Electronic supplementary information (ESI)

Dual-targeted inhibitors of mycobacterial aminoacyl-tRNA synthetases among N-benzylidene-N´-thiazol-2-yl-hydrazines

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Table of Contents

Section 1. Docking results for compounds 1 – 37

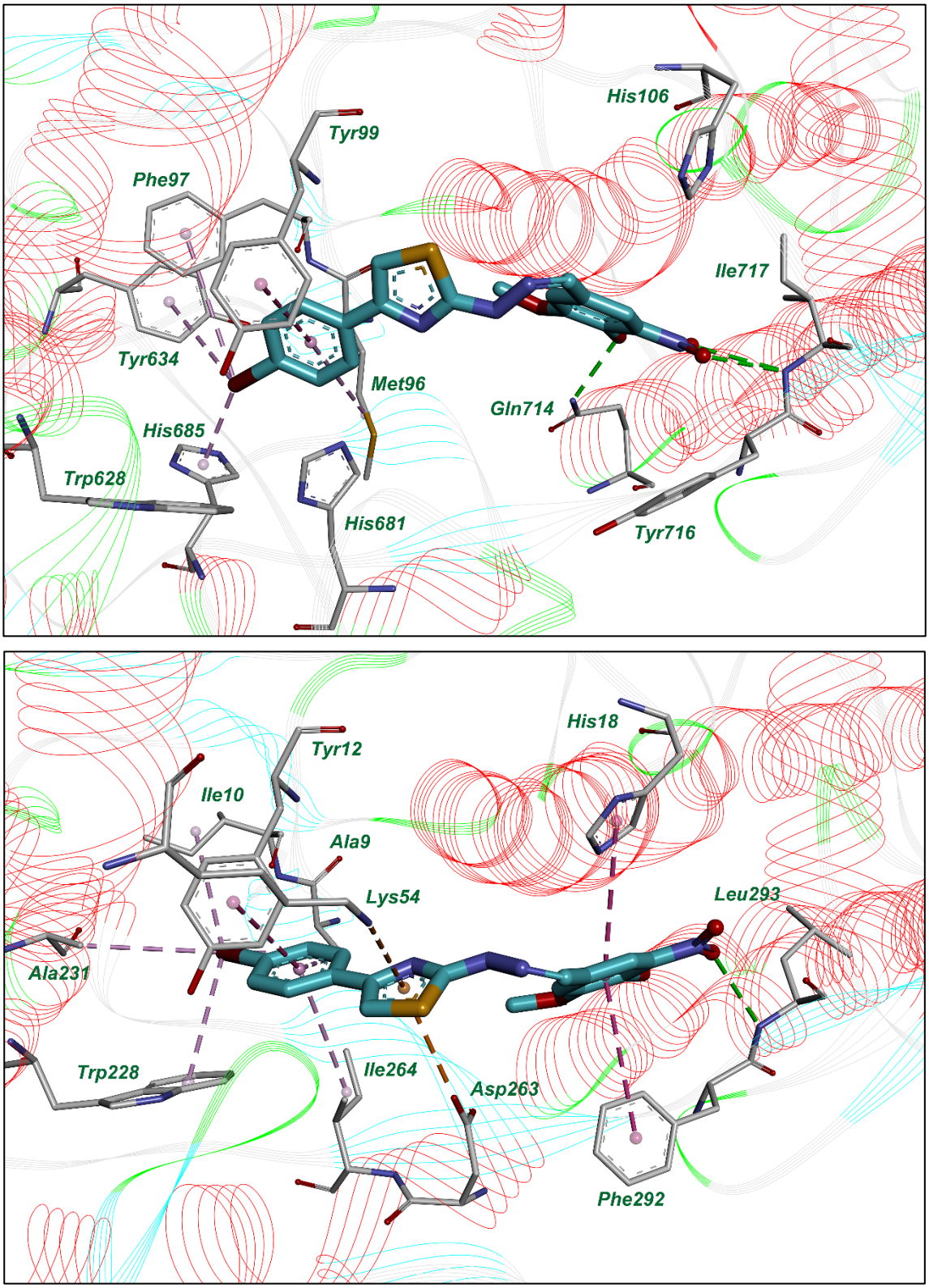
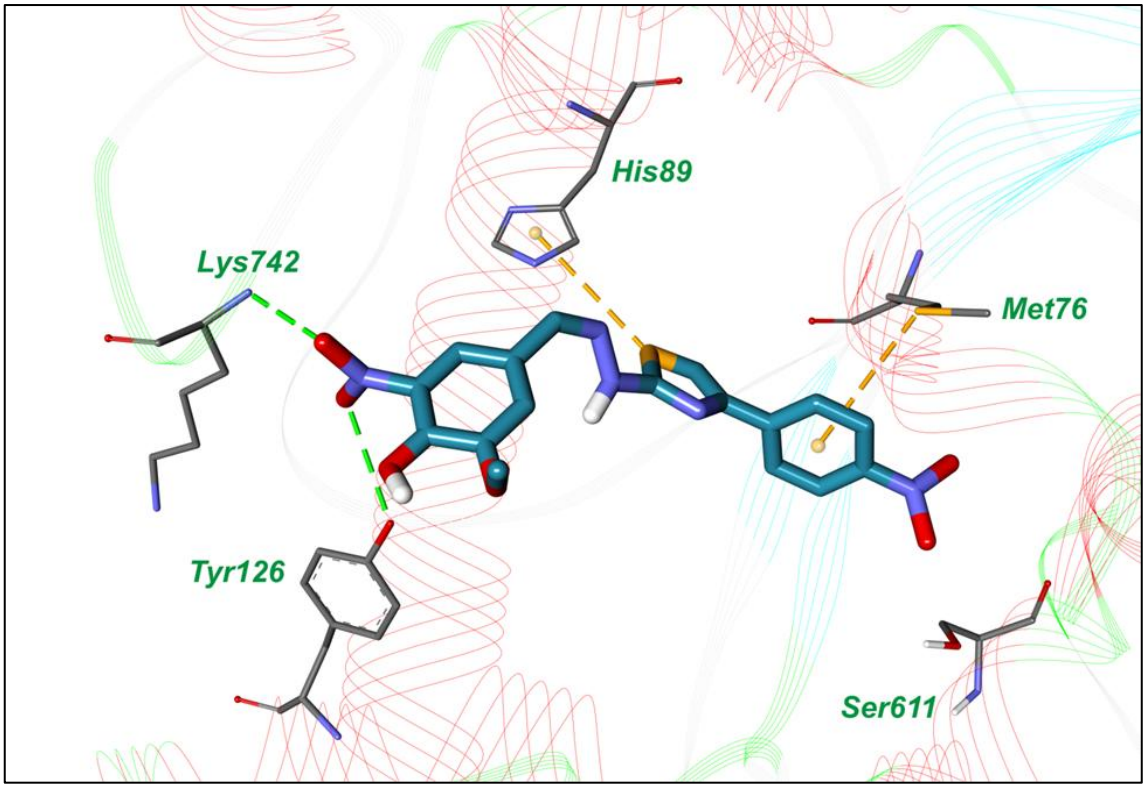


Figure S1-1. The complexes of compound **1** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-cation interactions – with orange color.



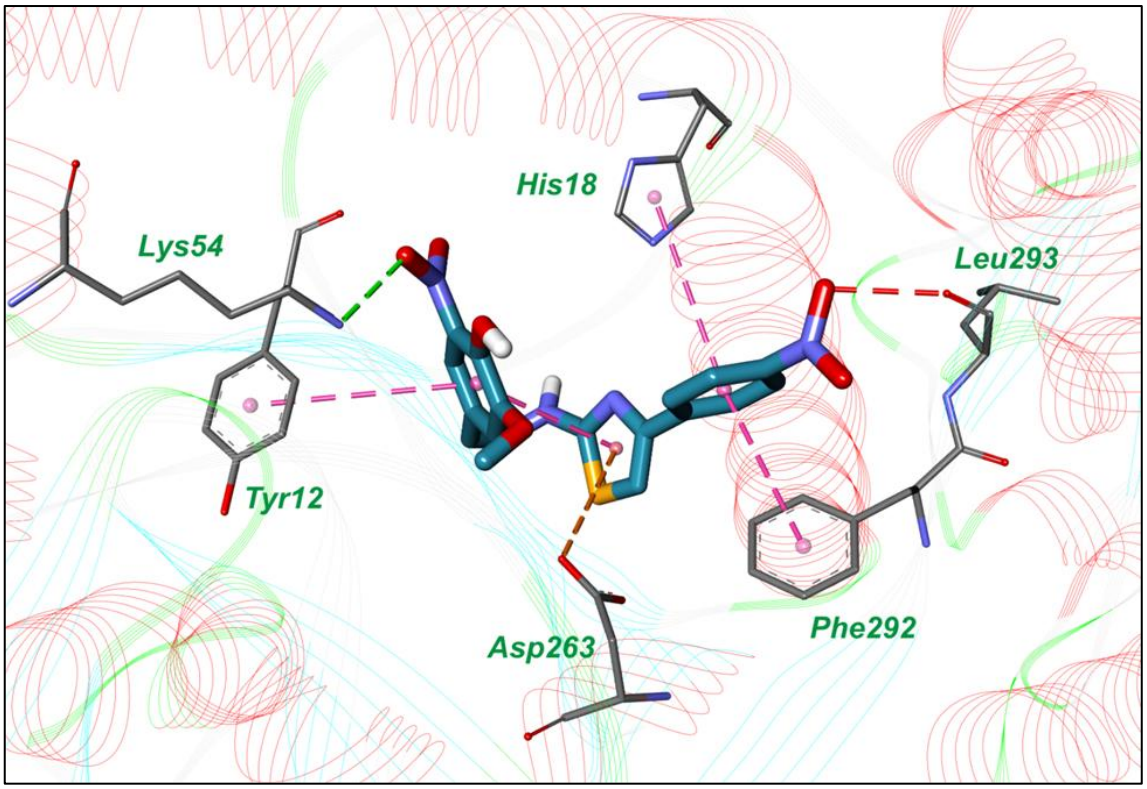


Figure S1-2. The complexes of compound **2** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

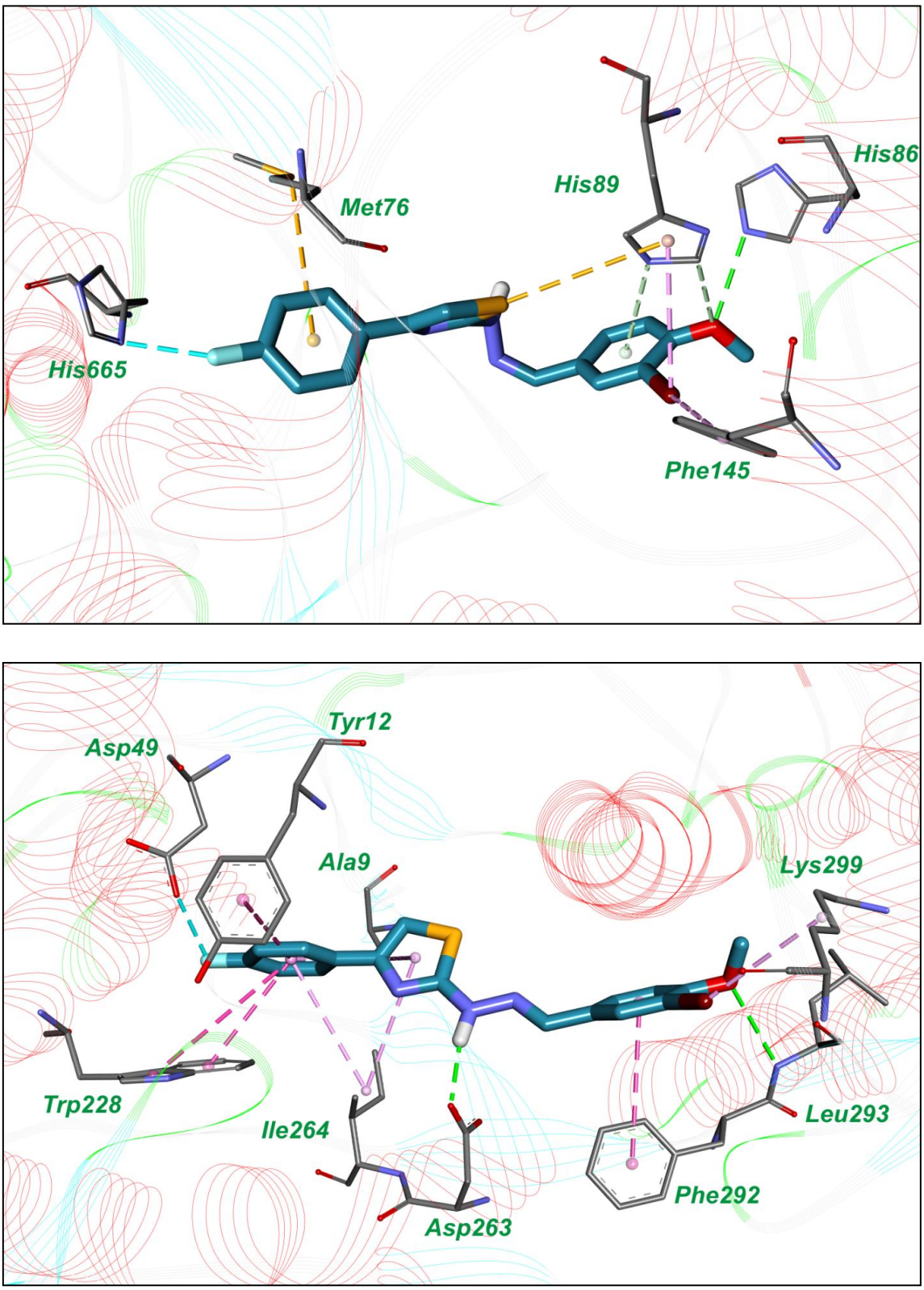


Figure S1-3. The complexes of compound **3** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color, halogen bonds – with blue color.

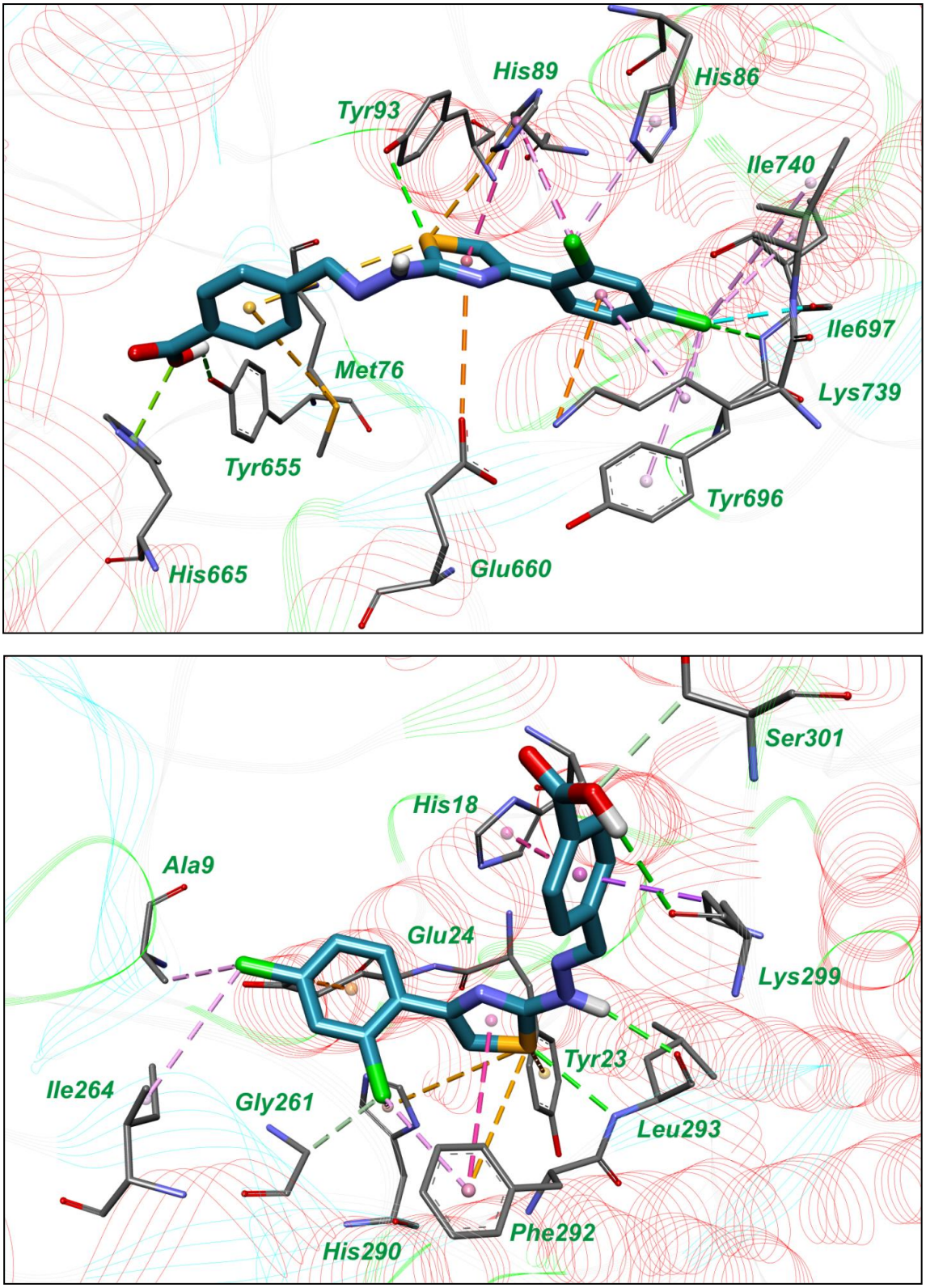
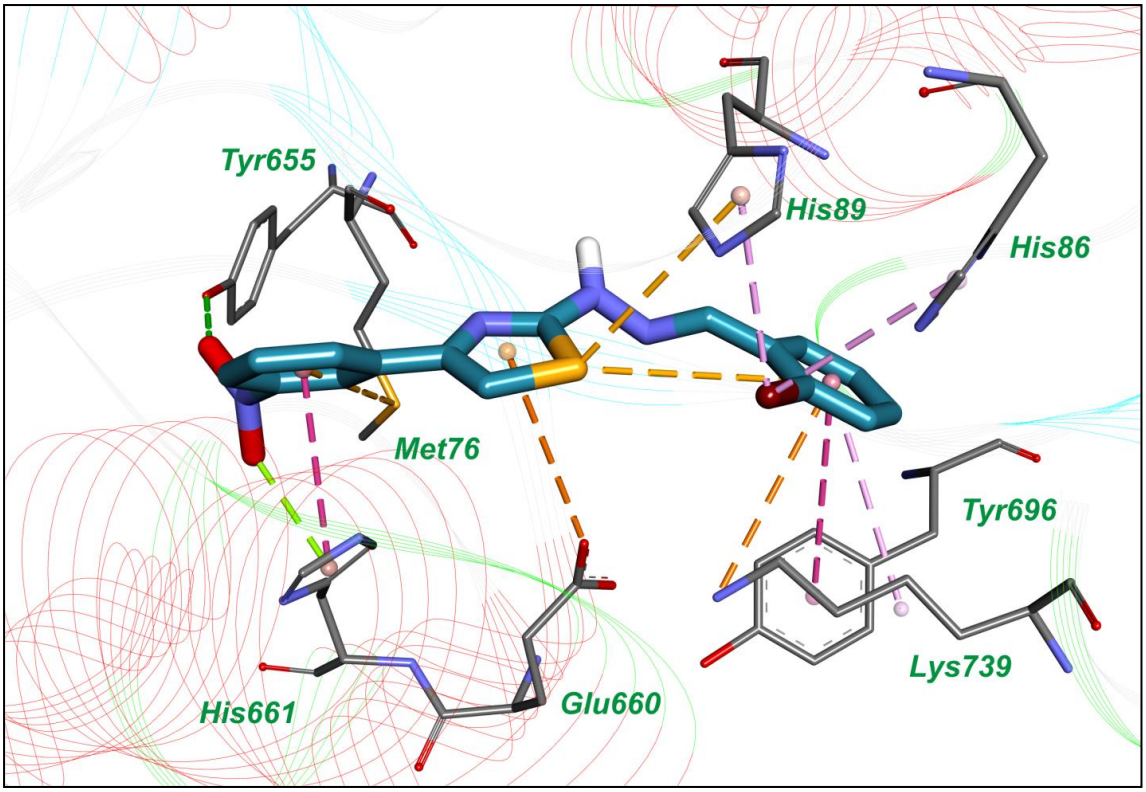


Figure S1-4. The complexes of compound **4** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color, halogen bonds – with blue color.



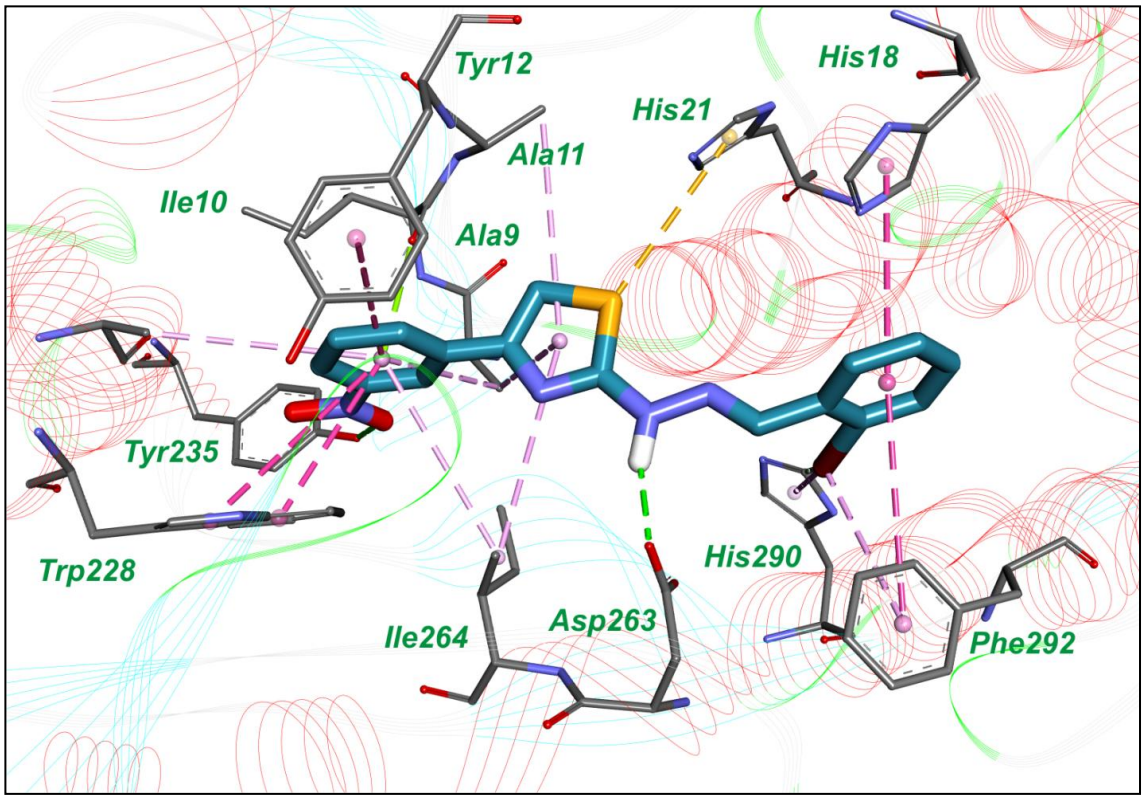


Figure S1-5. The complexes of compound **5** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

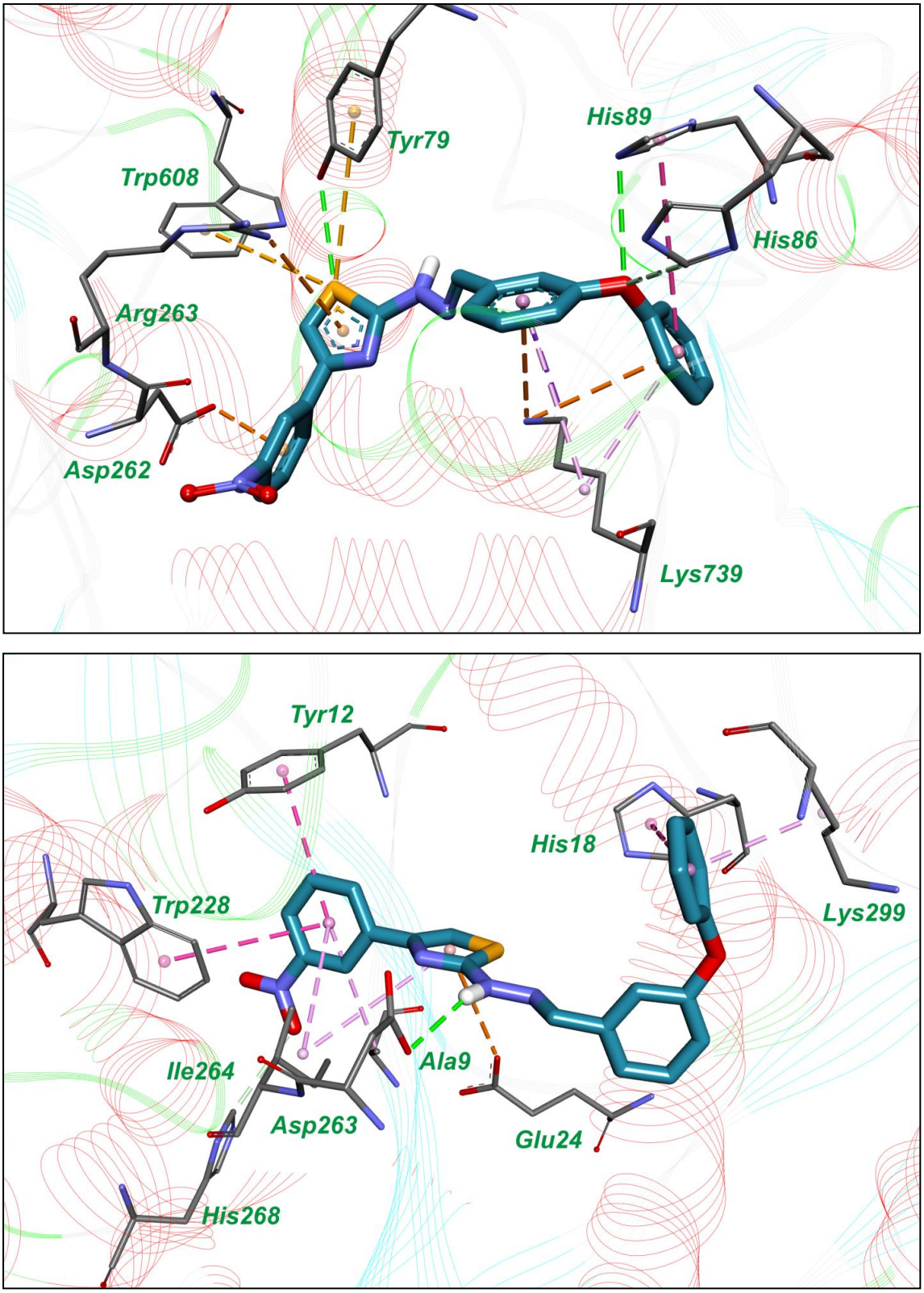
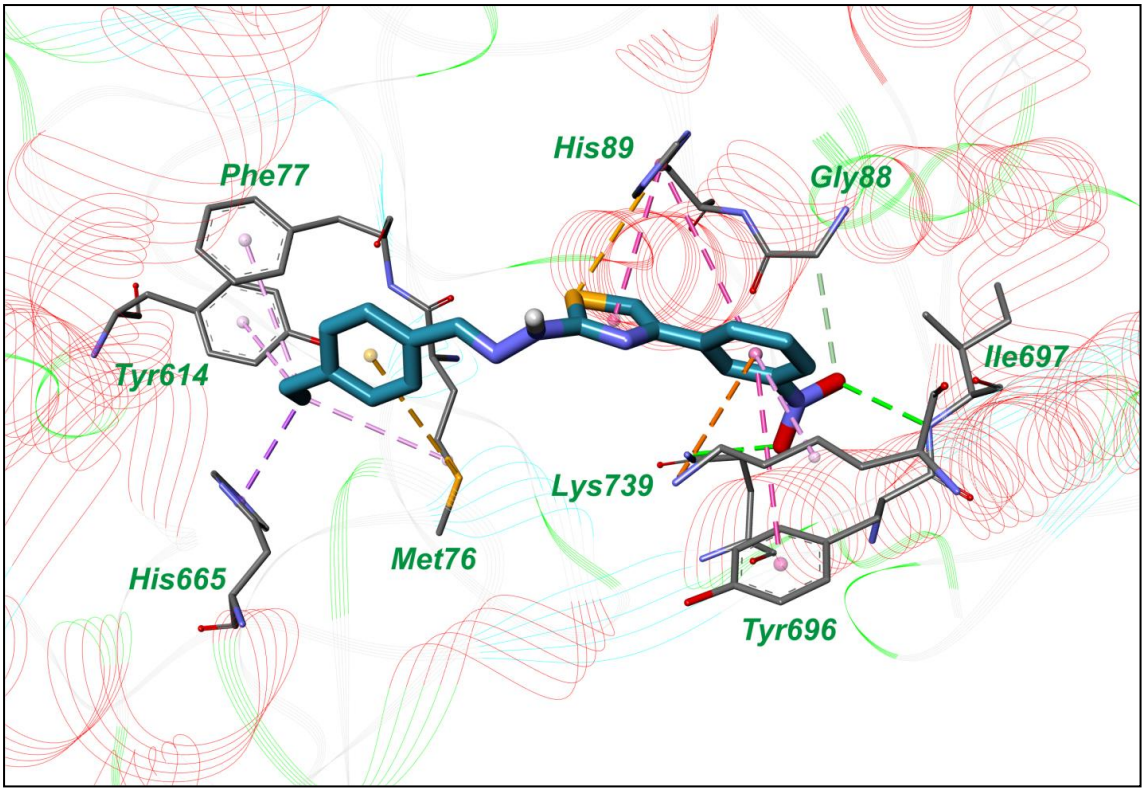


Figure S1-6. The complexes of compound **6** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.



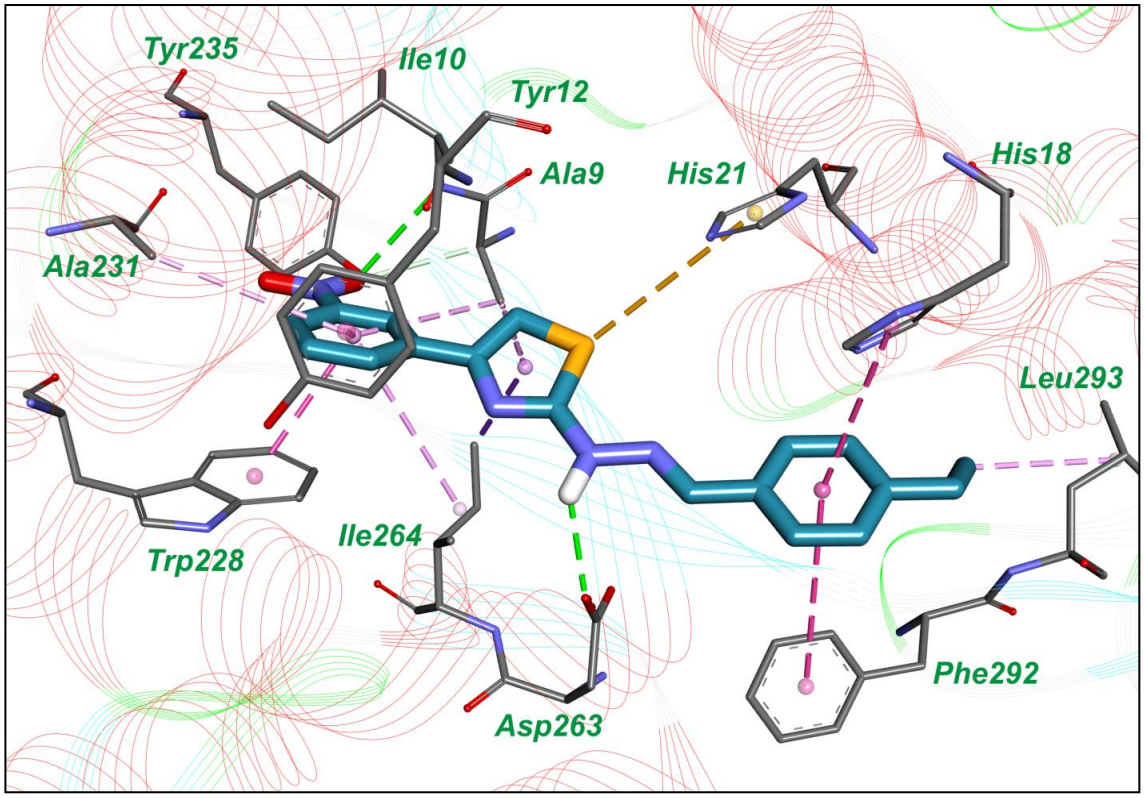


Figure S1-7. The complexes of compound **7** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

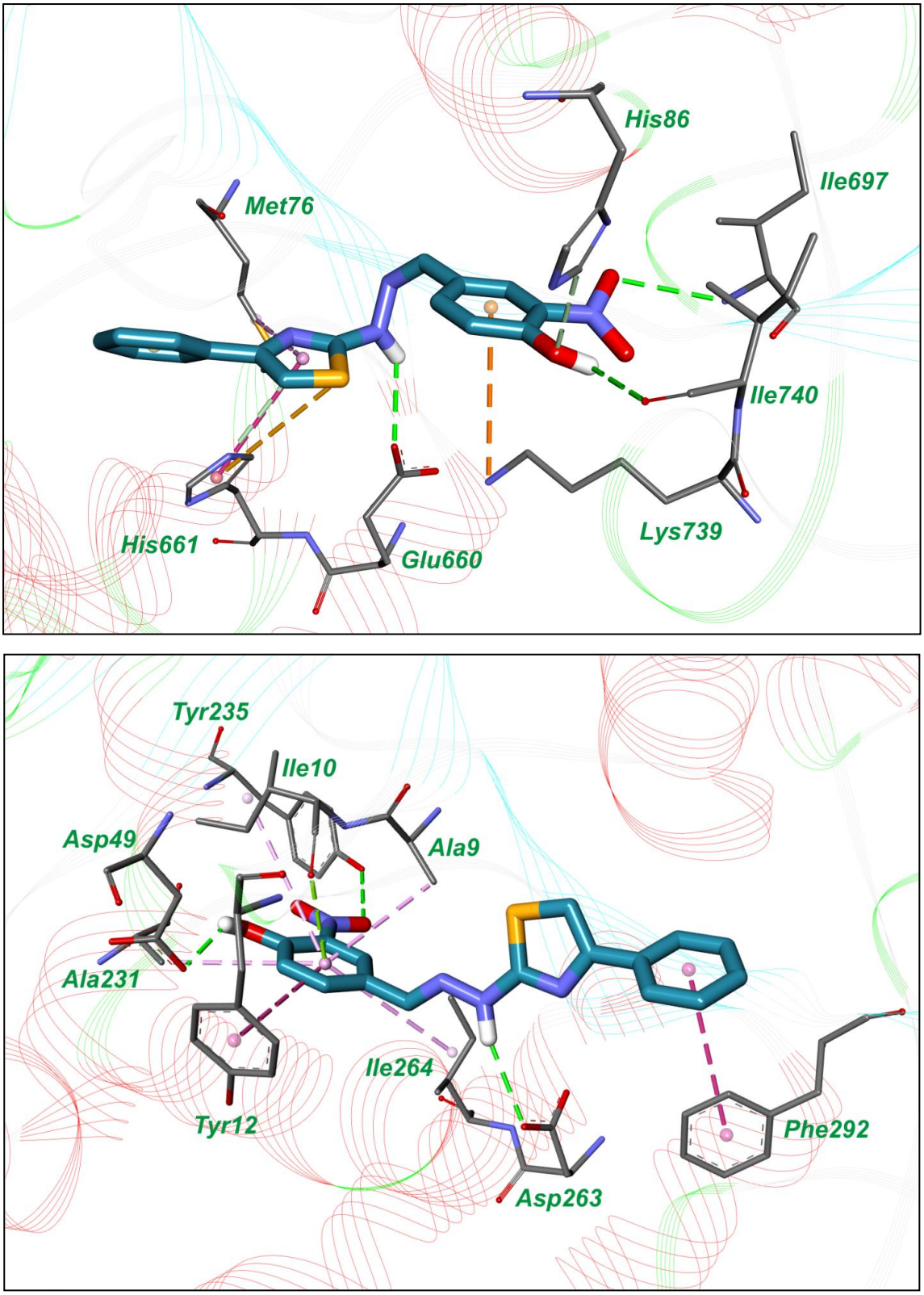


Figure S1-8. The complexes of compound **8** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

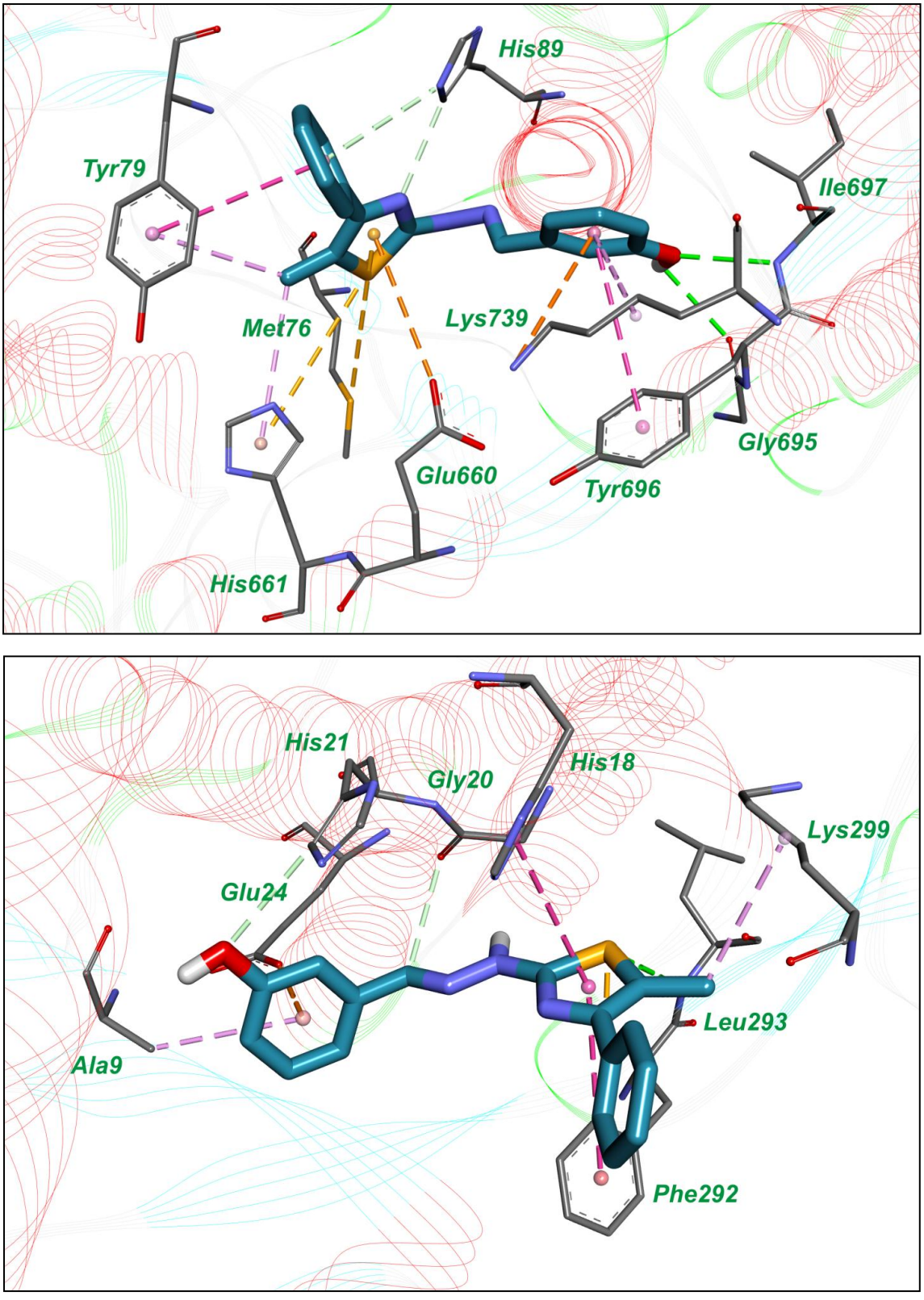


Figure S1-9. The complexes of compound **9** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

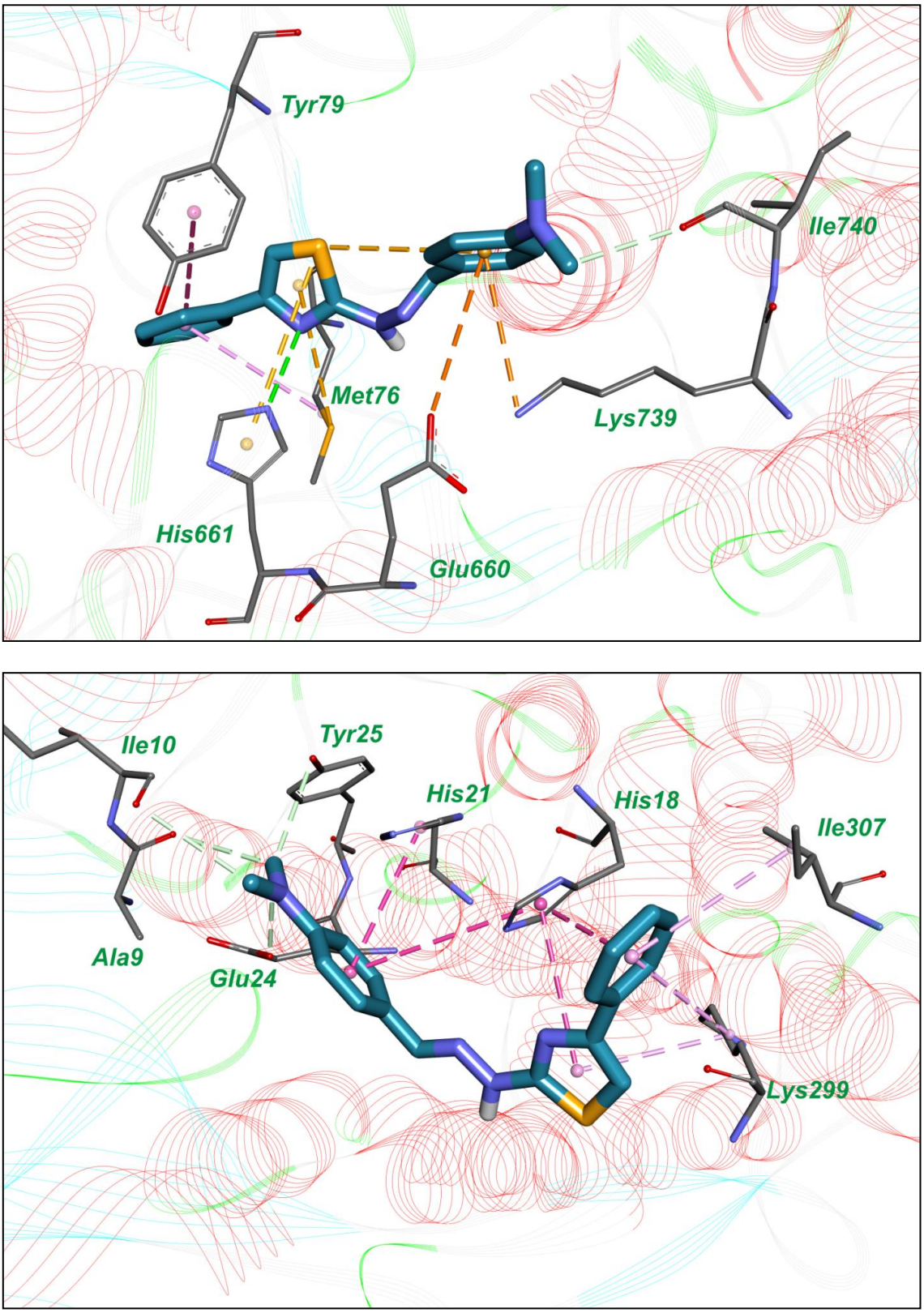
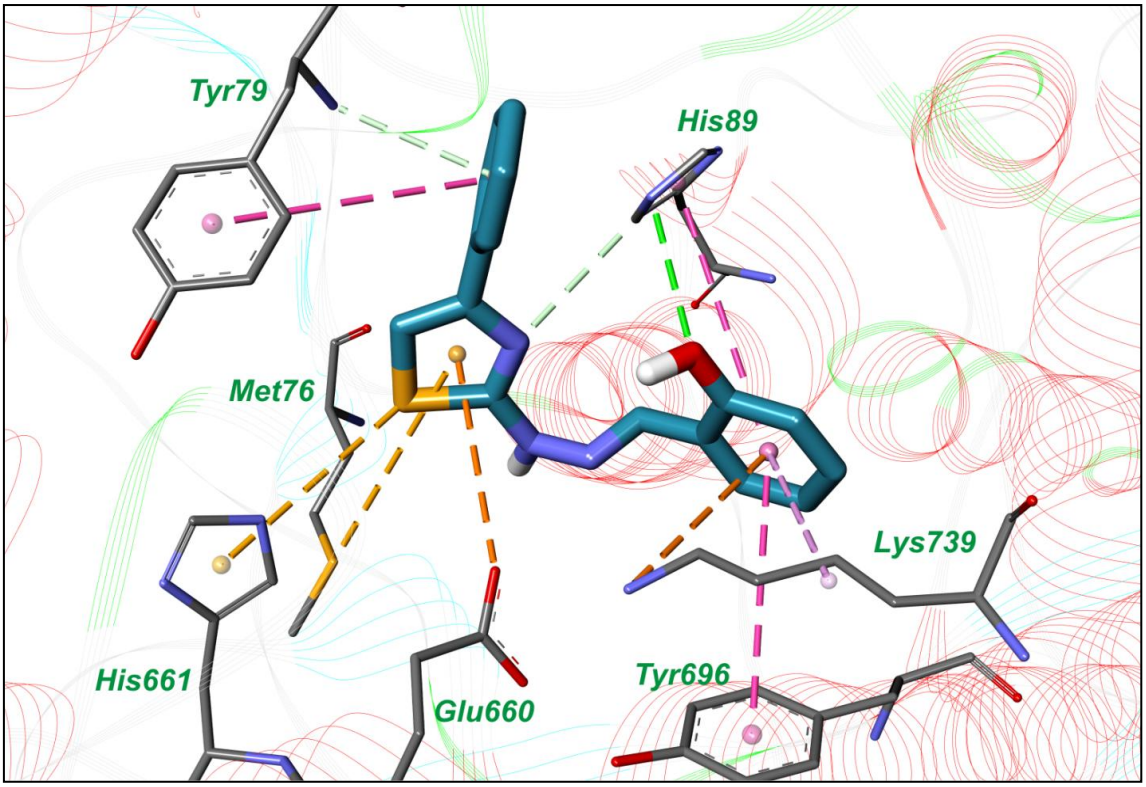


Figure S1-10. The complexes of compound **10** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.



