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ELECTRONIC SUPPORTING INFORMATION

FOR

Organo NHC catalyzed aqueous synthesis of 4β-isoxazole-podophyllotoxins: *In vitro* anticancer, caspases activation, tubulin polymerization inhibition and molecular docking studies

Rajkumar Nagavath,[a] Murali Krishna Thupurani,[b] Vinitha Badithapuram,[a] Ravinder Manchal,[a] Chandra Sekhar Vasam [c]* and Narasimha Swamy Thirukovela[a]*

[a]Department of Chemistry, Chaitanya (Deemed to be University)
Himayathnagar (V), Moinabad (M), Ranga Reddy, India
email; thirukovelann@chaitanya.edu.in

[b]Department of Biotechnology, Chaitanya (Deemed to be University)
Himayathnagar (V), Moinabad (M), Ranga Reddy, India

[c]Department of Pharmaceutical Chemistry
Telangana University, Nizamabad , T.S. India;
email : csvasam@telanganauniversity.ac.in

Experimental

SRB assay

All tumor cell lines have grown Dulbecco's revised Eagle's medium [comprising 10% FBS (10%) in humidified atmosphere of CO_2 (50%)] at 37 ^oC. The cell lines were trypsinized when sub-confluent from T25 flasks/60 mm dishes and sowed in 96-well plates in 100 μL aliquots at plating thicknesses dependent on doubling up time of discrete cell lines. The microtiter plates have been incubated at 37 ^oC, CO_2 (5%), air (95%) and 100% comparative moisture for 24 h earlier to adding of experimental drugs and incubated for 48 h with diverse concentration (0.01, 0.1, 1, 100 and 1000 μM) of synthesized hybrid molecules. After 48 h incubation at 37 ^oC, cell monolayers were fixed by adding 10% (wt/vol) cold CCl_3COOH and incubated at 4 ^oC for 1 h and stained with Sulforhodamine B (SRB) (0.057%) that dissolved in 1% AcOH for 30 min at RT. Unbound SRB was wash away with 1% AcOH. The protein-bound dye was dissolved in Tris base (10 mM) solution for OD caclulation at 510 nm by means of microplate reader. The GI_{50} was calculated from [(Ti-Tz)/ (C - Tz)] x 100 = 50, which is drug concentration ensuing in 50% reduction in net protein growth (measured using SRB staining) in control cells in the course of drug incubation.

Caspases 8, 9, 3/7 Assay

The caspase 3/7, 8, and 9 assay was performed based on the method instructions found in the manufacturer's kits. Briefly, add 100 μL approx (5×10^4 HeLa, MCF-7 and MIA PaCa2 cells/mL) were transferred to 96-well microtiter plates and maintained in incubator for 24 h. Compounds at different concentrations (05, 10, 15 and 20 μg/mL) are transferred to the cells and incubated for 24 h. Add Caspase-Glo 3/7, 8, and 9 reagents and plates were agitated gently for 30 sec. After one hour of incubation luminescence signal was recorded using GloMax-Multi Detection System.

Tubulin polymerization assay

This assay was performed according to manufacturer method as mentioned in tubulin polymerization kit (BK011, Cytoskeleton, Inc.). The reaction mixture in a finishing volume of 10 μL in PEM buffer (80 mM PIPES, 0.5 mM EGTA, 2 mM $MgCl_2$ and pH 6.9) in 384 well plates contained 2 mg/mL bovine brain tubulin, 10 lM fluorescent reporter, 1 mM GTP either in presence or absence of test hybrid molecules at 37 ^oC. The Tubulin polymerization was followed by observing the fluorescence improvement due to combination of fluorescence reporter keen on microtubules as polymerization continues. Fluorescence emission at 420 nm (here wavelength of excitation is 360 nm) was calculated for 1 h based on 1 min intervals in a multimode plate reader. The podophyllotoxin was then used under same experimental conditions. For the determination of IC_{50} values of tested compounds on tubulin polymerization, compounds have been pre-incubated with tubulin at variable (1, 2, 3, 4 and 5 μM) concentrations.

Procedure for the synthesis of chlorooximes. Aldehydes (1.5 mmol) (**2a-n**), $NH_2OH.HCl$ (1.5 mmol) (**3**) and NaoAc (1.5 mmol) in 1:1 aq. EtOH (2 mL) were added and resulting mixture was allowed stirring for 5 h at RT. After completion of reaction as designated by the TLC, the reaction was extracted twice with EtOAc (15 mL). The combined organic layer was dried under Na_2SO_4 and reduced using rotary evaporator. The purification was finally done by the 60-120 mesh size silica jel column chromatography using ethyl acetate/hexane as mobile phase.

The mixture of aldoximes (1.25 mmol) (**3a-n**) and *N*-chlorosuccinimide (**4**) (1.5 mmol) (**76**) in DMF (2 mL) was stirred at RT for 20 h. The reaction mixture was then poured into water and extracted twice with EtOAc (15 mL). The resulting ethyl acetate layer was washed

with brine solution and dried under Na_2SO_4. The excess of organic layer was concentrated using rotary evaporator to give corresponding chlorooximes (**5a-n**) which are directly used for next reaction deprived of any purification.

Procedure for the synthesis of 4β-isoxazole-podophyllotoxin (6a-n): Synthesis of (5R,8aR,9S)-9-((3-phenylisoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one (6a). A mixture of alkyne intermediate **1** (1.0 mmol), pre-catalyst **B** (0.05 mmol) and K_2CO_3 (0.15 mmol) in (7:3) H_2O/MeCN was stirred at RT for 20 min. Then, N-hydroxybenzimidoyl chloride (**5a**) (1 mmol) and K_2CO_3 (1.5 mmol) were added to same reaction mixture and stirring was continued for further 100 min. The progress of reaction as analyzed by the TLC, the reaction mixture was extracted twice with EtOAc (10 mL) and dried over Na_2SO_4 and the excess of organic layer was evaporated using rotary evaporator. Finally, the isolated crude product was purified by the 60-120 mesh size silica gel column chromatography using ethyl acetate/hexane (2:3) as mobile phase.

Characterization data

(5*R*,8a*R*,9*S*)-9-((3-phenylisoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6a): Colorless solid; M.P.: 156-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.95-3.03 (m,1H), 3.73 (s, 6H), 3.86 (s, 3H), 4.17 (d, 1H, *J* = 7.8 Hz), 4.48-4.60 (m, 2H), 4.92 (s, 2H), 5.02 (d, 1H, *J* = 5.6 Hz), 6.14 (s, 2H), 6.52 (s, 2H), 6.71 (s, 1H), 6.86 (s, 1H), 7.43-7.51 (m, 4H), 7.73-7.80 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 170.7, 163.3, 158.5, 147.1, 145.8, 141.8, 137.5, 132.2, 130.9, 130.3, 129.8, 128.6, 127.7, 110.1, 108.2, 107.3, 101.6, 98.1, 73.7, 67.9, 62.8, 56.9, 55.1, 45.8, 44.2, 40.4 ppm; MS (ESI): 572 $[M+H]^+$; CHN analysis for $C_{32}H_{29}NO_9$; Calculated (%): C, 67.24; H, 5.11; N, 2.45; Found (%): C, 67.22; H, 5.12; N, 2.48;

(5*R*,8a*R*,9*S*)-9-((3-(p-tolyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (**6b**): Colorless solid; M.P.: 161-163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.81 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.94-3.02 (m,1H), 3.75 (s, 6H), 3.85 (s, 3H), 4.18 (d, 1H, *J* = 7.8 Hz), 4.49-4.59 (m, 2H), 4.91 (s, 2H), 5.03 (d, 1H, *J* = 5.6 Hz), 6.13 (s, 2H), 6.52 (s, 2H), 6.72 (s, 1H), 6.85 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.52 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 170.5, 163.1, 158.5, 147.2, 145.7, 141.8, 140.5, 137.6, 132.2, 130.8, 129.9, 129.3, 127.3, 110.2, 108.4, 107.2, 101.5, 97.9, 73.6, 67.7, 62.8, 56.8, 54.9, 45.7, 44.3, 40.2, 22.1 ppm; MS (ESI): 586 $[M+H]^+$; CHN analysis for $C_{33}H_{31}NO_9$; Calculated (%): C, 67.68; H, 5.34; N, 2.39; Found (%): C, 67.66; H, 5.32; N, 2.41.

(5*R*,8a*R*,9*S*)-9-((3-(m-tolyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6c): Grey solid; M.P.: 161-163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.79 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.93-3.01 (m,1H), 3.74 (s, 6H), 3.86 (s, 3H), 4.17 (d, 1H, *J* = 7.8 Hz), 4.47-4.58 (m, 2H), 4.93 (s, 2H), 5.02 (d, 1H, *J* = 5.6 Hz), 6.14 (s, 2H), 6.53 (s, 2H), 6.71 (s, 1H), 6.86 (s, 1H), 7.27-7.35 (m, 1H), 7.41 (t, J = 7.3 Hz, 1H), 7.45-7.53 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 170.5, 162.6, 158.6, 147.3, 145.7, 141.9, 138.5, 137.7, 133.1, 132.1, 131.6, 129.8, 129.3, 128.4, 125.3, 110.1, 108.3, 107.4, 101.7, 98.1, 73.7, 67.8, 62.8, 56.9, 55.1, 45.6, 44.3, 40.3, 21.7 ppm; MS (ESI): 608 $[M+Na]^+$; CHN analysis for $C_{33}H_{31}NO_9$; Calculated (%): C, 67.68; H, 5.34; N, 2.39; Found (%): C, 67.71; H, 5.36; N, 2.37.

(5*R*,8a*R*,9*S*)-9-((3-(3,5-dimethylphenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-

one (**6d**): Colorless solid M.P.: 165-167; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 6H), 2.80 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.95-3.03 (m,1H), 3.74 (s, 6H), 3.86 (s, 3H), 4.16 (d, 1H, *J* = 7.8 Hz), 4.47-4.59 (m, 2H), 4.92 (s, 2H), 5.04 (d, 1H, *J* = 5.6 Hz), 6.15 (s, 2H), 6.51 (s, 2H), 6.71 (s, 1H), 6.86 (s, 1H), 7.16 (s, 1H), 7.46 (s, 2H), 7.52 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 170.3, 162.5, 158.7, 147.3, 145.6, 141.7, 138.8, 137.8, 133.2, 132.6, 132.2, 130.1, 126.8, 110.3, 108.4, 107.4, 101.6, 97.9, 73.7, 67.6, 62.9, 56.8, 55.1, 45.7, 44.3, 40.3, 21.9 ppm; MS (ESI): 600 $[M+H]^+$; CHN analysis for $C_{34}H_{33}NO_9$; Calculated (%): C, 68.10; H, 5.55; N, 2.34; Found (%): C, 68.13; H, 5.56; N, 2.36.

(5*R*,8a*R*,9*S*)-9-((3-(4-methoxyphenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxy phenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6e): Colorless solid M.P.: 166-168; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.80 (dd, 1H, *J* = 14.7, 12.9 Hz), 2.90-3.02 (m,1H), 3.73 (s, 6H), 3.87 (s, 6H), 4.16 (d, 1H, *J* = 7.8 Hz), 4.48-4.60 (m, 2H), 4.91 (s, 2H), 5.03 (d, 1H, *J* = 5.6 Hz), 6.13 (s, 2H), 6.51 (s, 2H), 6.70 (s, 1H), 6.84 (s, 1H), 6.95 (d, *J* = 7.5 Hz, 2H), 7.50 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 170.2, 163.2, 160.7, 158.6, 147.4, 145.5, 141.8, 137.7, 132.4, 130.5, 129.8, 122.8, 114.2, 110.4, 108.3, 107.4, 101.7, 98.1, 73.8, 67.7, 62.7, 56.7, 55.4, 54.8, 45.8, 44.2, 40.4 ppm; MS (ESI): 602 $[M+H]^+$; CHN analysis for $C_{33}H_{31}NO_{10}$; Calculated (%): C, 65.88; H, 5.19; N, 2.33; Found (%): C, 65.91; H, 5.17; N, 2.34.

(5*R*,8a*R*,9*S*)-9-((3-(4-chlorophenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6f): Colorless solid M.P.: 162-164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.95–3.04 (m,1H), 3.74 (s, 6H), 3.86 (s, 3H), 4.17 (d, 1H, *J* = 7.8 Hz), 4.47-4.59 (m, 2H), 4.94 (s, 2H), 5.04 (d, 1H, *J* = 5.6 Hz), 6.15 (s, 2H), 6.53 (s, 2H), 6.71 (s, 1H), 6.87 (s, 1H), 7.22 (d, 2H, *J* = 7.4 Hz), 7.52 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 170.6, 163.5, 158.7, 147.6, 145.7, 142.1, 137.8, 136.4, 132.3, 131.3, 129.9, 129.2, 128.1, 110.5, 108.5, 107.5, 101.8, 98.3, 73.7, 67.8, 62.8, 56.9, 55.2, 45.7, 44.4, 40.5 ppm; MS (ESI): 606 $[M+H]^+$; CHN analysis for $C_{32}H_{28}ClNO_9$; Calculated (%): C, 63.42; H, 4.66; N, 2.31; Found (%): 63.45; H, 4.65; N, 2.35.

