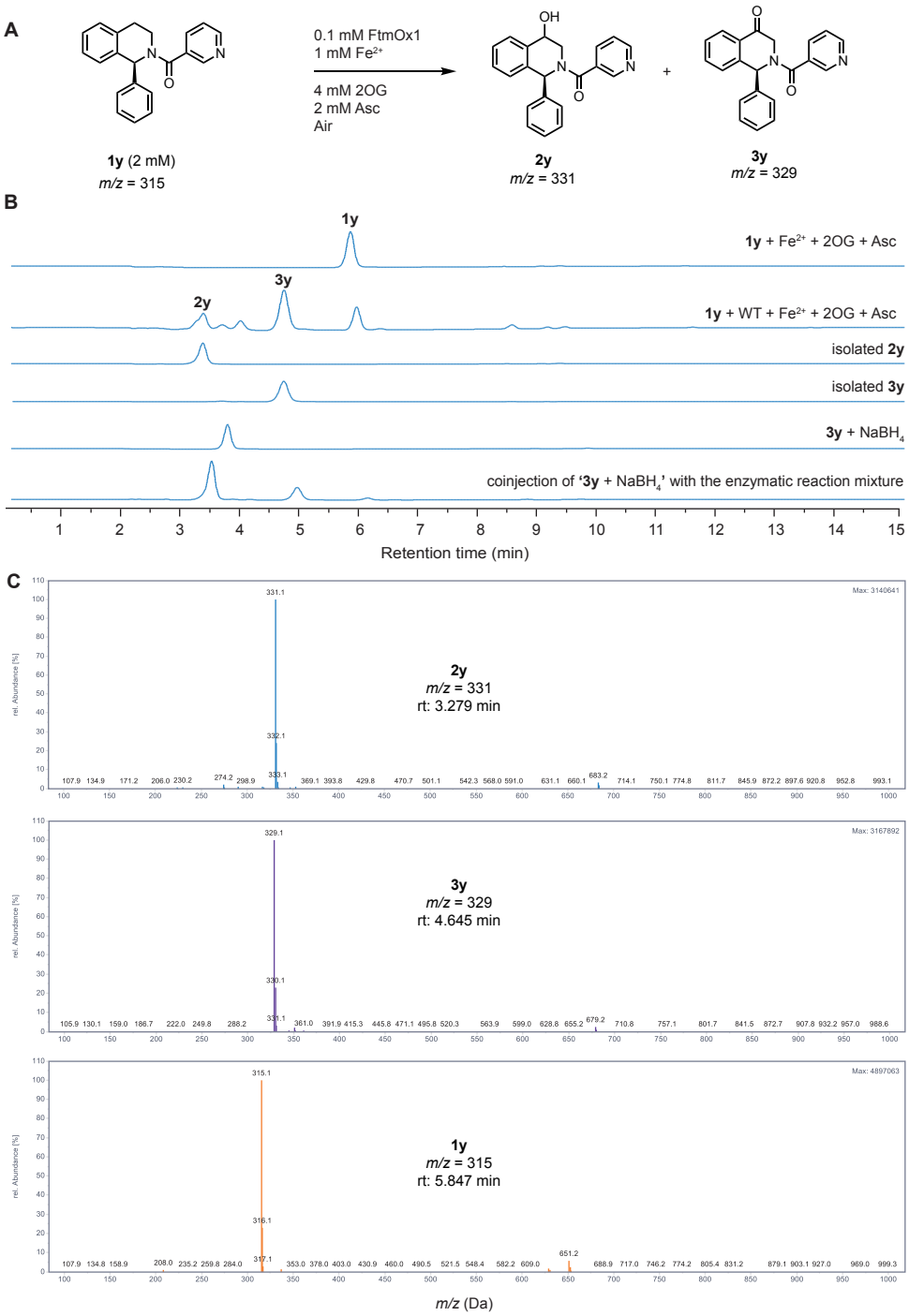


Figure S26. LC-MS analysis of the reaction of FtmOx1 with **1y**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1y** (*top spectrum*), the full reaction (*second from top*), the isolated **2y** (*third from top*)**,** the isolated **3y** (*third from bottom*), product reduced by $NaBH_4$ from **3y** (*second from bottom*)**,** and the co-injection of '**3y** + $NaBH_4$' with the enzymatic reaction mixture (*bottom spectrum*). **2y**, **3y**, **1y** and IS were eluted at 3.729 min, 4.645 min, 5.847 min and ~11.5 min, respectively. **C**) mass spectra of **2y** (*top spectrum*), **3y** (*middle spectrum*) and **1y** (*bottom*

spectrum).

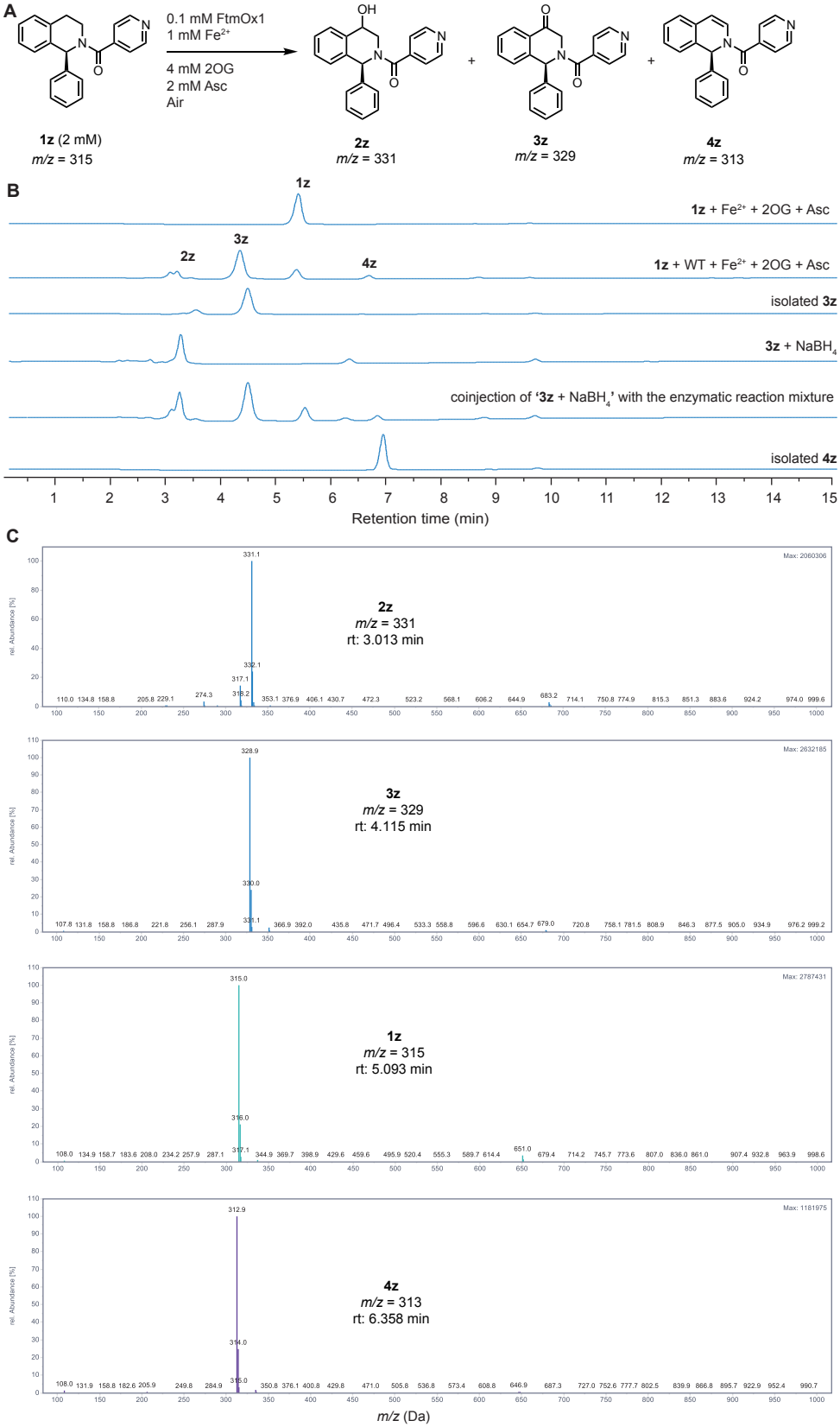


Figure S27. LC-MS analysis of the reaction of FtmOx1 with **1z**. **A**) reaction scheme. **B**) LC

spectra of synthesized substrate **1z** (*top spectrum*), the full reaction (*second from top*), the isolated **3z** (*third from top*), product reduced by $NaBH_4$ from **3z** (*third from bottom*)**,** the co-injection of '**3z** + $NaBH_4$' with the enzymatic reaction mixture (*second from bottom*) and the isolated **4z** (*bottom spectrum*). **2z**, **3z**, **1z**, **4z** and IS were eluted at 3.013 min, 4.115 min, 5.093 min, 6.358 min and ~11.5 min, respectively. **C**) mass spectra of **2z** (*top spectrum*), **3z** (*second from top*), **1z** (*second from bottom*) and **4z** (*bottom spectrum*).

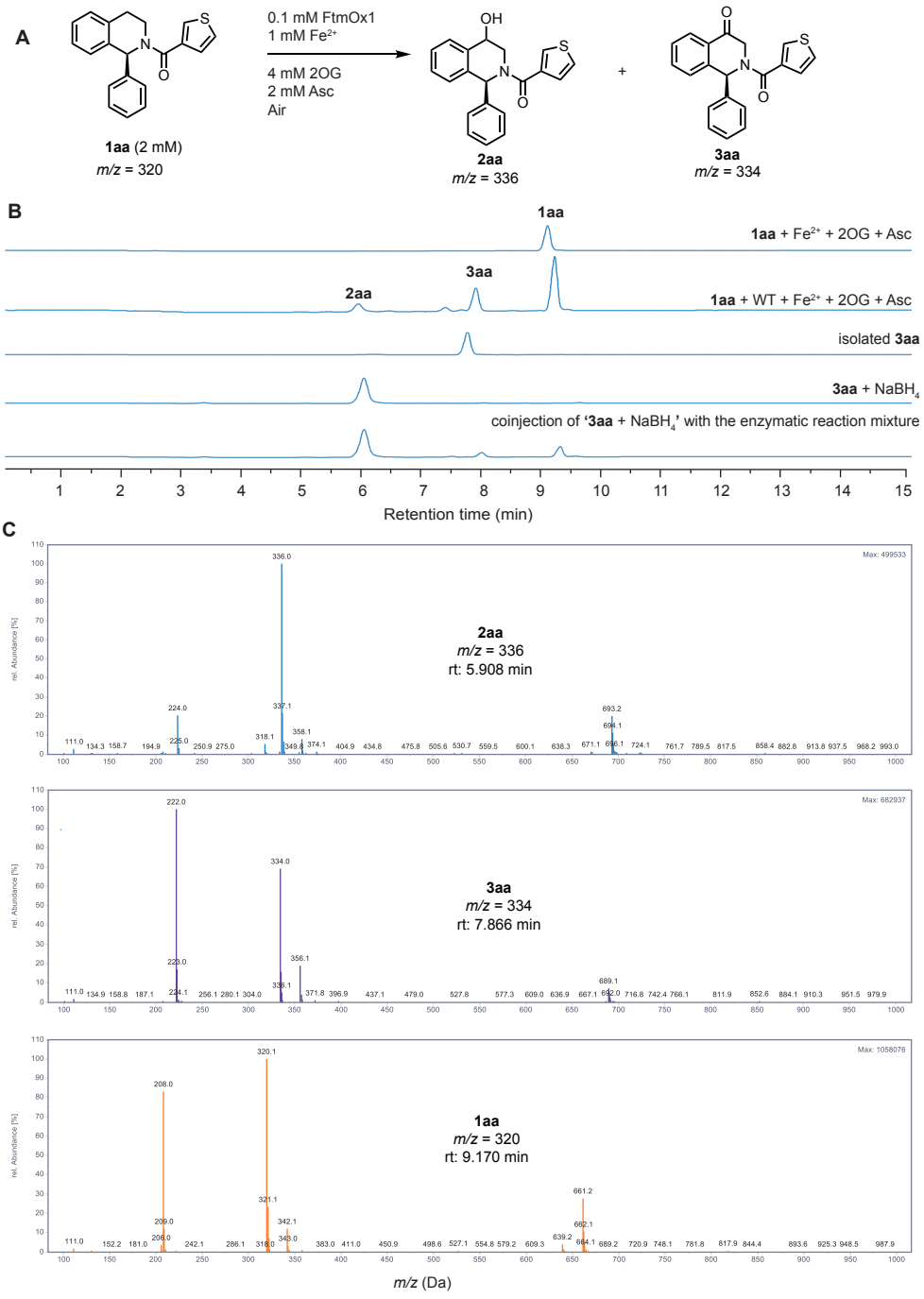


Figure S28. LC-MS analysis of the reaction of FtmOx1 with **1aa**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1aa** (*top spectrum*), the full reaction (*second from top*), the

isolated **3aa** (*middle spectrum*), product reduced by $NaBH_4$ from **3aa** (*second from bottom*) and the co-injection of '**3aa** + $NaBH_4$' with the enzymatic reaction mixture (*bottom spectrum*). **2aa**, **3aa**, **1aa** and IS were eluted at 5.908 min, 7.866 min and 9.170 min and ~11.5 min, respectively. **C**) mass spectra of **2aa** (*top spectrum*), **3aa** (*middle spectrum*) and **1aa** (*bottom spectrum*).

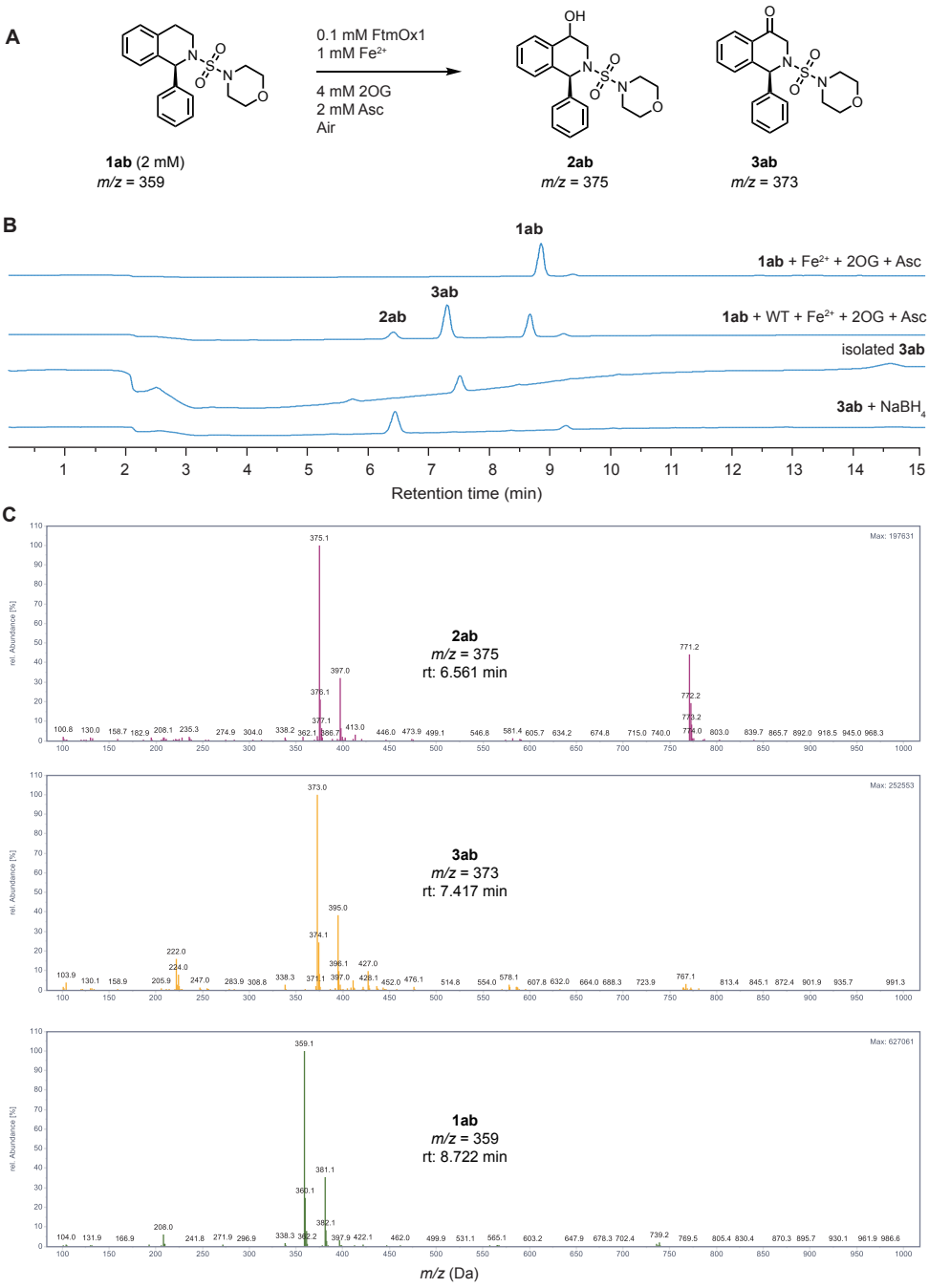


Figure S29. LC-MS analysis of the reaction of FtmOx1 with **1ab**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **1ab** (*top spectrum*), the full reaction (*second from top*), the isolated **3ab** (*second from bottom*) and the product reduced by $NaBH_4$ from **3ab** (*bottom spectrum*). **2ab**, **3ab**, **1ab** and IS were eluted at 6.561 min, 7.417 min, 8.722 min and ~11.5 min, respectively. **C**) mass spectra of **2ab** (*top spectrum*), **3ab** (*middle spectrum*) and **1ab** (*bottom spectrum*).

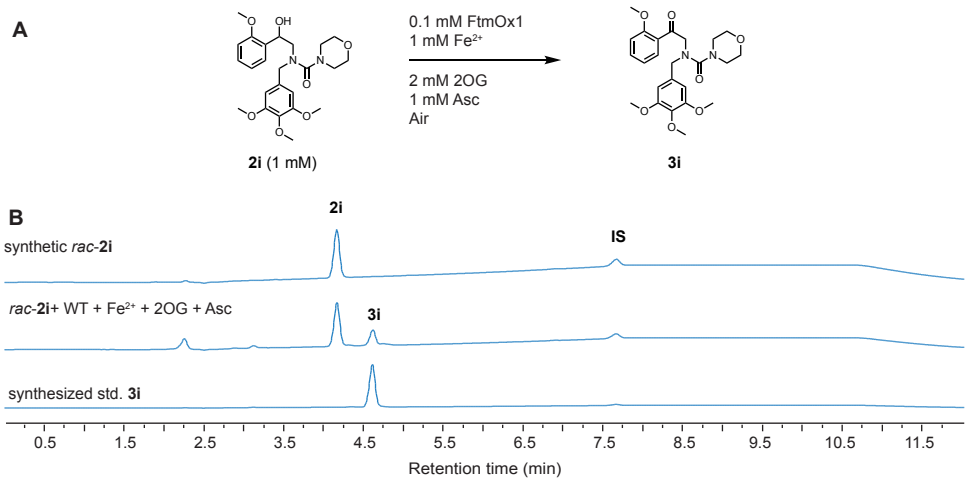


Figure S30. LC-MS analysis of the reaction of FtmOx1 with **2i**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2i** (*top spectrum*), the full reaction (*middle spectrum*) and synthesized **3i** (*bottom spectrum*). **2i**, **3i** and IS were eluted at 4.158 min, 4.625 min and ~7.7 min, respectively.

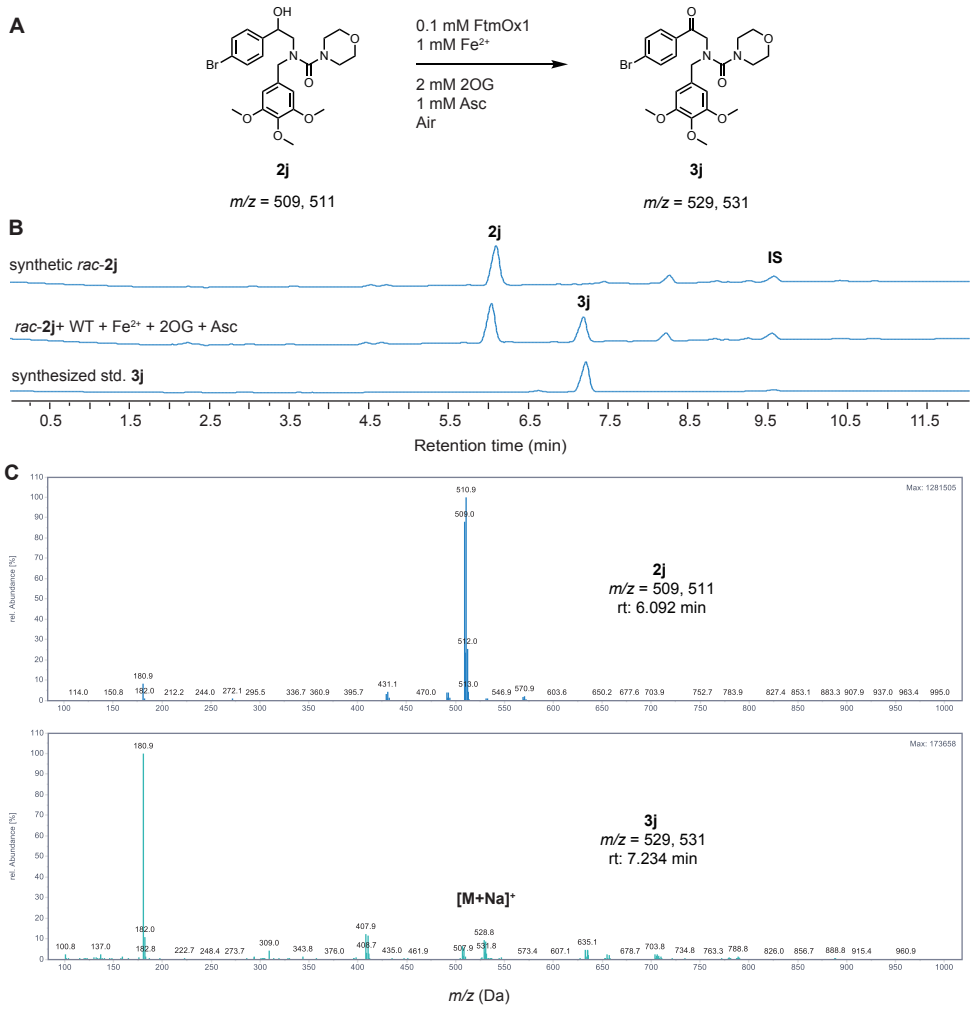


Figure S31. LC-MS analysis of the reaction of FtmOx1 with **2j**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2j** (*top spectrum*), the full reaction (*middle spectrum*) and

synthesized **3j** (*bottom spectrum*). **2j**, **3j** and IS were eluted at 6.092 min, 7.234 min and ~9.5 min, respectively. **C**) mass spectra of **2j** (*top spectrum*), **3j** (*bottom spectrum*).

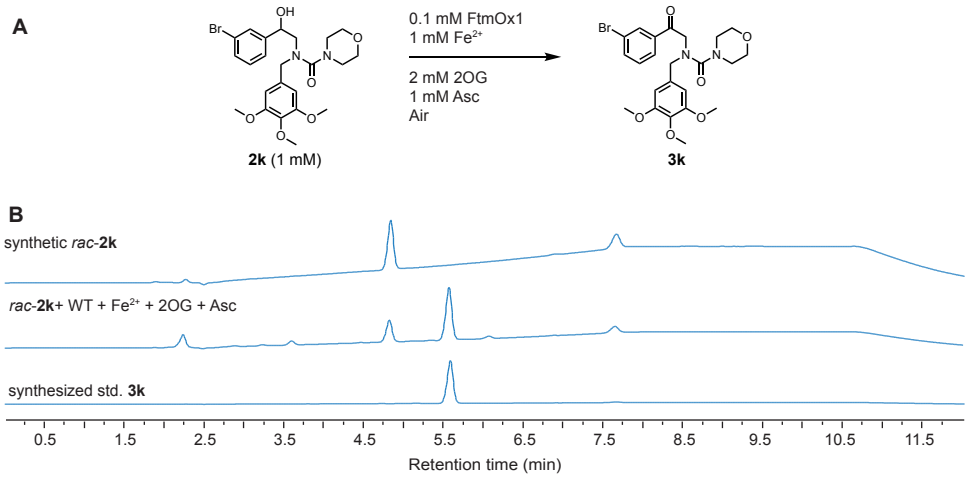


Figure S32. LC-MS analysis of the reaction of FtmOx1 with **2k**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2k** (*top spectrum*), the full reaction (*middle spectrum*) and synthesized **3k** (*bottom spectrum*). **2k**, **3k** and IS were eluted at 4.812 min, 5.616 min and ~7.7 min, respectively.

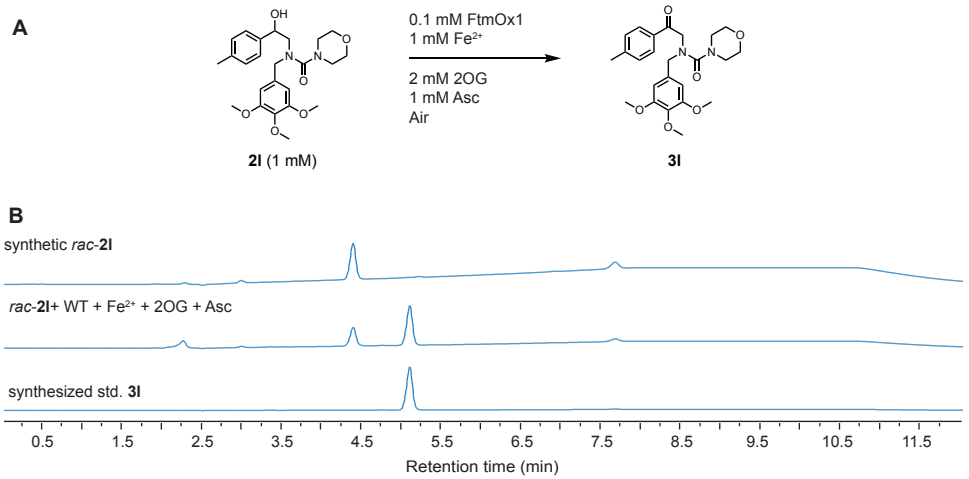


Figure S33. LC-MS analysis of the reaction of FtmOx1 with **2l**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2l** (*top spectrum*), the full reaction (*middle spectrum*) and synthesized **3l** (*bottom spectrum*). **2l**, **3l** and IS were eluted at 4.402 min, 5.126 min and ~7.7 min, respectively.

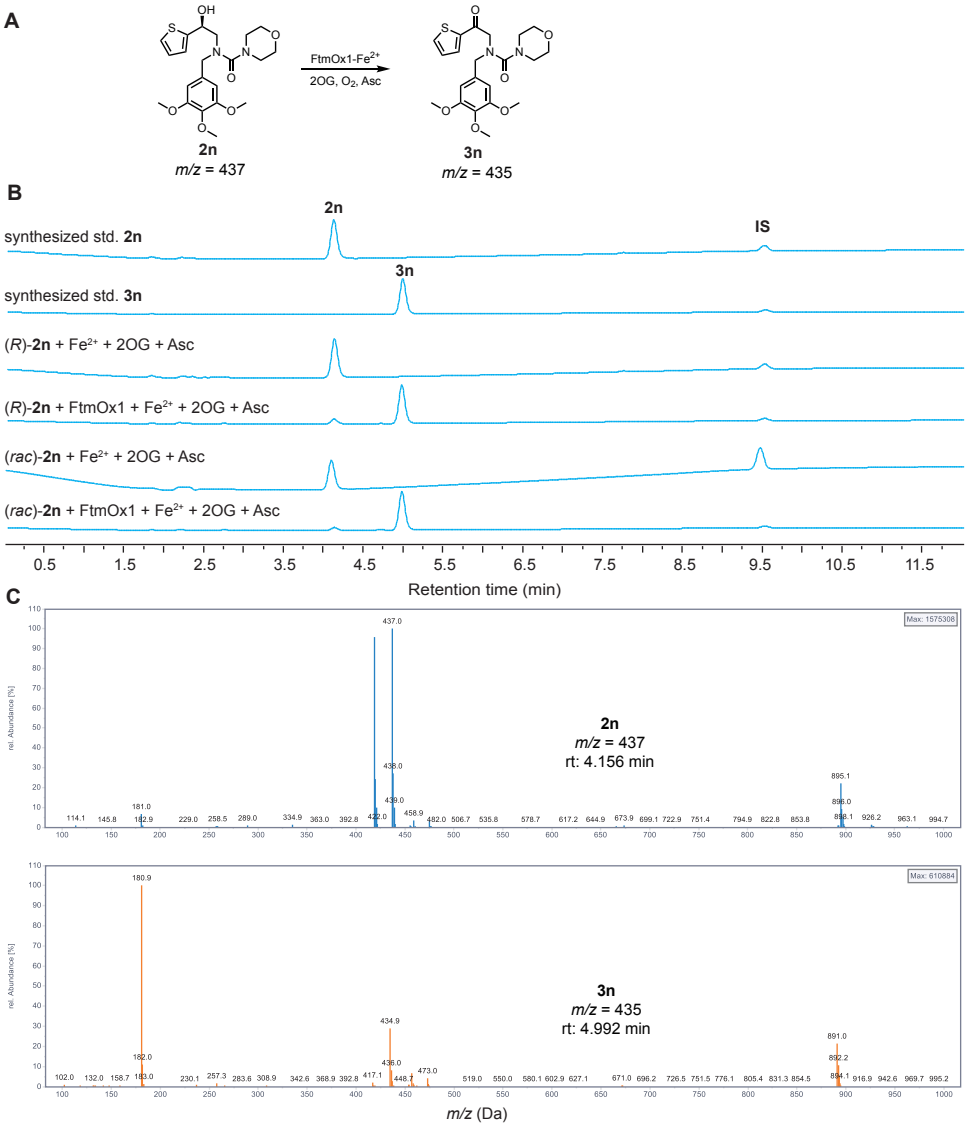


Figure S34. LC-MS analysis of the reaction of FtmOx1 with **2n** and *R*-**2n**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2n** and **3n** (*top, second from top spectrum*), the full reactions (*third from bottom, bottom spectrum*), each group omitting enzymes as control (*third from top*, *second from bottom spectrum*). **2n**, **3n** and IS were eluted at 4.156 min, 4.992 min and ~9.5 min, respectively. **C**) mass spectra of **2n** (*top spectrum*), **3n** (*bottom spectrum*).

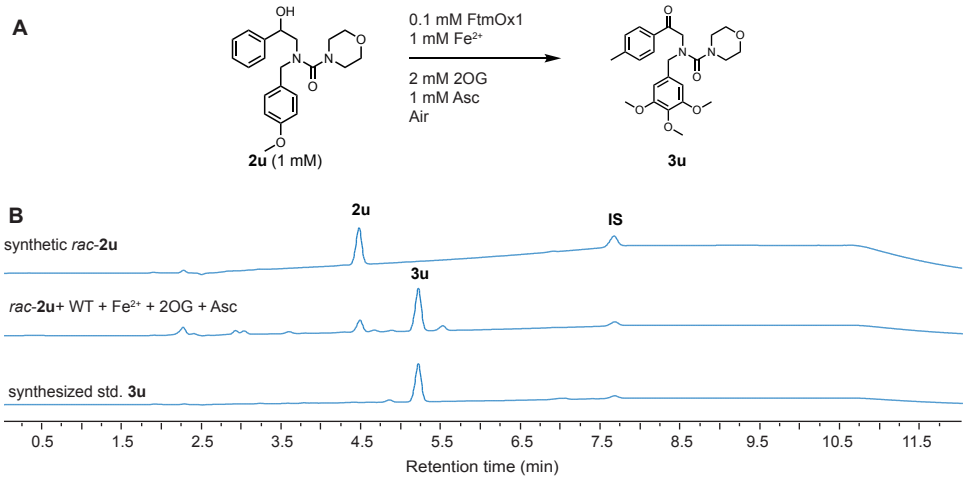


Figure S35. LC-MS analysis of the reaction of FtmOx1 with **2u**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2u** (*top spectrum*), the full reaction (*middle spectrum*) and synthesized **3u** (*bottom spectrum*). **2u**, **3u** and IS were eluted at 4.505 min, 5.208 min and ~7.7 min, respectively.

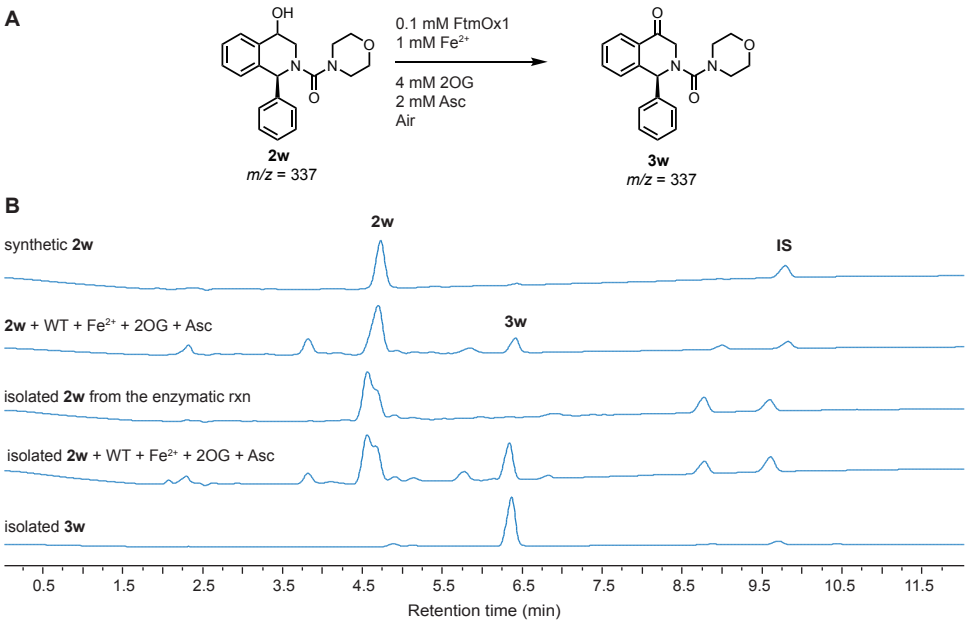


Figure S36. LC-MS analysis of the reaction of FtmOx1 with synthetic **2w** and isolated **2w**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2w** (*top spectrum*) and the full reaction of synthetic **2w** (*second from top spectrum*), isolated substrate **2w** (*middle spectrum*), the full reaction of isolated **2w** and synthesized **3w** (*second from bottom*, *bottom spectrum*). **2w**, **3w** and IS were eluted at 4.625 min, 6.355 min and ~9.5 min, respectively.

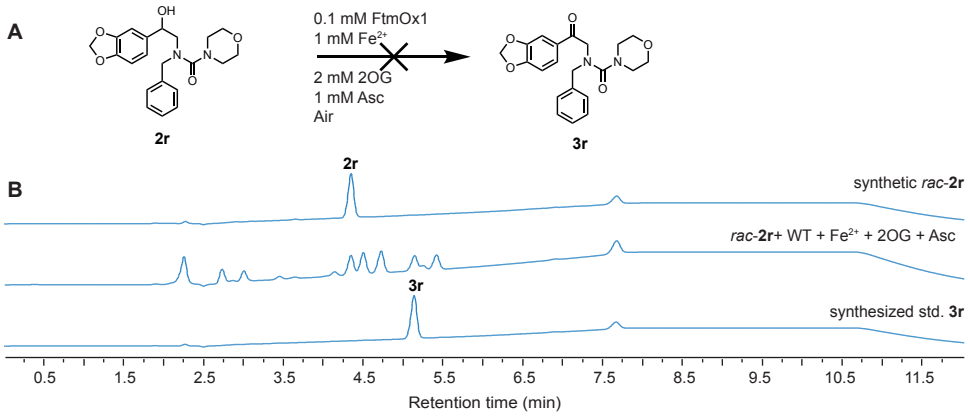


Figure S37. LC-MS analysis of the reaction of FtmOx1 with synthetic **2r**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate **2r** (*top spectrum*)**,** the full reaction (*middle spectrum*) and isolated **3r** (*bottom spectrum*). **2r**, **3r** and IS were eluted at 4.323 min, 5.179 min and ~7.7 min, respectively.

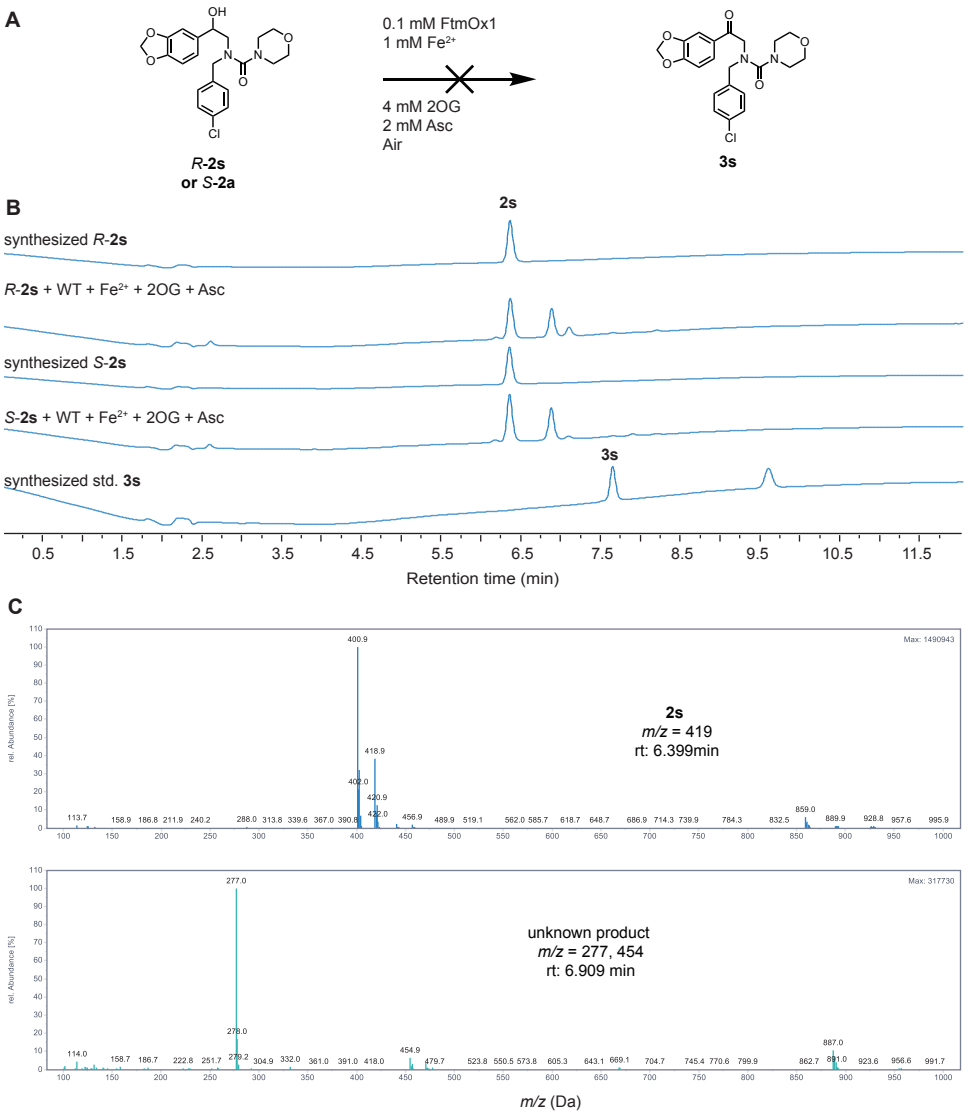


Figure S38. LC-MS analysis of the reaction of FtmOx1 with *S*-**2s** and *R*-**2s**. **A**) reaction scheme. **B**) LC spectra of synthesized substrate *R*-**2s** and the full reaction of synthesized *R*-**2s** (*second from top spectrum*), synthesized substrate *R*-**2s** (*middle spectrum*), the full reaction of synthesized *S*-**2s** (*second from bottom spectrum*) and the synthesized **3s** (*bottom spectrum*). **2s**, **3s** and IS were eluted at 6.399 min, 6.909 min and ~9.5 min, respectively. **C**) mass spectra of **2s** (*top spectrum*), and **3s** (*bottom spectrum*).

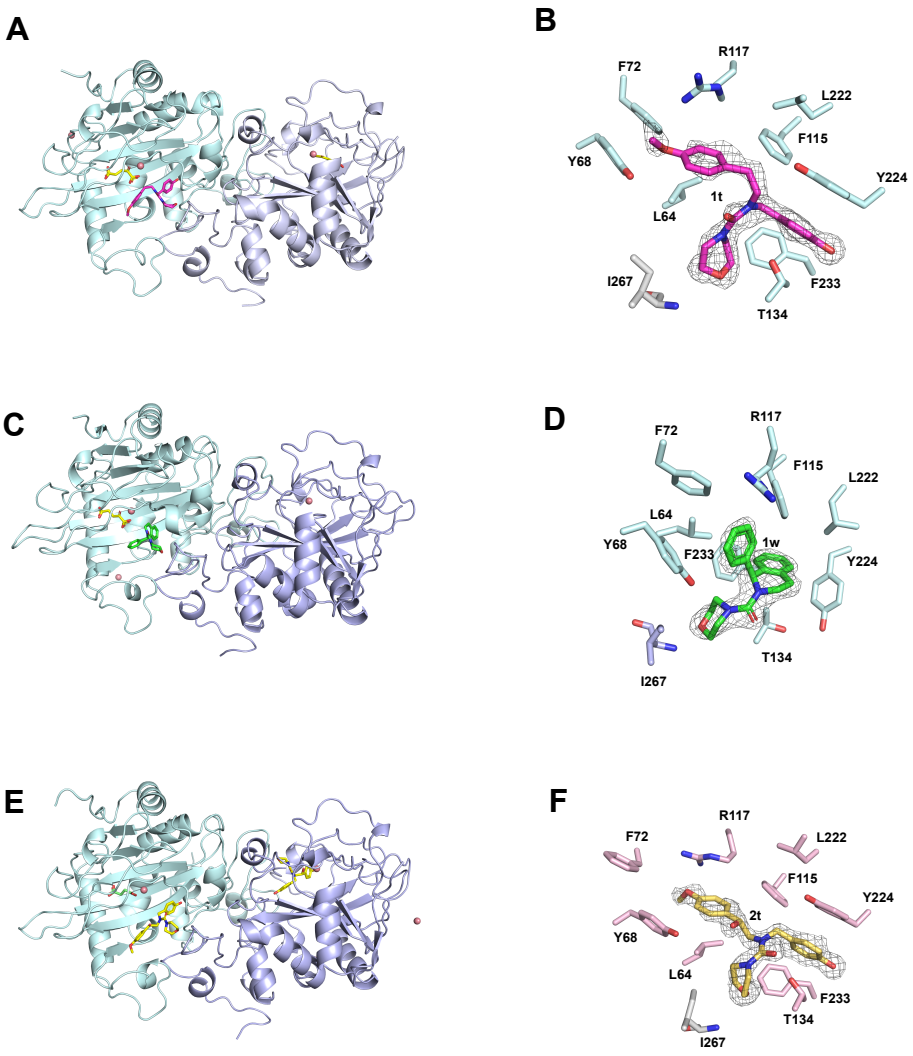


Figure S39. Overall structure of the protein ternary complex and its corresponding electron density map. The protein is displayed using a cartoon representation with different subunits colored distinctly. Ligands are shown in sticks format. An enlarged view of the binding pocket illustrating the spatial arrangement between the ligand and crucial residues. The overlaid mesh represents the 2mFo-Dfc electron density map, contoured at 0.8σ.(A) The overall structure of FtmOx1•Co^{2+}•2OG•**1t** (B) Active Site Details and Substrate Electron Density Map of **1t**. (C) The overall structure of FtmOx1•Co^{2+}•2OG•**1w.** (D) Active Site Details and Substrate Electron Density Map of **1w**. (E) The overall structure of FtmOx1•Co^{2+}•2OG•**2t.** (F) Active Site Details and Substrate Electron Density Map of **2t**.

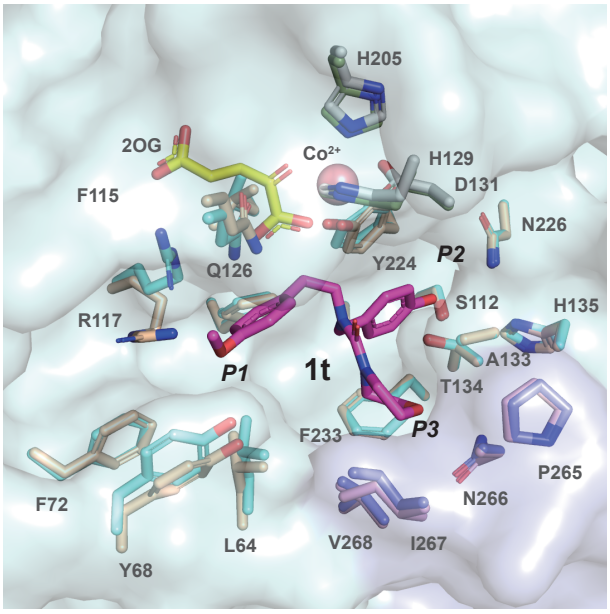


Figure S40. Structural comparison of the FtmOx1•2OG•**1t** complex with the apo-FtmOx1 conformation.

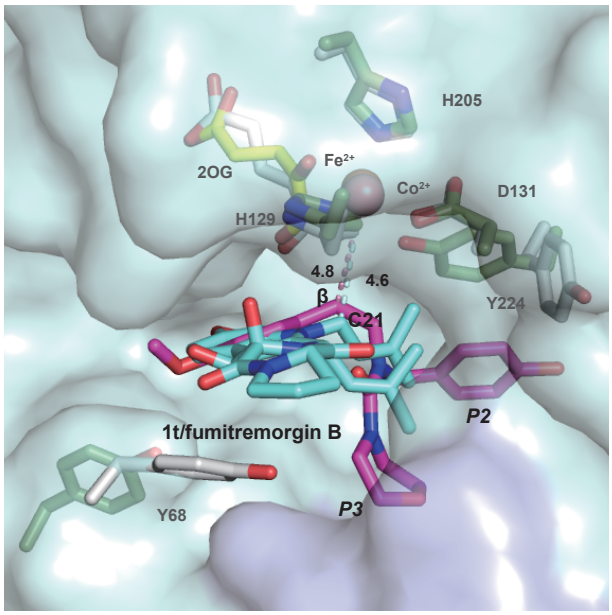


Figure S41. Structural overlay of FtmOx1 bound to the non-native substrate **1t** (magenta) and the native substrate fumitremorgin B (cyan), highlighting key differences in active-site interactions**.**

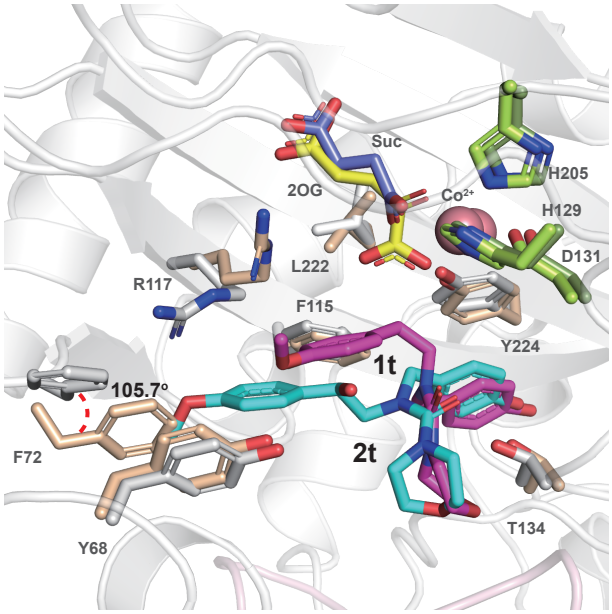


Figure S42. Structural overlay of FtmOx1 active sites showing conformational changes between substrate-bound (golden) and product-bound (gray) states.

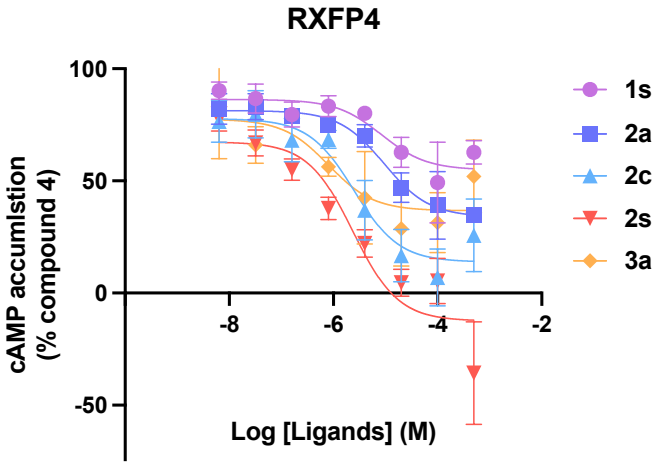


Figure S43. RXFP4 Activity Evaluation of Enzymatic Products.

Supplementary tables and figures

Supplementary methods

General Methods

All solvents were received from commercial sources without further purification. Commercially available reagents were used as received. Non-commercially available substrates were synthesized following reported protocols. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE III 500, Bruker AVANCE III 600 instruments. Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. Chemical shifts were reported in ppm (δ) with coupling constants (*J*) in hertz. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), quartet (q), and multiplet (m). All the analytical scale reactions were repeated at least twice independently using different batches of the enzyme.

Construction of FtmOx1 expression vectors

The DNA sequence encoding FtmOx1 from *Aspergillus fumigatus* was codon-optimized for expression in *Escherichia coli*, synthesized, and ligated with the pET28a vector at its NdeI and HindIII restriction sites (GenScript). The synthetic gene encodes an *N*-terminal His_6 tag, consisting of 20 amino acids (MGSSHHHHHHSSGLVPRGSH) sequence.

The full amino acid sequence is:

MGSSHHHHHHSSGLVPRGSHMTVDSKPQLQRLAADADVDRMCRLLEEDGAFILK
GLLPFDVVESFNRELDVQMAIPPPKGERLLADKYPPHFKYVPNVATTCPTFRNTVL
INPVIHAICEAYFQRTGDYWLSAAFLREIESGMPAQPFHRDDATHPLMHYQPLEAP
PVSLSVIFPLTEFTEENGATEVILGSHRWTEVGTPERDQAVLATMDPGDVLIVRQRV
VHAGGGNRTTAGKPRRVVLAYFNSVQLTPFETYRTMPREMVESMTVLGQRMLG
WRTMKPSDPNIVGINLIDDKRLENVLQLKAADSPA*

The full gene sequence is:

ATGGGCAGCAGCCATCATCATCATCATCACAGCAGCGGCCTGGTGCCGCGCGGC
AGCCATATGACCGTGGATAGCAAACCGCAACTGCAACGTCTGGCGGCGGATGC
GGATGTGGACCGTATGTGCCGTCTGCTGGAGGAAGATGGTGCGTTCATCCTGAA
GGGCCTGCTGCCGTTCGACGTGGTTGAGAGCTTTAACCGTGAACTGGATGTGC
AGATGGCGATCCCGCCGCCGAAAGGCGAGCGTCTGCTGGCGGACAAGTACCCG
CCGCACTTCAAATATGTGCCGAACGTTGCGACCACCTGCCCGACCTTTCGTAAC
ACCGTGCTGATCAACCCGGTTATCCACGCGATTTGCGAAGCGTACTTCCAACGT
ACCGGCGATTATTGGCTGAGCGCGGCGTTTCTGCGTGAGATTGAAAGCGGTATG
CCGGCGCAGCCGTTTCACCGTGACGATGCGACCCACCCGCTGATGCACTATCAG
CCGCTGGAGGCTCCGCCGGTTAGCCTGAGCGTTATCTTCCCGCTGACCGAGTTT
ACCGAGGAAAACGGCGCGACCGAAGTTATTCTGGGTAGCCATCGTTGGACCGA
GGTGGGTACCCCGGAACGTGATCAAGCGGTTCTGGCGACCATGGACCCGGGTG
ATGTGCTGATCGTTCGTCAACGTGTGGTTCATGCGGGTGGCGGTAACCGTACCA
CCGCGGGCAAGCCGCGTCGTGTGGTTCTGGCGTACTTCAACAGCGTGCAGCTG
ACCCCGTTTGAAACCTATCGTACCATGCCGCGTGAGATGGTGGAAAGCATGACC

GTTCTGGGCCAACGTATGCTGGGTTGGCGTACCATGAAACCGAGCGATCCGAA
CATCGTTGGTATTAACCTGATTGATGACAAGCGTCTGGAAAATGTTCTGCAACT
GAAAGCGGCGGACAGCCCGGCGTGA

A pRSFDuet expression vector containing an N-terminal His_6 tag and SUMO fusion protein was constructed by Gibson assembly method based on synthesized DNA sequence. The full gene sequence of the FtmOx1 His-SUMO construct is:

ATGTCGGACTCAGAAGTCAATCAAGAAGCTAAGCCAGAGGTCAAGCCAGAAGTCAAG
CCTGAGACTCACATCAATTTAAAGGTGTCCGATGGATCTTCAGAGATCTTCTTCAAGAT
CAAAAAGACCACTCCTTTAAGAAGGCTGATGGAAGCGTTCGCTAAAAGACAGGGTAA
GGAAATGGACTCCTTAAGATTCTTGTACGACGGTATTAGAATCCAAGCTGATCAGACCC
CTGAAGATTTGGACATGGAGGATAACGATATTATTGAGGCTCACAGAGAACAGATTGGT
GGAATGACCGTGGATAGCAAACCGCAACTGCAACGTCTGGCGGCGGATGCGGATGTG
GACCGTATGTGCCGTCTGCTGGAGGAAGATGGTGCGTTCATCCTGAAGGGCCTGCTGC
CGTTCGACGTGGTTGAGAGCTTTAACCGTGAACTGGATGTGCAGATGGCGATCCCGCC
GCCGAAAGGCGAGCGTCTGCTGGCGGACAAGTACCCGCCGCACTTCAAATATGTGCCG
AACGTTGCGACCACCTGCCCGACCTTTCGTAACACCGTGCTGATCAACCCGGTTATCC
ACGCGATTTGCGAAGCGTACTTCCAACGTACCGGCGATTATTGGCTGAGCGCGGCGTTT
CTGCGTGAGATTGAAAGCGGTATGCCGGCGCAGCCGTTTCACCGTGACGATGCGACCC
ACCCGCTGATGCACTATCAGCCGCTGGAGGCTCCGCCGGTTAGCCTGAGCGTTATCTTC
CCGCTGACCGAGTTTACCGAGGAAAACGGCGCGACCGAAGTTATTCTGGGTAGCCATC
GTTGGACCGAGGTGGGTACCCCGGAACGTGATCAAGCGGTTCTGGCGACCATGGACC
CGGGTGATGTGCTGATCGTTCGTCAACGTGTGGTTCATGCGGGTGGCGGTAACCGTAC
CACCGCGGGCAAGCCGCGTCGTGTGGTTCTGGCGTACTTCAACAGCGTGCAGCTGACC
CCGTTTGAAACCTATCGTACCATGCCGCGTGAGATGGTGGAAAGCATGACCGTTCTGG
GCCAACGTATGCTGGGTTGGCGTACCATGAAACCGAGCGATCCGAACATCGTTGGTATT
AACCTGATTGATGACAAGCGTCTGGAAAATGTTCTGCAACTGAAAGCGGCGGACAGC
CCGGCGTGA

Protein Expression and Purification

pET-28a plasmids containing genes were transformed using standard heat-shock protocols into chemically competent *E. coli* BL21(DE3) cells. *E. coli* cells containing the plasmid were selected on LB-AGAR plates with Kanamycin (50 μg/mL) and used to inoculate LB medium with Kanamycin (50 μg/mL). After incubation at 37°C overnight, pre-culture was used to inoculate fresh autoclaved medium (1 L) with Kanamycin (50 μg/mL). The cells were grown in 2 L shaking flask at 37 ºC (220 rpm) for about 4 h until OD_{600} reached 0.6~1.0 and then the culture was cool to 0 °C for 30 minutes and supplemented with 0.5 mM isopropyl β-D-thiogalactoside (IPTG). This culture was incubated at 18 °C for 16-18 h. Cells were harvested by centrifugation (8000 rpm, 10 min, 4 °C) and stored at -80 °C.

For purification, 5 g of cell pellet was suspended in 30 mL lysis buffer (50 mM Tris-HCl, 200 mM NaCl, 5% glycerol, pH 7.5). Cells were disrupted by high pressure

cell disrupter for 5-10 minutes. Lysates were centrifuged at 18000 rpm for 30 min at 4 ºC. The cleared lysate was loaded onto a Ni-NTA Beads (5 mL) and incubated at 4 ºC for half an hour. After incubation, let the liquid flow out at 4 ºC, wash with lysis buffer and elute with a gradient of 10 mL Tris Buffer (50 mM Tris-HCl, 200 mM NaCl, 5% glycerol, pH 7.5) containing different concentrations of imidazole (25 mM, 50 mM, 100 mM, 200 mM, 300 mM, 400 mM). Protein-containing fractions were collected and dialyzed against dialysis buffer (50 mM Tris-HCl, 200 mM NaCl, 5% glycerol, pH 7.5) including 1 mM EDTA for 2 hours, and then dialyzed again against dialysis buffer (50 mM Tris-HCl, 200 mM NaCl, 5% glycerol, pH 7.5). The protein was further concentrated, and its final concentration was determined by its absorbance at 280 nm using a calculated molar absorption coefficient of 26,930 M^{-1} cm^{-1} (https://web.expasy.org/protparam/). The protein was aliquoted and stored at -80 ºC.

E. coli BL21 (DE3) competent cells were transformed with pRSFDuet-based expression vectors encoding either wild-type (wt) or variant FtmOx1 using the heat-shock method. Transformants were selected on Luria-Bertani Broth (LB) agar plates containing 50 μg/mL kanamycin. A single colony was used to inoculate 10 mL of LB medium supplemented with 50 μg/mL kanamycin, and the culture was incubated overnight at 37 ºC with shaking at 220 rpm. Subsequently, 10 mL of this overnight culture was transferred into 1 L of LB medium, also containing 50 μg/mL kanamycin. The culture was grown at 37 ºC until reaching an optical density (OD_{600}) of approximately 0.6~0.8, at which point the incubation temperature was reduced to 18 ºC. Protein expression was induced by the addition of IPTG to a final concentration of 0.5 mM, and the cultures were incubated for an additional 16~18 hours at 18 ºC. The cells were harvested by centrifugation at 8000g for 15 min at 18 ºC, flash-frozen in liquid nitrogen, and stored at -80 ºC until further use.

All purification steps were performed at 4 ºC. Cell pellets were resuspended in Ni buffer A (25 mM Tris-HCl pH 8, 500 mM NaCl, and 2 mM 2-mercaptoethanol) containing protease inhibitor. The suspension was stirred on ice to homogeneity, and the cells were lysed by sonication. The supernatant and the cell debris were separated by centrifugation at 4 ºC for 30 min at 20,000g. The supernatant was mixed with Ni-IDA agarose resin, followed by eluting with washing buffer (25 mM Tris–HCl, pH 8.0, containing 500mM NaCl, 40 mM imidazole, and 2 mM 2-mercaptoethanol) using a gravity flow column. The bonded protein was eluted with eluting buffer containing 300mM imidazole. The eluate was supplemented with 0.5 mg of SUMO protease (Ulp1 from *Saccharomyces cerevisiae*) and dialyzed against 2Lof buffer B (25 mM Tris-HCl, pH 8.0, 500 mM NaCl) overnight at 4 ºC. Affinity chromatography was repeated; flow-through and wash fractions (with washing buffer) were collected. The fractions containing FtmOx1 were pooled, followed by two-step dialysis at 4 ºC, first against buffer C (25 mM Tris-HCl pH 8.0, 500 mM NaCl, and 10 mM EDTA) for 4 h and then against buffer D (25 mM Tris-HCl pH 8.0, 200 mM NaCl, and 2 mM 2-mercaptoethanol) for 4 h. This step was implemented to remove any metal ions retained through expression and purification The dialyzed sample was further purified by size-exclusion chromatography (SEC) using a HiLoad 16/600 Superdex 200 pg column in SEC buffer (25 mM Tris-HCl pH 7.4, 200 mM NaCl, and 2 mM Dithiothreitol). The protein was concentrated using an Amicon Ultra (Merck Millipore) at 2800 ×

g for 30 min at 4 °C. to be ~12 mg/mL, flash-frozen with liquid nitrogen, and stored at −80 °C. Protein purity was assessed by sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS-PAGE) stained with Coomassie Brilliant Blue.

Analytical scale of oxyfunctionalization by FtmOx1.

To a 2.5 mL reaction tube was added buffer (50 mM Tris-HCl, 200 mM NaCl, 5% glycerol, pH 7.5), wt or variants (0.1 mM, Tris-HCl buffer, pH 7.5), $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (1 mM, 100 mM in H_2O with 2.5 mM sulphuric acid), substrate (2 mM, 100 mM in DMSO, 4 μL), sodium ascorbate (2 mM, 0.1 M in H_2O), and 2-oxoglutarate (2OG, 4 mM, 100 mM in H_2O) sequentially. The total volume of the reaction was 200 μL and the final concentration for DMSO was 5 v/v%. The tube was uncapped and shaken at 800 rpm at room temperature for 2 h. And then, each tube was added 4 μL internal standard (IS) 9H-thioxanthen-9-one (0.002 mM final concetration, 1 mM stock in CH_3CN). To quench the reactions, ethyl acetate (600 μL) was added to the tube. The mixture was vortexed thoroughly and centrifuged (12000 rpm, 5 min). The organic phase (500 μL) was transferred to a new 1.7 mL tube, lyophilized, and re-dissolved in 200 μL of acetonitrile. The solution was transferred into HPLC vail inserts for LC-MS analysis. The product formation was confirmed by comparing MS spectra and the retention times in HPLC with the racemic standards. LC yields were determined relative to internal standard according to calibration curves. Enantiomeric excess (ee) was measured by chiral HPLC. Reactions for every substrate were set up in triplicate.

Reaction components were separated on an Agilent Zorbax Extend-C18 column (2.7 μm, 4.6 × 100 mm) initially in 50% solvent A (0.1% formic acid in water) and 50% solvent B (0.1% formic acid in acetonitrile). The column was developed at a flow rate of 0.4 mL/min. A gradient of 50% to 15% solvent A was applied from 0 min (the time of injection) to 5 min. The proportion of solvent A was kept at 15% from 5 min to 8 min. The column was then returned to 50% solvent A by a linear gradient from 8 min to 10 min and washed with 50% solvent A from 10 min to 12 min before the next injection.

Detection of the substrates, products and their derived products were achieved by electrospray ionization in the positive-ion mode (ESI^+) and the data of UV-Vis was monitored at 254 nm.

The ee values were determined by HPLC analysis on Shimadzu DGU-20A instrument with SPD-M40 PDA detector using Chiral columns [CHIRALEAK® AD-H, IA and IB (5 μm, 4.6 mm × 250 mm)], hexane (A) and isopropanol (B). And the isolated products were separated at the following solvent gradients. Method A:10 to 30 %B (0 – 30 min), 30 %B (30 – 50 min), 30 to 10 %B (50 – 65 min). Flow rate: 1 mL/min; Method B:10 to 18 %B (0 – 15 min), 18 %B (15 – 100 min), 18 to 10 %B (100 – 125 min). Flow rate: 1 mL/min; Method C: 5 to 13 %B (0 – 60 min), 13 %B (60 – 135min), 13 to 5 %B (135 – 145 min). The column was developed at a flow rate of 1 mL/min. And the data of UV-Vis was monitored at 254 nm. Additionally, the ee values of different products were detected by different conditions which were showed as in table below:

Table S1. The summary of chiral HPLC methods for enzymatic products.

Compd.	Elution condition	column	Compd.	Elution condition	column	Compd.	Elution condition	column
2a	A	AD	**2b**	A	AD	**2c**	A	AD
2d	A	AD	**2e**	A	AD	**2f**	B	IA
2g	A	IA	**2h**	A	IA	**2i**	A	AD
2j	A	AD	**2k**	A	AD	**2l**	A	AD
2m	A	AD	**2n**	A	AD	**2o**	A	AD
2p	A	IA	**2q**	A	IA	**2r**	A	AD
2s	A	AD	**2t**	A	IA	**2u**	A	AD
2v	C	IB						

TTNs determination

The reaction conditions were close as described above unless the amount of enzyme was 0.1 mM. TTNs were calculated based on measured protein concentration.

Preparative scale of oxyfunctionalization by FtmOx1.

To a 100 mL flask was added buffer (50 mM Tris-HCl, 200 mM NaCl, 5% glycerol, pH 7.5), FtmOx1 (0.2 mM, Tris-HCl buffer, pH 7.5), $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (1 mM, 100 mM in H_2O with 2.5mM sulphuric acid), substrate (2 mM, 0.1 M in DMSO; 4 mM, 0.2 M in DMSO), sodium ascorbate (2 mM, 0.1 M in H_2O), and 2OG (4 mM, 0.1 M in H_2O) sequentially. The resulting 50 mL-scale mixture was stirred in the air at 25 ℃ for 4 h. The reaction solution was extracted with 150 mL ethyl acetate for 3 times. The combined organic layer was concentrated *in vacuo* and purified by preparing liquid phase to provide hydroxylation product or ketone product as a colorless oily liquid.

Preparative isolation was conducted using a Waters 2545 Binary Gradient Module instrument with a Waters 2489 UV/visible detector using a SunFire column (Prep C18 OBD, 5 μm, 19 × 250 mm) under a gradient solvent system composed of water and acetonitrile, with a flow rate of 20.0 mL/min. For the first 5 min, the acetonitrile concentration was increased from 40 to 85%, then held for 7 min, and immediately returned to 40% to reequilibrate the column for another 1 min. Products were detected at 254 nm. Products amounts in the samples were calculated according to the recovery of IS.

X-ray crystallization and data collection methods

Crystallization

To facilitate the formation of stable ternary complexes of FtmOx1 with different substrates and 2-oxoglutarate (2OG) or Succinate, a final concentration of 1 mM $CoCl_2$ was added to the protein. Crystallization of FtmOx1·Co^{2+} was established by using a sitting-drop vapor-phase diffusion method, mixing the protein with a crystallization buffer (0.2 M Ammonium acetate, 0.05 M Sodium cacodylate trihydrate pH 6.5, 30% w/v Polyethylene glycol 8,000) at a ratio of 1:1 at 20 °C. The FtmOx1, 2OG and substrate complex was obtained using soaking methods. Crystal soaking was conducted by transferring the pre-formed FtmOx1·Co^{2+} crystals into crystallization mother liquor containing 5 mM 2OG and 10 mM substrate (50 mM in DMSO stocking buffer) and

incubated for 3 days at 20 °C. The crystals were cryoprotected by the addition of 25% v/v ethylene glycol (EG) in mother liquor before being vitrified in liquid nitrogen for data collection.

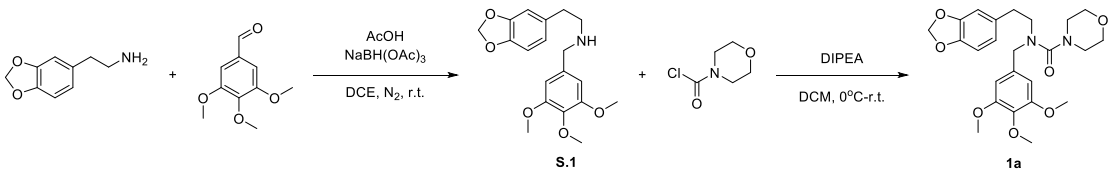
Crystal diffraction data were collected at beamline BL02U1, BL10U2, BL19U1 and BL18U1 at the National Center for Protein Sciences Shanghai (NCPSS) or the Shanghai Synchrotron Radiation Facility (SSRF). Data reduction and integration were achieved with the XDS software package. The crystal structure of FtmOx1 was solved with Phaser-MR[1] by using the apo-FtmOx1 (PDB ID 4Y5T) as a searching model. Iterative cycles of optimization were performed to improve the quality of the model using the refinement program PHENIX.Refine[1], followed by manual rebuilding in COOT[2]. The structure and restraints of **1t** or **2t** was generated in eLBOW from the PHENIX suite. Refinement statistics for each final model are summarized in Table S2. All structure figures were drawn by PyMol (http://pymol. sourceforge.net/) or USFC Chimera[3].

Table S2. Data collection and refinement statistics

Data collection	FtmOx1•Co^{2+}•2OG•**1t**	FtmOx1•Co^{2+}•succinate•**2t**
Space group	$P2_1\ 2_1\ 2_1$	$P2_1\ 2_1\ 2_1$
Wavelength(Å)	0.97918	0.97918
Cell dimensions		
α，β，γ (°)	74.22, 82.61, 92.12	74.14, 81.49, 91.89
α，β，γ (°)	90.0, 90.00, 90.00	90.0, 90.00, 90.00
Resolution (Å)	61.50-1.77(1.77-1.83)	30.48-1.69(1.75-1.69)
$CC_{1/2}$	0.999 (0.744)	0.997(0.529)
Completeness (%)	99.8(100)	98.4(92.4)
Average (I/σ)	5.5 (1.50)	6.2 (2.30)
Refinement		
Resolution	1.77-57.79	1.69-30.48
No. reflections used	56022	58197
R_{work}/R_{free}	0.1987/0.2434	0.2025/0.2531
Ramachandran		
Favored (%)	95.26	97.02%
Outliers (%)	0.1	0.18
RMSD		
Bond lengths (Å)	0.008	0.007
Bond angles (Å)	1.0	1.04

Synthesis and characterization of substrates and products

General procedure A (exemplified for the synthesis of **1a**)

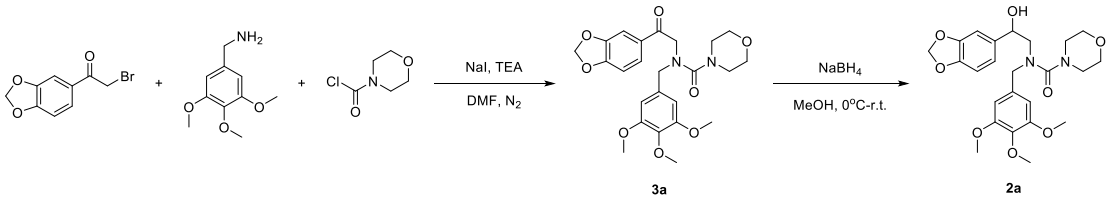


To a solution of 3,4-methylenedioxy-phenethylamin (11.22 mmol, 1.1 eq., 1.852 g) and

3,4,5-Trimethoxybenzaldehyde (10.2 mmol, 1 eq., 2 g) in DCE (20 mL) was added AcOH (5.1 mmol, 0.5 eq., 0.306 g) and $NaBH(OAc)_3$ (15.3 mmol, 1.5 eq., 3.244 g), then the flask was evacuated and backfilled with argon three times.The reaction was stirred at room temperature for 4 h. The mixture was poured into water and extracted with DCM. The combined organic layers were washed with brine and dried with Na_2SO_4. The solution was concentrated in vacuo and purified by column chromatography (DCM/MeOH v: v = 20:1) to provide 2.22 g (63% yield) of **S.1** as a white solid.

To a solution of **S.1** (2 mmol, 1 eq., 690 mg) and N,N-Diisopropylethylamine (DIPEA, 6 mmol, 3 eq., 774 mg) in DCM (20 mL) was slowly added 4-morpholinecarbonyl chloride (3 mmol, 1.5 eq., 447 mg) at 0℃. The mixture was then stirred at room temperature for 4 h. After being washed with saturated NH_4Cl and brine, the solvent was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (DCM/MeOH v: v = 100:1) to afford compound **1a** as a colorless oil (824 mg, 90%).

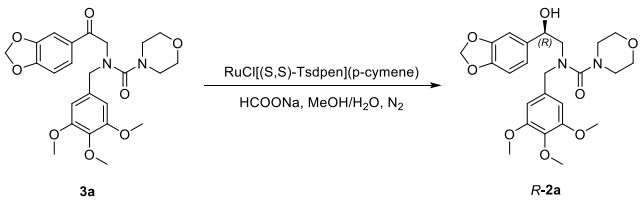
General procedure B (exemplified for the synthesis of **2a** and **3a**)



To a solution of 1-(benzo[d][1,3]dioxol-5-yl)-2-bromoethan-1-one (3.3 mmol, 1 eq., 800 mg) and NaI (0.33 mmol, 0.1 eq., 50 mg) in DMF (20 mL) under N_2, a solution of (3,4,5-trimethoxyphenyl)methanamine (5 mmol, 1.5 eq., 985 mg) and TEA (16.5 mmol, 5 eq., 1.67 g) in DMF (10 mL) was added. The raction mixture was stirred for 30 min, then 4-morpholinecarbonyl chloride (9.9 mmol, 3 eq., 1.48 g) was added. The reaction was stirred for 4 h. The mixture was poured into water and extracted with EtOAc. The combined organic layers was washed with saturated NH_4Cl and brine, the solvent was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (PE/EA v: v = 3:2) to afford compound **3a** as a yellow oil (623 mg, 40%).

To a solution of **3a** (1 mmol, 1 eq., 472 mg) in MeOH (20 mL) at 0℃, $NaBH_4$ (3 mmol, 3 eq., 114 mg) was gradually added. The mixture was then stirred at room temperature for 1 h. The mixture was poured into water and extracted with EtOAc. The combined organic layers was washed with brine, the solvent was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (PE/EA v: v = 1:4) to afford compound **2a** as a white solid (450 mg, 95%).

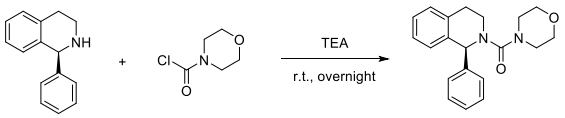
General procedure C (exemplified for the synthesis of *R*-**2a**) using adaptations of previously published methods.[4, 5]



To a solution of **3a** (236 mg, 0.5 mmol) in water-methanol mixture (1:1 v/v，25 mL)

was added RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) (7 mg, 0.01 mmol) and sodium formate (170 mg, 2.5 mmol). The mixture was vigorously stirred at room temperature under N_2 overnight. The reaction mixture was then extracted with DCM, washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (60% EA in PE) to afford compound *R*-**2a** as a colorless oil (201 mg, 85%).

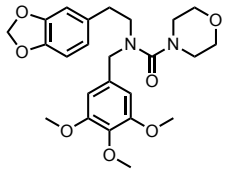
General procedure D (exemplified for the synthesis of **2w**)



2w

To a solution of (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (2 mmol, 1 eq., 210 mg) in DCM was added morpholine-4-carbonyl chloride (3 mmol, 1.5 eq., 450mg) and triethylamine (5 mmol, 2.5 eq., 694 ml). The mixture was vigorously stirred at room temperature overnight. The reaction mixture was then extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (PE/EA v: v = 2:1) to afford compound **2w** as a colorless oil (483 mg, 75%).

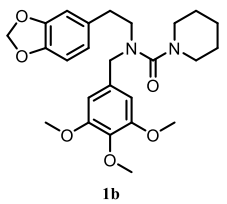
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1a):**



1a

Compound **1a** was obtained following the general procedure A in 57% yield (824 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d6) δ 6.81 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 1.6 Hz, 1H), 6.64 (dd, J = 7.9, 1.7 Hz, 1H), 6.54 (s, 2H), 5.95 (s, 2H), 4.29 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.54 (t, J = 4.7 Hz, 4H), 3.22 (t, J = 7.3 Hz, 2H), 3.08 (t, J = 4.7 Hz, 4H), 2.71 (t, J = 7.3 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.4, 147.6, 146.0, 136.8, 134.5, 133.5, 122.1, 109.6, 108.5, 104.9, 101.1, 66.3, 60.4, 56.3, 51.1, 49.6, 47.6, 33.4. **HRMS** (ESI, *m/z*)calcd for $C_{24}H_{31}N_2O_7^+$ $[M+H]^+$: 459.2126, found: 459.2144.

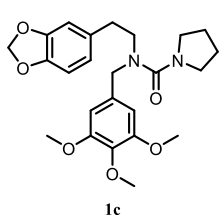
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)piperidine-1-carboxamide (1b):**



1b

Compound **1b** was obtained following the general procedure **A** in 55% yield (201 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.79 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 1.7 Hz, 1H), 6.62 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.53 (s, 2H), 5.94 (s, 2H), 4.25 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.17 (dd, *J* = 8.3, 6.4 Hz, 2H), 3.07 (t, *J* = 5.3 Hz, 4H), 2.70 (dd, *J* = 8.3, 6.4 Hz, 2H), 1.51 (q, *J* = 6.2 Hz, 2H), 1.45 (q, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.4, 153.4, 147.6, 145.9, 136.8, 134.8, 133.6, 122.0, 109.5, 108.5, 105.0, 101.1, 60.4, 56.2, 51.3, 49.9, 47.9, 33.5, 25.7, 24.7. **HRMS** (ESI, *m/z*:) calcd for $C_{25}H_{33}N_2O_6^+$ $[M+H]^+$: 457.2333, found: 457.2334.

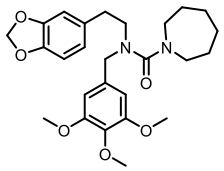
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)pyrrolidine-1-carboxamide (1c):**



1c

Compound **1c** was obtained following the general procedure **A** in 54% yield (380 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.79 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 6.62 (dd, J = 7.9, 1.7 Hz, 1H), 6.57 (s, 2H), 5.95 (s, 2H), 4.29 (s, 2H), 3.74 (s, 6H), 3.64 (s, 3H), 3.29 – 3.23 (m, 4H), 3.19 (dd, J = 9.0, 6.4 Hz, 2H), 2.71 (dd, J = 8.9, 6.4 Hz, 2H), 1.77 – 1.72 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 162.3, 153.3, 147.6, 145.9, 136.8, 135.0, 133.7, 122.0, 109.5, 108.5, 105.1, 101.1, 60.4, 56.3, 51.3, 49.5, 48.5, 33.7, 25.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_6^+$ $[M+H]^+$: 443.2177, found: 443.2193.

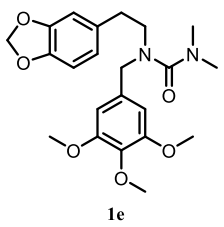
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)azepane-1-carboxamide (1d):**



1d

Compound **1d** was obtained following the general procedure **A** in 57% yield (211 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.79 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 6.54 (s, 2H), 5.95 (s, 2H), 4.20 (s, 2H), 3.73 (s, 6H), 3.63 (s, 3H), 3.26 (t, J = 5.9 Hz, 4H), 3.13 (dd, J = 8.5, 6.4 Hz, 2H), 2.70 (dd, J = 8.3, 6.4 Hz, 2H), 1.65 – 1.62 (m, 4H), 1.49 – 1.46 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.4, 153.3, 147.6, 145.9, 136.8, 135.0, 133.8, 122.0, 109.5, 108.5, 105.0, 101.1, 60.4, 56.2, 52.5, 50.5, 48.5, 33.6, 28.6, 27.4. **HRMS** (ESI, *m/z*) calcd for $C_{26}H_{35}N_2O_6^+$ $[M+H]^+$: 471.2490, found: 471.2492.

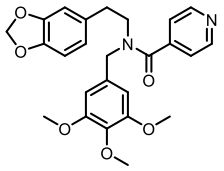
1-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-3,3-dimethyl-1-(3,4,5-trimethoxybenzyl)urea (1e):



1e

Compound **1e** was obtained following the general procedure **A** in 48% yield (201mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.80 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 6.55 (s, 2H), 5.95 (s, 2H), 4.24 (s, 2H), 3.74 (s, 6H), 3.64 (s, 3H), 3.19 – 3.14 (m, 2H), 2.73 (s, 6H), 2.70 (dd, J = 8.6, 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.6, 153.4, 147.6, 145.9, 136.9, 134.8, 133.7, 122.0, 109.5, 108.5, 105.1, 101.1, 60.4, 56.3, 51.8, 49.9, 38.7, 33.6. **HRMS** (ESI, *m/z*) calcd for $C_{22}H_{29}N_2O_6^+$ $[M+H]^+$: 417.2020, found: 417.2030.

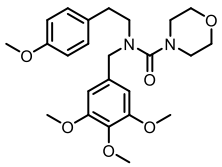
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)isonicotinamide (1f):**



1f

Compound **1f** was obtained following the general procedure **A** in 50% yield (225 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.66 (dd, J = 13.4, 5.0 Hz, 2H), 7.37 (d, J = 5.8 Hz, 1H), 7.20 (d, J = 5.7 Hz, 1H), 6.90 – 6.69 (m, 3H), 6.52 – 6.39 (m, 2H), 5.99 (d, J = 5.8 Hz, 2H), 4.72 (s, 1H), 4.29 (s, 1H), 3.83 (s, 4H), 3.78 (s, 2H), 3.70 (s, 2H), 3.66 (s, 1H), 3.61 (t, J = 7.4 Hz, 1H), 3.29 (t, J = 7.2 Hz, 1H), 2.86 (t, J = 7.4 Hz, 1H), 2.70 (t, J = 7.2 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 169.3, 169.0, 153.6, 153.5, 150.5, 150.3, 147.8, 146.3, 146.2, 144.5, 144.3, 137.3, 137.2, 133.5, 133.2, 132.7, 132.3, 122.1, 121.3, 121.2, 109.6, 109.5, 108.6, 105.5, 104.7, 101.2, 101.2, 60.4, 56.3, 52.5, 50.2, 47.3, 46.7, 33.9, 32.9. **HRMS** (ESI, *m/z*) calcd for $C_{25}H_{27}N_2O_6^+$ $[M+H]^+$: 451.1864, found: 451.1865.

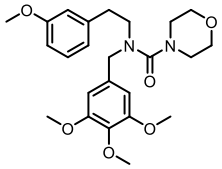
***N*-(4-methoxyphenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1g):**



1g

Compound **1g** was obtained following the general procedure **A** in 54% yield (239 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.12 – 7.07 (m, 2H), 6.86 – 6.82 (m, 2H), 6.54 (s, 2H), 4.30 (s, 2H), 3.75 (s, 6H), 3.71 (s, 3H), 3.64 (s, 3H), 3.56 – 3.50 (m, 4H), 3.22 (t, J = 7.5 Hz, 2H), 3.08 (t, J = 4.7 Hz, 4H), 2.73 (dd, J = 8.4, 6.5 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.2, 158.2, 153.4, 136.9, 134.5, 131.5, 130.1, 114.2, 105.0, 66.3, 60.4, 56.3, 55.5, 51.2, 49.7, 47.6, 32.8. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_6^+$ $[M+H]^+$: 445.2333, found: 445.2340.

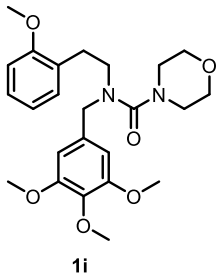
***N*-(3-methoxyphenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1h):**



1h

Compound **1h** was obtained following the general procedure **A** in 65% yield (289 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.21 – 7.16 (m, 1H), 6.78 – 6.73 (m, 3H), 6.55 (s, 2H), 4.31 (s, 2H), 3.74 (s, 6H), 3.72 (s, 3H), 3.64 (s, 3H), 3.55 – 3.51 (m, 4H), 3.26 (dd, J = 8.3, 6.5 Hz, 2H), 3.08 (t, J = 4.7 Hz, 4H), 2.77 (t, J = 7.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 159.7, 153.4, 141.3, 136.9, 134.4, 129.8, 121.5, 114.9, 112.0, 105.0, 66.3, 60.4, 56.3, 55.4, 51.2, 49.3, 47.6, 33.8. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_6^+$ $[M+H]^+$: 445.2333, found: 445.2344.

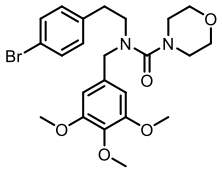
***N*-(2-methoxyphenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1i):**



1i

Compound **1i** was obtained following the general procedure **A** in 61% yield (270 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.18 (td, J = 7.9, 1.7 Hz, 1H), 7.10 (dd, J = 7.4, 1.7 Hz, 1H), 6.93 (dd, J = 8.3, 1.1 Hz, 1H), 6.84 (td, J = 7.4, 1.1 Hz, 1H), 6.55 (s, 2H), 4.32 (s, 2H), 3.74 (d, J = 1.5 Hz, 9H), 3.63 (s, 3H), 3.56 – 3.50 (m, 4H), 3.22 (dd, J = 8.5, 6.3 Hz, 2H), 3.06 (t, J = 4.6 Hz, 4H), 2.79 (dd, J = 8.4, 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.2, 157.7, 153.3, 136.8, 134.6, 130.8, 128.2, 127.3, 120.7, 111.1, 104.9, 66.3, 60.4, 56.2, 55.7, 50.8, 48.1, 47.7, 28.7. **HRMS** (ESI, *m/z*) calcd calcd. for $C_{24}H_{33}N_2O_6^+$ $[M+H]^+$: 445.2333, found: 445.2333.

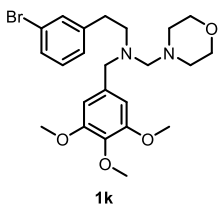
***N*-(4-bromophenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1j):**



1j

Compound **1j** was obtained following the general procedure **A** in 45% yield (221 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.46 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H), 6.53 (s, 2H), 4.30 (s, 2H), 3.74 (s, 6H), 3.64 (s, 3H), 3.55 – 3.51 (m, 4H), 3.26 (t, J = 7.2 Hz, 2H), 3.07 (t, J = 4.7 Hz, 4H), 2.78 (t, J = 7.2 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.4, 139.2, 136.9, 134.3, 131.6, 131.5, 119.6, 104.9, 66.3, 60.4, 56.3, 51.3, 49.0, 47.6, 33.0. **HRMS** (ESI, *m/z*) calcd for $C_{23}H_{30}BrN_2O_5^+$ $[M+H]^+$: 493.1333, found: 493.1339.

***N*-(3-bromophenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1k):**

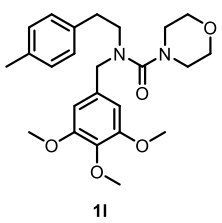


1k

Compound **1k** was obtained following the general procedure **A** in 48% yield (236 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.42 (t, J = 1.8 Hz, 1H), 7.39 (dt, J = 7.8, 1.6 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.22 – 7.19 (m, 1H), 6.54 (s, 2H), 4.29 (s, 2H), 3.74 (s, 6H), 3.64 (s, 3H), 3.55 – 3.51 (m,

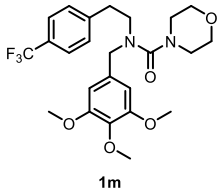
4H), 3.27 (t, *J* = 7.1 Hz, 2H), 3.05 (t, *J* = 4.7 Hz, 4H), 2.80 (t, *J* = 7.1 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.4, 142.7, 136.9, 134.3, 132.0, 130.8, 129.4, 128.4, 122.0, 105.0, 66.3, 60.4, 56.3, 51.1, 48.9, 47.6, 33.2. **HRMS** (ESI, *m/z*) calcd for $C_{23}H_{30}BrN_2O_5^+$ $[M+H]^+$: 493.1333, found: 493.1339.

***N*-(4-methylphenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1l):**


1l

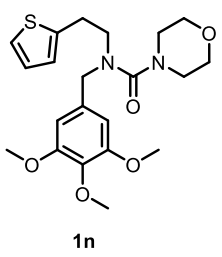
Compound **1l** was obtained following the general procedure **A** in 68% yield (291 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.10 – 7.04 (m, 4H), 6.54 (s, 2H), 4.30 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.56 – 3.50 (m, 4H), 3.22 (dd, *J* = 8.5, 6.4 Hz, 2H), 3.08 (t, *J* = 4.7 Hz, 4H), 2.75 (dd, *J* = 8.5, 6.4 Hz, 2H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.4, 136.8, 136.6, 135.5, 134.4, 129.3, 129.1, 104.9, 66.3, 60.4, 56.2, 51.2, 49.5, 47.6, 33.3, 21.1. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_5^+$ $[M+H]^+$: 429.2384, found: 429.2386.

***N*-(4-(trifluoromethyl)phenethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1m):**


1m

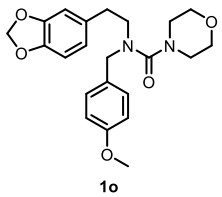
Compound **1m** was obtained following the general procedure **A** in 53% yield (650 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 2H), 6.54 (s, 2H), 4.32 (s, 2H), 3.74 (s, 6H), 3.64 (s, 3H), 3.51 (t, *J* = 4.7 Hz, 4H), 3.31 (t, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 4.7 Hz, 4H), 2.91 (t, *J* = 7.1 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.4, 144.9, 136.9, 134.3, 130.1, 127.4 (d, *J* = 31.6 Hz), 125.5 (q, *J* = 3.8 Hz), 124.9 (d, *J* = 271.9 Hz), 104.9, 66.3, 60.4, 56.3, 51.2, 48.8, 47.6, 33.5. **^{19}F NMR** (565 MHz, DMSO-d_6) δ -60.80. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{30}F_3N_2O_5^+$ $[M+H]^+$: 483.2101, found: 483.2105.

***N*-(2-(thiophen-2-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (1n):**


1n

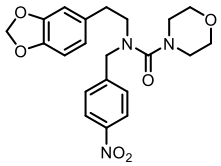
Compound **1n** was obtained following the general procedure **A** in 45% yield (189 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.33 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.86 (dd, *J* = 3.3, 1.2 Hz, 1H), 6.54 (s, 2H), 4.31 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.55 (t, *J* = 4.6 Hz, 4H), 3.27 (t, *J* = 7.2 Hz, 2H), 3.11 (t, *J* = 4.6 Hz, 4H), 3.03 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.4, 141.8, 136.9, 134.2, 127.4, 125.9, 124.6, 104.9, 66.3, 60.4, 56.3, 51.5, 49.3, 47.6, 27.8. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{29}N_2O_5S^+$ $[M+H]^+$: 421.1792, found: 421.1795.

***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(4-methoxybenzyl)morpholine-4-carboxamide (1o):**


1o

Compound **1o** was obtained following the general procedure **A** in 63% yield (251 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.61 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.95 (s, 2H), 4.28 (s, 2H), 3.73 (s, 3H), 3.55 – 3.51 (m, 4H), 3.15 (t, *J* = 7.4 Hz, 2H), 3.06 (t, *J* = 4.7 Hz, 4H), 2.67 (t, *J* = 7.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 158.9, 147.6, 146.0, 133.5, 130.4, 129.3, 122.0, 114.3, 109.5, 108.5, 101.1, 66.3, 55.5, 50.7, 49.0, 47.6, 33.3. **HRMS** (ESI, *m/z*) calcd for $C_{22}H_{27}N_2O_5^+$ $[M+H]^+$: 399.1914, found: 399.1922.

