

Supplementary Material

Trisodium citrate dihydrate catalyzed synthesis of fully and diversely functionalized novel piperidinone derivatives

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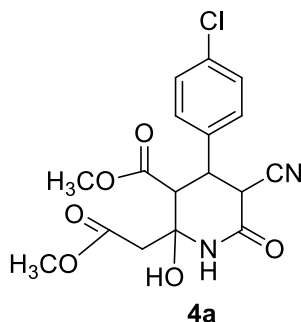
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Spectra FTIR, ¹H-NMR, ¹³C-NMR and HRMS of all the synthesized scaffolds.....S2

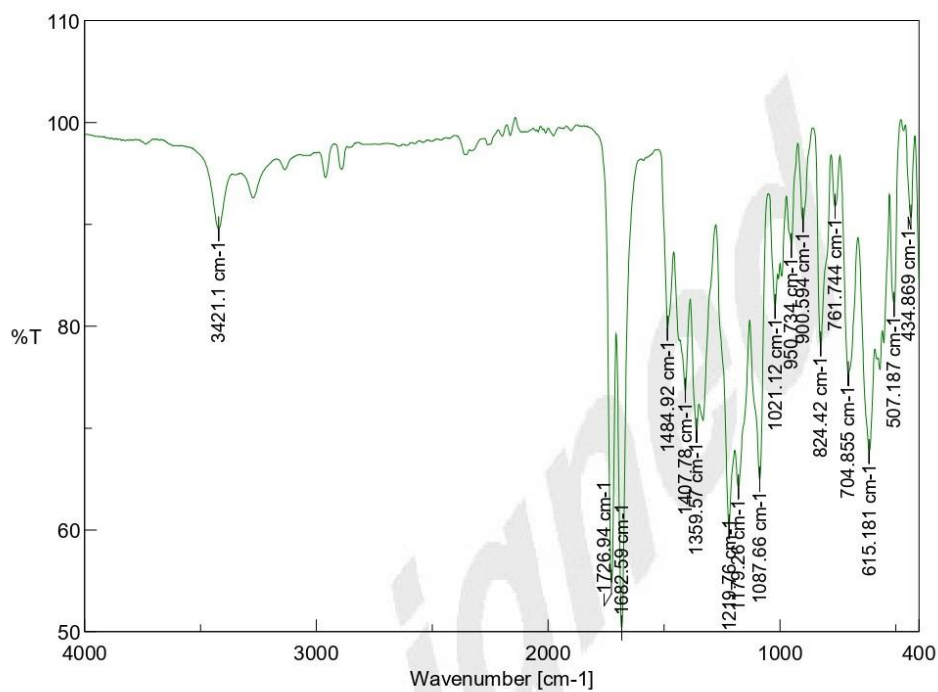
Characterization data along with scanned spectra of all the synthesized compounds are given below:

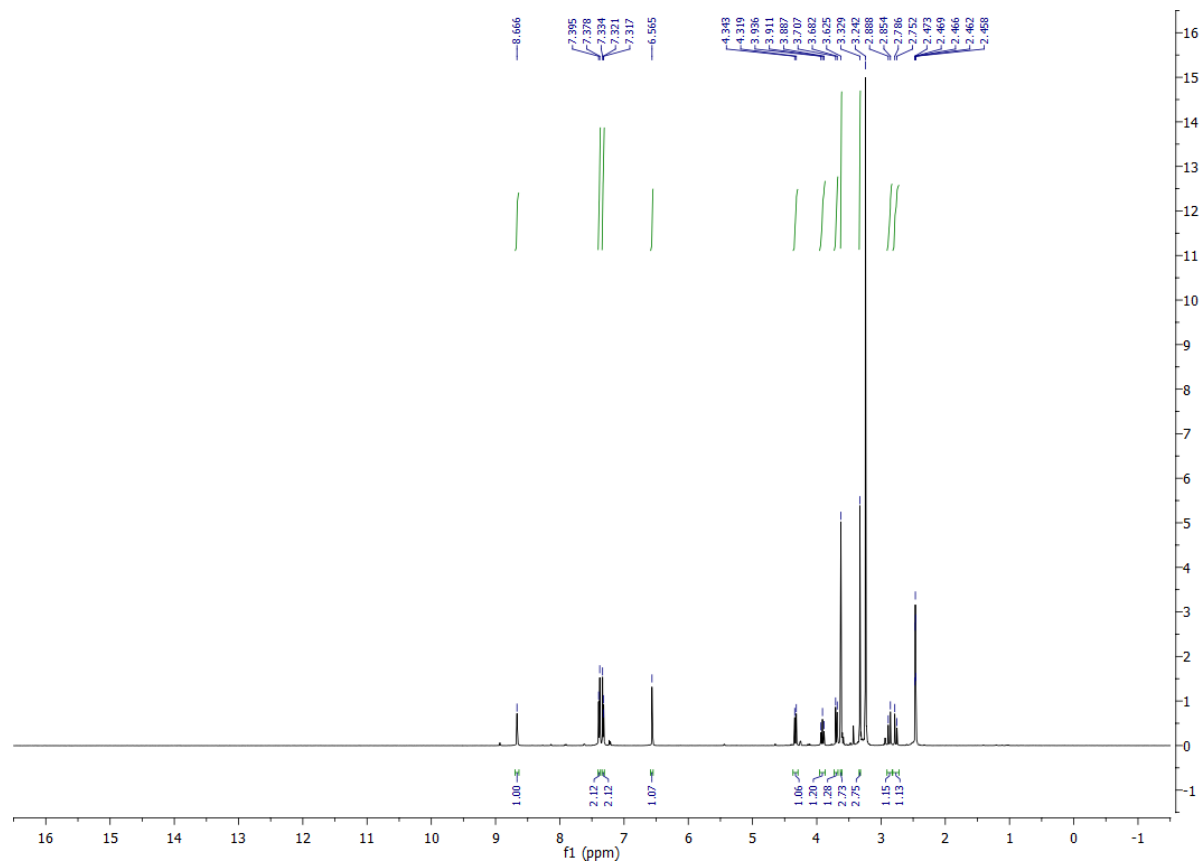


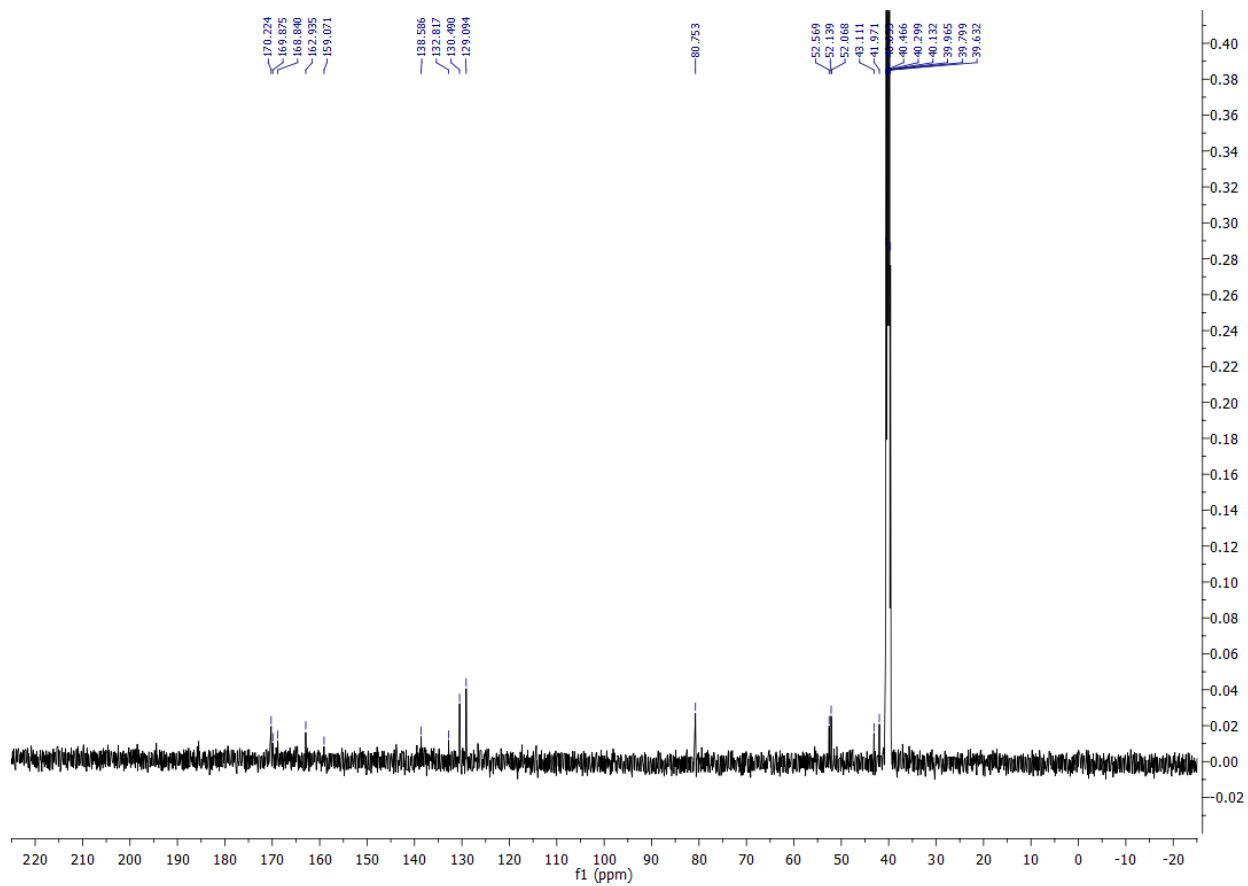
Methyl-4-(4-chlorophenyl)-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (4a). Light yellow solid, yield 97%; mp 142°C; FTIR (cm⁻¹): 3421, 1726, 1682, 1359, 1219, 1087, 615, 507, 434; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.67 (s, 1H, -NH), 7.39 (d, *J* = 8.5 Hz, 2H, aromatic H), 7.33 (d, *J* = 8.5 Hz, 2H, aromatic H), 6.57 (s, 1H, -OH), 4.33 (d, *J* = 12 Hz, 1H, -CH), 3.91 (t, *J* = 12.5 Hz, 1H, -CH), 3.69 (d, *J* = 12.5 Hz, 1H, aromatic H), 3.62 (s, 3H, -OCH₃), 3.33 (s, 3H, -OCH₃), 2.87 (d, *J* = 17 Hz, 1H), 2.77 (d, *J* = 17 Hz, 1H); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 170.22, 169.88, 168.84, 162.94, 159.07, 138.59, 132.82, 130.49 (2C), 129.09 (2C), 80.75, 52.57, 52.14, 52.07, 43.11, 41.97); HRMS (ESI-TOF) *m/z*: For C₁₇H₁₇ClN₂O₆ Calcd. [M]⁺ 380.0775; Found [M-H]⁻ 379.0355.

PID = 31131623-016939

BB MB S15-11.jws

Figure S1. FTIR spectrum of **4a**

Figure S2. ¹H NMR spectrum of **4a**

Figure S3. ¹³C NMR spectrum of **4a**

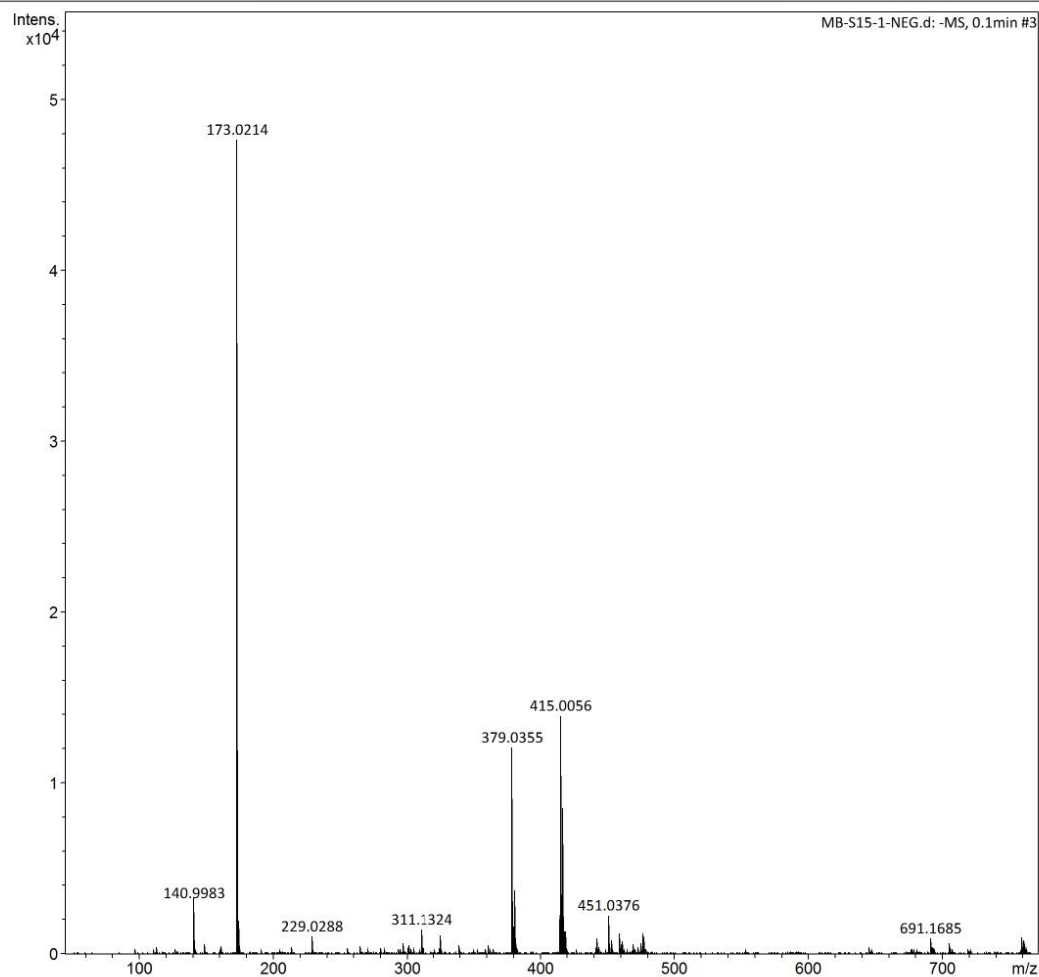
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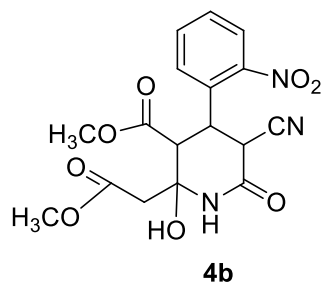
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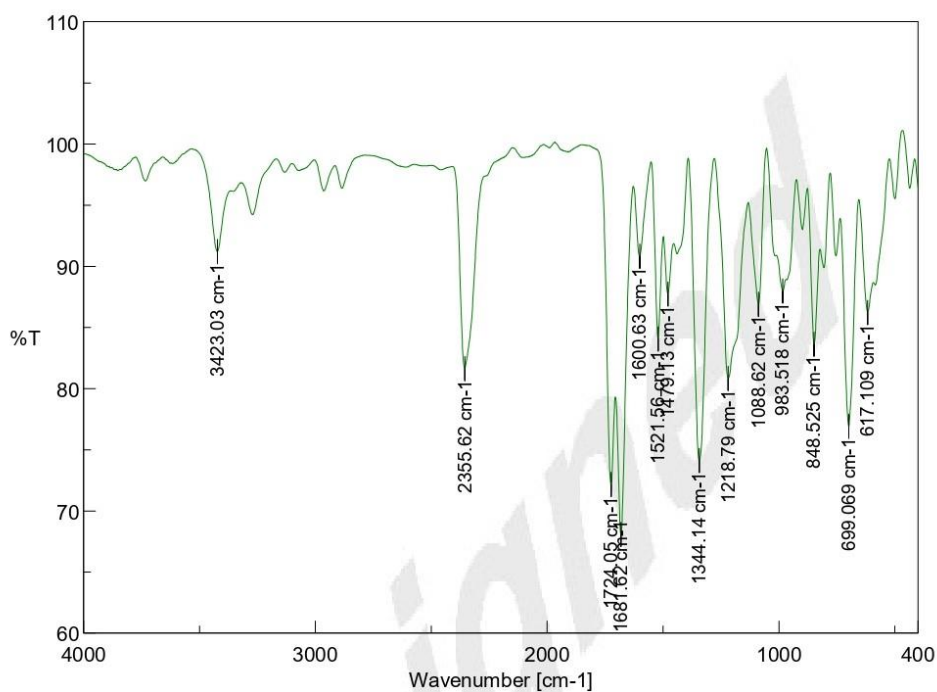
Figure S4. HRMS spectrum of **4a**