(5*R*,8a*R*,9*S*)-9-((3-(4-bromophenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6g): Light yellow solid M.P.: 178-180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.82 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.93-3.01 (m,1H), 3.75 (s, 6H), 3.85 (s, 3H), 4.16 (d, 1H, *J* = 7.8 Hz), 4.49-4.61 (m, 2H), 4.91 (s, 2H), 5.02 (d, 1H, *J* = 5.6 Hz), 6.16 (s, 2H), 6.52 (s, 2H), 6.70 (s, 1H), 6.85 (s, 1H), 7.33 (d, 2H, *J* = 7.9 Hz), 7.51 (s, 1H), 7.76 (d, *J* = 7.9 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 170.4, 163.3, 158.8, 147.4, 145.6, 141.9, 137.6, 132.2, 131.5, 129.9, 128.6, 127.3, 126.9, 110.4, 108.4, 107.6, 101.7, 98.1, 73.5, 67.7, 62.8, 56.8, 54.9, 45.6, 44.2, 40.3 ppm; MS (ESI): 650 $[M+H]^+$; CHN analysis for $C_{32}H_{28}BrNO_9$; Calculated (%): C, 59.09; H, 4.34; N, 2.15; O, 22.14; Found (%): C, 59.07; H, 4.37; N, 2.16.

(5*R*,8a*R*,9*S*)-9-((3-(4-fluorophenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6h): Colorless slid; 158-160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.84 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.95-3.03 (m,1H), 3.74 (s, 6H), 3.87 (s, 3H), 4.19 (d, 1H, *J* = 7.8 Hz), 4.50-4.62 (m, 2H), 4.94 (s, 2H), 5.04 (d, 1H, *J* = 5.6 Hz), 6.19 (s, 2H), 6.53 (s, 2H), 6.72 (s, 1H), 6.88 (s, 1H), 7.14 (d, 2H, *J* = 7.1 Hz), 7.53 (s, 1H), 7.61 (d, *J* = 7.1 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 170.5, 163.4, 161.9, 158.9, 147.6, 145.8, 142.1, 137.7, 132.5, 130.8, 130.1, 128.3, 113.5, 110.3,

108.5, 107.7, 101.8, 98.4, 73.8, 67.7, 62.9, 56.7, 55.1, 45.8, 44.3, 40.4 ppm; MS (ESI): 590 $[M+H]^+$; CHN analysis for $C_{32}H_{28}FNO_9$; Calculated (%): C, 65.19; H, 4.79; N, 2.38; Found (%): C, 65.21; H, 4.82; N, 2.35.

4-(5-((((5*S*,5a*R*,9*R*)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-5-yl)oxy)methyl)isoxazol-3-yl) benzonitrile (6i): Colorless solid M.P.: 166-168°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.94-3.02 (m,1H), 3.74 (s, 6H), 3.85 (s, 3H), 4.17 (d, 1H, *J* = 7.8 Hz), 4.47-4.59 (m, 2H), 4.92 (s, 2H), 5.03 (d, 1H, *J* = 5.6 Hz), 6.17 (s, 2H), 6.51 (s, 2H), 6.71 (s, 1H), 6.87 (s, 1H), 7.46-7.53 (m, 3H), 7.89 (d, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 170.6, 163.1, 158.6, 147.5, 145.6, 141.9, 137.8, 135.9, 132.4, 131.7, 130.2, 129.3, 119.2, 115.3, 110.5, 108.6, 107.5, 101.6, 98.2, 73.6, 67.5, 62.8, 56.9, 54.9, 45.6, 44.4, 40.5 ppm; MS (ESI): 619 $[M+Na]^+$; CHN analysis for $C_{33}H_{28}N_2O_9$; Calculated (%): C, 66.44; H, 4.73; N, 4.70; Found (%): C, 66.41; H, 4.75; N, 4.71.

(5*R*,8a*R*,9*S*)-9-((3-(4-nitrophenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6j): Colorless solid M.P.: 171-173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.84 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.95–3.04 (m,1H), 3.75 (s, 6H), 3.86 (s, 3H), 4.19 (d, 1H, *J* = 7.8 Hz), 4.49-4.61 (m, 2H), 4.95 (s, 2H), 5.05 (d, 1H, *J* = 5.6 Hz), 6.18 (s, 2H), 6.53 (s, 2H), 6.72 (s, 1H), 6.89 (s, 1H), 7.54 (s, 1H), 7.86 (d, *J* = 7.1 Hz, 2H), 8.21 (d, *J* = 7.1 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 170.7, 163.4, 158.9, 150.8, 147.8, 145.9, 142.1, 137.9, 136.1, 132.5, 130.1, 128.1, 126.3, 110.7, 108.7, 107.6, 101.7, 98.4, 73.8, 67.8, 62.7, 56.8, 55.2, 45.9, 44.7, 40.6 ppm; MS (ESI): 639 $[M+Na]^+$; CHN analysis for $C_{32}H_{28}N_2O_{11}$; Calculated (%): C, 62.34; H, 4.58; N, 4.54; O, 28.54; Found (%): C, 62.35; H, 4.60; N, 4.57.

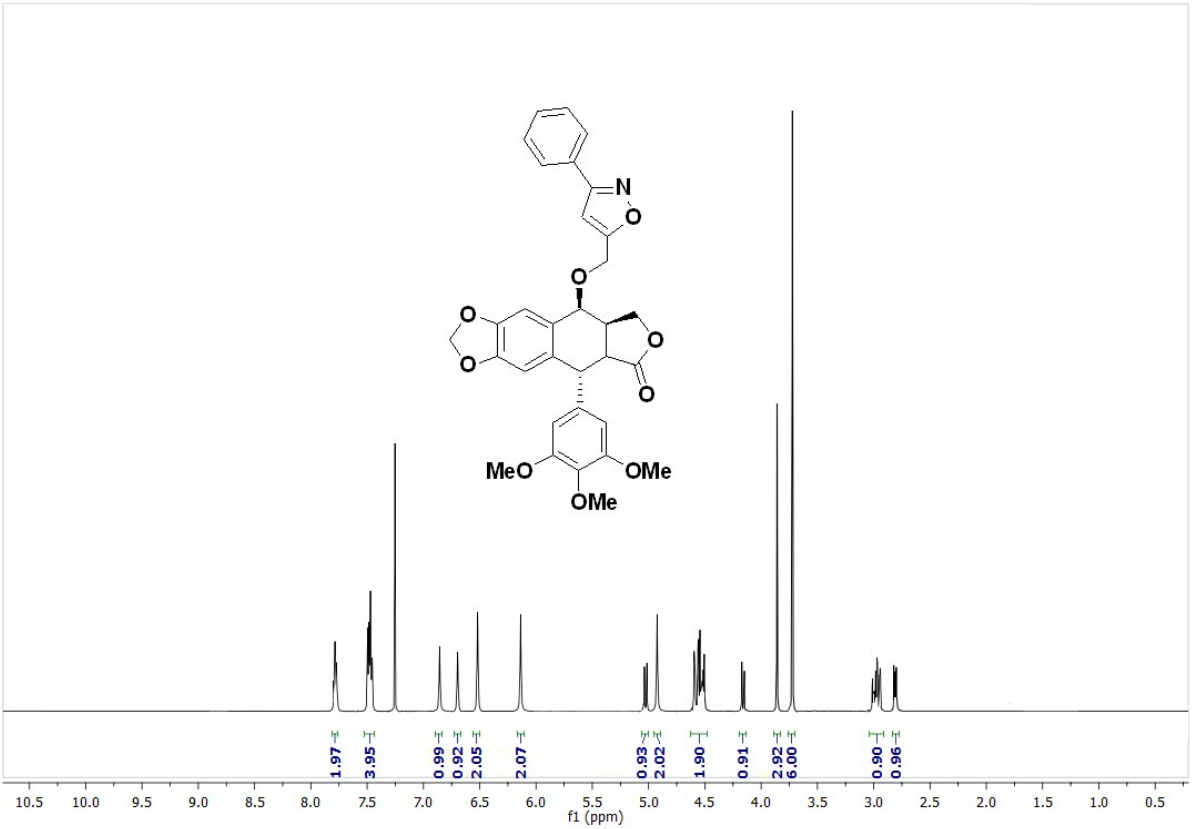
(5*R*,8a*R*,9*S*)-9-((3-(3-chlorophenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6k): Cream solid M.P.: 163-165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.93-3.01 (m,1H), 3.74 (s, 6H), 3.85 (s, 3H), 4.17 (d, 1H, *J* = 7.8 Hz), 4.47-4.58 (m, 2H), 4.91 (s, 2H), 5.02 (d, 1H, *J* = 5.6 Hz), 6.16 (s, 2H), 6.51 (s, 2H), 6.71 (s, 1H), 6.87 (s, 1H), 7.37-7.46 (m, 2H), 7.52-7.59 (m, 2H), 7.71 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 170.3, 162.2, 158.7, 147.6, 145.7, 141.8, 137.7, 133.4, 132.9, 132.3, 130.4, 129.8, 129.3, 127.3, 126.1, 110.5, 108.5, 107.6, 101.5, 97.9, 73.6, 67.5, 62.6, 56.7, 54.9, 45.7, 44.2, 40.3 ppm; MS (ESI): 606 $[M+H]^+$; CHN analysis for $C_{32}H_{28}ClNO_9$; Calculated (%): C, 63.42; H, 4.66; N, 2.31; Found (%): C, 63.40; H, 4.67; N, 2.34.

3-(5-((((5*S*,5a*R*,9*R*)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro [3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-5-yl)oxy)methyl)isoxazol-3-yl)benzonitrile (6l): Colorless solid M.P.: 165-167°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.94-3.03 (m, 1H), 3.75 (s, 6H), 3.87 (s, 3H), 4.16 (d, 1H, *J* = 7.8 Hz), 4.48-4.59 (m, 2H), 4.92 (s, 2H), 5.01 (d, 1H, *J* = 5.6 Hz), 6.17 (s, 2H), 6.52 (s, 2H), 6.70 (s, 1H), 6.86 (s, 1H), 7.53 (s, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.75-7.83 (m, 2H), 8.01 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 170.4 162.5, 158.8, 147.7, 145.8, 141.9, 137.8, 134.8, 134.3, 132.6, 132.1, 131.2, 129.9, 129.4, 119.1, 113.3, 110.6, 108.6, 107.7, 101.8, 98.1, 73.7, 67.7, 62.5, 56.9, 55.1, 45.8, 44.5, 40.4 ppm; MS (ESI): 597 $[M+H]^+$; CHN analysis for $C_{33}H_{28}N_2O_9$; Calculated (%): C, 66.44; H, 4.73; N, 4.70; O, 24.14; Found (%): C, 66.47; H, 4.75; N, 4.74.

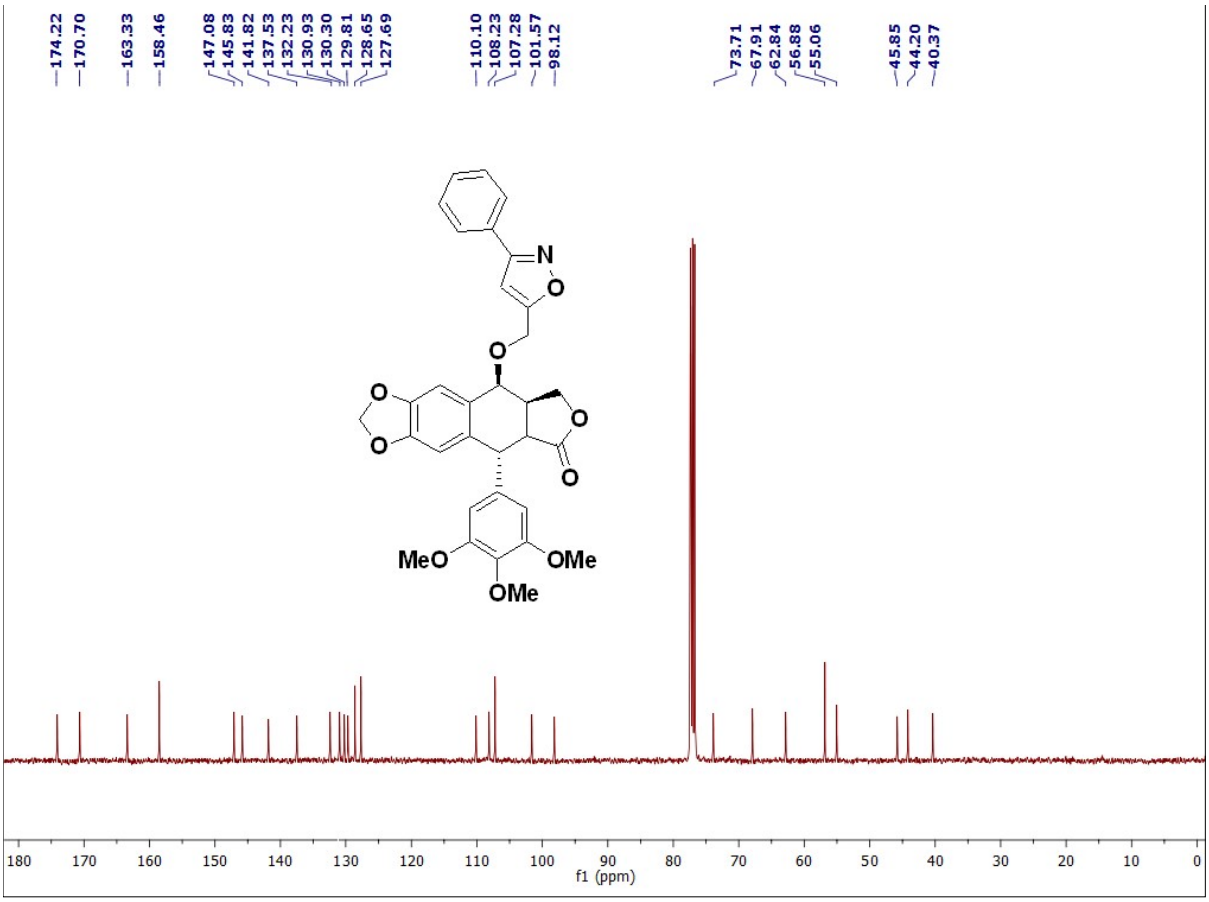
(5*R*,8a*R*,9*S*)-9-((3-(3,5-dichlorophenyl)isoxazol-5-yl)methoxy)-5-(3,4,5-trimethoxyphenyl)-5,8,8a,9-tetrahydrofuro[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-6(5a*H*)-one (6m): Colorless solid; M.P.: 168-170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.81 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.95-3.02 (m,1H), 3.76 (s, 6H), 3.86 (s, 3H), 4.18 (d, 1H, *J* = 7.8 Hz), 4.49-4.60

(m, 2H), 4.93 (s, 2H), 5.03 (d, 1H, *J* = 5.6 Hz), 6.18 (s, 2H), 6.52 (s, 2H), 6.71 (s, 1H), 6.85 (s, 1H), 7.41 (s, 1H), 7.51 (s, 1H), 7.65 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 170.5 162.3, 158.6, 147.4, 145.6, 141.7, 137.6, 134.9, 133.6, 132.4, 130.8, 129.8, 126.4, 110.7, 108.5, 107.6, 101.6, 98.2, 73.5, 67.6, 62.6, 56.8, 54.8, 45.7, 44.4, 40.3 ppm; MS (ESI): 641 $[M+H]^+$; CHN analysis for $C_{32}H_{27}Cl_2NO_9$; Calculated (%): C, 60.01; H, 4.25; N, 2.19; Found (%): C, 60.03; H, 4.27; N, 2.16.

