

Supplementary Materials

Title

Bifunctional Metformin-Phenolics Hybrids with Improved Anticancer and Antioxidant Properties: Evaluation on Glioma Cells

Authors

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1. Synthetic procedures and characterization

1.1 General procedure for the synthesis of **1a–g**

To the corresponding hydroxylated benzaldehyde dissolved in DMF (1.8 M, final concentration) were successively added K_2CO_3 (2.2 eq for each OH group) and 2-bromopropane (2.2 eq / OH group to protect) and the mixture was heated at 55 °C for 16 h. After cooling down to room temperature followed by addition of ethyl acetate, the mixture was washed with water and the organic layer was dried over $MgSO_4$, filtered and concentrated to afford the desired compound used without further purification.

1.1.1 2-Isopropoxybenzaldehyde **1a**

Title compound was obtained from 2-hydroxybenzaldehyde (3.2 mL, 41 mmol), K_2CO_3 (12.4 g, 90.2 mmol) and 2-bromopropane (8.5 mL, 90.2 mmol). Yellow pale oil (5 g, 80%). 1H NMR (300 MHz, $DMSO-d_6$) δ 10.37 (s, 1H, CHO), 7.67 (dd, 1H, $J = 7.7$ Hz and 1.8 Hz, H-6), 7.58 (td, 1H, $J = 7.5$ Hz and 2.0 Hz, H-4), 7.17 (bd, 1H, $J = 8.4$ Hz, H-5), 7.00 (bt, 1H, $J = 7.7$ Hz, H-3), 4.73 (sept, 1H, $J = 6.1$ Hz, $CH(CH_3)_2$), 1.30 (d, 6H, $J = 6.1$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $DMSO-d_6$) δ 189.7 (C=O), 160.6 (C-2), 136.6 (C-4), 128.0 (C-6), 125.5 (C-1), 120.8 (C-5), 115.3 (C-3), 71.2 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$). HRMS calc. for $C_{10}H_{13}O_2^+$ $[M+H]^+$ 165.0910, found 165.0911. Data in accordance with the literature [1].

1.1.2 3-Isopropoxybenzaldehyde **1b**

Title compound was obtained from 3-hydroxybenzaldehyde (3 g, 25 mmol), K_2CO_3 (7.6 g, 55 mmol) and 2-bromopropane (5 mL, 55 mmol). Colorless oil (4.1 g, quant. yield). 1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, CHO), 7.29 (bs, 1H, H-6), 7.26 (bs, 1H, H-2), 7.22 (bd, 1H, $J = 2.5$ Hz, H-4), 7.00 (m, 1H, H-5), 4.48 (sept, 1H, $J = 6.1$ Hz, $CH(CH_3)_2$), 1.22 (d, 6H, $J = 6.1$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2 (C=O), 158.7 (C-3), 138.0 (C-1), 130.2 (C-5), 123.1 (C-4, C-6), 114.4 (C-2), 70.4 ($CH(CH_3)_2$), 22.0 ($CH(CH_3)_2$). HRMS calc. for $C_{10}H_{13}O_2^+$ $[M+H]^+$ 165.0910, found 165.0913. Data in accordance with the literature [2].

1.1.3 4-Isopropoxybenzaldehyde **1c**

Title compound was obtained from 4-hydroxybenzaldehyde (3 g, 25 mmol), K_2CO_3 (7.6 g, 55 mmol) and 2-bromopropane (5 mL, 55 mmol). Colorless oil (4.1 g, quant. yield). 1H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H, CHO), 7.79 (d, 2H, $J = 8.4$ Hz, H-2), 6.95 (d, 2H, $J = 8.4$ Hz, H-3), 4.65 (sept, 1H, $J = 6.2$ Hz, $CH(CH_3)_2$), 1.36 (d, 6H, $J = 6.2$ Hz, $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8 (C=O), 163.2 (C-4), 132.1 (C-2), 129.7 (C-1), 115.9 (C-3), 70.4 ($CH(CH_3)_2$), 22.1 ($CH(CH_3)_2$). HRMS calc. for $C_{10}H_{13}O_2^+$ $[M+H]^+$ 165.0910, found 165.0911. Data in accordance with the literature [3].

1.1.4 3,5-Diisopropoxybenzaldehyde **1d**

Title compound was obtained from 3,5-dihydroxybenzaldehyde (2 g, 14.5 mmol), K_2CO_3 (8.8 g, 63.8 mmol, 4.4 eq) and 2-bromopropane (6.0 mL, 63.8 mmol, 4.4 eq). Red oil (3.2 g, quant. yield). 1H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H, CHO), 6.94 (s, 2H, H-2), 6.65 (s, 1H, H-4), 4.57 (sept, 2H, $J = 6.0$ Hz, $2 \times CH(CH_3)_2$), 1.33 (d, 12H, $J = 6.0$ Hz, $2 \times CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9 (C=O), 159.5 (C-3), 138.3 (C-1), 110.2 (C-4), 108.5 (C-2), 70.2 ($CH(CH_3)_2$), 21.8 ($CH(CH_3)_2$). HRMS calc. for $C_{13}H_{19}O_3^+$ $[M+H]^+$ 223.1329, found 223.1332. Data in accordance with the literature [4].

1.1.5 3,4-Diisopropoxybenzaldehyde **1e**

Title compound was obtained from 3,4-dihydroxybenzaldehyde (5 g, 36.2 mmol), K_2CO_3 (22 g, 159 mmol) and 2-bromopropane (15 mL, 159 mmol). Yellow pale oil (6.4 g, 80%). 1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H, CHO), 7.46-7.43 (m, 2H, H-2 and H-3), 6.99 (d, 1H,

$J = 8.8$ Hz, H-5), 4.64 (sept, 1H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 4.53 (sept, 1H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.40 (d, 6H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.36 (d, 6H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 190.9 (C=O), 155.0 (C-4), 149.0 (C-3), 130.1 (C-1), 126.4 (C-6), 116.1 (C-2), 114.9 (C-5), 72.4 ($\text{CH}(\text{CH}_3)_2$), 71.8 ($\text{CH}(\text{CH}_3)_2$), 22.1 ($\text{CH}(\text{CH}_3)_2$), 22.0 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{13}\text{H}_{19}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 223.1329, found 223.1329. Data in accordance with the literature [5].

1.1.6 4-Isopropoxy-3-methoxybenzaldehyde **1f**

Title compound was obtained from 4-hydroxy-3-methoxybenzaldehyde (5 g, 32.9 mmol), K_2CO_3 (10 g, 72.5 mmol) and 2-bromopropane (6.9 mL, 72.5 mmol). Yellow pale oil (5.8 g, 91%). ^1H NMR (300 MHz, CDCl_3) δ 9.83 (s, 1H, CHO), 7.42 (dd, 1H, $J = 7.9$ Hz and $J = 1.8$ Hz, H-6), 7.40 (bs, 1H, H-2), 6.97 (d, 1H, $J = 7.9$ Hz, H-5), 4.68 (sept, 1H, $J = 6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.91 (s, 3H, OCH_3), 1.42 (d, 6H, $J = 6.1$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 190.8 (C=O), 153.1 (C-3), 150.4 (C-4), 129.8.1 (C-1), 126.6 (C-6), 112.9 (C-5), 109.6 (C-2), 71.3 ($\text{CH}(\text{CH}_3)_2$), 56.0 (OCH_3), 21.9 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{11}\text{H}_{15}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 195.1016, found 195.1014. Data in accordance with the literature [6].

1.1.7 4-Isopropoxy-3,5-dimethoxybenzaldehyde **1g**

Title compound was obtained from 4-hydroxy-3,5-dimethoxybenzaldehyde (5 g, 27.5 mmol), K_2CO_3 (8.3 g, 60.5 mmol) and 2-bromopropane (5.7 mL, 60.5 mmol). Yellow pale oil (4.9 g, 81%). ^1H NMR (300 MHz, CDCl_3) δ 9.88 (s, 1H, CHO), 7.14 (s, 2H, H-2), 4.55 (sept, 1H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.92 (s, 6H, $2 \times \text{OCH}_3$), 1.33 (d, 6H, $J = 6.2$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 191.2 (C=O), 154.3 (C-3), 142.0 (C-4), 131.5 (C-1), 106.7 (C-2), 76.0 ($\text{CH}(\text{CH}_3)_2$), 56.2 (OCH_3), 22.5 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{12}\text{H}_{17}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 225.1121, found 225.1124. Data in accordance with the literature [7].

1.2 General procedure for the synthesis of **2a–h**

To the benzaldehyde derivative **1a–g**, dissolved in glacial acetic acid (0.5 M, final concentration) at room temperature was successively added malonic acid (2.2 eq) and piperidine (2.7 eq) dropwise and the mixture was heated at 120 °C for 1 day. The reaction mixture was allowed to cool at room temperature, poured onto a water/ice mixture and the precipitate was filtered off, washed with water and dried to afford the desired compound used without further purification.

1.2.1 (*E*)-3-(2-Isopropoxyphenyl)acrylic acid **2a**

Title compound was obtained from **1a** (5.0 g, 30.5 mmol), malonic acid (7.0 g, 67.1 mmol) and piperidine (8.1 mL, 82.3 mmol). Beige powder (6.45 g, 95%), mp 112.4 °C. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.83 (d, 1H, $J = 16.1$ Hz, Ar-CH=CH), 7.64 (d, 1H, $J = 7.7$ Hz, H-6), 7.34 (t, 1H, $J = 7.7$ Hz, H-5), 7.05 (d, 1H, $J = 8.3$ Hz, H-3), 6.93 (t, 1H, $J = 7.5$ Hz, H-4), 6.50 (d, 1H, $J = 16.1$ Hz, Ar-CH=CH), 4.66 (sept, 1H, $J = 5.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.28 (d, 6H, $J = 5.9$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 168.2 (C=O), 156.3 (C-2), 139.2 (Ar-CH=CH), 131.8 (C-4), 128.8 (C-6), 123.5 (C-1), 120.7 (Ar-CH=CH), 119.2 (C-1), 114.2 (C-3), 70.4 ($\text{CH}(\text{CH}_3)_2$), 21.9 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{12}\text{H}_{15}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 207.1016, found 207.1017. Data in accordance with the literature [8].

1.2.2 (*E*)-3-(3-Isopropoxyphenyl)acrylic acid **2b**

Title compound was obtained from **2b** (4.1 g, 25 mmol), malonic acid (5.70 g, 55 mmol) and piperidine (6.71 mL, 68.0 mmol). Beige powder (4.86 g, 94%), mp 93.3–94.3 °C. ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 7.28 (t, 1H, $J = 8.1$ Hz, H-5), 7.10 (bd, 1H, $J = 7.7$ Hz, H-6), 7.05 (d, 1H, $J = 1.9$ Hz, H-2), 6.92 (dd, 1H, $J = 8.1$ and 2.3 Hz, H-4), 6.43 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 6.33 (bs, 1H, OH), 4.57 (sept, 1H, $J = 6.3$

Hz, $\text{CH}(\text{CH}_3)_2$), 1.36 (d, 6H, $J = 6.3$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 166.2 (C=O), 158.5 (C-3), 146.1 (Ar-CH=CH), 136.0 (C-1), 130.1 (C-5), 120.9 (C-6), 118.9 (Ar-CH=CH), 118.3 (C-4), 115.4 (C-2), 70.3 ($\text{CH}(\text{CH}_3)_2$), 22.2 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{12}\text{H}_{13}\text{O}_3^-$ $[\text{M}-\text{H}]^-$ 205.0870, found 205.0868. Data in accordance with the literature [9].

1.2.3 (*E*)-3-(4-Isopropoxyphenyl)acrylic acid **2c**

Title compound was obtained from **1c** (4.1 g, 25 mmol), malonic acid (5.70 g, 55 mmol) and piperidine (6.71 mL, 68.0 mmol). Beige powder (4.30 g, 83%), mp 154.5 °C. ^1H NMR (300 MHz, CDCl_3) δ 9.16 (s, 1H, CO_2H), 7.70 (d, 1H, $J = 15.9$ Hz, Ar-CH=CH), 7.48 (d, 2H, $J = 8.8$ Hz, H-2), 6.89 (d, 2H, $J = 8.6$ Hz, H-3), 6.33 (d, 1H, $J = 15.9$ Hz, Ar-CH=CH), 4.60 (sept, 1H, $J = 6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.36 (d, 6H, $J = 6.1$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 160.1 (C=O), 145.9 (C-4, Ar-CH=CH), 130.1 (C-2), 126.9 (C-1), 116.0 (C-3), 115.7 (Ar-CH=CH), 70.2 ($\text{CH}(\text{CH}_3)_2$), 22.2 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{12}\text{H}_{13}\text{O}_3^-$ $[\text{M}-\text{H}]^-$ 205.0870, found 205.0868. Data in accordance with the literature [8].

1.2.4 (*E*)-3-(3,5-Diisopropoxyphenyl)acrylic acid **2d**

Title compound was obtained from **1d** (3.0 g, 13.5 mmol), malonic acid (3.1 g, 29.7 mmol) and piperidine (3.6 mL, 36.5 mmol). Beige powder (3.6 g, quant. yield), mp 115 °C (litt: 117–118 °C [10]). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.45 (d, 1H, $J = 15.9$ Hz, Ar-CH=CH), 6.73 (d, 2H, $J = 2.2$ Hz, H-2), 6.46 (d, 1H, $J = 16.1$ Hz, Ar-CH=CH), 6.43 (d, 1H, $J = 2.2$ Hz, H-4), 4.61 (sept, 2H, $J = 6.0$ Hz, $2 \times \text{CH}(\text{CH}_3)_2$), 1.22 (d, 12H, $J = 6.1$ Hz, $2 \times \text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 168.1 (C=O), 159.2 (C-3), 145.5 (Ar-CH=CH), 136.6 (C-1), 119.8 (Ar-CH=CH), 107.8 (C-2), 105.7 (C-4), 69.8 ($\text{CH}(\text{CH}_3)_2$), 22.1 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{15}\text{H}_{21}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 265.1434, found 265.1435.

1.2.5 (*E*)-3-(3,4-Diisopropoxyphenyl)acrylic acid **2e**

Title compound was obtained from **1e** (6.4 g, 28.8 mmol), malonic acid (6.6 g, 63.4 mmol) and piperidine (7.7 mL, 77.8 mmol). Beige powder (6.9 g, 91%), mp 115 °C (litt: 117–118 °C [10]). ^1H NMR (300 MHz, CDCl_3) δ 11.90 (bs, 1H, CO_2H), 7.74 (d, 1H, $J = 15.6$ Hz, Ar-CH=CH), 7.13 (bs, 2H, H-2 and H-6), 6.92 (d, 1H, $J = 8.6$ Hz, H-5), 6.32 (d, 1H, $J = 15.6$ Hz, Ar-CH=CH), 4.58 (sept, 1H, $J = 5.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 4.49 (sept, 1H, $J = 5.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.37 (m, 12H, $2 \times \text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 172.9 (C=O), 151.7 (C-4), 148.7 (C-3), 147.0 (Ar-CH=CH), 127.3 (C-6), 123.7 (Ar-CH=CH), 117.6 (C-2), 116.2 (C-5), 115.0 (C-1), 72.7 ($\text{CH}(\text{CH}_3)_2$), 72.0 ($\text{CH}(\text{CH}_3)_2$), 22.2 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{15}\text{H}_{21}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 265.1434, found 265.1534.

1.2.6 (*E*)-3-(4-Isopropoxy-3-methoxyphenyl)acrylic acid **2f**

Title compound was obtained from **1f** (5.8 g, 30.0 mmol), malonic acid (6.9 g, 66.0 mmol) and piperidine (8.0 mL, 81.0 mmol). Beige powder (5.4 g, 77%), mp 151 °C. ^1H NMR (300 MHz, CDCl_3) δ 11.70 (bs, 1H, CO_2H), 7.75 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 7.13 (d, 1H, $J = 8.3$ Hz, H-6), 7.10 (bs, 1H, H-2), 6.90 (d, 1H, $J = 8.3$ Hz, H-5), 6.33 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 4.63 (sept, 1H, $J = 6.1$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.91 (s, 3H, OCH_3), 1.42 (d, 6H, $J = 6.1$ Hz, $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ 172.8 (C=O), 150.3 (C-4), 150.0 (C-3), 147.0 (Ar-CH=CH), 126.9 (C-1), 122.9 (C-6), 114.8 (Ar-CH=CH), 114.3 (C-5), 110.6 (C-2), 71.3 ($\text{CH}(\text{CH}_3)_2$), 55.8 (OCH_3), 21.9 ($\text{CH}(\text{CH}_3)_2$). HRMS calc. for $\text{C}_{13}\text{H}_{17}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 237.1121, found 237.1122. Data in accordance with the literature [8].

1.2.7 (*E*)-3-(4-Isopropoxy-3,5-dimethoxyphenyl)acrylic acid **2g**

Title compound was obtained from **1g** (1.9 g, 10.4 mmol), malonic acid (2.4 g, 23.0 mmol) and piperidine (2.80 mL, 28.1 mmol). Beige powder (1.6 g, 59%), mp 159 °C. ^1H NMR (300 MHz, CDCl_3) δ 11.55 (bs, 1H, CO_2H), 7.73 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 6.79 (s, 2H, H-

2), 6.38 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 4.46 (sept, 1H, $J = 6.2$ Hz, CH(CH₃)₂), 3.88 (s, 6H, 2 × OCH₃), 1.32 (d, 6H, $J = 6.2$ Hz, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 172.6 (C=O), 154.1 (C-3), 147.20 (Ar-CH=CH), 138.7 (C-4), 129.2 (C-1), 116.3 (Ar-CH=CH), 105.6 (C-2), 75.8 (CH(CH₃)₂), 56.3 (OCH₃), 22.5 (CH(CH₃)₂). HRMS calc. for C₁₄H₁₉O₅⁺ [M+H]⁺ 267.1227, found 267.1227.

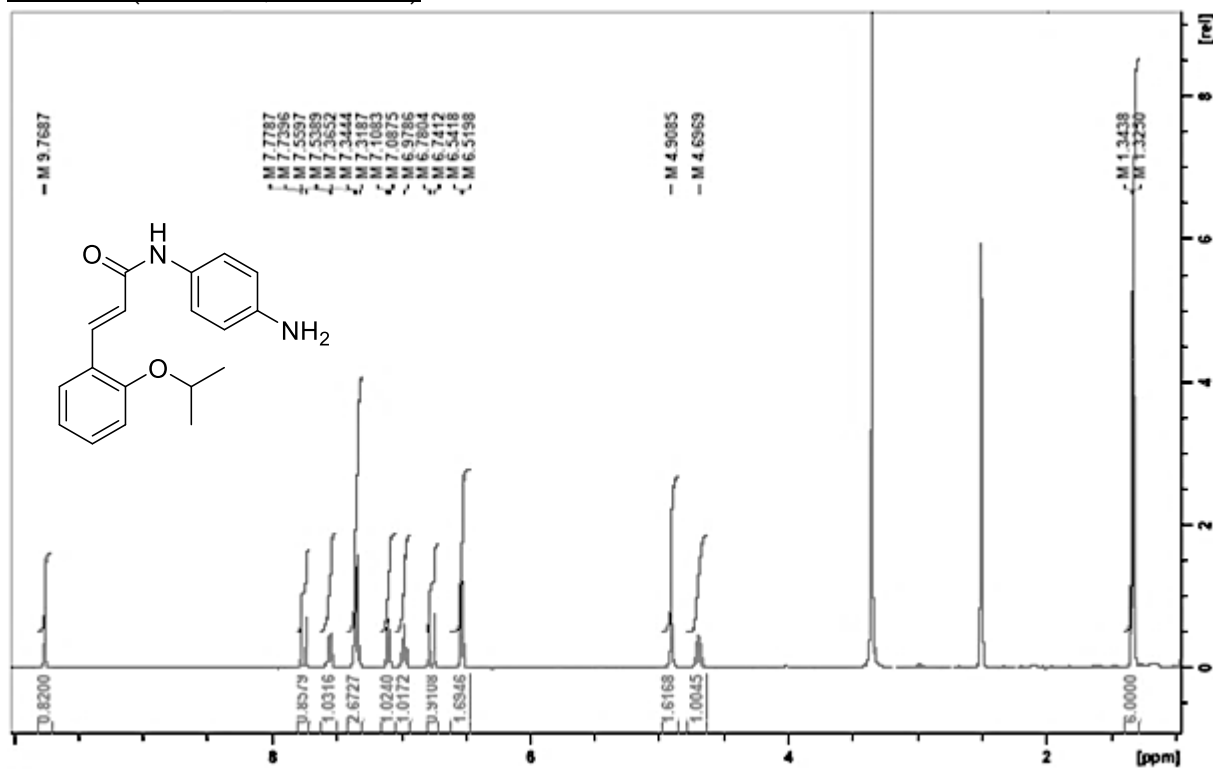
1.2.8 (*E*)-3-(3,4,5-Trimethoxyphenyl)acrylic acid **2h**

Title compound was obtained from commercial 3,4,5-trimethoxybenzaldehyde (450 mg, 2.74 mmol), malonic acid (628 mg, 6.03 mmol) and piperidine (730 μ L, 7.40 mmol). Since no precipitate was directly obtained using the general procedure described above, the aqueous layer was extracted with ethyl acetate (3 × 100 mL), the organic layers were gathered, dried over MgSO₄ and concentrated under vacuum to yield a beige powder (560 mg, 99%), mp 126 °C (litt: 127–128 °C [8]). ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 6.71 (s, 2H, 2 × H-2), 6.27 (d, 1H, $J = 15.8$ Hz, Ar-CH=CH), 3.80 (s, 9H, 3 × OCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 172.1 (C=O), 153.2 (C-3), 146.8 (Ar-CH=CH), 140.3 (C-4), 129.4 (C-1), 116.2 (Ar-CH=CH), 105.5 (C-2), 55.9 (OCH₃). HRMS calc. for C₁₂H₁₅O₅⁺ [M+H]⁺ 239.0914, found 239.0913. Data in accordance with the literature [11].

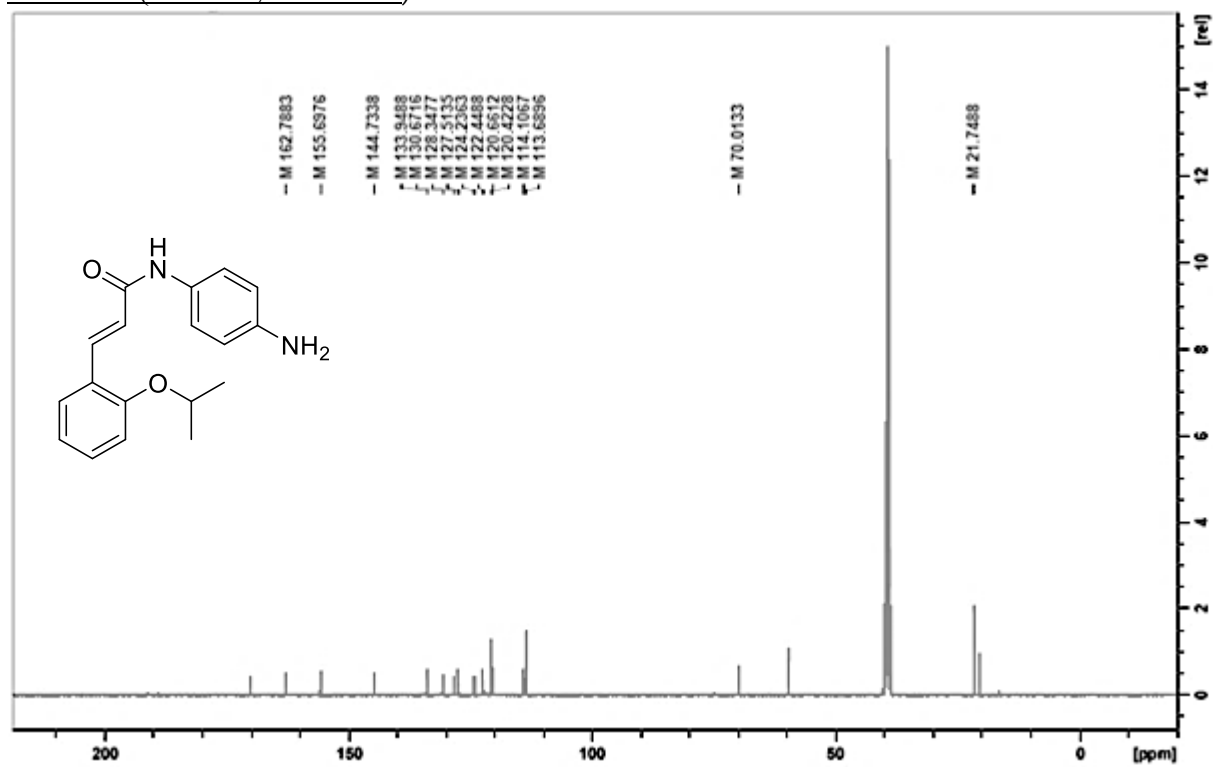
2. NMR spectra (^1H and ^{13}C) of metformin-phenolic acid hybrids and precursors

2.1. Spectra of **3a**

^1H NMR (300 MHz, $\text{DMSO}-d_6$)

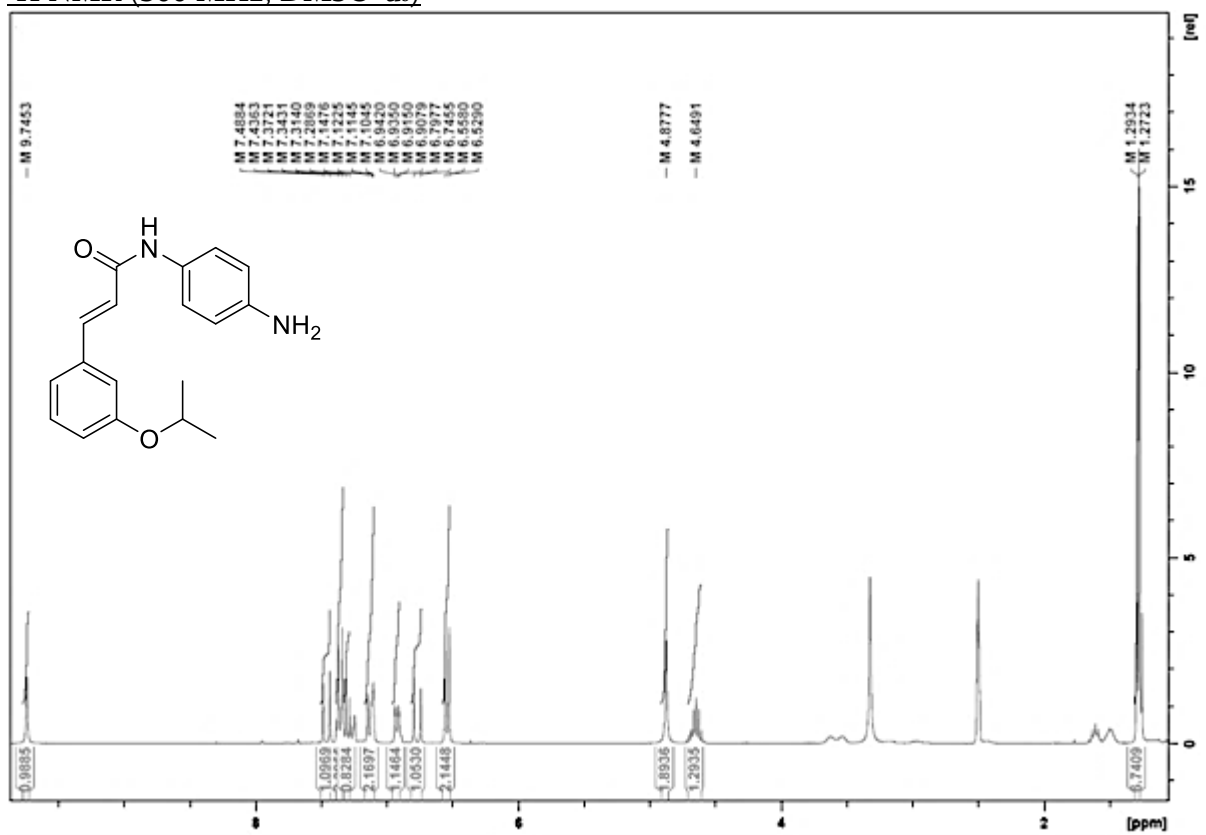


^{13}C NMR (75 MHz, $\text{DMSO}-d_6$)

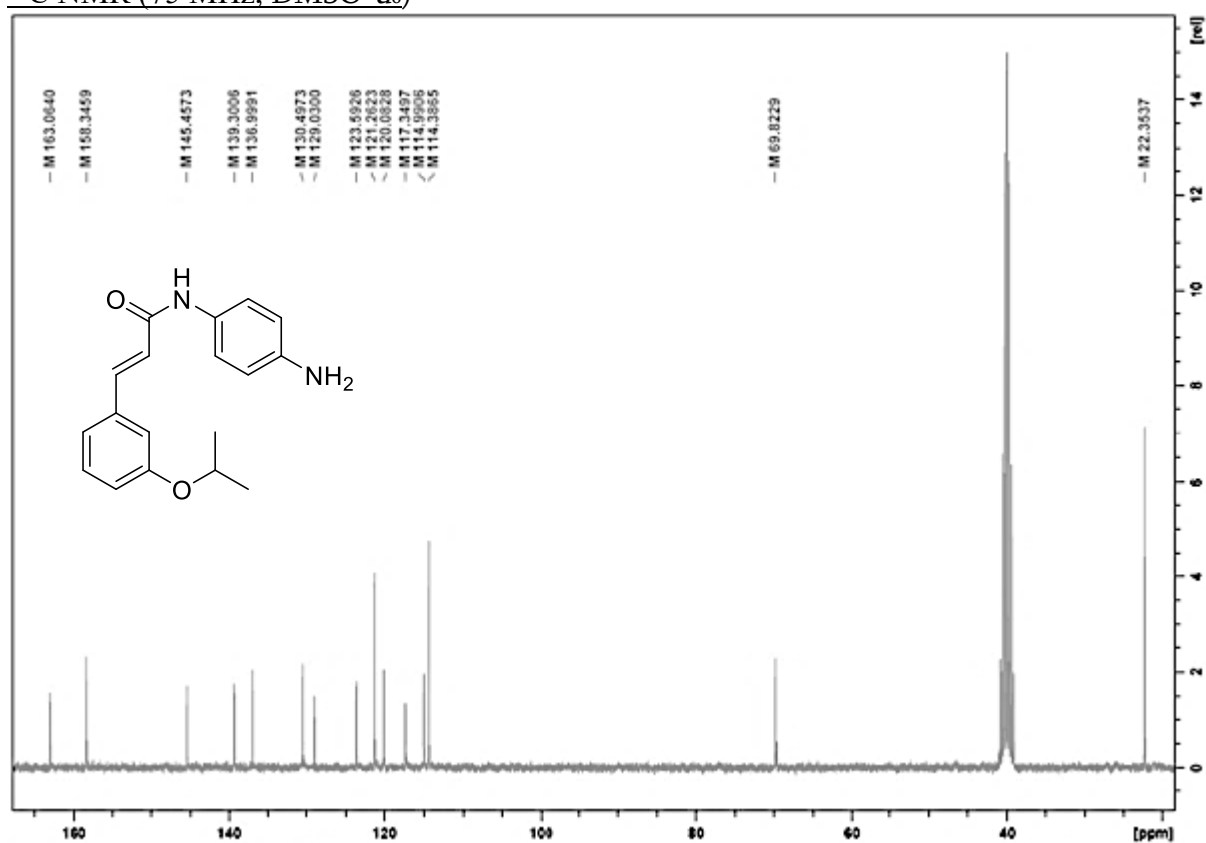


2.2. Spectra of **3b**

^1H NMR (300 MHz, $\text{DMSO}-d_6$)