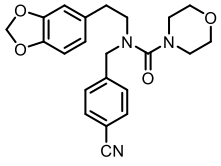
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(4-nitrobenzyl)morpholine-4-carboxamide (1p):**



1p

Compound **1p** was obtained following the general procedure **A** in 63% yield (762 mg) as yellow oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.22 – 8.17 (m, 2H), 7.54 – 7.49 (m, 2H), 6.81 (d, J = 7.9 Hz, 1H), 6.79 (d, J = 1.7 Hz, 1H), 6.65 (dd, J = 7.9, 1.7 Hz, 1H), 5.96 (s, 2H), 4.50 (s, 2H), 3.53 (t, J = 4.6 Hz, 4H), 3.25 (dd, J = 8.3, 6.4 Hz, 2H), 3.09 (t, J = 4.7 Hz, 4H), 2.74 (t, J = 7.3 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 163.9, 147.6, 147.4, 147.0, 146.0, 133.2, 128.9, 124.0, 122.2, 109.6, 108.5, 101.1, 66.3, 50.7, 50.6, 47.5, 33.5. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{24}N_3O_6^+$ $[M+H]^+$: 414.1660, found: 414.1670.

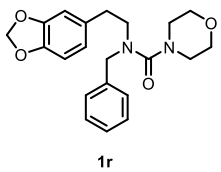
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(4-cyanobenzyl)morpholine-4-carboxamide (1q):**



1q

Compound **1q** was obtained following the general procedure **A** in 65% yield (902 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.80 (d, J = 8.3 Hz, 2H), 7.46 – 7.41 (m, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 1.7 Hz, 1H), 6.64 (dd, J = 7.9, 1.7 Hz, 1H), 5.96 (s, 2H), 4.45 (s, 2H), 3.53 (dd, J = 5.5, 3.9 Hz, 4H), 3.23 (dd, J = 8.3, 6.4 Hz, 2H), 3.07 (t, J = 4.7 Hz, 4H), 2.72 (dd, J = 8.3, 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.0, 147.6, 146.0, 145.1, 133.2, 132.8, 128.7, 122.1, 119.3, 110.2, 109.6, 108.5, 101.1, 66.3, 50.9, 50.4, 47.5, 33.5. **HRMS** (ESI, *m/z*) calcd for $C_{22}H_{24}N_3O_4^+$ $[M+H]^+$: 394.1761, found: 394.1761.

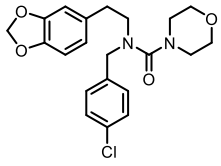
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-benzylmorpholine-4-carboxamide (1r):**



1r

Compound **1r** was obtained following the general procedure **A** in 72% yield (264 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.33 (t, J = 7.5 Hz, 2H), 7.28 – 7.21 (m, 3H), 6.80 (d, J = 7.8 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 6.61 (dd, J = 7.9, 1.7 Hz, 1H), 5.95 (s, 2H), 4.36 (s, 2H), 3.55 – 3.51 (m, 4H), 3.18 (dd, J = 8.3, 6.4 Hz, 2H), 3.06 (t, J = 4.7 Hz, 4H), 2.69 (dd, J = 8.2, 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.2, 147.6, 146.0, 138.7, 133.4, 128.9, 127.9, 127.5, 122.1, 109.6, 108.5, 101.1, 66.3, 51.3, 49.4, 47.6, 33.3. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{25}N_2O_4^+$ $[M+H]^+$: 369.1809, found: 369.1820.

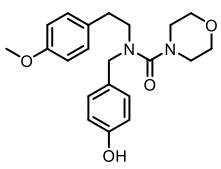
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(4-chlorobenzyl)morpholine-4-carboxamide (1s):**



1s

Compound **1s** was obtained following the general procedure **A** in 58% yield (233 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.41 – 7.36 (m, 2H), 7.29 – 7.24 (m, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 5.95 (s, 2H), 4.34 (s, 2H), 3.55 – 3.50 (m, 4H), 3.18 (dd, J = 8.3, 6.4 Hz, 2H), 3.06 (t, J = 4.7 Hz, 4H), 2.70 (dd, J = 8.2, 6.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.0, 147.6, 146.0, 137.9, 133.3, 132.0, 129.8, 128.8, 122.1, 109.6, 108.5, 101.1, 66.3, 50.5, 49.7, 47.6, 33.4. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{24}ClN_2O_4^+$ $[M+H]^+$: 403.1419, found: 403.1426.

***N*-(4-hydroxybenzyl)-*N*-(4-methoxyphenethyl)morpholine-4-carboxamide(1t):**

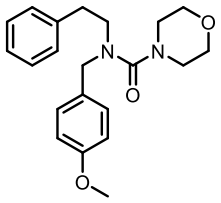


1t

Compound **1t** was obtained following the general procedure **A** in 55% yield (205 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.33 (s, 1H),

7.05 (dd, *J* = 10.8, 8.2 Hz, 4H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 2H), 4.23 (s, 2H), 3.70 (s, 3H), 3.58 – 3.50 (m, 4H), 3.13 (t, *J* = 7.3 Hz, 2H), 3.05 (t, *J* = 4.6 Hz, 4H), 2.68 (t, *J* = 7.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.18, 158.17, 156.93, 131.60, 130.08, 129.29, 128.49, 115.69, 114.20, 66.35 (d, *J* = 6.9 Hz), 55.46, 50.83, 48.78, 47.68, 32.75. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{27}N_2O_4^+$ $[M+H]^+$: 371.1966, found: 371.1971.

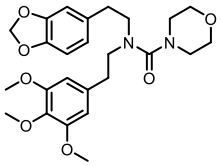
N-(4-methoxybenzyl)-N-phenethylmorpholine-4-carboxamide(1u):



1u

Compound **1u** was obtained following the general procedure **A** in 65% yield (312 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.27 (t, *J* = 7.2 Hz, 2H), 7.17 (ddd, *J* = 12.3, 7.9, 5.3 Hz, 5H), 6.92 – 6.87 (m, 2H), 4.29 (s, 2H), 3.73 (d, *J* = 1.4 Hz, 3H), 3.52 (t, *J* = 4.6 Hz, 4H), 3.19 (t, *J* = 7.4 Hz, 2H), 3.05 (t, *J* = 4.6 Hz, 4H), 2.76 (t, *J* = 7.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.15, 158.87, 139.76, 130.32, 129.28, 129.16, 128.74, 126.55, 114.35, 66.31, 55.50, 50.74, 48.74, 47.64, 33.66. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{27}N_2O_3^+$ $[M+H]^+$: 355.2016, found: 355.2022.

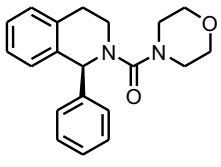
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N*-(3,4,5-trimethoxyphenethyl)morpholine-4-carboxamide (1v):**



1v

Compound **1v** was obtained following the general procedure **A** in 40% yield (189 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.83 – 6.79 (m, 2H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.49 (s, 2H), 5.95 (s, 2H), 3.75 (d, *J* = 1.4 Hz, 6H), 3.60 (d, *J* = 1.4 Hz, 3H), 3.47 (t, *J* = 4.6 Hz, 4H), 3.35 – 3.29 (m, 4H), 2.91 (t, *J* = 4.6 Hz, 4H), 2.68 (q, *J* = 7.0 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 163.9, 153.1, 147.6, 145.9, 136.3, 135.6, 133.6, 122.1, 109.6, 108.5, 106.5, 101.1, 66.3, 60.4, 56.2, 49.4, 49.4, 47.6, 34.5, 33.9. **HRMS** (ESI, *m/z*) calcd for $C_{25}H_{33}N_2O_7^+$ $[M+H]^+$: 473.2283, found: 473.2289.

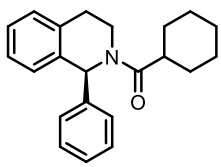
(*S*)-morpholino(1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone 1w:



1w

Compound **1w** was obtained following the general procedure **D** in 89% yield 335 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 3H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.07 (s, 1H), 3.57 (dddd, *J* = 29.8, 11.1, 6.4, 3.0 Hz, 5H), 3.27 – 3.14 (m, 3H), 3.08 (ddd, *J* = 13.2, 6.6, 3.1 Hz, 2H), 2.92 (ddd, *J* = 16.5, 10.4, 6.1 Hz, 1H), 2.80 (dt, *J* = 16.5, 4.0 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 163.39, 143.40, 136.14, 135.05, 129.25, 128.77, 128.62 (d, *J* = 3.6 Hz), 127.53, 127.19, 126.28, 66.38, 58.86, 47.58, 41.20, 28.49. **HRMS** (ESI, *m/z*) calcd for $C_{20}H_{22}N_2O_2$ $[M+H]^+$: 323.1754, found: 323.1769.

(*S*)-cyclohexyl(1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone(1x):

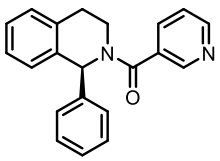


1x

Compound **1x** was obtained following the general procedure **D** in 77% yield (250mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.23 (tq, *J* = 17.4, 5.9, 4.2 Hz, 7H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.75 (s, 1H), 3.87 (dt, *J* = 13.4, 5.0 Hz, 1H), 3.39 (ddd, *J* = 14.2, 10.1, 4.6 Hz, 1H), 2.93 (ddd, *J* = 16.2, 10.1, 5.9 Hz, 1H), 2.81 (dt, *J* = 16.3, 4.4 Hz, 1H), 2.66 (t, *J* = 10.8 Hz, 1H), 1.66 – 1.63 (m, 5H), 1.49 – 1.43 (m, 1H), 1.35 – 1.22 (m, 3H), 1.18 (t, *J* = 12.4 Hz,

1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 174.46, 143.23, 135.82, 135.29, 129.12, 128.91, 128.63, 128.12, 127.44 (d, J = 3.3 Hz), 126.51, 54.80, 40.07, 29.80, 29.45, 29.13, 26.05, 25.61 (d, J = 14.7 Hz). **HRMS**(ESI, *m/z*) calcd for $C_{22}H_{26}NO^+$ $[M+H]^+$: 320.2009, found: 320.2006.

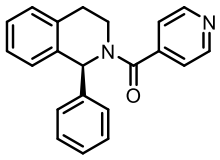
(*S*)-(1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)(pyridin-3-yl)methanone(1y):



1y

Compound **1y** was obtained following the general procedure **D** in 66% yield (232mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.67 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.48 (dd, J = 7.8, 4.8 Hz, 1H), 7.34 (d, J = 7.1 Hz, 3H), 7.27 (d, J = 5.0 Hz, 6H), 7.22 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 7.3 Hz, 2H), 6.86 (s, 1H), 3.53 (s, 1H), 3.40 (t, J = 12.7 Hz, 2H), 3.03 (ddd, J = 16.6, 10.6, 6.1 Hz, 1H), 2.80 (dt, J = 16.4, 4.2 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 167.74, 150.97, 147.56, 142.75, 134.79, 132.54, 129.36, 128.91, 127.89, 126.70, 124.10, 55.62, 41.77, 28.88. **HRMS**(ESI, *m/z*) calcd for $C_{21}H_{19}N_2O^+$ $[M+H]^+$: 315.1492, found: 315.1488.

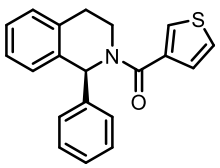
(*S*)-(1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)(pyridin-4-yl)methanone(1z):



1z

Compound **1z** was obtained following the general procedure **D** in 69% yield (247mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.68 (d, J = 5.1 Hz, 3H), 7.41 (d, J = 5.0 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.30 – 7.22 (m, 6H), 7.17 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 3.47 – 3.36 (m, 2H), 3.32 (d, J = 4.9 Hz, 0H), 3.00 (ddd, J = 17.1, 11.1, 6.1 Hz, 1H), 2.77 (dt, J = 16.5, 3.6 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 167.73, 150.65, 144.05, 142.65, 134.84 (d, J = 5.1 Hz), 129.39, 128.98 (d, J = 15.2 Hz), 128.65, 127.95, 127.55 (d, J = 25.4 Hz), 126.72, 121.25, 55.39, 41.49, 28.79. **HRMS**(ESI, *m/z*) calcd for $C_{21}H_{19}N_2O^+$ $[M+H]^+$: 315.1492, found: 315.1490.

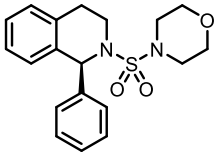
(*S*)-(1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)(thiophen-3-yl)methanone9(1aa):



1aa

Compound **1aa** was obtained following the general procedure **D** in 79% yield (278mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.63 (t, J = 3.9 Hz, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.29 – 7.18 (m, 7H), 7.16 (d, J = 7.5 Hz, 1H), 6.81 (s, 1H), 3.78 (s, 1H), 3.42 – 3.35 (m, 1H), 3.04 (s, 1H), 2.80 (d, J = 16.4 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 165.59, 142.79, 136.90, 135.25 (d, J = 42.0 Hz), 129.35, 128.83, 127.79, 127.57 (d, J = 13.6 Hz), 127.19, 126.85, 126.64, 55.76, 41.38, 28.97. **HRMS**(ESI, *m/z*) calcd for $C_{20}H_{18}NOS^+$ $[M+H]^+$: 320.1104, found: 320.1101.

(*S*)-4-((1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)morpholine(1ab):

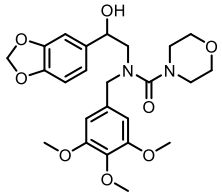


1ab

Compound **1ab** was obtained following the general procedure **D** in 59% yield (262mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.33 (t, J = 7.7 Hz, 2H), 7.27 (q, J = 7.3 Hz, 3H), 7.20 (d, J = 7.8 Hz, 3H), 7.09 (d, J = 7.8 Hz, 1H), 5.97 (s, 1H), 3.67 – 3.61 (m, 1H), 3.48 (tdd, J = 14.2, 8.2, 3.2 Hz, 4H), 3.30 (dd, J = 14.2, 3.9 Hz, 1H), 3.05 – 2.95 (m, 3H), 2.89 (dt, J = 12.4, 3.7 Hz, 2H), 2.81 (dd, J = 16.6, 3.9 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 142.29, 135.18, 134.39, 129.52, 128.77 (d, J = 4.9 Hz), 128.64, 128.02, 127.68, 126.63, 65.86, 59.61,

55.35, 46.38, 27.56. **HRMS**(ESI, *m/z*) calcd for $C_{19}H_{23}N_2O_3S^+$ $[M+H]^+$: 359.1424, found: 359.1422.

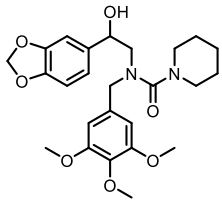
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (2a):**



2a

Compound **2a** was obtained following the general procedure **B** in 38% yield (450 mg) as white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 6.87 – 6.81 (m, 2H), 6.76 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.52 (s, 2H), 5.99 – 5.95 (m, 2H), 5.44 (d, *J* = 4.4 Hz, 1H), 4.73 (dt, *J* = 7.4, 4.9 Hz, 1H), 4.36 (d, *J* = 15.6 Hz, 1H), 4.27 (d, *J* = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.59 – 3.47 (m, 4H), 3.20 (dd, *J* = 13.9, 7.5 Hz, 1H), 3.17 – 3.09 (m, 3H), 3.09 – 3.01 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 164.3, 153.4, 147.5, 146.6, 138.4, 136.7, 134.5, 119.8, 108.2, 106.9, 104.8, 101.2, 70.7, 66.3, 60.4, 56.2, 55.3, 52.1, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_8^+$ $[M+H]^+$: 475.2075, found: 475.2072.

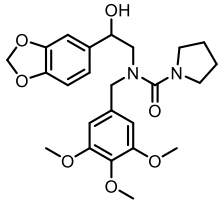
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)piperidine-1-carboxamide (2b):**



2b

Compound **2b** was obtained following the general procedure **B** in 36% yield (170 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.86 – 6.80 (m, 2H), 6.76 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.52 (s, 2H), 5.97 (dd, *J* = 4.7, 1.0 Hz, 2H), 5.44 (d, *J* = 4.4 Hz, 1H), 4.71 (dt, *J* = 7.4, 4.9 Hz, 1H), 4.32 (d, *J* = 15.6 Hz, 1H), 4.24 (d, *J* = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.17 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.13 – 3.00 (m, 5H), 1.54 – 1.47 (m, 2H), 1.46 – 1.40 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.6, 153.4, 147.5, 146.6, 138.5, 136.7, 134.8, 119.8, 108.2, 106.9, 104.8, 101.2, 70.9, 60.4, 56.2, 55.5, 52.3, 47.9, 25.7, 24.7. **HRMS** (ESI, *m/z*) calcd for $C_{25}H_{33}N_2O_7^+$ $[M+H]^+$: 473.2282, found: 473.2285.

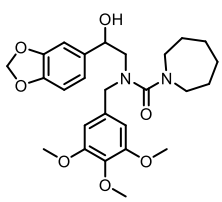
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)pyrrolidine-1-carboxamide (2c):**



2c

Compound **2c** was obtained following the general procedure **B** in 35% yield (160 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.83 (dd, *J* = 4.7, 3.1 Hz, 2H), 6.75 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.54 (s, 2H), 5.97 (d, *J* = 3.6 Hz, 2H), 5.51 (d, *J* = 4.3 Hz, 1H), 4.73 (dt, *J* = 8.4, 4.6 Hz, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 4.24 (d, *J* = 16.1 Hz, 1H), 3.74 (s, 6H), 3.64 (s, 3H), 3.28 – 3.20 (m, 5H), 3.12 (dd, *J* = 14.1, 4.8 Hz, 1H), 1.80 – 1.66 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 162.6, 153.3, 147.5, 146.6, 138.7, 136.7, 134.9, 119.7, 108.2, 106.8, 104.8, 101.2, 71.1, 60.4, 56.3, 55.5, 52.3, 48.4, 25.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_7^+$ $[M+H]^+$: 459.2126, found: 459.2127.

***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)azepane-1-carboxamide (2d):**

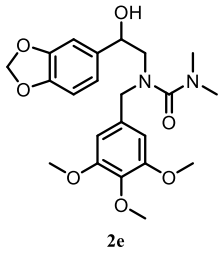


2d

Compound **2d** was obtained following the general procedure **B** in 36% yield (175 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.83 (dd, *J* = 4.8, 3.1 Hz, 2H), 6.75 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.54 (s, 2H), 5.96 (d, *J* = 4.1

Hz, 2H), 5.43 (d, *J* = 4.3 Hz, 1H), 4.68 (dt, *J* = 7.3, 5.0 Hz, 1H), 4.26 (d, *J* = 15.8 Hz, 1H), 4.18 (d, *J* = 15.7 Hz, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 3.23 (t, *J* = 5.8 Hz, 4H), 3.17 – 3.04 (m, 2H), 1.64 – 1.58 (m, 4H), 1.48 – 1.43 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.6, 153.3, 147.5, 146.6, 138.7, 136.6, 134.9, 119.8, 108.2, 106.9, 104.8, 101.2, 70.9, 60.4, 56.2, 56.1, 53.3, 48.5, 28.5, 27.4. **HRMS** (ESI, *m/z*) calcd for $C_{26}H_{35}N_2O_7^+$ $[M+H]^+$: 487.2439, found: 487.24412.

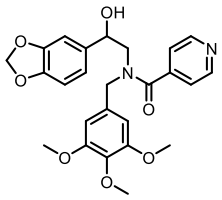
1-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-3,3-dimethyl-1-(3,4,5-trimethoxybenzyl)urea (2e):



2e

Compound **2e** was obtained following the general procedure **B** in 35% yield (151 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.83 (dd, *J* = 4.8, 3.1 Hz, 2H), 6.75 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.53 (s, 2H), 5.99 – 5.95 (m, 2H), 5.44 (d, *J* = 4.4 Hz, 1H), 4.70 (dt, *J* = 8.3, 4.7 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 4.20 (d, *J* = 15.7 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.18 (dd, *J* = 14.0, 7.8 Hz, 1H), 3.08 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.72 (s, 6H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.9, 153.4, 147.5, 146.6, 138.6, 136.8, 134.7, 119.7, 108.2, 106.8, 105.0, 101.2, 70.8, 60.4, 56.3, 55.7, 52.7, 38.7. **HRMS** (ESI, *m/z*) calcd for $C_{22}H_{29}N_2O_7^+$ $[M+H]^+$: 433.1969, found: 433.1970.

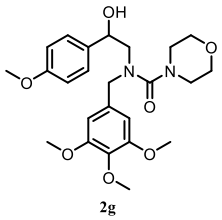
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)isonicotinamide (2f):**



2f

Compound **2f** was obtained following the general procedure **B** in 31% yield (145 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.7 – 8.6 (m, 2H), 7.3 – 7.3 (m, 2H), 7.0 – 6.8 (m, 2H), 6.7 (s, 1H), 6.6 – 6.5 (m, 1H), 6.3 (s, 1H), 6.0 – 6.0 (m, 2H), 5.7 – 5.6 (m, 1H), 5.0 – 4.8 (m, 1H), 4.8 – 4.6 (m, 1H), 4.5 – 4.2 (m, 1H), 3.8 (s, 4H), 3.7 (s, 2H), 3.7 (s, 2H), 3.6 (s, 1H), 3.6 – 3.4 (m, 1H), 3.3 – 3.1 (m, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 169.7, 169.4, 153.6, 153.5, 150.5, 150.2, 147.7, 146.9, 146.8, 144.5, 137.9, 137.3, 137.2, 137.1, 133.5, 132.7, 121.8, 121.2, 119.8, 119.5, 108.4, 106.9, 106.6, 105.3, 104.5, 101.3, 70.6, 70.1, 60.4, 56.3, 53.5, 52.7, 48.0. **HRMS** (ESI, *m/z*) calcd for $C_{25}H_{27}N_2O_7^+$ $[M+H]^+$: 467.1813, found: 467.1814.

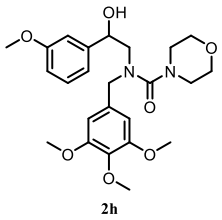
***N*-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxa mide (2g):**



2g

Compound **2g** was obtained following the general procedure **B** in 40% yield (184 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.22 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.52 (s, 2H), 5.40 (d, *J* = 4.3 Hz, 1H), 4.76 (dt, *J* = 7.8, 4.8 Hz, 1H), 4.38 (d, *J* = 15.6 Hz, 1H), 4.28 (d, *J* = 15.6 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 3H), 3.63 (s, 3H), 3.57 – 3.48 (m, 4H), 3.21 (dd, *J* = 14.0, 7.8 Hz, 1H), 3.17 – 3.02 (m, 5H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.4, 158.9, 153.4, 136.8, 136.3, 134.5, 127.7, 113.9, 104.9, 70.5, 66.3, 60.4, 56.3, 55.5, 55.3, 52.1, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_7^+$ $[M+H]^+$: 461.2282, found: 461.2282.

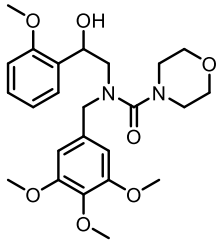
***N*-(2-hydroxy-2-(3-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxa mide (2h):**



2h

Compound **2h** was obtained following the general procedure **B** in 32% yield (147 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.23 (t, J = 7.8 Hz, 1H), 6.90 – 6.85 (m, 2H), 6.83 – 6.78 (m, 1H), 6.53 (s, 2H), 5.52 (d, J = 4.4 Hz, 1H), 4.80 (dt, J = 7.6, 4.7 Hz, 1H), 4.40 (d, J = 15.6 Hz, 1H), 4.30 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.73 (s, 3H), 3.63 (s, 3H), 3.57 – 3.48 (m, 4H), 3.25 – 3.15 (m, 2H), 3.15 – 3.02 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.4, 159.6, 153.4, 146.1, 136.8, 134.5, 129.5, 118.8, 113.0, 112.0, 104.8, 70.9, 66.3, 60.4, 56.2, 55.4, 55.3, 52.1, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_7^+$ $[M+H]^+$: 461.2282, found: 461.2280.

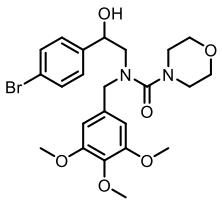
***N*-(2-hydroxy-2-(2-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxa mide (2i):**



2i

Compound **2i** was obtained following the general procedure **B** in 41% yield (187 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.42 (dd, J = 7.5, 1.8 Hz, 1H), 7.21 (td, J = 7.8, 1.8 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.52 (s, 2H), 5.37 (d, J = 4.4 Hz, 1H), 5.14 (dt, J = 7.9, 3.8 Hz, 1H), 4.45 (d, J = 15.6 Hz, 1H), 4.35 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.69 (s, 3H), 3.63 (s, 3H), 3.57 – 3.49 (m, 4H), 3.24 (dd, J = 14.1, 8.0 Hz, 1H), 3.20 – 3.14 (m, 1H), 3.14 – 3.04 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.5, 156.1, 153.3, 136.7, 134.8, 132.0, 128.5, 127.1, 120.7, 110.9, 104.7, 66.3, 65.3, 60.4, 56.2, 55.7, 54.0, 51.6, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_7^+$ $[M+H]^+$: 461.2282, found: 461.2296.

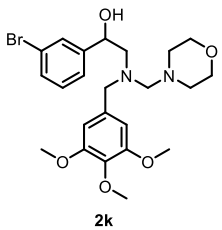
***N*-(2-(4-bromophenyl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxami de (2j):**



2j

Compound **2j** was obtained following the general procedure **B** in 34% yield (173 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.53 – 7.51 (m, 2H), 7.30 – 7.27 (m, 2H), 6.53 (s, 2H), 5.62 (d, J = 4.4 Hz, 1H), 4.82 (dt, J = 7.1, 5.0 Hz, 1H), 4.38 (d, J = 15.7 Hz, 1H), 4.31 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.64 (s, 3H), 3.59 – 3.45 (m, 4H), 3.25 – 3.15 (m, 2H), 3.15 – 3.08 (m, 2H), 3.07 – 3.01 (m, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.3, 153.4, 143.7, 136.8, 134.4, 131.3, 128.8, 120.5, 104.9, 70.4, 66.3, 60.4, 56.3, 55.0, 52.3, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{23}H_{30}BrN_2O_6^+$ $[M+H]^+$: 509.1282, found: 509.1288.

***N*-(2-(3-bromophenyl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxami de (2k):**



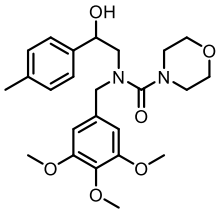
2k

Compound **2k** was obtained following the general procedure **B** in 28% yield (142 mg) as white solid.

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (t, J = 1.8 Hz, 1H), 7.44 (dt, J = 7.6, 1.7 Hz, 1H), 7.31 (d, J = 2.3 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.53 (s, 2H), 5.65 (d, J = 4.5 Hz, 1H), 4.83 (q, J = 5.7 Hz, 1H), 4.38 (d, J = 15.4 Hz, 1H), 4.31 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.56 – 3.47 (m, 4H),

3.26 – 3.18 (m, 2H), 3.14 – 3.07 (m, 2H), 3.06 – 3.00 (m, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.3, 153.4 (d, J = 2.3 Hz), 147.2, 136.8, 134.4, 130.7, 130.3, 129.4, 125.7, 121.9, 104.8, 70.4, 66.3, 60.4, 56.2, 54.9, 52.2, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{23}H_{30}B_rN_2O_6^+$ $[M+H]^+$: 509.1282, found: 509.1281.

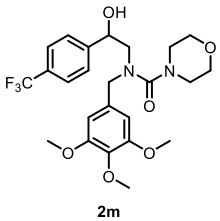
***N*-(2-hydroxy-2-(p-tolyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (2l):**



2l

Compound **2l** was obtained following the general procedure **B** in 54% yield (239 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.19 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 6.53 (s, 2H), 5.44 (d, J = 4.3 Hz, 1H), 4.78 (dt, J = 8.2, 4.6 Hz, 1H), 4.40 (d, J = 15.6 Hz, 1H), 4.29 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.57 – 3.48 (m, 4H), 3.24 – 3.15 (m, 2H), 3.14 – 3.10 (m, 2H), 3.09 – 3.02 (m, 2H), 2.27 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.4, 153.4, 141.3, 136.7, 136.6, 134.5, 129.0, 126.5, 104.8, 70.7, 66.3, 60.4, 56.2, 55.4, 52.1, 47.6, 21.2. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{33}N_2O_6^+$ $[M+H]^+$: 445.2333, found: 445.2334.

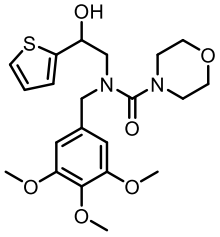
***N*-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (2m):**



2m

Compound **2m** was obtained following the general procedure **B** in 60% yield (503 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.69 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 6.53 (s, 2H), 5.73 (d, J = 4.5 Hz, 1H), 4.94 (q, J = 5.8 Hz, 1H), 4.38 (q, J = 15.7 Hz, 2H), 3.74 (s, 6H), 3.64 (s, 3H), 3.54 – 3.46 (m, 4H), 3.24 (d, J = 6.3 Hz, 2H), 3.09 (ddd, J = 13.3, 6.1, 3.6 Hz, 2H), 3.02 (ddd, J = 13.1, 6.1, 3.4 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.3, 153.4, 149.1, 136.9, 134.4, 128.2 (q, J = 31.3 Hz), 127.4, 125.3 (d, J = 4.0 Hz), 124.8 (d, J = 271.9 Hz), 104.9, 70.5, 66.3, 60.4, 56.3, 55.0, 52.3, 47.5. **^{19}F NMR** (565 MHz, DMSO-d_6) δ -60.82. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{30}F_3N_2O_6^+$ $[M+H]^+$: 499.2050, found: 499.2059.

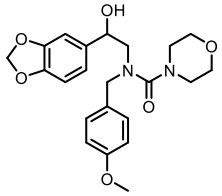
***N*-(2-hydroxy-2-(thiophen-2-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (2n):**



2n

Compound **2n** was obtained following the general procedure **B** in 27% yield (117 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.41 (dd, J = 5.0, 1.2 Hz, 1H), 6.96 (dd, J = 4.9, 3.5 Hz, 1H), 6.94 (d, J = 3.5 Hz, 1H), 6.53 (s, 2H), 5.90 (d, J = 4.7 Hz, 1H), 5.12 – 5.06 (m, 1H), 4.39 (d, J = 15.6 Hz, 1H), 4.31 (d, J = 15.7 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.58 – 3.49 (m, 4H), 3.31 – 3.22 (m, 2H), 3.18 – 3.12 (m, 2H), 3.11 – 3.05 (m, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.3, 153.4, 148.6, 136.8, 134.3, 127.0, 124.9, 123.9, 104.8, 67.2, 66.3, 60.4, 56.2, 55.3, 52.4, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{29}N_2O_6S^+$ $[M+H]^+$: 437.1741, found: 437.1741.

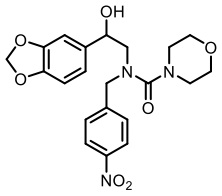
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(4-methoxybenzyl)morpholine-4-carboxamide (2o):**



2o

Compound **2o** was obtained following the general procedure **B** in 45% yield (186 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.12 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.85 – 6.80 (m, 2H), 6.73 (dd, J = 8.0, 1.7 Hz, 1H), 5.97 (d, J = 2.2 Hz, 2H), 5.40 (d, J = 4.5 Hz, 1H), 4.68 (dt, J = 7.3, 5.1 Hz, 1H), 4.35 (d, J = 15.1 Hz, 1H), 4.24 (d, J = 15.2 Hz, 1H), 3.73 (s, 3H), 3.56 – 3.47 (m, 4H), 3.16 (dd, J = 13.9, 7.4 Hz, 1H), 3.13 – 3.07 (m, 2H), 3.06 – 2.99 (m, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.3, 158.8, 147.5, 146.6, 138.4, 130.4, 129.3, 119.8, 114.3, 108.2, 106.9, 101.2, 70.6, 66.3, 55.5, 54.4, 51.6, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{22}H_{27}N_2O_6^+$ $[M+H]^+$: 415.1864, found: 415.1864.

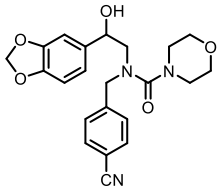
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(4-nitrobenzyl)morpholine-4-carboxamide (2p):**



2p

Compound **2p** was obtained following the general procedure **B** in 43% yield (405 mg) as orange solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.22 – 8.16 (m, 2H), 7.52 – 7.48 (m, 2H), 6.90 – 6.81 (m, 2H), 6.78 (dd, J = 8.0, 1.6 Hz, 1H), 5.98 (dd, J = 3.9, 1.1 Hz, 2H), 5.50 (d, J = 4.4 Hz, 1H), 4.75 (dt, J = 7.7, 4.8 Hz, 1H), 4.60 – 4.50 (m, 2H), 3.58 – 3.48 (m, 4H), 3.24 (dd, J = 14.1, 7.7 Hz, 1H), 3.20 – 3.09 (m, 3H), 3.06 (ddd, J = 13.1, 5.7, 3.7 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 162.8, 147.5, 147.4, 147.0, 146.7, 138.2, 128.9, 124.0, 119.8, 108.2, 106.9, 101.2, 70.8, 66.3, 56.1, 51.6, 47.5. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{24}N_3O_7^+$ $[M+H]^+$: 430.1609, found: 430.1606.

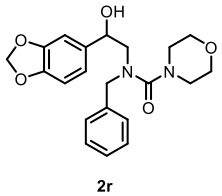
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(4-cyanobenzyl)morpholine-4-carboxamide (2q):**



2q

Compound **2q** was obtained following the general procedure **B** in 56% yield (406 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.81 – 7.77 (m, 2H), 7.44 – 7.40 (m, 2H), 6.87 – 6.82 (m, 2H), 6.76 (dd, J = 7.9, 1.6 Hz, 1H), 5.99 – 5.96 (m, 2H), 5.46 (d, J = 4.3 Hz, 1H), 4.73 (dt, J = 7.9, 4.4 Hz, 1H), 4.54 – 4.44 (m, 2H), 3.58 – 3.47 (m, 4H), 3.22 (dd, J = 14.1, 7.7 Hz, 1H), 3.17 – 3.09 (m, 3H), 3.05 (ddd, J = 13.1, 5.8, 3.7 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 147.5, 146.7, 145.2, 138.2, 132.8, 128.7, 119.8, 119.3, 110.2, 108.2, 106.9, 101.2, 70.8, 66.3, 56.0, 51.8, 47.5. **HRMS** (ESI, *m/z*) calcd for $C_{22}H_{24}N_3O_5^+$ $[M+H]^+$: 410.1710, found: 410.1706.

***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-benzylmorpholine-4-carboxamide (2r):**

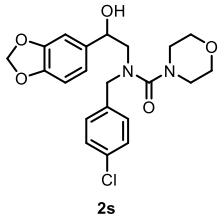


2r

Compound **2r** was obtained following the general procedure **B** in 48% yield (184 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.33 (t, J = 7.6 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.22 – 7.18 (m, 2H), 6.86 – 6.81 (m, 2H), 6.73 (dd, J = 7.9, 1.7 Hz, 1H), 5.97 (q, J = 1.0 Hz, 2H), 5.44 (d, J = 4.5 Hz, 1H), 4.70 (dt, J = 7.5, 5.0 Hz, 1H), 4.43 (d, J = 15.5 Hz, 1H), 4.33 (d, J = 15.5 Hz, 1H), 3.56 – 3.47 (m, 4H), 3.18 (dd, J = 14.0, 7.5 Hz, 1H), 3.13 – 3.00 (m, 5H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.3, 147.5, 146.6, 138.7, 138.4, 128.9, 127.9, 127.5, 119.8, 108.2, 106.9,

101.2, 70.6, 66.3, 54.9, 52.1, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{25}N_2O_5^+$ $[M+H]^+$: 385.1758, found: 385.1759.

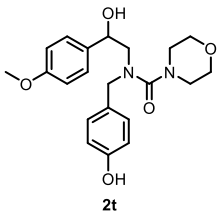
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(4-chlorobenzyl)morpholine-4-carboxamide (2s):**



2s

Compound **2s** was obtained following the general procedure **B** in 42% yield (156 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.38 (d, J = 8.4 Hz, 0H), 7.24 (d, J = 8.3 Hz, 0H), 6.85 – 6.81 (m, 0H), 6.75 (dd, J = 8.0, 1.7 Hz, 0H), 5.97 (d, J = 2.4 Hz, 0H), 5.41 (d, J = 4.5 Hz, 0H), 4.70 (dt, J = 7.5, 5.0 Hz, 0H), 4.41 (d, J = 15.5 Hz, 0H), 4.34 (d, J = 15.6 Hz, 0H), 3.56 – 3.47 (m, 0H), 3.19 (dd, J = 14.0, 7.5 Hz, 0H), 3.14 – 3.06 (m, 0H), 3.07 – 3.00 (m, 0H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.2, 147.5, 146.7, 138.3, 137.9, 132.0, 129.8, 128.8, 119.8, 108.2, 106.9, 101.2, 70.7, 66.3, 55.2, 51.4, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{24}ClN_2O_5^+$ $[M+H]^+$: 419.1368, found: 419.1369.

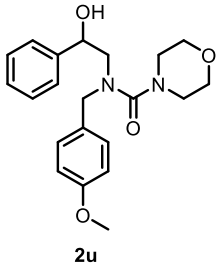
***N*-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-*N*-(4-hydroxybenzyl)morpholine-4-carboxamide (2t):**



2t

Compound **2t** was obtained following the general procedure **B** in 38% yield (140 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.34 (s, 1H), 7.20 – 7.16 (m, 2H), 7.02 – 6.94 (m, 2H), 6.89 – 6.85 (m, 2H), 6.74 – 6.70 (m, 2H), 5.36 (d, J = 4.4 Hz, 1H), 4.69 (dt, J = 7.6, 5.0 Hz, 1H), 4.31 (d, J = 15.0 Hz, 1H), 4.16 (d, J = 15.0 Hz, 1H), 3.72 (s, 3H), 3.59 – 3.47 (m, 4H), 3.20 – 3.12 (m, 1H), 3.12 – 2.96 (m, 5H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.40, 158.87, 156.92, 136.32, 129.31, 128.47, 127.67, 115.68, 113.85, 70.33, 66.37, 66.31, 55.51, 55.35, 54.19, 51.66, 47.67, 47.30. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{27}N_2O_5^+$ $[M+H]^+$: 387.1915, found: 387.1919.

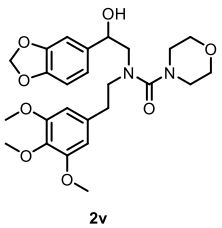
***N*-(2-hydroxy-2-phenylethyl)-*N*-(4-methoxybenzyl)morpholine-4-carboxamide (2u):**



2u

Compound **2u** was obtained following the general procedure **B** in 45% yield (185 mg) as colorless oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.34 – 7.26 (m, 4H), 7.26 – 7.21 (m, 1H), 7.15 – 7.11 (m, 2H), 6.91 – 6.87 (m, 2H), 5.48 (d, J = 4.4 Hz, 1H), 4.78 (dt, J = 7.7, 4.9 Hz, 1H), 4.38 (d, J = 15.1 Hz, 1H), 4.25 (d, J = 15.1 Hz, 1H), 3.73 (s, 3H), 3.55 – 3.46 (m, 4H), 3.20 (dd, J = 14.0, 7.7 Hz, 1H), 3.15 – 3.06 (m, 3H), 3.02 (ddd, J = 13.1, 6.0, 3.6 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.38, 158.86, 144.33, 130.32, 129.28, 128.43, 127.52, 126.53, 114.34, 70.88, 66.31, 55.35, 54.42, 51.64, 47.64. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{27}N_2O_4^+$ $[M+H]^+$: 371.1966, found:371.1976.

***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxyphenethyl)morpholine-4-carboxamide (2v):**

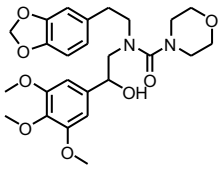


2v

Compound **2v** was obtained following the general procedure **B** in 35% yield (171 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.90 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.78 (dd, J = 8.0, 1.6 Hz, 1H), 6.47 (s, 2H), 5.97 (dd, J = 4.7, 1.1 Hz, 2H), 5.39 (d, J = 4.4 Hz, 1H), 4.67 – 4.61 (m,

1H), 3.75 (s, 6H), 3.60 (s, 3H), 3.49 – 3.41 (m, 4H), 3.40 – 3.35 (m, 1H), 3.34 – 3.27 (m, 2H), 3.24 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.95 – 2.82 (m, 4H), 2.72 – 2.61 (m, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.1, 153.1, 147.5, 146.6, 138.5, 136.2, 135.6, 119.9, 108.1, 107.0, 106.4, 101.2, 70.9, 66.3, 60.4, 56.2, 55.1, 50.2, 47.6, 34.4. **HRMS** (ESI, *m/z*) calcd for $C_{25}H_{33}N_2O_8^+$ $[M+H]^+$: 489.2231, found: 489.2232.

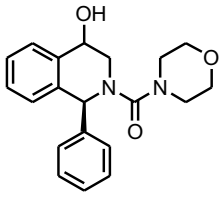
***N*-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-*N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)morpholine-4-carboxamide (2v'):**



2v'

Compound **2v'** was obtained following the general procedure **B** in 37% yield (189 mg) as colorless oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.82 – 6.76 (m, 2H), 6.66 – 6.61 (m, 3H), 5.95 (d, *J* = 1.3 Hz, 2H), 5.42 (d, *J* = 4.7 Hz, 1H), 4.65 (q, *J* = 5.7 Hz, 1H), 3.77 (d, *J* = 1.3 Hz, 6H), 3.62 (d, *J* = 1.3 Hz, 3H), 3.58 – 3.53 (m, 2H), 3.45 (q, *J* = 5.5 Hz, 4H), 3.34 (d, *J* = 11.1 Hz, 2H), 3.14 (t, *J* = 4.5 Hz, 2H), 2.96 – 2.82 (m, 4H), 2.66 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.12, 153.05, 147.58, 145.90, 140.13, 136.91, 133.59, 122.10, 109.58, 108.48, 103.83, 101.09, 71.35, 66.37, 66.28, 60.39, 56.28, 55.36, 55.26, 50.26, 47.67, 47.30, 33.85. **HRMS** (ESI, *m/z*) calcd for $C_{25}H_{33}N_2O_8^+$ $[M+H]^+$: 489.2232, found: 489.2240.

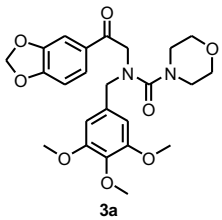
((1*S*)-4-hydroxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)(morpholino)methanone (2w):



2w

Compound **2w** was obtained following the general procedure **B** in 68% yield (23 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.24 (td, *J* = 6.9, 6.3, 1.4 Hz, 1H), 7.20 – 7.16 (m, 3H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.02 (s, 1H), 5.71 (d, *J* = 6.2 Hz, 1H), 4.69 (dt, *J* = 9.8, 6.0 Hz, 1H), 3.66 (dd, *J* = 13.0, 5.8 Hz, 1H), 3.57 (dddd, *J* = 35.1, 11.6, 6.6, 3.1 Hz, 4H), 3.20 (ddd, *J* = 13.3, 6.6, 3.0 Hz, 2H), 3.09 – 3.01 (m, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 163.17, 143.27, 139.60, 135.58, 128.97, 128.57, 128.16, 127.65, 127.33, 127.24, 127.17, 66.37, 64.95, 59.08, 48.01, 47.50. **HRMS** (ESI, *m/z*) calcd for $C_{20}H_{23}N_2O_3^+$ $[M+H]^+$:339.1703, found: 339.1710.

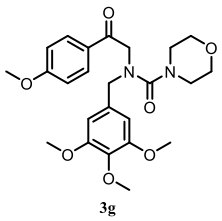
***N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (3a):**



3a

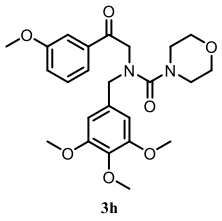
Compound **3a** was obtained following the general procedure **B** in 40% yield (623 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.60 (h, *J* = 8.2, 1.8 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.62 (s, 2H), 6.13 (s, 2H), 4.54 (s, 2H), 4.43 (s, 2H), 3.75 (s, 6H), 3.64 (s, 3H), 3.57 (q, *J* = 7.9, 6.2 Hz, 5H), 3.18 – 3.12 (m, 5H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 193.92, 163.93, 153.50, 152.10, 148.29, 136.94, 133.84, 130.26, 124.57, 108.55, 107.68, 104.73, 102.50, 66.25, 60.38, 56.24, 54.21, 53.27, 47.67, 47.30. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{29}N_2O_8^+$ $[M+H]^+$: 473.1919, found: 473.1925.

***N*-(2-(4-methoxyphenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (3g):**


3g

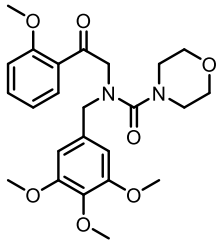
Compound **3g** was obtained following the general procedure **B** in 42% yield (192 mg) as lightyellow solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.96 – 7.92 (m, 2H), 7.05 – 7.01 (m, 2H), 6.61 (s, 2H), 4.55 (s, 2H), 4.42 (s, 2H), 3.84 (s, 3H), 3.73 (s, 6H), 3.63 (s, 3H), 3.56 (t, *J* = 4.7 Hz, 5H), 3.15 (t, *J* = 4.7 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 194.2, 164.0, 163.8, 153.5, 136.8, 133.9, 130.6, 128.6, 114.4, 104.6, 66.2, 60.4, 56.2, 56.0, 54.0, 53.3, 47.7. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_7^+$ $[M+H]^+$: 459.2126, found: 459.2137.

***N*-(2-(3-methoxyphenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (3h):**


3h

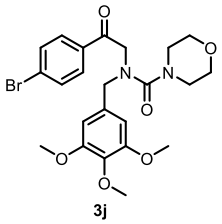
Compound **3h** was obtained following the general procedure **B** in 35% yield (161 mg) as light yellow solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.55 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.25 – 7.20 (m, 1H), 6.62 (s, 2H), 4.59 (s, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.74 (s, 6H), 3.63 (s, 3H), 3.56 (t, *J* = 4.7 Hz, 4H), 3.17 – 3.11 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 195.8, 163.9, 159.9, 153.5, 137.1, 136.8, 133.8, 130.4, 120.7, 119.9, 112.8, 104.6, 66.2, 60.4, 56.2, 55.8, 54.6, 53.3, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_7^+$ $[M+H]^+$: 459.2126, found: 459.2133.

***N*-(2-(2-methoxyphenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (3i):**


3i

Compound **3i** was obtained following the general procedure **B** in 72% yield (1243 mg) as yellow oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.61 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.60 (s, 2H), 4.39 (d, *J* = 2.7 Hz, 4H), 3.84 (d, *J* = 1.0 Hz, 3H), 3.73 (d, *J* = 1.1 Hz, 6H), 3.64 (d, *J* = 1.0 Hz, 3H), 3.55 (t, *J* = 4.6 Hz, 4H), 3.15 – 3.10 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 197.7, 163.9, 158.9, 153.5, 136.9, 134.6, 133.8, 130.2, 126.5, 121.1, 112.8, 104.9, 66.2, 60.4, 58.4, 56.3, 53.3, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_7^+$ $[M+H]^+$: 459.2126, found: 459.2132.

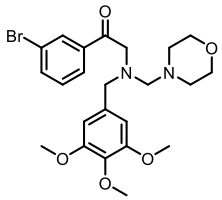
***N*-(2-(4-bromophenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (3j):**


3j

Compound **3j** was obtained following the general procedure **B** in 78% yield (1420 mg) as yellow solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 6.61 (s, 2H), 4.57 (s, 2H), 4.43 (s, 2H), 3.74 (d, *J* = 1.1 Hz, 6H), 3.63 (d, *J* = 1.0 Hz, 3H), 3.56 (t, *J* = 4.7 Hz, 4H), 3.15 (t, *J* = 4.6 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 195.4, 163.8, 153.5, 136.9, 134.8, 133.8, 132.3, 130.3, 128.0, 104.6, 66.2, 60.4, 56.3, 54.4, 53.4, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{23}H_{28}BrN_2O_6^+$ $[M+H]^+$: 507.1125, found: 507.1130.

***N*-(2-(3-bromophenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide**

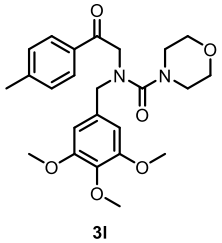
(3k):



3k

Compound **3k** was obtained following the general procedure **B** in 60% yield (398 mg) as yellow solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.08 (t, J = 1.8 Hz, 1H), 7.94 (dd, J = 7.8, 1.4 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.49 (t, J = 7.9 Hz, 1H), 6.61 (s, 2H), 4.58 (s, 2H), 4.43 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.55 (t, J = 4.7 Hz, 4H), 3.14 (t, J = 4.6 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 195.3, 163.8, 153.5, 137.8, 136.9, 136.5, 133.8, 131.5, 130.8, 127.3, 122.6, 104.7, 66.2, 60.4, 56.3, 54.6, 53.4, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{23}H_{28}BrN_2O_6^+$ $[M+H]^+$: 507.1125, found: 507.1131.

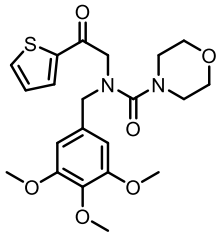
***N*-(2-oxo-2-(p-tolyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(3l):**



3l

Compound **3n** was obtained following the general procedure **B** in 33% yield (142 mg) as light yellow oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.10 – 7.02 (m, 4H), 6.53 (s, 2H), 4.30 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.53 (t, J = 4.6 Hz, 4H), 3.22 (dd, J = 8.5, 6.4 Hz, 2H), 3.08 (t, J = 4.6 Hz, 4H), 2.25 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 164.14, 153.41, 136.91, 136.60, 135.50, 134.43, 129.31, 129.06, 104.99, 66.33, 60.45, 56.29, 51.23, 49.55, 47.62, 33.32, 21.07. **HRMS** (ESI, *m/z*) calcd for $C_{24}H_{31}N_2O_6^+$ $[M+H]^+$: 443.2177, found: 443.2175.

***N*-(2-oxo-2-(thiophen-2-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (3n):**

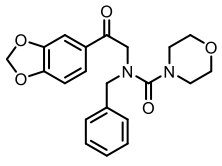


3n

Compound **3n** was obtained following the general procedure **B** in 30% yield (130 mg) as light yellow oil. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.03 (dd, J = 5.0, 1.1 Hz, 1H), 7.99 (dd, J = 3.8, 1.1 Hz, 1H), 7.24 (dd, J = 4.9, 3.8 Hz, 1H), 6.62 (s, 2H), 4.53 (s, 2H), 4.44 (s, 2H), 3.74 (s, 6H), 3.63 (s, 3H), 3.59 – 3.53 (m, 4H), 3.16 (t, J = 4.7 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 189.2, 163.8, 153.5, 142.0, 136.9, 135.4, 133.7, 133.6, 129.2, 104.7, 66.2, 60.4, 56.2, 54.3, 53.4, 47.6.

HRMS (ESI, *m/z*) calcd for $C_{21}H_{27}N_2O_6S^+$ $[M+H]^+$: 435.1584, found: 435.1597.

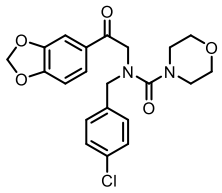
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoethyl)-*N*-benzylmorpholine-4-carboxamide (3r):**



3r

Compound **3r** was obtained following the general procedure **B** in 63% yield (674 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.57 (dd, J = 8.2, 1.7 Hz, 1H), 7.43 (d, J = 1.7 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.31 – 7.23 (m, 3H), 7.01 (d, J = 8.2 Hz, 1H), 6.13 (s, 2H), 4.51 (s, 2H), 4.47 (s, 2H), 3.54 (t, J = 4.6 Hz, 4H), 3.12 (t, J = 4.7 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 193.8, 164.0, 152.1, 148.3, 138.3, 130.1, 129.0, 127.6, 127.6, 124.6, 108.6, 107.7, 102.5, 66.2, 54.2, 53.1, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{23}N_2O_5^+$ $[M+H]^+$: 383.1601, found: 383.1610.

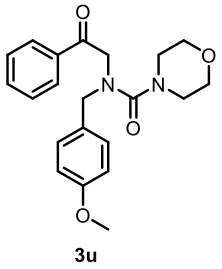
***N*-(2-(benzo[*d*][1,3]dioxol-5-yl)-2-oxoethyl)-*N*-(4-chlorobenzyl)morpholine-4-carboxamide (3s):**



3s

Compound **3s** was obtained following the general procedure **B** in 46% yield (191 mg) as light yellow solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.59 (dd, J = 8.2, 1.7 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.2 Hz, 1H), 6.14 (s, 2H), 4.54 (s, 2H), 4.44 (s, 2H), 3.54 (t, J = 4.7 Hz, 4H), 3.11 (t, J = 4.7 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 193.8, 163.9, 152.2, 148.3, 137.6, 132.1, 130.1, 129.6, 128.9, 124.6, 108.6, 107.7, 102.5, 66.2, 54.5, 52.4, 47.6. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{22}ClN_2O_5^+$ $[M+H]^+$: 417.1212, found: 417.1224.

N-(4-methoxybenzyl)-N-(2-oxo-2-phenylethyl)morpholine-4-carboxamide(3u):

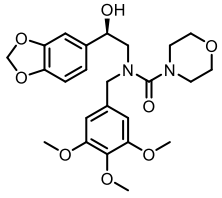


3u

Compound **3s** was obtained following the general procedure **B** in 53% yield (215 mg) as white solid. **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.91 – 7.81 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 7.19 – 7.15 (m, 2H), 6.89 – 6.84 (m, 2H), 4.52 (d, J = 2.1 Hz, 4H), 3.78 (s, 3H), 3.70 (t, J = 4.7 Hz, 4H), 3.35 (t, J = 4.7 Hz, 4H). **^{13}C NMR** (151 MHz, Chloroform-*d*) δ 195.45, 164.37, 159.18, 135.44, 133.47 (d, J = 2.9 Hz), 128.70 (d, J = 6.5 Hz), 127.79, 114.29, 77.33, 77.12, 76.90, 66.60, 55.28, 52.83, 52.43, 47.62. **HRMS** (ESI, *m/z*) calcd for $C_{21}H_{25}N_2O_4^+$ $[M+H]^+$: 369.1809, found: 369.1811.

Isolated enzymatic products from the scale-up reactions:

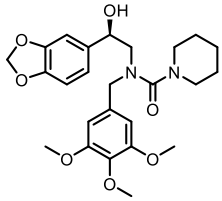
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide (WT-2a)：



2a

Compound **2a** was isolated from the reaction of wt in 42% yield (16 mg) as a white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 6.87 – 6.84 (m, 1H), 6.83 (s, 1H), 6.76 (dd, J = 7.9, 1.6 Hz, 1H), 6.52 (s, 2H), 5.99 – 5.95 (m, 2H), 5.44 (d, J = 4.4 Hz, 1H), 4.73 (dt, J = 7.4, 4.9 Hz, 1H), 4.36 (d, J = 15.6 Hz, 1H), 4.27 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.59 – 3.47 (m, 4H), 3.20 (dd, J = 14.0, 7.5 Hz, 1H), 3.17 – 3.12 (m, 1H), 3.15 – 3.09 (m, 2H), 3.09 – 3.01 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 164.32, 153.38, 147.50, 146.64, 138.38, 136.75, 134.51, 119.83, 108.21, 106.95, 104.83, 101.21, 70.69, 66.31, 60.43, 56.23, 55.29, 52.08, 47.59, 21.23, 14.55.

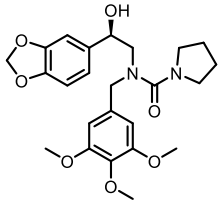
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)piperidine-1-carboxamide(2b):



2b

Compound **2b** was isolated from the reaction of P69D in 35% yield (12 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.84 (dd, J = 4.7, 3.1 Hz, 2H), 6.75 (dd, J = 8.0, 1.6 Hz, 1H), 6.52 (s, 2H), 5.97 (d, J = 4.5 Hz, 2H), 5.43 (d, J = 4.0 Hz, 1H), 4.72 – 4.69 (m, 1H), 4.32 (d, J = 15.6 Hz, 1H), 4.24 (d, J = 15.6 Hz, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 3.17 (dd, J = 13.9, 7.5 Hz, 1H), 3.13 – 3.06 (m, 2H), 3.06 – 3.00 (m, 2H), 1.47 (dq, J = 39.2, 5.7 Hz, 6H).

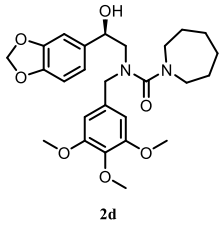
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)pyrrolidine-1-carboxamide(2c):



2c

Compound **2c** was isolated from the reaction of wt in 30% yield (10 mg) as a white solid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 6.83 (dd, J = 4.8, 3.1 Hz, 2H), 6.74 (dd, J = 8.0, 1.6 Hz, 1H), 6.54 (s, 2H), 5.99 – 5.94 (m, 2H), 5.52 (s, 1H), 4.73 (dd, J = 7.8, 4.8 Hz, 1H), 4.40 (d, J = 16.1 Hz, 1H), 4.23 (d, J = 16.1 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.28 – 3.18 (m, 5H), 3.11 (dd, J = 14.1, 4.8 Hz, 1H), 1.77 – 1.67 (m, 4H).

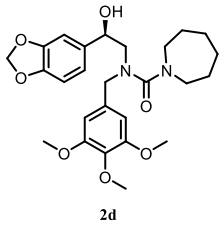
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)azepane-1-carboxamide（2d):



2d

Compound **2d** was isolated from the reaction of wt in 23% yield (8 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.83 (dd, J = 4.7, 3.1 Hz, 2H), 6.75 (dd, J = 8.0, 1.6 Hz, 1H), 6.54 (s, 2H), 5.96 (d, J = 4.1 Hz, 2H), 5.42 (d, J = 4.4 Hz, 1H), 4.71 – 4.65 (m, 1H), 4.26 (d, J = 15.7 Hz, 1H), 4.18 (d, J = 15.7 Hz, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 3.23 (t, J = 5.8 Hz, 4H), 3.14 (dd, J = 13.9, 7.3 Hz, 1H), 3.08 (dd, J = 13.9, 5.4 Hz, 1H), 1.61 (d, J = 6.2 Hz, 4H), 1.46 (dd, J = 6.3, 3.1 Hz, 4H).

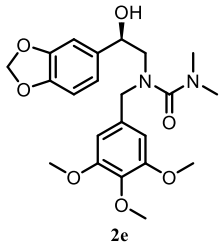
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)azepane-1-carboxamide（2d):



2d

Compound **2d** was isolated from the reaction of P69D in 28% yield (10 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.85 – 6.80 (m, 2H), 6.75 (dd, J = 8.0, 1.6 Hz, 1H), 6.54 (s, 2H), 5.96 (dd, J = 4.2, 0.9 Hz, 2H), 5.41 (d, J = 4.4 Hz, 1H), 4.68 (q, J = 4.9, 3.0 Hz, 1H), 4.26 (d, J = 15.7 Hz, 1H), 4.18 (d, J = 15.7 Hz, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 3.24 (t, J = 5.8 Hz, 4H), 3.18 – 3.06 (m, 2H), 1.63 – 1.60 (m, 4H), 1.46 (p, J = 2.9 Hz, 4H).

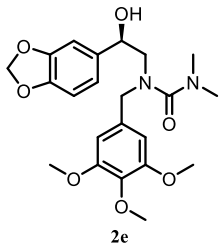
(*R*)-1-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-3,3-dimethyl-1-(3,4,5-trimethoxybenzyl)urea(2e):



2e

Compound **2e** was isolated from the reaction of wt in 8% yield (3 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.85 – 6.81 (m, 2H), 6.74 (dd, J = 7.9, 1.6 Hz, 1H), 6.53 (s, 2H), 5.97 (d, J = 3.2 Hz, 2H), 5.45 (d, J = 4.5 Hz, 1H), 4.69 (dt, J = 8.4, 4.5 Hz, 1H), 4.34 (d, J = 15.7 Hz, 1H), 4.19 (d, J = 15.7 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.17 (dd, J = 14.0, 7.8 Hz, 1H), 3.07 (dd, J = 14.0, 4.9 Hz, 1H), 2.71 (s, 6H).

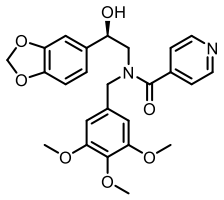
(*R*)-1-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-3,3-dimethyl-1-(3,4,5-trimethoxybenzyl)urea(2e):



2e

Compound **2e** was isolated from the reaction of P69D in 15% yield (5 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.83 (d, J = 7.8 Hz, 2H), 6.74 (d, J = 7.7 Hz, 1H), 6.53 (s, 2H), 5.97 (d, J = 3.3 Hz, 2H), 5.45 (d, J = 4.4 Hz, 1H), 4.70 (dd, J = 8.4, 4.4 Hz, 1H), 4.33 (d, J = 15.7 Hz, 1H), 4.19 (d, J = 15.7 Hz, 1H), 3.73 (s, 6H), 3.63 (s, 3H), 3.16 (dd, J = 14.0, 7.9 Hz, 1H), 3.08 (td, J = 14.7, 13.9, 5.0 Hz, 1H), 2.71 (s, 6H).

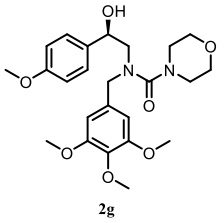
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)isonicotinamide(2f):



2f

Compound **2f** was isolated from the reaction of wt in 12% yield (5 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.63 (d, J = 5.3 Hz, 2H), 7.30 (dd, J = 11.2, 5.1 Hz, 2H), 6.92 – 6.84 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.66 (s, 1H), 6.56 (d, J = 8.8 Hz, 1H), 6.34 (s, 1H), 5.98 (dd, J = 20.5, 5.1 Hz, 2H), 5.66 (s, 1H), 4.93 (d, J = 2.9 Hz, 0H), 4.84 (d, J = 15.0 Hz, 1H), 4.71 (dd, J = 8.2, 4.7 Hz, 1H), 4.59 (d, J = 14.9 Hz, 1H), 4.43 (d, J = 16.4 Hz, 0H), 4.18 (d, J = 16.4 Hz, 0H), 3.80 (s, 4H), 3.73 (s, 3H), 3.65 (s, 2H), 3.62 (s, 1H), 3.26 – 3.21 (m, 1H), 3.12 (dd, J = 14.6, 4.7 Hz, 1H).

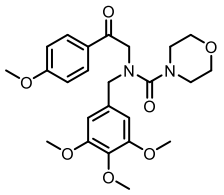
(*R*)-*N*-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(2g):



2g

Compound **2g** was isolated from the reaction of P69D in 13% yield (5 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.21 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.52 (s, 2H), 5.39 (d, J = 4.3 Hz, 1H), 4.82 – 4.70 (m, 1H), 4.37 (d, J = 15.6 Hz, 1H), 4.27 (d, J = 15.6 Hz, 1H), 3.73 (d, J = 8.0 Hz, 9H), 3.63 (s, 3H), 3.52 (dt, J = 8.6, 4.3 Hz, 4H), 3.21 (dd, J = 14.0, 7.7 Hz, 1H), 3.16 – 3.10 (m, 3H), 3.04 (dt, J = 13.4, 4.4 Hz, 2H).

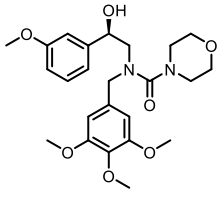
***N*-(2-(4-methoxyphenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(3g):**



3g

Compound **3g** was isolated from the reaction of P69D in 2% yield (1 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.93 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.60 (s, 2H), 4.54 (s, 2H), 4.41 (s, 2H), 3.83 (s, 3H), 3.74 – 3.70 (m, 8H), 3.64 – 3.61 (m, 4H), 3.56 (t, J = 4.5 Hz, 5H), 3.14 (t, J = 4.7 Hz, 4H).

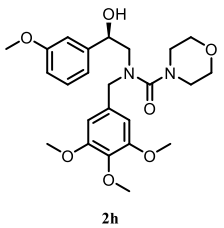
(*R*)-*N*-(2-hydroxy-2-(3-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(2h):



2h

Compound **2h** was isolated from the reaction of wt in 22% yield (8 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.23 (t, J = 7.8 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.80 (dd, J = 8.2, 2.6 Hz, 1H), 6.53 (s, 2H), 5.51 (s, 1H), 4.79 (dd, J = 7.6, 5.0 Hz, 1H), 4.40 (d, J = 15.6 Hz, 1H), 4.29 (d, J = 15.6 Hz, 1H), 3.73 (d, J = 5.9 Hz, 9H), 3.63 (s, 3H), 3.53 – 3.51 (m, 4H), 3.26 – 3.10 (m, 4H), 3.08 – 3.03 (m, 2H).

(*R*)-*N*-(2-hydroxy-2-(3-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(2h):

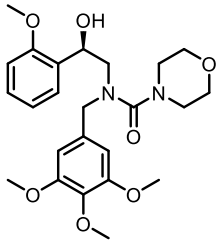


2h

Compound **2h** was isolated from the reaction of P69D in 18% yield (7 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.23 (t, J = 7.8 Hz, 1H), 6.87 (t, J = 5.6 Hz, 2H), 6.80 (dd, J = 8.2, 2.6 Hz, 1H), 6.52 (s, 2H), 5.50 (d, J = 4.4 Hz, 1H), 4.79 (dt, J = 8.2, 4.8 Hz, 1H), 4.39 (d, J = 15.6 Hz, 1H),

4.29 (d, *J* = 15.6 Hz, 1H), 3.73 (d, *J* = 5.3 Hz, 9H), 3.63 (s, 3H), 3.55 – 3.48 (m, 4H), 3.19 (dd, *J* = 15.7, 6.3 Hz, 2H), 3.16 – 3.08 (m, 2H), 3.08 – 3.02 (m, 2H).

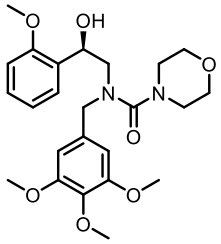
(*R*)-*N*-(2-hydroxy-2-(2-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carbo xamide(2i):



2i

Compound **2i** was isolated from the reaction of wt in 21% yield (8 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.42 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.52 (s, 2H), 5.36 (d, *J* = 4.5 Hz, 1H), 5.14 (dt, *J* = 8.2, 4.3 Hz, 1H), 4.44 (d, *J* = 15.5 Hz, 1H), 4.35 (d, *J* = 15.6 Hz, 1H), 3.74 (s, 6H), 3.69 (s, 3H), 3.63 (s, 3H), 3.53 (t, *J* = 4.9 Hz, 4H), 3.24 (dd, *J* = 14.1, 8.0 Hz, 1H), 3.17 (d, *J* = 4.0 Hz, 1H), 3.11 (dtt, *J* = 18.0, 12.9, 4.2 Hz, 4H).

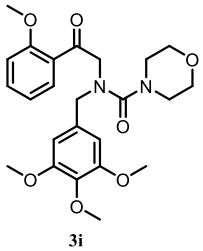
(*R*)-*N*-(2-hydroxy-2-(2-methoxyphenyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carbo xamide(2i):



2i

Compound **2i** was isolated from the reaction of P69D in 16% yield (6 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.42 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.24 – 7.18 (m, 1H), 6.97 – 6.89 (m, 2H), 6.51 (s, 2H), 5.37 – 5.31 (m, 1H), 5.14 (dt, *J* = 8.8, 4.4 Hz, 1H), 4.44 (d, *J* = 15.5 Hz, 1H), 4.34 (d, *J* = 15.6 Hz, 1H), 3.74 (d, *J* = 1.7 Hz, 6H), 3.69 (d, *J* = 1.6 Hz, 3H), 3.63 (d, *J* = 1.6 Hz, 3H), 3.52 (d, *J* = 5.0 Hz, 4H), 3.30 (s, 2H), 3.24 (dd, *J* = 14.2, 8.0 Hz, 1H), 3.17 (d, *J* = 4.2 Hz, 1H), 3.15 – 3.05 (m, 2H).

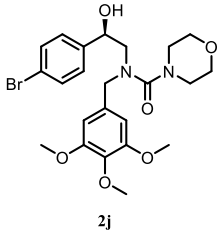
***N*-(2-(2-methoxyphenyl)-2-oxoethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(3i):**



3i

Compound **3i** was isolated from the reaction of wt in 10% yield (5 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.85 – 6.81 (m, 2H), 6.74 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.54 (s, 2H), 5.97 (d, *J* = 3.8 Hz, 2H), 5.52 (d, *J* = 4.3 Hz, 1H), 4.73 (dt, *J* = 8.4, 4.6 Hz, 1H), 4.40 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 16.1 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.25 – 3.19 (m, 6H), 3.11 (dd, *J* = 14.1, 4.8 Hz, 1H).

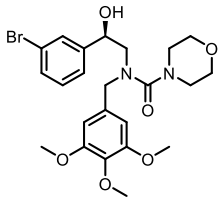
(*R*)-*N*-(2-(4-bromophenyl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carbox amide(2j):



2j

Compound **2j** was isolated from the reaction of wt in 15% yield (6 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.53 – 7.49 (m, 2H), 7.29 – 7.25 (m, 2H), 6.52 (s, 2H), 5.60 (dd, *J* = 4.5, 1.3 Hz, 1H), 4.81 (q, *J* = 5.7 Hz, 1H), 4.37 (d, *J* = 15.6 Hz, 1H), 4.30 (d, *J* = 15.6 Hz, 1H), 3.74 (d, *J* = 1.3 Hz, 6H), 3.63 (d, *J* = 1.3 Hz, 3H), 3.51 (q, *J* = 4.8 Hz, 4H), 3.24 – 3.14 (m, 2H), 3.11 (dt, *J* = 13.5, 4.5 Hz, 2H), 3.03 (dt, *J* = 13.3, 4.5 Hz, 2H).

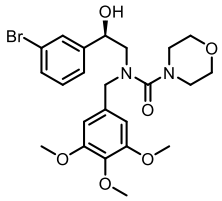
(*R*)-*N*-(2-(3-bromophenyl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carbox amide(2k):



2k

Compound **2k** was isolated from the reaction of wt in 25% yield (9 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.50 (t, J = 1.8 Hz, 1H), 7.44 (dt, J = 7.7, 1.7 Hz, 1H), 7.30 (dt, J = 15.2, 7.6 Hz, 2H), 6.53 (s, 2H), 5.66 (d, J = 4.5 Hz, 1H), 4.82 (q, J = 5.7 Hz, 1H), 4.37 (d, J = 15.6 Hz, 1H), 4.31 (d, J = 15.5 Hz, 1H), 3.75 (s, 6H), 3.64 (s, 3H), 3.56 – 3.48 (m, 4H), 3.27 – 3.18 (m, 2H), 3.10 (ddd, J = 13.2, 5.9, 3.7 Hz, 2H), 3.04 (ddd, J = 9.4, 6.0, 2.8 Hz, 2H).

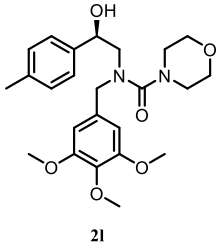
(*R*)-*N*-(2-(3-bromophenyl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carbox amide(2k):



2k

Compound **2k** was isolated from the reaction of P69D in 18% yield (6 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.50 (s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.33 – 7.26 (m, 2H), 6.52 (s, 2H), 5.69 – 5.55 (m, 1H), 4.81 (d, J = 6.5 Hz, 1H), 4.37 (d, J = 15.6 Hz, 1H), 4.30 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.52 (q, J = 4.6 Hz, 4H), 3.26 – 3.17 (m, 2H), 3.10 (dt, J = 13.6, 4.3 Hz, 2H), 3.05 – 3.00 (m, 2H).

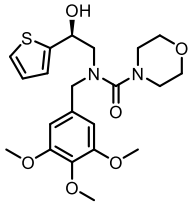
(*R*)-*N*-(2-hydroxy-2-(p-tolyl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(2l) :



2l

Compound **2l** was isolated from the reaction of wt in 30% yield (13 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.19 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.7 Hz, 2H), 6.52 (s, 2H), 5.44 (d, J = 4.3 Hz, 1H), 4.78 (dt, J = 8.4, 4.8 Hz, 1H), 4.39 (d, J = 15.5 Hz, 1H), 4.28 (d, J = 15.6 Hz, 1H), 3.74 (s, 6H), 3.63 (s, 3H), 3.52 (dt, J = 8.6, 4.2 Hz, 4H), 3.13 (dq, J = 9.4, 3.7 Hz, 2H), 3.05 (ddd, J = 13.1, 6.0, 3.6 Hz, 2H).

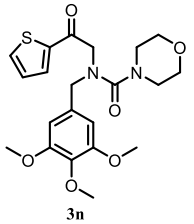
(*S*)-*N*-(2-hydroxy-2-(thiophen-2-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxa mide(2n):



2n

Compound **2n** was isolated from the reaction of wt in 32% yield (14 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.40 (dd, J = 5.0, 1.2 Hz, 1H), 6.99 – 6.92 (m, 2H), 6.53 (s, 2H), 5.92 (d, J = 4.7 Hz, 1H), 5.11 – 5.05 (m, 1H), 4.39 (d, J = 15.6 Hz, 1H), 4.30 (d, J = 15.6 Hz, 1H), 3.74 (s, 7H), 3.64 (s, 3H), 3.54 (dt, J = 6.1, 3.0 Hz, 4H), 3.32 – 3.22 (m, 2H), 3.18 – 3.13 (m, 2H), 3.12 – 3.05 (m, 2H).

***N*-(2-oxo-2-(thiophen-2-yl)ethyl)-*N*-(3,4,5-trimethoxybenzyl)morpholine-4-carboxamide(3n):**

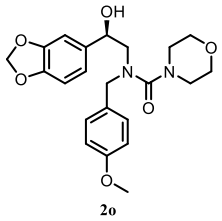


3n

Compound **3n** was isolated from the reaction of wt in 13% yield (5 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.03 (d, J = 4.9 Hz, 1H), 7.98 (d, J = 3.8 Hz, 1H), 7.28 – 7.21 (m, 1H), 6.61 (s, 2H), 4.52 (s, 2H), 4.43 (s, 2H), 3.73 (s, 7H), 3.63 (s, 3H), 3.56 (t, J = 4.6 Hz, 4H), 3.15 (t, J = 4.6 Hz, 4H).

(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(4-methoxybenzyl)morpholine-4-carb

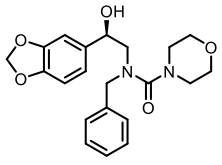
oxamide(2o):



2o

Compound **2o** was isolated from the reaction of P69D in 33% yield (13 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.12 (d, J = 8.3 Hz, 2H), 6.91 – 6.86 (m, 2H), 6.85 – 6.80 (m, 2H), 6.72 (dd, J = 8.0, 1.7 Hz, 1H), 5.97 (d, J = 2.0 Hz, 2H), 5.40 (d, J = 4.5 Hz, 1H), 4.67 (q, J = 5.7 Hz, 1H), 4.34 (d, J = 15.1 Hz, 1H), 4.23 (d, J = 15.1 Hz, 1H), 3.73 (s, 3H), 3.55 – 3.47 (m, 4H), 3.18 – 3.06 (m, 3H), 3.02 (ddd, J = 11.4, 7.7, 4.0 Hz, 3H).

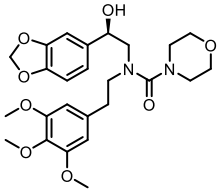
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-benzylmorpholine-4-carboxamide(2r)
:



2r

Compound **2r** was isolated from the reaction of P69D in 11% yield (4 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.42 – 7.14 (m, 6H), 6.85 – 6.80 (m, 2H), 6.73 (dd, J = 8.0, 1.7 Hz, 1H), 5.97 (d, J = 1.9 Hz, 2H), 5.42 (d, J = 4.5 Hz, 1H), 4.69 (d, J = 8.4 Hz, 1H), 4.42 (d, J = 15.5 Hz, 1H), 4.32 (d, J = 15.5 Hz, 1H), 3.55 – 3.49 (m, 4H), 3.18 (dd, J = 14.0, 7.4 Hz, 1H), 3.13 – 3.00 (m, 5H).

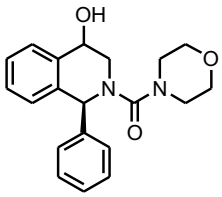
(*R*)-*N*-(2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyethyl)-*N*-(3,4,5-trimethoxyphenethyl)morpholi ne-4-carboxamide(2v):



2v

Compound **2v** was isolated from the reaction of P69D in 15% yield (6 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 6.90 (d, J = 1.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.77 (dd, J = 7.9, 1.6 Hz, 1H), 6.47 (s, 2H), 5.97 (d, J = 4.4 Hz, 2H), 5.38 (d, J = 4.4 Hz, 1H), 4.65 – 4.62 (m, 1H), 3.74 (s, 6H), 3.60 (s, 3H), 3.44 (dt, J = 6.1, 3.1 Hz, 4H), 3.43 – 3.35 (m, 1H), 3.30 (dd, J = 14.1, 7.2 Hz, 2H), 3.23 (dd, J = 13.9, 5.6 Hz, 1H), 2.94 – 2.82 (m, 5H), 2.66 (tt, J = 9.9, 4.9 Hz, 2H).

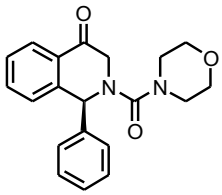
((1*S*)-4-hydroxy-1-phenyl-3,4-dihydroisoquinolin-2(1H)-yl)(morpholino)methanone (2w):



2w

Compound **2w** was isolated from the reaction of WT in 10% yield (18 mg) as a white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.51 (d, J = 7.8 Hz, 1H), 7.25 – 7.07 (m, 7H), 6.88 (d, J = 7.7 Hz, 1H), 5.95 (s, 1H), 5.66 (d, J = 6.2 Hz, 1H), 4.62 (dt, J = 9.7, 6.0 Hz, 1H), 3.59 (dd, J = 13.0, 5.8 Hz, 1H), 3.54 – 3.41 (m, 4H), 3.12 (ddd, J = 13.2, 6.6, 3.1 Hz, 2H), 3.04 – 2.87 (m, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 163.17, 143.27, 139.60, 135.58, 128.97, 128.57, 128.16, 127.65, 127.34, 127.24, 127.16, 66.37, 64.94, 59.07, 48.01, 47.50.

(*S*)-2-(morpholine-4-carbonyl)-1-phenyl-2,3-dihydroisoquinolin-4(1H)-one 3w:

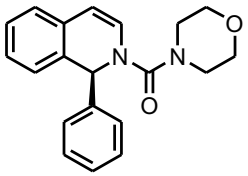


3w

Compound **3w** was isolated from the reaction of wt in 50% yield (90 mg) as a transparent liquid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.95 (dd, J = 7.8, 1.4 Hz, 1H), 7.73 (td, J = 7.5, 1.4 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.35 (dd, J = 8.2, 6.5 Hz, 2H), 7.32 – 7.28 (m, 1H), 7.05 (dd, J = 7.3, 1.9 Hz, 2H), 6.26 (s, 1H), 4.08 (dd, J = 18.5, 1.3 Hz, 1H), 3.67 (d, J = 18.5 Hz, 1H), 3.62 (dt, J = 5.9, 3.9 Hz, 4H), 3.31 – 3.17 (m, 4H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 193.53, 163.11, 142.40, 138.98, 134.87, 130.56, 129.19, 128.91, 128.85, 128.28, 128.20, 126.87,

66.27, 59.33, 52.27, 47.23. **HRMS** (ESI, *m/z*) calcd for $C_{20}H_{20}N_2O_3$ $[M+H]^+$: 337.1547, found: 337.1566.

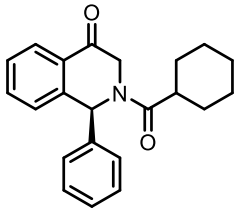
(*S*)-morpholino(1-phenylisoquinolin-2(1H)-yl)methanone 4w:



4w

Compound **3w** was isolated from the reaction of wt in 10% yield (18 mg) as a transparent liquid. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.39 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.28 – 7.08 (m, 8H), 6.76 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.13 (s, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 3.65 (ddd, *J* = 11.4, 6.4, 3.0 Hz, 2H), 3.57 (ddd, *J* = 11.4, 6.5, 3.0 Hz, 2H), 3.30 (ddd, *J* = 9.5, 6.5, 3.2 Hz, 1H), 3.16 (ddd, *J* = 13.2, 6.5, 3.0 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 159.10, 142.33, 133.06, 131.11, 129.05, 128.37, 128.15, 127.51, 127.40, 127.23, 126.92, 124.93, 107.68, 66.23, 58.75, 47.67. **HRMS**(ESI, *m/z*) calcd for $C_{20}H_{21}N_2O_2^+$ $[M+H]^+$: 321.1598, found: 321.1599.

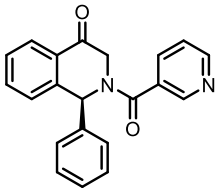
(*S*)-2-(cyclohexanecarbonyl)-1-phenyl-2,3-dihydroisoquinolin-4(1H)-one(3x):



3x

Compound **3x** was isolated from the reaction of wt in 20% yield (30 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 6.7 Hz, 3H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.13 (s, 1H), 6.96 (d, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 32.0 Hz, 1H), 4.66 (d, *J* = 18.7 Hz, 1H), 3.85 (d, *J* = 18.7 Hz, 1H), 2.72 (s, 1H), 1.72 – 1.60 (m, 5H), 1.33 (dt, *J* = 24.4, 12.4 Hz, 4H), 1.21 – 1.12 (m, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 192.59, 174.82, 142.42, 139.30, 135.05, 130.68, 130.11, 129.36 – 129.10 (m), 128.92, 128.56, 128.17 (d, *J* = 13.1 Hz), 127.60 (d, *J* = 19.0 Hz), 127.08, 126.90, 53.83, 50.78, 29.66 – 29.36 (m), 29.36 – 29.06 (m), 29.01, 25.97, 25.39 (d, *J* = 13.3 Hz). **HRMS**(ESI, *m/z*) calcd for $C_{22}H_{24}NO_2^+$ $[M+H]^+$: 334.1802, found: 334.1800.

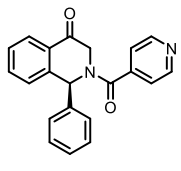
(*S*)-2-nicotinoyl-1-phenyl-2,3-dihydroisoquinolin-4(1H)-one(3y):



3y

Compound **3y** was isolated from the reaction of wt in 35% yield (43 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.81 – 8.57 (m, 2H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.53 (dd, *J* = 16.1, 8.9 Hz, 1H), 7.33 (dtd, *J* = 53.1, 19.9, 18.5, 10.6 Hz, 4H), 7.16 (s, 1H), 6.99 (d, *J* = 19.5 Hz, 1H), 6.29 (s, 0H), 5.06 (s, 0H), 4.30 – 3.96 (m, 1H), 3.60 – 3.15 (m, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 191.52, 168.14, 165.58, 151.49, 136.48, 135.17, 130.60, 129.38, 128.82 – 127.98 (m), 127.20 (d, *J* = 11.4 Hz), 124.02, 121.63, 56.15, 29.48. **HRMS**(ESI, *m/z*) calcd for $C_{21}H_{17}N_2O_2^+$ $[M+H]^+$: 329.1285, found: 329.1282.

(*S*)-2-isonicotinoyl-1-phenyl-2,3-dihydroisoquinolin-4(1H)-one(3z):

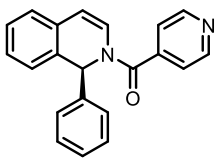


3z

Compound **3z** was isolated from the reaction of wt in 10% yield (15 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.71 – 8.68 (m, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.79 – 7.76 (m, 2H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.43 (s, 2H), 7.35 (s, 1H), 7.24 (q, *J* = 7.1, 6.6 Hz, 1H), 7.16 – 7.13 (m, 2H), 6.96 (s, 1H), 4.03 (d, *J* = 9.1 Hz, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ

150.69, 135.22, 130.55, 129.41, 128.51 (d, *J* = 30.3 Hz), 127.16 (d, *J* = 22.9 Hz), 121.79, 55.35, 29.47. **HRMS**(ESI, *m/z*) calcd for $C_{21}H_{17}N_2O_2^+$ $[M+H]^+$: 329.1285, found: 329.1283.

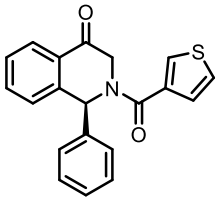
(*S*)-(1-phenylisoquinolin-2(1H)-yl)(pyridin-4-yl)methanone(4z):



4z

Compound **4z** was isolated from the reaction of wt in 10% yield (15 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.73 (d, *J* = 5.0 Hz, 2H), 7.49 – 7.46 (m, 3H), 7.30 (dq, *J* = 13.7, 7.1, 6.5 Hz, 6H), 7.22 (d, *J* = 7.1 Hz, 2H), 6.82 (s, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 6.04 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 167.09, 150.74, 142.12, 141.83, 132.52, 130.04 (d, *J* = 22.8 Hz), 128.91, 128.19 – 127.73 (m), 126.84 (d, *J* = 15.6 Hz), 125.61, 122.55, 110.79, 56.71. **HRMS**(ESI, *m/z*) calcd for $C_{21}H_{17}N_2O^+$ $[M+H]^+$: 313.1336, found: 313.1333.

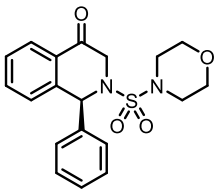
(*S*)-1-phenyl-2-(thiophene-3-carbonyl)-2,3-dihydroisoquinolin-4(1H)-one(3aa):



3aa

Compound **3aa** was isolated from the reaction of wt in 13% yield (23 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 3.0 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.35 (dt, *J* = 27.2, 7.4 Hz, 3H), 7.26 (d, *J* = 5.0 Hz, 1H), 7.08 (s, 4H), 4.48 (s, 1H), 4.19 – 3.80 (m, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 192.17, 165.80, 141.94, 138.78, 135.55, 135.16, 130.62, 129.35, 129.03 (d, *J* = 26.2 Hz), 128.62 – 128.08 (m), 127.71, 127.22, 29.51 (d, *J* = 12.6 Hz). **HRMS**(ESI, *m/z*) calcd for $C_{20}H_{16}NO_2S^+$ $[M+H]^+$: 334.0896, found: 334.0892.

(*S*)-2-(morpholinosulfonyl)-1-phenyl-2,3-dihydroisoquinolin-4(1H)-one(3ab):

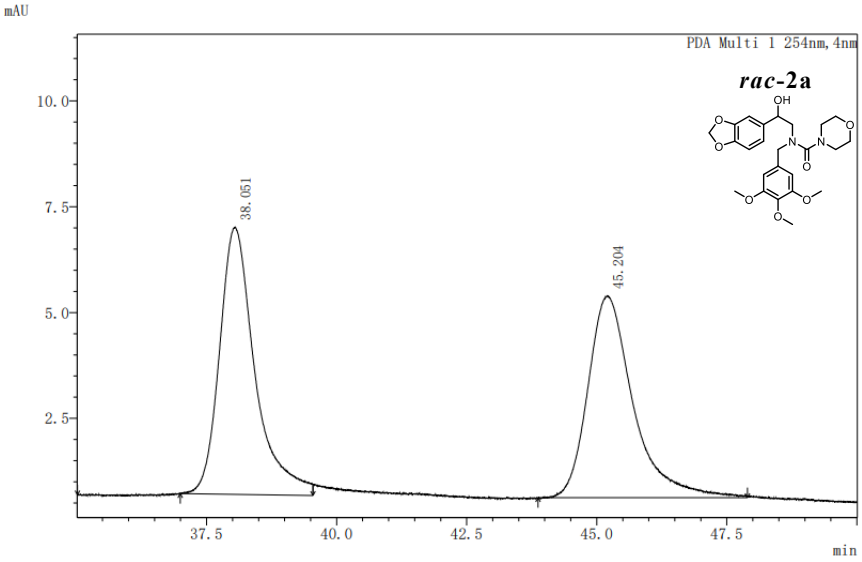


3ab

Compound **3ab** was isolated from the reaction of wt in 27% yield (43 mg) as white solid. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.06 – 8.02 (m, 1H), 7.76 (td, *J* = 7.5, 1.4 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.15 – 7.11 (m, 2H), 6.33 (s, 1H), 4.14 (d, *J* = 18.7 Hz, 1H), 3.82 (d, *J* = 18.9 Hz, 1H), 3.42 (t, *J* = 4.7 Hz, 4H), 3.04 – 2.88 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 192.15, 141.66, 138.26, 135.34, 130.26 (d, *J* = 8.2 Hz), 129.23, 128.72 (d, *J* = 3.2 Hz), 126.94, 65.80, 59.44, 50.59, 46.64. **HRMS**(ESI, *m/z*) calcd for $C_{19}H_{21}N_2O_4S^+$ $[M+H]^+$: 373.1217, found: 373.1216.