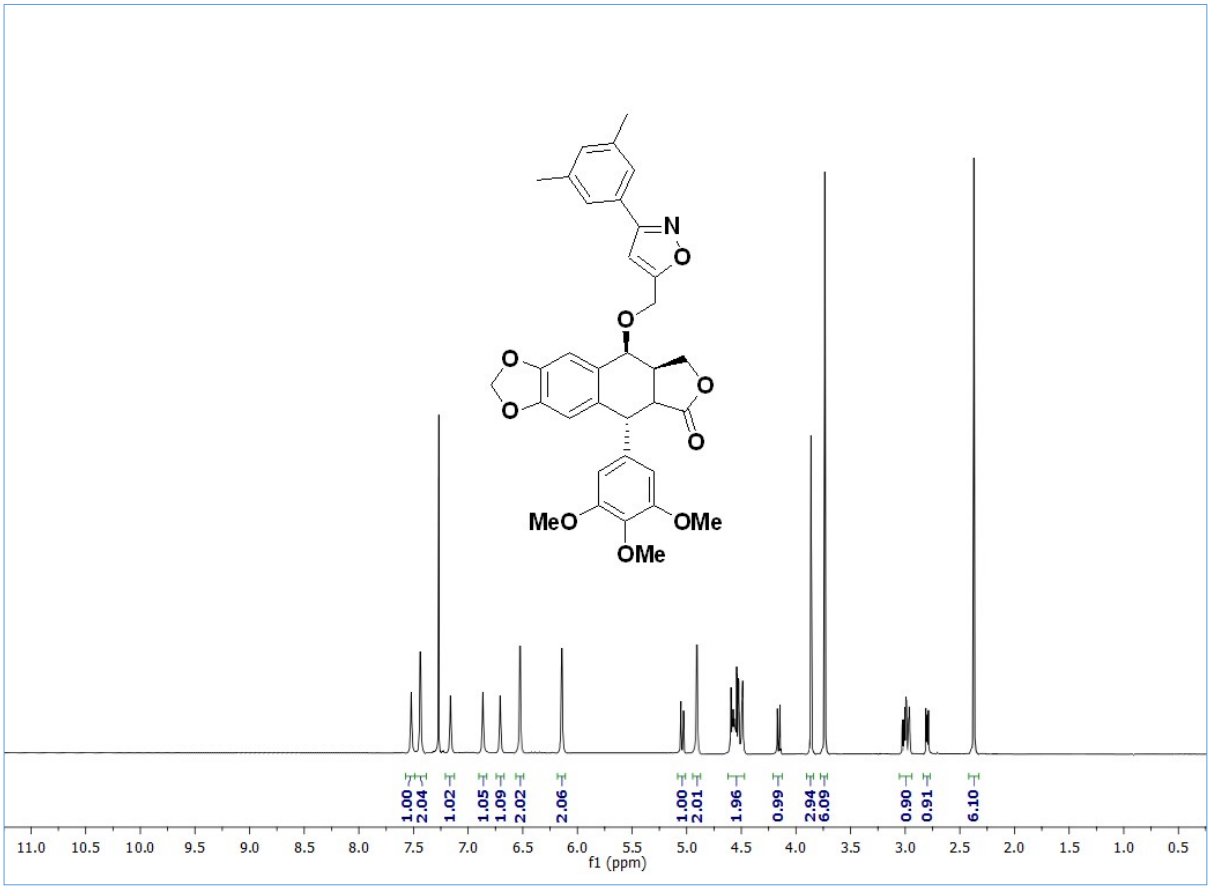
5-(5-((((5*S*,5a*R*,9*R*)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro [3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-5-yl)oxy)methyl)isoxazol-3-yl)isophthalonitrile (6n): Light orange solid; M.P.: 172-174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.82 (dd, 1H, *J* = 14.8, 6.6 Hz), 2.94-3.03 (m,1H), 3.75 (s, 6H), 3.85 (s, 3H), 4.17 (d, 1H, *J* = 7.8 Hz), 4.48-4.60 (m, 2H), 4.92 (s, 2H), 5.04 (d, 1H, *J* = 5.6 Hz), 6.17 (s, 2H), 6.51 (s, 2H), 6.70 (s, 1H), 6.87 (s, 1H), 7.52 (s, 1H), 7.80 (s, 1H), 8.21 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 170.6, 162.7, 158.8, 147.8, 145.7, 142.1, 137.7, 136.8, 135.8, 132.7, 132.1, 130.1, 118.9, 115.3, 110.6, 108.7, 107.5, 101.7, 98.3, 73.6, 67.7, 62.5, 56.9, 55.1, 45.9, 44.6, 40.5 ppm; MS (ESI): 622 $[M+H]^+$; CHN analysis for $C_{34}H_{27}N_3O_9$; Calculated (%): C, 65.70; H, 4.38; N, 6.76; Found (%): C, 65.72; H, 4.41; N, 6.79.