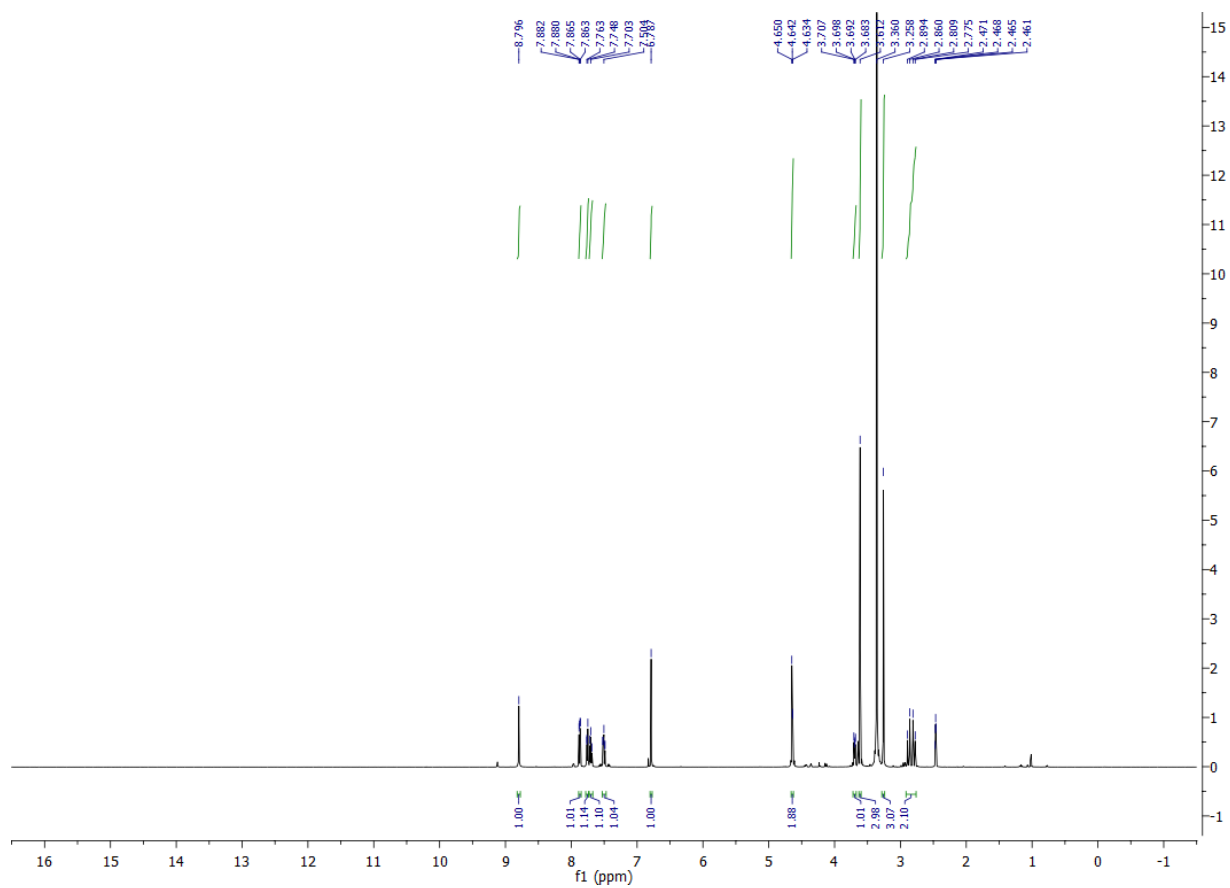


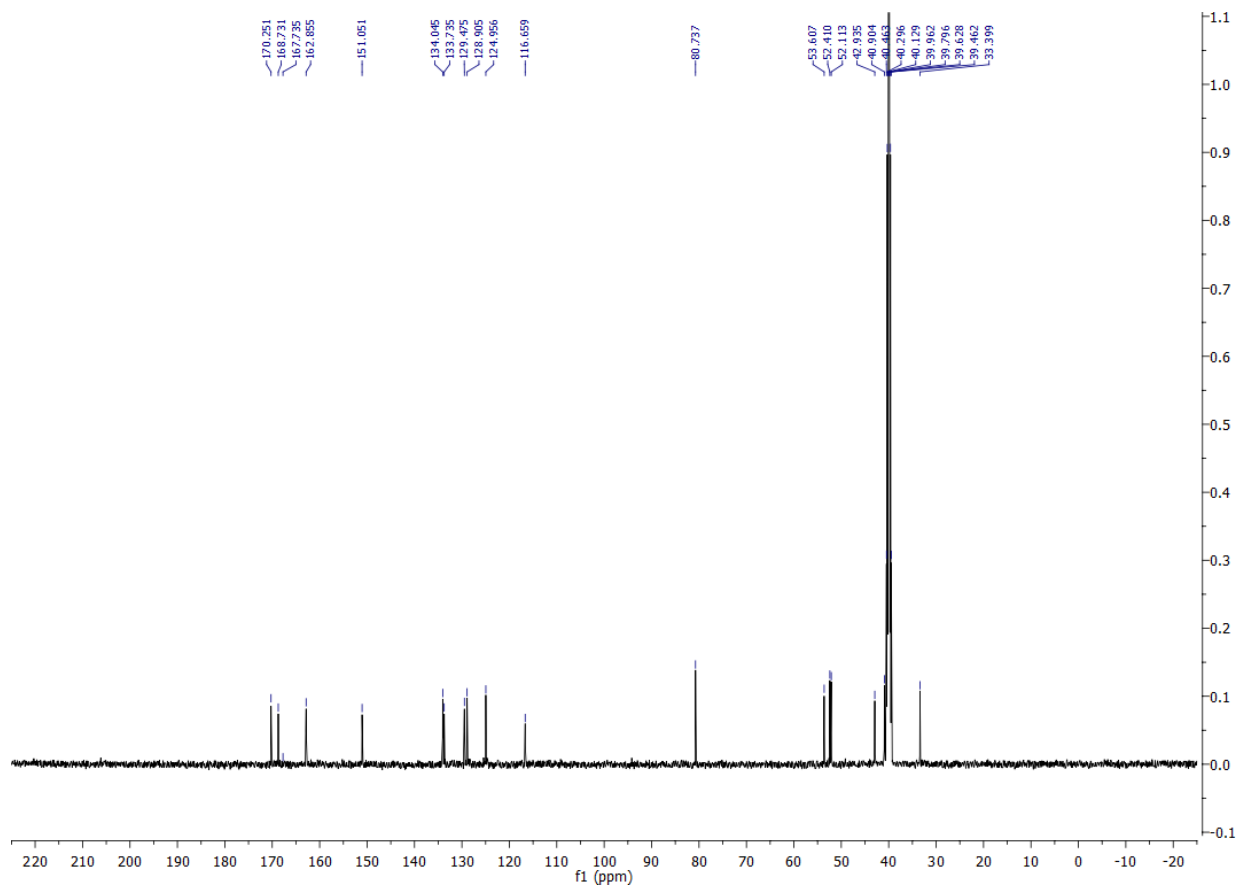
Methyl-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-4-(2-nitrophenyl)-6-oxopiperidine-3-carboxylate (4b). Light yellow solid, yield 90%; mp 153-155°C; FTIR (cm⁻¹): 3423, 2355, 1681, 1344, 1218 848, 699, 617; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.80 (s, 1H, -NH), 7.88-7.86 (m, 1H, aromatic H), 7.77-7.69 (m, 2H, aromatic H), 7.52-7.49 (m, 1H, aromatic H), 6.79 (s, 1H, OH), 4.65-4.63 (m, 2H, -CH), 3.71-3.69 (m, 1H, -CH), 3.68 (s, 3H, -OCH₃), 3.26 (s, 3H, -OCH₃), 2.88 (dd, *J* = 17 Hz, 2H, -CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 170.25, 168.73, 167.74, 162.86, 151.05, 134.05, 133.74, 129.48, 128.96, 124.96, 116.66, 80.74, 53.61, 52.41, 52.11, 42.94, 40.94); HRMS (ESI-TOF) *m/z*: For C₁₇H₁₇N₃O₈ Calcd. [M+Na]⁺ 414.1016; Found [M+Na]⁺ 414.1050.

PID = 30083047-071244

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Figure S5. FTIR spectrum of **4b**

Figure S6. ^1H NMR spectrum of **4b**

Figure S7. ¹³C NMR spectrum of **4b**

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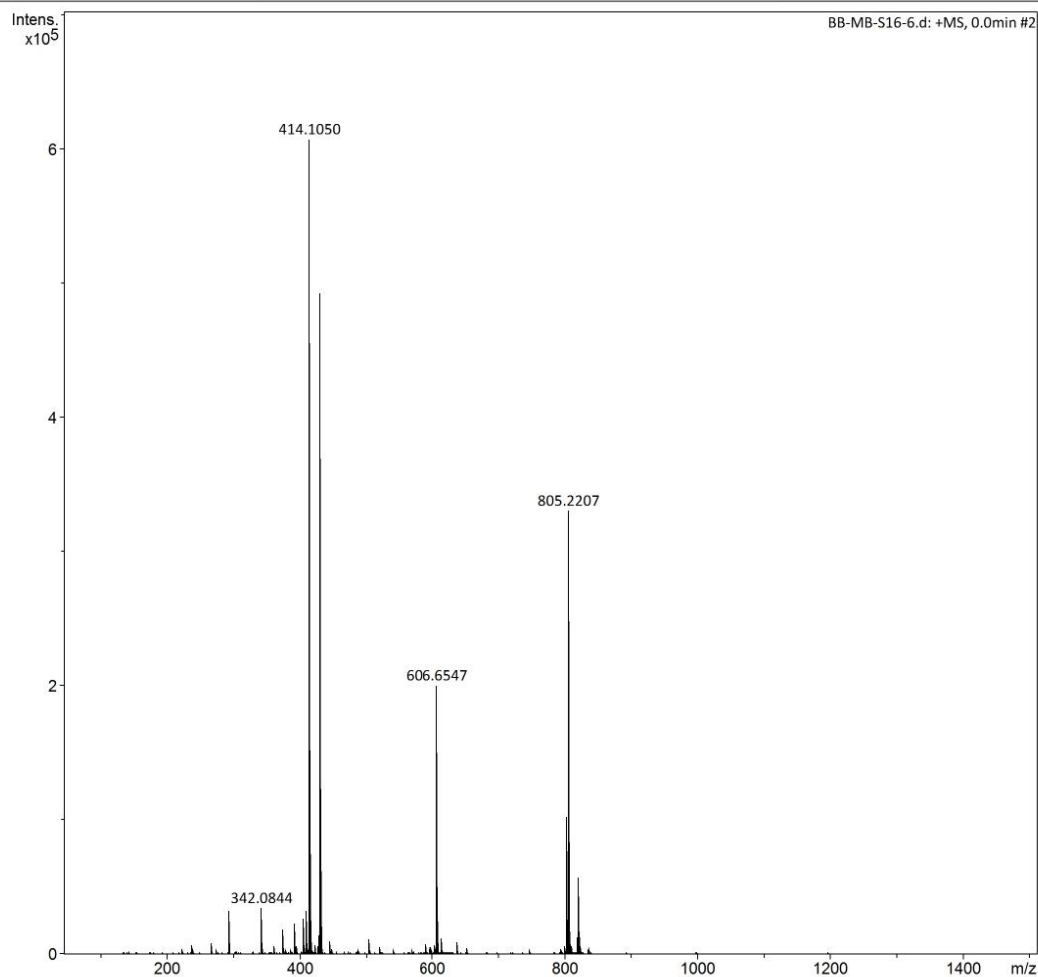
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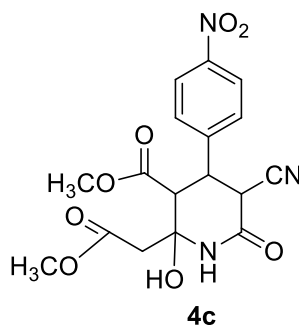
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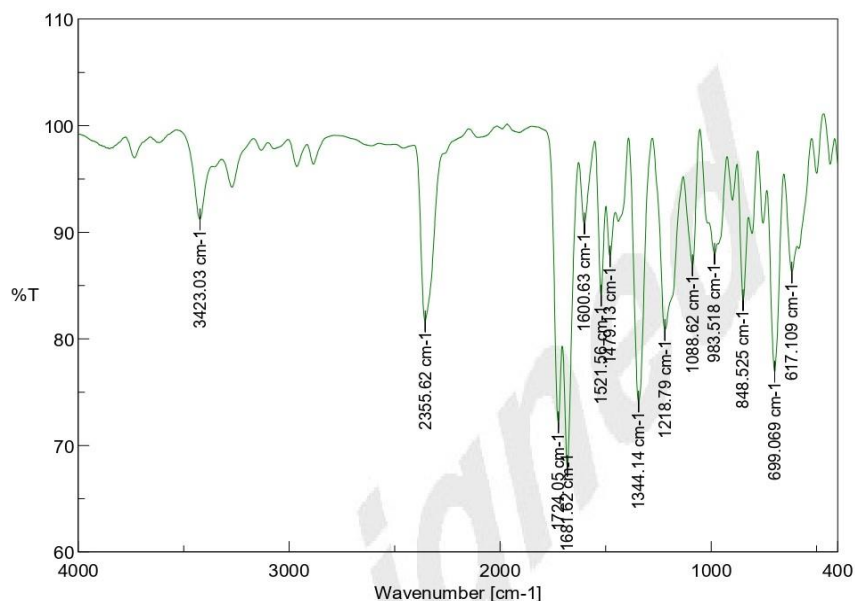
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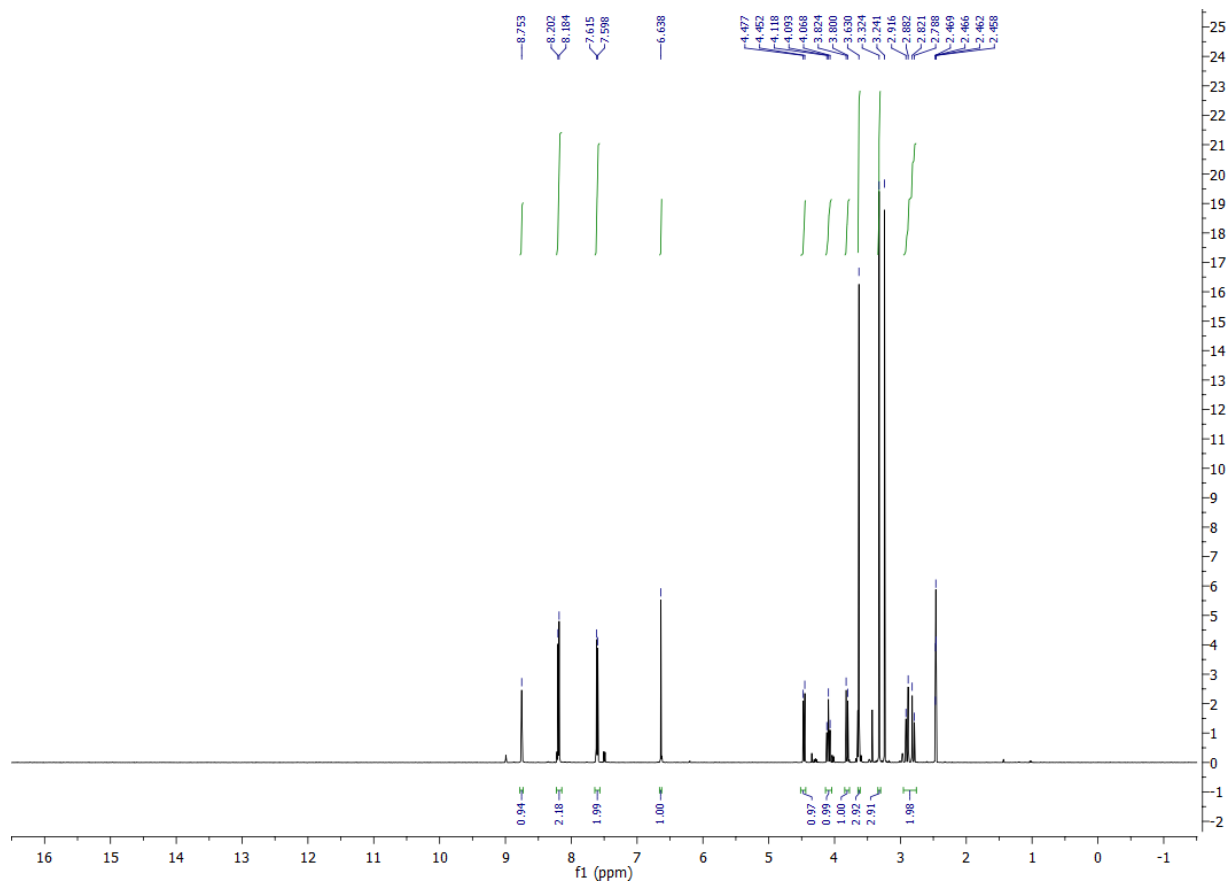


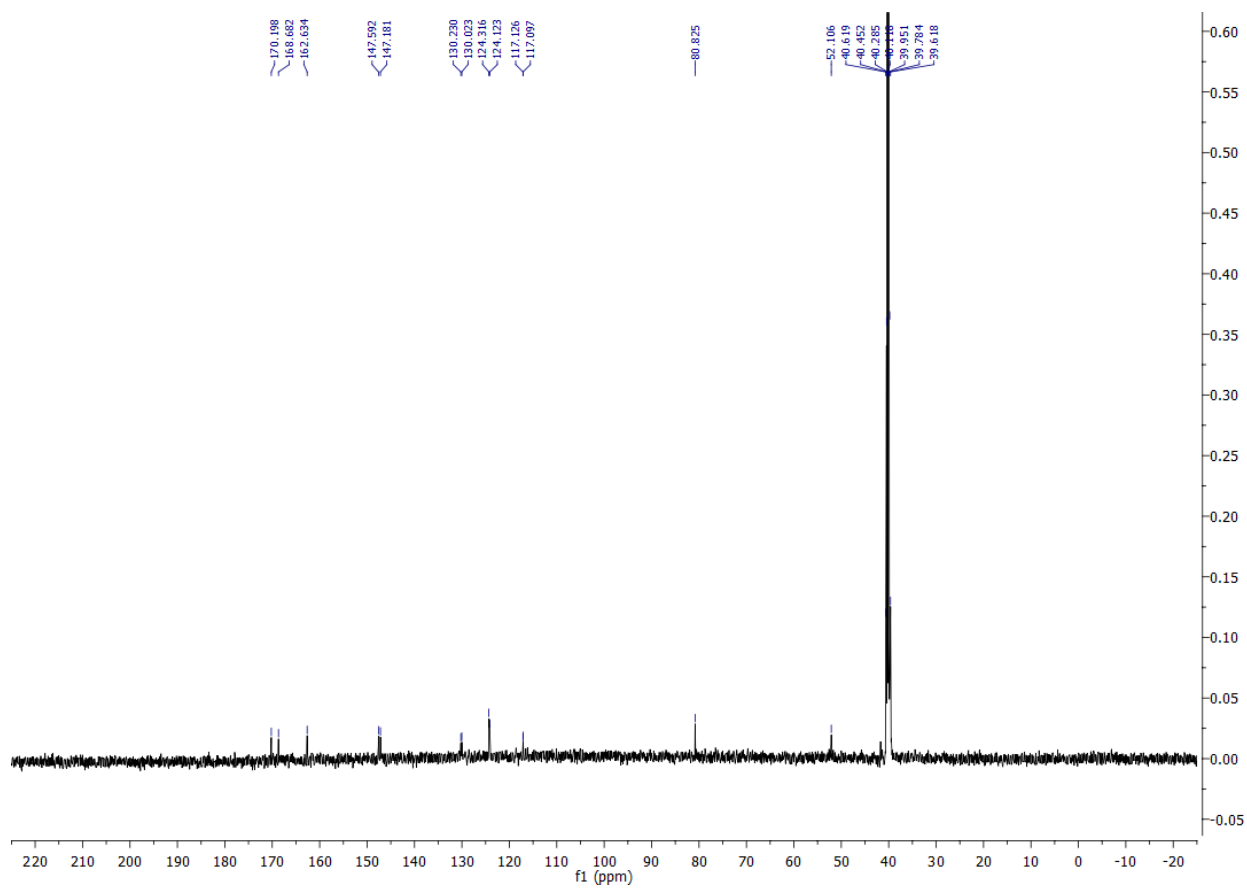
Methyl-5-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-4-(4-nitrophenyl)-6-oxopiperidine-3-carboxylate (4c). Light yellow solid, yield 94%; mp 140°C; FTIR (cm⁻¹): 3423, 2355, 1681, 1344, 1218, 848, 699, 617; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.75 (s, 1H, -NH), 8.19 (d, *J* = 9 Hz, 2H, aromatic H), 7.61 (d, *J* = 8.5 Hz, 2H, aromatic H), 6.64 (s, 1H, -OH), 4.46 (d, *J* = 12.5 Hz, 1H, -CH), 4.09 (t, *J* = 12.5 Hz, 1H, -CH), 3.81 (d, *J* = 12.5 Hz, 1H, aromatic H), 3.63 (s, 3H, -OCH₃), 3.32 (s, 3H, -OCH₃), 2.85 (dd, *J* = 17 Hz, 2H, -CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 170.20, 168.68, 162.63, 147.59 (2C), 147.18, 130.02, 124.32 (2C), 124.12 (2C), 117.13, 117.10, 80.83, 52.11, 40.62, 40.46); HRMS (ESI-TOF) *m/z*: For C₁₇H₁₇N₃O₈ Calcd. [M+Na]⁺ 414.1016; Found [M+Na]⁺414.1050