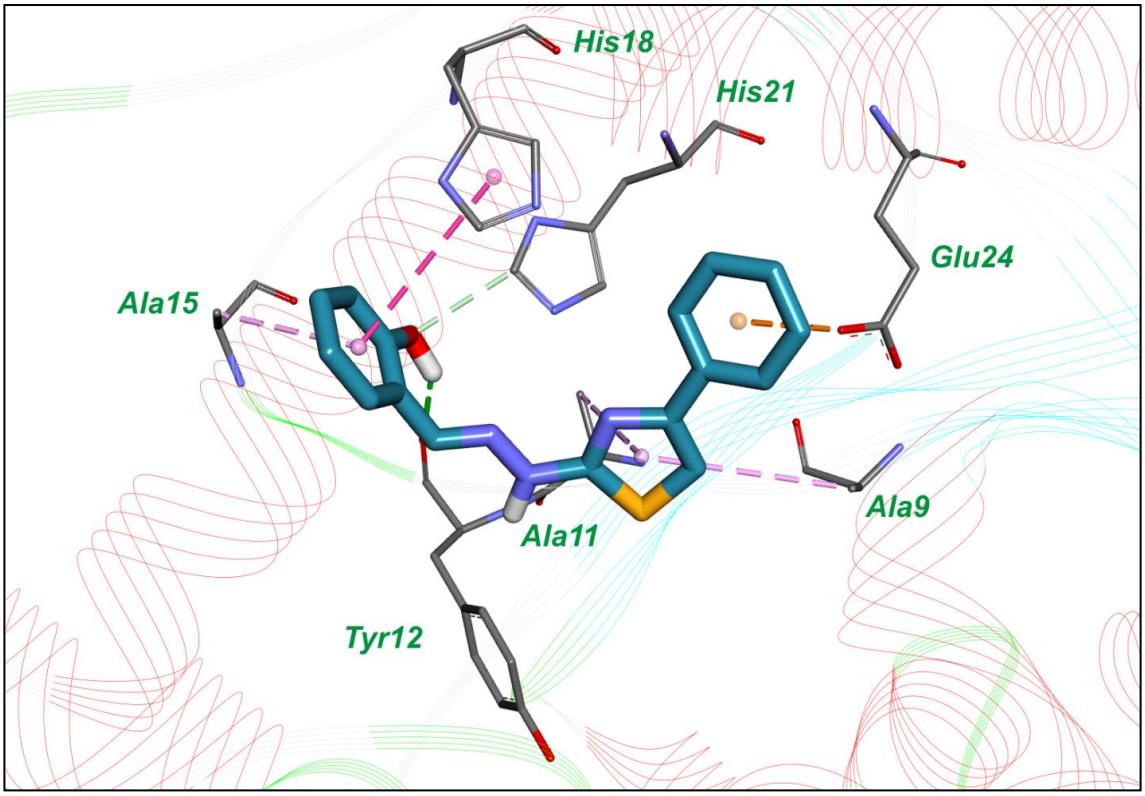
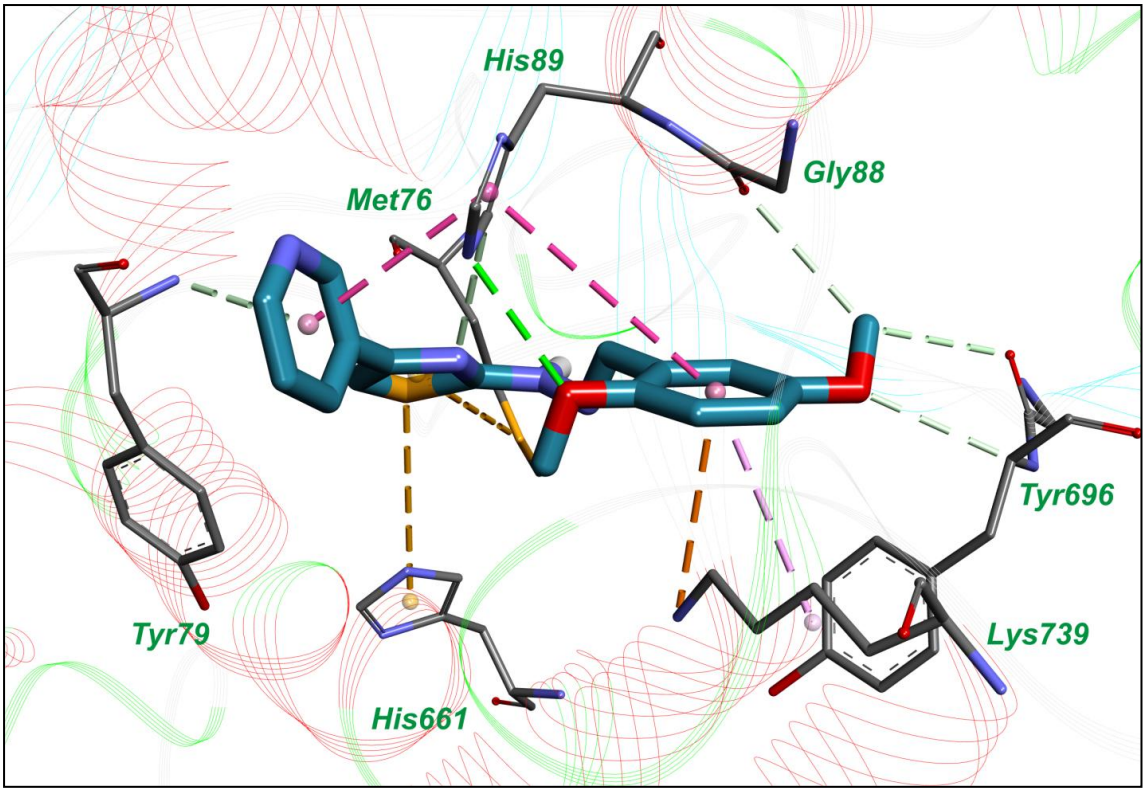


Figure S1-11. The complexes of compound **11** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.



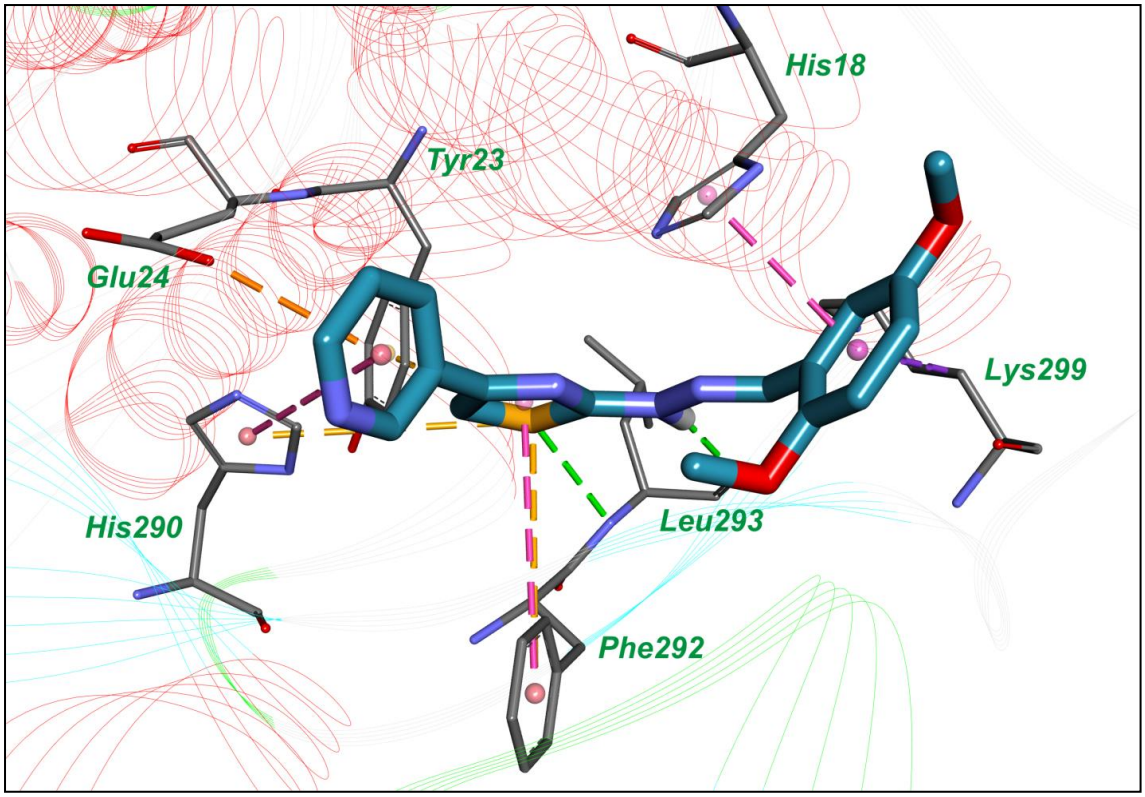
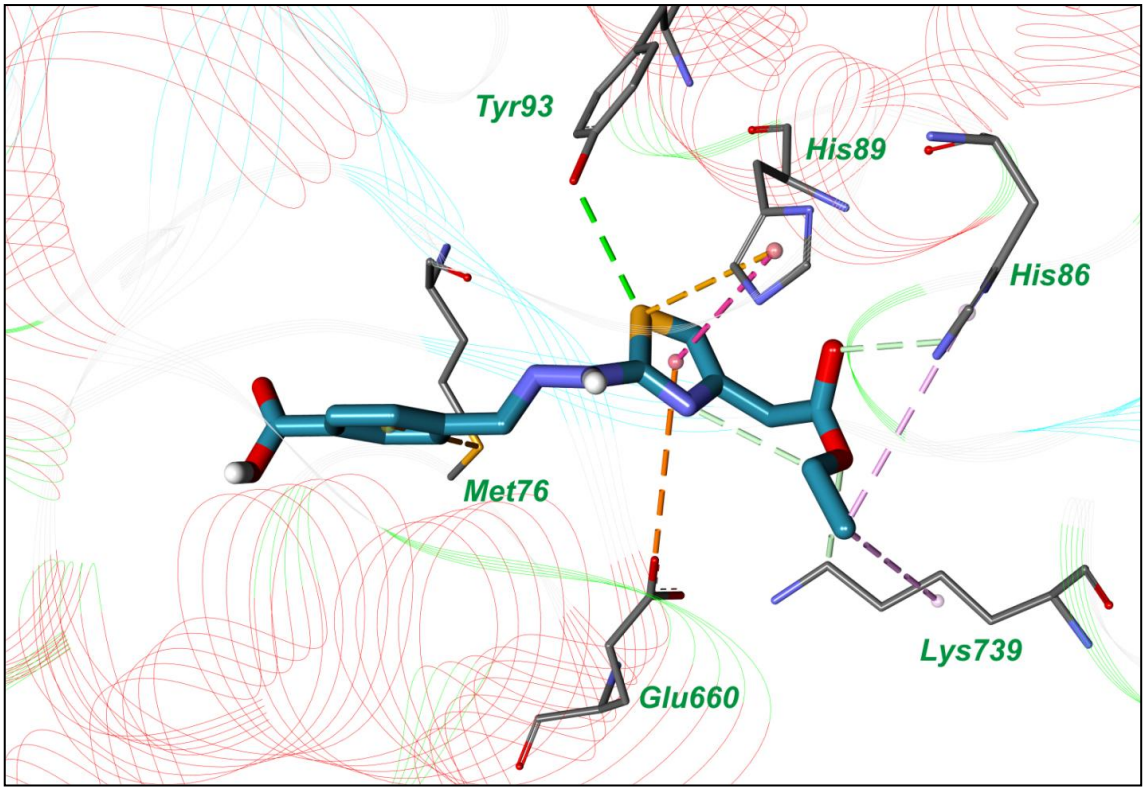


Figure S1-12. The complexes of compound **12** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.



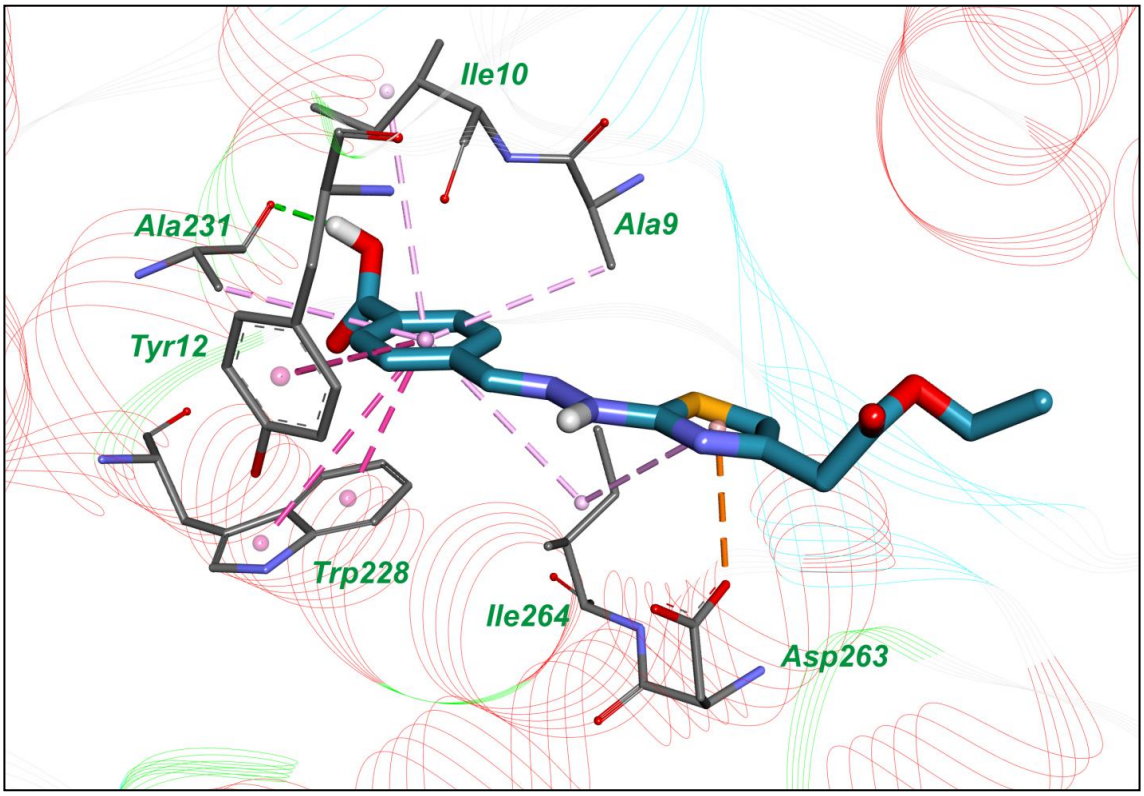


Figure S1-13. The complexes of compound **13** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

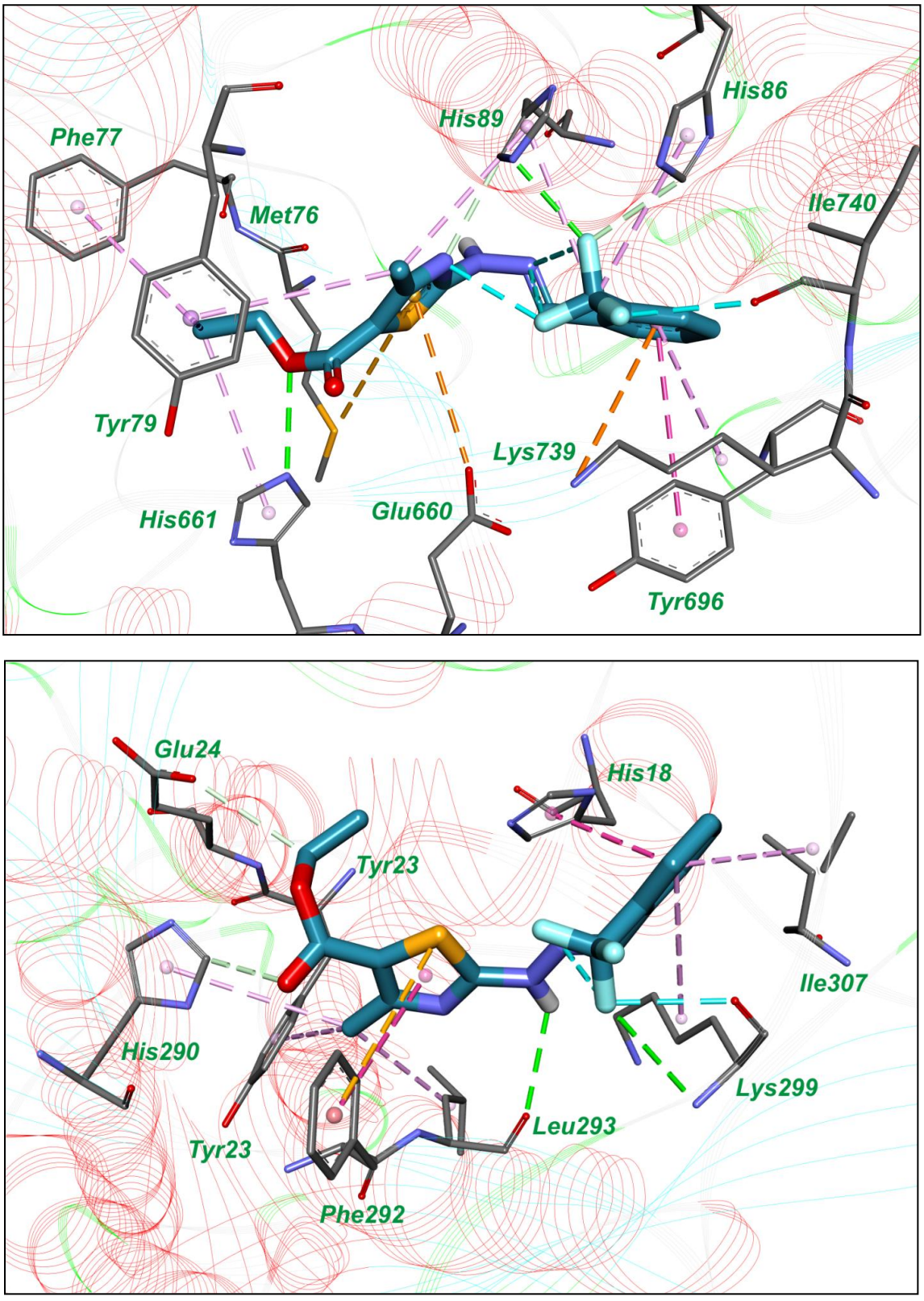
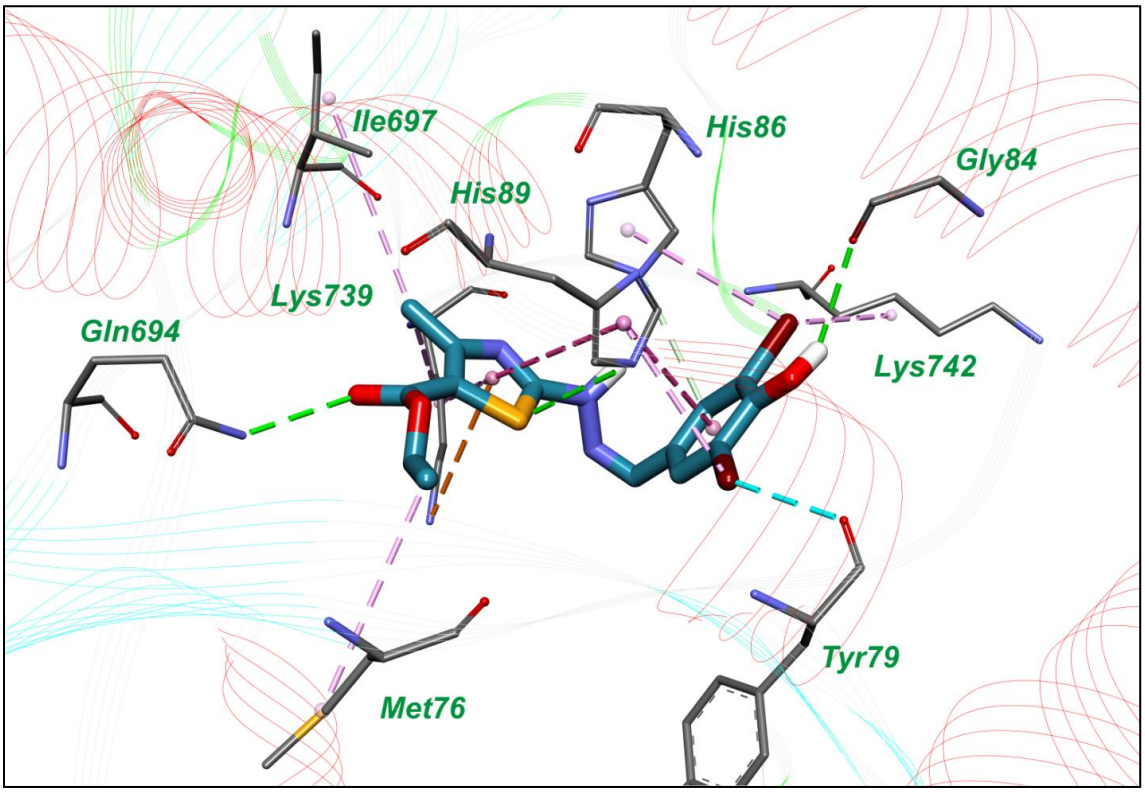


Figure S1-14. The complexes of compound **14** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color, halogen bonds – with blue color.



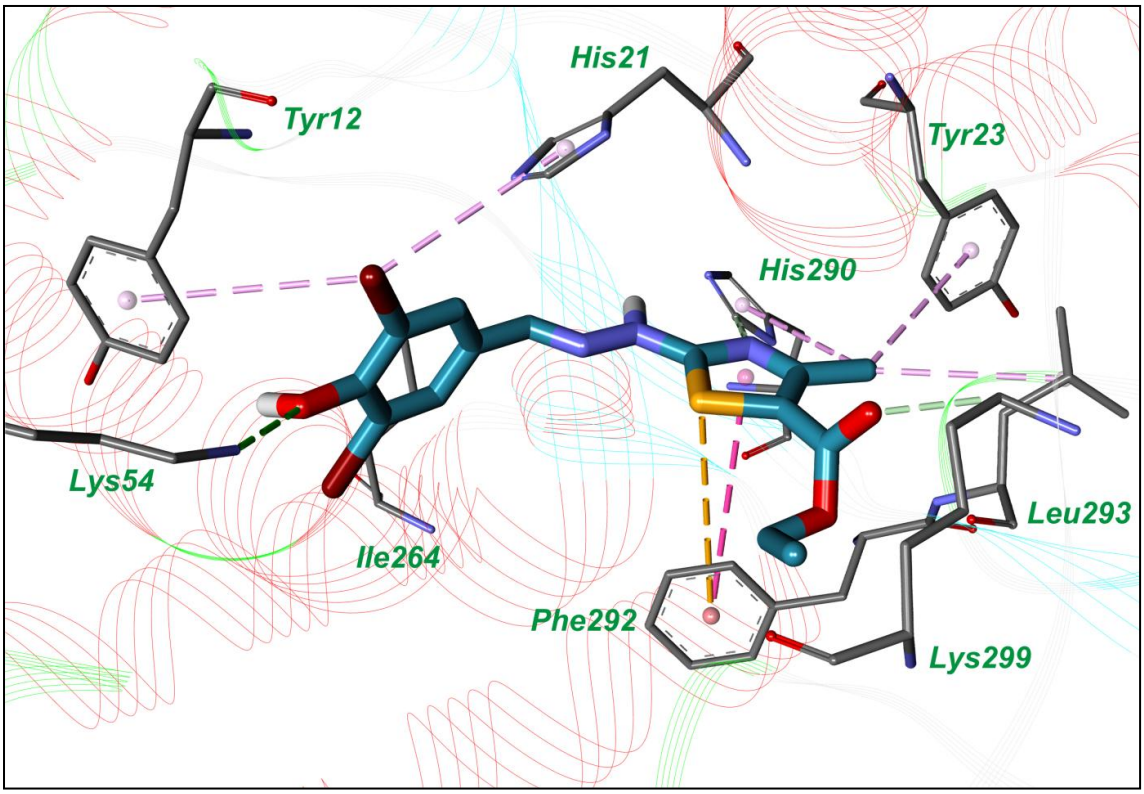


Figure S1-15. The complexes of compound **15** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color, halogen bonds – with blue color.

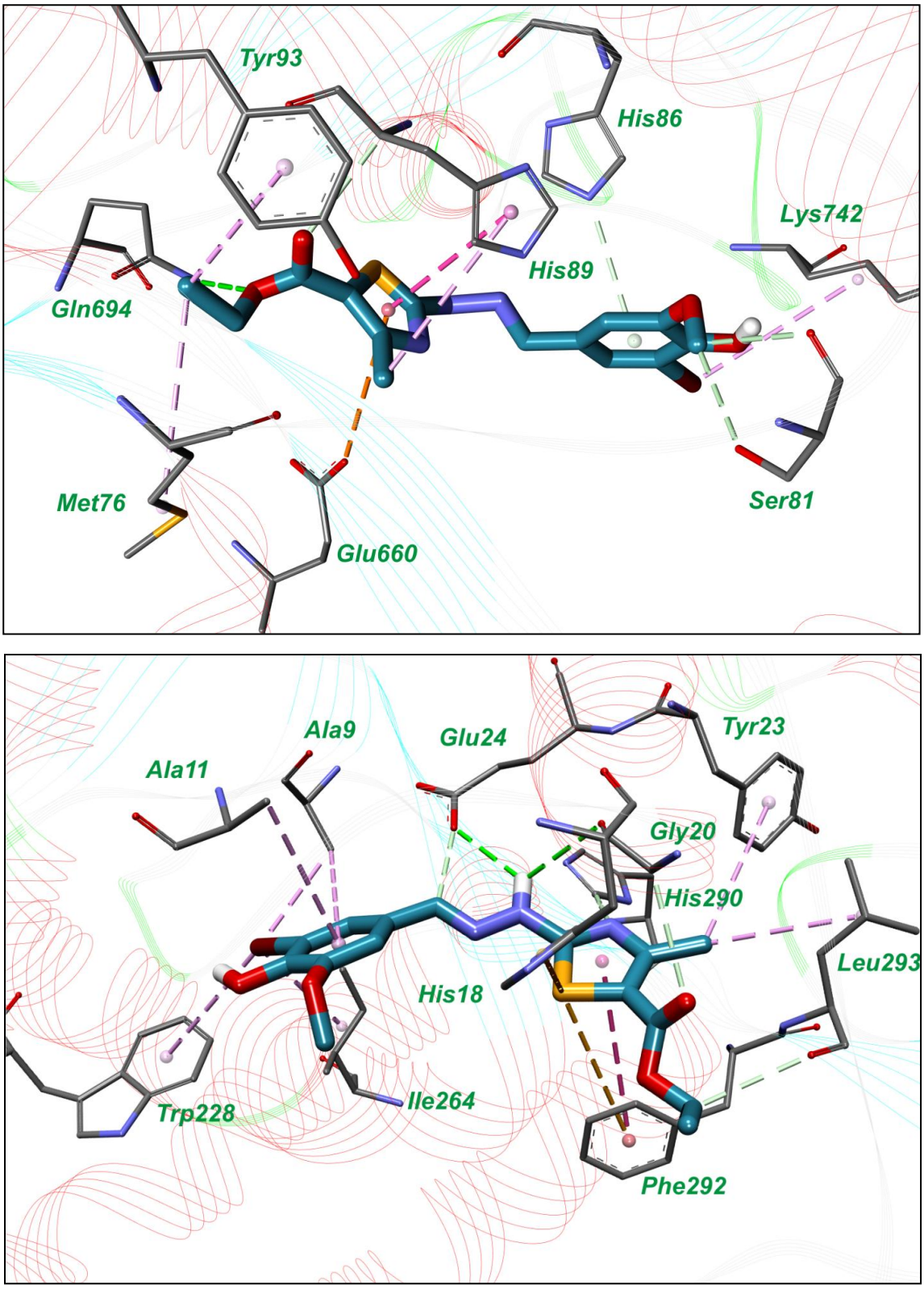


Figure S1-16. The complexes of compound **16** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-cation interactions – with orange color.

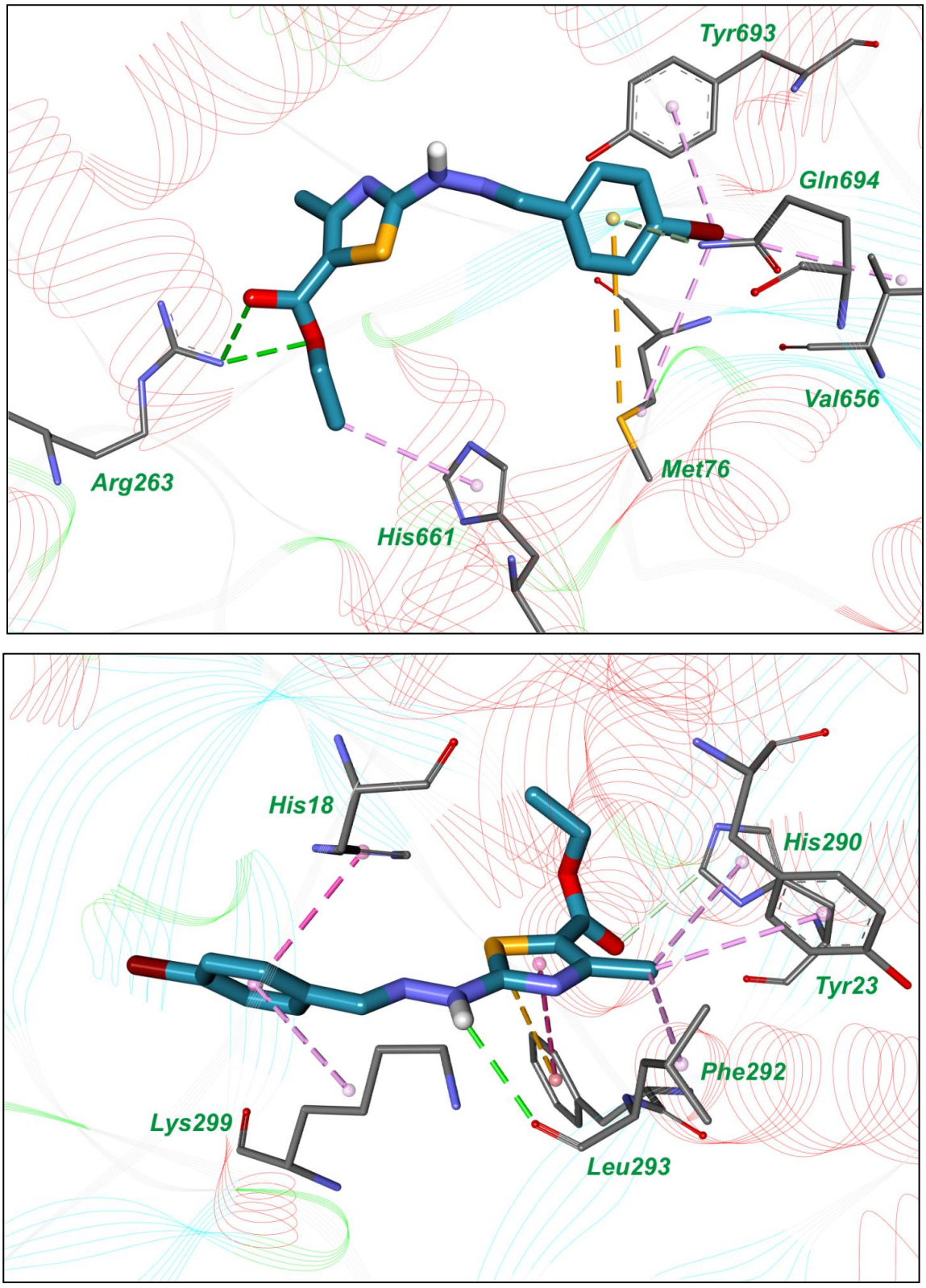


Figure S1-17. The complexes of compound **17** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color, halogen bonds – with blue color.

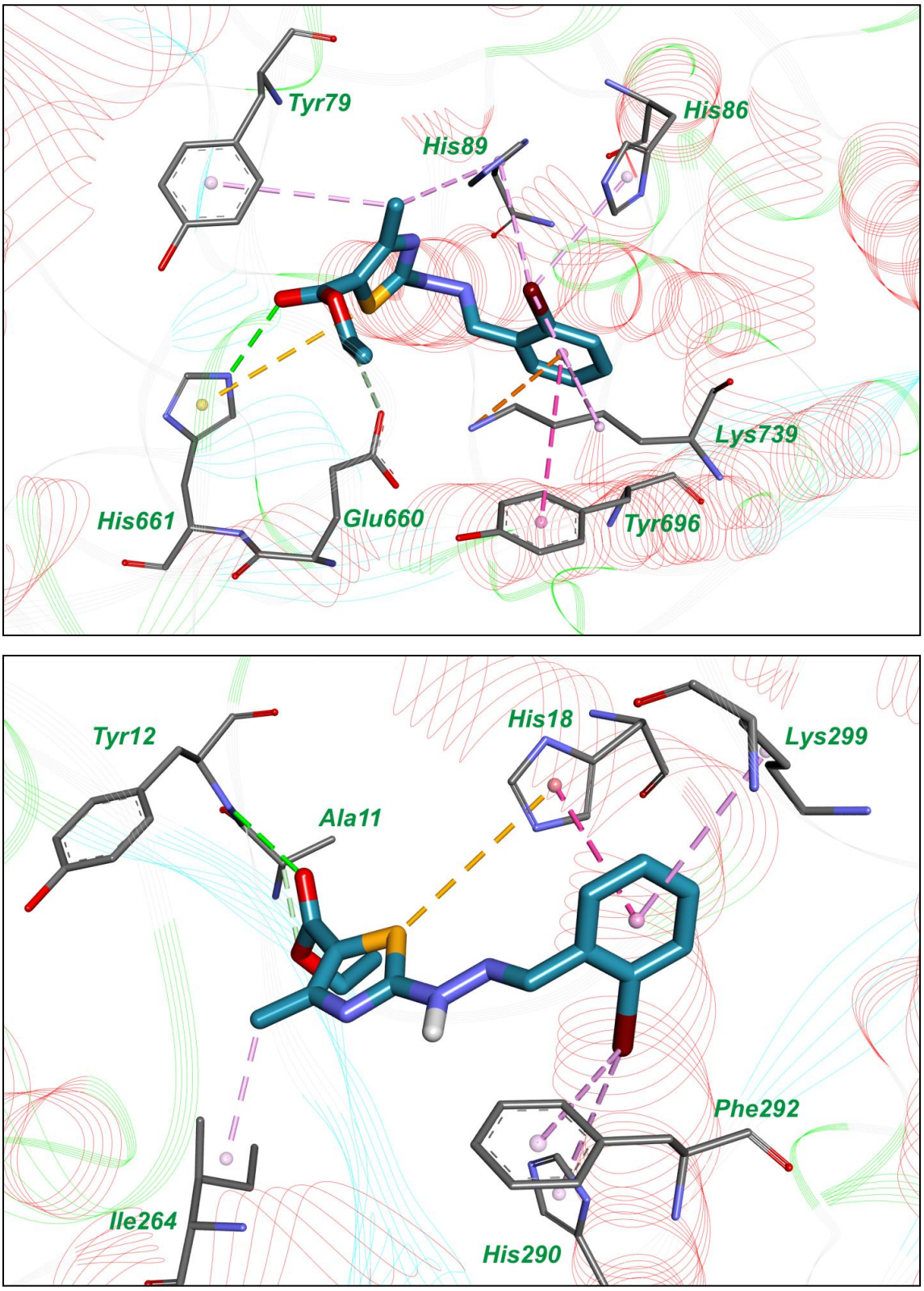


Figure S1-18. The complexes of compound **18** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

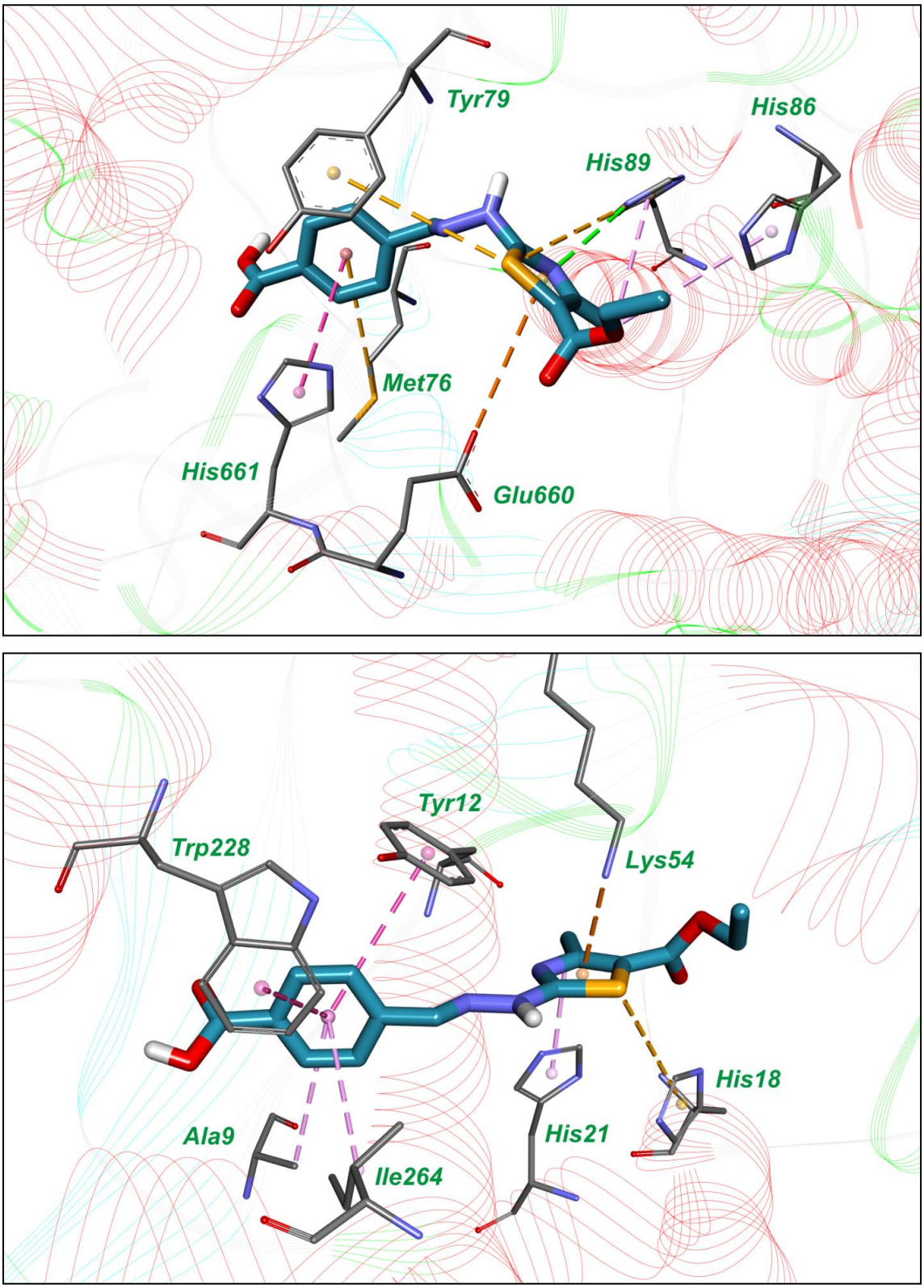


Figure S1-19. The complexes of compound **19** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