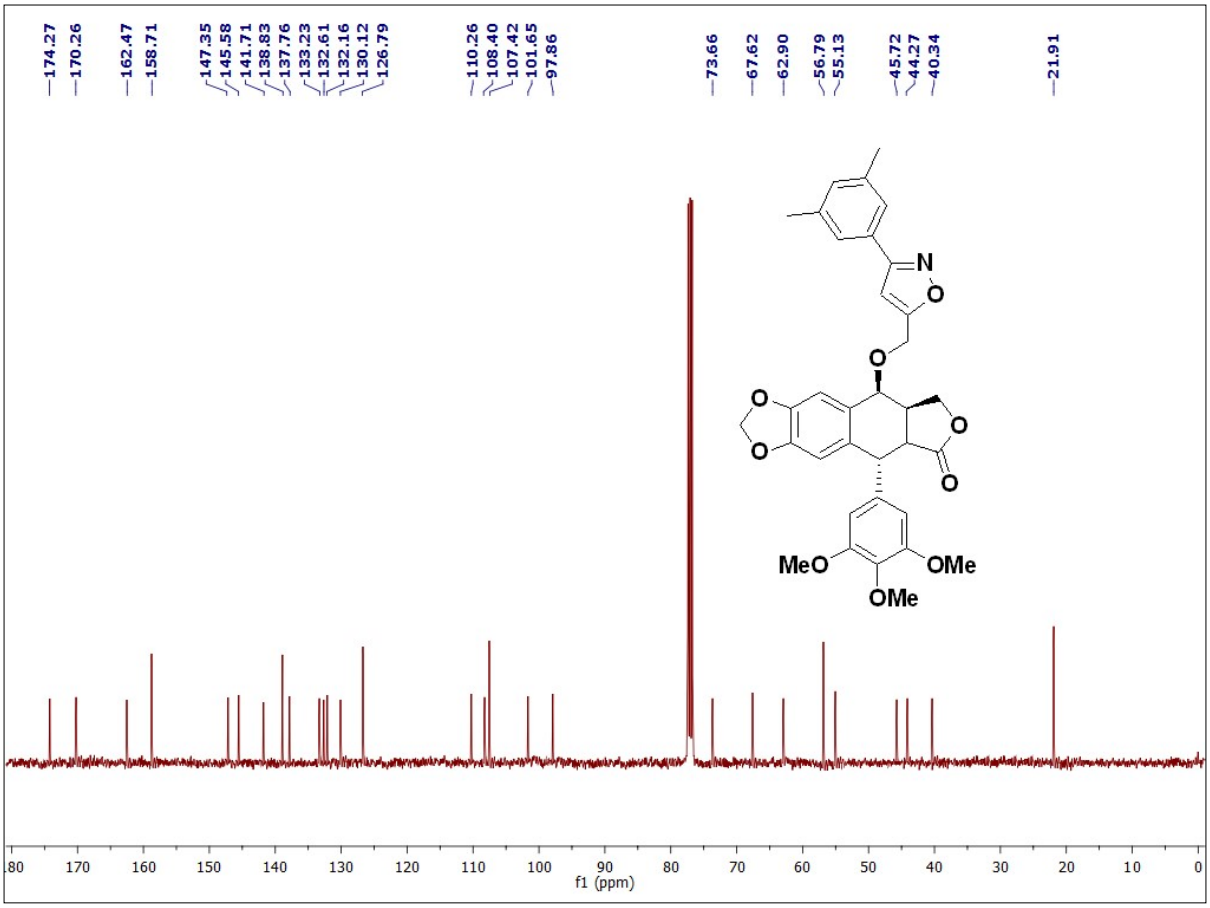
^{1}H NMR spectrum of compound **6a**



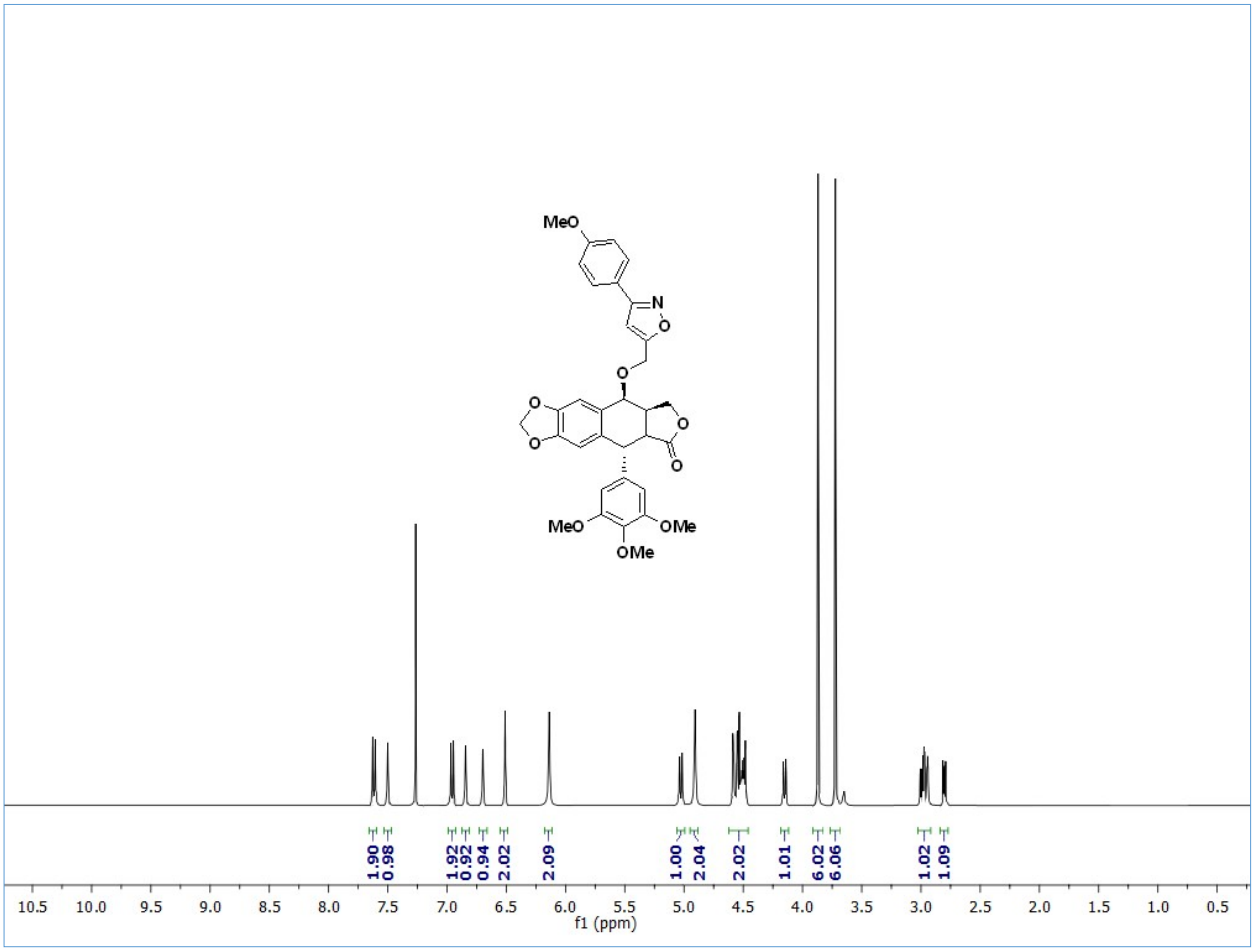
^{13}C NMR spectrum of compound **6a**



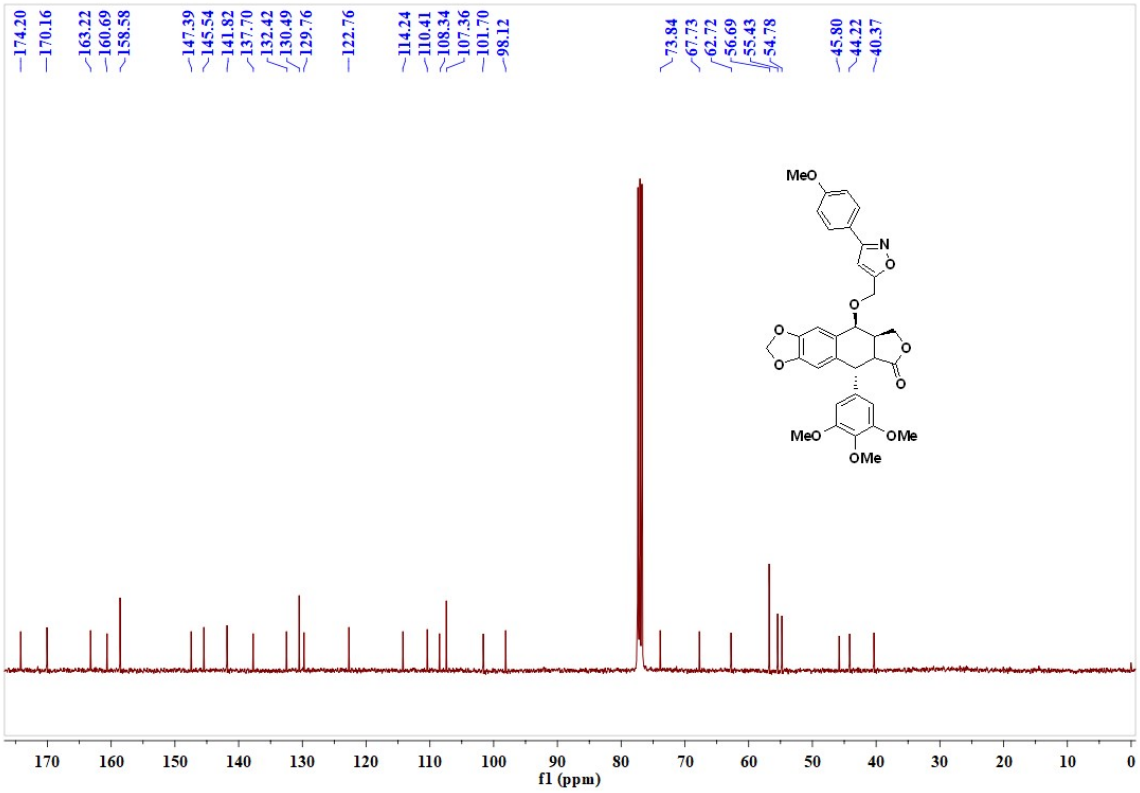
^{1}H NMR spectrum of compound **6d**



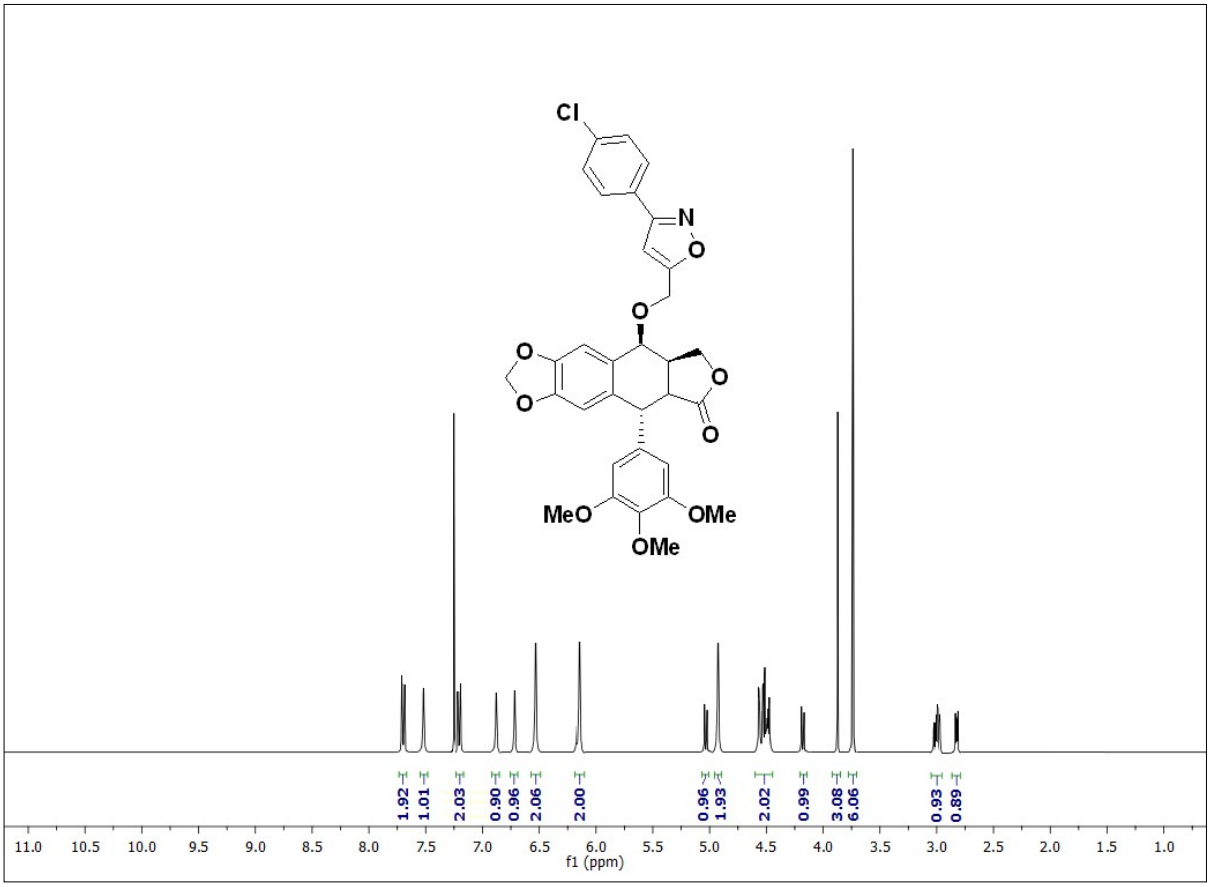
^{13}C NMR spectrum of compound **6d**



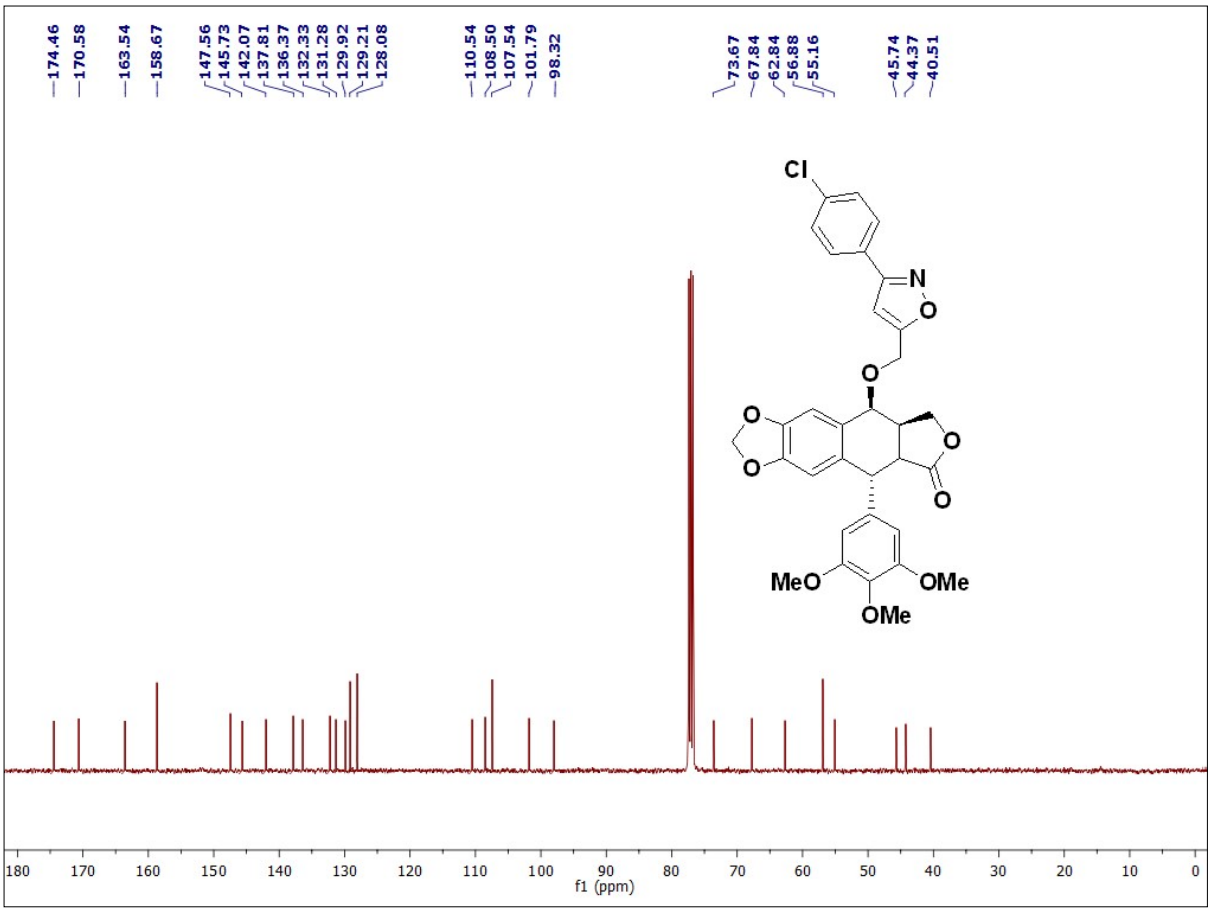