Chiral HPLC chromatograms

Chiral analysis of racemic product std. *rac*-2a:

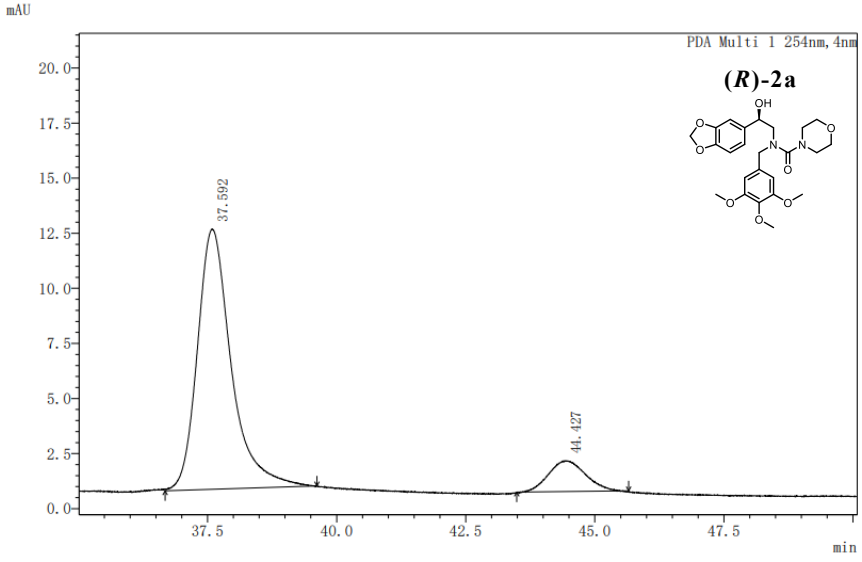


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	38.051	298317	6307	50.873	36.992	0.000
2	45.204	288077	4765	49.127	43.872	0.000
总计		586393	11072	100.000		

Chiral analysis of the chemically synthesized (*R*)-2a:

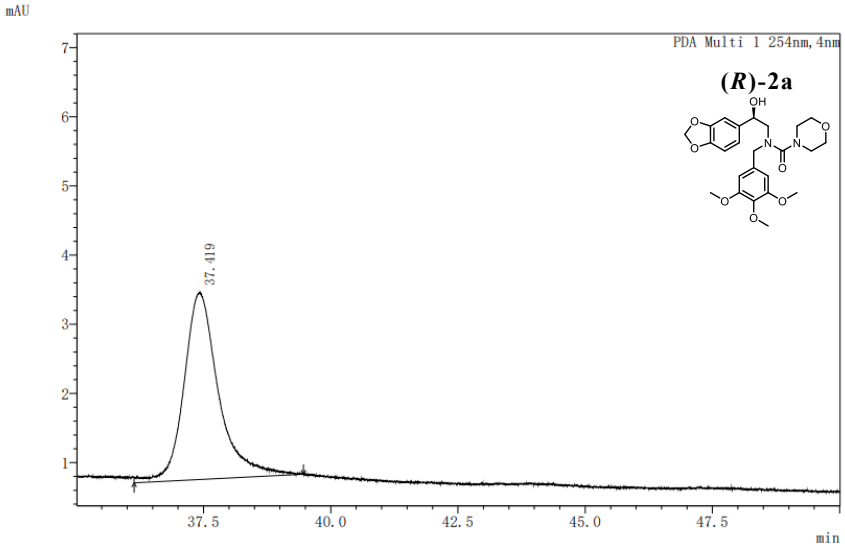


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	37.592	538728	11810	88.674	36.680	0.000
2	44.427	68811	1385	11.326	43.488	0.000
总计		607539	13195	100.000		

Chiral analysis of enzymatic (*R*)-2a from the reaction of FtmOx1:

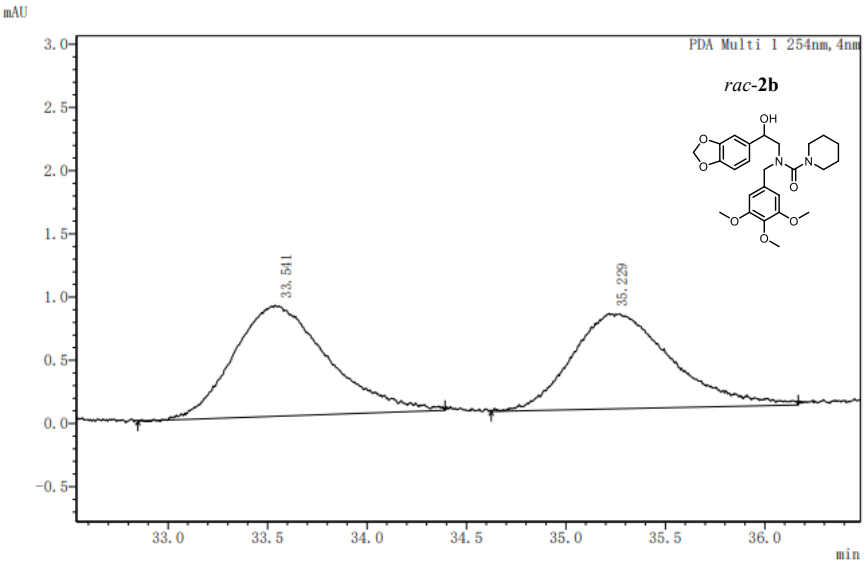


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	37.419	128230	2702	100.000	36.136	0.000
总计		128230	2702	100.000		

Chiral analysis of compound *rac*-2b

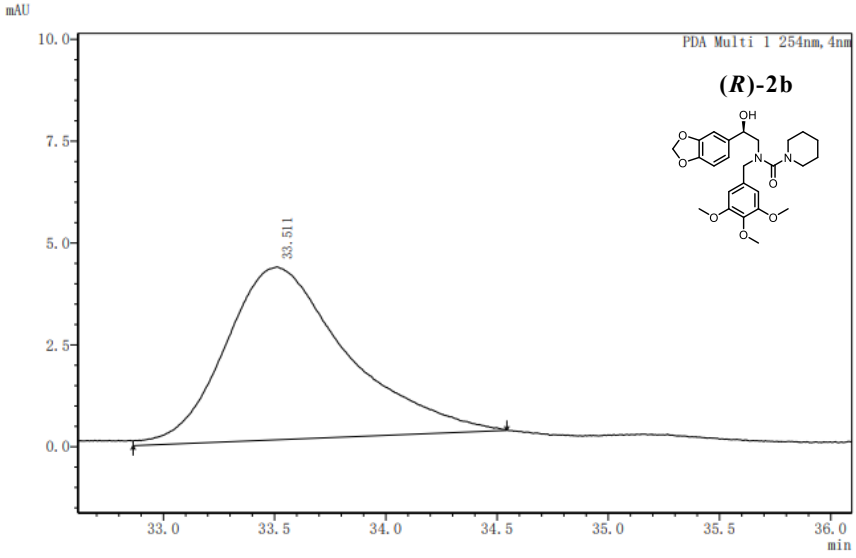


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	33.541	29053	874	52.434	32.848	0.000
2	35.229	26356	752	47.566	34.624	0.000
总计		55408	1626	100.000		

Chiral analysis of enzymatic (*R*)-2b

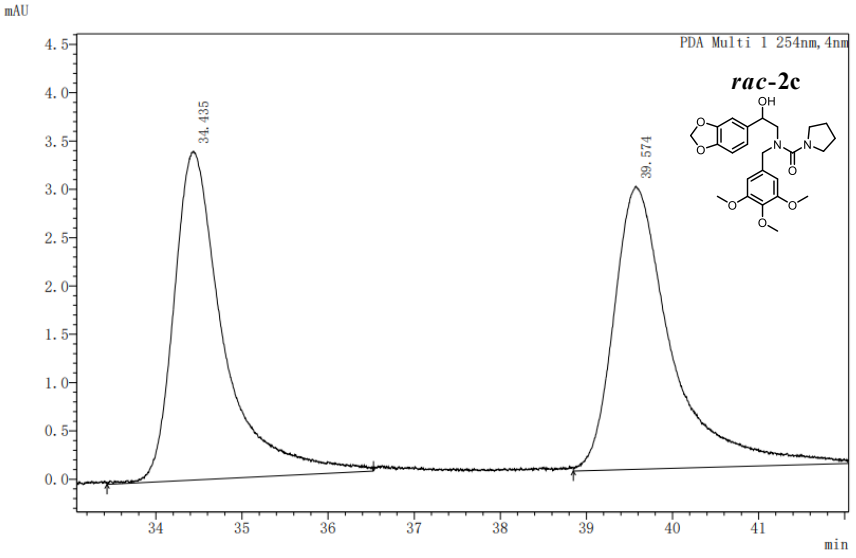


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	33.511	162024	4241	100.000	32.864	0.000
总计		162024	4241	100.000		

Chiral analysis of compound *rac*-2c

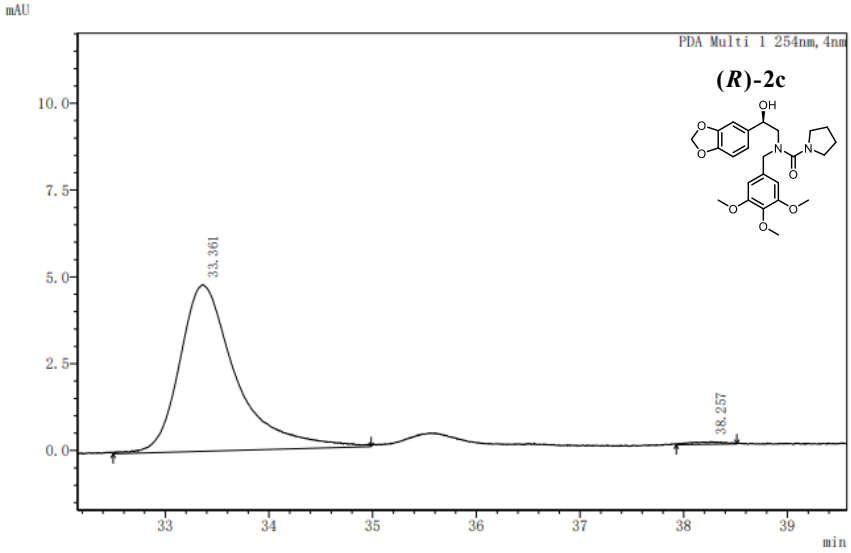


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	34.435	136805	3399	49.842	33.432	0.000
2	39.574	137675	2924	50.158	38.848	0.000
总计		274480	6324	100.000		

Chiral analysis of enzymatic (*R*)-2c

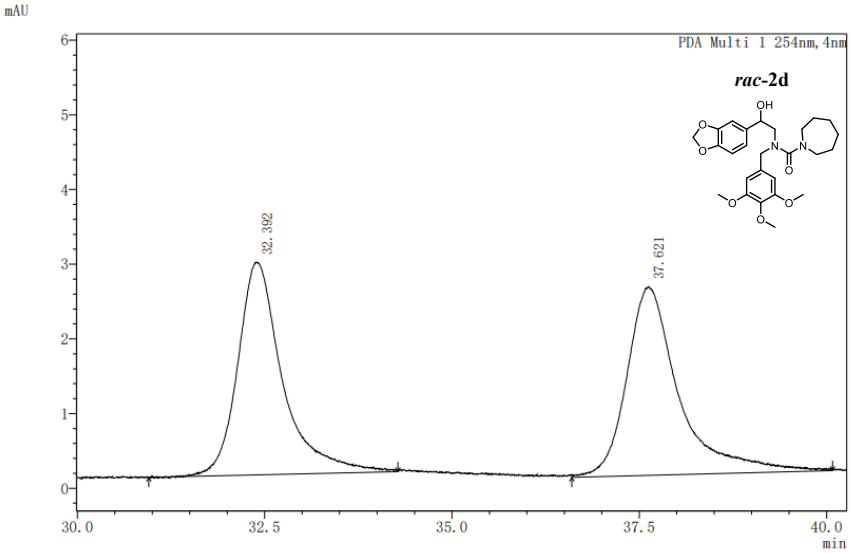


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	33.361	181467	4793	99.135	32.496	0.000
2	38.257	1583	67	0.865	37.928	0.000
总计		183050	4860	100.000		

Chiral analysis of compound *rac*-2d

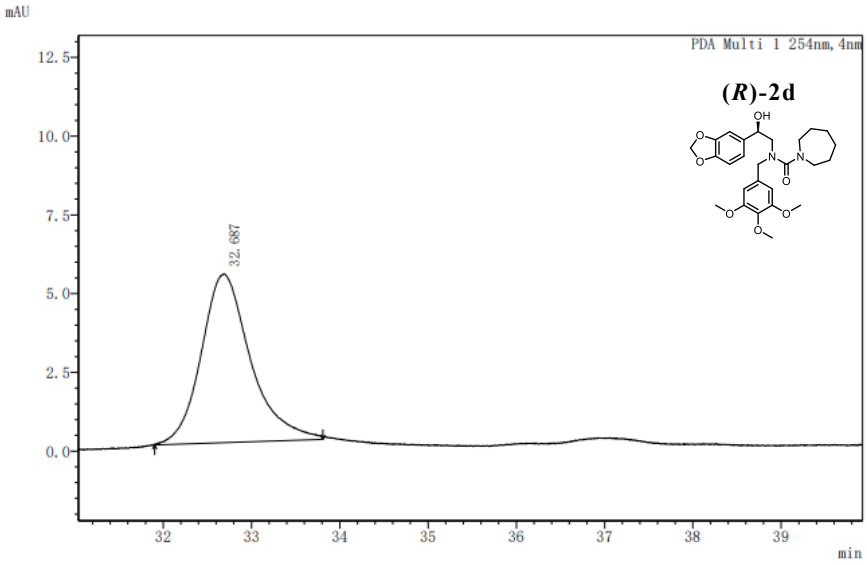


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	32.392	118471	2845	49.147	30.952	0.000
2	37.621	122581	2528	50.853	36.600	0.000
总计		241052	5372	100.000		

Chiral analysis of enzymatic (*R*)-2d from the reaction of FtmOx1

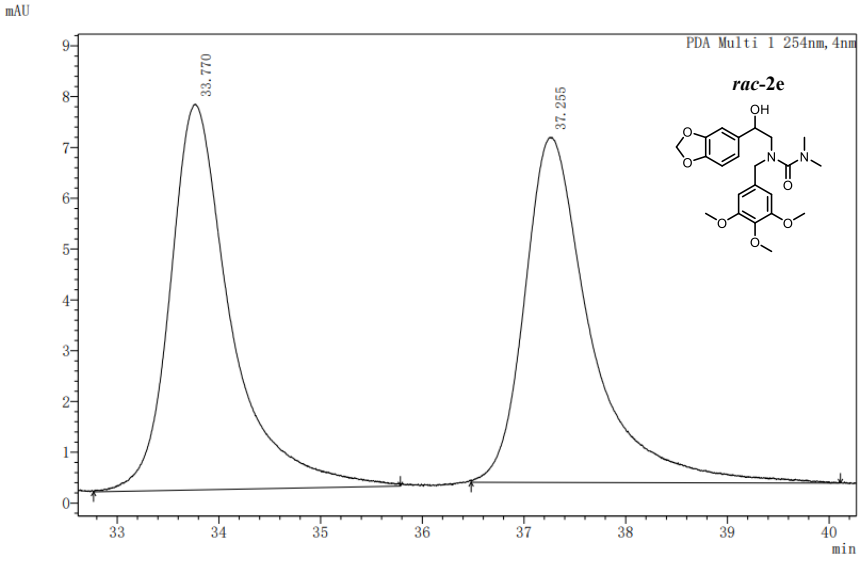


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	32.687	208495	5360	100.000	31.904	0.000
总计		208495	5360	100.000		

Chiral analysis of compound *rac*-2e

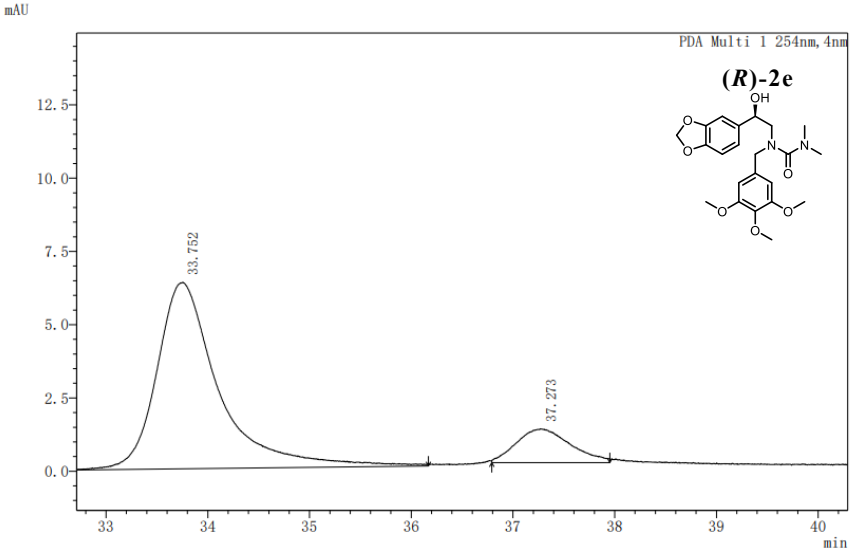


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	33.770	315762	7587	50.704	32.768	0.000
2	37.255	306992	6787	49.296	36.480	0.000
总计		622754	14374	100.000		

Chiral analysis of enzymatic (*R*)-2e from the reaction of FtmOx1

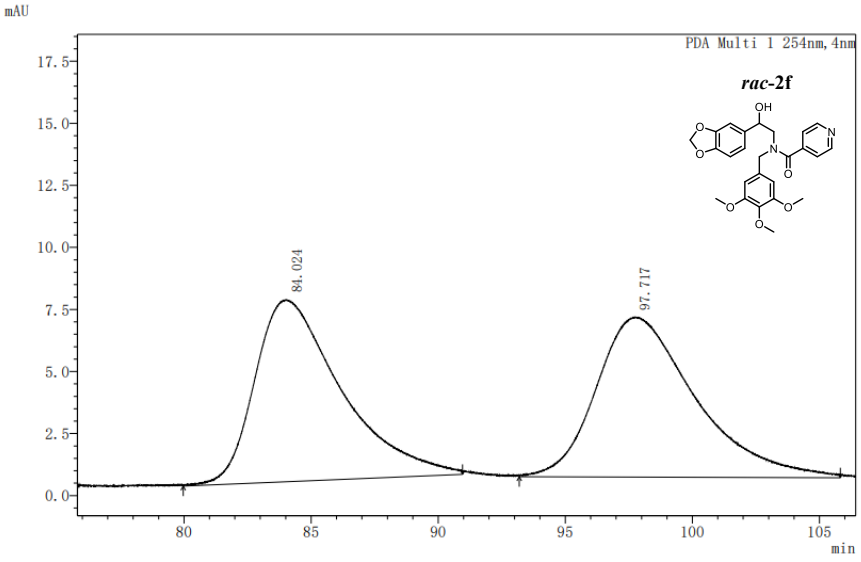


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	33.752	270247	6359	86.448	32.232	0.000
2	37.273	42367	1146	13.552	36.792	0.000
总计		312614	7505	100.000		

Chiral analysis of compound *rac*-2f

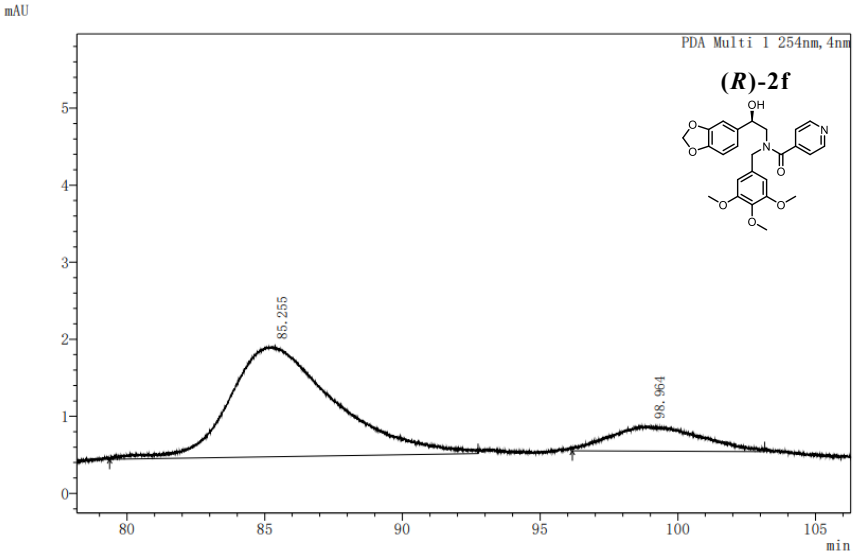


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	84.024	1731218	7319	49.727	79.968	0.000
2	97.717	1750213	6439	50.273	93.192	0.000
总计		3481431	13757	100.000		

Chiral analysis of enzymatic (*R*)-2f from the reaction of 1f with FtmOx1

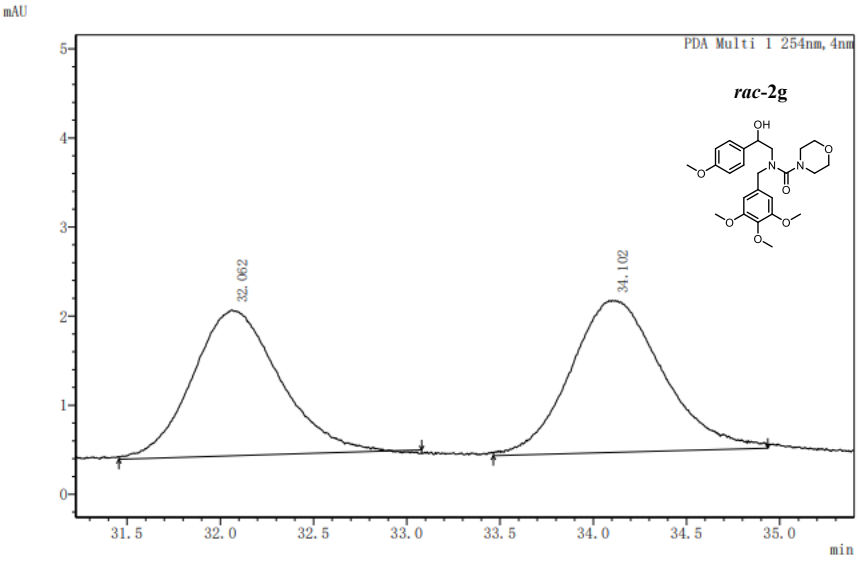


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	85.255	380493	1428	83.662	79.368	0.000
2	98.964	74303	326	16.338	96.168	0.000
总计		454796	1755	100.000		

Chiral analysis of compound *rac*-2g

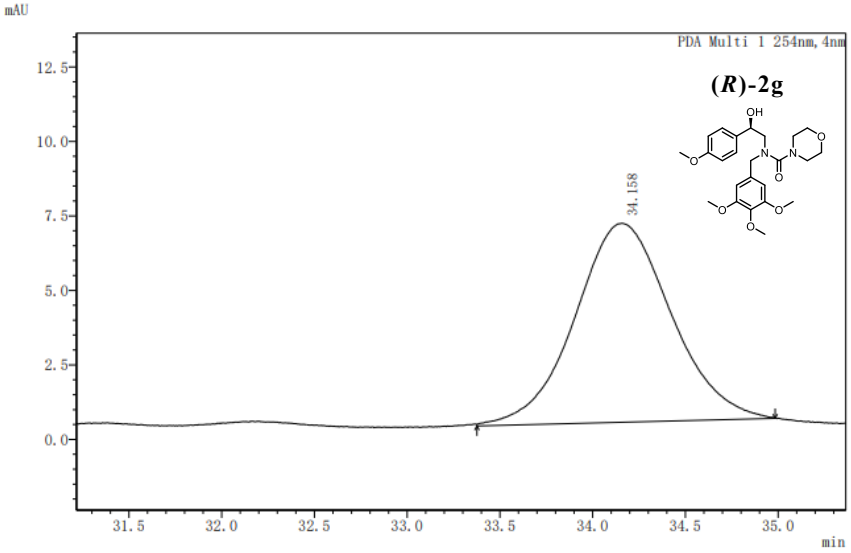


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	32.062	53118	1634	47.498	31.456	0.000
2	34.102	58714	1703	52.502	33.464	0.000
总计		111832	3338	100.000		

Chiral analysis of enzymatic (*R*)-2g from the reaction of 1g with FtmOx1

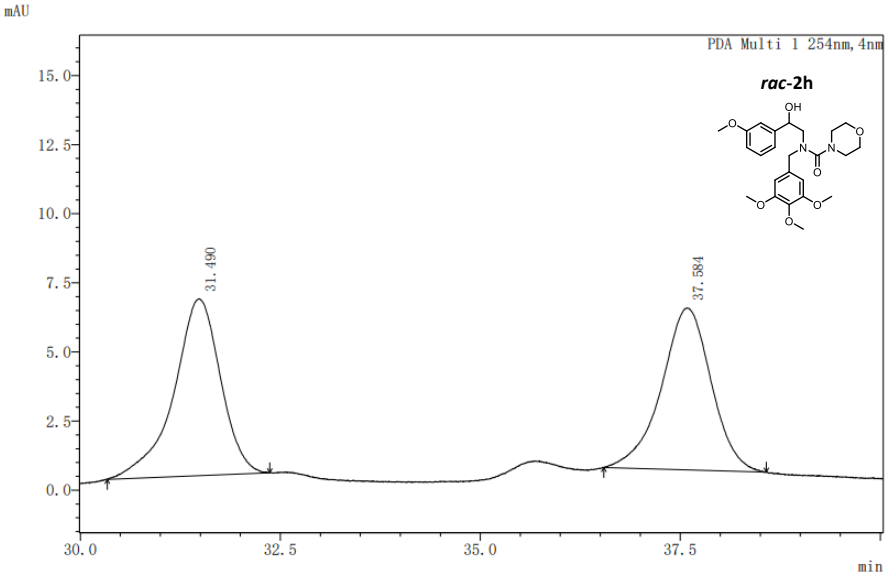


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	34.158	240981	6674	100.000	33.376	0.000
总计		240981	6674	100.000		

Chiral analysis of compound *rac*-2h

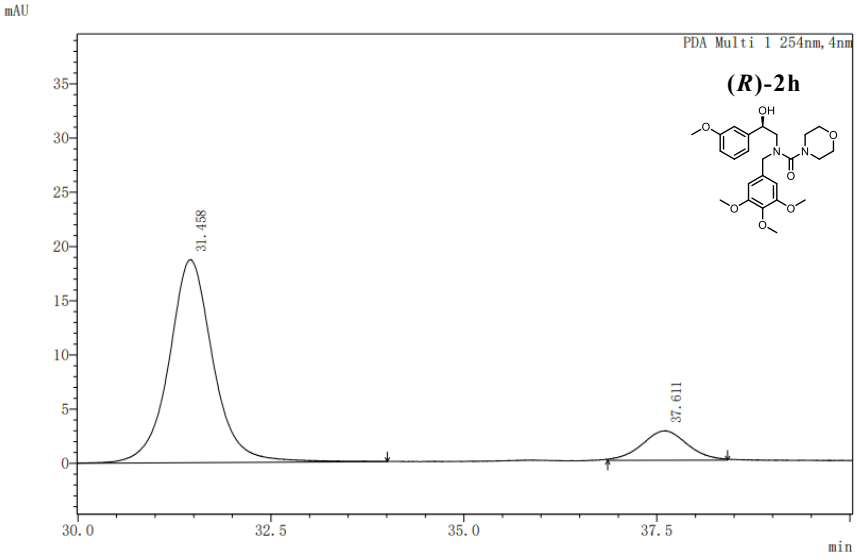


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	31.490	259504	6391	50.581	30.336	0.000
2	37.584	253541	5855	49.419	36.544	0.000
总计		513045	12246	100.000		

Chiral analysis of enzymatic compound (*R*)-2h

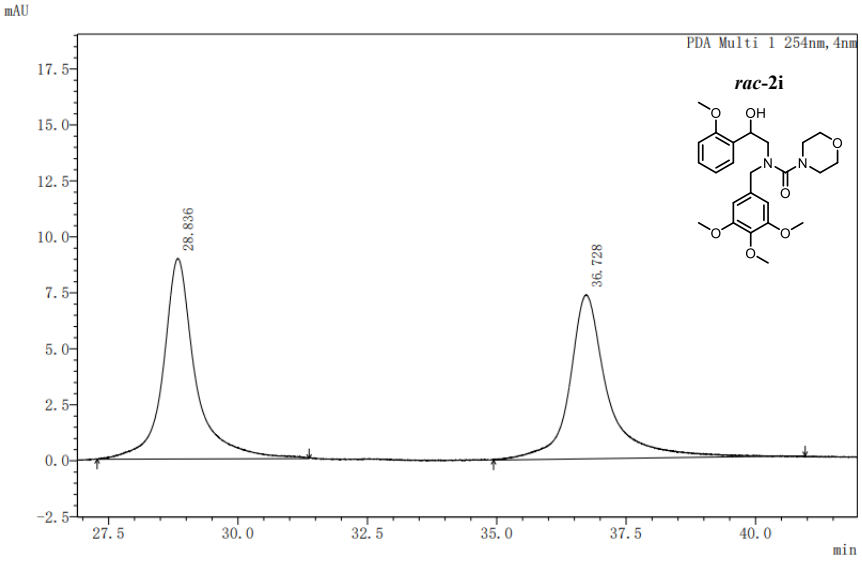


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	31.458	744501	18713	87.030	29.832	0.000
2	37.611	110949	2701	12.970	36.864	0.000
总计		855450	21414	100.000		

Chiral analysis of compound *rac*-2i

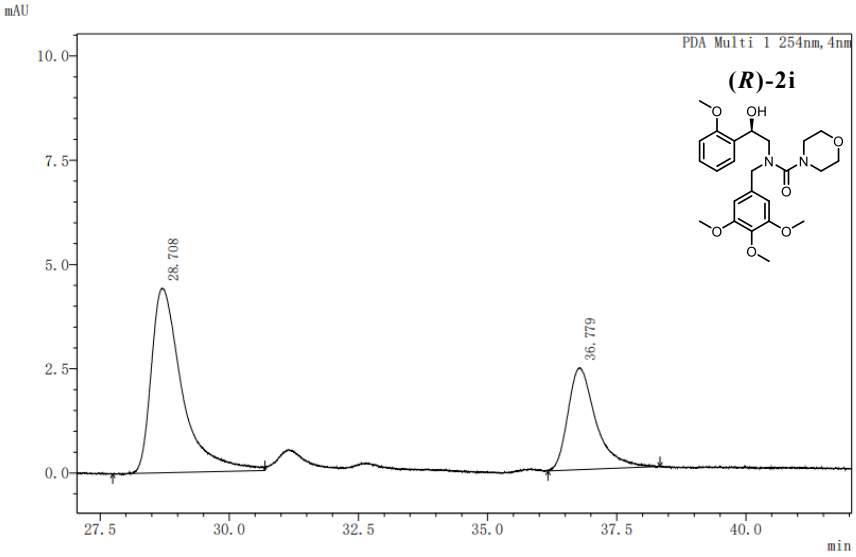


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	28.836	390424	8954	50.843	27.280	0.000
2	36.728	377479	7322	49.157	34.936	0.000
总计		767903	16276	100.000		

Chiral analysis of enzymatic compound (*R*)-2i

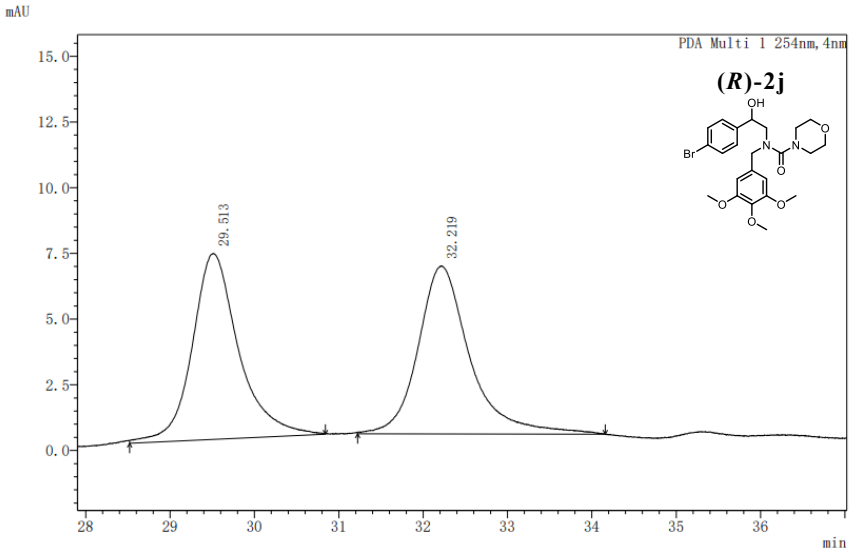


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	28.708	183171	4418	66.465	27.744	0.000
2	36.779	92419	2446	33.535	36.168	0.000
总计		275590	6863	100.000		

Chiral analysis of compound *rac*-1j

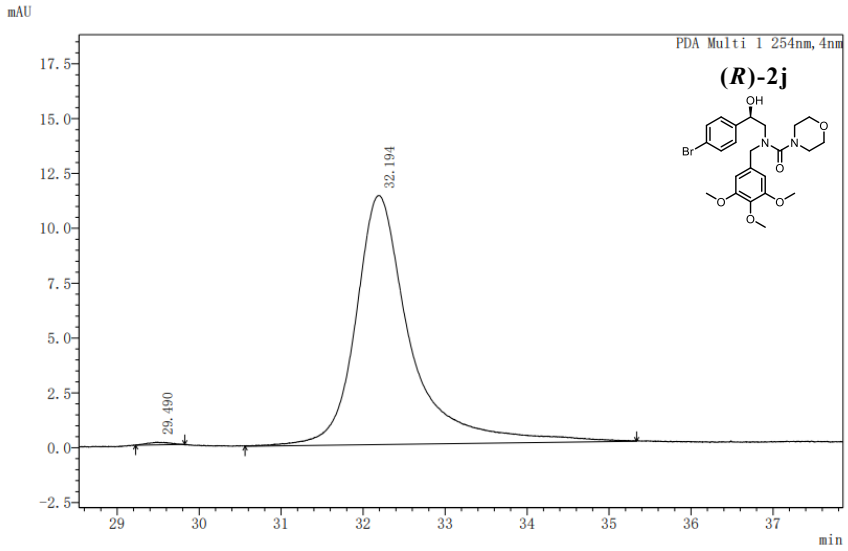


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	浓度	浓度单位	标记
1	29.513	271861	7074	0.000		M
2	32.219	273418	6390	0.000		M
总计		545279	13464			

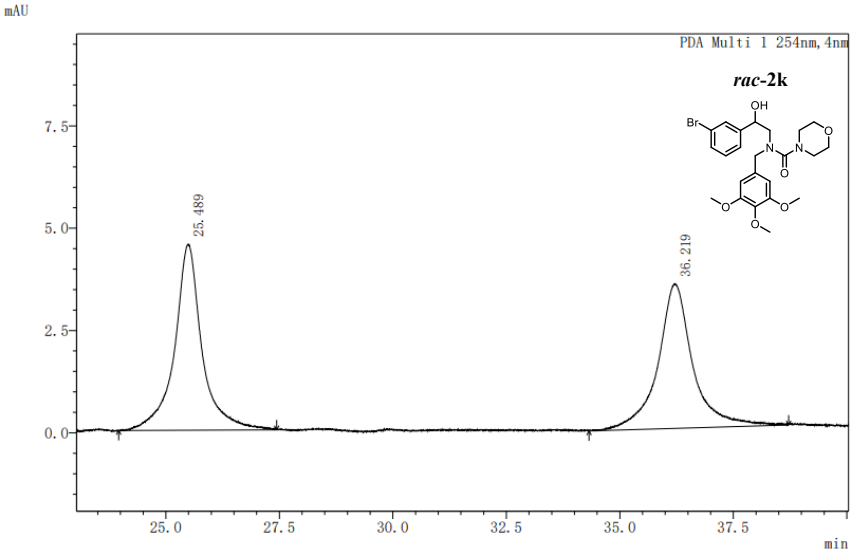
Chiral analysis of enzymatic compound (*R*)-2j



<峰表>
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	29.490	2340	119	0.440	29.224	0.000
2	32.194	529825	11348	99.560	30.560	0.000
总计		532165	11467	100.000		

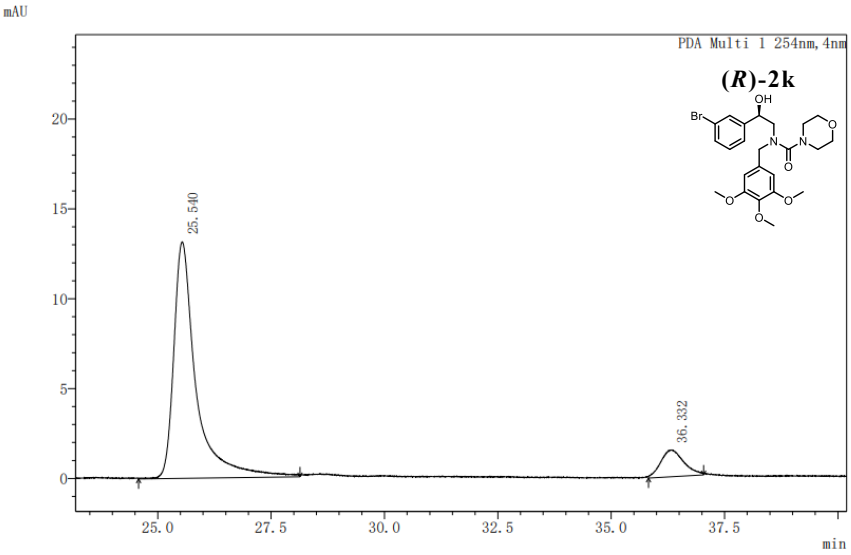
Chiral analysis of compound *rac*-2k



<峰表>
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	25.489	191973	4544	50.211	23.960	0.000
2	36.219	190359	3534	49.789	34.320	0.000
总计		382332	8078	100.000		

Chiral analysis of enzymatic compound (*R*)-2k

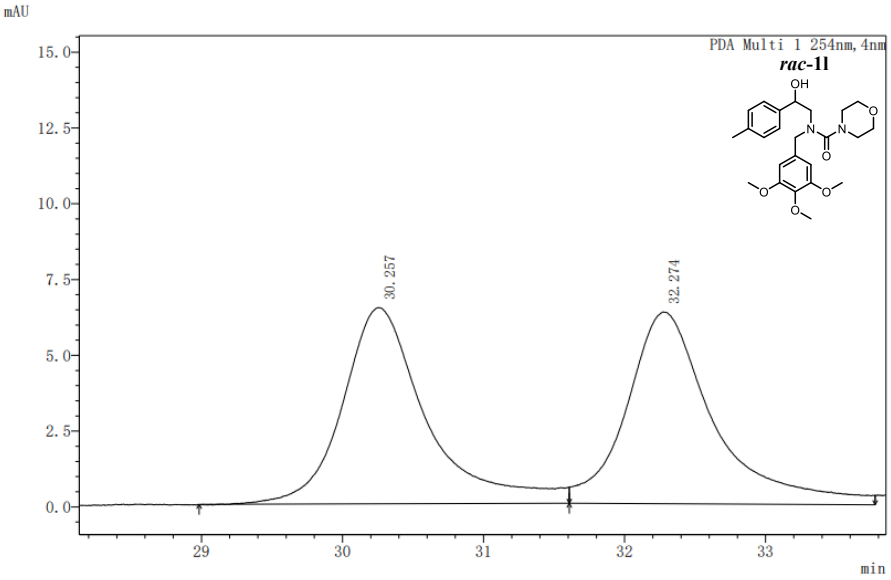


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	25.540	449200	13160	89.804	24.576	0.000
2	36.332	50999	1466	10.196	36.016	0.000
总计		500199	14625	100.000		

Chiral analysis of compound *rac*-1l

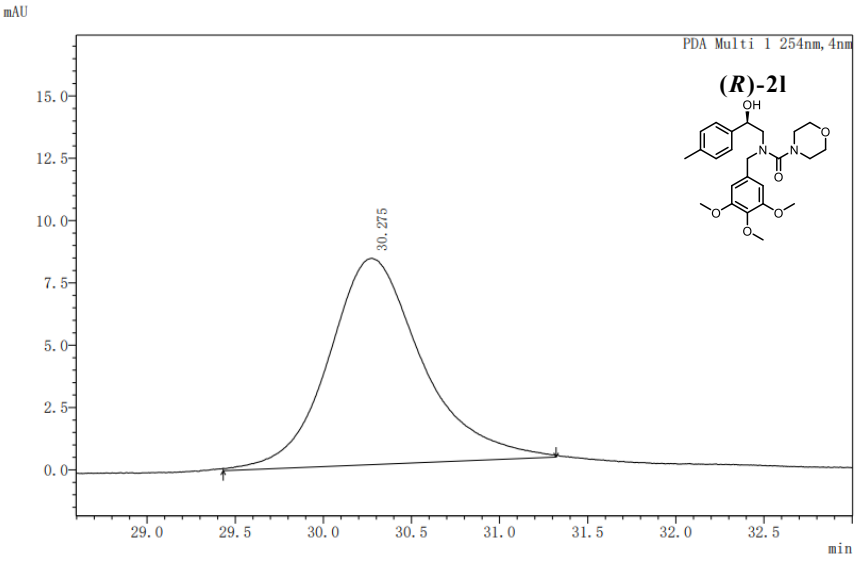


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	30.257	267597	6467	49.746	28.984	0.000
2	32.274	270332	6320	50.254	31.608	0.000
总计		537929	12787	100.000		

Chiral analysis of enzymatic compound (*R*)-2l

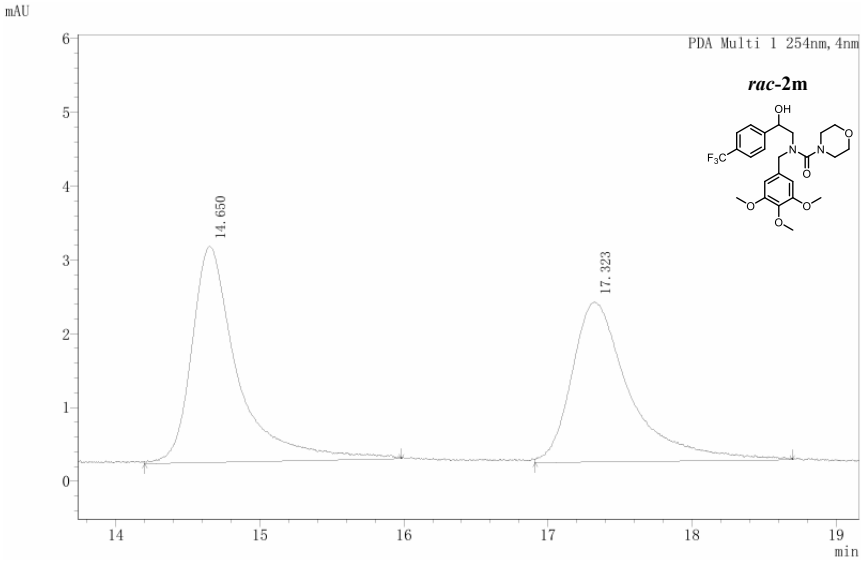


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	30.275	306304	8276	100.000	29.432	0.000
总计		306304	8276	100.000		

Chiral analysis of compound *rac*-2m

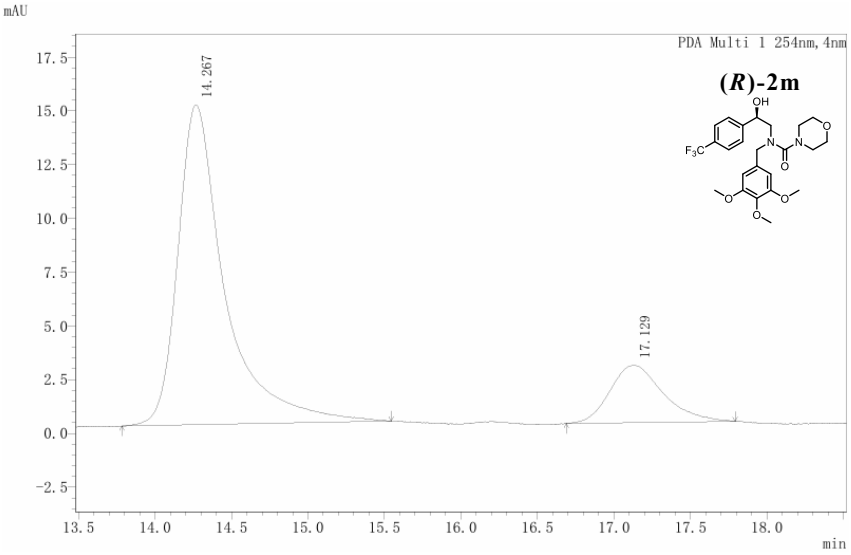


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	14.650	65344	2924	51.719	14.200	0.000
2	17.323	60999	2167	48.281	16.912	0.000
总计		126343	5092	100.000		

Chiral analysis of enzymatic compound (*R*)-2m

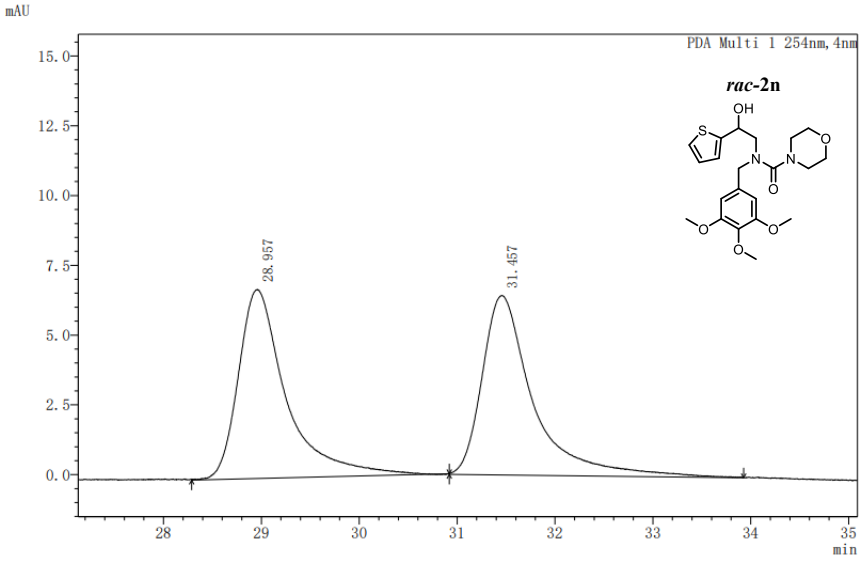


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	14.267	318176	14867	83.076	13.784	0.000
2	17.129	64817	2663	16.924	16.688	0.000
总计		382993	17530	100.000		

Chiral analysis of compound *rac*-2n

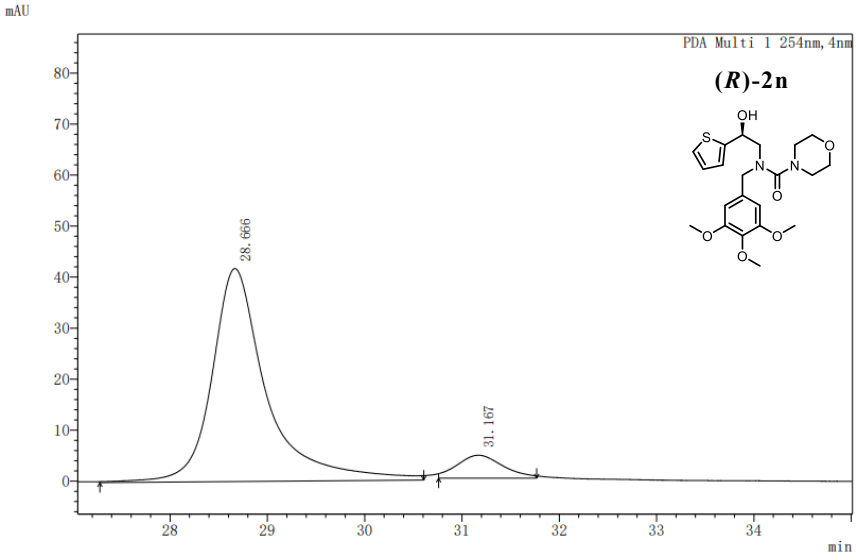


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	28.957	230173	6768	49.757	28.288	0.000
2	31.457	232418	6426	50.243	30.920	0.000
总计		462591	13194	100.000		

Chiral analysis of enzymatic compound (*R*)-2n

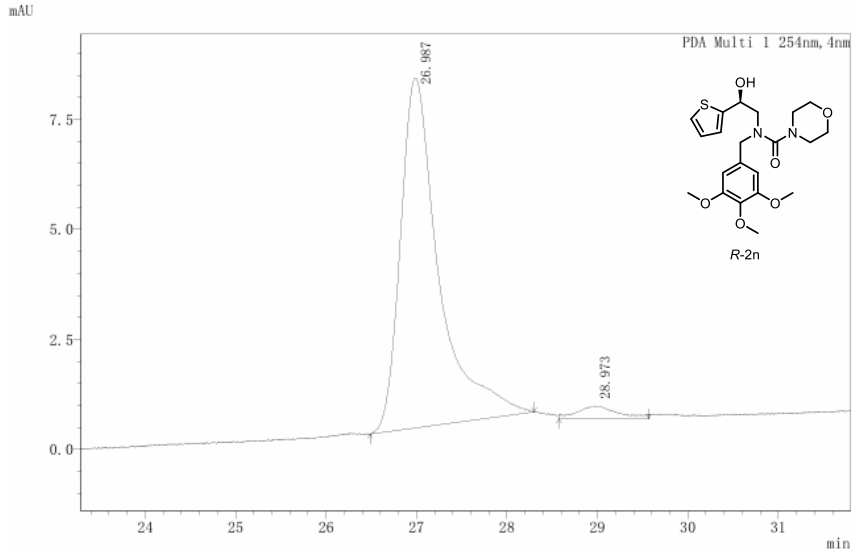


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	28.666	1636782	41769	91.720	27.280	0.000
2	31.167	147769	4491	8.280	30.760	0.000
总计		1784551	46260	100.000		

Chiral analysis of chemically synthesized (*R*)-2n

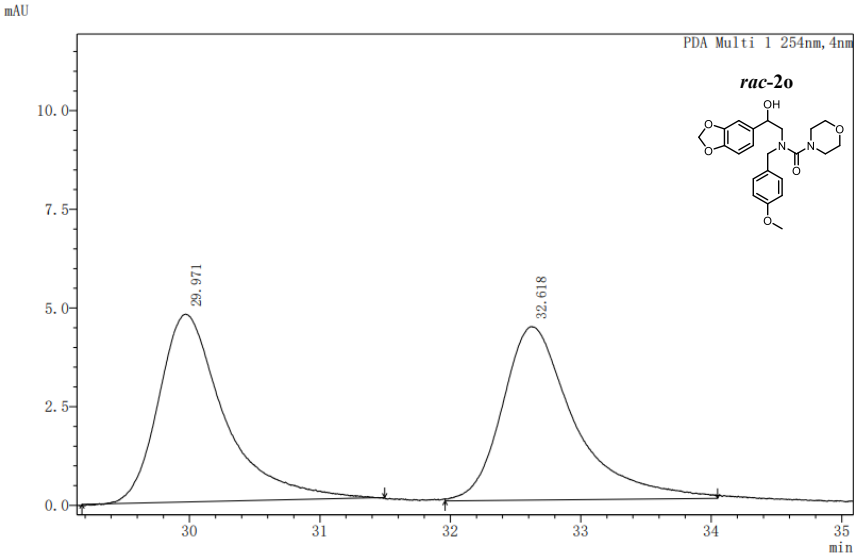


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	26.987	235851	7947	96.301	26.488	0.000
2	28.973	9058	286	3.699	28.576	0.000
总计		244909	8233	100.000		

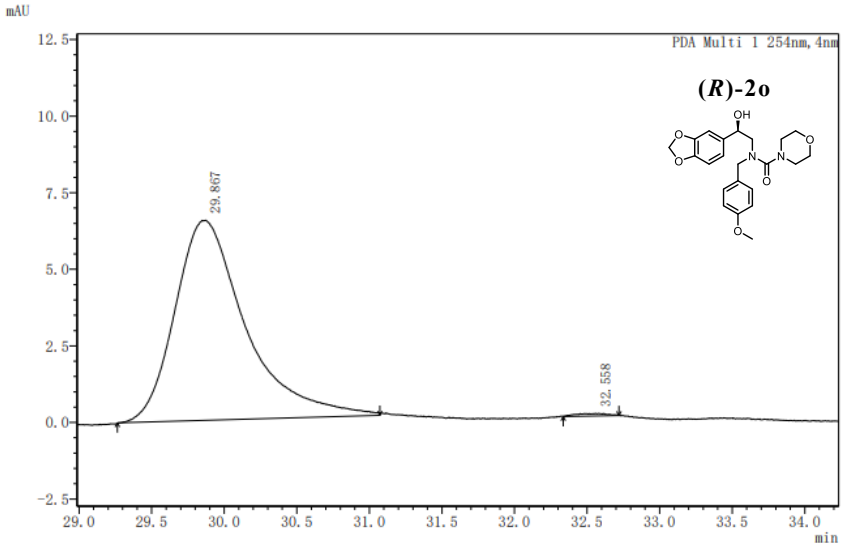
Chiral analysis of compound *rac*-2o



<峰表>
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	29.971	166308	4756	49.592	29.176	0.000
2	32.618	169047	4392	50.408	31.960	0.000
总计		335355	9148	100.000		

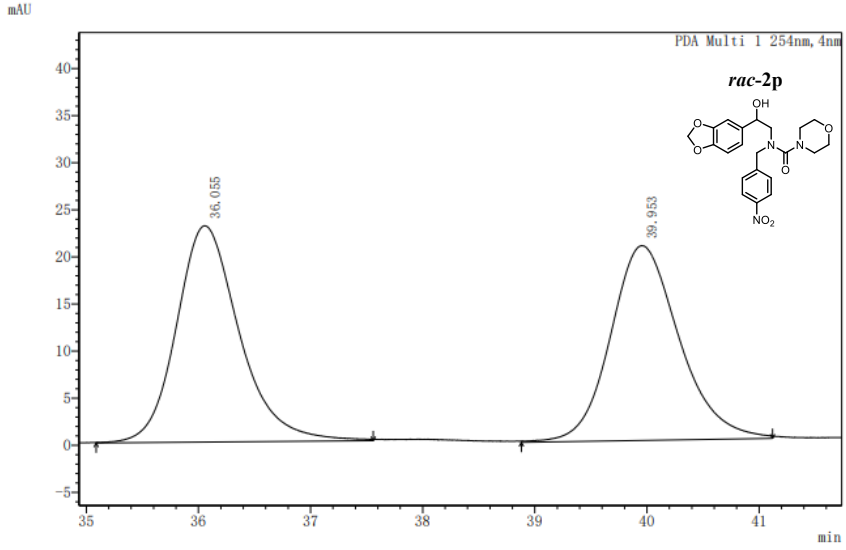
Chiral analysis of enzymatic compound (*R*)-2o



<峰表>
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	29.867	221549	6524	99.412	29.264	0.000
2	32.558	1311	83	0.588	32.336	0.000
总计		222859	6607	100.000		

Chiral analysis of compound *rac*-2p

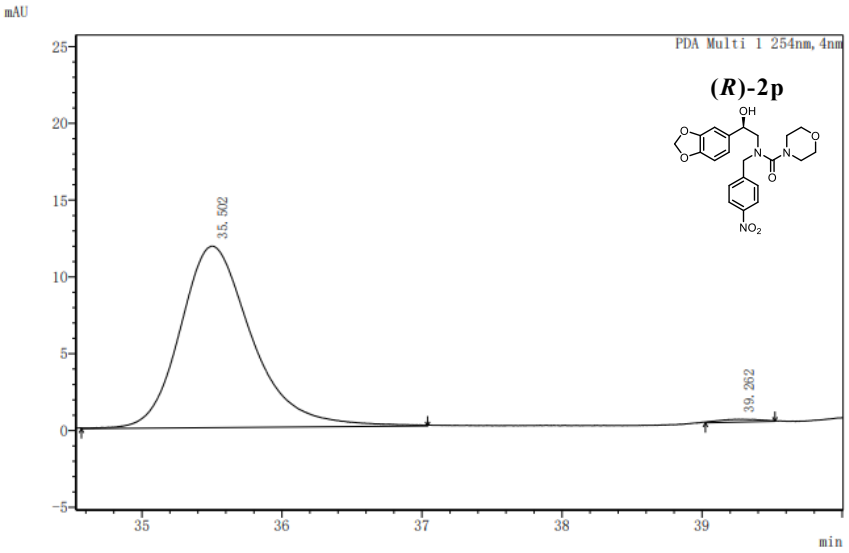


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	36.055	897566	22962	50.393	35.088	0.000
2	39.953	883574	20677	49.607	38.880	0.000
总计		1781140	43639	100.000		

Chiral analysis of enzymatic compound (*R*)-2p

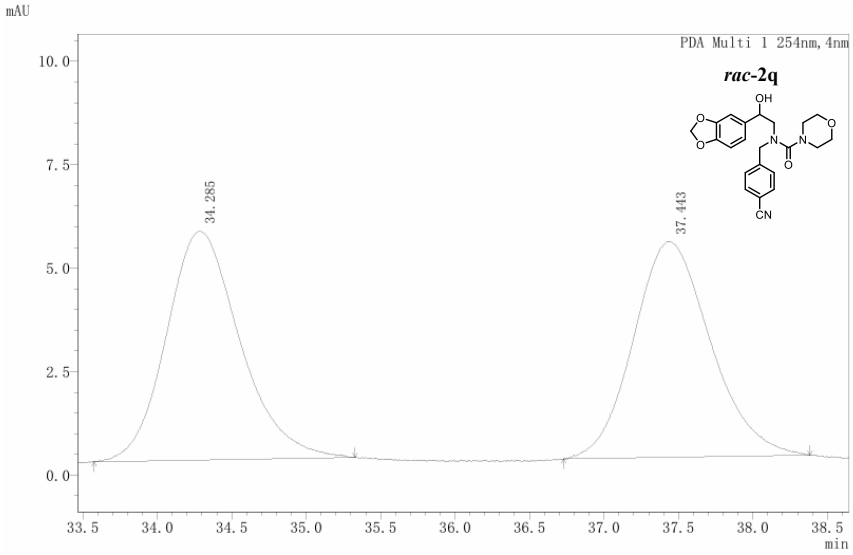


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	35.502	421732	11812	99.136	34.568	0.000
2	39.262	3675	184	0.864	39.024	0.000
总计		425407	11996	100.000		

Chiral analysis of compound *rac*-2q

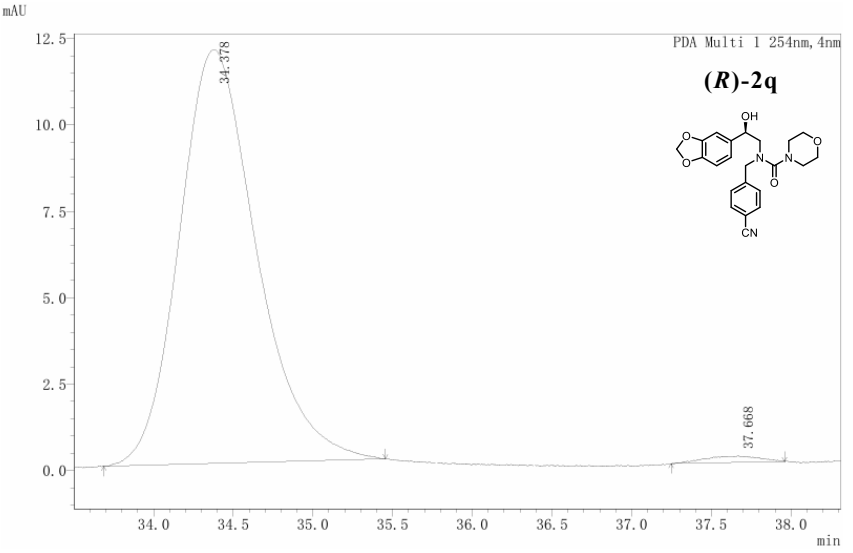


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	34.285	190123	5537	50.295	33.576	0.000
2	37.443	187890	5207	49.705	36.728	0.000
总计		378013	10744	100.000		

Chiral analysis of enzymatic compound (*R*)-2q

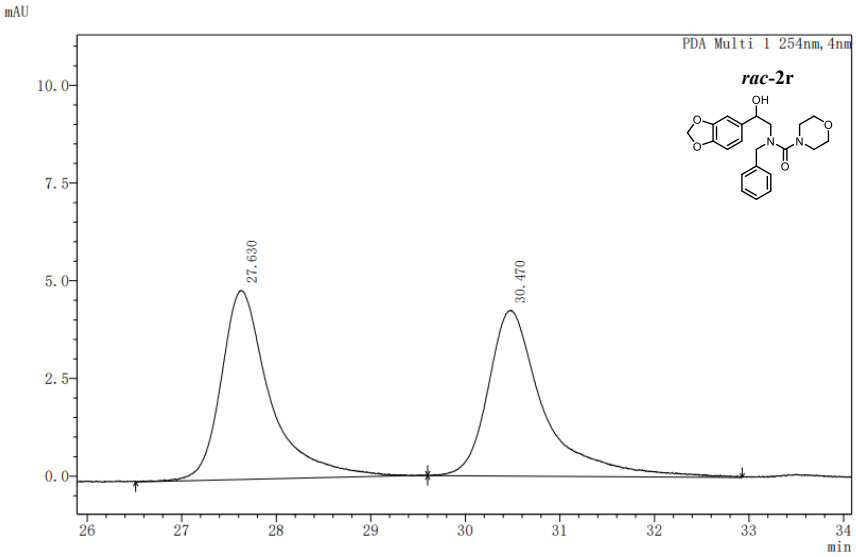


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	34.378	403698	11978	0.000			
2	37.668	4308	180	0.000		M	
总计		408006	12158				

Chiral analysis of compound *rac*-2r

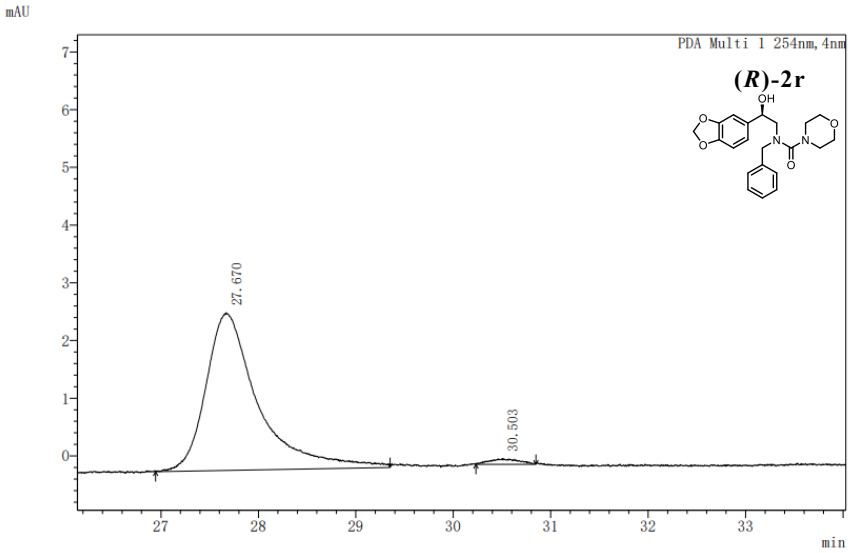


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	27.630	173755	4835	50.026	26.512	0.000
2	30.470	173573	4240	49.974	29.600	0.000
总计		347328	9075	100.000		

Chiral analysis of enzymatic compound (*R*)-2r

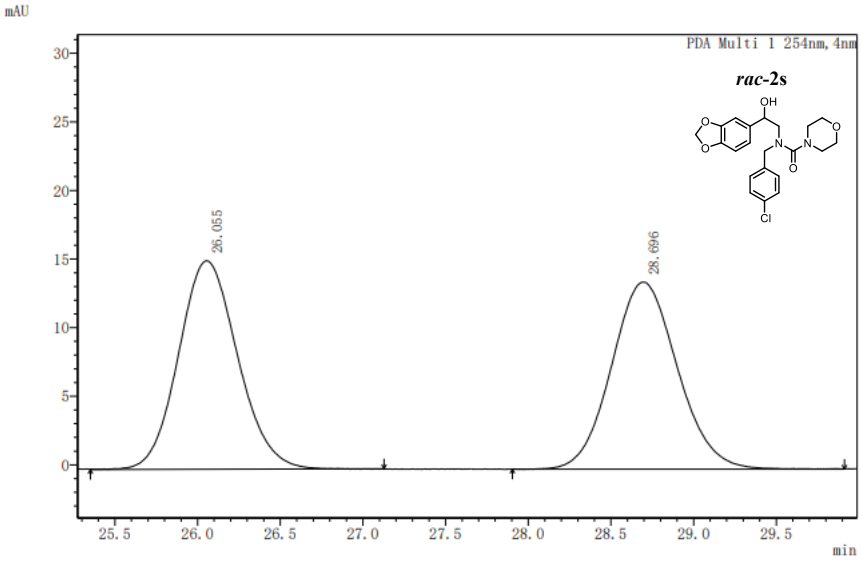


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	27.670	101460	2722	98.040	26.944	0.000
2	30.503	2028	95	1.960	30.232	0.000
总计		103488	2817	100.000		

Chiral analysis of compound *rac*-2s

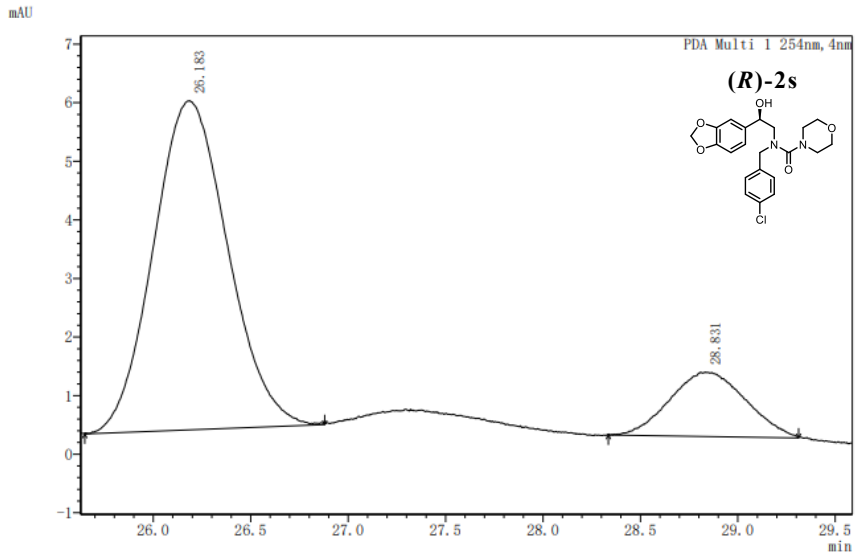


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	26.055	378250	15199	49.933	25.352	0.000
2	28.696	379270	13637	50.067	27.904	0.000
总计		757520	28836	100.000		

Chiral analysis of enzymatic compound (*R*)-2s

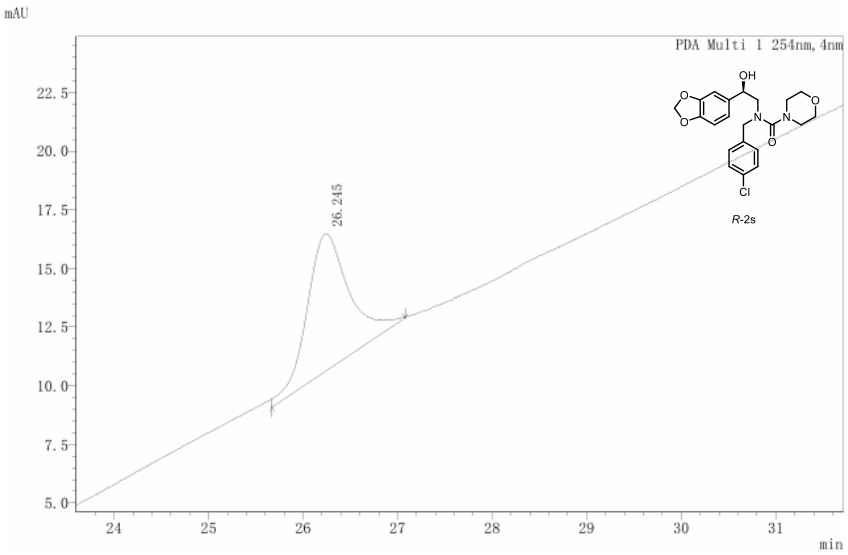


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	26.183	149531	5614	83.414	25.648	0.000
2	28.831	29732	1095	16.586	28.336	0.000
总计		179263	6709	100.000		

Chiral analysis of chemically synthesized compound (*R*)-2s

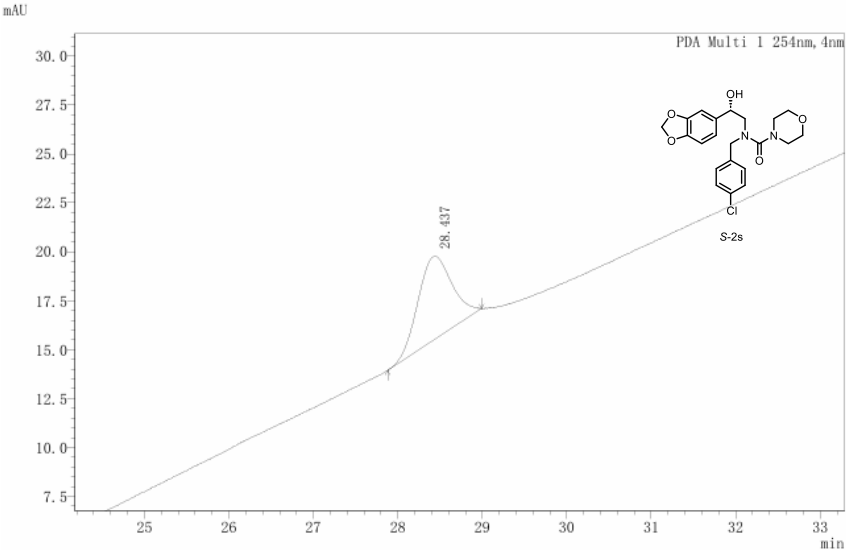


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	26.245	180796	5844	0.000		M	
总计		180796	5844				

Chiral analysis of chemically synthesized compound (*S*)-2s

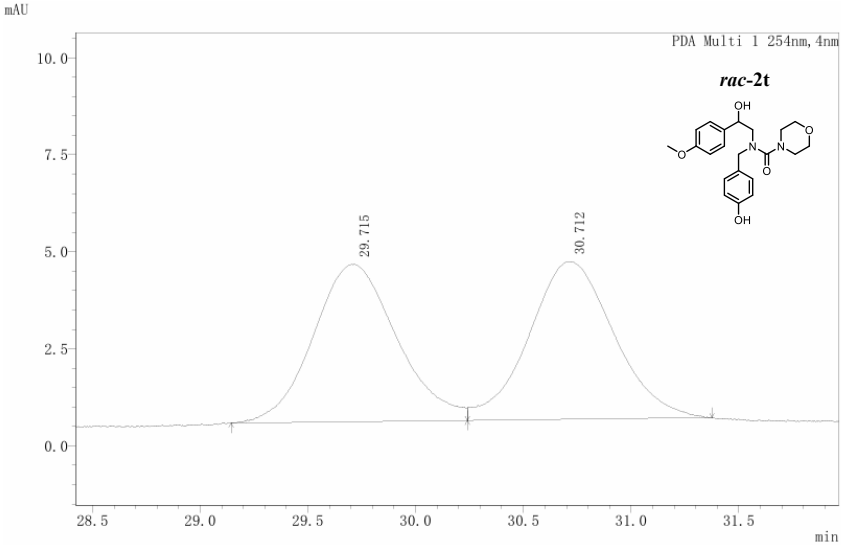


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	浓度	浓度单位	标记	化合物名
1	28.437	119446	4257	0.000			
总计		119446	4257				

Chiral analysis of compound *rac*-2t

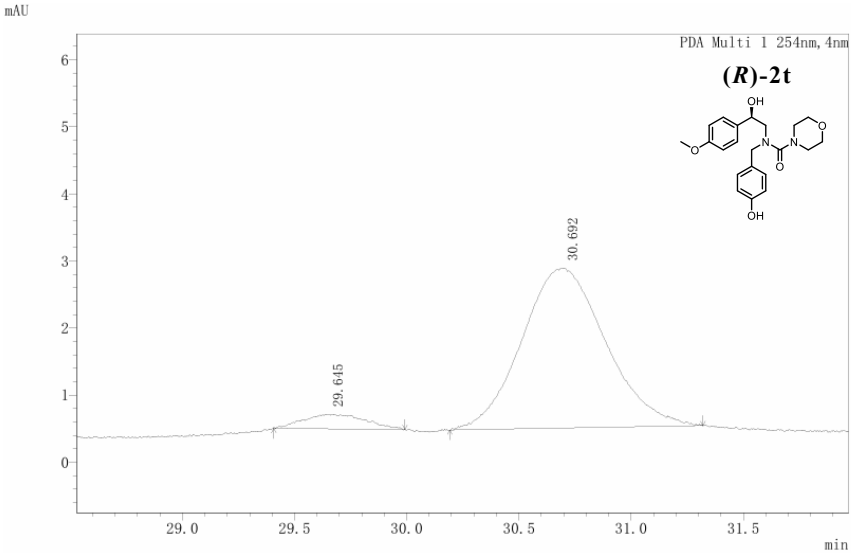


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	29.715	109325	4052	49.555	29.144	0.000
2	30.712	111286	4062	50.445	30.240	0.000
总计		220611	8114	100.000		

Chiral analysis of enzymatic (*R*)-2t

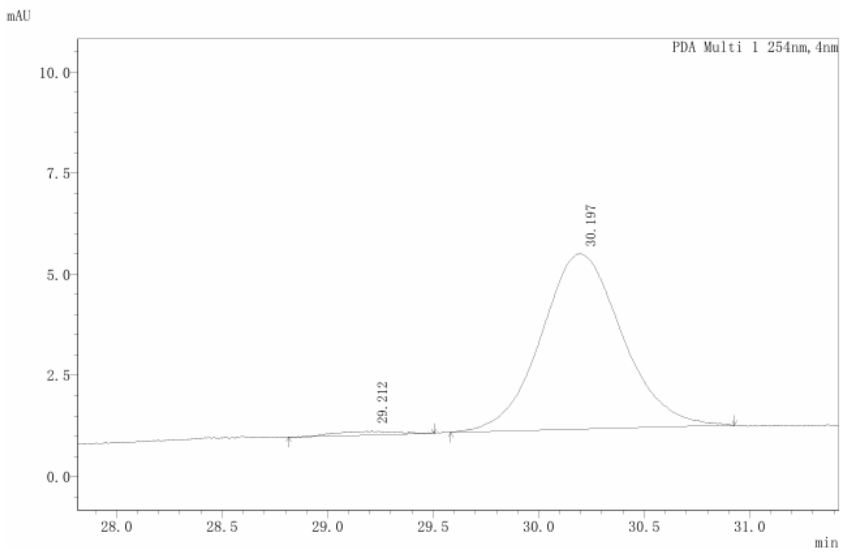


〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	29.645	4130	216	6.250	29.408	0.000
2	30.692	61947	2383	93.750	30.192	0.000
总计		66077	2599	100.000		

Chiral analysis of synthetic (*R*)-2t



〈峰表〉

PDA Ch1 254nm

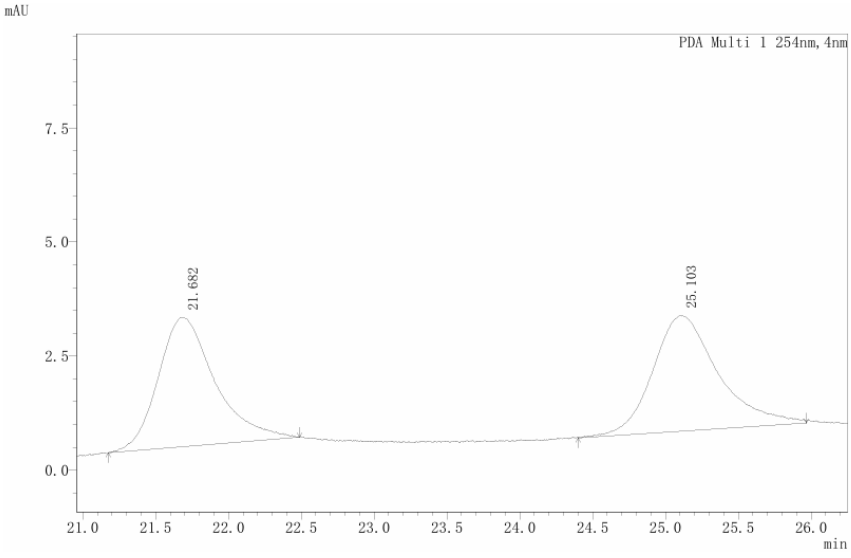
峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	29.212	2081	98	1.766	28.816	0.000
2	30.197	115753	4332	98.234	29.584	0.000
总计		117834	4430	100.000		

Chiral analysis of compound *rac*-2u

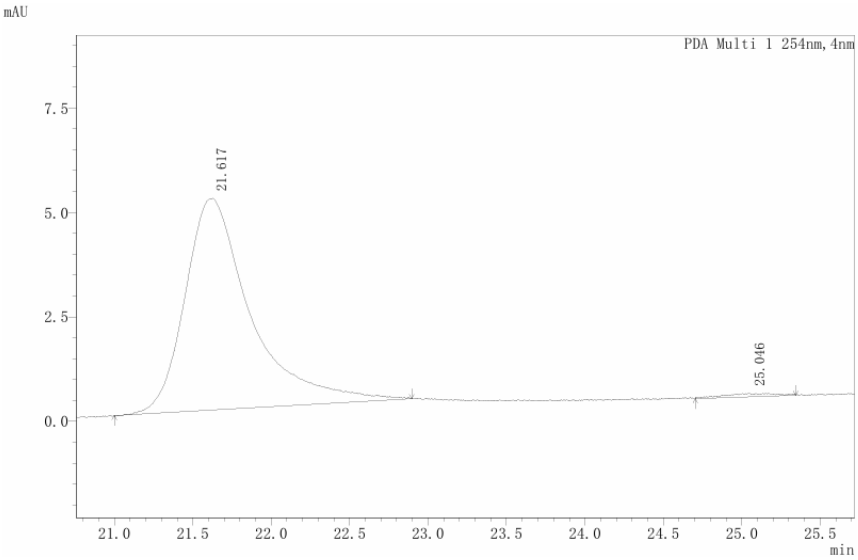
〈峰表〉

PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	21.682	76928	2832	49.249	21.176	0.000
2	25.103	79274	2538	50.751	24.400	0.000
总计		156201	5370	100.000		



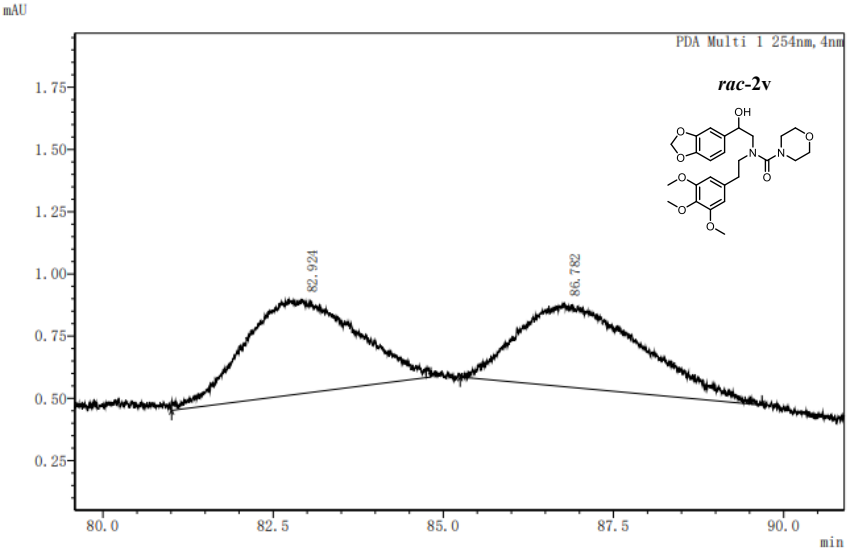
Chiral analysis of enzymatic compound (*R*)-2u



<峰表>
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	21.617	148138	5060	98.754	21.000	0.000
2	25.046	1869	82	1.246	24.704	0.000
总计		150006	5142	100.000		

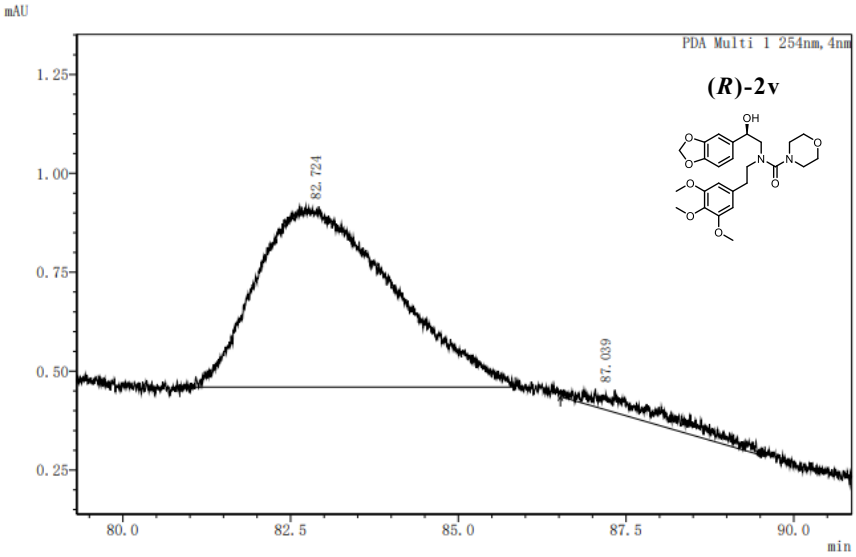
Chiral analysis of compound *rac*-1v



<峰表>
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	82.924	43993	376	50.918	81.008	0.000
2	86.782	42406	331	49.082	85.248	0.000
总计		86399	707	100.000		

Chiral analysis of enzymatic (*R*)-2v

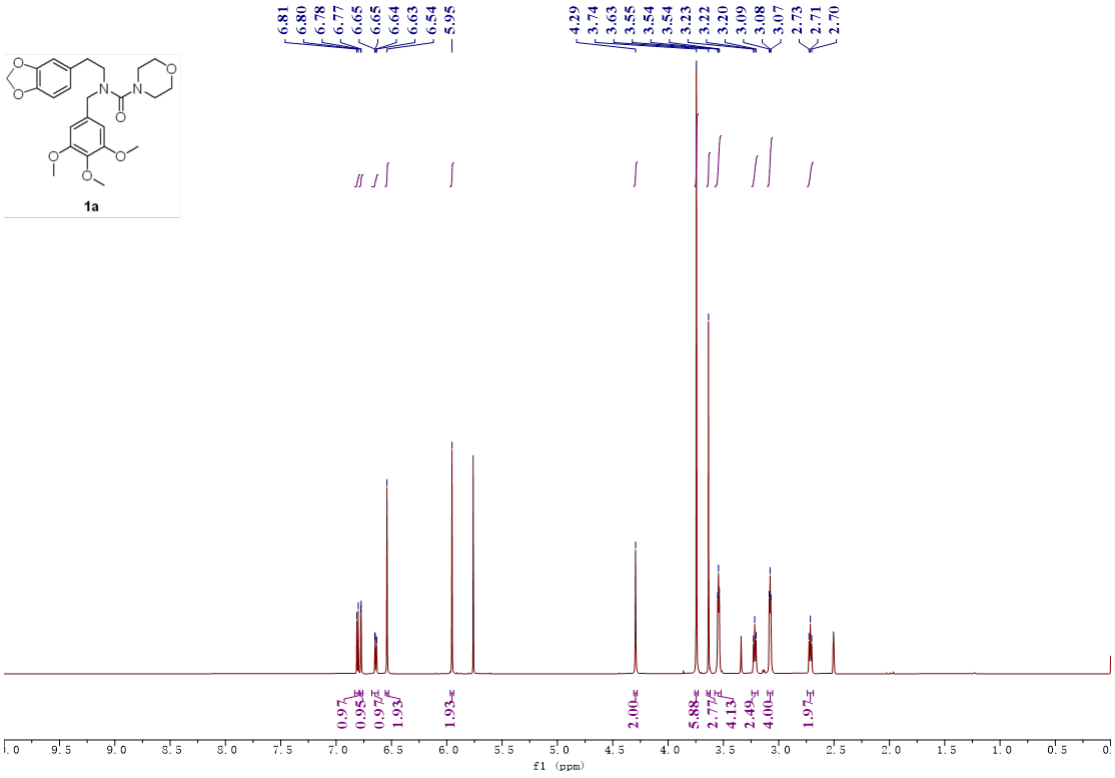


<峰表>

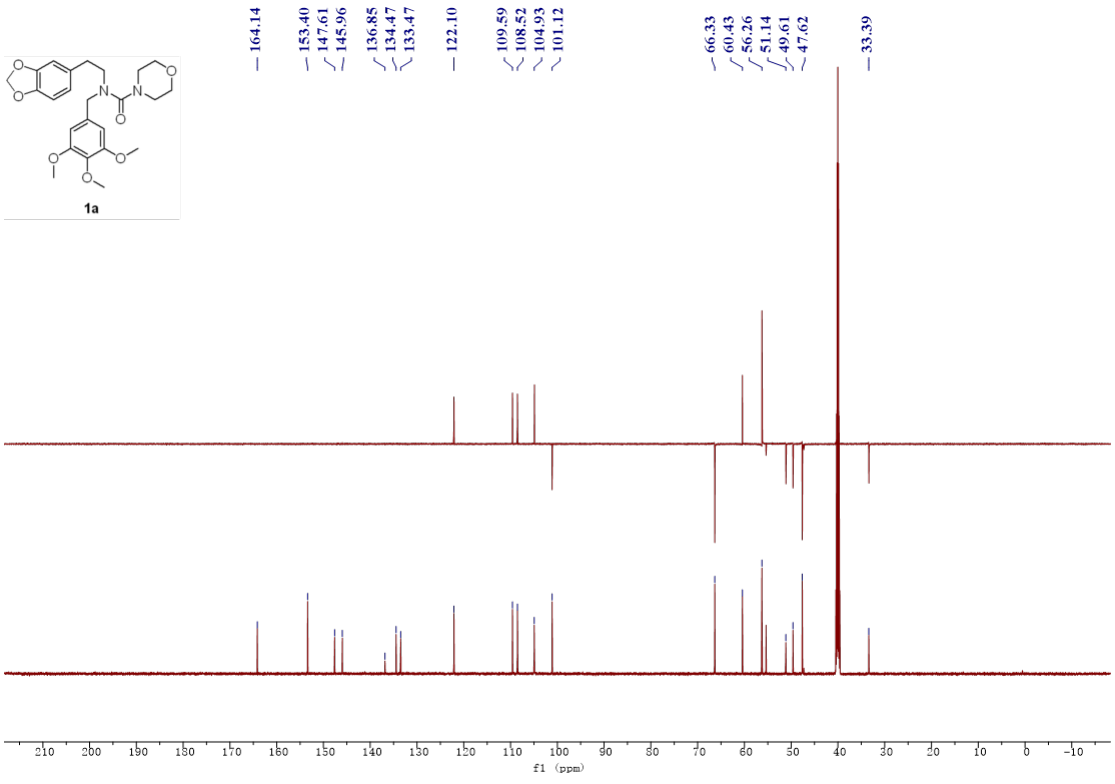
PDA Ch1 254nm

峰号	保留时间	面积	高度	面积%	峰开始	浓度
1	82.724	63858	455	93.799	80.848	0.000
2	87.039	4222	41	6.201	86.520	0.000
总计		68080	495	100.000		

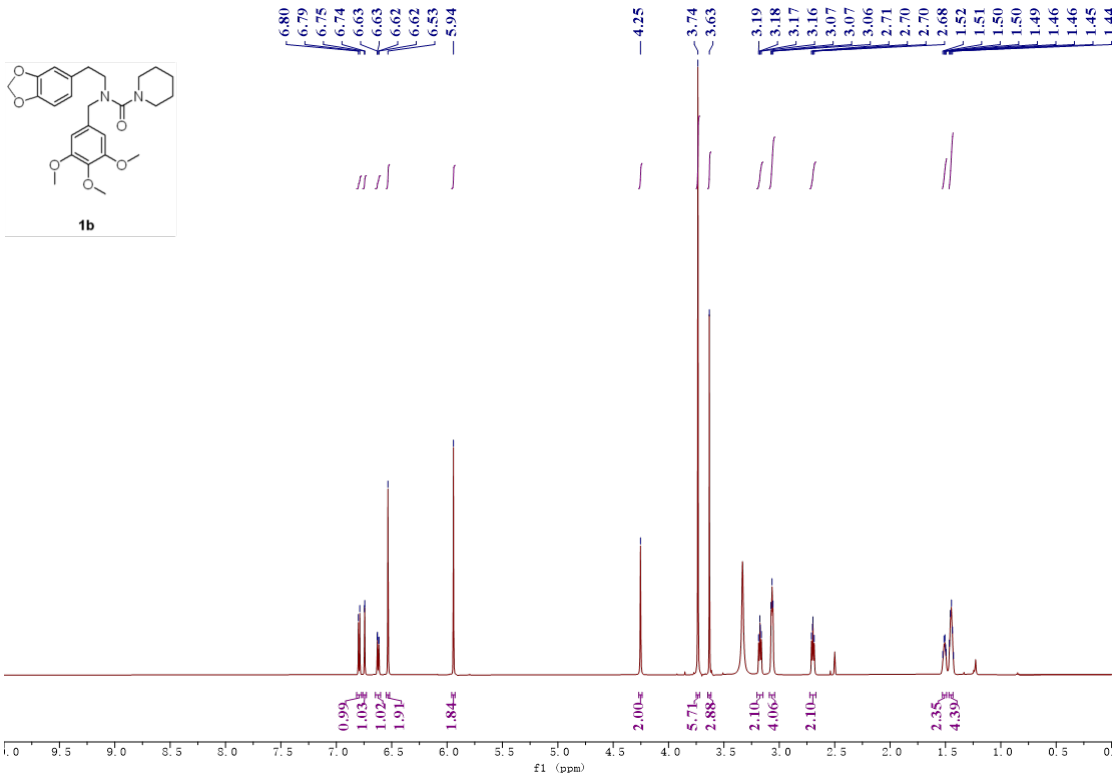
NMR spectra



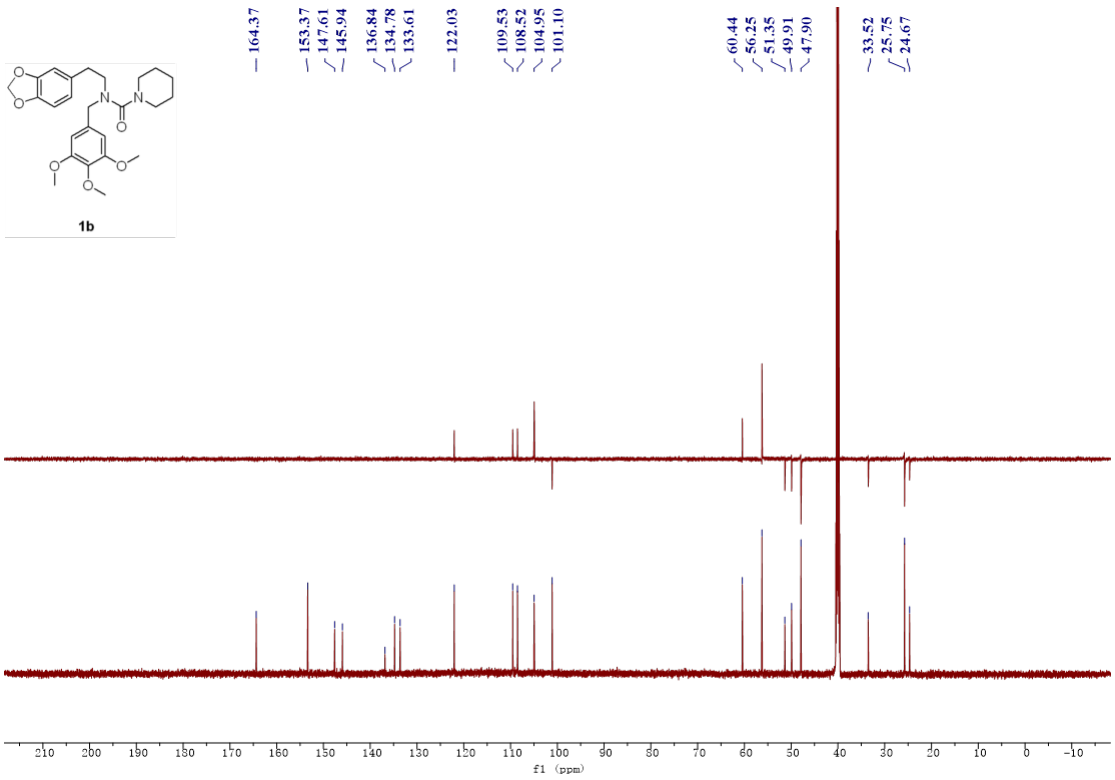
^{1}H NMR spectrum of compound **1a** in DMSO-d_6