PID = 30083047-071244

BB MB S15-2 22.jws

Figure S9. FTIR spectrum of **4c**

Figure S10. ^1H NMR spectrum of **4c**

Figure S11. ^{13}C NMR spectrum of 4c

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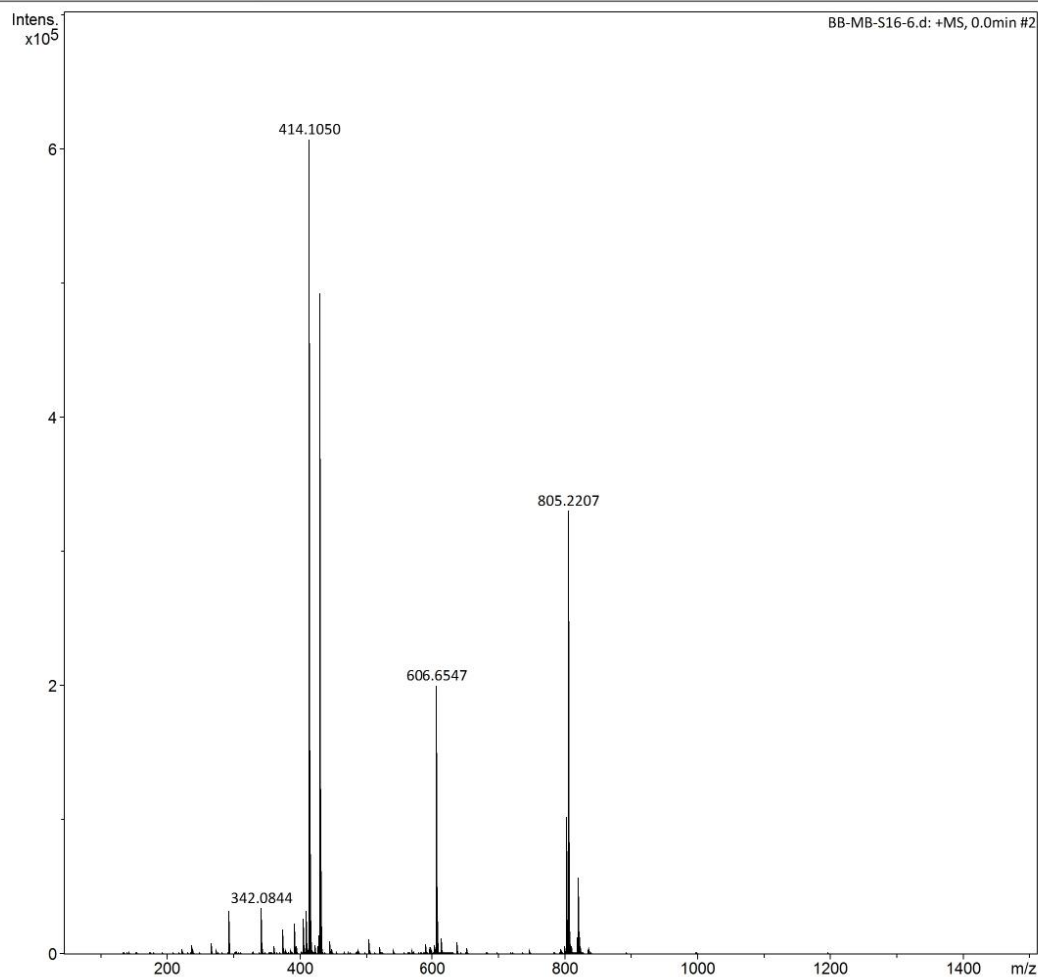
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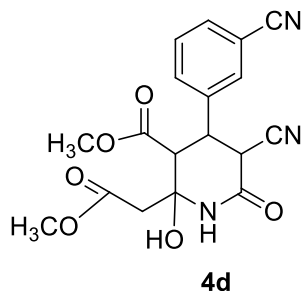
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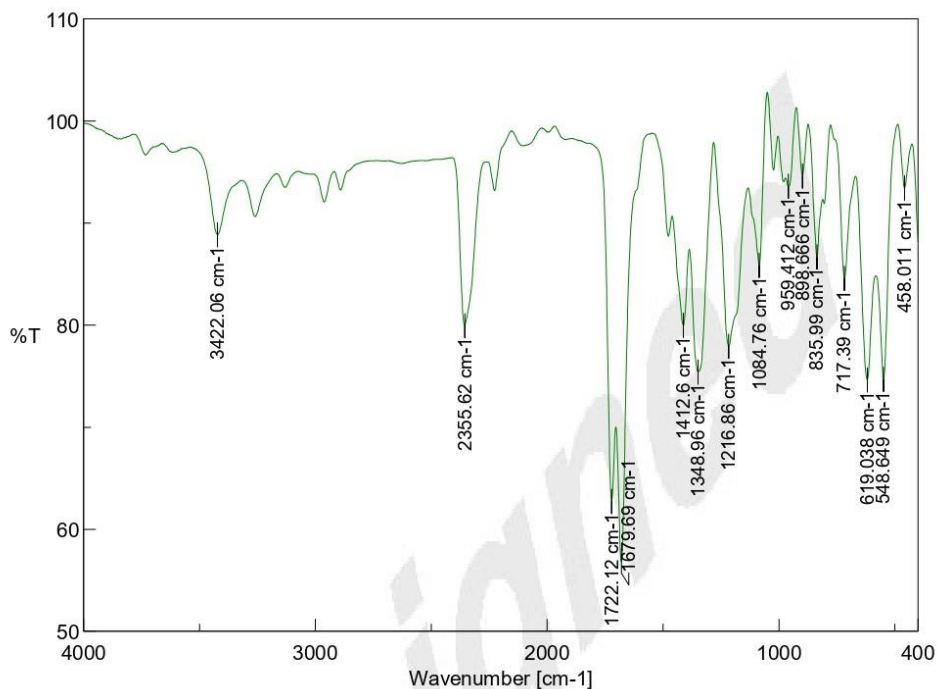
Figure S12. HRMS spectrum of **4c**

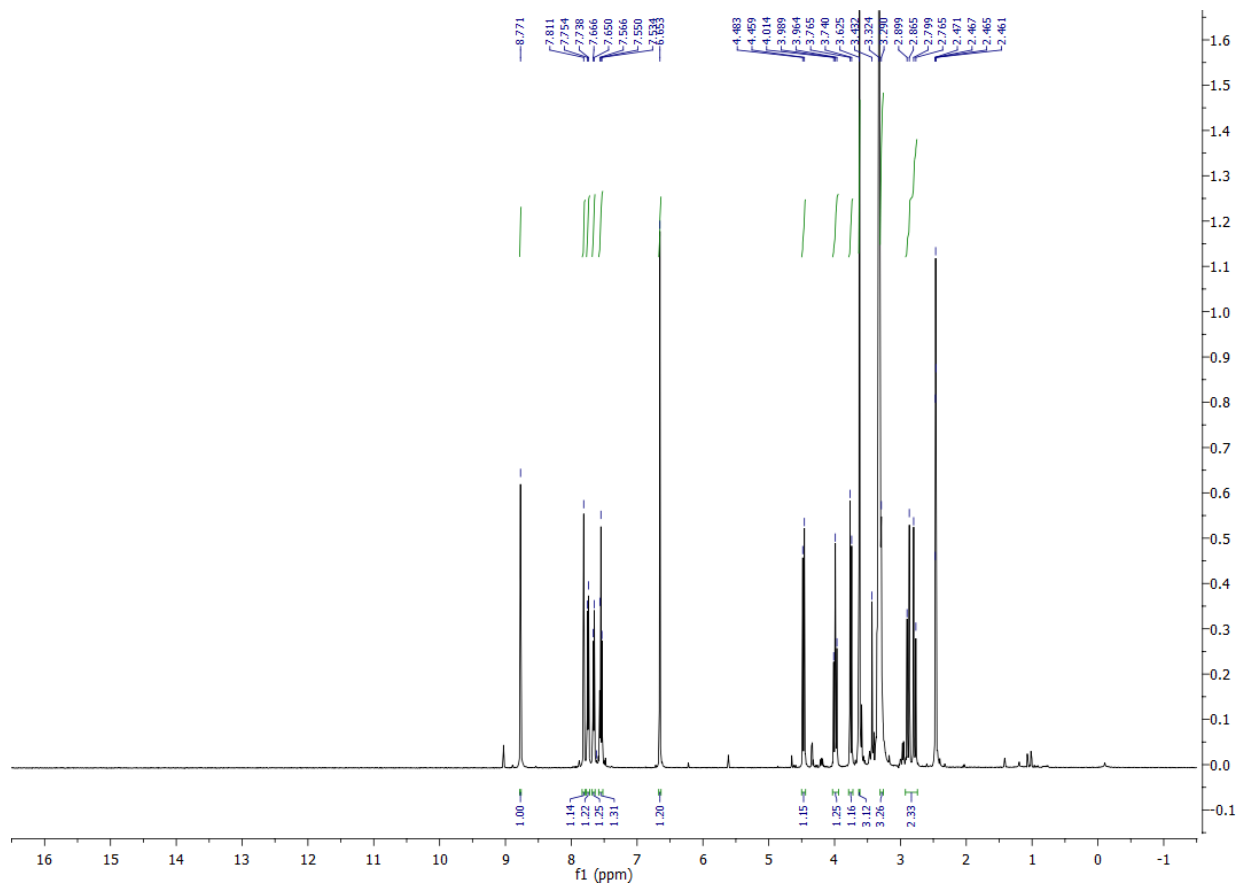


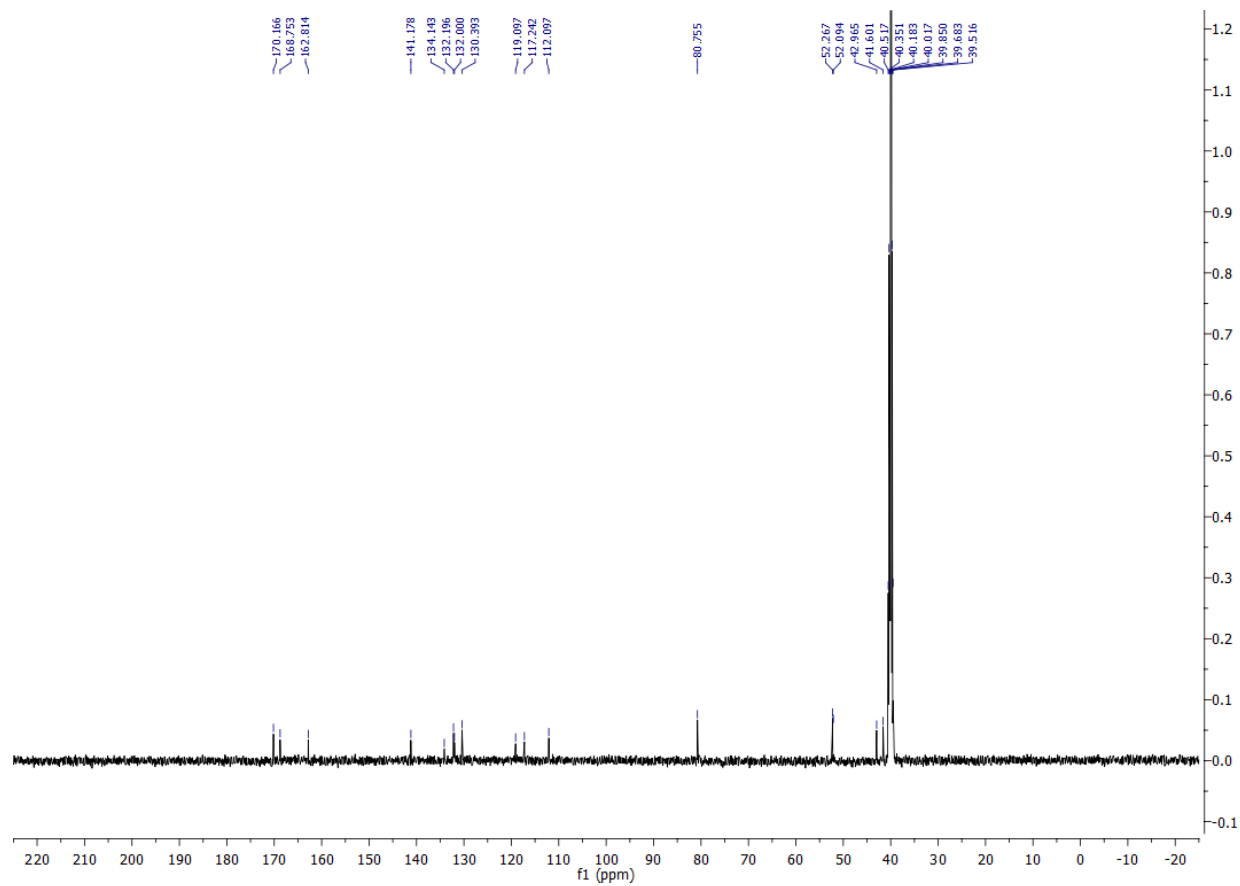
Methyl-5-cyano-4-(3-cyanophenyl)-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (4d) White solid, yield 91%; mp 163°C; 3422, 2355, 1722, 1679, 1348, 1216, 619, 548, 458; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.77 (s, 1H, -NH), 7.81 (s, 1H, aromatic H), 7.75 (d, J = 8 Hz, 1H, aromatic H), 7.75 (d, J = 8 Hz, 1H, -CH), 7.55 (d, J = 8 Hz, 1H, -CH), 6.65 (s, 1H, -OH), 4.47 (d, J = 12 Hz, 1H, -CH), 3.99 (t, J = 12.5 Hz, 1H, -CH), 3.75 (d, J = 12.5 Hz, 1H, -CH), 3.63 (s, 3H, -OCH₃), 3.32 (s, 3H, -OCH₃), 2.83 (dd, J = 17 Hz, 2H, -CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 170.17, 168.75, 162.81, 141.18, 134.14, 132.20, 132.00 (2C), 119.10, 117.24, 112.10, 80.76, 52.27 (2C), 52.09 (2C), 42.97, 41.60); HRMS (ESI-TOF) m/z: For C₁₈H₁₇N₃O₆ Calcd. [M]⁺ 371.1117; Found [M-H]⁻ 370.0476.

PID = 30083047-004301

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Figure S13. FTIR spectrum of **4d**

Figure S14. ^1H NMR spectrum of **4d**

Figure S15. ^{13}C NMR spectrum of **4d**

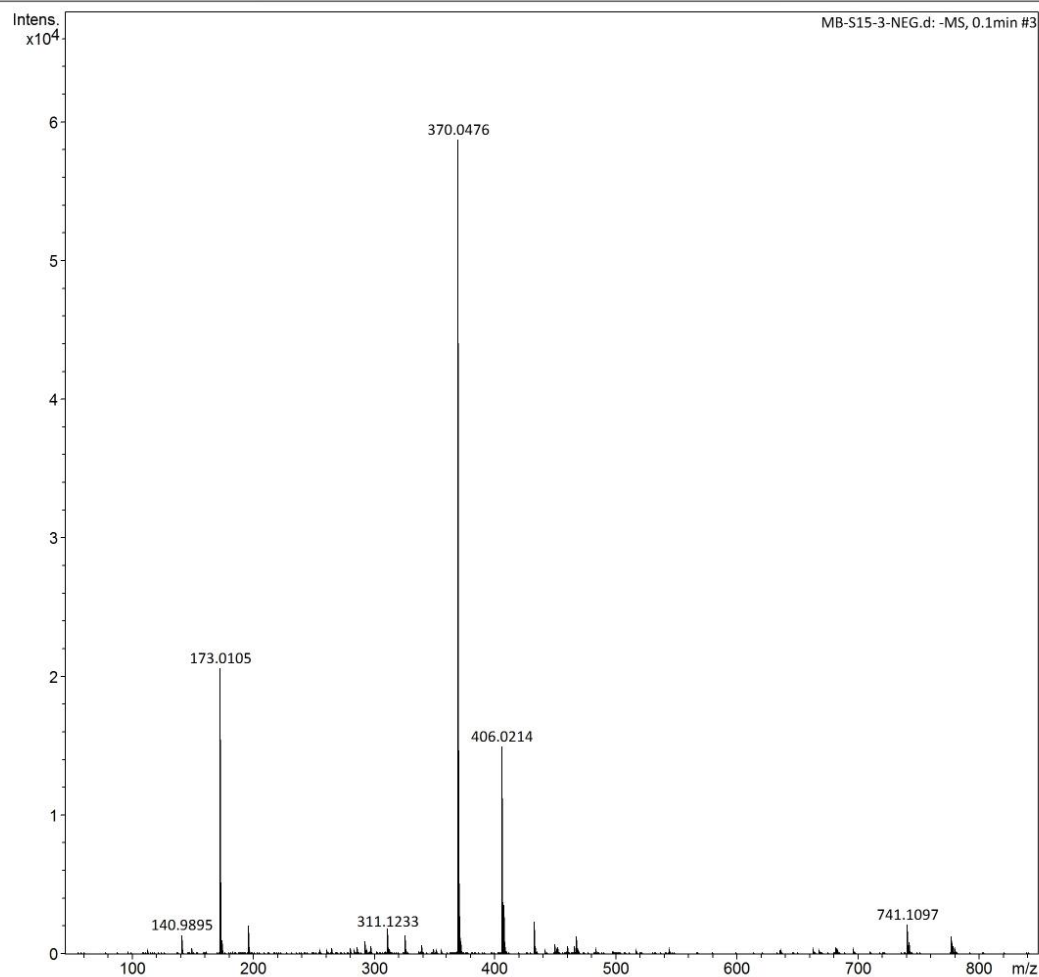
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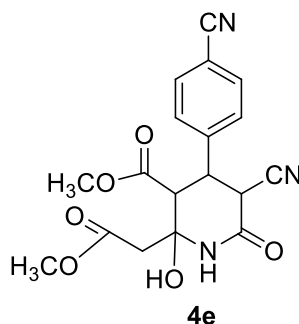
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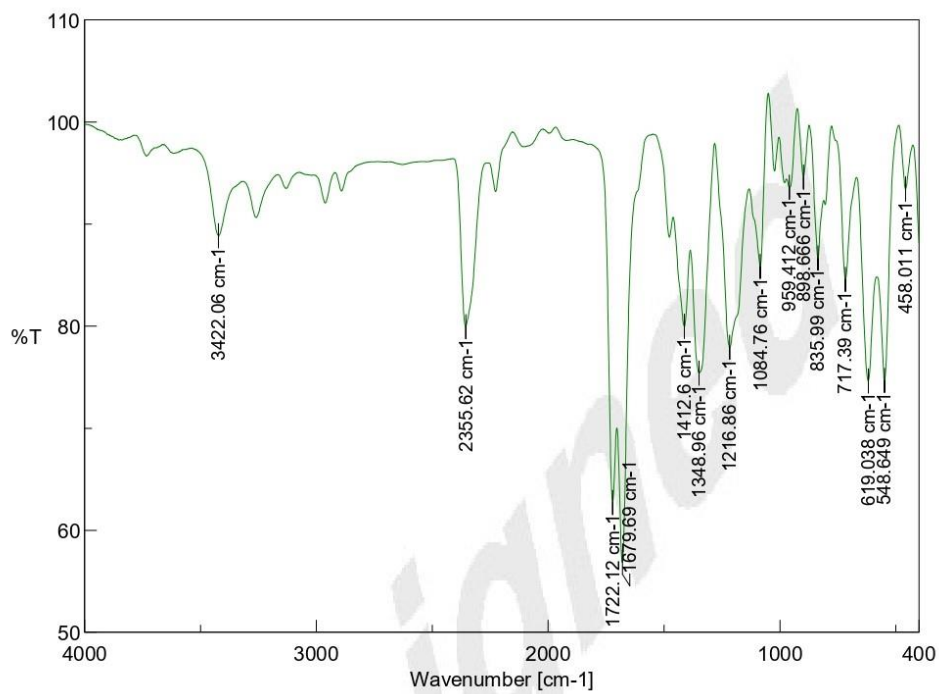
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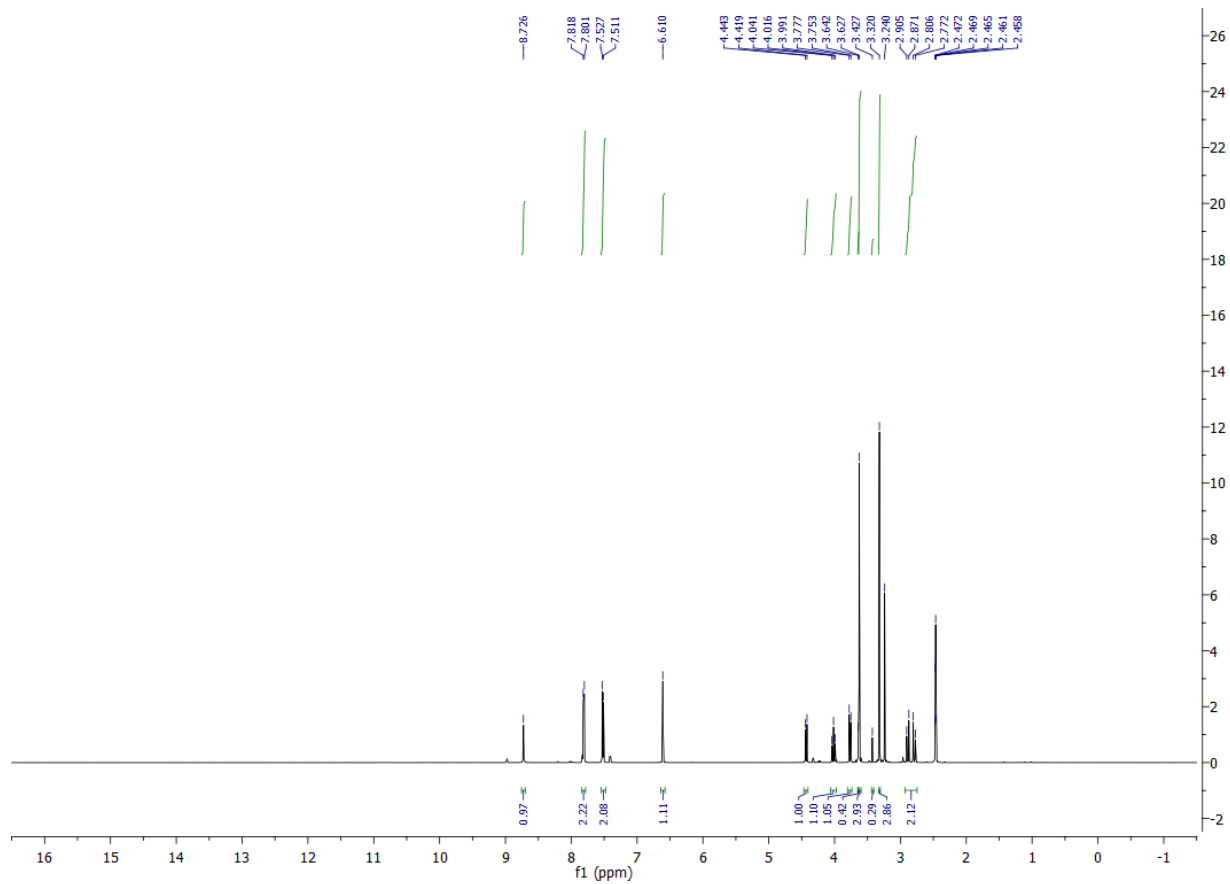