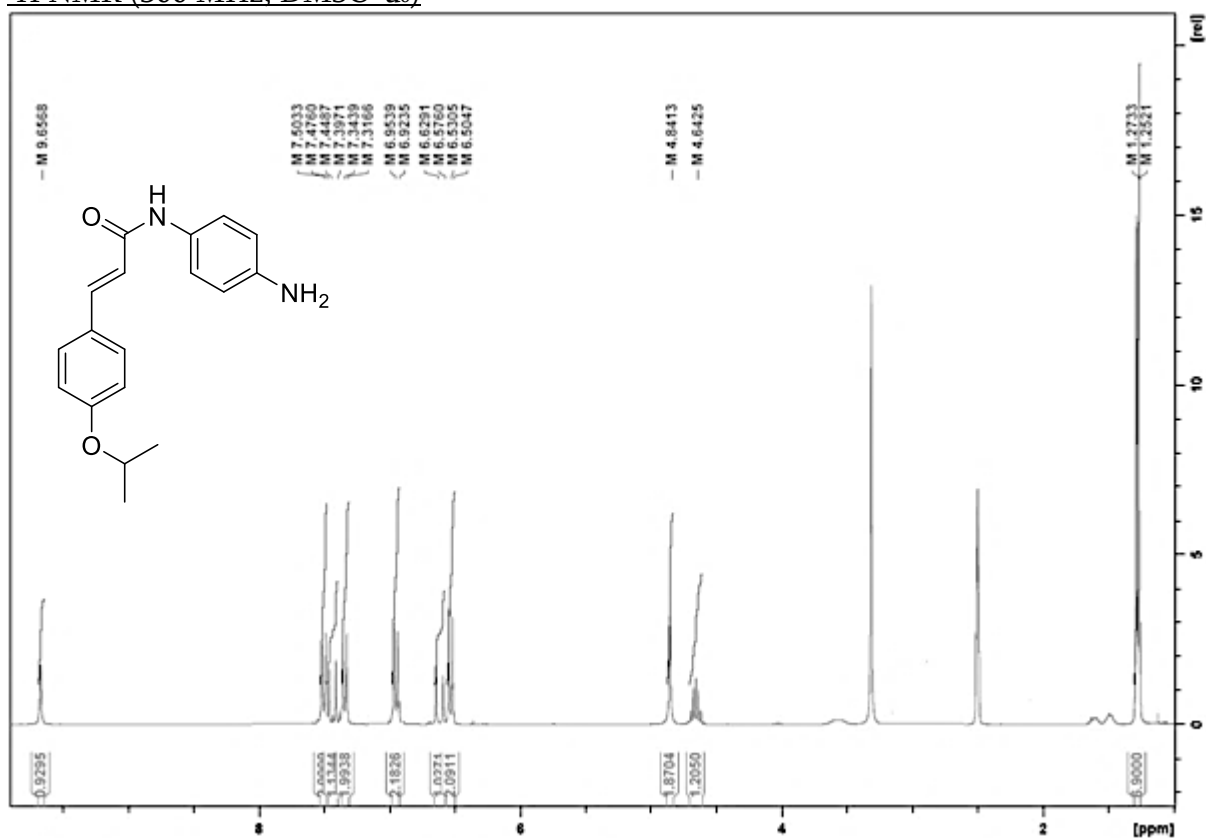


^{13}C NMR (75 MHz, $\text{DMSO}-d_6$)

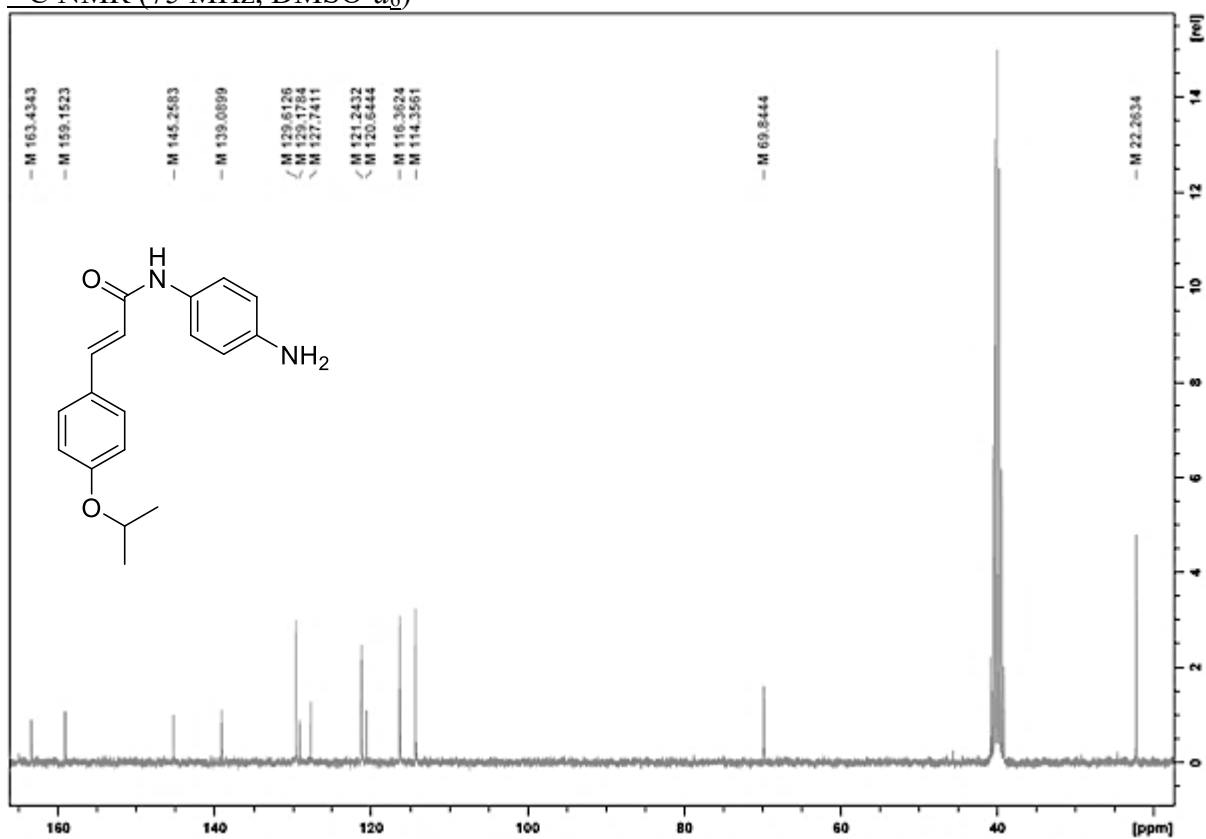


2.3. Spectra of **3c**

^1H NMR (300 MHz, $\text{DMSO}-d_6$)

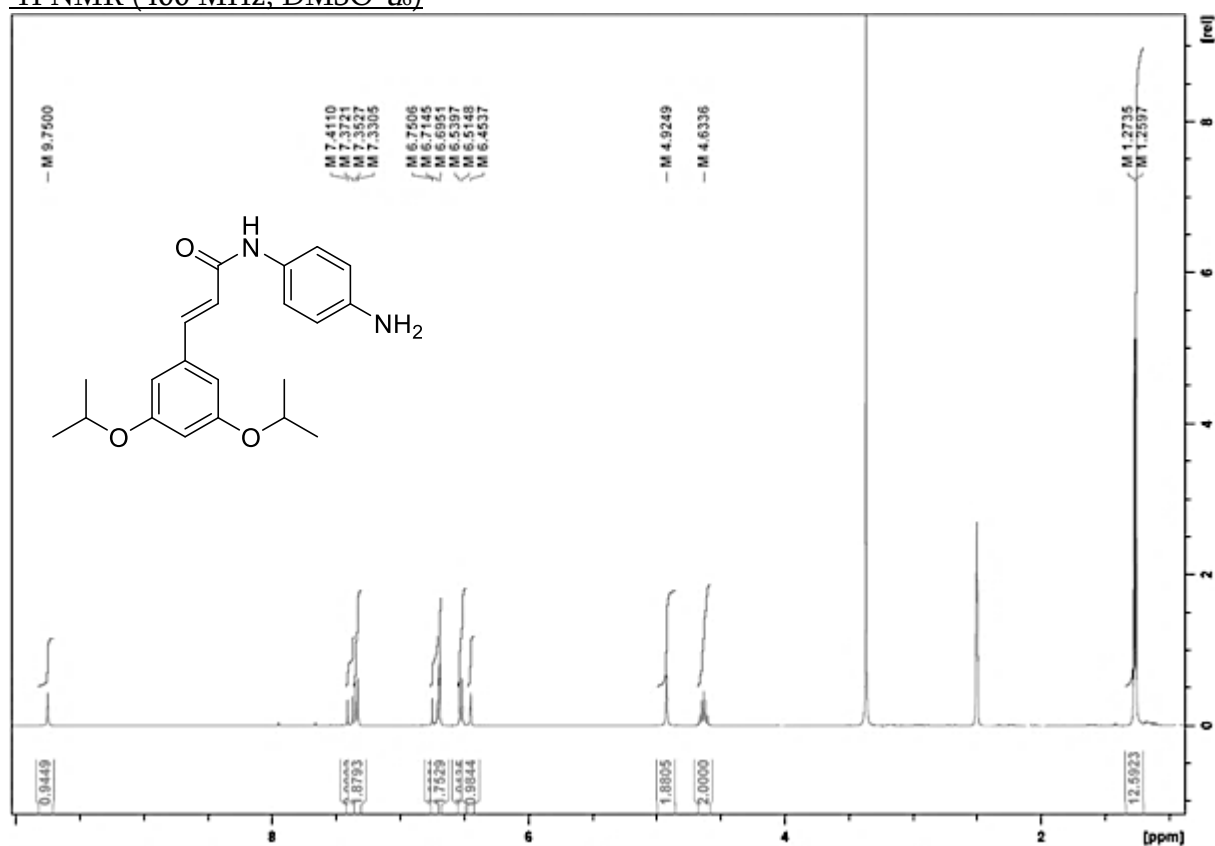


^{13}C NMR (75 MHz, $\text{DMSO}-d_6$)

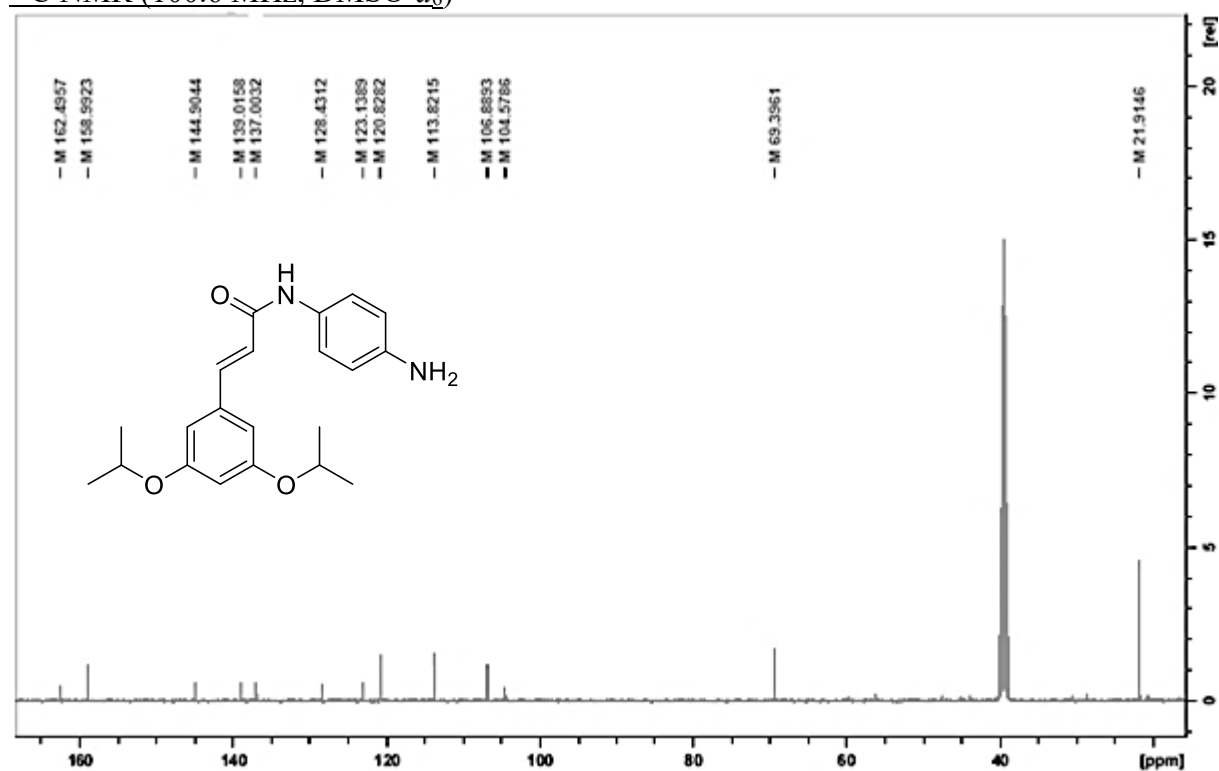


2.4. Spectra of **3d**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

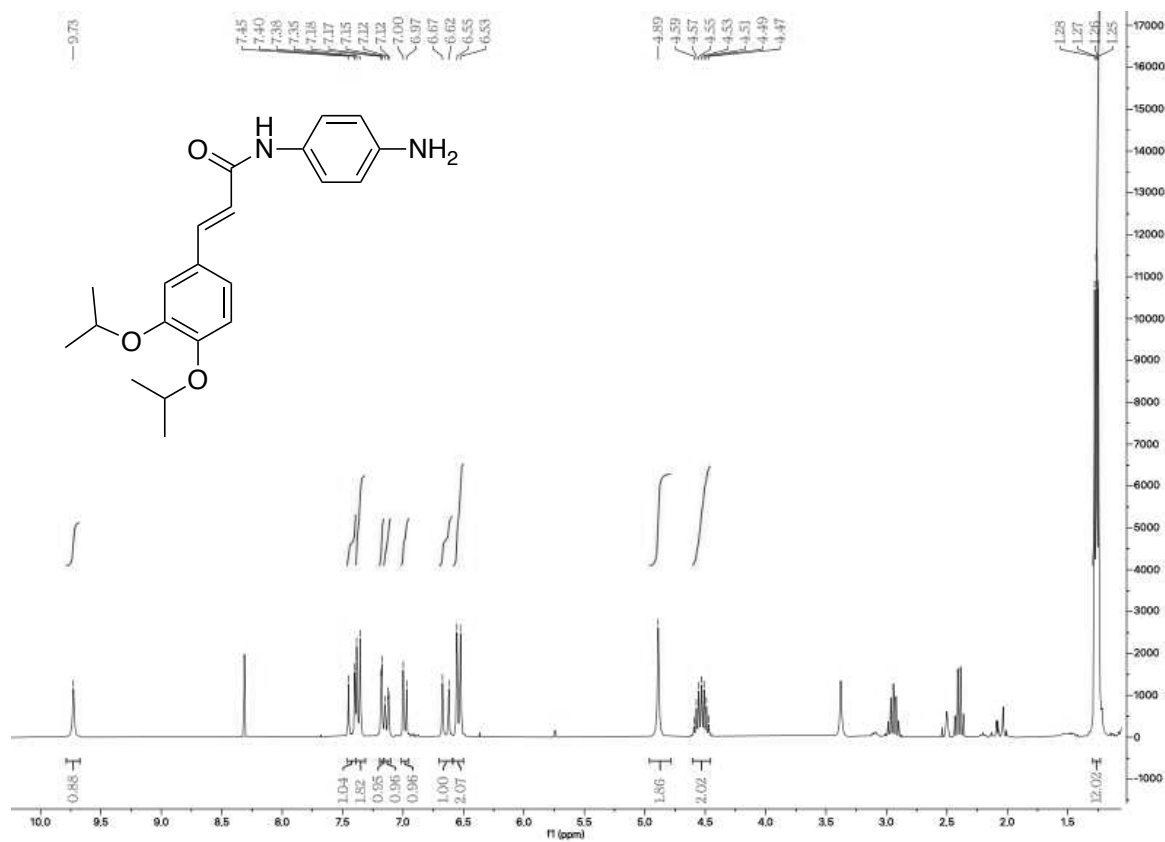


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

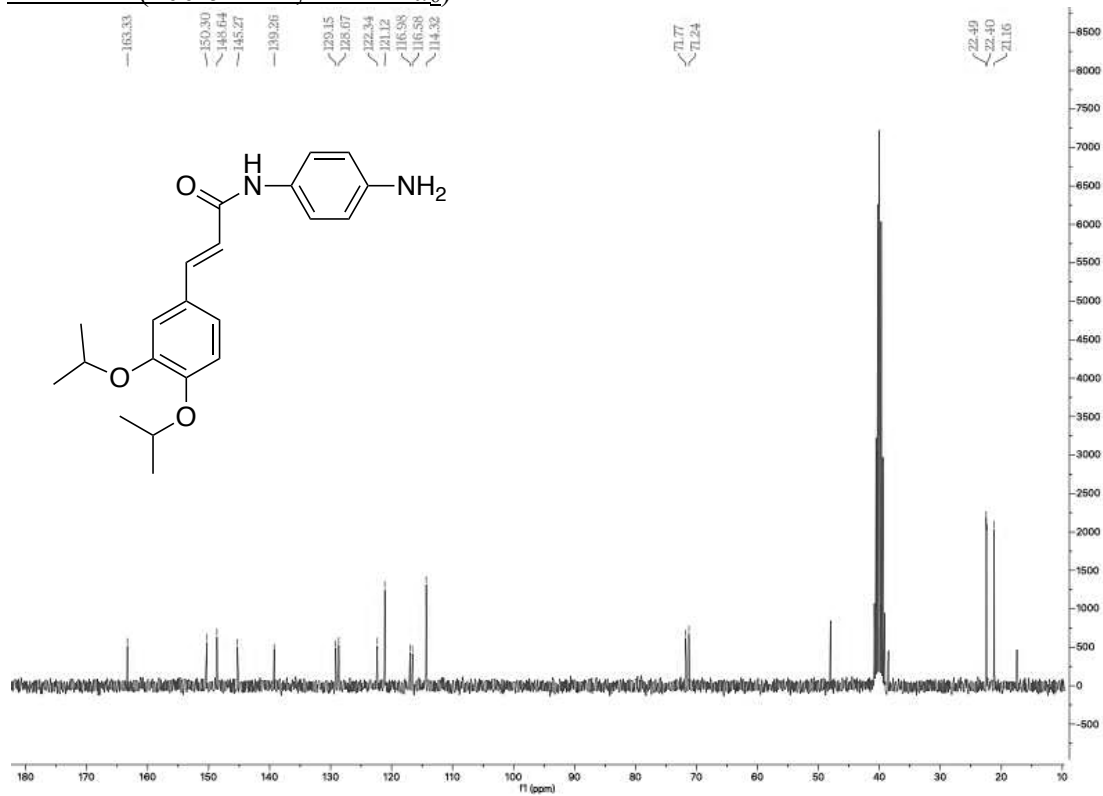


2.5. Spectra of **3e**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

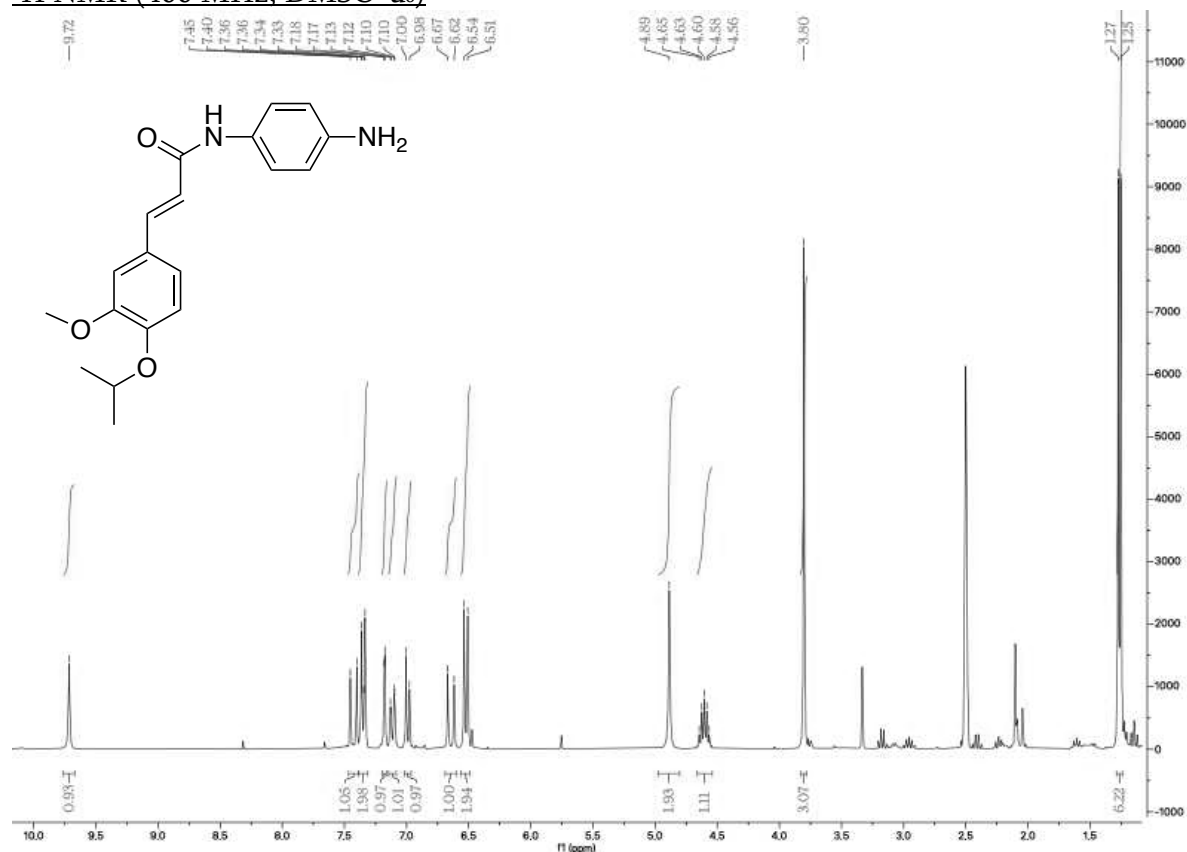


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

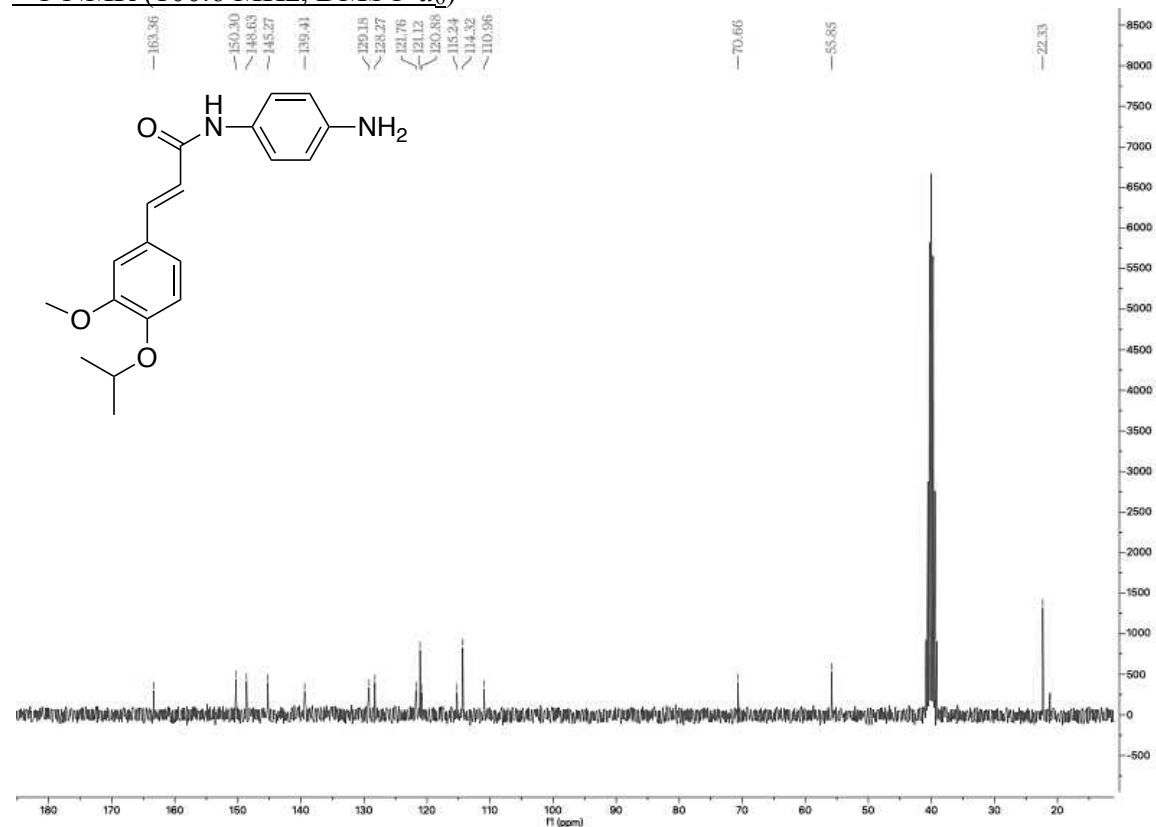


2.6. Spectra of **3f**

¹H NMR (400 MHz, DMSO-*d*₆)

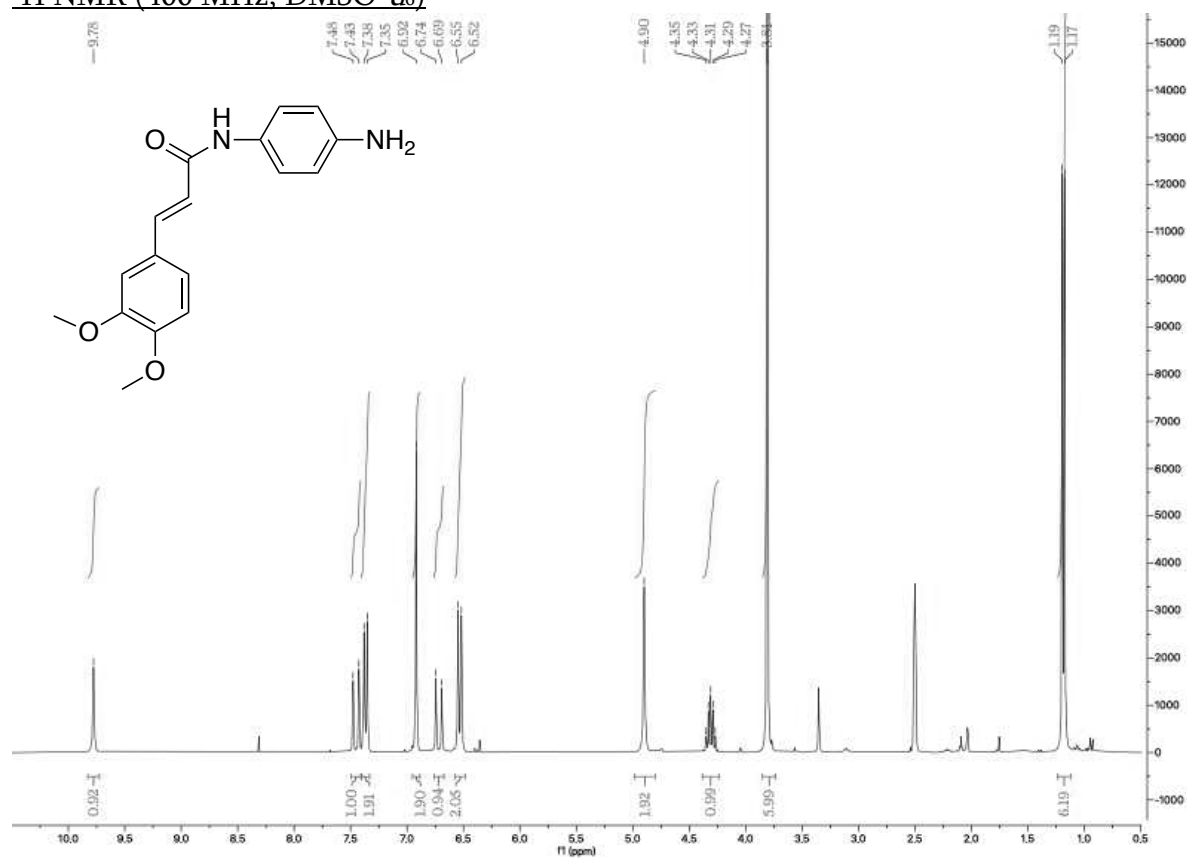


¹³C NMR (100.6 MHz, DMSO-*d*₆)

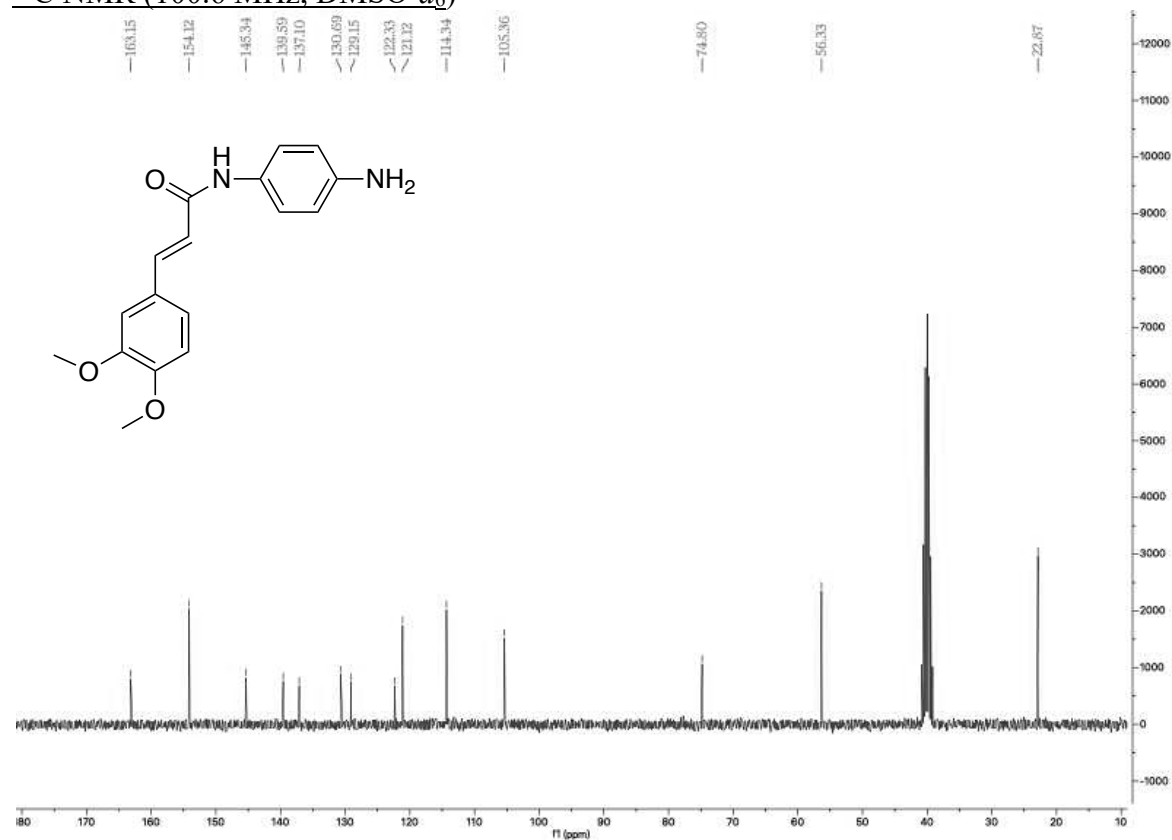


2.7. Spectra of **3g**

¹H NMR (400 MHz, DMSO-*d*₆)

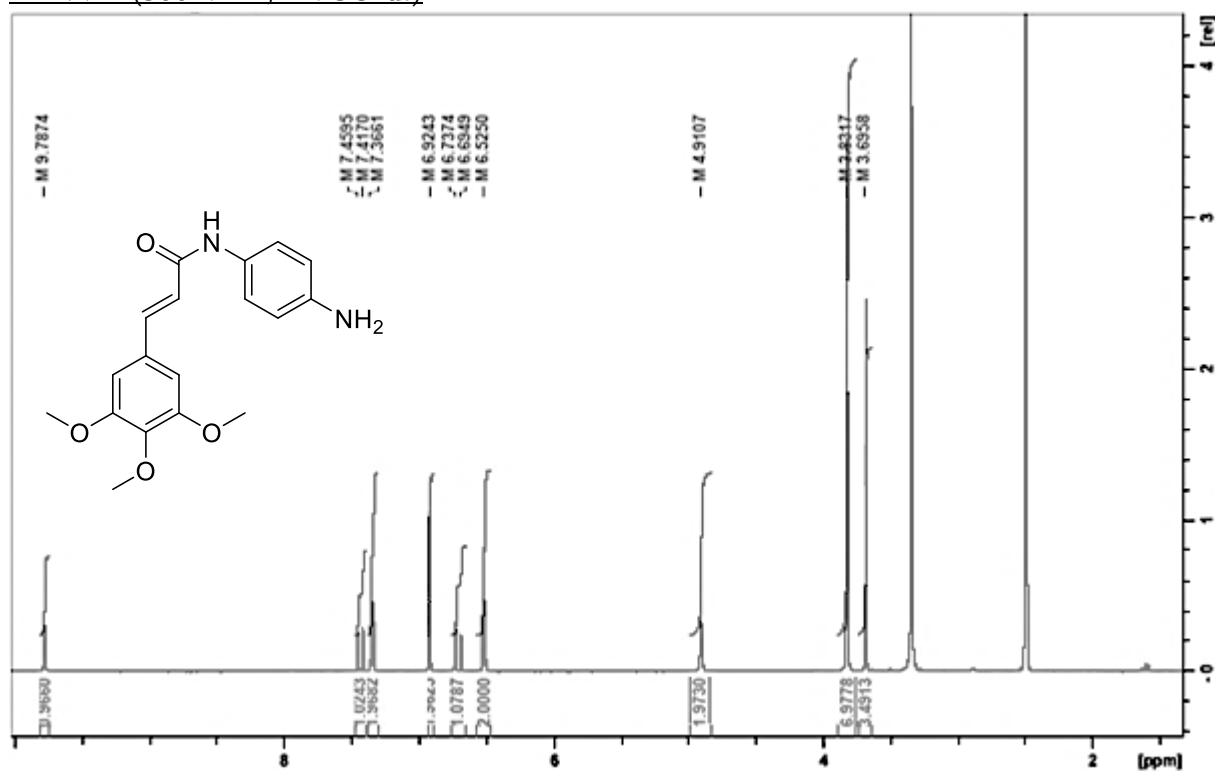


¹³C NMR (100.6 MHz, DMSO-*d*₆)