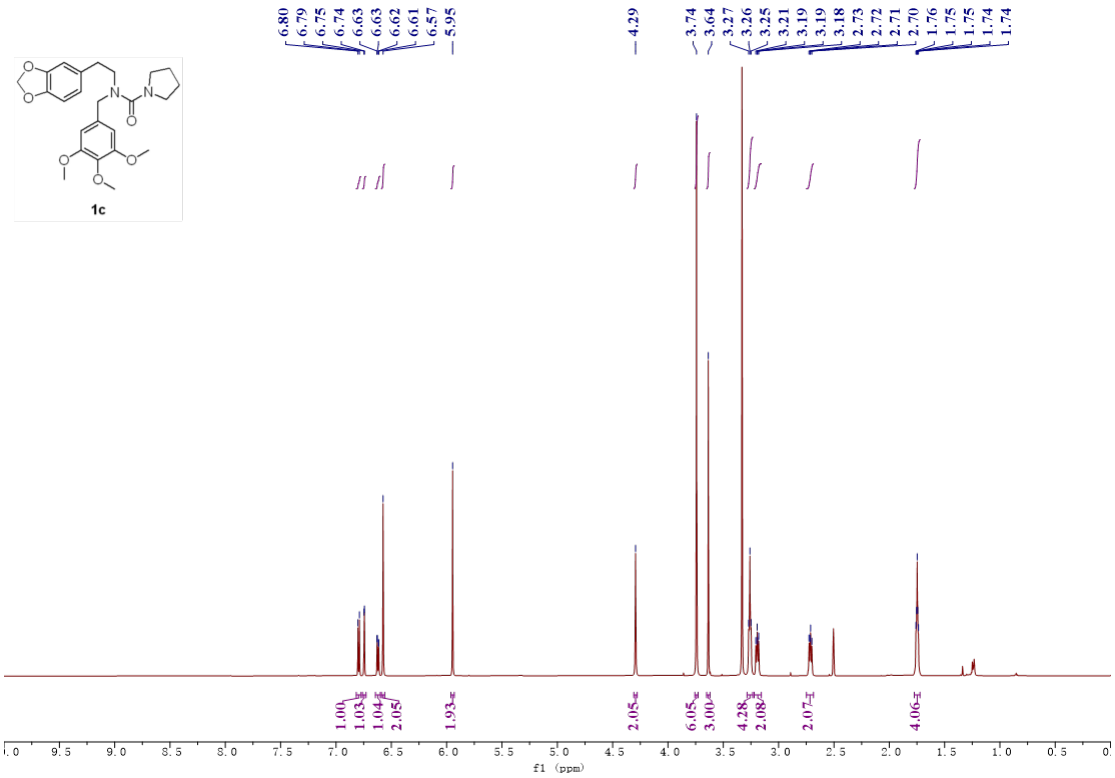
^{13}C NMR spectrum of compound **1a** in DMSO-d_6



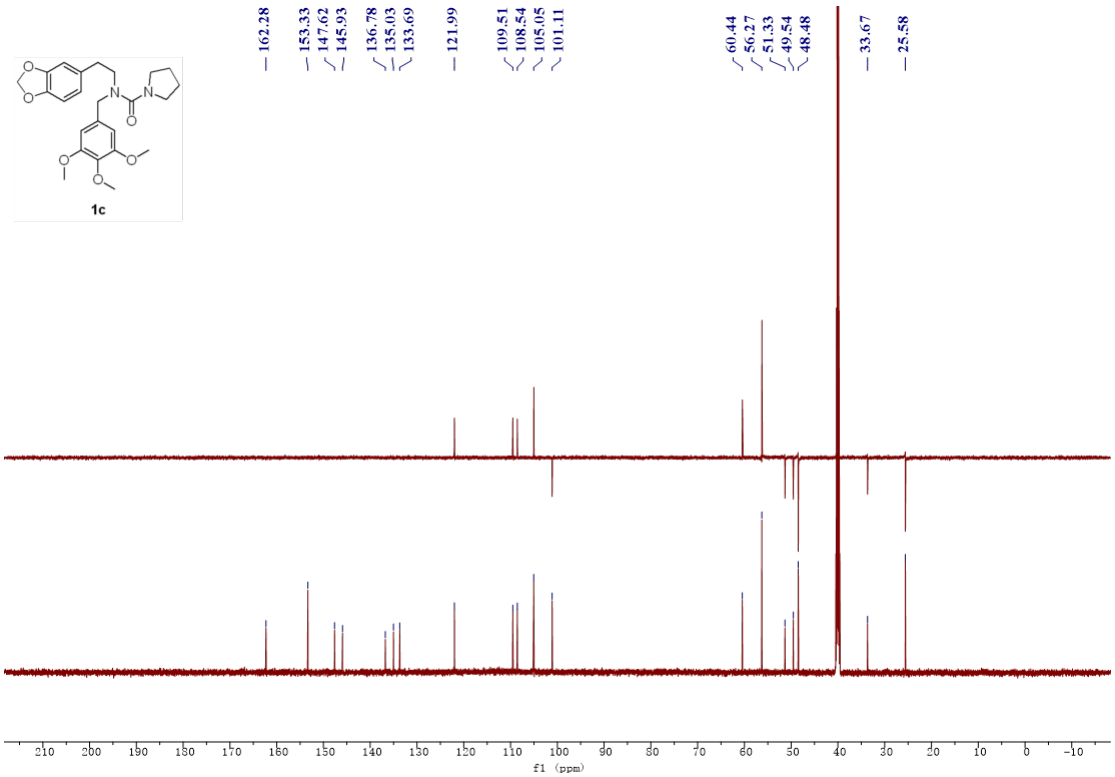
^{1}H NMR spectrum of compound **1b** in DMSO-d_6



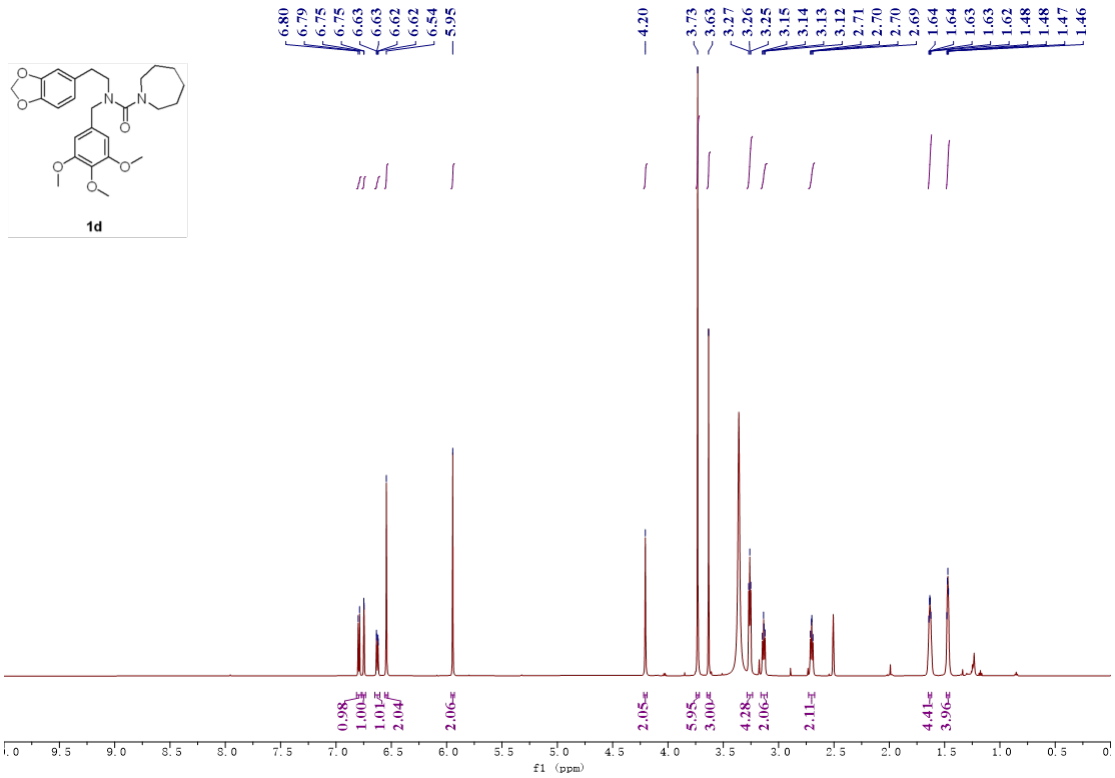
^{13}C NMR spectrum of compound **1b** in DMSO-d_6



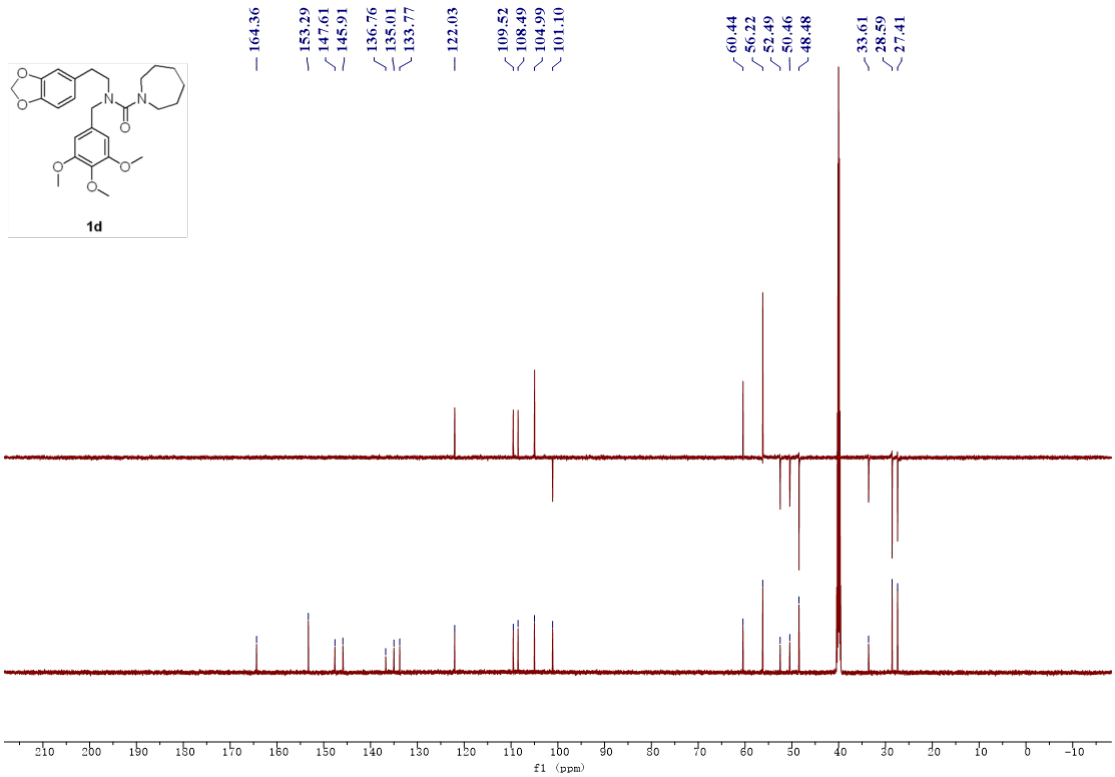
^{1}H NMR spectrum of compound **1c** in DMSO-d_6



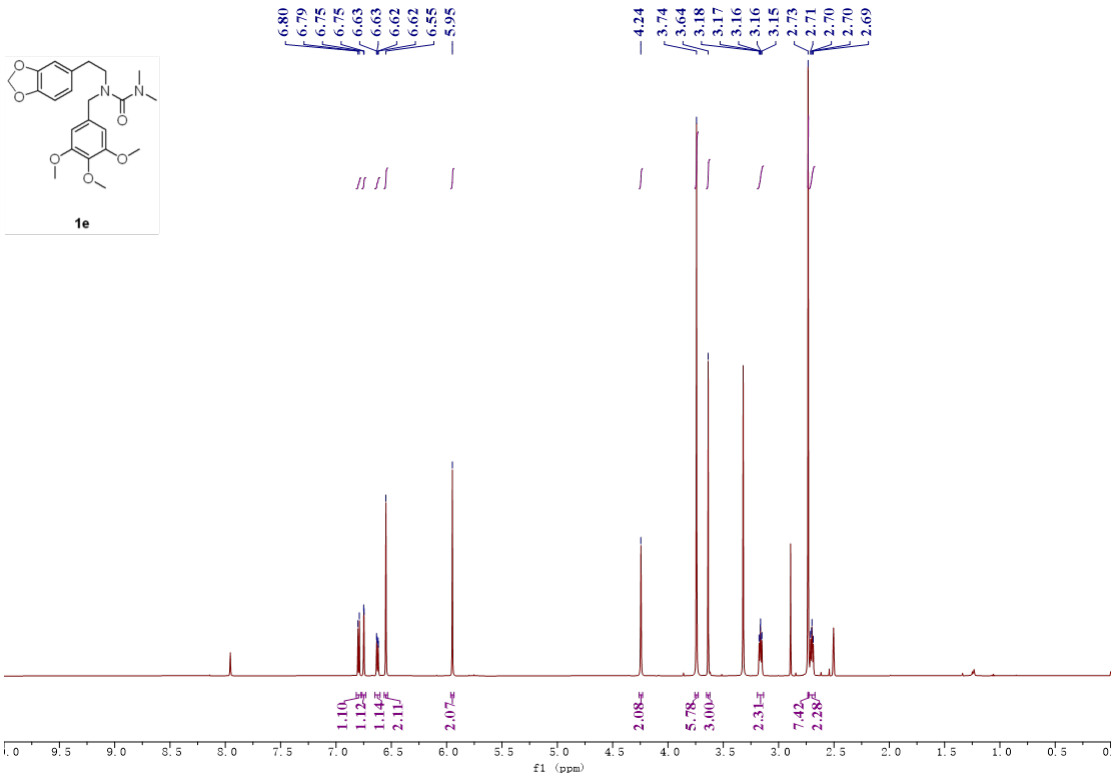
^{13}C NMR spectrum of compound **1c** in DMSO-d_6



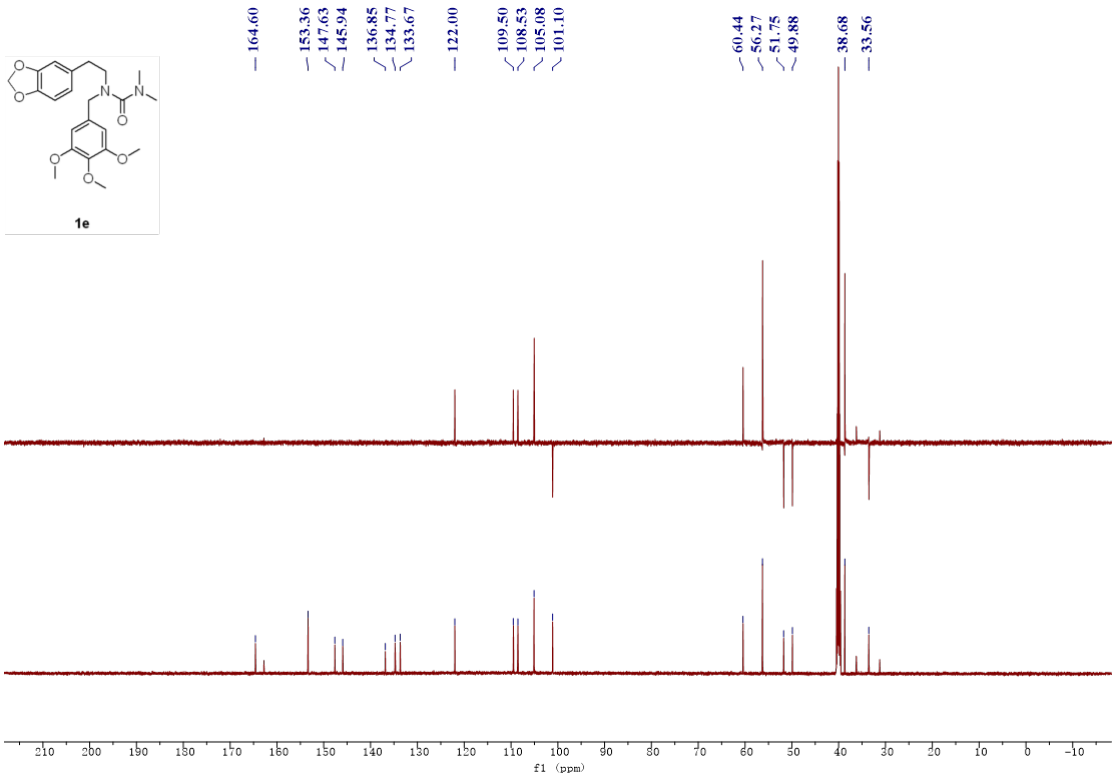
^{1}H NMR spectrum of compound **1d** in DMSO-d_6



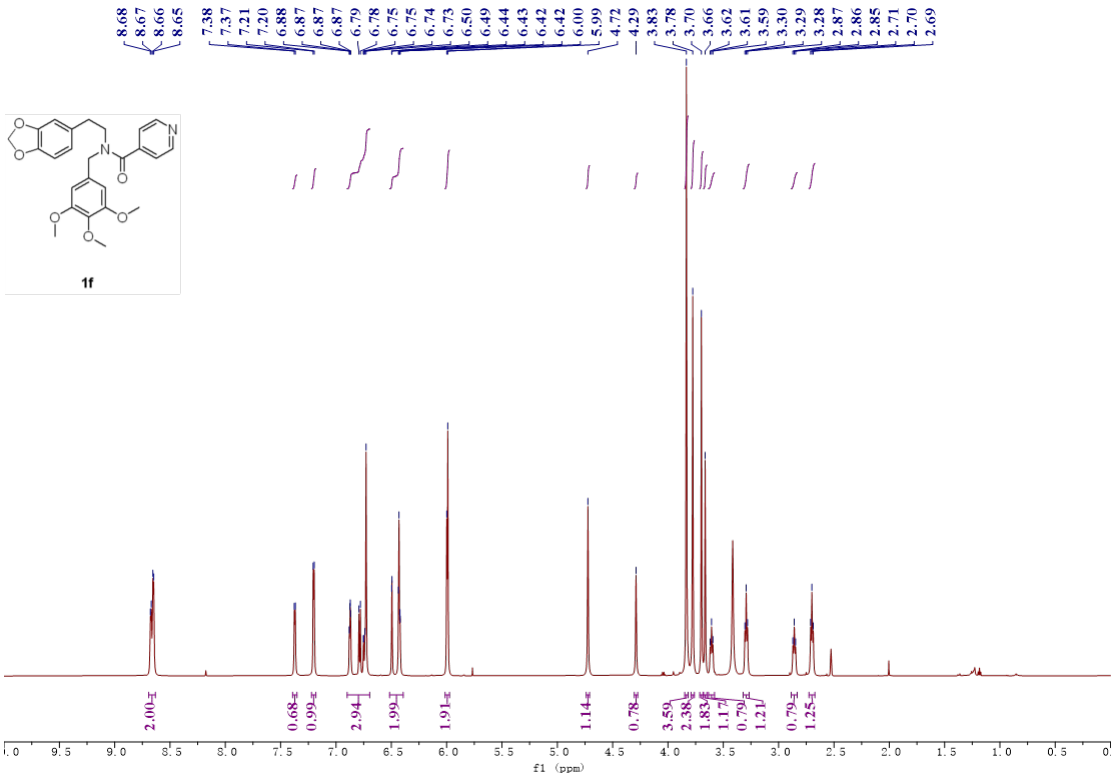
^{13}C NMR spectrum of compound **1d** in DMSO-d_6



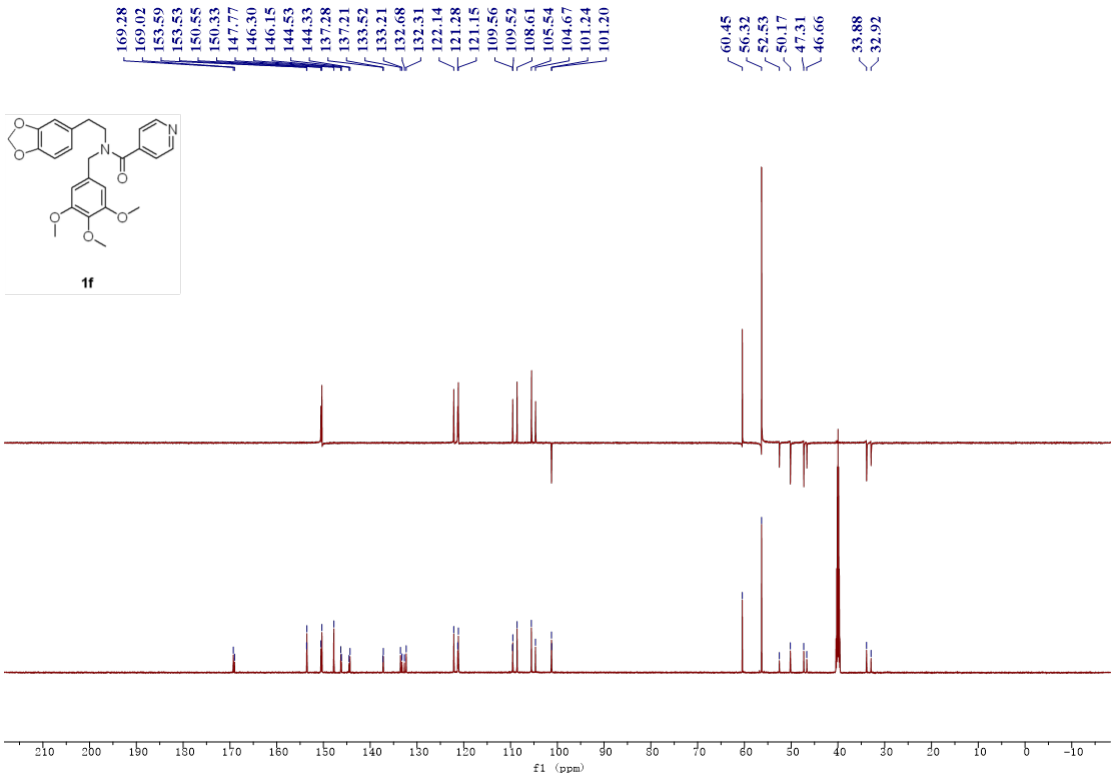
^{1}H NMR spectrum of compound **1e** in DMSO-d_6



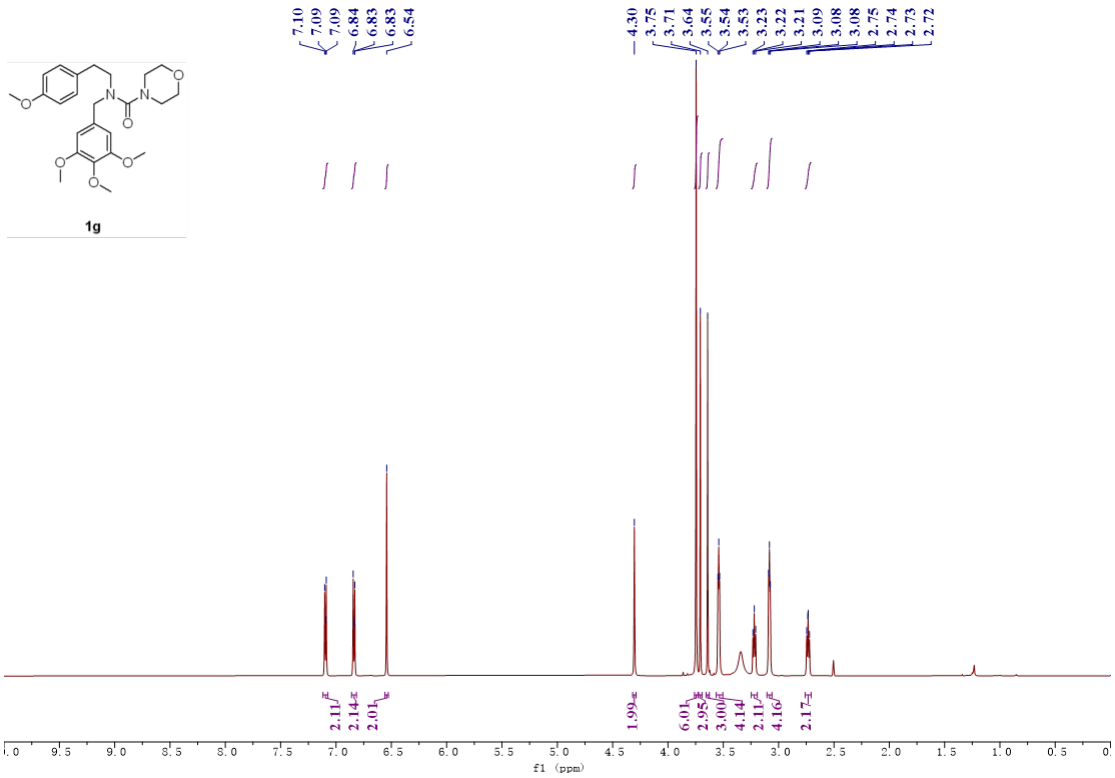
^{13}C NMR spectrum of compound **1e** in DMSO-d_6



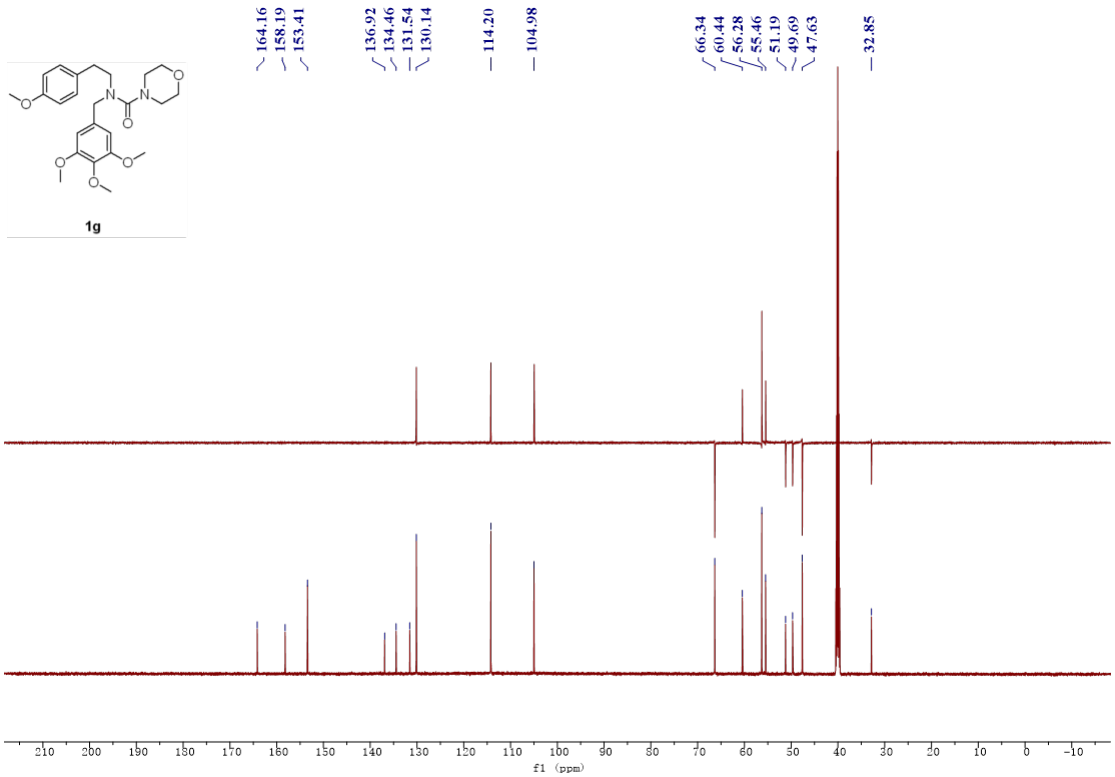
^{1}H NMR spectrum of compound **1f** in DMSO-d_6



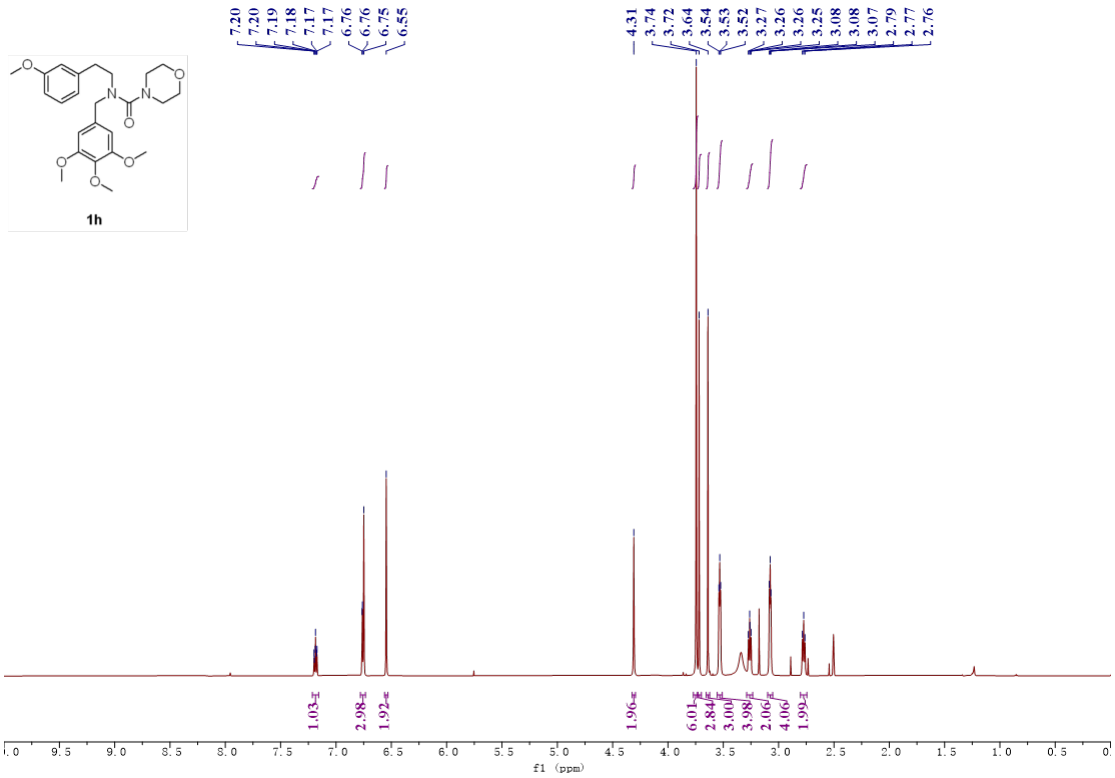
^{13}C NMR spectrum of compound **1f** in DMSO-d_6



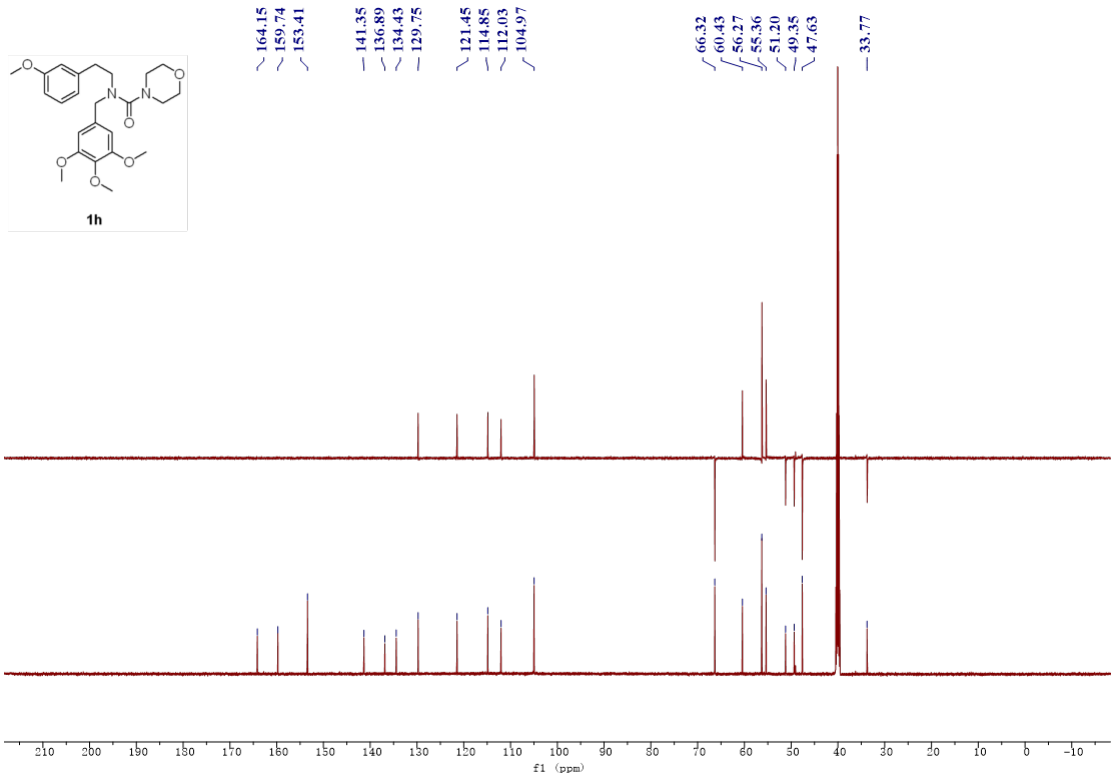
^{1}H NMR spectrum of compound **1g** in DMSO-d_6



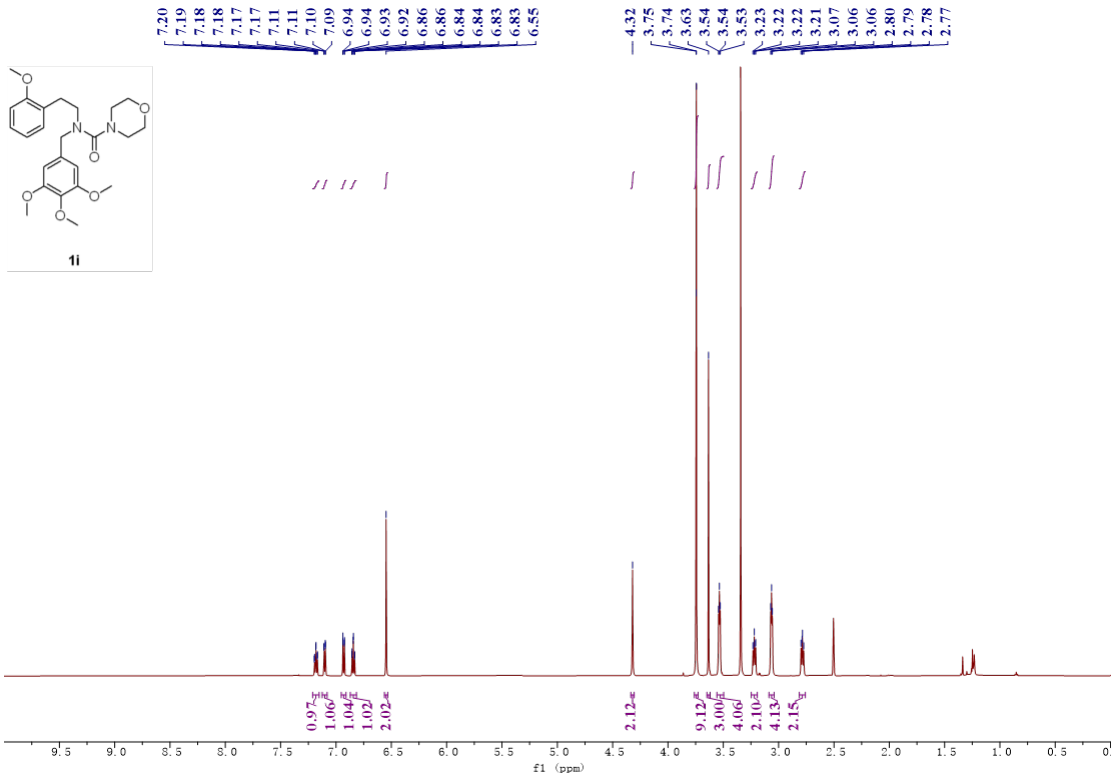
^{13}C NMR spectrum of compound **1g** in DMSO-d_6



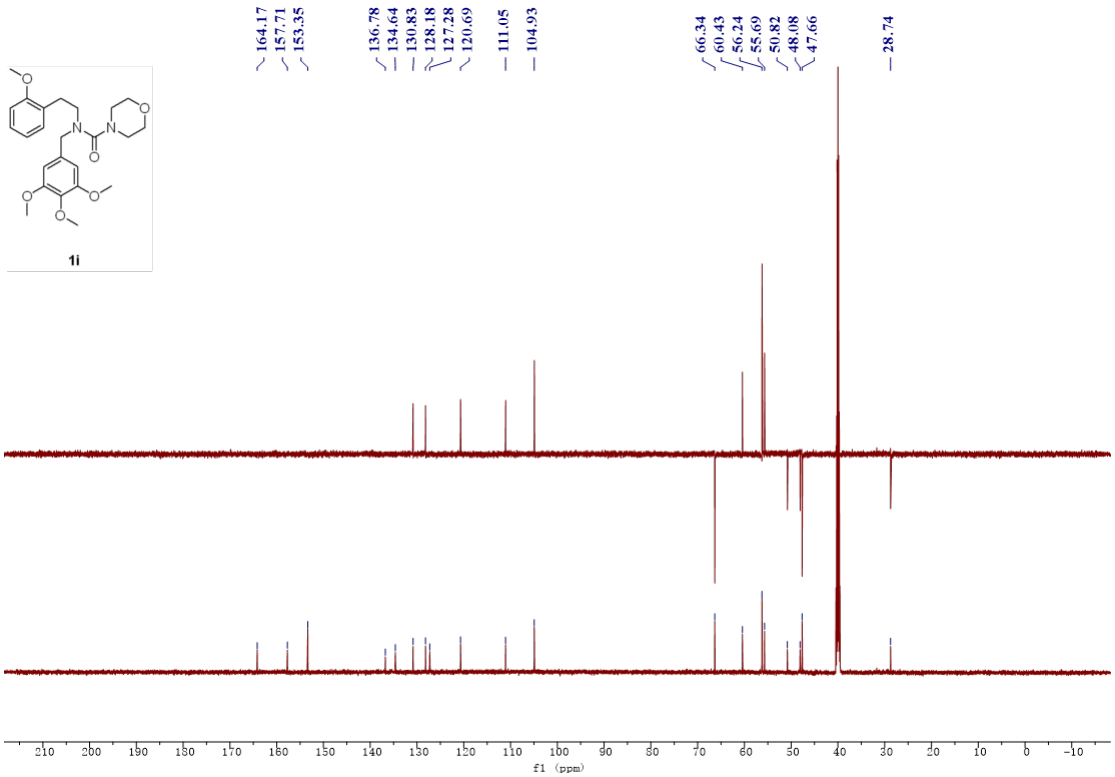
^{1}H NMR spectrum of compound **1h** in DMSO-d_6



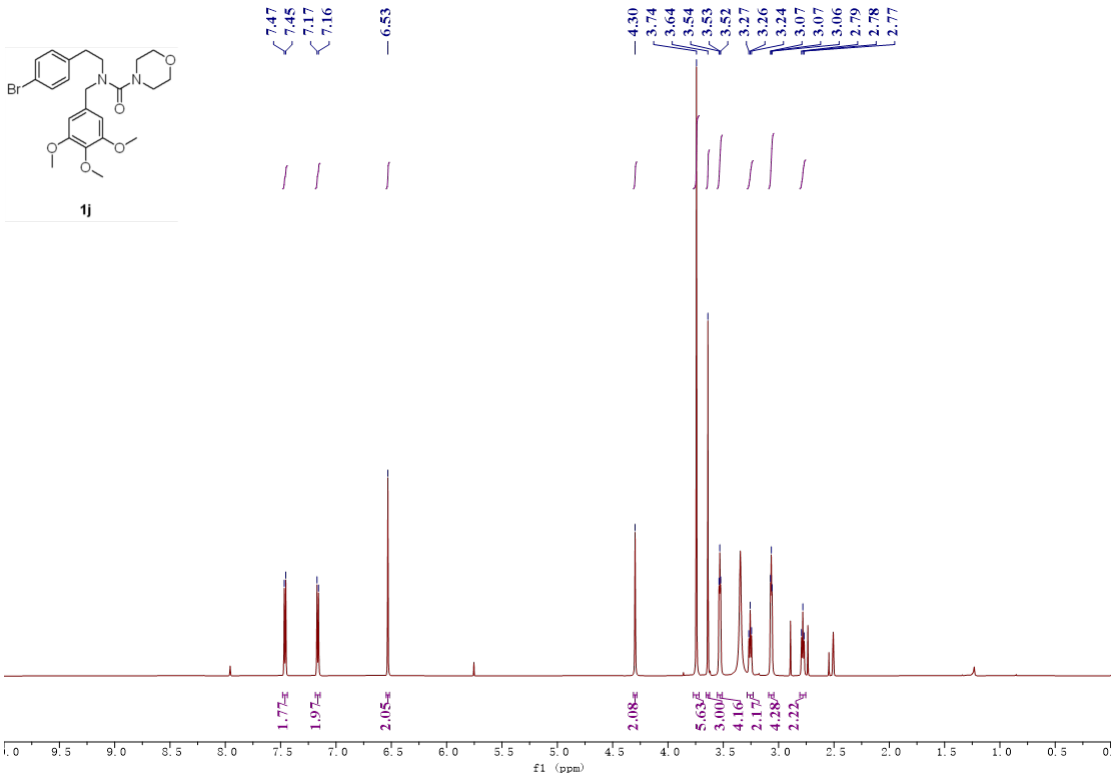
^{13}C NMR spectrum of compound **1h** in DMSO-d_6



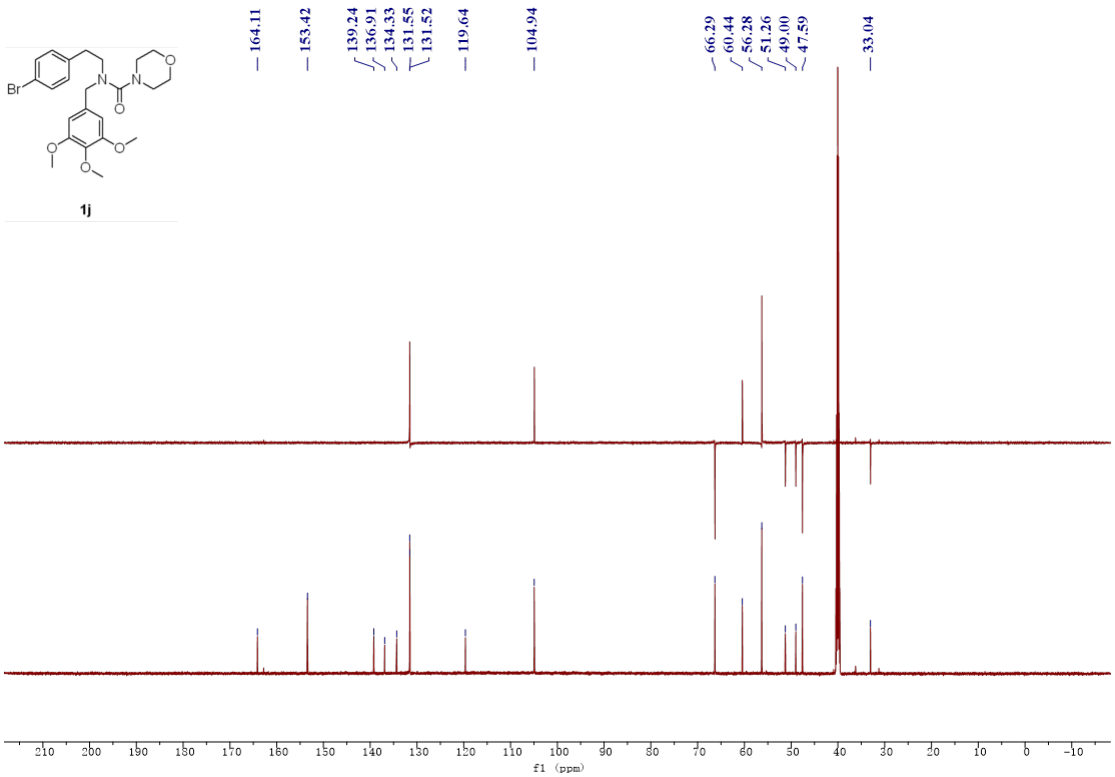
^{1}H NMR spectrum of compound **1i** in DMSO-d_6



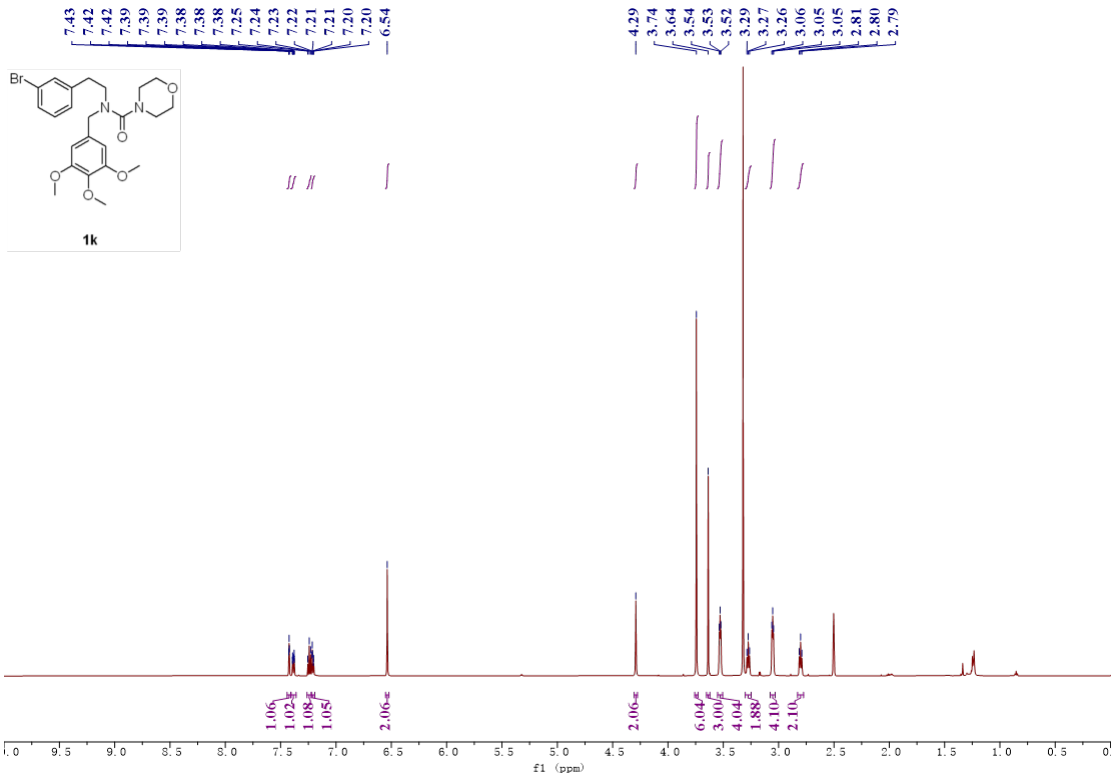
^{13}C NMR spectrum of compound **1i** in DMSO-d_6



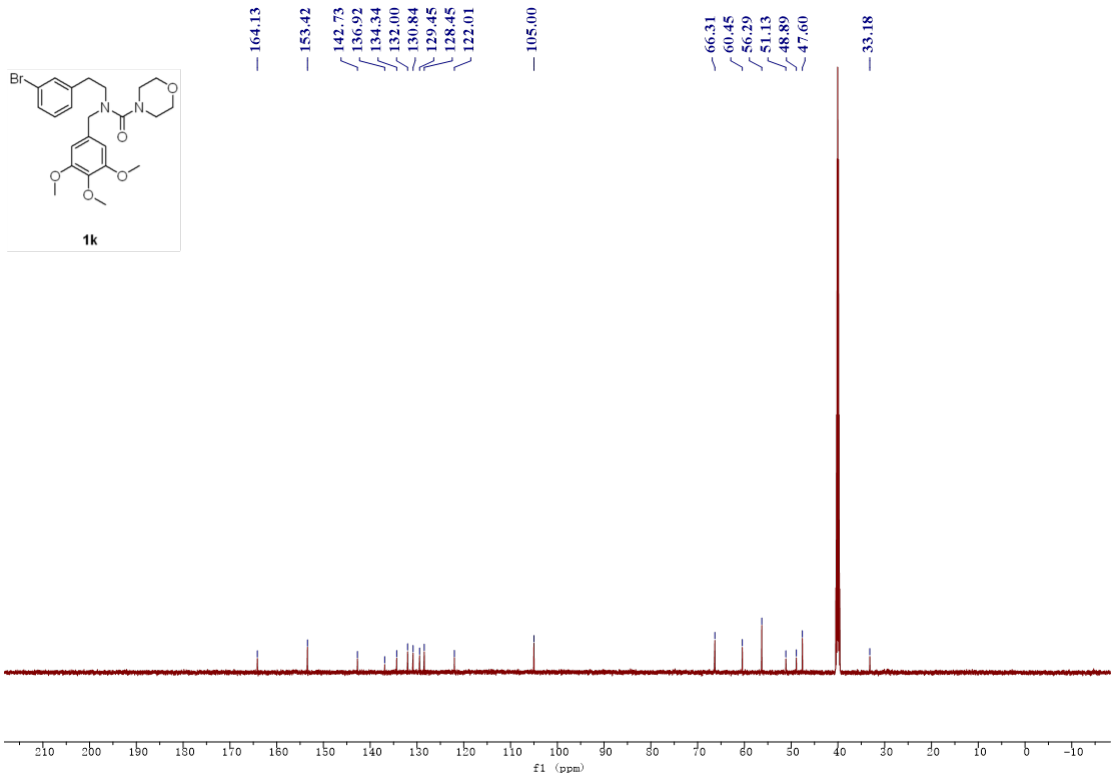
^{1}H NMR spectrum of compound **1j** in DMSO-d_6



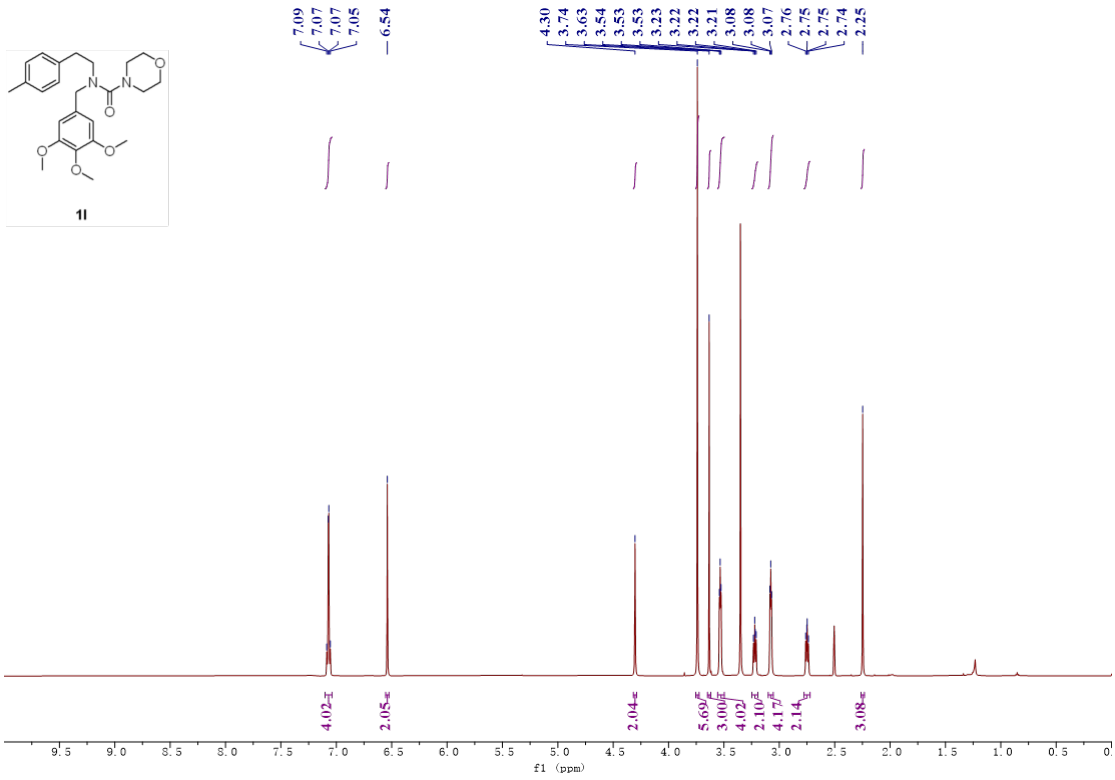
^{13}C NMR spectrum of compound **1j** in DMSO-d_6



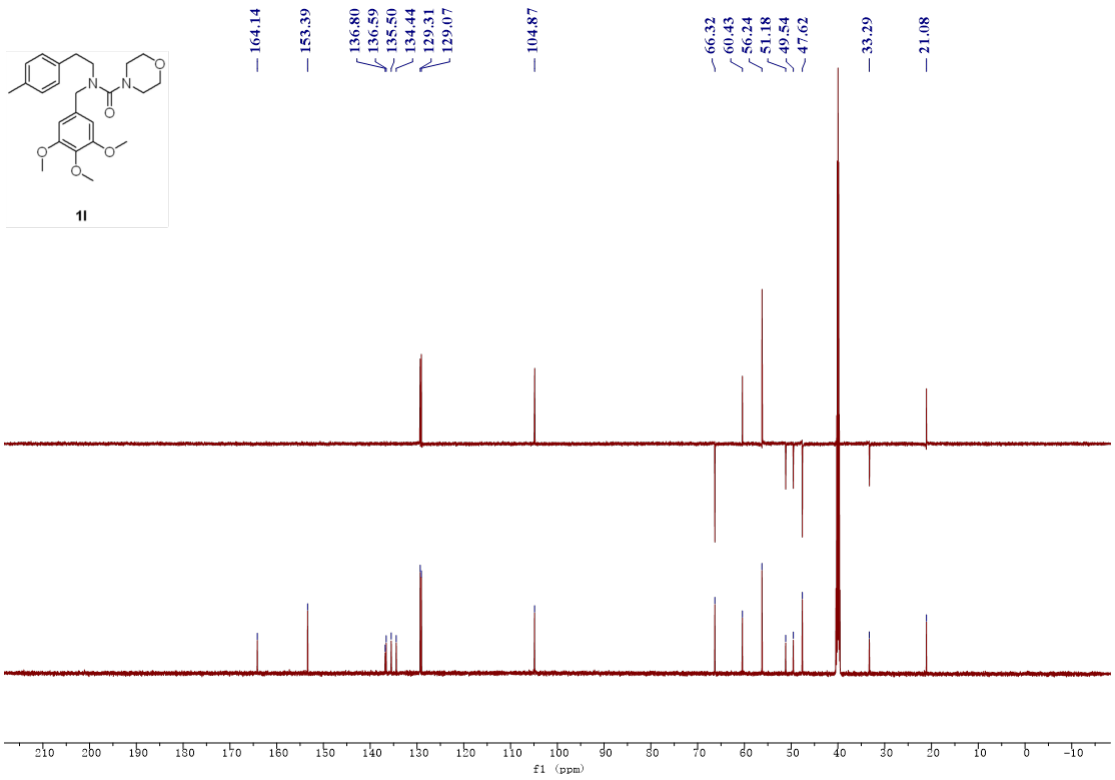
^{1}H NMR spectrum of compound **1k** in DMSO-d_6



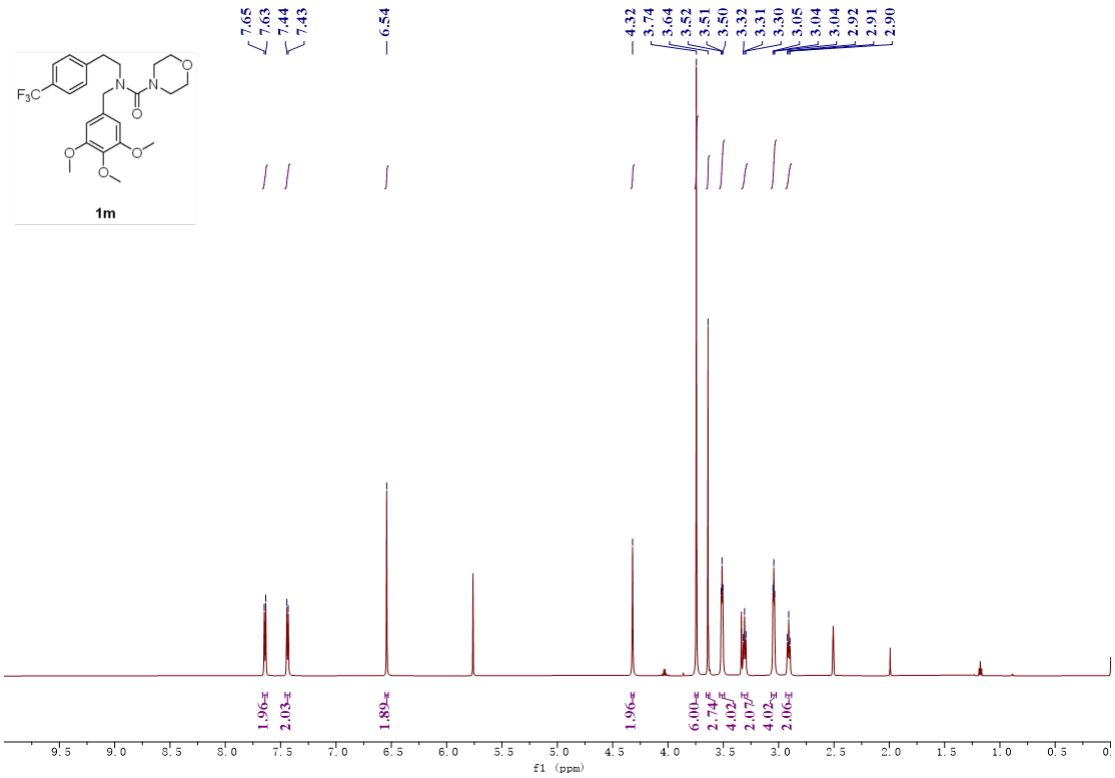
^{13}C NMR spectrum of compound **1k** in DMSO-d_6



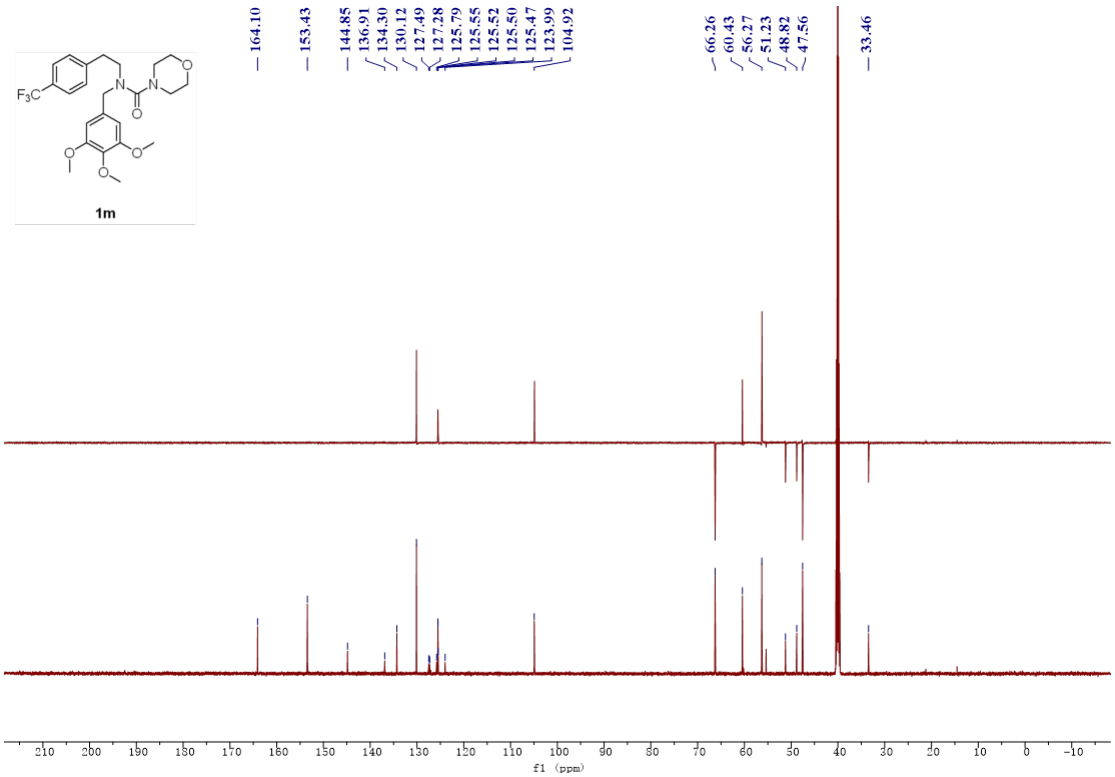
^{1}H NMR spectrum of compound **1l** in DMSO-d_6



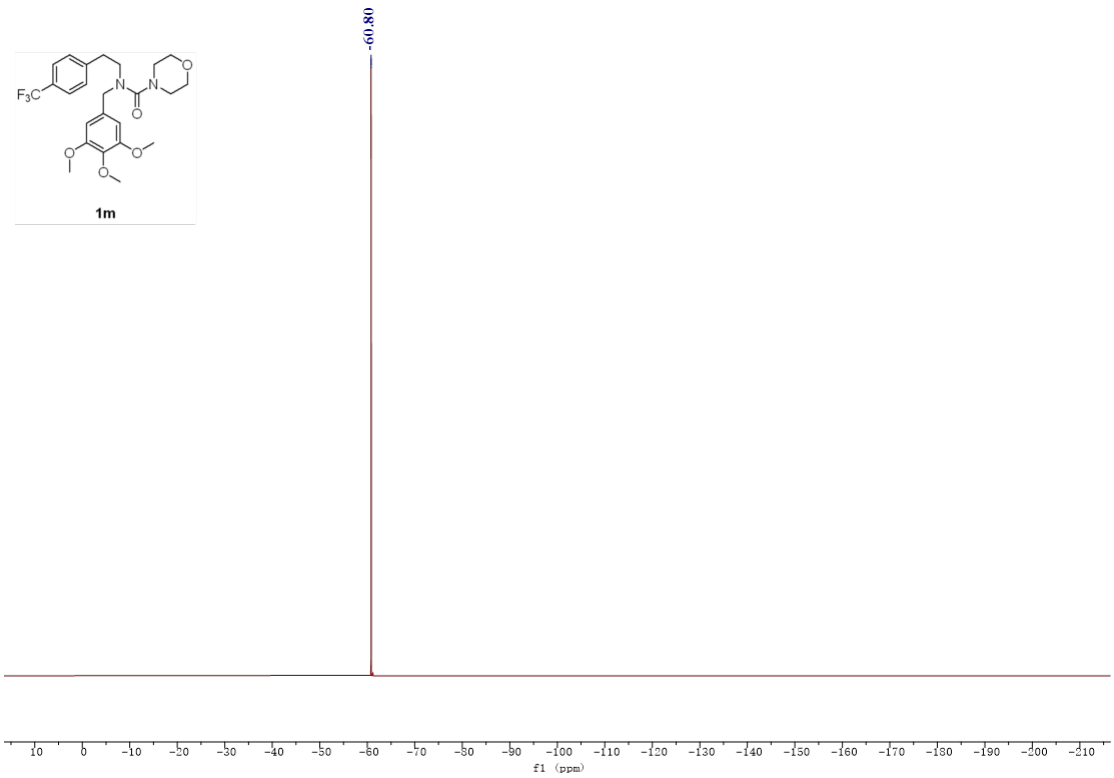
^{13}C NMR spectrum of compound **1l** in DMSO-d_6



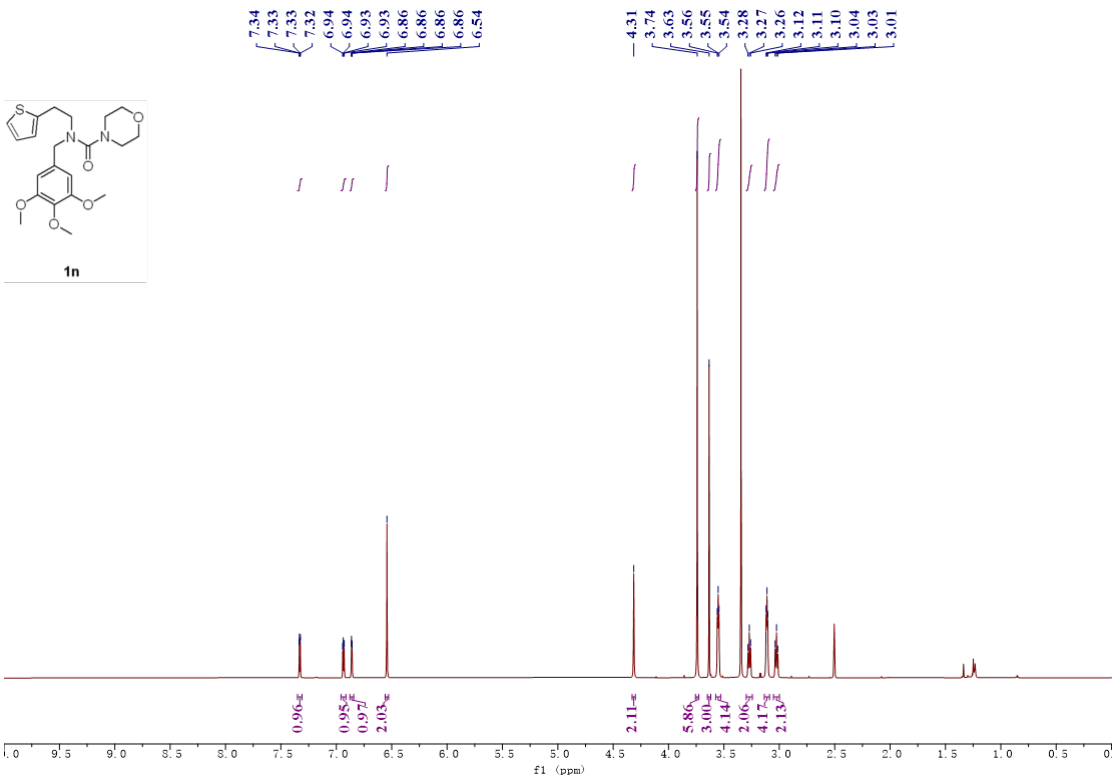
^{1}H NMR spectrum of compound **1m** in DMSO-d_6



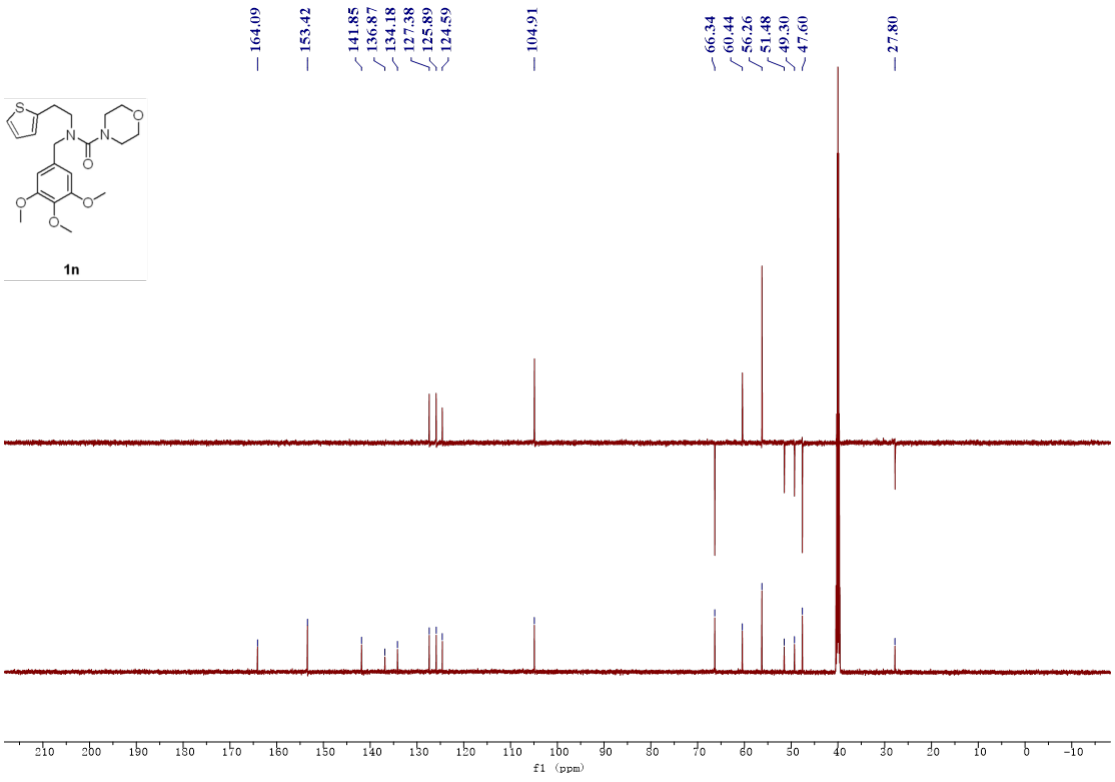
^{13}C NMR spectrum of compound **1m** in DMSO-d_6



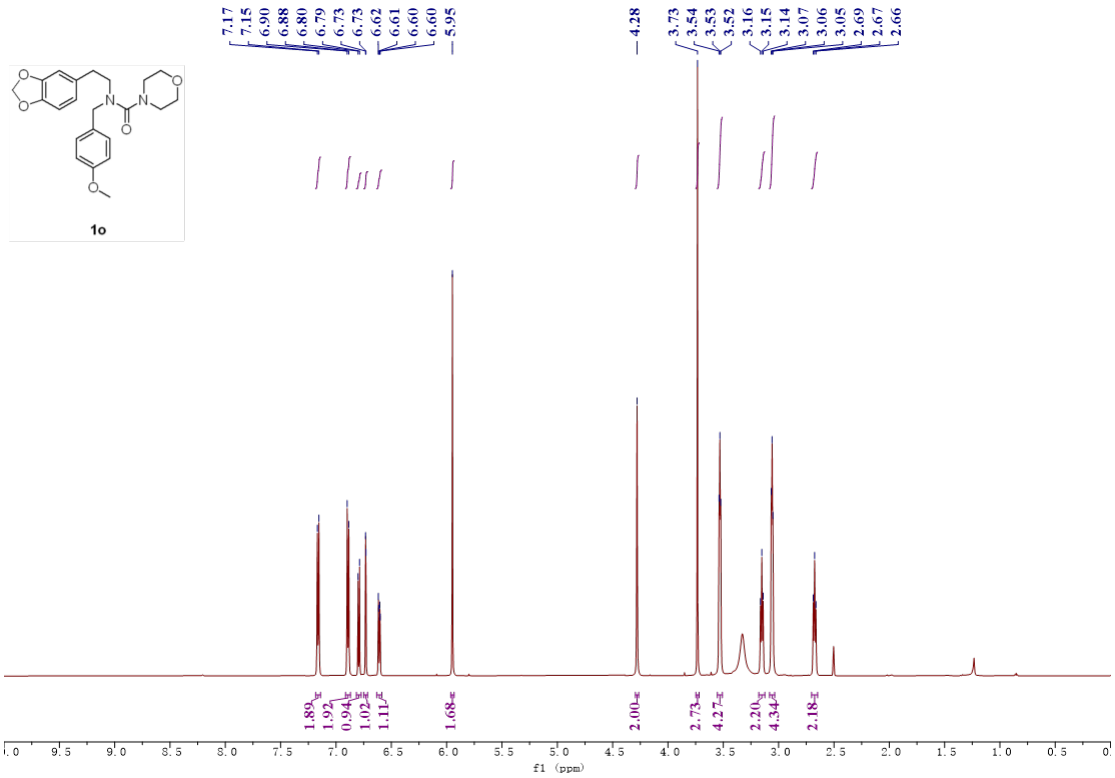
^{19}F NMR spectrum of compound **1m** in DMSO-d_6



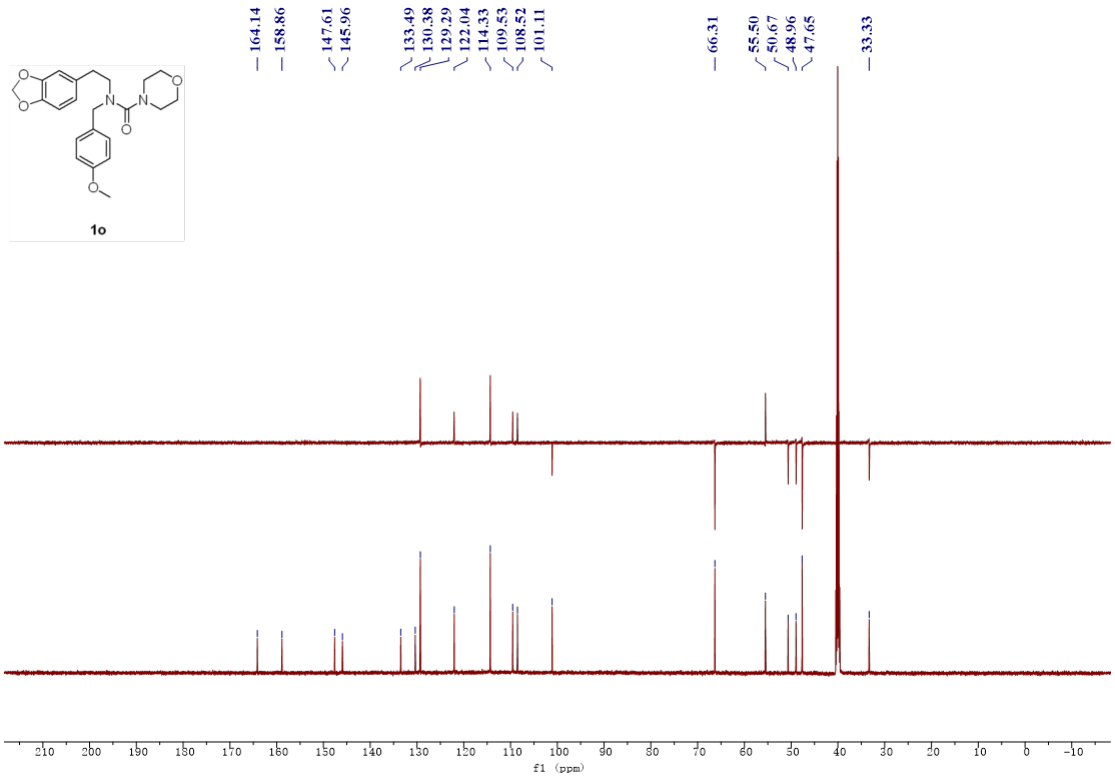
^{1}H NMR spectrum of compound **1n** in DMSO-d_6



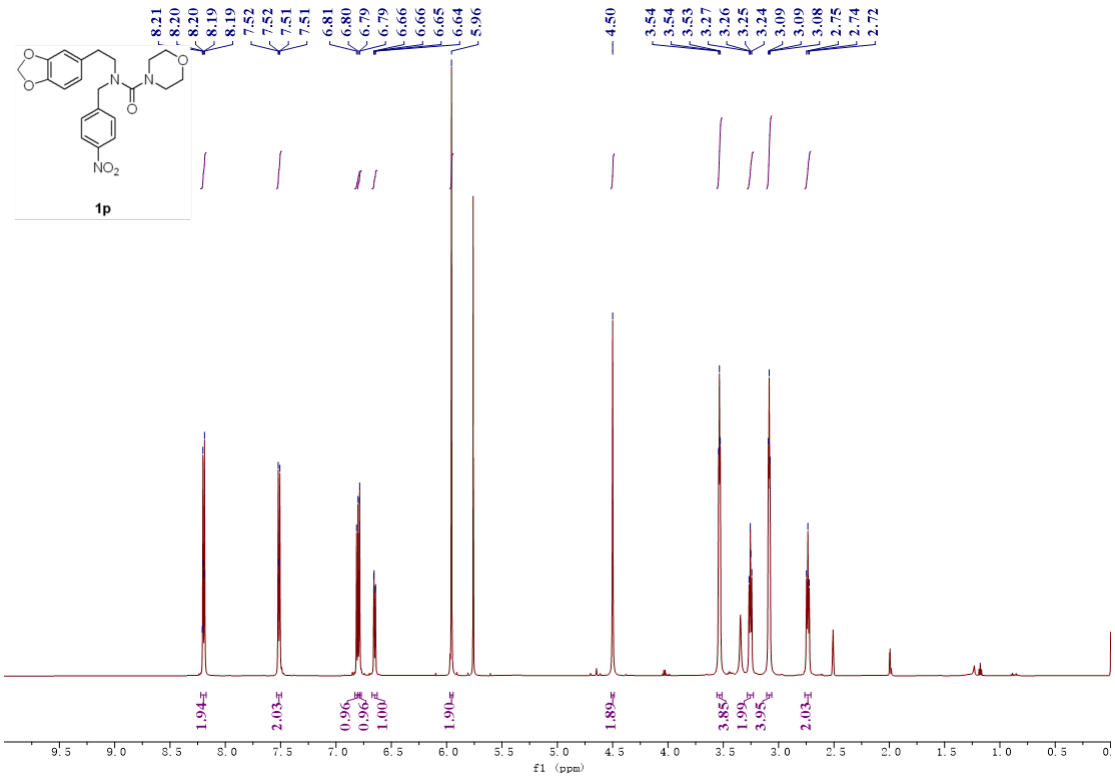
^{13}C NMR spectrum of compound **1n** in DMSO-d_6



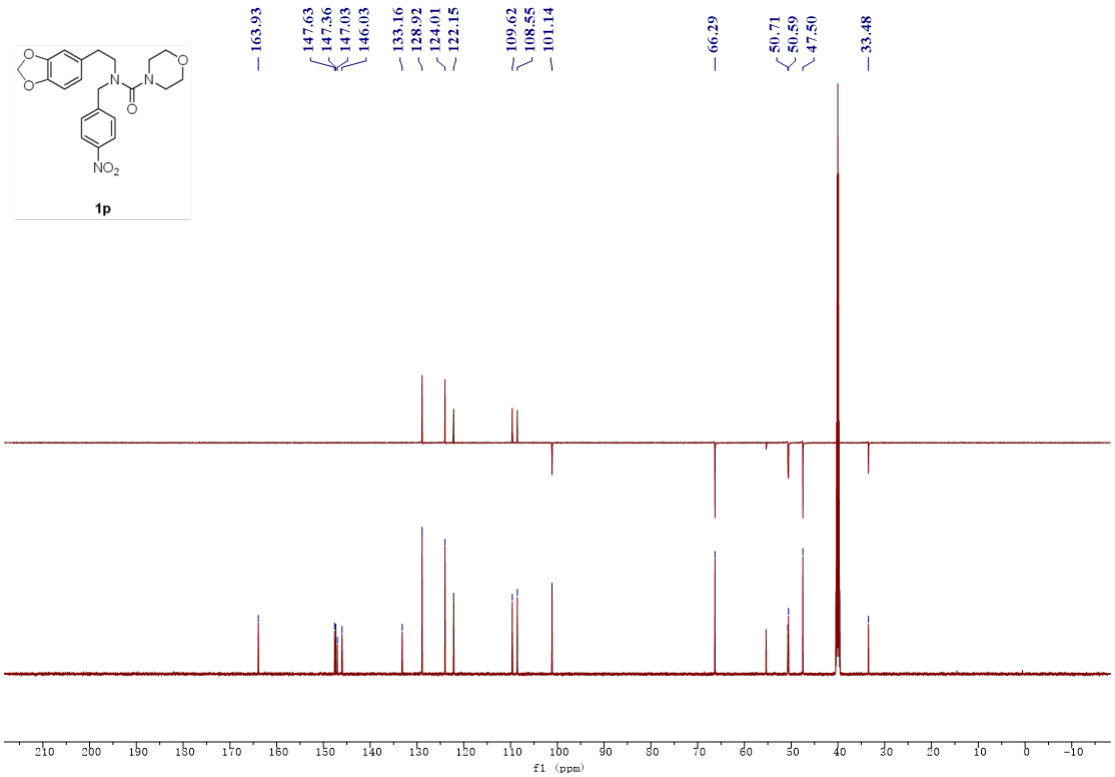
^{1}H NMR spectrum of compound **1o** in DMSO-d_6



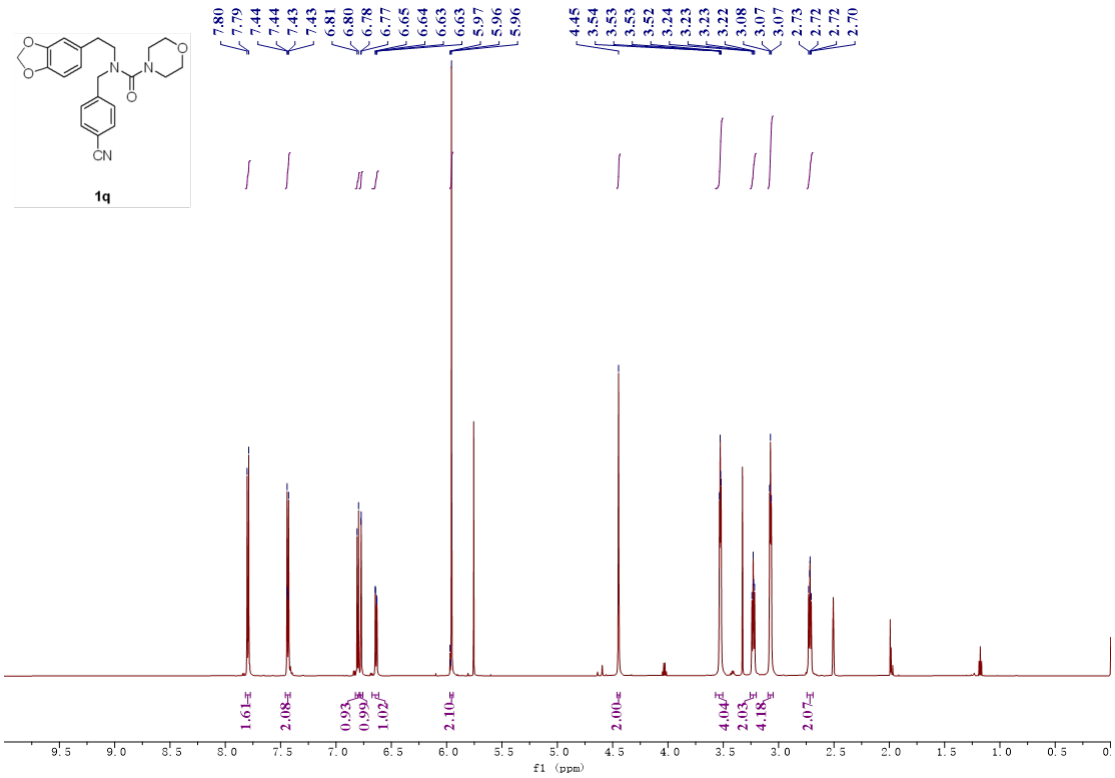
^{13}C NMR spectrum of compound **1o** in DMSO-d_6



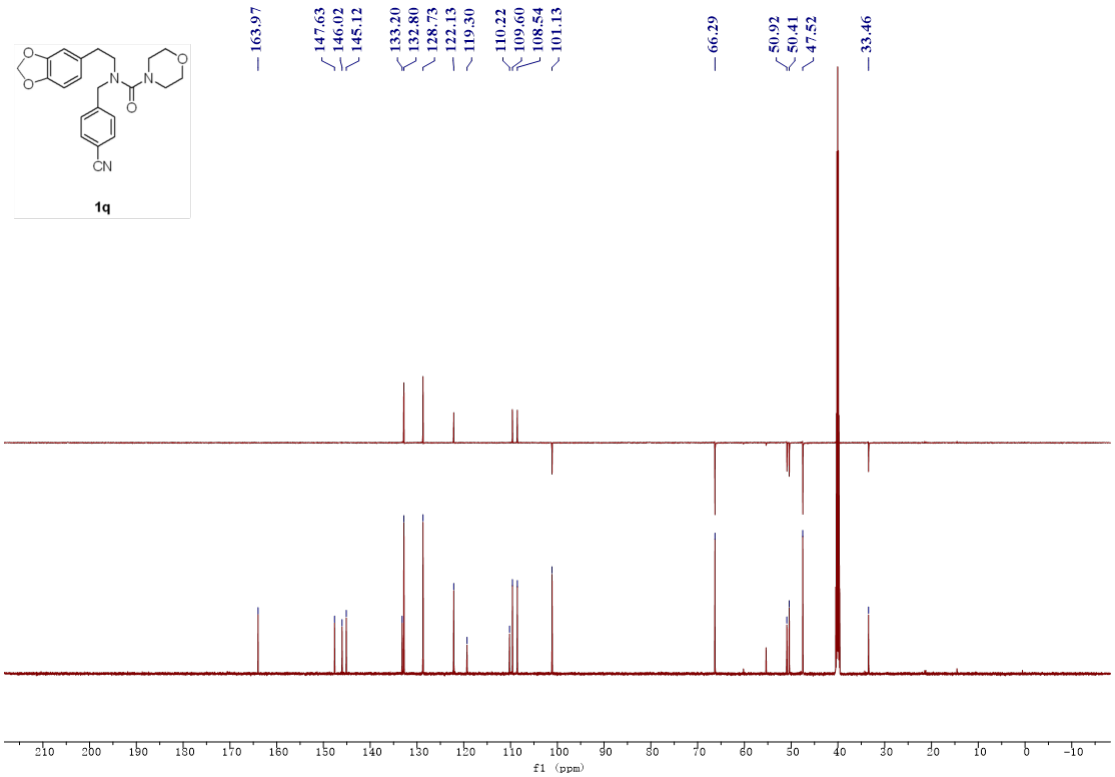
^{1}H NMR spectrum of compound **1p** in DMSO-d_6



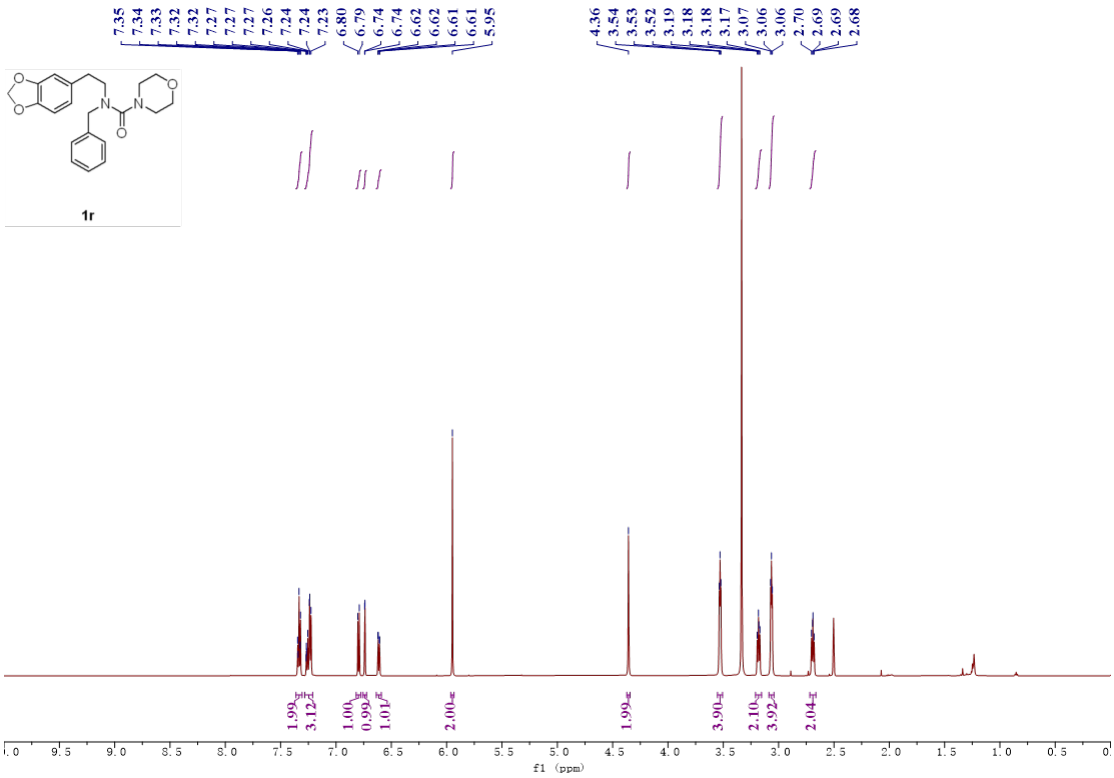
^{13}C NMR spectrum of compound **1p** in DMSO-d_6