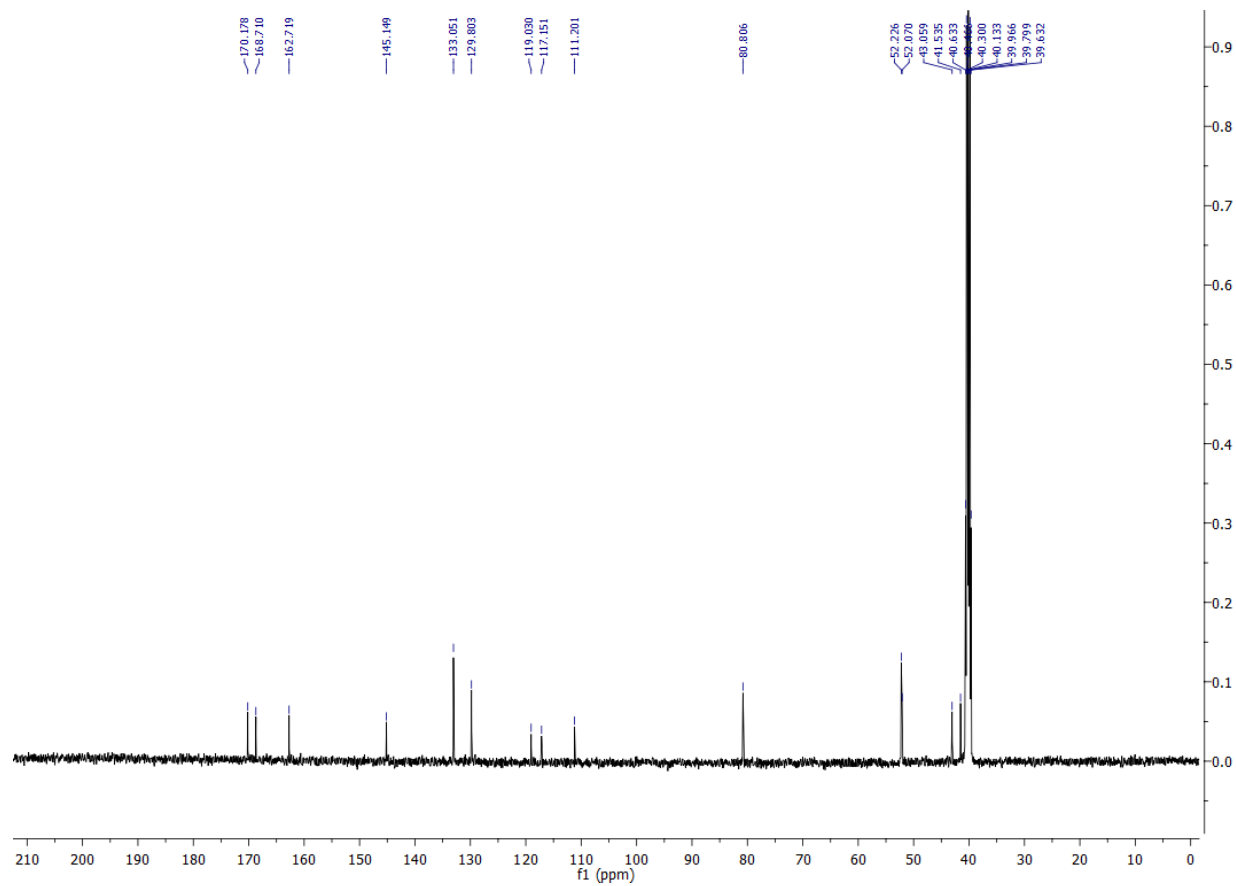
Methyl-5-cyano-4-(4-cyanophenyl)-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxopiperidine-3-carboxylate (4e). White solid, yield 95%; mp 151°C; FTIR (cm⁻¹): 3422, 2355, 1722, 1679, 1348, 1216, 619, 548, 458; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.73 (s, 1H, -NH), 7.81(d, *J* = 8.5 Hz, 2H, aromatic H), 7.52 (d, *J* = 8 Hz, 2H, aromatic H), 6.61 (s, 1H, -OH), 4.43 (d, *J* = 12 Hz, 1H, -CH), 4.02 (t, *J* = 12.5 Hz, 1H, -CH), 3.77 (d, *J* = 12 Hz, 1H, aromatic H), 3.63 (s, 3H, -OCH₃), 3.32 (s, 3H, -OCH₃), 2.84 (dd, *J* = 17 Hz, 2H, -CH₂); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 170.18, 168.71, 162.72, 145.15, 133.05 (2C), 129.80 (2C), 119.03, 117.15, 111.20, 80.81, 52.23 (2C), 52.07 (2C), 43.06, 41.54); HRMS (ESI-TOF) *m/z*: For C₁₈H₁₇N₃O₆ Calcd. [M]⁺ 371.1117; Found [M-H]⁻ 370.0476

PID = 30083047-004301

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Figure S17. FTIR spectrum of **4e**

Figure S18. ^1H NMR spectrum of **4e**

Figure S19. ^{13}C NMR spectrum of **4e**

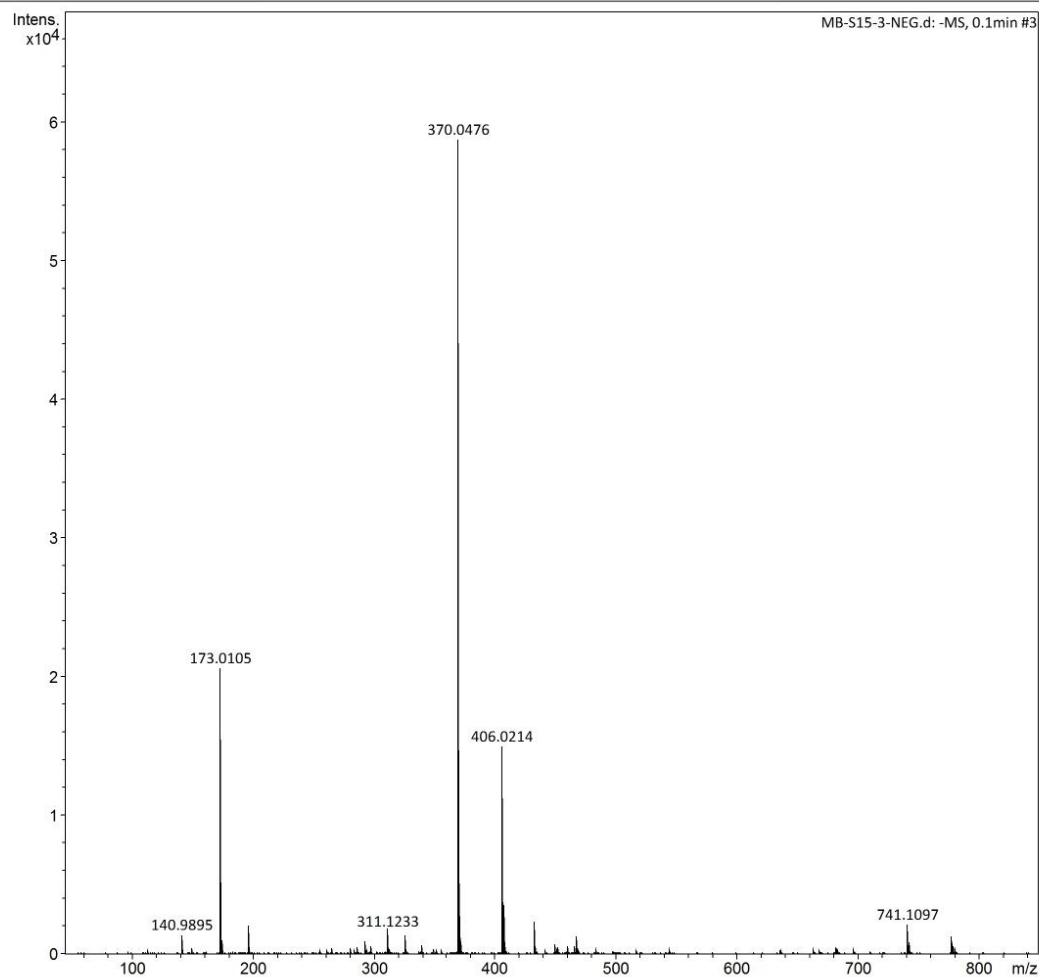
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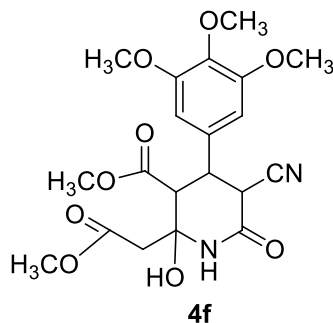
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Figure S20. HRMS spectrum of **4e**



Methyl-cyano-2-hydroxy-2-(2-methoxy-2-oxoethyl)-6-oxo-4-(3,4,5-trimethoxyphenyl)piperidine-3-carboxylate (4f) White solid, yield 98%; mp 181-182°C; ^1H NMR (500 MHz, DMSO- d_6) δ_{H} /ppm: 8.65 (s, 1H, -NH), 6.59 (s, 2H, aromatic H), 6.61 (s, 1H, -OH), 4.41 (d, $J = 12$ Hz, 1H, -CH), 3.80 (t, $J = 12.5$ Hz, 1H, -CH), 3.73 (s, 6H, 2X -OCH₃), 3.64 (d, $J = 8.5$ Hz, 1H, -CH), 3.62 (s, 3H, -OCH₃), 3.61 (s, 3H, -OCH₃), 3.36 (s, 3H, -OCH₃), 2.79 (dd, $J = 16.5$ Hz, 2H, -CH₂); ^{13}C NMR (125 MHz, DMSO- d_6) δ_{C} /ppm: 170.25, 169.07, 163.31, 153.21 (2C), 137.23, 135.07, 117.65, 105.99, 80.67, 60.48 (2C), 56.49 (2C), 52.84 (2C), 52.14, 52.09, 43.06, 41.99); HRMS (ESI-TOF) m/z : For C₂₀H₂₄N₂O₉ Calcd. [M+Na]⁺ 459.1482; Found [M+Na]⁺ 459.1274

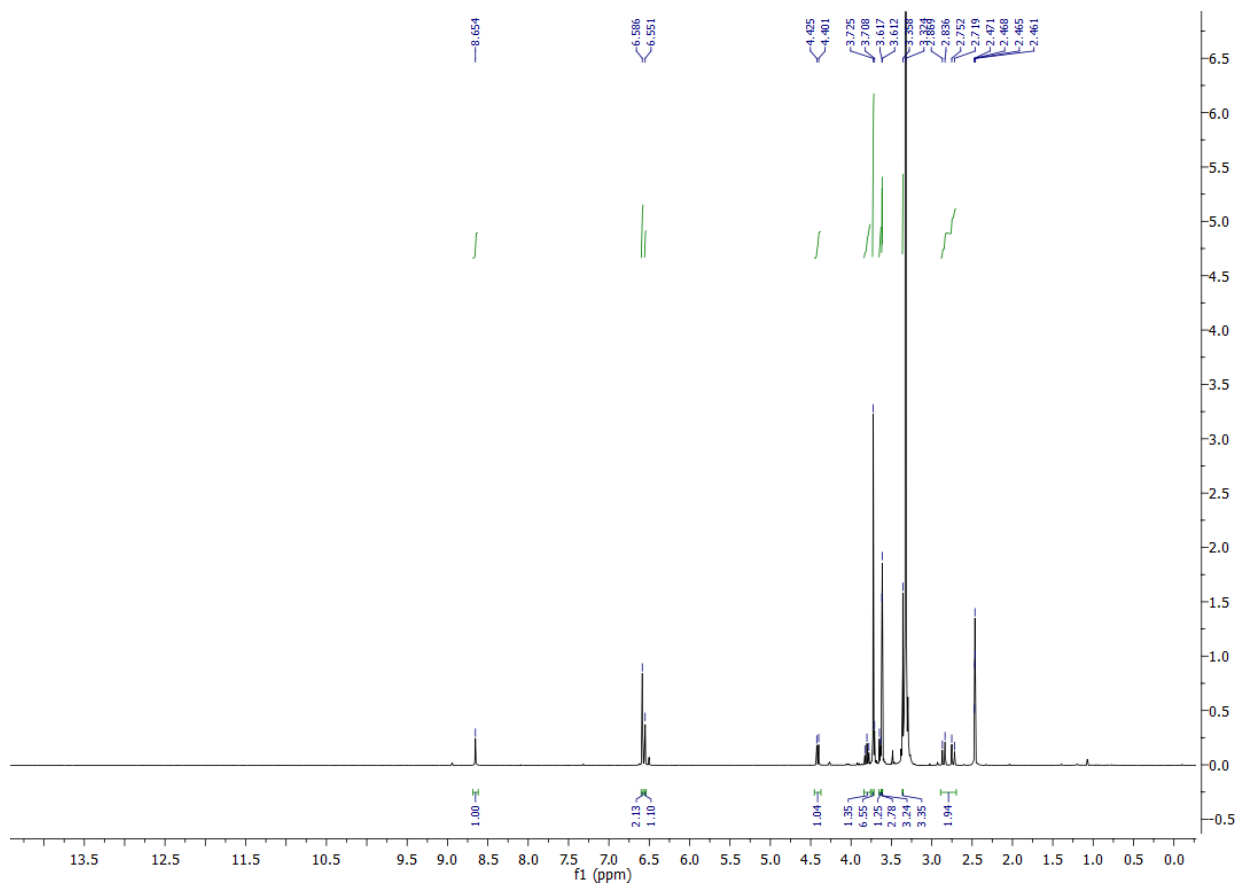
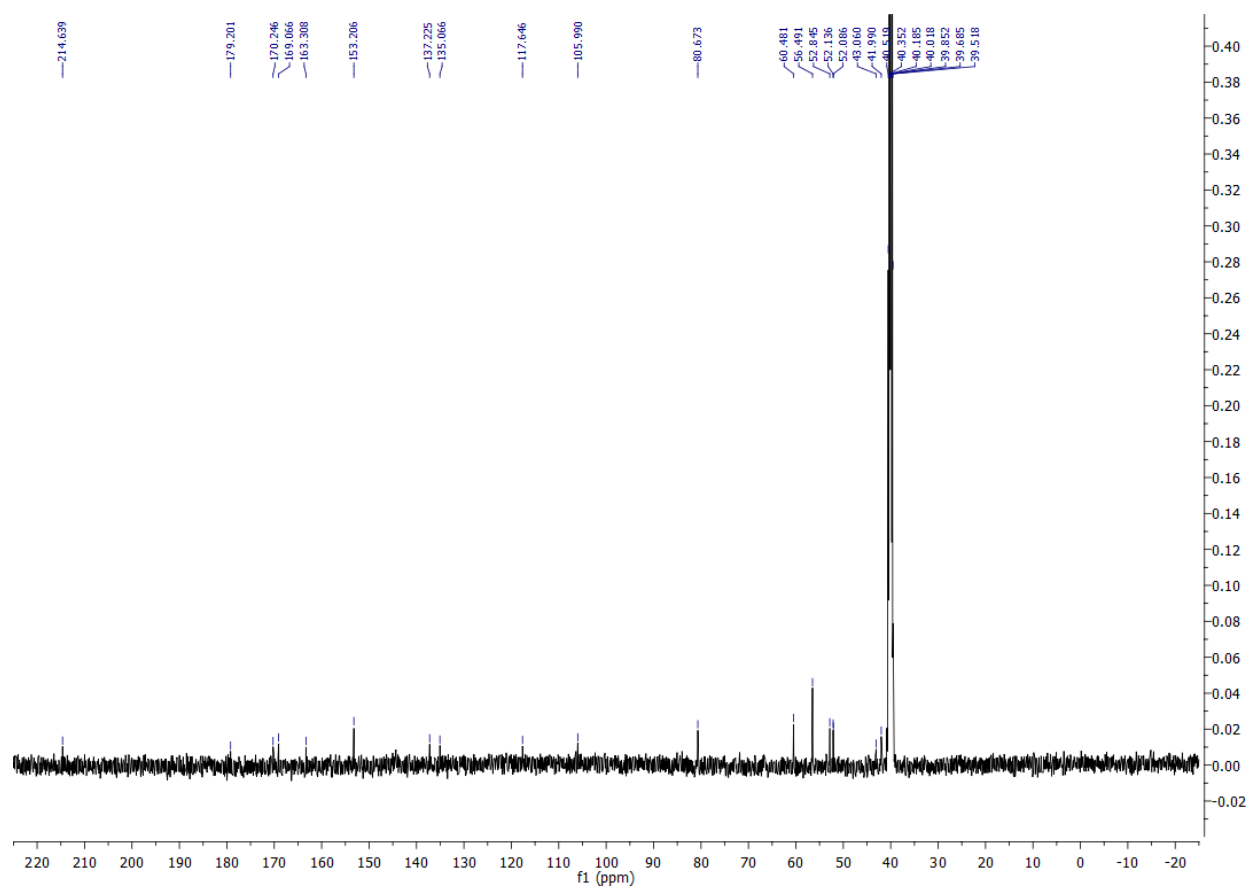