^{1}H NMR spectrum of compound **6e**



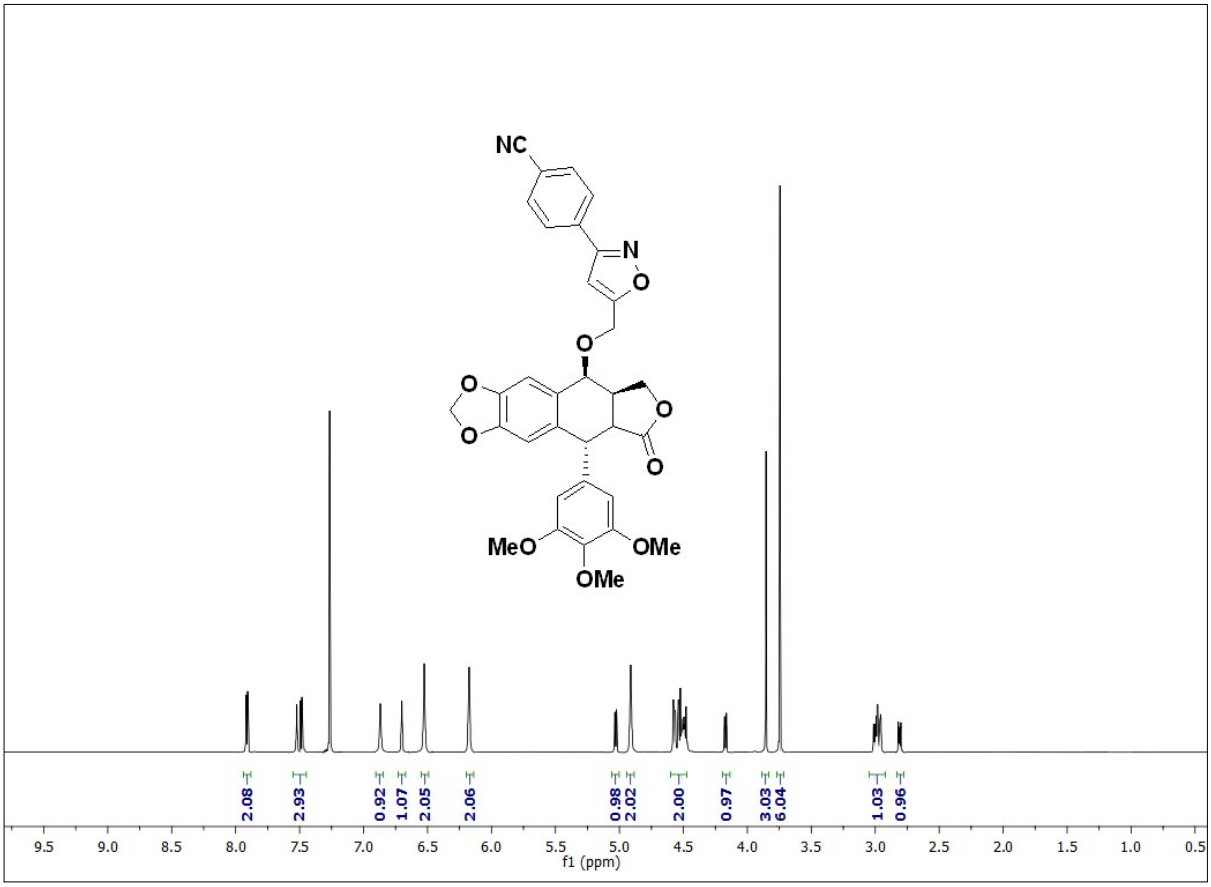
^{13}C NMR spectrum of compound **6e**



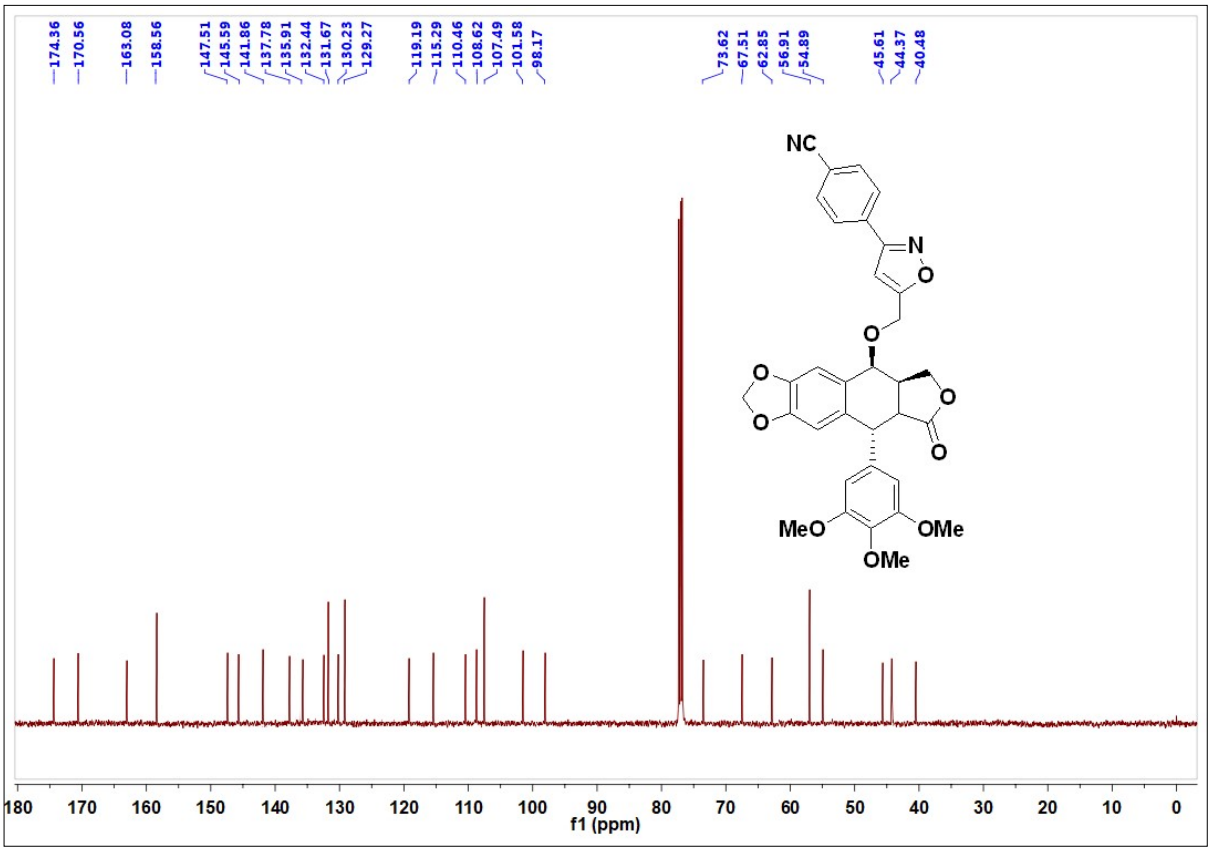
^{1}H NMR spectrum of compound **6f**



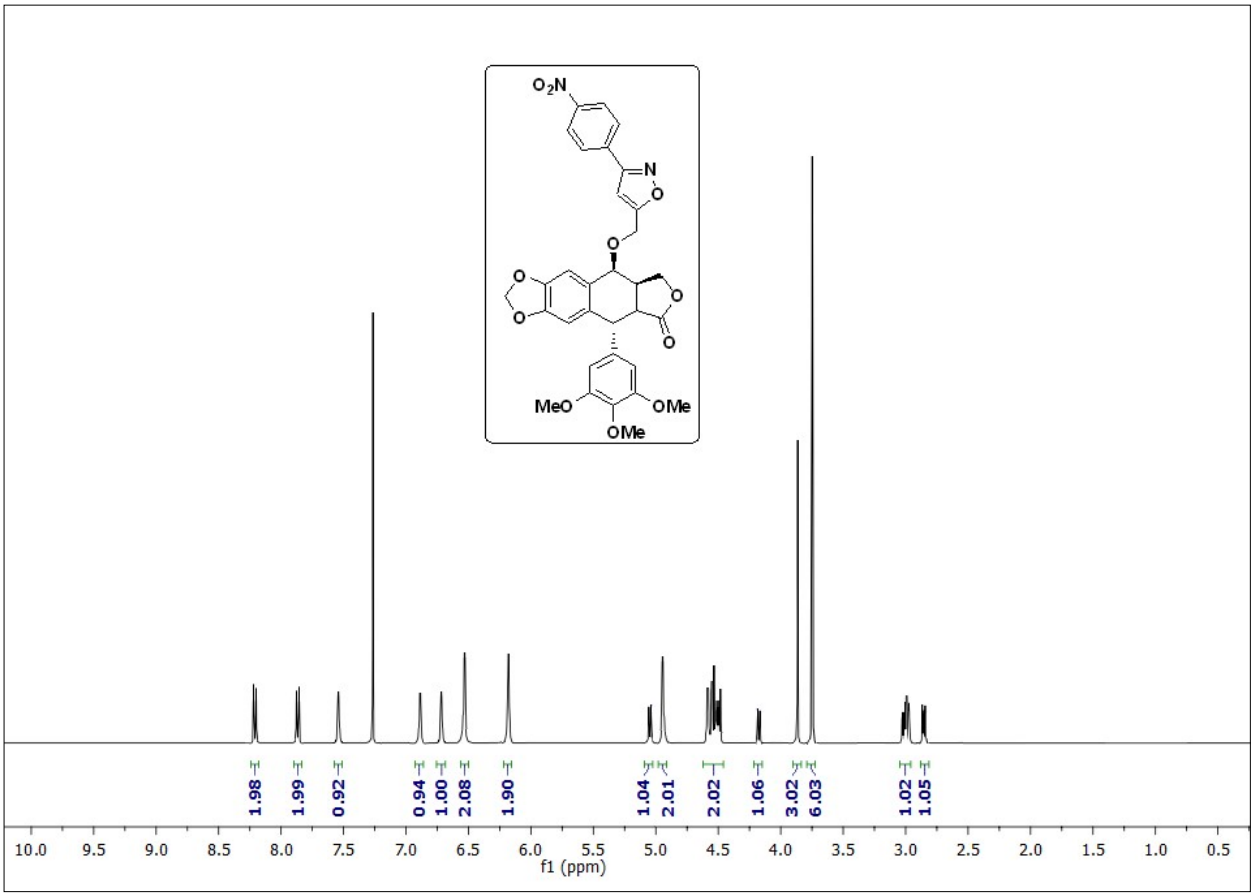
^{13}C NMR spectrum of compound **6f**



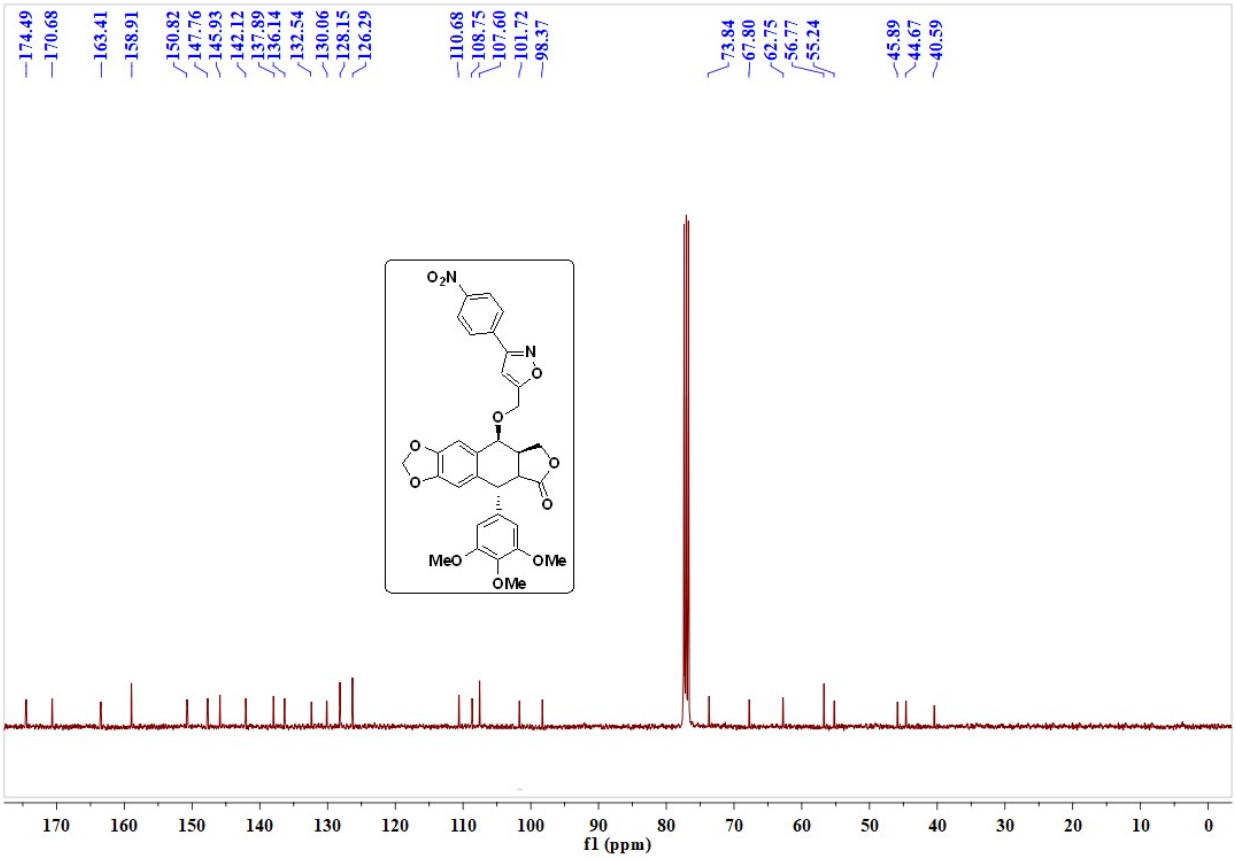
^{1}H NMR spectrum of compound **6i**