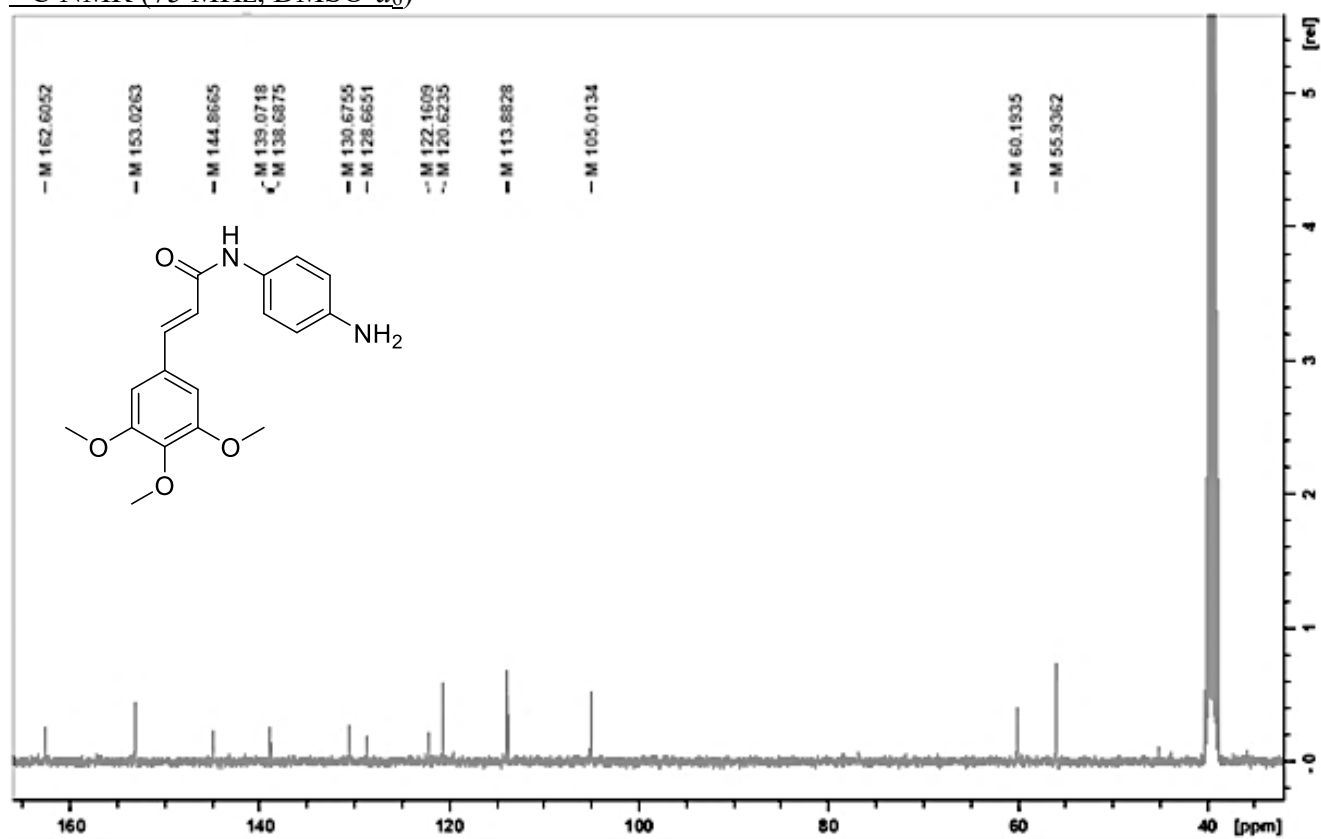


2.8. Spectra of **3h**

^1H NMR (300 MHz, DMSO- d_6)

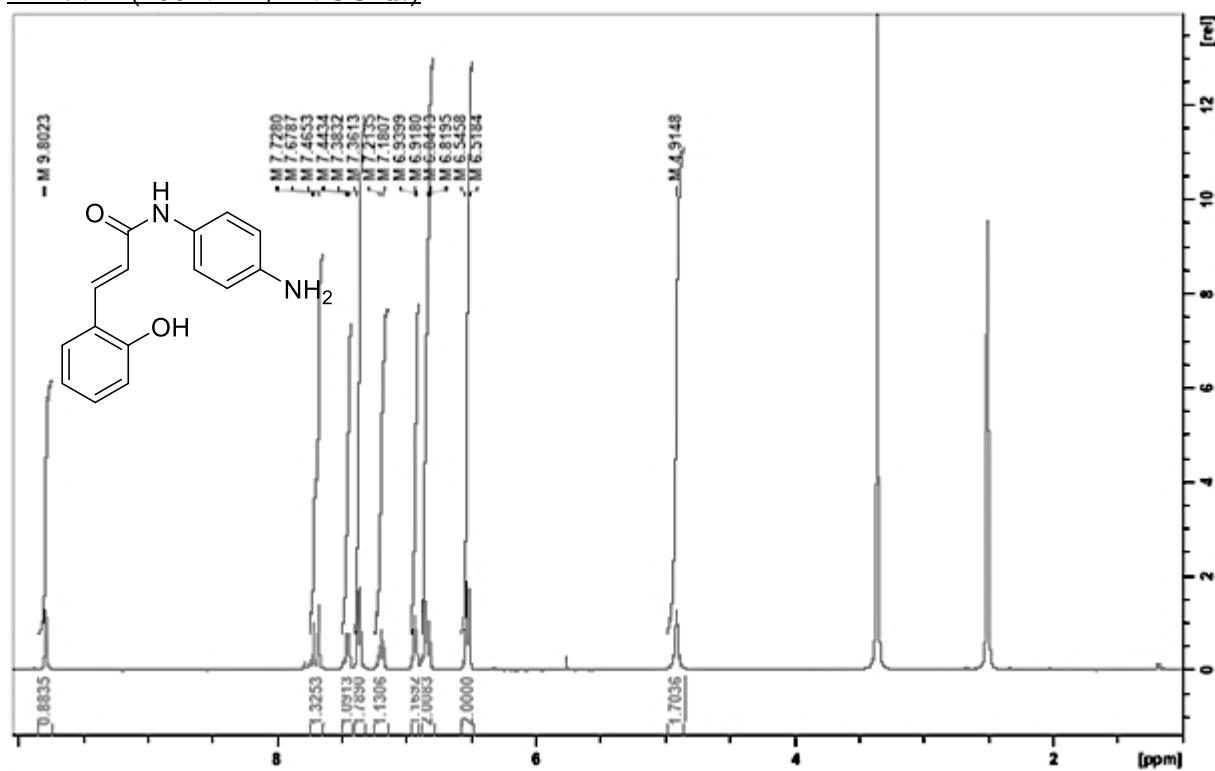


^{13}C NMR (75 MHz, DMSO- d_6)

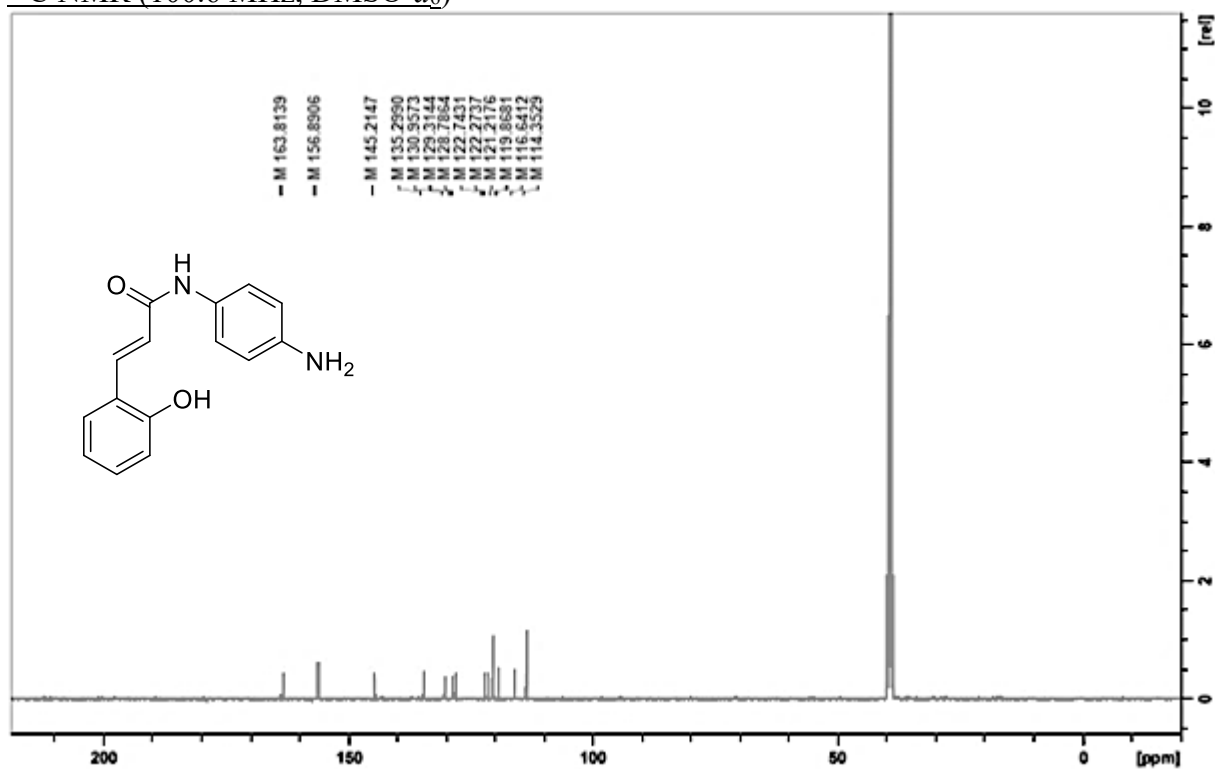


2.9. Spectra of **4a**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

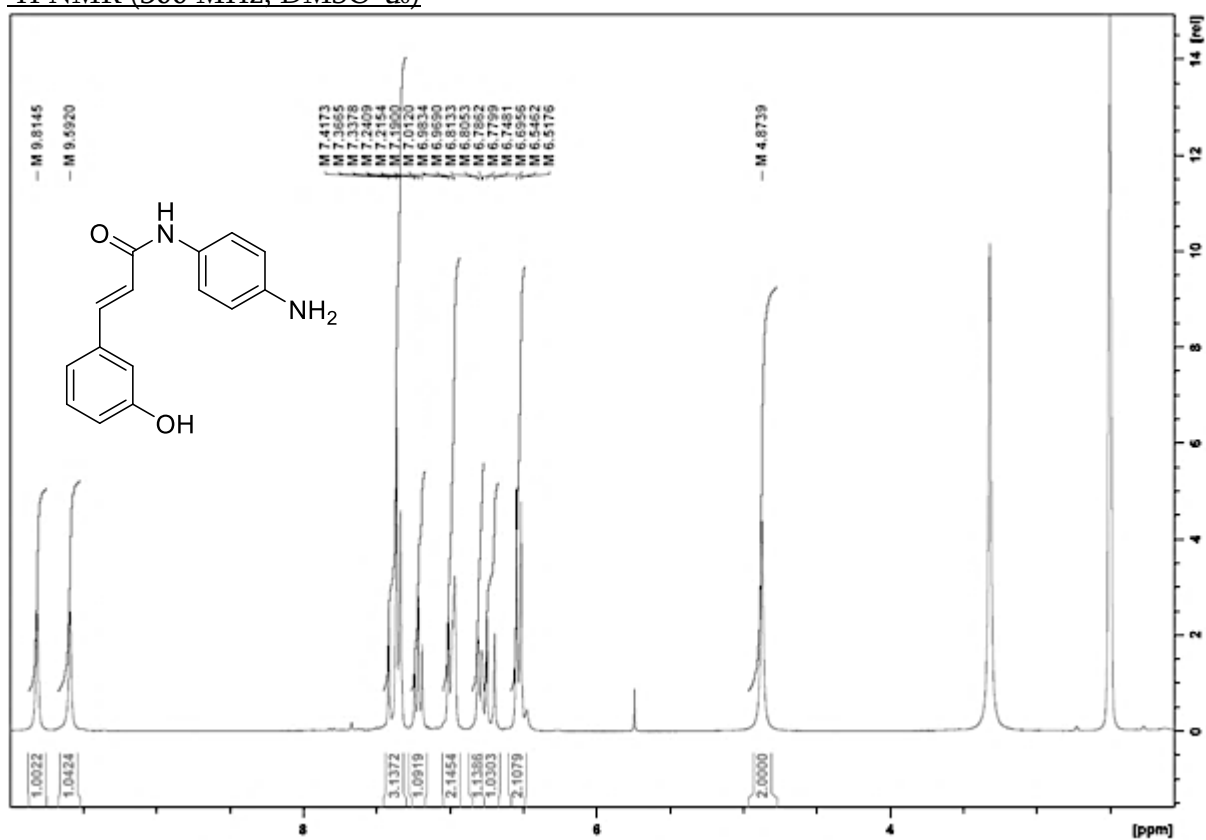


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

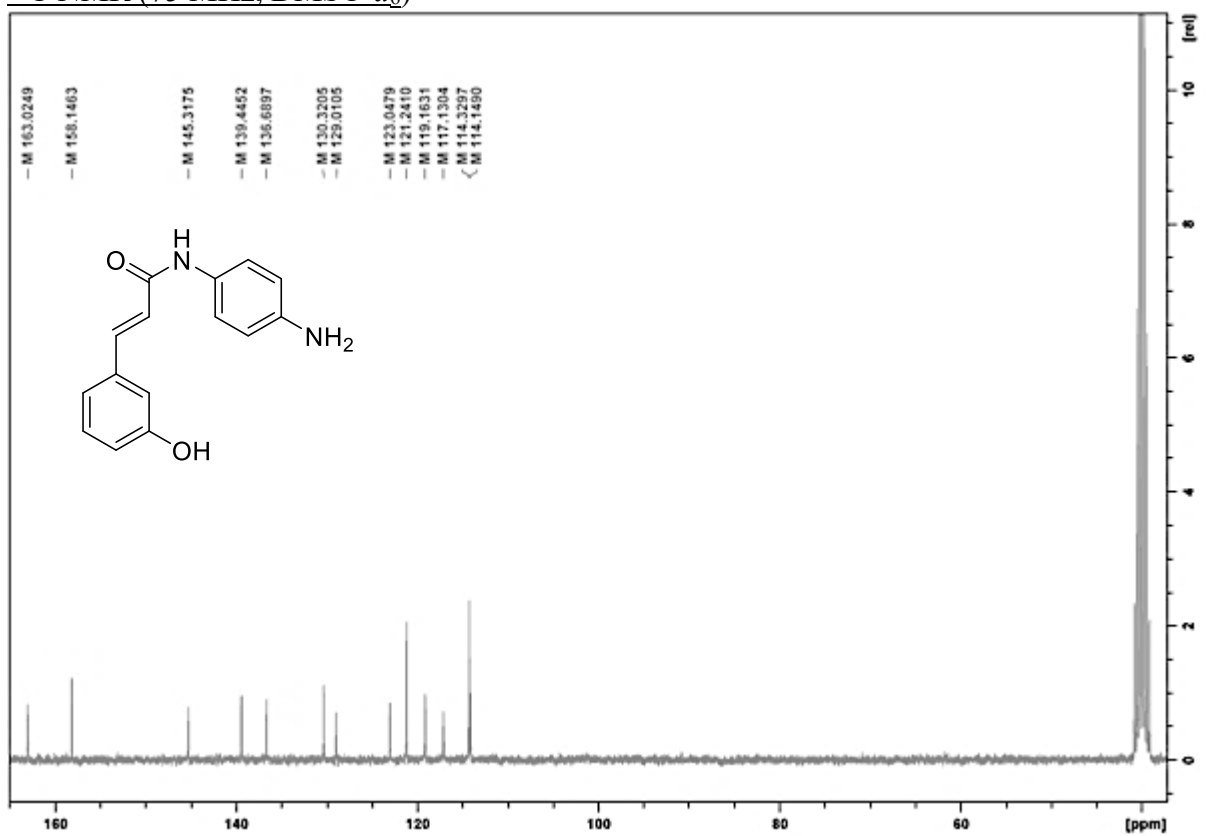


2.10. Spectra of **4b**

^1H NMR (300 MHz, $\text{DMSO}-d_6$)

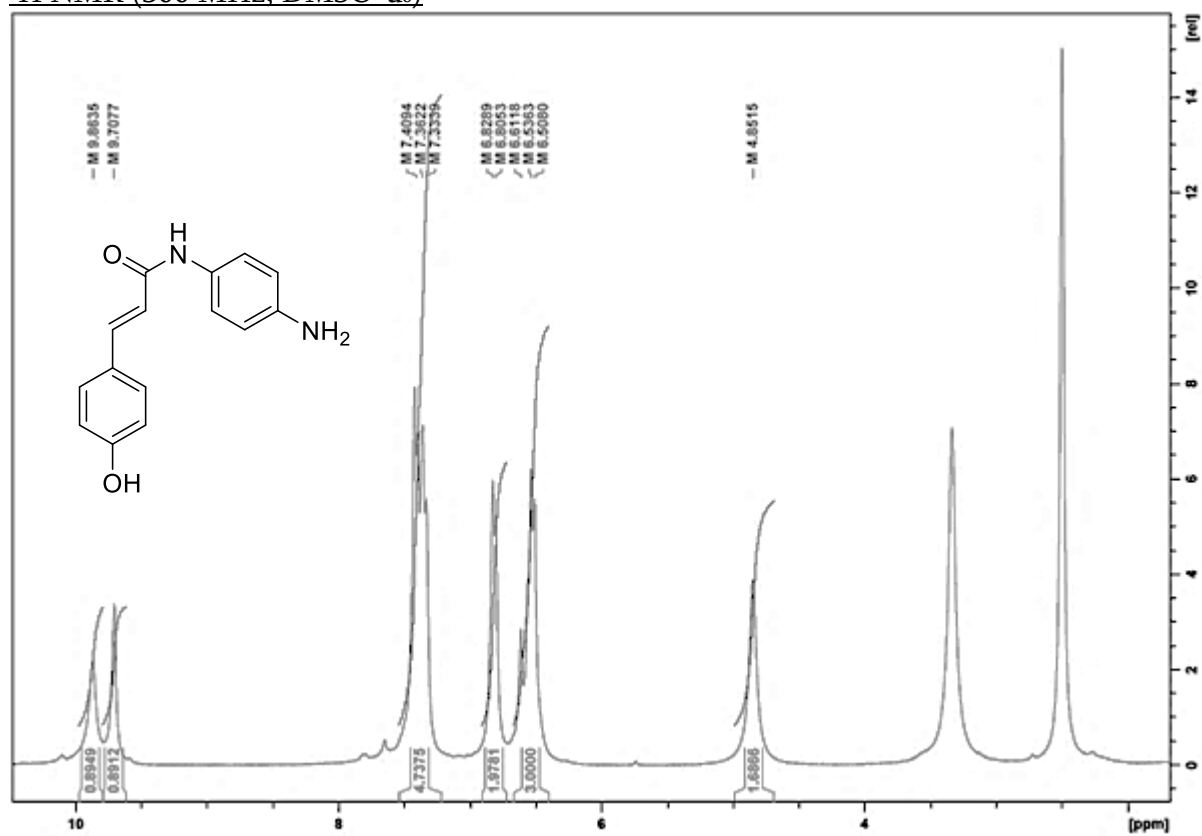


^{13}C NMR (75 MHz, $\text{DMSO}-d_6$)

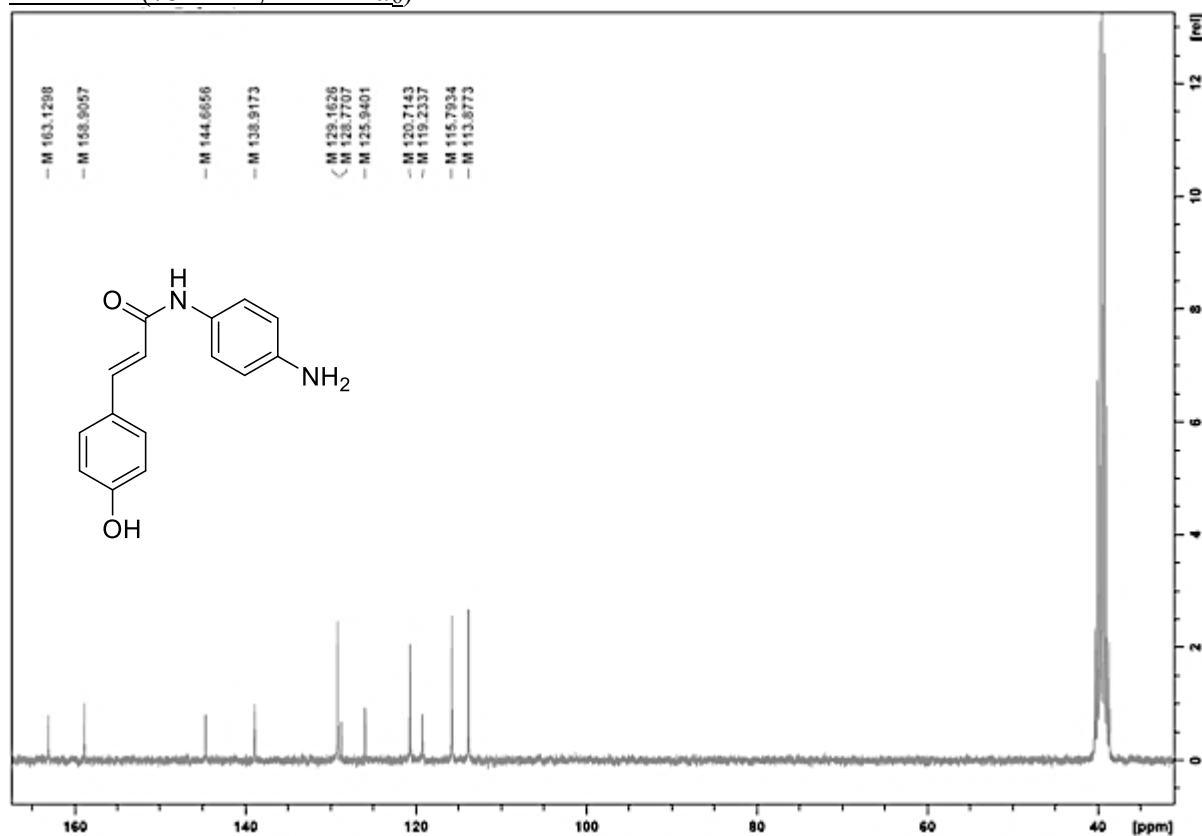


2.11. Spectra of **4c**

^1H NMR (300 MHz, $\text{DMSO}-d_6$)

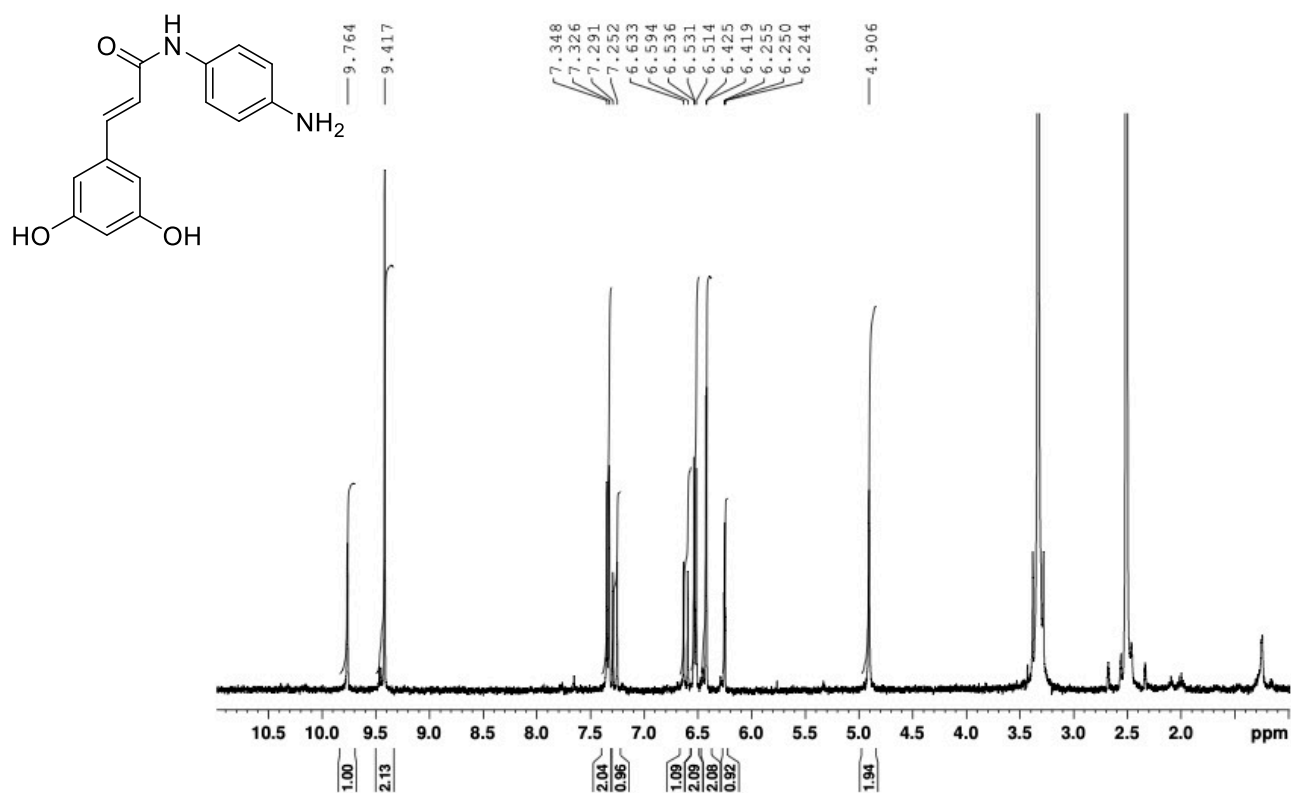


^{13}C NMR (75 MHz, $\text{DMSO}-d_6$)

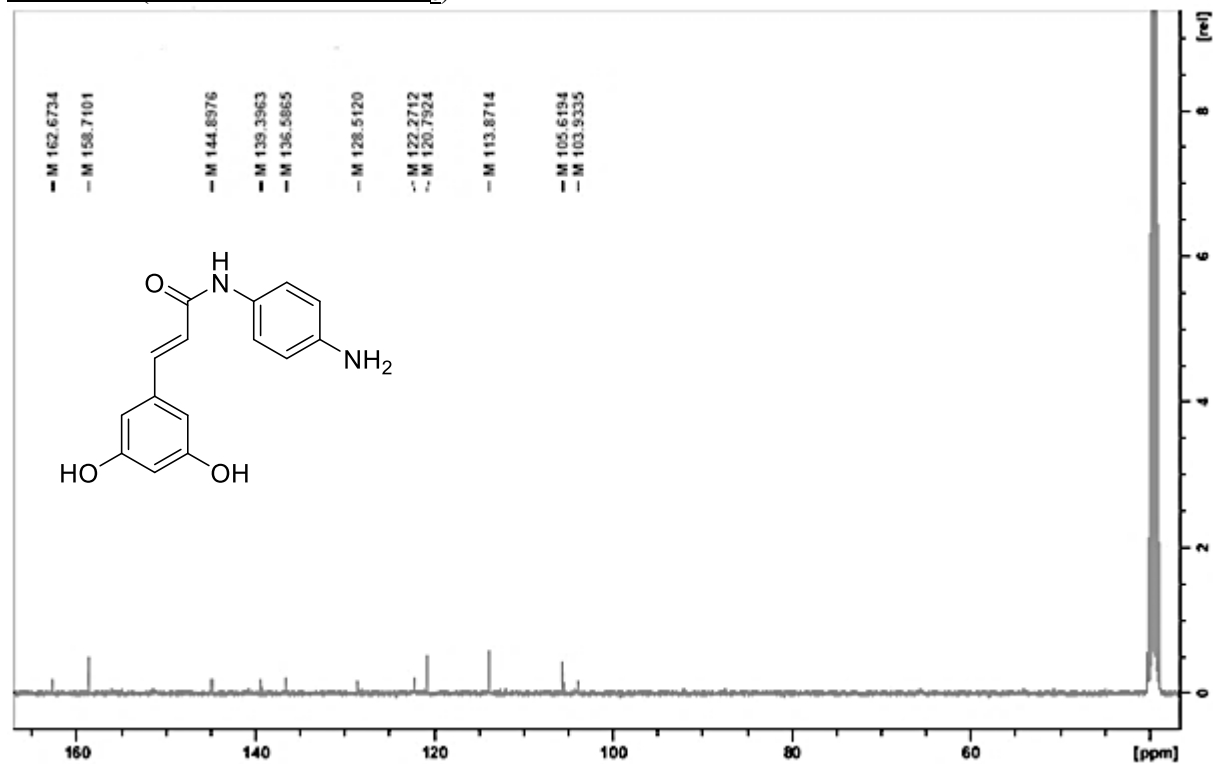


2.12. Spectra of **4d**

^1H NMR (400 MHz, DMSO- d_6)

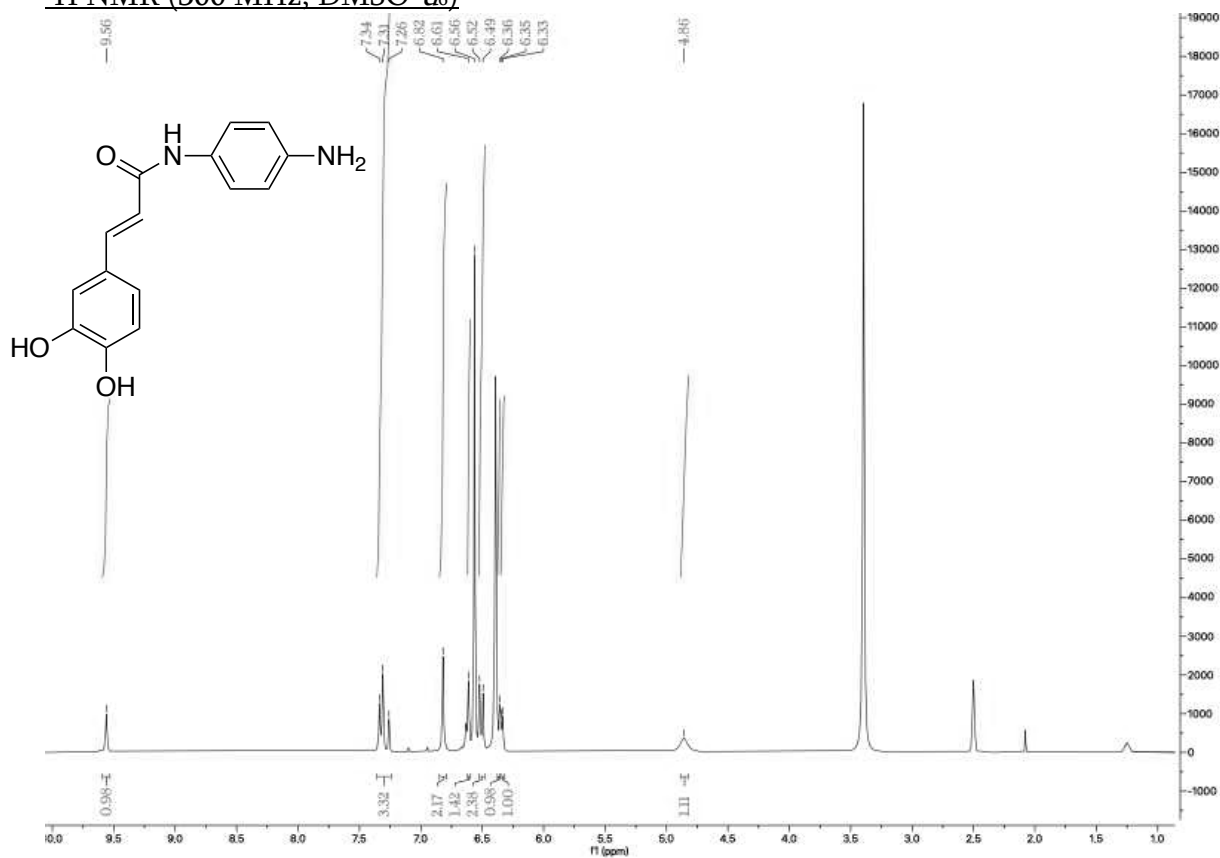


^{13}C NMR (100.6 MHz, DMSO- d_6)