Figure S21. ^1H NMR spectrum of **4f**

Figure S22. ^{13}C NMR spectrum of **4f**

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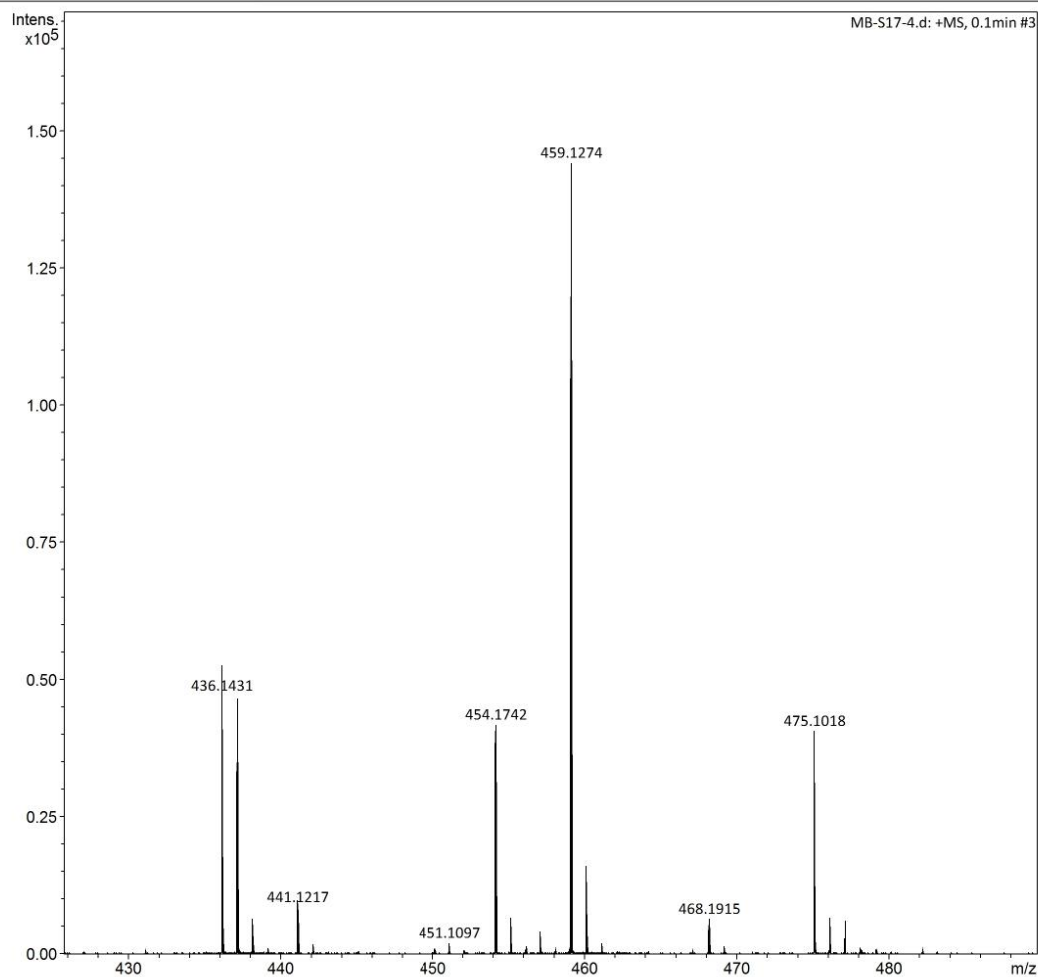
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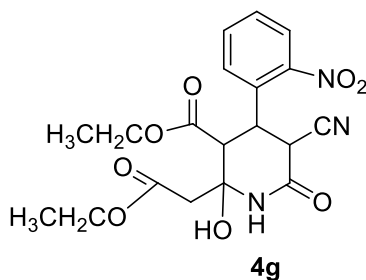
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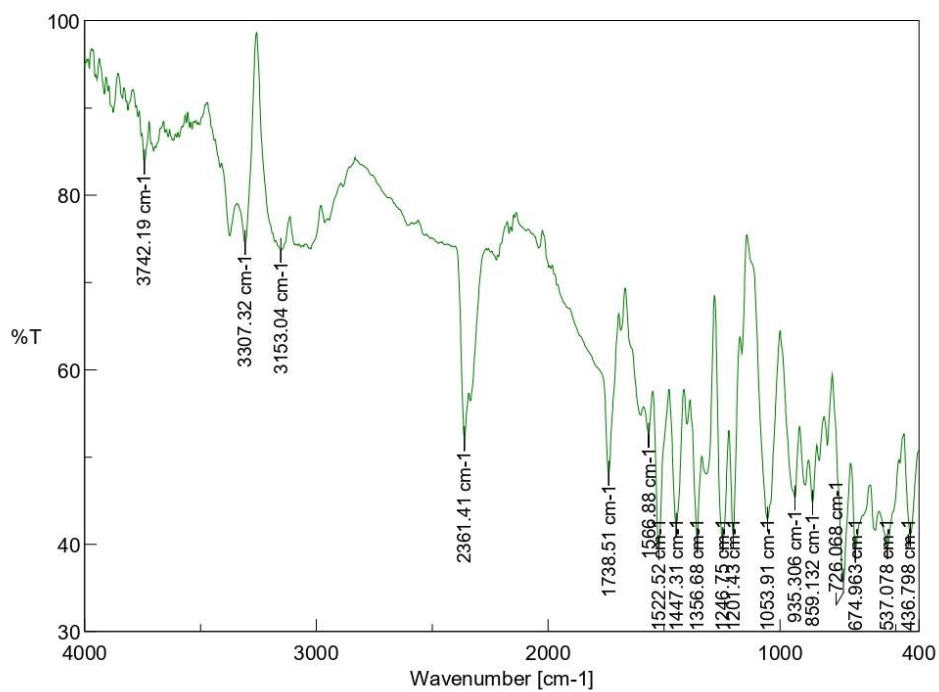
Figure S23. HRMS spectrum of **4f**

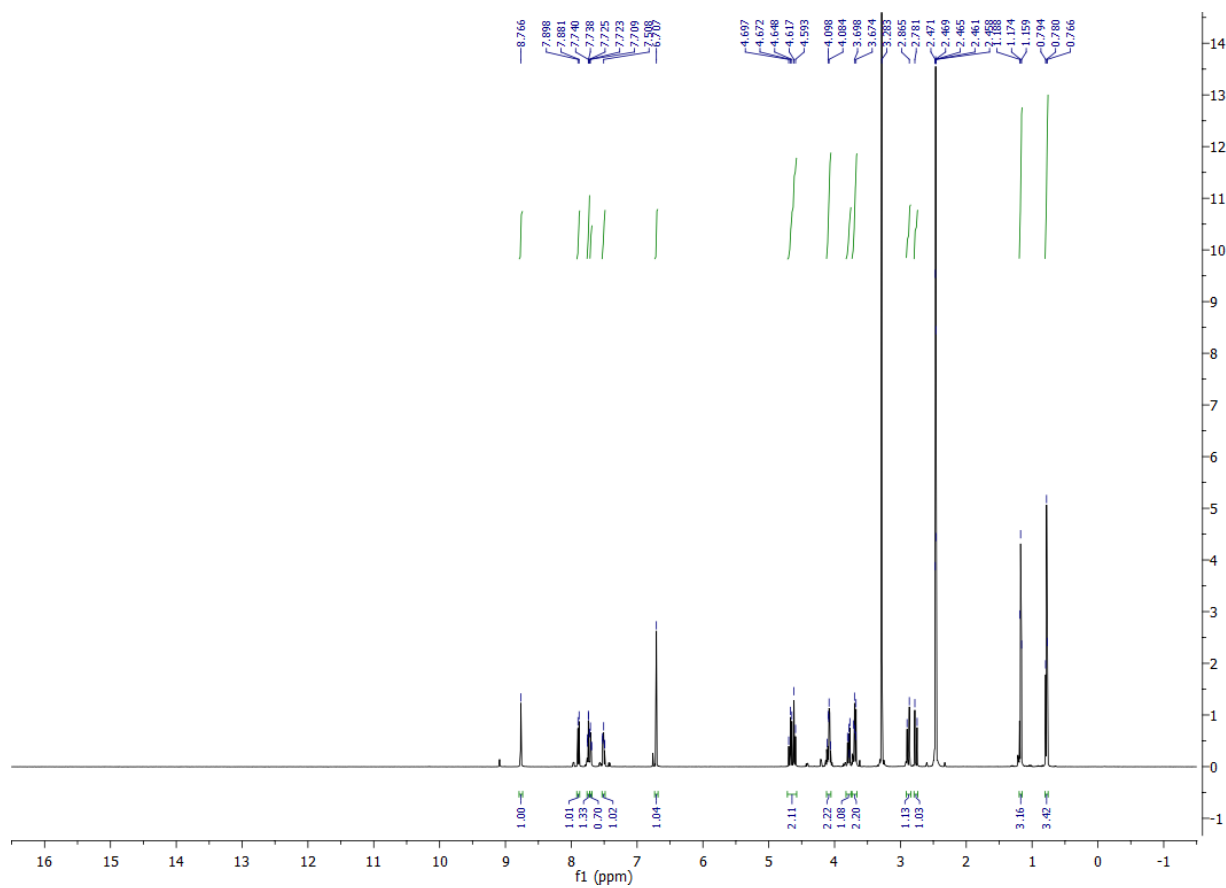


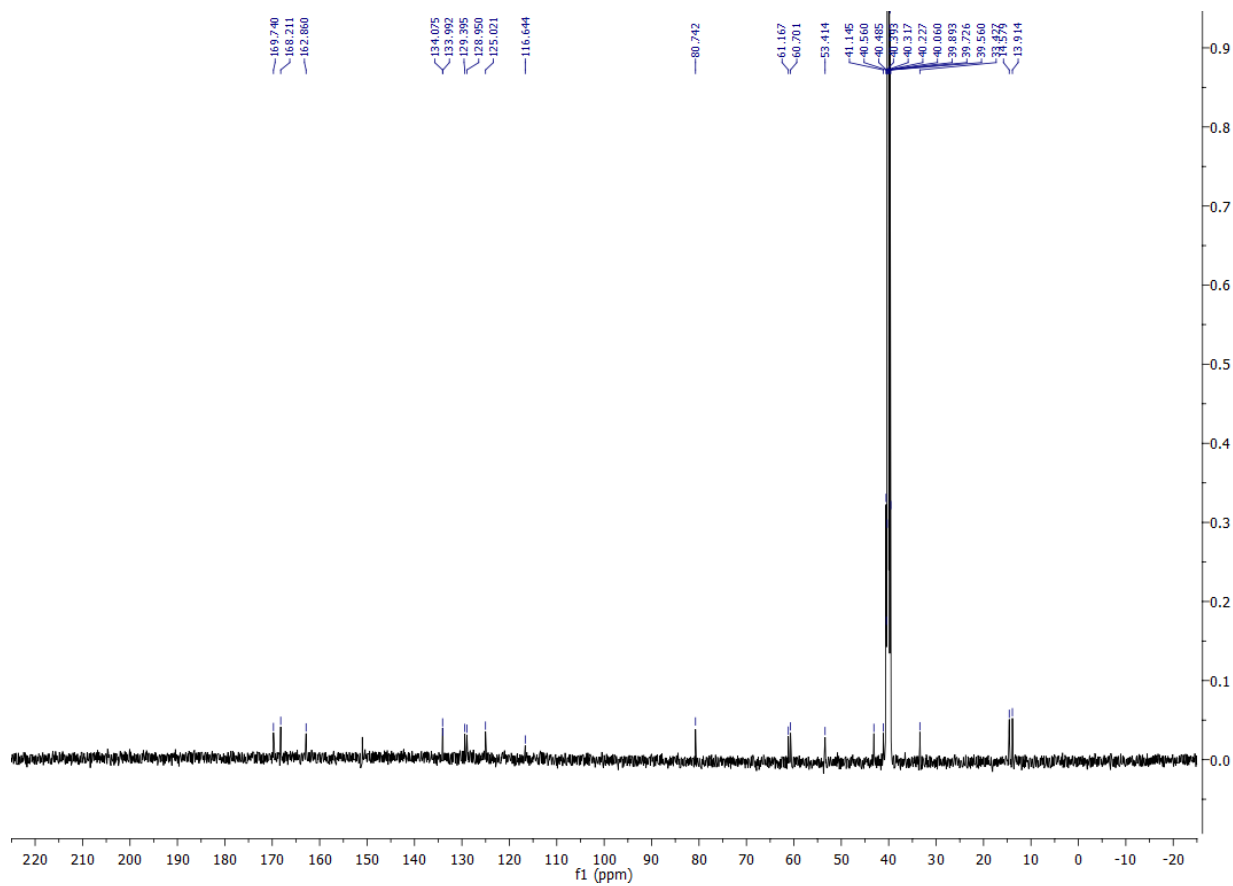
Ethyl-5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-(2-nitrophenyl)-6-oxopiperidine-3-carboxylate (4g). Light yellow solid, yield 89%; mp 161-163°C; FTIR (cm⁻¹): 3742, 3307, 3153, 2361, 1738, 1356, 1053, 649, 537, 436; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.76 (s, 1H, -NH), 7.89 (d, *J* = 8.5 Hz, 1H, aromatic H), 7.76-7.71 (m, 1H, aromatic H), 7.70 (d, *J* = 8 Hz, 1H, aromatic H), 7.51 (td, *J* = 17 Hz, *J* = 8 Hz, *J* = 7.5 Hz, 1H, aromatic H), 6.71, (s, 1H, OH), 4.69-4.59 (m, 2H, -CH), 4.11-4.060 (m, 2H, -OCH₂), 3.80-3.77 (m, 1H, -CH), 3.71-3.67 (m, 2H, -OCH₂), 2.88 (d, *J* = 17 Hz, 1H, -CH₂), 2.76 (d, *J* = 17 Hz, 1H, -CH₂), 1.17 (t, *J* = 7 Hz, 3H, -CH₃), 0.78 (t, *J* = 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 169.74, 168.21 (2C), 162.86, 134.07, 133.99, 129.39, 128.96, 125.02, 116.64, 80.74, 61.17, 60.70, 53.41, 41.15, 40.56, 33.43, 14.58, 13.91; HRMS (ESI-TOF) *m/z*: For C₁₉H₂₁N₃O₈ Calcd. [M+Na]⁺ 442.1329; Found [M+Na]⁺ 442.1194

PID = 19204072-001452

ETRB TUN

Figure S24. FTIR spectrum of **4g**

Figure S25. ^1H NMR spectrum of **4g**

Figure S26. ^{13}C NMR spectrum of **4g**

Display Report

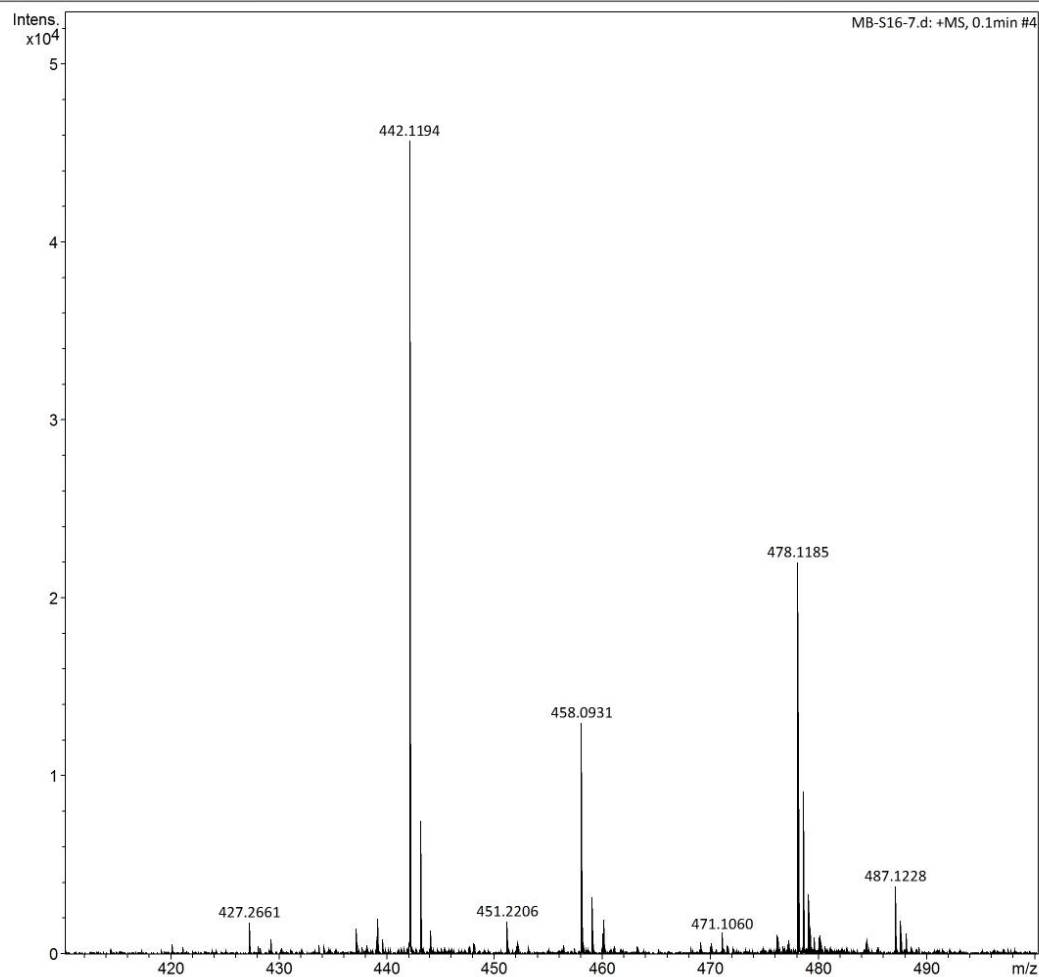
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Method Tune_pos_Standard.m
Sample Name MEOH
Comment

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Operator HRMS
Instrument maXis impact 1819696.00160