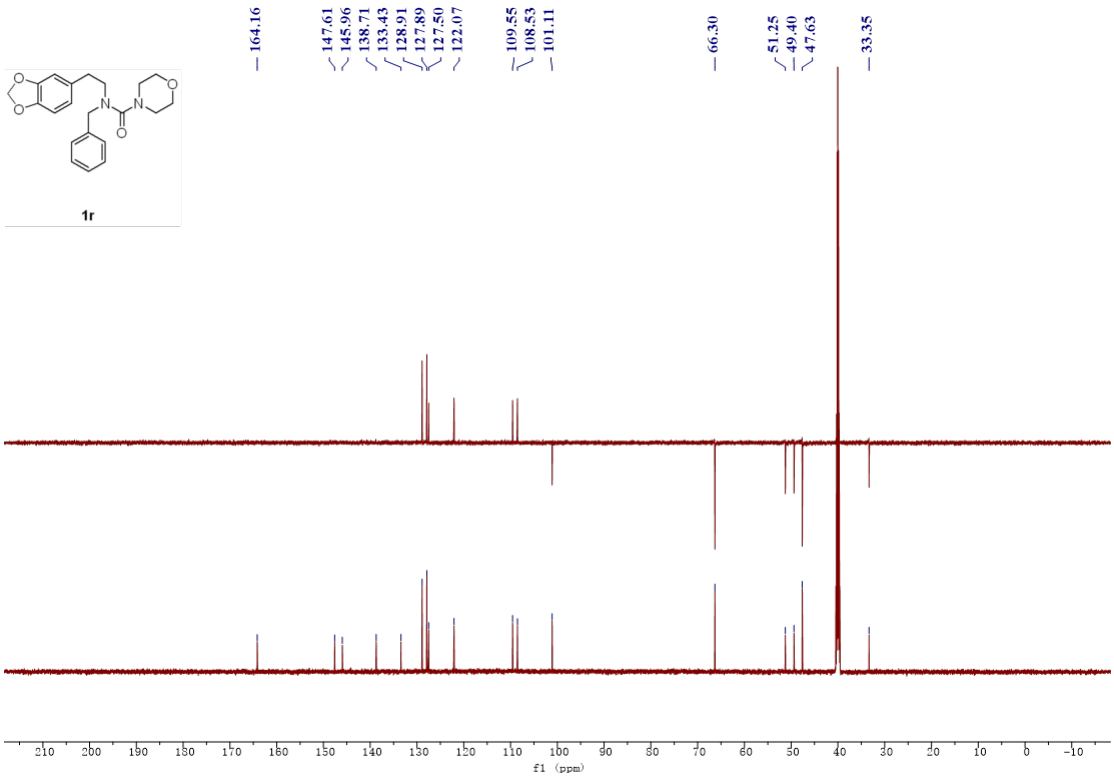
^{1}H NMR spectrum of compound **1q** in DMSO-d_6



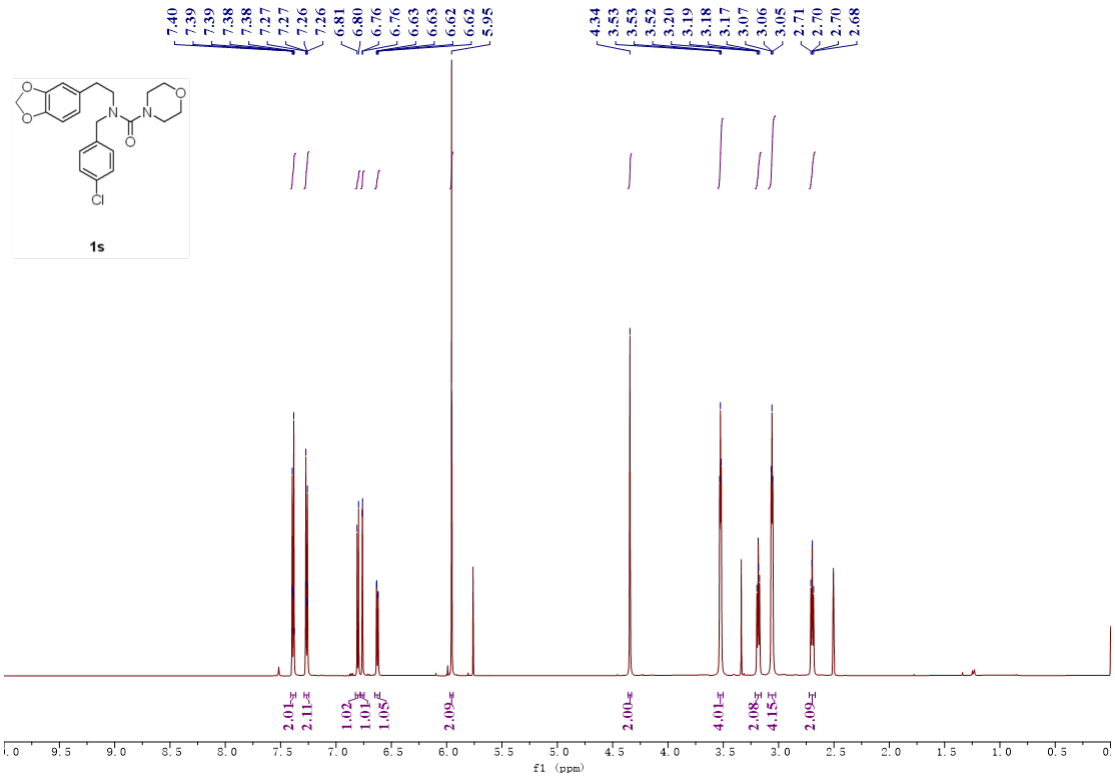
^{13}C NMR spectrum of compound **1q** in DMSO-d_6



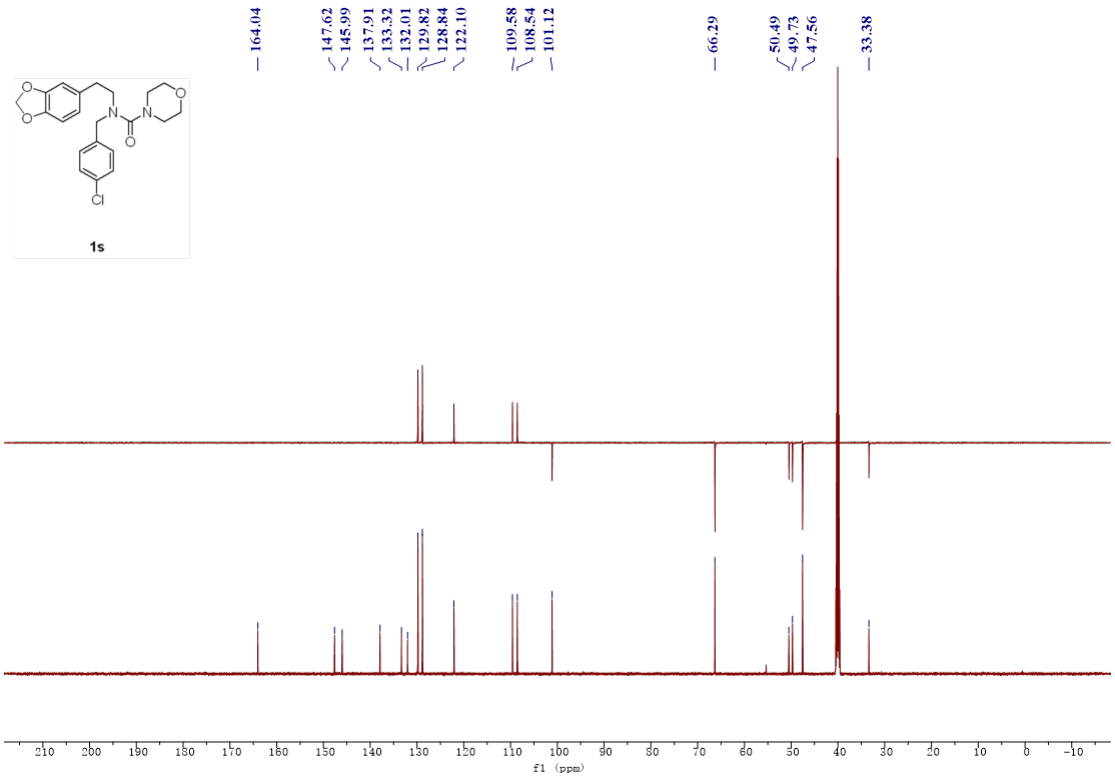
^{1}H NMR spectrum of compound **1r** in DMSO-d_6



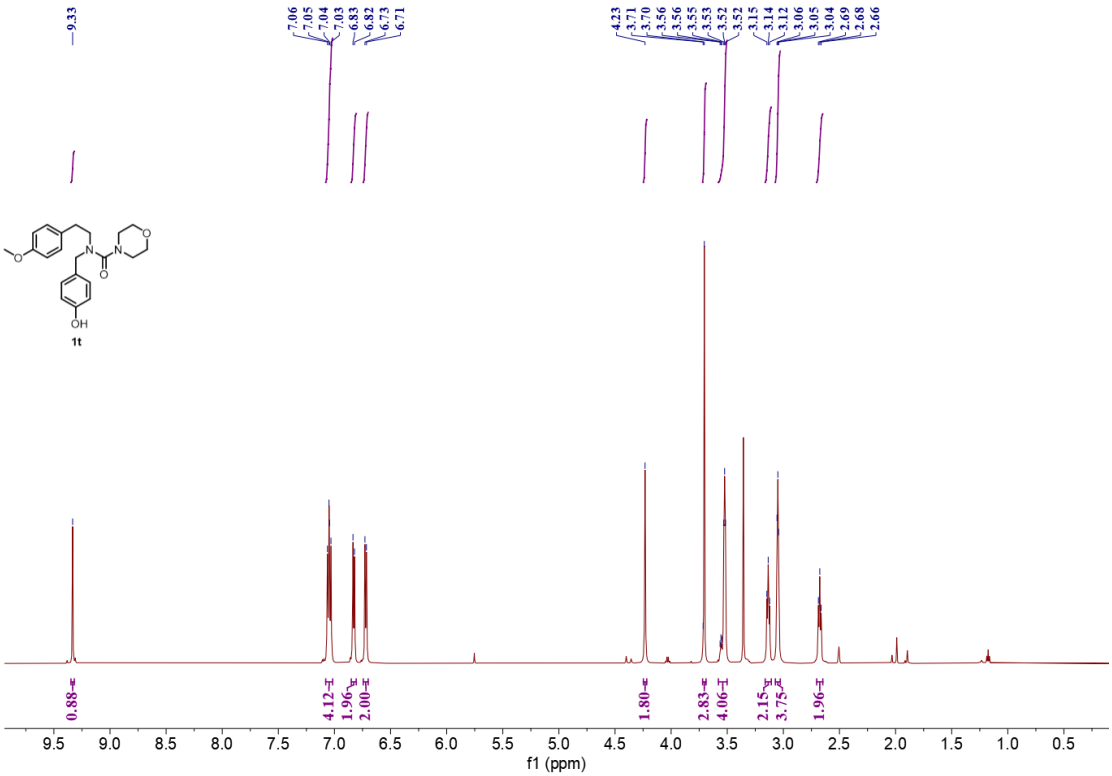
^{13}C NMR spectrum of compound **1r** in DMSO-d_6



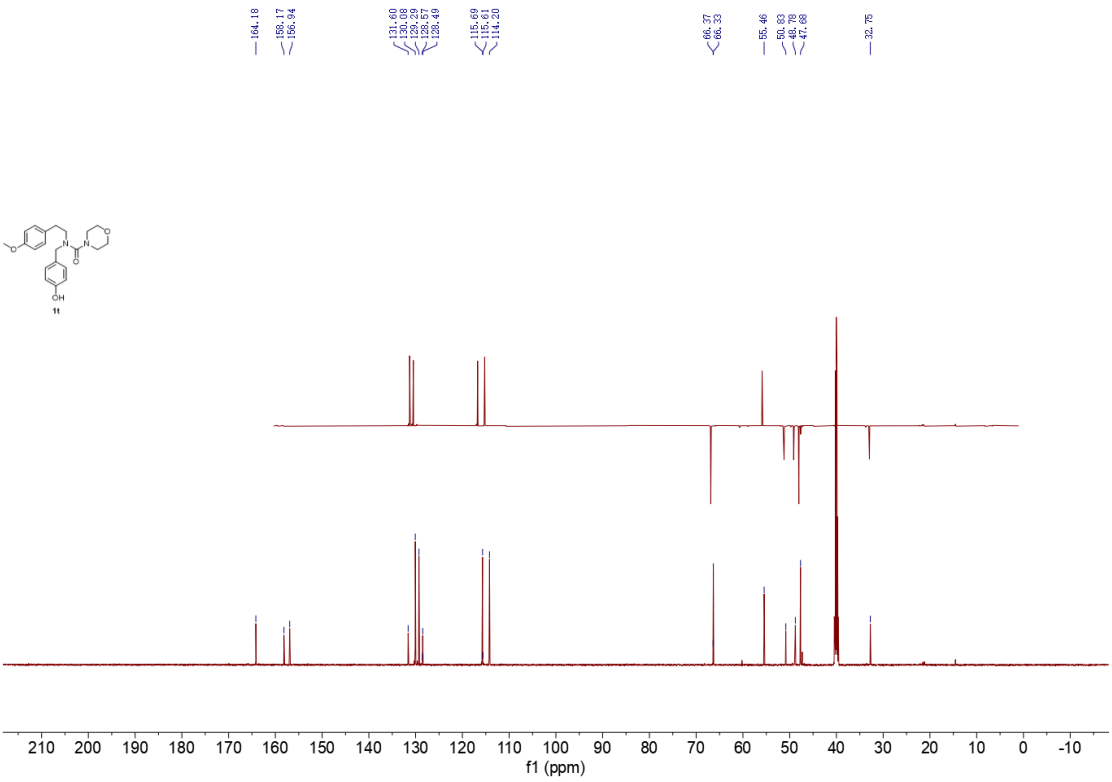
^{1}H NMR spectrum of compound **1s** in DMSO-d_6



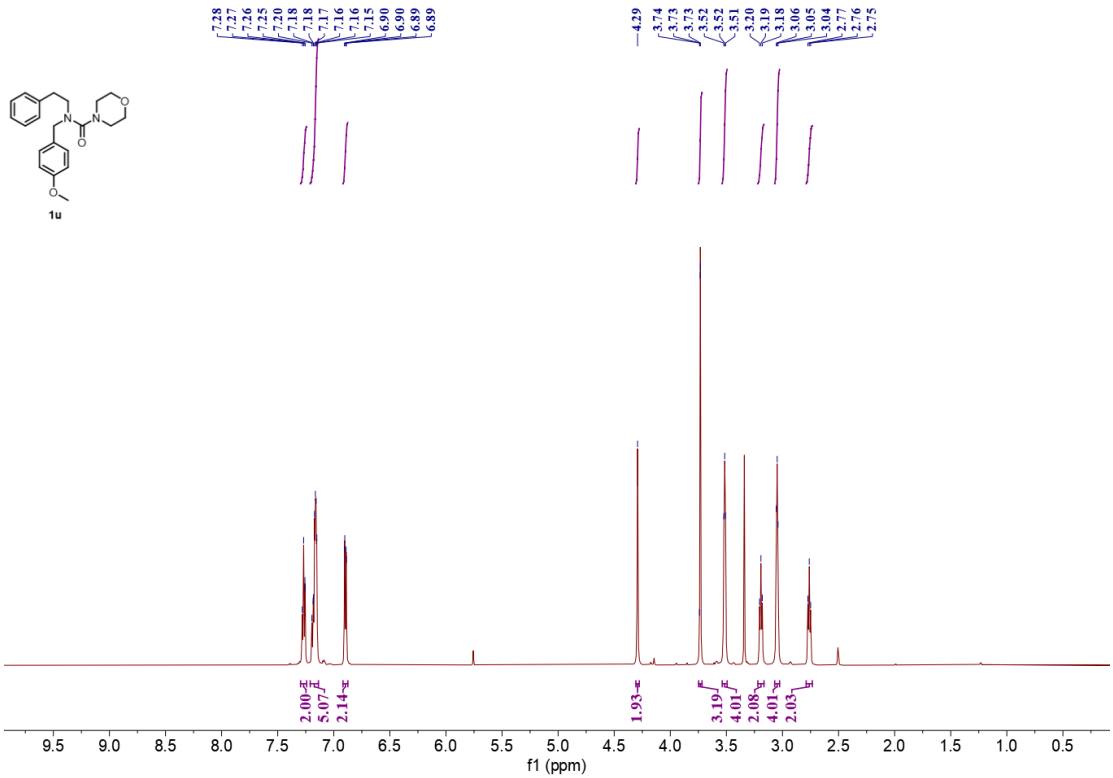
^{13}C NMR spectrum of compound **1s** in DMSO-d_6



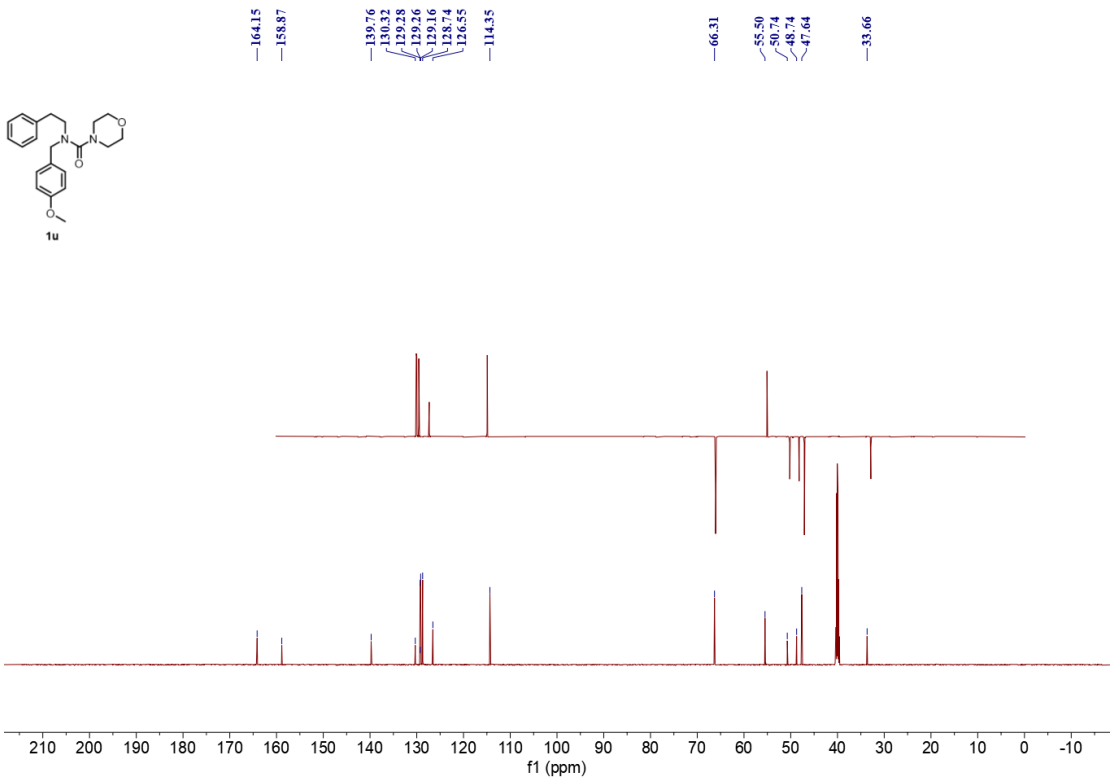
^{1}H NMR spectrum of compound **1t** in DMSO-d_6



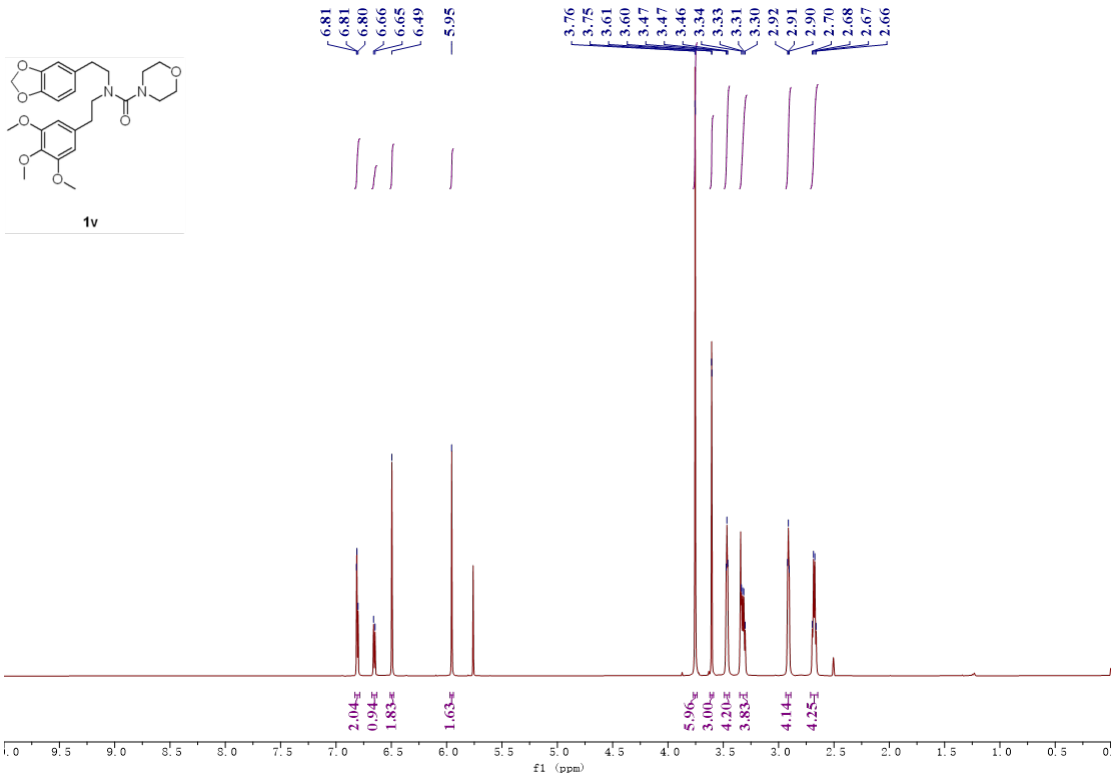
^{13}C NMR spectrum of compound **1t** in DMSO-d_6



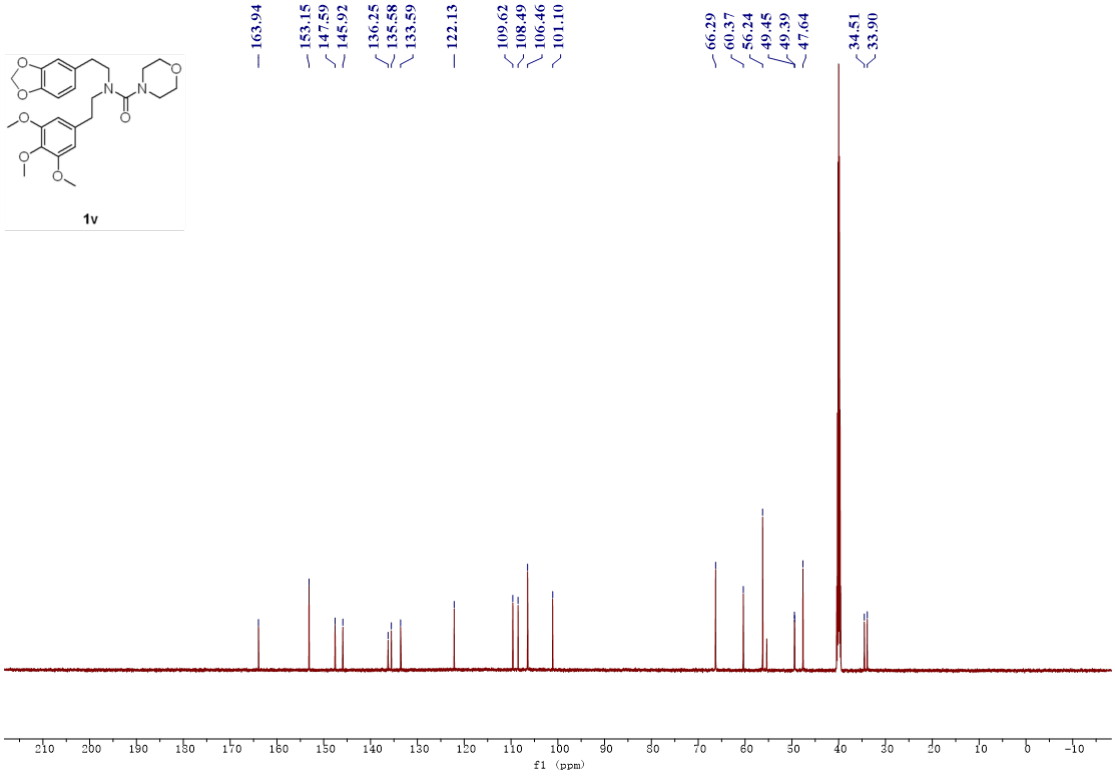
^{1}H NMR spectrum of compound **1u** in DMSO-d_6



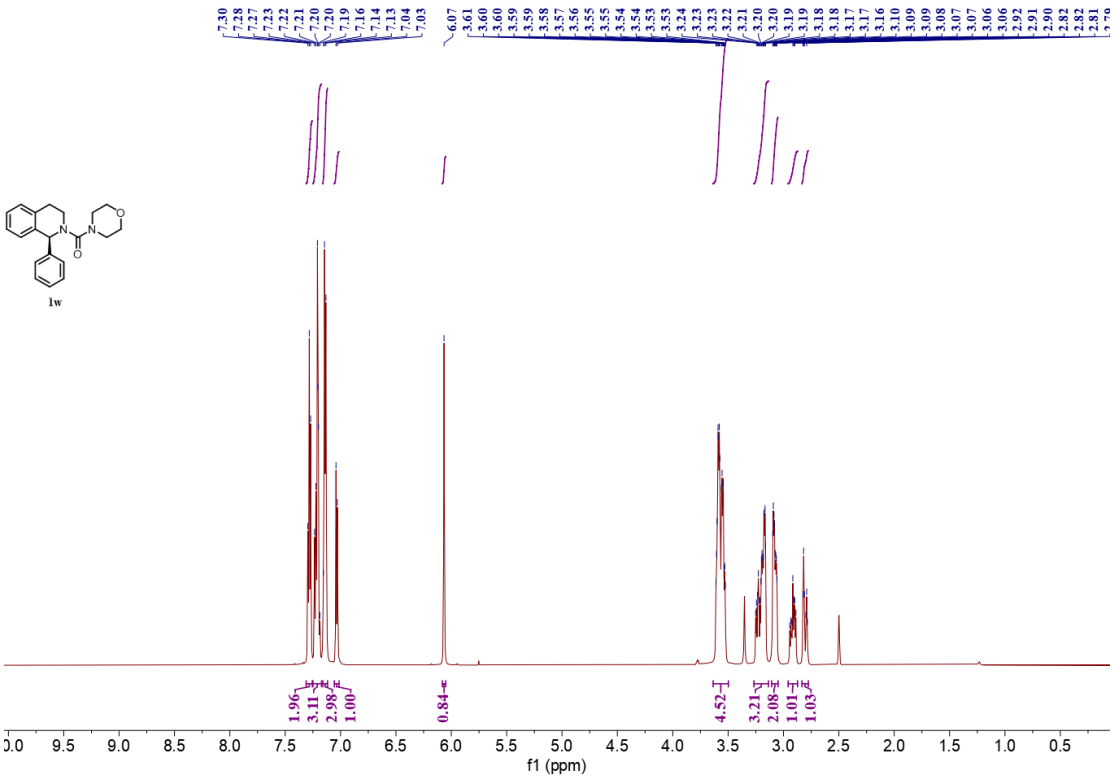
^{13}C NMR spectrum of compound **1u** in DMSO-d_6



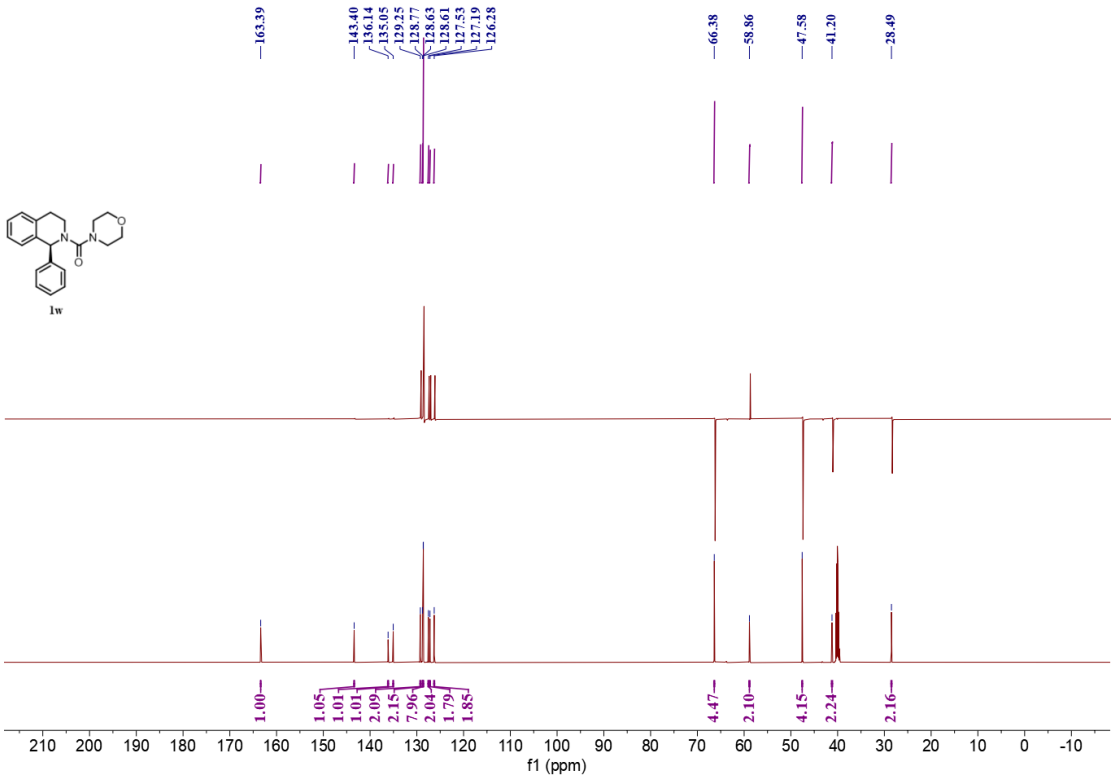
^{1}H NMR spectrum of compound **1v** in DMSO-d_6



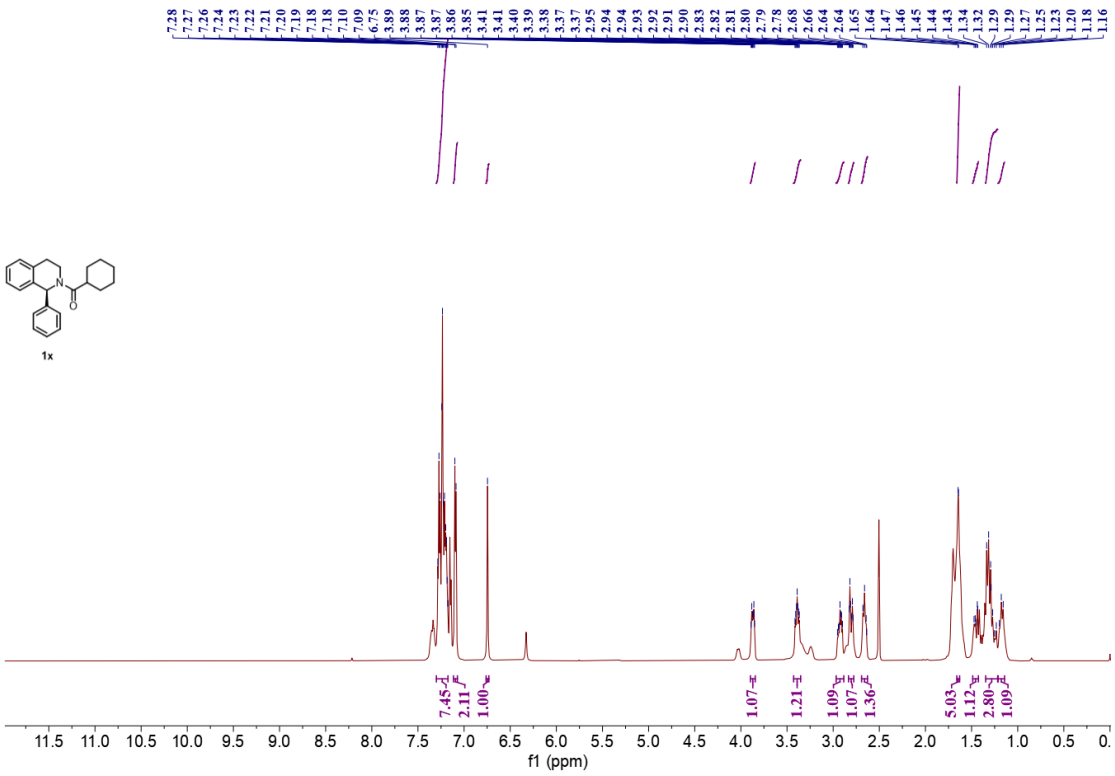
^{13}C NMR spectrum of compound **1v** in DMSO-d_6



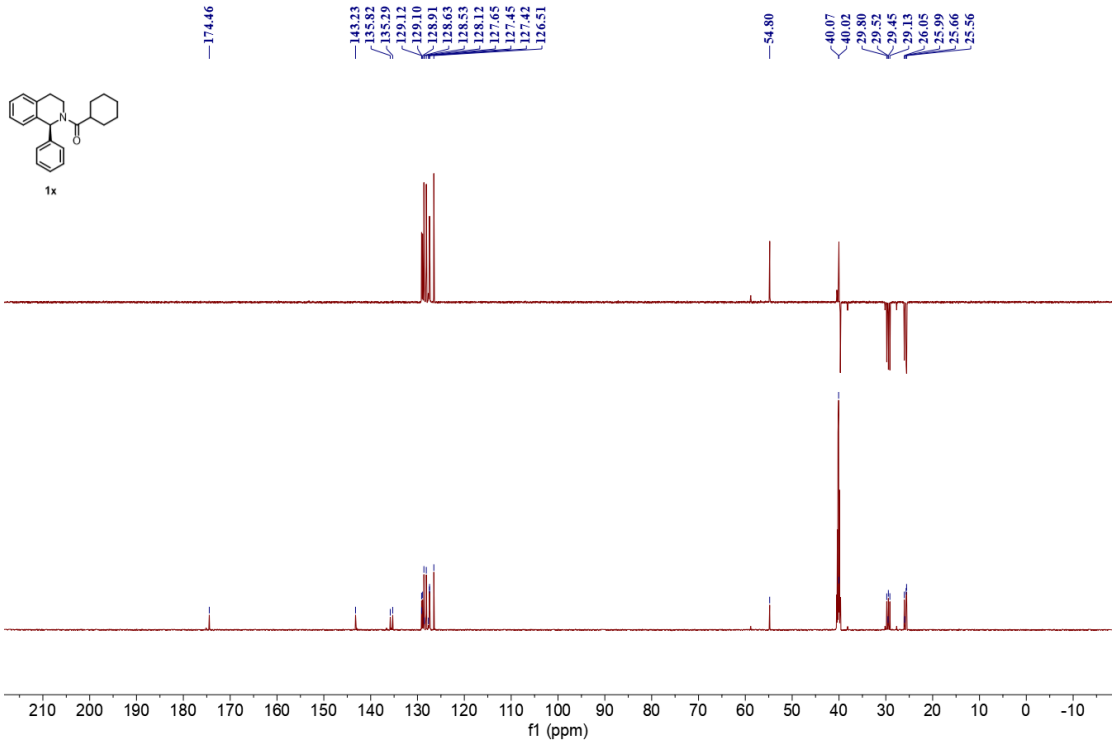
^{1}H NMR spectrum of compound **1w** in DMSO-d_6



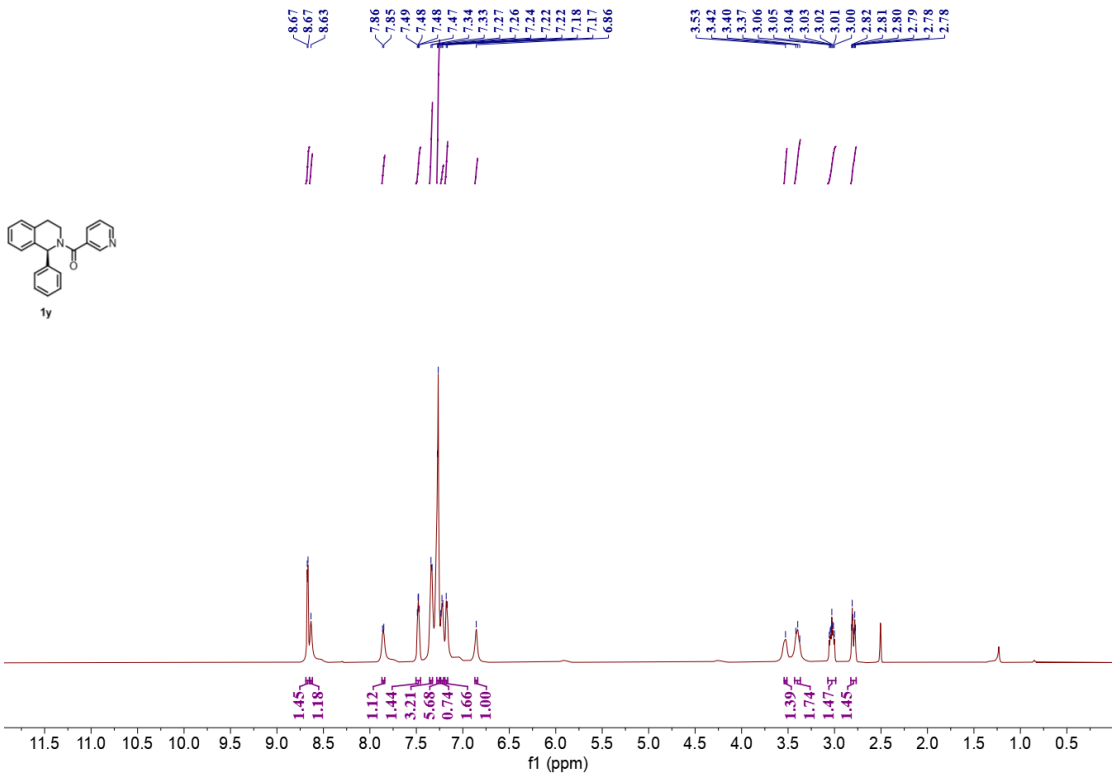
^{13}C NMR spectrum of compound **1w** in DMSO-d_6



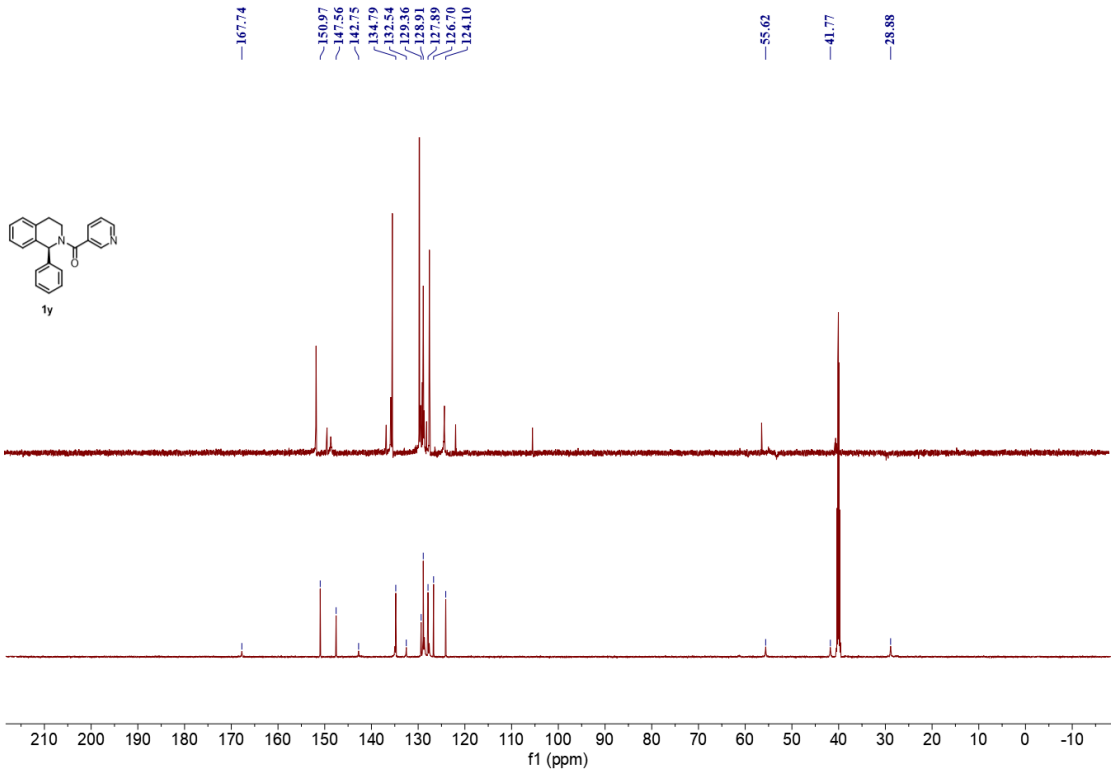
^{1}H NMR spectrum of compound **1x** in DMSO-d_6



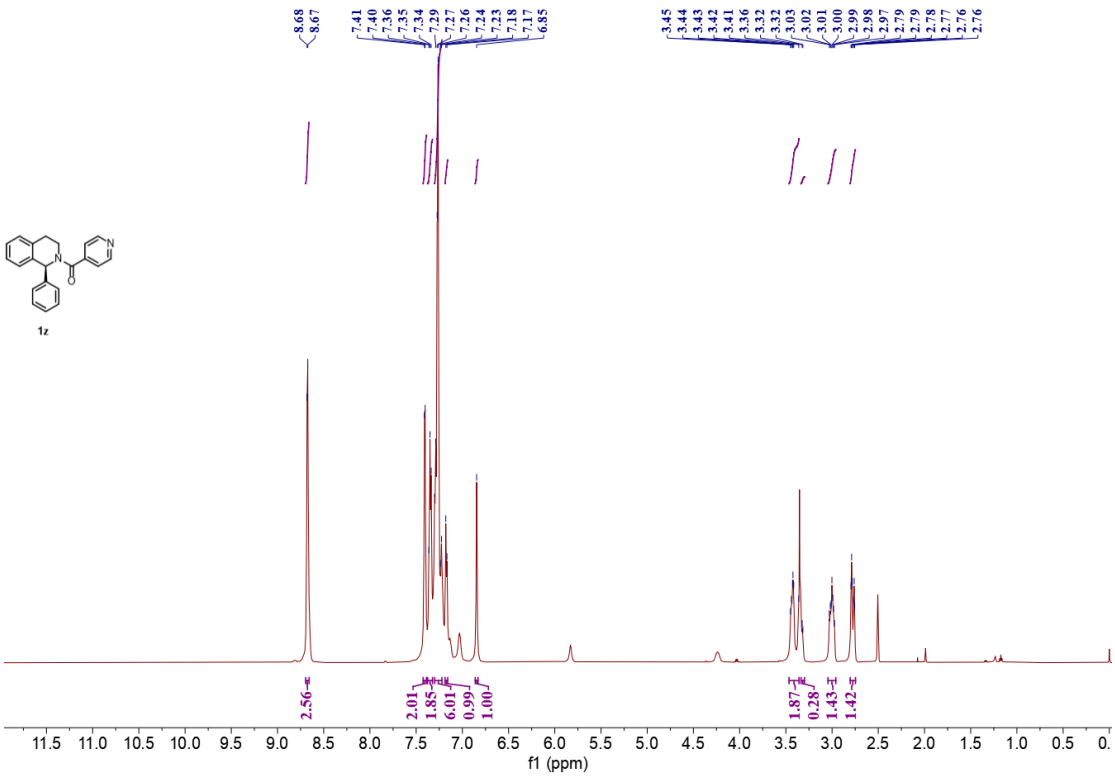
^{13}C NMR spectrum of compound **1x** in DMSO-d_6



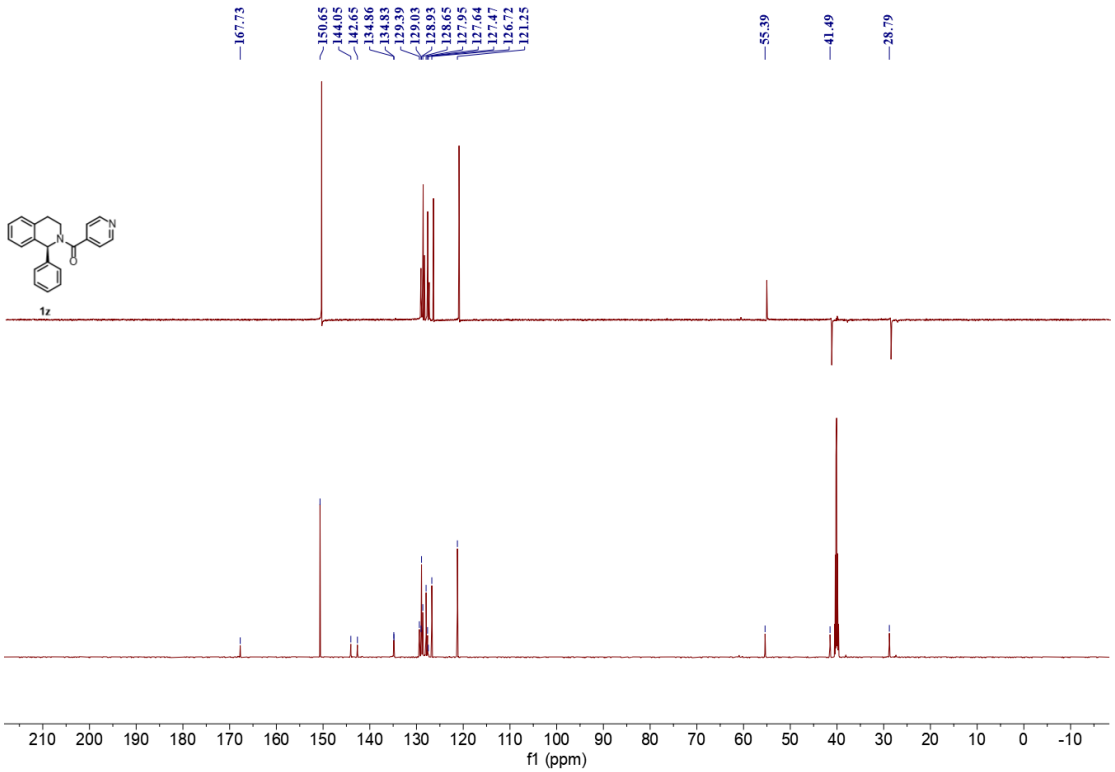
^{1}H NMR spectrum of compound **1y** in DMSO-d_6



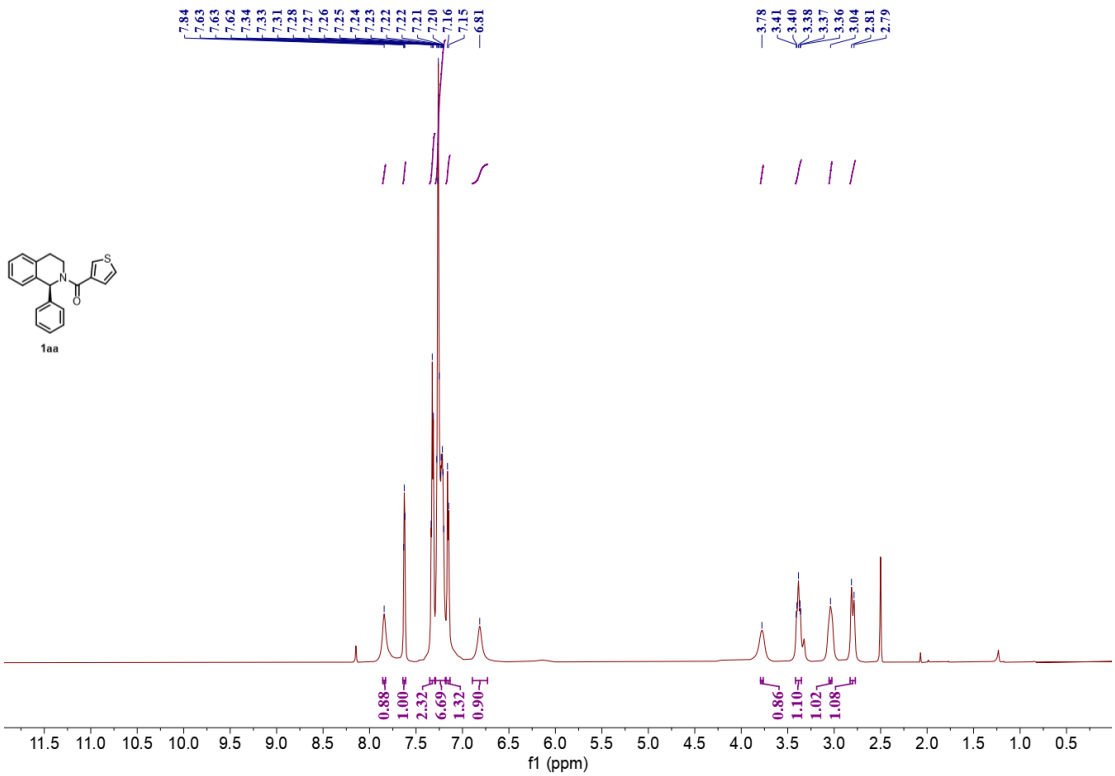
^{13}C NMR spectrum of compound **1y** in DMSO-d_6



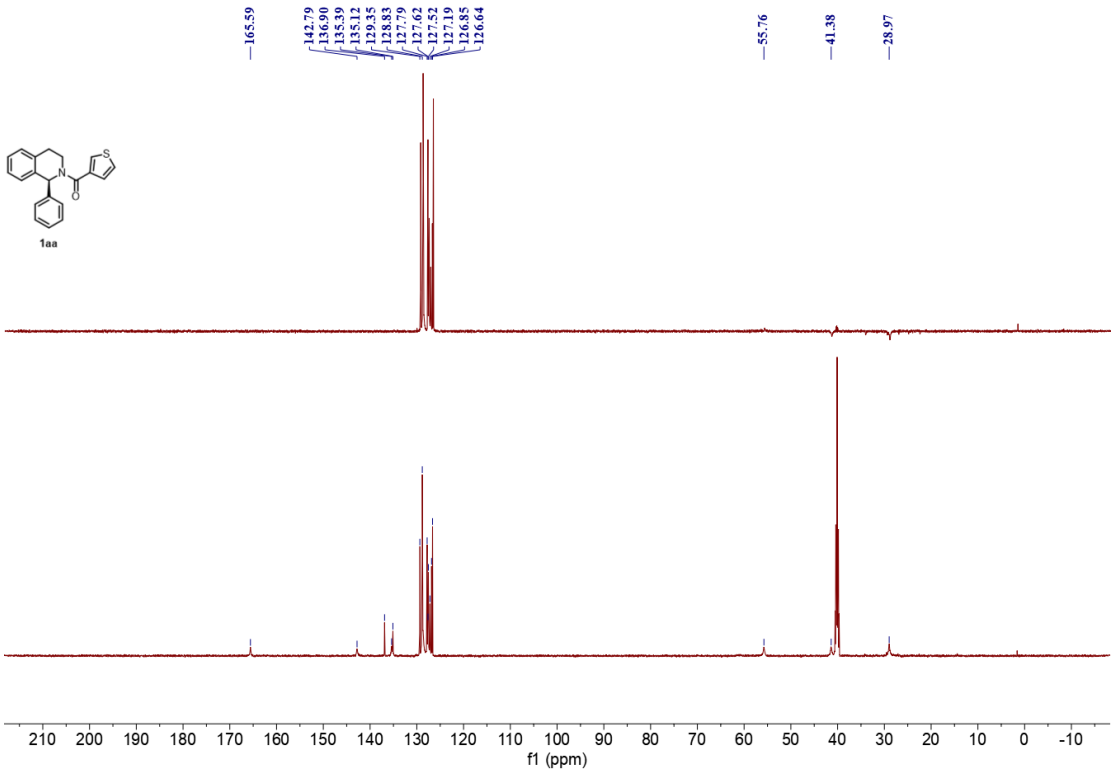
^{1}H NMR spectrum of compound **1z** in DMSO-d_6



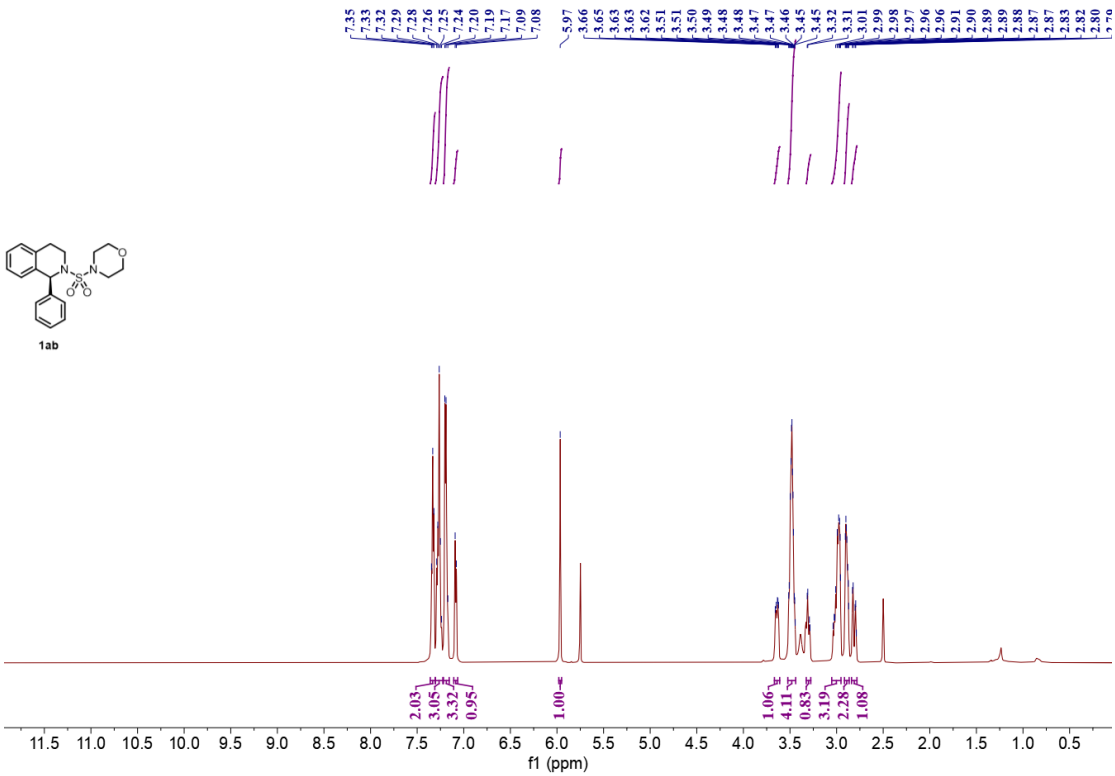
^{13}C NMR spectrum of compound **1z** in DMSO-d_6



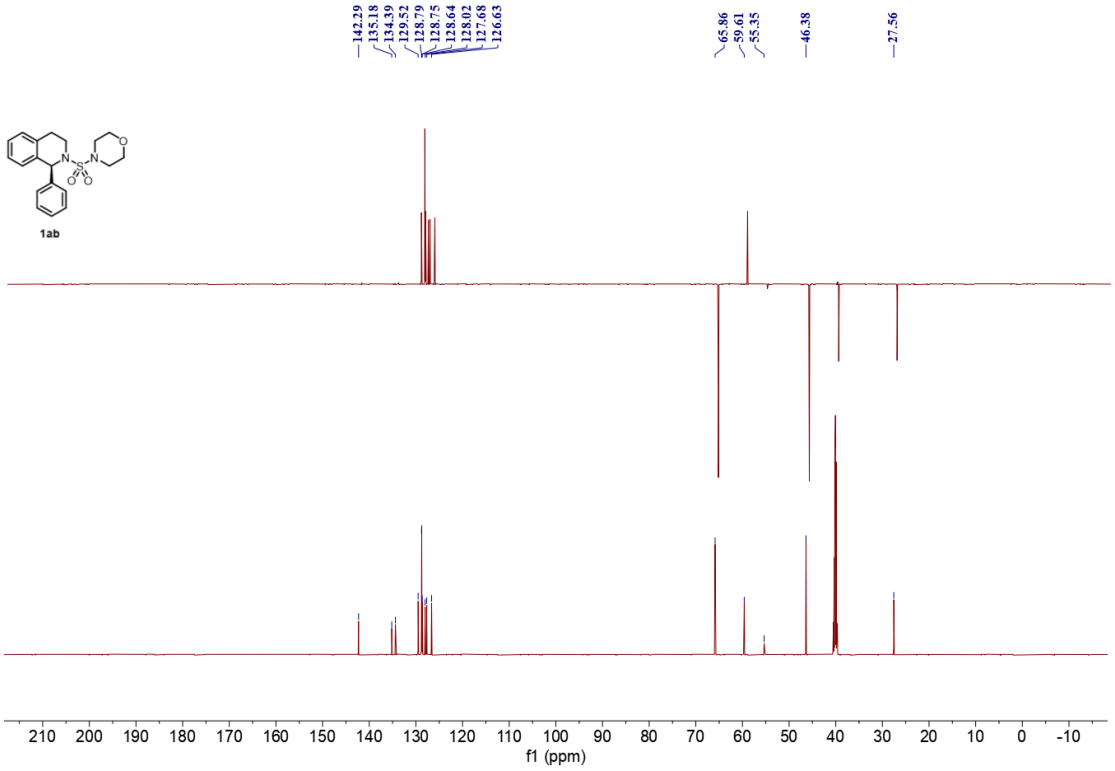
^{1}H NMR spectrum of compound **1aa** in DMSO-d_6



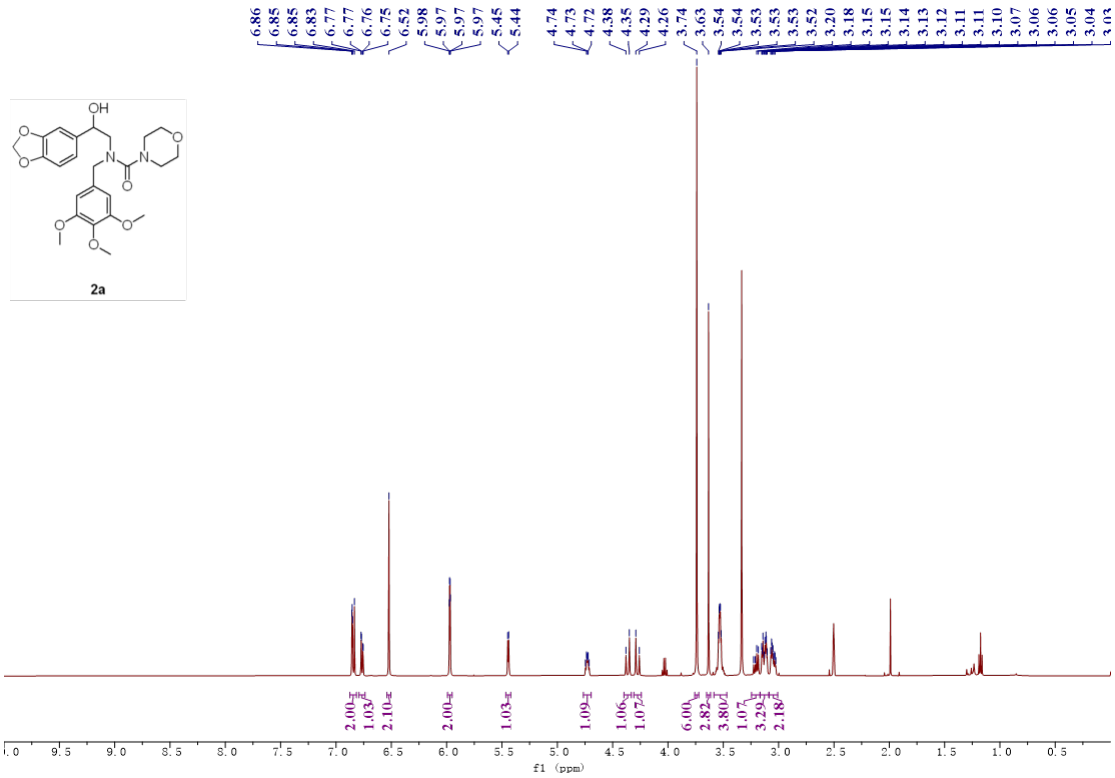
^{13}C NMR spectrum of compound **1aa** in DMSO-d_6



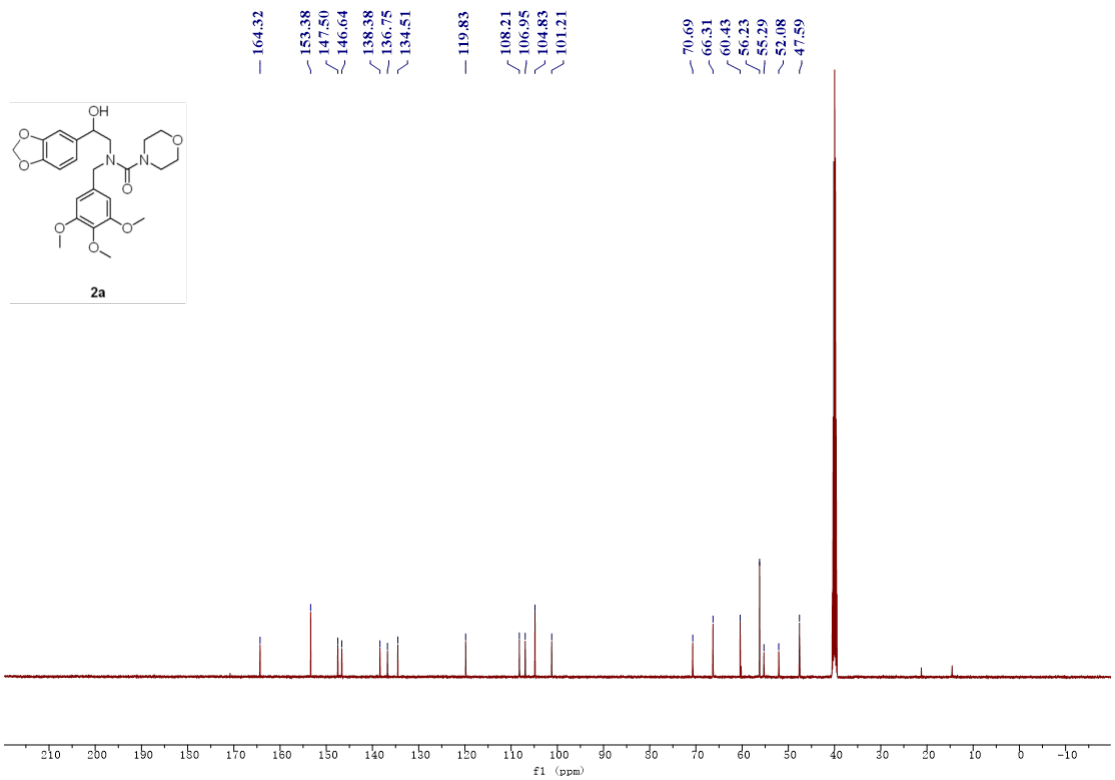
^{1}H NMR spectrum of compound **1ab** in DMSO-d_6



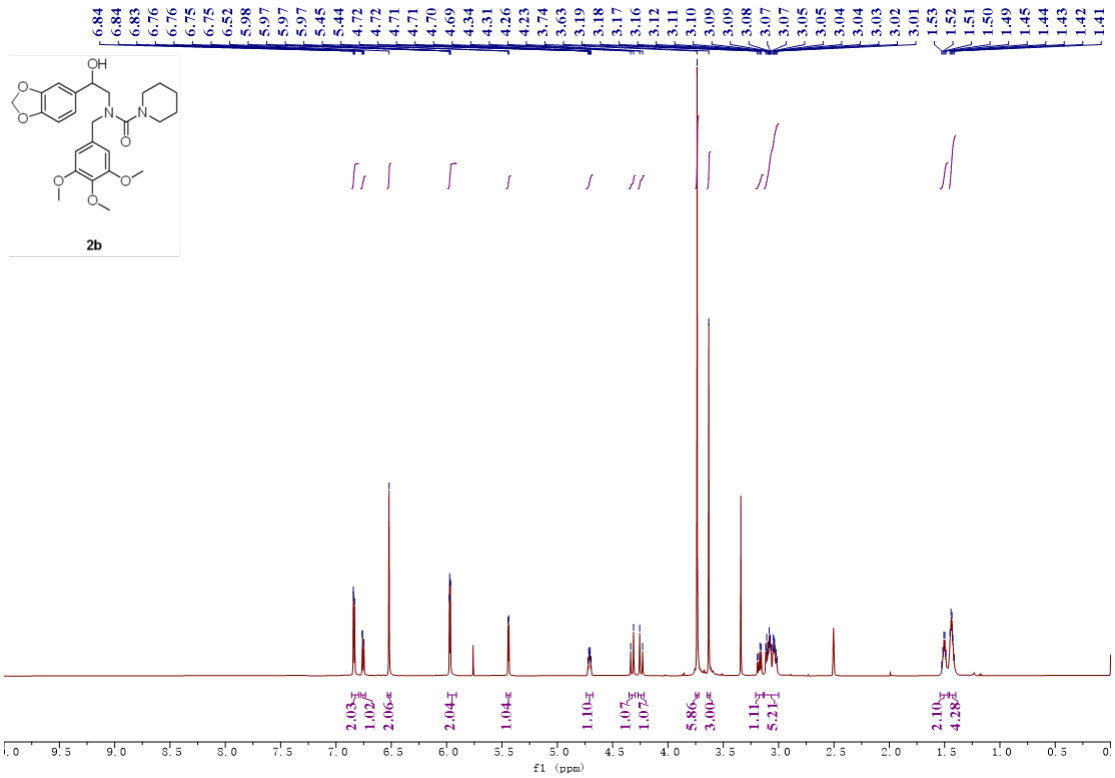
^{13}C NMR spectrum of compound **1ab** in DMSO-d_6



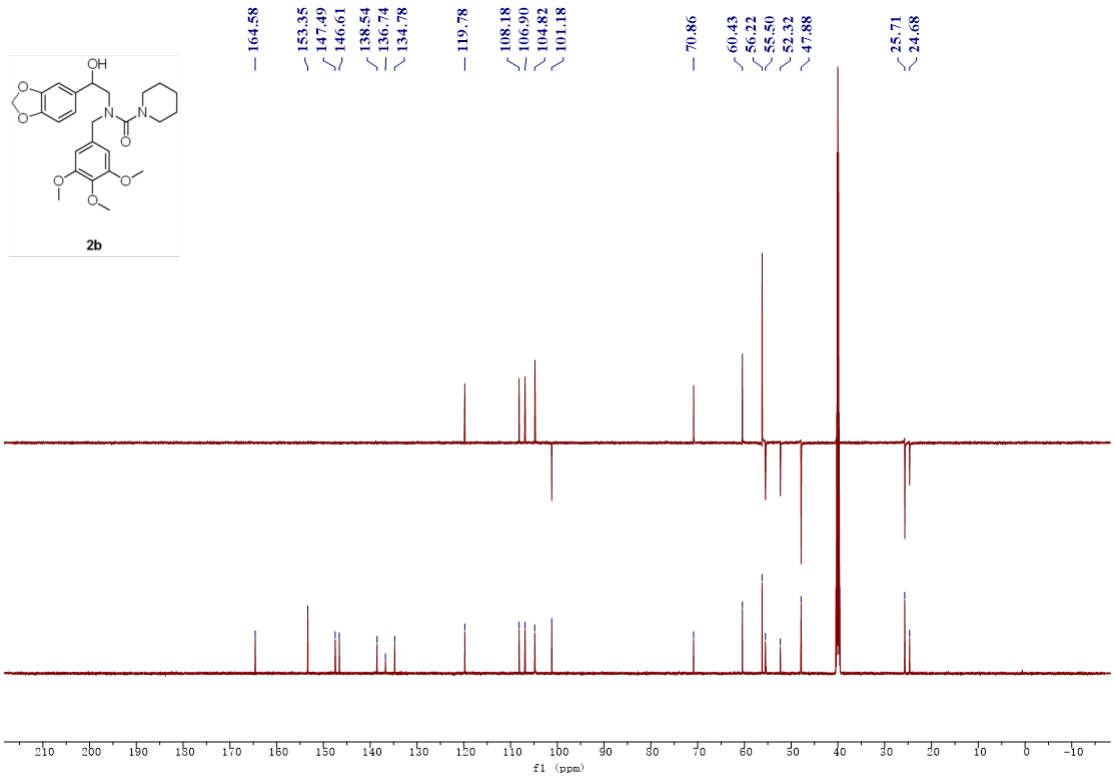
^{1}H NMR spectrum of compound **2a** in DMSO-d_6



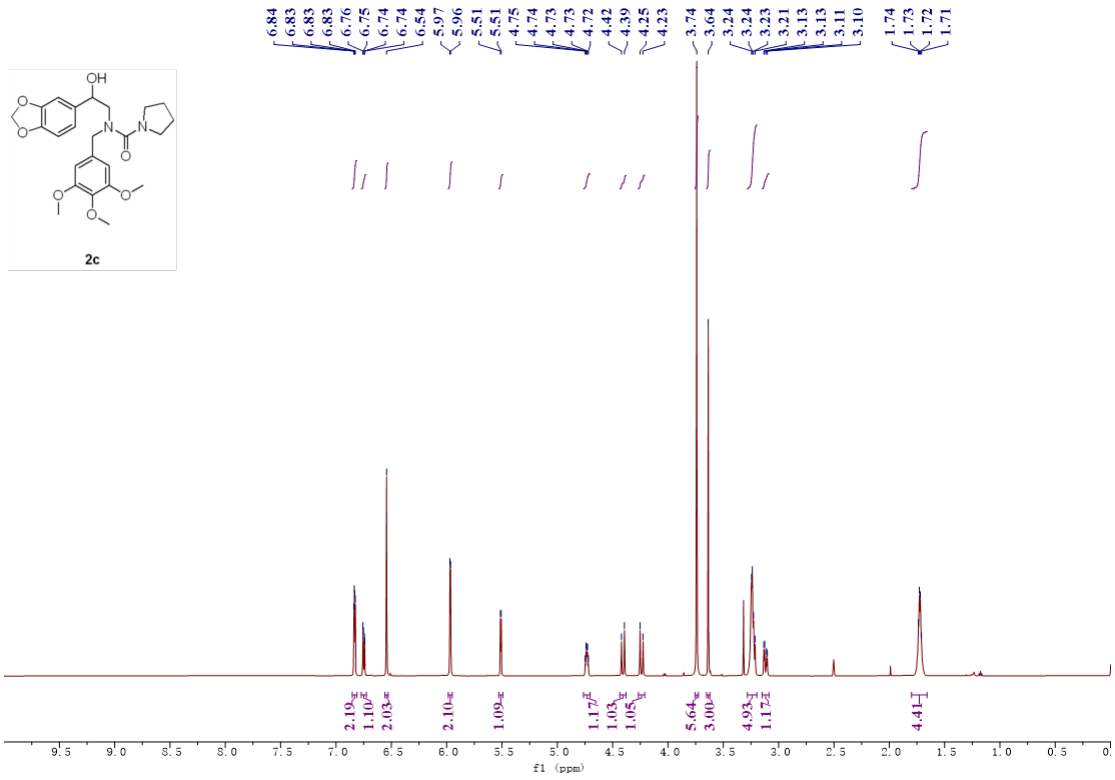
^{13}C NMR spectrum of compound **2a** in DMSO-d_6



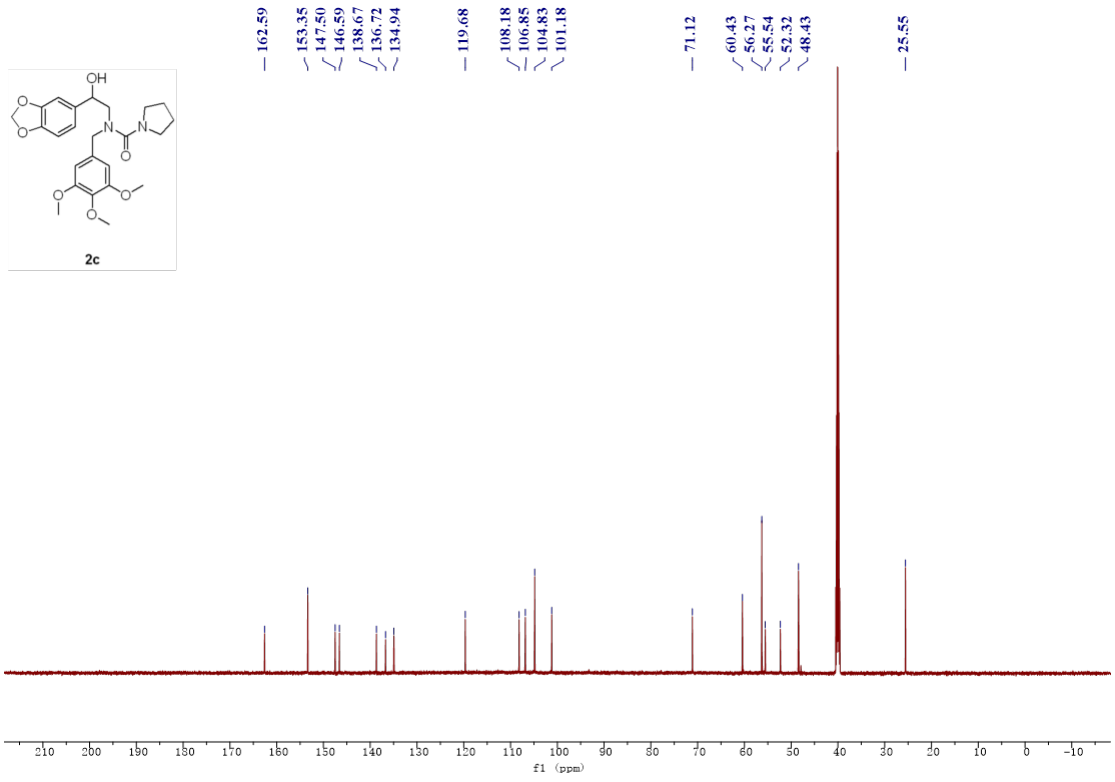
^{1}H NMR spectrum of compound **2b** in DMSO-d_6



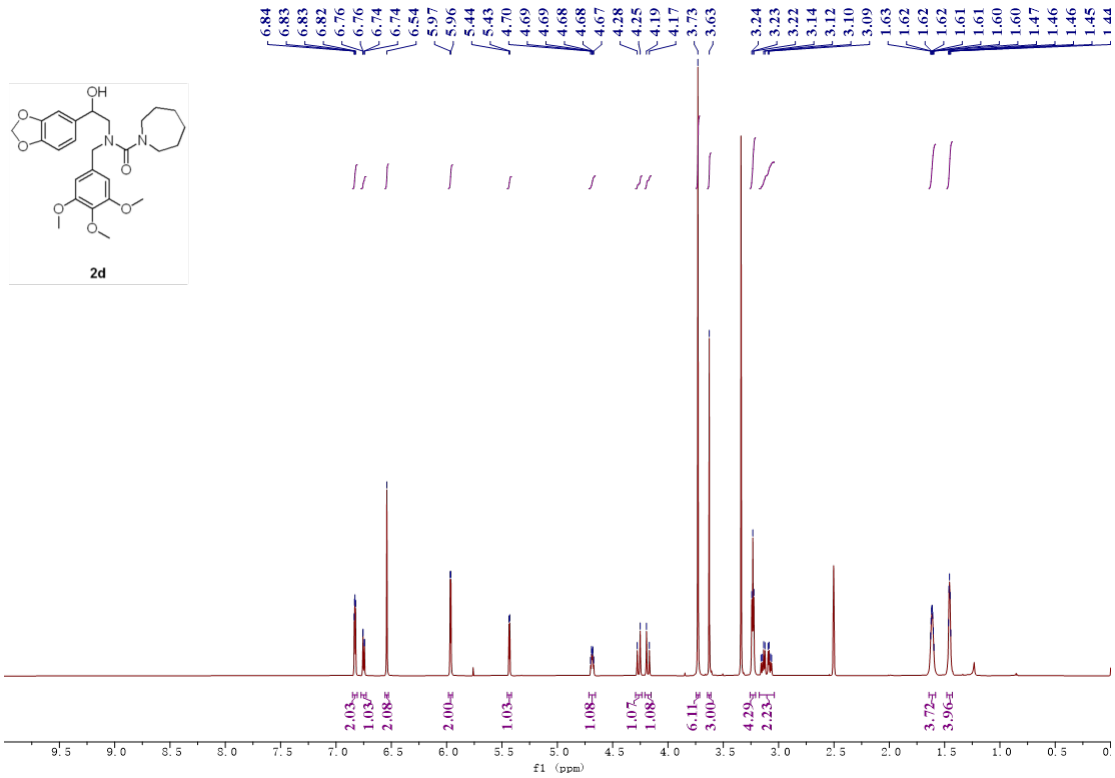
^{13}C NMR spectrum of compound **2b** in DMSO-d_6



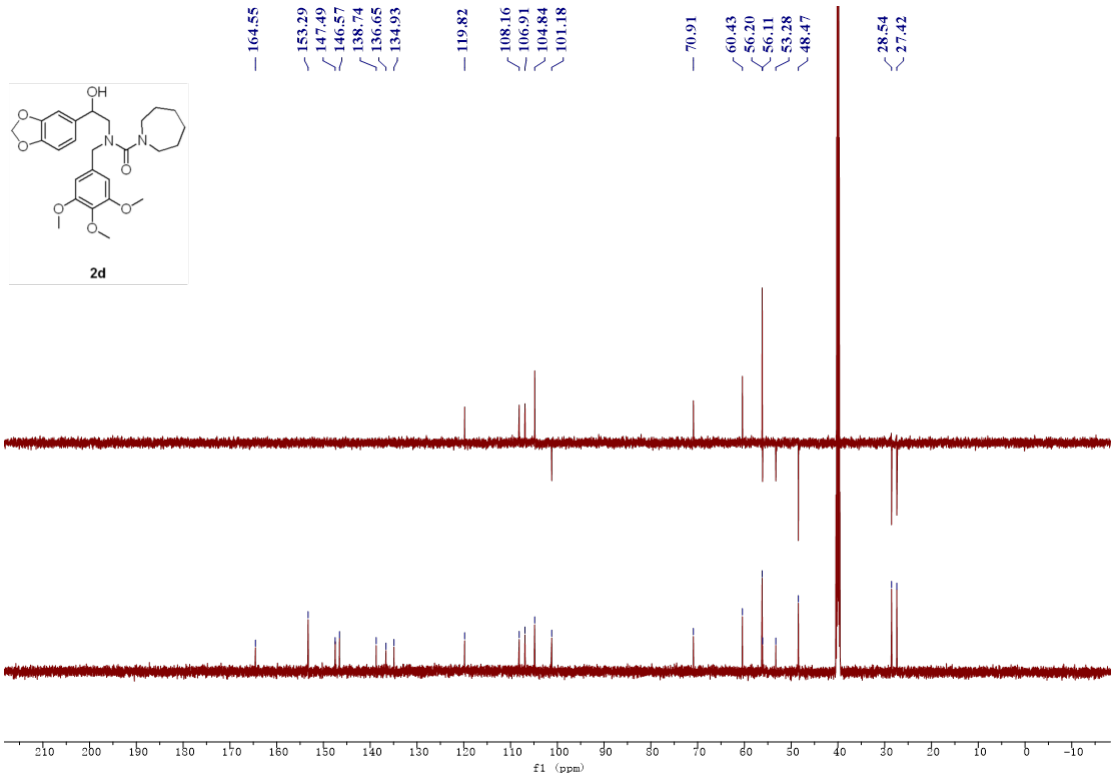
^{1}H NMR spectrum of compound **2c** in DMSO-d_6



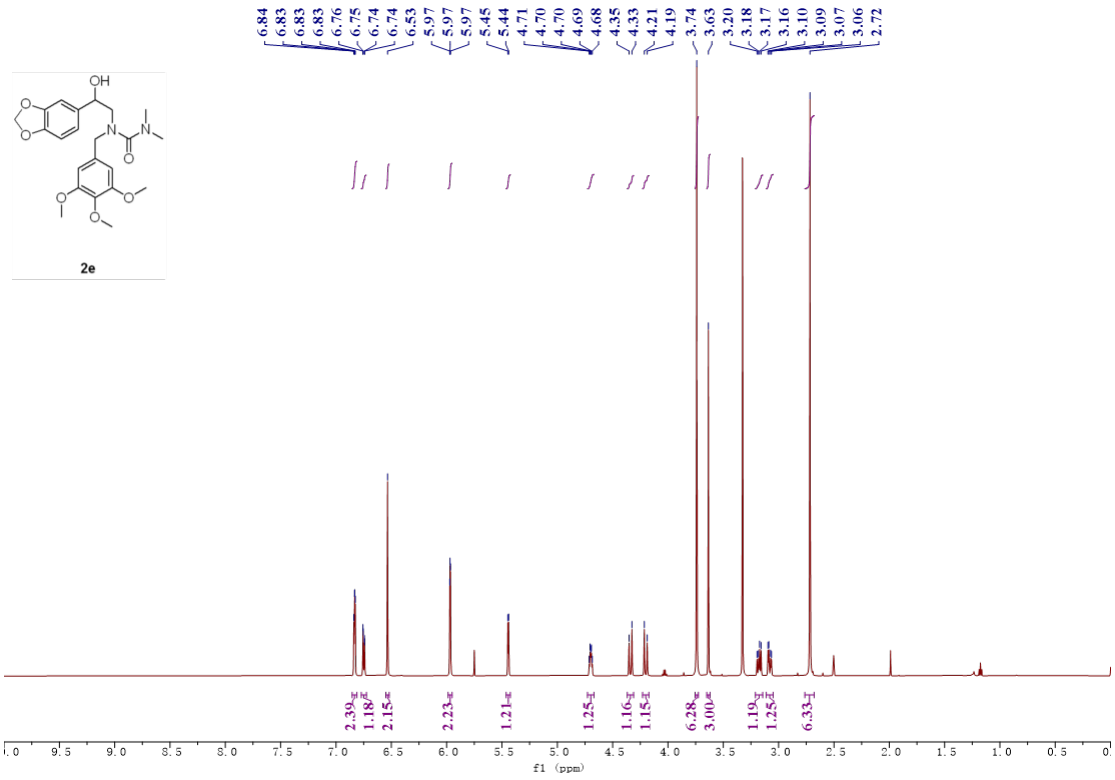
^{13}C NMR spectrum of compound **2c** in DMSO-d_6



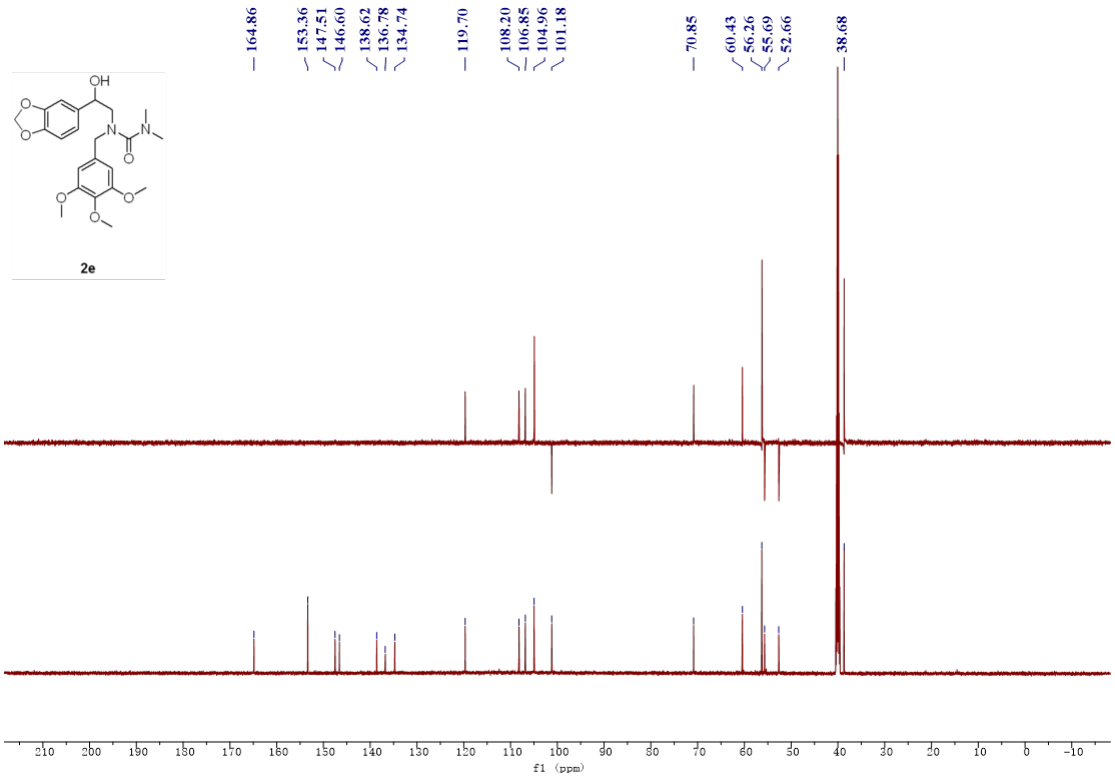
^{1}H NMR spectrum of compound **2d** in DMSO-d_6



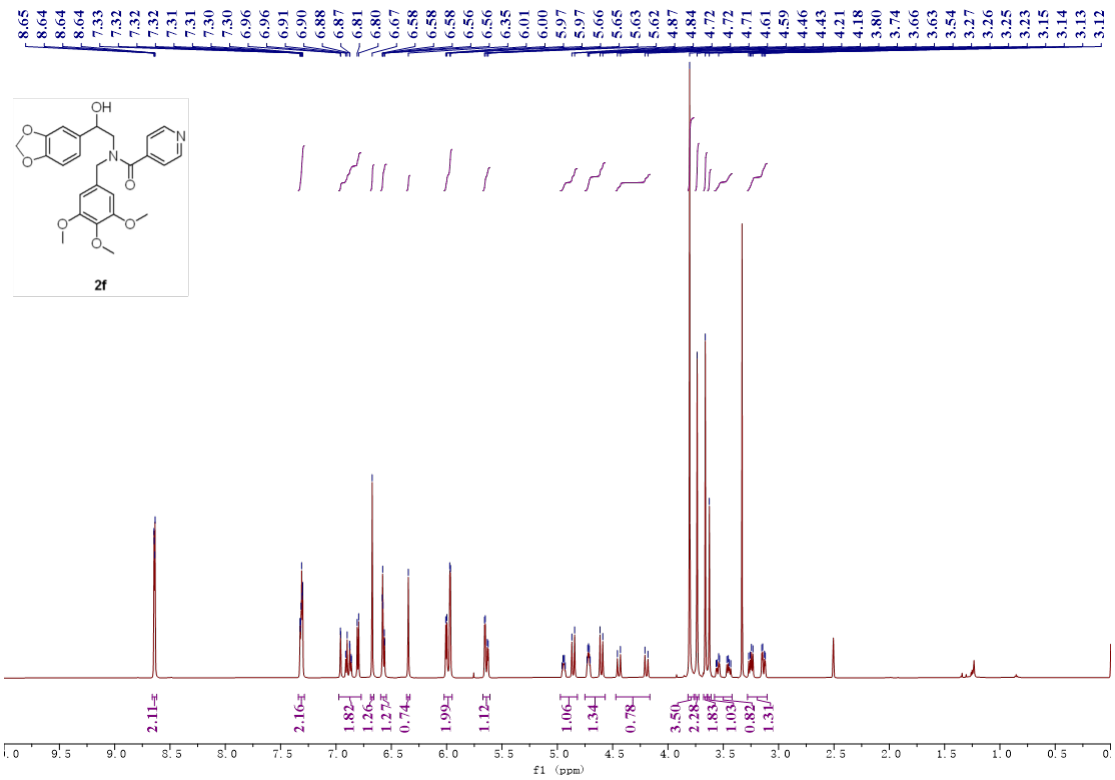
^{13}C NMR spectrum of compound **2d** in DMSO-d_6



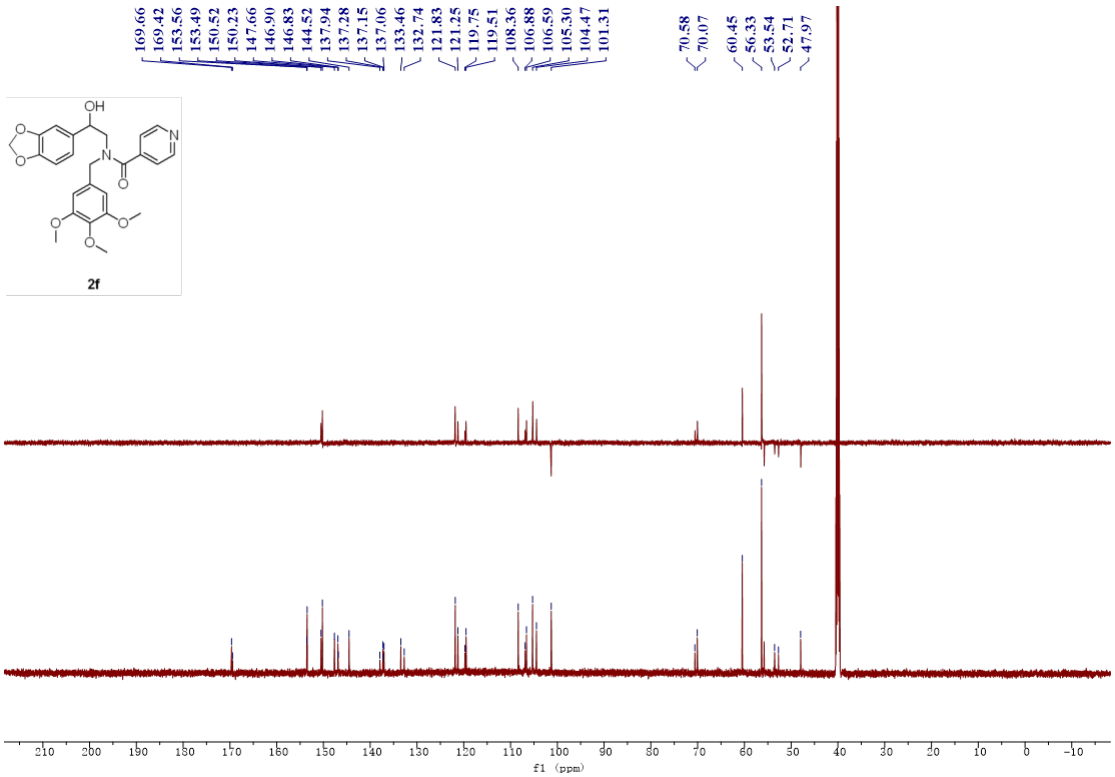
^{1}H NMR spectrum of compound **2e** in DMSO-d_6