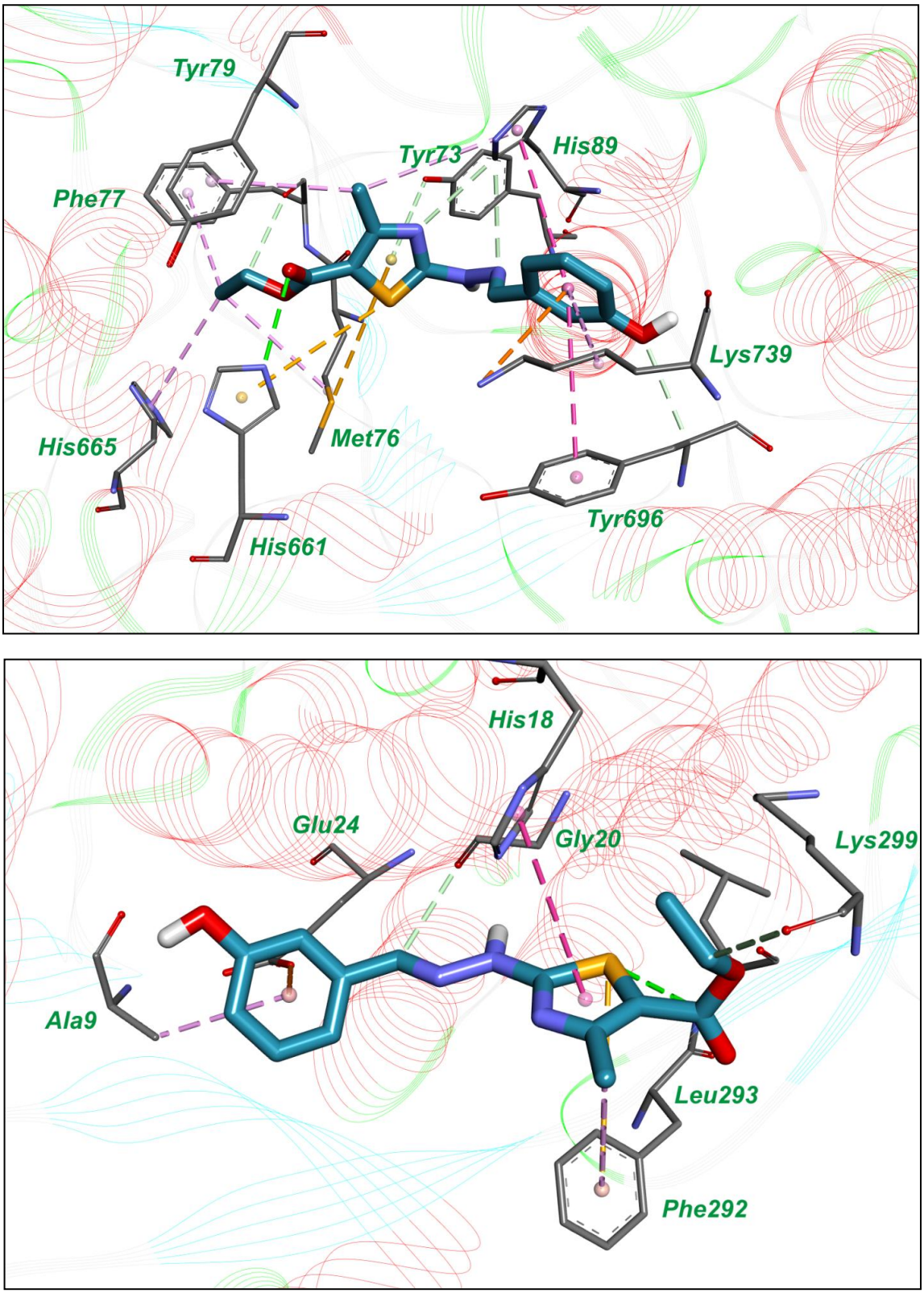


Figure S1-20. The complexes of compound **20** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

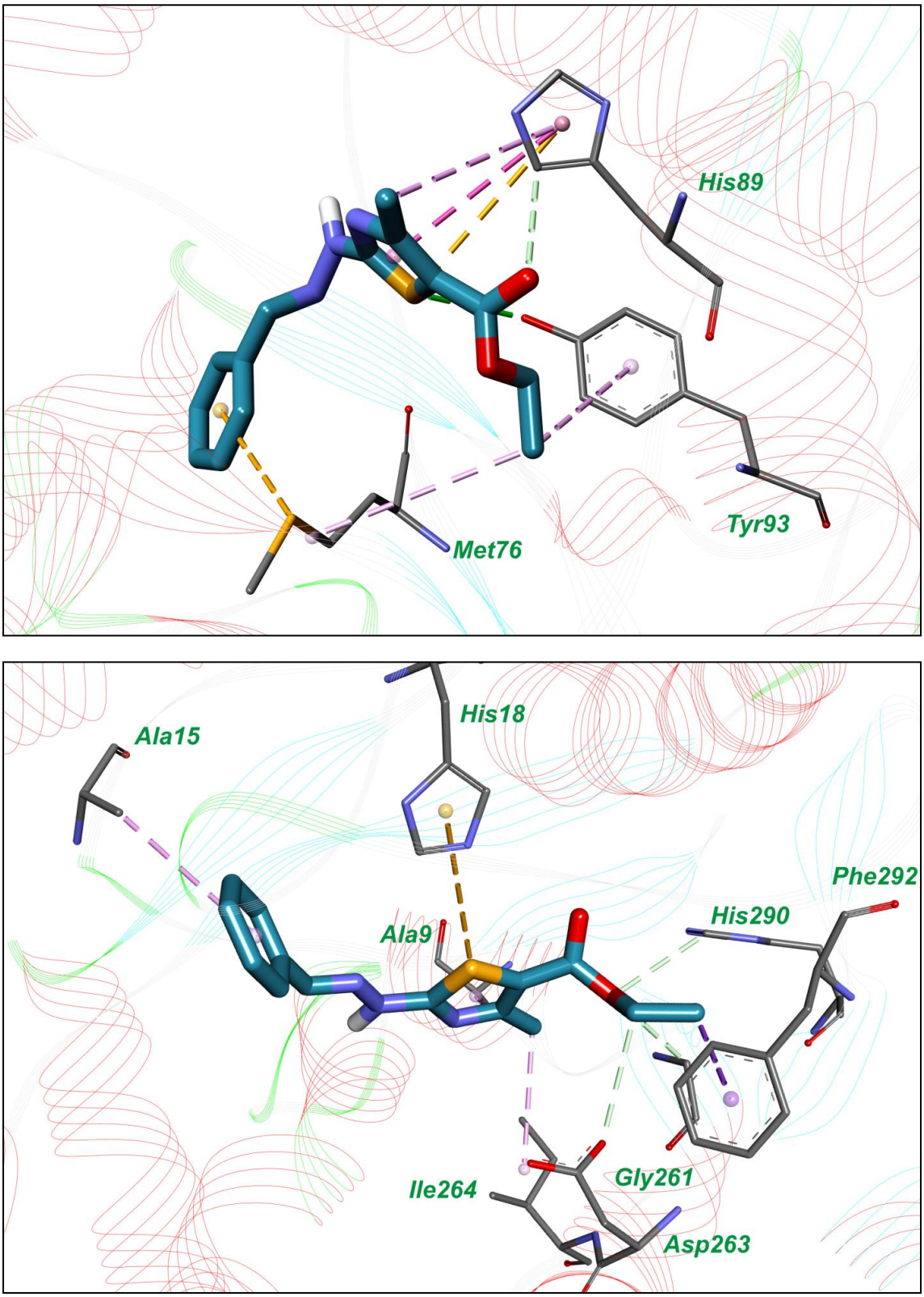


Figure S1-21. The complexes of compound **21** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

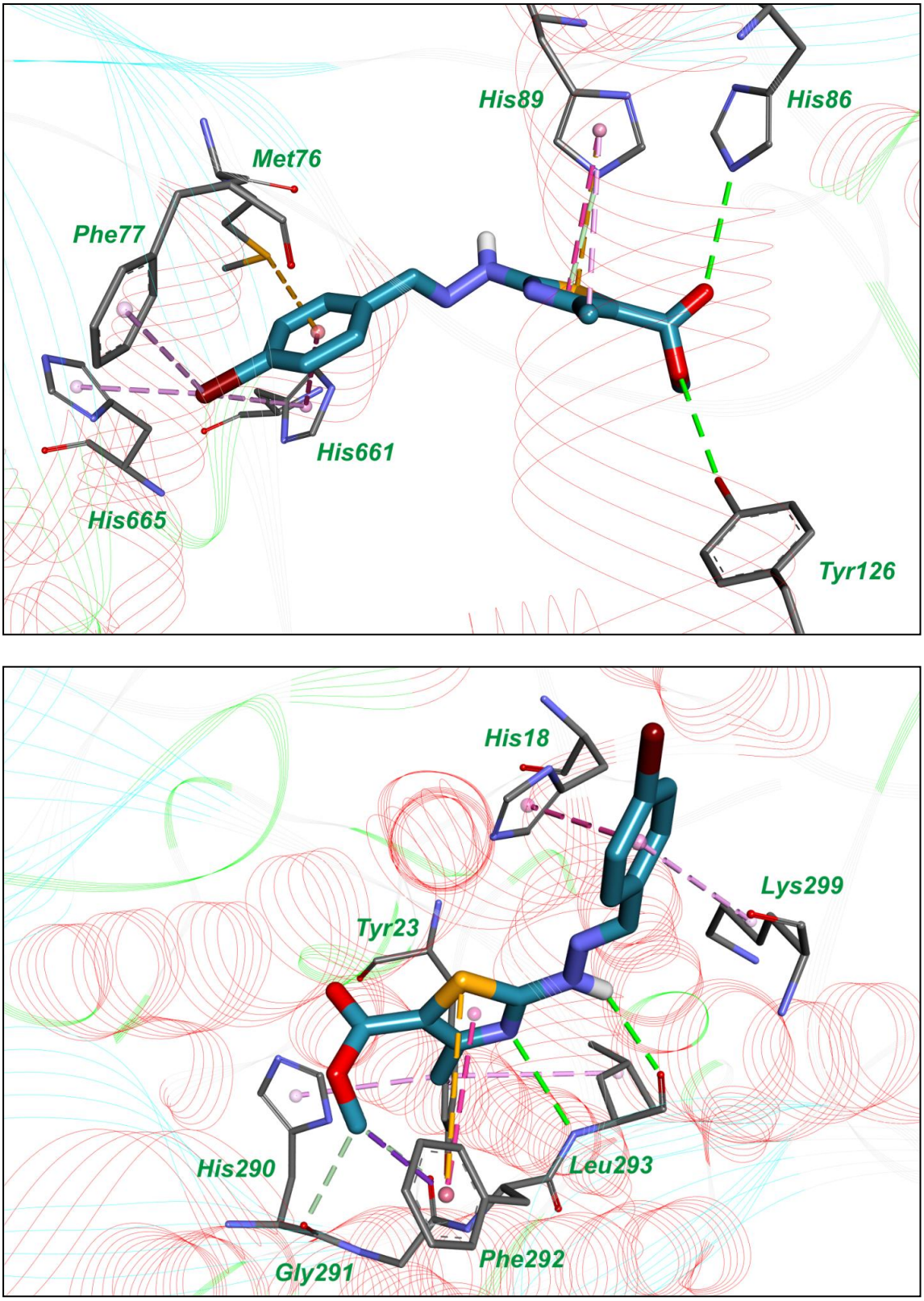


Figure S1-22. The complexes of compound **22** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

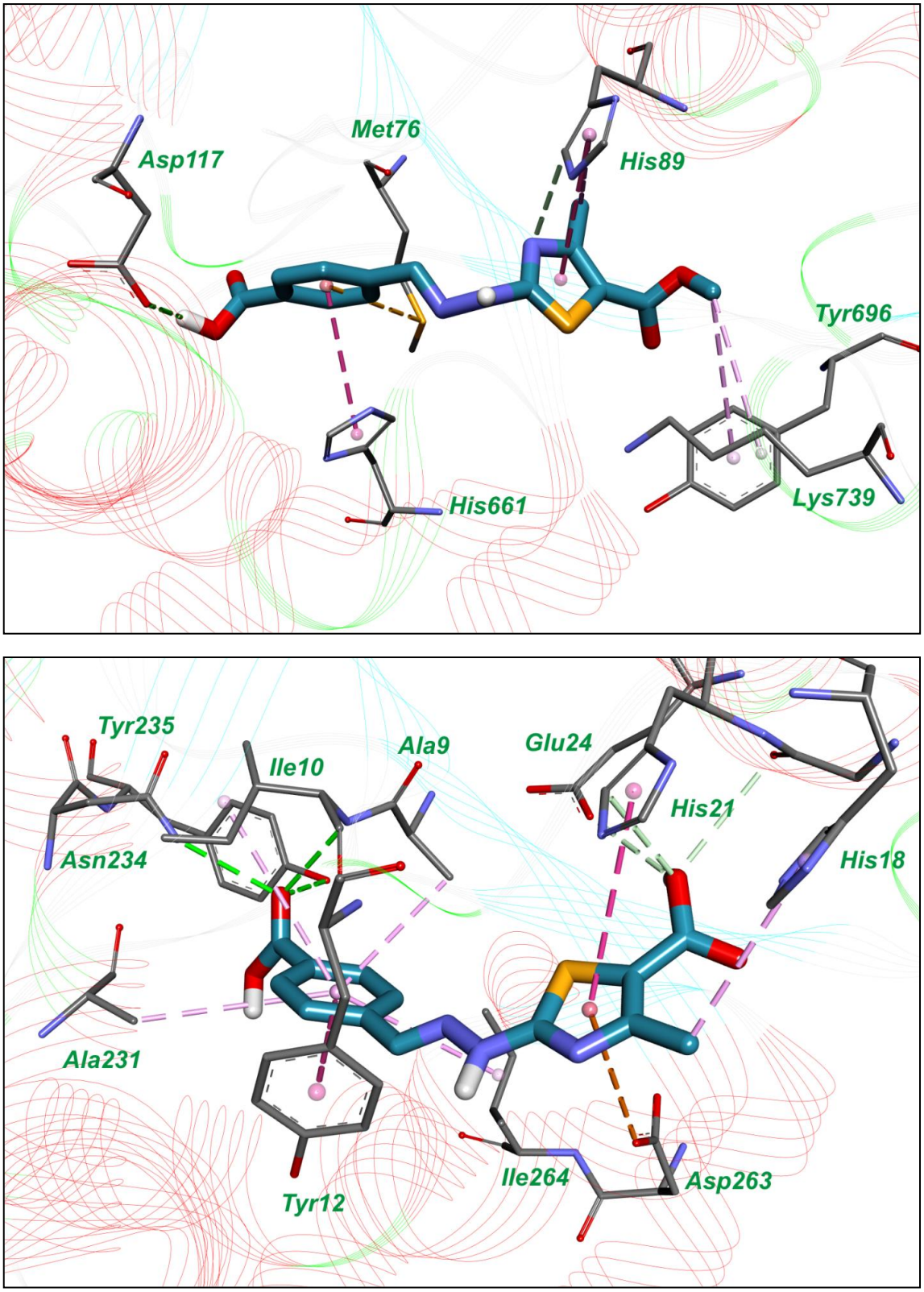


Figure S1-23. The complexes of compound **23** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-cation interactions – with orange color.

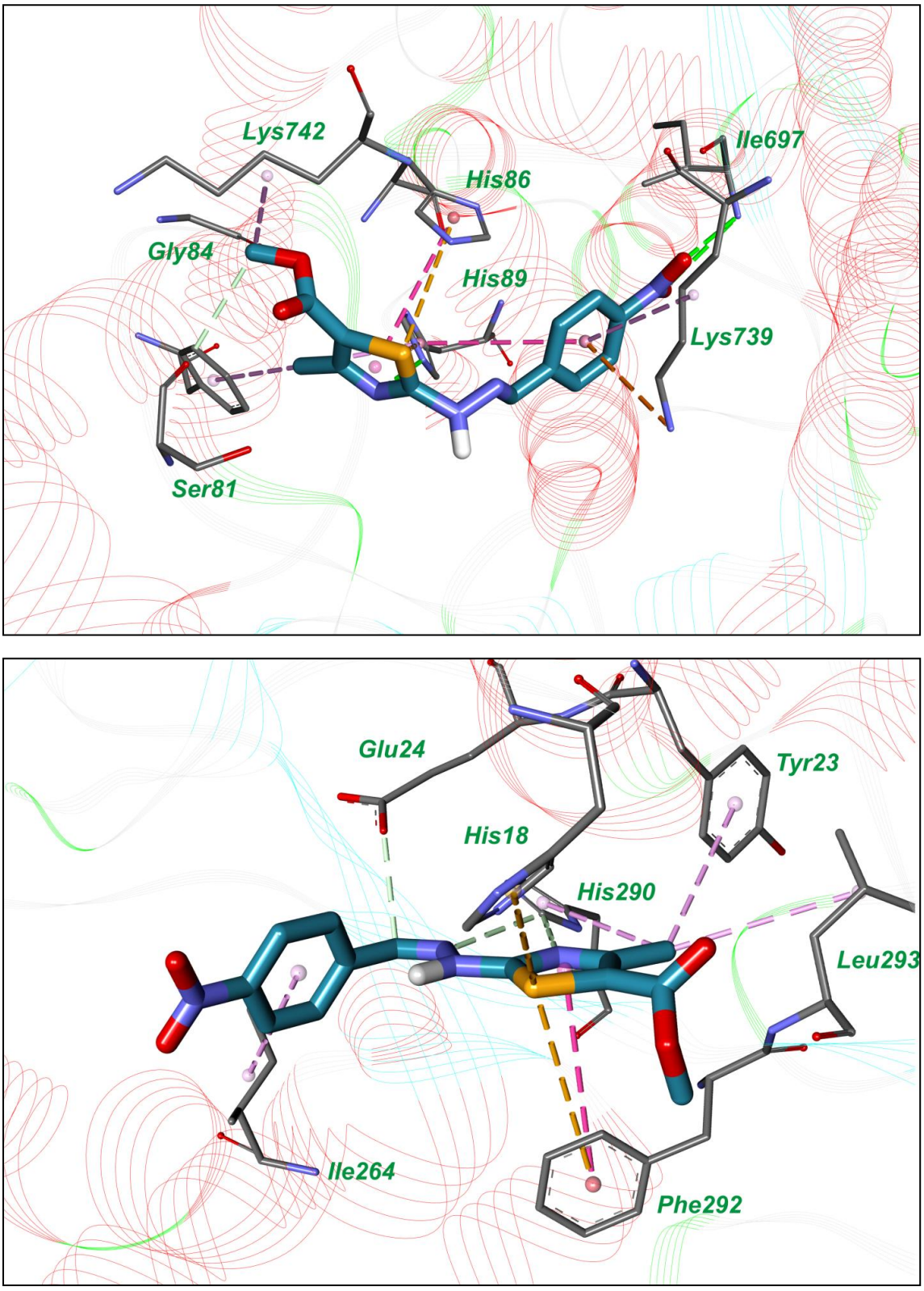


Figure S1-24. The complexes of compound **24** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

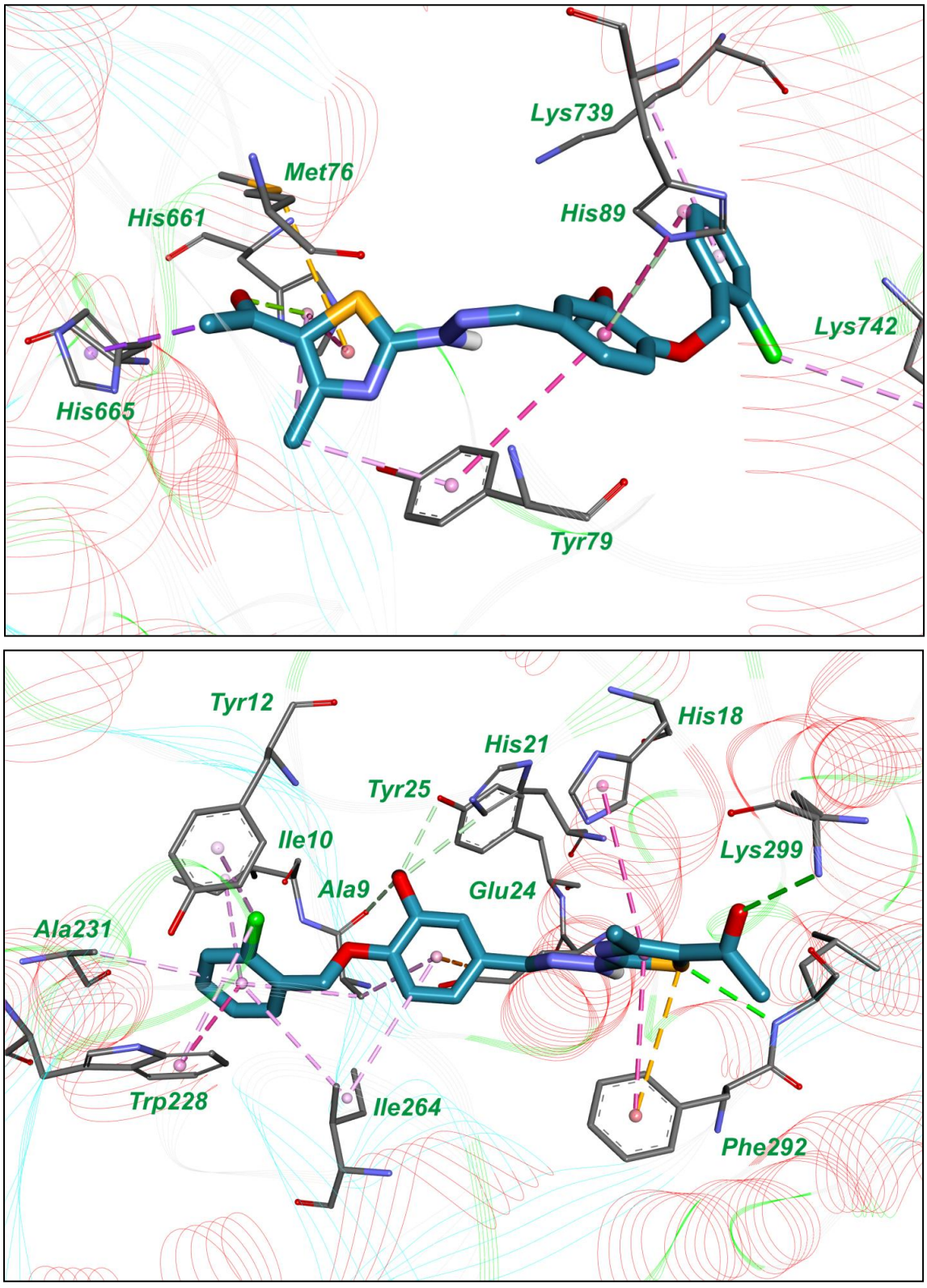


Figure S1-25. The complexes of compound **25** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

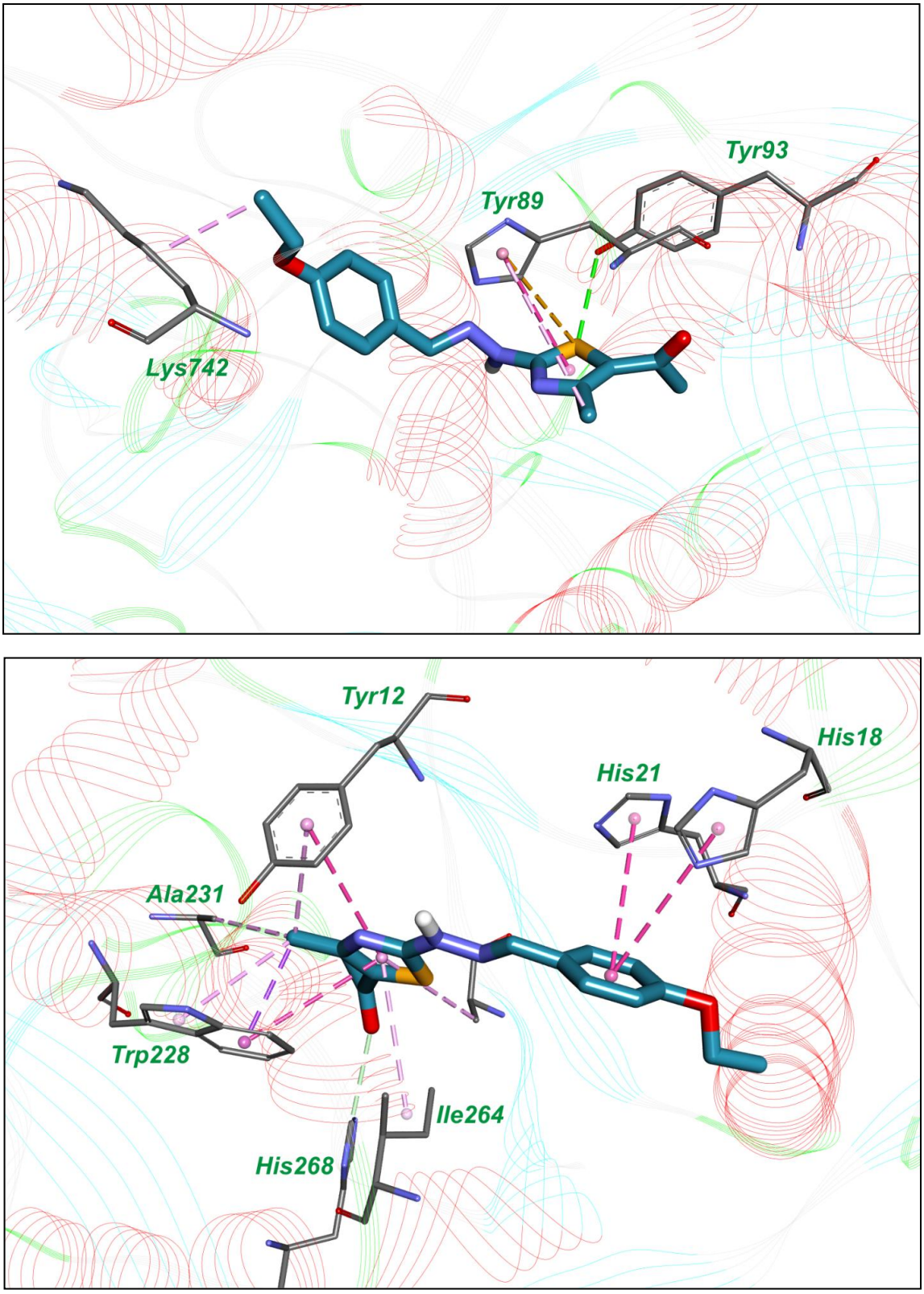


Figure S1-26. The complexes of compound **26** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

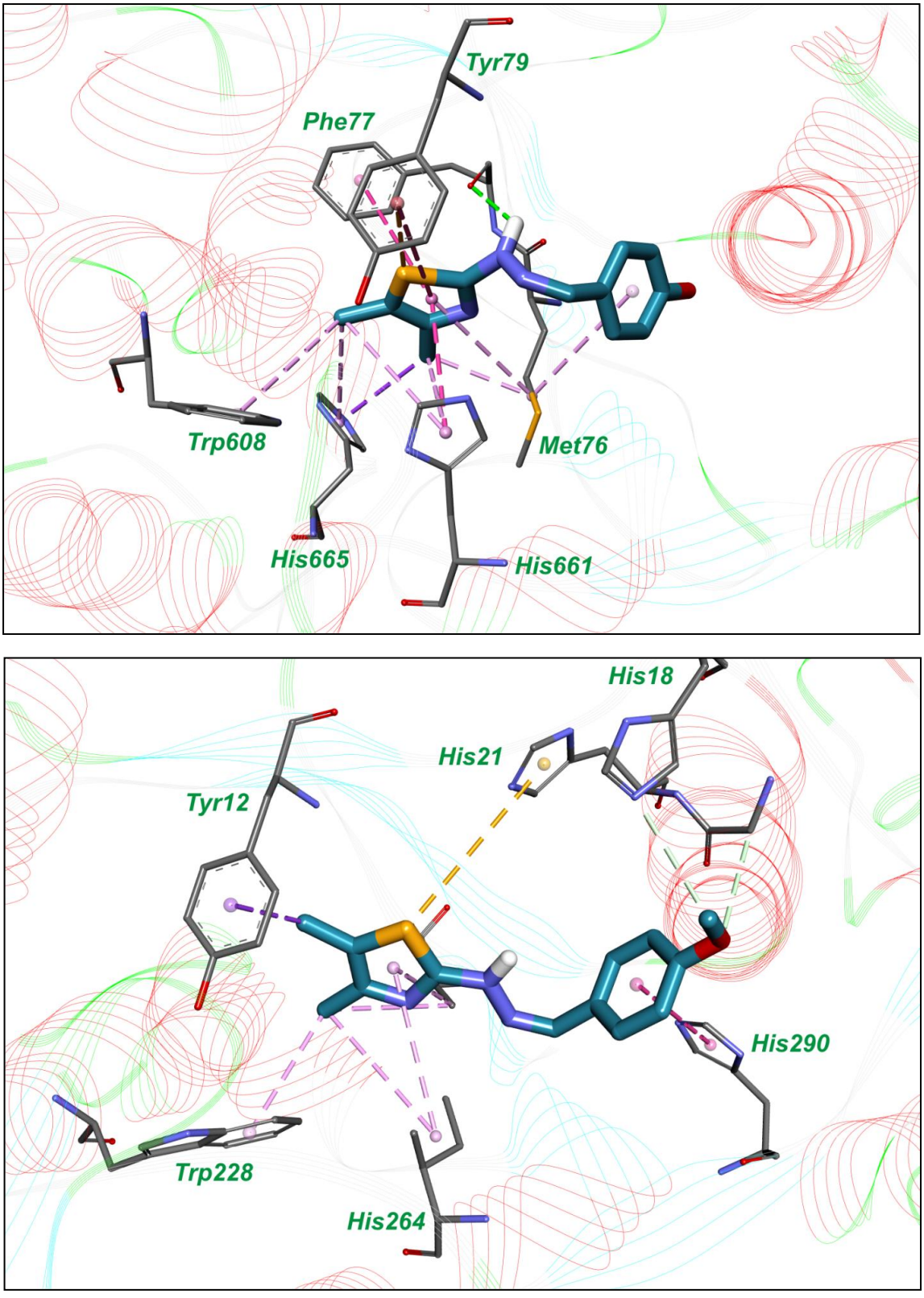


Figure S1-27. The complexes of compound **27** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

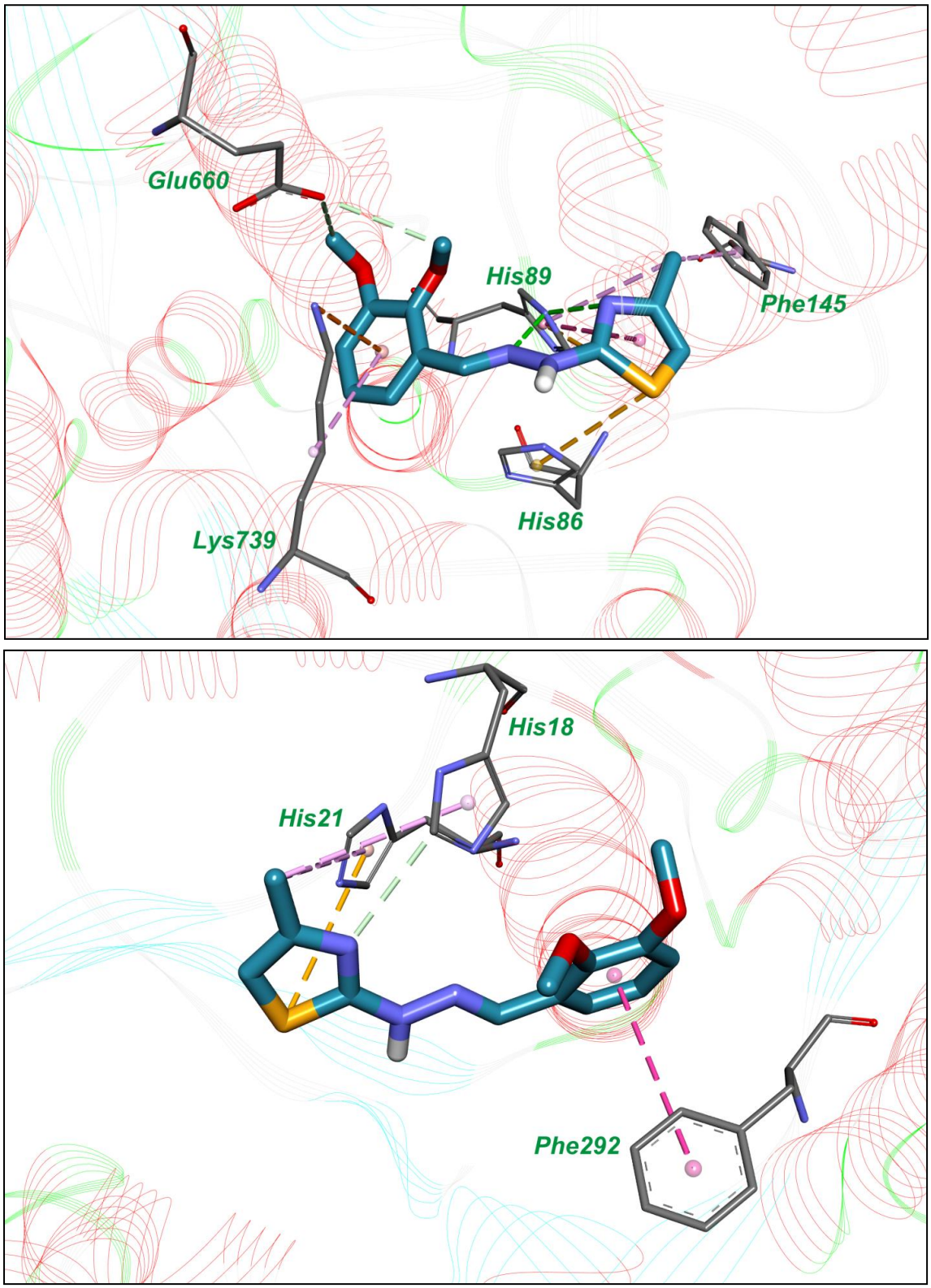


Figure S1-28. The complexes of compound **28** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

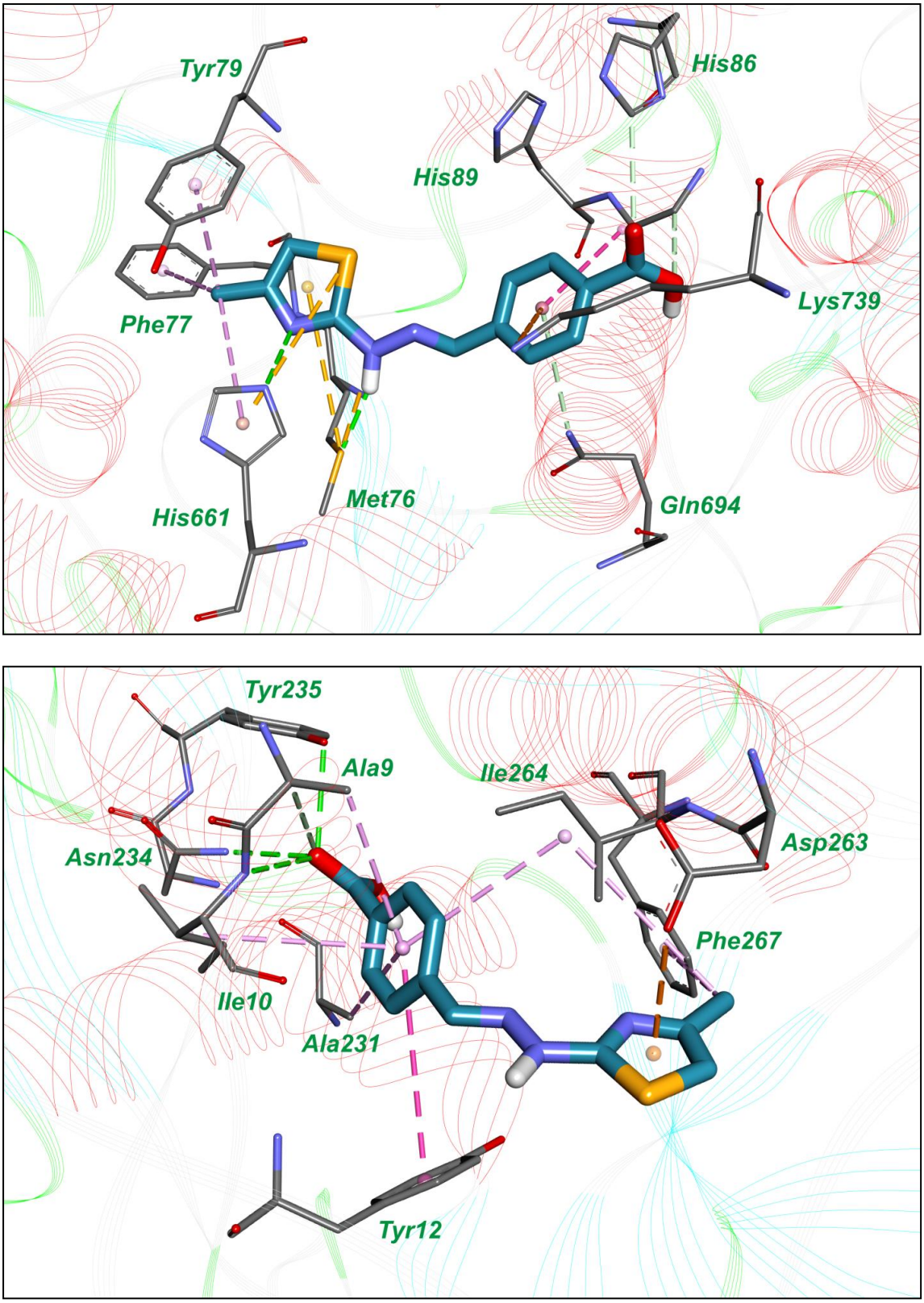


Figure S1-29. The complexes of compound **29** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

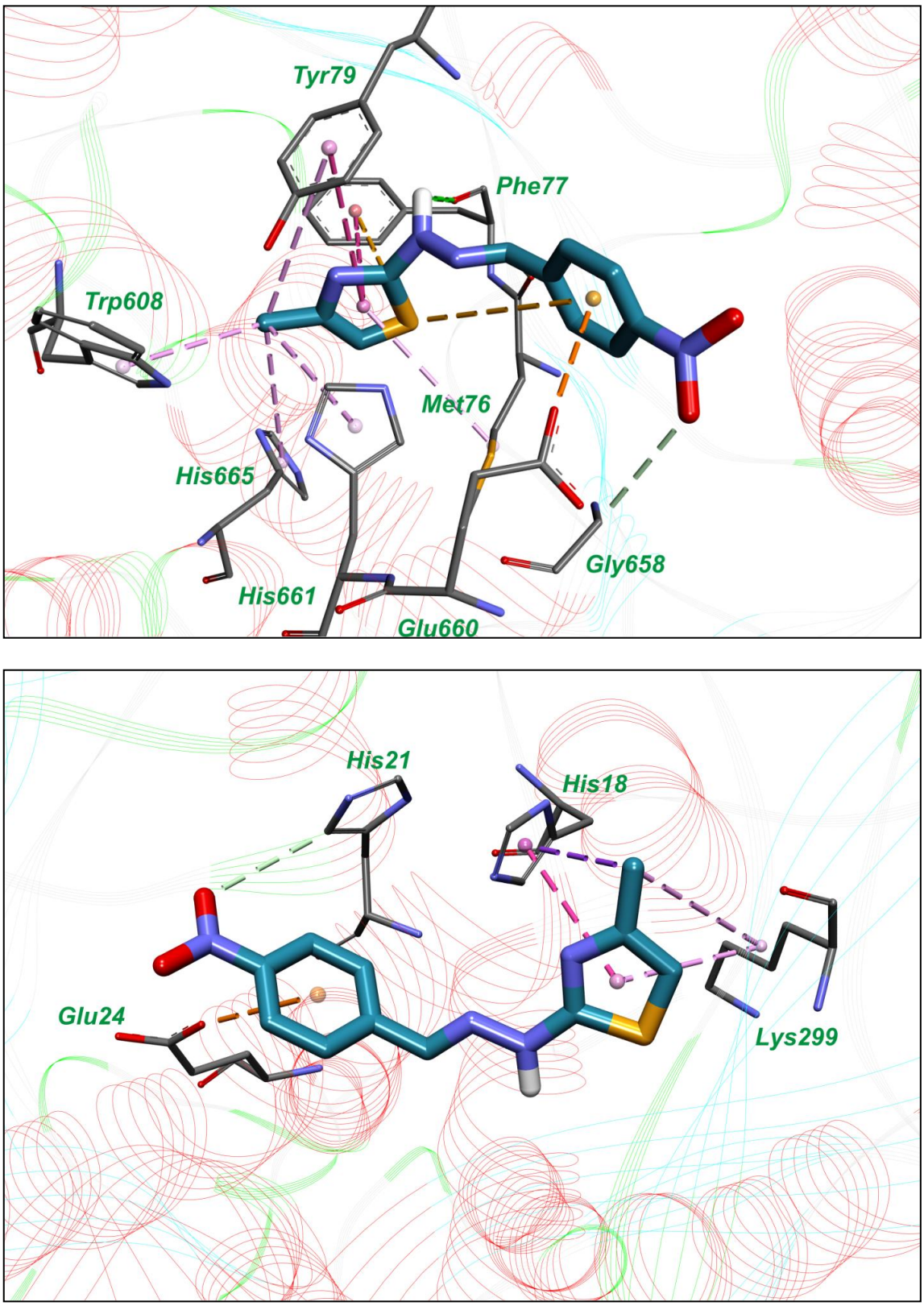


Figure S1-30. The complexes of compound **30** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

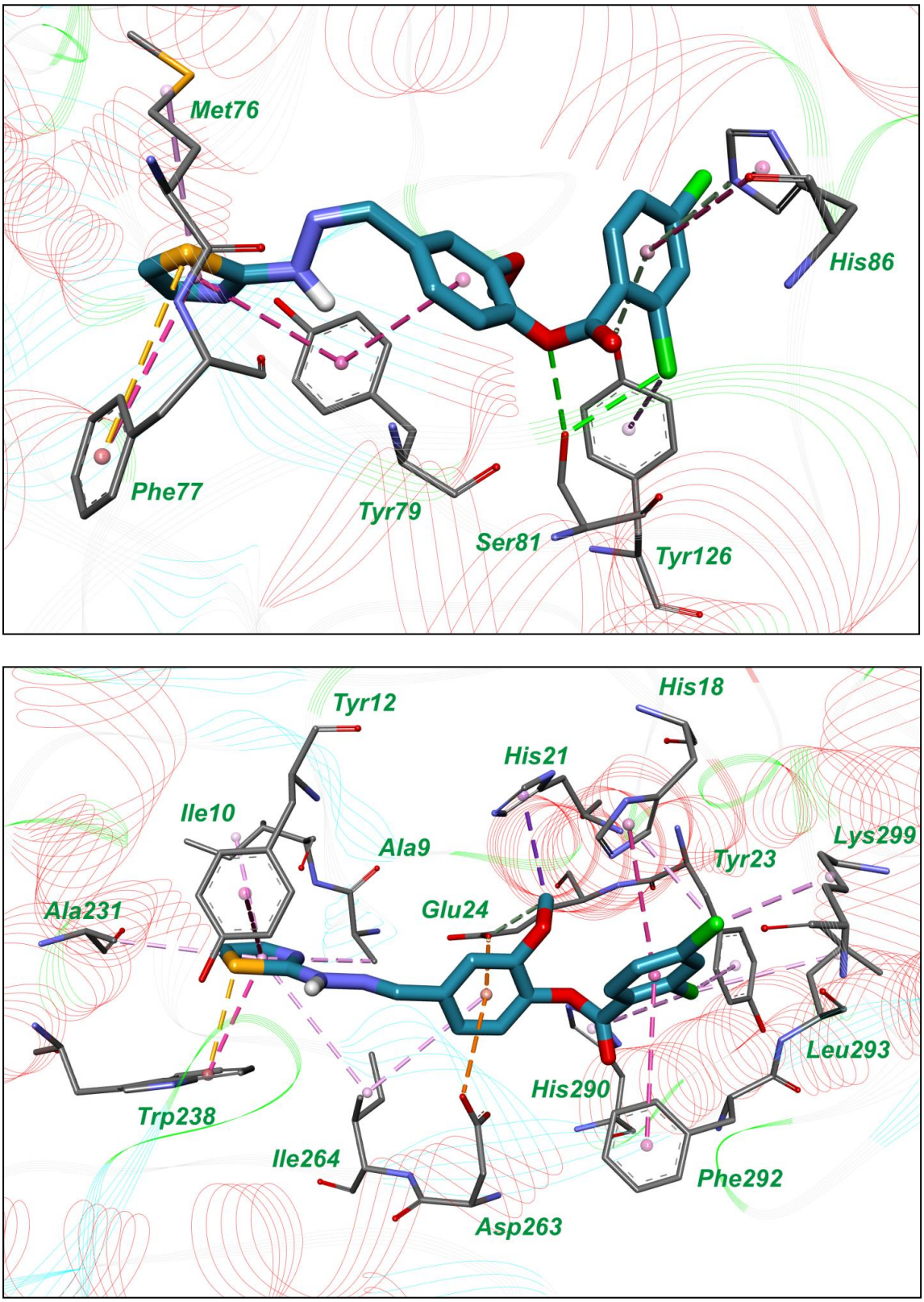


Figure S1-31. The complexes of compound **31** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

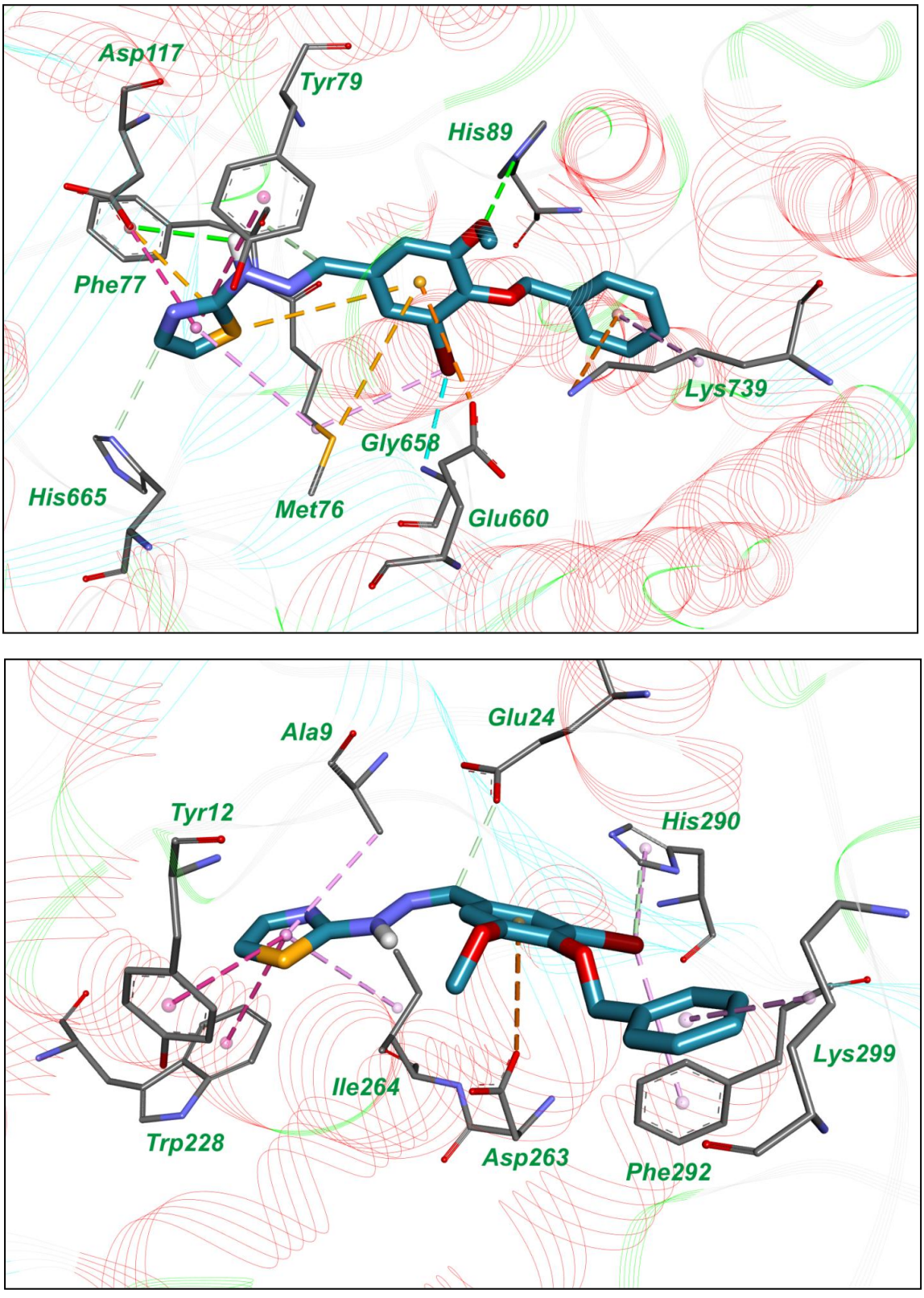


Figure S1-32. The complexes of compound **32** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color, halogen bonds – with blue color.