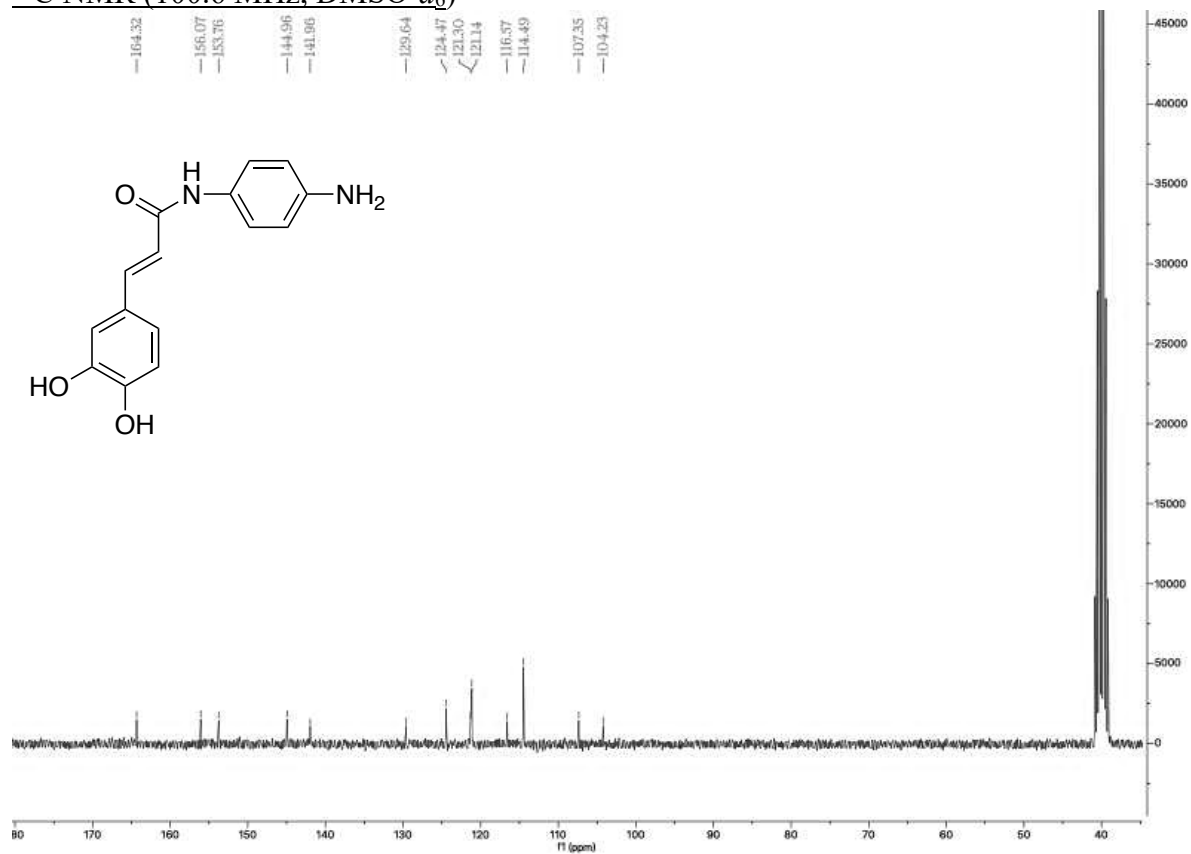


2.13. Spectra of **4e**

¹H NMR (300 MHz, DMSO-*d*₆)

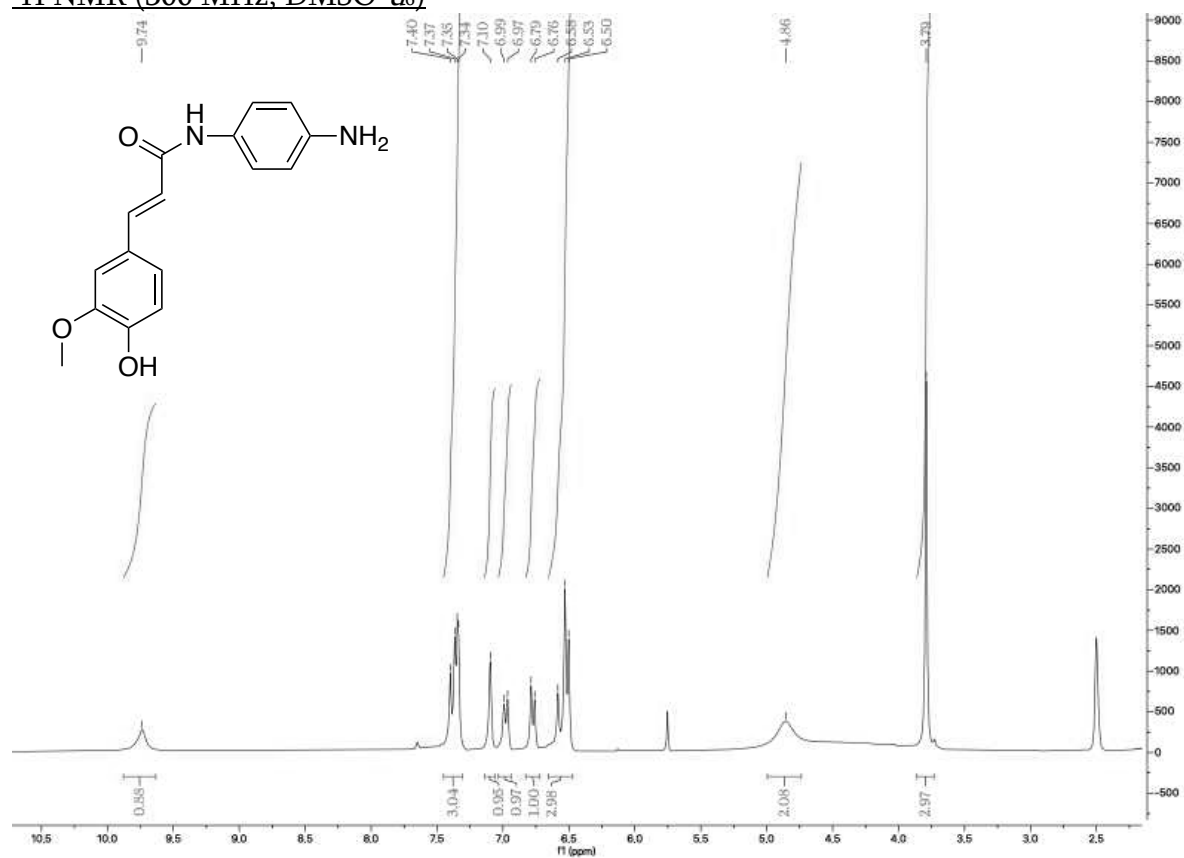


¹³C NMR (100.6 MHz, DMSO-*d*₆)

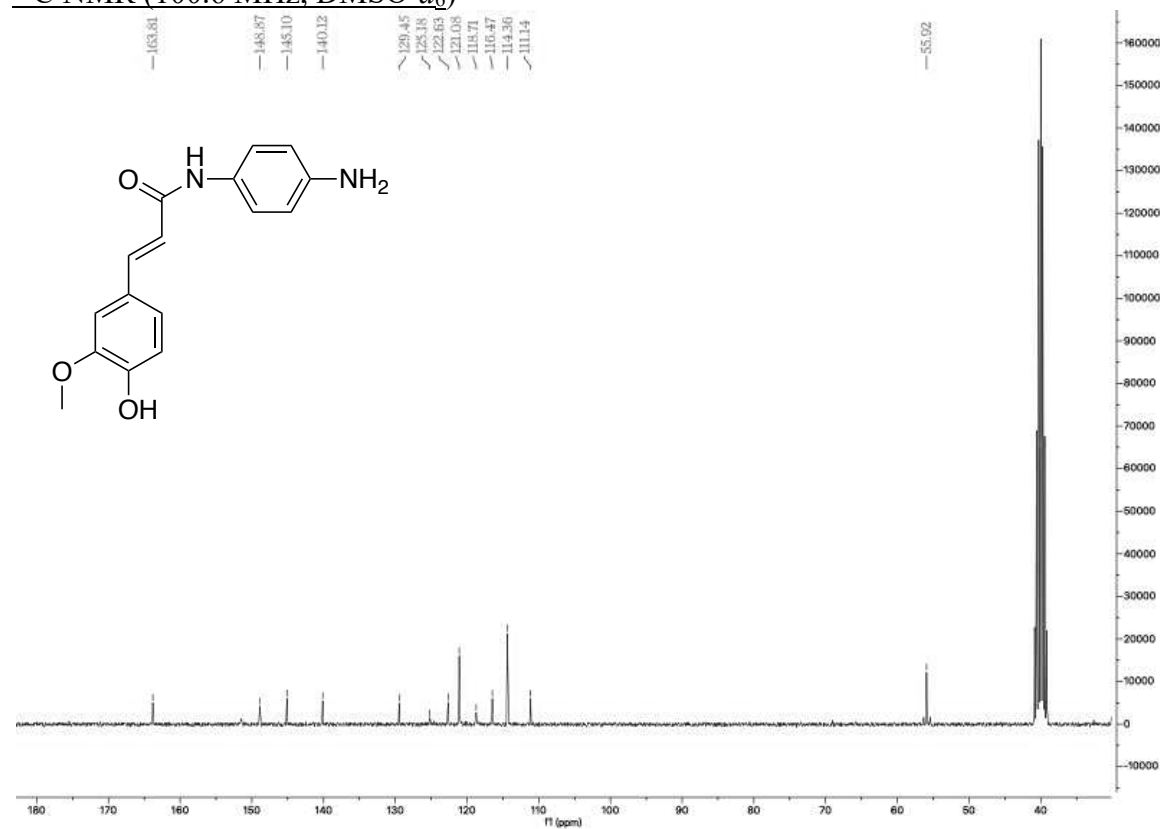


2.14. Spectra of **4f**

¹H NMR (300 MHz, DMSO-*d*₆)

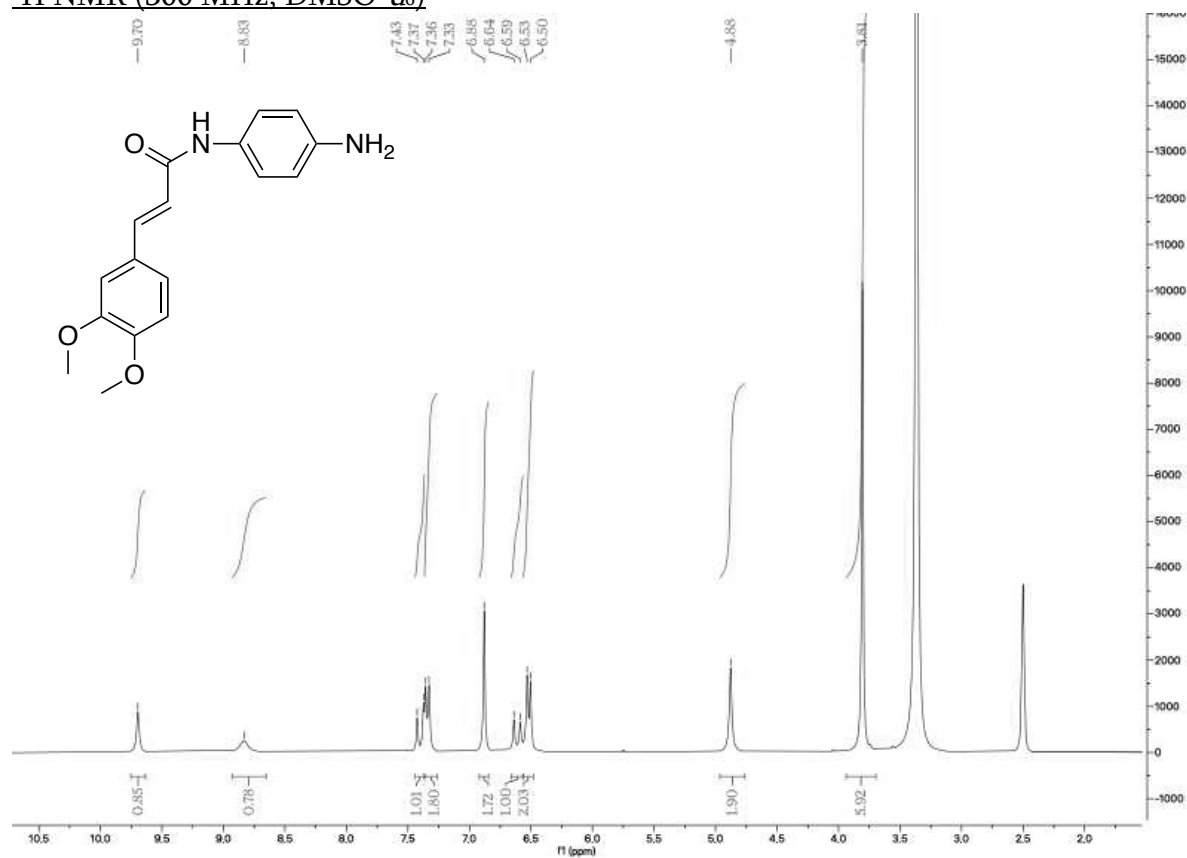


¹³C NMR (100.6 MHz, DMSO-*d*₆)

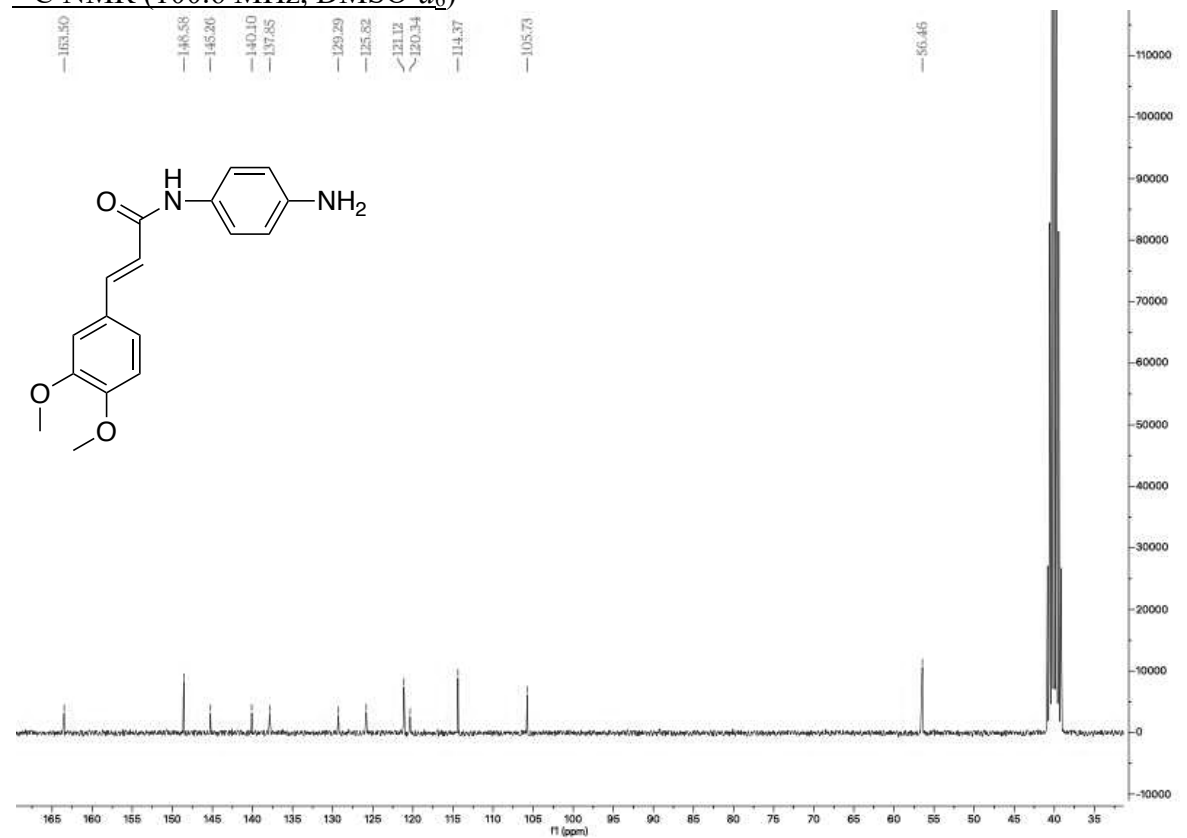


2.15. Spectra of **4g**

¹H NMR (300 MHz, DMSO-*d*₆)

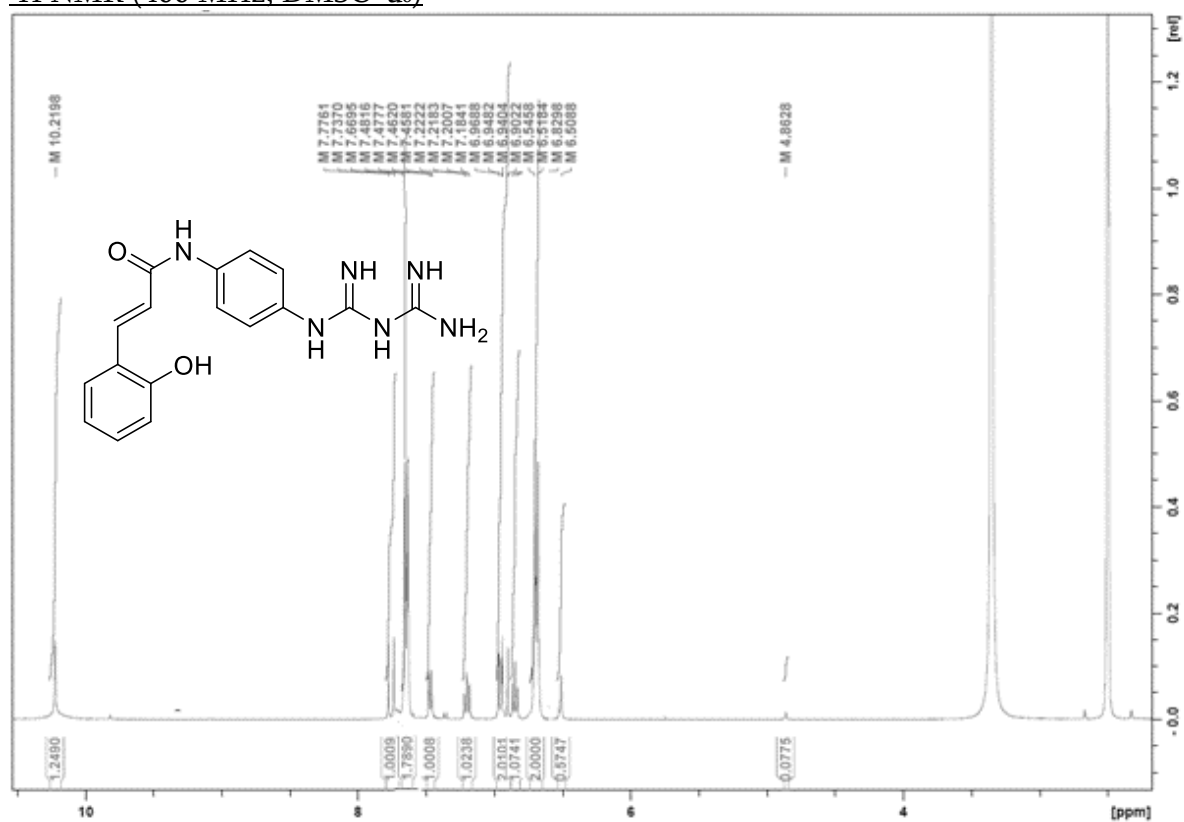


¹³C NMR (100.6 MHz, DMSO-*d*₆)

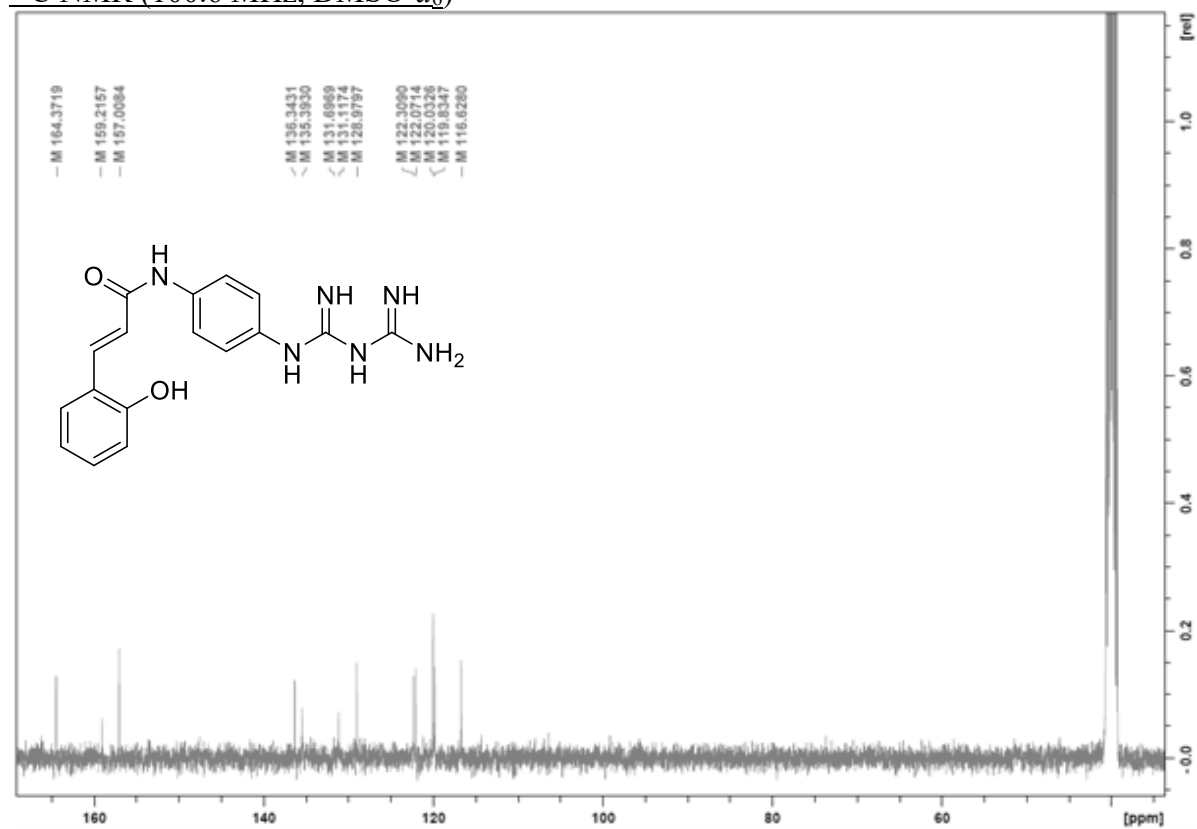


2.16. Spectra of **5a**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

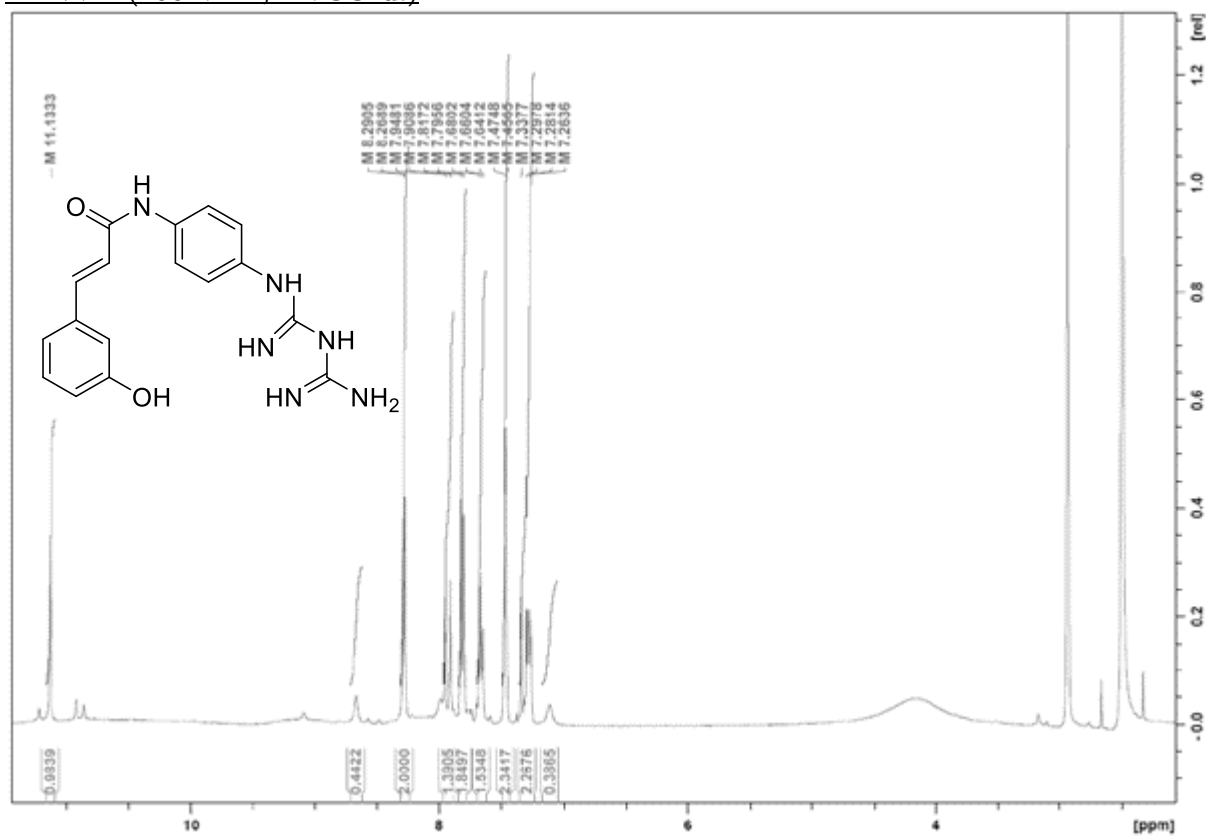


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

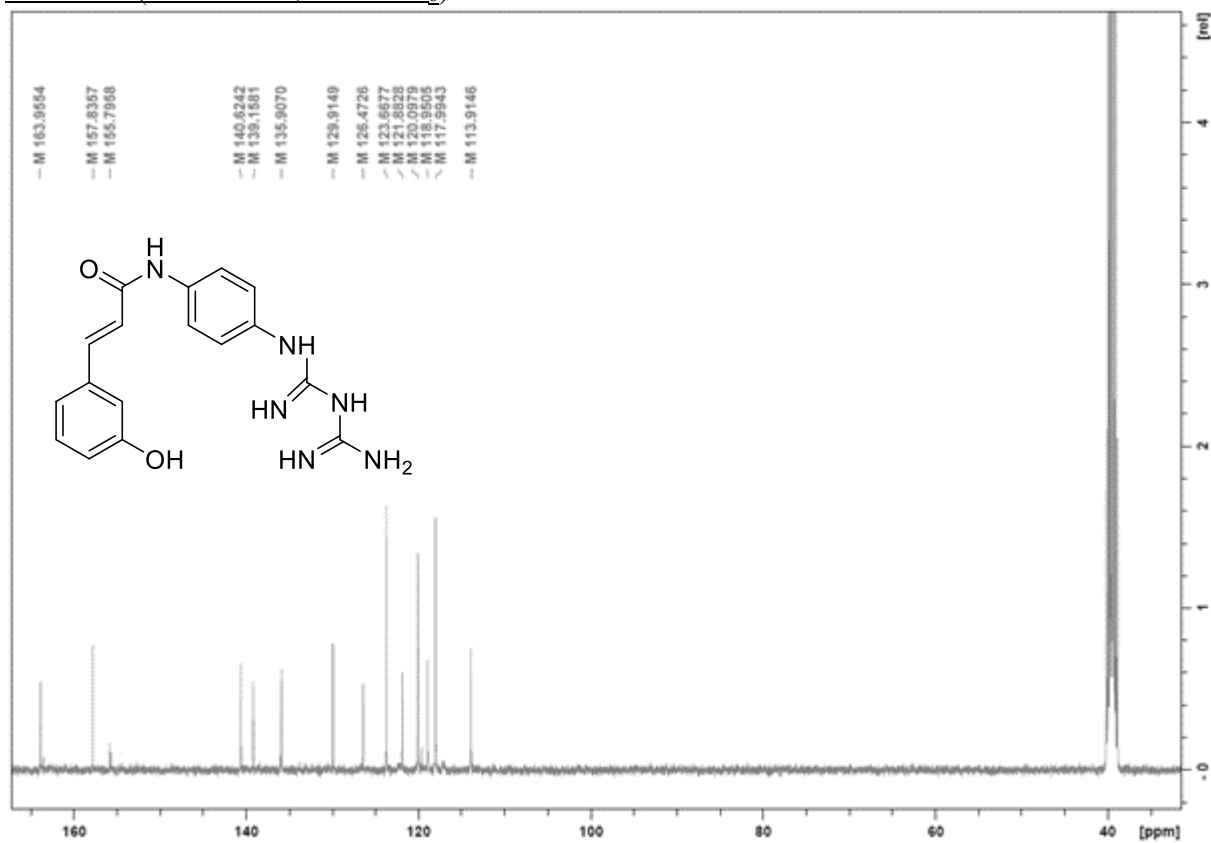


2.17. Spectra of **5b**

^1H NMR (400 MHz, DMSO- d_6)

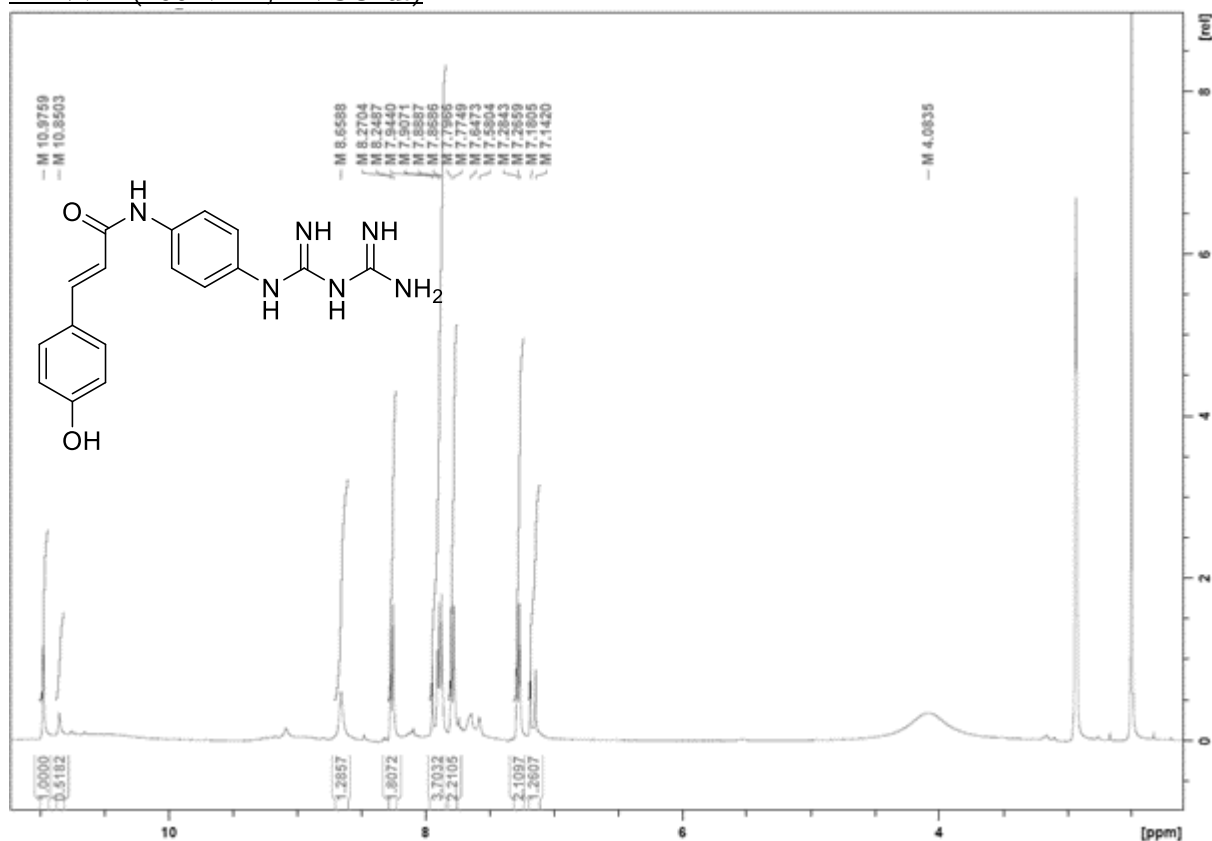


^{13}C NMR (100.6 MHz, DMSO- d_6)