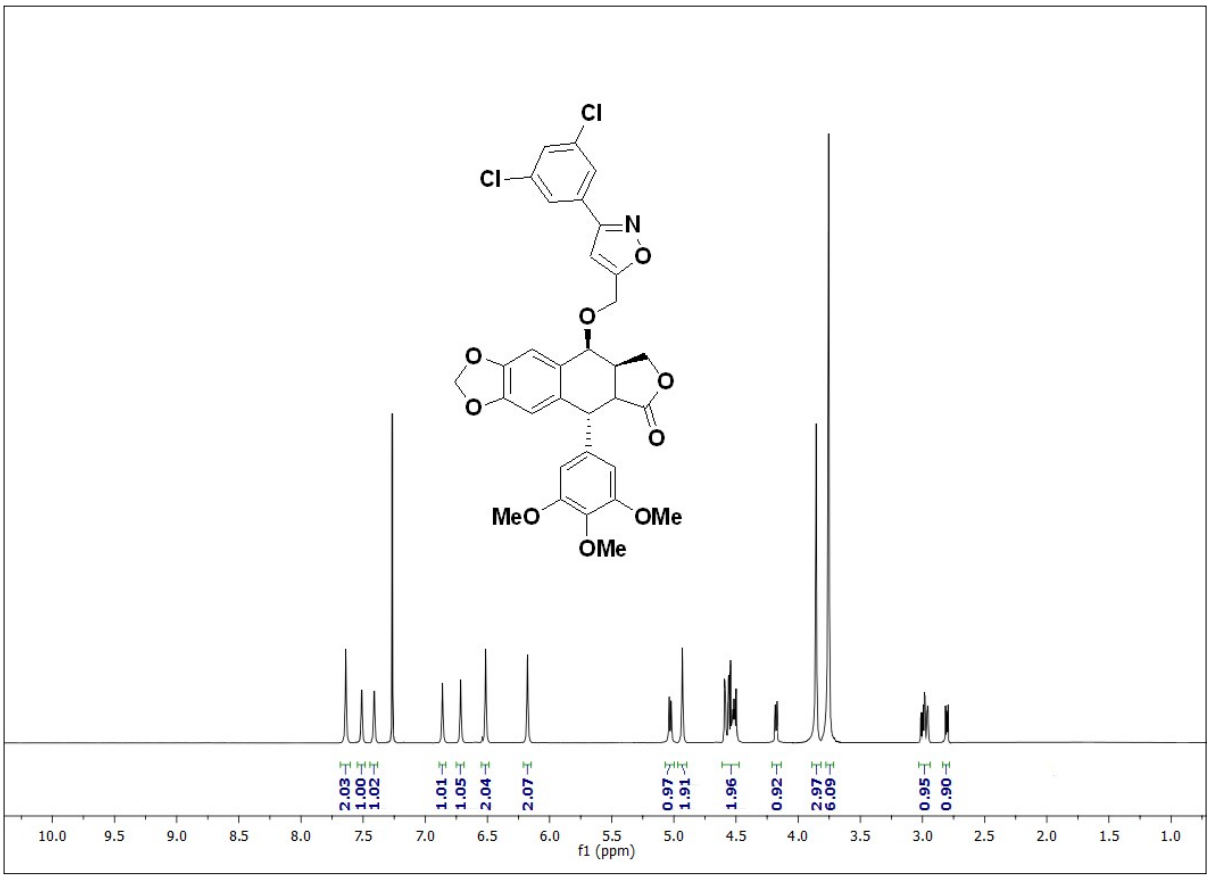
^{13}C NMR spectrum of compound **6i**



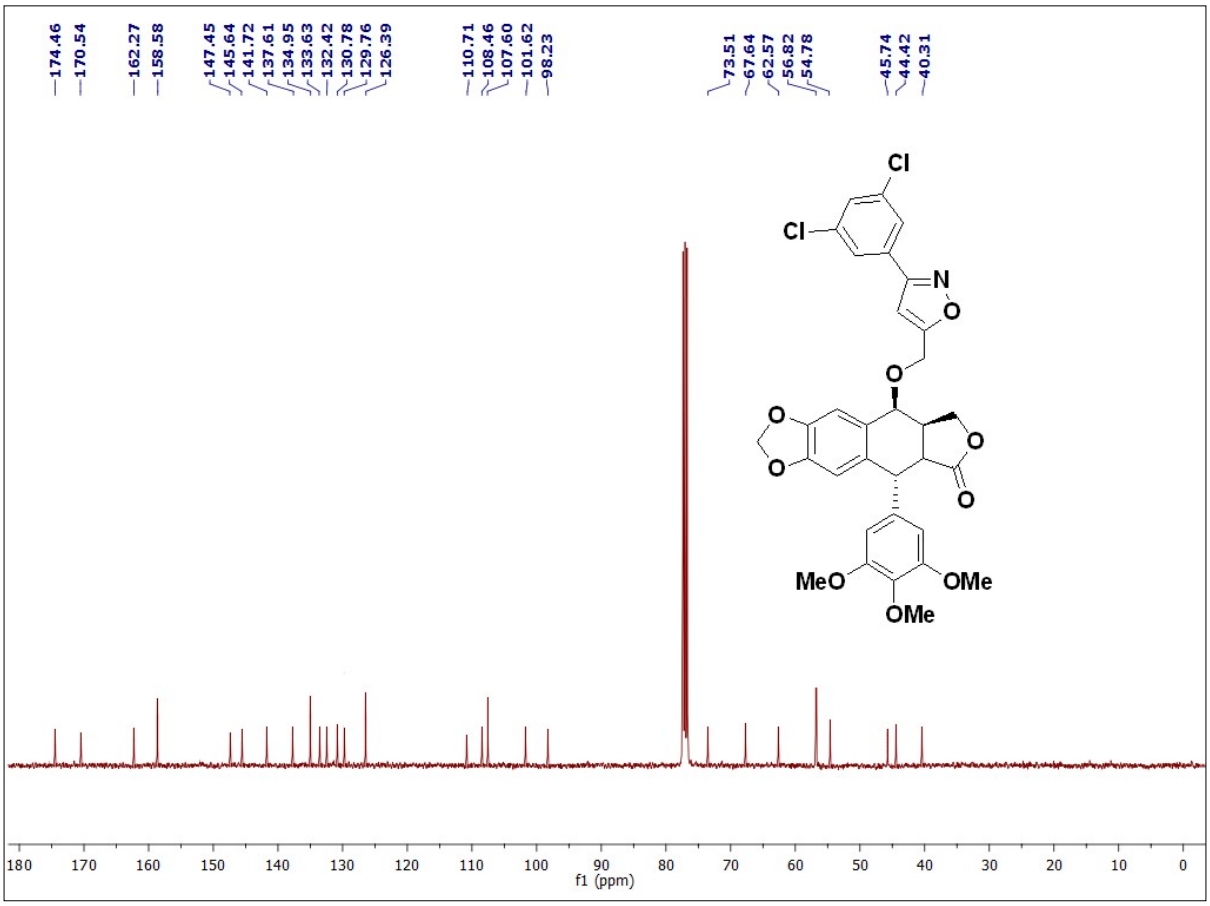
^{1}H NMR spectrum of compound **6j**



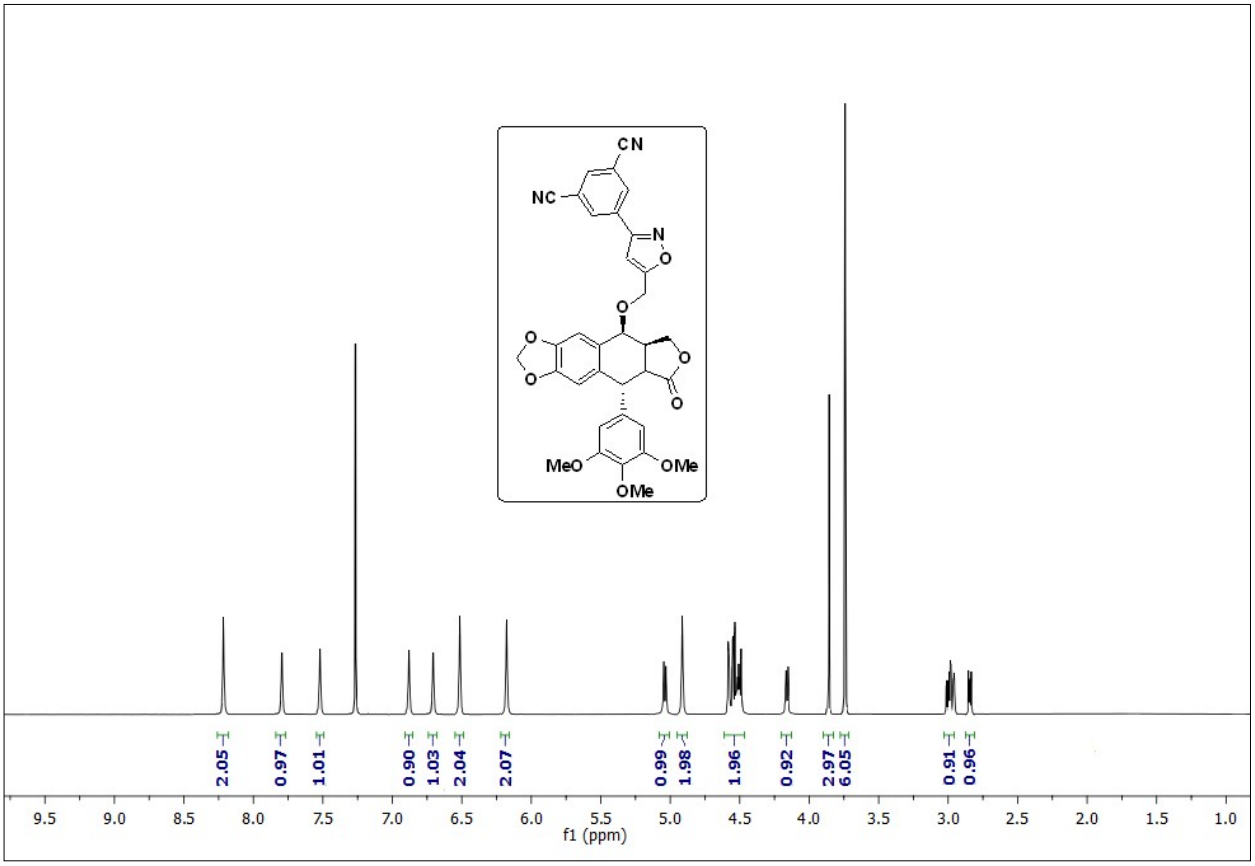
^{13}C NMR spectrum of compound **6j**



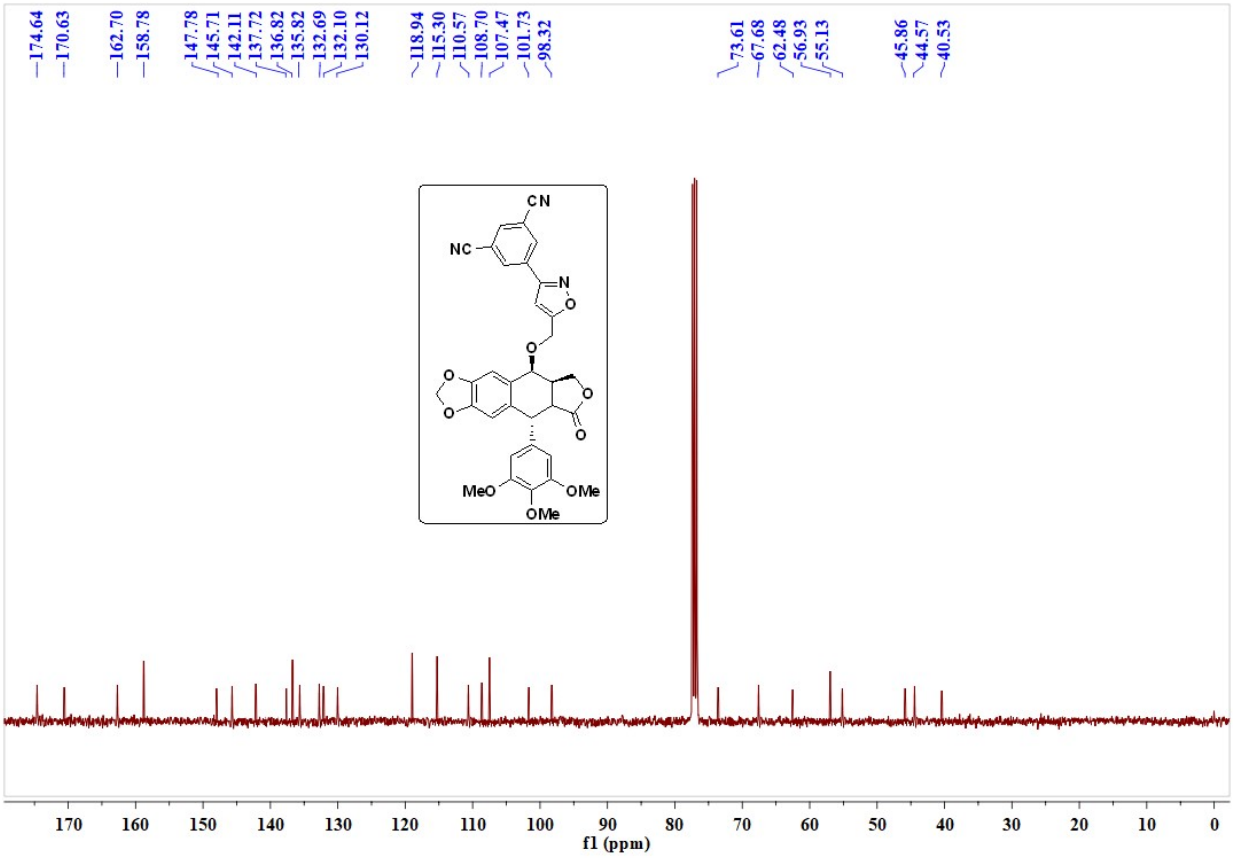
^{1}H NMR spectrum of compound **6m**



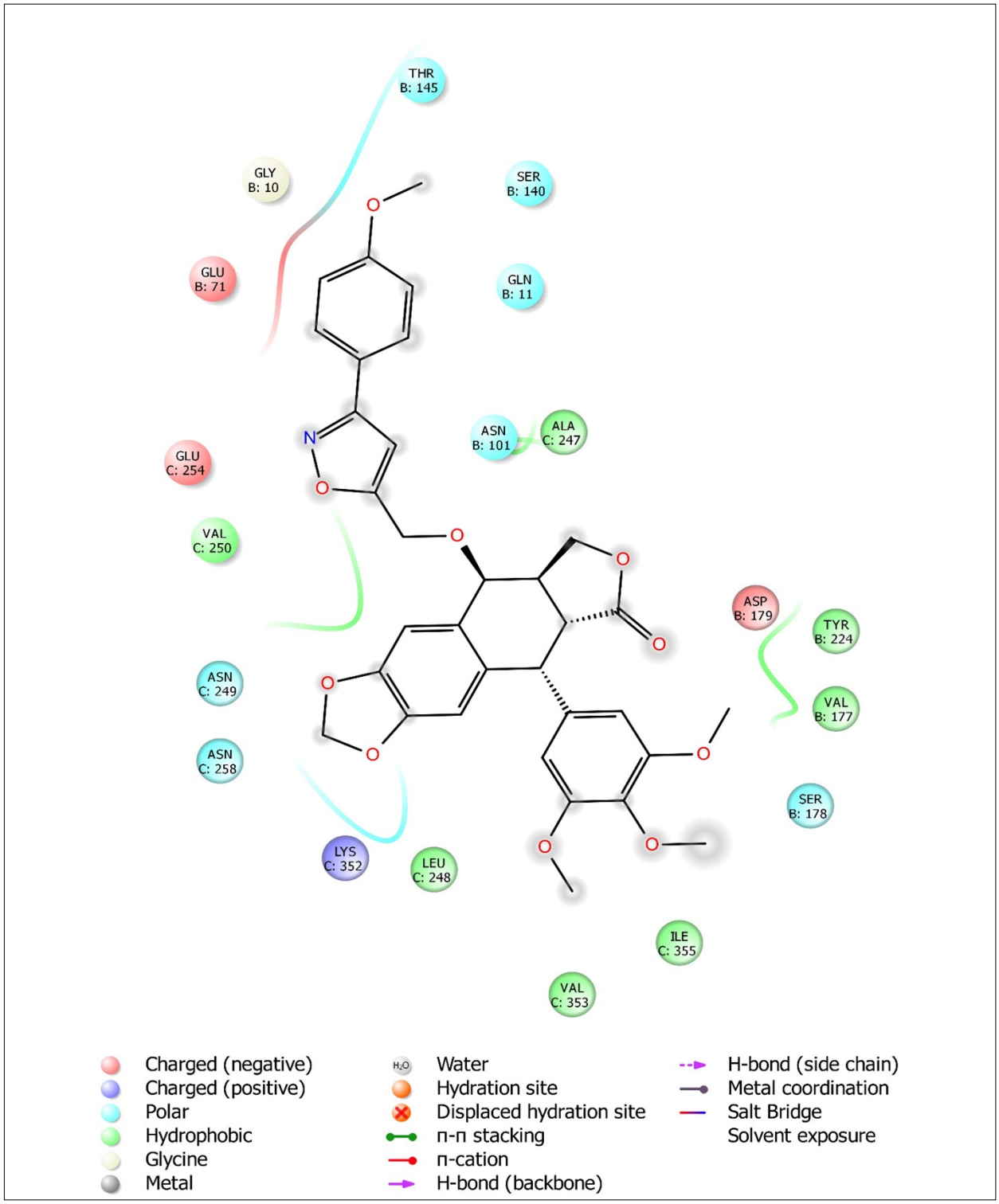