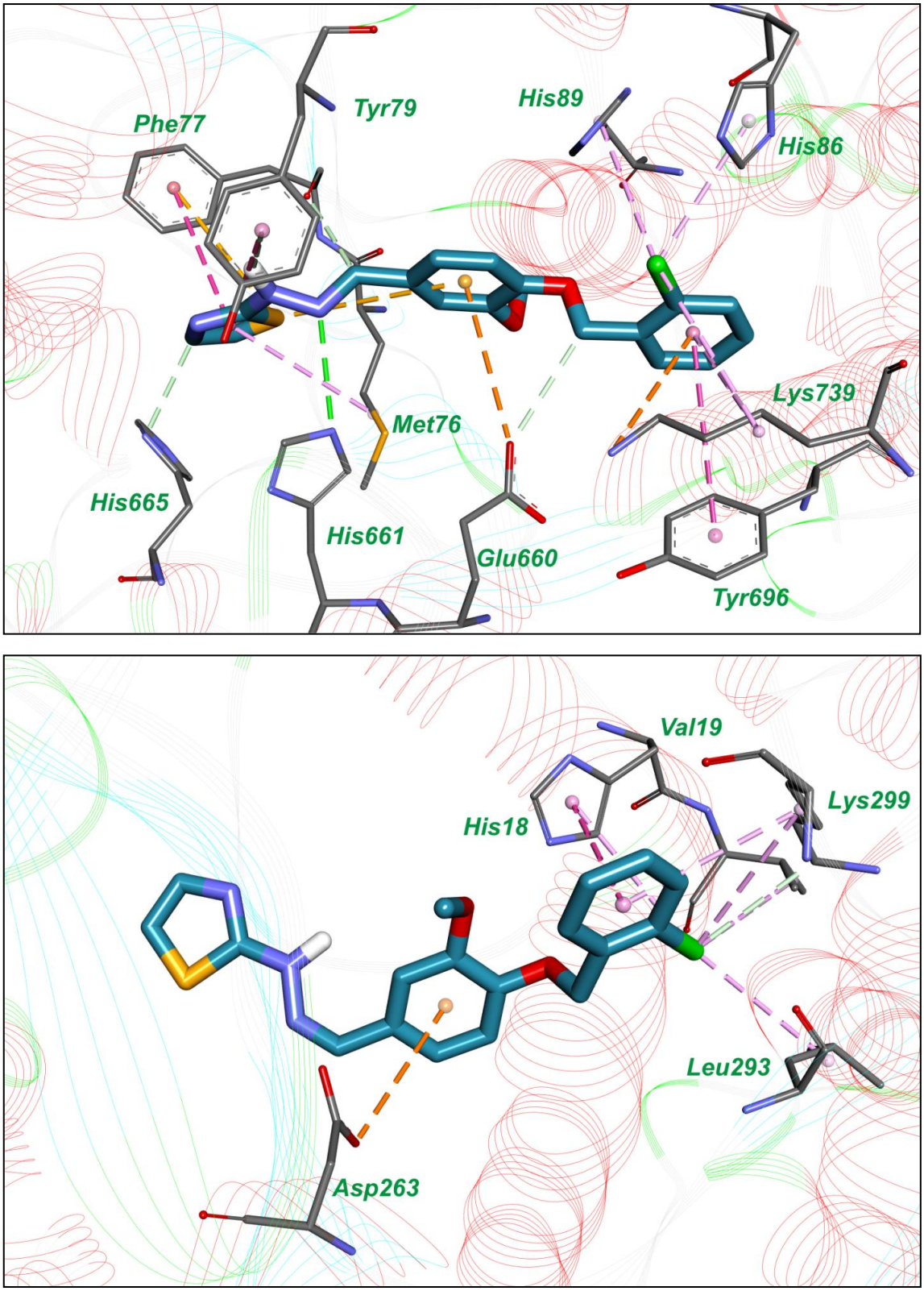
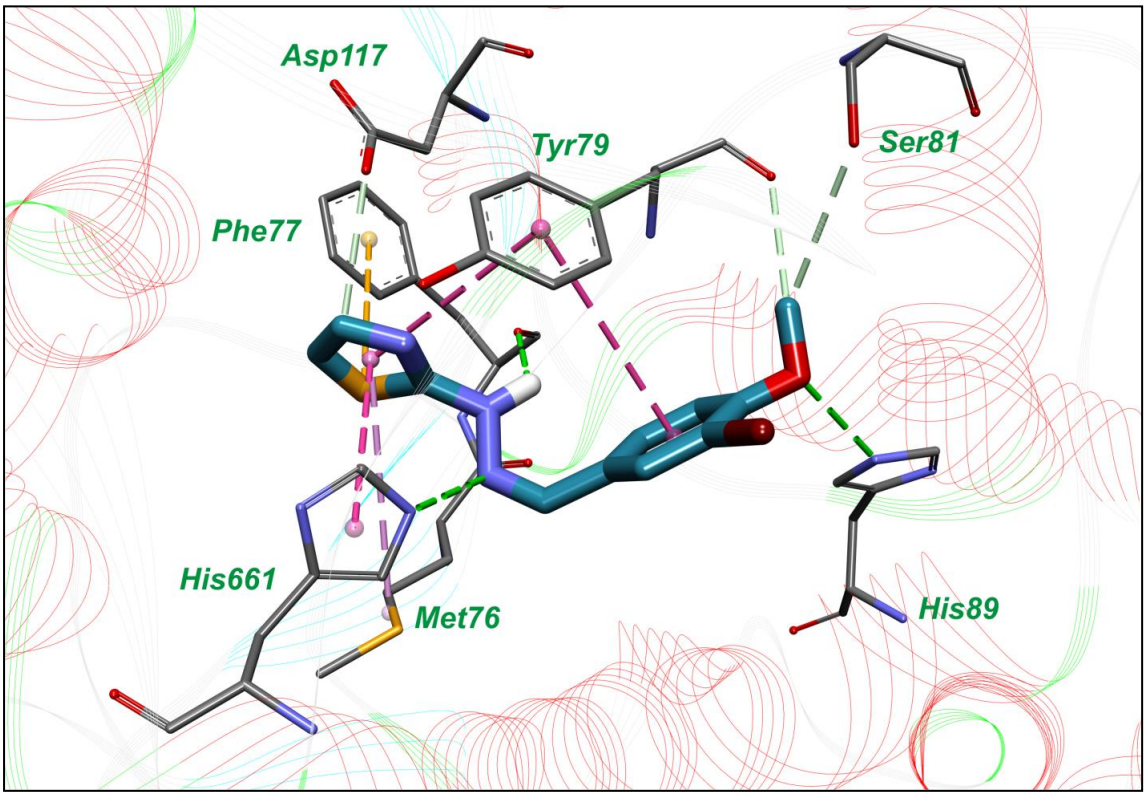


Figure S1-33. The complexes of compound **33** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.



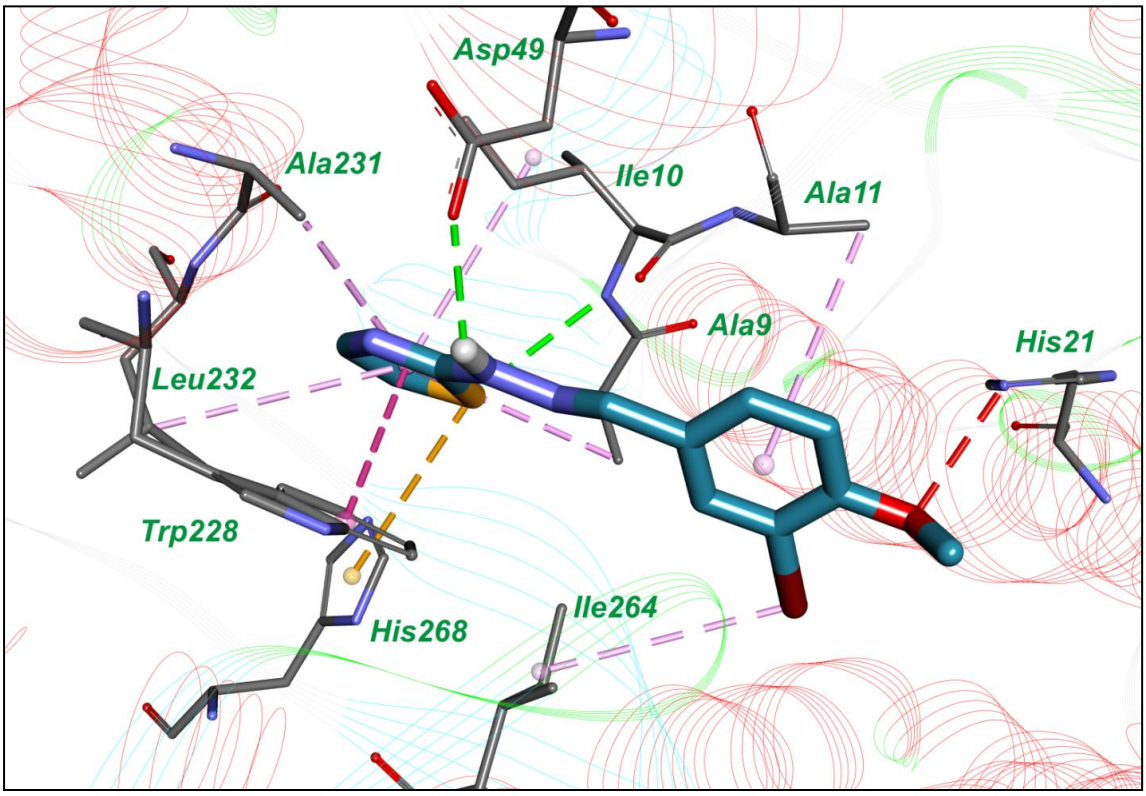


Figure S1-34. The complexes of compound **34** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

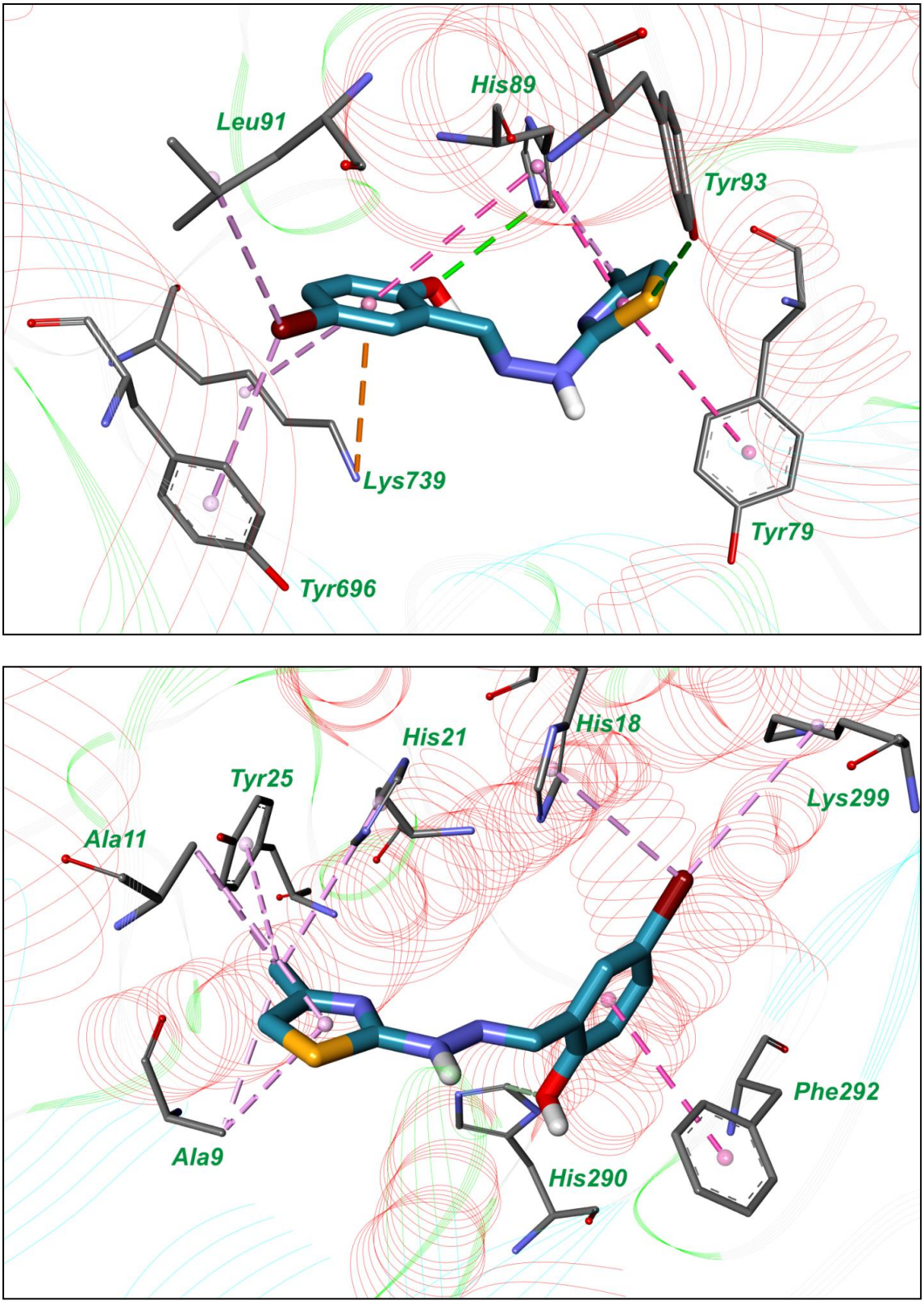


Figure S1-35. The complexes of compound **35** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-cation interactions – with orange color.

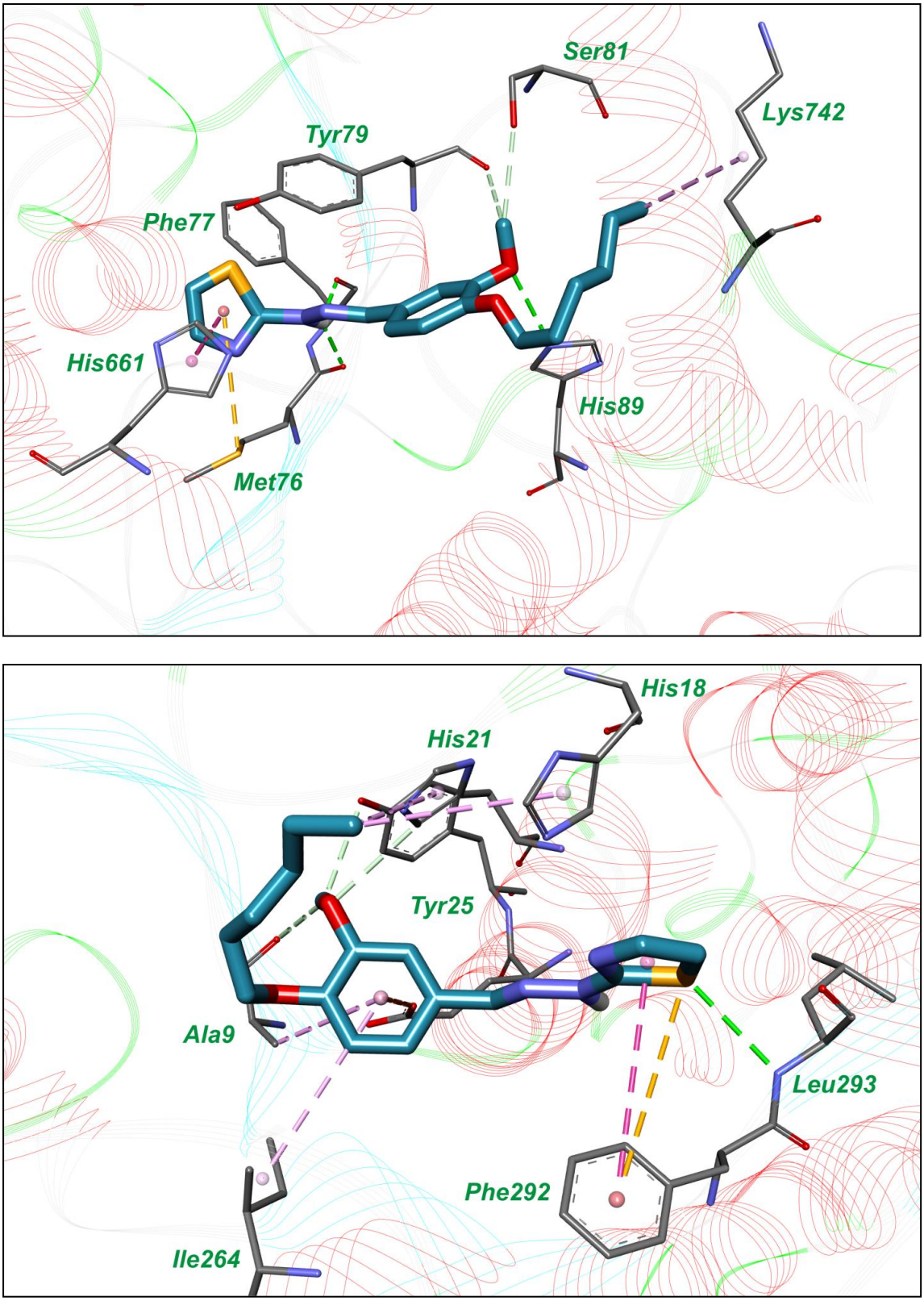


Figure S1-36. The complexes of compound **36** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-sulfur interactions are shown with yellow color, π-cation interactions – with orange color.

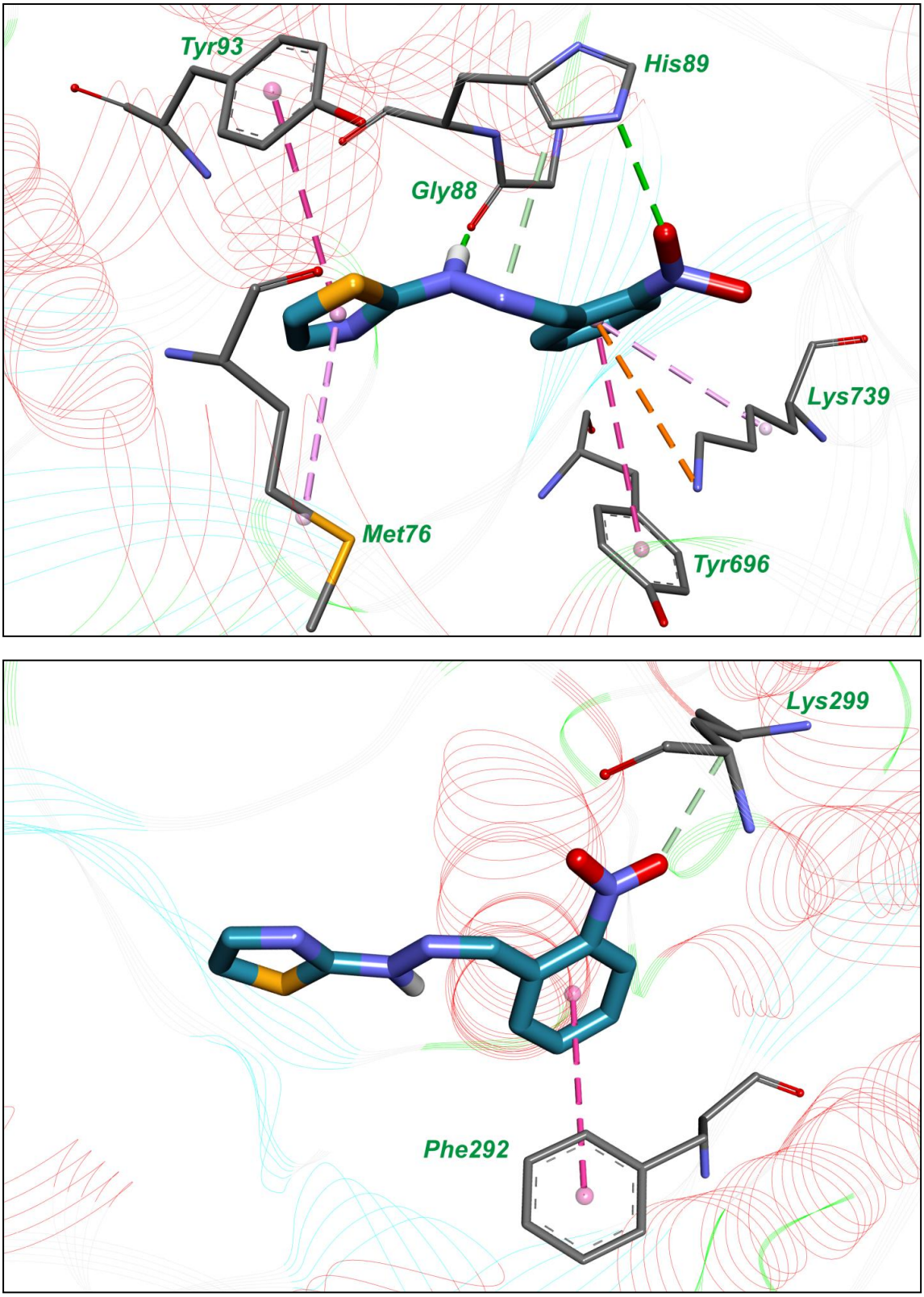


Figure S1-37. The complexes of compound **37** with *M. tuberculosis* leucyl-tRNA synthetase (top panel) and methionyl-tRNA syntetase (bottom panel). Hydrogen bonds are indicated with green dotted lines, hydrophobic interactions are represented with magenta colors, π-cation interactions – with orange color.

Section 2. Synthesis and characteristics of compounds 3 – 37, 3a, 5a, 5b

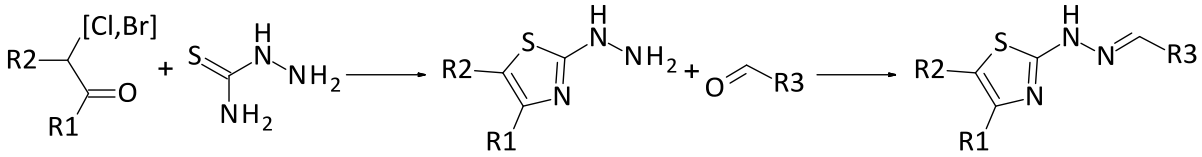
Materials and instrumentation

Starting materials and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded on a Varian Mercury+ 300 MHz instrument at 302 MHz and 76 MHz frequencies for ^{1}H and ^{13}C spectra respectively. Chemical shifts δ are described as parts per million downfield from an internal standard of tetramethylsilane, and spin multiplicities are given as s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), q (quartet), quintet (quintet) or m (multiplet). HPLC–MS analysis was performed using the Agilent 1100 LC/MSD SL separations module and Mass Quad G1956B mass detector with electrospray ionization (+ve or -ve ion mode as indicated), and HPLC was performed using a Zorbax SB-C18, Rapid Resolution HT cartridge, 4.6 mm x 30 mm, 1.8 µm i.d. column (Agilent P/N 823975-902) at a temperature of 40°C with gradient elution of 0 – 100 % CH_3CN (with 1 mL/L HCOOH)/H_2O (with 1 mL/L HCOOH) at a flow rate of 3 mL/min and a run time of 2.8 min. Compounds were detected at 215 nm using a diode array G1315B detector. All tested compounds gave 95% purity as determined by these methods.

Synthesis and characterization

General procedure for the compounds 3-37 synthesis

N-Benzylidene-N'-thiazol-2-yl-hydrazine derivatives were synthesized in one pot manner (Scheme 1). Primarily 1,3-thiazole-2-hydrazine salt formed in reaction of correspondent α-chloro- or α-bromo-ketone with thiosemicarbazide in iPrOH solution.[1,2] Hydrazine salt without isolation was basified with sodium carbonate, and then correspondent aldehyde was added. Unsubstituted 2-hydrazinothiazole hydrochloride was prepared separately starting from 2-aminothiazole.[3]



Scheme S1. Synthesis of N-Benzylidene-N'-thiazol-2-yl-hydrazine derivatives.

General procedure of N-Benzylidene-N'-thiazol-2-ylhydrazine derivatives synthesis

12 mmol of correspondent halogenoketone and 0.91 g (10 mmol) of thiosemicarbazide were mixed in 30 ml of iPrOH and refluxed for 20 min. until bulky precipitate of 2-hydrazinothiazole halogenide salt formed. Then 2.12 g (20 mmol) of sodium carbonate were added. Reaction mixture was refluxed for additional 1–2 min, 10 mmol of correspondent aldehyde were added and refluxing was continued for 1–2 h. During that time heavy bulky precipitate substantially decreased in volume. After evaporation of solvent 20 ml of acetonitrile were added, mixture was heated to reflux and resulted solution or suspension was decanted from heavy inorganic solid material. Mixture was allowed to cool to room temperature, and then precipitate of product was filtered and dried on the air. Following substances were obtained:

N-(3-Bromo-4-methoxy-benzylidene)-N'-[4-(4-fluoro-phenyl)-thiazol-2-yl]-hydrazine (**3**): yield 53%, as beige powder, m.p. 235-237°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.34 (s, 1H), 7.90 (s, 1H), 7.77 (d, *J* = 10.9 Hz, 3H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.16 (t, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.46, 163.94 (d, *J* = 246.6 Hz), 156.69, 152.41, 141.58, 131.16 (d, *J* = 8.0 Hz), 130.70, 128.57, 128.06, 115.52 (d, *J* = 21.6 Hz), 113.12, 112.16, 56.79. MS (ESI) Calculated m/z 406.0024; Found m/z 405.80 (M+); t_R = 1.208 min.

4-{[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-hydrazonomethyl}-benzoic acid (**4**): yield 21%, as beige powder, m.p. 303-305°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.38 (br s, 1H) 7.96 (t, *J* = 27.1 Hz, 2H), 7.68 (d, *J* = 30.6 Hz, 2H), 7.42 (d, *J* = 18.1 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 167.62, 146.48, 140.68, 138.70, 132.95, 132.61, 132.49, 131.99, 131.66, 130.18, 127.89, 126.61, 110.01. MS (ESI) Calculated m/z 392.0027; Found m/z 392 (M+); t_R = 1.167 min.

N-(2-Bromo-benzylidene)-N'-[4-(3-nitro-phenyl)-thiazol-2-yl]-hydrazine (**5**): yield 42%, as golden powder, m.p. 155-156°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.31 (s, 1H), 8.23 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 7.62 (dd, *J* = 15.5, 7.3 Hz, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.83, 153.37, 144.61, 141.30, 138.27, 136.70, 135.89, 135.28, 133.17, 131.71, 127.75, 127.11, 125.09, 111.74. MS (ESI) Calculated m/z 402.9864; Found m/z 404.80 (M+); t_R = 1.249 min.

N-[4-(3-Nitro-phenyl)-thiazol-2-yl]-N'-(3-phenoxy-benzylidene)-hydrazine (**6**): yield 63%, as orange powder, m.p. 156-157°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.32 (s, 1H), 8.62 (s, 1H), 8.23 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 1H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.57 (s, 1H), 7.39 (dt, *J* = 6.9, 2.7 Hz, 4H), 7.26 (s, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.97 (dt, *J* = 5.6, 2.4 Hz, 1H), 3.39 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.60, 162.33, 161.48, 153.38, 145.89, 141.50, 141.28, 136.66, 135.64, 135.27, 128.90, 127.13, 126.82, 125.10, 124.49, 124.05, 120.63, 111.65. MS (ESI) Calculated m/z 417.1021; Found m/z 417 (M+); t_R = 1.291 min.

N-(4-Ethyl-benzylidene)-N'-[4-(3-nitro-phenyl)-thiazol-2-yl]-hydrazine (**7**): yield 26%, as lemon yellow powder, m.p. 172-173°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.25 (d, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 3H), 7.21 (d, *J* = 6.9 Hz, 2H), 2.58 (q, *J* = 7.0 Hz, 2H), 1.14 (q, *J* = 5.9 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.85, 148.21, 148.10, 145.19, 141.58, 136.24, 131.92, 131.47, 130.07, 128.17, 126.31, 121.86, 119.90, 106.06, 28.06, 15.34. MS (ESI) Calculated m/z 353.1072; Found m/z 353 (M+); t_R = 1.270 min.

2-Nitro-4-[(4-phenyl-thiazol-2-yl)-hydrazonomethyl]-phenol (**8**): yield 38%, as brick red powder, m.p. 223-224°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.45 (s, 1H), 8.10 (s, 1H), 8.00 (s, 1H), 7.92 – 7.75 (m, 3H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.27 (s, 2H), 7.18 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.31, 157.94, 155.67, 144.44, 142.11, 139.81, 137.28, 133.77, 132.70, 131.29, 130.69, 128.24, 124.96, 108.80. MS (ESI) Calculated m/z 341.0708; Found m/z 341 (M+); t_R = 1.125 min.

3-[(5-Methyl-4-phenyl-thiazol-2-yl)-hydrazonomethyl]-phenol (**9**): yield 32%, as beige powder, m.p. 155-156°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.89 (br s, 1H), 9.60 (br s, 1H), 7.90 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.47 – 7.34 (m, 2H), 7.31 (d, *J* = 12.0 Hz, 2H), 7.25 – 7.15 (m, 1H), 7.11 (s, 1H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.77 (d, *J* = 6.7 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 164.75, 158.09, 145.84, 141.30, 136.27, 135.64, 130.24, 128.69, 128.29, 127.45, 118.27, 117.29, 116.95, 112.37, 12.72. MS (ESI) Calculated m/z 310.1014; Found m/z 310 (M+); t_R = 1.002 min.

Dimethyl-{4-[(4-phenyl-thiazol-2-yl)-hydrazonomethyl]-phenyl}-amine (**10**): yield 40%, as dark grey powder, m.p. 190-192°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.85 (s, 1H), 7.91 (s, 1H), 7.83 (d, *J* = 6.9 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.42 – 7.31 (m, 2H), 7.28 (d, *J* = 6.6 Hz, 1H), 7.22 (s, 1H), 6.71 (d, *J* = 7.8 Hz, 2H), 2.92 (s, 6H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.89, 151.41, 150.87, 142.75, 135.28, 129.00, 127.99, 127.86, 125.93, 122.39, 112.38, 103.37, 40.25. MS (ESI) Calculated m/z 323.1330; Found m/z 323.20 (M+); t_R = 1.167 min

2-[(4-Phenyl-thiazol-2-yl)-hydrazonomethyl]-phenol (**11**): yield 52%, as beige powder, m.p. 171-172°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 10.14 (s, 1H), 8.34 (s, 1H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 6.6 Hz, 2H), 7.31 – 7.11 (m, 3H), 7.04 – 6.76 (m, 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.39, 156.43, 150.80, 140.42, 134.99, 130.94, 129.04, 128.01, 127.03, 125.97, 120.53, 119.94, 116.59, 103.69. MS (ESI) Calculated m/z 296.0858; Found m/z 296 (M+); t_R = 1.126 min.

N-(2,5-Dimethoxy-benzylidene)-N'-(4-pyridin-3-yl-thiazol-2-yl)-hydrazine (**12**): yield 27%, as yellowish powder, m.p. 203-204°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.23 (s, 1H), 9.05 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.44 (m, 1H), 7.41 (s, 1H), 7.28 (s, 1H), 7.07 – 6.85 (m, 2H), 3.77 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.90, 158.41, 156.74, 153.55, 152.90, 151.99, 141.90, 137.81, 135.48, 128.91, 128.18, 121.35, 118.36, 114.46, 110.46, 61.33, 60.54. MS (ESI) Calculated m/z 341.1072; Found m/z 341 (M+); t_R = 0.879 min.

4-[(4-Ethoxycarbonylmethyl-thiazol-2-yl)-hydrazonomethyl]-benzoic acid (**13**): yield 69%, as white powder, m.p. 243-244°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.76 (br s, 3H), 8.37 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 3H), 7.82 (d, *J* = 7.9 Hz, 2H), 6.88 (s, 1H), 4.08 (q, *J* = 6.9 Hz, 2H), 3.76 (s, 2H), 2.50 (d, *J* = 11.6 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 4H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.53, 167.74, 167.23, 145.63, 138.78, 137.87, 132.26, 130.19, 127.48, 126.74, 107.81, 61.11, 34.91, 14.49. MS (ESI) Calculated m/z 334.0862; Found m/z 334 (M+); t_R = 0.880 min.

4-Methyl-2-[N'-(2-trifluoromethyl-benzylidene)-hydrazino]-thiazole-5-carboxylic acid ethyl ester (**14**): yield 16%, as beige powder, m.p. 184-186°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.66 (s, 1H), 8.36 (s, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.0 Hz, 1H), 4.16 (q, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 1.23 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.23, 166.93, 144.15, 144.04, 137.96, 136.98, 134.82, 131.97, 131.68, 127.50 (q, *J* = 274.2 Hz), 65.34, 22.15, 19.40. MS (ESI) Calculated m/z 358.0837; Found m/z 358 (M+); t_R = 1.188 min.

2-[N'-(3,5-Dibromo-4-hydroxy-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid ethyl ester (**15**): yield 67%, as gray powder, m.p. 275-276°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.41 (s, 1H), 7.90 (s, 1H), 7.78 (s, 2H), 4.16 (q, *J* = 6.6 Hz, 2H), 2.42 (s, 3H), 1.23 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.05, 166.99, 162.85, 157.06, 146.98, 135.34, 133.83, 117.38, 114.01, 65.29, 22.11, 19.50. MS (ESI) Calculated m/z 460.9044; Found m/z 463.80 (M+); t_R = 1.064 min.

2-[N'-(3-Bromo-4-hydroxy-5-methoxy-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid ethyl ester (**16**): yield 56%, as grayish powder, m.p. 253-254°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.34 (s, 1H), 7.17 (s, 1H), 4.17 (q, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 2.43 (s, 3H), 1.23 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.52, 162.38, 158.50, 149.40, 147.87, 144.43, 125.21, 124.03, 110.39, 108.83, 60.42, 56.52, 17.53, 14.79. MS (ESI) Calculated m/z 414.0123; Found m/z 413.80 (M+); t_R = 1.023 min.

2-[N'-(4-Bromo-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid ethyl ester (**17**): yield 57%, as ivory crystals, m.p. 193-194°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.64 (s, 2H), 8.12 (s, 1H), 7.57 (s, 4H), 4.15 (q, *J* = 6.9 Hz, 2H), 2.44 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.02, 161.99, 156.81, 144.57, 133.49, 132.21, 129.01, 123.59, 109.59, 60.75, 16.95, 14.69. MS (ESI) Calculated m/z 368.0068; Found m/z 370 (M+); t_R = 1.188 min.

2-[N'-(2-Bromo-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid ethyl ester (**18**): yield 24%, as ivory flakes, m.p. 200-201°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 4.16 (q, *J* = 7.05 Hz, 2H), 2.44 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.48, 162.21, 158.40, 142.75, 133.54, 133.09,

131.73, 128.51, 127.31, 123.40, 110.02, 60.59, 17.48, 14.71. MS (ESI) Calculated m/z 368.0068; Found m/z 370 (M+); t_R = 1.168 min.

2-[N'-(4-Carboxy-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid ethyl ester (**19**): yield 89%, as mustard powder, m.p. 320-325°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 4.18 (q, 2H), 2.44 (s, 3H), 1.23 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.69, 168.30, 162.29, 158.46, 144.10, 137.33, 134.91, 130.12, 126.72, 109.59, 60.54, 17.47, 14.73. MS (ESI) Calculated m/z 334.0862; Found m/z 334 (M+); t_R = 0.940 min.

2-[N'-(3-Hydroxy-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid ethyl ester (**20**): yield 45%, as white powder, m.p. 242-244°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.06 – 7.88 (m, 1H), 7.26 – 7.16 (m, 1H), 7.14 (s, 1H), 7.02 (d, *J* = 6.4 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 4.25 – 4.03 (m, 2H), 2.46 – 2.35 (m, 2H), 1.24 (dt, *J* = 6.7, 3.5 Hz, 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.75, 167.10, 163.48, 162.83, 149.57, 140.51, 135.04, 123.62, 122.35, 117.26, 113.95, 65.21, 22.30, 19.49. MS (ESI) Calculated m/z 306.0912; Found m/z 306 (M+); t_R = 0.940 min.

2-(N'-Benzylidene-hydrazino)-4-methyl-thiazole-5-carboxylic acid ethyl ester (**21**): yield 74%, as beige powder, m.p. 196-197°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.65 (d, *J* = 5.7 Hz, 2H), 7.39 (d, *J* = 6.1 Hz, 3H), 4.17 (q, *J* = 6.7 Hz, 2H), 2.45 (s, 3H), 1.23 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.45, 167.06, 163.31, 149.50, 139.19, 134.93, 133.99, 131.82, 114.23, 65.25, 22.27, 19.47. MS (ESI) Calculated m/z 290.0963; Found m/z 290 (M+); t_R = 1.084 min.

2-[N'-(4-Bromo-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid methyl ester (**22**): yield 77%, as ivory flakes, m.p. 210-211°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.57 (s, 4H), 3.70 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.76, 162.65, 158.52, 143.56, 133.75, 132.20, 128.85, 123.31, 109.20, 51.88, 17.43. MS (ESI) Calculated m/z 353.9912; Found m/z 356 (M+); t_R = 1.125 min.