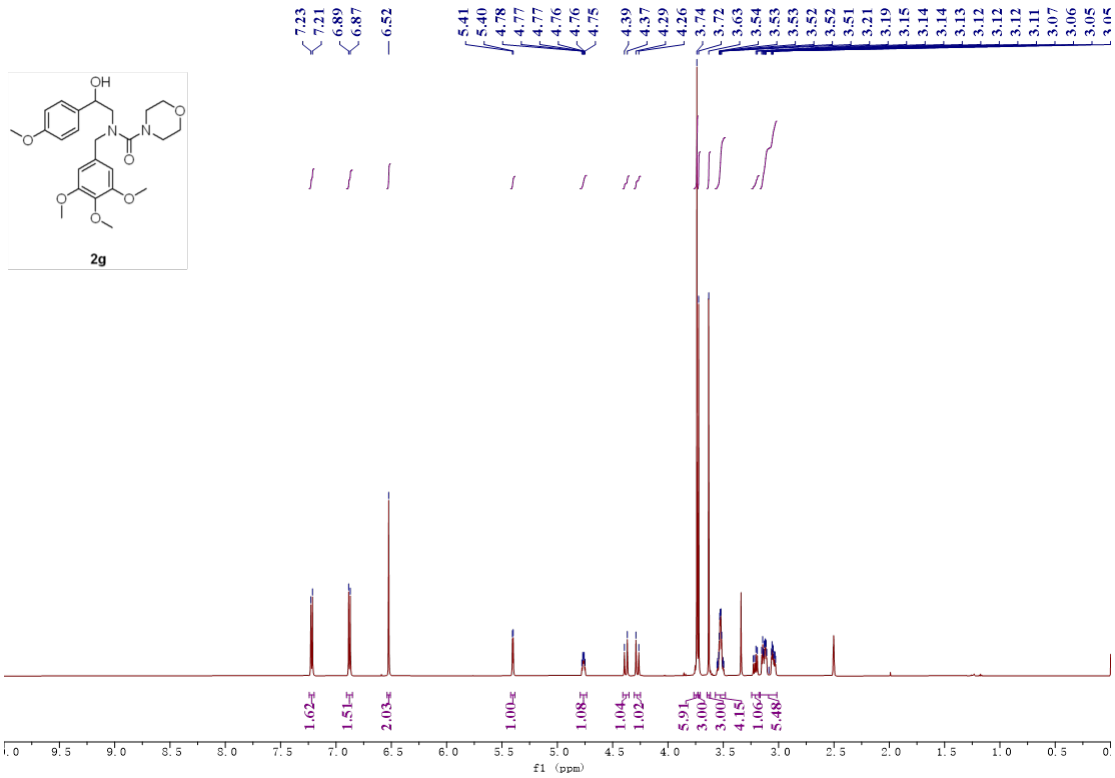
^{13}C NMR spectrum of compound **2e** in DMSO-d_6



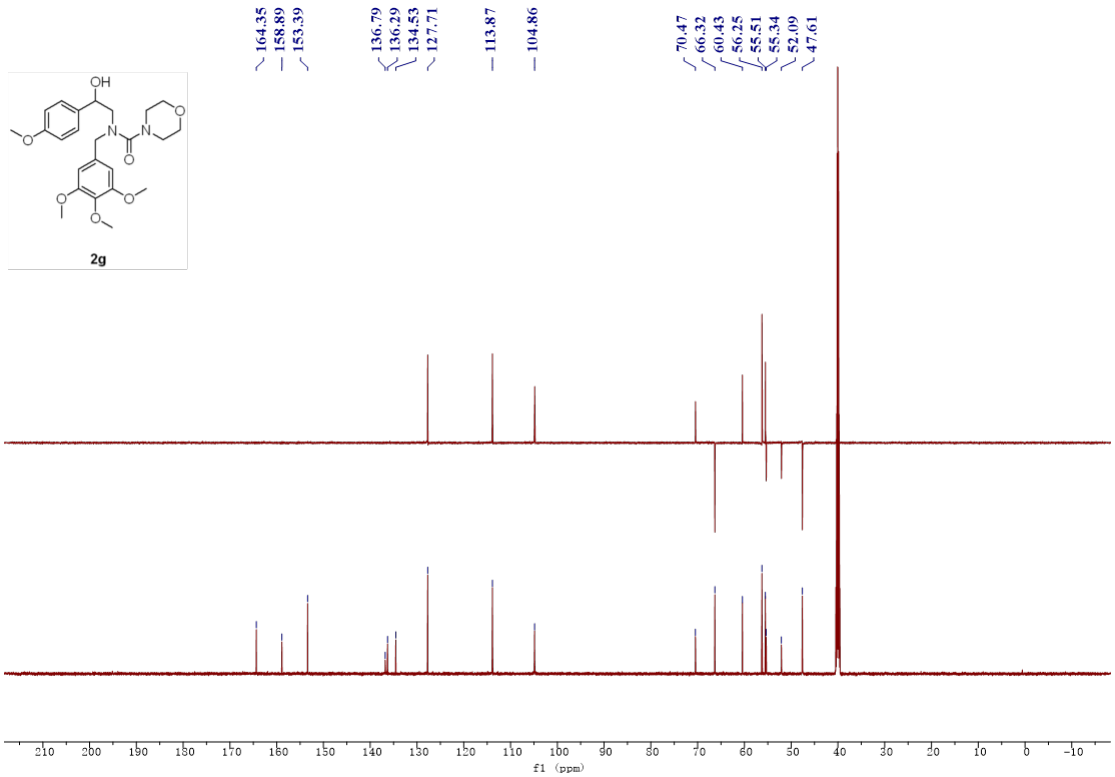
^{1}H NMR spectrum of compound **2f** in DMSO-d_6



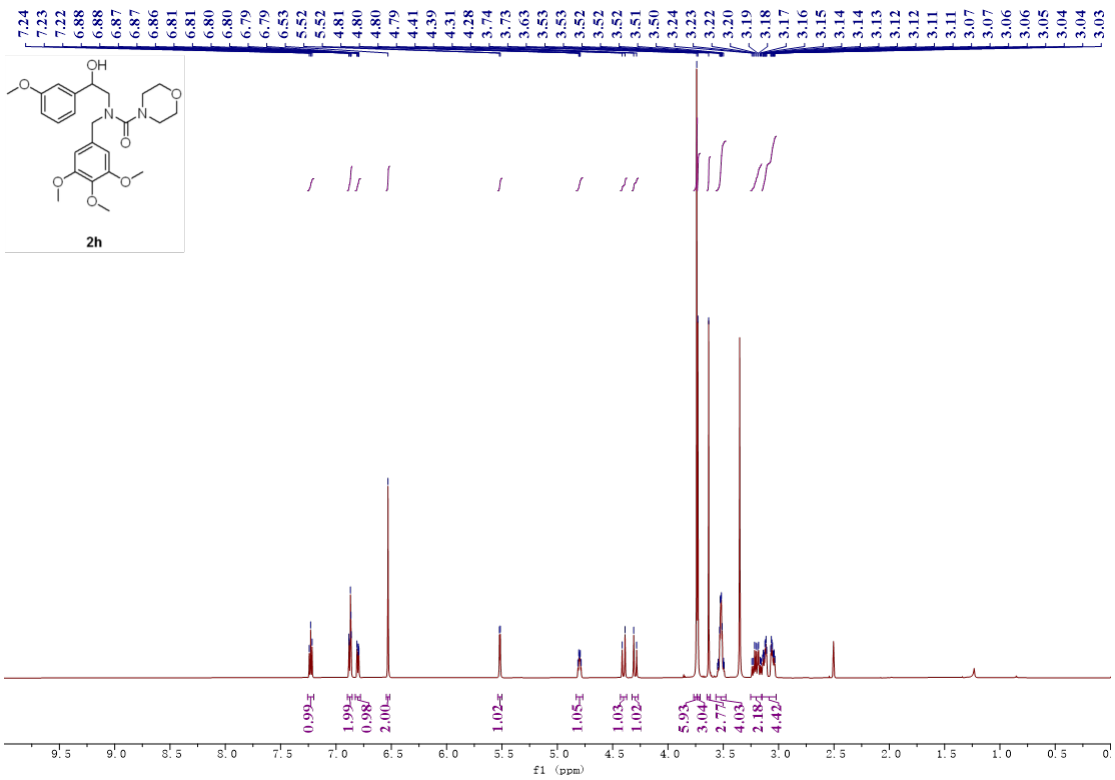
^{13}C NMR spectrum of compound **2f** in DMSO-d_6



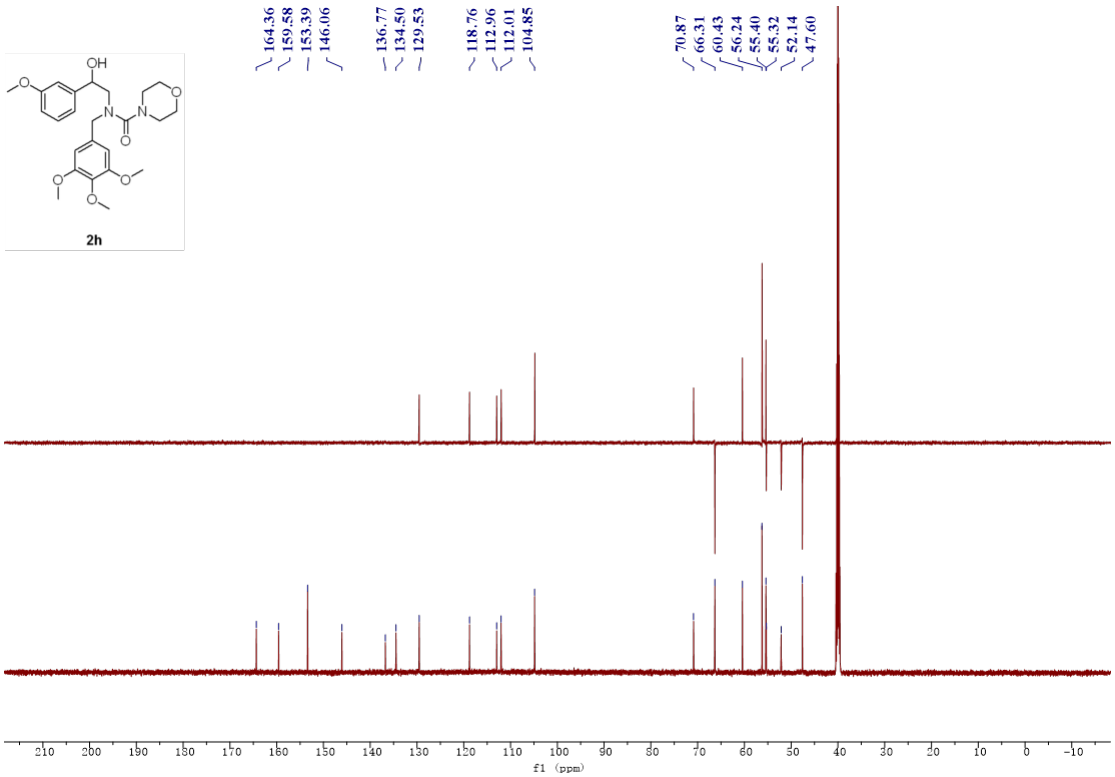
^{1}H NMR spectrum of compound **2g** in DMSO-d_6



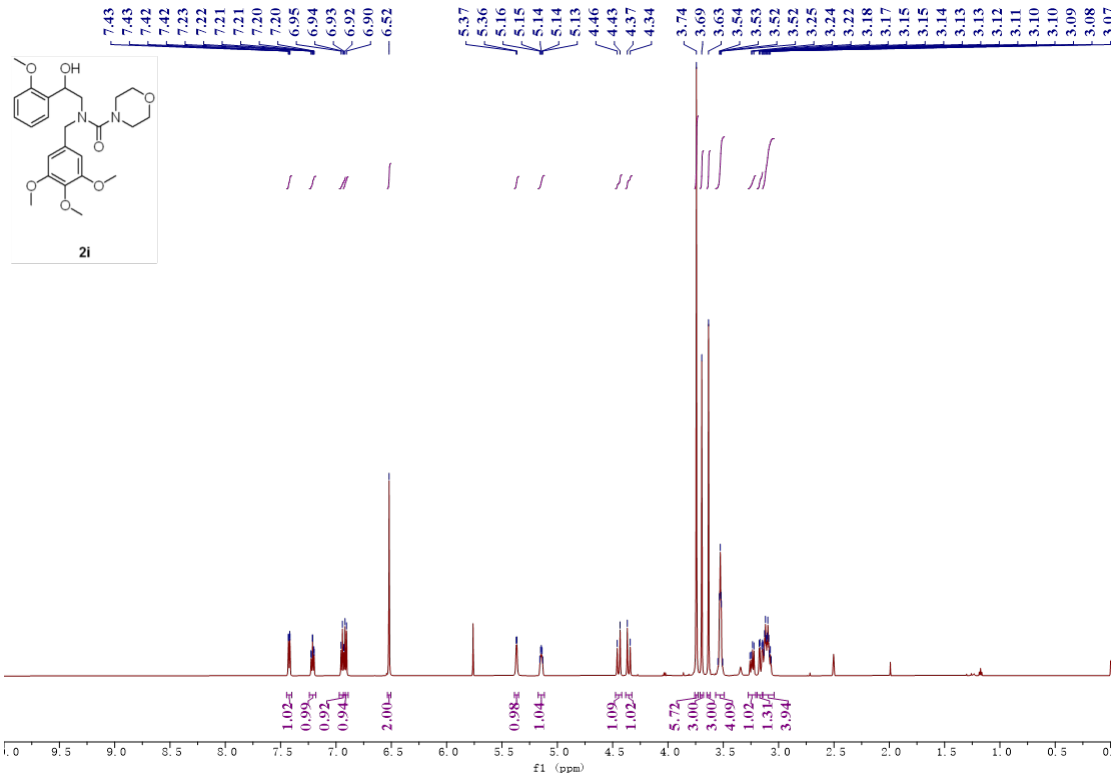
^{13}C NMR spectrum of compound **2g** in DMSO-d_6



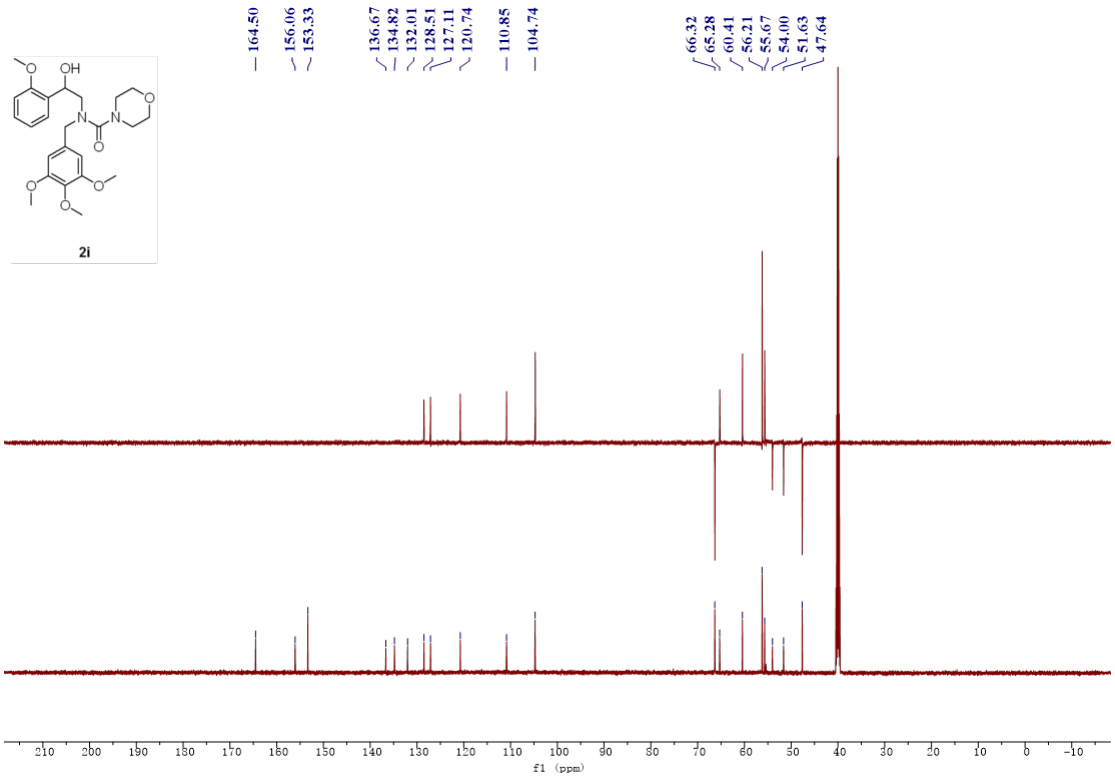
^{1}H NMR spectrum of compound **2h** in DMSO-d_6



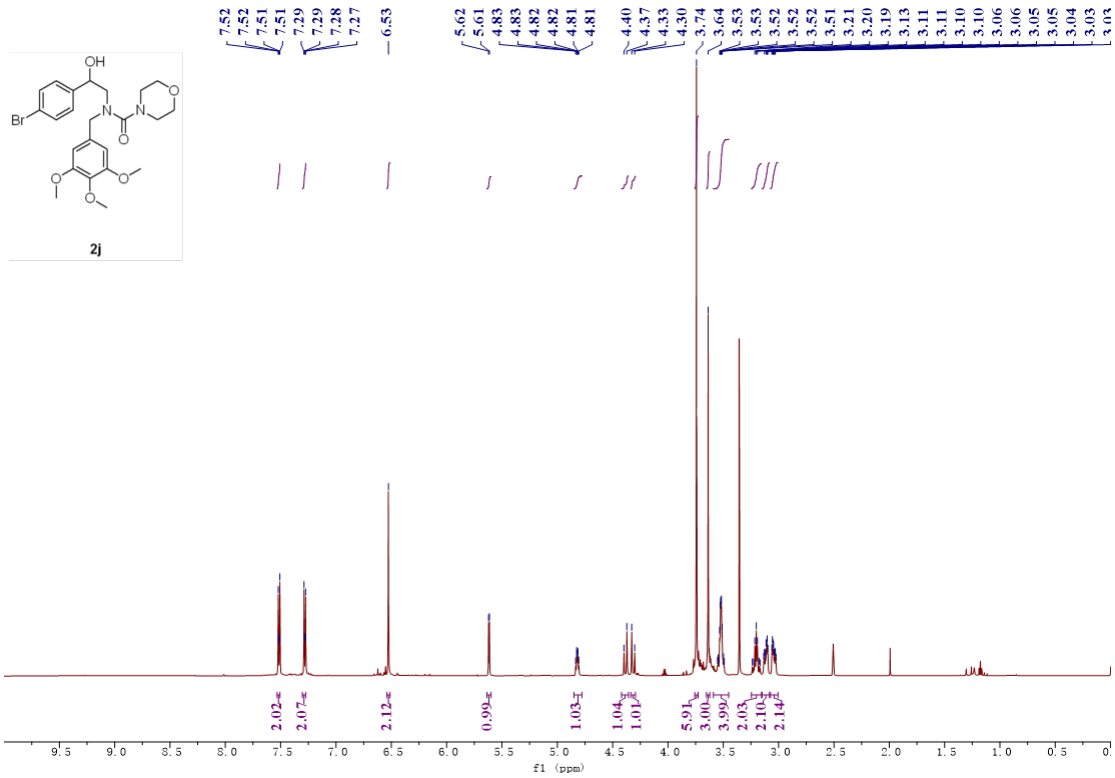
^{13}C NMR spectrum of compound **2h** in DMSO-d_6



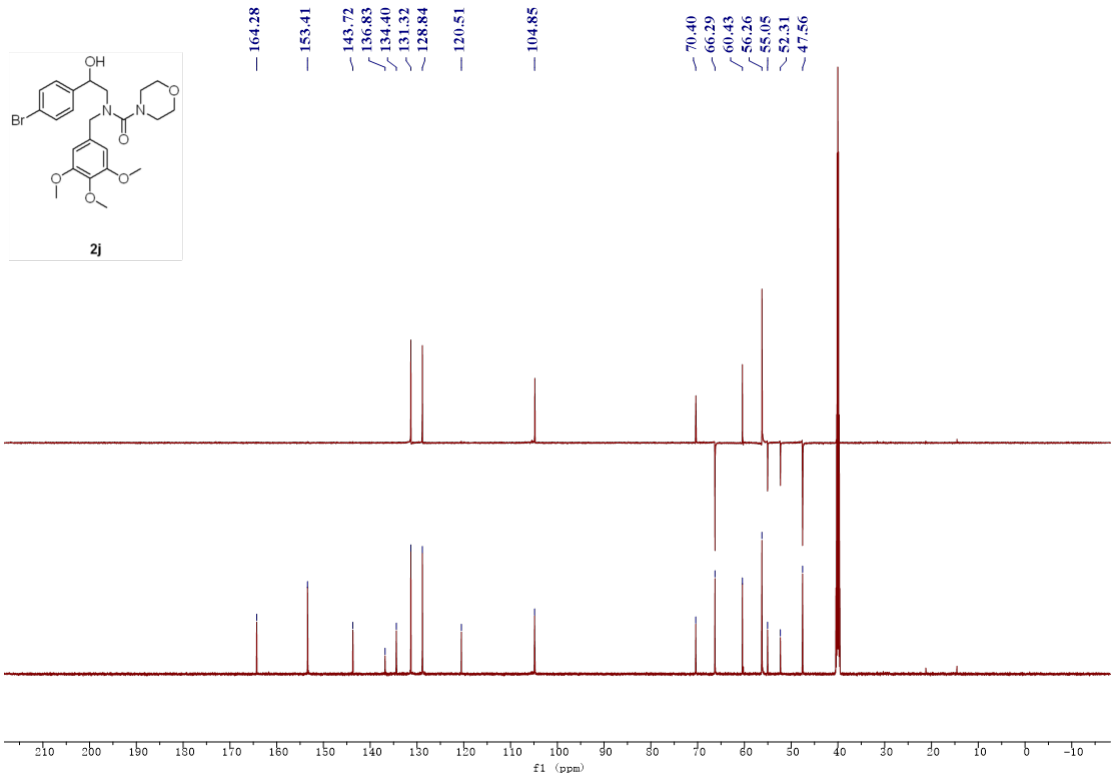
^{1}H NMR spectrum of compound **2i** in DMSO-d_6



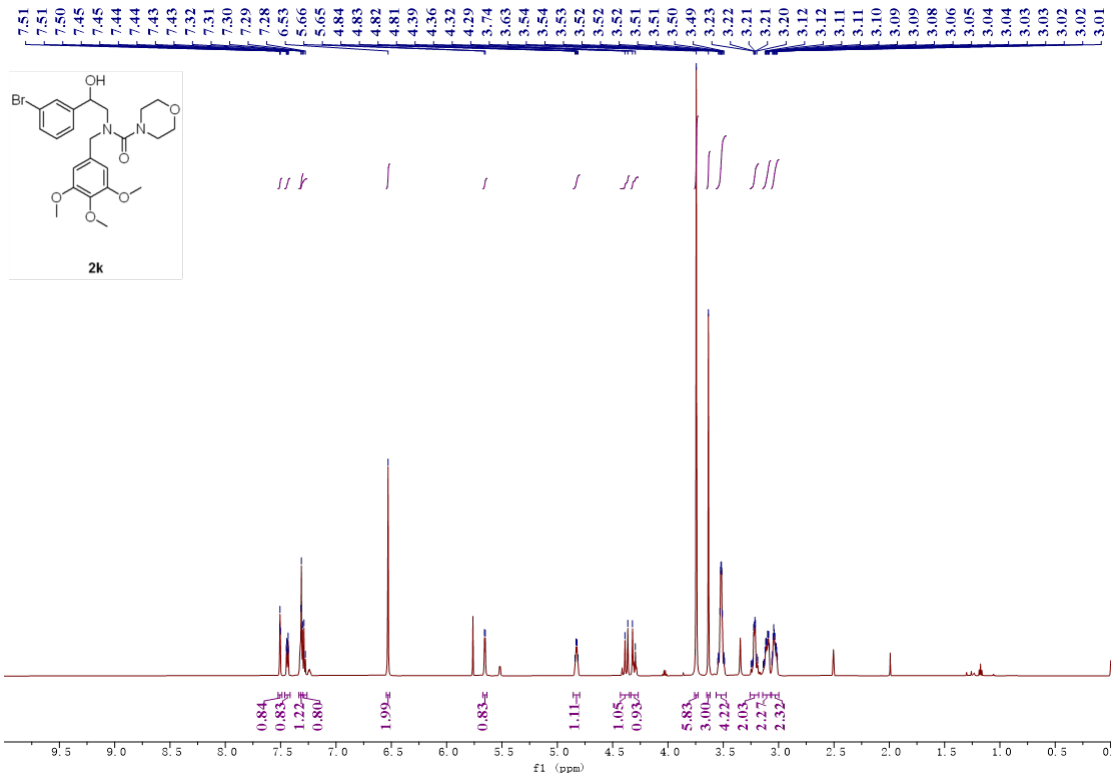
^{13}C NMR spectrum of compound **2i** in DMSO-d_6



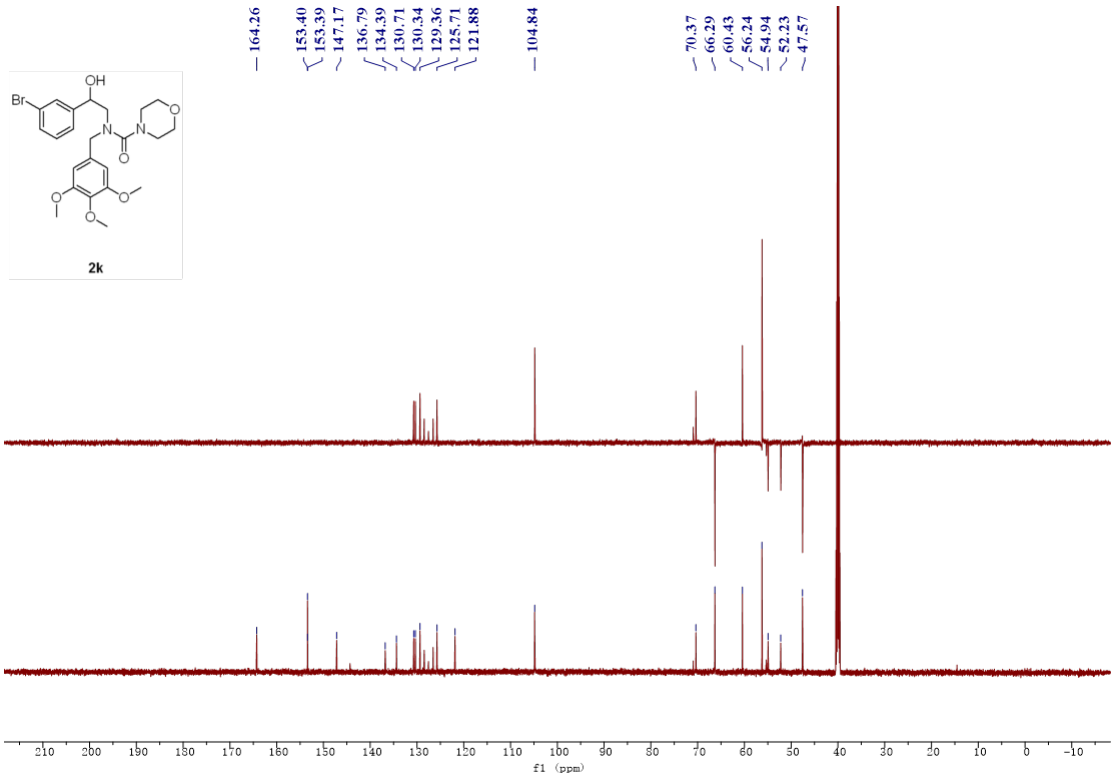
^{1}H NMR spectrum of compound **2j** in DMSO-d_6



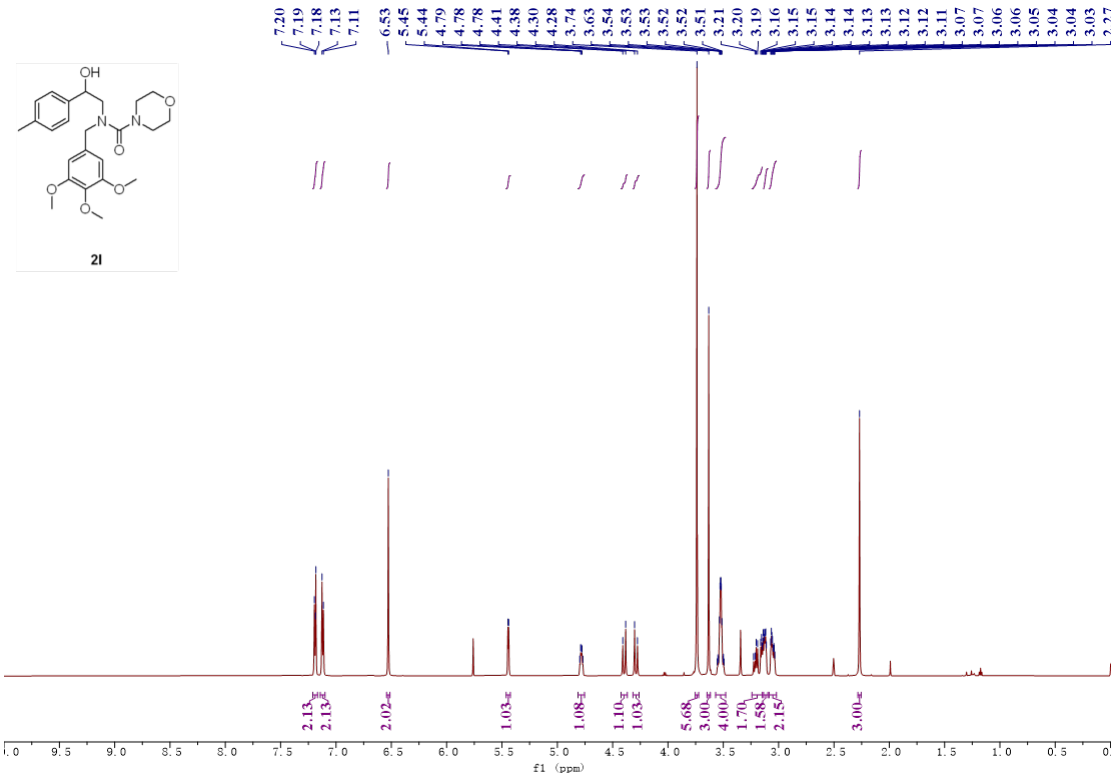
^{13}C NMR spectrum of compound **2j** in DMSO-d_6



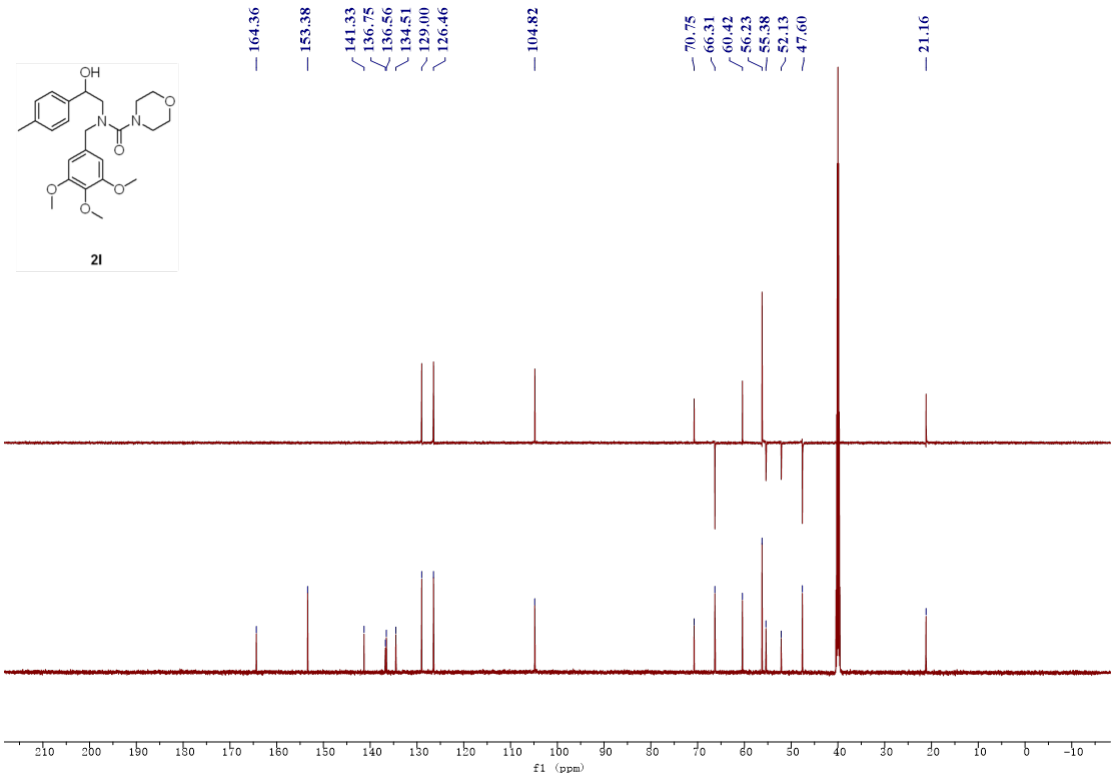
^{1}H NMR spectrum of compound **2k** in DMSO-d_6



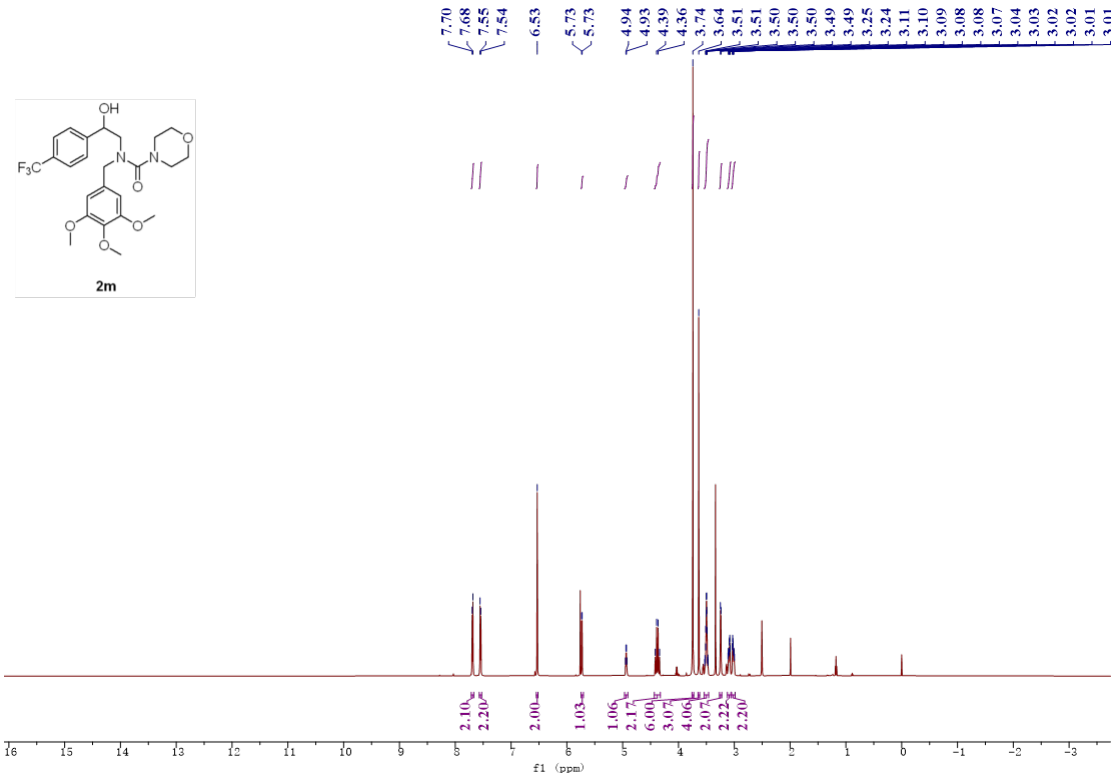
^{13}C NMR spectrum of compound **2k** in DMSO-d_6



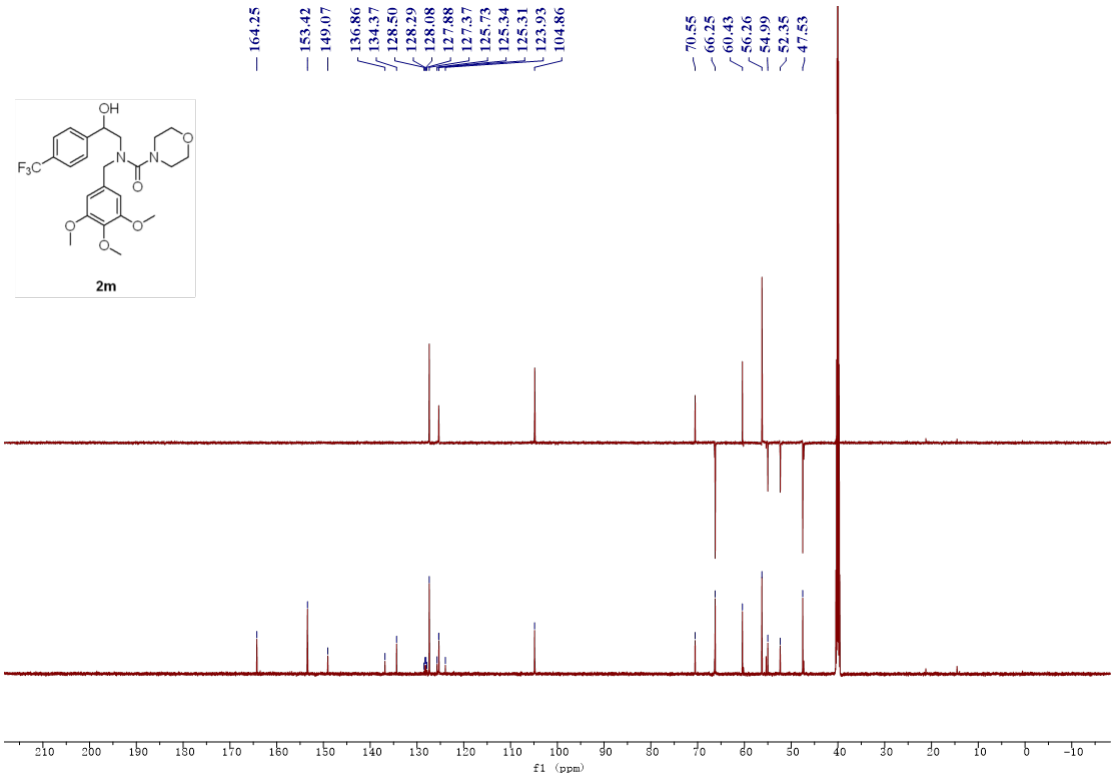
^{1}H NMR spectrum of compound **2l** in DMSO-d_6



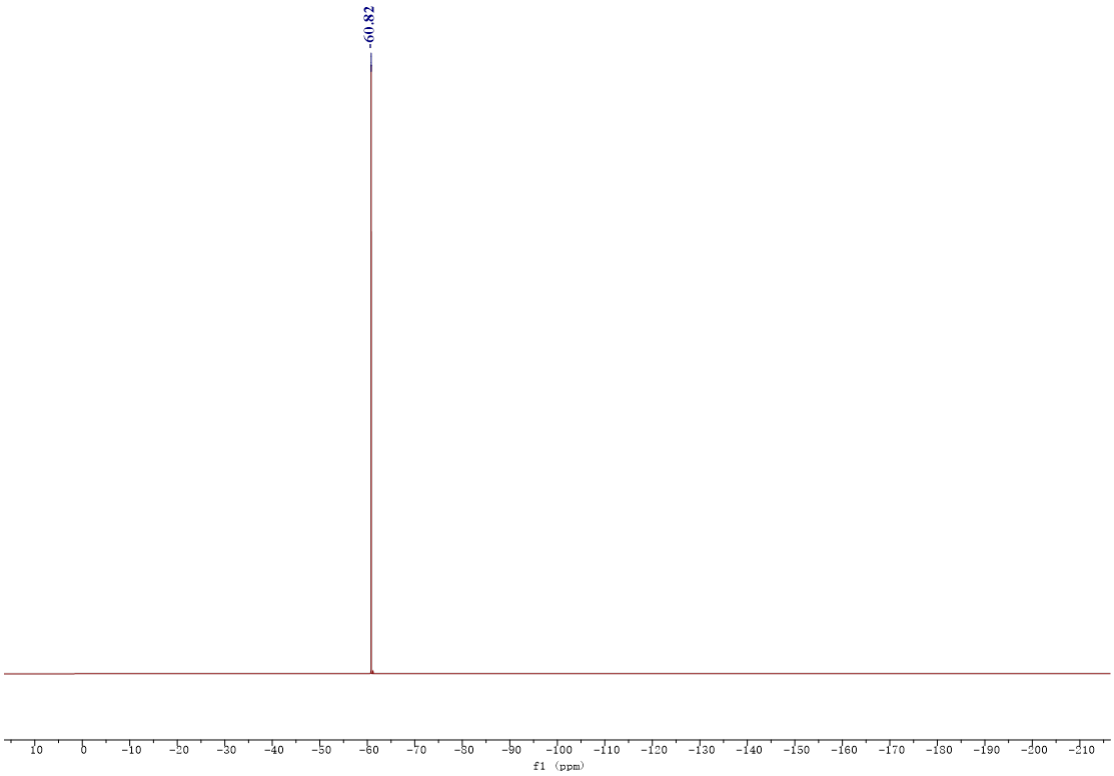
^{13}C NMR spectrum of compound **2l** in DMSO-d_6



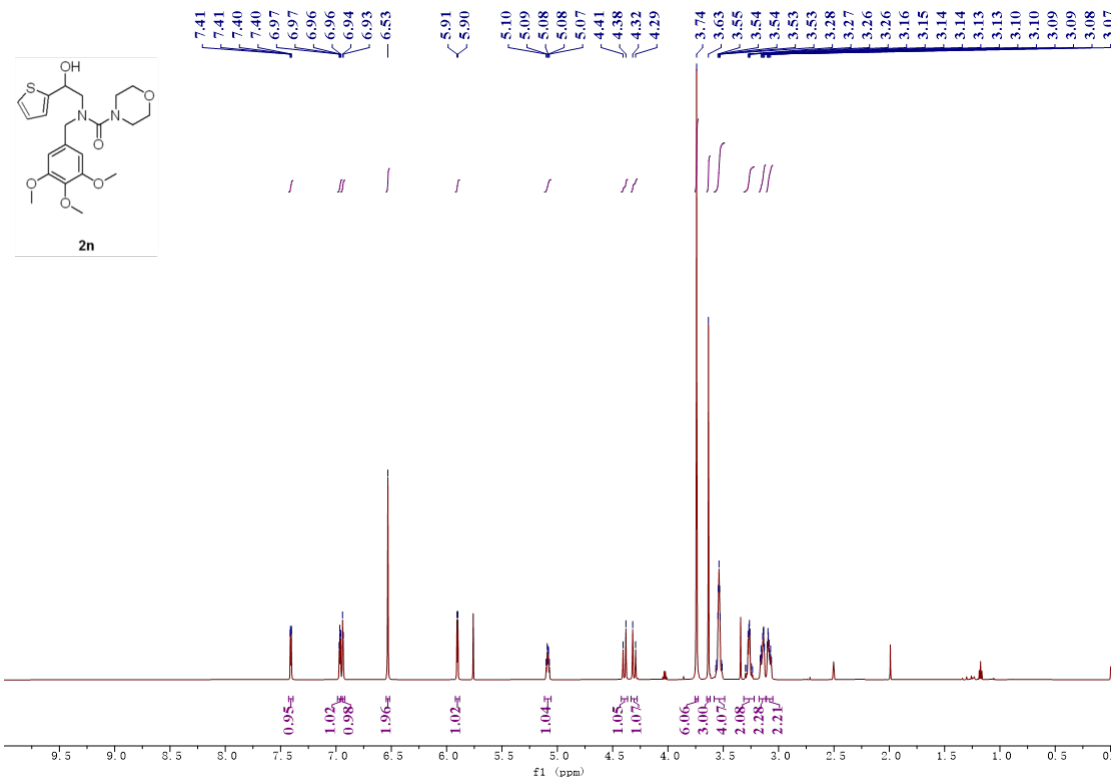
^{1}H NMR spectrum of compound **2m** in DMSO-d_6



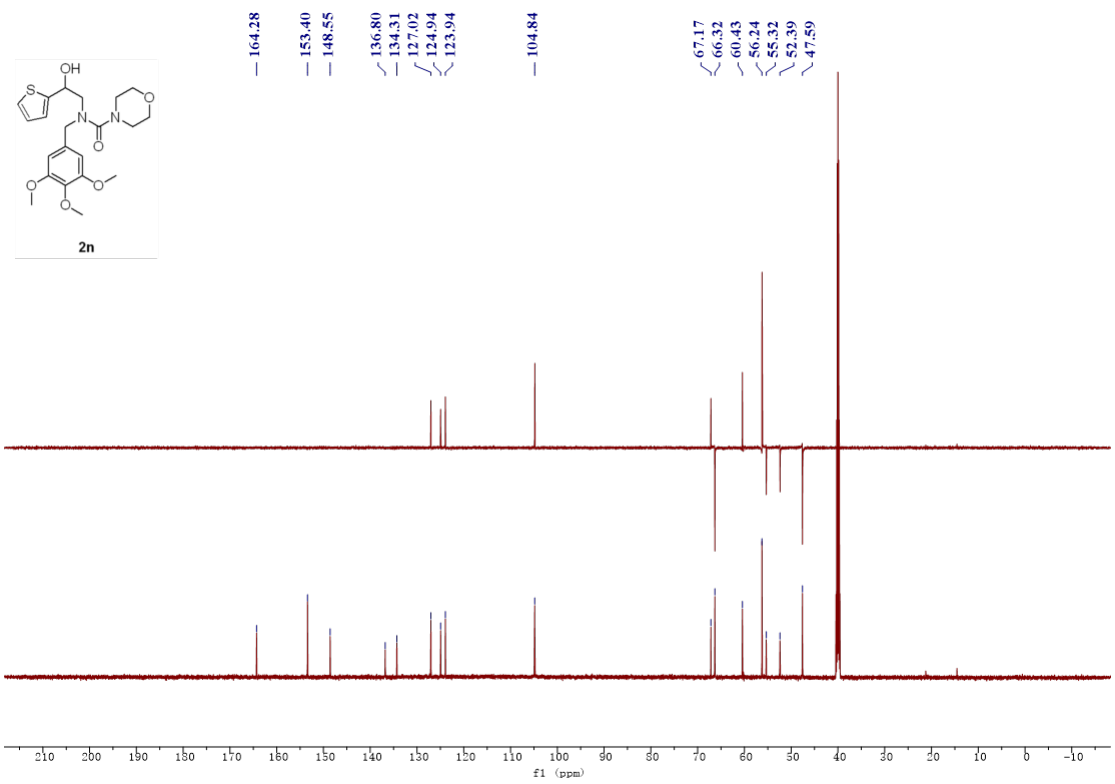
^{13}C NMR spectrum of compound **2m** in DMSO-d_6



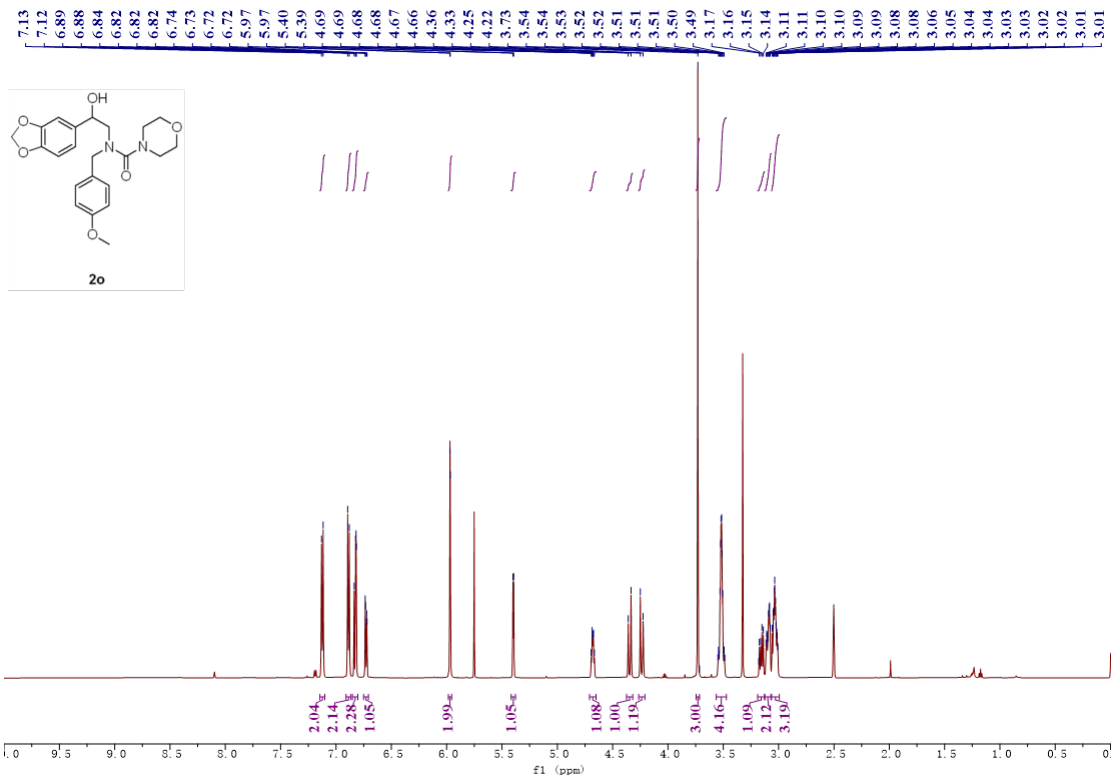
^{19}F NMR spectrum of compound **2m** in DMSO-d_6



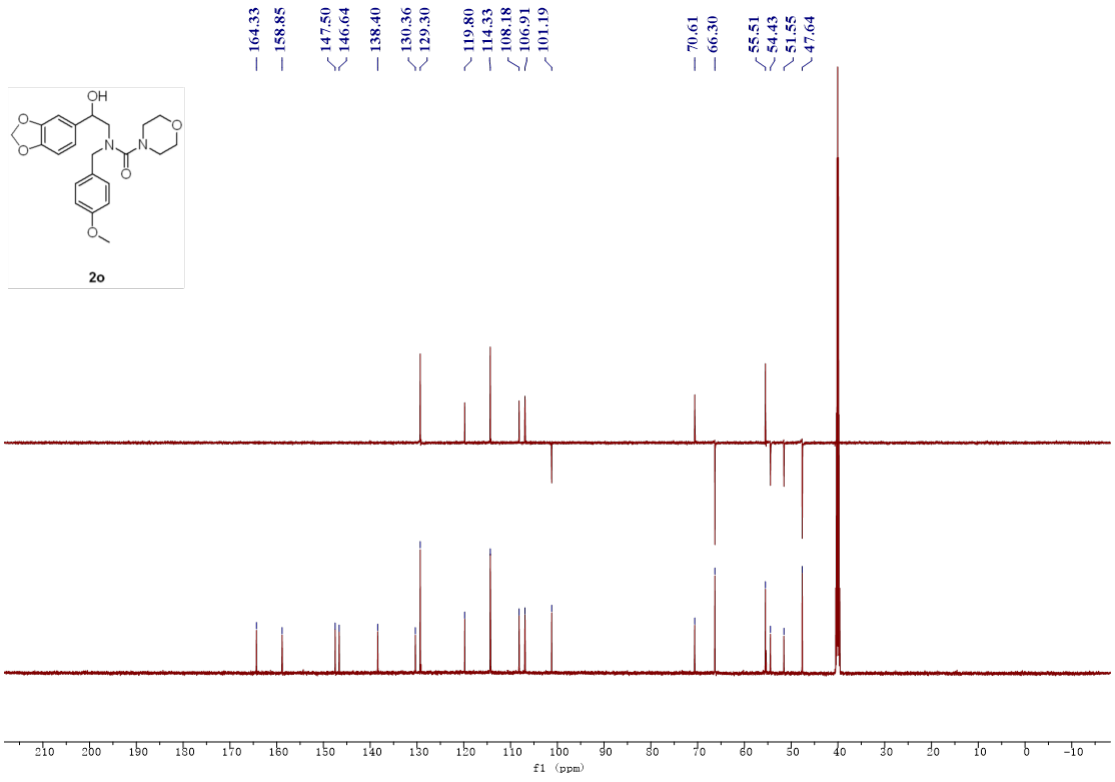
^{1}H NMR spectrum of compound **2n** in DMSO-d_6



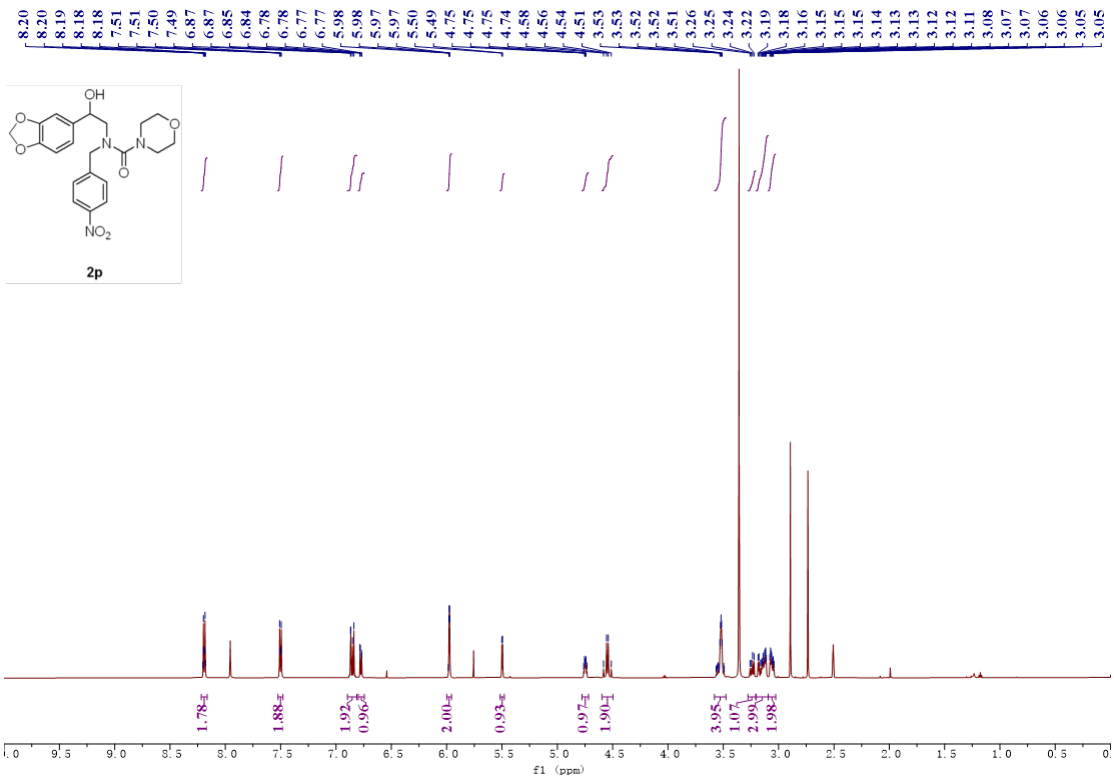
^{13}C NMR spectrum of compound **2n** in DMSO-d_6



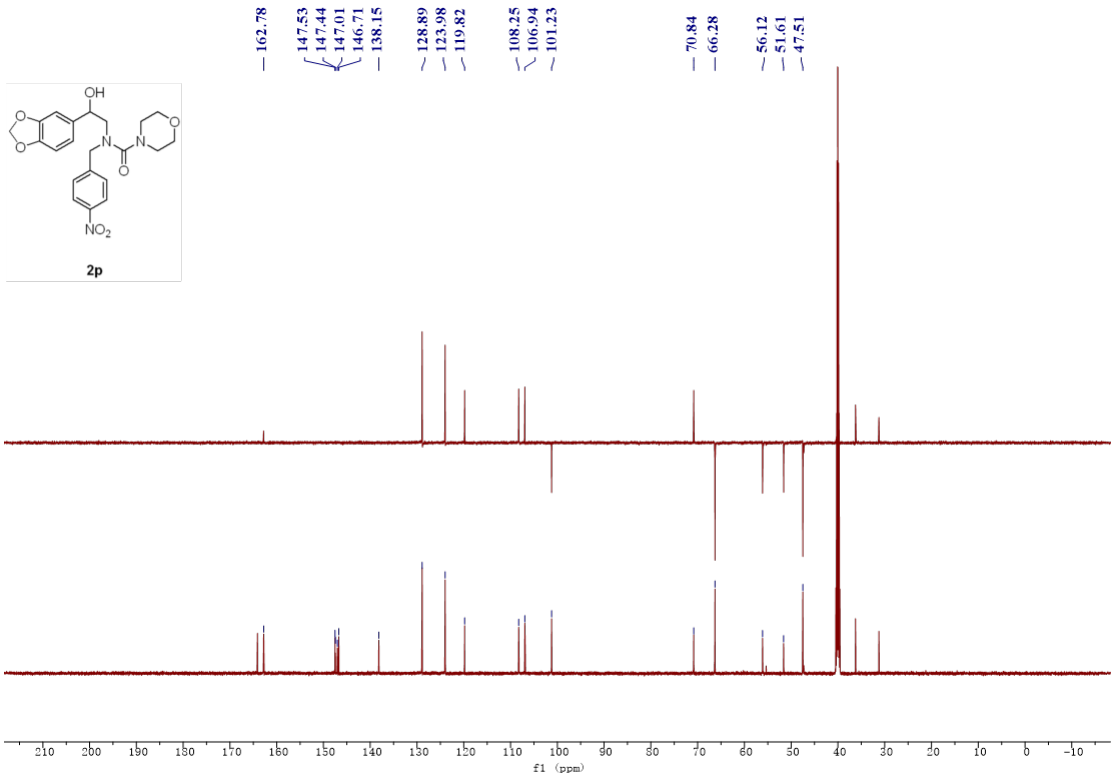
^{1}H NMR spectrum of compound **2o** in DMSO-d_6



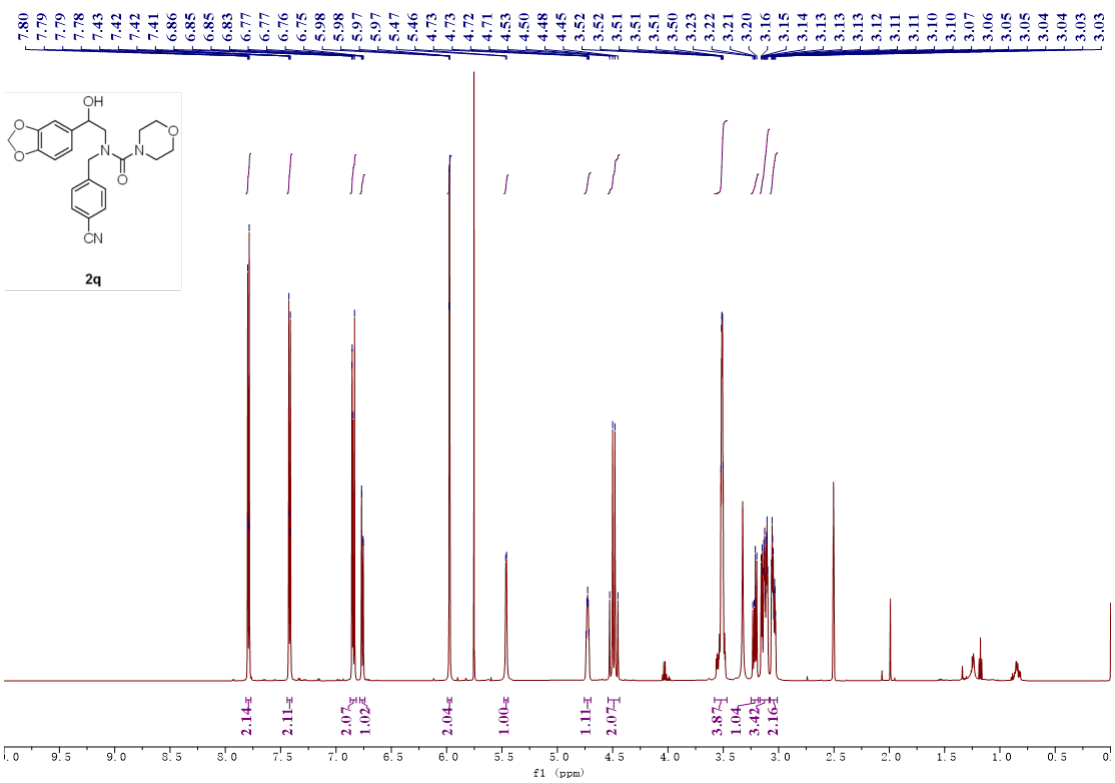
^{13}C NMR spectrum of compound **2o** in DMSO-d_6



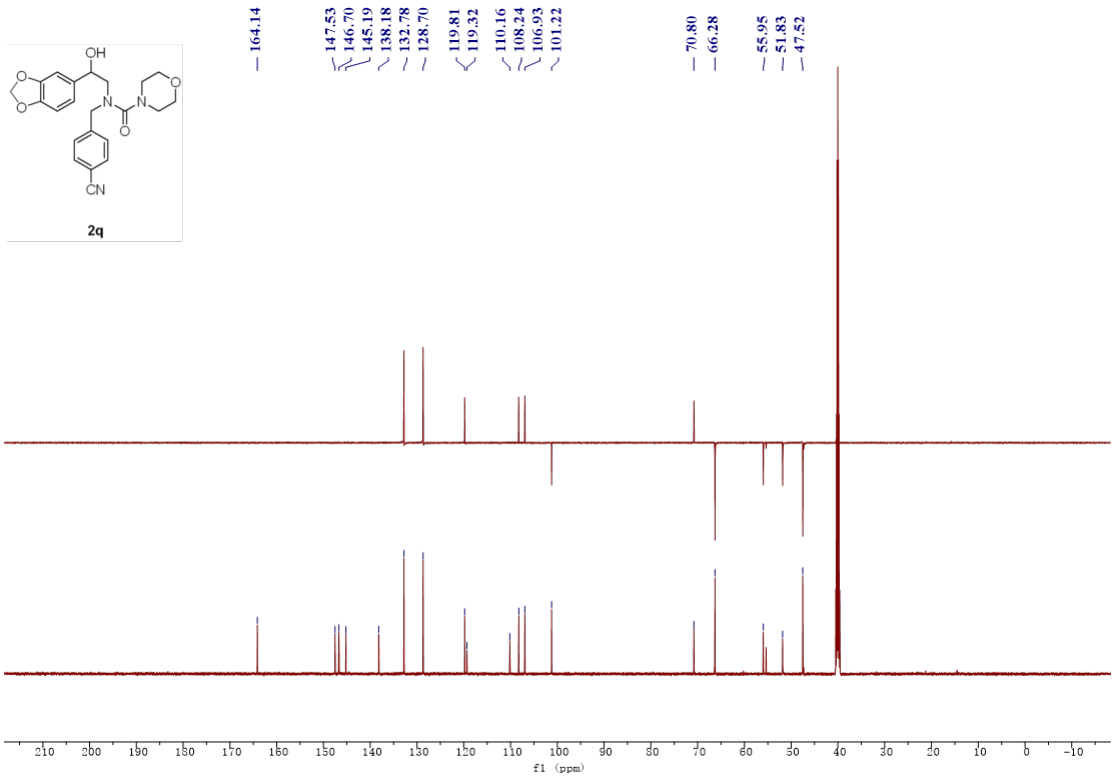
^{1}H NMR spectrum of compound **2p** in DMSO-d_6



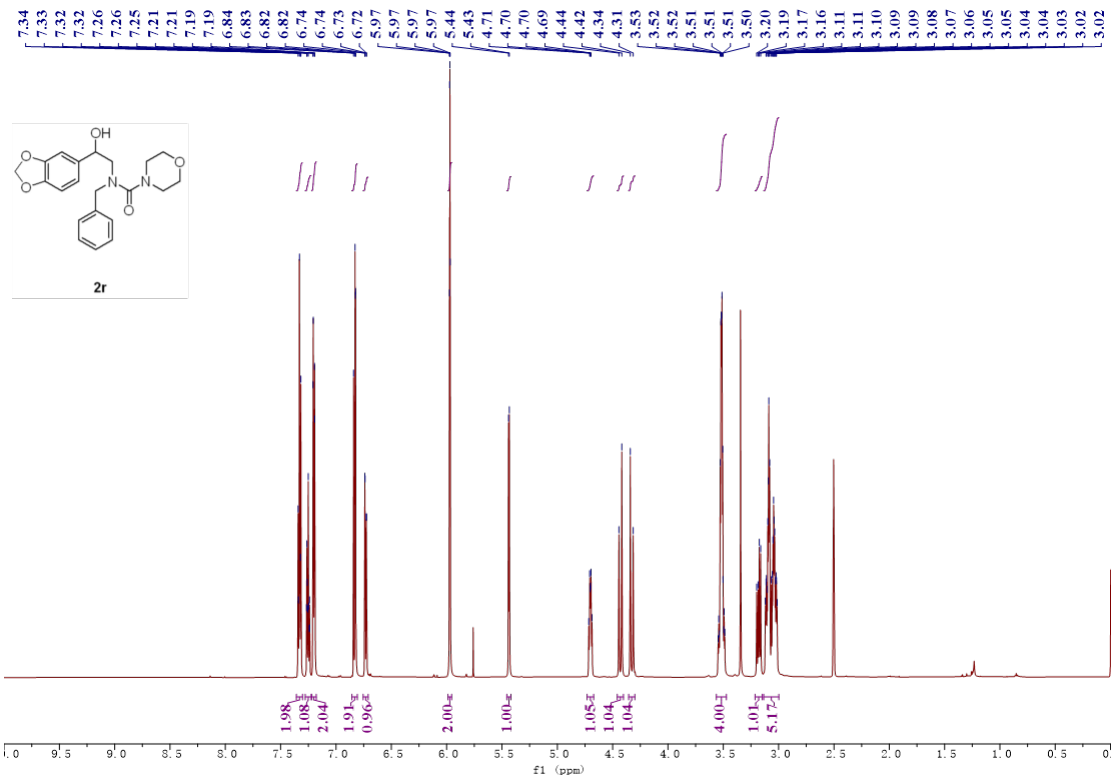
^{13}C NMR spectrum of compound **2p** in DMSO-d_6



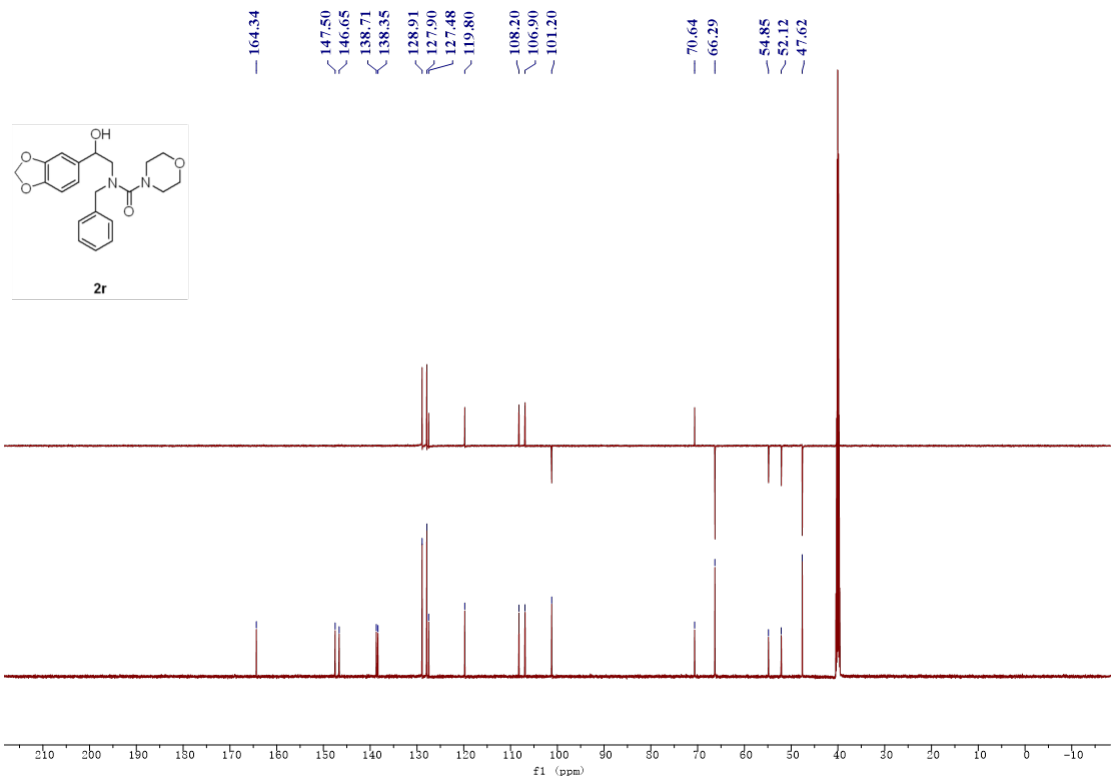
^{1}H NMR spectrum of compound **2q** in DMSO-d_6



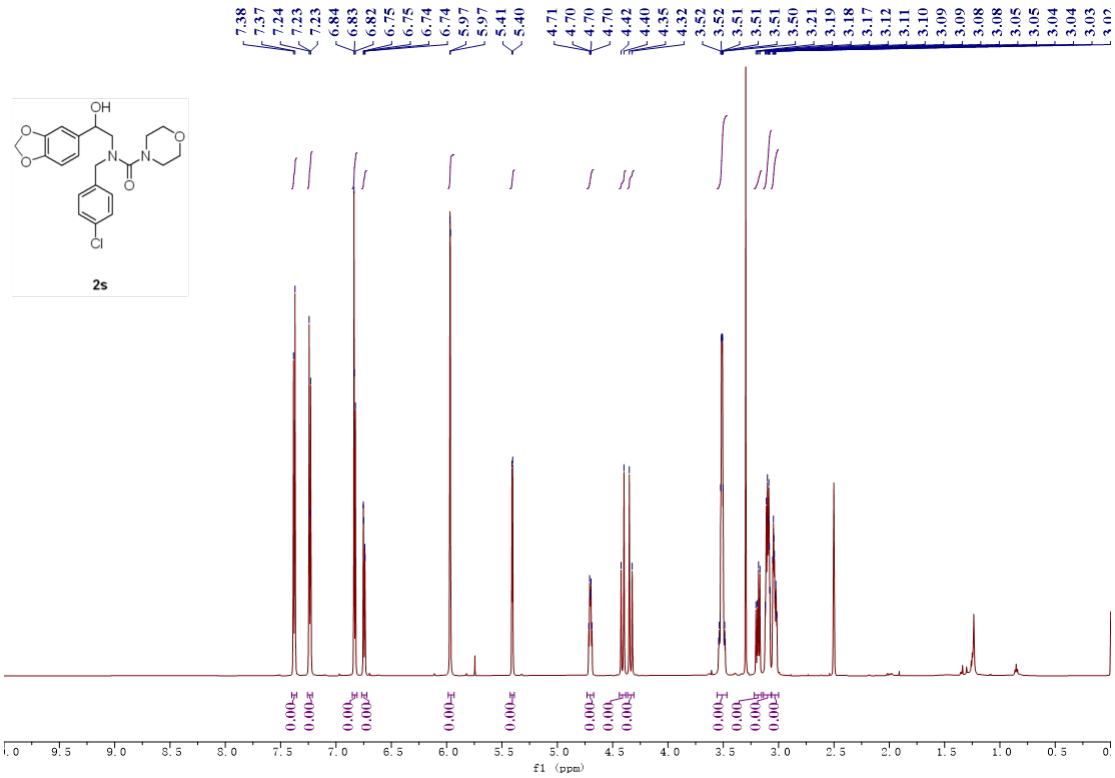
^{13}C NMR spectrum of compound **2q** in DMSO-d_6



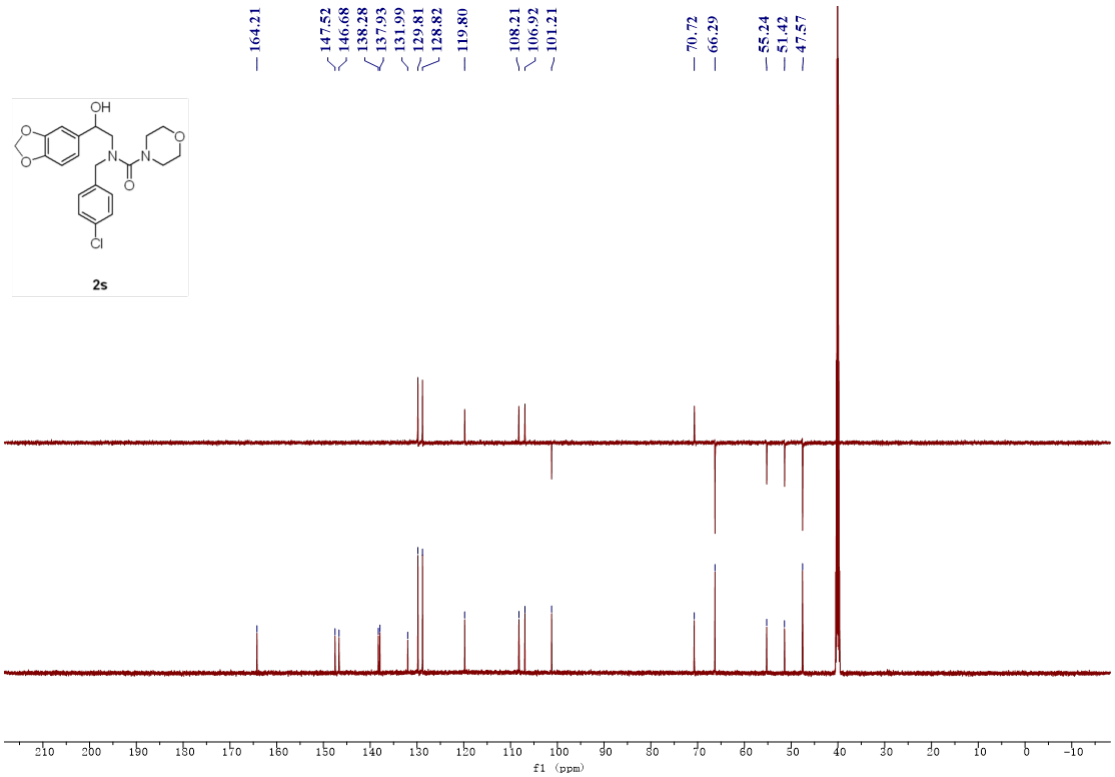
^{1}H NMR spectrum of compound **2r** in DMSO-d_6



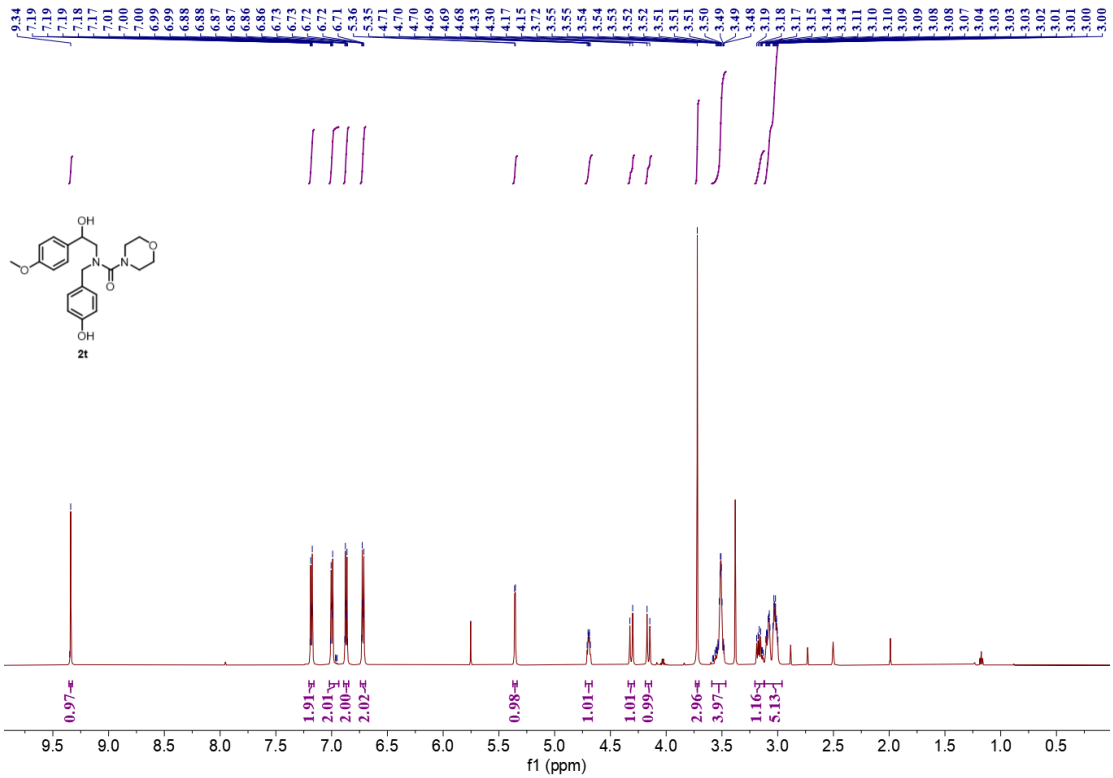
^{13}C NMR spectrum of compound **2r** in DMSO-d_6



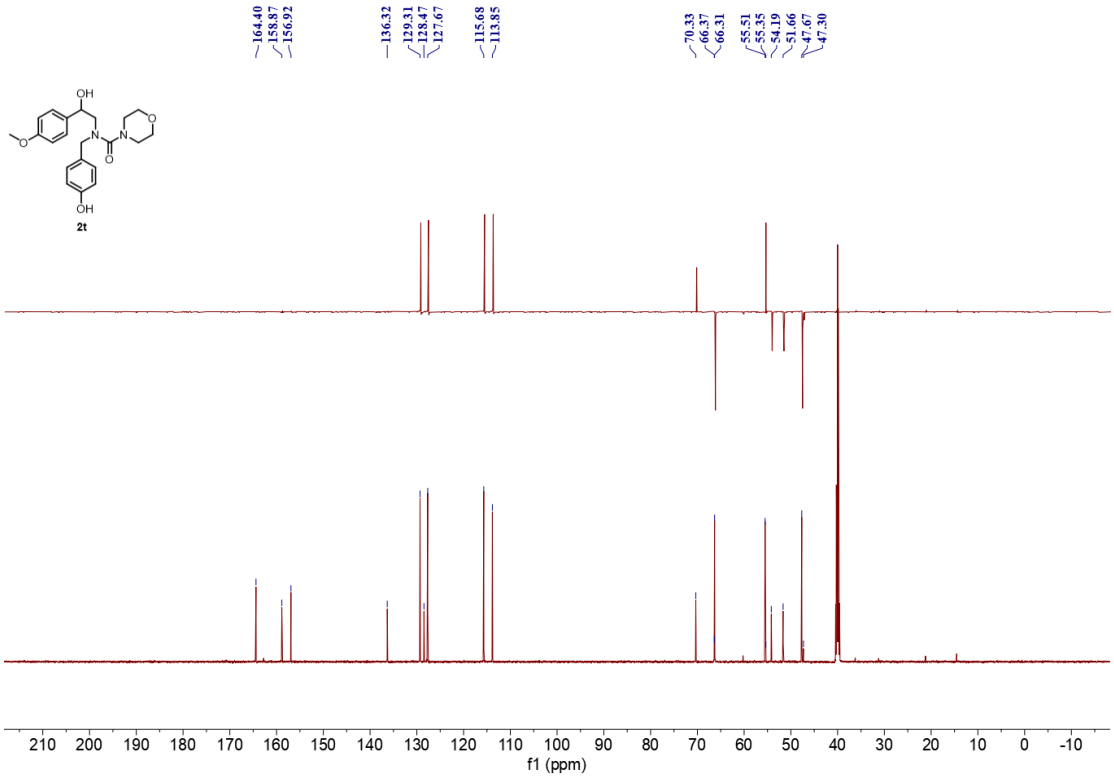
^{1}H NMR spectrum of compound **2s** in DMSO-d_6



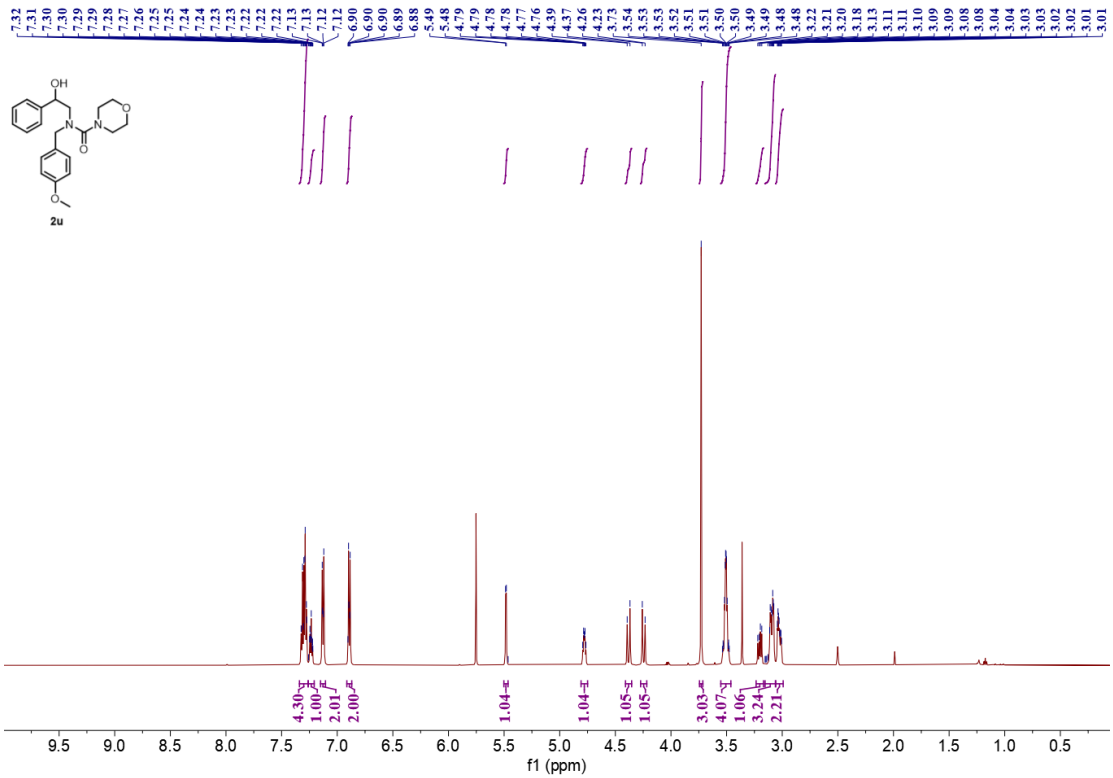
^{13}C NMR spectrum of compound **2s** in DMSO-d_6



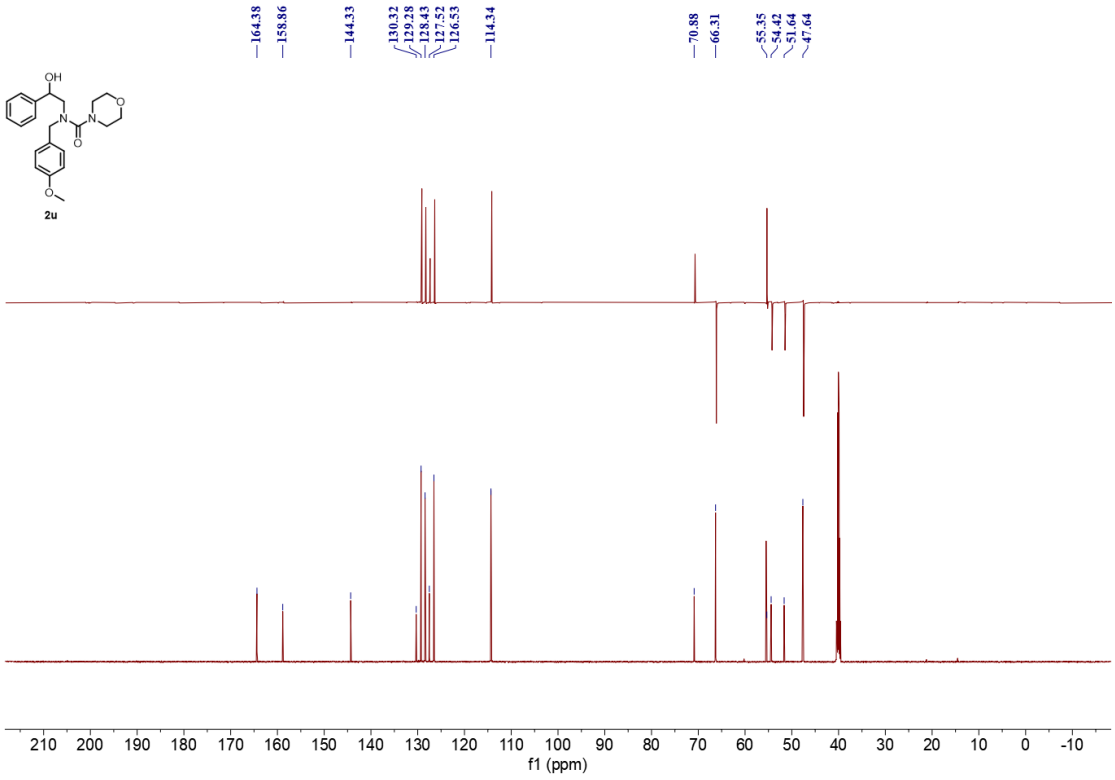
^{1}H NMR spectrum of compound **2t** in DMSO-d_6



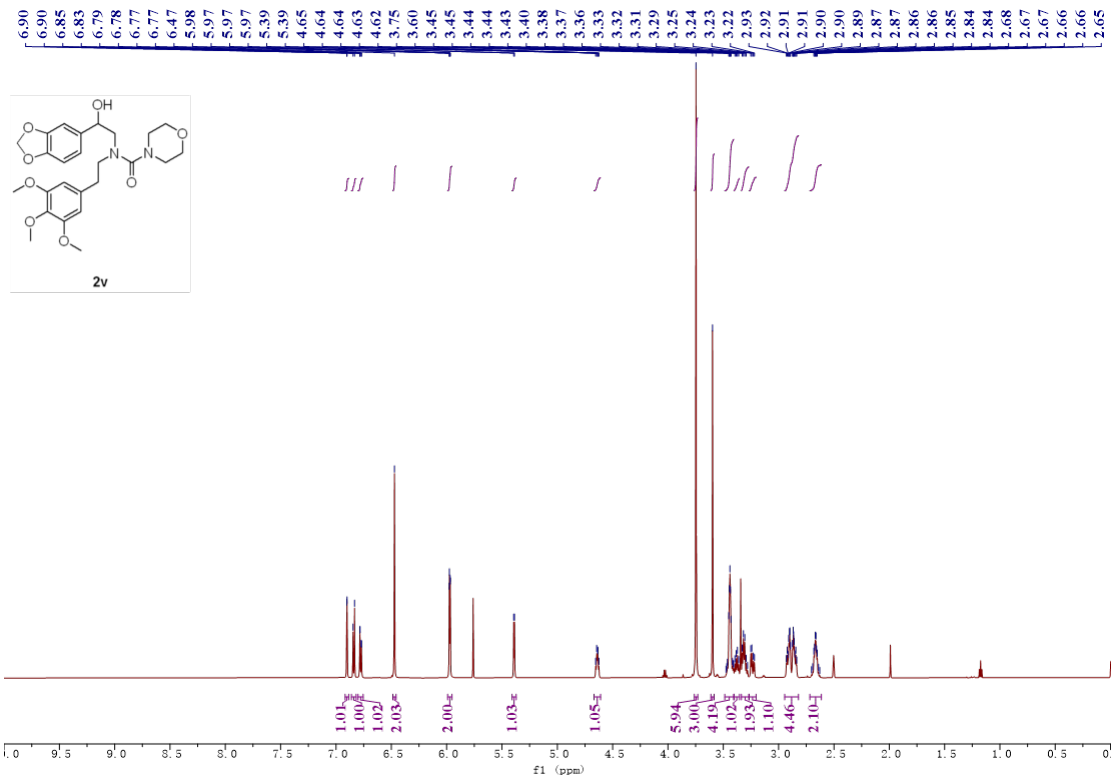
^{13}C NMR spectrum of compound **2t** in DMSO-d_6



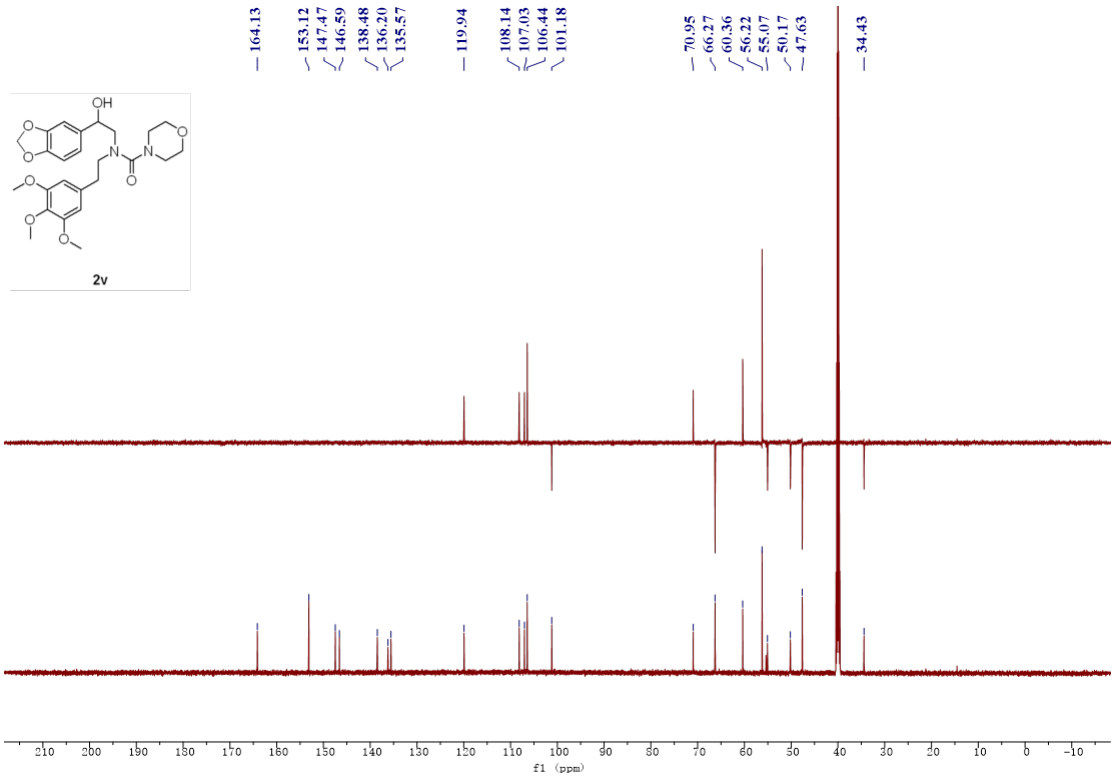
^{1}H NMR spectrum of compound **2u** in DMSO-d_6