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MB-S16-7.d

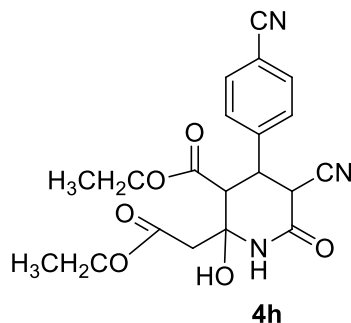
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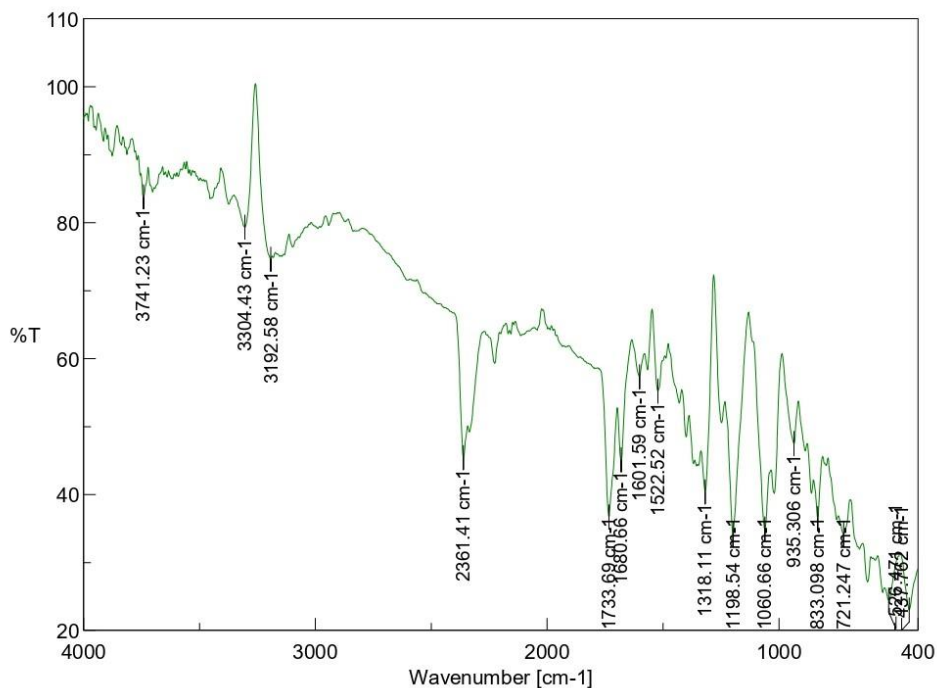
Figure S27.HRMS spectrum of **4g**

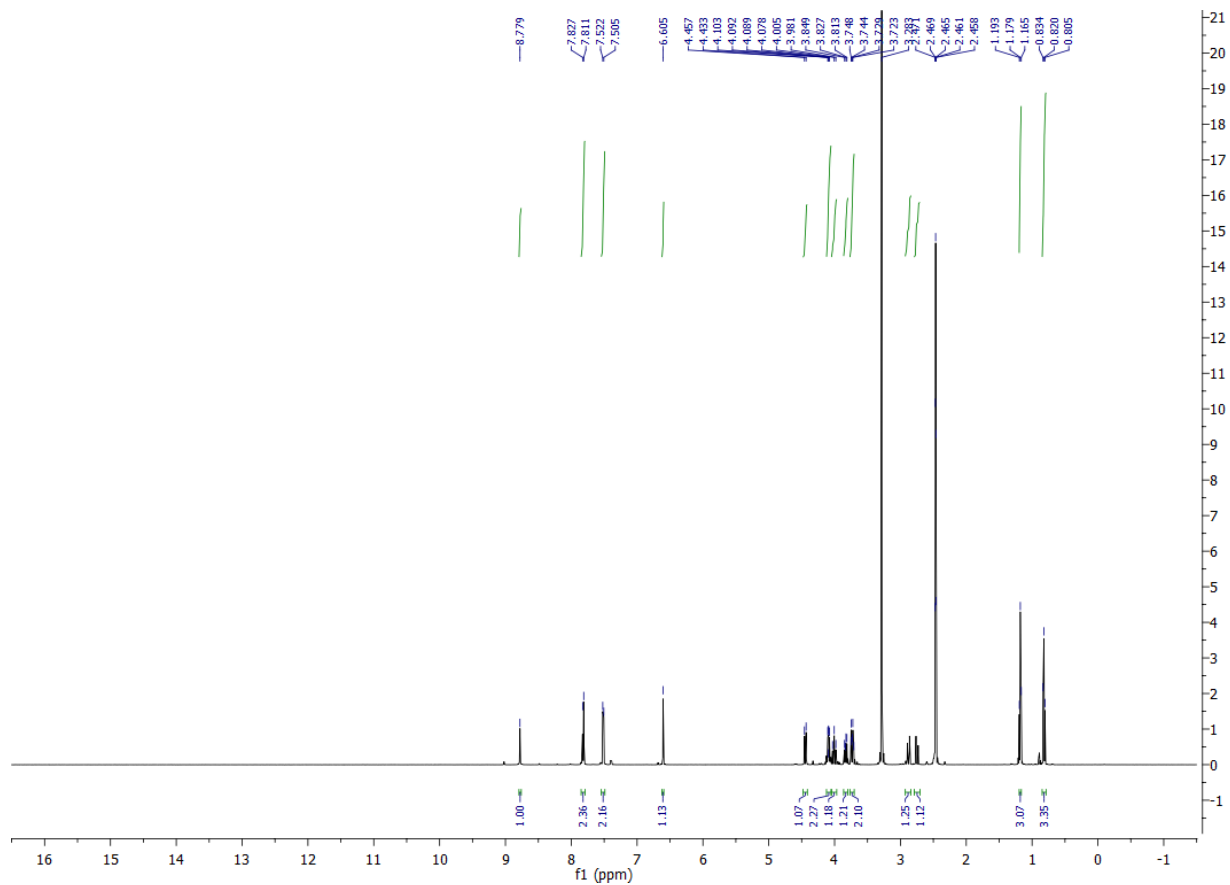


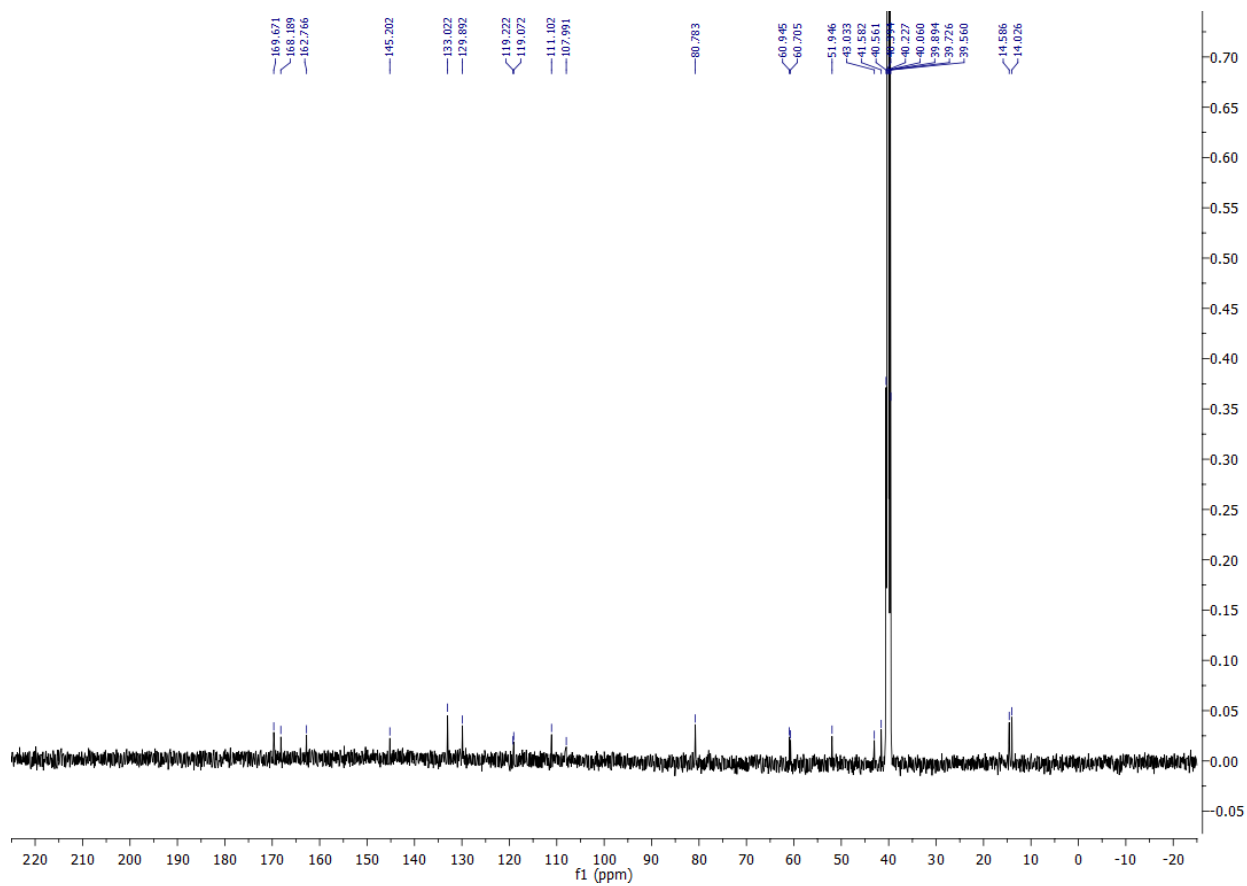
Ethyl-5-cyano-4-(4-cyanophenyl)-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-6-oxopiperidine-3-carboxylate (4h). Light yellow solid, yield 93%; mp 155°C; FTIR (cm⁻¹): 3741, 3304, 3192, 2361, 1733, 1318, 1060, 721, 526, 437; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.78 (s, 1H, -NH), 7.82 (d, *J* = 8 Hz, 2H, aromatic H), 7.51 (d, *J* = 8.5 Hz, 2H, aromatic H), 6.60 (s, 1H, OH), 4.57-4.33 (d, *J* = 12 Hz, 1H, -CH), 4.10-4.078 (m, 2H, -OCH₂), 4.00 (t, *J* = 12.5 Hz, 1H, -CH), 3.85-3.81 (m, 1H, -CH), 3.75-3.70 (m, 2H, -OCH₂), 2.88 (d, *J* = 17 Hz, 1H, -CH₂), 2.76 (d, *J* = 17 Hz, 1H, -CH₂), 1.77 (t, *J* = 7 Hz, 3H, -CH₃), 0.82 (t, *J* = 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 169.67, 168.19 (2C), 162.76, 145.20, 133.07 (2C), 129.89, 119.22, 119.072, 111.10, 107.99, 80.78, 60.94, 60.70, 51.95, 43.03, 41.58, 14.59, 14.03; HRMS (ESI-TOF) *m/z*: For C₂₀H₂₁N₃O₈ Calcd. [M+K]⁺ 438.1430; Found [M+K]⁺ 438.1109

PID = 19204072-022060

VRSB

Figure S28. FTIR spectrum of **4h**

Figure S29. ^1H NMR spectrum of **4h**

Figure S30. ^{13}C NMR spectrum of **4h**

Display Report

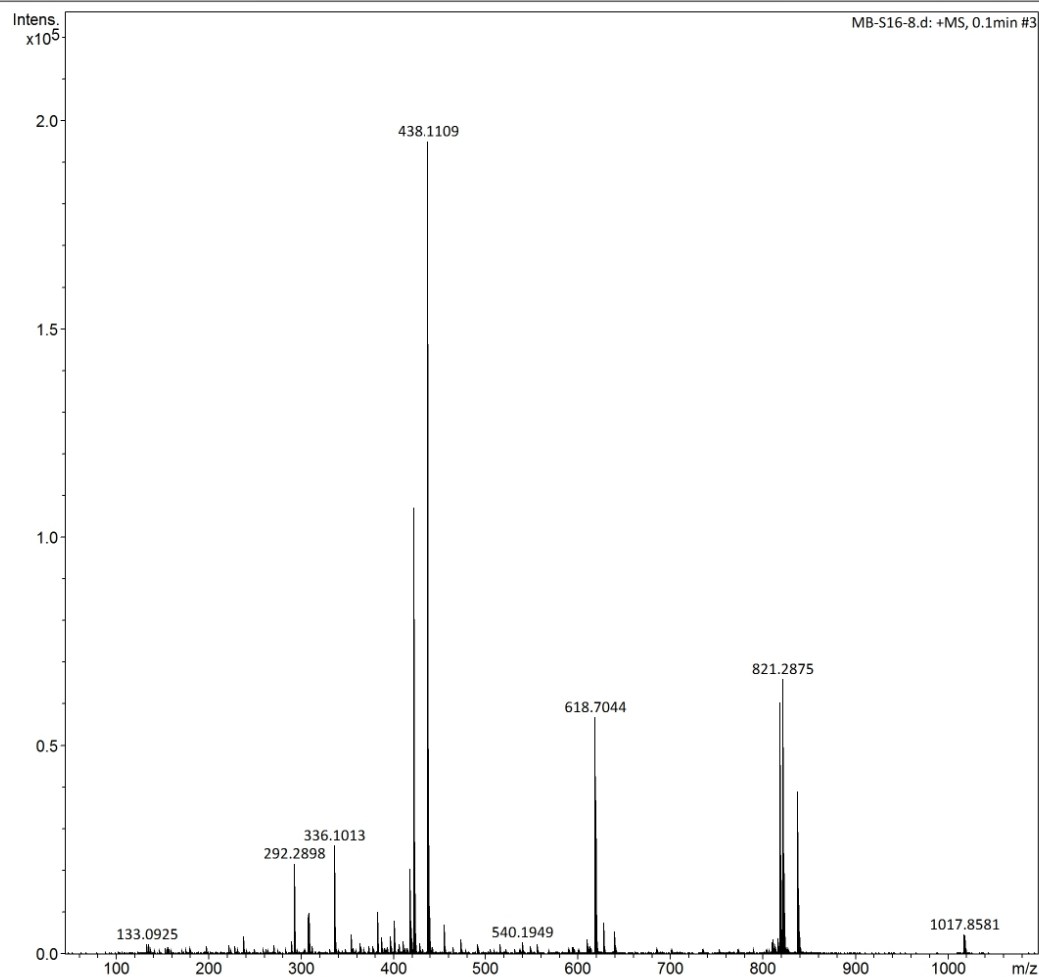
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Comment

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Operator HRMS
Instrument maXis impact 1819696.00160

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Scan End	1500 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
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MB-S16-8.d

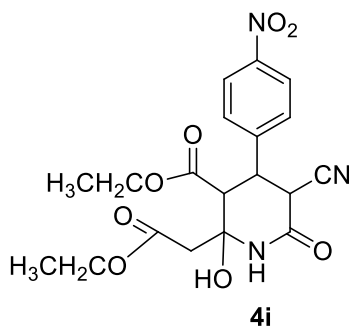
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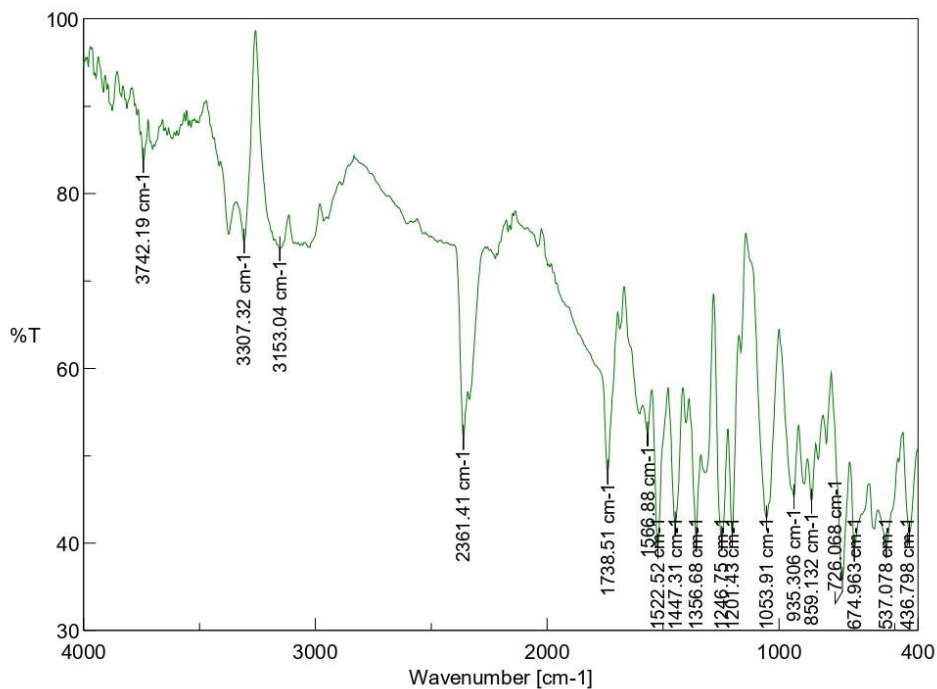
Figure S31.HRMS spectrum of 4h