2-[N'-(4-Carboxy-benzylidene)-hydrazino]-4-methyl-thiazole-5-carboxylic acid methyl ester (**23**): yield 80%, as yellow power, m.p. 305-310°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.71 (br s, 1H), 8.12 (s, 1H), 7.94 (s, 2H), 7.74 (s, 2H), 3.70 (s, 4H), 2.47 (s, 4H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.64, 167.31, 162.65, 158.52, 143.71, 138.43, 131.76, 130.22, 127.01, 109.49, 51.95, 17.40. MS (ESI) Calculated m/z 320.0705; Found m/z 320 (M+); t_R = 0.879 min.

4-Methyl-2-[N'-(4-nitro-benzylidene)-hydrazino]-thiazole-5-carboxylic acid methyl ester (**24**): yield 66%, as orangish power, m.p. 275-277°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.62 (s, 2H), 8.14 (d, *J* = 7.4 Hz, 3H), 7.79 (d, *J* = 8.3 Hz, 2H), 3.68 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.25, 162.34, 157.24, 147.75, 142.73, 140.57, 127.82, 124.34, 109.74, 52.03, 16.96. MS (ESI) Calculated m/z 321.0658; Found m/z 321 (M+); t_R = 1.043 min.

1-(2-{N'-[4-(2-Chloro-benzyloxy)-3-methoxy-benzylidene]-hydrazino}-4-methyl-thiazol-5-yl)-ethanone (**25**): yield 53%, as yellow crystals, m.p. 202-203°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.37 (s, 2H), 7.29 (s, 1H), 7.16 (s, 1H), 7.08 (s, 1H), 5.14 (s, 2H), 3.80 (s, 3H), 2.46 (s, 3H), 2.36 (s, 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 161.64, 154.51, 154.30, 150.06, 147.53, 139.32, 137.81, 135.40, 135.11, 134.54, 132.92, 132.56, 125.83, 118.55, 118.10, 114.21, 72.67, 60.74, 34.62, 23.47. MS (ESI) Calculated m/z 430.0992; Found m/z 430 (M+); t_R = 1.105 min.

1-{2-[N'-(4-Ethoxy-benzylidene)-hydrazino]-4-methyl-thiazol-5-yl}-ethanone (**26**): yield 39%, as grey powder, m.p. 170-171°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.01 (d, *J* = 2.7 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.6 Hz, 2H), 6.94 (dd, *J* = 8.4, 2.6 Hz, 2H), 4.02 (dd, *J* = 6.7, 3.0 Hz, 2H), 2.48 – 2.42 (m, 3H), 2.36 (d, *J* = 2.8 Hz,

3H), 1.30 (q, *J* = 6.6 Hz, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 193.83, 174.25, 165.17, 161.32, 150.04, 133.49, 131.62, 126.78, 119.91, 68.42, 34.67, 23.33, 19.73. MS (ESI) Calculated m/z 304.1120; Found m/z 304 (M+); t_R = 1.002 min.

N-(4,5-Dimethyl-thiazol-2-yl)-N'-(4-methoxy-benzylidene)-hydrazine (**27**): yield 44%, as gray powder, m.p. 188-189°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 4H), 2.12 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 170.03, 165.16, 146.31, 146.02, 132.75, 132.65, 119.41, 117.78, 60.37, 19.31, 15.98. MS (ESI) Calculated m/z 262.1014; Found m/z 262 (M+); t_R = 0.817 min.

N-(2,3-Dimethoxy-benzylidene)-N'-(4-methyl-thiazol-2-yl)-hydrazine (**28**): yield 13%, as beige powder, m.p. 153-155°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.04 (dt, *J* = 17.3, 7.6 Hz, 2H), 6.34 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.15, 157.86, 152.74, 152.23, 141.68, 133.21, 129.46, 121.64, 118.33, 107.65, 66.19, 60.86, 22.31. MS (ESI) Calculated m/z 278.0963; Found m/z 278 (M+); t_R = 0.899 min.

4-[(4-Methyl-thiazol-2-yl)-hydrazonomethyl]-benzoic acid (**29**): yield 82%, as olive powder, m.p. 292-295°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 8.02 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 2H), 6.36 (s, 1H), 2.14 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.08, 172.19, 152.30, 145.24, 143.87, 135.86, 134.97, 131.24, 107.89, 22.14. MS (ESI) Calculated m/z 262.0650; Found m/z 262 (M+); t_R = 0.755 min.

N-(4-Methyl-thiazol-2-yl)-N'-(4-nitro-benzylidene)-hydrazine (**30**): yield 83%, as tile red powder, m.p. 260-262°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.15 (br s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 8.05 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 6.39 (s, 1H), 2.14 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.11, 152.08, 146.31, 144.04, 133.32, 131.97, 129.27, 108.19, 21.99. MS (ESI) Calculated m/z 263.0603; Found m/z 263 (M+); t_R = 0.961 min.

2,4-Dichloro-benzoic acid 2-methoxy-4-(thiazol-2-yl-hydrazonomethyl)-phenyl ester (**31**): yield 24%, as brown power, m.p. 145-147°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.81 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.33 (s, 3H), 6.96 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.56, 162.21, 151.46, 143.71, 140.48, 138.69, 135.07, 134.64, 133.86, 133.73, 131.26, 128.34, 127.45, 123.68, 119.94, 111.00, 109.74, 56.51. MS (ESI) Calculated m/z 422.0133; Found m/z 421.80 (M+); t_R = 1.167 min.

N-(4-Benzyloxy-3-bromo-5-methoxy-benzylidene)-N'-thiazol-2-yl-hydrazine (**32**): yield 62%, as dark brown power, m.p. 155-157°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.92 (s, 1H), 7.45 (d, *J* = 10.0 Hz, 4H), 7.40 – 7.25 (m, 5H), 7.22 (s, 1H), 6.83 (s, 1H), 4.98 (s, 2H), 3.87 (s, 4H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.24, 154.11, 145.34, 139.74, 139.04, 137.22, 132.56, 128.75, 128.67, 128.53, 122.23, 117.95, 110.22, 109.15, 74.55, 56.52. MS (ESI) Calculated m/z 418.0225; Found m/z 420 (M+); t_R = 1.147 min.

N-[4-(2-Chloro-benzyloxy)-3-methoxy-benzylidene]-N'-thiazol-2-yl-hydrazine (**33**): yield 78%, as grey powder, m.p. 179-180°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.94 (s, 1H), 7.57 (dd, *J* = 5.4, 3.7 Hz, 1H), 7.48 (dd, *J* = 5.4, 3.7 Hz, 1H), 7.36 (dd, *J* = 5.7, 3.5 Hz, 2H), 7.27 (s, 1H), 7.20 (d, *J* = 3.5 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 3.5 Hz, 1H), 5.14 (s, 2H), 3.80 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 174.14, 154.52, 153.88, 146.36, 143.95, 139.37, 137.82, 135.36, 135.08, 134.54, 133.27, 132.54, 125.13, 118.60, 113.98, 113.54, 72.67, 60.66. MS (ESI) Calculated m/z 374.0730; Found m/z 374 (M+); t_R = 1.064 min.

N-(3-Bromo-4-methoxy-benzylidene)-N'-thiazol-2-yl-hydrazine (**34**): yield 27%, as brown powder, m.p. 193-194°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.86 (s, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 6.80 (s, 1H), 3.85 (s, 4H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.29, 156.42, 140.04, 139.04, 130.40, 129.16, 127.74, 113.22, 111.69, 108.89, 56.83. MS (ESI) Calculated m/z 311.9806; Found m/z 313.80 (M+); t_R = 0.961 min.

4-Bromo-2-[(4-methyl-thiazol-2-yl)-hydrazonomethyl]-phenol (**35**): yield 51%, as olive powder, m.p. 201-202°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.26 (s, 1H), 7.76 – 7.64 (m, 1H), 7.31 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.32 (s, 1H), 2.13 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 173.23, 160.60, 149.36, 145.50, 137.75, 133.78, 127.52, 123.54, 115.84, 106.56, 21.31. MS (ESI) Calculated m/z 311.9806; Found m/z 314 (M+); t_R = 1.024 min.

N-(4-Hexyloxy-3-methoxy-benzylidene)-N'-thiazol-2-yl-hydrazine (**36**): yield 43%, as light brown powder, m.p. 148-149°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.28 – 7.14 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 3.92 (br s, 3H), 3.78 (s, 4H), 1.67 (br s, 2H), 1.36 (br s, 2H), 1.25 (br s, 5H), 0.84 (br s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 169.45, 149.82, 149.57, 141.73, 139.16, 127.73, 120.50, 113.10, 109.04, 108.62, 68.61, 55.82, 31.46, 29.12, 25.65, 22.53, 14.34. MS (ESI) Calculated m/z 334.1589; Found m/z 334 (M+); t_R = 1.146 min.

N-(2-Nitro-benzylidene)-N'-thiazol-2-yl-hydrazine (**37**): yield 48%, as brick red powder, m.p. 221-222°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.25 (br s, 1H), 8.38 (s, 1H), 8.14 – 7.80 (m, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 3.3 Hz, 1H), 6.88 (d, *J* = 3.3 Hz, 1H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.96, 147.78, 139.04, 136.56, 133.86, 129.96, 129.13, 127.82, 125.08, 109.84. MS (ESI) Calculated m/z 249.0446; Found m/z 249 (M+); t_R = 0.920 min.

N-(3-Bromo-4-methoxy-benzylidene)-N'-(4-methyl-thiazol-2-yl)-hydrazine (**3a**): yield 38%, as grayish powder, m.p. 182-183°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.31 (s, 1H), 3.85 (s, 4H), 2.14 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.45, 156.37, 147.39, 140.19, 130.38, 129.26, 127.71, 113.20, 111.67, 102.54, 56.81, 17.41. MS (ESI) Calculated m/z 325.9963; Found m/z 326 (M+); t_R = 0.940 min.

N-(2-Bromo-benzylidene)-N'-(4-phenyl-thiazol-2-yl)-hydrazine (**5a**): yield 35%, as beige powder, m.p. 182-183°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 12.53 (br s, 1H), 8.32 (s, 1H), 7.95 – 7.67 (m, 3H), 7.59 (br s, 1H), 7.51 – 7.35 (m, 4H), 7.32 – 7.12 (m, 2H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.52, 153.13, 141.10, 134.22, 133.52, 133.28, 131.37, 129.01, 128.72, 128.56, 128.14, 128.01, 127.19, 125.98, 123.13, 112.86. MS (ESI) Calculated m/z 358.0014; Found m/z 358 (M+); t_R = 1.249 min.

N-(2-Bromo-benzylidene)-N'-(4-methyl-thiazol-2-yl)-hydrazine (**5b**): yield 23%, as beige crystalline solid, m.p. 198-200°C. ^{1}H NMR (302 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 6.6 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 6.36 (s, 1H), 2.14 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6) δ 168.53, 147.72, 139.53, 133.78, 133.51, 130.96, 128.43, 126.90, 122.85, 103.11, 17.47. MS (ESI) Calculated m/z 295.9857; Found m/z 296 (M+); t_R = 1.023 min.

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1. Nandi J. Bose, *Ind. Chem. Soc*., 1930, **7**, 733.
2. K. Takrouri, T. Chen, E. Papadopoulos, R. Sahoo, E. Kabha, H. Chen, S. Cantel, G. Wagner, J. A. Halperin, B. H. Aktas, M. Chorev, *Eur. J. Med. Chem.,* 2014, **77**, 361.
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Supplementary figures S2. ^{1}H NMR, ^{13}C NMR and HPLS-MS spectra.

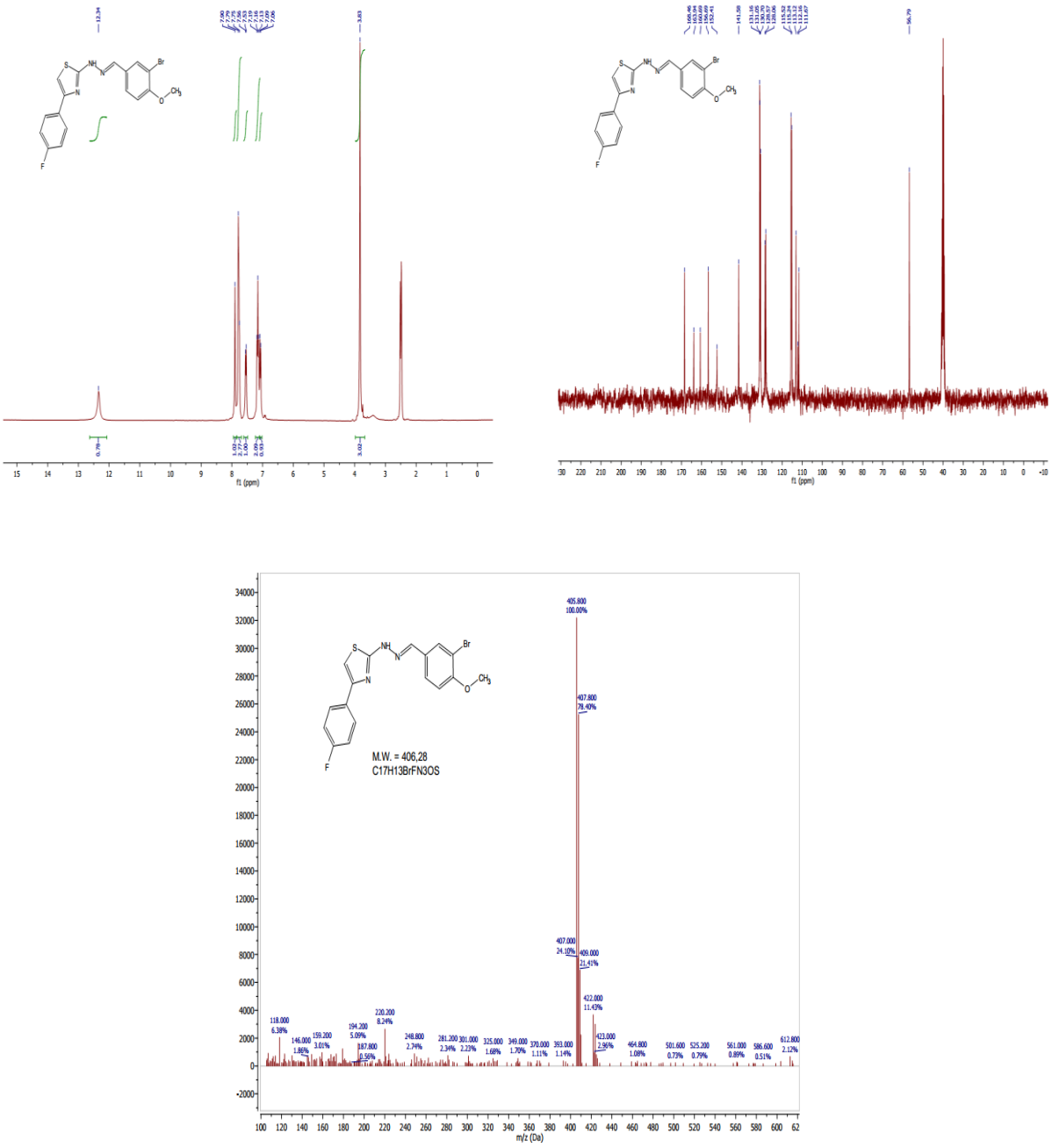
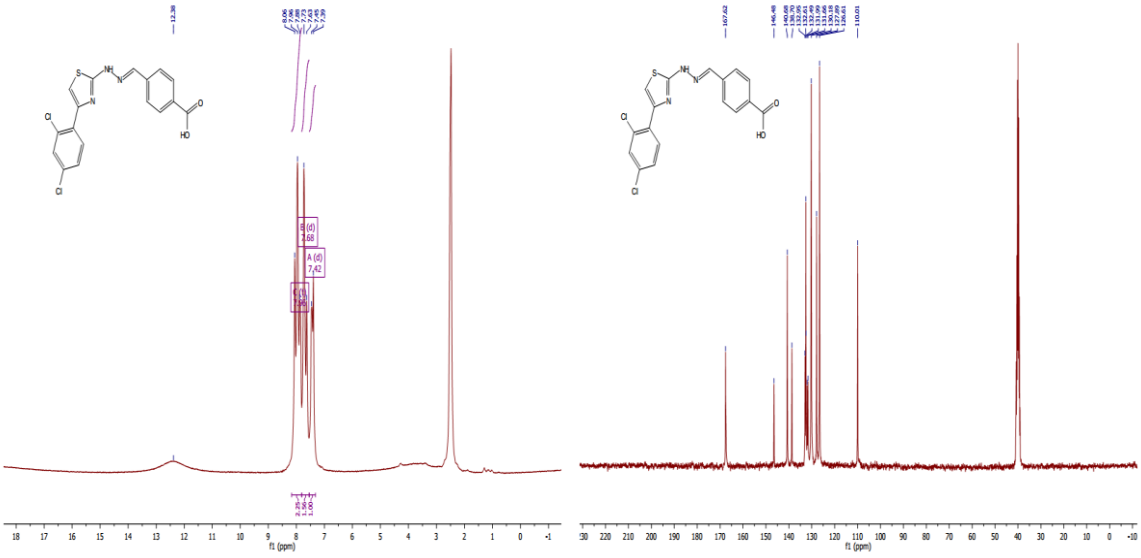


Figure S2-1. Spectra of compound **3**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



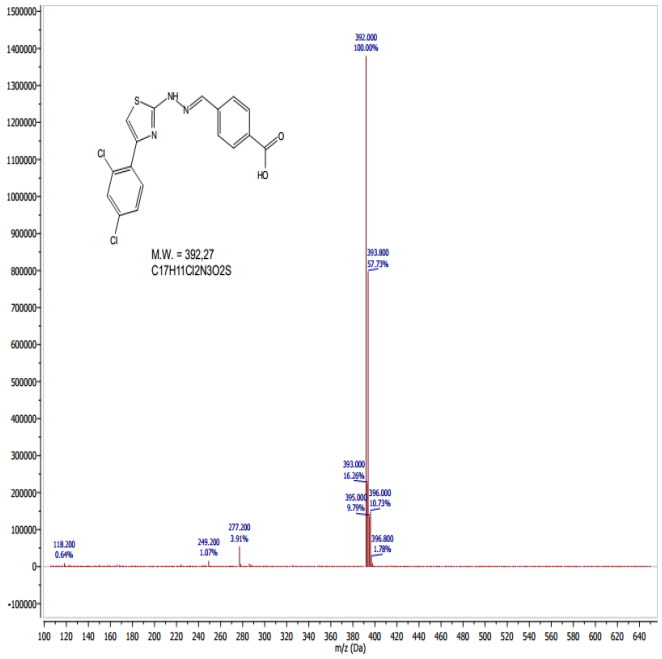


Figure S2-2. Spectra of compound **4**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

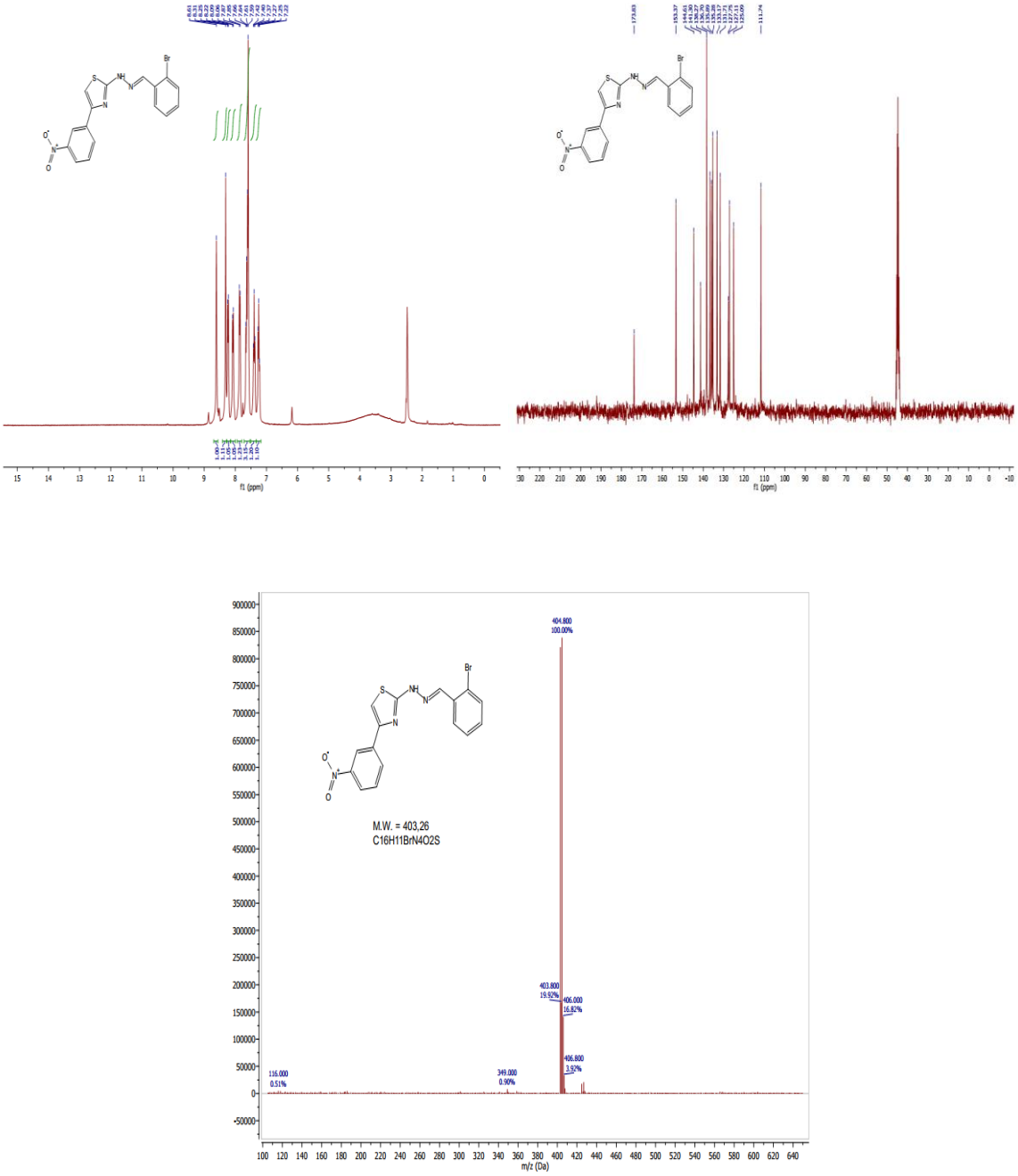
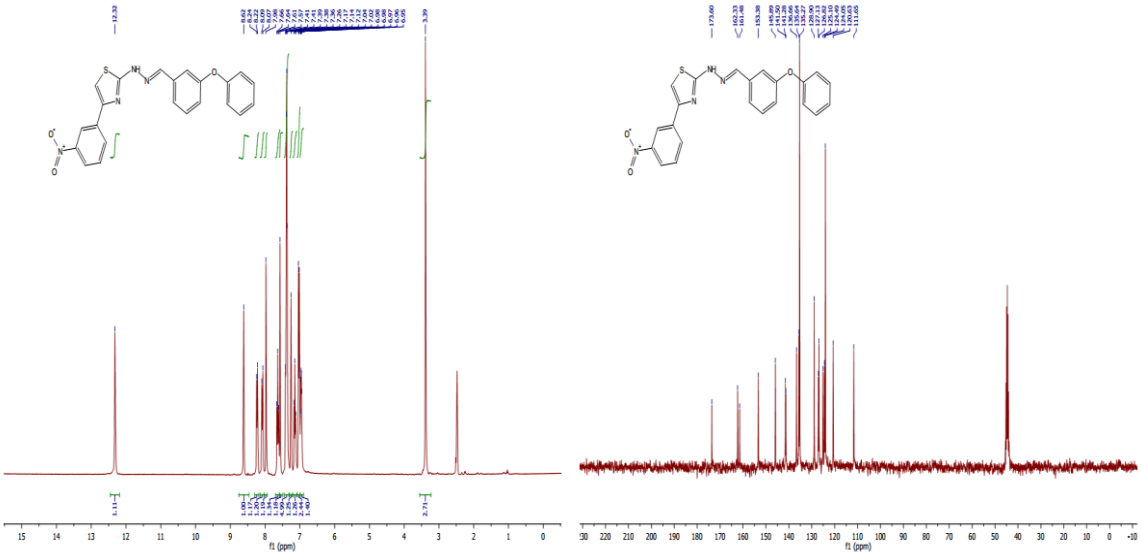


Figure S2-3. Spectra of compound **5**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



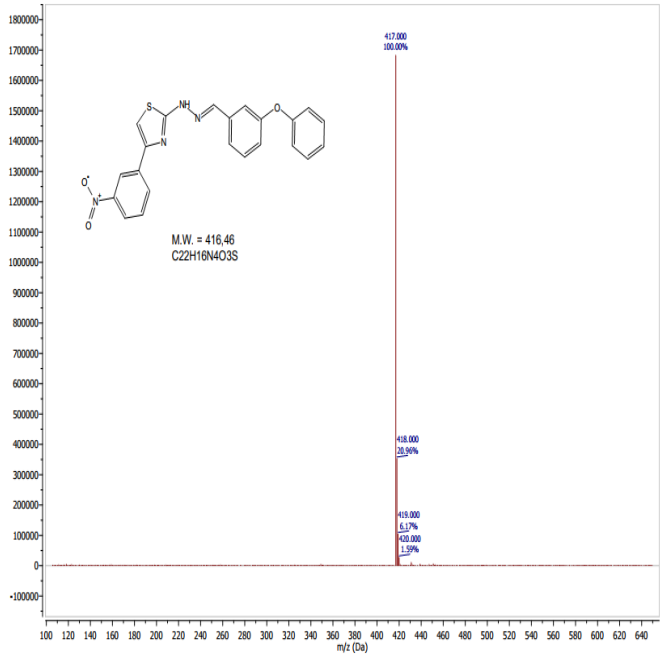


Figure S2-4. Spectra of compound **6**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

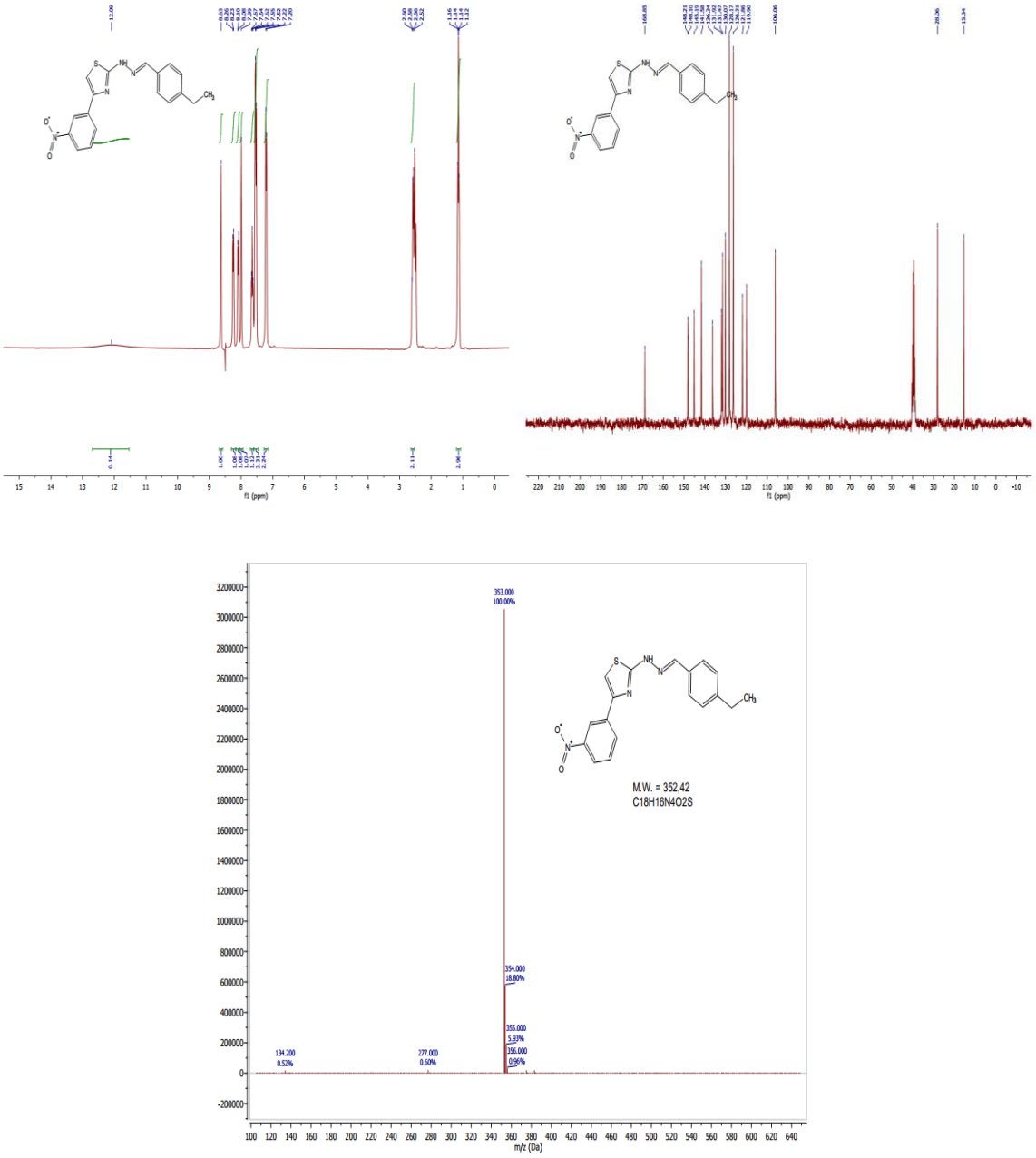
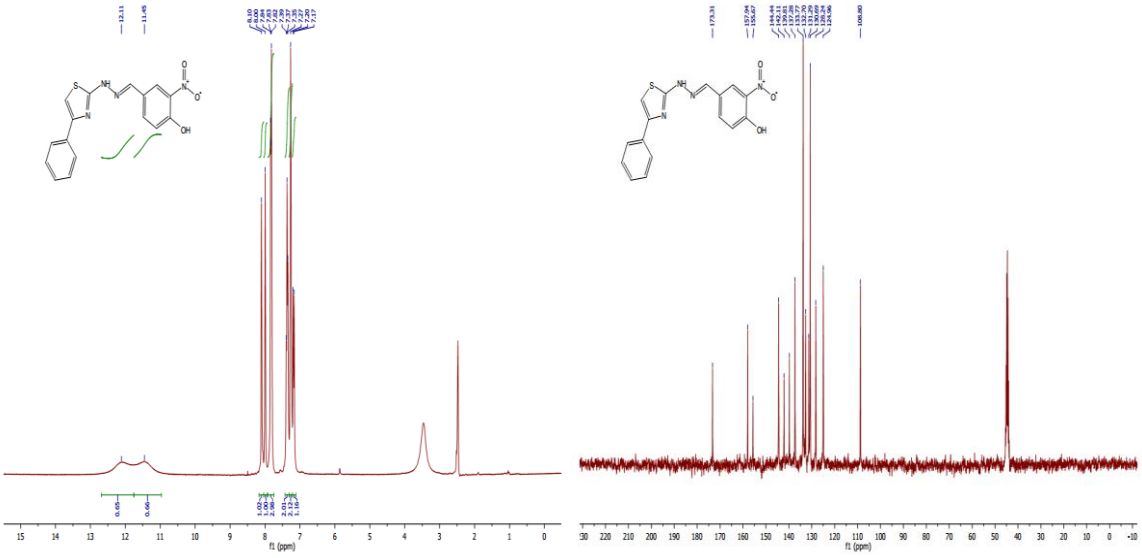


Figure S2-5. Spectra of compound **7**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



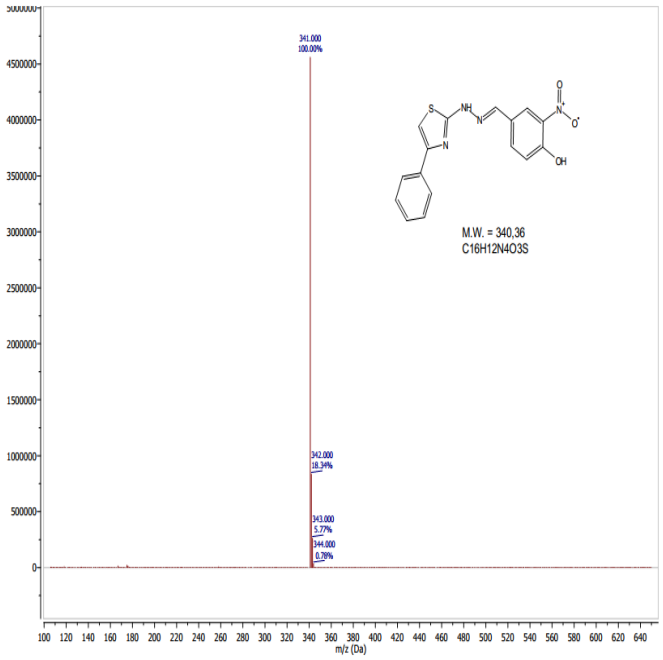


Figure S2-6. Spectra of compound **8**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

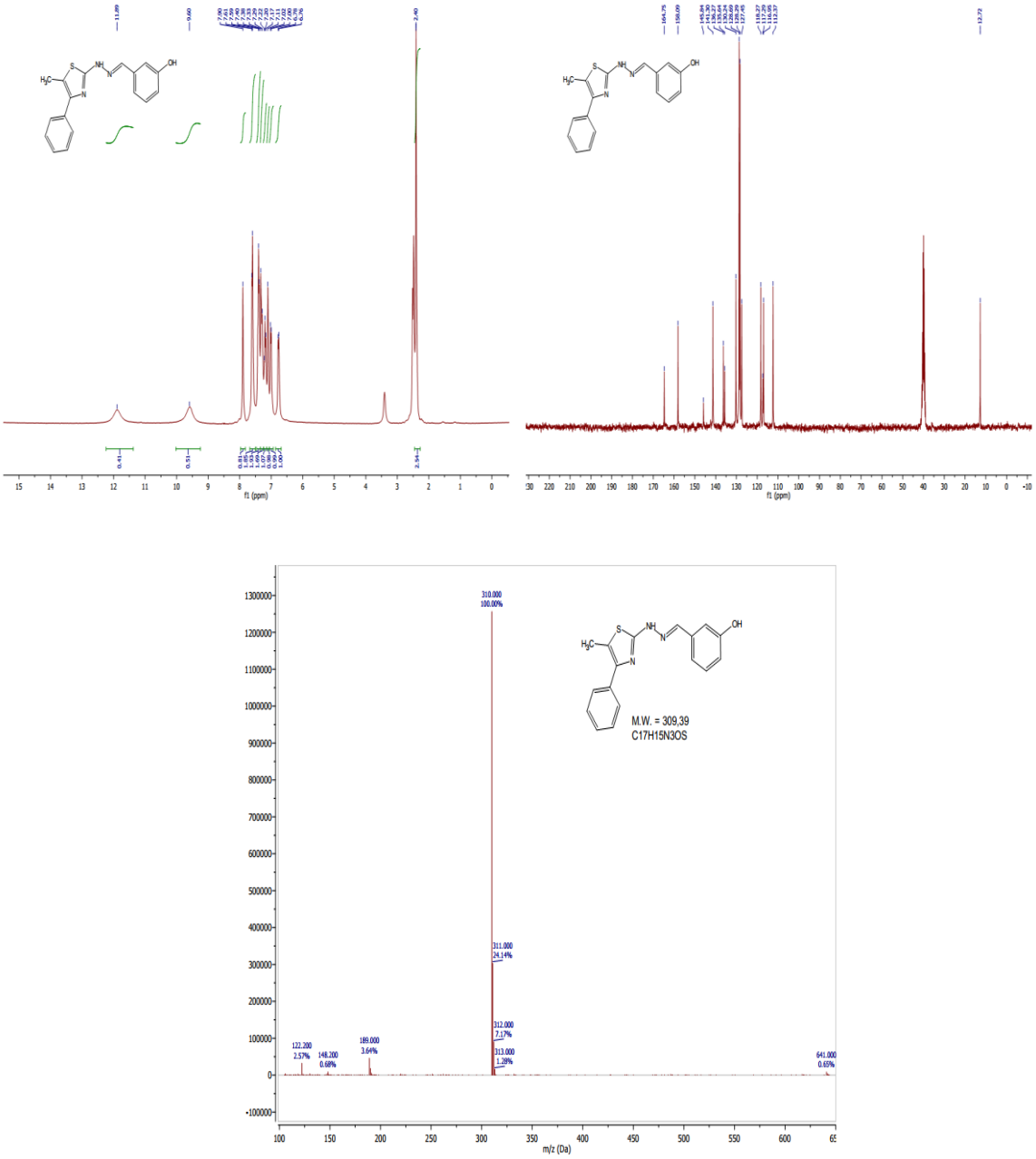


Figure S2-7. Spectra of compound **9**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

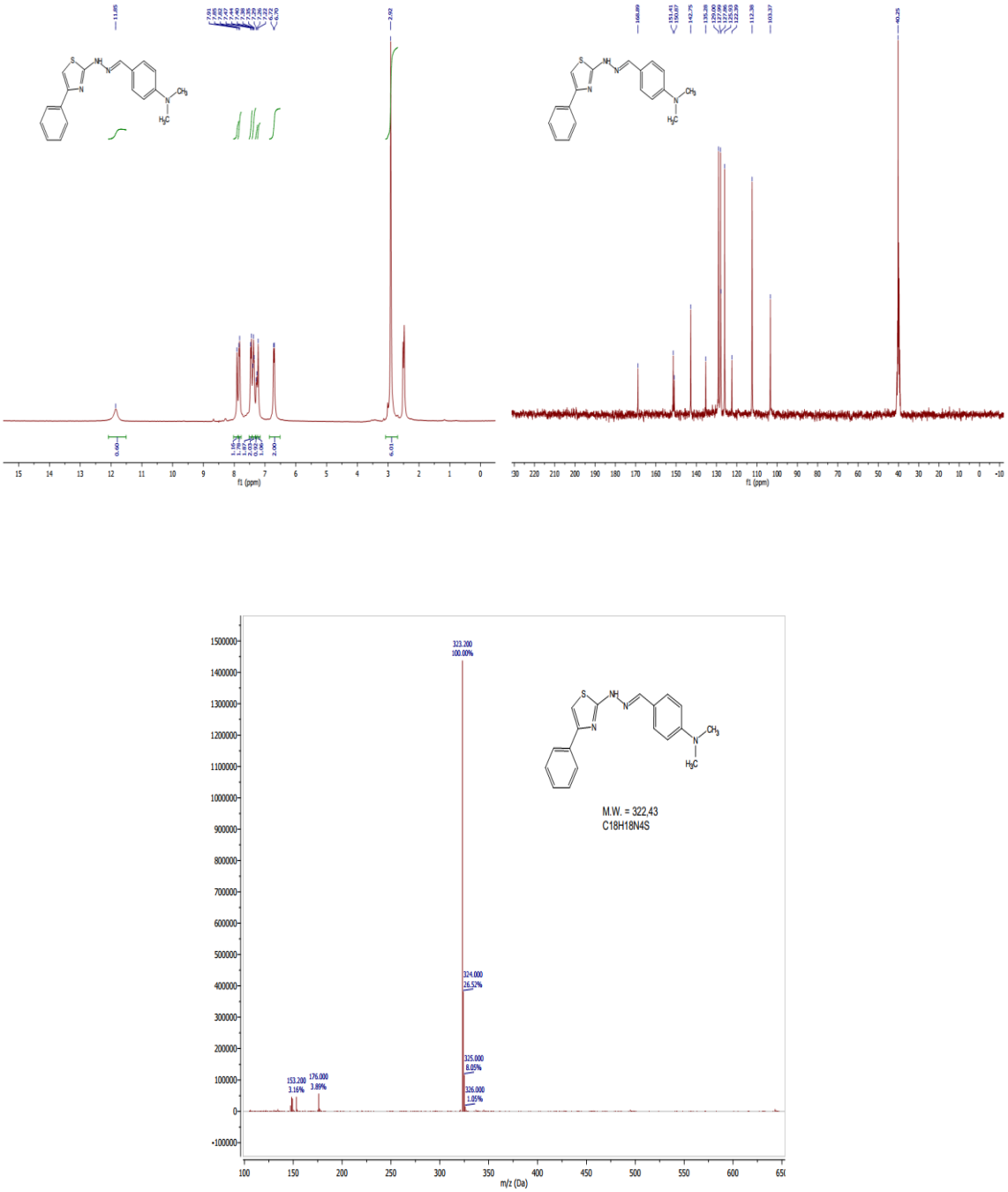


Figure S2-8. Spectra of compound **10**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

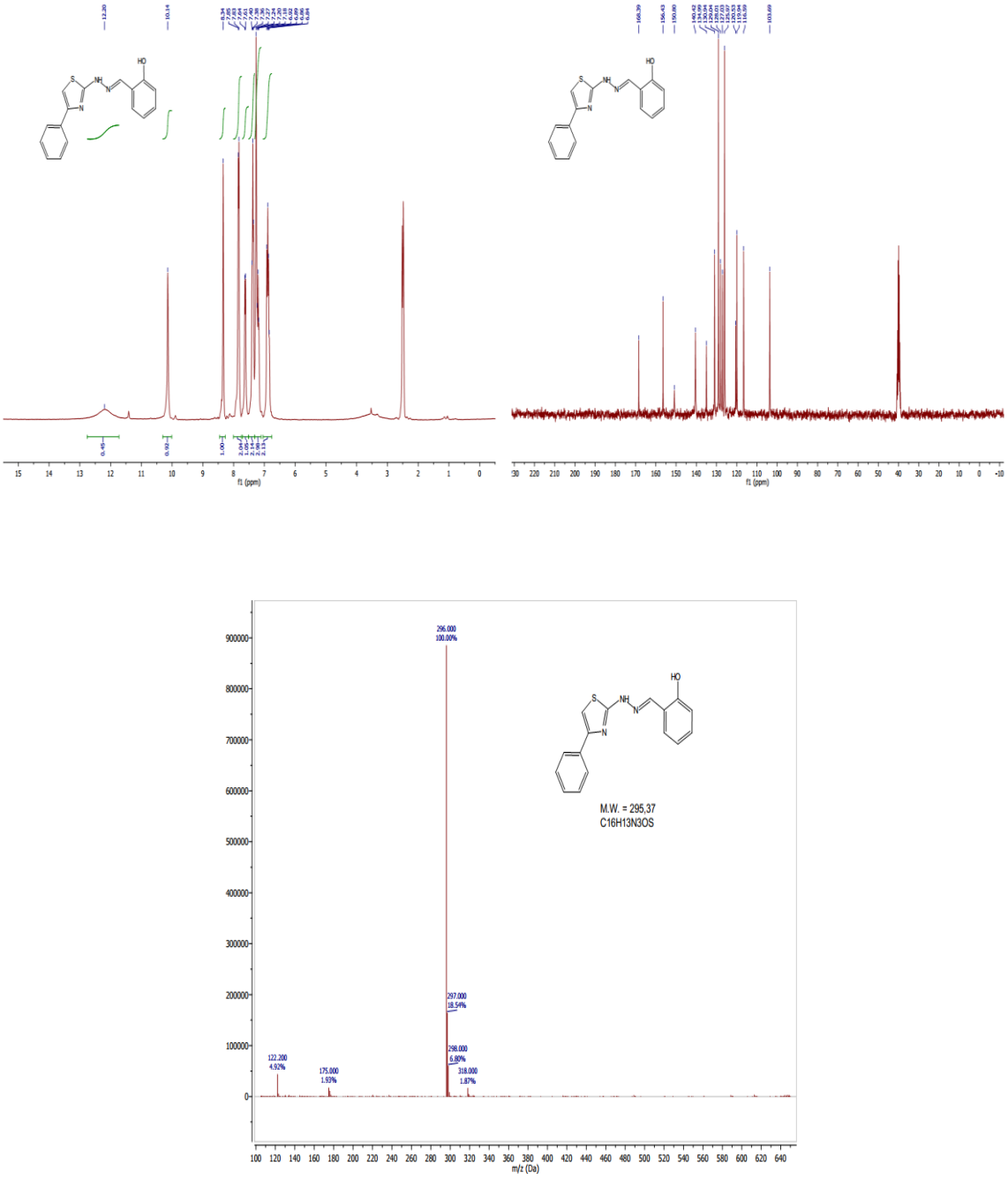


Figure S2-9. Spectra of compound **11**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