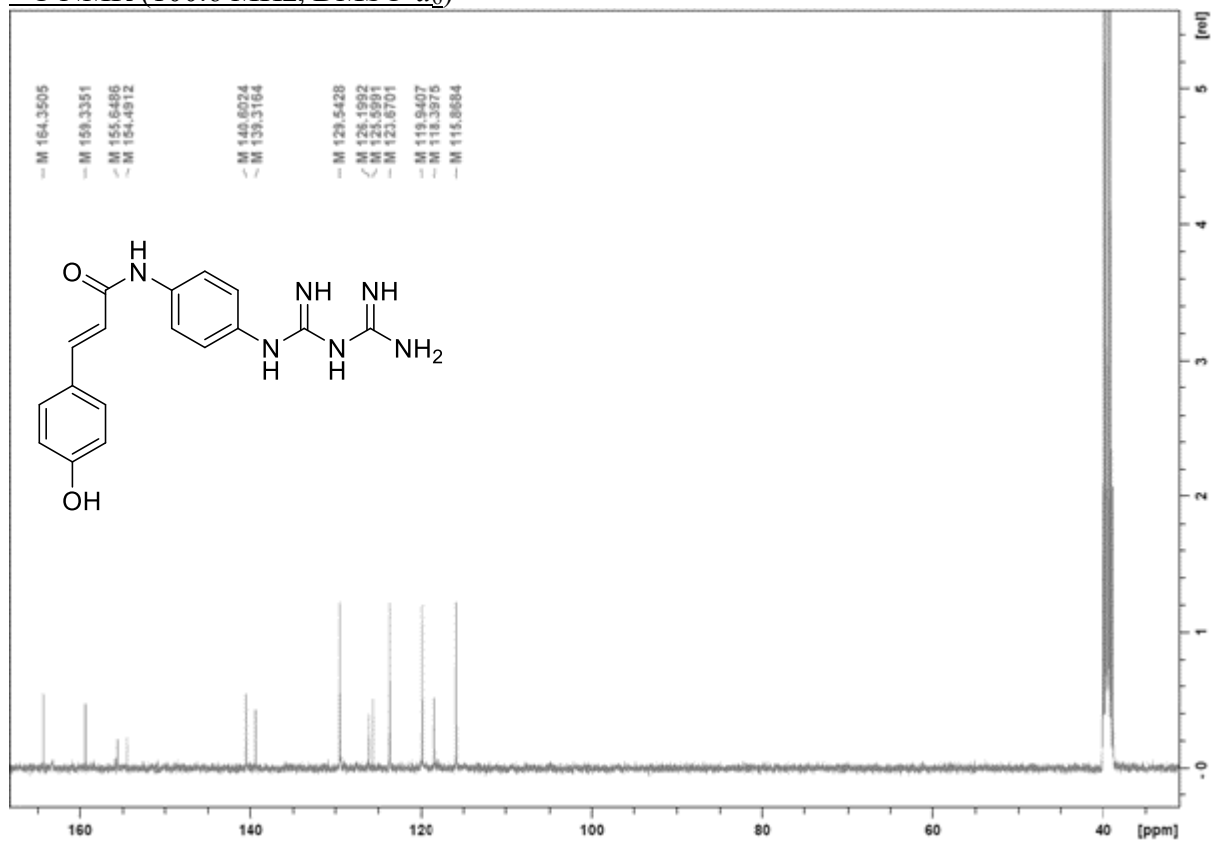


2.18. Spectra of **5c**

¹H NMR (400 MHz, DMSO-*d*₆)

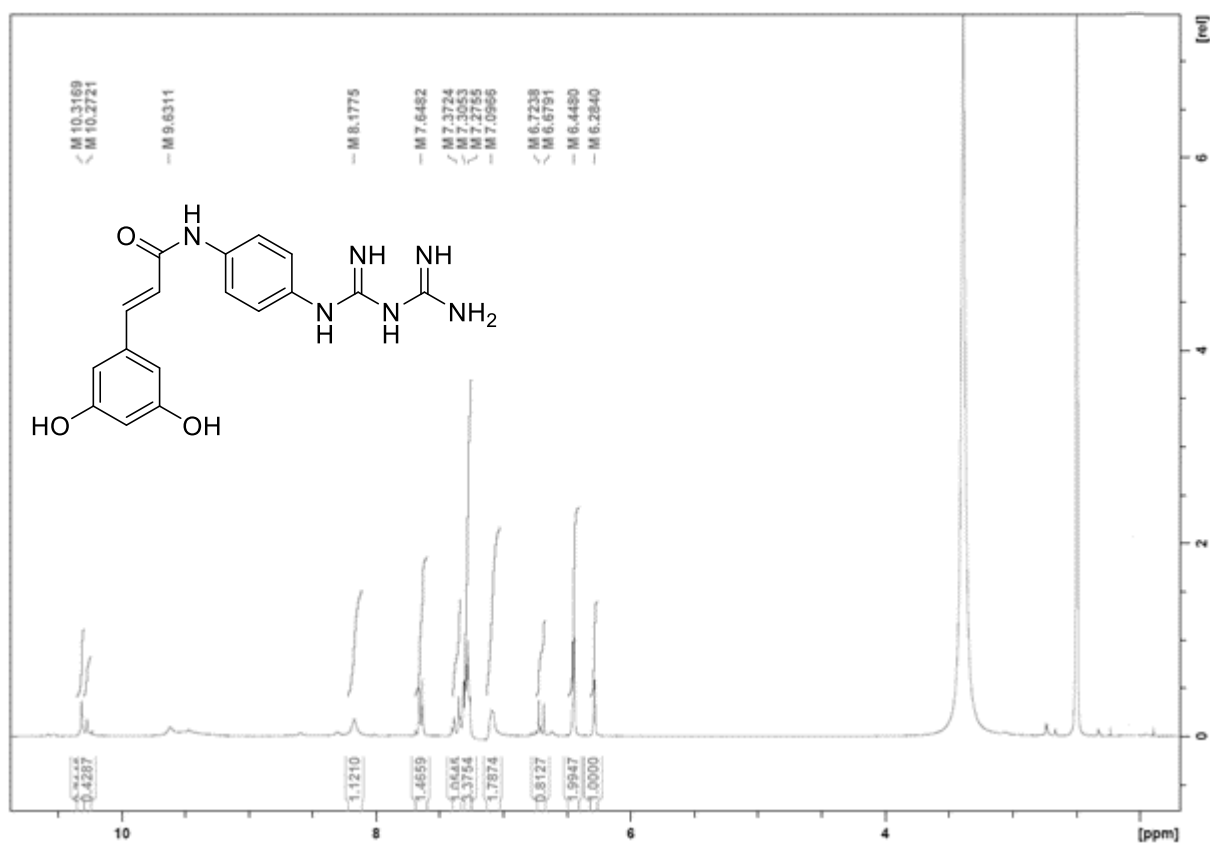


¹³C NMR (100.6 MHz, DMSO-*d*₆)

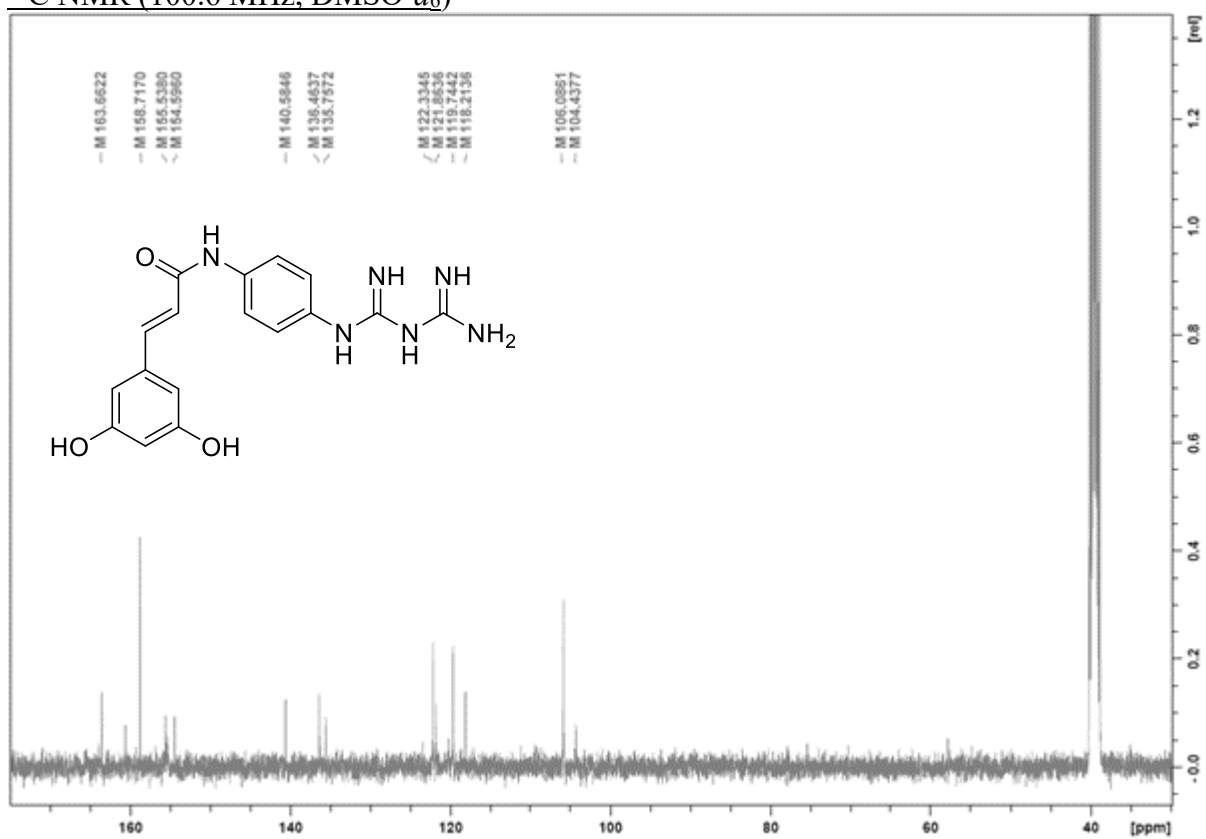


2.19. Spectra of **5d**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

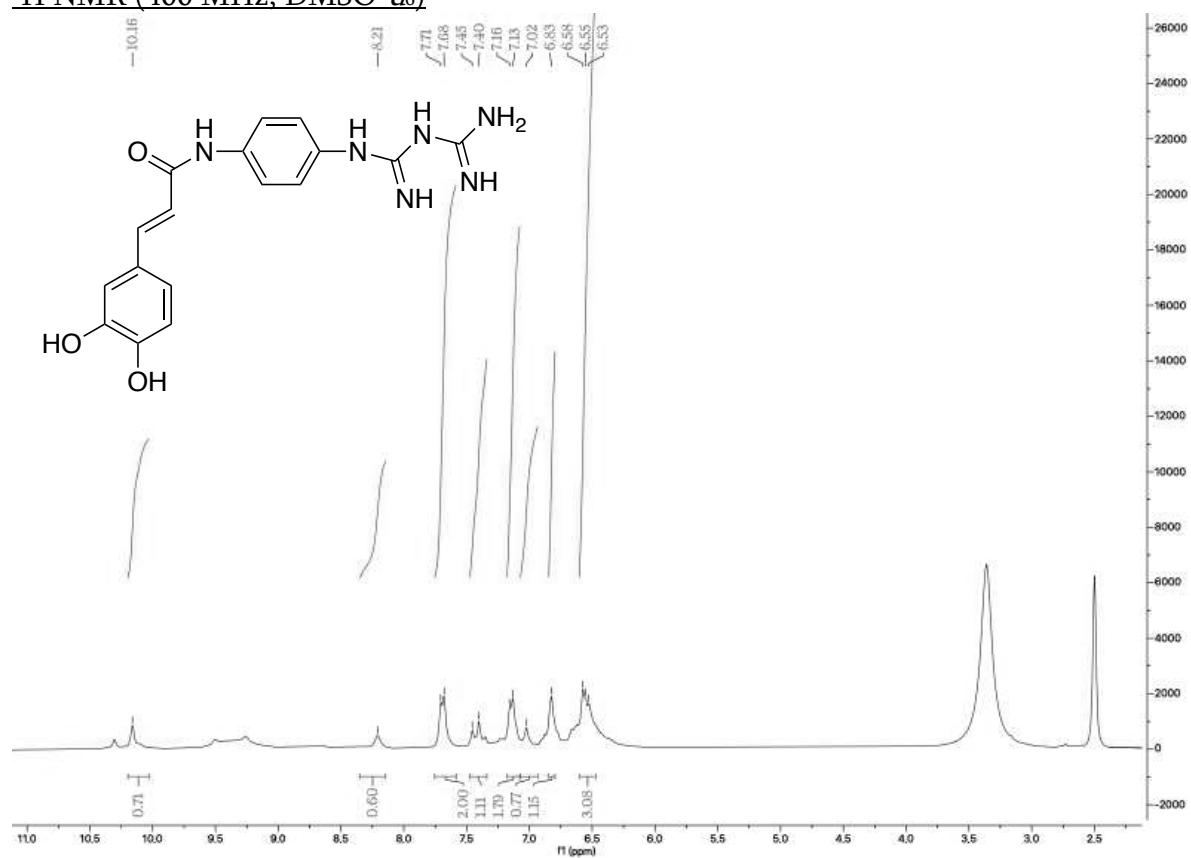


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

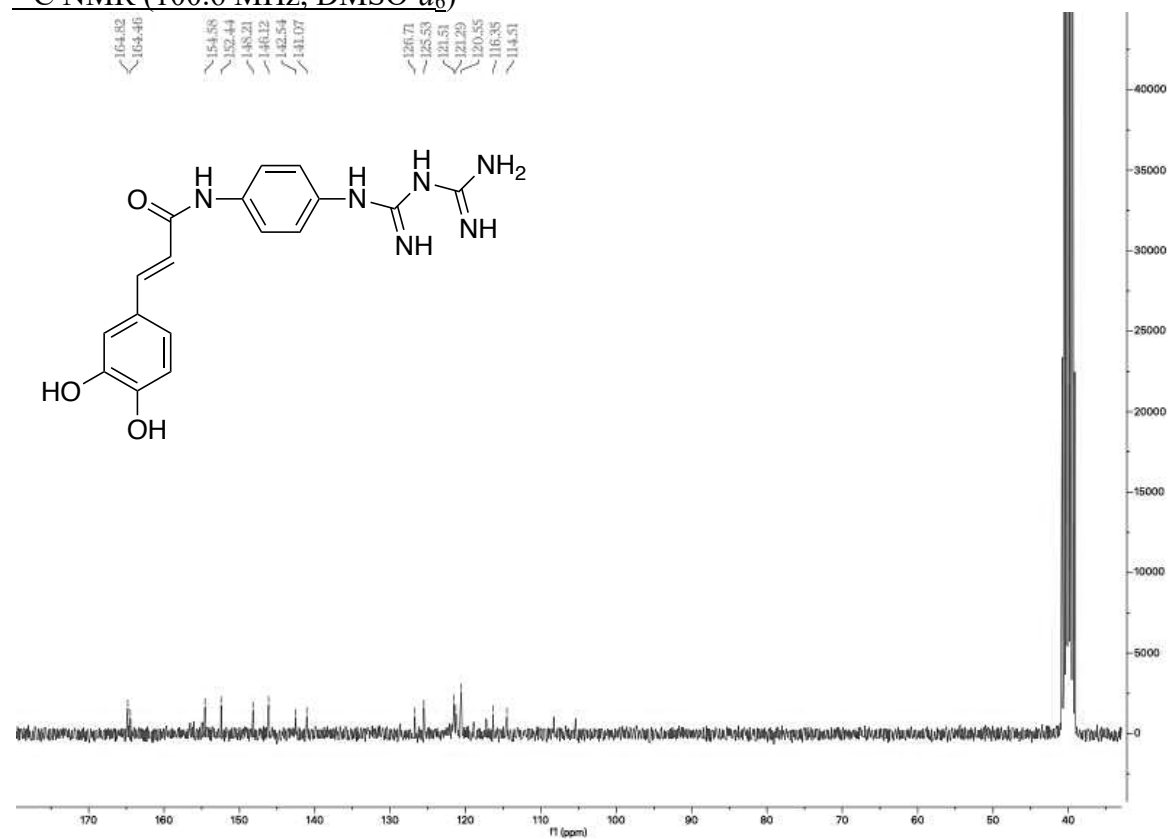


2.20. Spectra of **5e**

¹H NMR (400 MHz, DMSO-*d*₆)

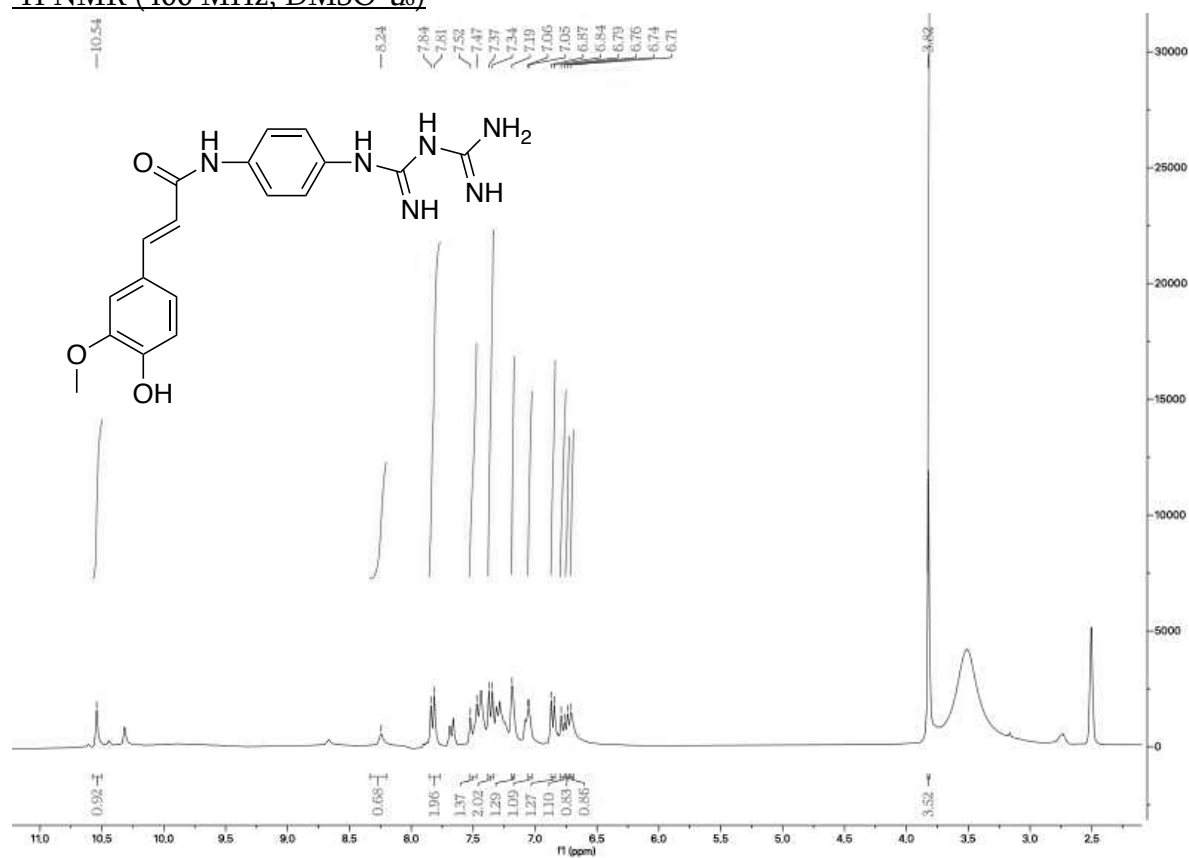


¹³C NMR (100.6 MHz, DMSO-*d*₆)

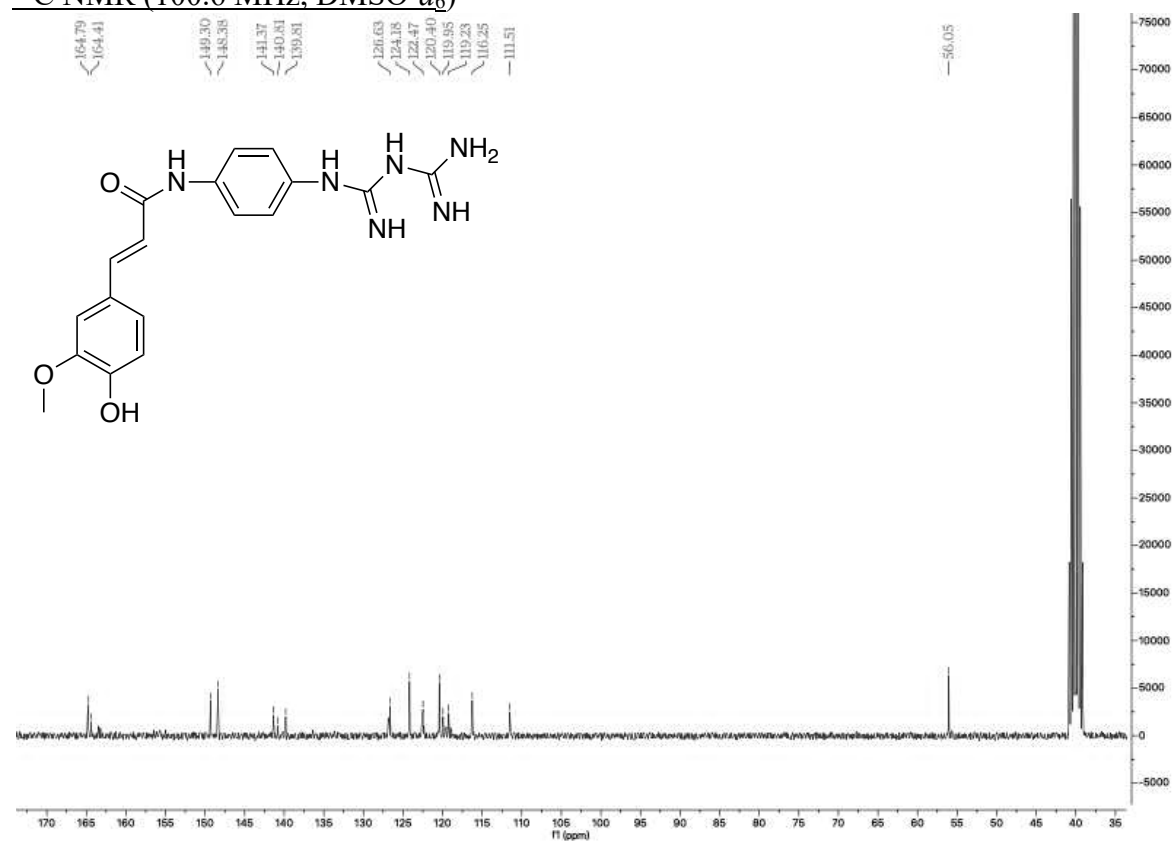


2.21. Spectra of **5f**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

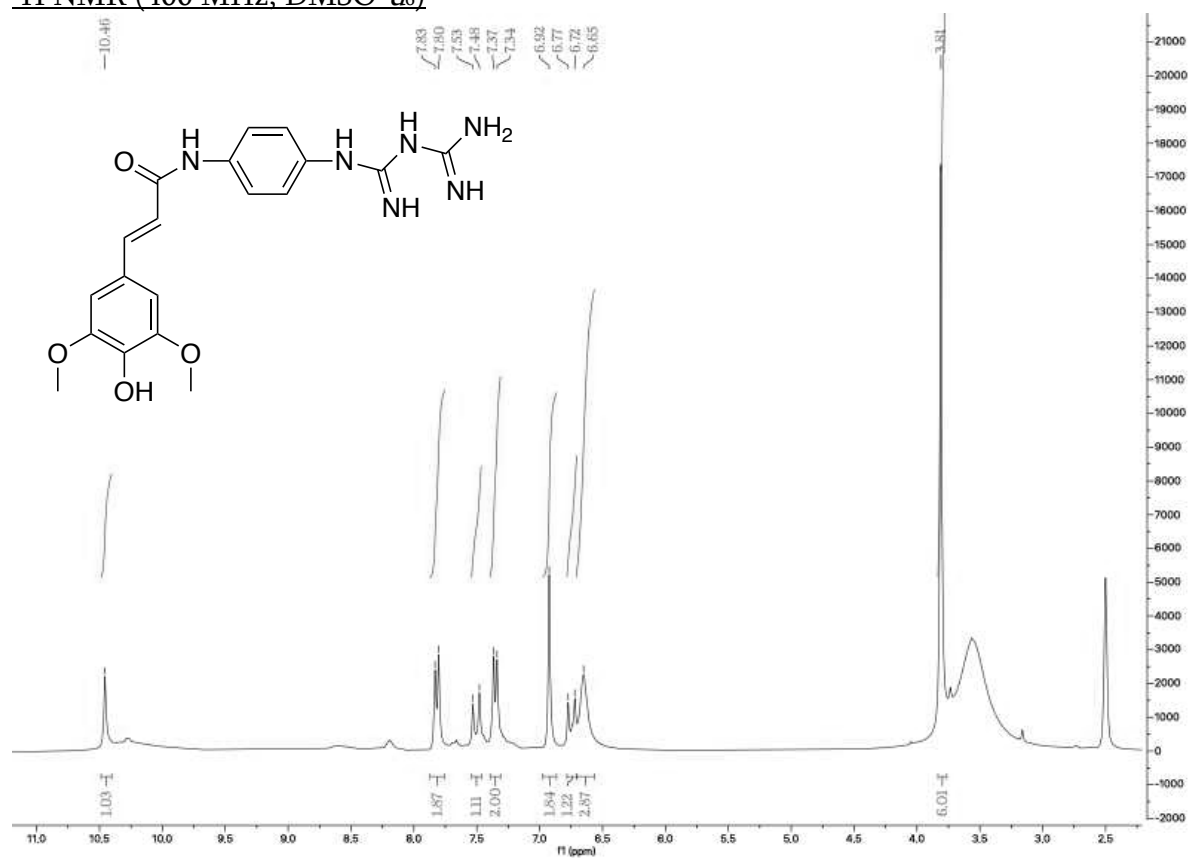


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

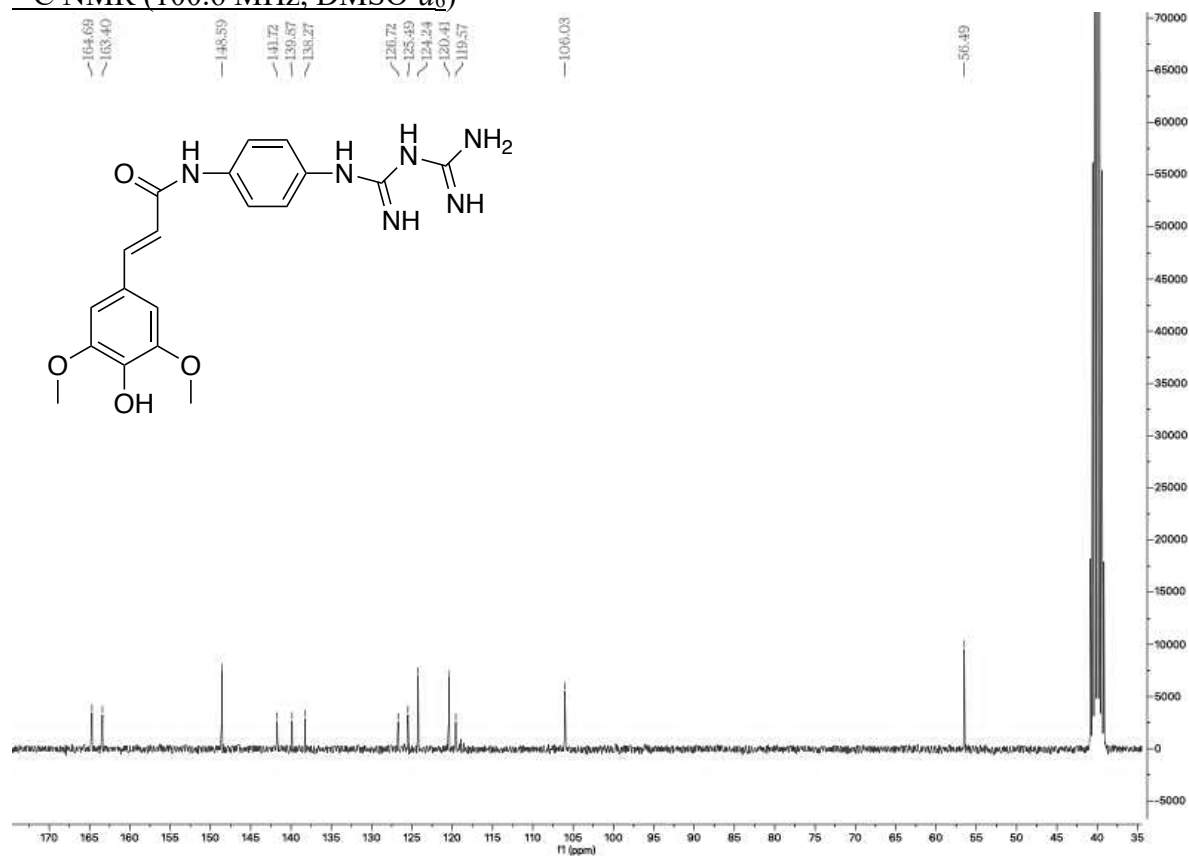


2.22. Spectra of **5g**

^1H NMR (400 MHz, DMSO- d_6)

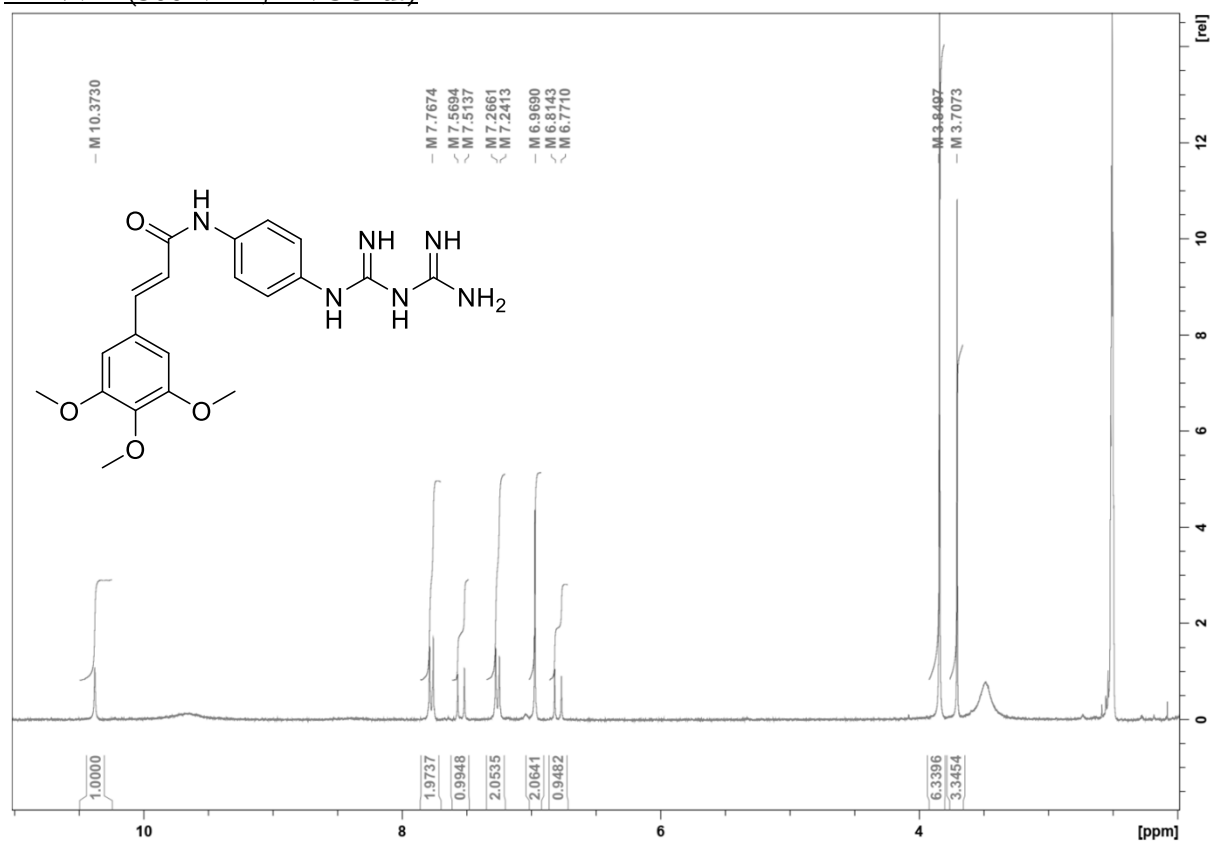


^{13}C NMR (100.6 MHz, DMSO- d_6)