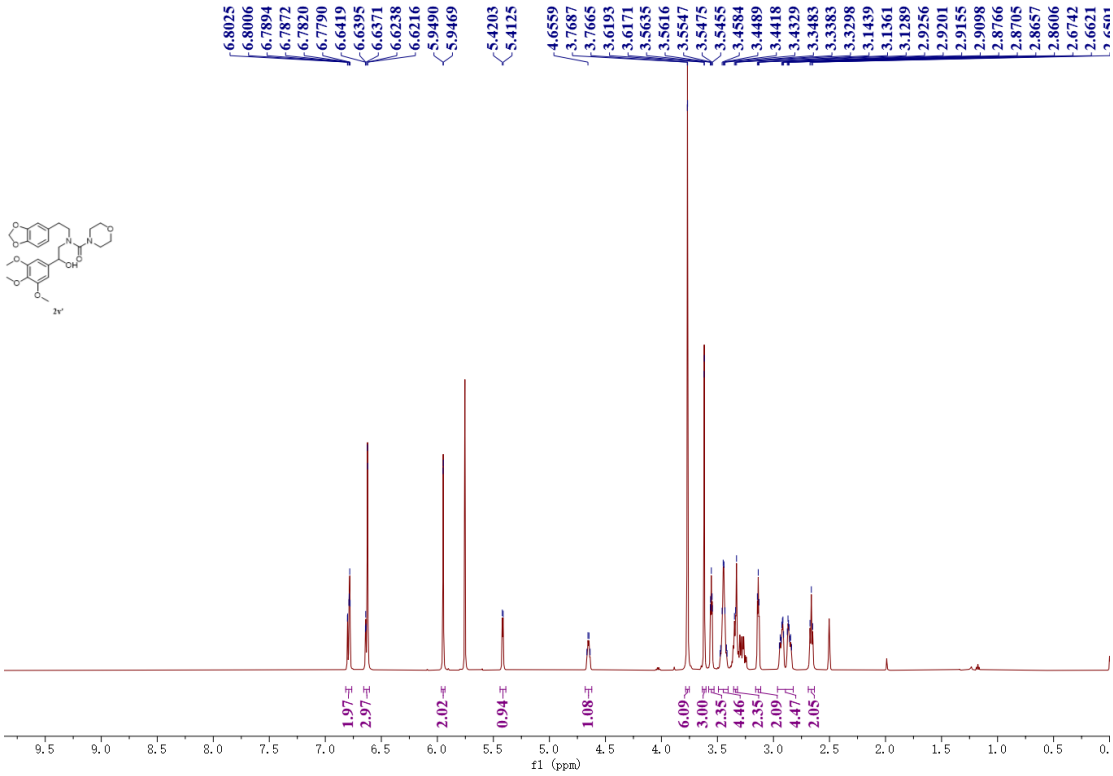
^{13}C NMR spectrum of compound **2u** in DMSO-d_6



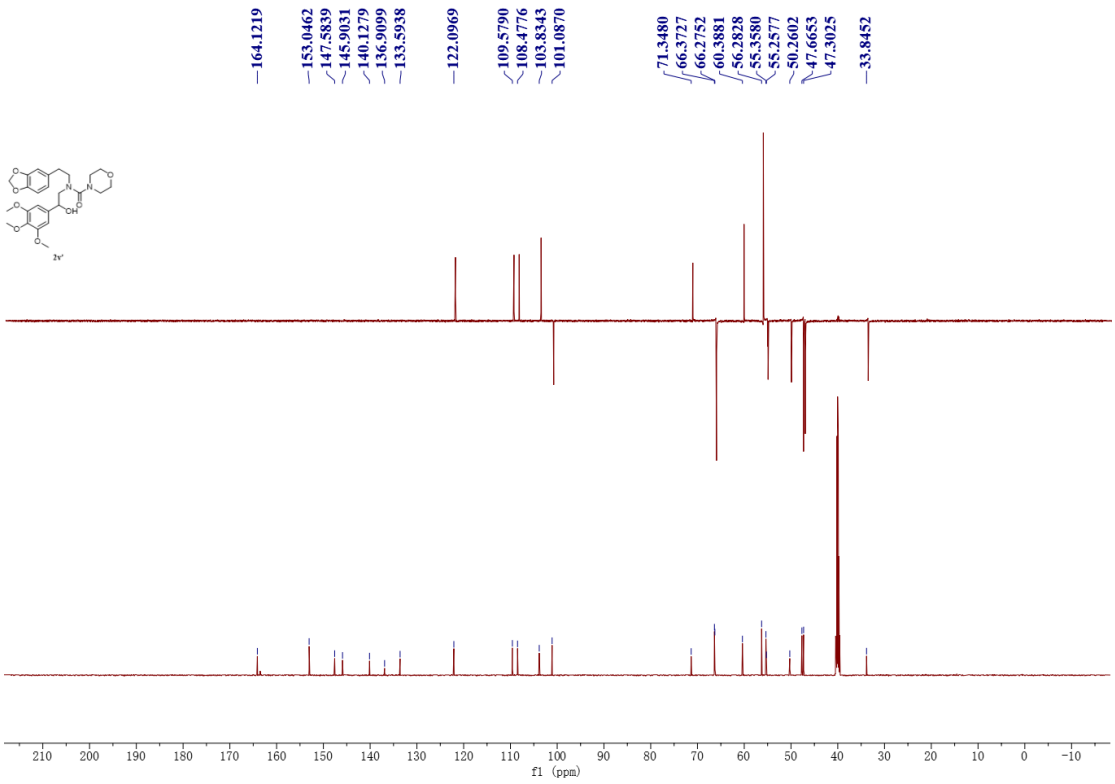
^{1}H NMR spectrum of compound **2v** in DMSO-d_6



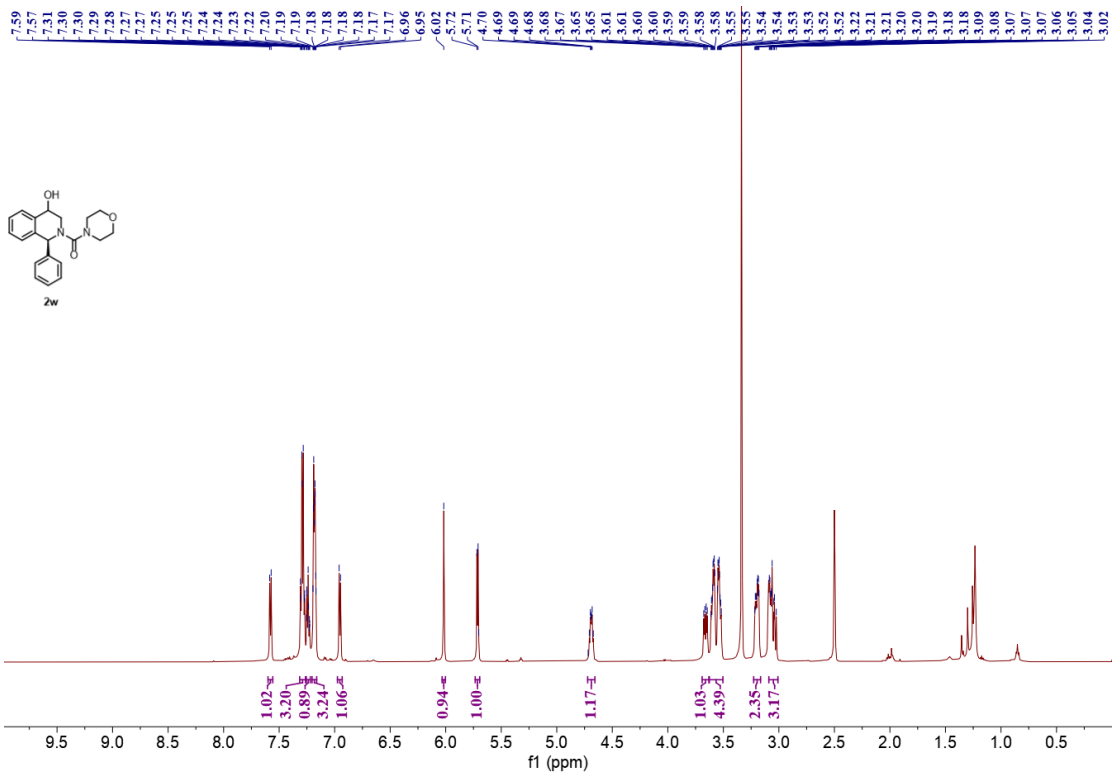
^{13}C NMR spectrum of compound **2v** in DMSO-d_6



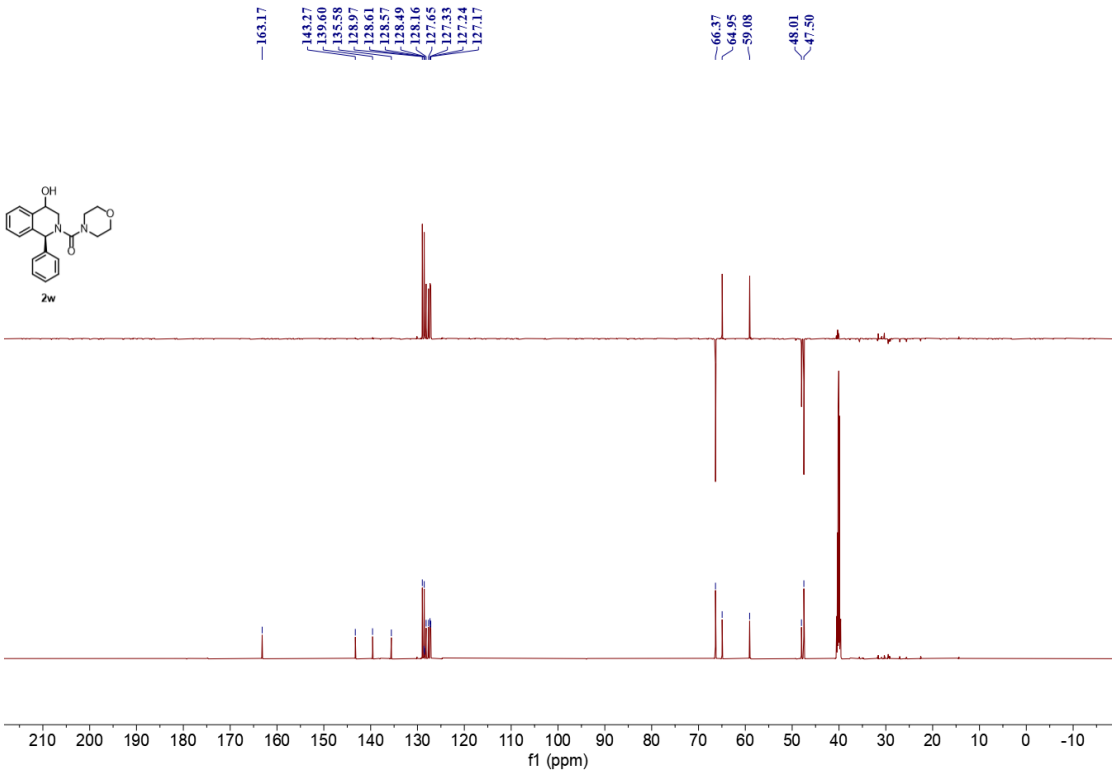
^{1}H NMR spectrum of compound **2v'** in DMSO-d_6



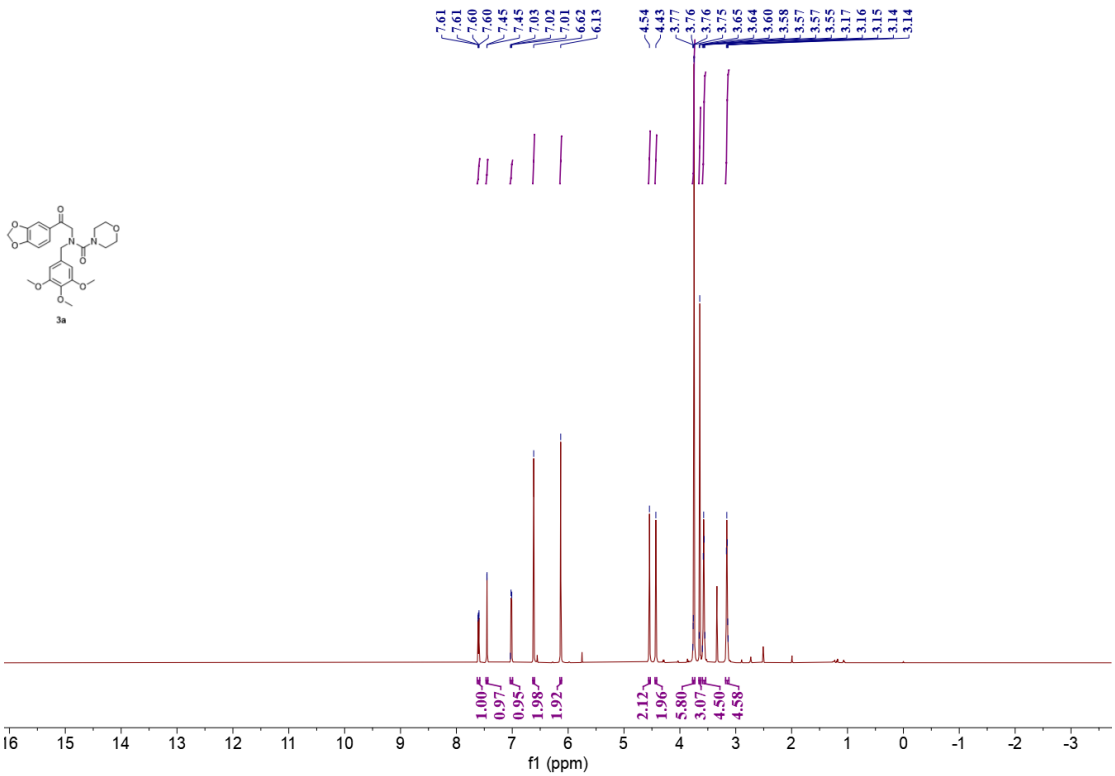
^{13}C NMR spectrum of compound **2v'** in DMSO-d_6



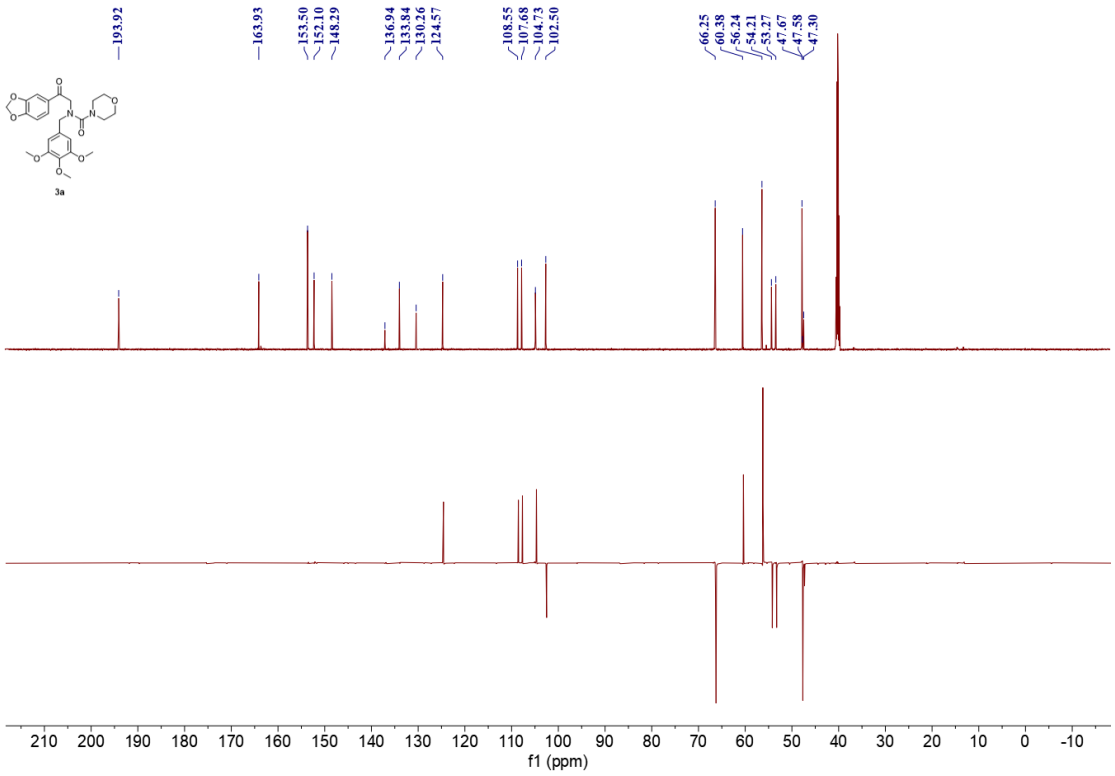
^{1}H NMR spectrum of compound **2w** in DMSO-d_6



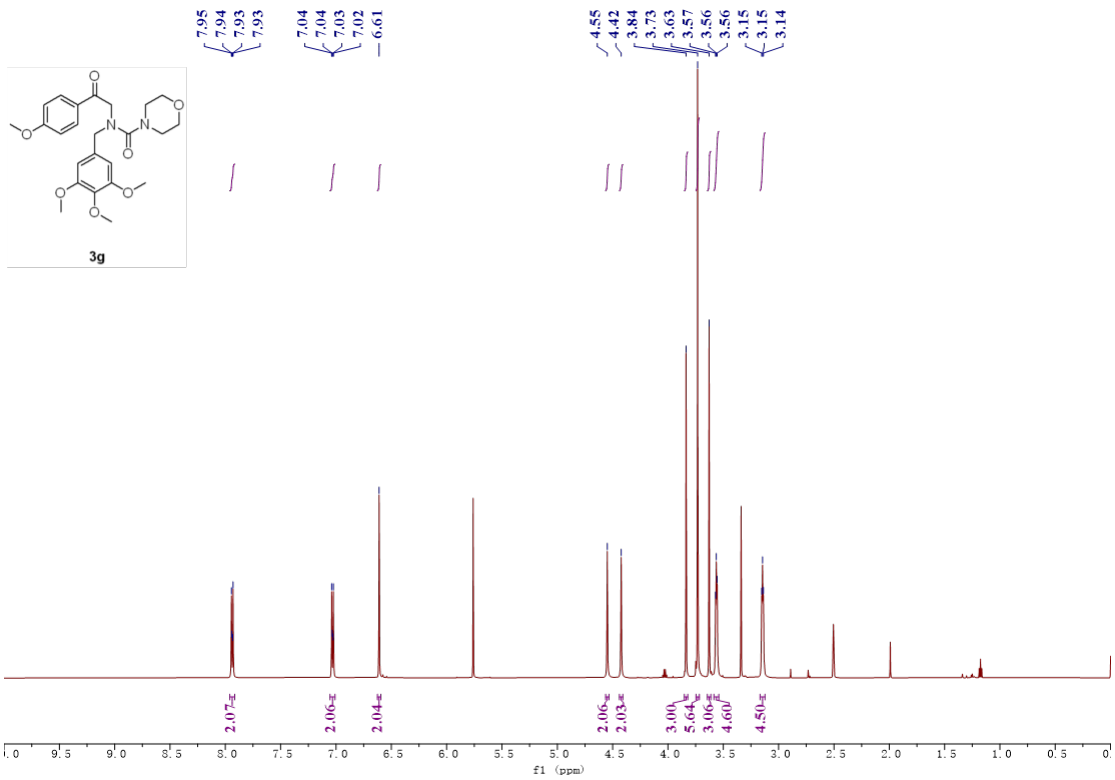
^{13}C NMR spectrum of compound **2w** in DMSO-d_6



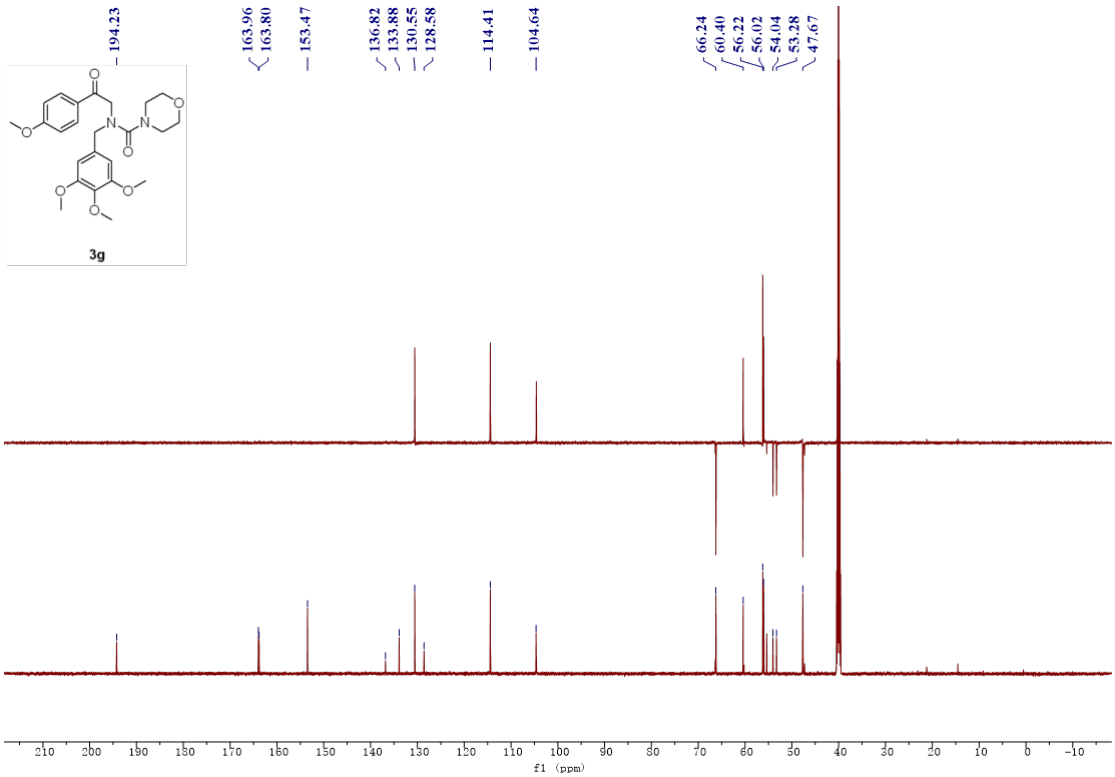
^{1}H NMR spectrum of compound **3a** in DMSO-d_6



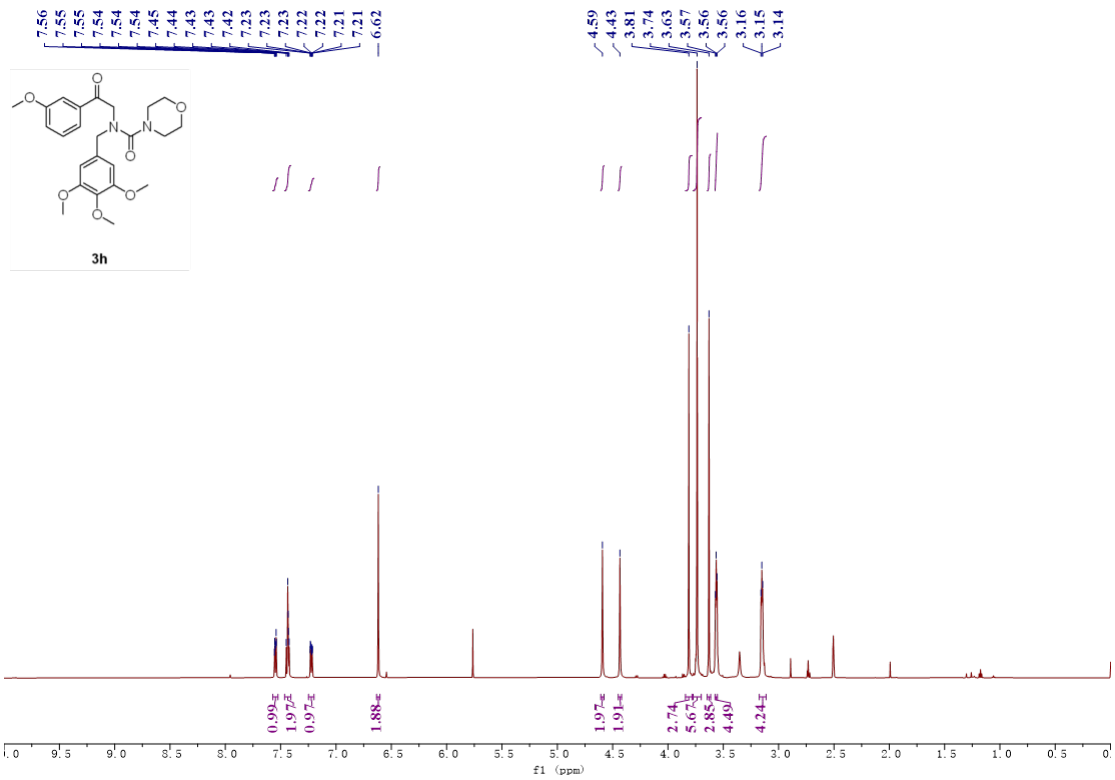
^{13}C NMR spectrum of compound **3a** in DMSO-d_6



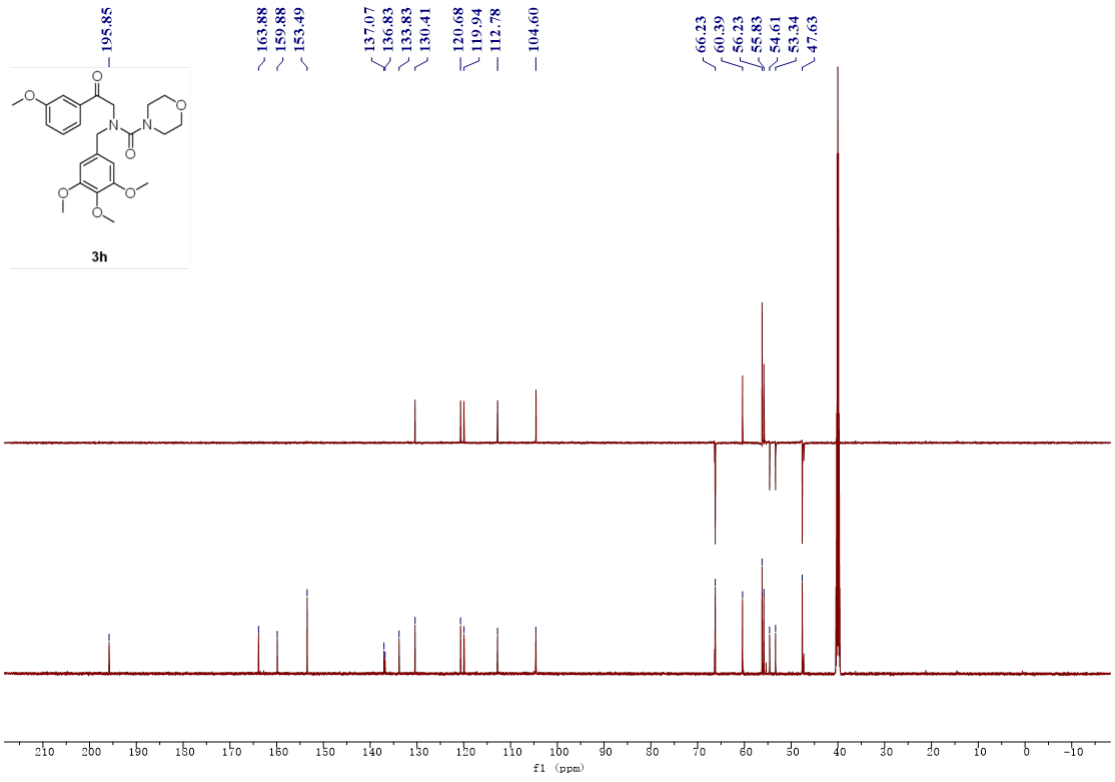
^{1}H NMR spectrum of compound **3g** in DMSO-d_6



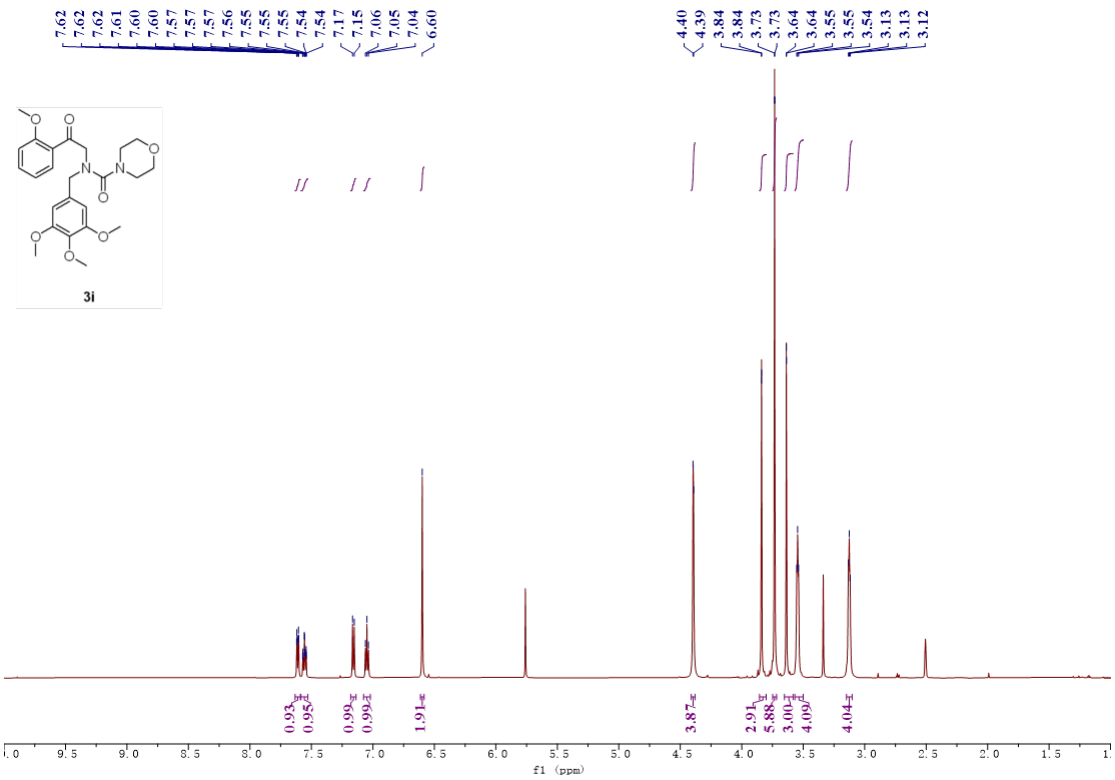
^{13}C NMR spectrum of compound **3g** in DMSO-d_6



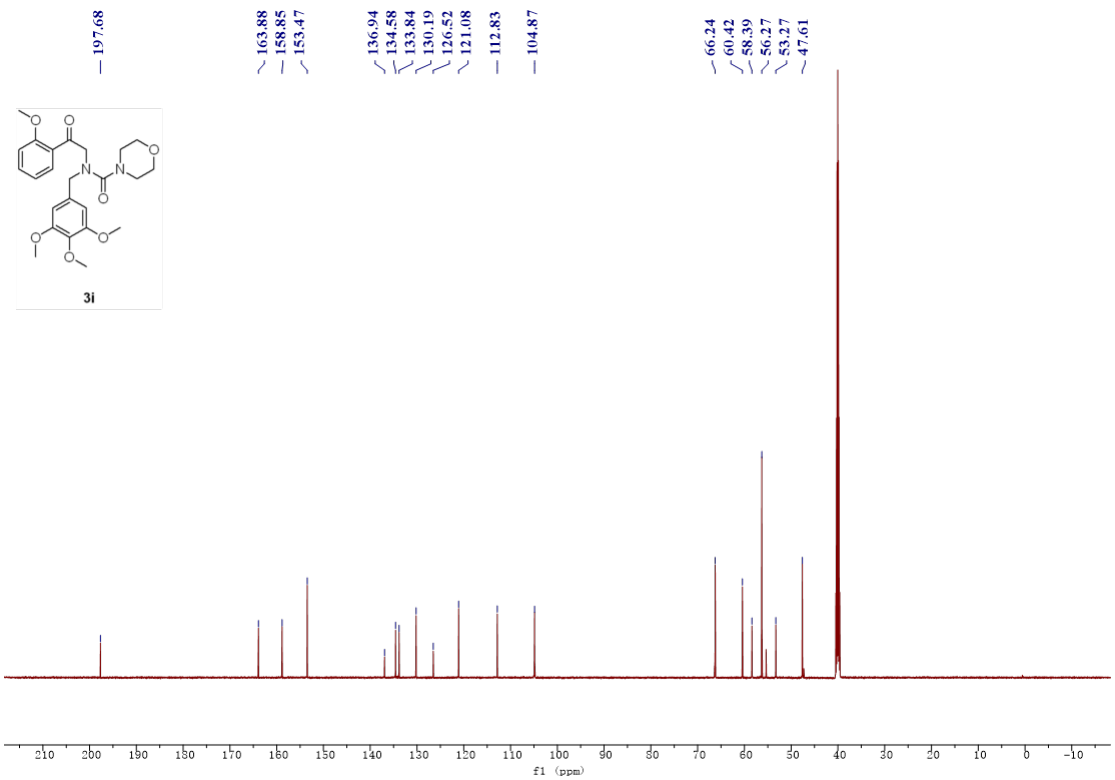
^{1}H NMR spectrum of compound **3h** in DMSO-d_6



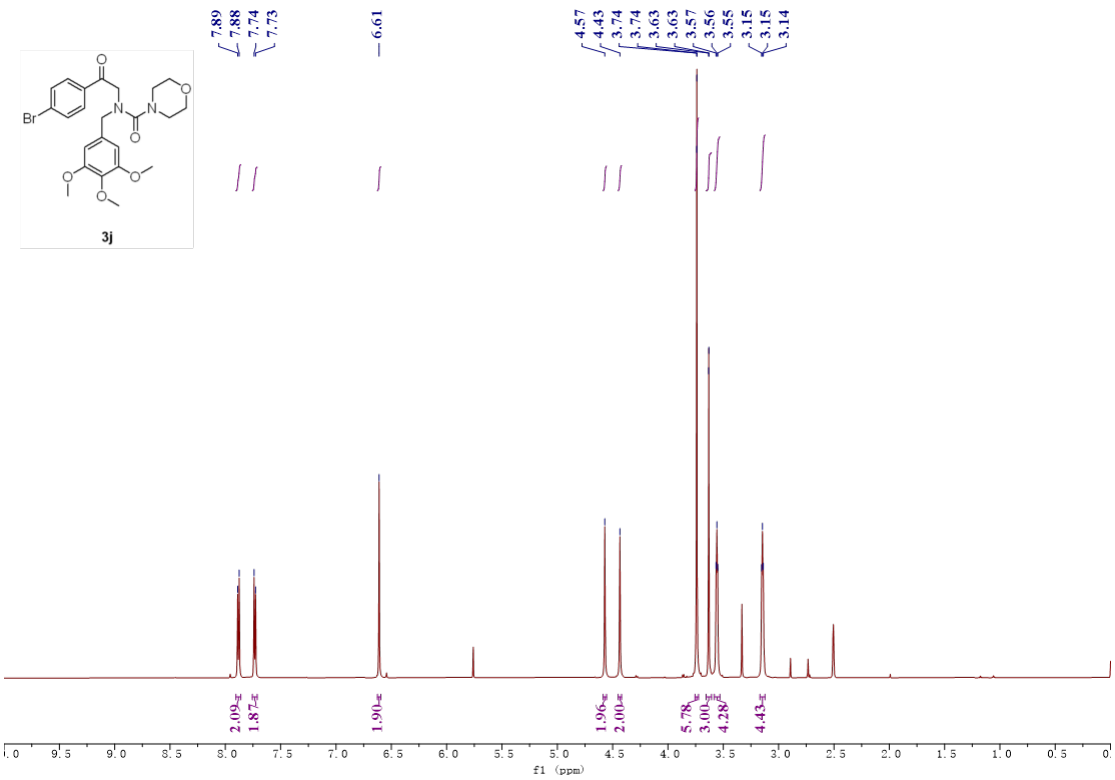
^{13}C NMR spectrum of compound **3h** in DMSO-d_6



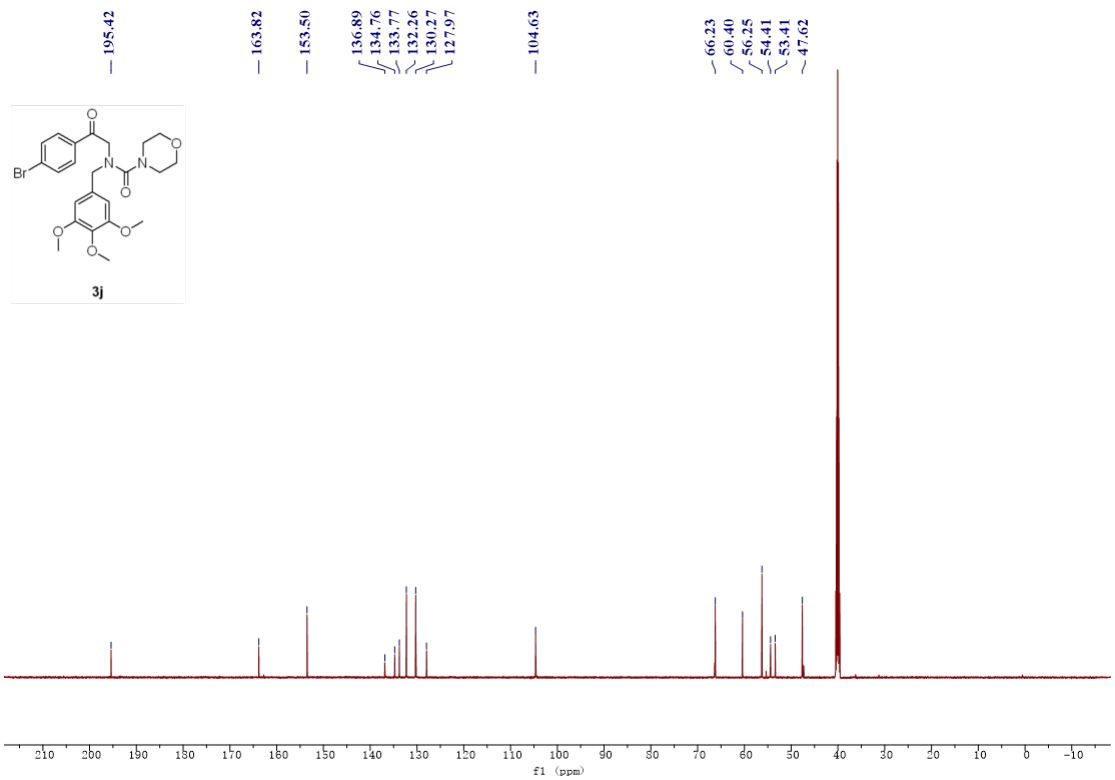
^{1}H NMR spectrum of compound **3i** in DMSO-d_6



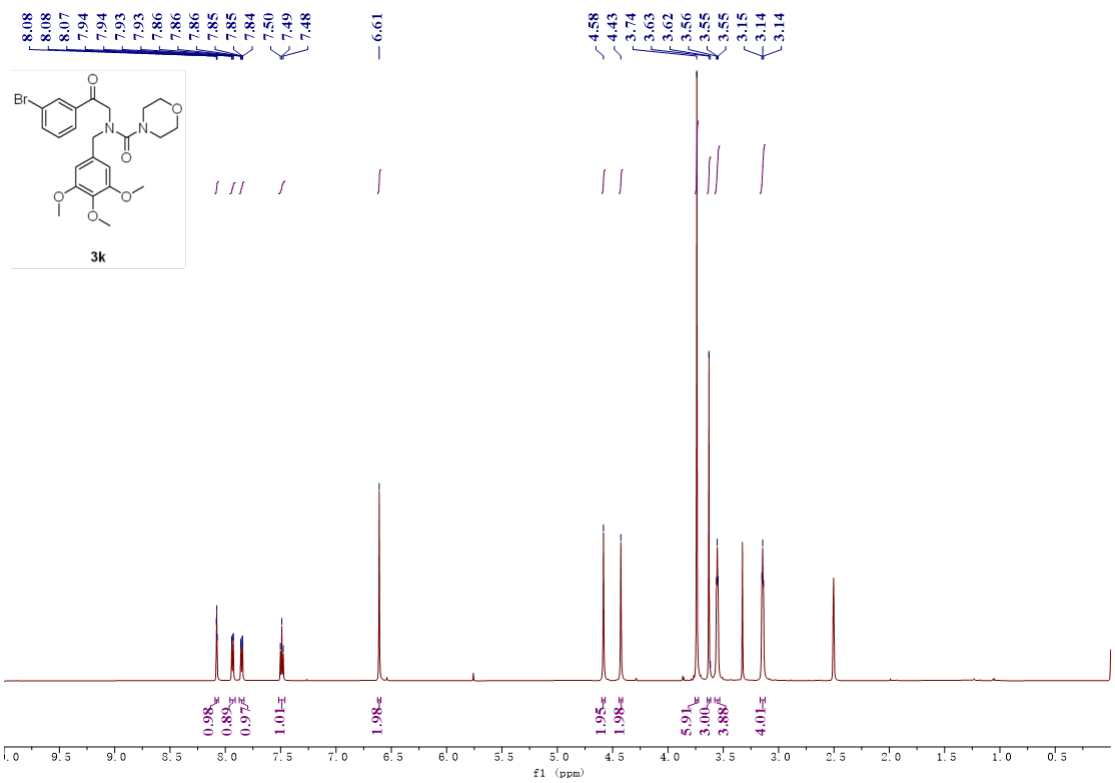
^{13}C NMR spectrum of compound **3i** in DMSO-d_6



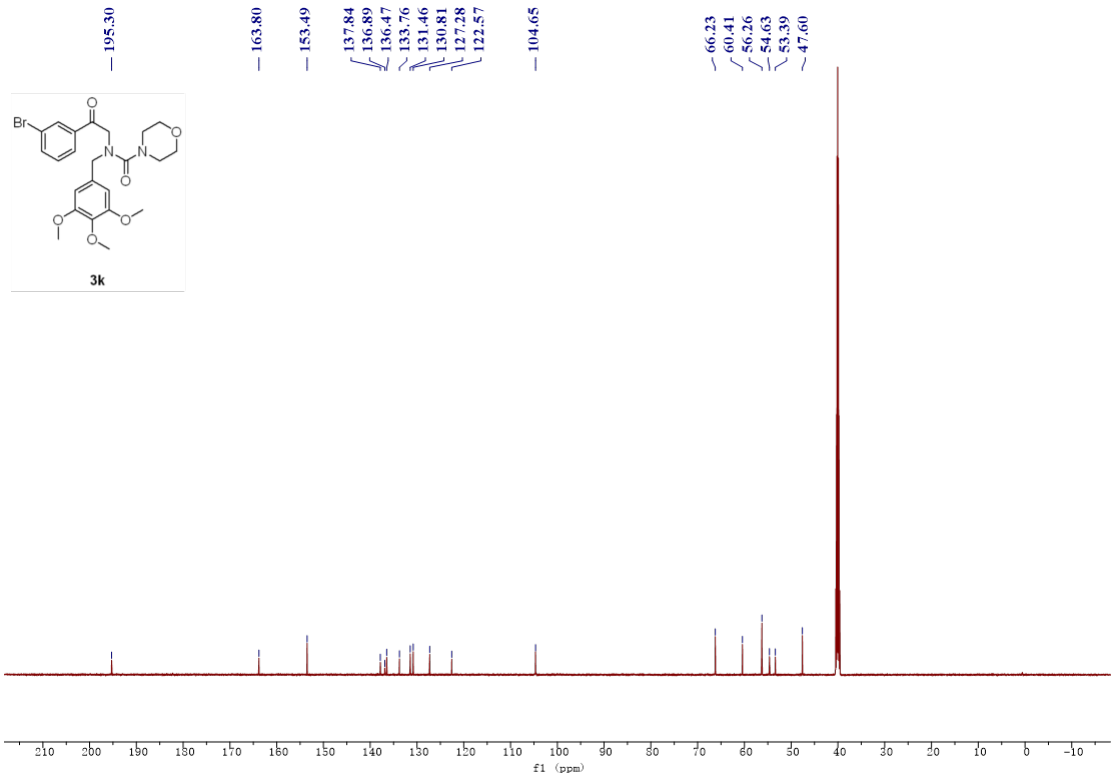
^{1}H NMR spectrum of compound **3j** in DMSO-d_6



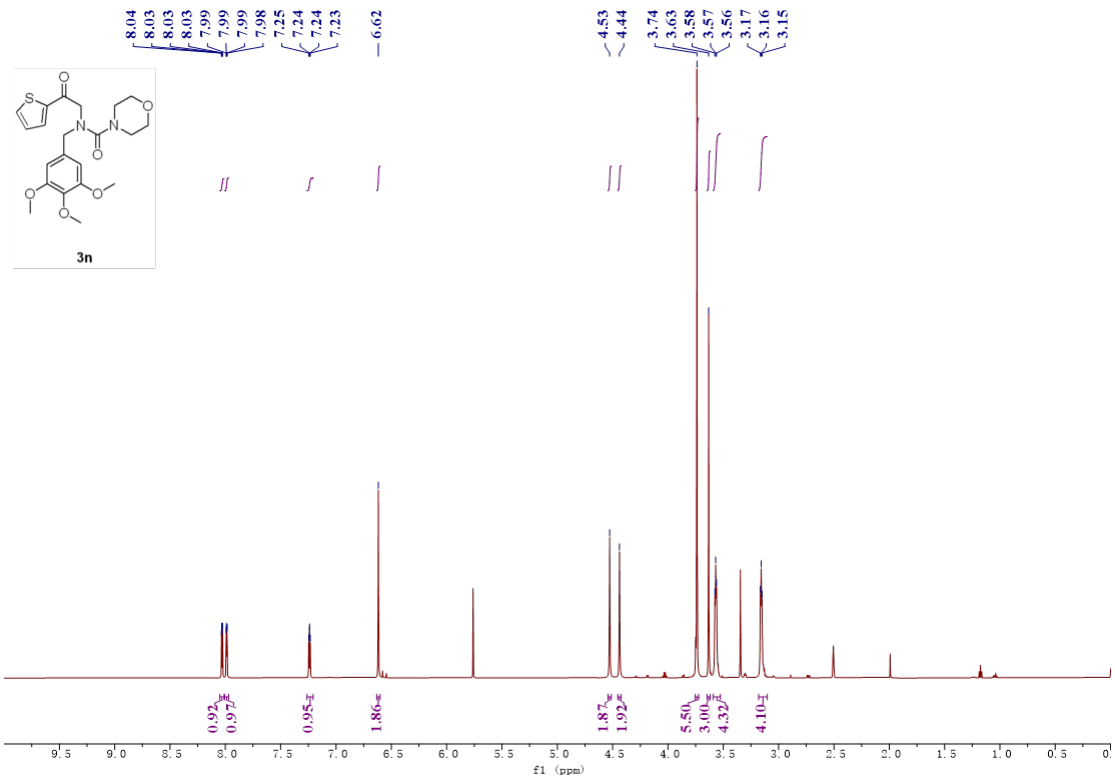
^{13}C NMR spectrum of compound **3j** in DMSO-d_6



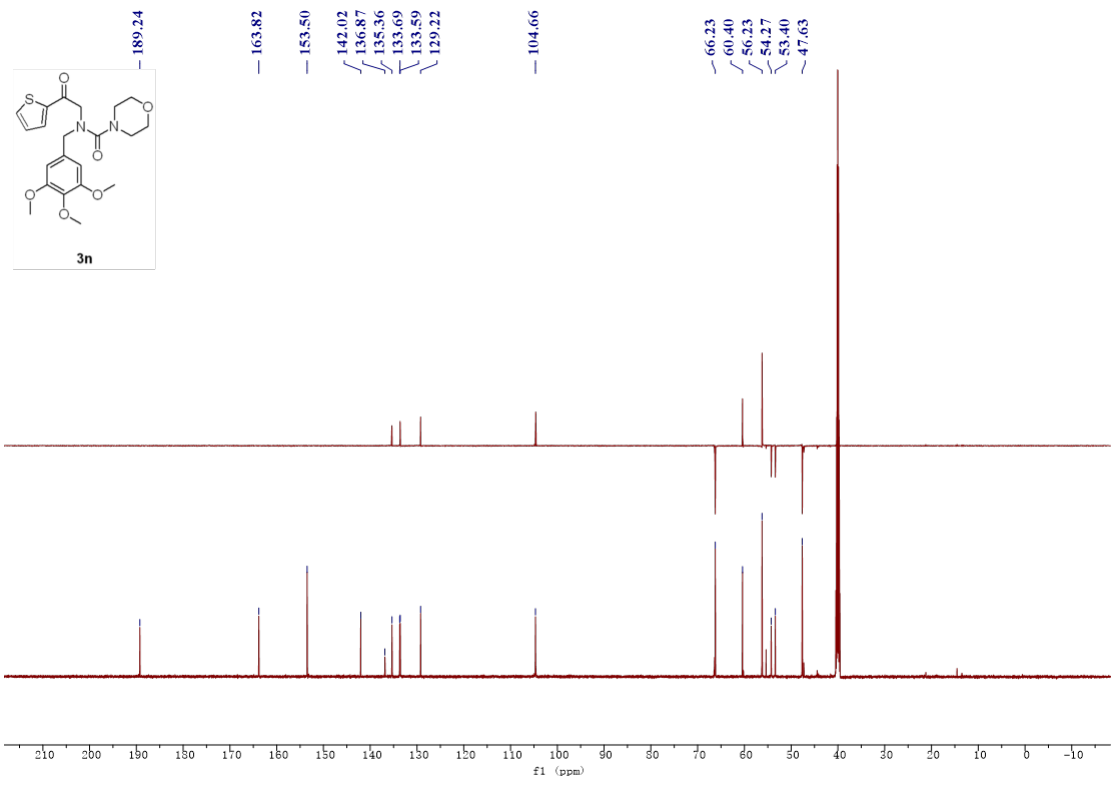
^{1}H NMR spectrum of compound **3k** in DMSO-d_6



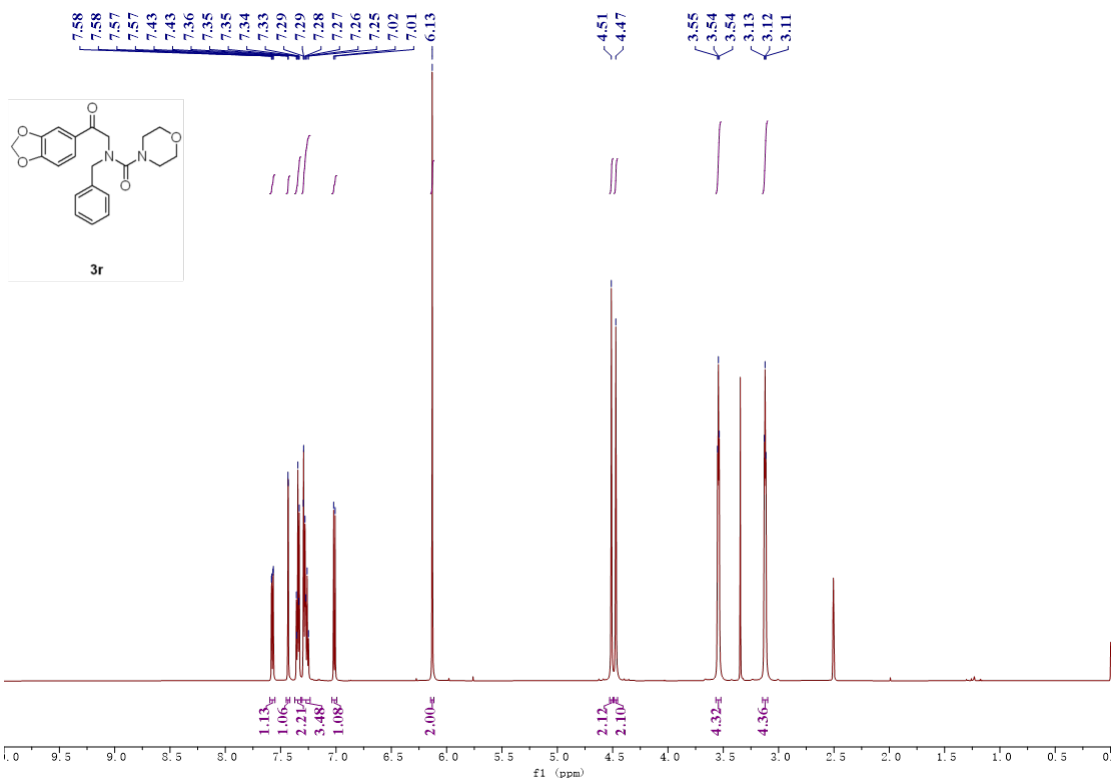
^{13}C NMR spectrum of compound **3k** in DMSO-d_6



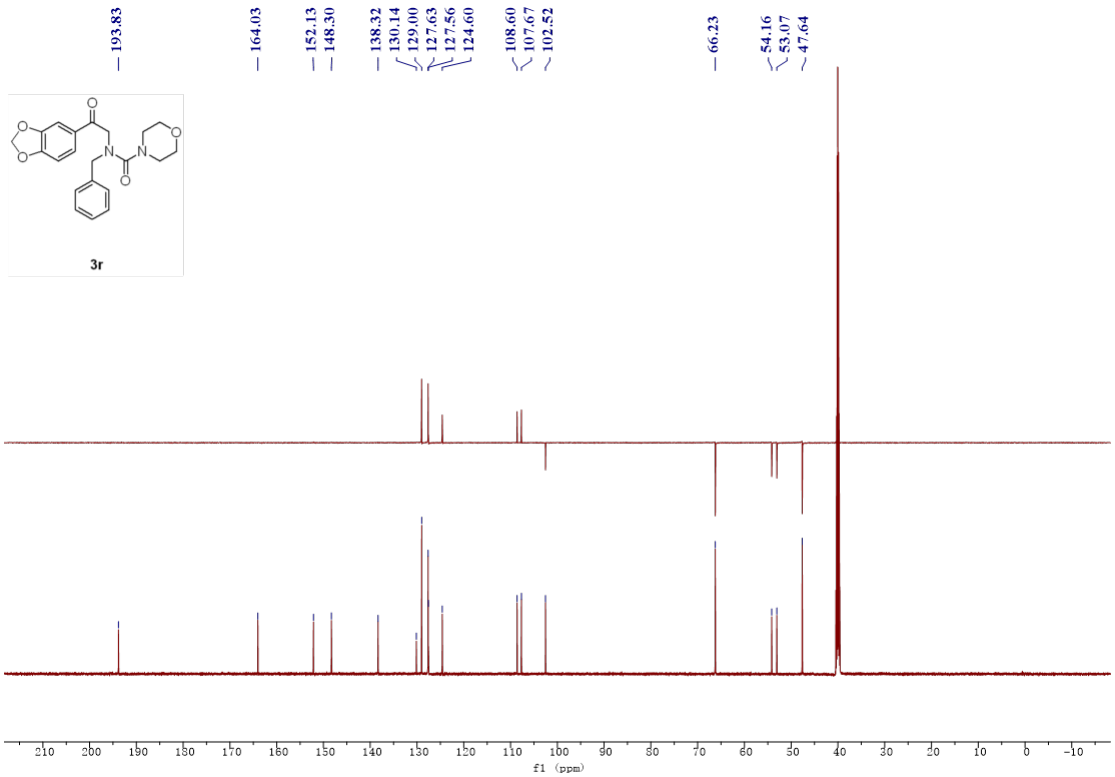
^{1}H NMR spectrum of compound **3n** in DMSO-d_6



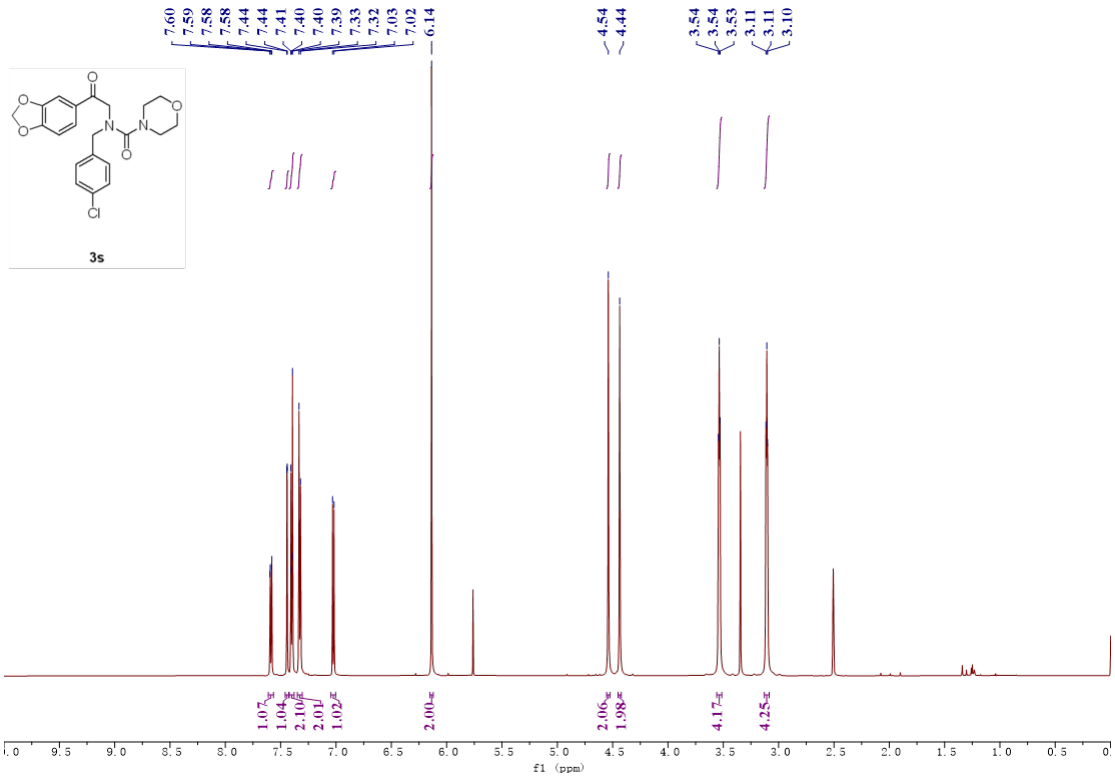
^{13}C NMR spectrum of compound **3n** in DMSO-d_6



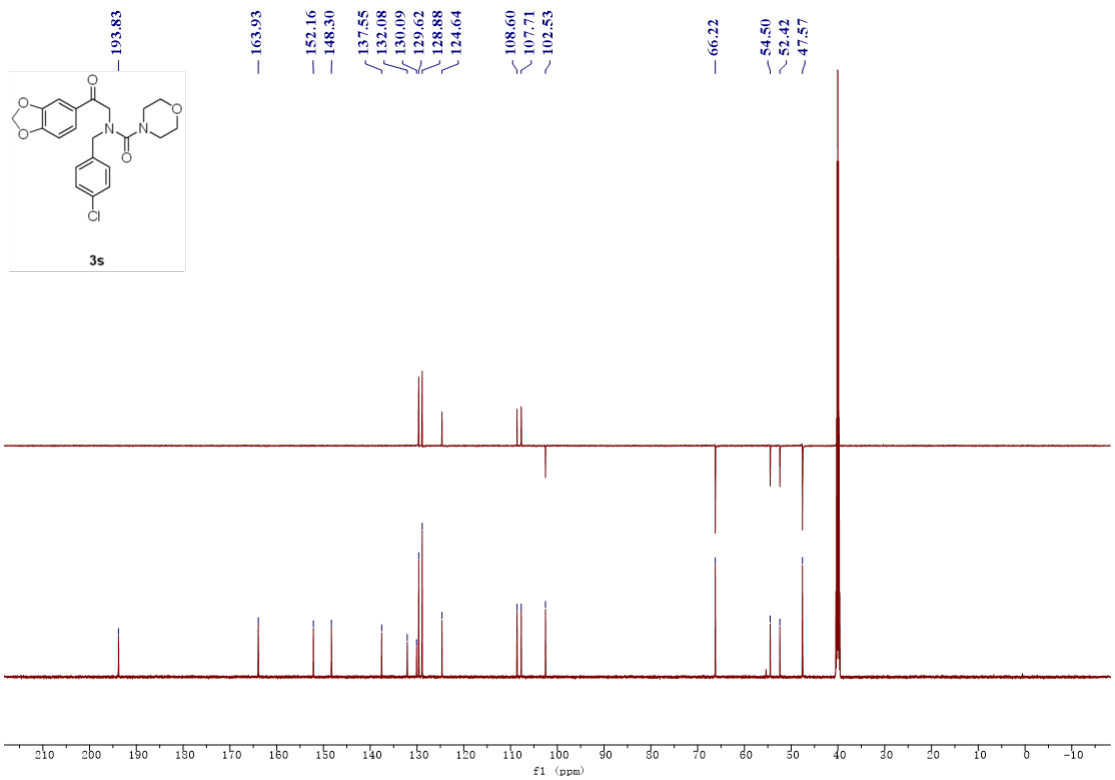
^{1}H NMR spectrum of compound **3r** in DMSO-d_6



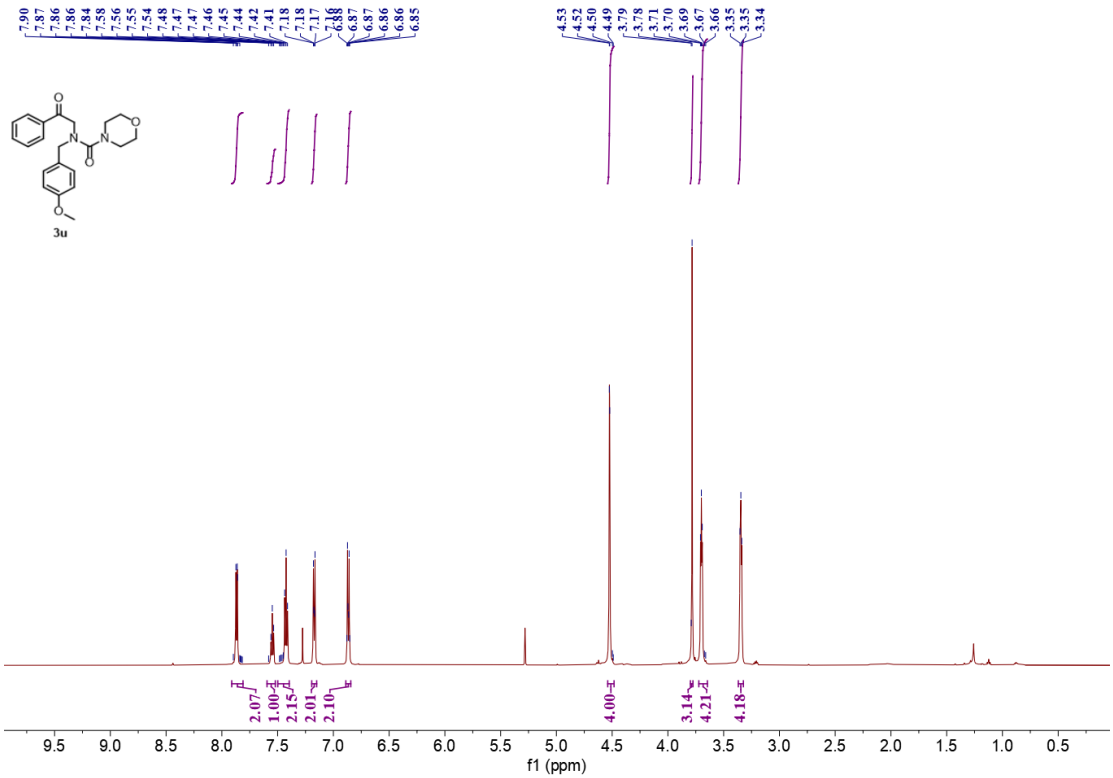
^{13}C NMR spectrum of compound **3r** in DMSO-d_6



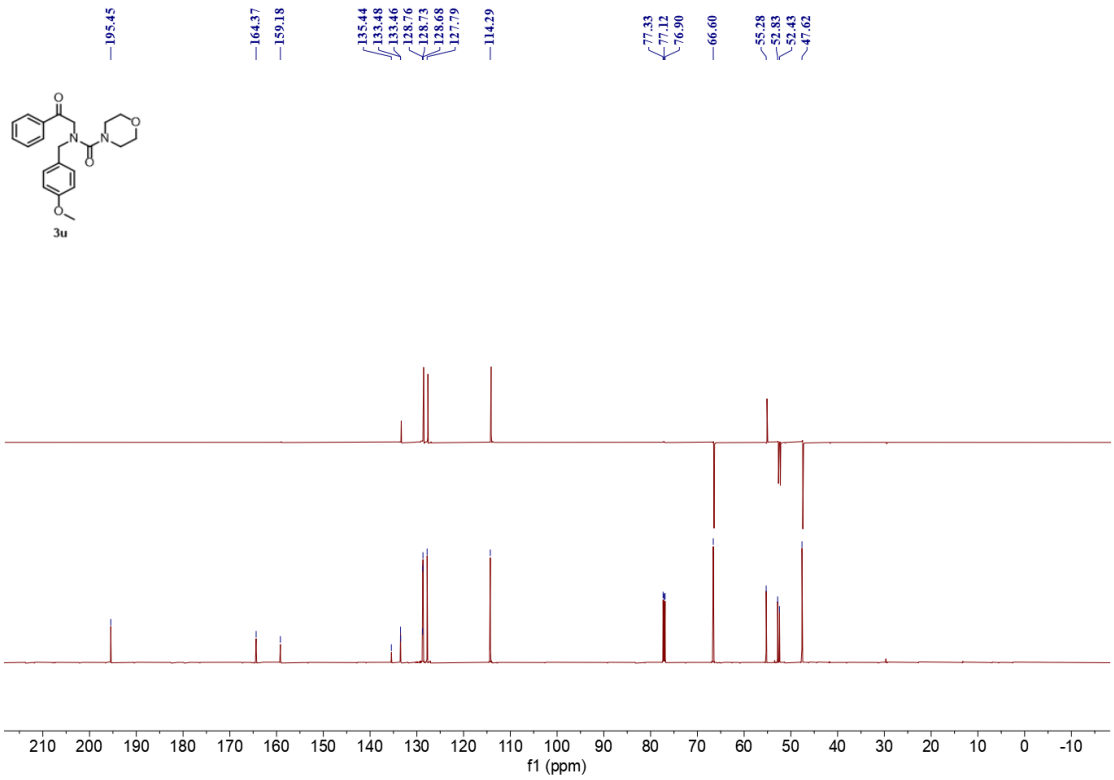
^{1}H NMR spectrum of compound **3s** in DMSO-d_6



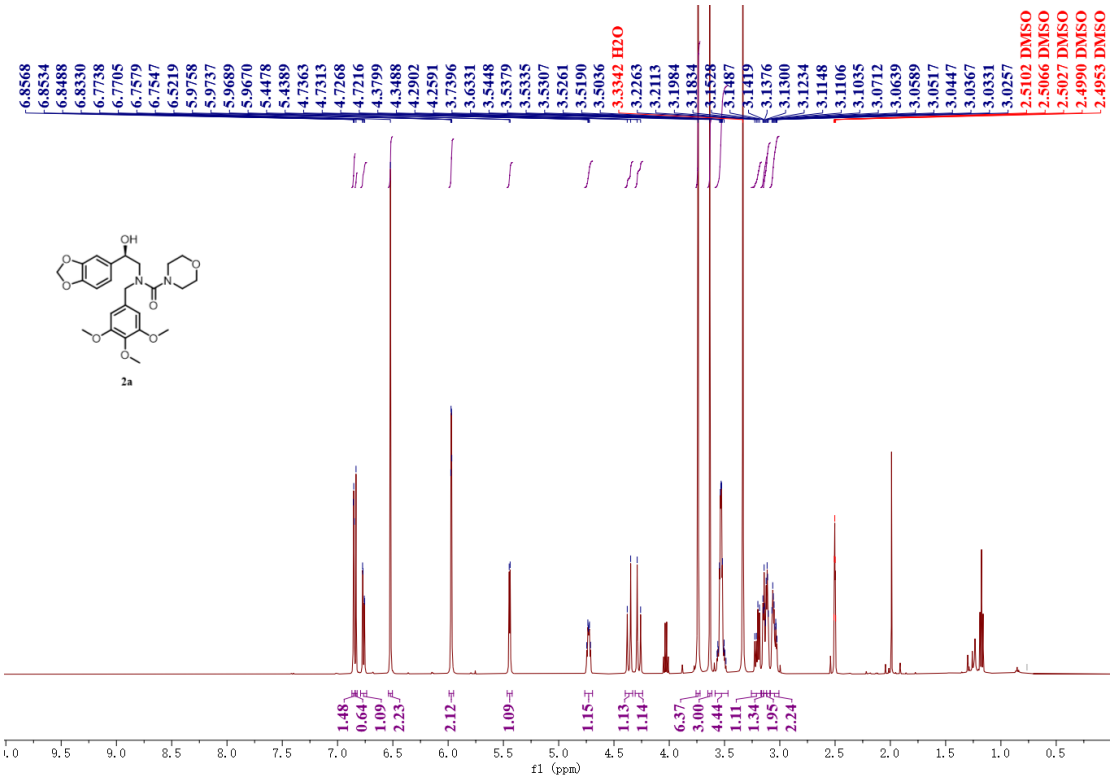
^{13}C NMR spectrum of compound **3s** in DMSO-d_6



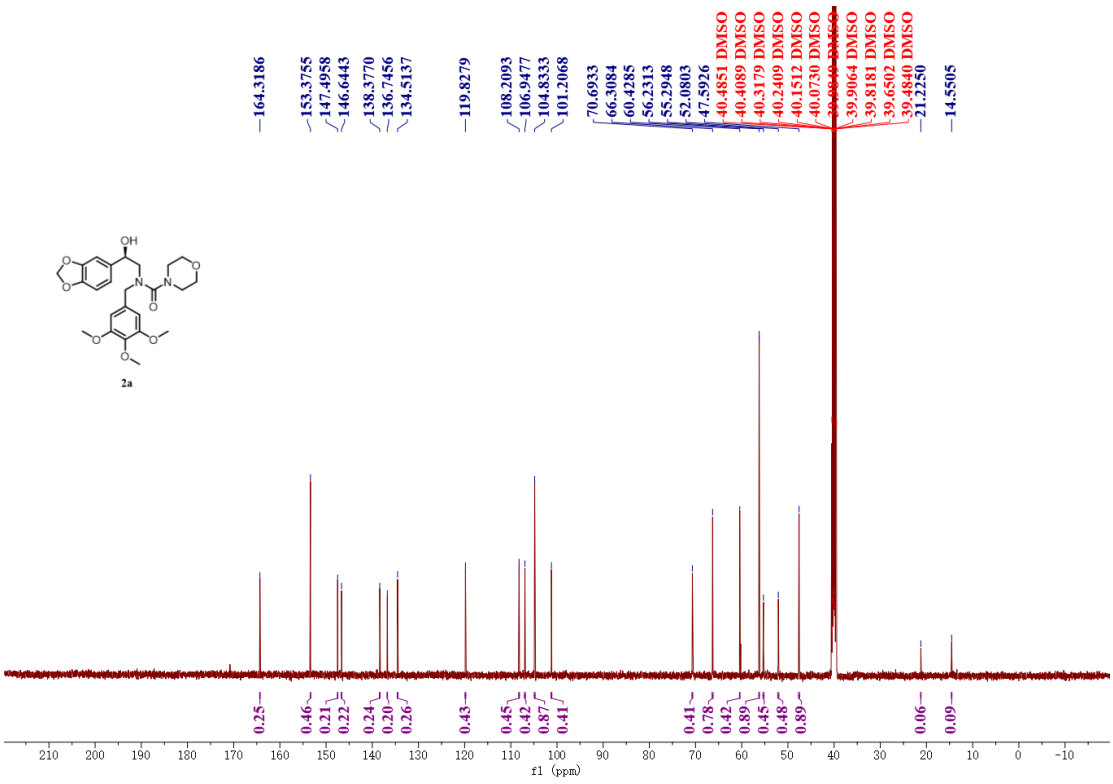
^{1}H NMR spectrum of compound **3u** in DMSO-d_6



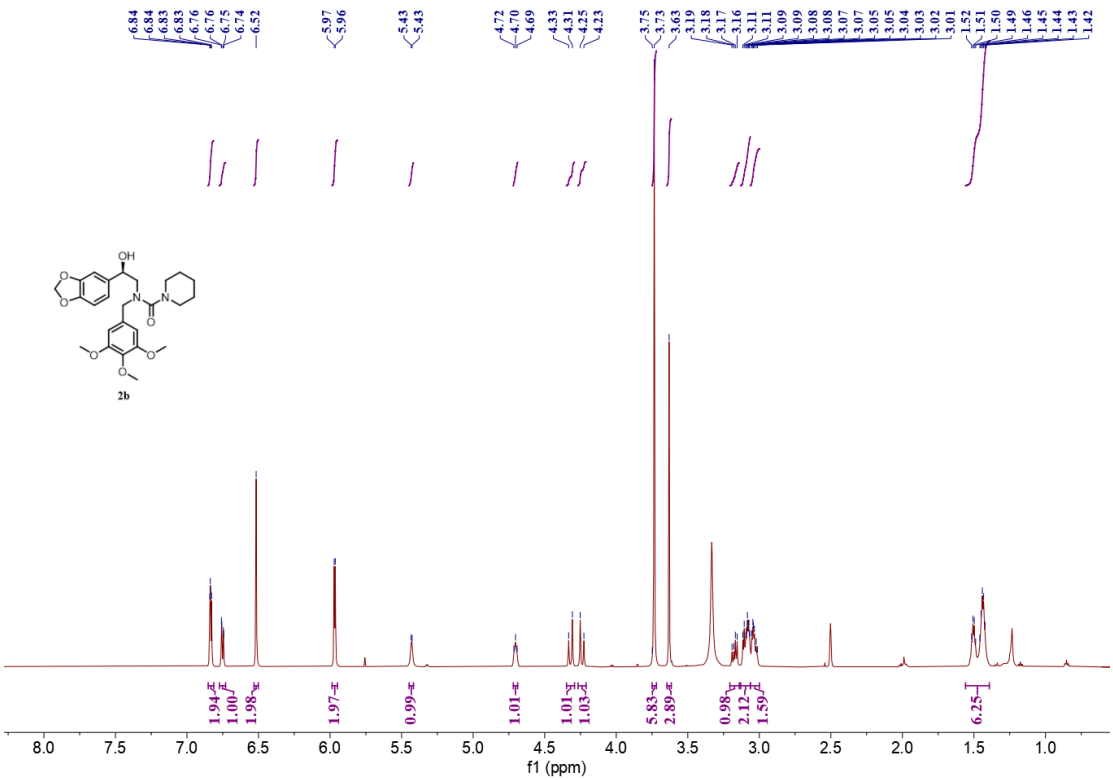
^{13}C NMR spectrum of compound **3u** in DMSO-d_6



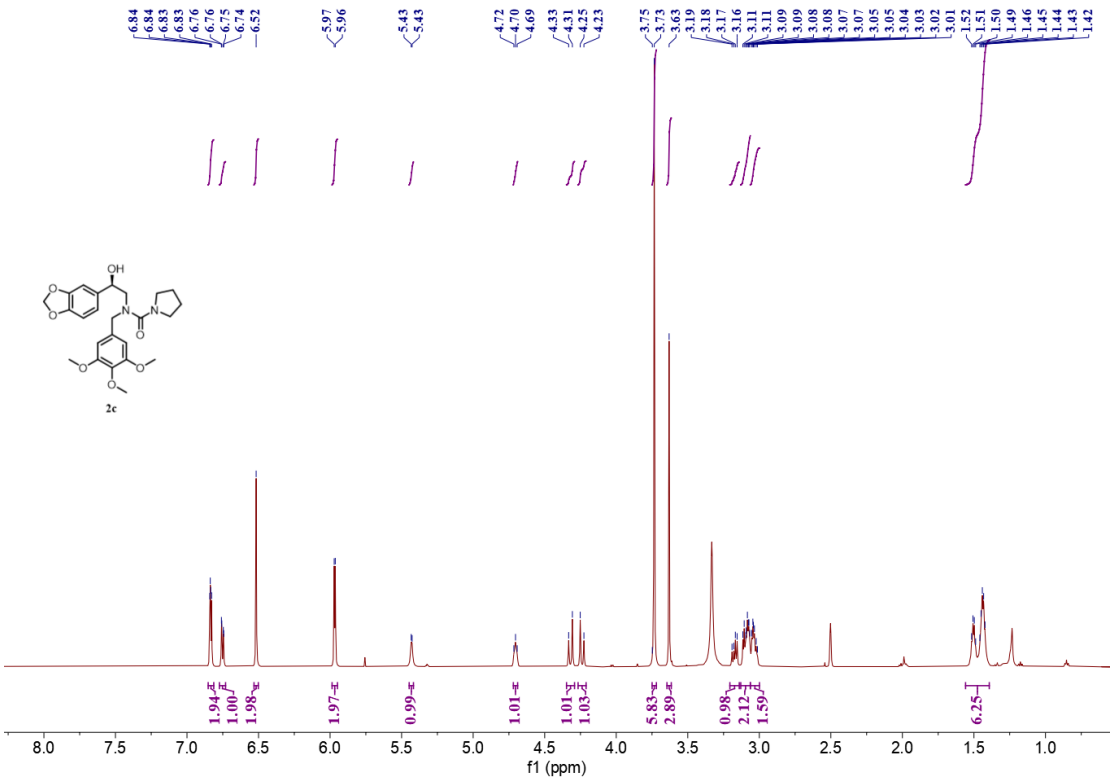
^{1}H NMR spectrum (500 MHz, DMSO-d_6) of isolated **2a** from the reaction of wt



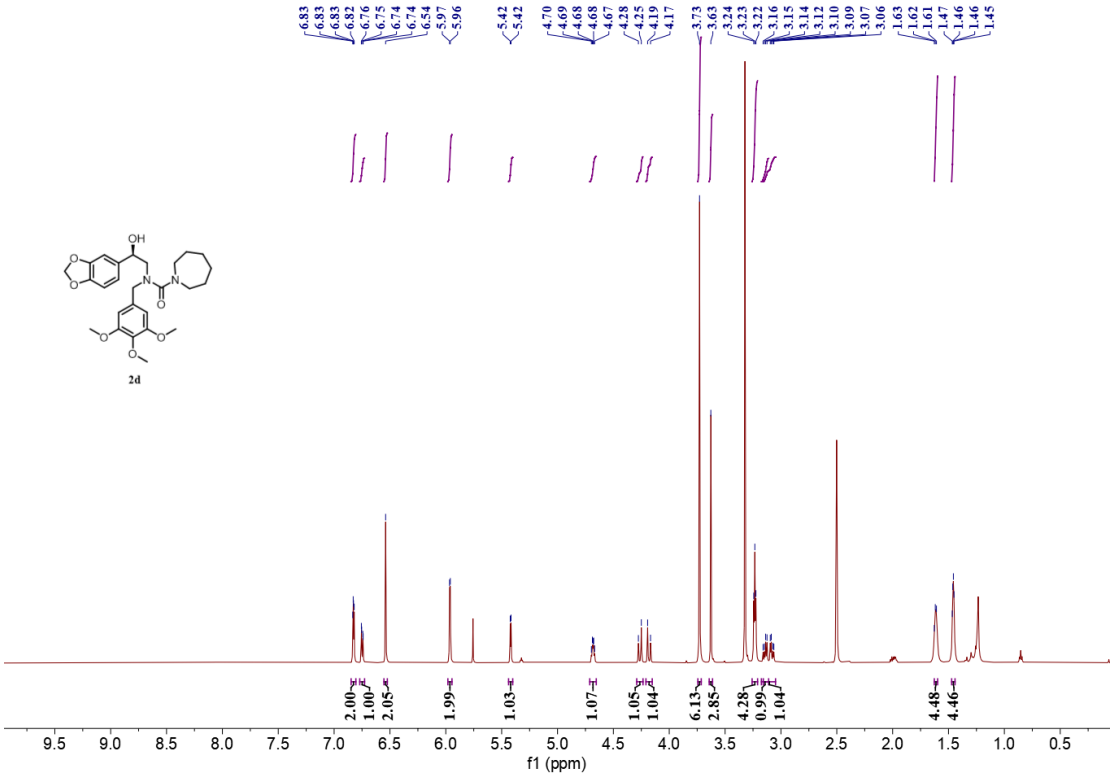
^{13}C NMR spectrum (500 MHz, DMSO-d_6) of isolated **2a** from the reaction of wt



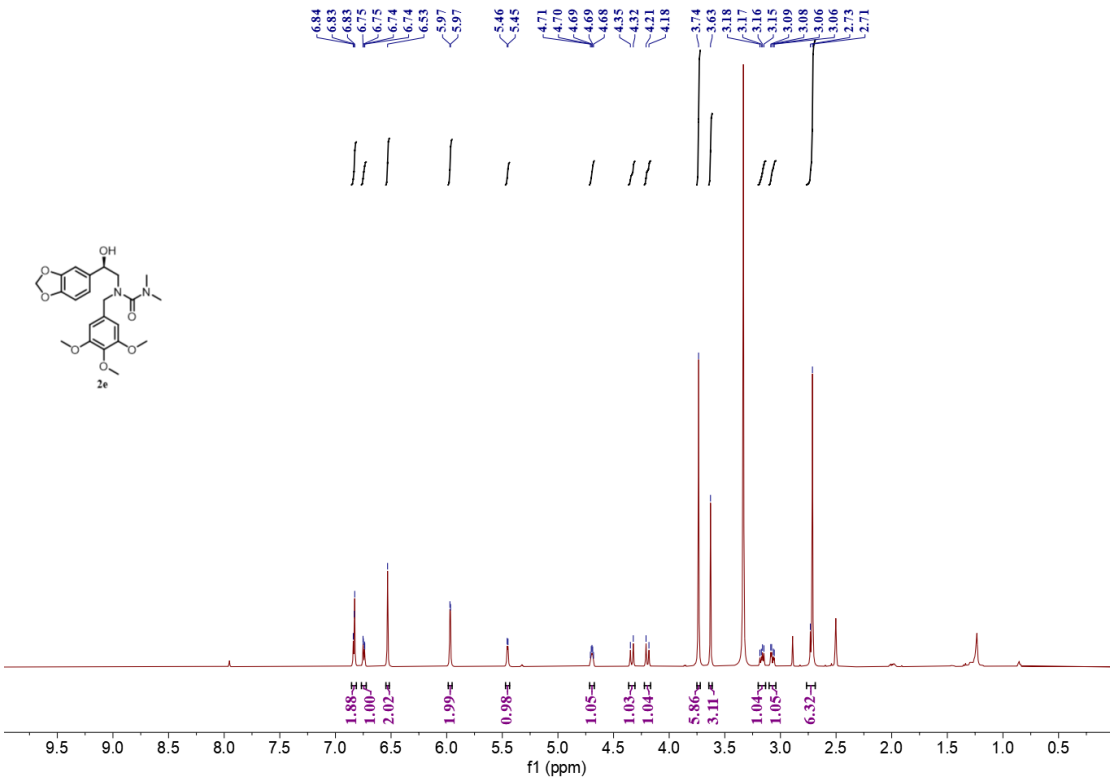
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2b** from the enzymatic reaction



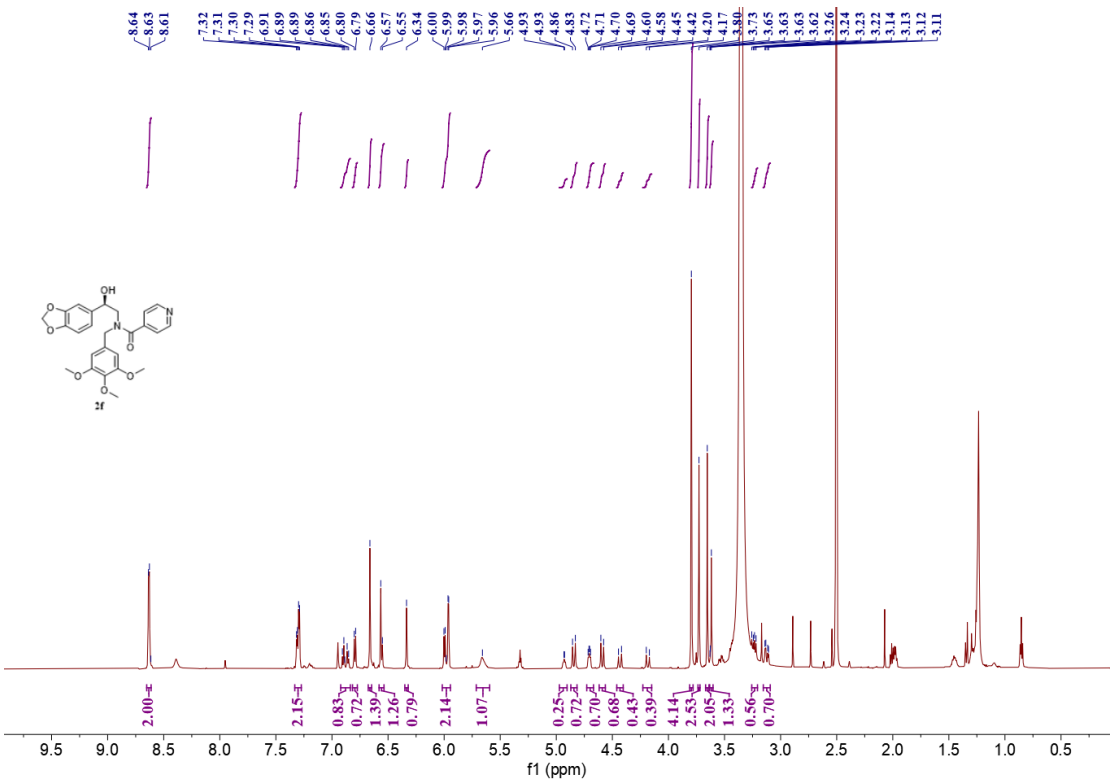
^{1}H NMR spectrum (500 MHz, DMSO-d_6) of isolated **2c** from the reaction of wt



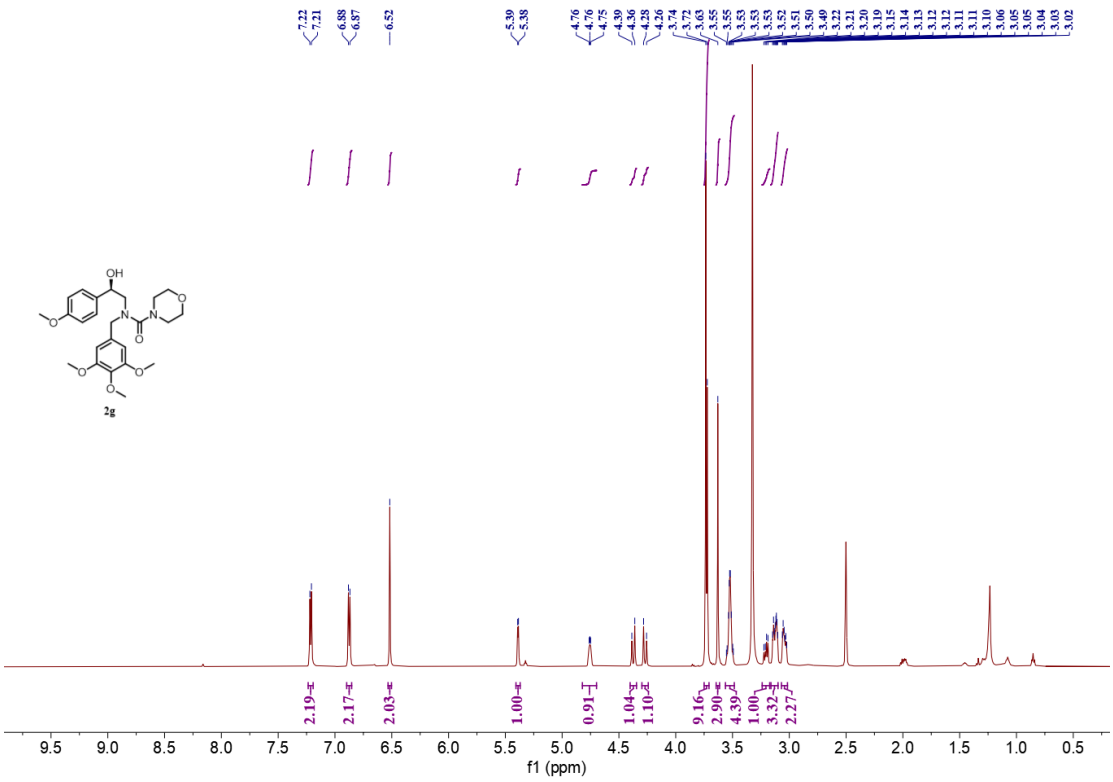
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2d** from the reaction of wt



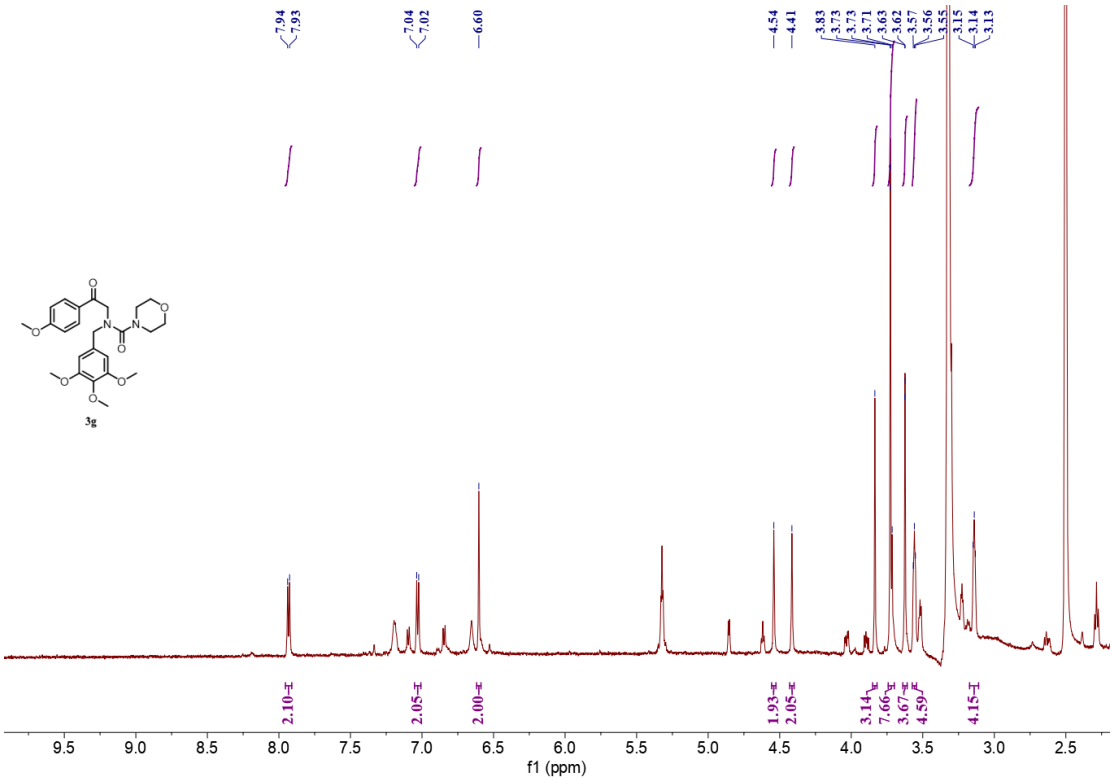
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2e** from the reaction of wt