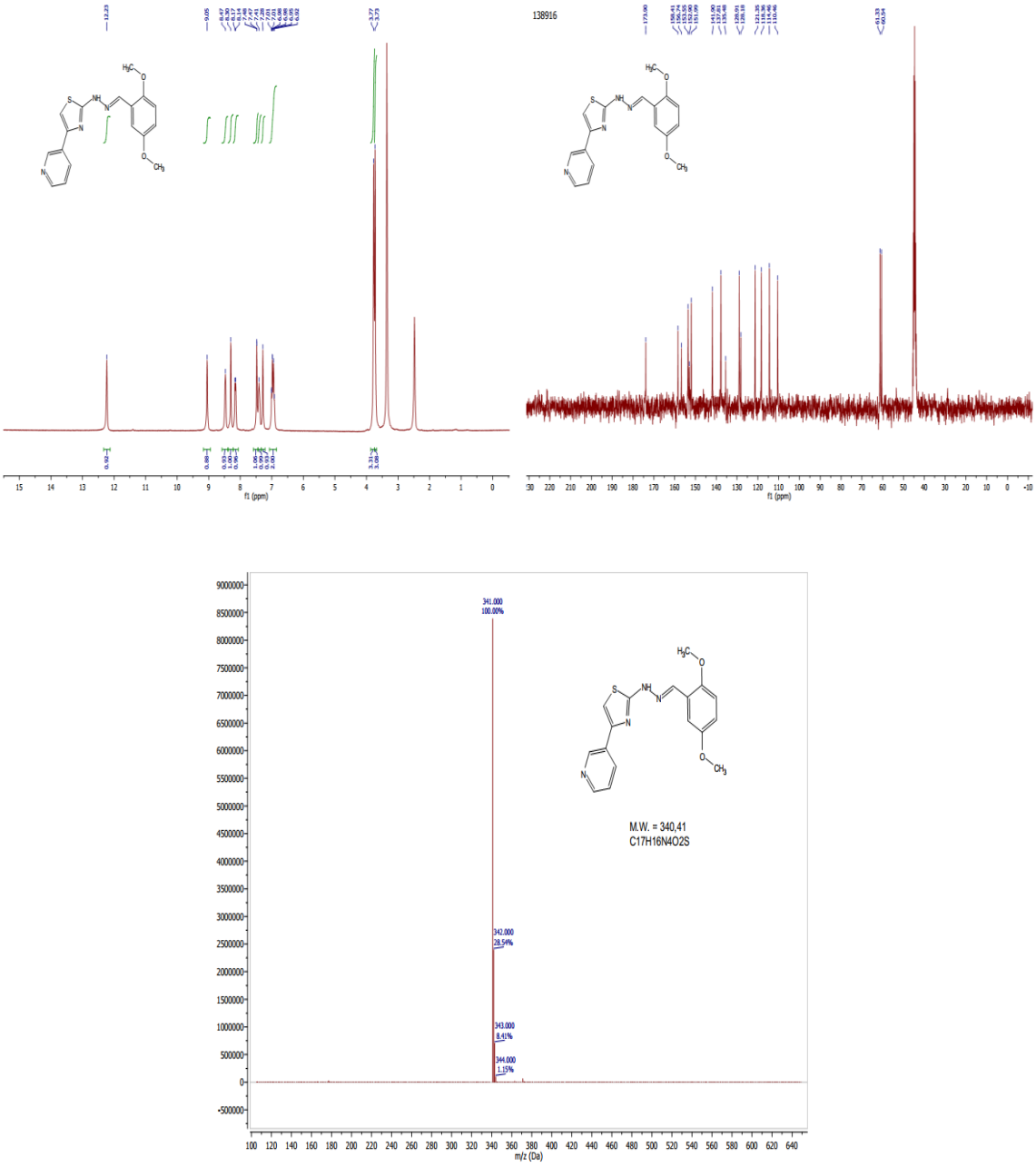
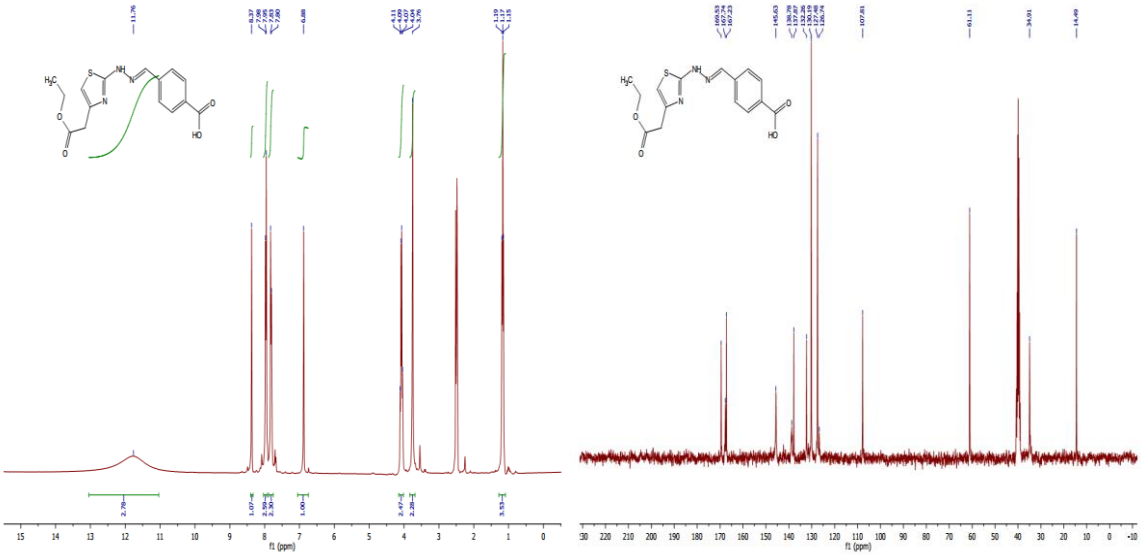


Figure S2-10. Spectra of compound **12**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



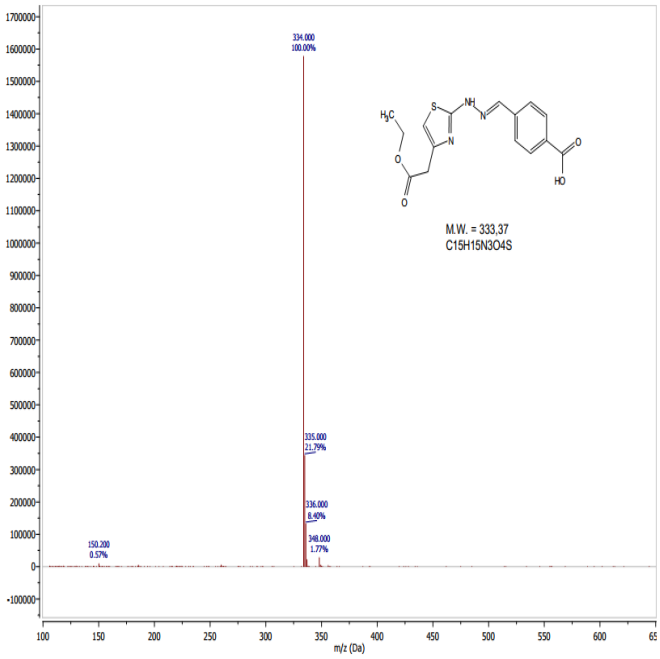
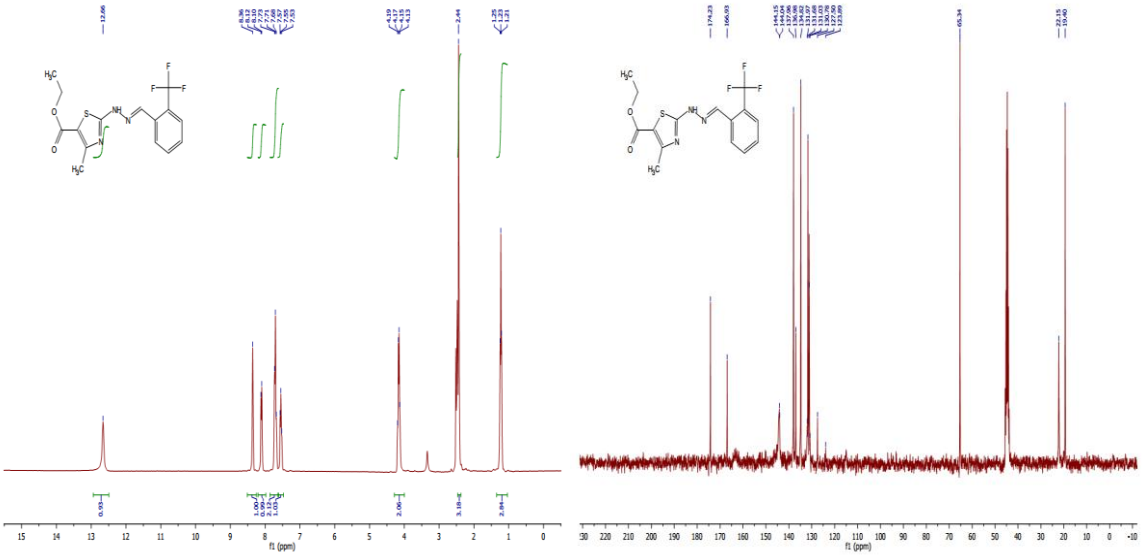


Figure S2-11. Spectra of compound **13**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



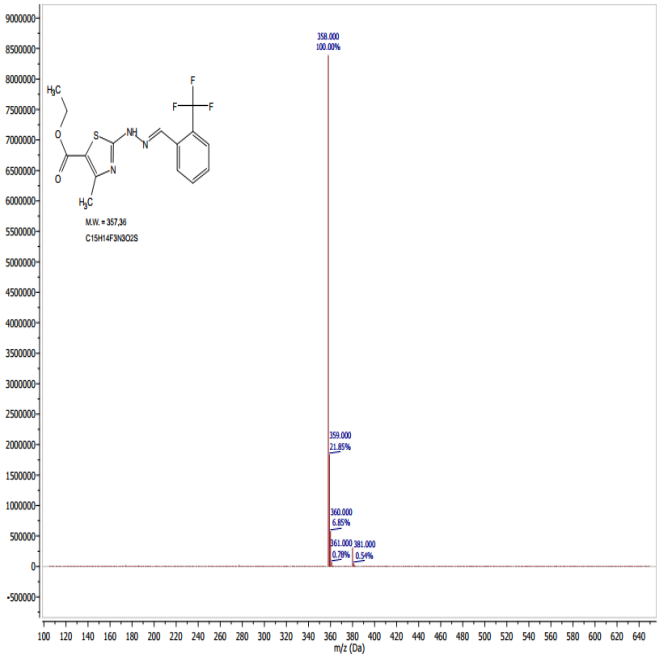
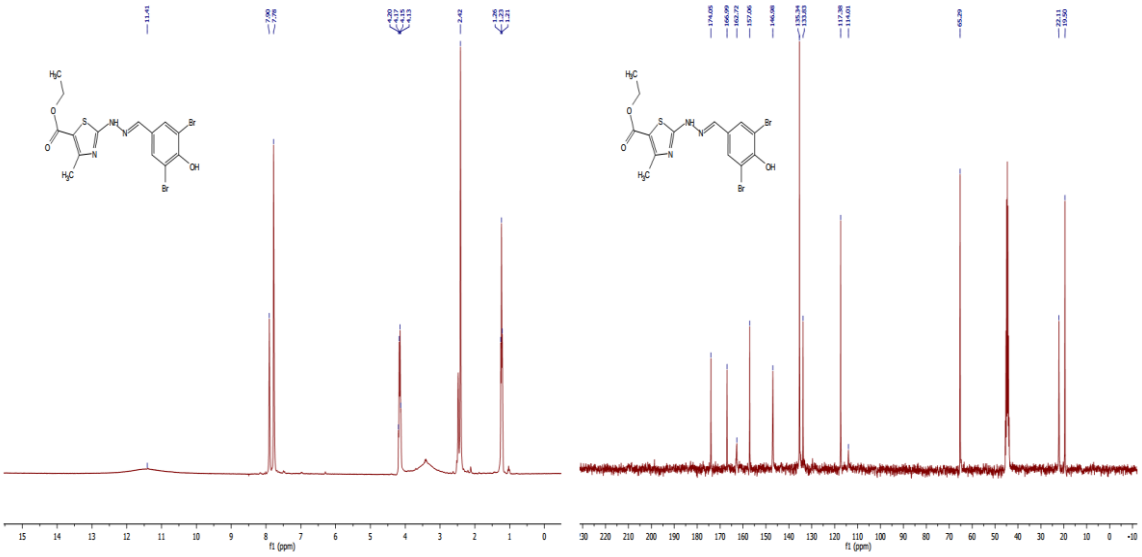


Figure S2-12. Spectra of compound **14**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



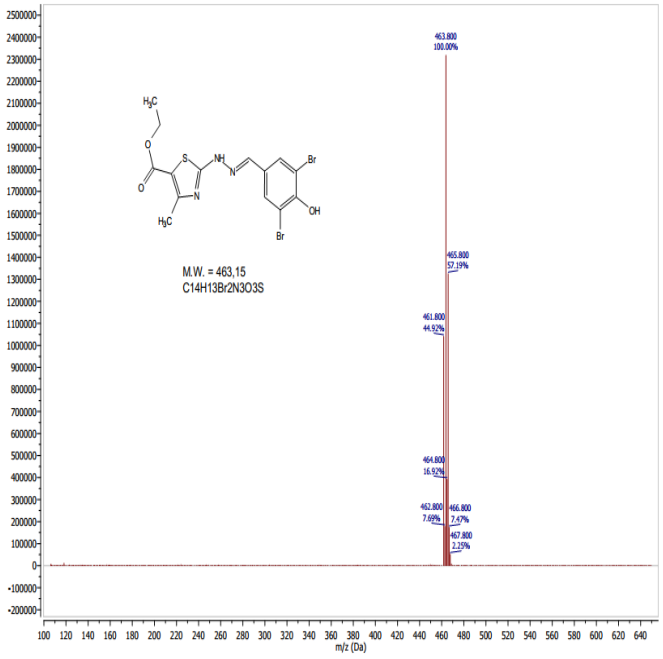
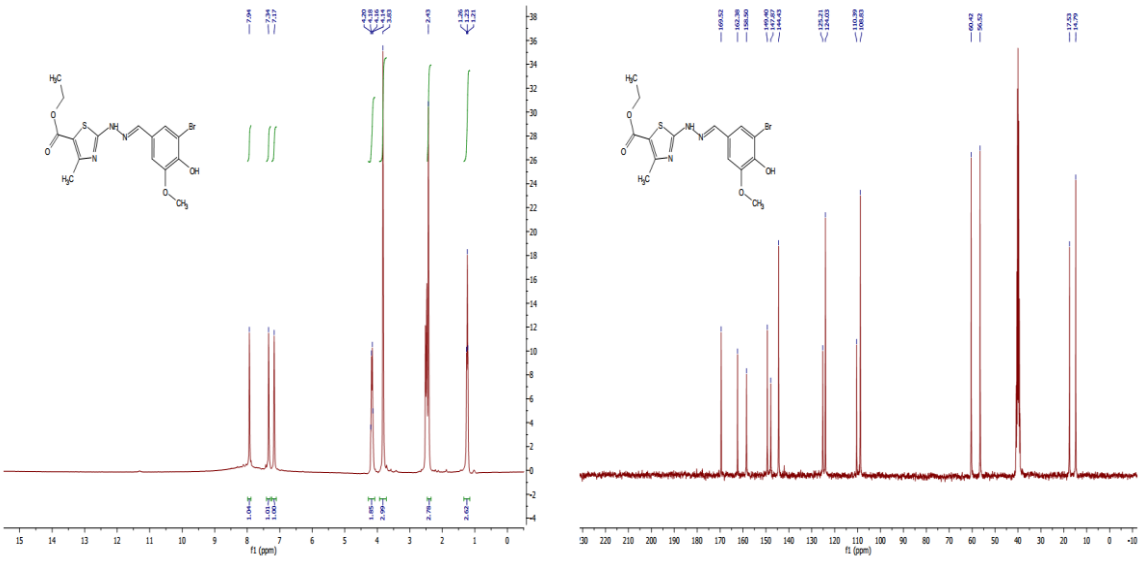


Figure S2-13. Spectra of compound **15**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



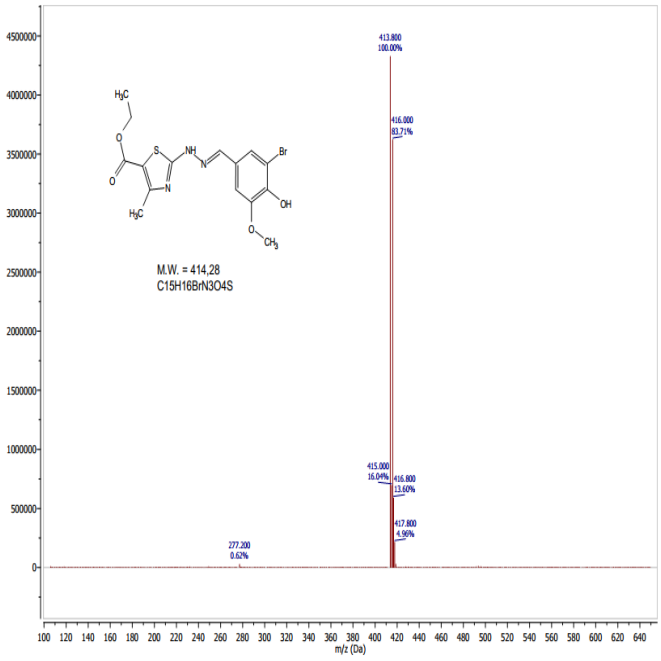


Figure S2-14. Spectra of compound **16**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

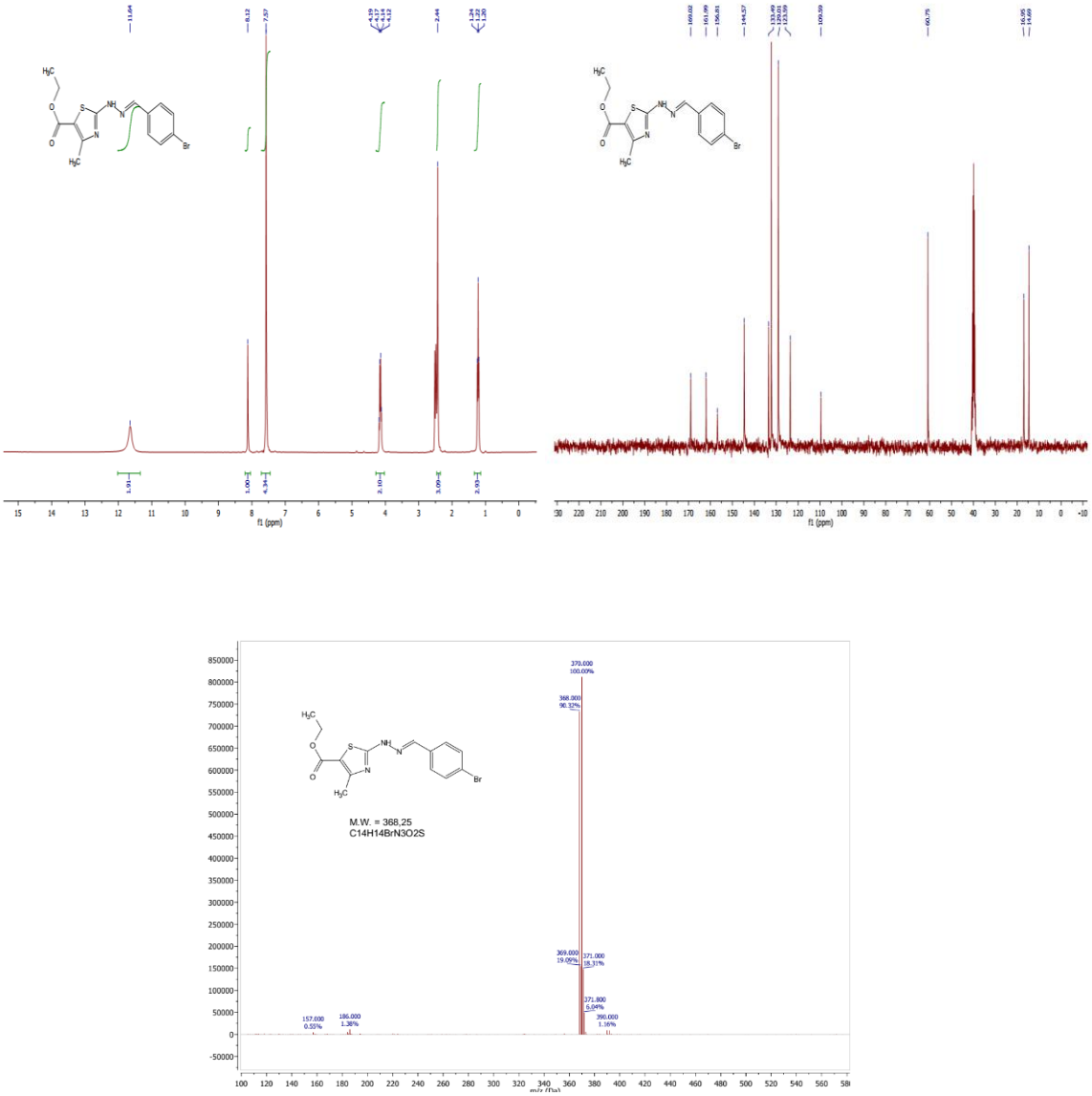
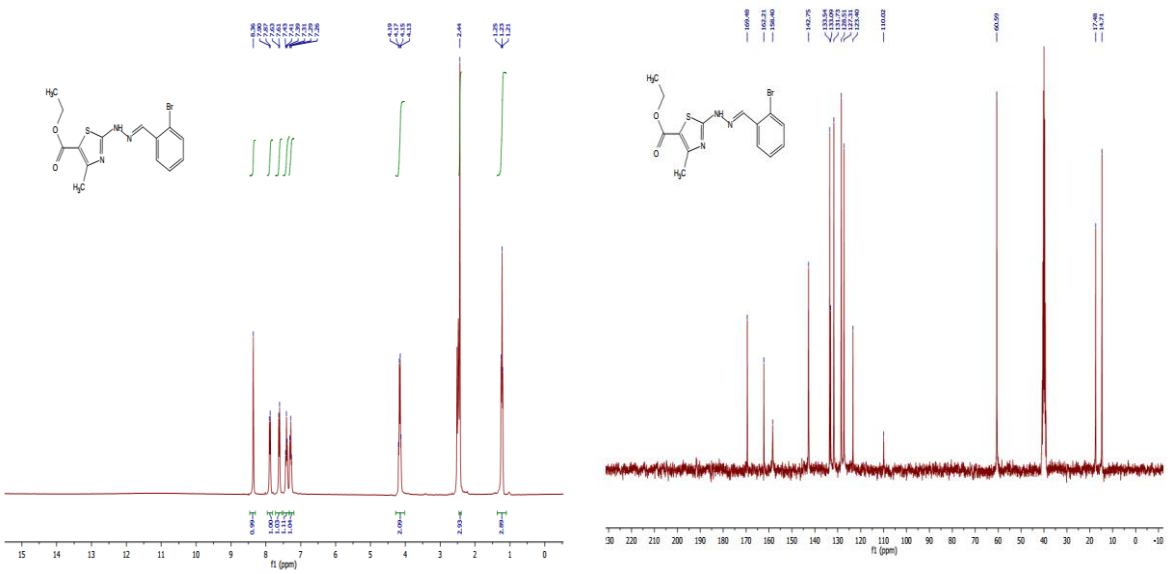


Figure S2-15. Spectra of compound **17**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



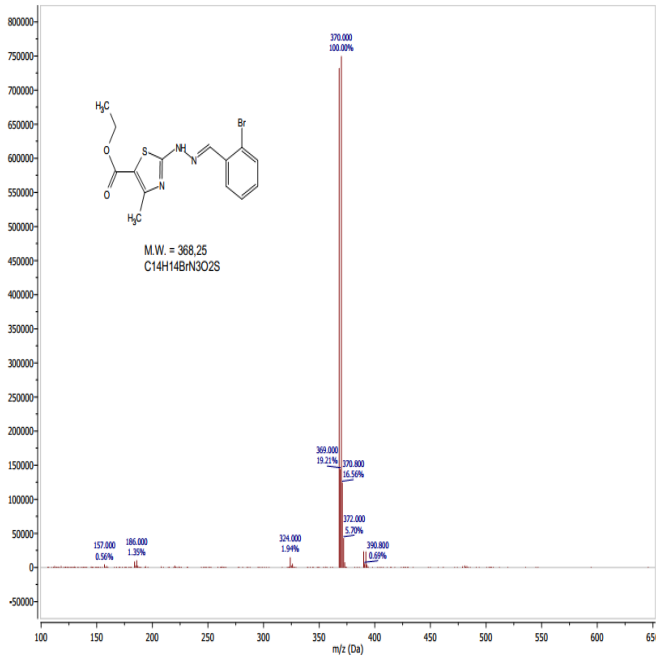


Figure S2-16. Spectra of compound **18**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

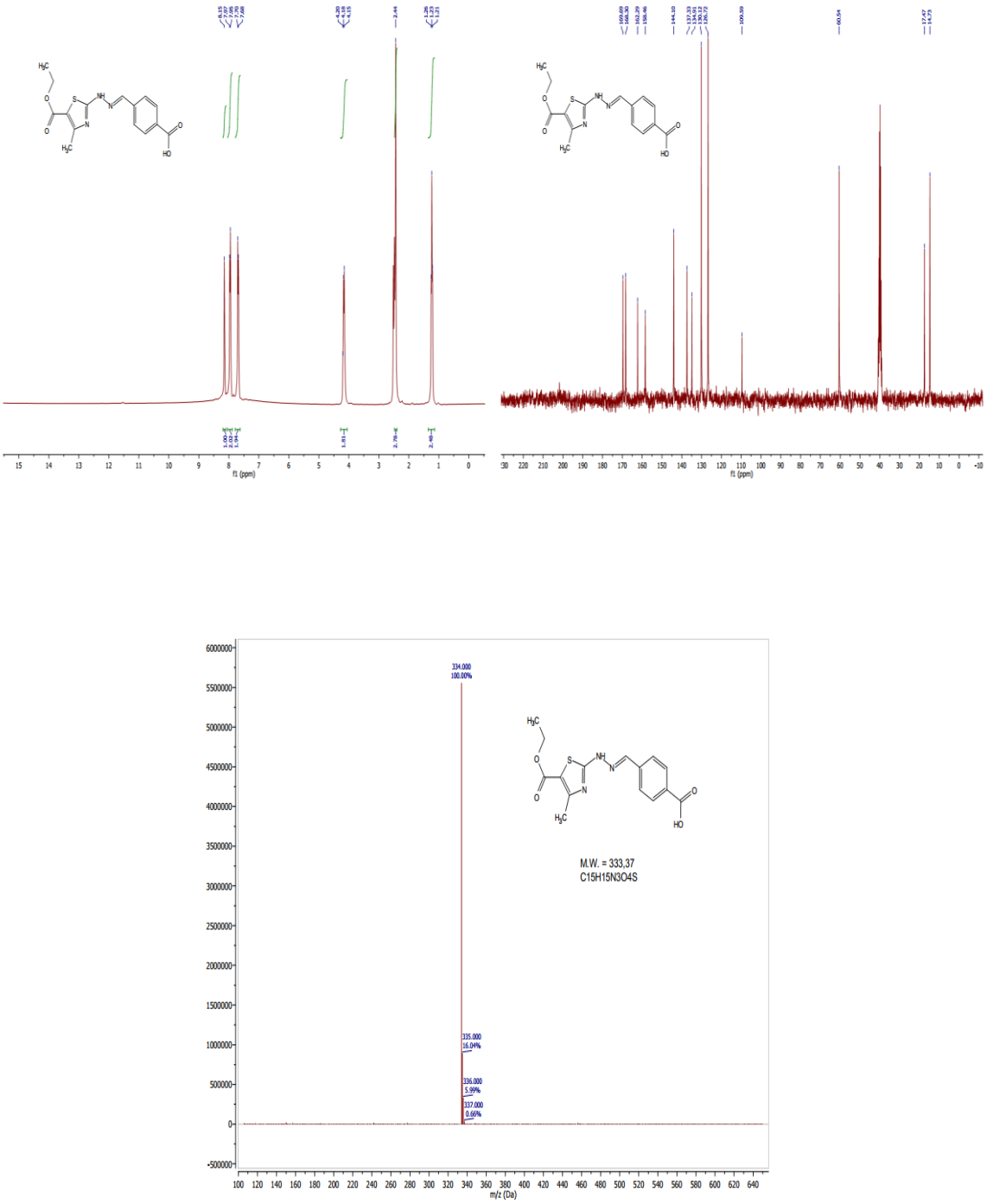
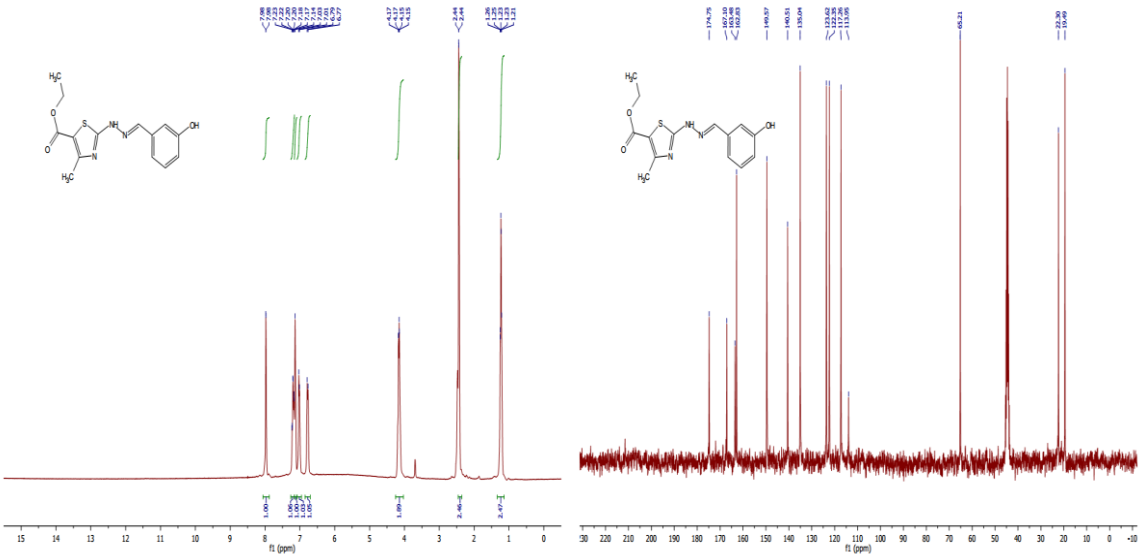


Figure S2-17. Spectra of compound **19**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



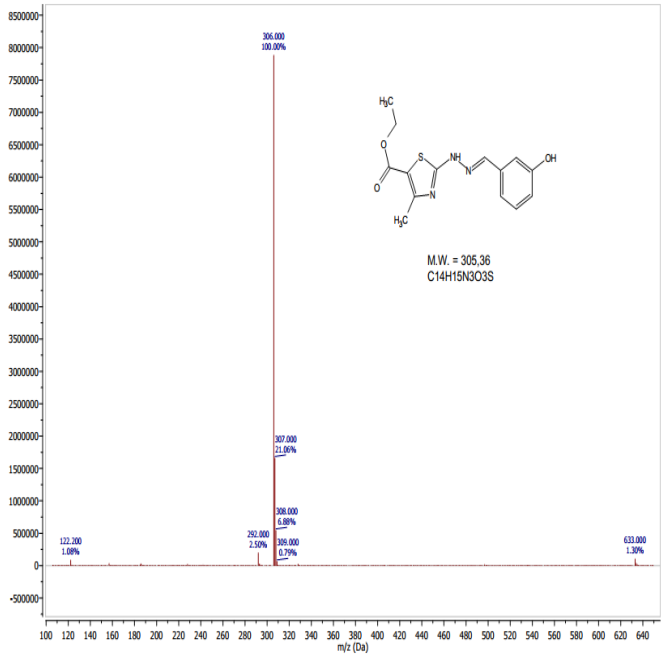
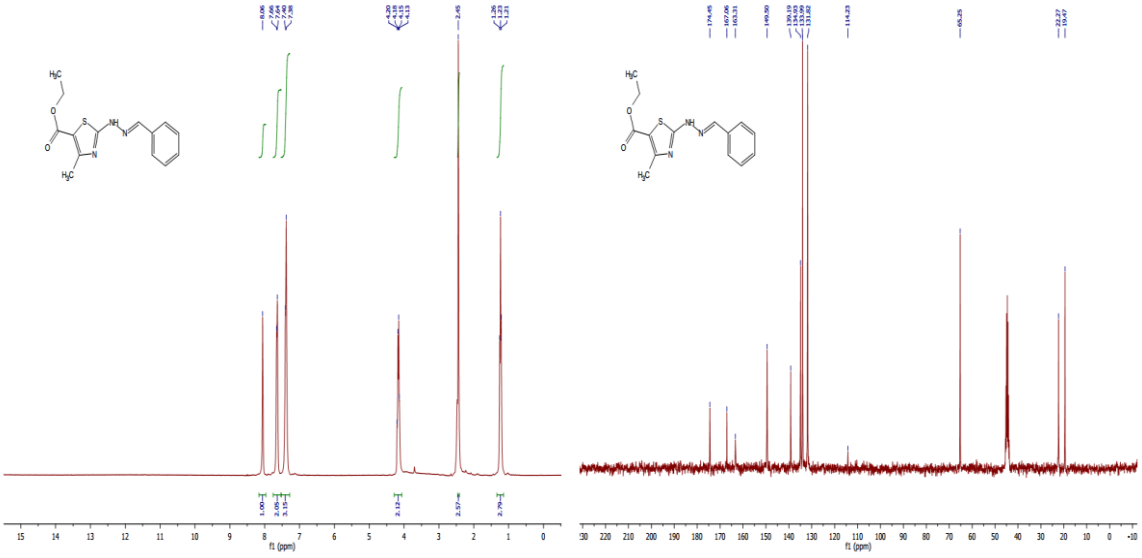


Figure S2-18. Spectra of compound **20**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



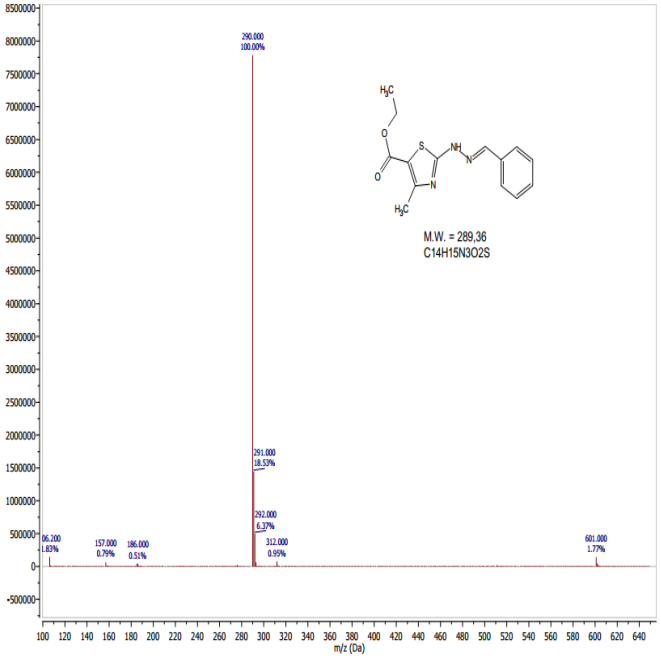
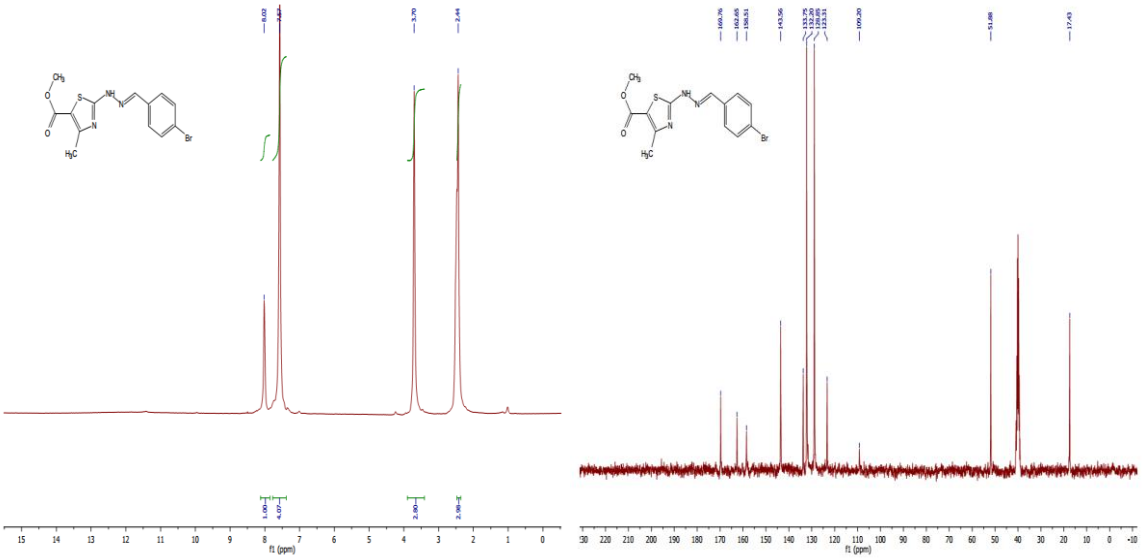


Figure S2-19. Spectra of compound **21**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



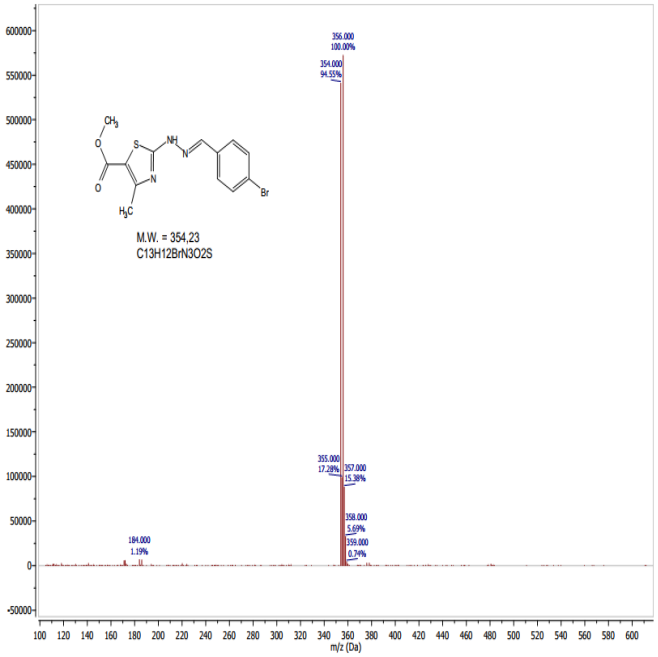
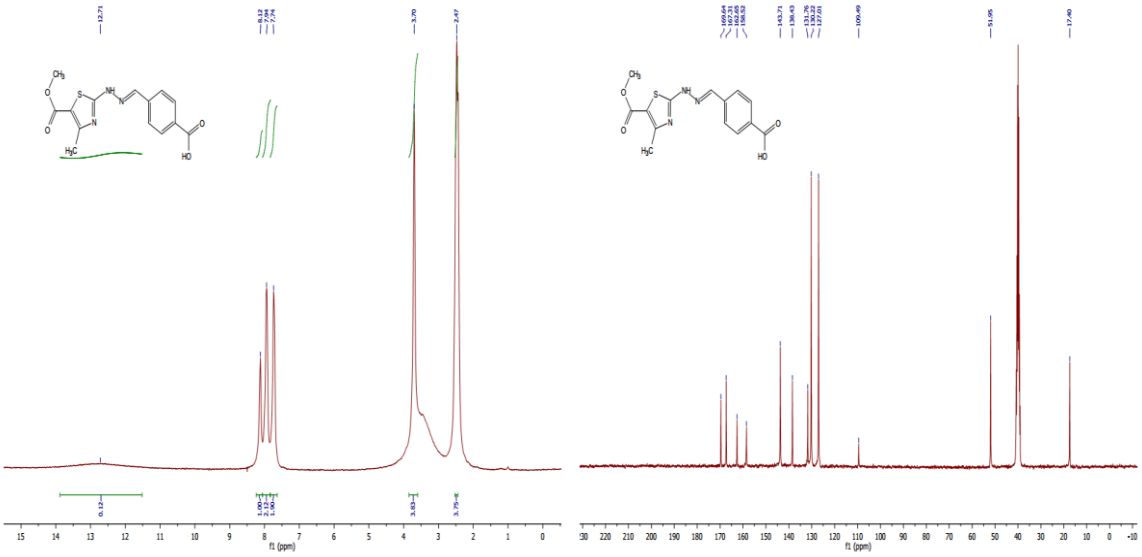


Figure S2-20. Spectra of compound **22**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