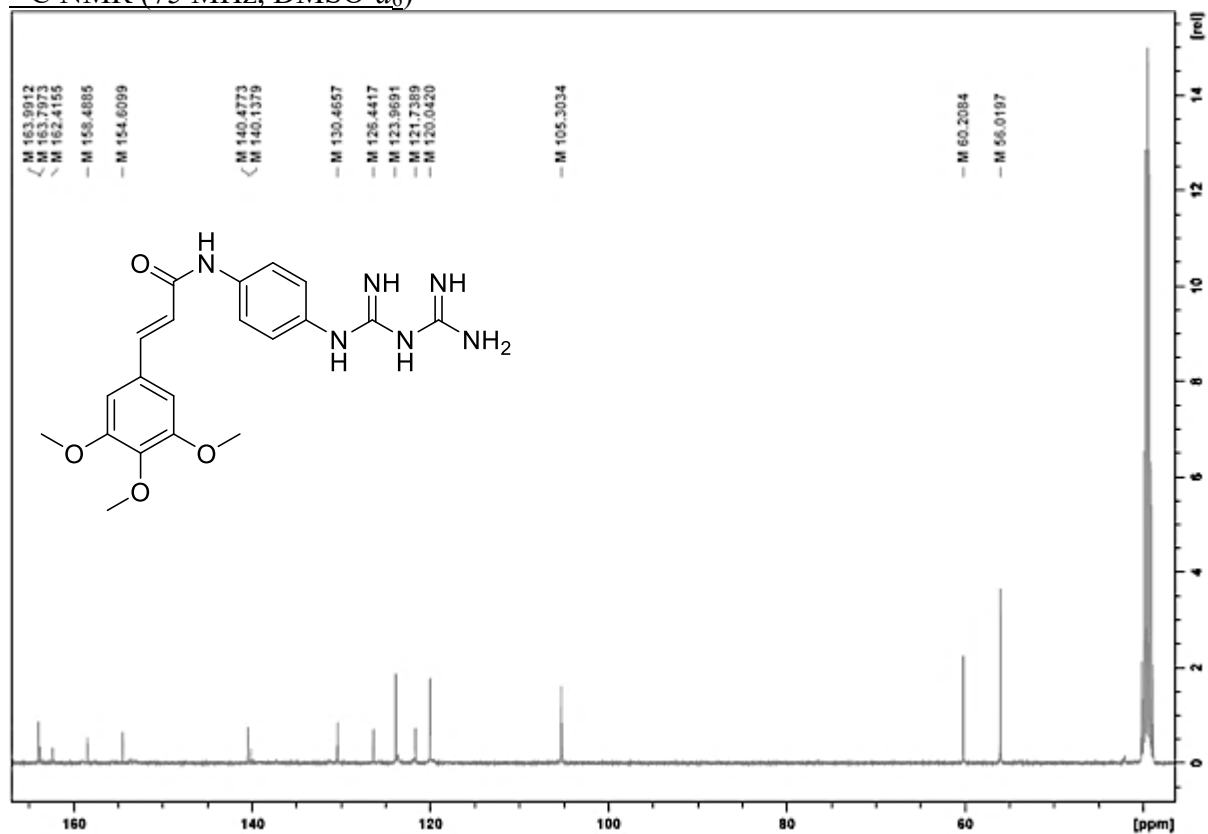


2.23. Spectra of **5h**

^1H NMR (300 MHz, DMSO- d_6)



^{13}C NMR (75 MHz, DMSO- d_6)



3. Procedure for the synthesis of compounds 6-7

3.1 2-(4-Isopropoxyphenyl)acetic acid (6)

Title compound was obtained by stirring a mixture in DMF (20 mL) of commercial 4-hydroxyphenylacetic acid (2.0 g, 13.2 mmol), K₂CO₃ (6.0 g, 43.4 mmol, 3.3 eq) and 2-bromopropane (5.7 mL, 60.5 mmol, 4.6 eq) for 16 h at 110 °C according to the procedure reported by Pasturel *et al.* [12]. After cooling the reaction mixture to room temperature water (20 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The gathered organic layers were dried over MgSO₄, filtered and concentrated to yield isopropyl 2-(4-isopropoxyphenyl)acetate as a colorless oil (6.2 g, quant). ¹H NMR (300 MHz, CDCl₃) δ 7.17 (d, 2H, *J* = 8.6 Hz, H-2), 6.83 (d, 2H, *J* = 8.6 Hz, H-3), 5.00 (sept, 1H, *J* = 6.4 Hz, CO₂CH(CH₃)₂), 4.51 (sept, 1H, *J* = 6.1 Hz, OCH(CH₃)₂), 3.50 (s, 2H, CH₂), 1.32 (d, 6H, *J* = 6.1 Hz, OCH(CH₃)₂), 1.22 (d, 6H, *J* = 6.2 Hz, CO₂CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 171.4 (C=O), 156.9 (C-4), 130.1 (C-2), 126.2 (C-1), 115.9 (C-3), 69.9 (OCH(CH₃)₂), 68.0 (CO₂CH(CH₃)₂), 40.8 (CH₂), 22.0 (OCH(CH₃)₂), 21.7 (CO₂CH(CH₃)₂). To perform saponification, the residue, dissolved in water:THF (1:1, v/v) (40 mL), was added NaOH (7.4 g, 185 mmol, 14 eq) and refluxed for 16 h. After gradual cooling of the mixture down to room temperature, then to 0 °C, concentrated HCl was added as to reach pH 1. Ethyl acetate (50 mL) was added and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The gathered organic layers were dried over MgSO₄, filtered and concentrated. The residue was crystallized in ethyl acetate:n-hexane (1:9, v/v; 20 mL) to give **8**. White crystals (1.31 g, 51%), mp 60 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.13 (d, 2H, *J* = 8.6 Hz, H-2), 6.82 (d, 2H, *J* = 8.6 Hz, H-3), 4.53 (sept, 1H, *J* = 6.1 Hz, CH(CH₃)₂), 3.45 (s, 2H, CH₂), 1.22 (d, 6H, *J* = 6.1 Hz, CH(CH₃)₂); ¹³C NMR (75 MHz, CDCl₃) δ 173.6 (C=O), 156.6 (C-4), 130.8 (C-2), 127.1 (C-1), 115.9 (C-3), 70.0 (CH(CH₃)₂), 40.3 (CH₂), 22.2 (CH(CH₃)₂). HRMS calc. for C₁₁H₁₅O₃⁺ [M+H]⁺ 193.0870, found 193.0868.

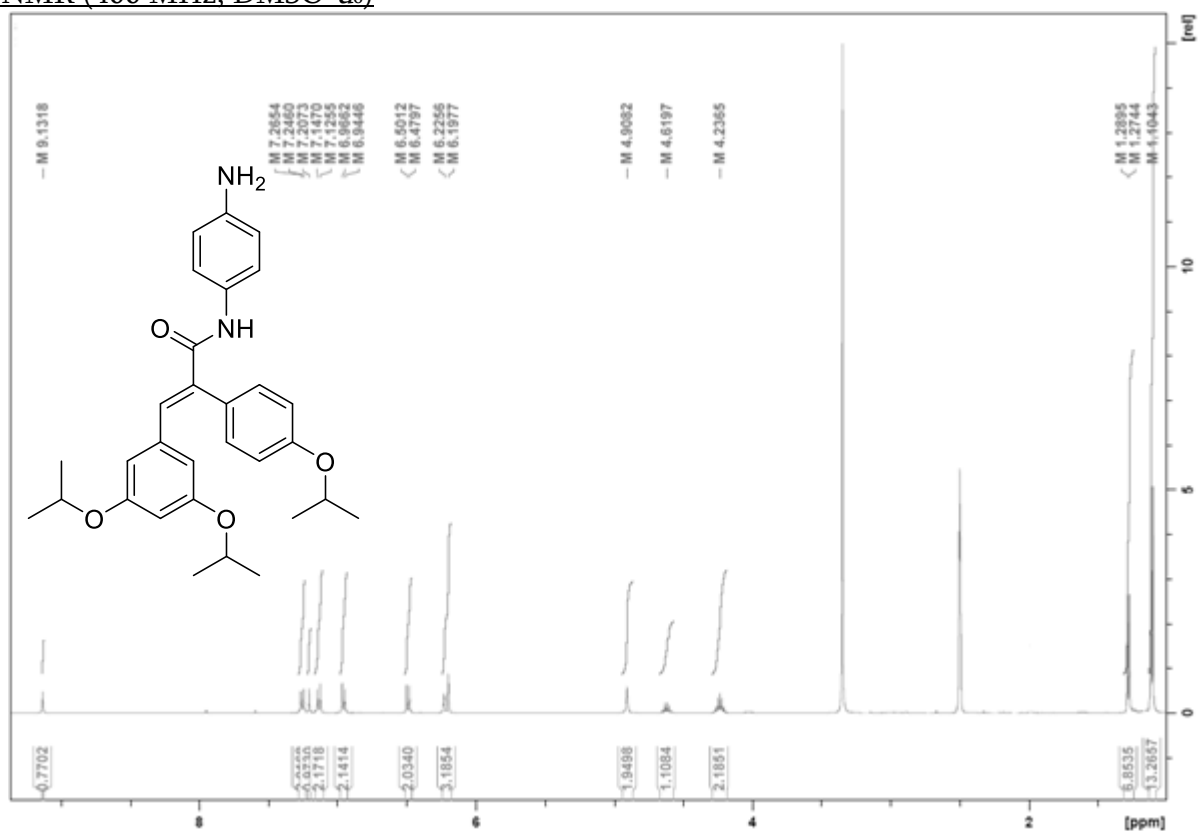
3.2 (*E*)-3-(3,5-Diisopropoxyphenyl)-2-(4-isopropoxyphenyl)acrylic acid (7)

Compounds **6** (500 mg, 2.58 mmol, 1 eq) and **1d** (572 mg, 2.58 mmol, 1 eq) were mixed under argon in a mixture of acetic anhydride (500 μL) and triethylamine (250 μL) in a sealed tube and stirred at 100 °C for 1 day [13]. The solution was allowed to cool to room temperature and diluted with ethyl acetate (10 mL). The organic layer was washed with water (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried over MgSO₄, filtered and concentrated and the residue was dissolved in acetic acid (10 mL). The solution was poured over a mixture of water and ice (20 g / 20g) and the precipitate was filtered off to yield a yellow powder (700 mg, 68%), mp 166 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.7 (bs, 1H, CO₂H), 7.61 (s, 1H, =CH_{vinyl}), 7.06 (d, 2H, *J* = 6.9 Hz, H_{ortho} monosubstituted), 6.93 (d, 2H, *J* = 6.9 Hz, H_{meta} monosubstituted), 6.26 (m, 1H, H_{para} disubstituted), 6.23 (m, 2H, H_{ortho} disubstituted); 4.61 (sept, 1H, *J* = 6.0 Hz, CH(CH₃)₂), 4.22 (sept, 2H, *J* = 6.0 Hz, 2 × CH(CH₃)₂), 1.28 (d, 6H, 1H, *J* = 5.90 Hz, CH(CH₃)₂), 1.10 (d, 12H, *J* = 6.1 Hz, 2 × CH(CH₃)₂); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 169.0 (C=O), 158.6 (C_{meta} disubstituted), 157.4 (C_{para} monosubstituted), 139.4 (CH=C), 136.8 (C_{ipso} disubstituted), 133.6 (C=CH), 131.1 (C_{ortho} monosubstituted), 128.7 (C_{ipso} monosubstituted), 115.9 (C_{meta} monosubstituted), 109.7 (C_{ortho} disubstituted), 105.2 (C_{para} disubstituted), 69.6 (CH(CH₃)₂), 69.5 (CH(CH₃)₂), 22.3 (CH(CH₃)₂), 22.2 (CH(CH₃)₂). HRMS calc. for C₂₄H₂₉O₅⁻ [M-H]⁻ 397.1993, found 397.1995.

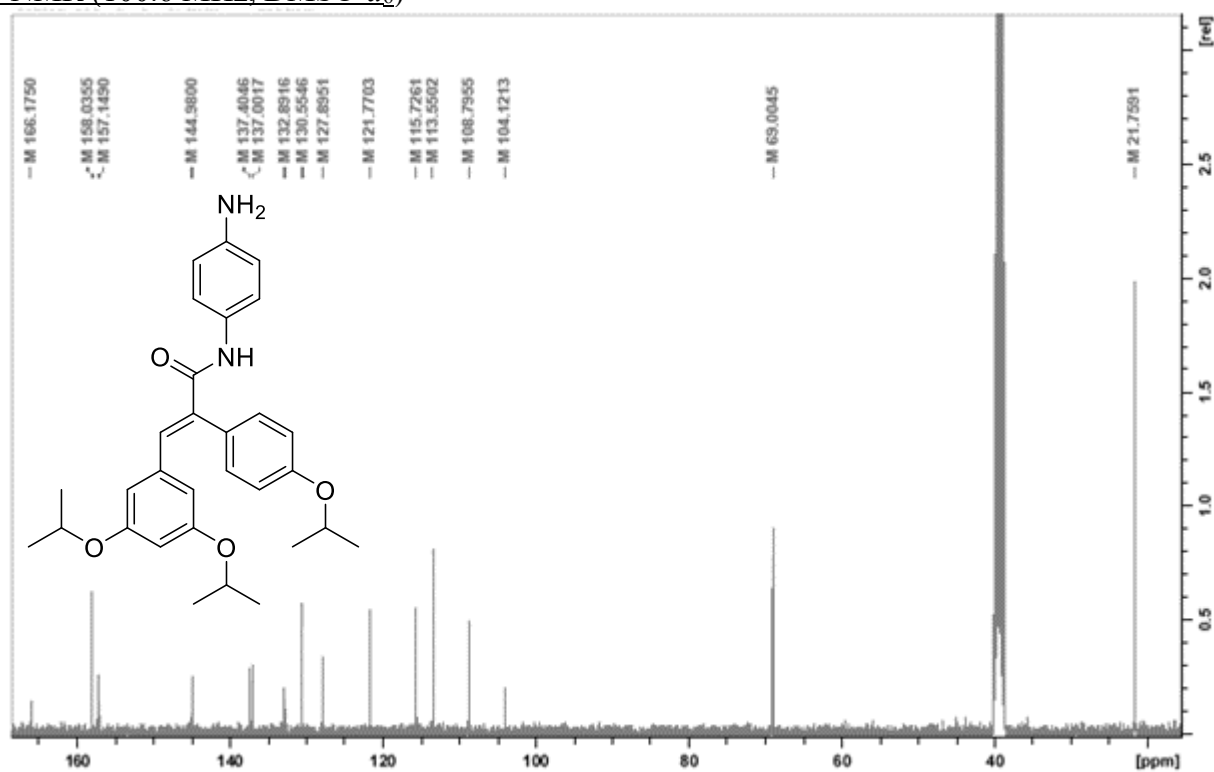
4. NMR spectra (^1H and ^{13}C) of metformin-resveratrol hybrids

4.1 Spectra of **8**

^1H NMR (400 MHz, $\text{DMSO}-d_6$)

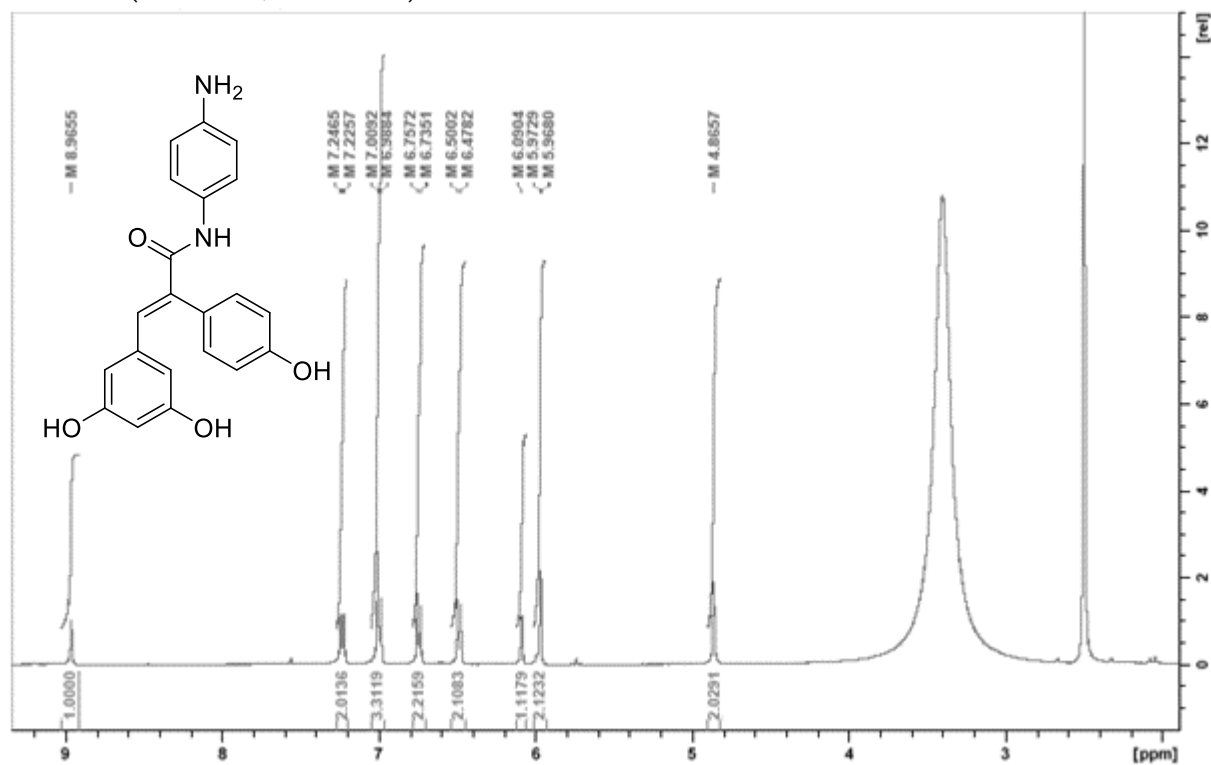


^{13}C NMR (100.6 MHz, $\text{DMSO}-d_6$)

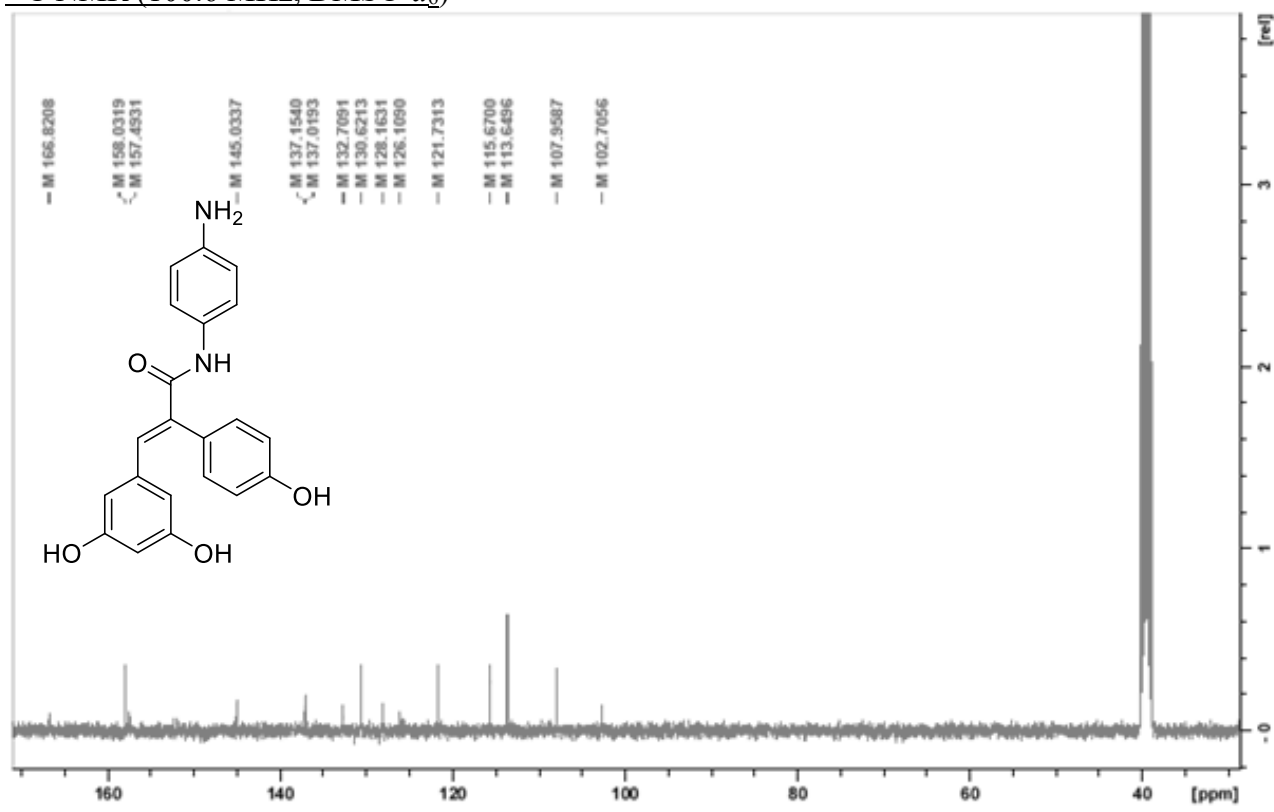


4.2 Spectra of **9**

^1H NMR (400 MHz, $\text{DMSO-}d_6$)

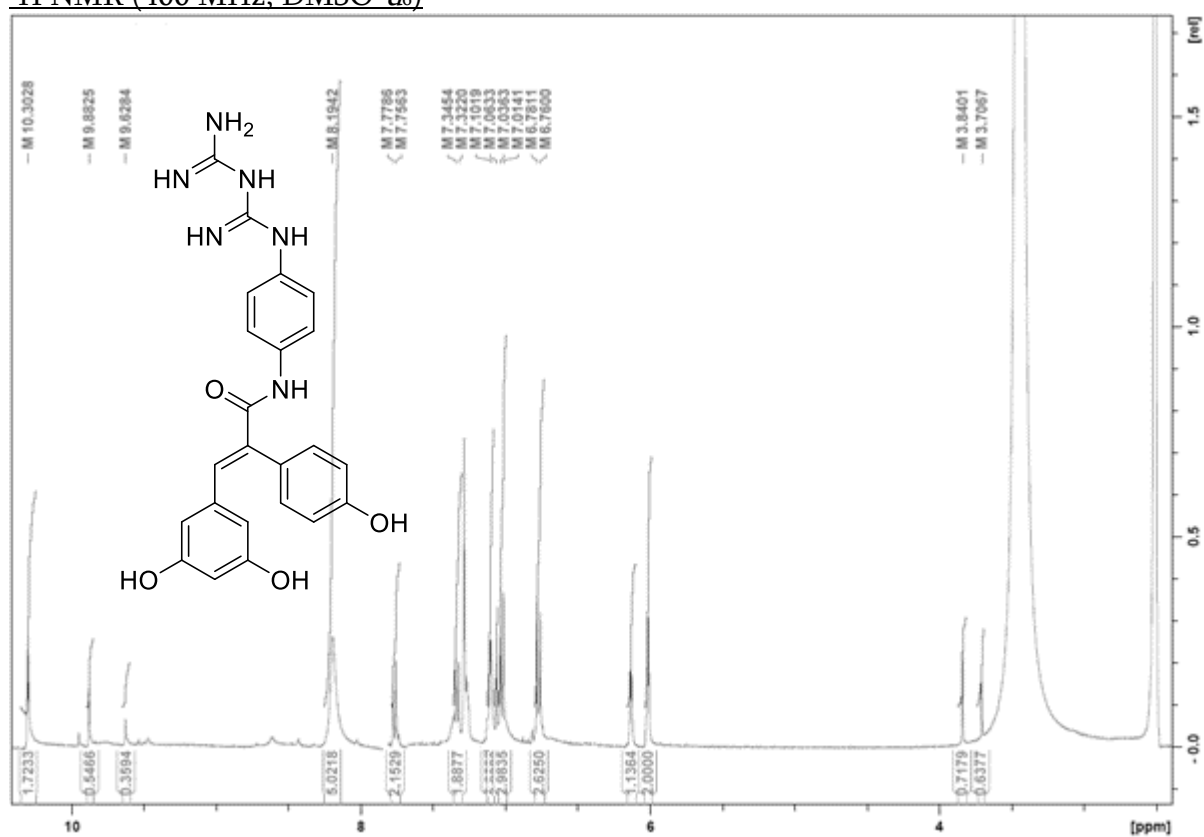


^{13}C NMR (100.6 MHz, $\text{DMSO-}d_6$)

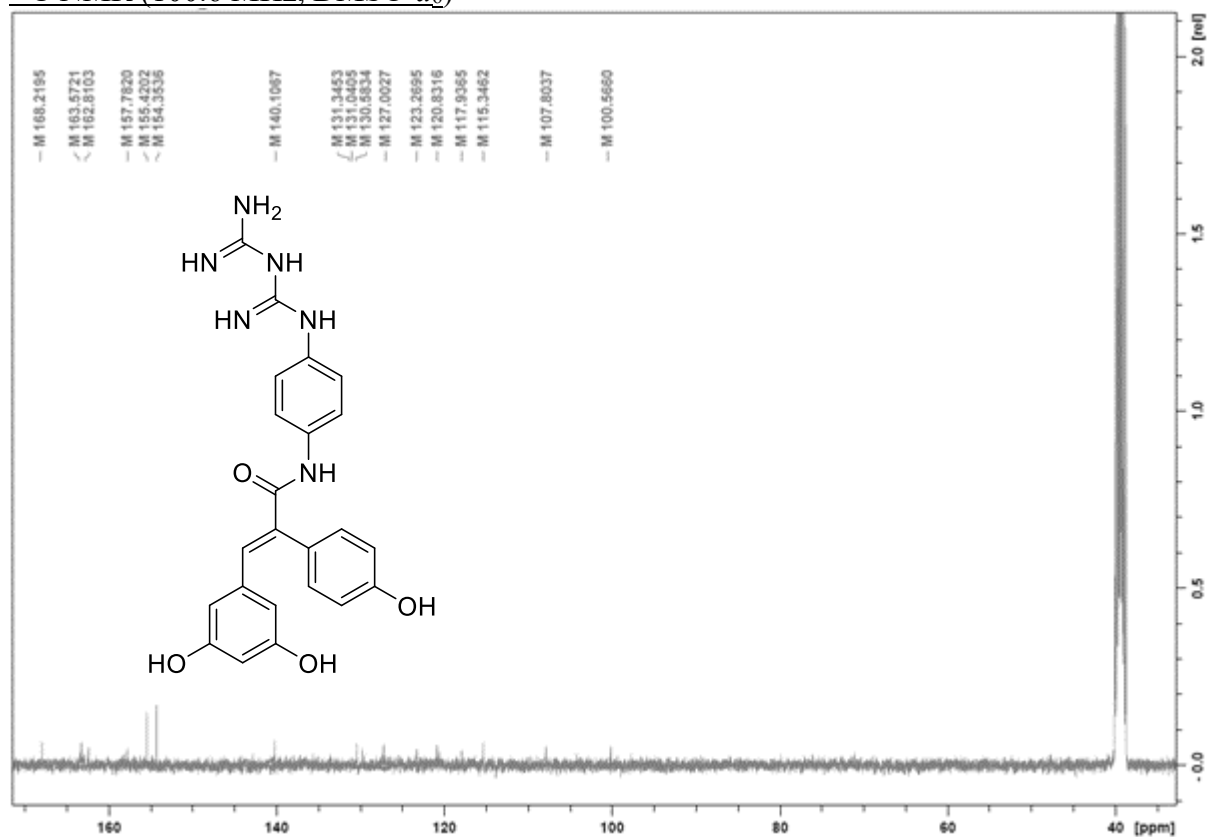


4.3 Spectra of **10**

¹H NMR (400 MHz, DMSO-*d*₆)



¹³C NMR (100.6 MHz, DMSO-*d*₆)



5. Calculated AlogP values for metformin, phenolic acids and hybrid derivatives (**Table S1**)

Compound	AlogP ^b
5a	1.64
5b	1.66
5c	1.66
5d	1.32
5e	1.34
5f	1.77
5g	1.90
5h	2.07
10	3.12
metformin	-1.41
caffeic acid	1.67
ferulic acid	1.58
sinapic acid	1.63
salicylic acid	1.96
gallic acid	1.17

Table S1. Predicted lipophilicity (AlogP) values of metformin, phenolic acids, and hybrid compounds (**5a-5h, 10**) were determined using the Virtual Computational Chemistry Laboratory software at ALOGPS 2.1 homepage available online at www.vcclab.org/lab/alogps/ (accessed on November 3rd 2025).

6. Impact of a 4 h treatment with metformin, **5a** or **5h** on serine threonine kinase (STK) and tyrosine kinase (PTK) activity as compared to control (DMSO 0.01%) using kinomic Pamgene assay.

6.1 List of kinases significantly inhibited or activated by metformin in GBM9 and U87 cells (**Table S2**)

Table S2 summarizes the kinases identified as significantly modulated following treatment with metformin, based on PamGene kinase activity profiling. Kinase activity (setStat) and specificity (pSpecificityScore) values were derived from the BioNavigator analysis pipeline. Kinases with pSpecificityScore < 0.05 were considered significantly altered. Positive setStat values indicate kinase activation, while negative values correspond to inhibition. Data are presented separately for U87 differentiated cells and GBM9 stem-like cells, highlighting distinct signaling reprogramming patterns induced by metformin.