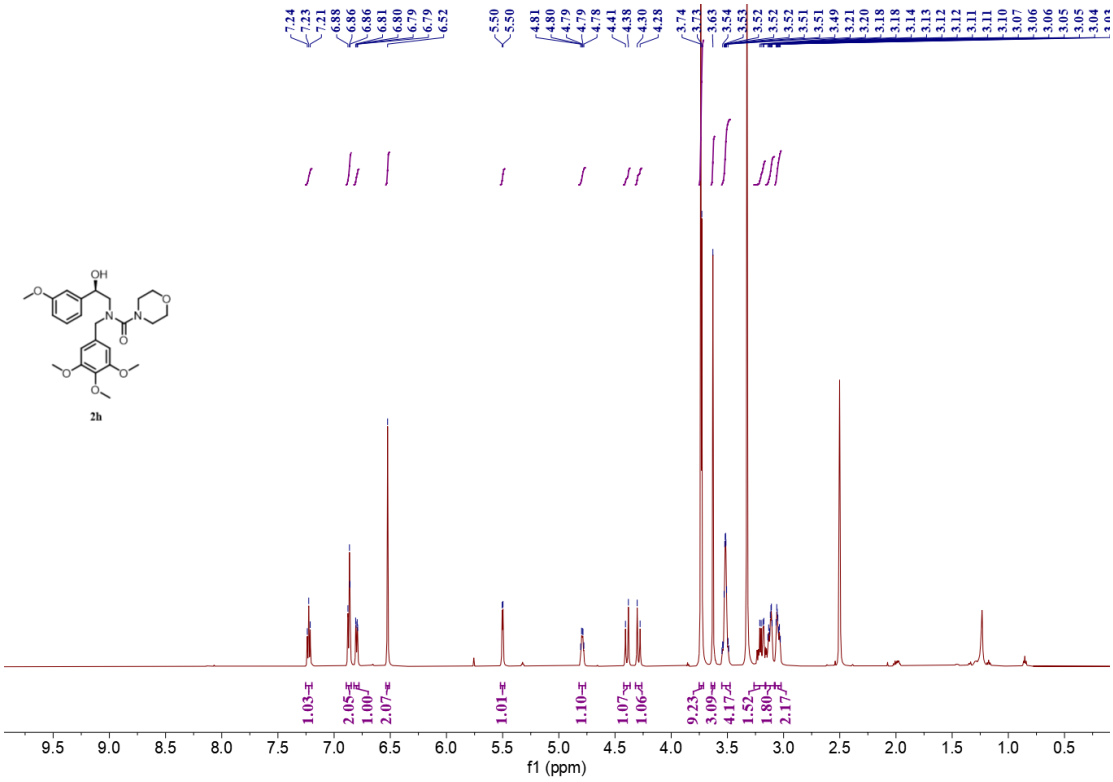
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2f** from the reaction of wt



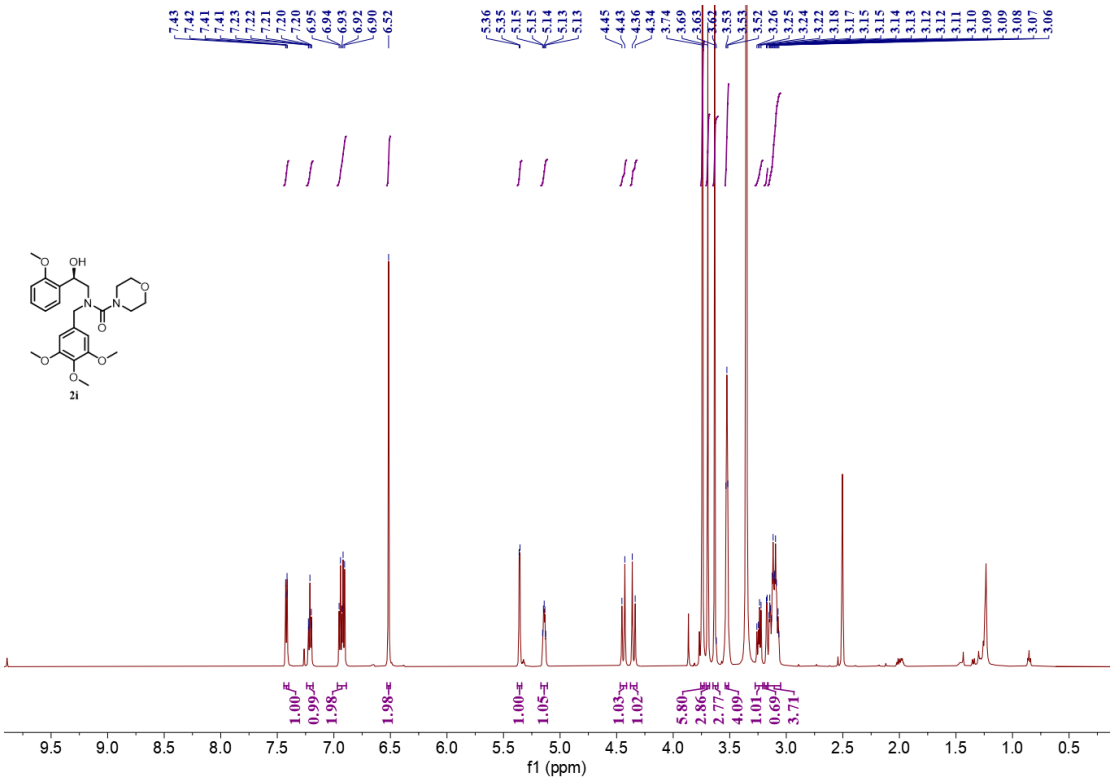
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2g** from the enzymatic reaction



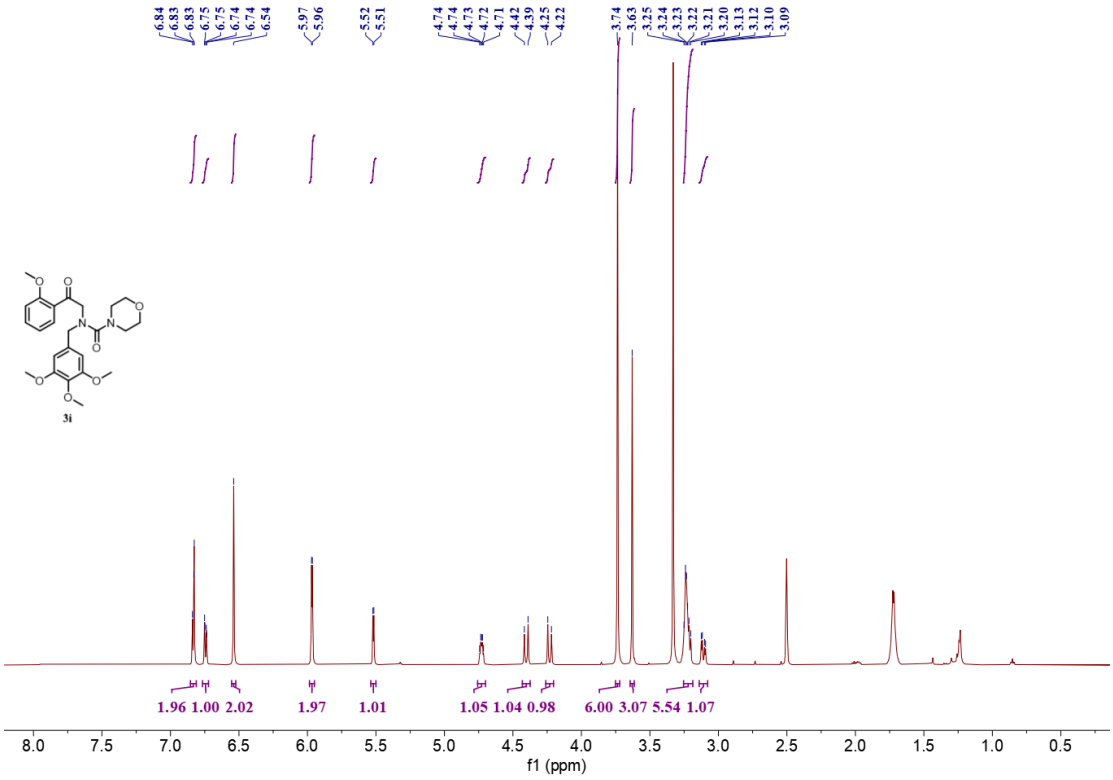
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3g** from the enzymatic reaction



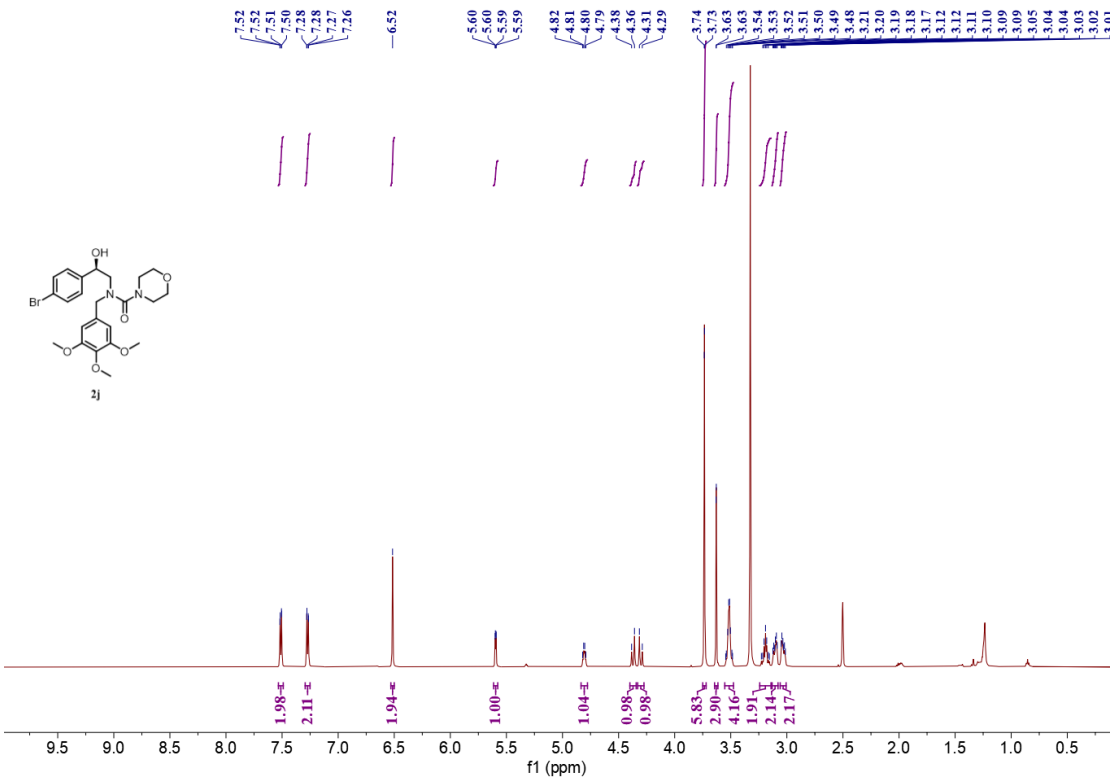
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2h** from the enzymatic reaction P69D



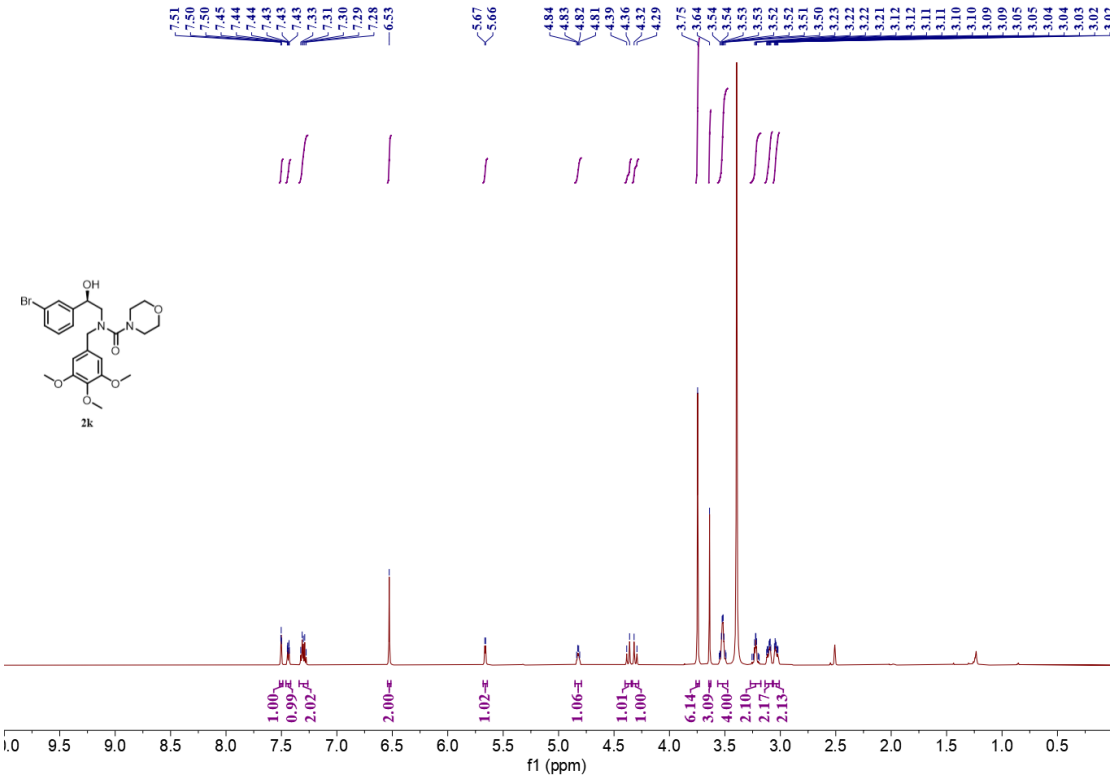
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2i** from the reaction of wt



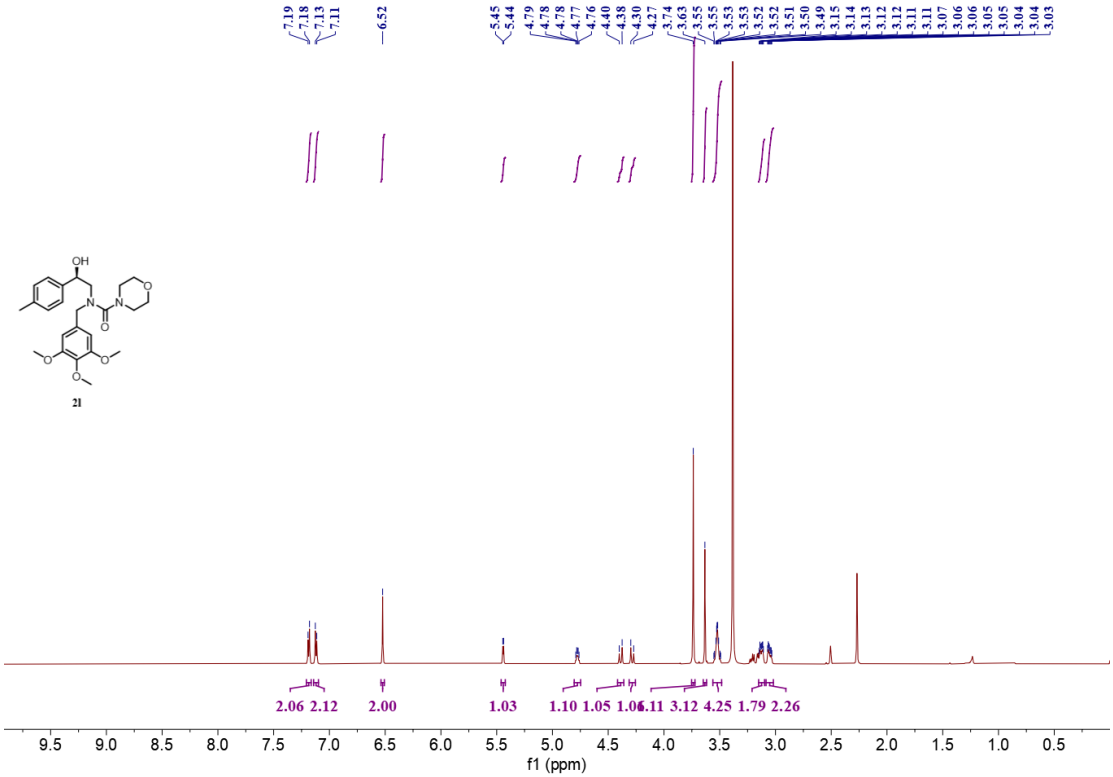
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3i** from the reaction of wt



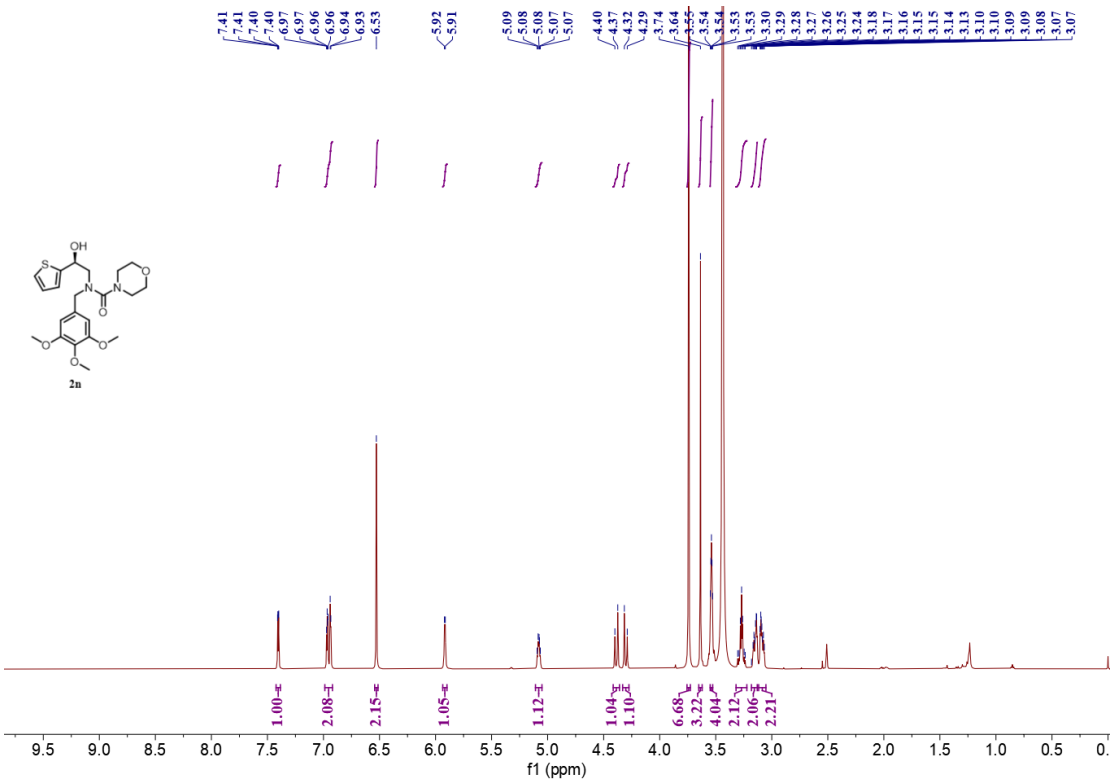
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2j** from the reaction of wt



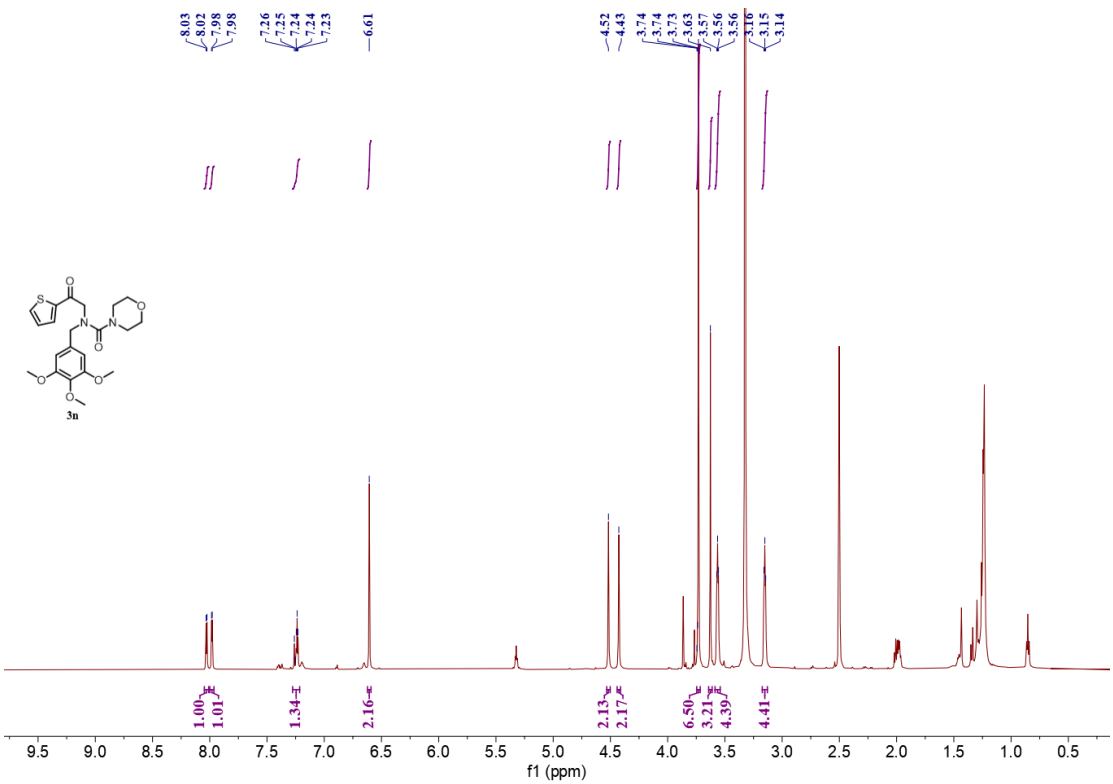
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2k** from the reaction of wt



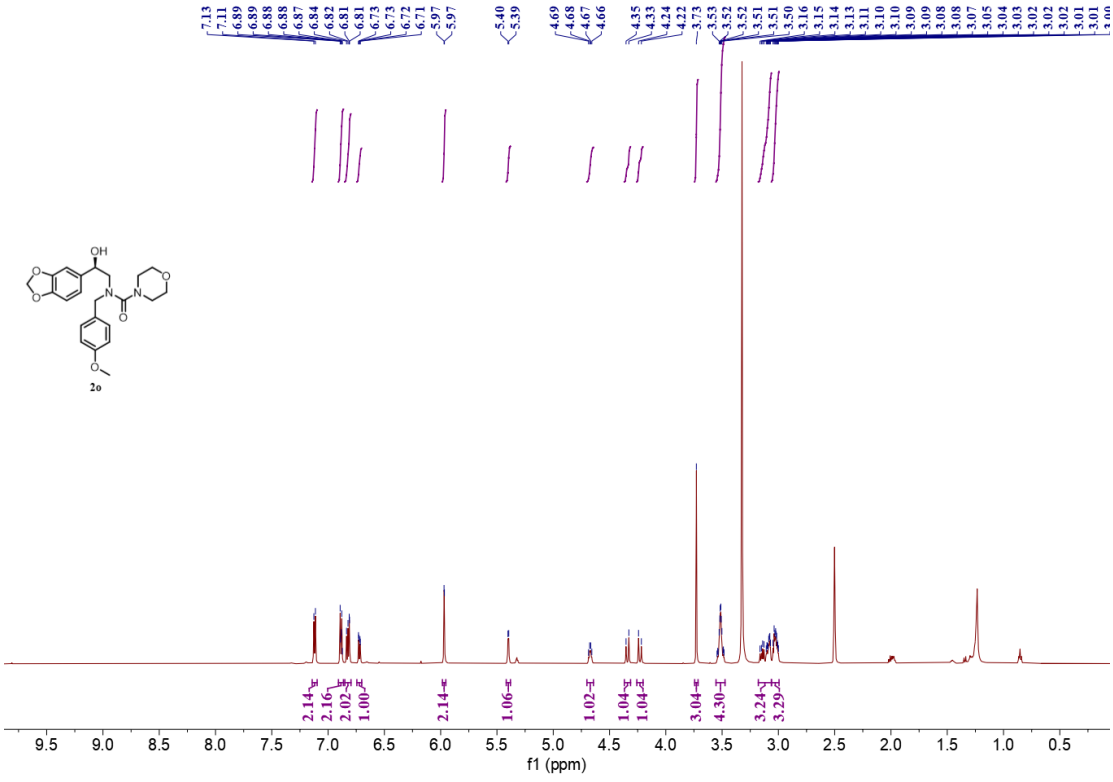
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2l** from the reaction of wt



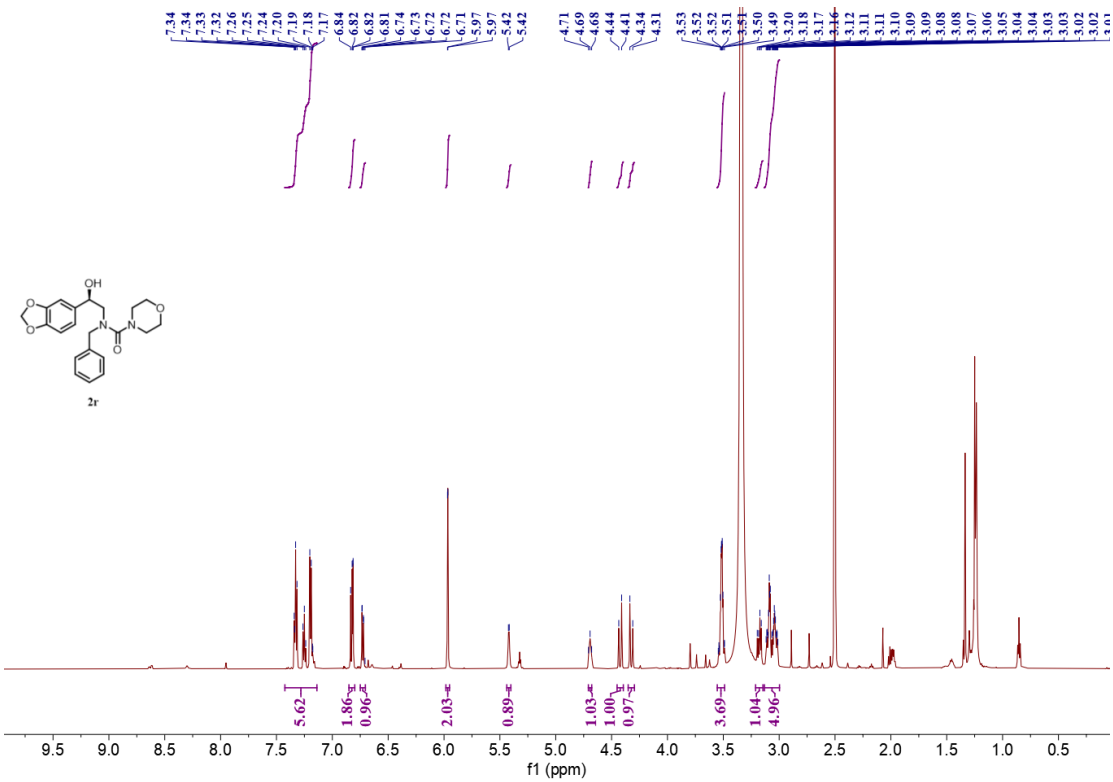
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2n** from the reaction of wt



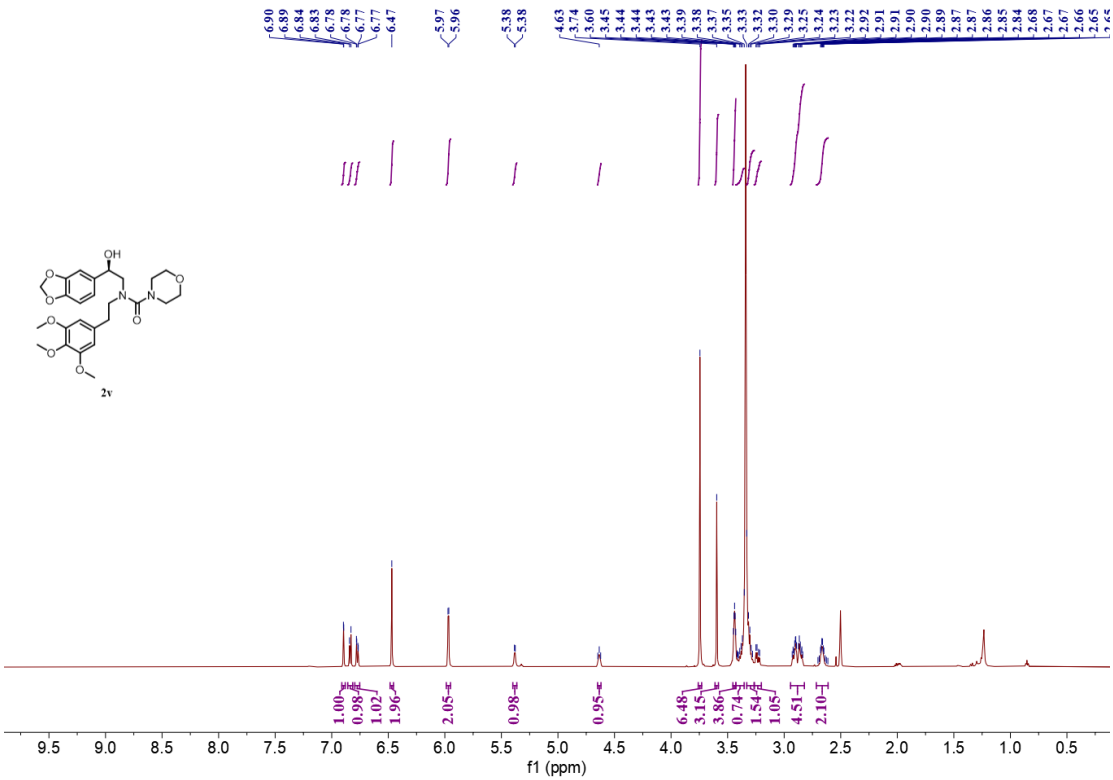
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3n** from the reaction of wt



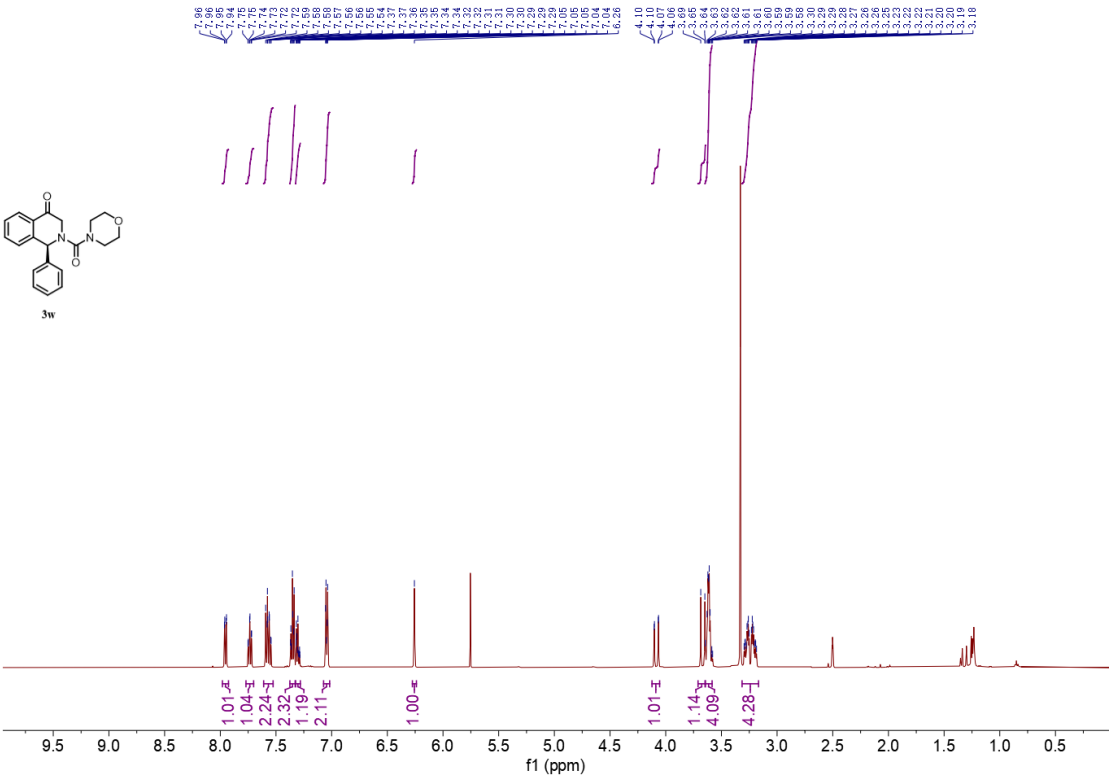
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2o** from the enzymatic reaction



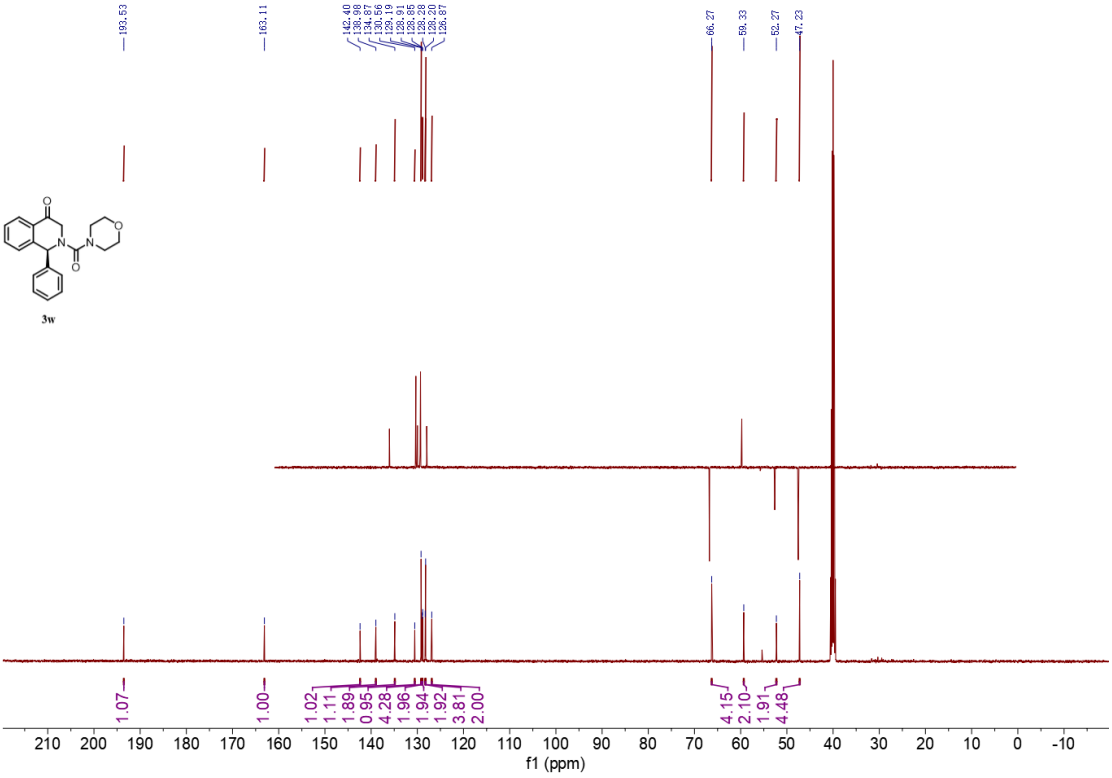
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2r** from the enzymatic reaction



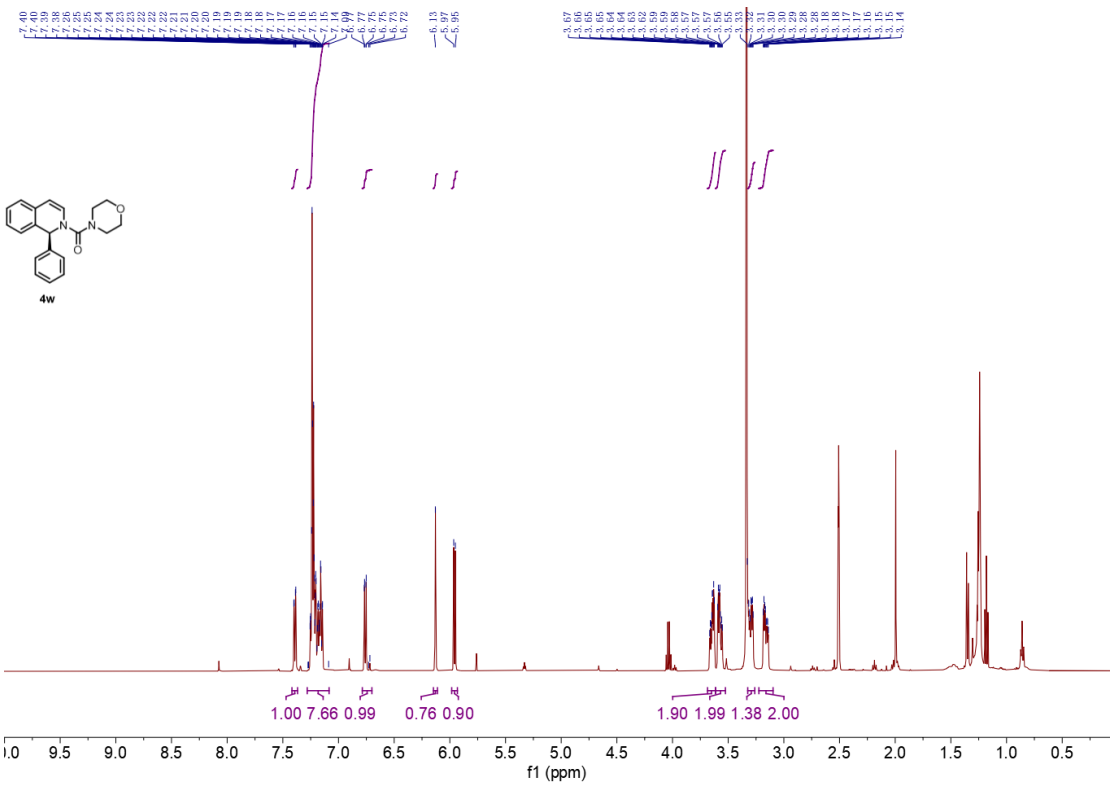
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2v** from the enzymatic reaction



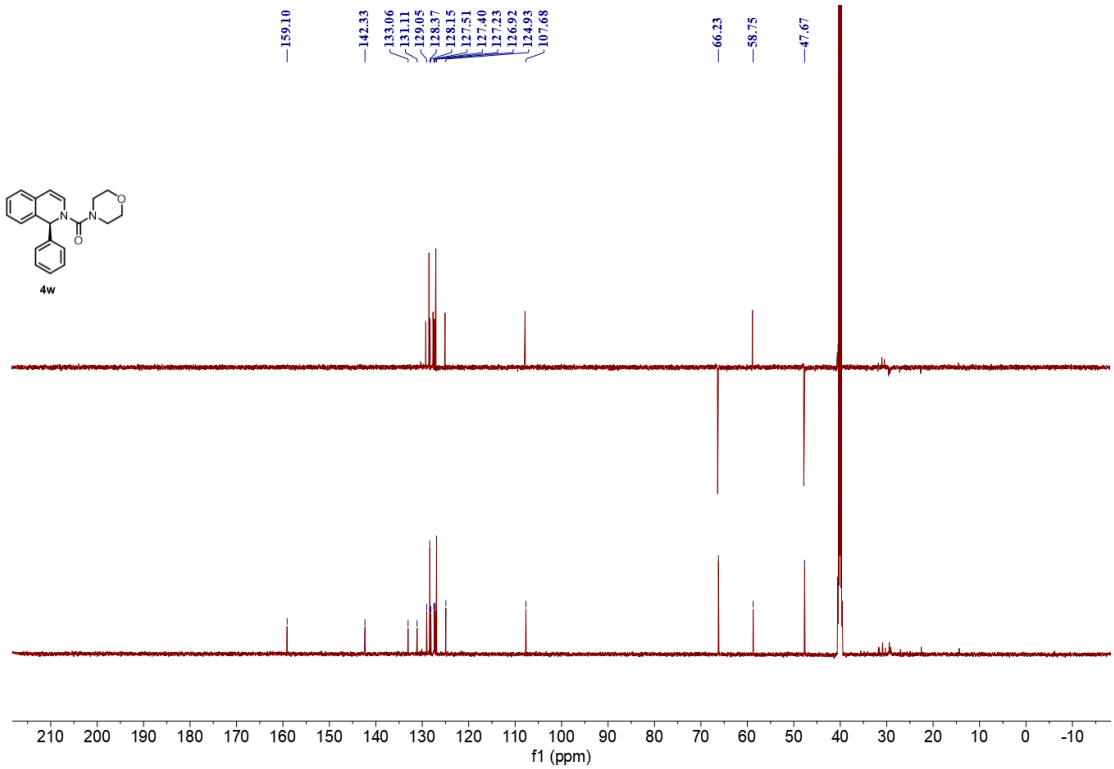
^{1}H NMR spectrum of compound **3w** in DMSO-d_6



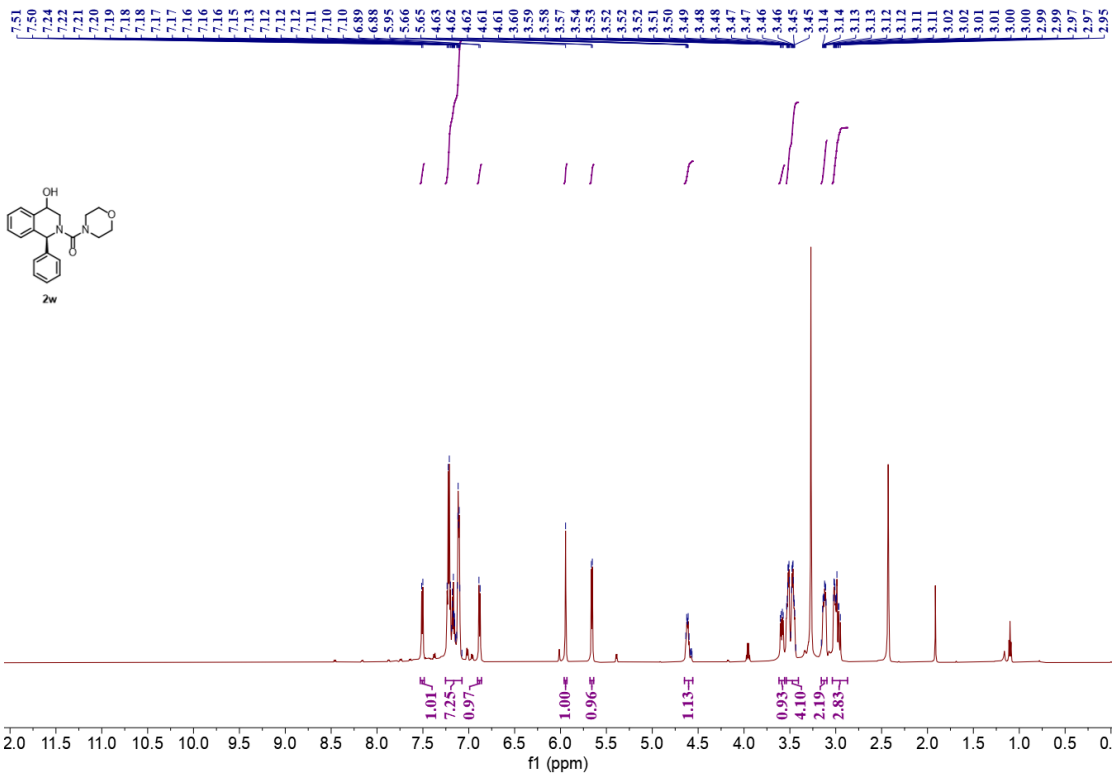
^{13}C NMR spectrum of compound **3w** in DMSO-d_6



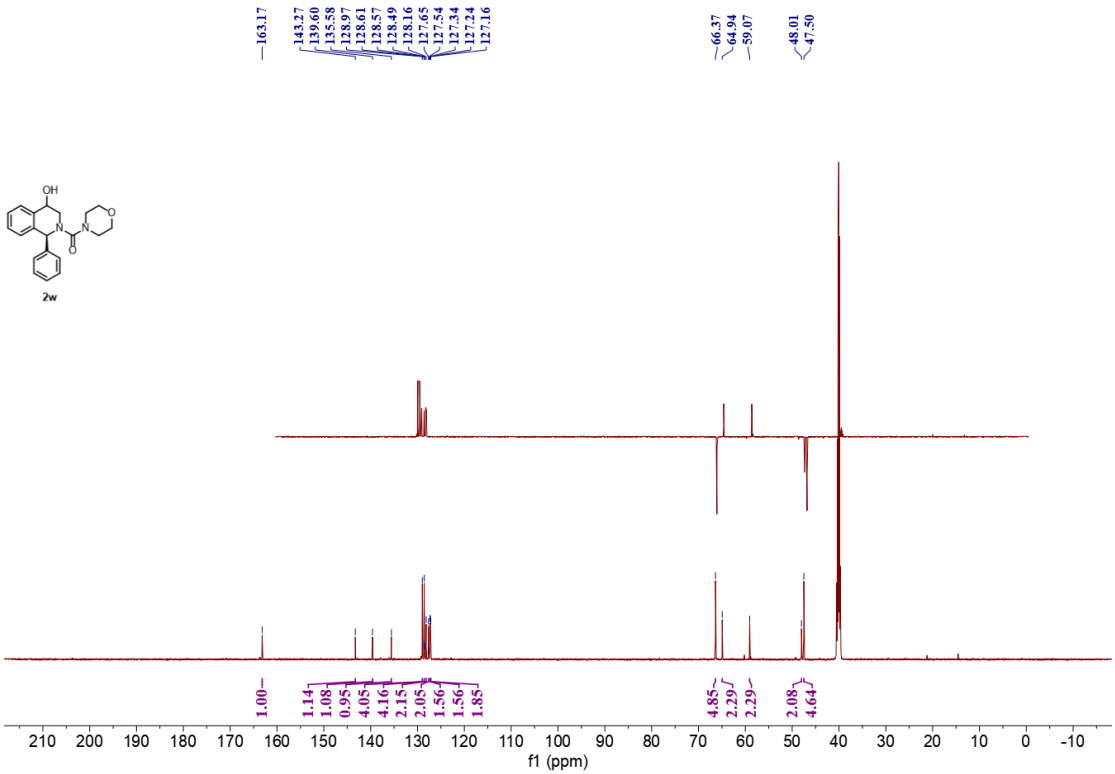
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **4w** from the enzymatic reaction



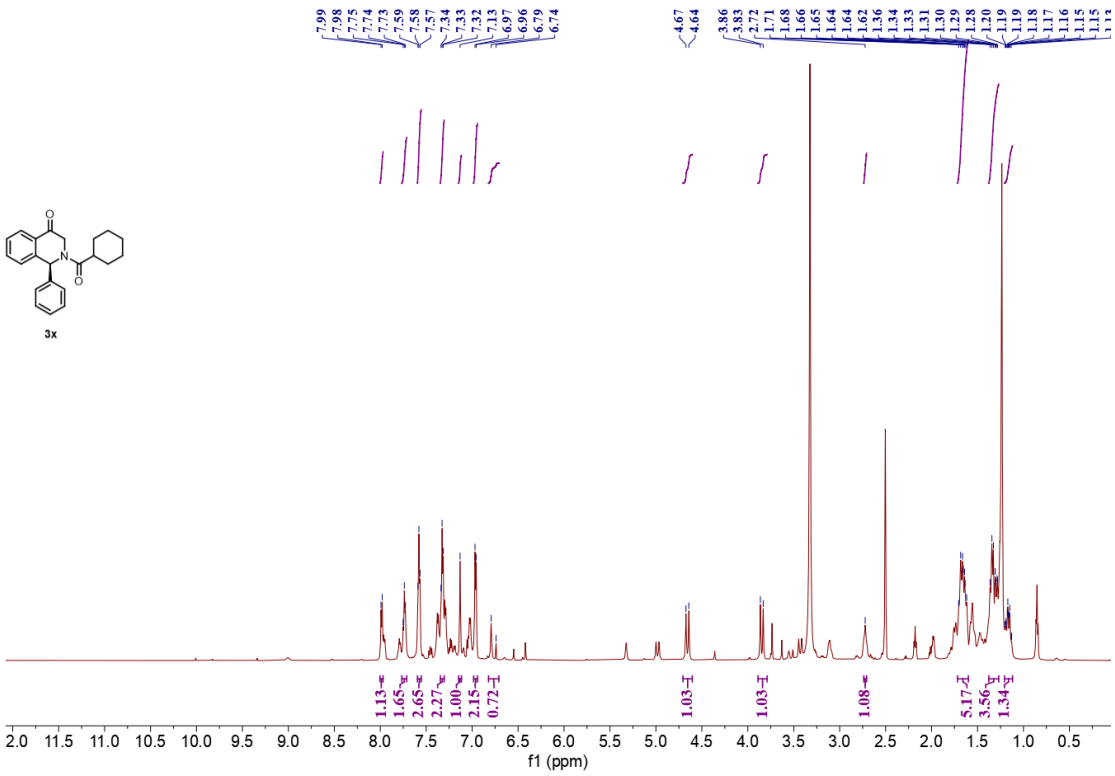
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **4w** from the enzymatic reaction



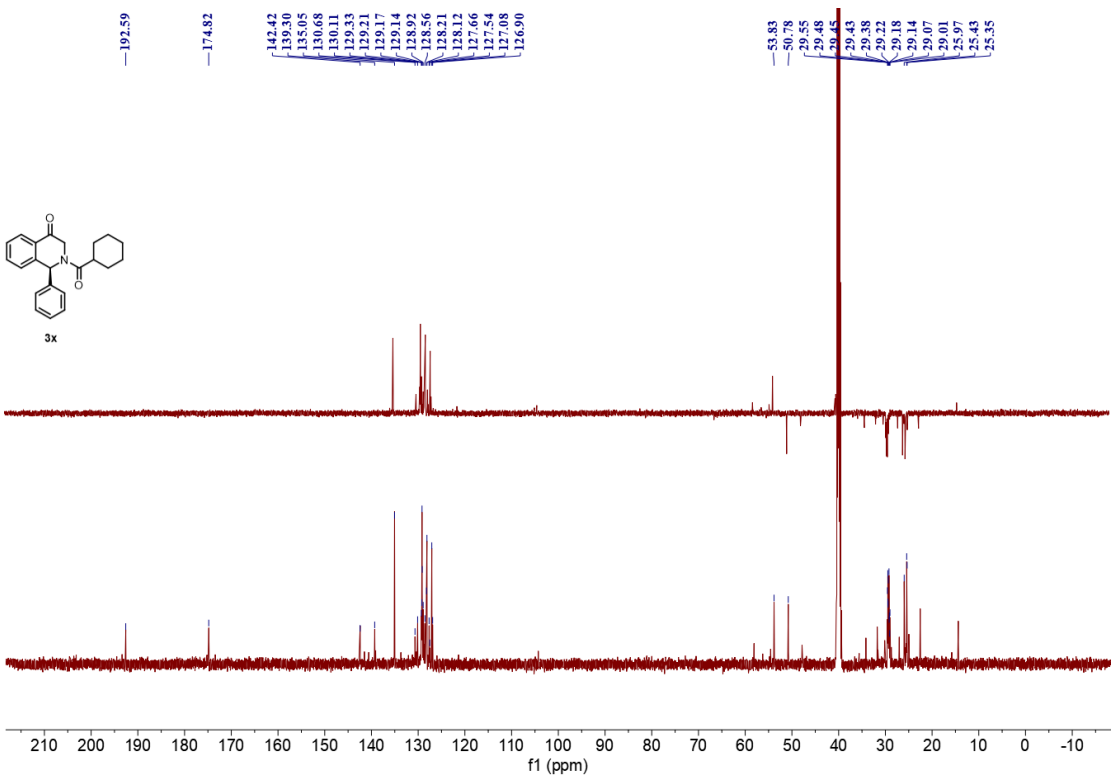
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2w** from the enzymatic reaction



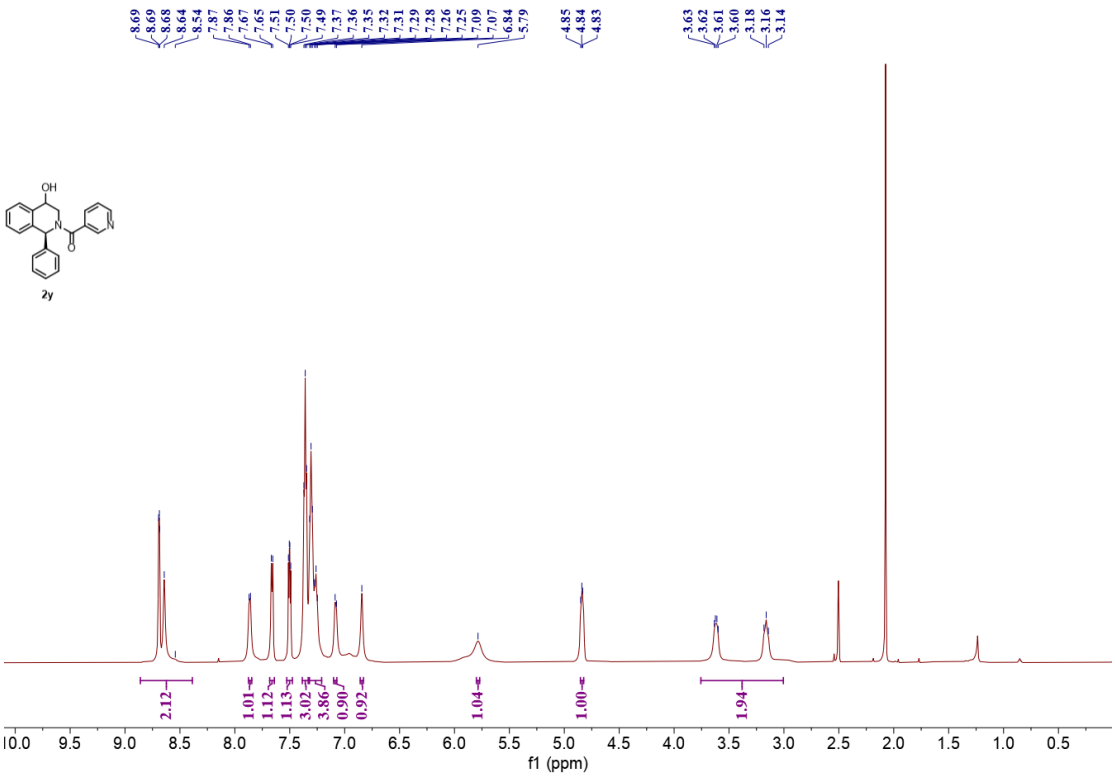
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **2w** from the enzymatic reaction



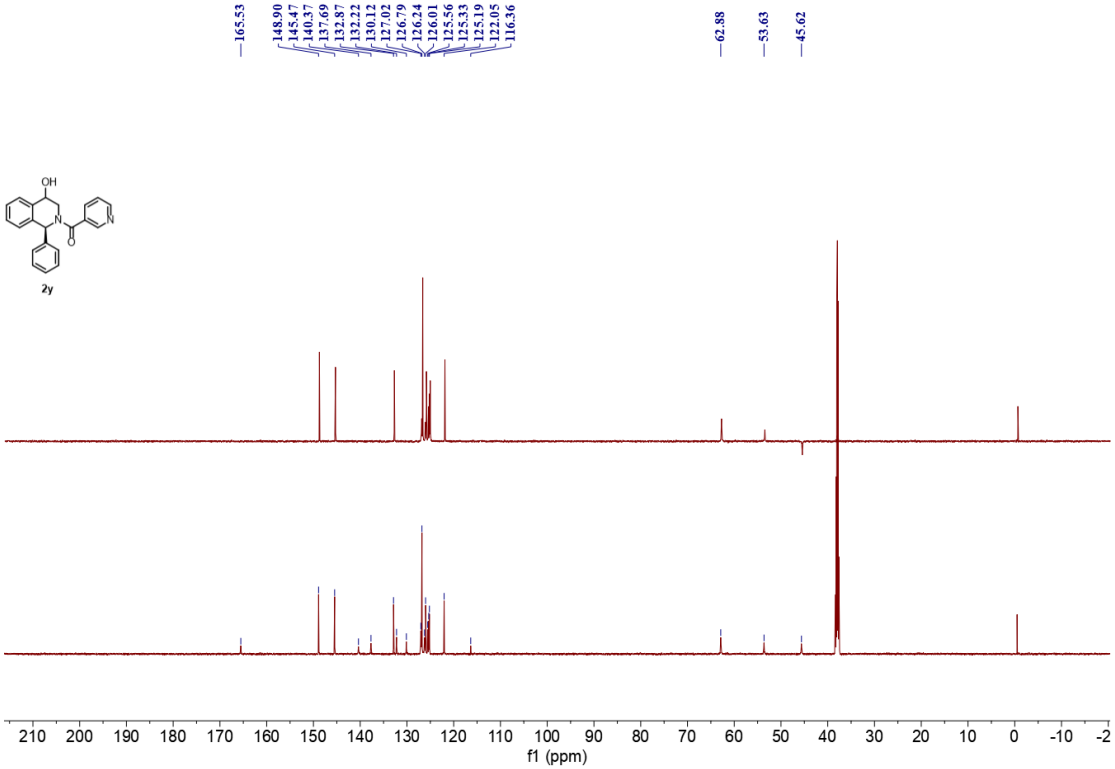
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3x** from the enzymatic reaction



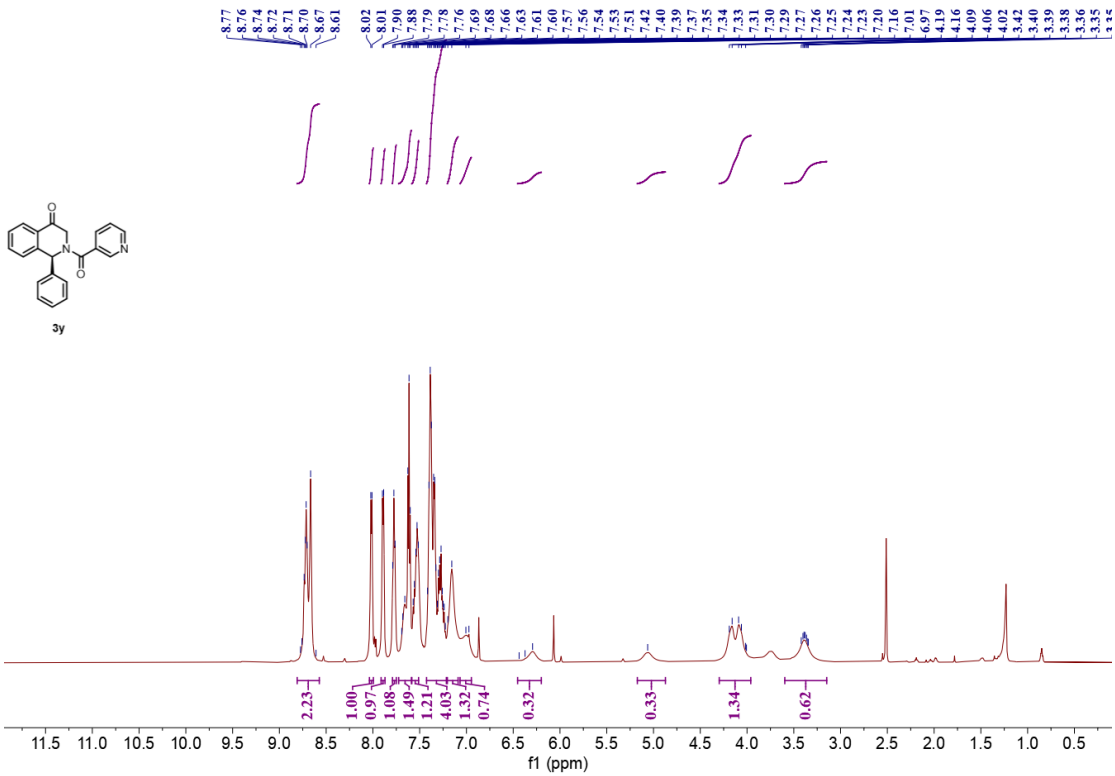
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **3x** from the enzymatic reaction



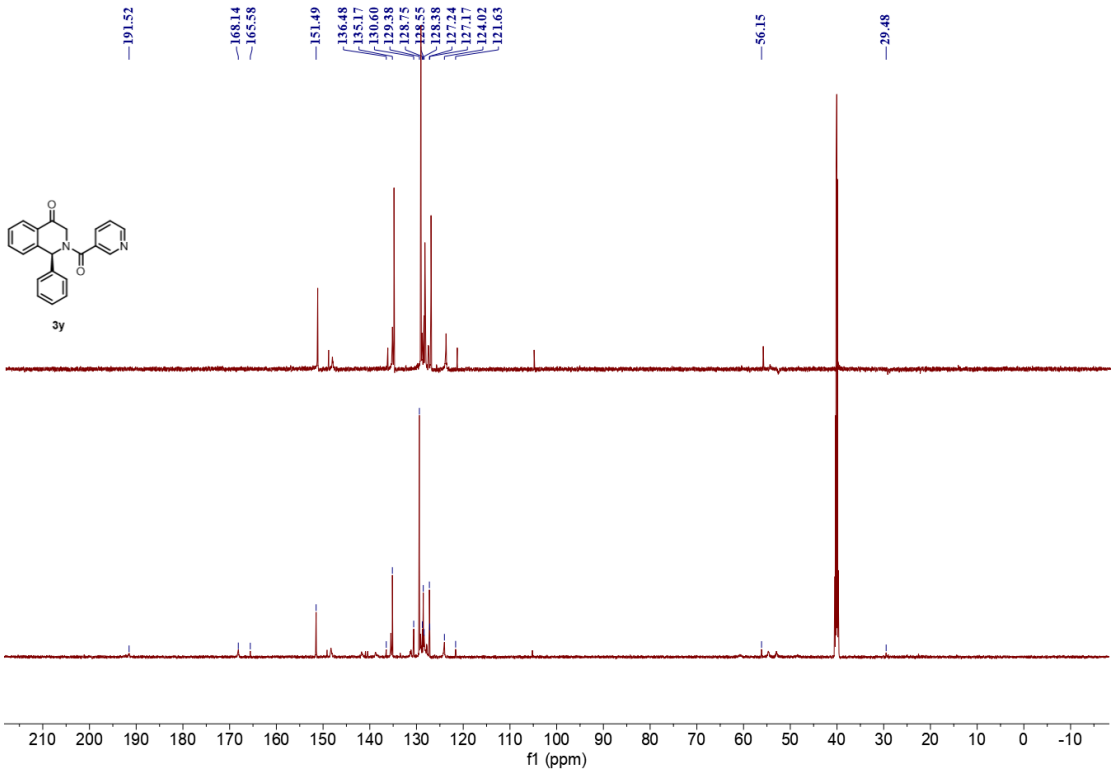
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2y** from the enzymatic reaction



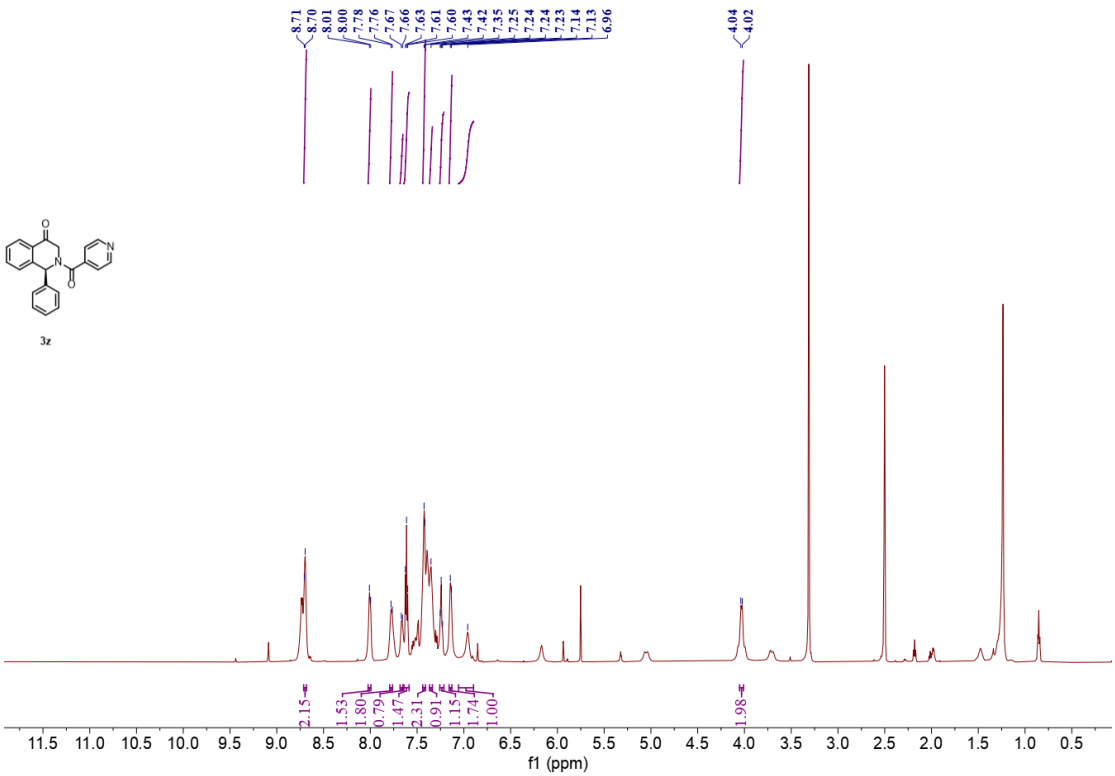
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **2y** from the enzymatic reaction



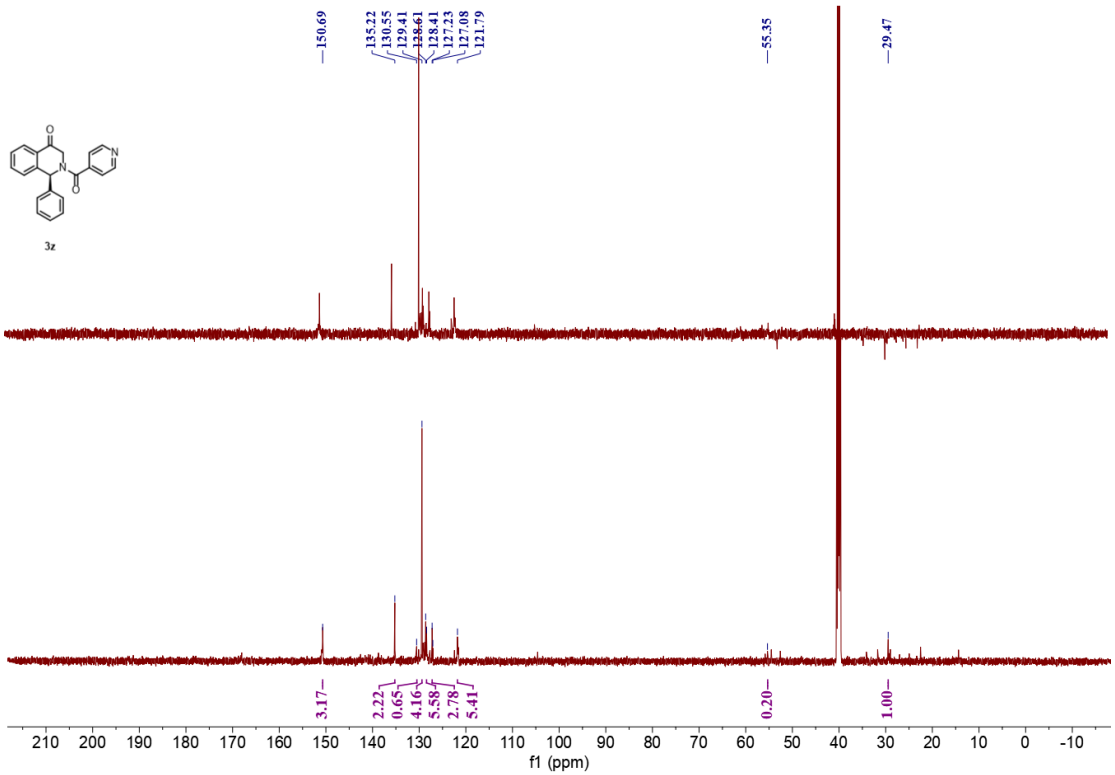
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3y** from the enzymatic reaction



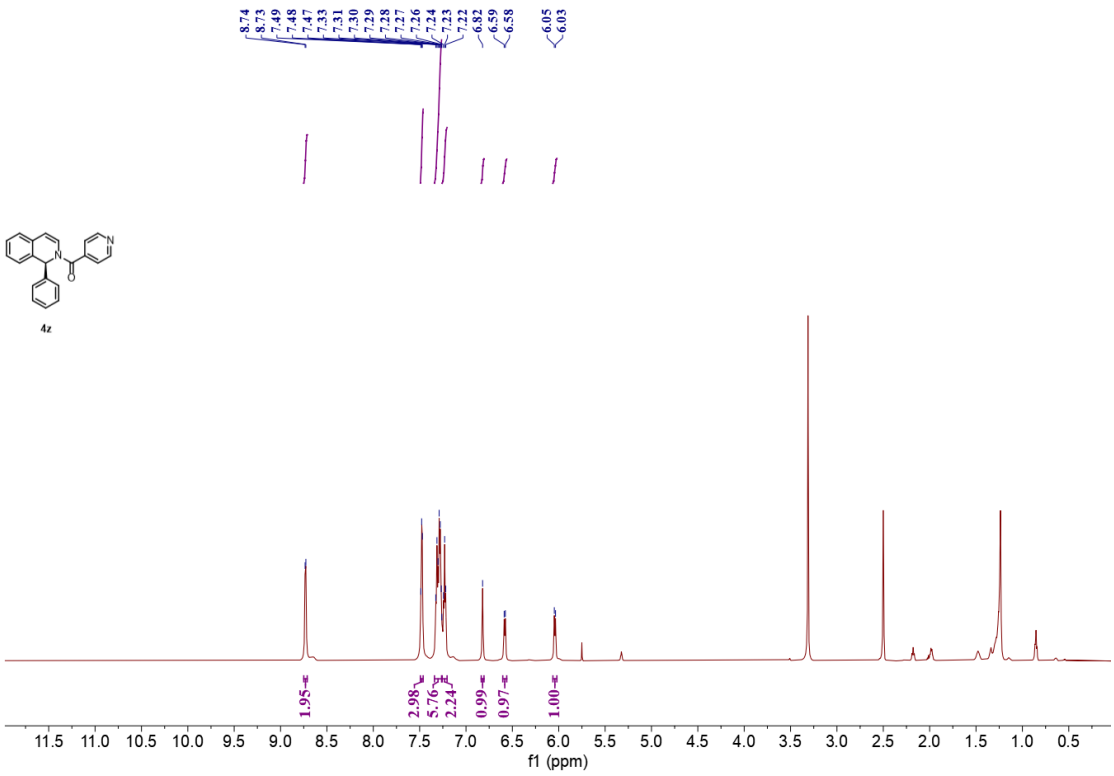
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **3y** from the enzymatic reaction



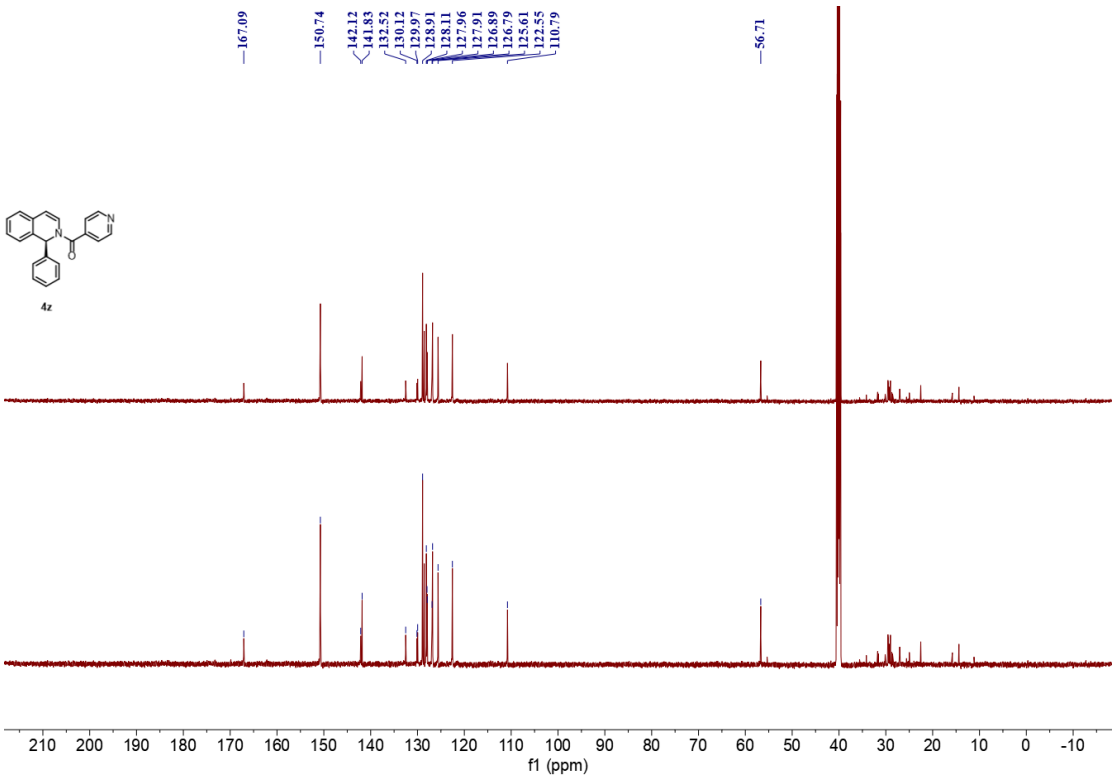
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3z** from the enzymatic reaction



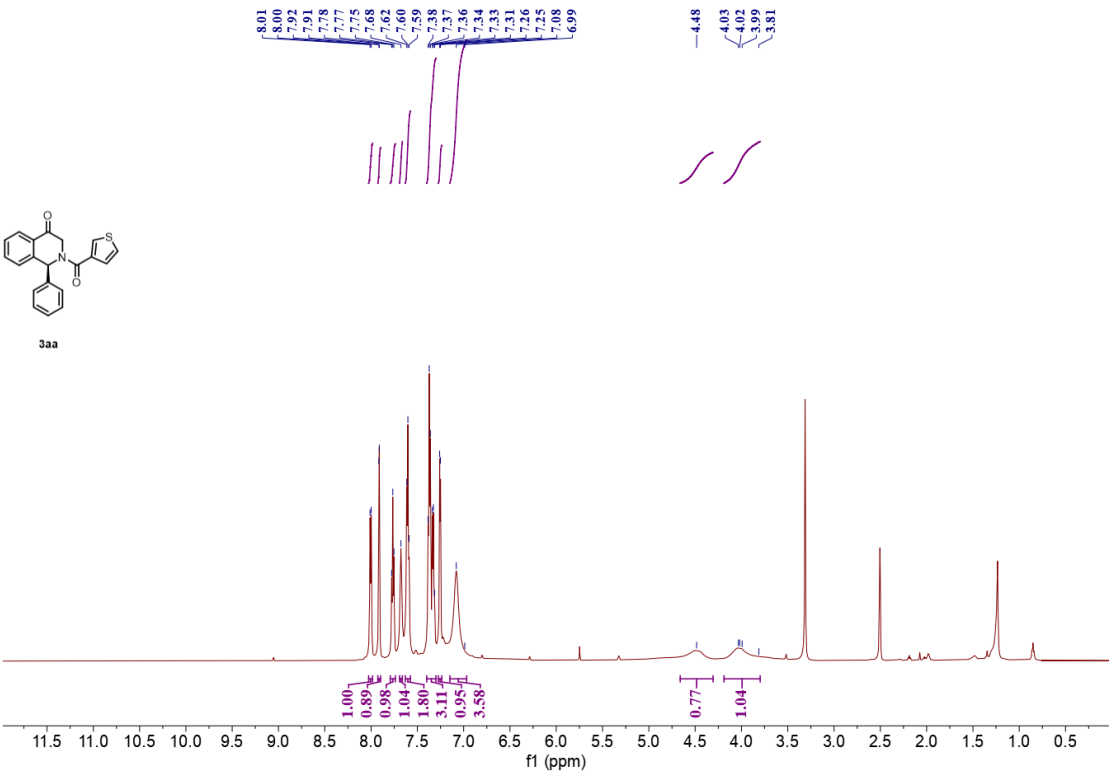
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **3z** from the enzymatic reaction



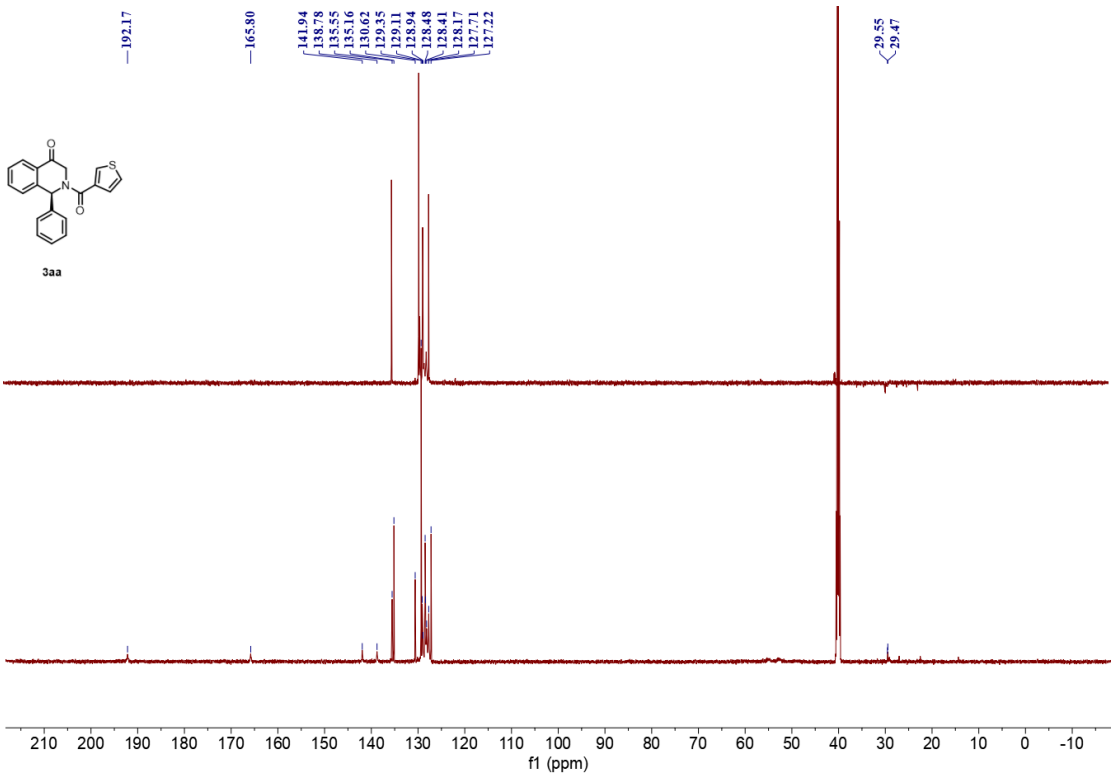
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **4z** from the enzymatic reaction



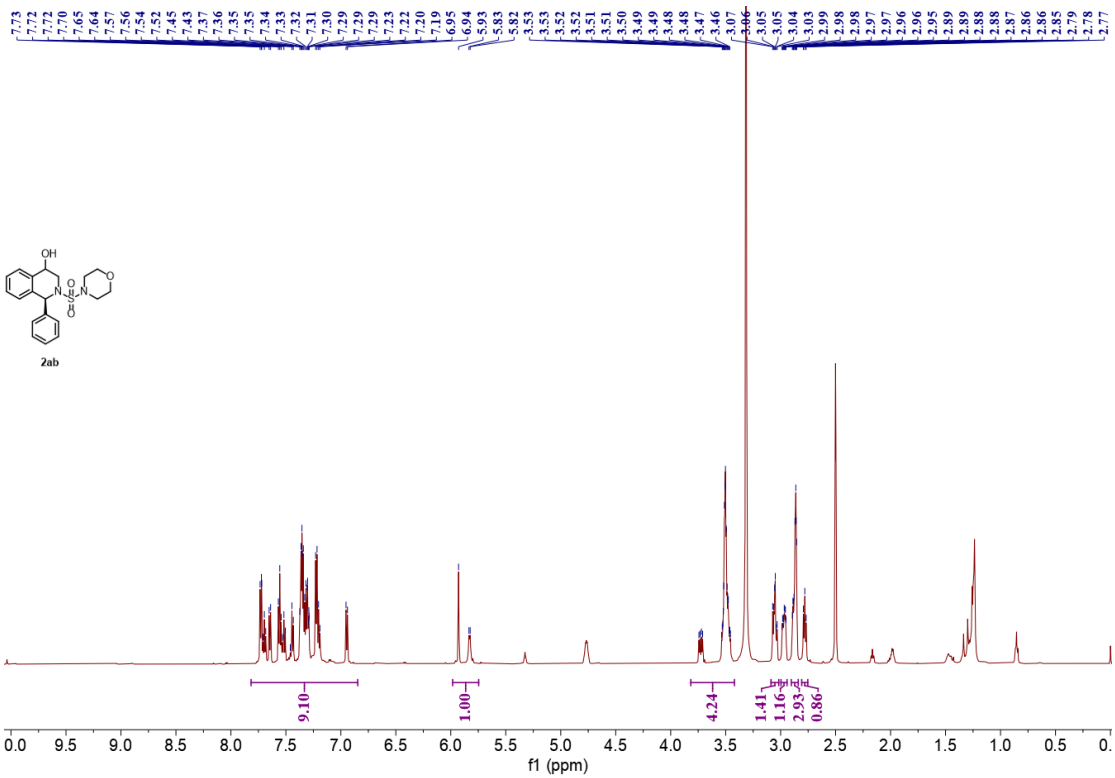
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **4z** from the enzymatic reaction



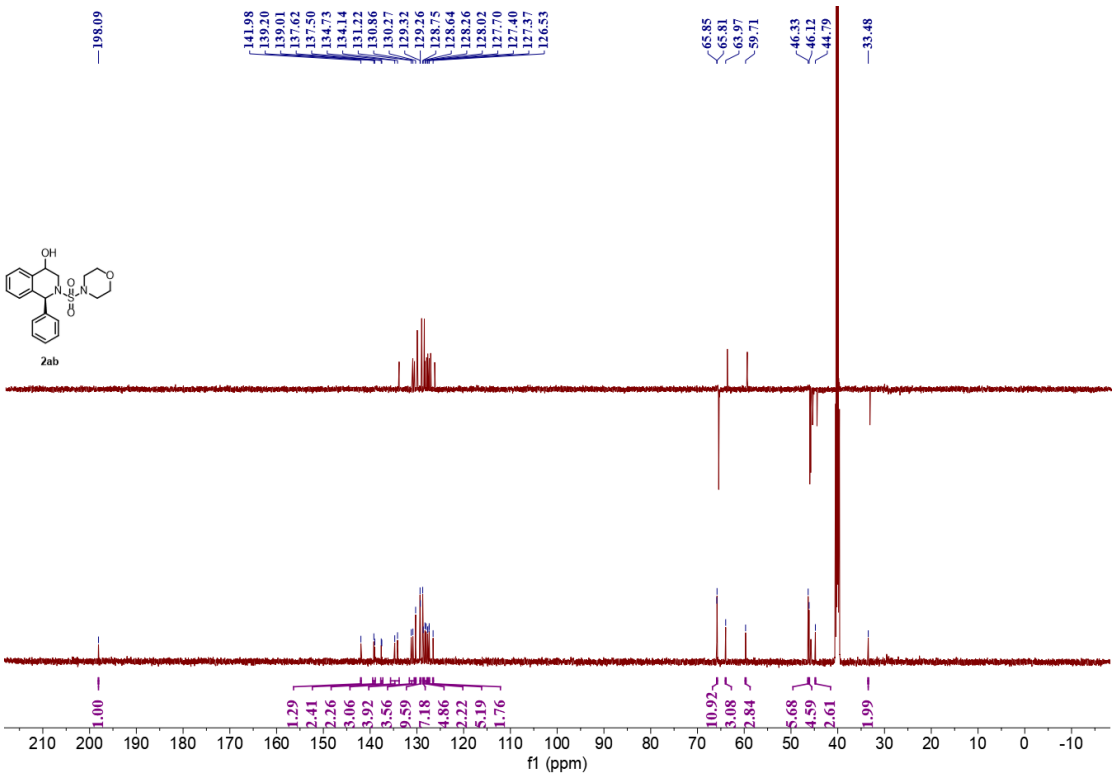
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3aa** from the enzymatic reaction



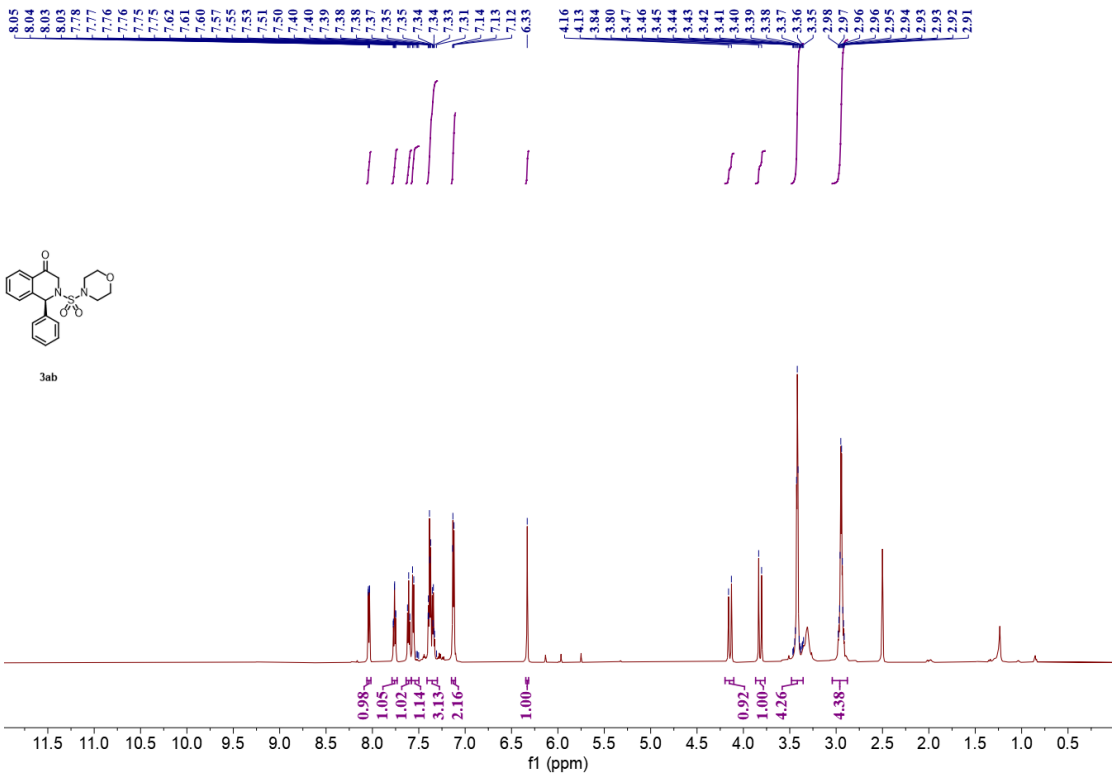
^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **3aa** from the enzymatic reaction



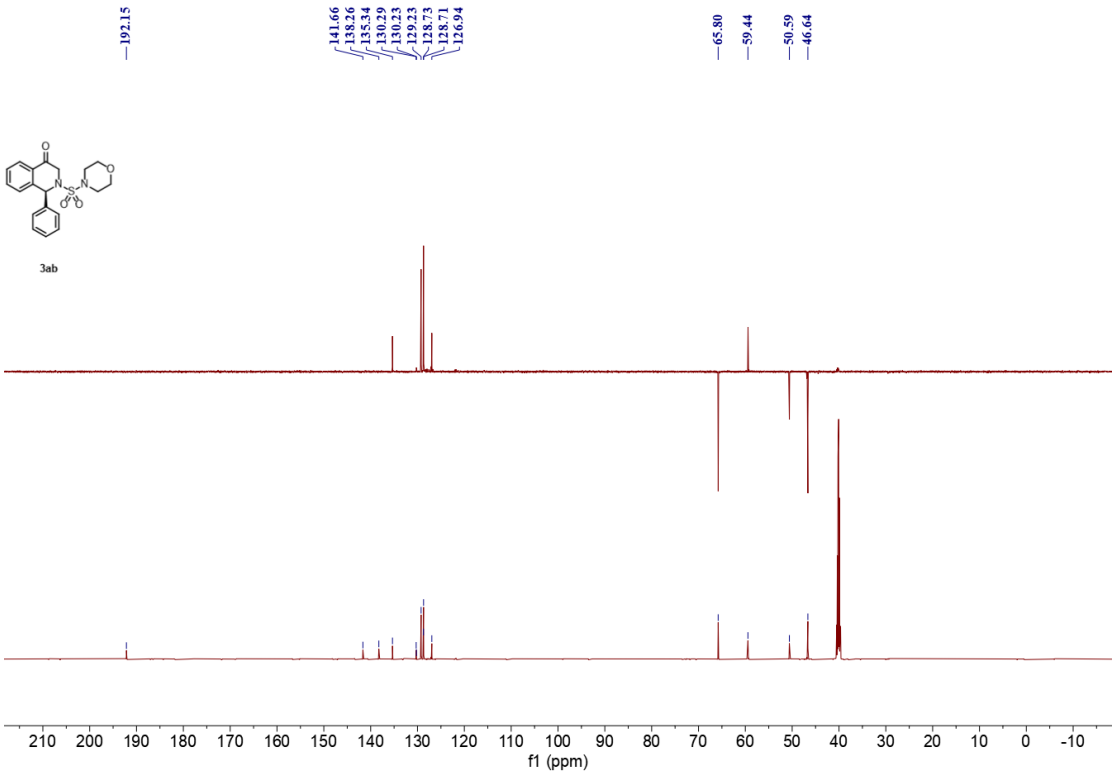
^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **2ab** from the enzymatic reaction



^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **2ab** from the enzymatic reaction



^{1}H NMR spectrum (600 MHz, DMSO-d_6) of isolated **3ab** from the enzymatic reaction



^{13}C NMR spectrum (600 MHz, DMSO-d_6) of isolated **3ab** from the enzymatic reaction

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