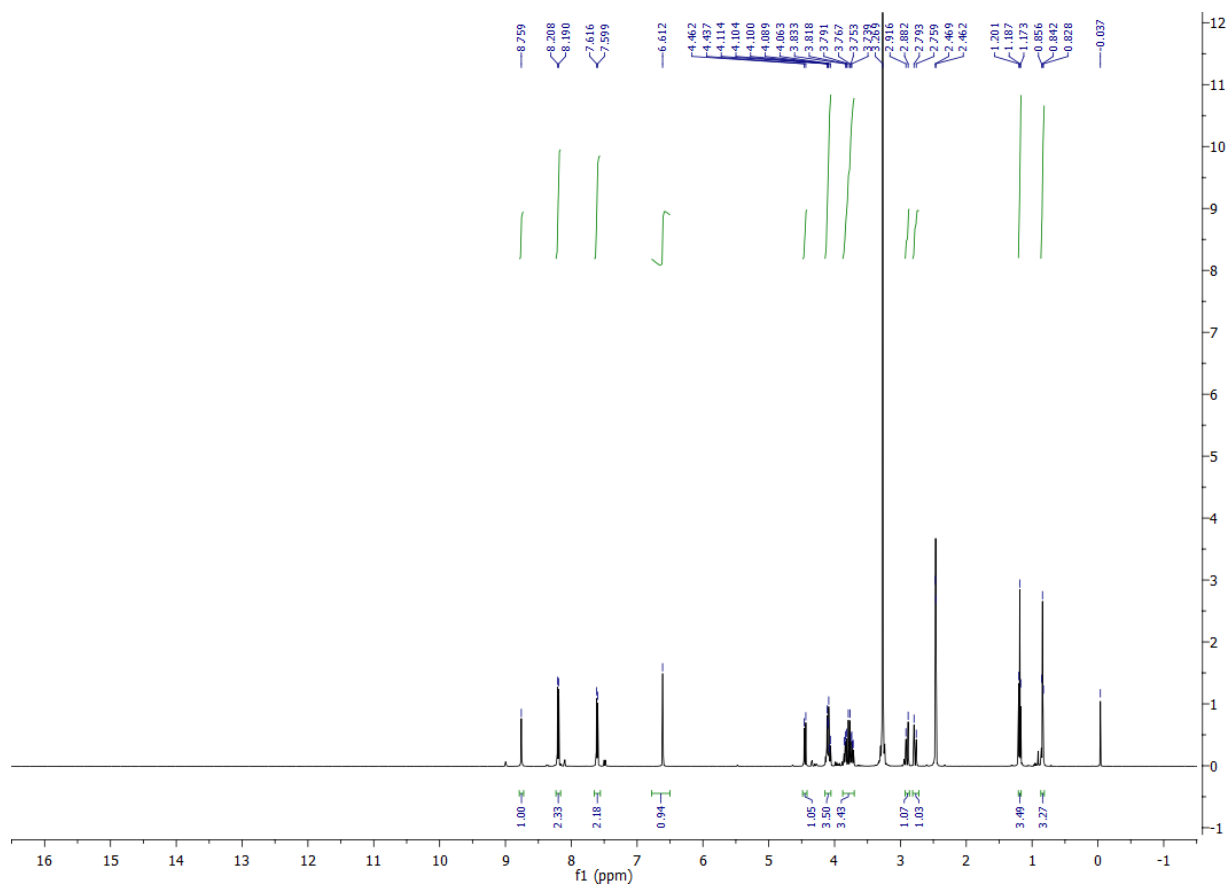


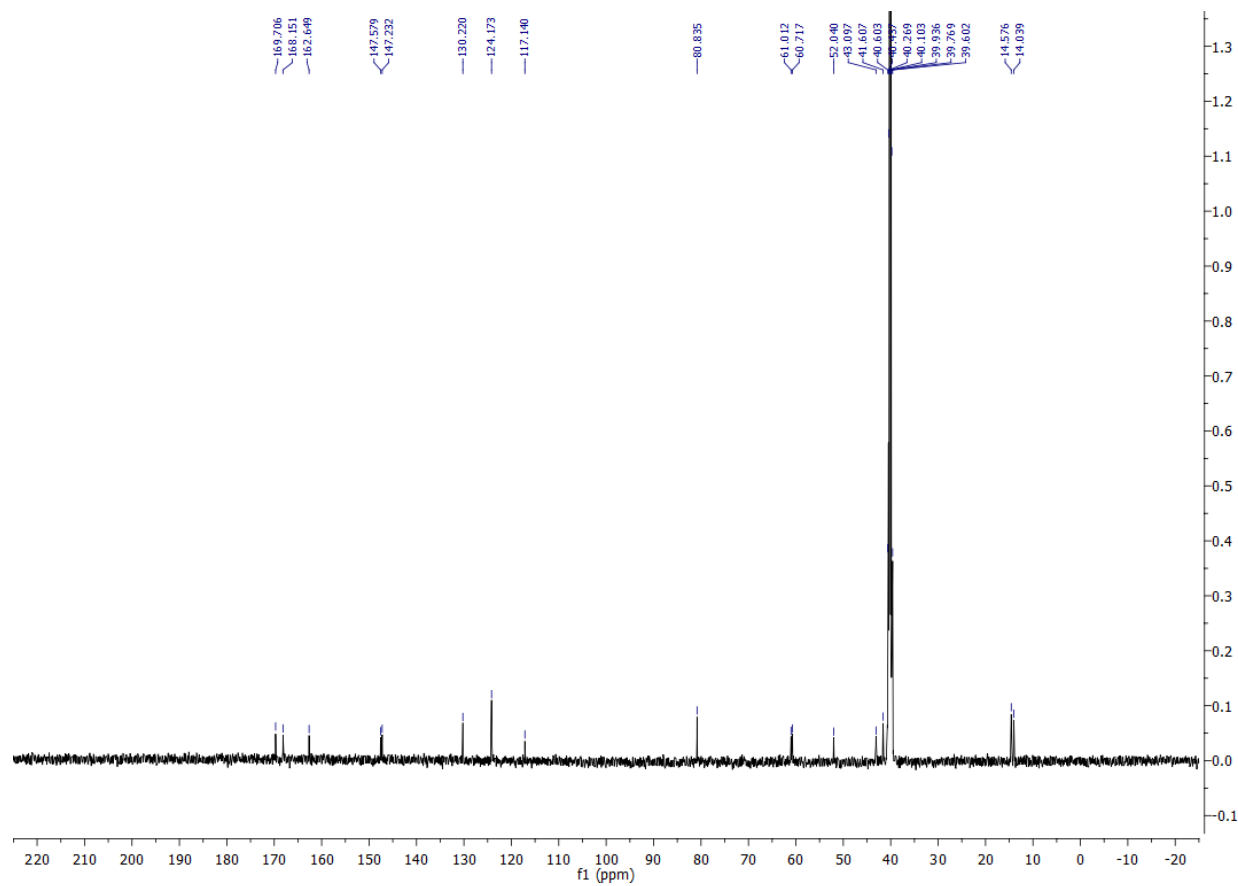
Ethyl-5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-(4-nitrophenyl)-6-oxopiperidine-3-carboxylate (4i). Light yellow solid, yield 91%; mp 162°C; FTIR (cm⁻¹): 3742, 3307, 3153, 2361, 1738, 1356, 1053, 649, 537, 436; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.76 (s, 1H, -NH), 8.20 (d, *J* = 9 Hz, 2H, aromatic H), 7.61 (d, *J* = 8.5 Hz, 2H, aromatic H), 6.61 (s, 1H, OH), 4.45 (d, *J* = 12.5 Hz, 1H, -CH), 4.11-4.06 (m, 2H, -OCH₂, 1H, -CH), 3.85-3.71 (m, 2H, -OCH₂, 1H, -CH), 2.89 (d, *J* = 17 Hz, 1H, -CH₂), 2.78 (d, *J* = 17 Hz, 1H, -CH₂), 1.87 (t, *J* = 7 Hz, 3H, -CH₃), 0.84 (t, *J* = 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 169.70, 168.15, 162.65, 147.58, 147.23, 130.22 (2C), 124.17 (2C), 117.14, 80.84, 61.01, 60.72, 52.04, 43.10, 41.61 (2C), 14.58, 14.04; HRMS (ESI-TOF) *m/z*: For C₁₉H₂₁N₃O₈ Calcd. [M+Na]⁺ 442.1329; Found [M+Na]⁺ 442.1194

PID = 19204072-001452

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Figure S32. FTIR spectrum of **4i**

Figure S33. ^1H NMR spectrum of **4i**

Figure S34. ^{13}C NMR spectrum of **4i**

Display Report

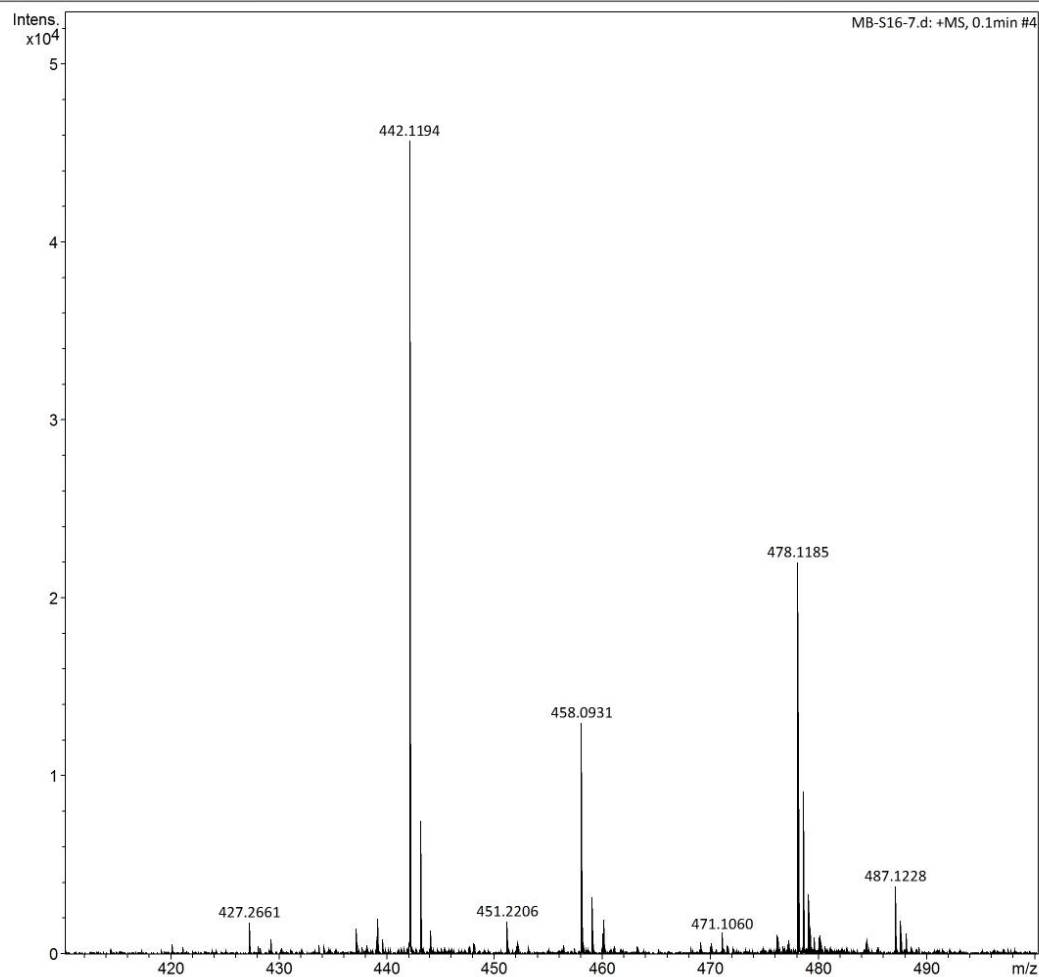
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Method Tune_pos_Standard.m
Sample Name MEOH
Comment

Acquisition Date 5/29/2024 2:24:39 PM
Operator HRMS
Instrument maXis impact 1819696.00160

Acquisition Parameter

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MB-S16-7.d

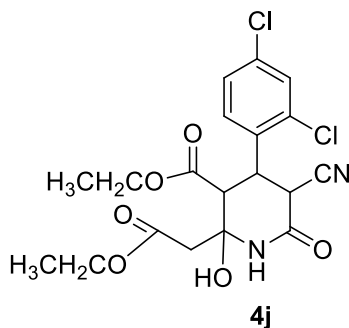
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by: HRMS

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Figure S35. HRMS spectrum of **4i**



Ethyl-5-cyano-4-(2,4-dichlorophenyl)-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-6-oxopiperidine-3-carboxylate (4j). White solid, yield 94%; mp 174°C; FTIR (cm⁻¹): 3741, 3377, 3297, 2360, 1717, 1519, 1355, 1054, 625, 518, 436; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.70 (s, 1H, -NH), 7.60 (d, *J* = 2 Hz, 1H, aromatic H), 7.48 (d, *J* = 8.5 Hz, 1H, aromatic H), 7.43 (dd, *J* = 2 Hz, 1H, aromatic H) 6.66 (s, 1H, OH), 4.60 (d, *J* = 12 Hz, 1H, -CH), 4.31 (d, *J* = 12 Hz, 1H, -CH), 4.12-4.08 (m, 2H, -OCH₂), 3.87-3.83 (m, 1H, -CH), 3.76-3.71 (m, 2H, -OCH₂), 2.90 (d, *J* = 16.5 Hz, 1H, -CH₂), 2.78 (d, *J* = 17 Hz, 1H, -CH₂), 1.18 (t, *J* = 7 Hz, 3H, -CH₃), 0.84 (t, *J* = 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 169.77, 168.16, 162.74, 136.91, 136.03, 133.22, 129.72, 128.42, 117.47, 116.75, 80.83, 60.96, 60.71, 52.54, 43.26, 41.59 (2C), 14.57, 13.96; HRMS (ESI-TOF) *m/z*: For C₁₉H₂₀Cl₂N₂O₆ Calcd. [M+Na]⁺ 465.0596; Found [M+Na]⁺ 465.0704

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VGDHT HD X

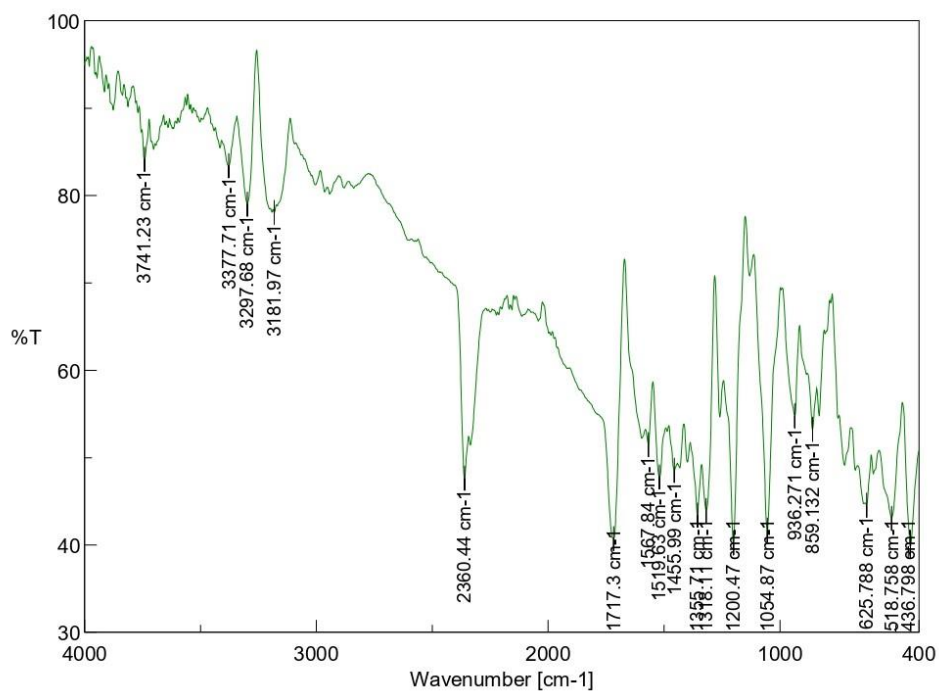
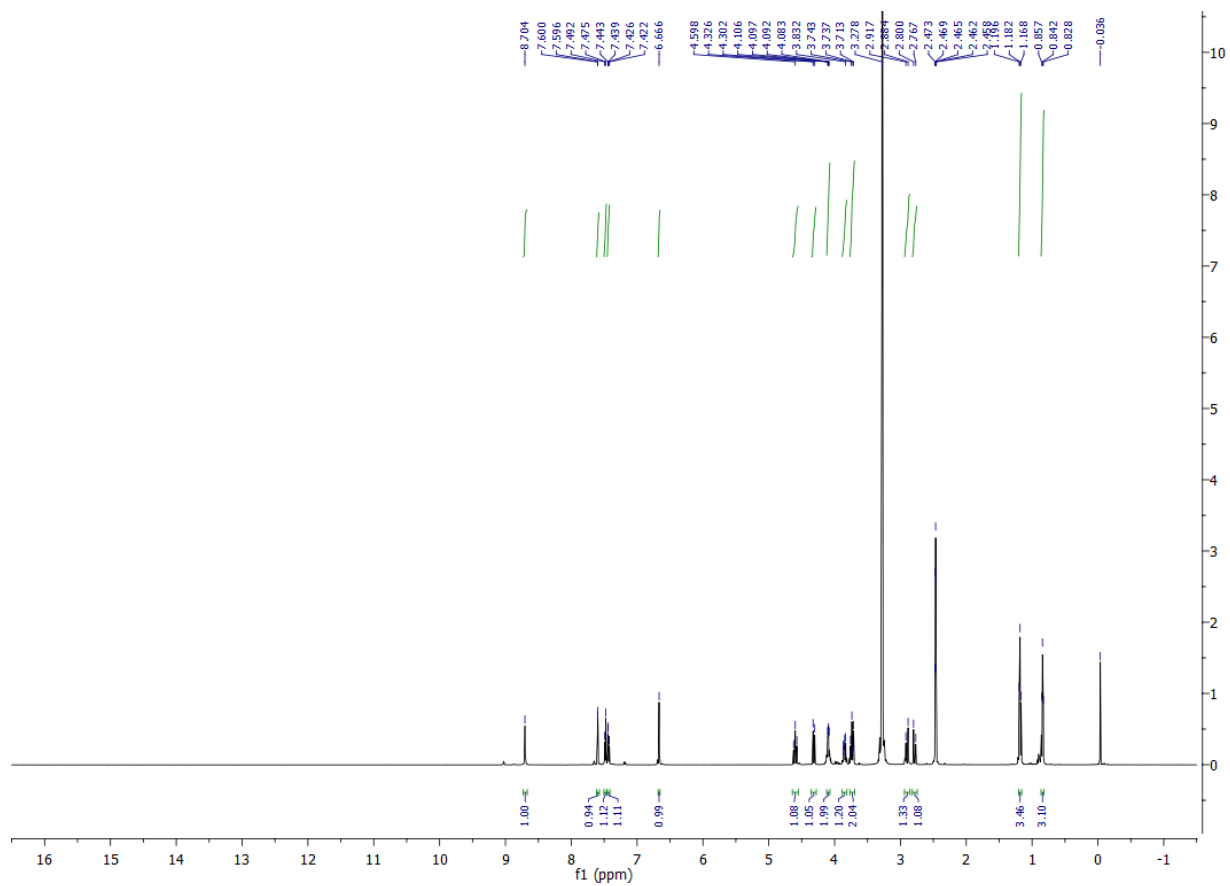
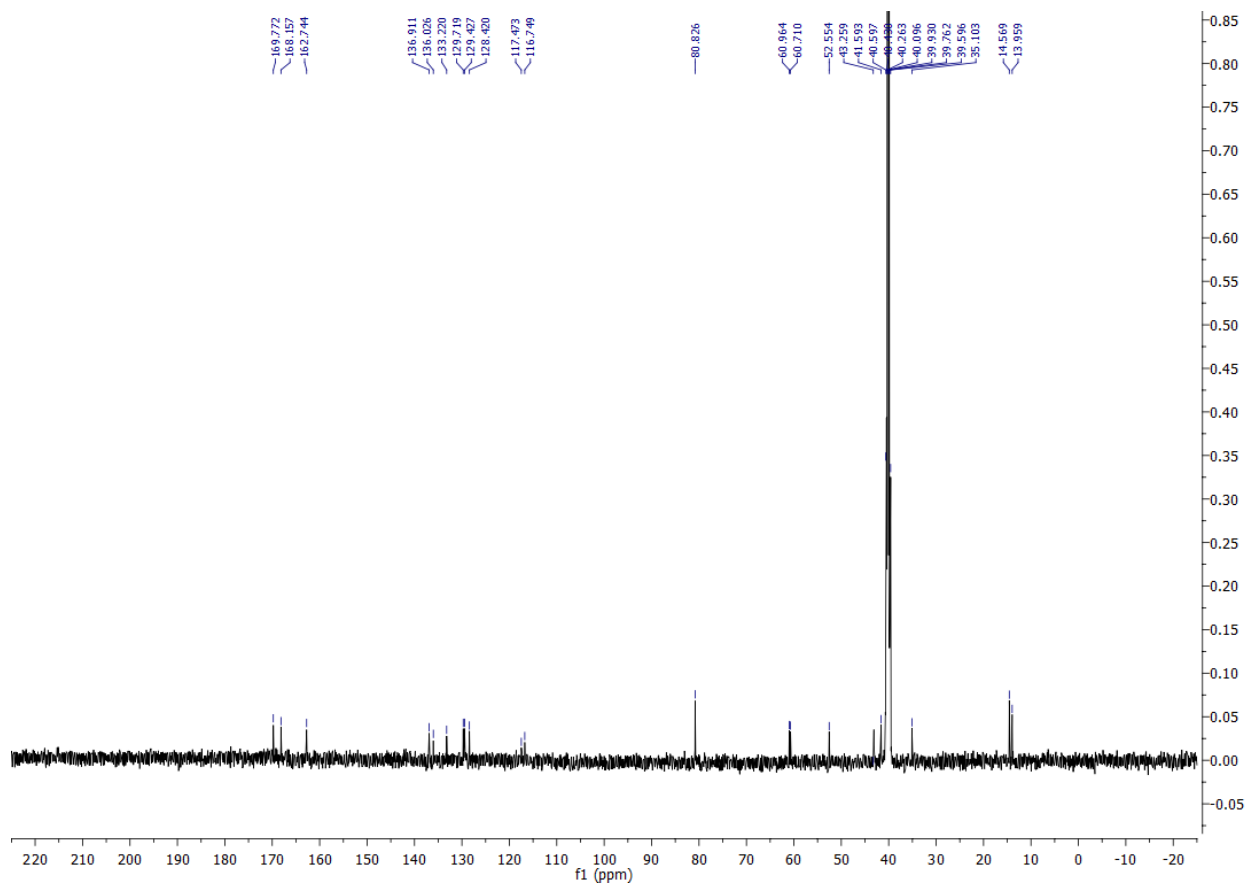