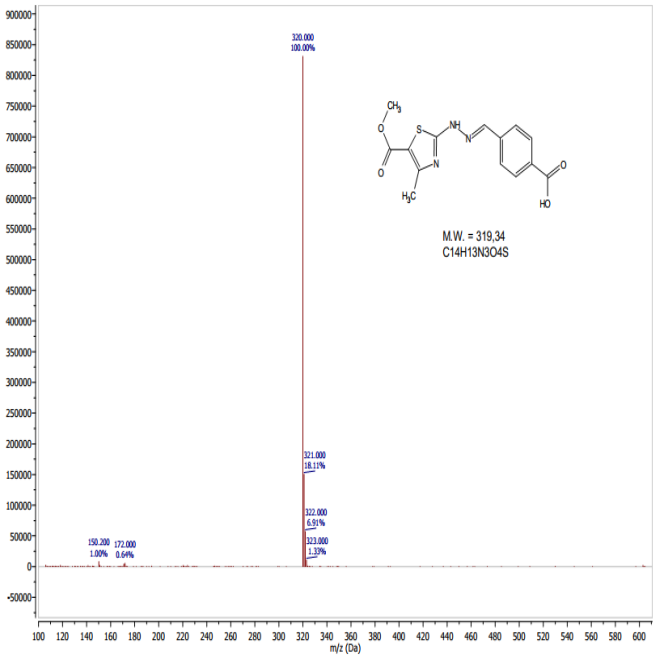
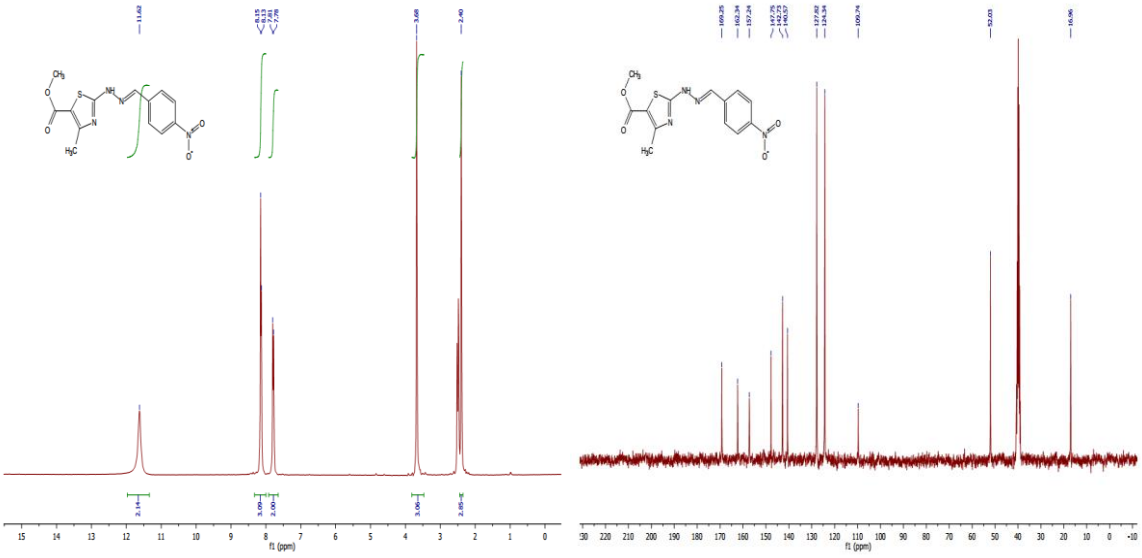


Figure S2-21. Spectra of compound **23**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



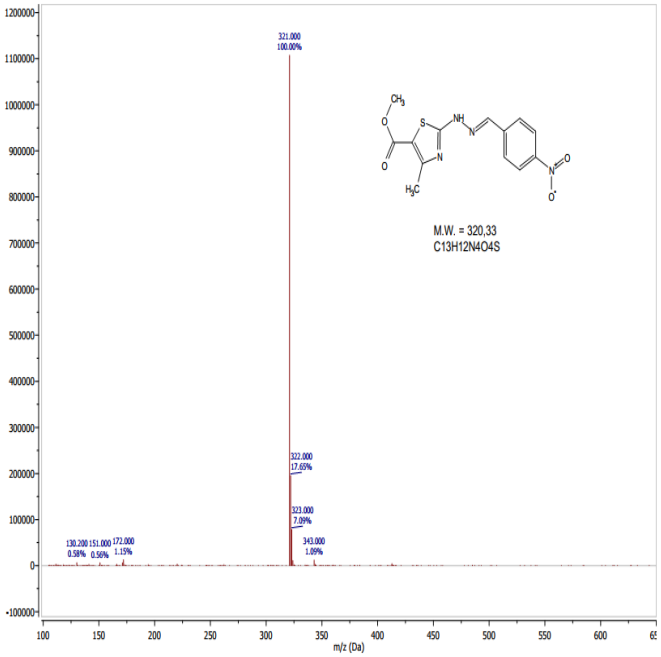
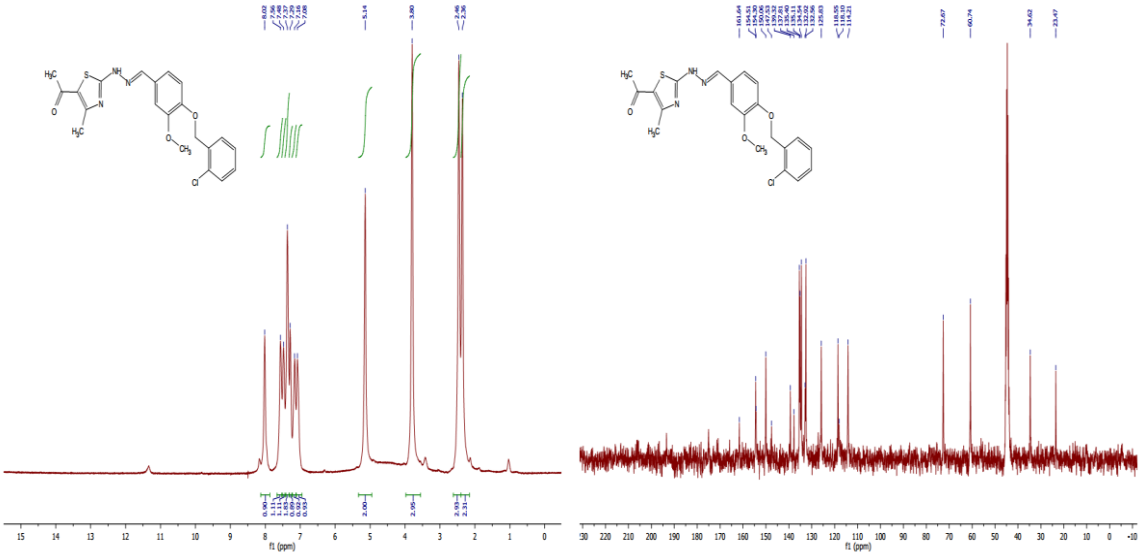


Figure S2-22. Spectra of compound **24**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



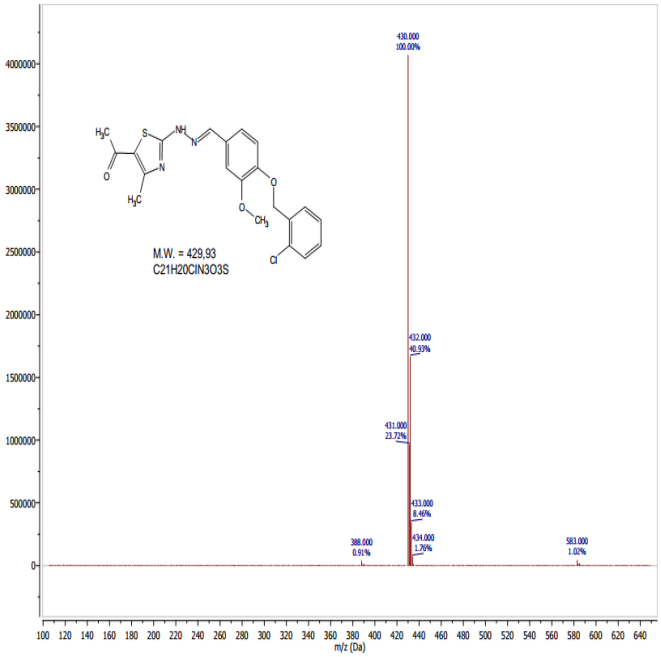
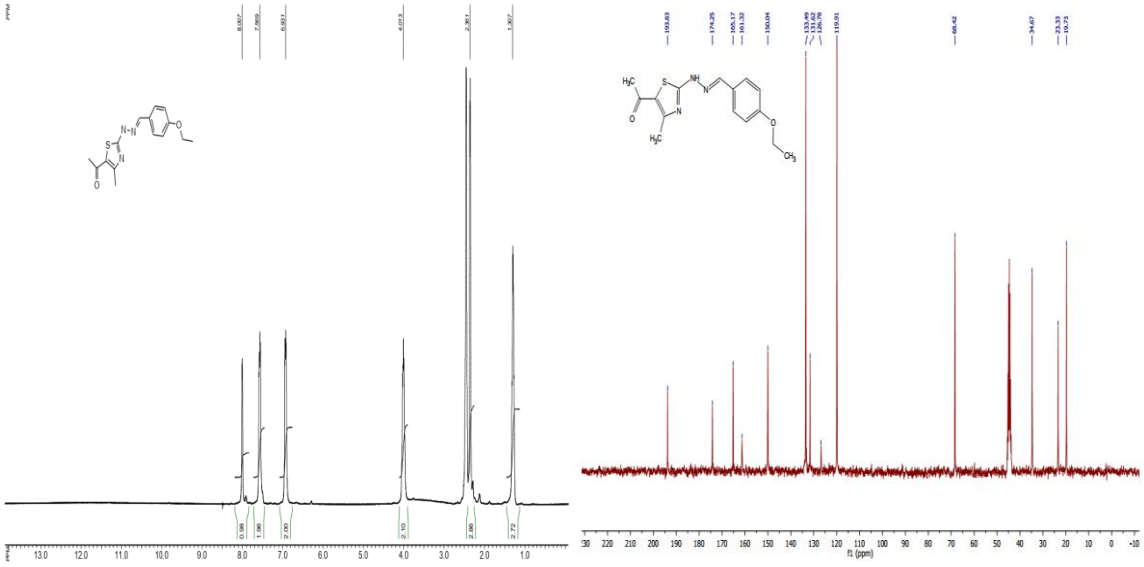


Figure S2-23. Spectra of compound **25**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



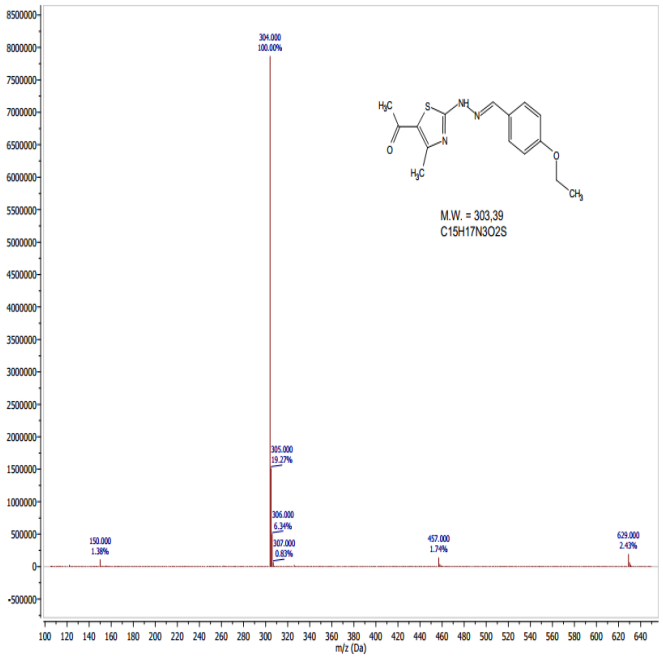


Figure S2-24. Spectra of compound **26**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

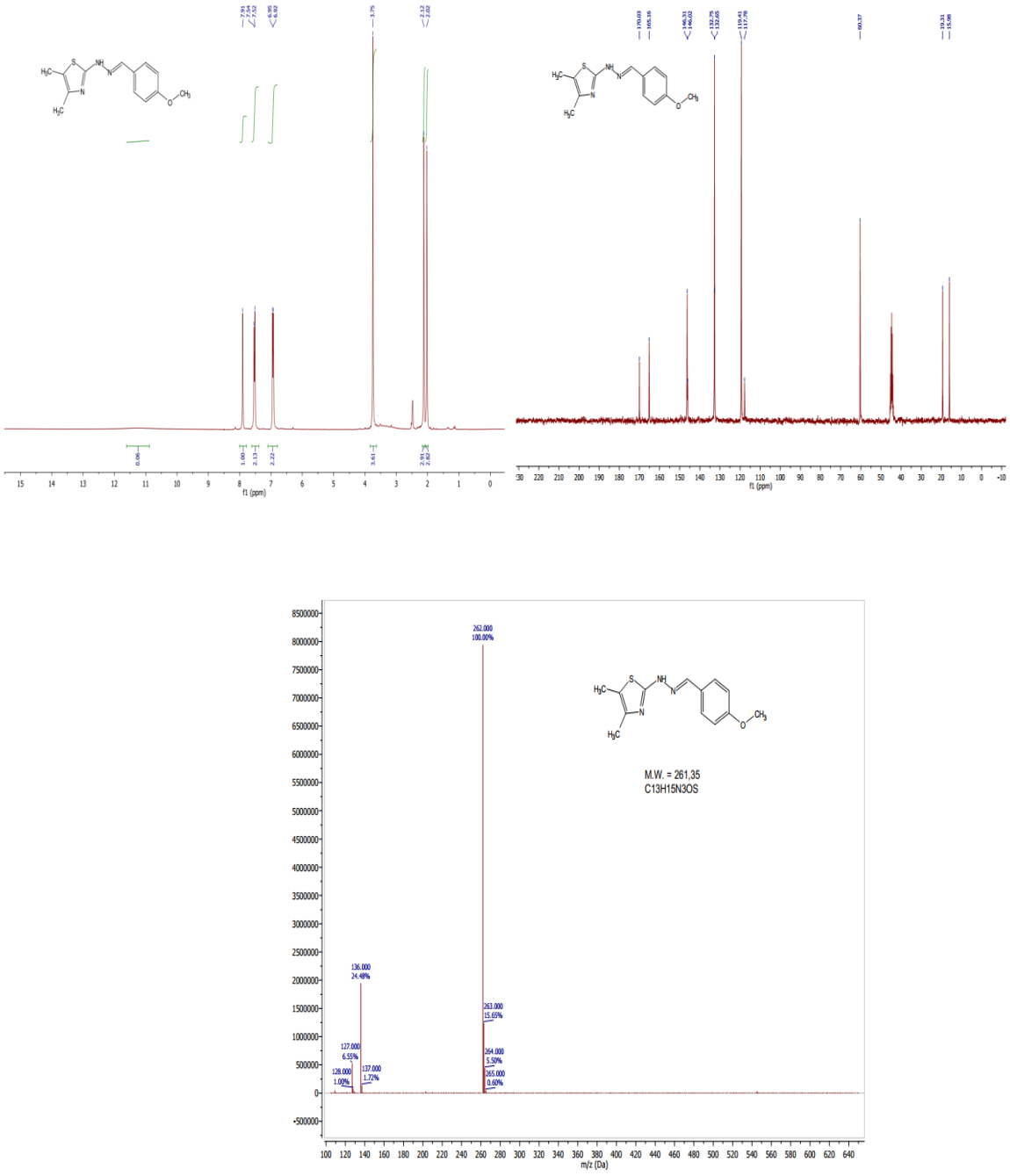


Figure S2-25. Spectra of compound **27**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

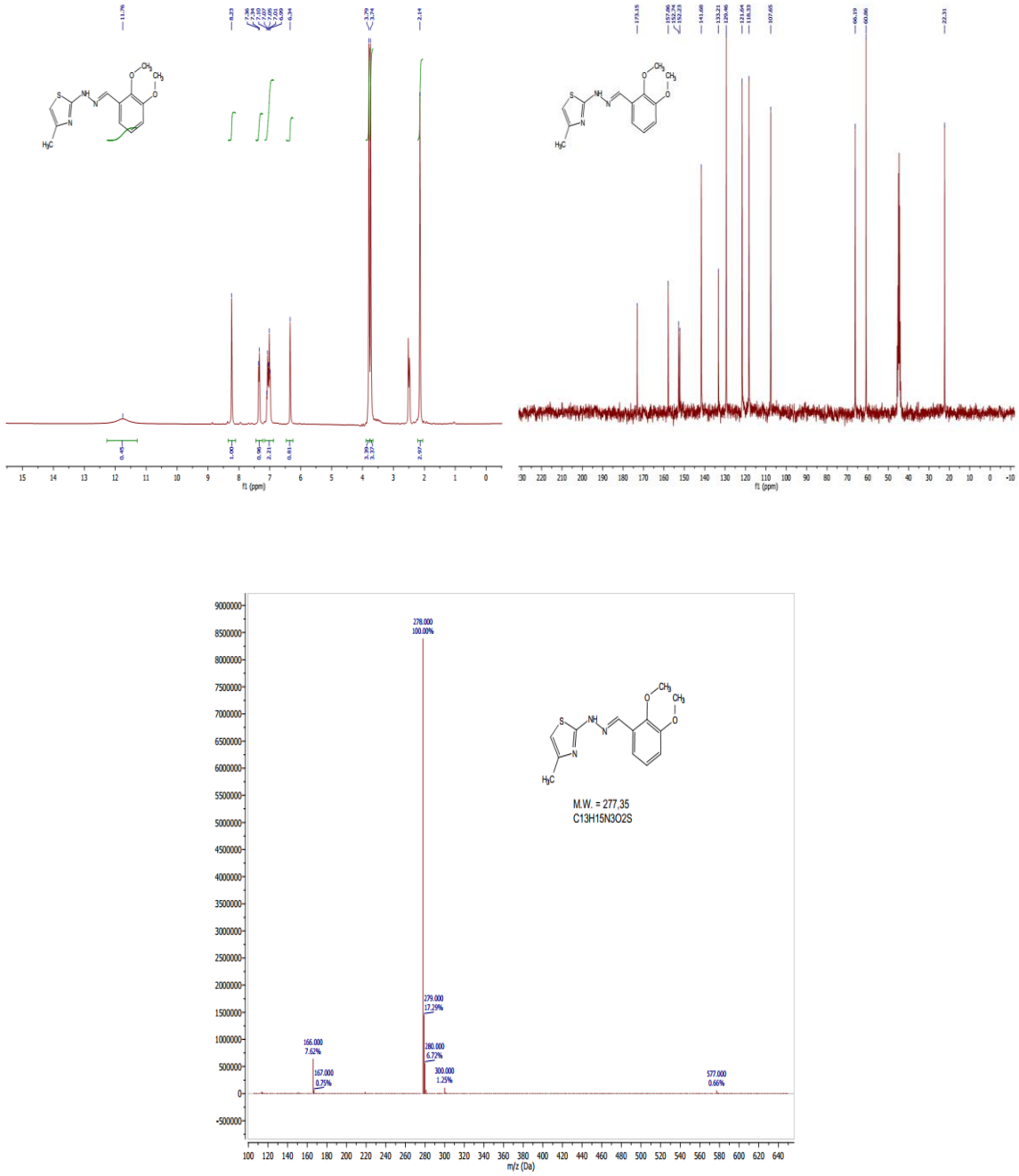
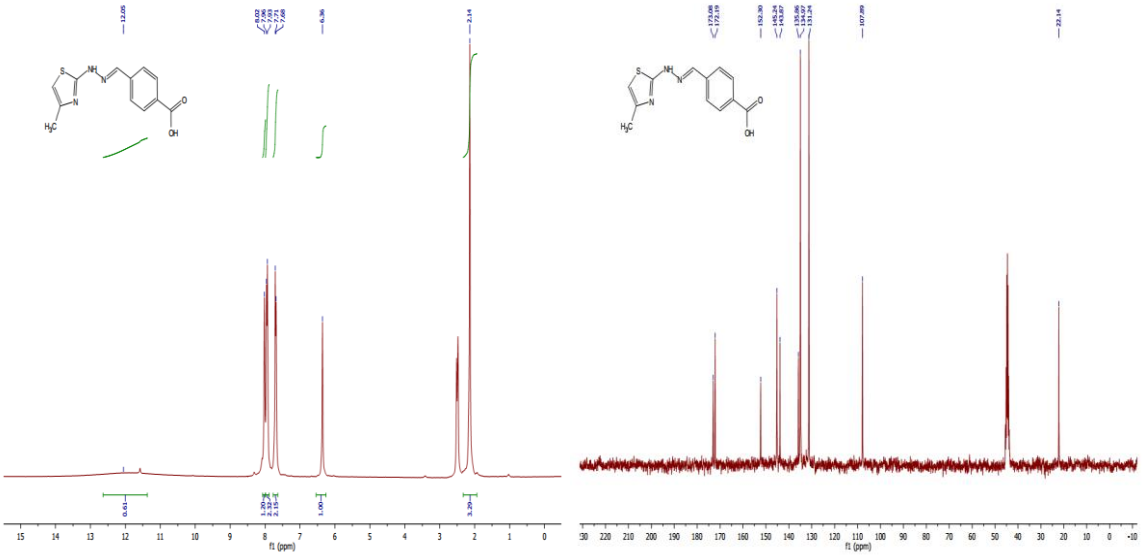


Figure S2-26. Spectra of compound **28**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



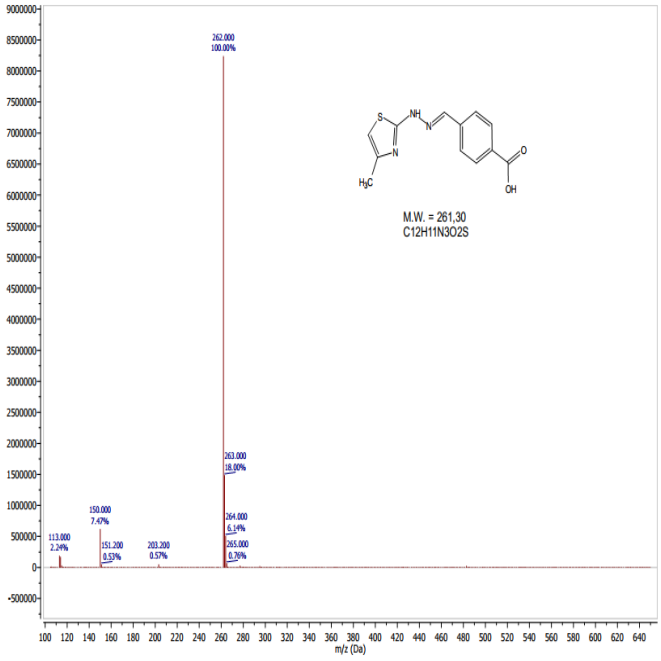
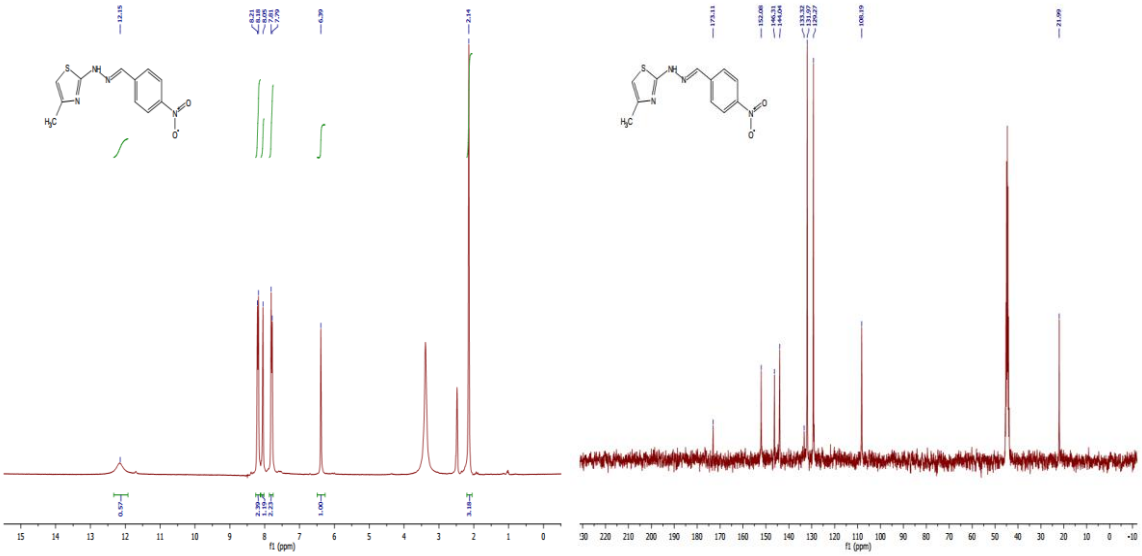


Figure S2-27. Spectra of compound **29**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



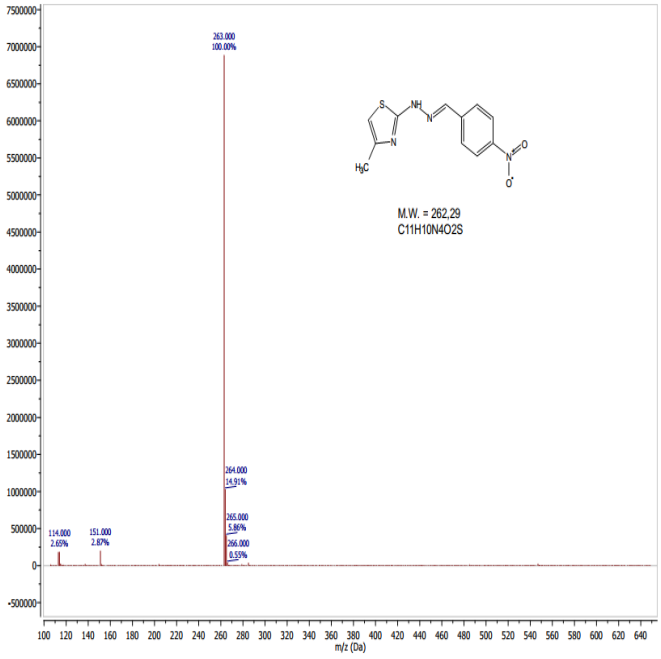


Figure S2-28. Spectra of compound **30**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

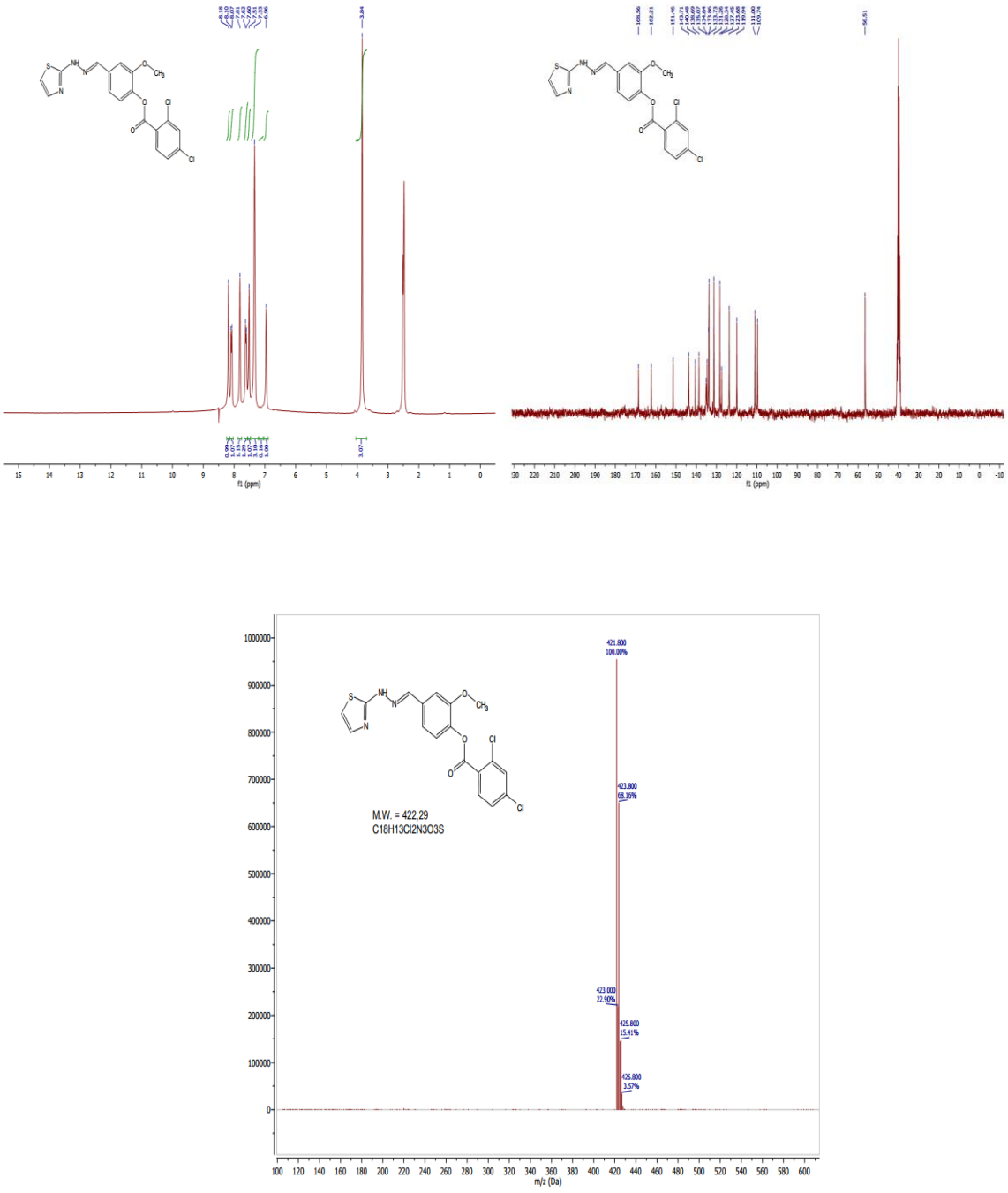
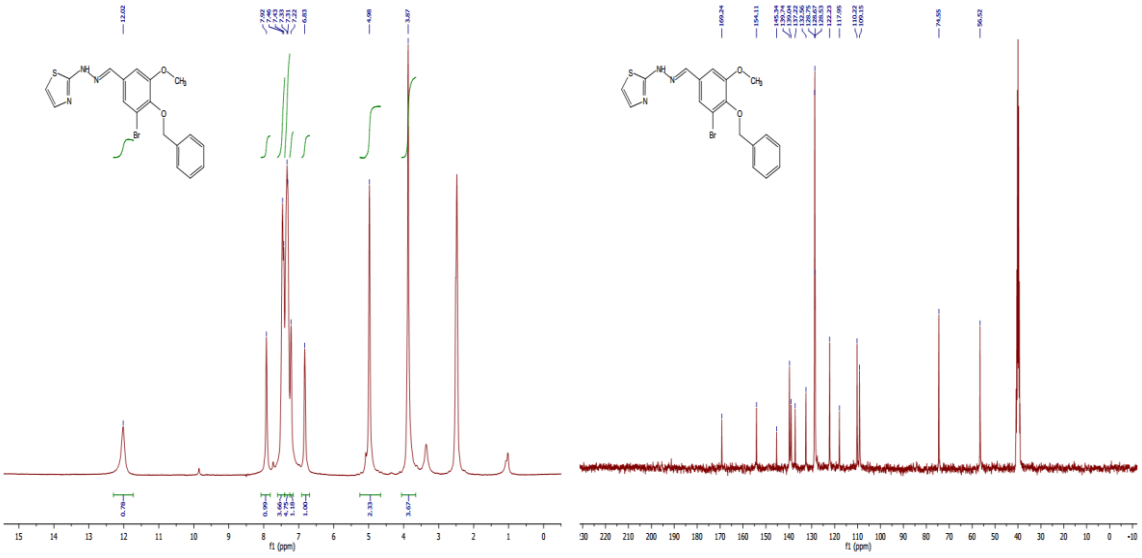


Figure S2-29. Spectra of compound **31**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



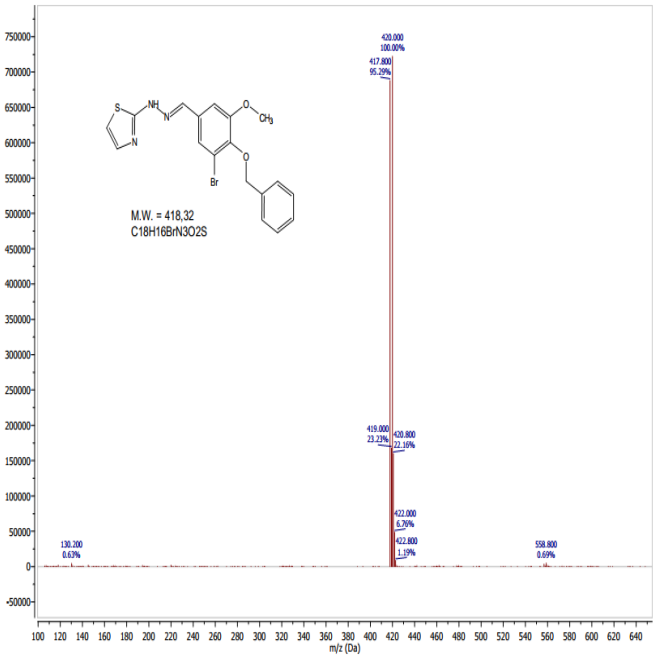
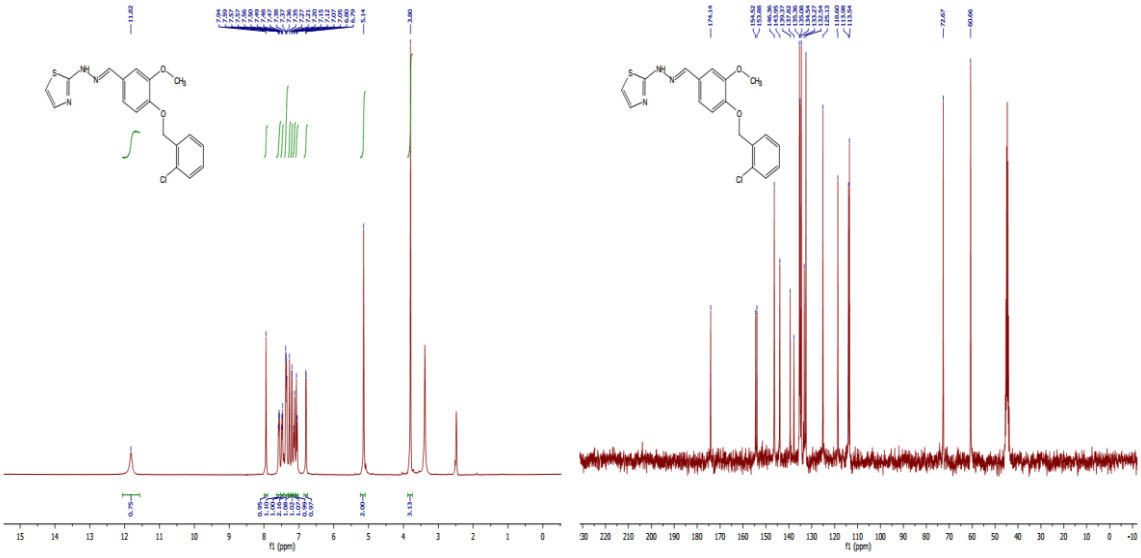


Figure S2-30. Spectra of compound **32**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



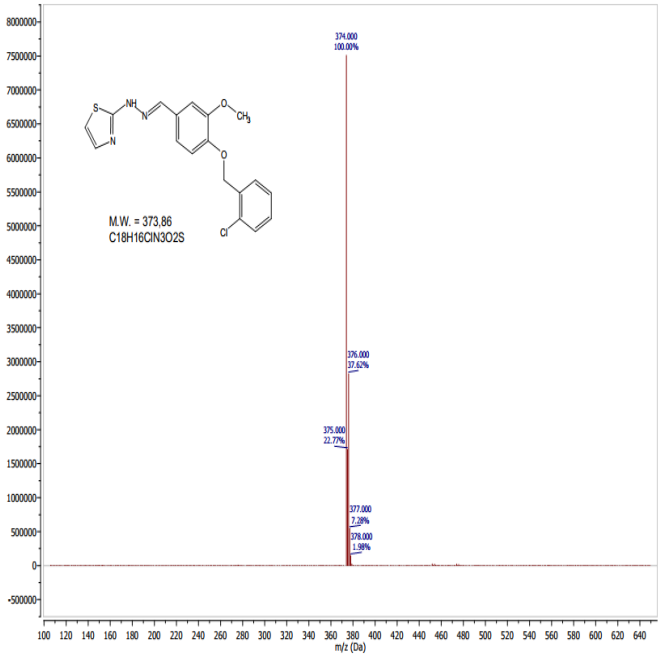
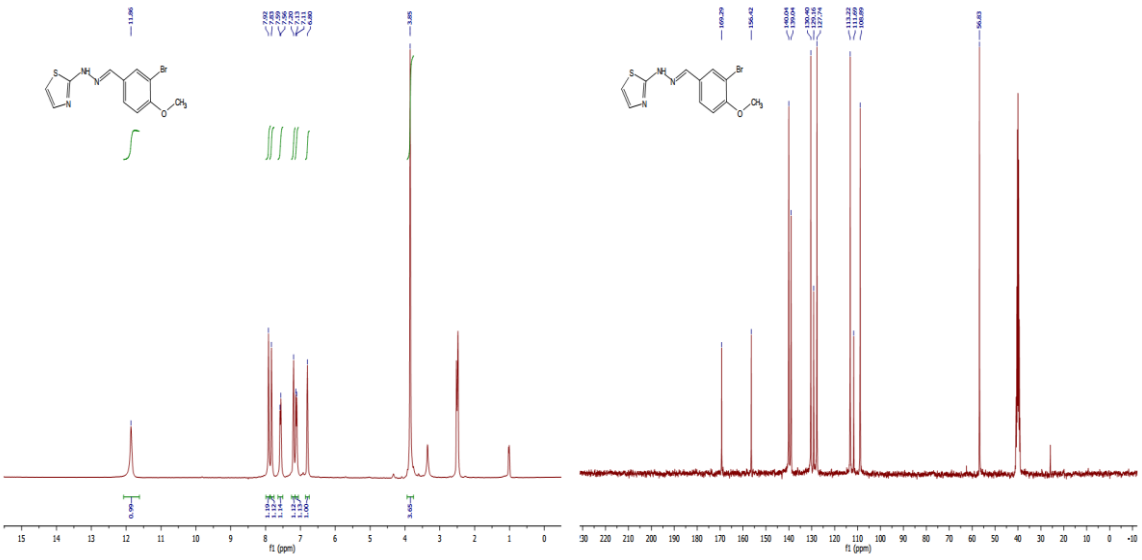


Figure S2-31. Spectra of compound **33**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



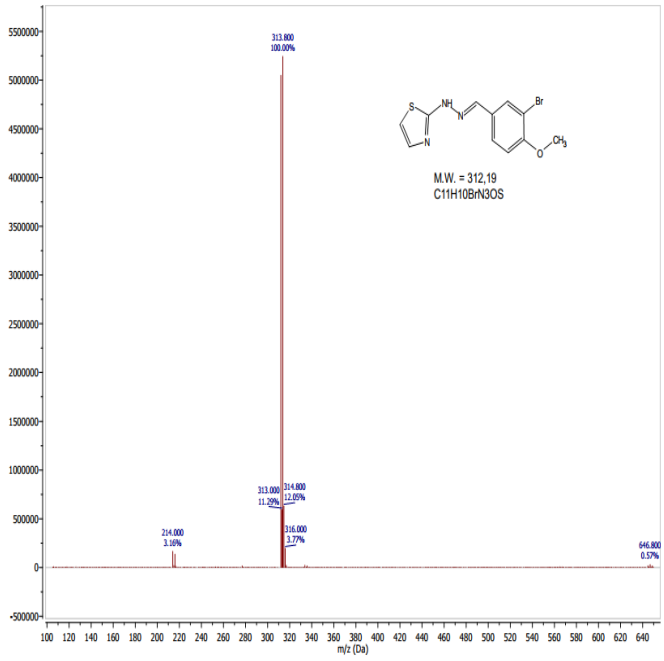
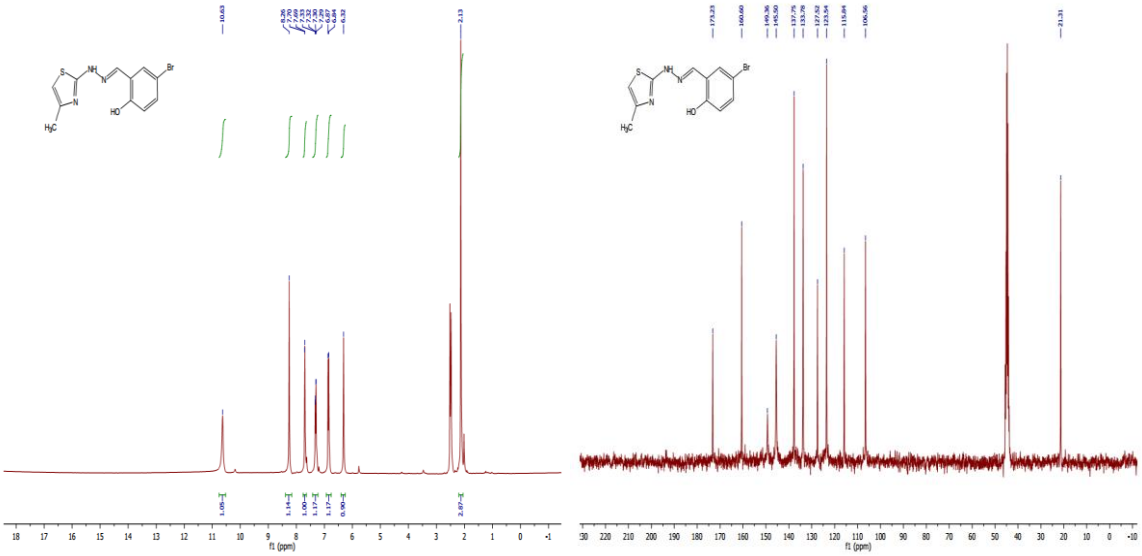


Figure S2-32. Spectra of compound **34**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



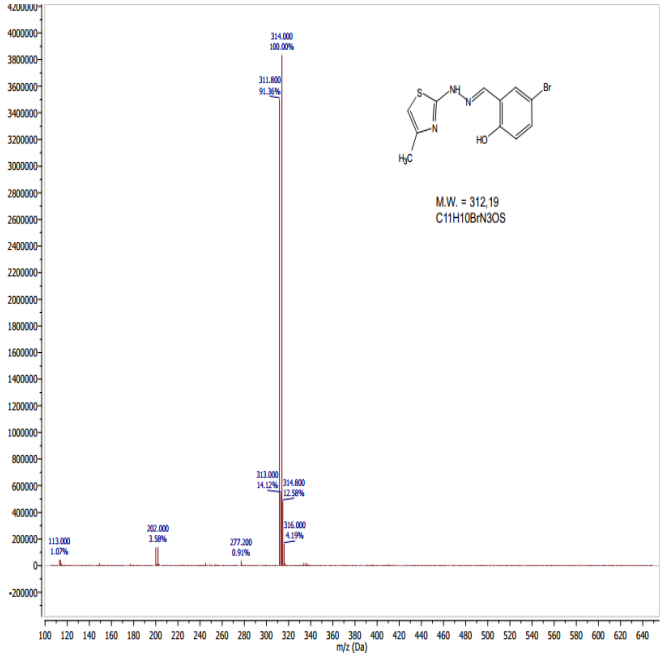


Figure S2-33. Spectra of compound **35**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

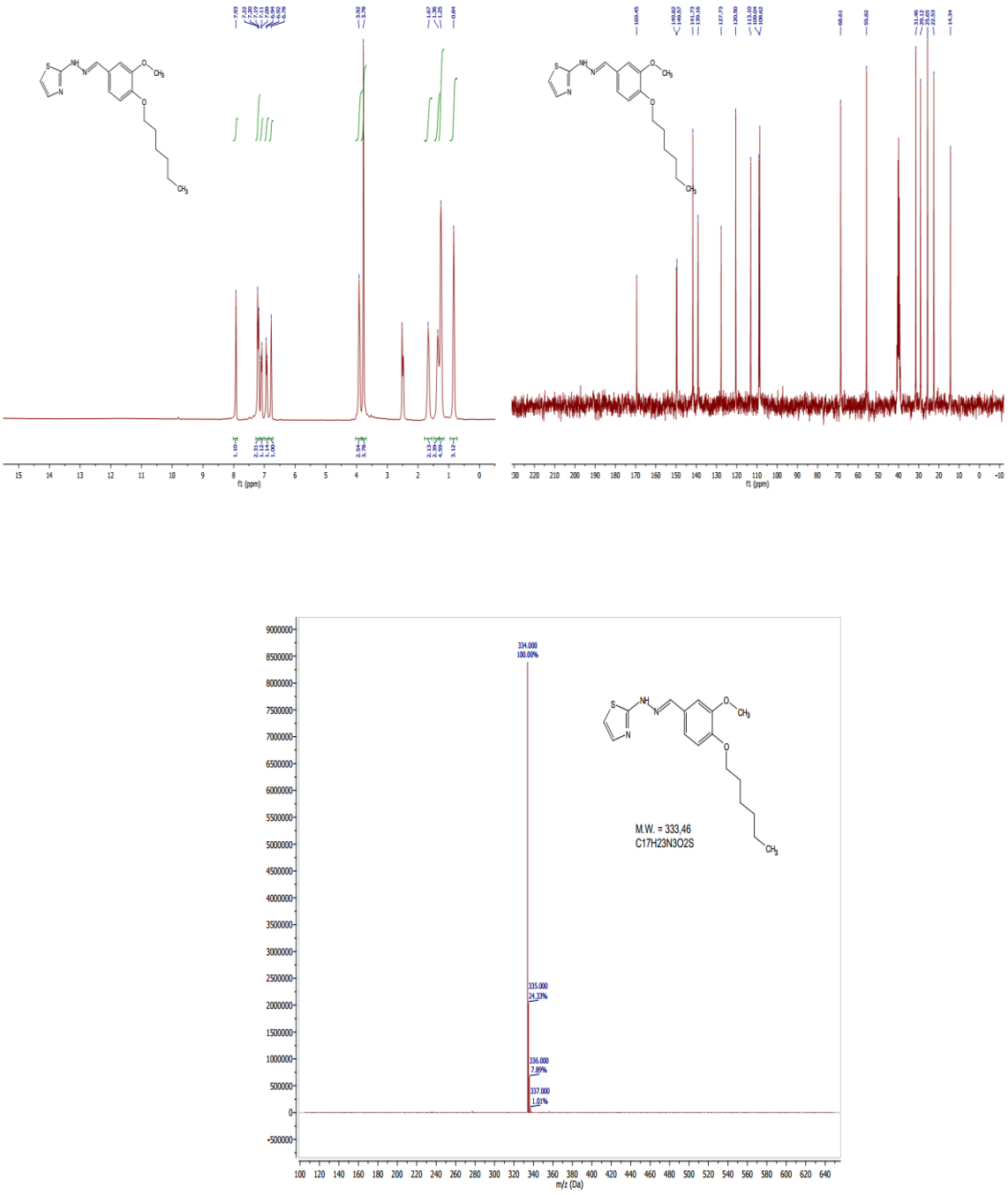
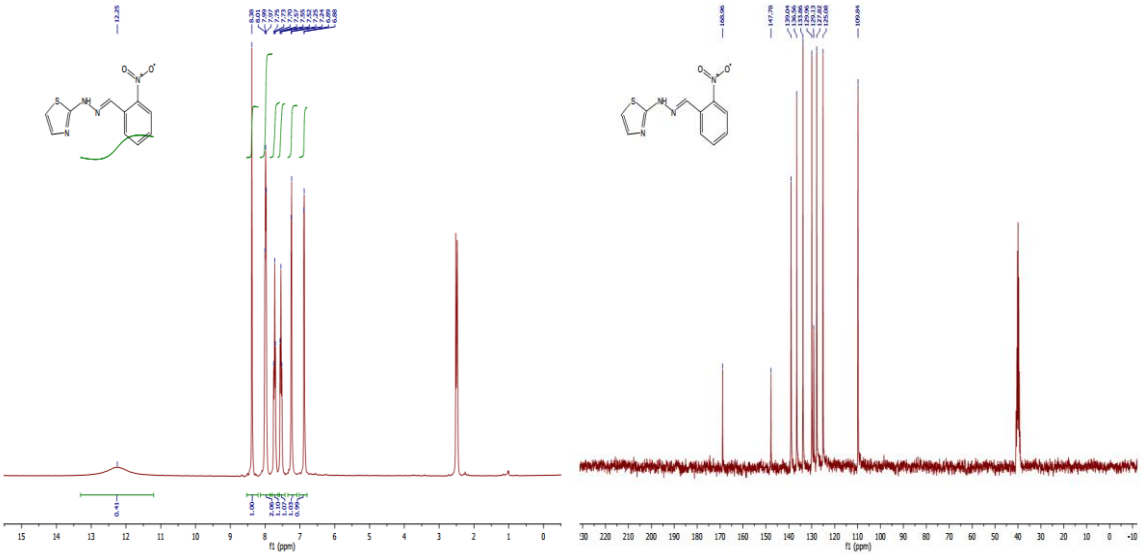


Figure S2-34. Spectra of compound **36**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.