Kinases inhibited by Metformin in U87											
kinase Name	Normalized.K inase.Stat	specificit yScore	sensitivit yScore	setStat	Peptide s.in.Set	pSpecificityS core	pSensitivi tyScore	finalScore	Ce ll	ty pe	gene
ANPa (NPR1)	- 0.064971016 5101066	0.918	NA	- 0.584739148 59096	9	0.037157318 7987575	NA	0.037157318 7987575	U8 7	S T K	ANPNPR 1
CDK2	- 0.032982346 7483218	0.97	NA	- 0.527717547 973149	16	0.013228265 7337552	NA	0.013228265 7337552	U8 7	S T K	CDK2
ERK1	- 0.026023938	1	NA	- 0.546502715	21	8.694587126 28891e-05	NA	0	U8 7	S T	ERK1

	8564106			984622						K	
ERK2 (MAPK 1)	- 0.0204537454465023	0.996	NA	- 0.409074908930047	20	0.00174066157630127	NA	0.00174066157630127	U87	STK	ERK2MA PK1
ERK5 (MAPK 7)	- 0.0409361574093059	0.978	NA	- 0.6959146759582	17	0.00966114521239857	NA	0.00966114521239857	U87	STK	ERK5MA PK7
IKKb (IKBKI NASE)	- 0.00336248535242434	0.996	NA	- 0.00672497070484868	2	0.00174066157630127	NA	0.00174066157630127	U87	STK	IKKIKBKI NASE
MAK	- 0.0101577830140023	0.988	NA	- 0.060946698084014	6	0.00524305541237188	NA	0.00524305541237188	U87	STK	MAK
ZC4	- 0.00434827358572437	0.99	NA	- 0.00869654717144874	2	0.00436480540245009	NA	0.00436480540245009	U87	STK	ZC4
Kinases activated by Metformin in U87											
kinase Name	Normalized.K inase.Stat	specificityScore	sensitivityScore	setStat	Peptide s.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
ALK	5.62331101596251	0.892	NA	61.8564211755876	11	0.0496351456238769	NA	0.0496351456238769	U87	PTK	ALK
FLT1	3.20579297846675	0.916	NA	6.41158595693351	2	0.0381045263321496	NA	0.0381045263321496	U87	PTK	FLT1
LTK	4.84585748201164	0.926	NA	33.9210023740815	7	0.0333890133180656	NA	0.0333890133180656	U87	PTK	LTK
MER (MERT K)	5.42576124943797	0.906	NA	59.6833737438177	11	0.0428718023231869	NA	0.0428718023231869	U87	PTK	MERMERTK
PYK2 (PTK2 B)	5.53780077377327	0.898	NA	55.3780077377327	10	0.0467236633326956	NA	0.0467236633326956	U87	PTK	PYK2PTK 2B
TRKA (NTRK 1)	3.15809239900877	0.944	NA	9.4742771970263	3	0.025028005701931	NA	0.025028005701931	U87	PTK	TRKANTR K1
TRKB (NTRK 2)	3.02420911990388	0.998	NA	12.0968364796155	4	0.000869458712628891	NA	0.000869458712628891	U87	PTK	TRKBNT RK2
TRKC (NTRK 3)	3.34312975103838	0.97	NA	13.3725190041535	4	0.0132282657337552	NA	0.0132282657337552	U87	PTK	TRKCNT RK3
CDK6	0.0515209048325717	0.906	NA	0.154562714497715	3	0.0428718023231869	NA	0.0428718023231869	U87	STK	CDK6
ERK7 (BI916 334)	0.0390653710368892	0.934	NA	0.156261484147557	4	0.0296531237699066	NA	0.0296531237699066	U87	STK	ERK7BI9 16334
ICK	0.0176503310857877	0.972	NA	0.0706013243431508	4	0.0123337350737254	NA	0.0123337350737254	U87	STK	ICK
JNK1 (MAPK 8)	0.126956311266079	0.926	NA	2.4121699140555	19	0.0333890133180656	NA	0.0333890133180656	U87	STK	JNK1MA PK8
JNK2 (MAPK 9)	0.0215011518752431	0.992	NA	0.322517278128647	15	0.00348832784582135	NA	0.00348832784582135	U87	STK	JNK2MA PK9
JNK3	0.126956311	0.926	NA	2.412169914	19	0.033389013	NA	0.033389013	U8	S	JNK3MA

(MAPK 10)	266079			0555		3180656		3180656	7	T K	PK10
p38a MAPK (MAPK 14)	0.113847721 961469	0.894	NA	1.821563551 38351	16	0.048662481 2040823	NA	0.048662481 2040823	U8 7	S T K	38MAPK MAPK14
p38b MAPK (MAPK 11)	0.012970542 5251843	0.998	NA	0.181587595 352581	14	0.000869458 712628891	NA	0.000869458 712628891	U8 7	S T K	38MAPK MAPK11
p38d MAPK (MAPK 13)	0.124958438 282519	0.928	NA	2.499168765 65039	20	0.032452023 7811379	NA	0.032452023 7811379	U8 7	S T K	38MAPK MAPK13
Kinases inhibited by Metformin in GBM											
kinase Name	Normalized.K inase.Stat	specificit yScore	sensitivit yScore	setStat	Peptide s.in.Set	pSpecificityS core	pSensitivi tyScore	finalScore	Ce ll	ty p e	gene
CHED (CDC2 L5)	- 0.021332133 3003678	0.94	NA	- 0.042664266 6007356	2	0.026872146 4003014	NA	0.026872146 4003014	G B M	S T K	CHEDCD C2L5
ERK7 (BI916 334)	- 0.021332133 3003678	0.94	NA	- 0.042664266 6007356	2	0.026872146 4003014	NA	0.026872146 4003014	G B M	S T K	ERK7BI9 16334
Kinases activated by Metformin in GBM											
kinase Name	Normalized.K inase.Stat	specificit yScore	sensitivit yScore	setStat	Peptide s.in.Set	pSpecificityS core	pSensitivi tyScore	finalScore	Ce ll	ty p e	gene
CTK (MATK)	0.130896244 730268	0.928	NA	1.832547426 22375	14	0.032452023 7811379	NA	0.032452023 7811379	G B M	P T K	CTKMAT K
FGR	0.102883428 33519	0.944	NA	0.823067426 681519	8	0.025028005 701931	NA	0.025028005 701931	G B M	P T K	FGR
FRK	0.138513072 331746	0.962	NA	2.770261446 63493	20	0.016824927 9621871	NA	0.016824927 9621871	G B M	P T K	FRK
HCK	0.106472253 799438	0.994	NA	1.597083806 99158	15	0.002613615 60268669	NA	0.002613615 60268669	G B M	P T K	HCK
LYN	0.099861477 3605809	0.976	NA	1.098476250 96639	11	0.010550182 3333082	NA	0.010550182 3333082	G B M	P T K	LYN
SRC	0.117420679 046994	0.964	NA	1.643889506 65792	14	0.015922966 0971692	NA	0.015922966 0971692	G B M	P T K	SRC
YES1	0.124935969 328269	0.93	NA	1.624167601 2675	13	0.031517051 4460649	NA	0.031517051 4460649	G B M	P T K	YES1
ANPa (NPR1)	0.041005021 5780064	0.916	NA	0.287035151 046045	7	0.038104526 3321496	NA	0.038104526 3321496	G B M	S T K	ANPNPR 1
ATR	0.003004046 56843248	0.996	NA	0.009012139 70529744	3	0.001740661 57630127	NA	0.001740661 57630127	G B M	S T K	ATR
RAF1	0.016853701 3839605	0.964	NA	0.033707402 767921	2	0.015922966 0971692	NA	0.015922966 0971692	G B M	S T K	RAF1

6.2 List of kinases significantly inhibited or activated by **5a** in GBM9 and U87 cells (Table S3)

Table S3 summarizes the kinases identified as significantly modulated following treatment with compound **5a**, based on PamGene kinase activity profiling. Kinase activity (setStat) and specificity (pSpecificityScore) values were derived from the BioNavigator analysis pipeline. Kinases with pSpecificityScore < 0.05 were considered significantly altered. Positive setStat values indicate kinase activation, while negative values correspond to inhibition. Data are presented separately for U87 differentiated cells and GBM9 stem-like cells, highlighting distinct signaling reprogramming patterns induced by **5a**.

Kinases inhibited by 5a in U87											
kinaseName	Normalized. Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptide s.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
FLT1	-3.2705279291147	0.934	NA	-6.54105585822939	2	0.0296531237699066	NA	0.0296531237699066	U87	PTK	FLT1
LTK	-4.46528951342754	0.922	NA	-31.2570265939928	7	0.0352690789463706	NA	0.0352690789463706	U87	PTK	LTK
RON	-2.50336034248613	0.964	NA	-2.50336034248613	1	0.0159229660971692	NA	0.0159229660971692	U87	PTK	RON
TRKA (NTRK1)	-3.34168451185104	0.97	NA	-10.0250535355531	3	0.0132282657337552	NA	0.0132282657337552	U87	PTK	TRKANTRK1
TRKB (NTRK2)	-3.30687842854596	0.992	NA	-13.2275137141838	4	0.00348832784582135	NA	0.00348832784582135	U87	PTK	TRKBNTRK2
TRKC (NTRK3)	-3.59853668569017	0.978	NA	-14.3941467427607	4	0.00966114521239857	NA	0.00966114521239857	U87	PTK	TRKCNTRK3
ANPb (NPR2)	-0.0326199060755653	0.986	NA	-0.0326199060755653	1	0.0061230850587888	NA	0.0061230850587888	U87	STK	ANPNPR2
CDK2	-0.0972268471369751	0.976	NA	-1.26394901278068	13	0.0105501823333082	NA	0.0105501823333082	U87	STK	CDK2
CDK7	-0.0430591381252201	0.97	NA	-0.258354828751321	6	0.0132282657337552	NA	0.0132282657337552	U87	STK	CDK7
CDKL4 (AA626859)	-0.0865356248286718	0.942	NA	-0.778820623458046	9	0.0259490972071227	NA	0.0259490972071227	U87	STK	CDKL4AA626859
CDKL5 (STK9)	-0.0844812136170159	0.96	NA	-0.675849708936128	8	0.0177287669604316	NA	0.0177287669604316	U87	STK	CDKL5STK9
DAPK2	-0.0326199060755653	0.986	NA	-0.0326199060755653	1	0.0061230850587888	NA	0.0061230850587888	U87	STK	DAPK2
ERK1	-0.0821866207755805	0.99	NA	-1.31498593240929	16	0.00436480540245009	NA	0.00436480540245009	U87	STK	ERK1
ERK2 (MAPK1)	-0.0854910684222482	0.992	NA	-1.28236602633372	15	0.00348832784582135	NA	0.00348832784582135	U87	STK	ERK2MAPK1
IKKE	-	0.986	NA	-	1	0.006123085	NA	0.006123085	U87	S	IKKE

	0.032619906 0755653			0.032619906 0755653		0587888		0587888	7	T K	
JNK1 (MAPK8)	- 0.135260562 305085	0.98	NA	- 2.164168996 88136	16	0.008773924 30750515	NA	0.008773924 30750515	U8 7	S T K	JNK1MAP K8
JNK2 (MAPK9)	- 0.062100080 1547809	0.99	NA	- 0.745200961 85737	12	0.004364805 40245009	NA	0.004364805 40245009	U8 7	S T K	JNK2MAP K9
JNK3 (MAPK10)	- 0.135260562 305085	0.98	NA	- 2.164168996 88136	16	0.008773924 30750515	NA	0.008773924 30750515	U8 7	S T K	JNK3MAP K10
PIM2	- 0.191245027 974222	0.97	NA	- 3.059920447 58756	16	0.013228265 7337552	NA	0.013228265 7337552	U8 7	S T K	PIM2
RAF1	- 0.052335455 8900755	0.936	NA	- 0.104670911 780151	2	0.028724151 2618947	NA	0.028724151 2618947	U8 7	S T K	RAF1
TBK1	- 0.032619906 0755653	0.986	NA	- 0.032619906 0755653	1	0.006123085 0587888	NA	0.006123085 0587888	U8 7	S T K	TBK1
p38a MAPK (MAPK14)	- 0.052527436 5859052	0.988	NA	- 0.682856675 616768	13	0.005243055 41237188	NA	0.005243055 41237188	U8 7	S T K	38MAPK MAPK14
p38d MAPK (MAPK13)	- 0.114955641 012914	0.984	NA	- 1.839290256 20662	16	0.007004901 56865849	NA	0.007004901 56865849	U8 7	S T K	38MAPK MAPK13
p38g MAPK (MAPK12)	- 0.079810060 2679163	0.982	NA	- 0.957720723 214995	12	0.007888512 21305034	NA	0.007888512 21305034	U8 7	S T K	38MAPK MAPK12
Kinases activated by 5a in U87											
kinaseName	Normalized. Kinase.Stat	specificit yScore	sensitivit yScore	setStat	Peptide s.in.Set	pSpecificityS core	pSensitivi tyScore	finalScore	Ce ll	ty p e	gene
ADCK3 (LOC569 97)	0.085108842 3220755	0.928	NA	0.425544211 610377	5	0.032452023 7811379	NA	0.032452023 7811379	U8 7	S T K	ADCK3LO C56997
ANPa (NPR1)	0.043576870 1132563	0.982	NA	0.435768701 132563	10	0.007888512 21305034	NA	0.007888512 21305034	U8 7	S T K	ANPNPR1
CDK1 (CDC2)	0.116499595 394615	0.948	NA	1.164995953 94615	10	0.023191662 6619338	NA	0.023191662 6619338	U8 7	S T K	CDK1CD C2
CDK3	0.144395744 781907	0.892	NA	0.866374468 691441	6	0.049635145 6238769	NA	0.049635145 6238769	U8 7	S T K	CDK3
ERK5 (MAPK7)	0.020300386 2590553	0.996	NA	0.284205407 626774	14	0.001740661 57630127	NA	0.001740661 57630127	U8 7	S T K	ERK5MAP K7
ERK7 (BI91633 4)	0.027834761 1096422	0.966	NA	0.111339044 438569	4	0.015022873 5845067	NA	0.015022873 5845067	U8 7	S T K	ERK7BI91 6334
ICK	0.084996270 4041364	0.92	NA	0.254988811 212409	3	0.036212172 6544447	NA	0.036212172 6544447	U8 7	S T K	ICK
MAK	0.027922377 5141202	0.976	NA	0.111689510 056481	4	0.010550182 3333082	NA	0.010550182 3333082	U8 7	S T K	MAK
SCYL2	0.037427941	0.964	NA	0.037427941	1	0.015922966	NA	0.015922966	U8	S	SCYL2FL

(FLJ10074)	8190364			8190364		0971692		0971692	7	T K	J10074
p38b MAPK (MAPK11)	0.083702804 1956148	0.978	NA	0.920730846 151763	11	0.009661145 21239857	NA	0.009661145 21239857	U8 7	S T K	38MAPK MAPK11
Kinases inhibited by 5a in GBM											
kinaseName	Normalized. Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptide s.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
FLT3	- 0.496351040 065407	0.9	NA	- 2.481755200 32703	5	0.045757490 5606751	NA	0.045757490 5606751	G B M	P T K	FLT3
JAK1_d2	- 0.396522424 72279	0.978	NA	- 0.396522424 72279	1	0.009661145 21239857	NA	0.009661145 21239857	G B M	P T K	JAK12
JAK2	- 0.459989070 729029	0.932	NA	- 0.919978141 458058	2	0.030584087 6460186	NA	0.030584087 6460186	G B M	P T K	JAK2
ROR1	- 0.396522424 72279	0.978	NA	- 0.396522424 72279	1	0.009661145 21239857	NA	0.009661145 21239857	G B M	P T K	ROR1
ROR2	- 0.396522424 72279	0.978	NA	- 0.396522424 72279	1	0.009661145 21239857	NA	0.009661145 21239857	G B M	P T K	ROR2
SRM (SRMS)	- 0.509678457 647769	0.952	NA	- 6.116141491 77323	12	0.021363051 6155257	NA	0.021363051 6155257	G B M	P T K	SRMSRM S
MAPKAP K3	- 0.087571440 1259882	0.92	NA	- 1.488714482 1418	17	0.036212172 6544447	NA	0.036212172 6544447	G B M	S T K	MAPKAP K3
PKACa (PRKAC A)	- 0.102269334 973334	0.976	NA	- 2.761272044 28003	27	0.010550182 3333082	NA	0.010550182 3333082	G B M	S T K	PKACPRK ACA
PKACb PRKACB	- 0.111905025 150604	0.91	NA	- 2.797625628 76509	25	0.040958607 6789064	NA	0.040958607 6789064	G B M	S T K	PKACPRK ACB
RSK4 (RPS6KA 6)	- 0.092679566 8276001	0.902	NA	- 1.482873069 2416	16	0.044793462 4580583	NA	0.044793462 4580583	G B M	S T K	RSK4RPS 6KA6
mTOR/F RAP	- 0.022980753 4028989	0.936	NA	- 0.068942260 2086966	3	0.028724151 2618947	NA	0.028724151 2618947	G B M	S T K	TORFRAP
Kinases activated by 5a in GBM											
kinaseName	Normalized. Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptide s.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
CK1a1 (CSNK1A 1)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	CK11CSN K1A1
CK2a1 (CSNK2A 1)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	CK21CSN K2A1
CK2a2 (CSNK2A 2)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	CK22CSN K2A2
CLK3	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	CLK3
GPRK4	0.004907671	1	NA	0.004907671	1	0.000174066	NA	0	G	S	GPRK4GP

(GPRK2L)	20435498			20435498		157630127			B M	T K	RK2L
HSER (GUCY2C)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	HSENGU CY2C
IKKa (CHUK)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	IKKCHUK
NEK10	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	NEK10
Nuak2 (DKFZP4 34J037)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	N2DKFZP 434J037
PCTAIRE 1 (PCTK1)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	PCTAIRE1 PCTK1
PCTAIRE 2 (PCTK2)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	PCTAIRE2 PCTK2
PCTAIRE 3	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	PCTAIRE3
PFTAIRE 1 (PFTK1)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	PFTAIRE1 PFTK1
PINK1	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	PINK1
SPEG (KIAA129 7)	0.004907671 20435498	1	NA	0.004907671 20435498	1	0.000174066 157630127	NA	0	G B M	S T K	SPEGKIA A1297

6.3 List of kinases significantly inhibited or activated by **5h** in GBM9 and U87 cells (**Table S4**)

Table S4 summarizes the kinases identified as significantly modulated following treatment with compound **5h**, based on PamGene kinase activity profiling. Kinase activity (setStat) and specificity (pSpecificityScore) values were derived from the BioNavigator analysis pipeline. Kinases with pSpecificityScore < 0.05 were considered significantly altered. Positive setStat values indicate kinase activation, while negative values correspond to inhibition. Data are presented separately for U87 differentiated cells and GBM9 stem-like cells, highlighting distinct signaling reprogramming patterns induced by **5h**.

Kinases inhibited by 5h in U87											
kinaseName	Normalized.Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptide s.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
ERBB2	-3.9156835270675	0.942	NA	-19.5784176353375	5	0.0259490972071227	NA	0.0259490972071227	U87	PTK	ERBB2
FER	-3.22246122761871	0.9	NA	-6.44492245523742	2	0.0457574905606751	NA	0.0457574905606751	U87	PTK	FER
MER (MERTK)	-4.15106174783928	0.984	NA	-41.5106174783928	10	0.00700490156865849	NA	0.00700490156865849	U87	PTK	MERMERTK
RON	-1.91123936581053	1	NA	-1.91123936581053	1	0.000174066157630127	NA	0	U87	PTK	RON
TRKA (NTRK1)	-3.19788565596013	0.96	NA	-9.59365696788039	3	0.0177287669604316	NA	0.0177287669604316	U87	PTK	TRKANTRK1
TRKB (NTRK2)	-3.2010453223583	0.98	NA	-12.8041812894332	4	0.00877392430750515	NA	0.00877392430750515	U87	PTK	TRKBNTRK2
TRKC (NTRK3)	-3.24699419075924	0.972	NA	-12.987976763037	4	0.0123337350737254	NA	0.0123337350737254	U87	PTK	TRKCNTRK3
ADCK3 (LOC56997)	-0.197714045621856	0.988	NA	-1.58171236497485	8	0.00524305541237188	NA	0.00524305541237188	U87	STK	ADCK3LOC56997
CDK1 (CDC2)	-0.363546633471559	0.98	NA	-4.72610623513027	13	0.00877392430750515	NA	0.00877392430750515	U87	STK	CDK1CDC2
CDK2	-0.505467359777815	0.958	NA	-8.59294511622286	17	0.0186344909214556	NA	0.0186344909214556	U87	STK	CDK2
CDK7	-0.367807438011474	0.92	NA	-2.57465206608032	7	0.0362121726544447	NA	0.0362121726544447	U87	STK	CDK7
CDKL5 (STK9)	-0.392686161233142	0.922	NA	-3.53417545109828	9	0.0352690789463706	NA	0.0352690789463706	U87	STK	CDKL5STK9
DYRK1A	-0.147494285528632	0.904	NA	-0.294988571057264	2	0.0438315695246367	NA	0.0438315695246367	U87	STK	DYRK1A
ERK5 (MAPK7)	-0.511897836811069	0.954	NA	-9.21416106259925	18	0.0204516252959049	NA	0.0204516252959049	U87	STK	ERK5MAPK7
ERK7	-	0.916	NA	-	5	0.038104526	NA	0.038104526	U87	S	ERK7BI91

(BI916334)	0.32418763281176			1.6209381640588		3321496		63321496	7	T K	6334
ICK	-0.215752930890892	0.926	NA	-0.863011723563567	4	0.0333890133180656	NA	0.0333890133180656	U87	S T K	ICK
IKKb (IKBKIN ASE)	-0.0389367981234278	0.966	NA	-0.0778735962468556	2	0.0150228735845067	NA	0.0150228735845067	U87	S T K	IKKIKBKIN ASE
PDK1 (PDPK1)	-0.0129499125567217	0.99	NA	-0.0258998251134434	2	0.00436480540245009	NA	0.00436480540245009	U87	S T K	PDK1PDPK1
PRKY	-0.241255912169447	0.948	NA	-1.68879138518613	7	0.0231916626619338	NA	0.0231916626619338	U87	S T K	PRKY
mTOR/FRAP	-0.474120309381999	0.902	NA	-4.74120309381999	10	0.0447934624580583	NA	0.0447934624580583	U87	S T K	TORFRAP
Kinases activated by 5h in U87											
kinaseName	Normalized. Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptides.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
ANPa (NPR1)	0.179772047854754	0.996	NA	1.61794843069279	9	0.00174066157630127	NA	0.00174066157630127	U87	S T K	ANPNPR1
RSKL2	0.0243858324842931	0.99	NA	0.0731574974528794	3	0.00436480540245009	NA	0.00436480540245009	U87	S T K	RSKL2
TAO1	0.152720118727865	0.948	NA	0.152720118727865	1	0.0231916626619338	NA	0.0231916626619338	U87	S T K	TAO1
TAO2 (PSK)	0.152720118727865	0.948	NA	0.152720118727865	1	0.0231916626619338	NA	0.0231916626619338	U87	S T K	TAO2PSK
TAO3 (JIK)	0.152720118727865	0.948	NA	0.152720118727865	1	0.0231916626619338	NA	0.0231916626619338	U87	S T K	TAO3JIK
Kinases inhibited by 5h in GBM											
kinaseName	Normalized. Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptides.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
BTK	-0.14301137611484	0.894	NA	-0.7150568805742	5	0.0486624812040823	NA	0.0486624812040823	GBM	P T K	BTK
FES	-0.141004900043953	0.914	NA	-0.70502450219764	5	0.0390538042661686	NA	0.0390538042661686	GBM	P T K	FES
FGFR2	-0.130906529744456	0.898	NA	-0.523626118977824	4	0.0467236633326956	NA	0.0467236633326956	GBM	P T K	FGFR2
FGFR3	-0.130906529744456	0.898	NA	-0.523626118977824	4	0.0467236633326956	NA	0.0467236633326956	GBM	P T K	FGFR3
FGFR4	-0.148618391866685	0.97	NA	-1.48618391866685	10	0.0132282657337552	NA	0.0132282657337552	GBM	P T K	FGFR4
FRK	-0.22459801850503	0.922	NA	-4.49196037010059	20	0.0352690789463706	NA	0.0352690789463706	GBM	P T K	FRK
LTK	-0.184464441450476	0.916	NA	-1.84464441450476	10	0.0381045263321496	NA	0.0381045263321496	GBM	P T K	LTK

SRM (SRMS)	- 0.199412154791525	0.92	NA	- 2.3929458574983	12	0.0362121726544447	NA	0.0362121726544447	G B M	P T K	SRMSRMS
TEC	- 0.195201618765967	0.954	NA	- 3.12322590025547	16	0.0204516252959049	NA	0.0204516252959049	G B M	P T K	TEC
TYRO3	- 0.213601725982024	0.894	NA	- 3.20402588973036	15	0.0486624812040823	NA	0.0486624812040823	G B M	P T K	TYRO3
Kinases activated by 5h in GBM											
kinaseName	Normalized. Kinase.Stat	specificityScore	sensitivityScore	setStat	Peptides.in.Set	pSpecificityScore	pSensitivityScore	finalScore	Cell	type	gene
EPHA4	0.0241269960765853	0.94	NA	0.0241269960765853	1	0.0268721464003014	NA	0.0268721464003014	G B M	P T K	EPHA4
EPHB4	0.0241269960765853	0.94	NA	0.0241269960765853	1	0.0268721464003014	NA	0.0268721464003014	G B M	P T K	EPHB4
ANPa (NPR1)	0.235421431876305	0.96	NA	1.88337145501044	8	0.0177287669604316	NA	0.0177287669604316	G B M	S T K	ANPNPR1
CDK4	0.0234240872296013	0.938	NA	0.0234240872296013	1	0.0277971616209356	NA	0.0277971616209356	G B M	S T K	CDK4
DCAMKL2 (BI035543)	0.285455680314429	0.92	NA	2.56910112282986	9	0.0362121726544447	NA	0.0362121726544447	G B M	S T K	DCAMKL2 BI035543
DMPK2 (HSMDB KIN)	0.0234240872296013	0.938	NA	0.0234240872296013	1	0.0277971616209356	NA	0.0277971616209356	G B M	S T K	DMPK2HS MDPKIN
DNAPK/ PRKDC	0.00694338014585466	0.976	NA	0.00694338014585466	1	0.0105501823333082	NA	0.0105501823333082	G B M	S T K	DNAPKPR KDC
NDR1 (NDR)	0.0730733302569579	0.994	NA	0.292293321027832	4	0.00261361560268669	NA	0.00261361560268669	G B M	S T K	NDR1NDR
PKACa (PRKACA)	0.368846323948465	0.93	NA	9.95885074660854	27	0.0315170514460649	NA	0.0315170514460649	G B M	S T K	PKACPRK ACA
PKACb PRKACB	0.354125467053165	0.954	NA	9.20726214338228	26	0.0204516252959049	NA	0.0204516252959049	G B M	S T K	PKACPRK ACB
RSK1 (RPS6KA2)	0.332039937326592	0.936	NA	5.64467893455206	17	0.0287241512618947	NA	0.0287241512618947	G B M	S T K	RSK1RPS6 KA2
RSK2 (RPS6KA3)	0.314722567144657	0.974	NA	6.6091739100378	21	0.0114410431213845	NA	0.0114410431213845	G B M	S T K	RSK2RPS6 KA3
RSK3 (RPS6KA1)	0.34901019558522	0.912	NA	6.980203917044	20	0.0400051616715838	NA	0.0400051616715838	G B M	S T K	RSK3RPS6 KA1
RSK4 (RPS6KA6)	0.332918986443589	0.934	NA	5.9925417559846	18	0.0296531237699066	NA	0.0296531237699066	G B M	S T K	RSK4RPS6 KA6

7. Effect of DMSO on Akt, ERK1/2 and AMPK α phosphorylation on U87 cells (**Figure S1**)

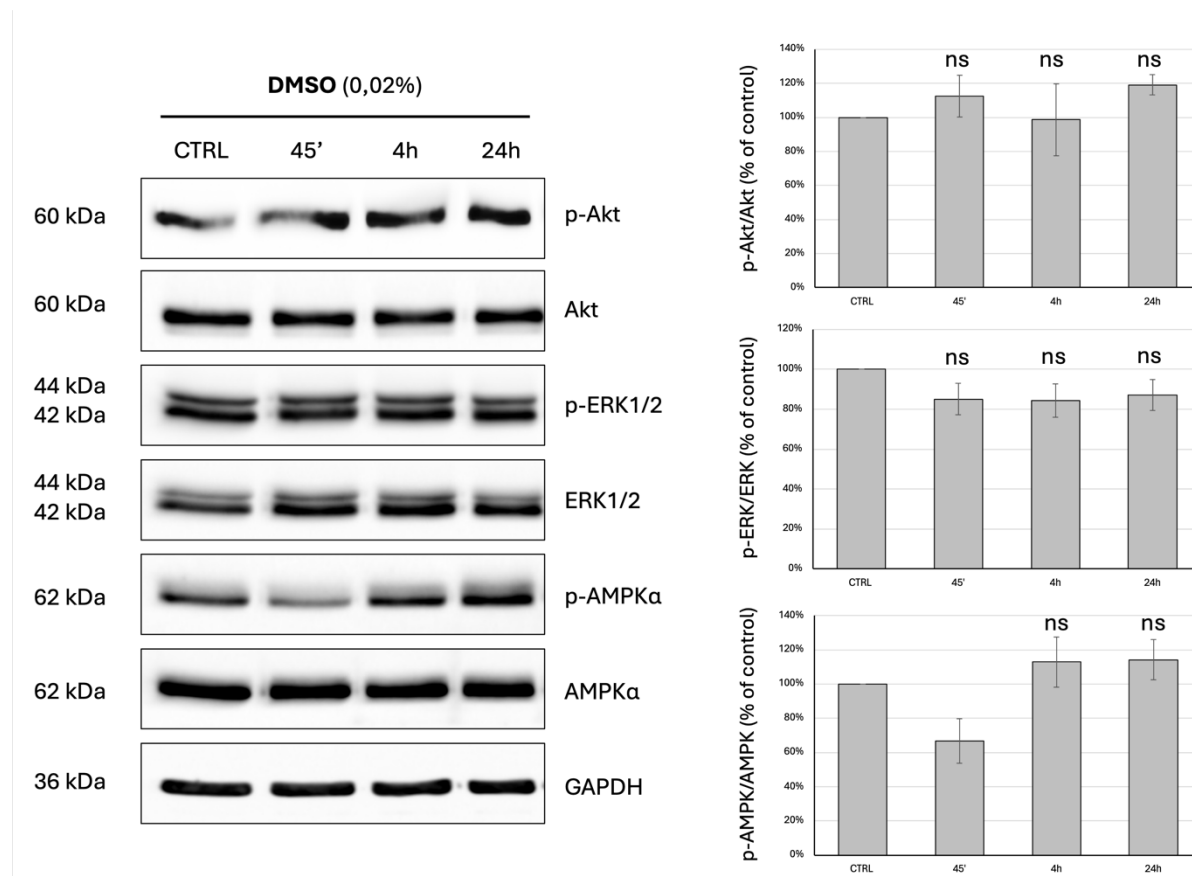


Figure S1. Cells were treated with complemented MEM medium containing 0.02% DMSO, the volume added as a co-solvent in all experiments with the tested hybrids. After incubation for varying times at 37 °C, band intensities (left panel) were quantified using ImageJ and are expressed as the ratio of phosphorylated protein/total protein (right panel). CTRL corresponds to initial time point. Values represent the mean $\pm$ SEM of three independent experiments made in triplicate. Statistical analyses of the data were performed using one-way analysis of variance (ANOVA), followed, if significant ($P < 0.05$), by *a posteriori* Dunnett's multiple comparisons test. Differences between groups were found not significant: ns

8. Original, uncropped Western blot images (**Figure S2-10**)

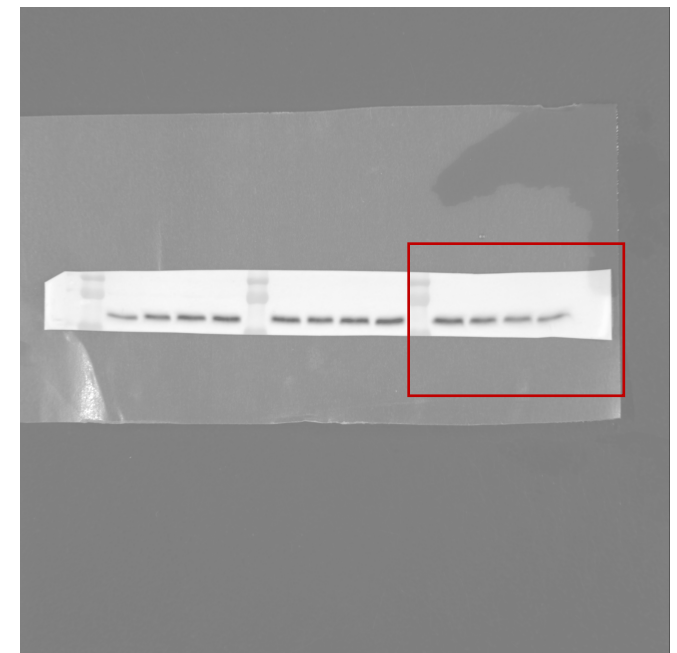
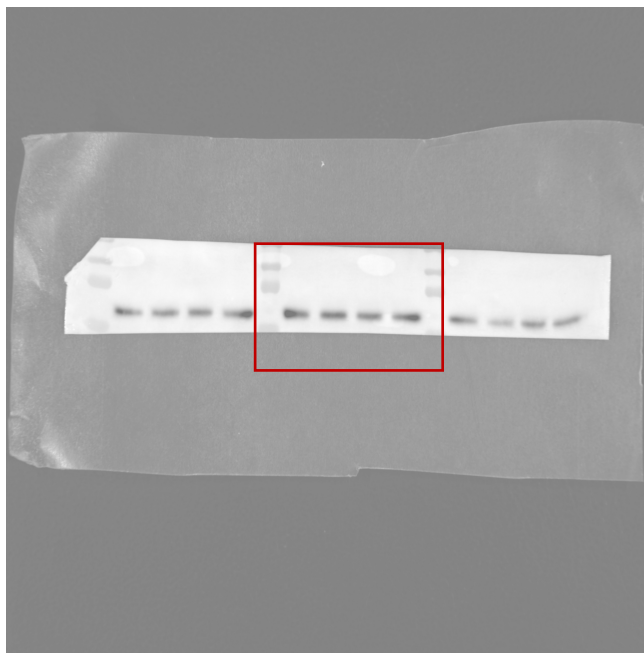
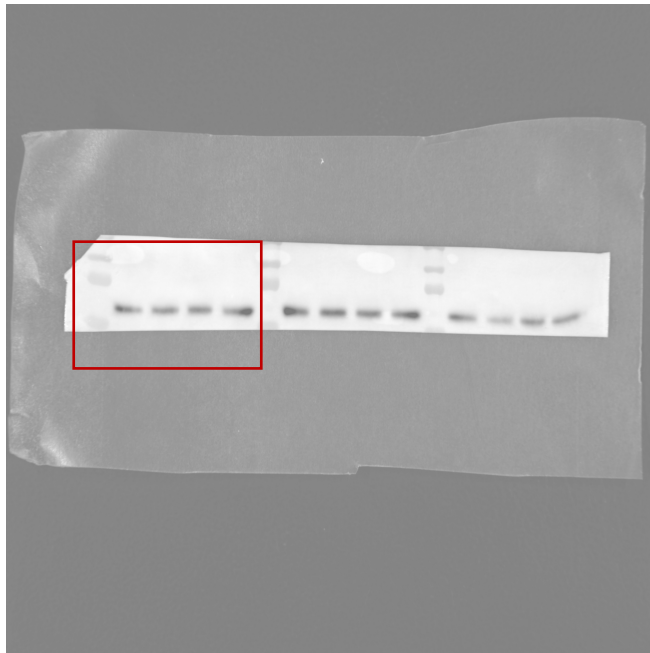
8.1 Western blot source images for Akt (**Figure S2**)