^{13}C NMR spectrum of compound **6m**



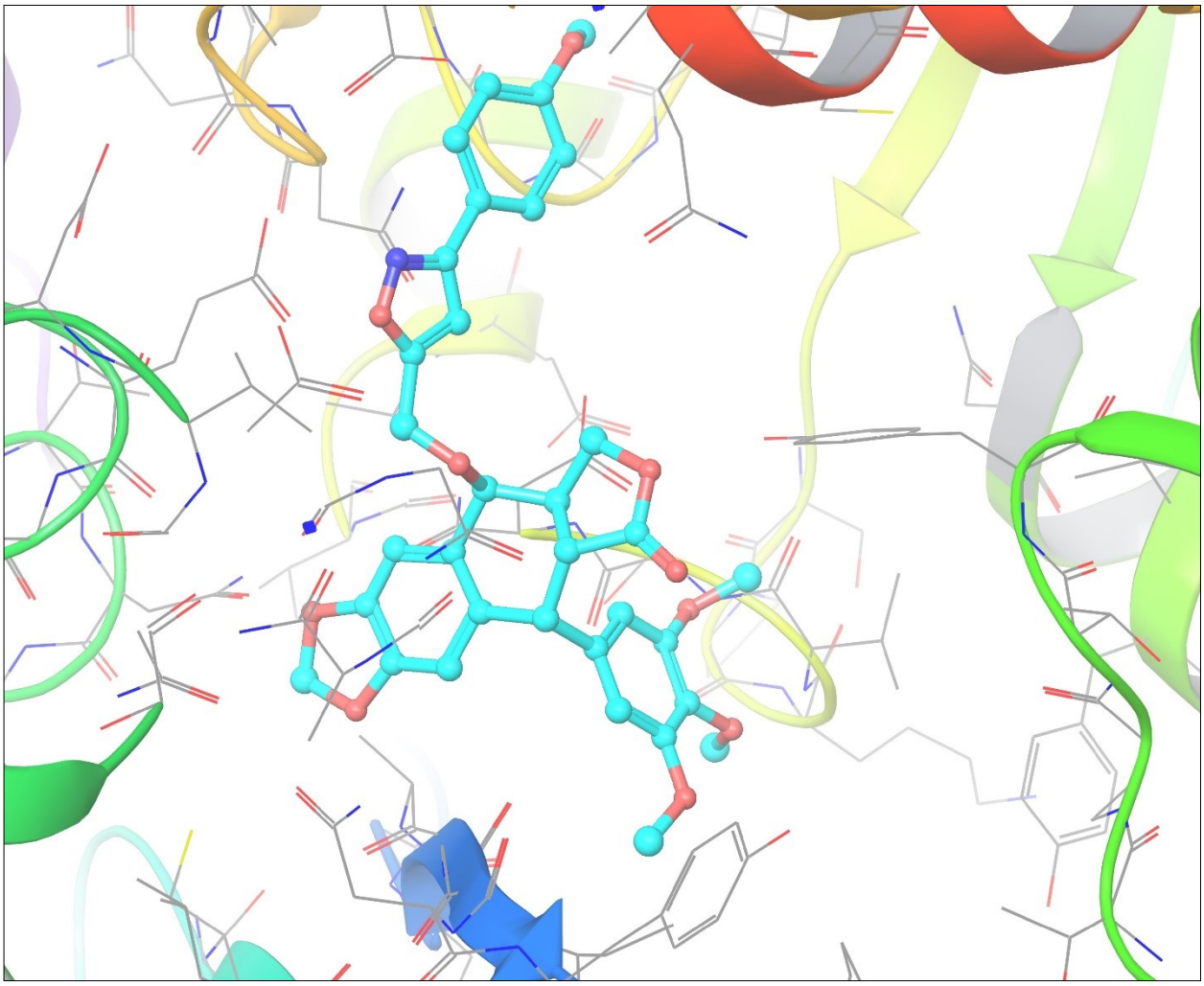
^{1}H NMR spectrum of compound **6n**



^{13}C NMR spectrum of compound **6n**



2D-molecular docking figure of compound **6e**



3D-molecular docking figure of compound **6e**

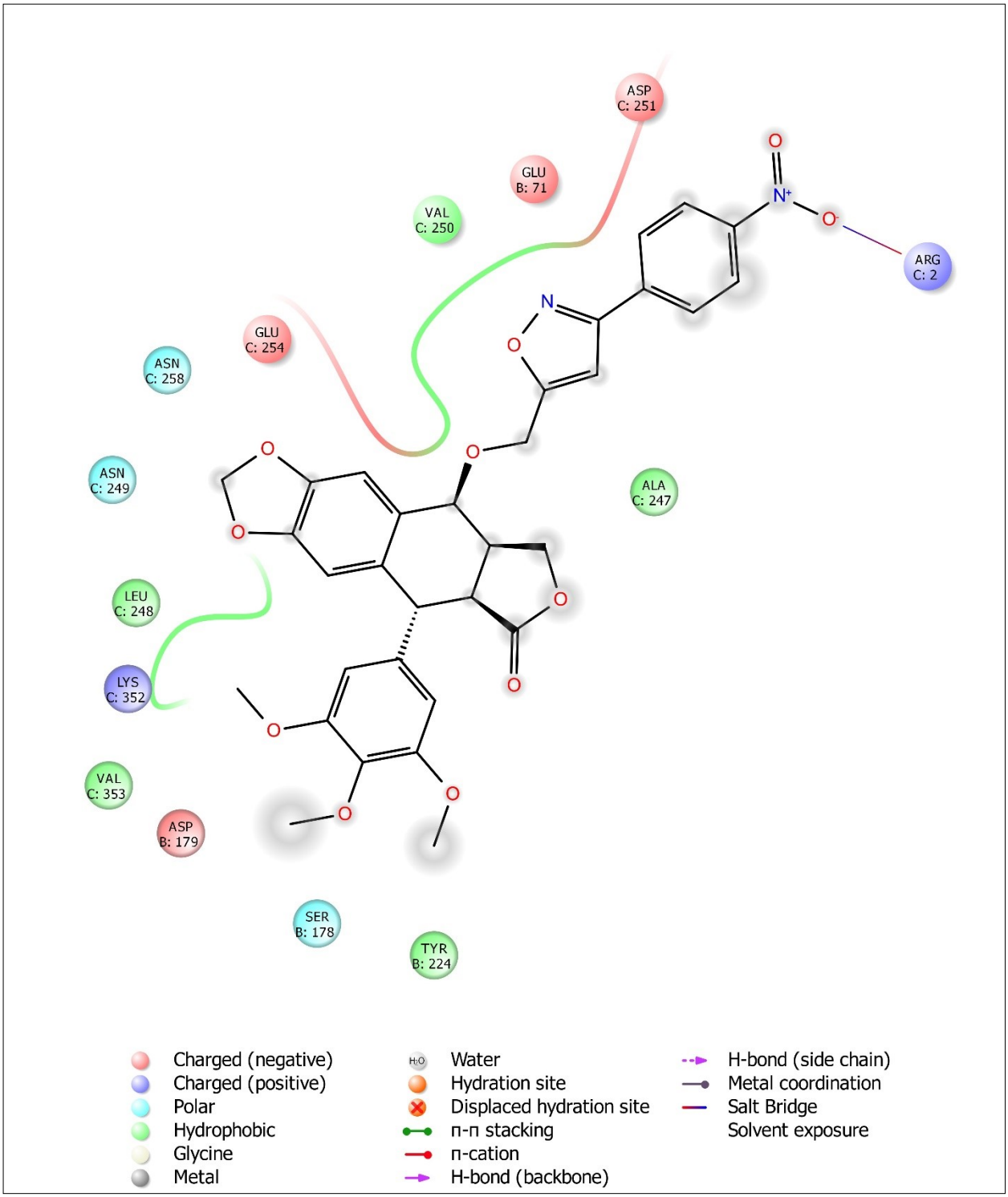
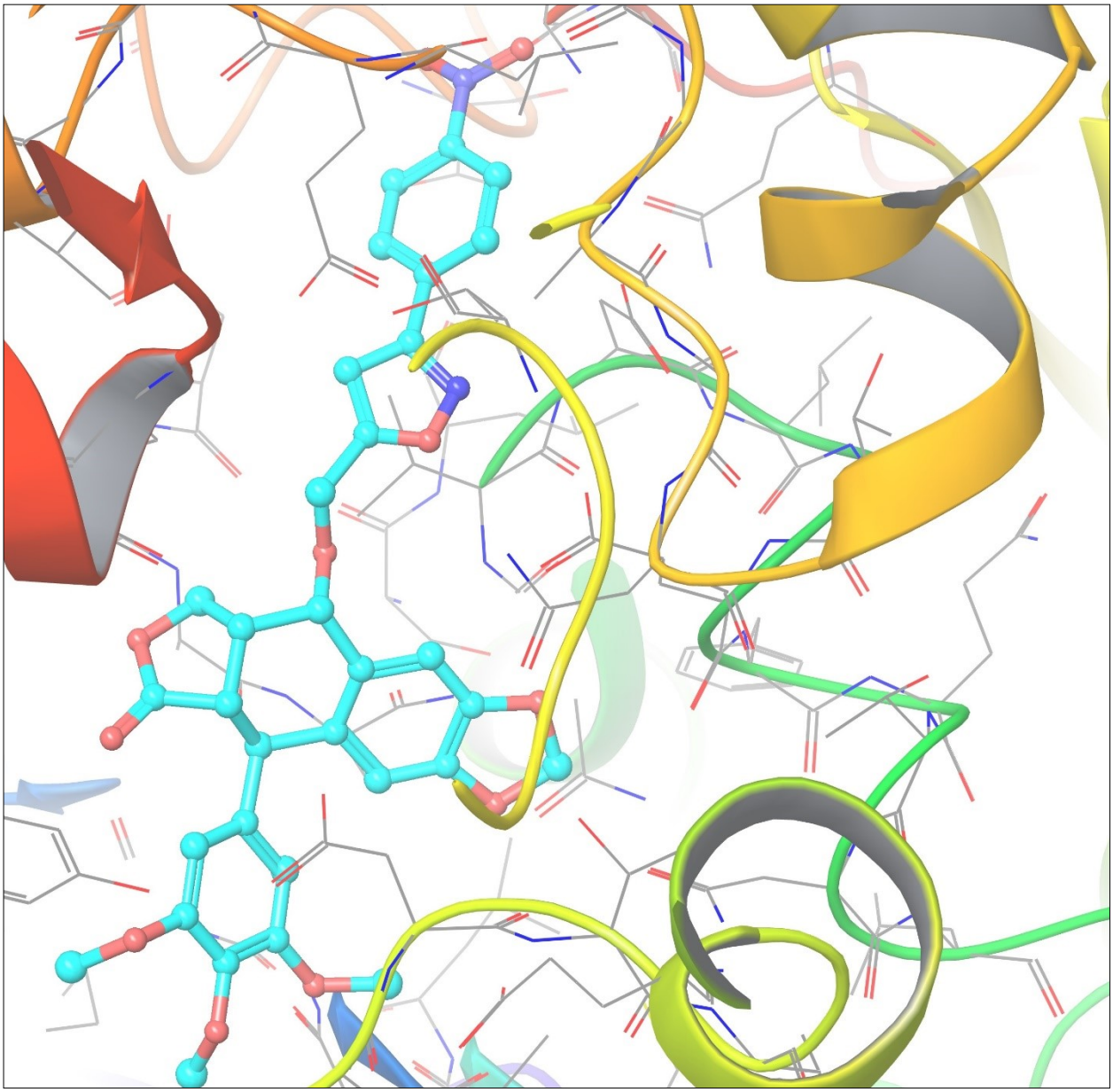
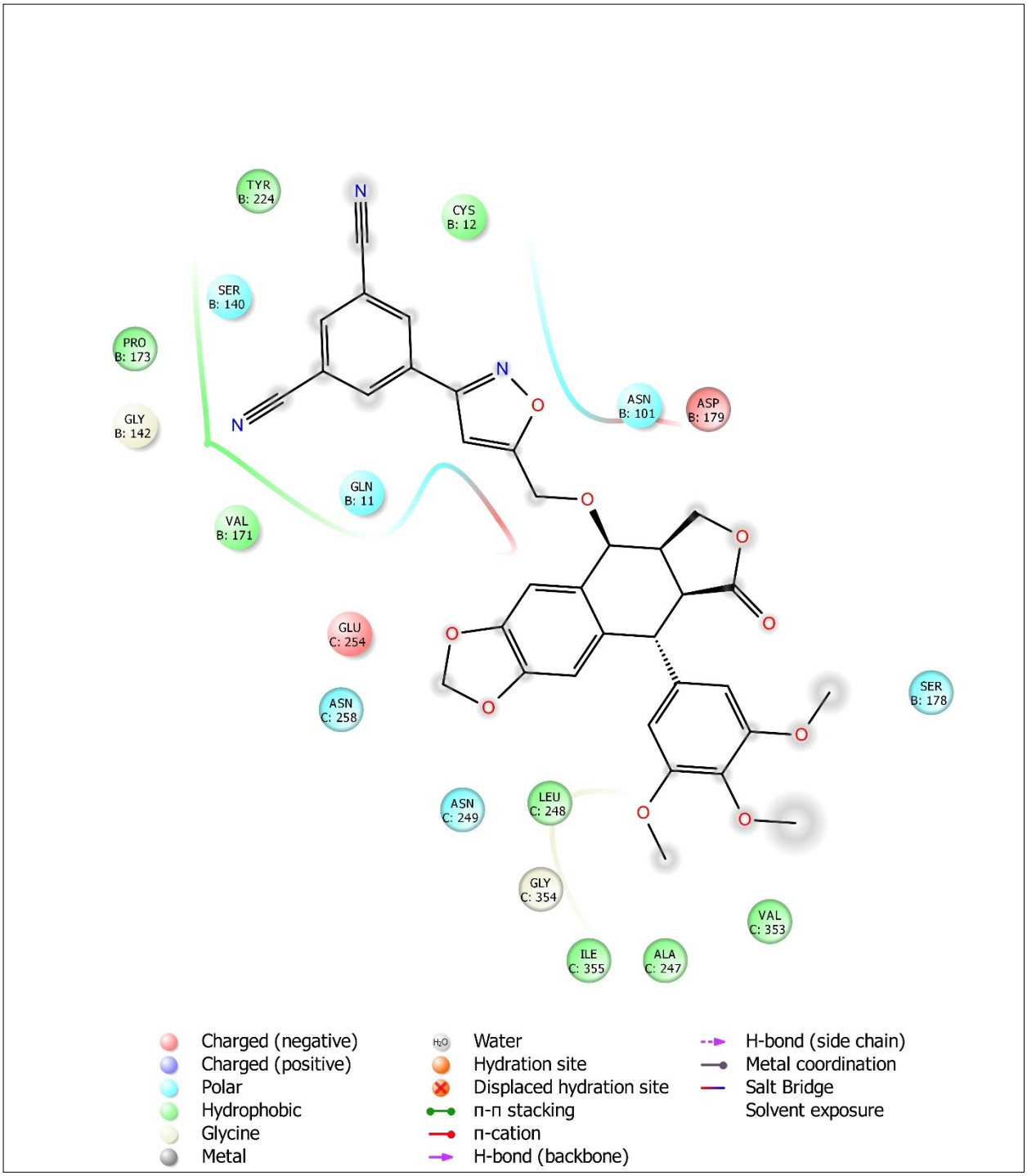