Figure S36. FTIR spectrum of 4j

Figure S37. ^1H NMR spectrum of **4j**

Figure S38. ^{13}C NMR spectrum of **4j**

Display Report

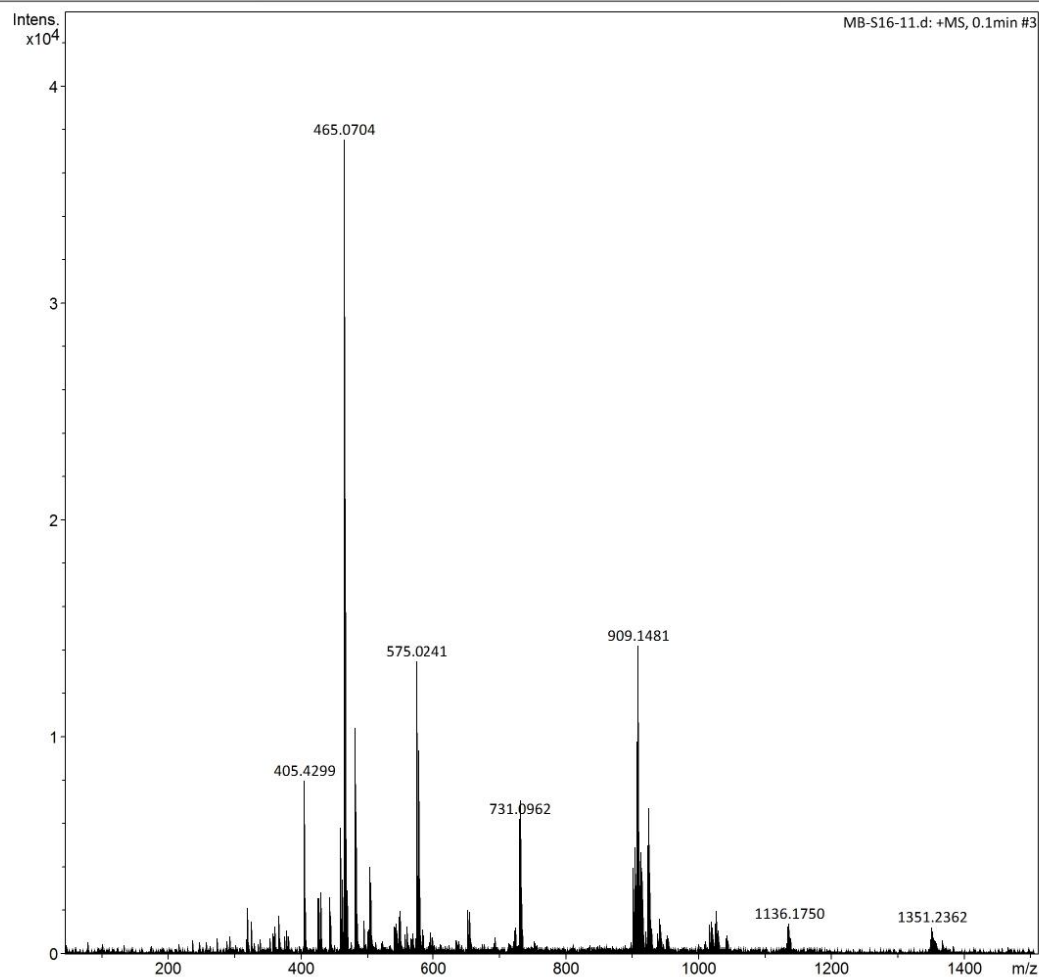
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Sample Name
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Instrument maXis impact 1819696.00160

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MB-S16-11.d

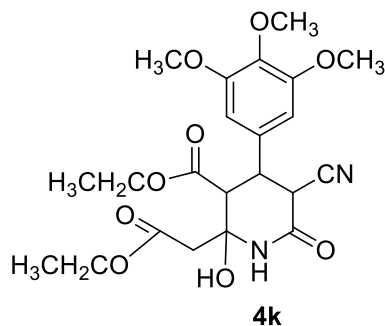
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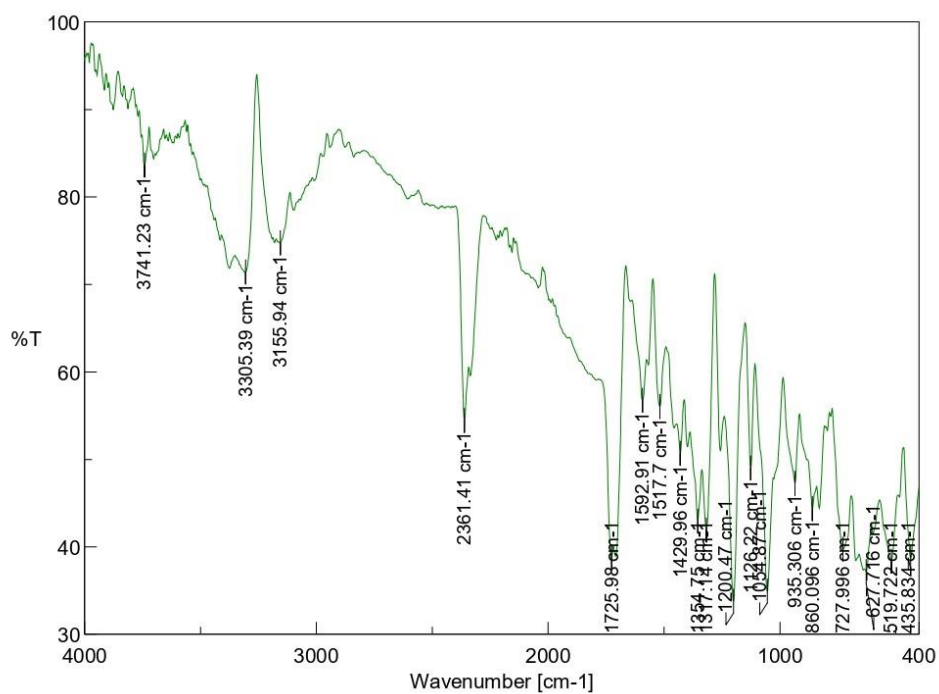
Figure S39.HRMS spectrum of 4j

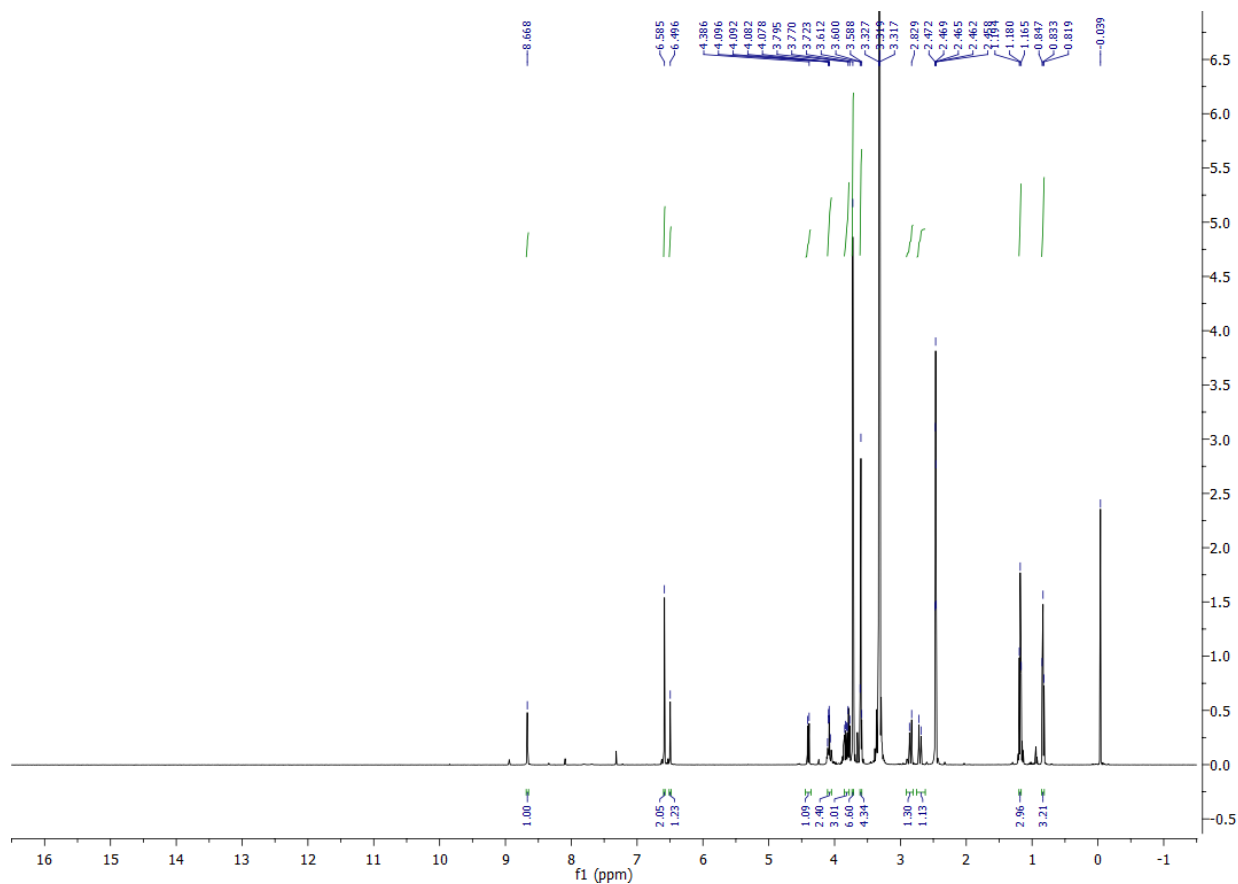


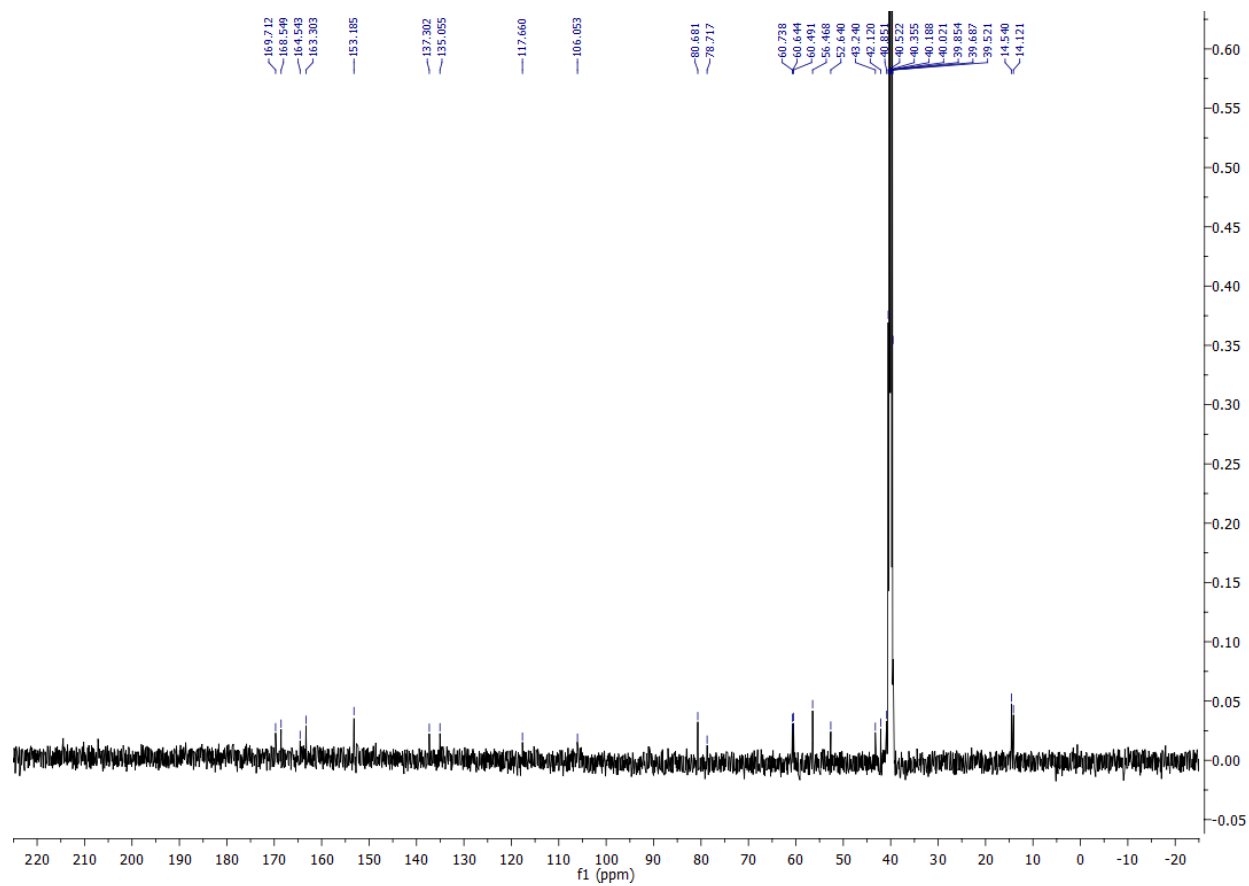
Ethyl-5-cyano-2-(2-ethoxy-2-oxoethyl)-2-hydroxy-6-oxo-4-(3,4,5-trimethoxyphenyl)piperidine-3-carboxylate (4k). White solid, yield 98%; mp 197°C; FTIR (cm⁻¹): 3741, 3305, 3155, 2361, 1725, 1517, 1317, 1054, 627, 519, 435; ¹H NMR (500 MHz, DMSO-d₆) δ_H/ppm: 8.67 (s, 1H, -NH), 6.59 (s, 2H, aromatic H), 6.49 (s, 1H, OH), 4.39 (d, *J* = 12.5 Hz, 1H, -CH), 4.11 (m, 2H, -OCH₂), 3.88-3.79 (m, 2H, -OCH₂, 1H, -CH), 3.72 (s, 6H, 2 x -OCH₃), 3.6 (t, 3H, -OCH₃, 1H, -CH), 2.85 (d, *J* = 16.5 Hz, 1H, -CH₂), 2.70 (d, *J* = 17 Hz, 1H, -CH₂), 1.19-1.165 (m, 3H, -CH₃), 0.83 (t, *J* = 7 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, DMSO-d₆) δ_C/ppm: 169.71, 168.55, 164.54, 163.30, 153.18, 137.30, 135.05, 117.66, 106.05, 80.68, 78.71, 60.74, 60.64, 60.49, 56.47, 52.64 (2C), 43.24, 42.12 (2C), 14.54, 14.12; HRMS (ESI-TOF) *m/z*: For C₂₂H₂₈N₂O₉ Calcd. [M+Na]⁺ 487.1693; Found [M+Na]⁺ 487.1756

PID = 19204072-122476

VHFBJYB

Figure S40. FTIR spectrum of **4k**

Figure S41. ^1H NMR spectrum of **4k**

Figure S42. ^{13}C NMR spectrum of **4k**

Display Report

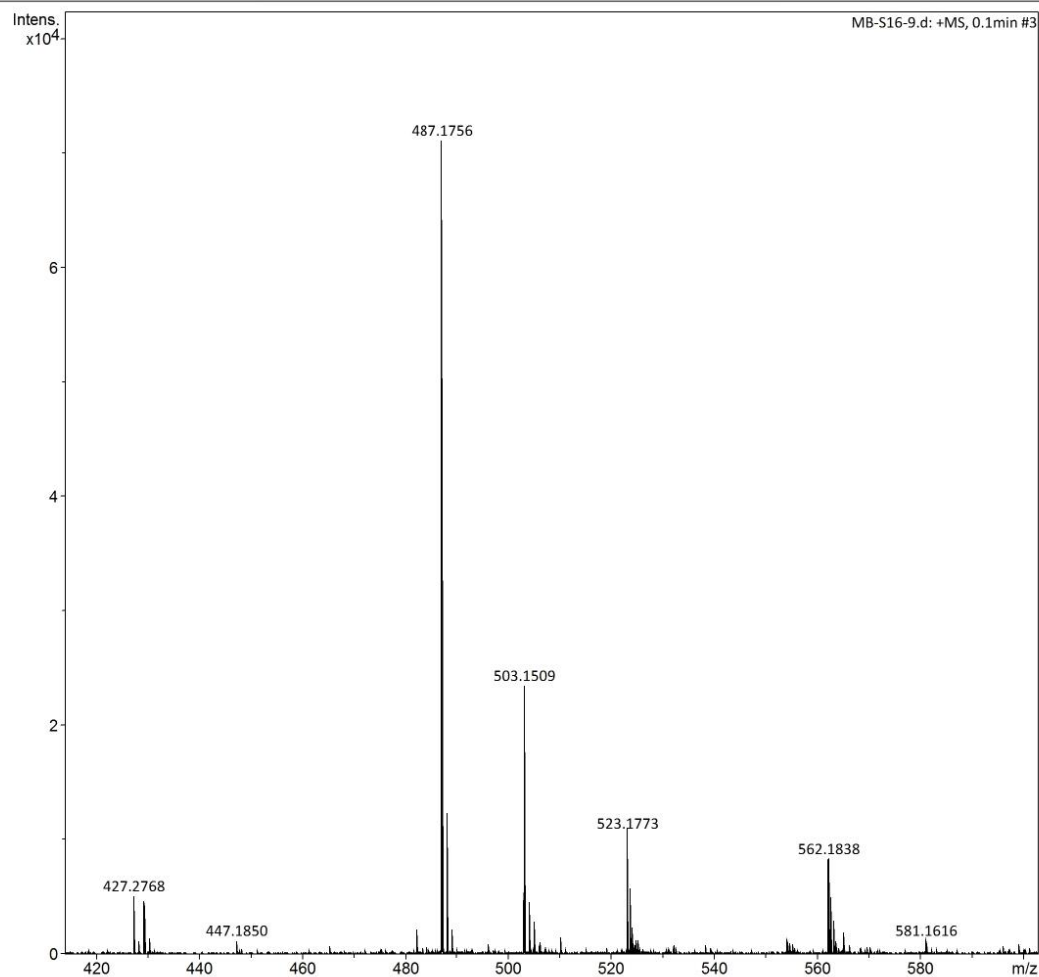
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Instrument maXis impact 1819696.00160

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Figure S43. HRMS spectrum of **4k**