Akt

Metformin

5a

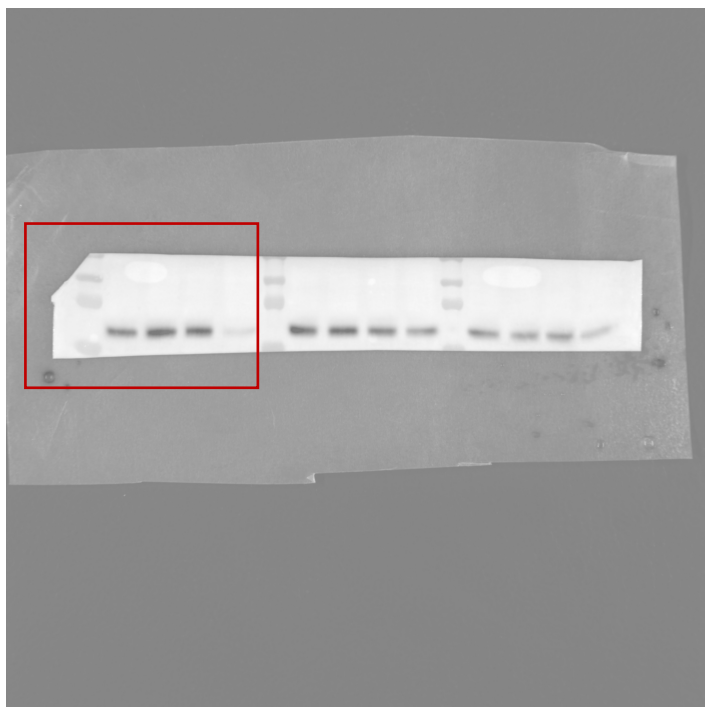
5h



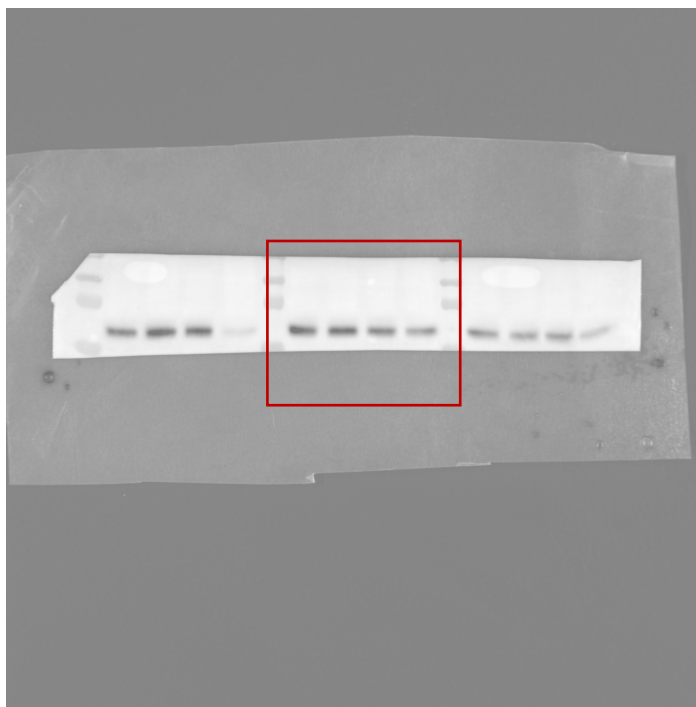
8.2 Western blot source images for P-Akt (**Figure S3**)

P-Akt

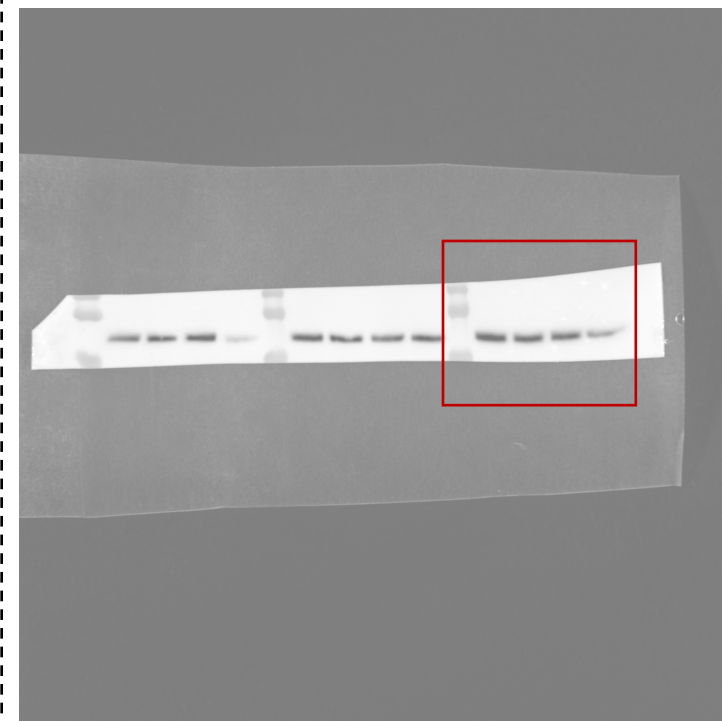
Metformin



5a



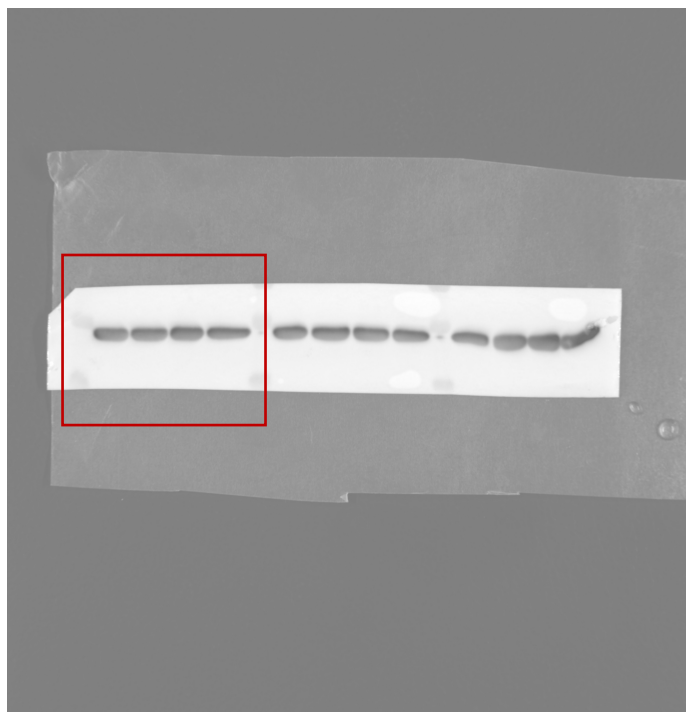
5h



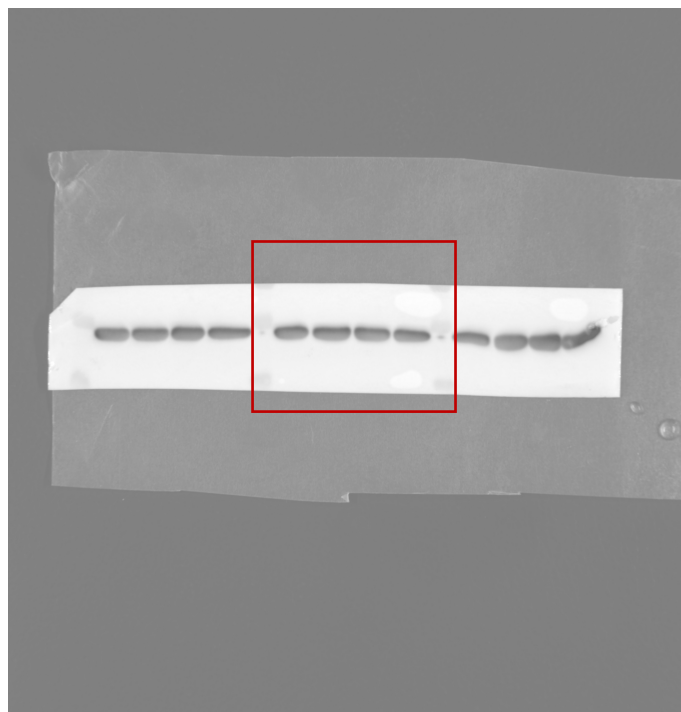
8.3 Western blot source images for GAPDH (loading control for Akt and P-Akt) (**Figure S4**)

GAPDH

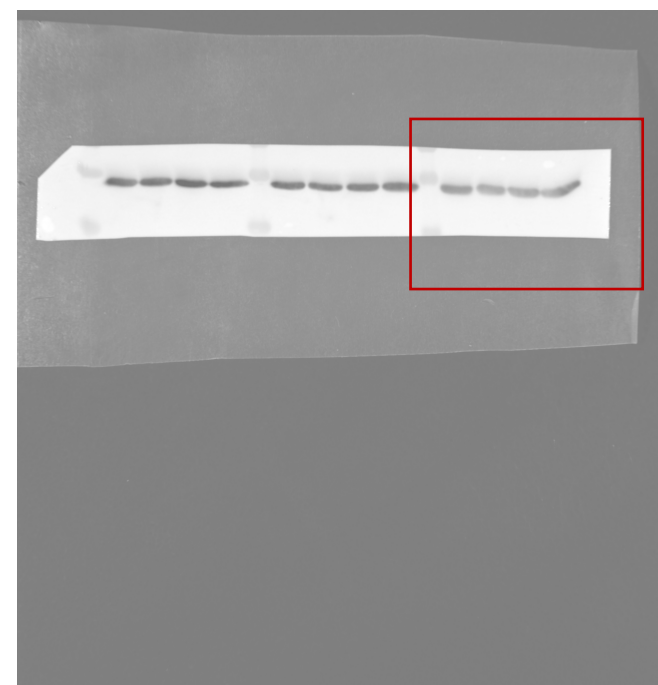
Metformin



5a



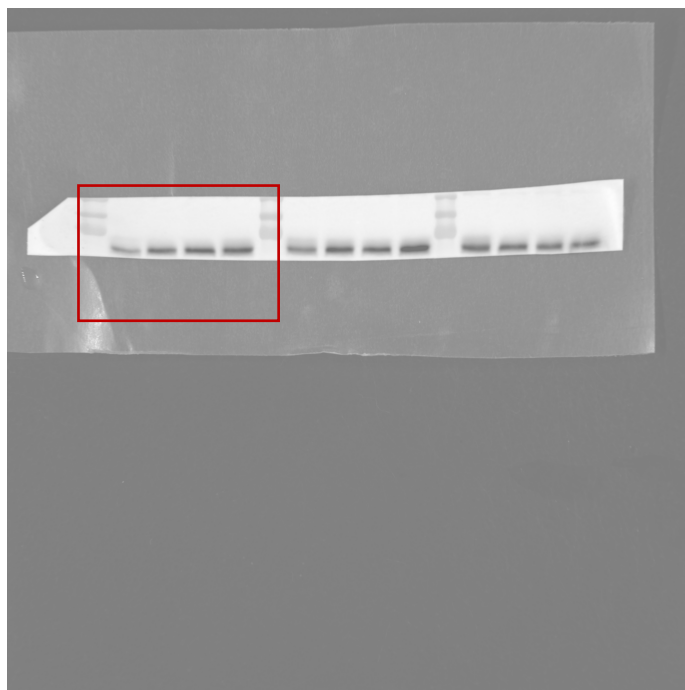
5h



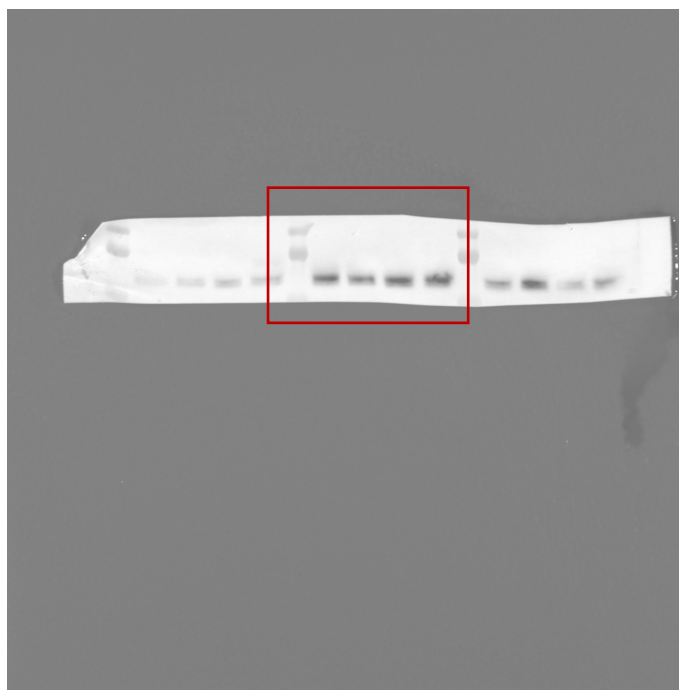
8.4 Western blot source images for AMPK (**Figure S5**)

AMPK

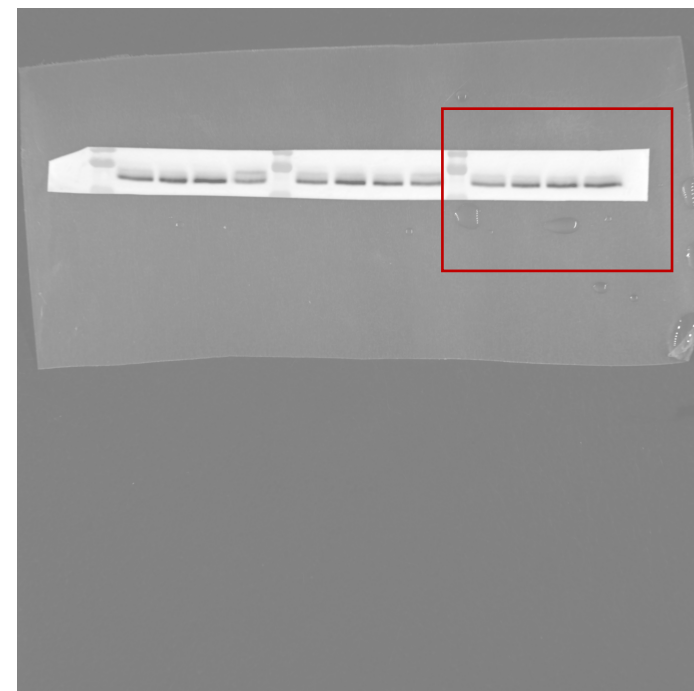
Metformin



5a



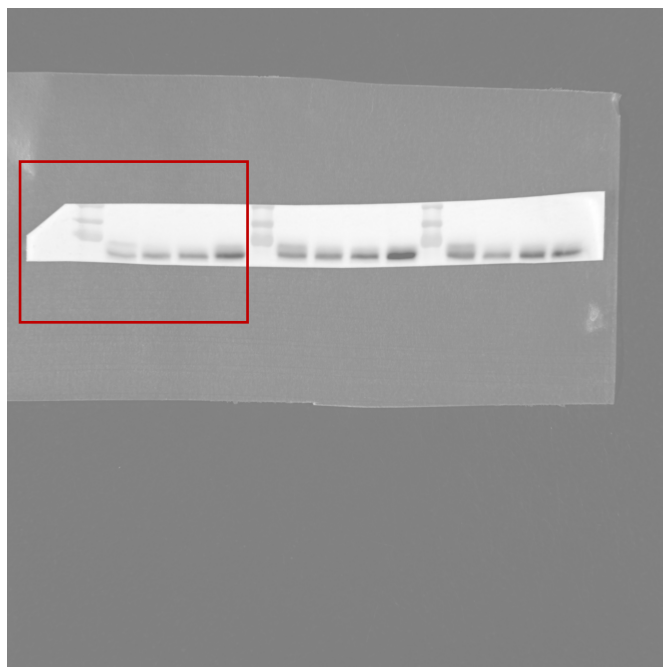
5h



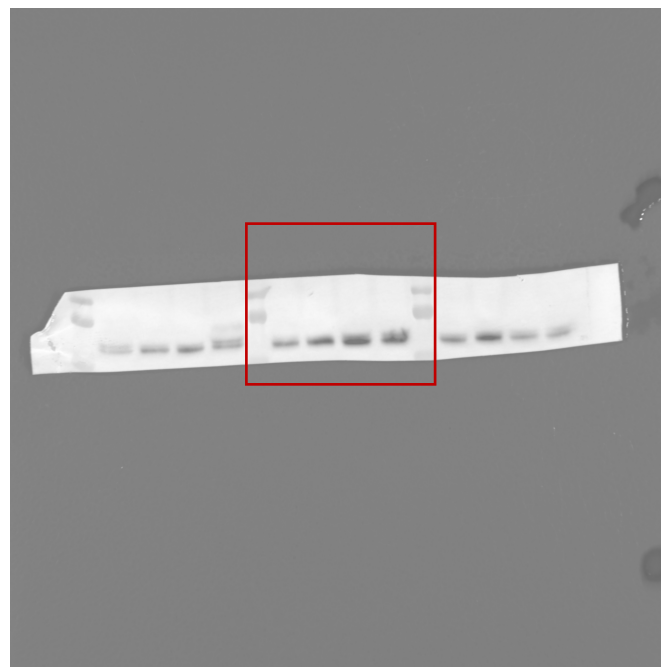
8.5 Western blot source images for P-AMPK (**Figure S6**)

P-AMPK

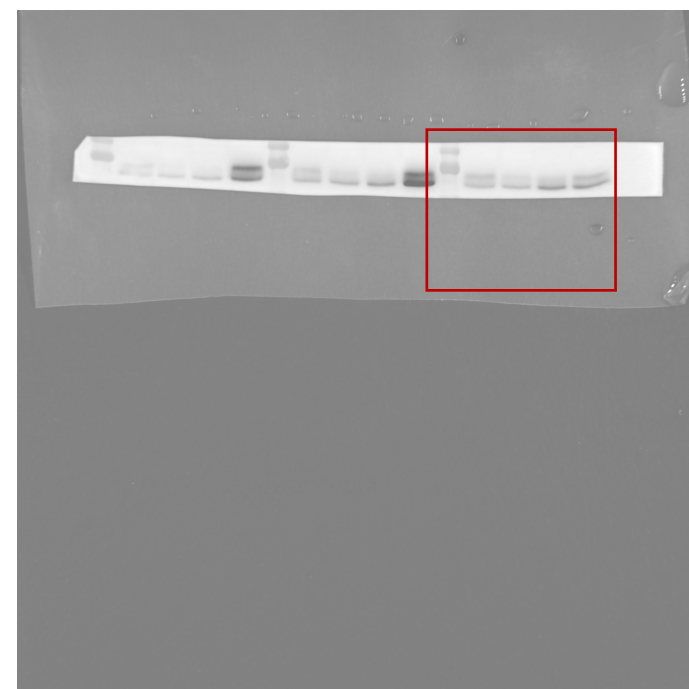
Metformin



5a



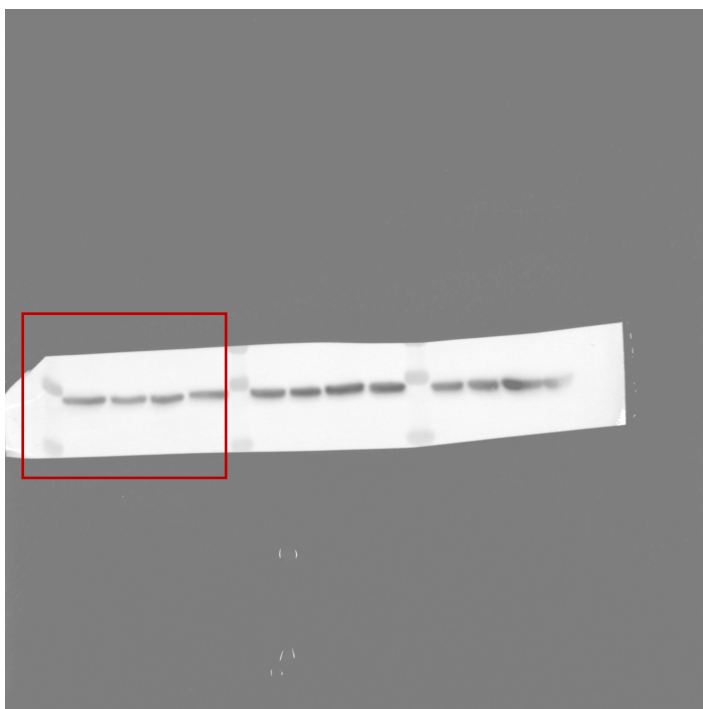
5h



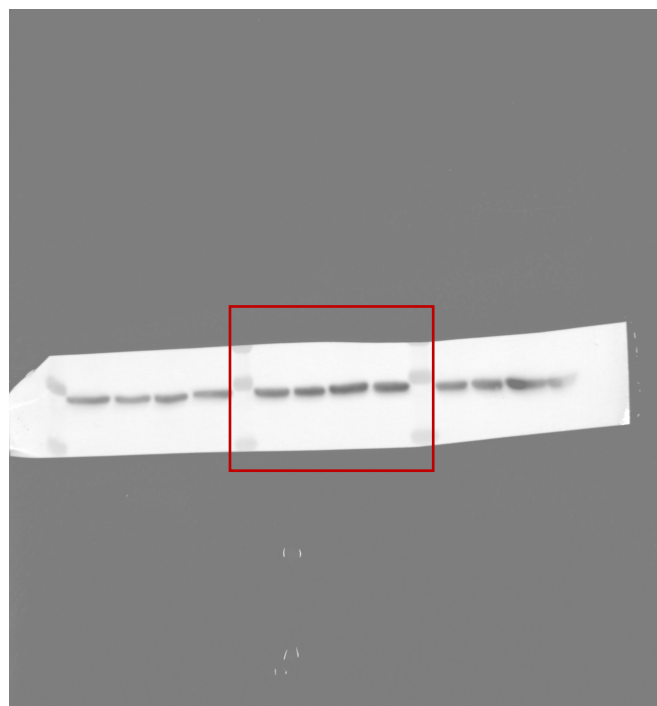
8.6 Western blot source images for GAPDH (loading control for AMPK and P-AMPPK) (**Figure S7**)

GAPDH

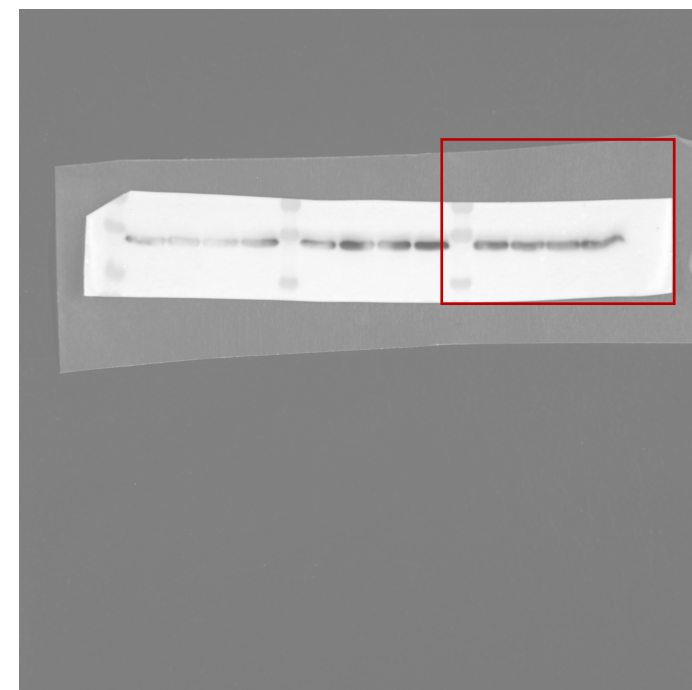
Metformin



5a



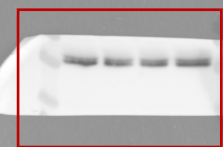
5h



8.7 Western blot source images for ERK1/2 (**Figure S8**)

ERK1/2

Metformin



5a



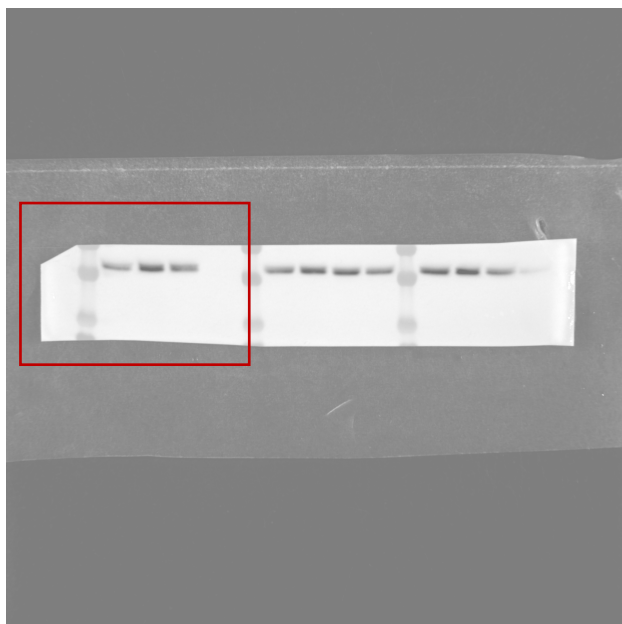
5h



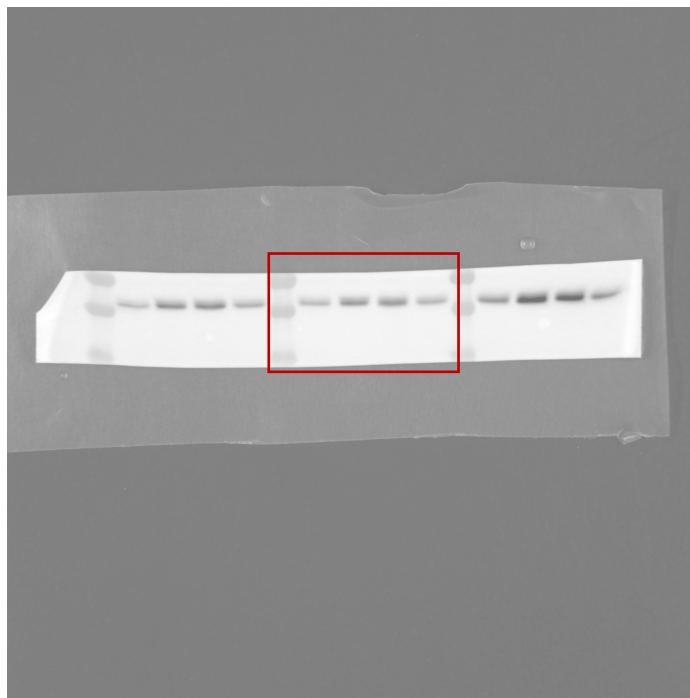
8.8 Western blot source images for P-ERK1/2 (**Figure S9**)

P-ERK1/2

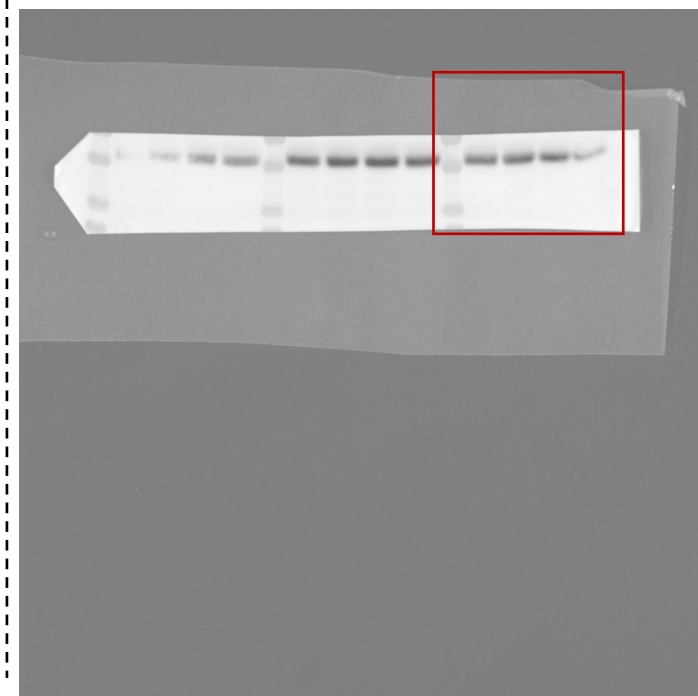
Metformin



5a



5h



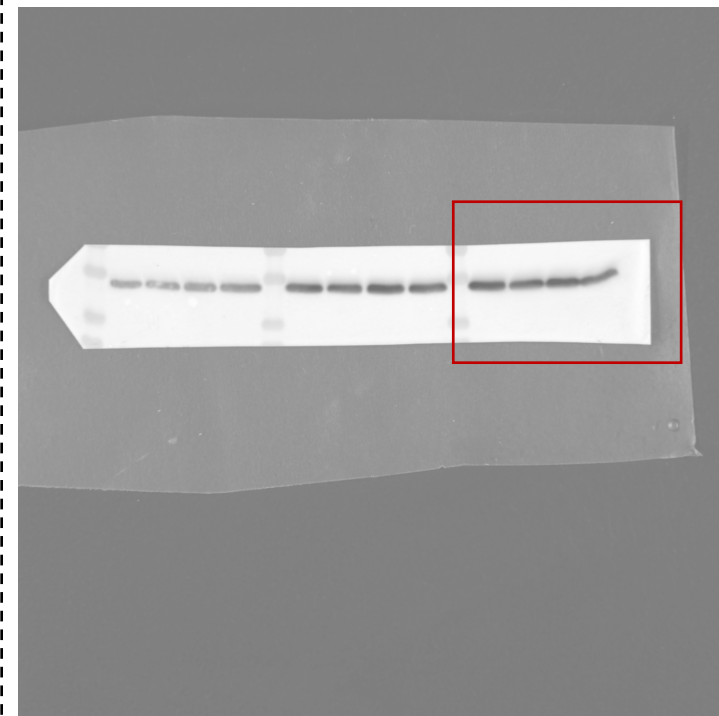
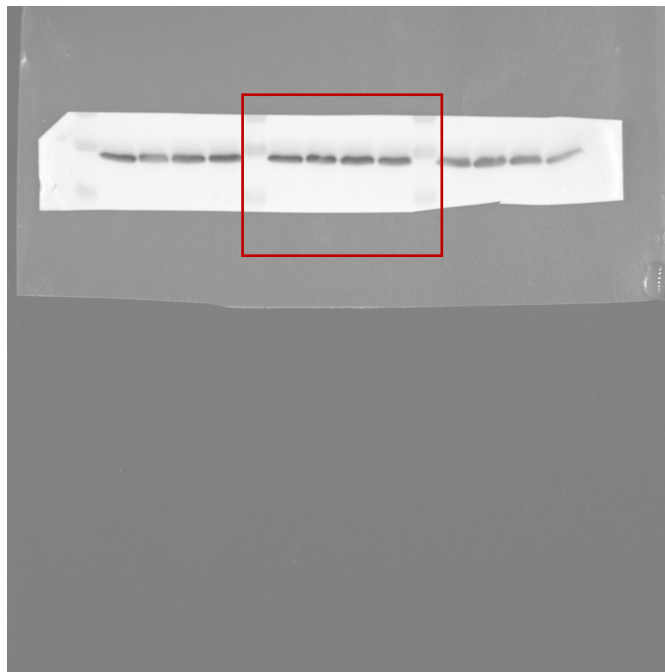
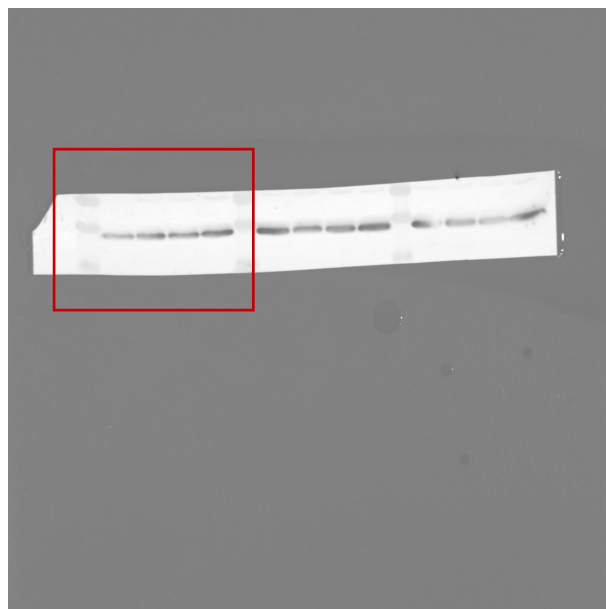
8.9 Western blot source images for GAPDH (loading control for ERK1/2 and P-ERK1/2) (**Figure S10**)

Metformin

GAPDH

5a

5h



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