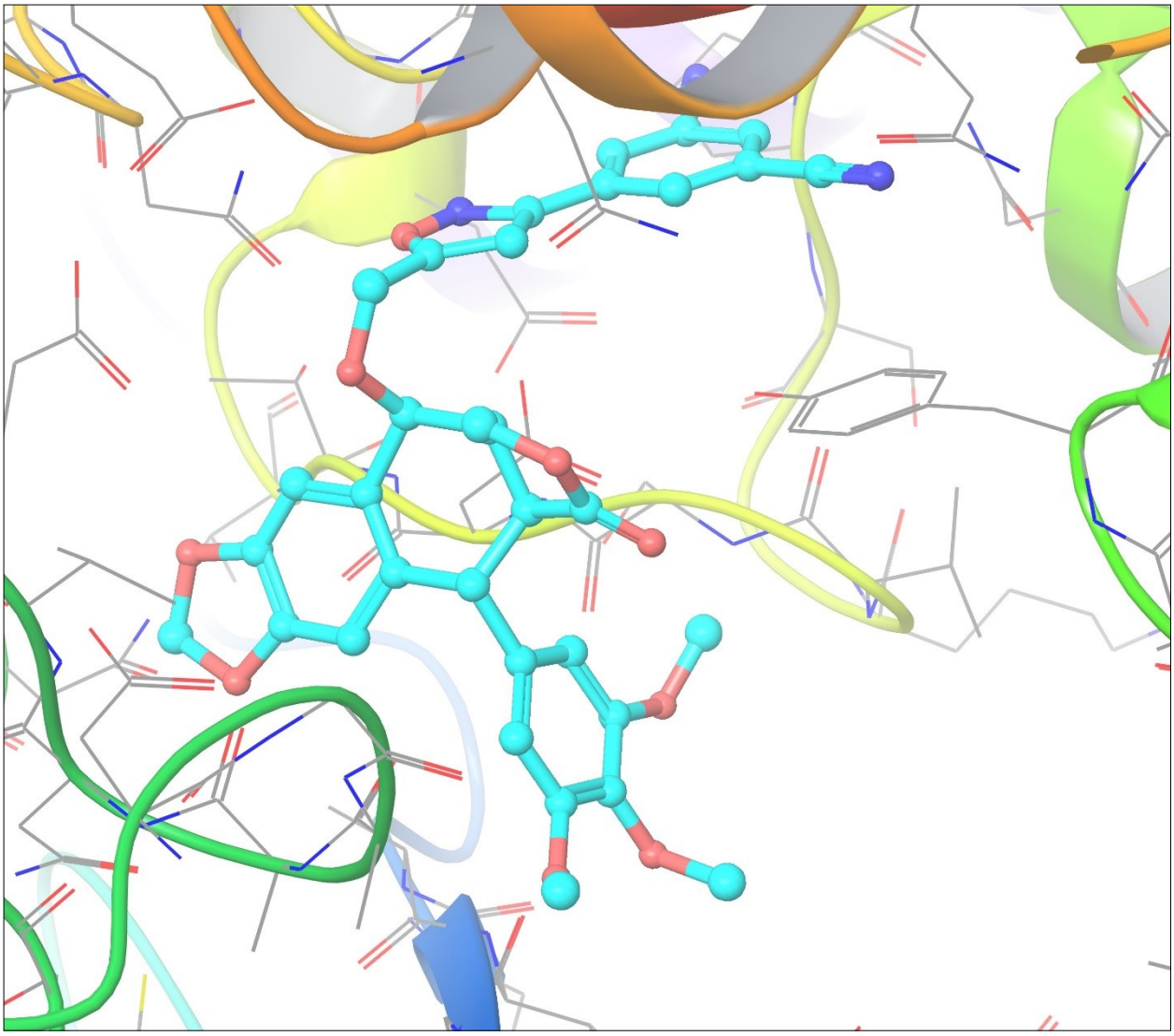
Figure 4.7. 2D-molecular docking figure of compound **6j**



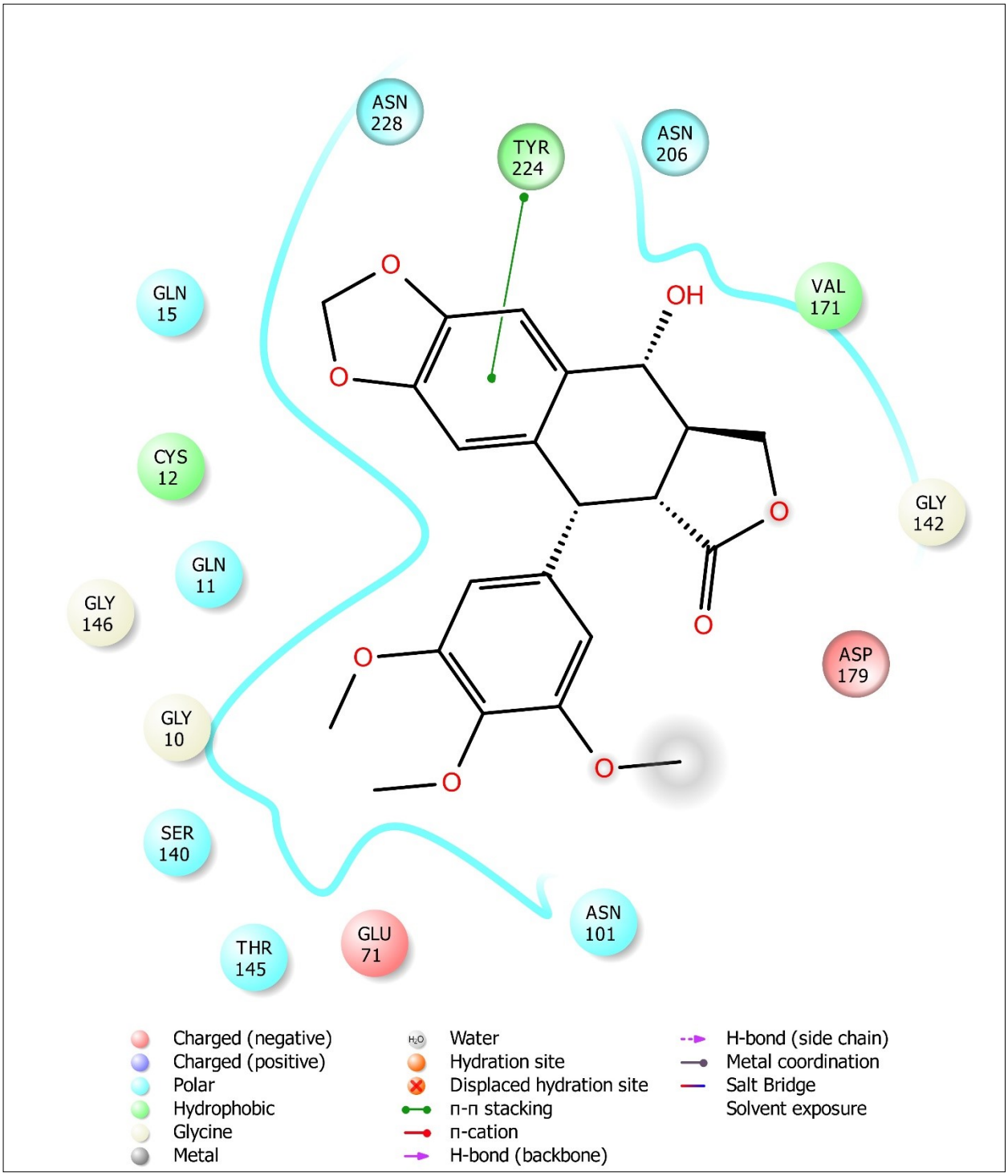
3D-molecular docking figure of compound **6j**



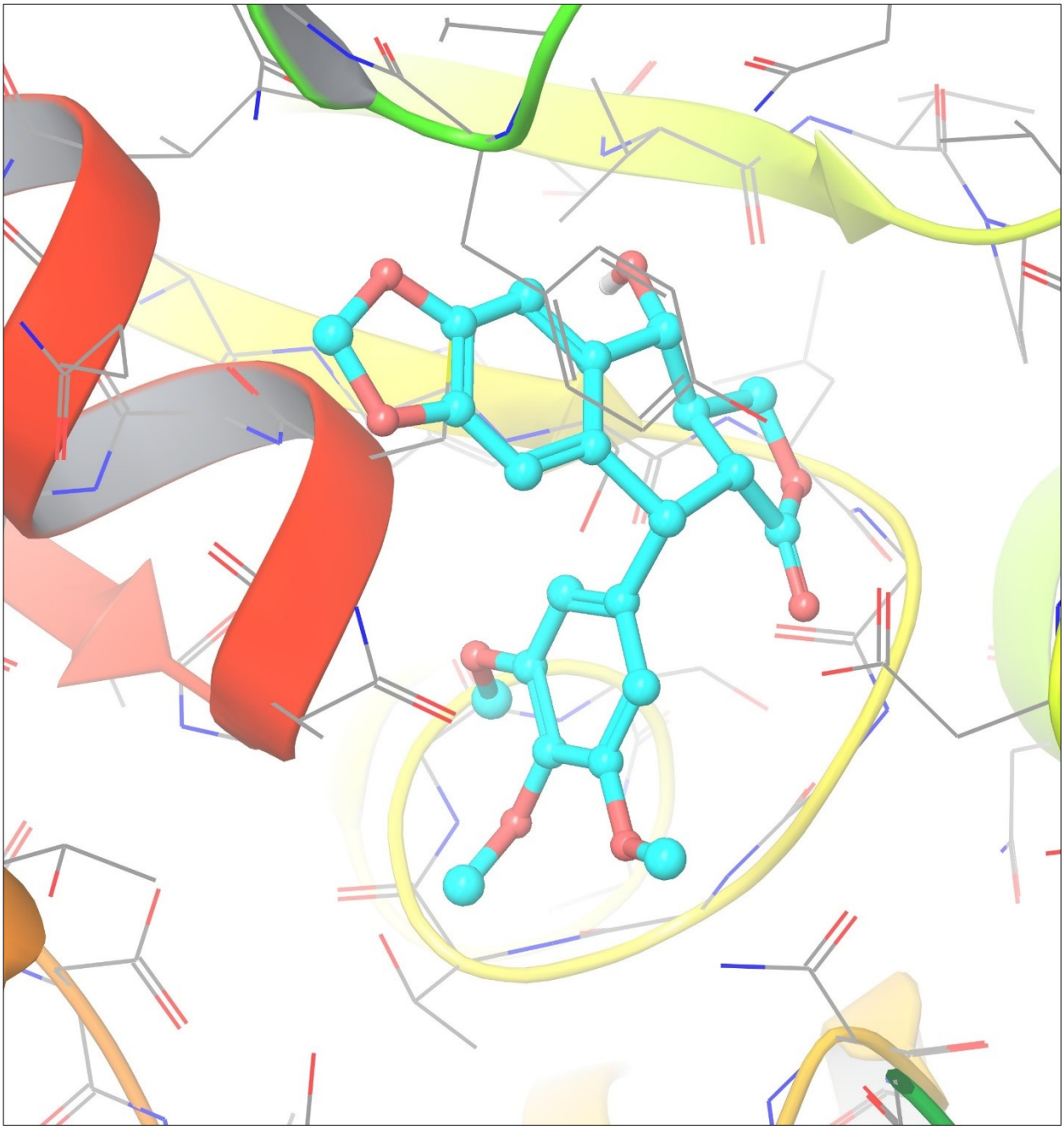
3D-molecular docking figure of compound **6n**



3D-molecular docking figure of compound **6n**



2D-molecular docking figure of compound podophyllotoxin



3D-molecular docking figure of compound podophyllotoxin