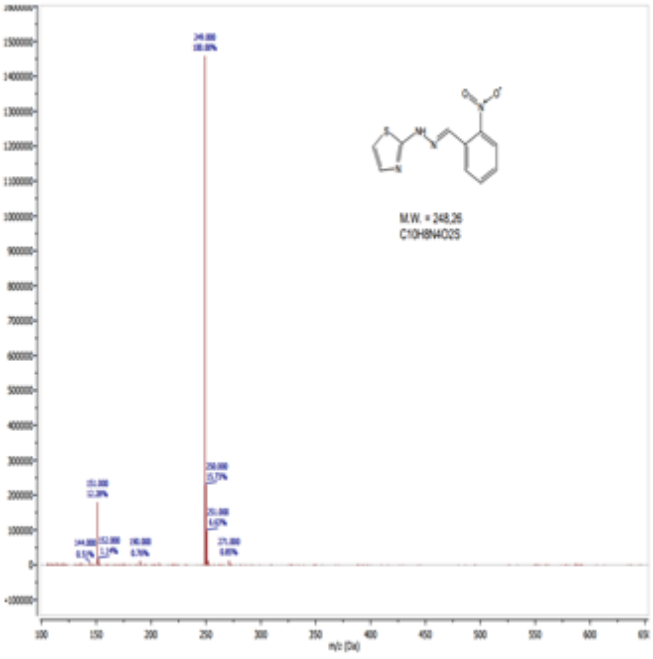


Figure S2-35. Spectra of compound **37**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

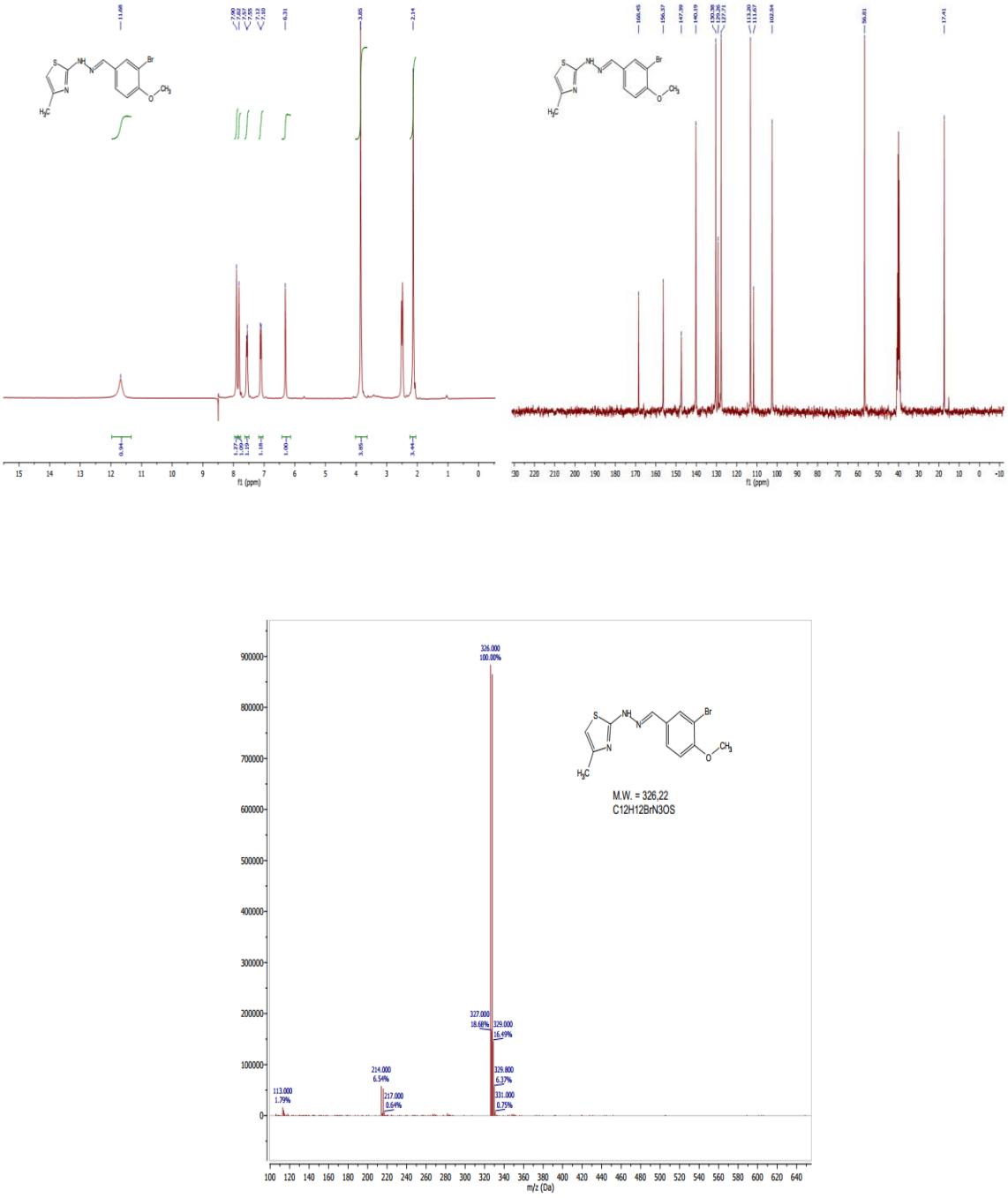


Figure S2-36. Spectra of compound **3a**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

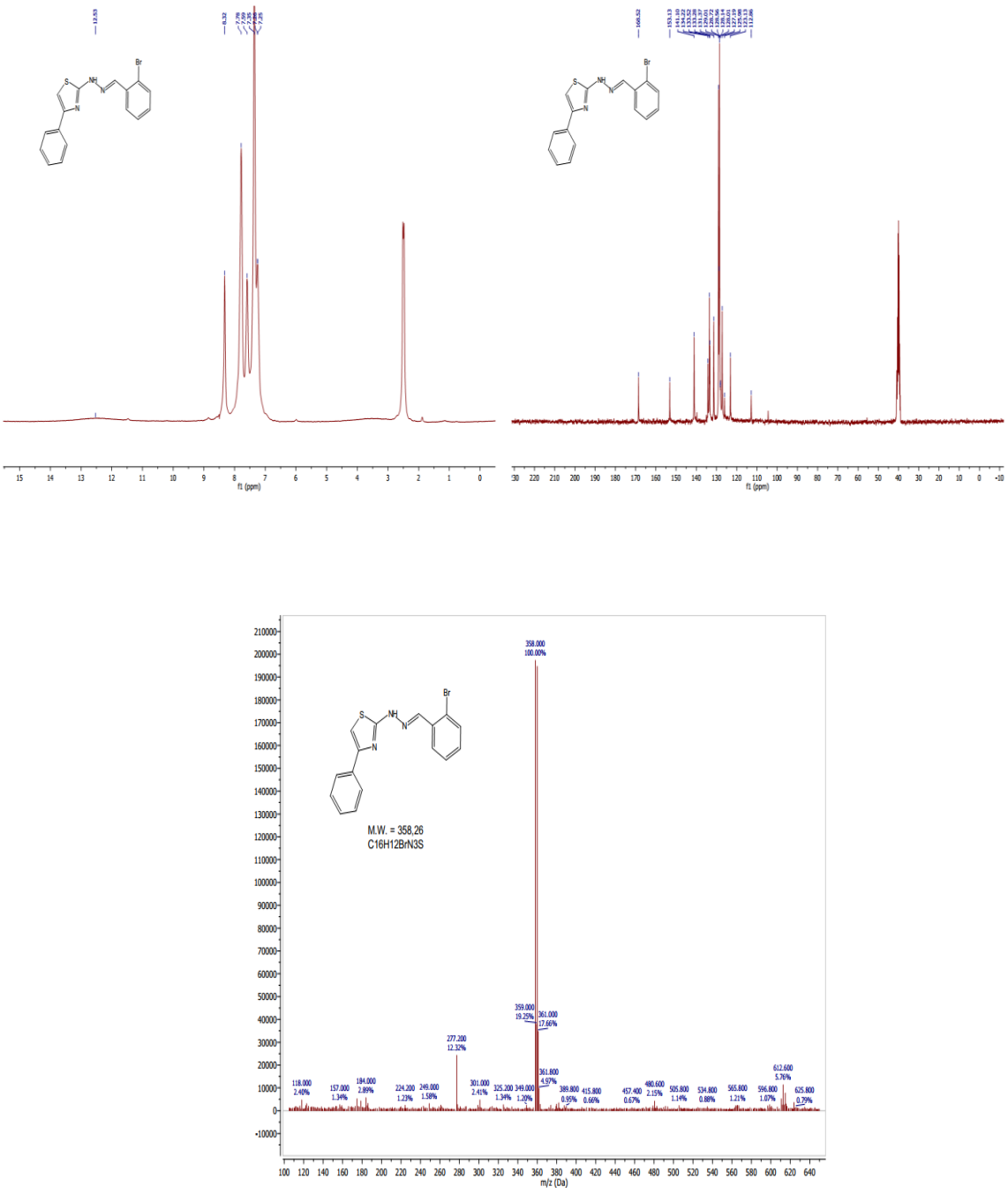


Figure S2-37. Spectra of compound **5a**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

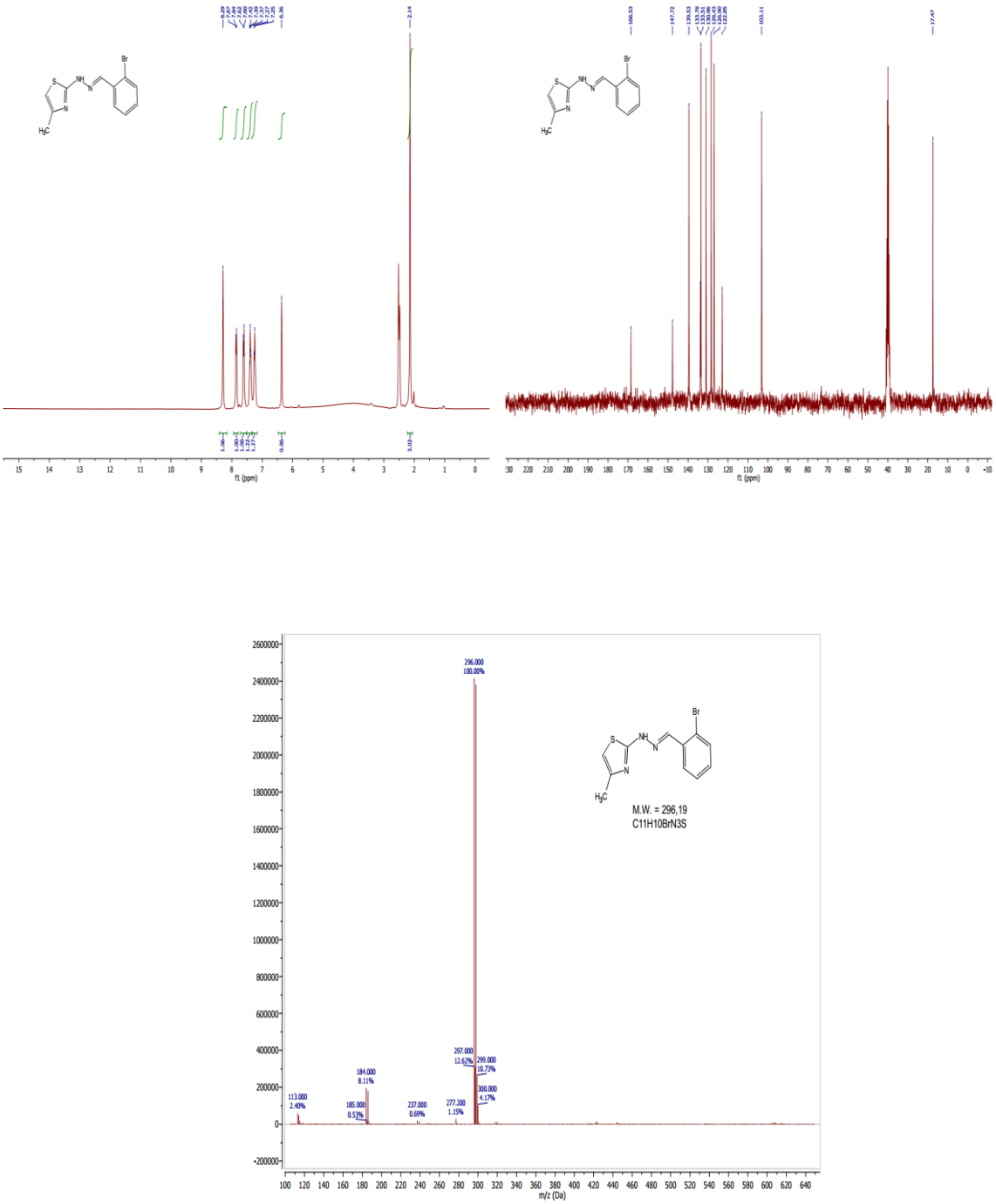


Figure S2-38. Spectra of compound **5b**. ^{1}H NMR spectrum (left top panel) was recorded in DMSO-d_6 at 302 MHz. ^{13}C NMR spectrum (right top panel) was recorded in DMSO-d_6 at 76 MHz. Bottom panel - HPLC–MS spectrum.

Section 3. Biological assays

Table S1. Monitoring of impact of compounds on steps downstream the aminoacylation reaction in enzymatic activity assays

Compound number	BIOMOL GREEN signal (%)	
	Set 1	Set 2
DMSO	100	100
1	80	82
2	100	100
3	93	100
4	96	100
5	100	100
6	NT	93
8	100	81
9	83	92
10	78	85
12	96	99
13	NT	100
14	NT	99
15	96	98
16	93	95
17	86	87
18	100	98
21	93	99
22	88	93
24	96	99
25	82	75
26	100	90
28	NT	100
30	96	97
31	65	70
32	77	73
33	86	79
34	94	93
35	93	100
36	NT	92
37	NT	100

Set 1: compounds were incubated at concentration of 50 μM in presence of 0.25 U mL^{-1} iPPase and 5 μM inorganic pyrophosphate. After 10 min, the treatment with BIOMOL® Green reagent followed.
Set 2: compounds were combined with 10 μM Phosphate Standard and treated with BIOMOL® GREEN reagent.
The values represent average value from two independent experiments.
NT – not tested.

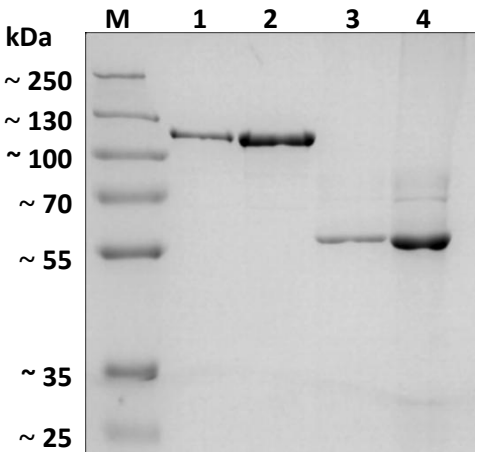
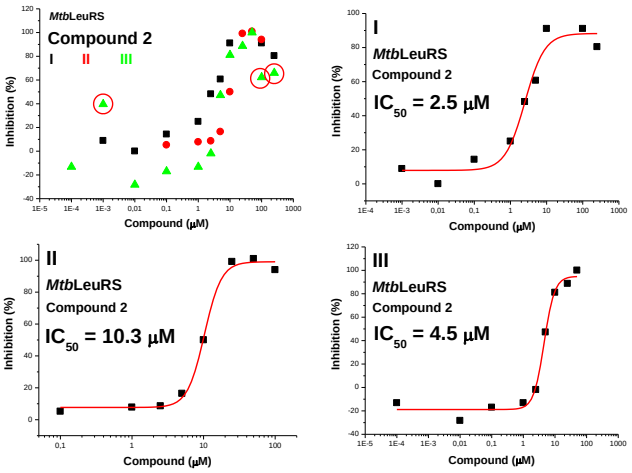


Figure S3-1. Analysis of purified *Mtb*LeuRS and *Mtb*MetRS using SDS-PAGE. Electrophoresis was performed on 10% SDS-polyacrylamide gel and proteins were detected by Coomassie Brilliant Blue staining. Lines 1 and 2 – *Mtb*LeuRS; lines 3 and 4 – *Mtb*MetRS; line M – protein marker, PageRuler™ Plus (Thermo Scientific).

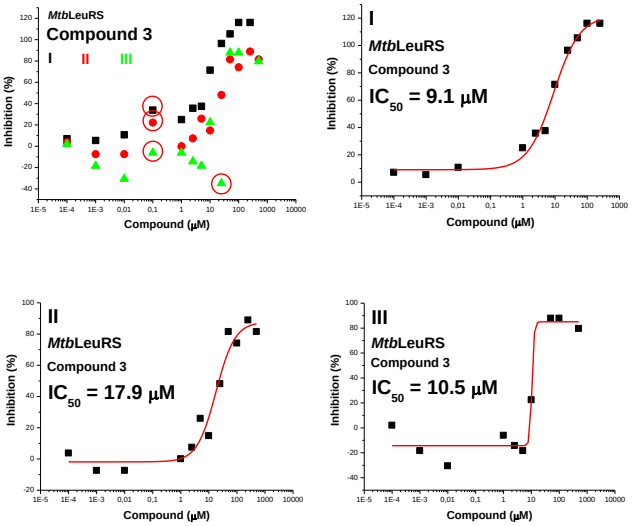
Compound 2

	Inhibition (%)		
	I	II	III
0.1 nM			-13.2
1 nM	8.9		39.6
10 nM	0.0		-28.3
100 nM	14.3	5.2	-17.0
1 µM	25.0	7.8	-13.2
2.5 µM	48.2	8.6	-1.9
5 µM	60.7	16.4	47.2
10 µM	91.1	50.0	81.1
25 µM		99.1	88.7
50 µM		100.9	100.0
100 µM	91.1	94.0	62.3
250 µM	80.4		66.0



Compound 3

	Inhibition (%)		
	I	II	III
0.1 nM	7.1	3.7	2
1 nM	5.4	-7.4	-18.4
10 nM	10.7	-7.4	-30.6
100 nM	33.9	22.2	-6.1
1 µM	25	0.0	-6.1
2.5 µM	35.7	7.4	-14.3
5 µM	37.5	25.9	-18.4
10 µM	71.4	14.8	22.4
25 µM	96.4	48.1	-34.7
50 µM	105.4	81.5	87.8
100 µM	116.1	74.1	87.8
250 µM	116.1	88.9	
500 µM		81.5	79.6



Compound 3a

	Inhibition (%)	
	I	II
0.1 nM	-15.2	-17.6
1 nM	45.5	23.5
10 nM	-9.1	-5.9
100 nM	3.0	
1 µM	15.2	23.5
10 µM	3.0	5.9
100 µM	51.5	47.1
250 µM	75.8	100.0

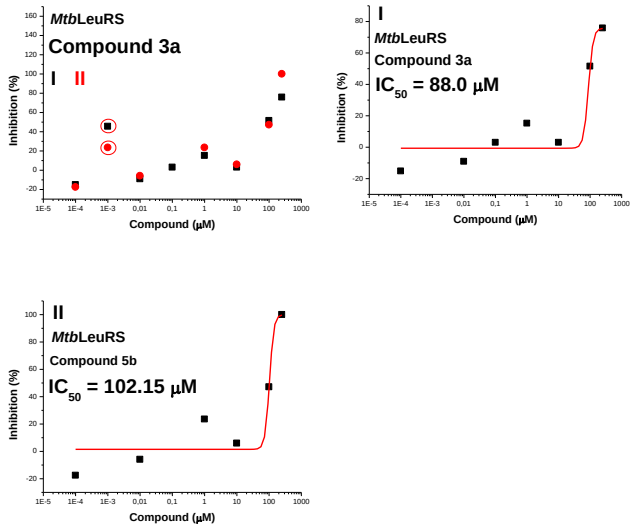
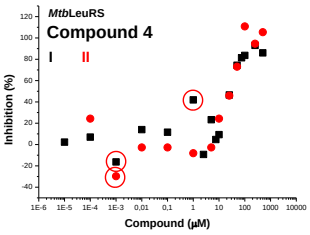
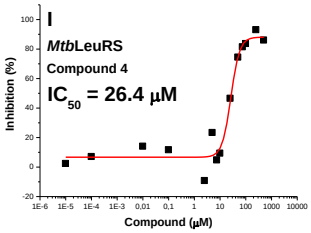


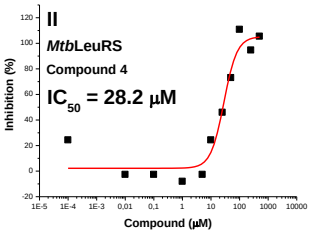
Figure S3-2. Inhibition of *Mtb*LeuRS in presence of compounds **2, 3, 3a, 4, 5, 5a, and 5b**. Percent reductions in enzyme activity were plotted against inhibitor concentrations from 0.01 nM to 500 µM.

Compound 4

	Inhibition (%)	
	I	II
0.01 nM	2.3	
0.1 nM	7	24.3
1 nM	-16.3	-29.7
10 nM	14	-2.7
100 nM	11.6	-2.7
1 µM	41.9	-8.1
2.5 µM	-9.3	
5 µM	23.3	-2.7
7.5 µM	4.7	
10 µM	9.3	24.3
25 µM	46.5	45.9
50 µM	74.4	73
75 µM	81.4	
100 µM	83.6	110.8
250 µM	93	94.6
500 µM	86	105.4

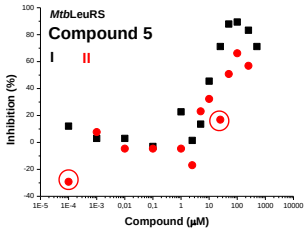


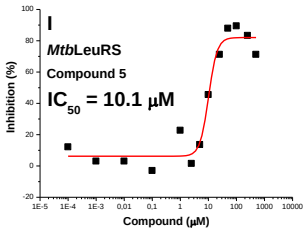




Compound 5

	Inhibition (%)	
	I	II
0.1 nM	12.1	-29.2
1 nM	3	7.7
10 nM	3	-4.6
100 nM	-3	-4.6
1 µM	22.7	-4.6
2.5 µM	1.5	-16.9
5 µM	13.6	23.1
10 µM	45.5	32.3
25 µM	71.2	16.9
50 µM	87.9	50.8
100 µM	89.4	66.2
250 µM	83.3	56.9
500 µM	71.2	26.2





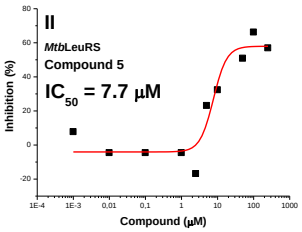
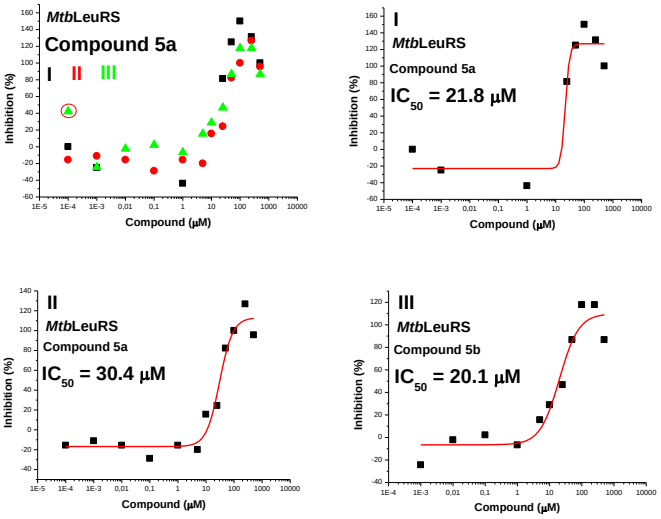


Figure S3-2 (Continued). Inhibition of *Mtb*LeuRS in presence of compounds **2, 3, 3a, 4, 5, 5a, and 5b**. Percent reductions in enzyme activity were plotted against inhibitor concentrations from 0.01 nM to 500 µM.

Compound 5a

	Inhibition (%)		
	I	II	III
0.1 nM	0.0	-15.6	42.2
1 nM	-25.0	-11.1	-24.4
10 nM		-15.6	-2.2
100 nM		-28.9	2.2
1 µM	43.8	-15.6	-6.7
5 µM		-20.0	15.6
10 µM		15.6	28.9
25 µM	81.3	24.4	46.7
50 µM	125.0	82.2	86.7
100 µM	150.0	100.0	117.8
250 µM	131.3	126.7	117.8
500 µM	100.0	95.6	86.7



Compound 5b

	Inhibition (%)		
	I	II	III
0.1 nM	4.8	-23.1	-13.7
1 nM	0.0	-15.4	-21.6
10 nM	0.0	7.7	-5.9
100 nM	-33.3	-46.2	5.9
1 µM	4.8	-38.5	-5.9
10 µM	0.0		-2.0
25 µM		23.1	25.5
50 µM		100.0	49.0
75 µM		107.7	84.3
100 µM	119.0	115.4	103.9
250 µM	128.6		119.6
500 µM			111.8

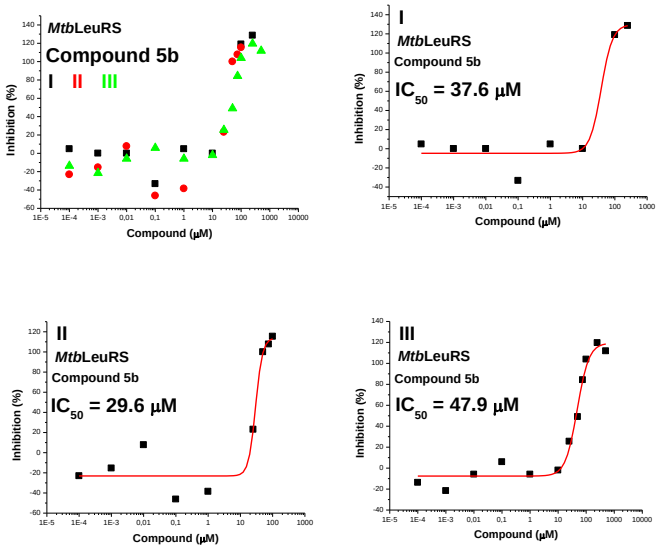
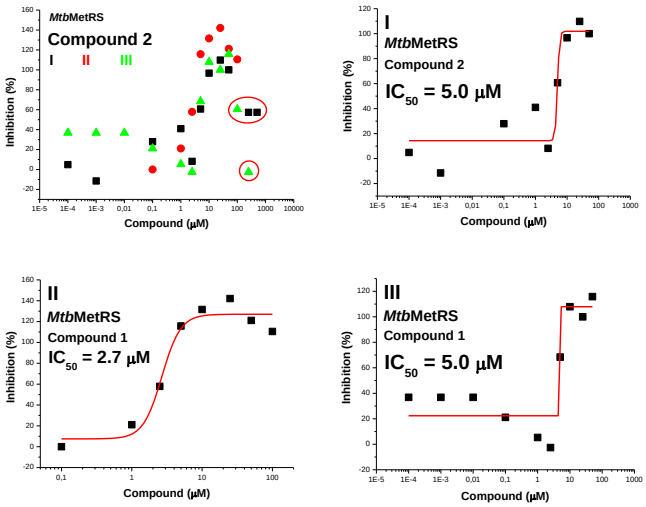


Figure S3-2 (Continued). Inhibition of *Mtb*LeuRS in presence of compounds **2, 3, 3a, 4, 5, 5a, and 5b**. Percent reductions in enzyme activity were plotted against inhibitor concentrations from 0.01 nM to 500 µM.

Compound 2

	Inhibition (%)		
	I	II	III
0.1 nM	4.9		36.8
1 nM	-11.5		36.8
10 nM			36.8
100 nM	27.9	0	21.1
1 µM	41	21.1	5.3
2.5 µM	8.2	57.9	-2.6
5 µM	60.7	115.8	68.4
10 µM	96.7	131.6	107.9
25 µM	109.8	142.1	100
50 µM	100	121.1	115.8
100 µM		110.5	60.5
250 µM	57.4		-2.6
500 µM	57.4		



Compound 3

	Inhibition (%)			
	I	II	III	IV
0.1 nM	12.5		9.7	0
1 nM	-6.3			14.3
10 nM	3.1		22.6	9.5
100 nM	6.3	-3.6	29.0	-9.5
1 µM	34.4	0		19
2.5 µM	25	17.9		66.7
5 µM	40.6	3.6	29.0	57.1
10 µM	71.9	53.6	41.9	90.5
25 µM		100	80.6	104.8
50 µM	96.9	100	112.9	119
100 µM	96.9	114.3	119.4	100
250 µM	103.1		132.3	71.4
500 µM	106.3		132.3	52.4

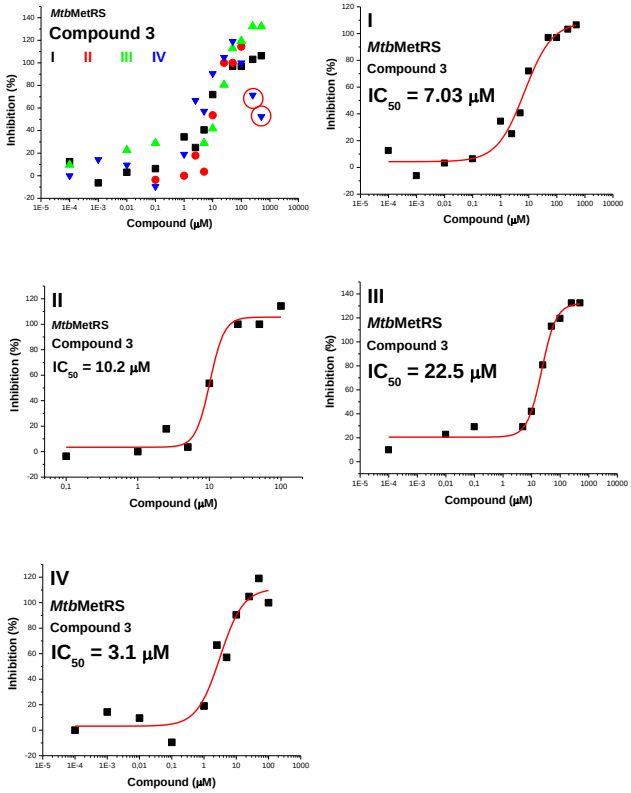
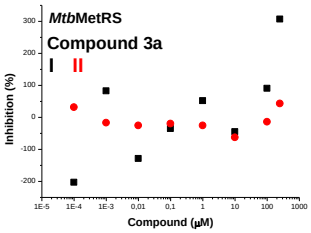


Figure S3-3. Inhibition of *Mtb*MetRS in presence of compounds **2, 3, 3a, 4, 5, 5a, and 5b**. Percent reductions in enzyme activity were plotted against inhibitor concentrations from 0.01 nM to 500 µM.

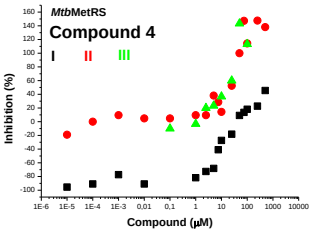
Compound 3a

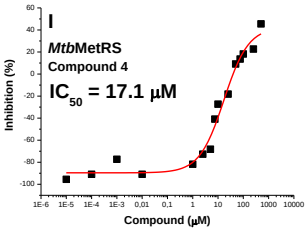
	Inhibition (%)	
	I	II
0.1 nM	-203.2	31.4
1 nM	82.3	-17.1
10 nM	-129.0	-25.7
100 nM	-35.5	-20.0
1 µM	51.6	-25.7
10 µM	-45.2	-62.9
100 µM	90.3	-14.3
250 µM	306.5	42.9

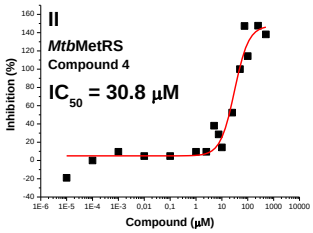


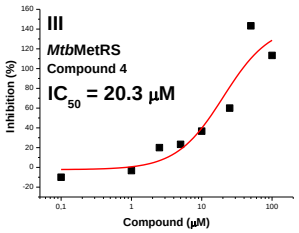
Compound 4

	Inhibition (%)		
	I	II	III
0.01 nM	-95.5	-19	
0.1 nM	-90.9	0	
1 nM	-77.3	9.5	
10 nM	-90.9	4.8	
100 nM		4.8	-10
1 µM	-81.8	9.5	-3.3
2.5 µM	-72.7	9.5	20
5 µM	-68.2	38.1	23.3
7.5 µM	-40.9	28.6	
10 µM	-27.3	14.3	36.7
25 µM	-18.2	52.4	60
50 µM	9.1	100	143.3
75 µM	13.6	147.3	
100 µM	18.2	114.3	113.3
250 µM	22.7	147.6	
500 µM	45.5	138.1	



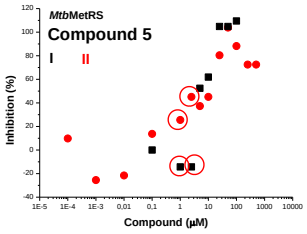


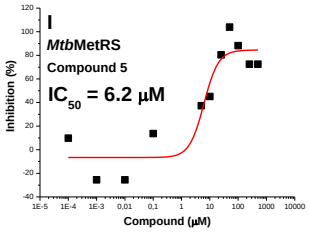




Compound 5

	Inhibition (%)	
	I	II
0.01 nM		
0.1 nM	9.8	
1 nM	-25.5	
10 nM	-21.6	
100 nM	13.7	0
1 µM	25.5	-14.3
2.5 µM	45.1	-14.3
5 µM	37.3	52.4
10 µM	45.1	61.9
25 µM	80.4	104.8
50 µM	103.9	104.8
100 µM	88.2	109.5
250 µM	72.5	
500 µM	72.5	





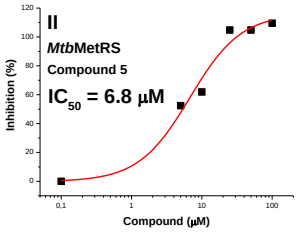
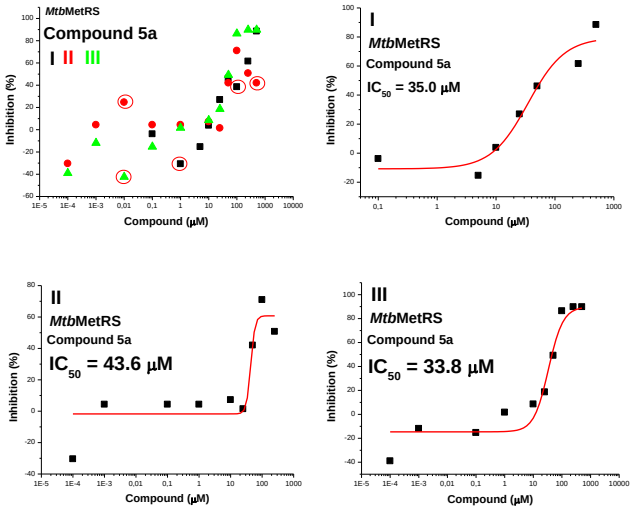


Figure S3-3 (Continued). Inhibition of *Mtb*MetRS in presence of compounds **2, 3, 3a, 4, 5, 5a, and 5b**. Percent reductions in enzyme activity were plotted against inhibitor concentrations from 0.01 nM to 500 µM.

Compound 5a

	Inhibition (%)		
	I	II	III
0.1 nM		-30.4	-39.0
1 nM		4.4	-11.9
10 nM		24.6	-42.4
100 nM	-3.9	4.4	-15.3
1 µM	-30.8	4.4	1.7
5 µM	-15.4		
10 µM	3.9	7.3	8.5
25 µM	26.9	1.5	18.6
50 µM	46.2	42.0	49.2
100 µM	38.5	71.0	86.4
250 µM	61.5	50.7	89.8
500 µM	88.5	42.0	89.8



Compound 5b

	Inhibition (%)	
	I	II
0.1 nM	-66.7	16.42
1 nM	25.9	-7.46
10 nM	-48.2	-19.4
100 nM	-18.5	-22.39
1 µM	7.4	7.46
10 µM	-51.9	-25.37
25 µM	-18.5	16.42
50 µM	22.2	1.49
100 µM	22.2	19.4
250 µM	103.7	73.13
500 µM	107.4	76.12

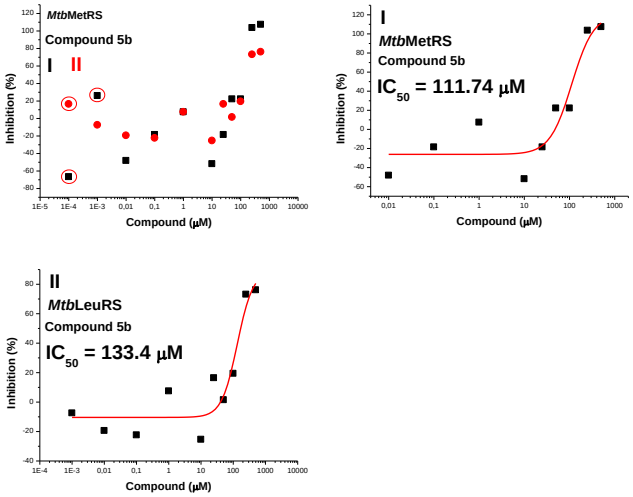


Figure S3-3 (Continued). Inhibition of *Mtb*MetRS in presence of compounds **2, 3, 3a, 4, 5, 5a, and 5b**. Percent reductions in enzyme activity were plotted against inhibitor concentrations from 0.01 nM to 500 µM.

Table S2. Viability (MTT assay) of HEK293 and HepG2 cells exposed to compound **3**.

Compound **3** (μM)	Cell viability† (%)	
	HEK293	**HepG2**
6.25	97 ± 9	99 ± 7
12.5	96 ± 8	98 ± 5
25	99 ± 11	96 ± 6
50	100 ± 7	93 ± 2
100	95 ± 12	88 ± 2

The values represent the mean ± s.d. of three independent experiments.

†Expressed as a percentage relative to the control wells. Control wells did not contain compound **3**.